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Supporting Information

Concise Synthesis of Hemigossypol via Sequential Palladium-Catalyzed Regiospecific Oxygenations of Naphthalene Ring

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Scheme S1. Synthesis of compound 3.

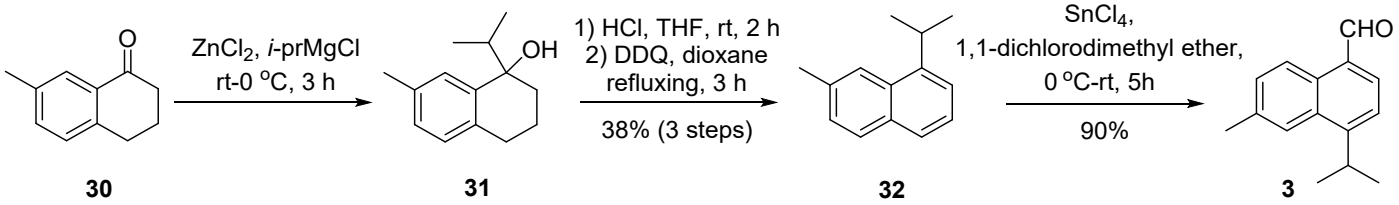
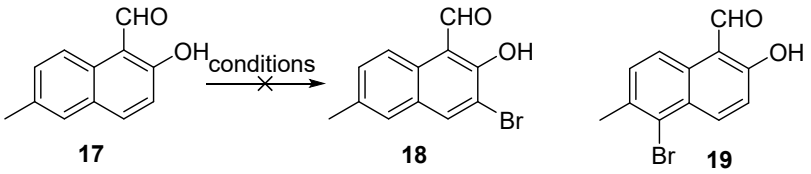


Table S1. Halogenation of compound 17 under various conditions



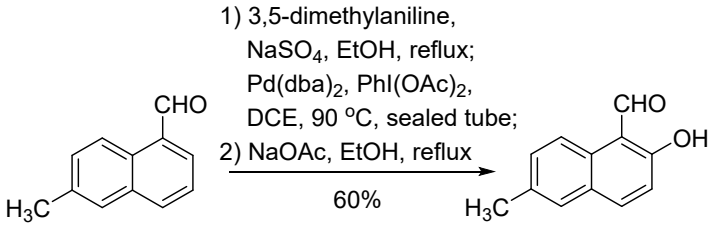
entry	conditions[a]	product	Yield (%)
1	Br_2, $AlCl_3$, DCM, rt, 1 h	18	94
2	Br_2, AcOH, 90 °C, 6 h	18	54
3	NBS, AIBN, CCl_4, reflux, 1 h	np[b]	
4	Py·HBr_3, DCM, rt, 12 h	np[b]	
5	SO_2Cl_2,TEMP, toluone, 70 °C, 6 h	np[b]	
6	NaOCl, KOH, H_2O, rt, 1h	np[b]	
7	NIS, PEG-400, rt, 12 h	nr[c]	
8	KIO_3, H_3PO_4, I_2, AcOH, EtOH, rt, 12 h	nr[c]	
9	HIO_3, I_2, EtOH, H_2O, rt, 12 h	nr[c]	
10	NIS, $AlCl_3$, DCM, -20 °C-rt, 12 h	nr[c]	
11	chloramine T, NaI, DMF, rt, 12 h	nr[c]	

[a]Reaction was performed with 0.2 mmol of **17**; all yields are reported as isolated yields. [b]np = no product. [c]nr = no reaction.

1. General materials and methods.

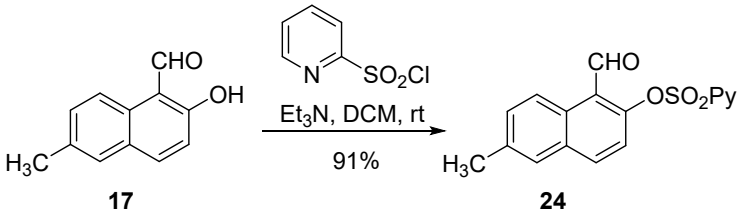
^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded at ambient temperature on Bruker AV-500, VNMRS 600 and Inova 400 instruments. The chemical shifts were reported in δ (ppm) using the δ 7.26 signal of $CDCl_3$ and δ 2.50 signal of DMSO-d_6 (^{1}H NMR), the δ 77.16 signal of $CDCl_3$ and δ 39.52 signal of DMSO-d_6 (^{13}C NMR) as internal standards. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HR-ESI-MS experiments were carried out using a Finnigan MAT 95 (EI/CI) or on a Thermo Fisher Scientific LTQ Orbitrap XL or Thermo Fisher Scientific Q Exactive Plus in the positive mode. All commercially available reagents were used without further purification, purchased from Acros or Aldrich and used without further purification unless otherwise noted. Solvents were predistilled according to standard laboratory methods. The progress of the reactions was monitored by analytical thin-layer chromatography (TLC) from Jiangyou Chemical Co., Ltd (Yantai, China). Visualization of the developed TLC plates was performed with ultraviolet irradiation (254 nm) or by staining with basic potassium permanganate solution. And silica gel (200-300 mesh) for column chromatography was purchased from Haiyang Chemical Co., Ltd (Qingdao, China), particle size 0.040-0.063 mm (230-240 mesh, flash).

2. Procedure for Synthesis of hemigossypol



5 **17**

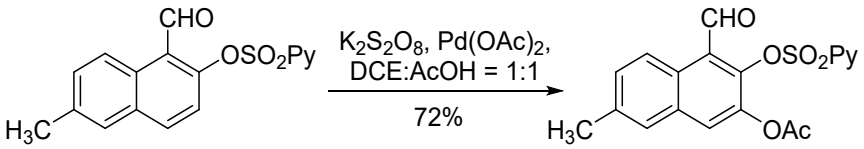
2-Hydroxy-6-methyl-1-naphthaldehyde (17). To a stirring solution of naphthaldehyde **5** (1.7 g, 10 mmol) in EtOH (100 mL, 0.1 M) at room temperature was added 3,5-dimethylaniline (1.33 g, 11 mmol) and sodium sulfate (14.2 g, 100 mmol). The reaction mixture was refluxed with stirring for 12 h. The reaction mixture was cooled and filtered. The filtrate was concentrated *in vacuo* and recrystallized with EtOH at -20 °C. The precipitates was filtered to give the imime intermediate as yellow powders. In a sealed tube with magnetic stir bar was charged with the imine intermediate (2.73 g, 10 mmol), $Pd(dba)_2$ (287 mg, 0.5 mmol), and $PhI(OAc)_2$ (8.05 g, 25 mmol) in anhydrous DCE (0.1 M, 100 mL). The reaction tube was sealed and heated to 90 °C by using an oil bath for 7 h. The reaction mixture was then treated with silica gel (3 g, 200-300 mesh) with stirring at the reflux temperature for 1 h. The resulting mixture was cooled to room temperature and filtrated. The filtrate was concentrated to obtain the crude 2-acetoxyl product. NaOAc (25 mL, 1.0 M in H_2O) was added to the crude 2-acetoxyl product dissolved in EtOH (100 mL, 0.1 M) and refluxed for 12 h. The resulting mixture was cooled and neutralized by the addition of 1N HCl aqueous solution. The organic phase was separated and the remaining aqueous layer extracted with EtOAc twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. After removing the volatiles, the residue was purified by column chromatography (EtOAc/n-hexane = 1/30) to afford the product **17** as a yellow power (1.12 g, 6 mmol, 60% in two steps total yield). R_f 0.60 (10:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.05 (s, 1H), 10.80 (s, 1H), 8.25 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 9.0 Hz, 1H), 7.58 (s, 1H), 7.46 (dd, J = 8.5, 1.5 Hz, 1H), 7.11 (d, J = 9.0 Hz, 1H), 2.50 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.4, 164.4, 138.8, 134.2, 131.3, 131.0, 128.8, 128.2, 119.2, 118.6, 111.4, 21.3. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{12}H_{11}O_2$ 187.0759, found 187.0762.



17 **24**

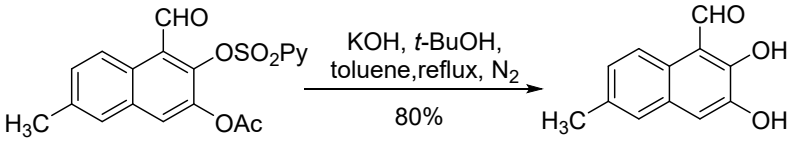
1-Formyl-6-methylnaphthalen-2-yl pyridine-2-sulfonate (24). To a stirring solution of compound **17** (930 mg,

5.0 mmol) in DCM (25 mL, 0.2 M) at room temperature was added Et_3N (1.01 g, 10 mmol) and pyridine-2-sulfonyl chloride (1.77 g, 10 mmol). The reaction mixture was poured into water and extracted with DCM twice. The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/2) to afford compound **24** as an off-white power (1.47 g, 4.5 mmol, 91%). R_f 0.30 (2:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.56 (s, 1H), 9.03 (d, *J* = 9.0 Hz, 1H), 8.80 (d, *J* = 4.5 Hz, 1H), 8.02 (d, *J* = 7.5 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.95 (td, *J* = 7.5, 1.5 Hz, 1H), 7.64-7.62 (m, 2H), 7.52-7.49 (m, 2H), 2.51 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 190.5, 153.0, 152.8, 151.0, 138.7, 137.3, 136.1, 132.7, 132.4, 128.9, 128.7, 127.5, 125.6, 124.5, 121.3, 21.6. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{17}H_{14}NO_4S$ 328.0644, found 328.0647.



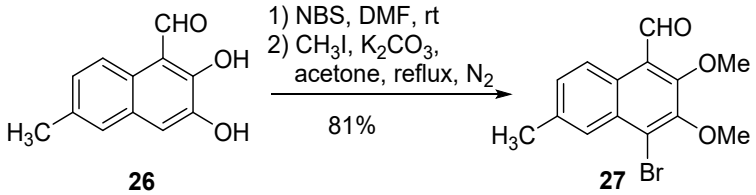
24 **25**

4-Formyl-7-methyl-3-((pyridin-2-ylsulfonyl)oxy)naphthalen-2-yl acetate (25). To a solution of compound **24** (1.47 g, 4.5 mmol) in a mixture solution DCE (9 mL, 0.5 M) and AcOH (9 mL, 0.5 M) was added $K_2S_2O_8$ (2.43 g, 9.0 mmol) and $Pd(OAc)_2$ (101 mg, 0.45 mmol) at room temperature. The mixture was stirred at 80 °C for 48 h in a sealed tube. Upon completion, the resulting mixture was cooled. The reaction mixture was poured into water and extracted with DCM twice. The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/1) to afford compound **25** as an orange power (1.25 g, 3.2 mmol, 72%). R_f 0.30 (1:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.33 (s, 1H), 9.01 (d, *J* = 9.0 Hz, 1H), 8.84 (d, *J* = 4.0 Hz, 1H), 8.05 (d, *J* = 7.5 Hz, 1H), 8.00 (td, *J* = 8.0, 1.5 Hz, 1H), 7.85 (s, 1H), 7.69 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H), 7.60 (s, 1H), 7.49 (dd, *J* = 9.0, 1.5 Hz, 1H), 2.51 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.8, 168.7, 153.3, 151.2, 145.5, 140.9, 138.8, 138.1, 132.6, 132.0, 128.8, 127.9, 127.2, 126.9, 125.6, 124.8, 124.5, 21.6, 21.0. HRMS (ESI) m/z $[M-CH_3CO+2H]^+$calcd for $C_{17}H_{14}NO_5S$ 344.0593, found 344.0587.



25 **26**

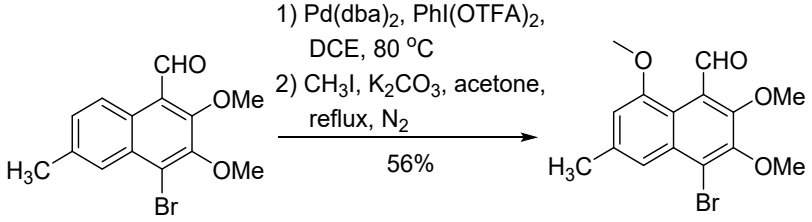
2,3-Dihydroxy-6-methyl-1-naphthaldehyde (26). To a solution of compound **25** (1.15 g, 3.0 mmol) in toluene (15 mL, 0.2 M) was added KOH (840 mg, 15 mmol) and *t*-BuOH (2.2 g, 28.5 mmol). The reaction mixture was heated to reflux under N_2 by using an oil bath for 4 h. The resulting mixture was cooled and neutralized by the addition of 1N HCl aqueous solution. The organic phase was separated and the remaining aqueous layer extracted with EtOAc twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. After removing the volatiles, the residue was purified by column chromatography (EtOAc/n-hexane = 1/5) to afford the product **26** as a yellow power (485 mg, 2.4 mmol, 80%). R_f 0.50 (2:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.48 (s, 1H), 10.75 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.49 (s, 1H), 7.45 (s, 1H), 7.33 (dd, *J* = 9.0, 2.0 Hz, 1H), 5.94 (s, 1H), 2.48 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.3, 154.3, 144.5, 135.2, 129.0, 128.9, 127.7, 126.0, 118.8, 118.5, 111.8, 21.7. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{12}H_{11}O_3$ 203.0708, found 203.0714.



26 **27**

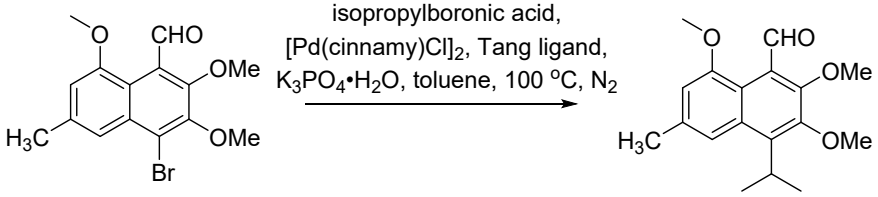
4-Bromo-2,3-dimethoxy-6-methyl-1-naphthaldehyde (27). NBS (374 mg, 2.1 mmol) was added to a solution of compound **25** (383 mg, 1.9 mmol) in DMF (19 mL, 0.1 M) at room temperature and stirred for 1 h. The reaction mixture was poured into water and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford the corresponding brominated product without further purification.

To a solution of crude brominated product in acetone (19 mL) was added CH_3I (809 mg, 5.7 mmol) and K_2CO_3 (787 mg, 5.7 mmol). After refluxed under N_2 by using an oil bath for 6 h, the resulting mixture was cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc twice. The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/10) to afford compound **27** as a white power (474 mg, 1.5 mmol, 81% in two steps total yield). R_f 0.50 (5:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.77 (s, 1H), 9.11 (d, J = 8.5 Hz, 1H), 8.04 (s, 1H), 7.45 (dd, J = 9.0, 2.0 Hz, 1H), 4.09 (s, 3H), 3.99 (s, 3H), 2.55 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 159.2, 149.8, 137.5, 131.3, 130.1, 126.6, 126.4, 125.4, 125.0, 122.9, 63.3, 61.1, 21.9. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{14}H_{14}BrO_3$ 309.0126, found 309.0142.



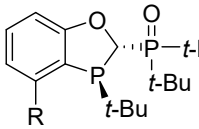
27 **28**

4-Bromo-2,3,8-trimethoxy-6-methyl-1-naphthaldehyde (28). To a stirring solution of compound **27** (308 mg, 1.0 mmol) in DCE (5.0 mL, 0.2 M) was added fresh $Pd(dba)_2$ (17.3 mg, 0.03 mmol), $PhI(OTFA)_2$ (860 mg, 2.0 mmol), and 2-aminobenzenesulfonic acid (17.3 mg, 0.1 mmol) at room temperature. The reaction mixture was stirred at 80 °C by using an oil bath for 8 h. The resulting mixture was cooled to room temperature and filtrated. The filtrate was concentrated under 30 °C to obtain the crude product. To a solution of the above crude product in acetone (10 mL，0.1 M) was added CH_3I (284 mg, 2.0 mmol) and K_2CO_3 (276 mg, 2.0 mmol). After refluxed under N_2 by using an oil bath for 6 h, the resulting mixture was cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc twice. The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/30) to afford compound **28** as a yellow power (189 mg, 0.56 mmol, 56% in two steps total yield). R_f 0.50 (5:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.63 (s, 1H), 6.70 (s, 1H), 3.97 (s, 3H), 3.93 (s, 6H), 2.52 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 193.3, 155.0, 150.8, 148.9, 137.7, 131.4, 129.2, 119.3, 118.9, 118.0, 108.4, 63.2, 61.0, 56.2, 22.4. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{15}H_{16}BrO_4$ 339.0232, found 339.0218.



28 **29**

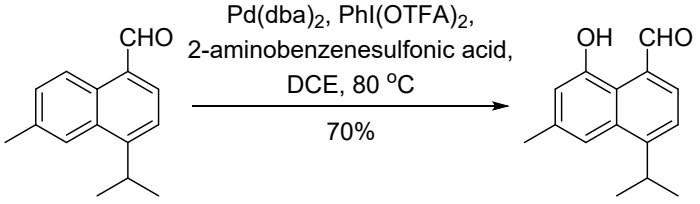
Tang ligand:



R	yield	*i*-Pr/*n*-Pr
NMe_2	83%	20/1
OMe	45%	3/1

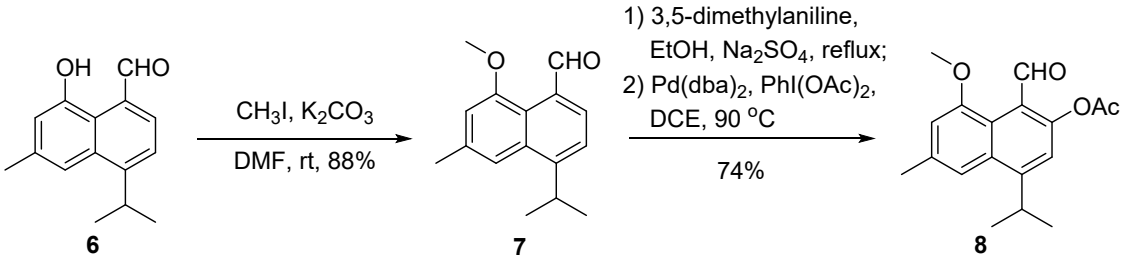
4-Isopropyl-2,3,8-trimethoxy-6-methyl-1-naphthaldehyde (29). Isopropylboronic (51 mg, 0.6 mmol), $[Pd(cinnamy)Cl]_2$ (4.6 mg, 0.009 mmol), Ligand (7 mg, 0.018 mmol) and $K_3PO_4 \cdot H_2O$ (210 mg, 0.9 mmol) were added to a solution of compound **28** (101 mg, 0.3 mmol) in dry toluene (1.5 mL, 0.2 M) under N_2 atmosphere. The reaction mixture was stirred at 100 °C by using an oil bath for 24 h. The resulting mixture was cooled to room temperature. The reaction mixture was poured into water and extracted with EtOAc twice. The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/30) to afford compound **29** as a white power (75 mg, 0.25 mmol, 83 % yield). R_f 0.30 (10:1 hexane/EtOAc). ^1H NMR (500 MHz, $CDCl_3$) δ 10.65 (s, 1H), 7.53 (s, 1H), 6.64 (s, 1H), 3.88-3.91 (m, 10H), 2.49 (s, 3H), 1.49 (d, J = 7.0 Hz, 6H).^{13}C NMR (125 MHz, $CDCl_3$) δ 194.0, 155.5, 149.2, 137.9, 135.4, 131.3, 127.8, 119.0, 116.4, 107.3×2, 62.4, 61.1, 56.0, 31.6, 22.6, 22.1×2. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{18}H_{23}O_4$ 303.1596, found 303.1609.

3. Synthesis of compound 9, 11 and 12



3 **6**

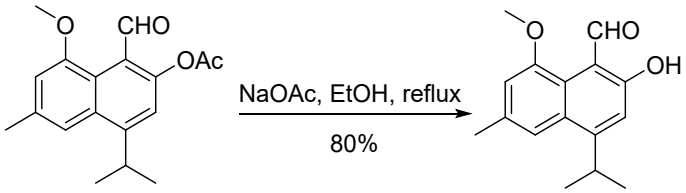
8-Hydroxy-4-isopropyl-6-methyl-1-naphthaldehyde (6). To a solution of compound **3** (2.12 g, 10 mmol) in DCE (50 mL, 0.2 M) was added 2-aminobenzenesulfonic acid (173 mg, 1.0 mmol), $Pd(dba)_2$ (173 mg, 0.3 mmol) and $PhI(OTFA)_2$ (8.6 g, 20 mmol). The reaction mixture was stirred at 80 °C by using an oil bath for 12 h. The resulting mixture was cooled to room temperature and filtered. The filtrate was poured into water and extracted with DCM twice. The combined organic phases were washed with brine, dried over Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/20) to afford compound **6** as a yellow power (1.6 g, 7.0 mmol, 70 % yield). R_f 0.50 (10:1 hexane/EtOAc). ^1H NMR (500 MHz, $CDCl_3$) δ 11.84 (s, 1H), 9.78 (s, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.55 (d, J = 7.0 Hz, 1H), 7.54 (s, 1H), 7.06 (s, 1H), 3.84-3.76 (m, 1H), 2.53 (s, 3H), 1.46 (s, 3H), 1.45 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.5, 156.1, 155.7, 142.5, 138.9, 134.3, 130.3, 120.9, 119.9, 117.2, 114.9, 29.9, 23.23×2, 21.8. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{15}H_{17}O_2$ 229.1229, found 229.1245.



6 7 8

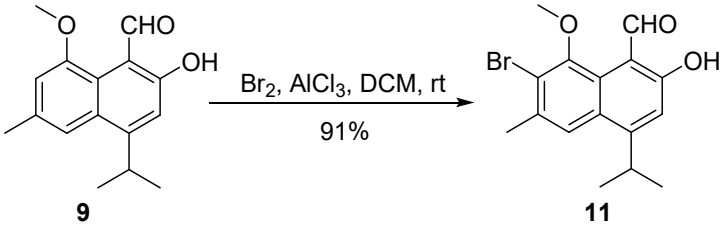
4-Isopropyl-8-methoxy-6-methyl-1-naphthaldehyde (7). To a stirring solution of compound **6** (1.6 g, 7.0 mmol) in DMF (14 mL, 0.5 M) was add K_2CO_3 (1.4 g, 10 mmol) and MeI (1.4 g, 10 mmol) at room temperature. The reaction mixture was stirred for 2 h. The reaction mixture was poured into water and extracted with EA twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solution was concentrated *in vacuo* to afford compound **7** (1.5 g, 6.2 mmol, 88%).

1-Formyl-4-isopropyl-8-methoxy-6-methylnaphthalen-2-yl acetate (8). To a stirring solution of compound **7** (1.45 g, 6.0 mmol) in EtOH (60 mL, 0.1 M) was add 3,5-dimethylaniline (799 mg, 6.6 mmol) and sodium sulfate (8.5 g, 60 mmol) at room temperature. The reaction mixture was refluxed with stirring for 12 h. The reaction mixture was cooled and filtered. The filtrate was concentrated *in vacuo* and recrystallized with EtOH. The precipitates was filtered to give the imime intermediate as yellow powders. In a sealed tube with magnetic stir bar was charged with the imine intermediate (2.07 g, 6.0 mmol), $Pd(dba)_2$ (172 mg, 0.3 mmol), and $PhI(OAc)_2$ (4.83 g, 15 mmol) in anhydrous DCE (60 mL, 0.1 M). The reaction tube was sealed and heated to 90 °C by using an oil bath for 7 h. The reaction mixture was then treated with silica gel (3 g, 200-300 mesh) with stirring at the reflux temperature for 1 h. The resulting mixture was cooled to room temperature and filtrated. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/10) to afford compound **8** as a yellow power (1.32 g, 4.4 mmol, 74% in two steps total yield). R_f 0.50 (5:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.55 (s, 1H), 7.51 (s, 1H), 7.09 (s, 1H), 6.77 (s, 1H), 3.93 (s, 3H), 3.73-3.64 (m, 1H), 2.53 (s, 3H), 2.32 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.4, 169.9, 156.1, 149.3, 144.8, 136.2, 131.3, 124.2, 122.4, 118.5, 115.8, 108.8, 55.9, 29.1, 23.2×2, 22.4, 21.0. HRMS (ESI) m/z [M-CH_3CO+2H]$^+$calcd for $C_{16}H_{19}O_3$ 259.1334, found 259.1347.



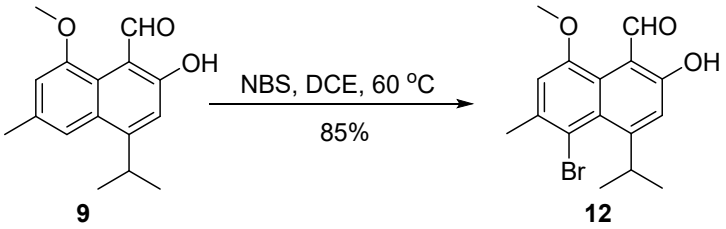
8 9

2-Hydroxy-4-isopropyl-8-methoxy-6-methyl-1-naphthaldehyde (9). NaOAc (10 mL, 1.0 M) was added to the compound **8** (1.2 g, 4.0 mmol) dissolved in EtOH (40 mL, 0.1 M) and refluxed for 12 h. The resulting mixture was cooled and neutralized by the addition of 1N HCl aqueous solution. The organic phase was separated and the remaining aqueous layer extracted with EtOAc twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. After removing the volatiles, the residue was purified by column chromatography (EtOAc/n-hexane = 1/50) to afford the product **9** as a yellow power (825 mg, 3.2 mmol, 80%). R_f 0.70 (20:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 14.01 (s, 1H), 11.12 (s, 1H), 7.51 (s, 1H), 7.07 (s, 1H), 6.91 (s, 1H), 3.99 (s, 3H), 3.70-3.62 (m, 1H), 2.51 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.8, 165.1, 156.3, 156.0, 133.6, 128.4, 122.0, 116.7, 116.3, 112.2, 111.0, 55.7, 29.5, 23.11×2, 21.90. HRMS (ESI) m/z [M+H]$^+$calcd for $C_{16}H_{19}O_3$ 259.1334, found 259.1356.



9 11

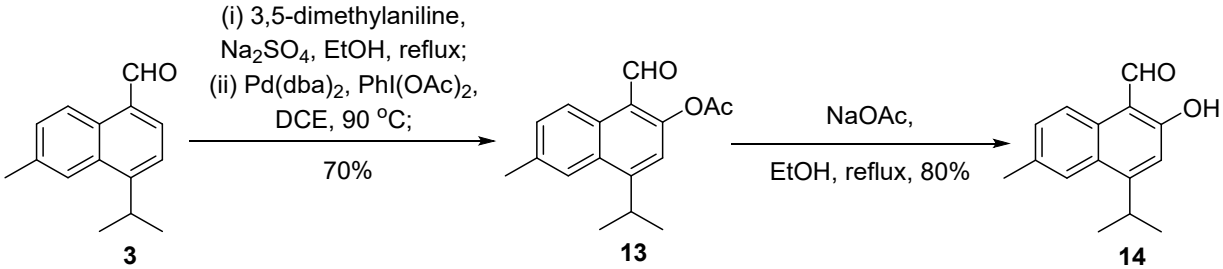
7-Bromo-2-hydroxy-4-isopropyl-8-methoxy-6-methyl-1-naphthaldehyde (11). To a stirring solution of compound **9** (258 mg, 1.0 mmol) in DCM (10 mL, 0.1 M) was add $AlCl_3$ (13.3 mg, 0.1 mmol) and Br_2 (174.6 mg, 1.1 mmol) at room temperature for 1 h. The reaction mixture was poured into water and extracted with DCM twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/50) to afford methoxylated product **11** as a yellow power (305 mg, 0.91 mmol, 91%). R_f 0.60 (20:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.92 (s, 1H), 11.07 (s, 1H), 7.75 (s, 1H), 7.08 (s, 1H), 3.79 (s, 3H), 3.67-3.59 (m, 1H), 2.58 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.8, 165.7, 156.5, 153.2, 134.6, 127.2, 125.8, 122.3, 121.4, 116.7, 110.8, 59.6, 29.4, 23.8, 23.1×2. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{16}H_{18}BrO_3$ 337.0439, found 337.0442.



9 12

5-Bromo-2-hydroxy-4-isopropyl-8-methoxy-6-methyl-1-naphthaldehyde (12). To a solution of compound **9** (258 mg, 1.0 mmol) in DCE (5 mL, 0.2 M) was add NBS (195 mg, 1.1 mmol) at room temperature. The mixture was stirred at 60 °C by using an oil bath for 3 h, then cooled down. The mixture was added another NBS (195 mg, 1.1 mmol) and stirred at 60 °C for 3 h. The resulting mixture was cooled and poured into water, extracted with DCM twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/50) to afford methoxylated product **12** as a yellow power (285 mg, 0.85 mmol, 85%). R_f 0.40 (20:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.50 (s, 1H), 10.89 (s, 1H), 7.22 (s, 1H), 6.87 (s, 1H), 4.67-4.59 (m, 1H), 3.96 (s, 3H), 2.57 (s, 3H), 1.33 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.0, 164.1, 158.6, 155.0, 136.5, 128.9, 126.5, 120.0, 113.3, 112.1, 111.6, 56.4, 31.4, 25.9, 25.3×2. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{16}H_{18}BrO_3$ 337.0439, found 337.0434.

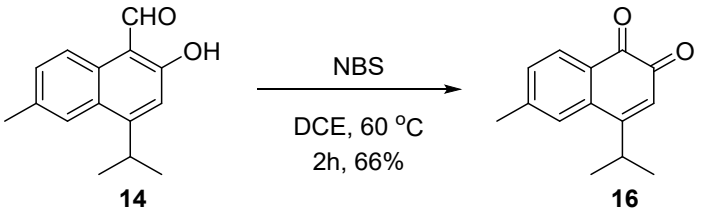
4. Synthesis of compound 14 and 16.



3 13 14

2-Hydroxy-4-isopropyl-6-methyl-1-naphthaldehyde (14). To a stirring solution of compound **3** (1.27 g, 6.0 mmol) in DCE (12 mL, 0.5 M) was added 3,5-dimethylaniline (799 mg, 6.6 mmol) and dry $MgSO_4$ (3.6 g, 30 mmol) at room temperature. The reaction tube was sealed and stirred at 75 °C for 12 h. The reaction mixture was cooled and filtered. The filtrate was concentrated *in vacuo* and EtOH (1 mL) was added. The mixture was then stored at -20 °C for 24-48 h until the yellow solid precipitated. The precipitates were filtered to give the imime

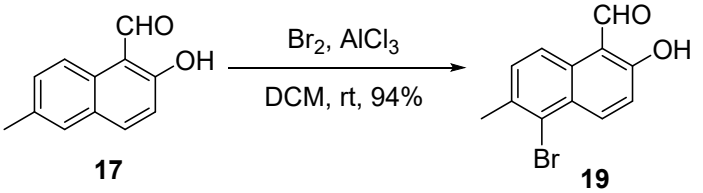
intermediate. In a sealed tube with a magnetic stir bar was charged with the imine intermediate (1.89 g, 6.0 mmol), $Pd(dba)_2$ (172 mg, 0.3 mmol), and $PhI(OAc)_2$ (4.83 g, 15 mmol) in anhydrous DCE (60 mL, 0.1 M). The reaction tube was sealed and heated to 90 °C by using an oil bath for 5 h. The reaction mixture was then treated with silica gel (3 g, 200-300 mesh) with stirring at the reflux temperature for 1 h. The resulting mixture was cooled to room temperature and filtrated. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/10) to afford compound **13** as a yellow oil (1.13 g, 4.2 mmol, 70%) for next step. To a solution of compound **13** (1.1 g, 4.0 mmol) in EtOH (20 mL, 0.2 M) was added NaOAc (5 mL, 2.0 M) and then refluxed for 12 h. The resulting mixture was cooled and neutralized by the addition of 1N HCl aqueous solution. The organic phase was separated and the remaining aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. After removing the volatiles, the residue was purified by column chromatography (EtOAc/n-hexane = 1/50) to afford product **14** as a yellow powder (730 mg, 3.2 mmol, 80%). R_f 0.70 (20:1 hexane/EtOAc). ^1H NMR (500 MHz, $CDCl_3$) δ 13.12 (s, 1H), 10.74 (s, 1H), 8.28 (d, J = 8.5 Hz, 1H), 7.87 (s, 1H), 7.44 (d, J = 8.5 Hz, 1H), 7.07 (s, 1H), 3.76-3.69 (m, 1H), 2.53 (s, 3H), 1.40 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.8, 164.3, 157.2, 133.8, 131.4, 130.4, 126.4, 123.9, 119.2, 115.3, 110.2, 29.2, 23.0×2, 21.6. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{15}H_{17}O_2$ 229.1229, found 229.1216.



14 **16**

4-Isopropyl-6-methylnaphthalene-1,2-dione (16). To a solution of compound **14** (228 mg, 1.0 mmol) in DCE (5 mL, 0.2 M) was add NBS (195 mg, 1.1 mmol) at room temperature. The mixture was stirred at 60 °C by using an oil bath for 2 h, then cooled down. The resulting mixture was cooled and poured into water, extracted with DCM twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (DCM/n-hexane = 1/2) to afford methoxylated product **16** as a yellow power (141 mg, 0.66 mmol, 66%). R_f 0.30 (10:1 hexane/EtOAc). ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 1H), 7.35 (s, 1H), 7.31 (d, *J* = 8.5 Hz, 1H), 6.32 (s, 1H), 3.27-3.22 (m, 1H), 2.44 (s, 3H), 1.31 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.4, 179.5, 163.2, 146.8, 134.8, 131.0, 130.7, 129.5, 126.5, 123.5, 29.1, 22.4, 22.0. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{14}H_{15}O_2$ 215.1072, found 215.1200.

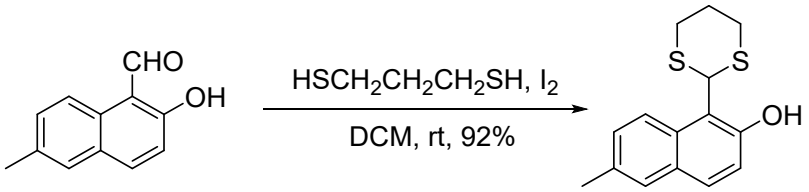
5. Synthesis of compound 19, 20 and 22.



17 **19**

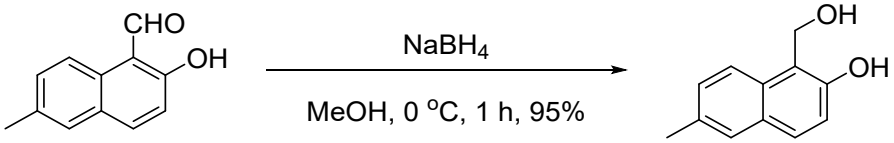
5-Bromo-2-hydroxy-6-methyl-1-naphthaldehyde (19). To a stirring solution of compound **17** (94 mg, 0.5 mmol) in DCM (10 mL, 0.1 M) was added $AlCl_3$ (6.7 mg, 0.1 mmol) and Br_2 (87.9 mg, 0.55 mmol) at room temperature for 1 h. The reaction mixture was poured into water and extracted with DCM twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/50) to afford product **19** as a yellow powder (124 mg, 0.47 mmol, 94%). R_f 0.60 (20:1 hexane/EtOAc). ^1H NMR (500 MHz, $CDCl_3$) δ 13.70 (s, 1H), 10.76 (s, 1H), 8.24-8.23 (m, 2H), 7.52 (s, 1H), 7.49 (dd, *J* = 9.0, 1.5 Hz, 1H), 2.51 (s, 3H). ^{13}C

NMR (125 MHz, $CDCl_3$) δ 193.3, 160.5, 140.8, 135.2, 131.7, 130.2, 128.7, 127.9, 118.6, 112.7, 112.1, 21.3. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{12}H_{10}BrO_2$ 264.9864, found 264.9866.



17 **20**

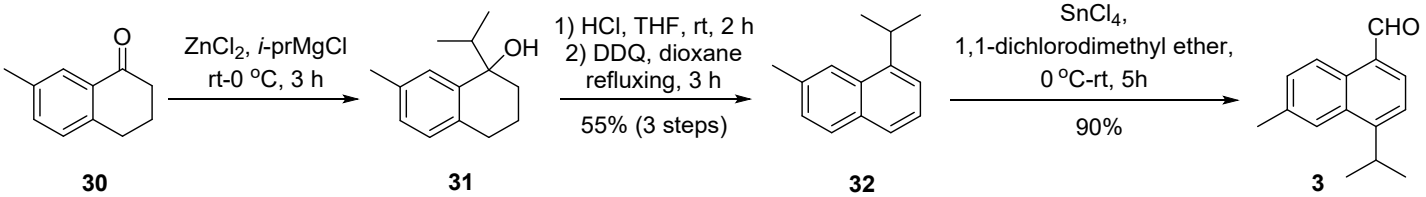
1-(1,3-Dithian-2-yl)-6-methylnaphthalen-2-ol (20). To a stirring solution of compound **17** (93 mg, 0.5 mmol) in DCM (2.5 mL, 0.2 M) was added I_2 (12.7 mg, 0.1 mmol) and 1,3-Dimercaptopropane (0.055 mL, 0.55 mmol) at room temperature for 1 h. The reaction mixture was poured into saturated sodium thiosulfate solution and extracted with DCM twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/20) to afford product **20** as a yellow powder (130 mg, 0.47 mmol, 92%). R_f 0.1 (10:1 hexane/EtOAc). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.15 (s, 1H), 8.80 (d, J = 9.0 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.53 (s, 1H), 7.28 (dd, J = 9.0, 3.5 Hz, 1H), 7.15 (d, J = 9.0 Hz, 1H), 6.29 (s, 1H), 3.16-3.11 (m, 2H), 2.95-2.92 (m, 2H), 2.40 (s, 3H), 2.20-2.17 (m, 1H), 1.87-1.79 (m, 1H). ^{13}C NMR (125 MHz, DMSO-d_6) δ 150.9, 132.0, 131.3, 129.5, 129.3×2, 127.8, 127.5, 126.2, 118.3, 116.5, 44.2, 32.5, 26.0, 21.3. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{15}H_{17}OS_2$ 277.0721, found 277.0745.



17 **22**

1-(Hydroxymethyl)-6-methylnaphthalen-2-ol (22). To a stirring solution of compound **17** (93 mg, 0.5 mmol) in THF (5 mL, 0.1 M) was added $NaBH_4$ (19 mg, 0.5 mmol) at 0 °C. The reaction mixture was then stirred at rt for 1 h. The reaction mixture was poured into water and extracted with EA twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (EtOAc/n-hexane = 1/10) to afford product **22** as a yellow power (89 mg, 0.48 mmol, 95%). R_f 0.2 (5:1 hexane/EtOAc). ^{1}H NMR (500 MHz, Methanol-d_4) δ 7.93 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.50 (s, 1H), 7.30 (dd, J = 8.5, 1.5 Hz, 1H), 7.06 (d, J = 9.0 Hz, 1H), 5.11 (s, 2H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, Methanol-d_4) δ 153.9, 133.1, 130.5, 130.0, 129.6, 128.3×2, 123.9, 119.0, 118.4, 56.3, 21.3. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{12}H_{13}O_2$ 189.0916, found 189.0900.

4. Synthesis of compound 3.



30 **31** **32** **3**

1-Isopropyl-7-methylnaphthalene (31). To a solution of *i*-prMgCl (1.0 M in THF, 1.1 mL,1.1 mmol) was added $ZnCl_2$ (13.6 mg, 0.1 mmol) at room temperature under nitrogen atmosphere. This solution was stirred at that temperature for 1 h. Then, the solution was cooled to 0 °C, and 7-methyl-3,4-dihydro-2H-naphthalen-1-one **30** (160 mg, 1.0 mmol) was added at 0 °C. The mixture was stirred for 2 h at 0 °C, and the reaction was monitored by TLC (compound **30** can not be comsumed completely, and the product **31** can not be distinguished from **30** in TLC). The resulting mixture was quenched by saturated aqueous NH_4Cl, extracted with EtOAc, and washed by

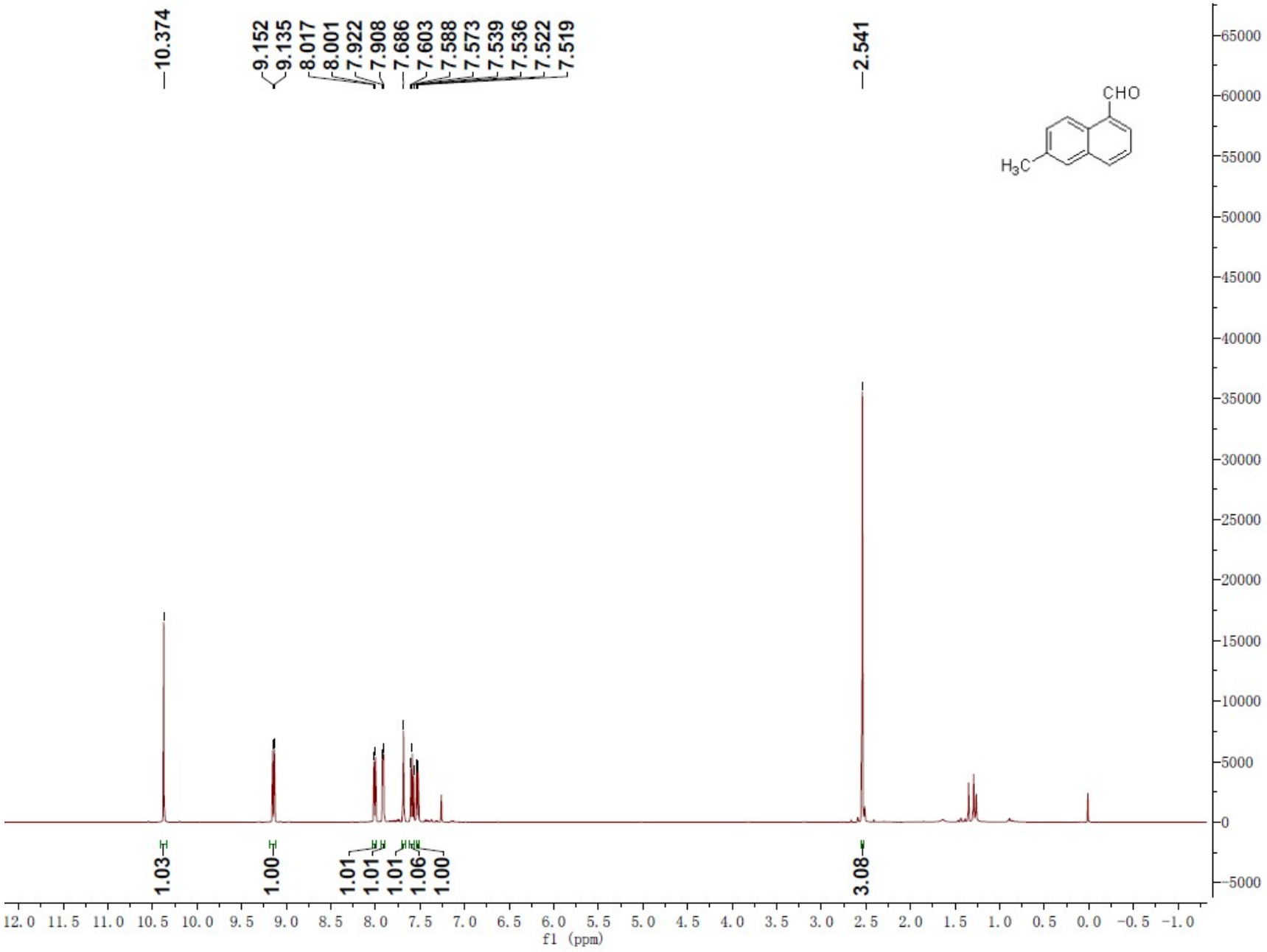
brine. The combined extracts were dried over $MgSO_4$. The organic phase was concentrated *in vacuo* to afford the mixture of **30** and **31**.

HCl (1 mL, 6 M) was added to a solution of crude product **31** in THF (1 mL, 0.5 M) at room temperature for 2 h. The reaction mixture was poured into water and extracted with EtOAc twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The filtrate was concentrated *in vacuo* to afford the corresponding product without further purification. To to a solution of the crude product in dioxane (3 mL, 0.3 M) was added DDQ (250 mg, 1.1 mmol) and mixture was refluxed for about 3 h. The resulting mixture was cooled and poured into water, extracted with EtOAc twice. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, and filtered. The solution was concentrated *in vacuo* and the residue was purified by column chromatography (petroleum ether) to afford product **32** as a colorless oil (101 mg, 0.55 mmol, 55% in three steps total yield). R_f 0.5 (petroleum ether). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.76 (d, *J* = 8.5 Hz, 1H), 7.66 (dd, *J* = 6.5, 2.5 Hz, 1H), 7.41-7.36 (m, 2H), 7.31 (d, *J* = 8.5 Hz, 1H), 3.77-3.72 (m, 1H), 2.56 (s, 3H), 1.41 (s, 3H), 1.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 135.3, 132.2, 131.6, 128.9, 127.5, 126.1, 124.9, 122.5, 121.9, 29.9, 28.5, 23.7, 22.4. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{14}H_{17}$ 185.1330, found 185.1302.

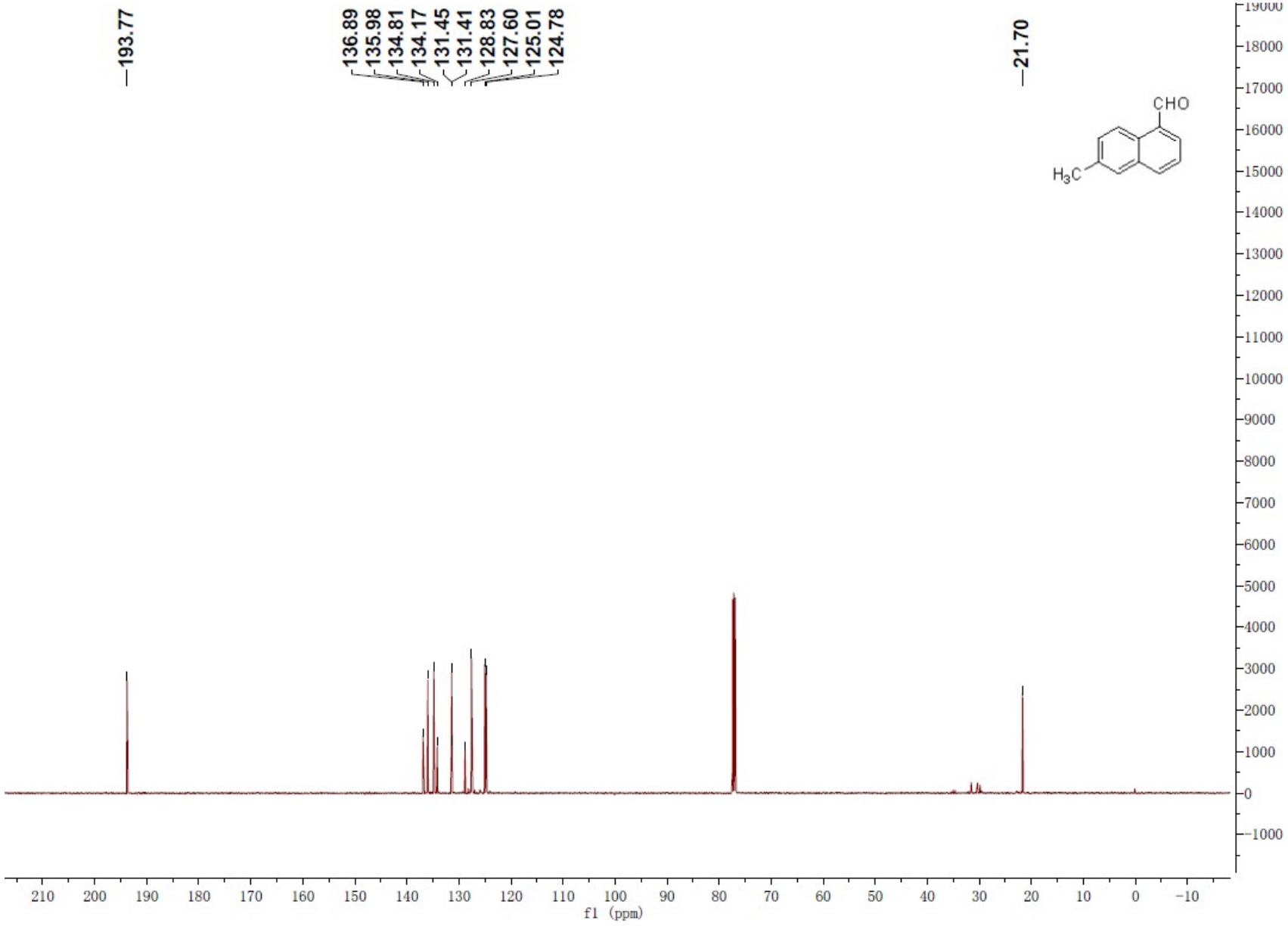
4-Isopropyl-6-methyl-1-naphthaldehyde (3). A solution of α,α-dichloromethyl methyl ether (46 mg, 0.4 mmol) in DCM (2 mL, 0.2 M) was cooled in an ice bath and then treated dropwise with $SnCl_4$ (125.5 mg, 0.48 mmol). After stirring for 45 minutes, a solution of compound **32** (73.6 mg, 0.4 mmol) in DCM (0.4 mL, 1.0 M) was added. The mixture was allowed to slowly warm to room temperature and stirred for 5h. The mixture was poured into ice water and extracted with DCM twice. The combined organics were washed with H_2O, brine, dried over anhydrous Na_2SO_4, and filtered. After removing the volatiles, the residue was purified by silica gel column chromatography (EtOAc/n-hexane = 1/50) to give compound **3** as a yellow oil (76.4 mg, 0.36 mmol, 90%). R_f 0.50 (50:1 hexane/EtOAc). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.31 (s, 1H), 9.24 (d, *J* = 9.0 Hz, 1H), 7.98 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.52 (dd, *J* = 9.0, 1.0 Hz, 1H), 3.85-3.79 (m, 1H), 2.58 (s, 3H), 1.44 (s, 3H), 1.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.6, 152.5, 136.6, 136.4, 131.9, 130.6, 129.7, 129.3, 125.6, 122.9, 121.3, 29.2, 23.5×2, 22.3. HRMS (ESI) m/z $[M+H]^+$calcd for $C_{15}H_{17}O$ 213.1279, found 213.1253.

5. ^{1}H NMR and ^{13}C NMR Spectra

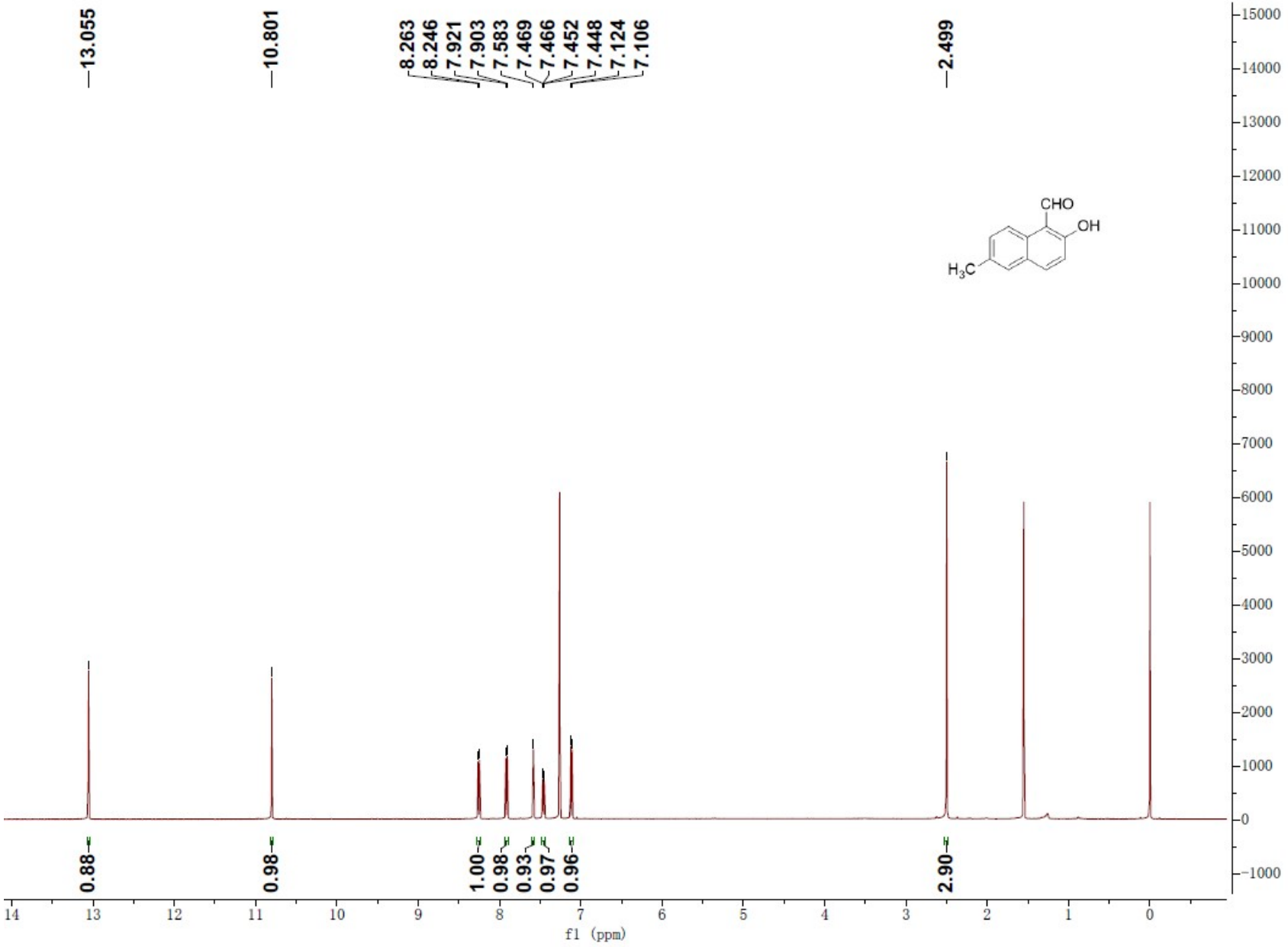
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 5



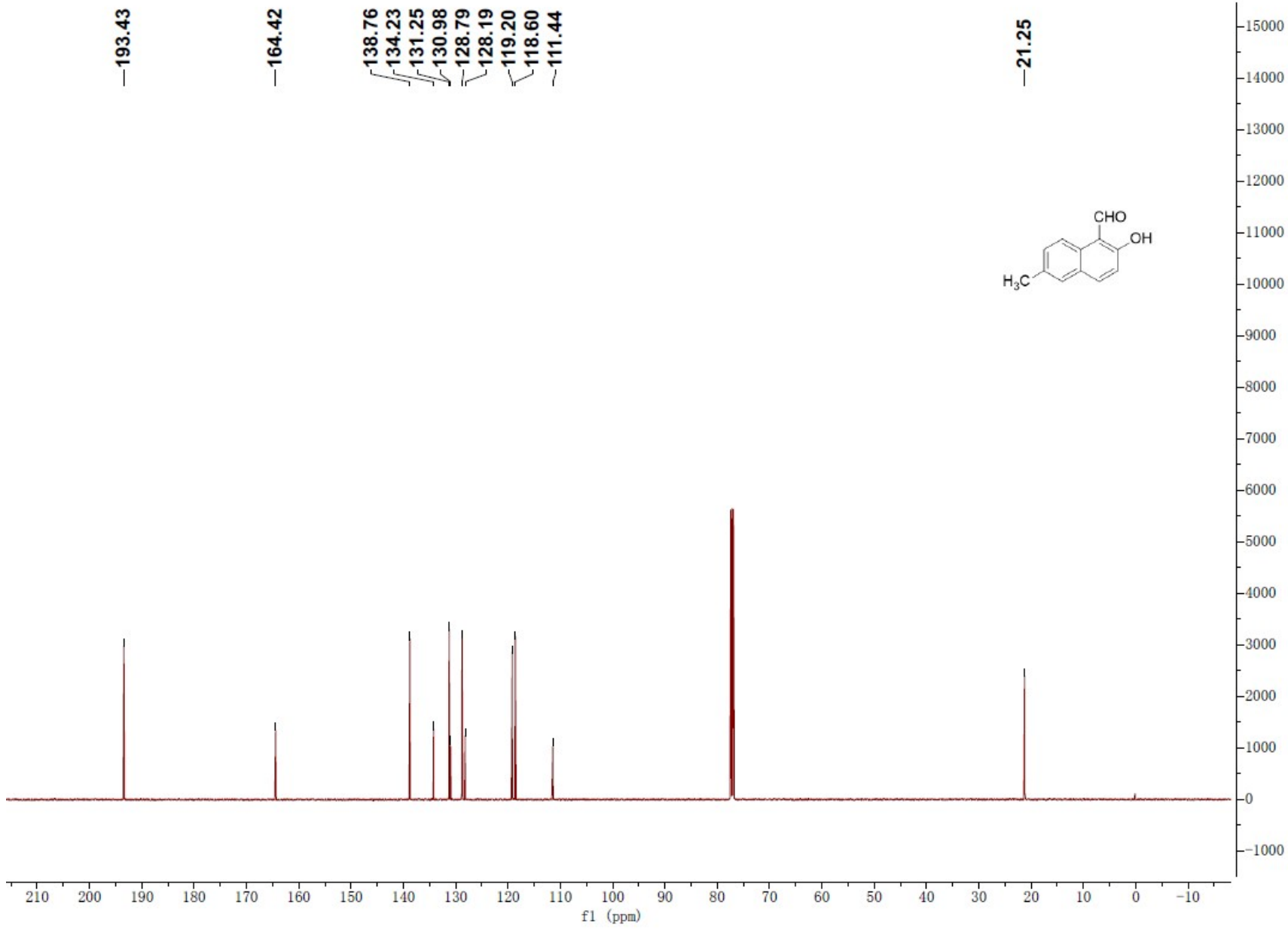
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 5



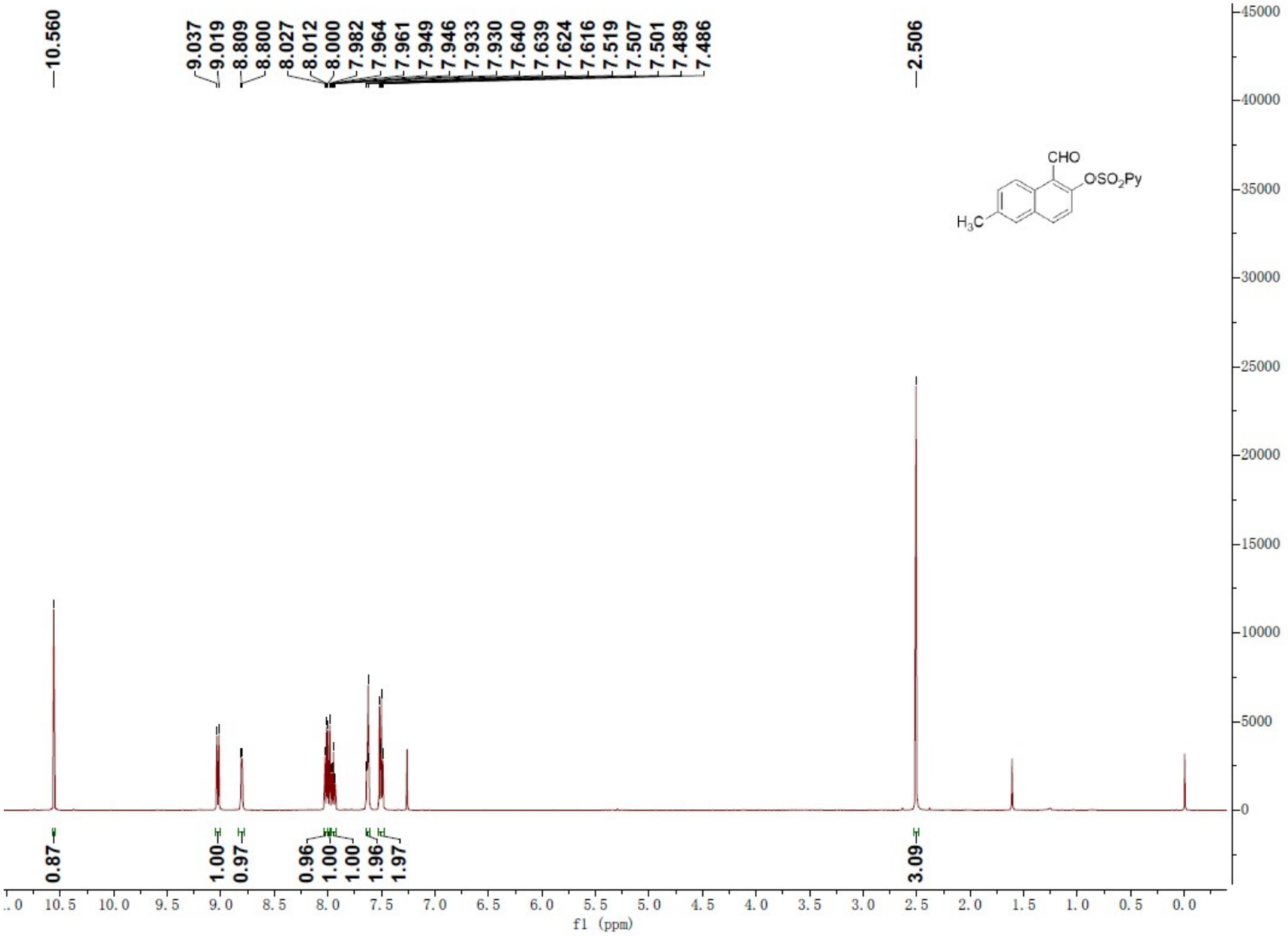
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 17



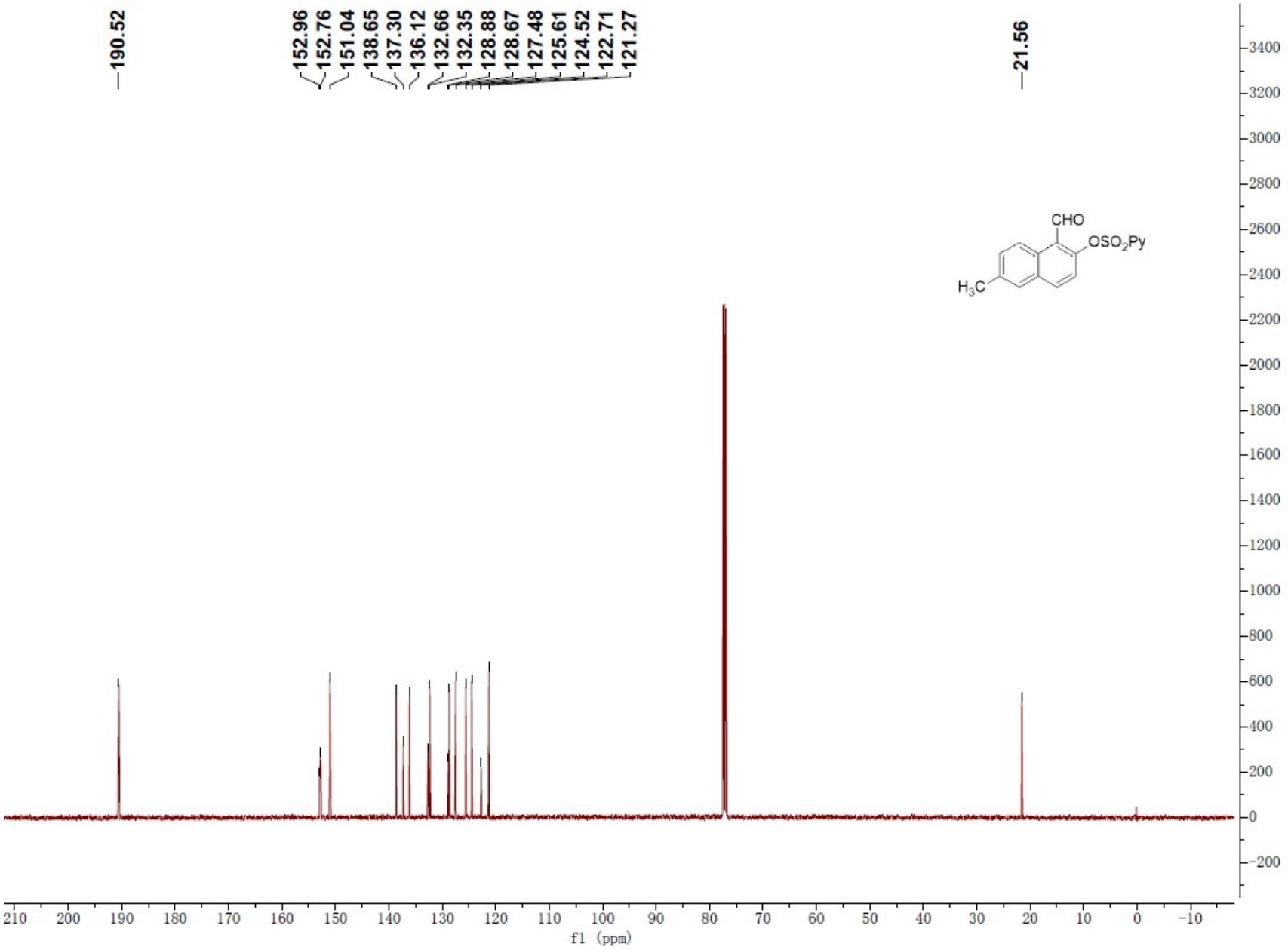
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 17



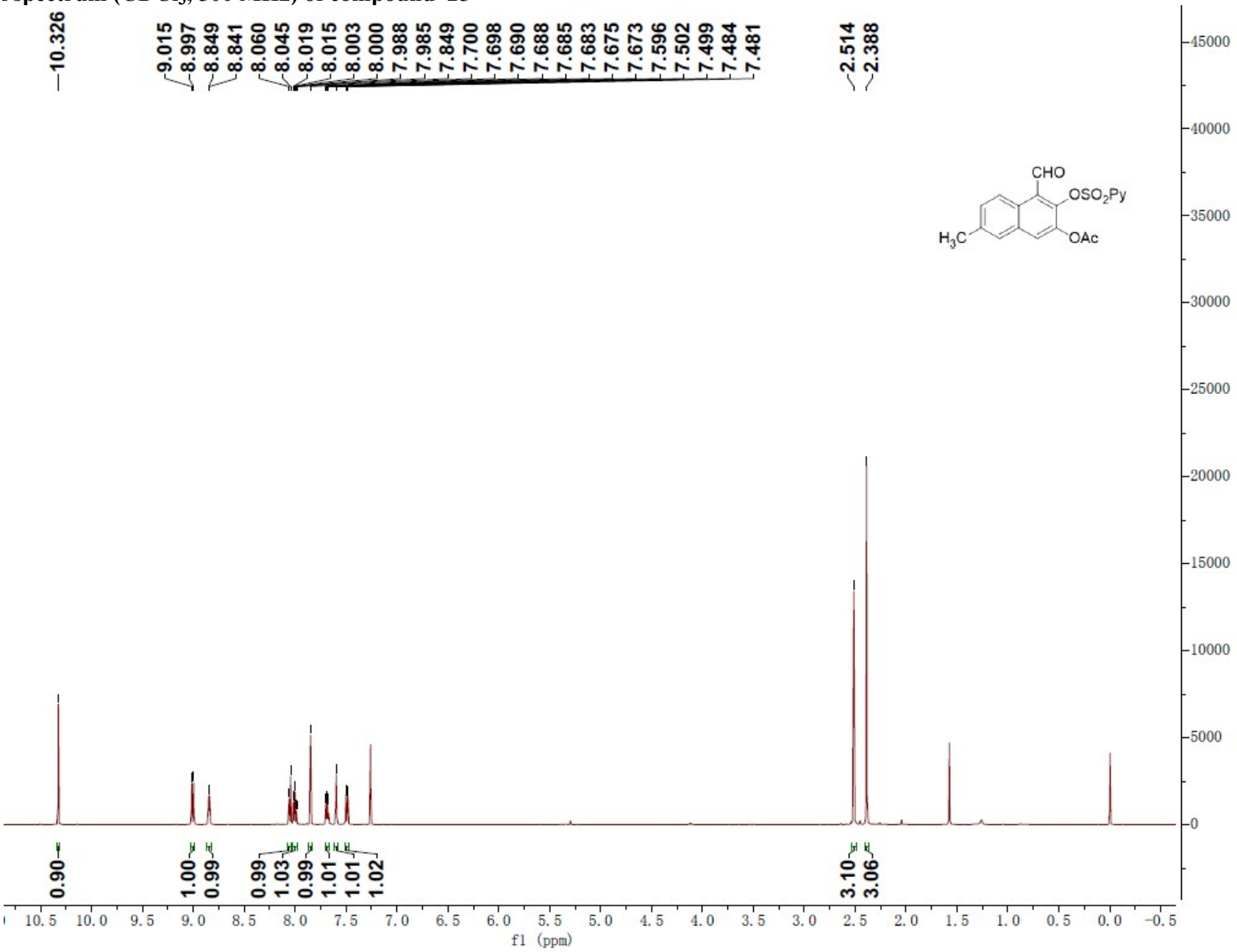
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 24



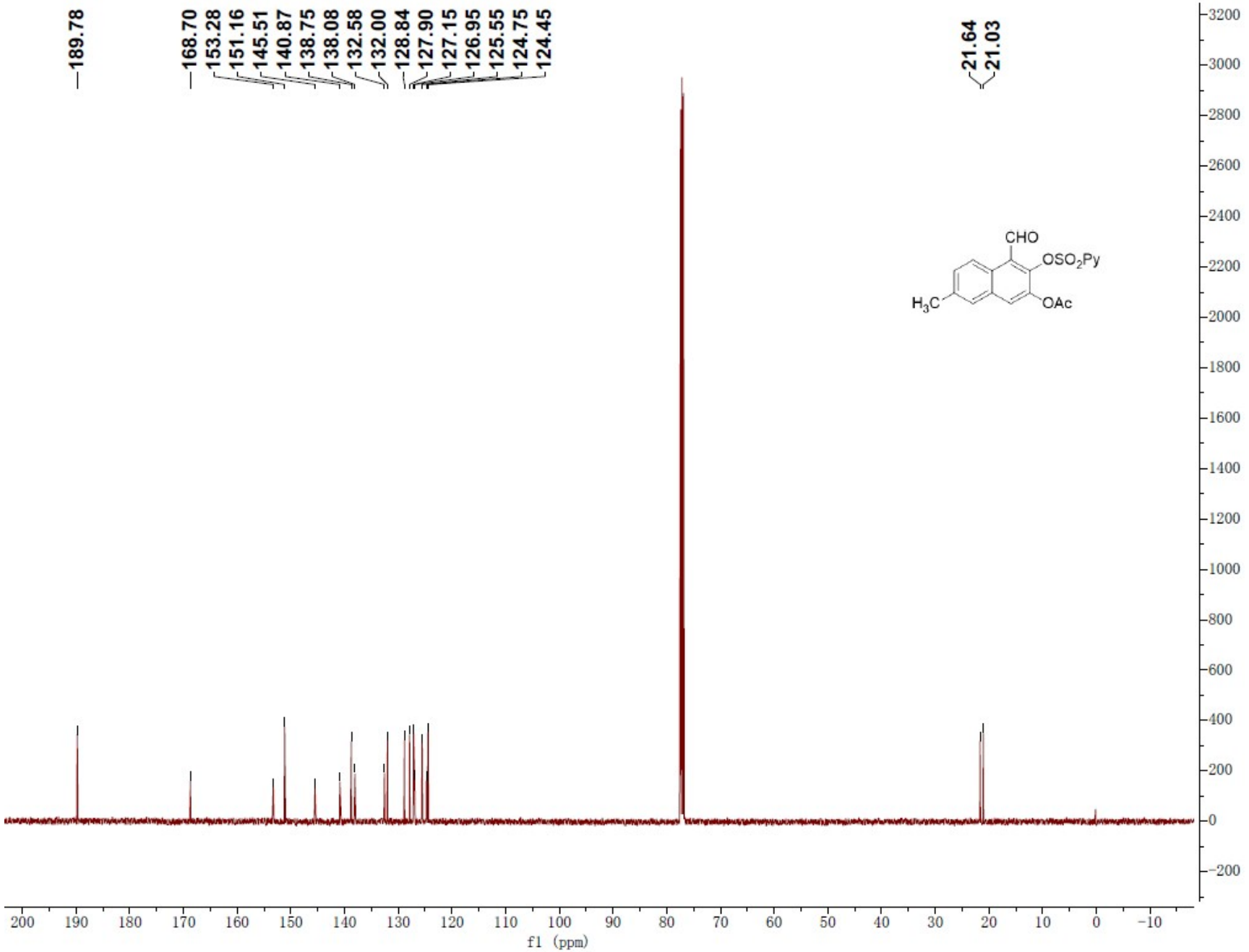
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 24



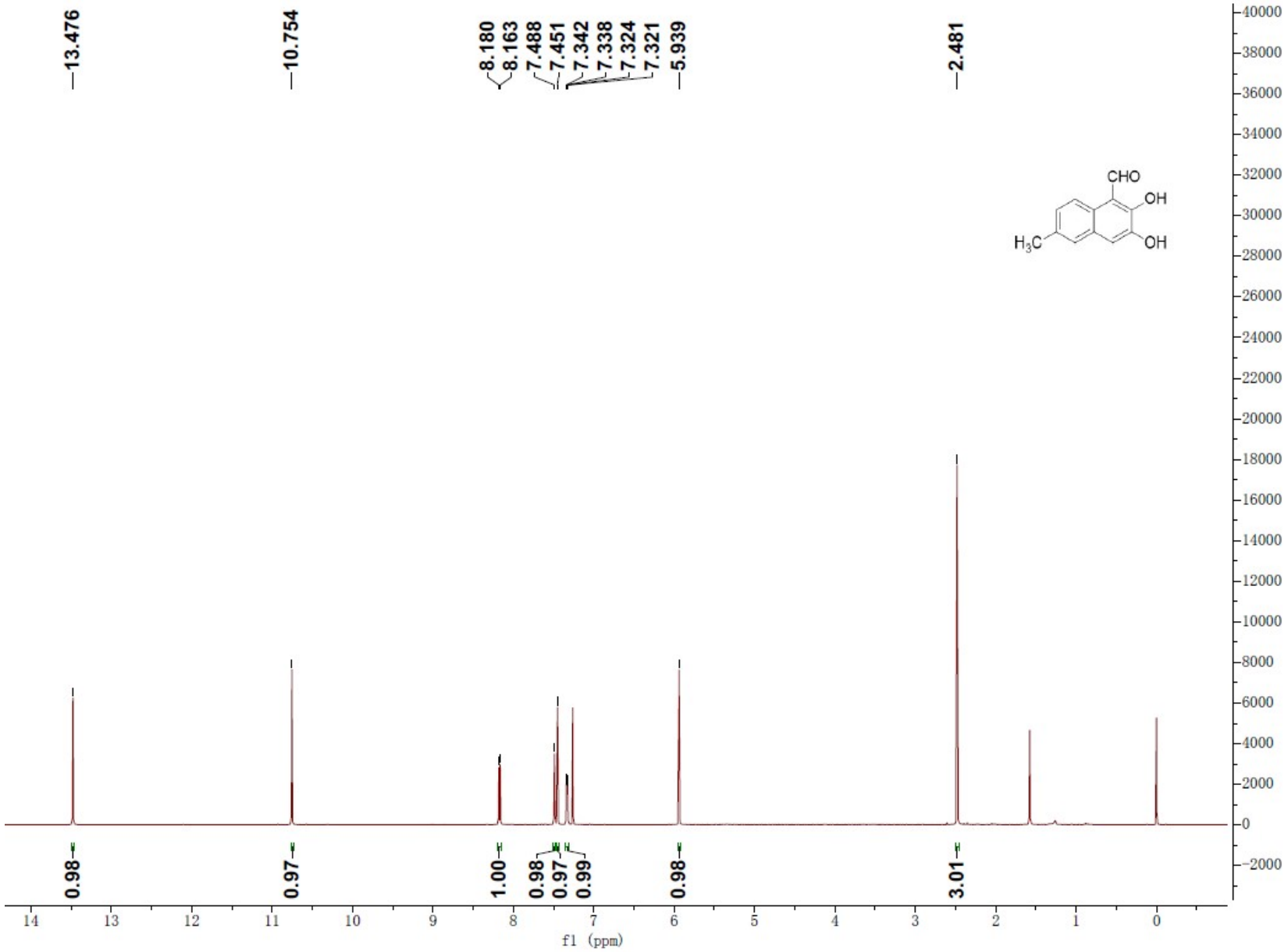
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 25



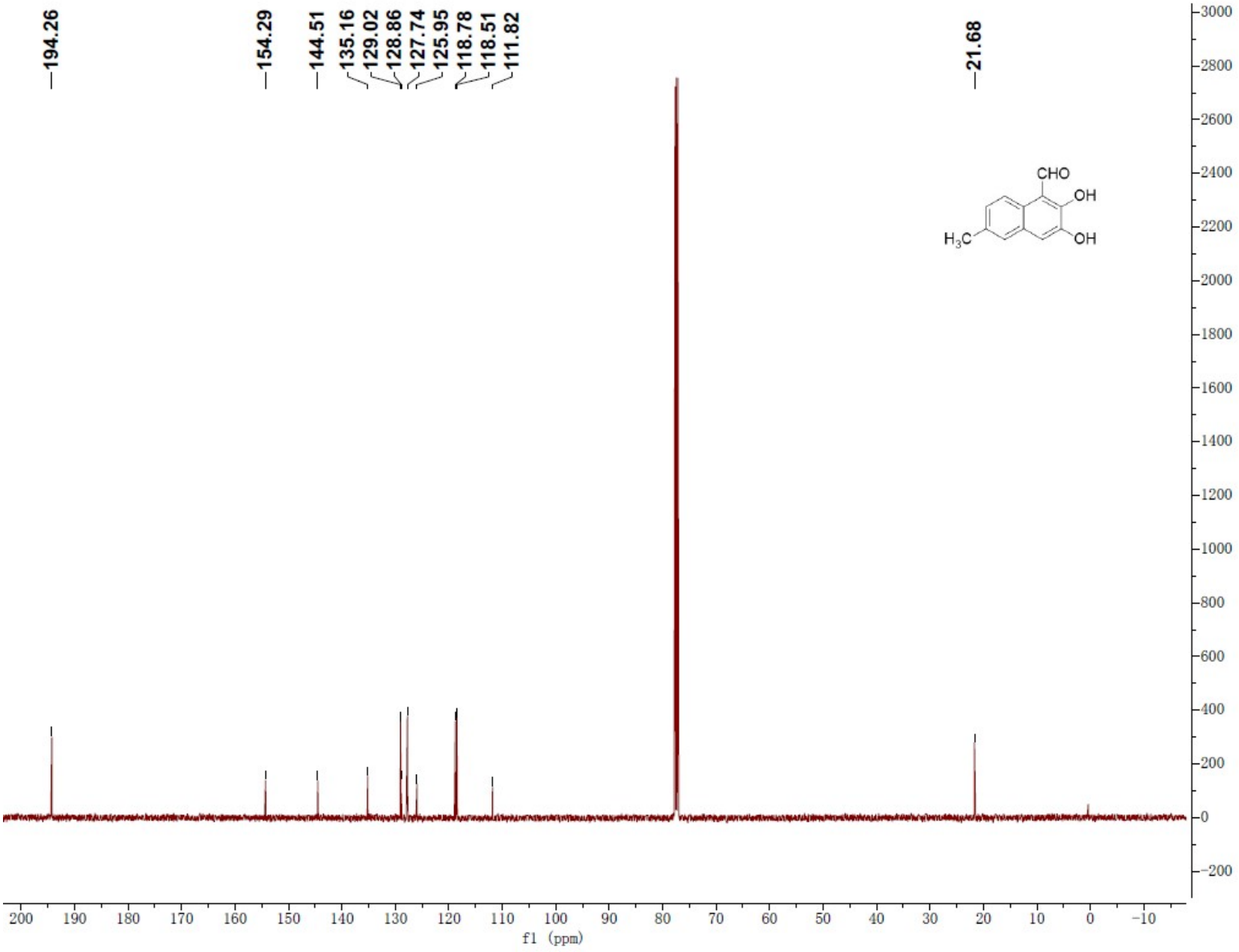
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 25



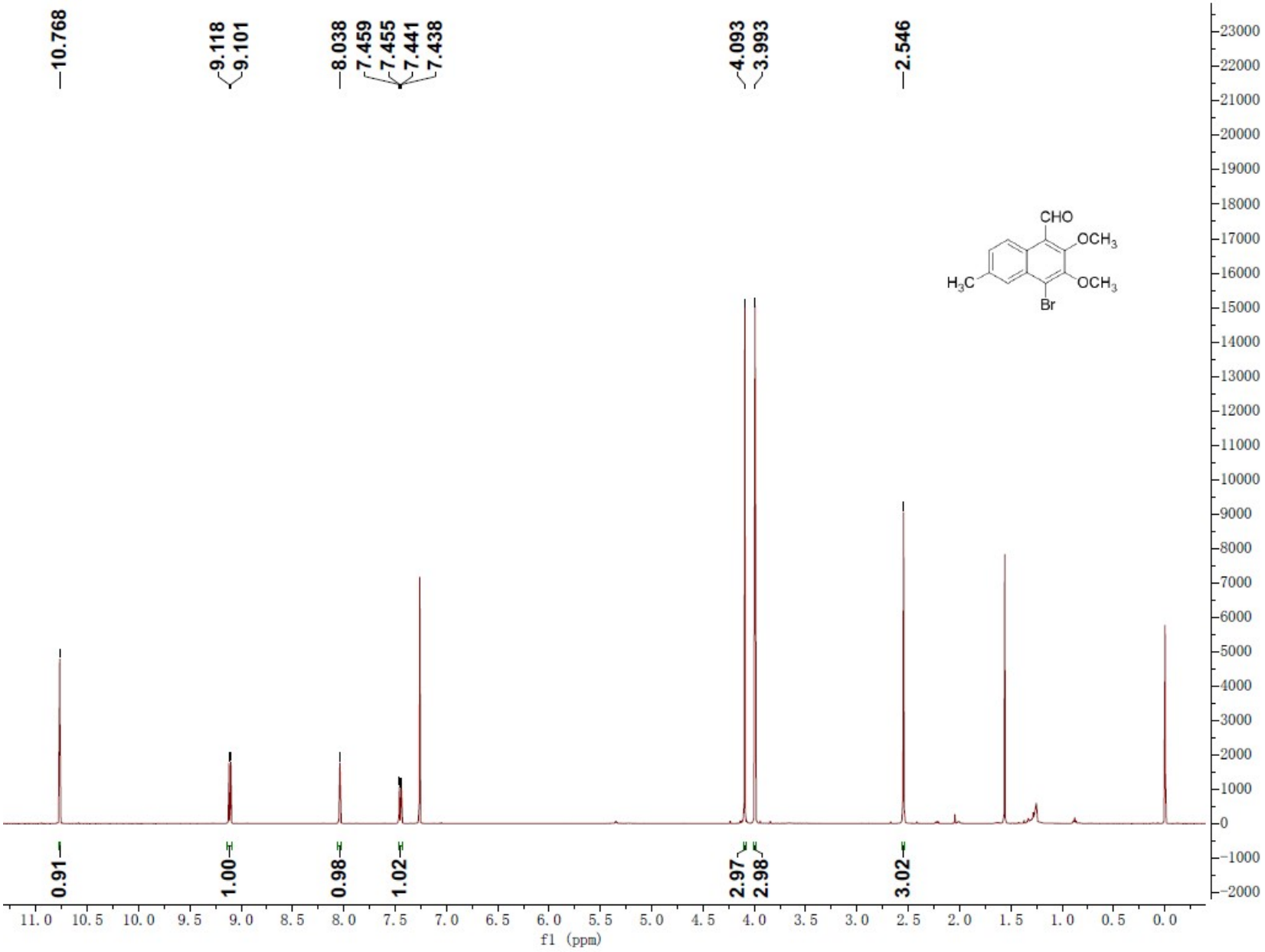
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 26



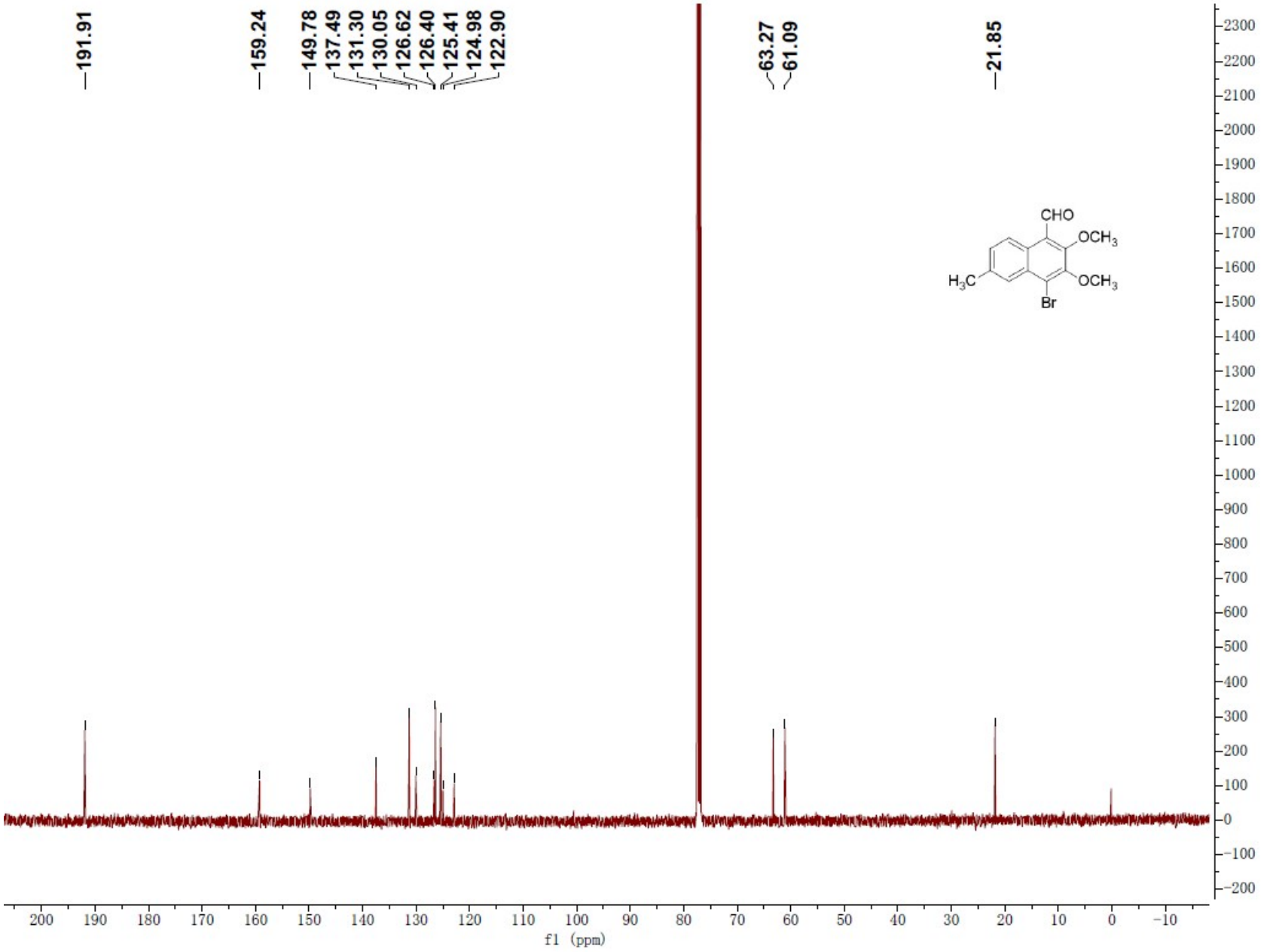
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 26



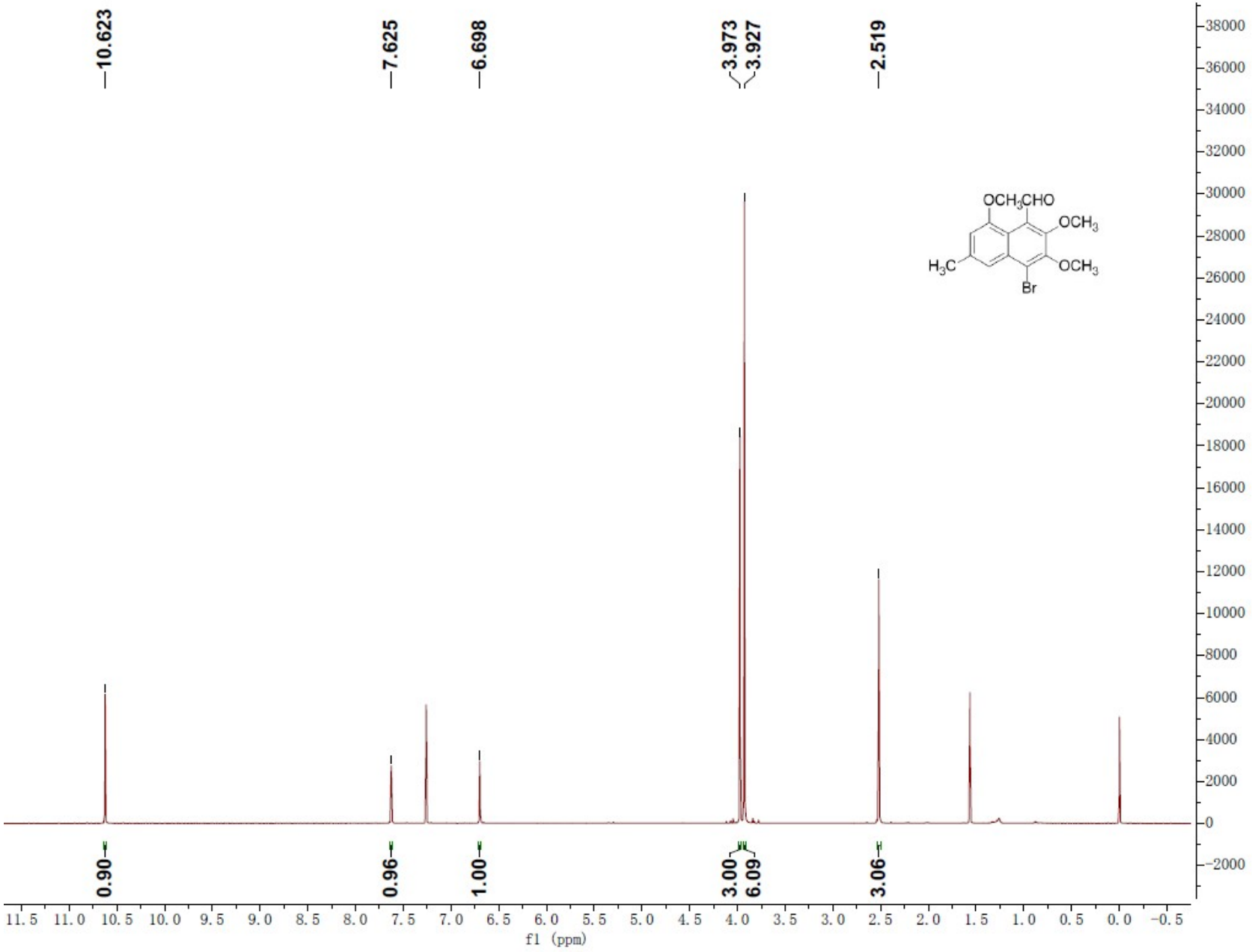
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 27



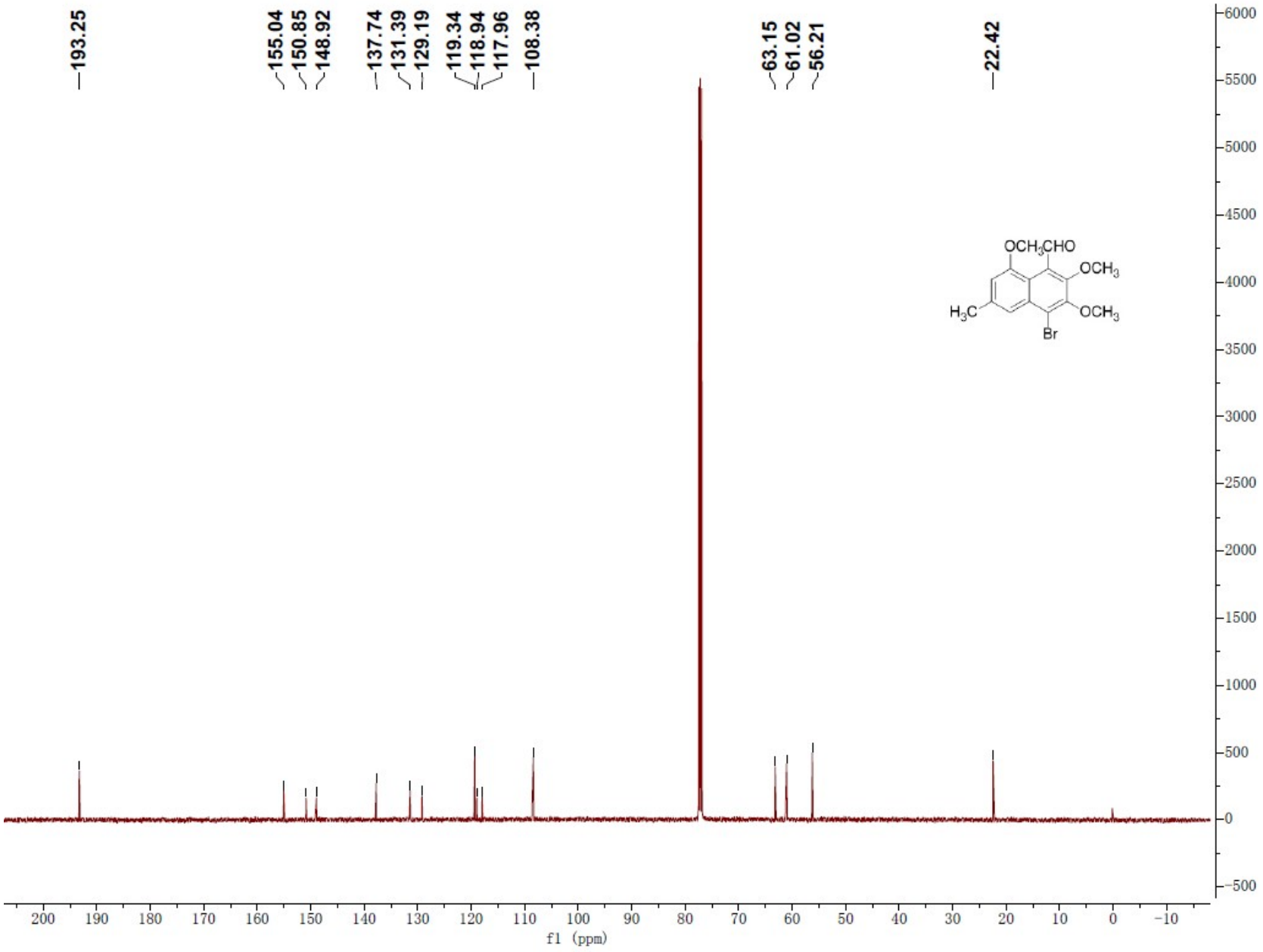
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 27



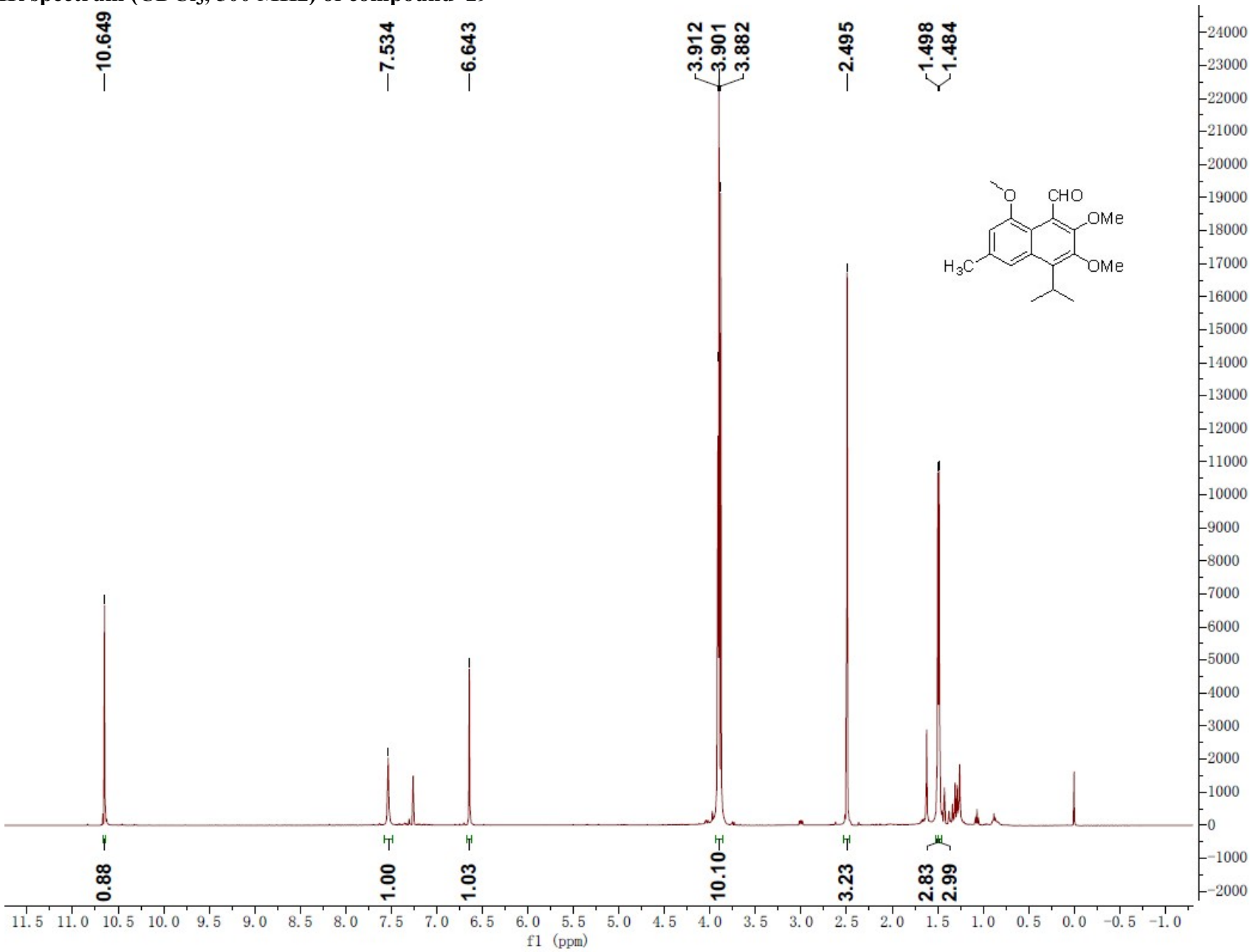
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 28



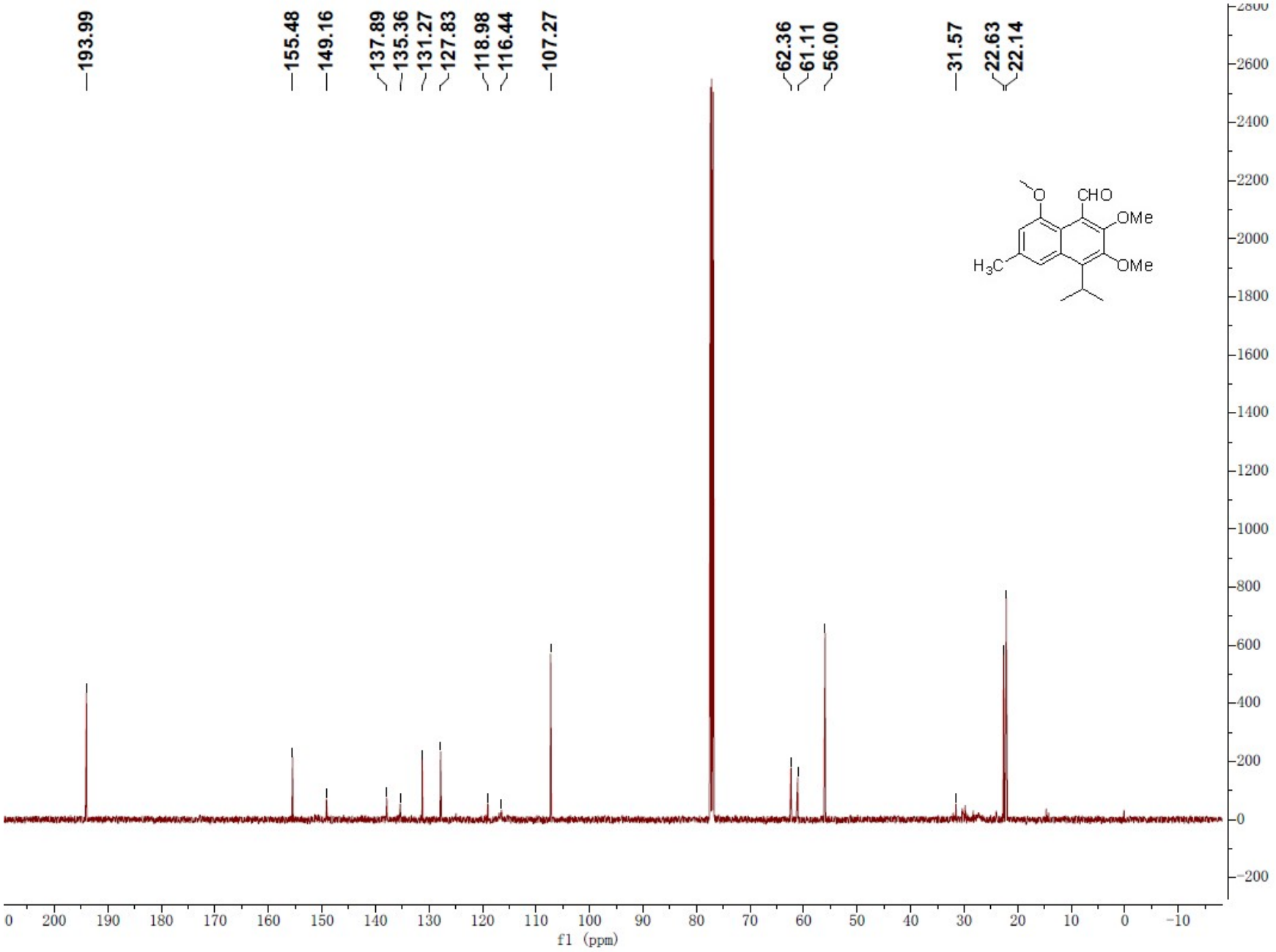
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 28



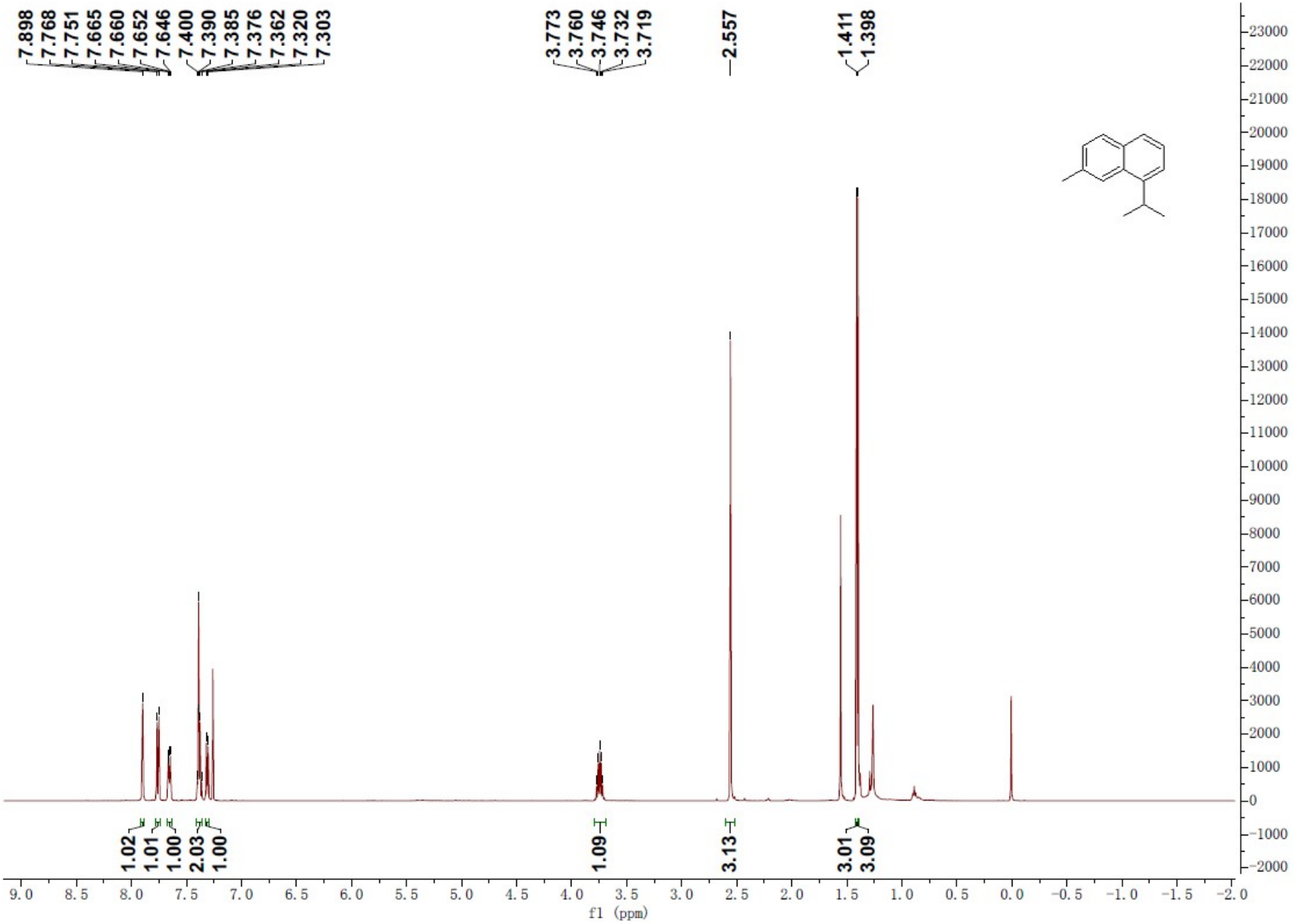
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 29



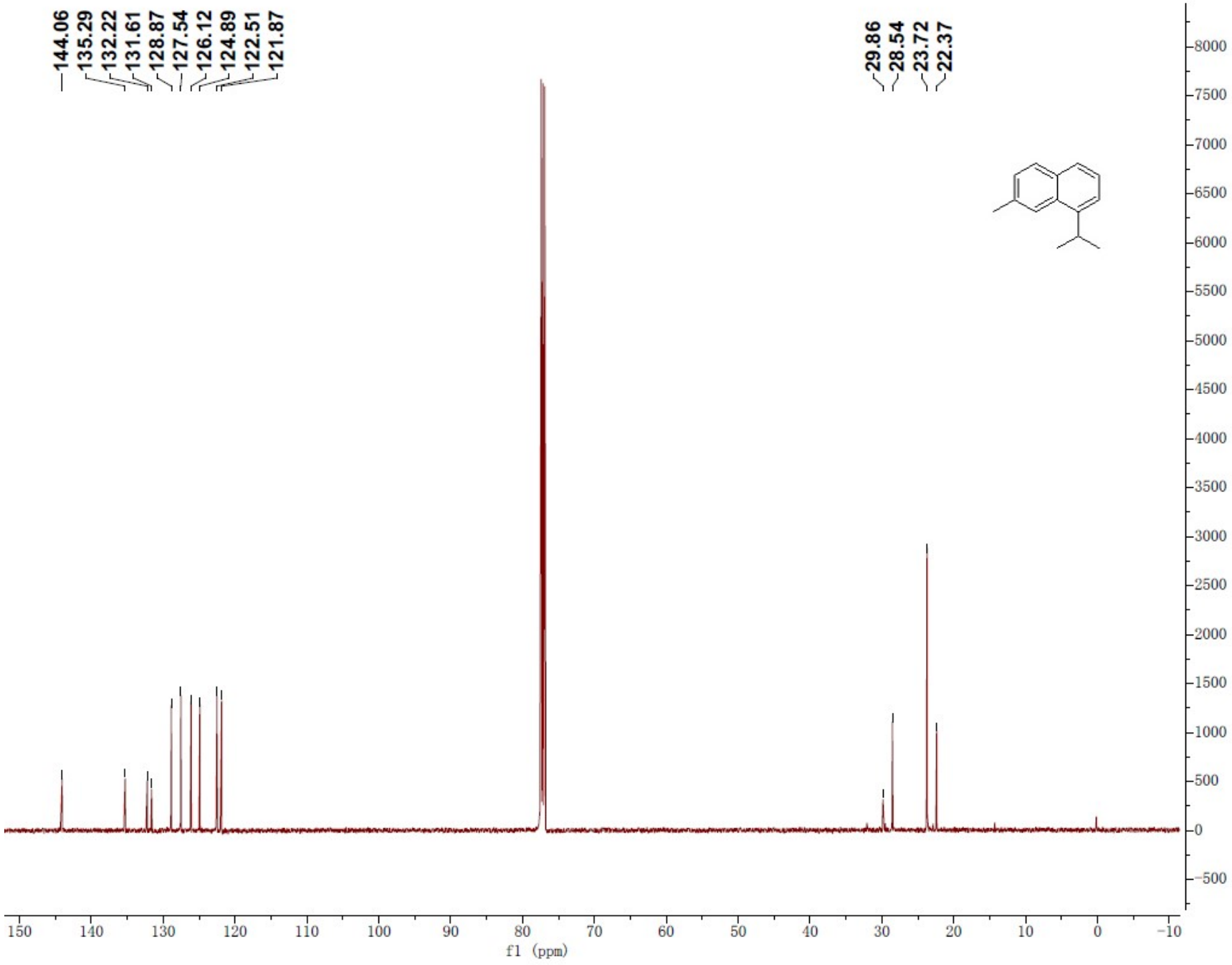
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 29



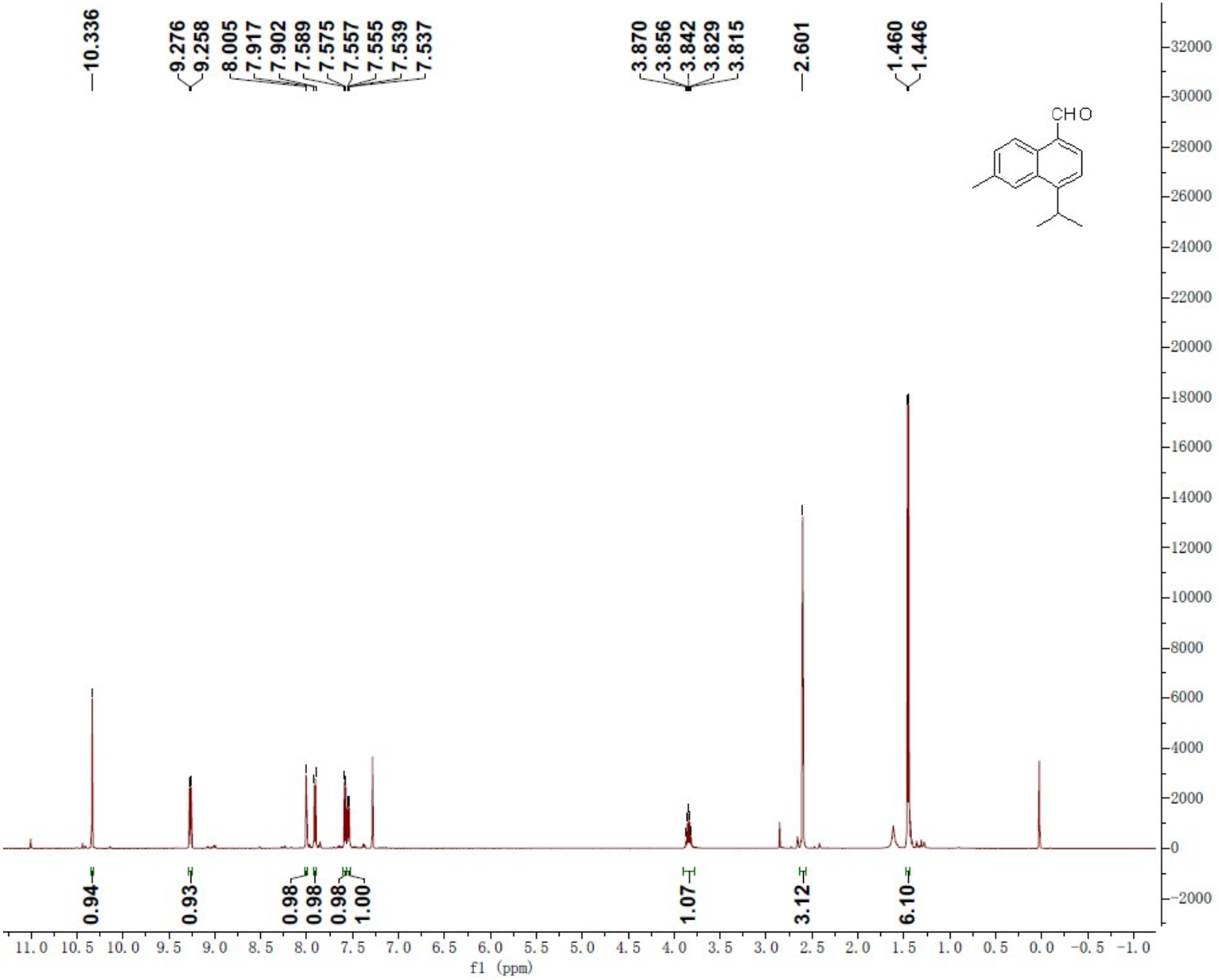
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 32



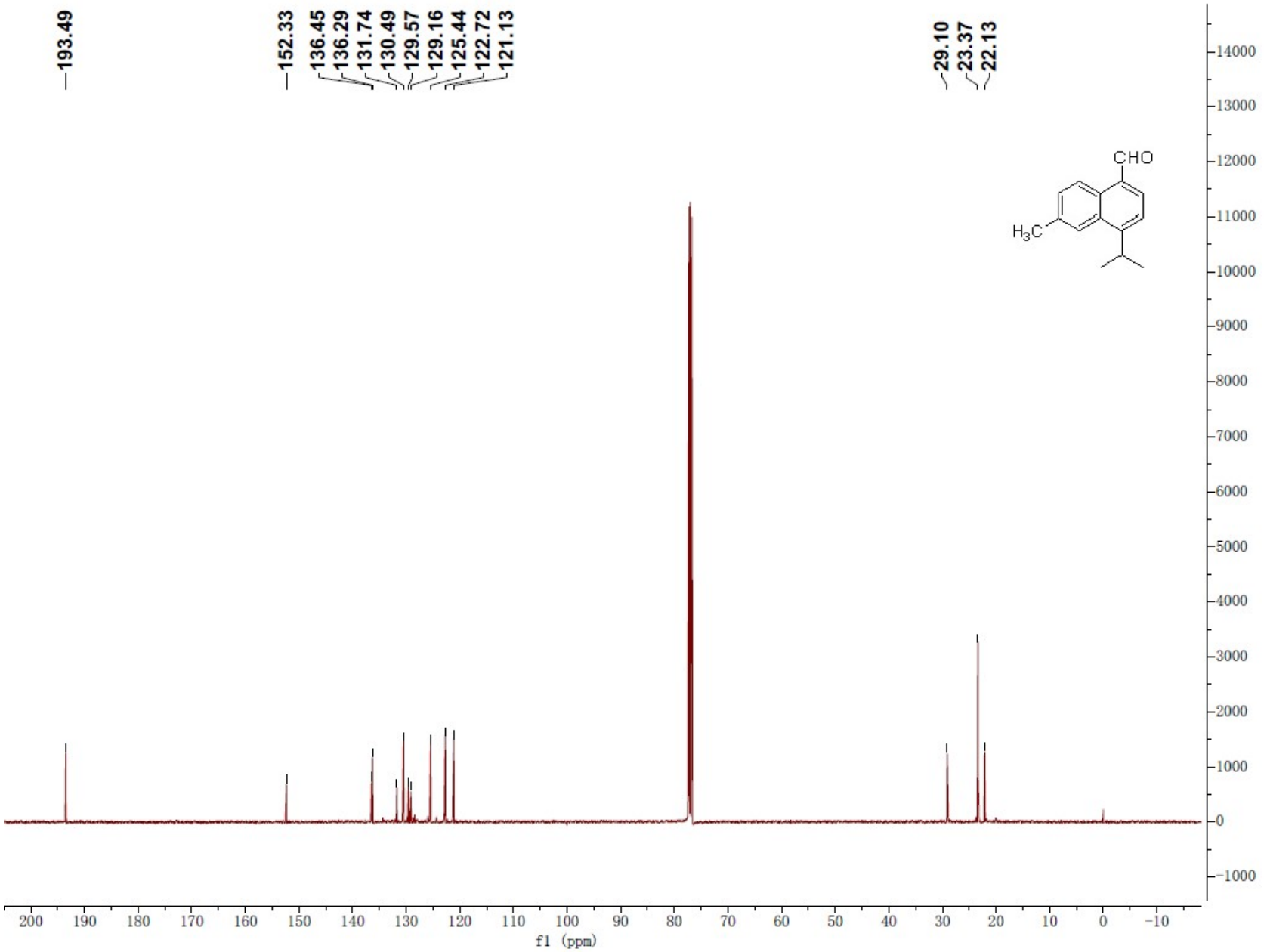
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 32



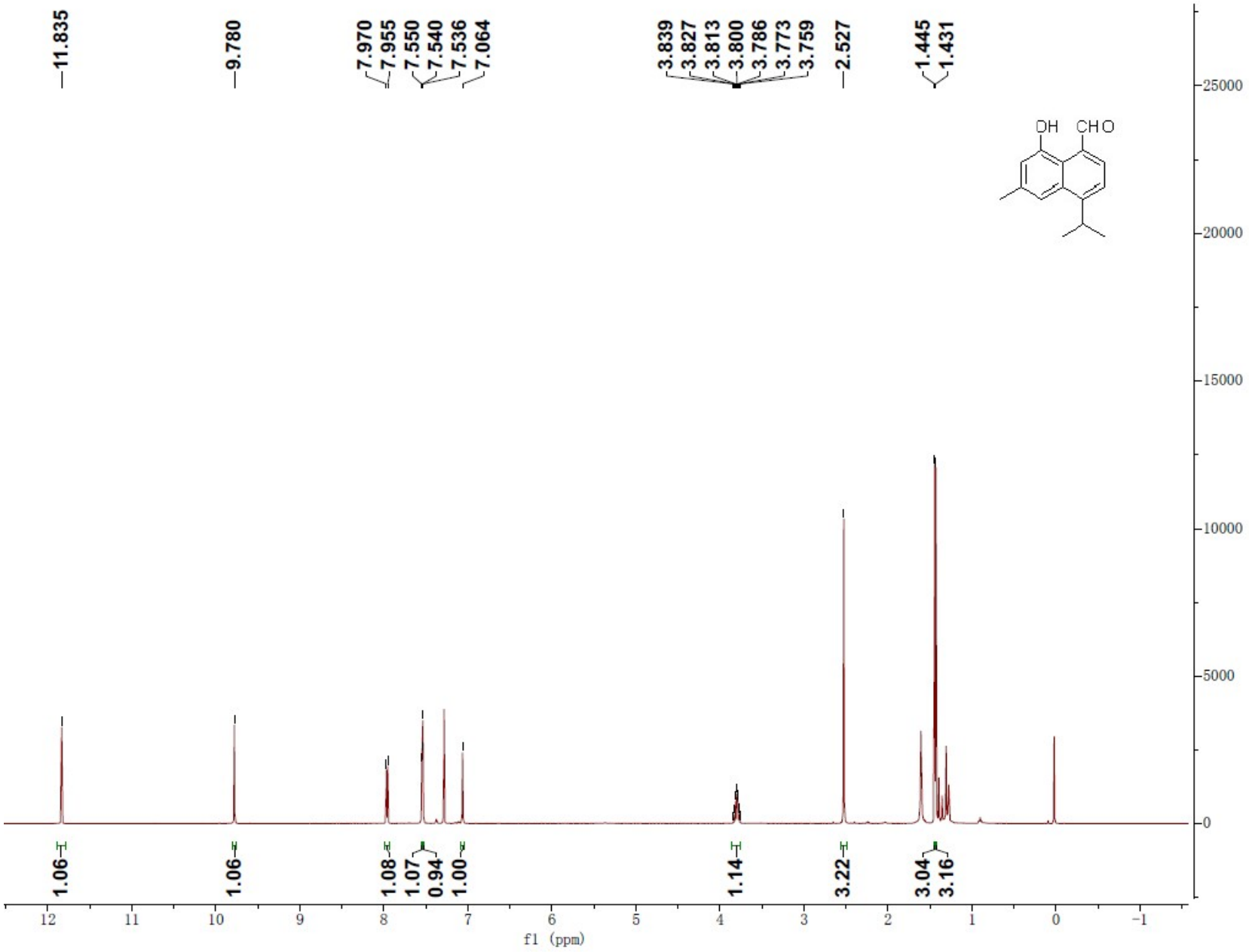
^{13}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 3



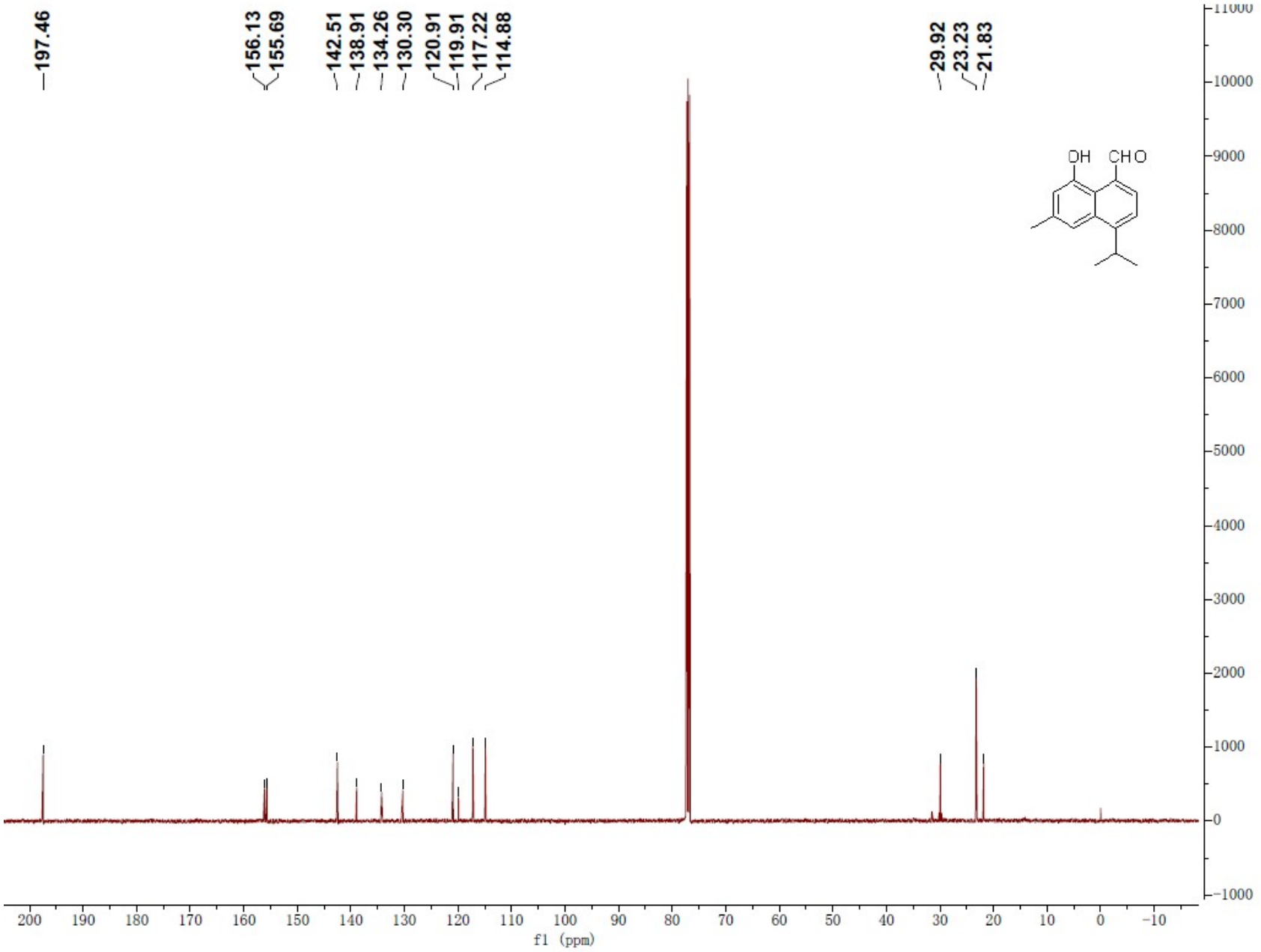
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 3



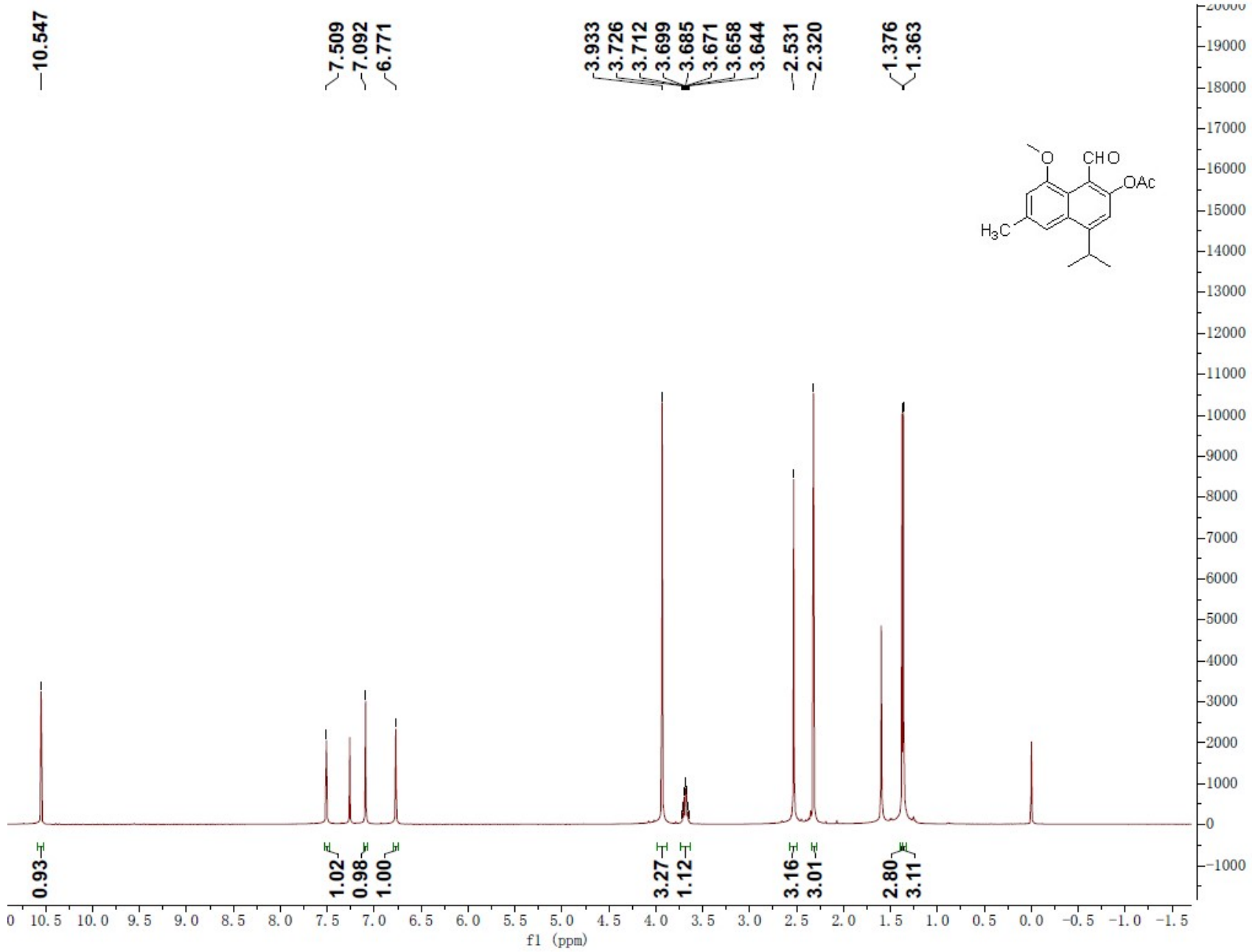
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 6



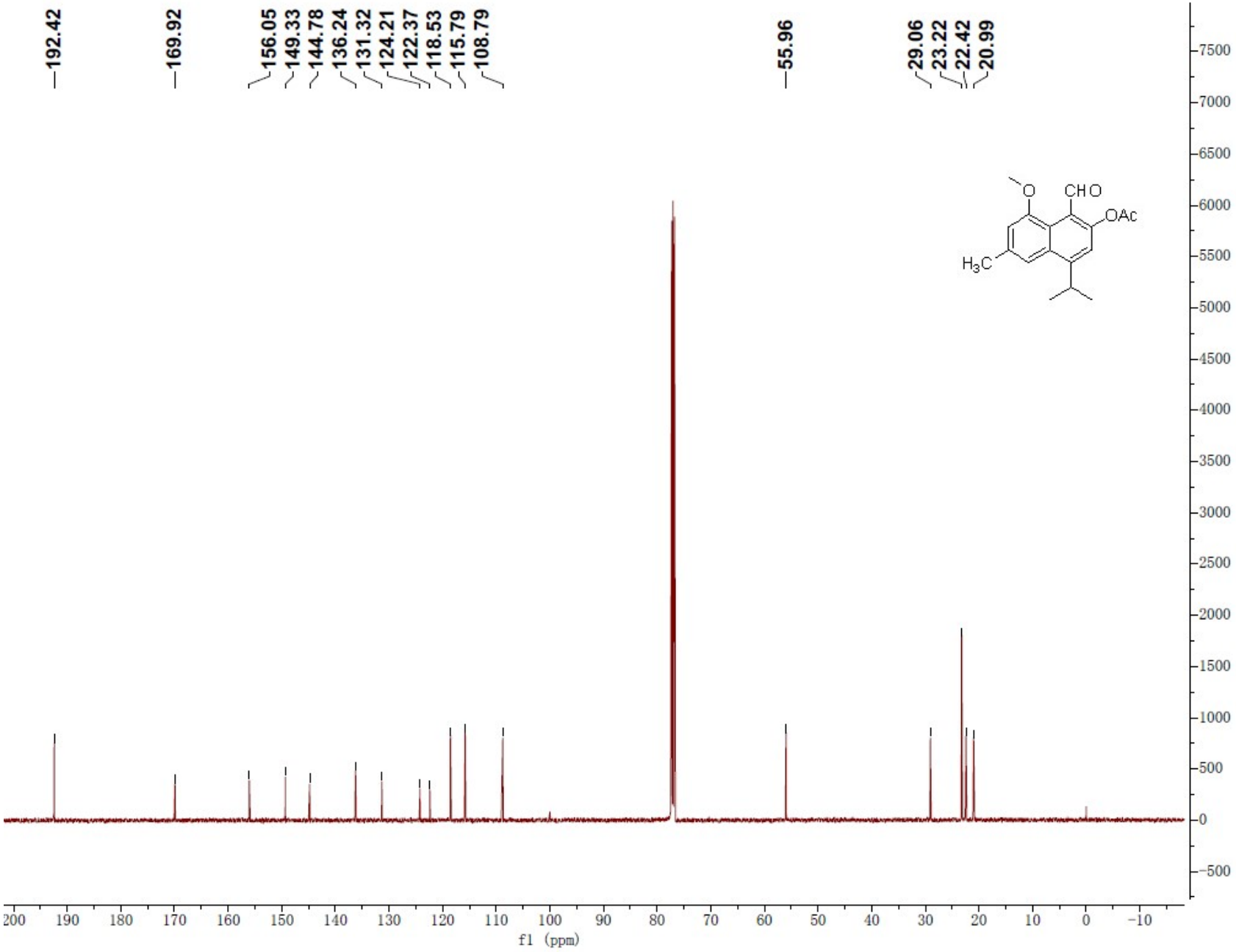
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 6



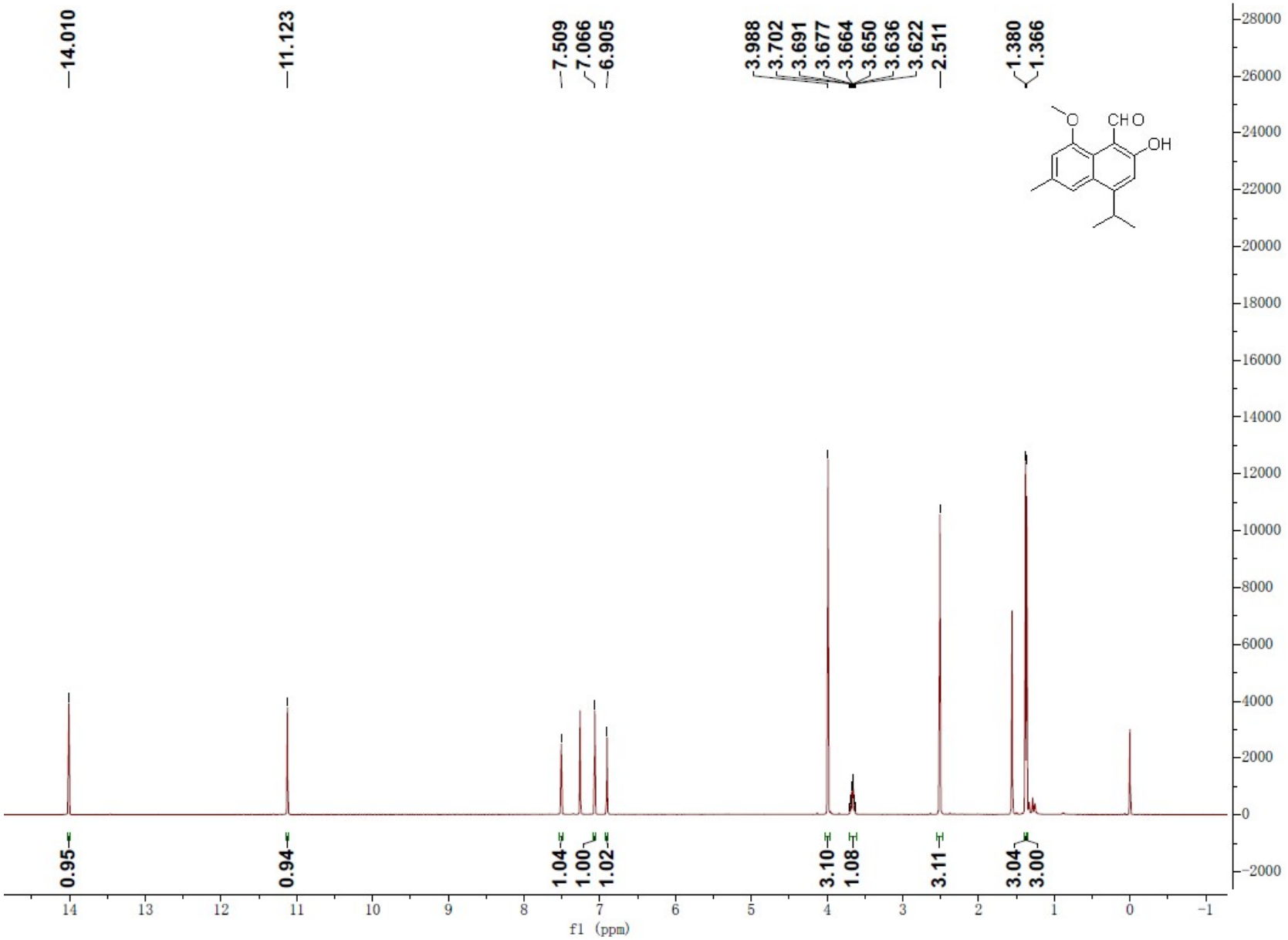
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 8



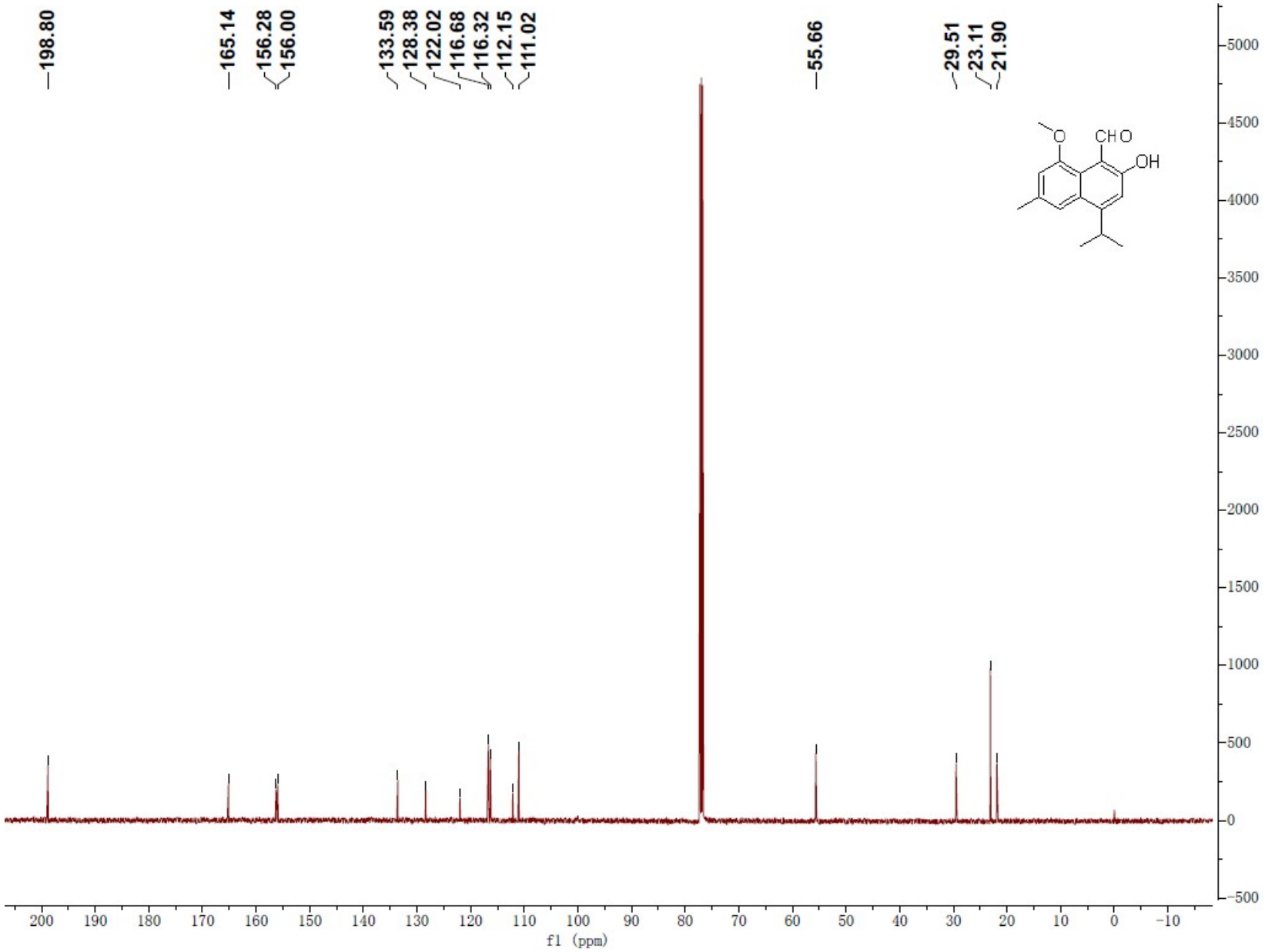
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 8



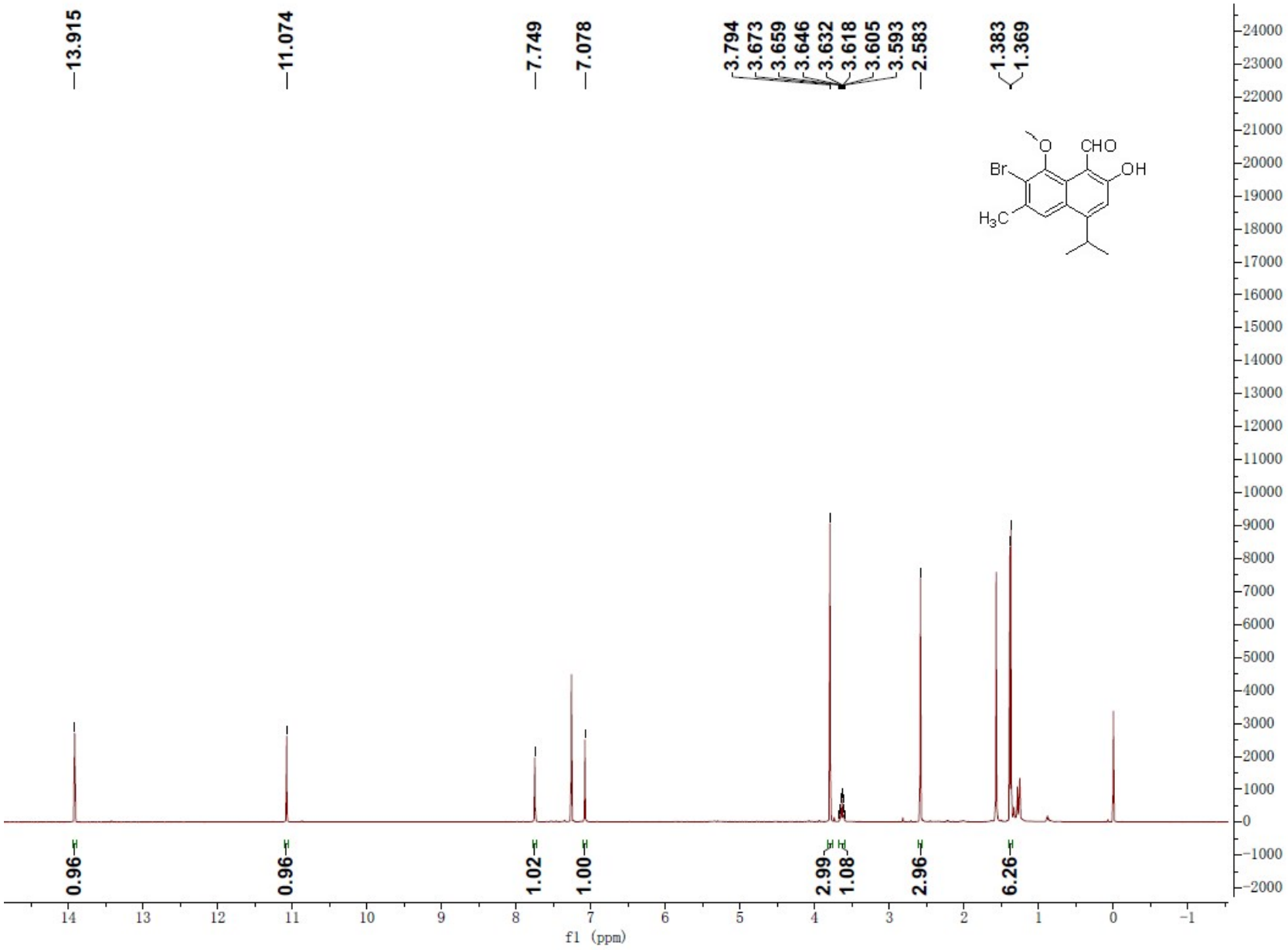
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 9



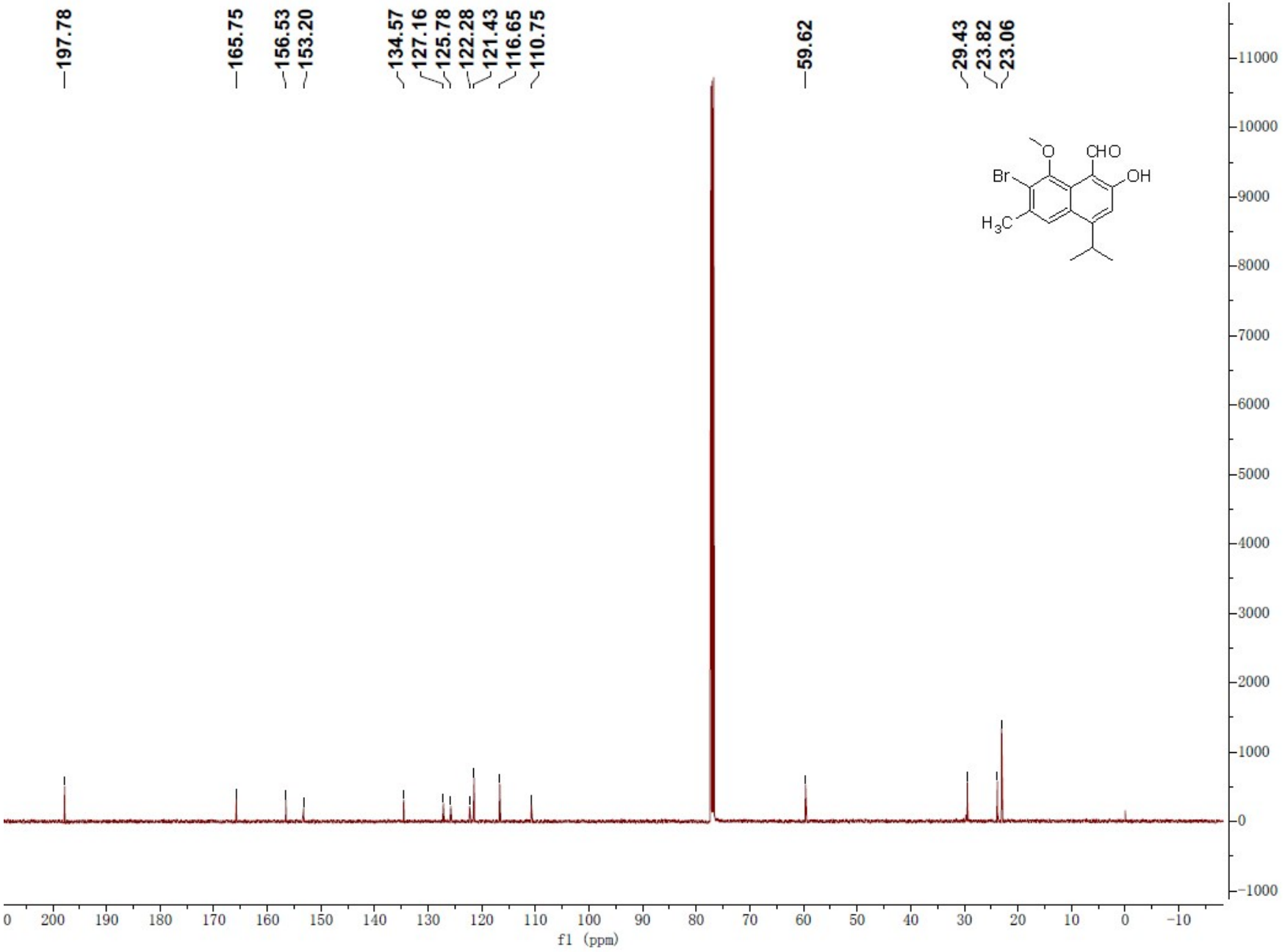
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 9



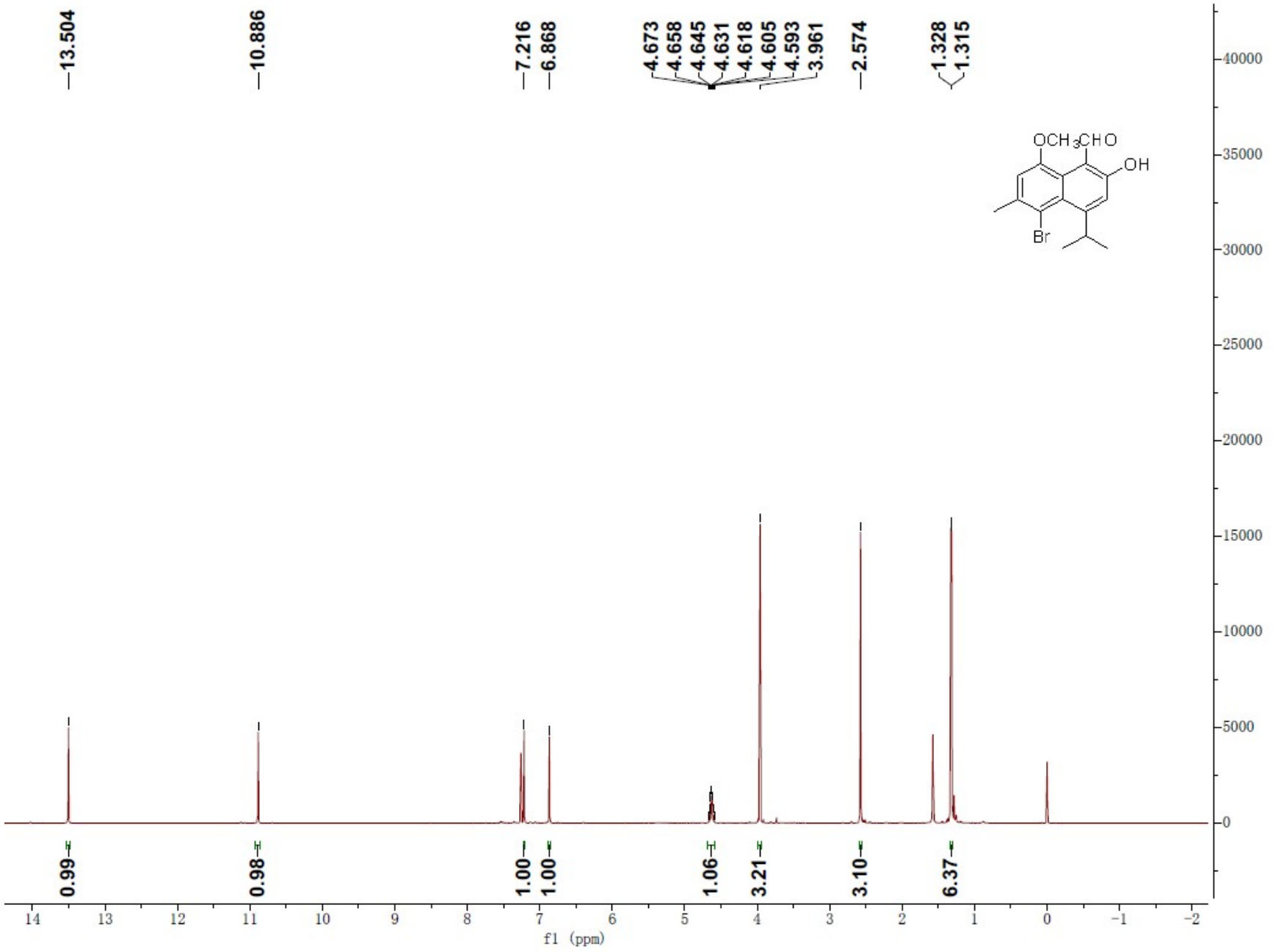
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 11



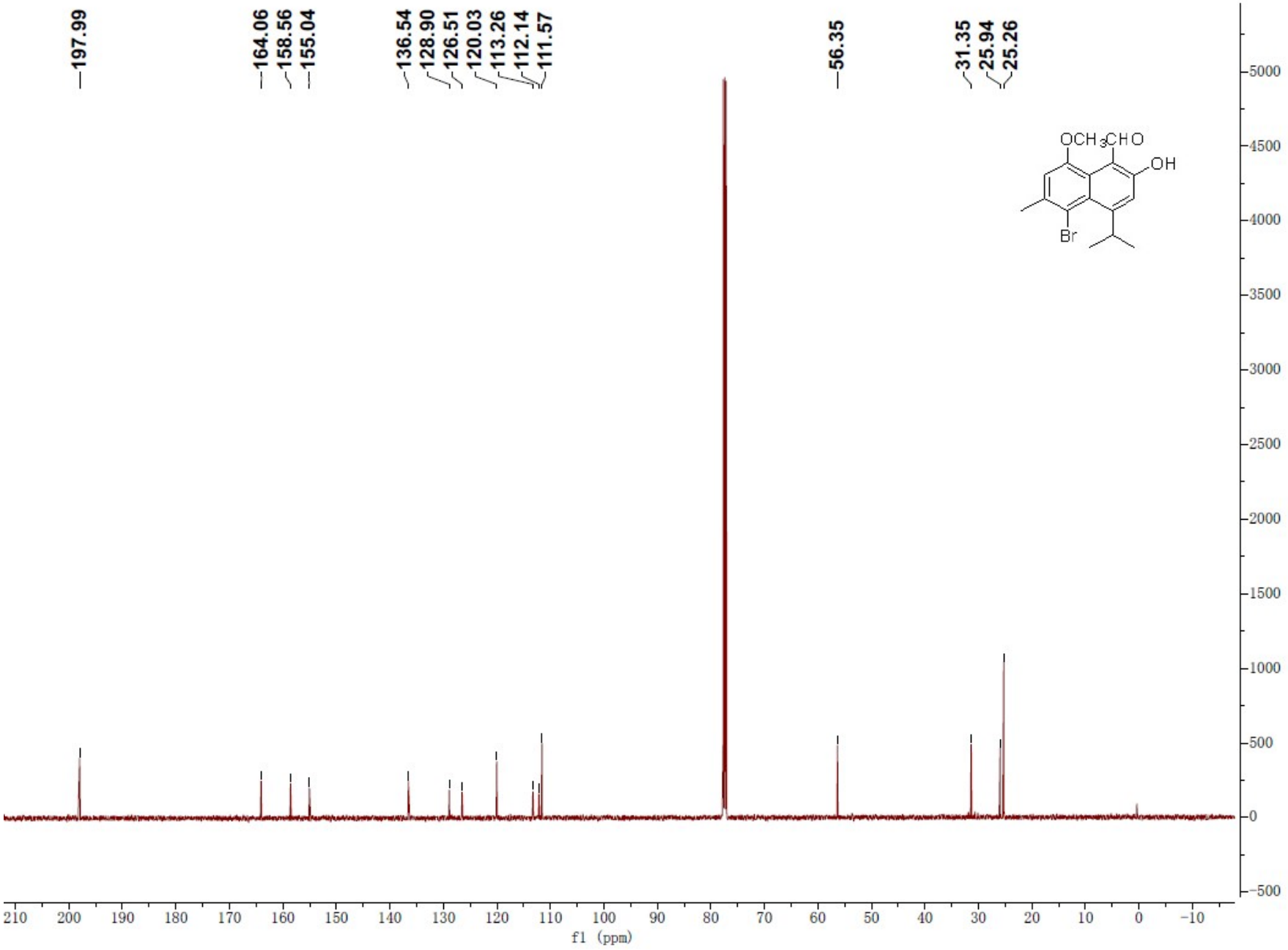
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 11



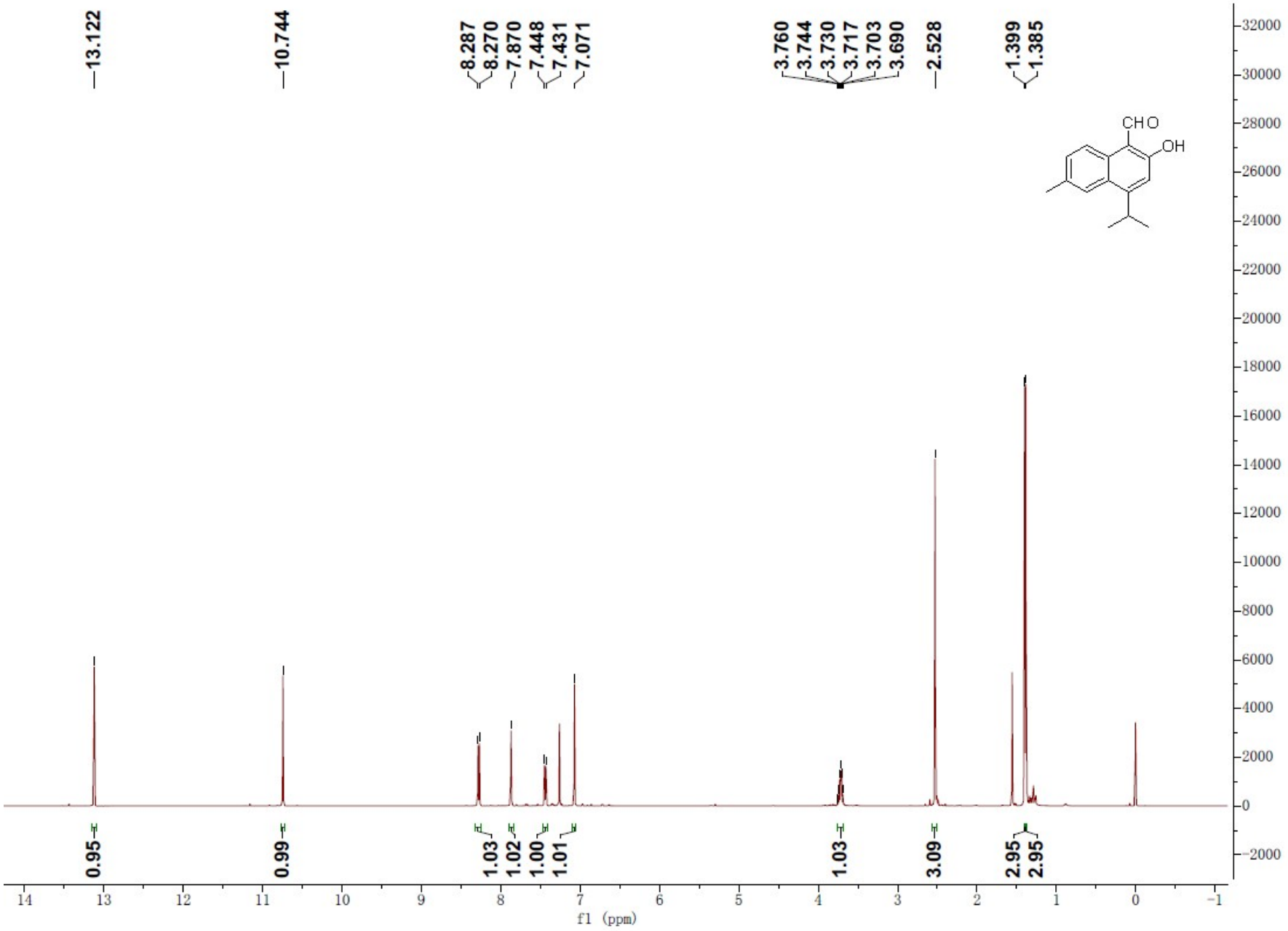
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 12



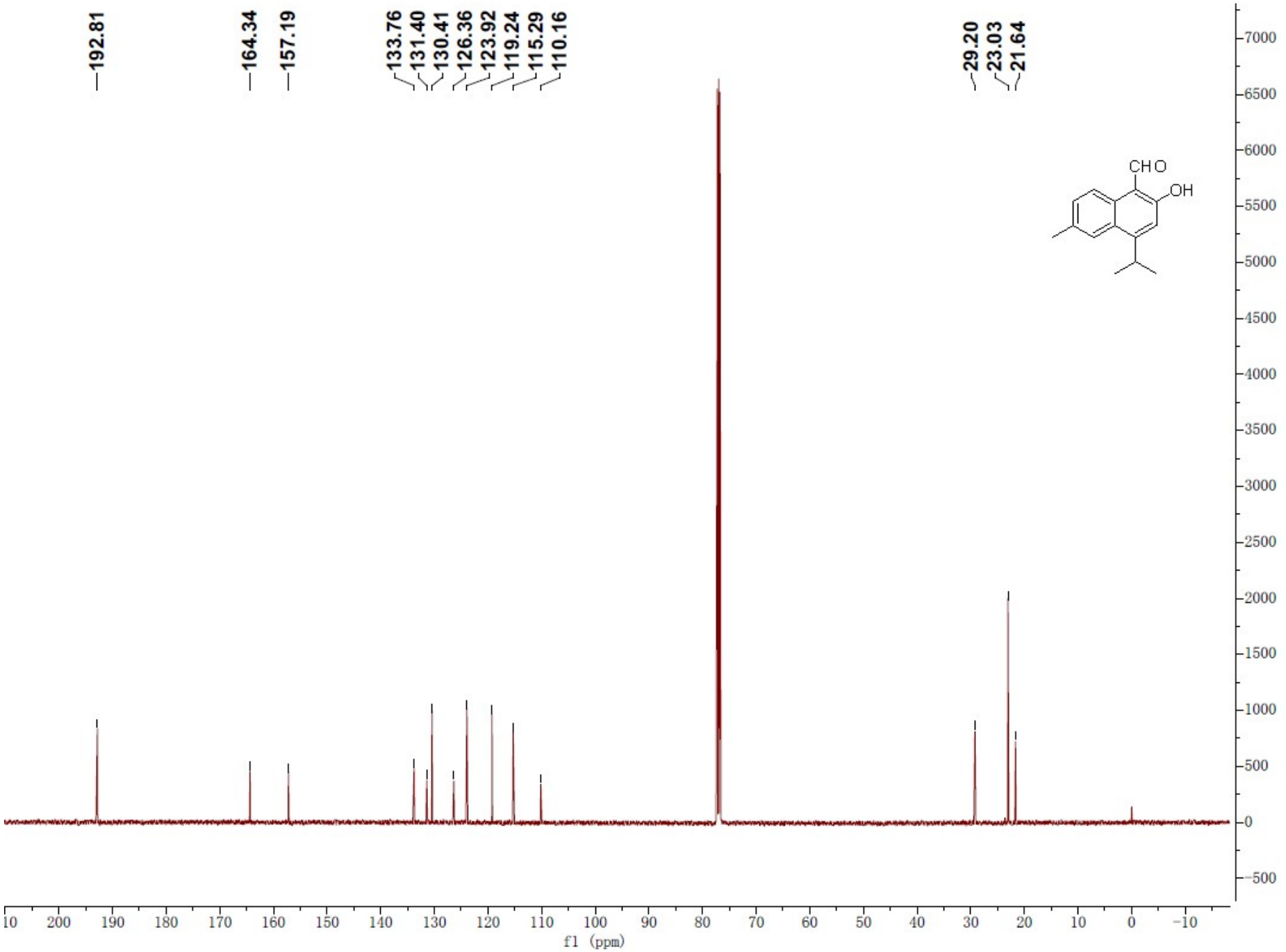
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 12



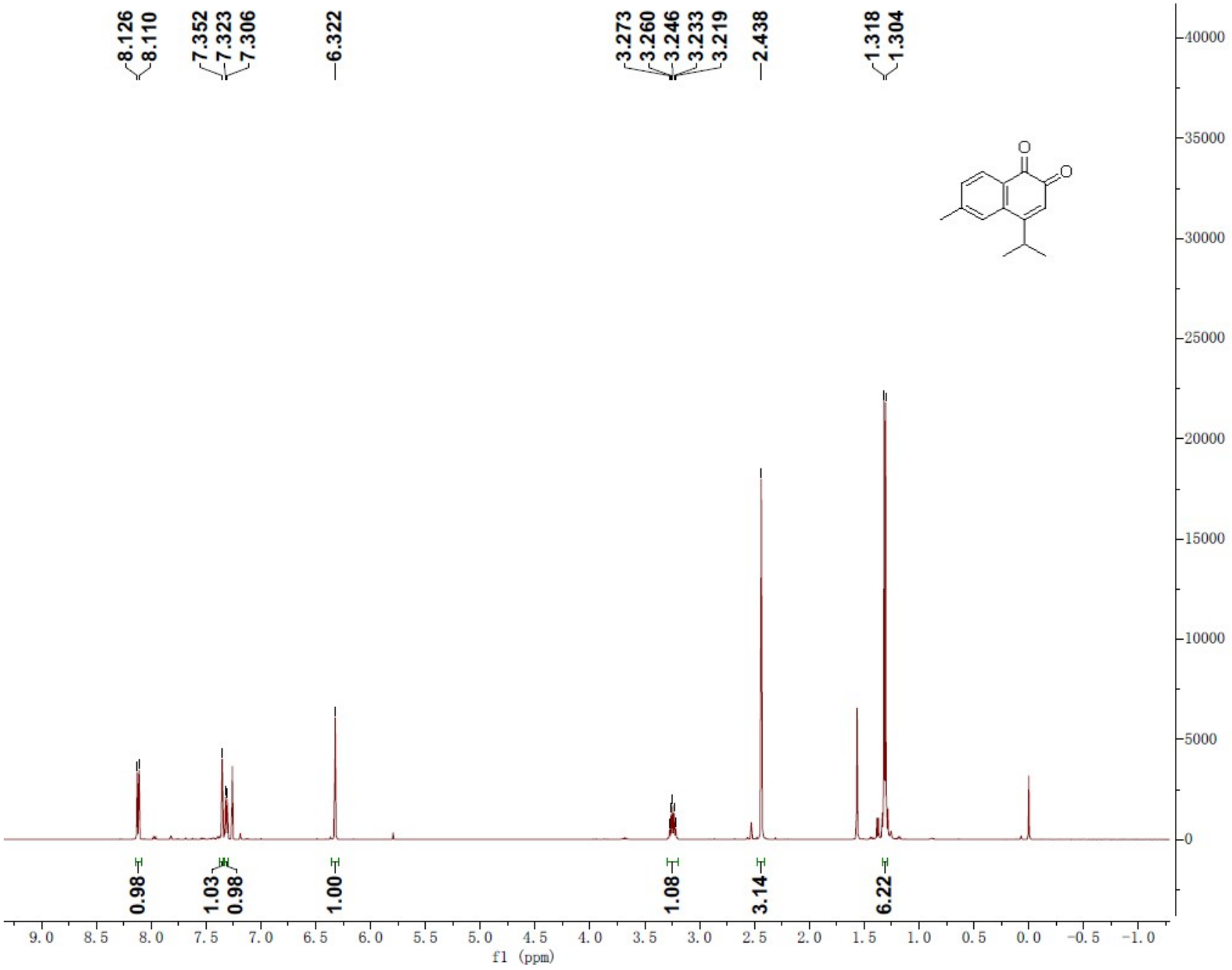
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 14



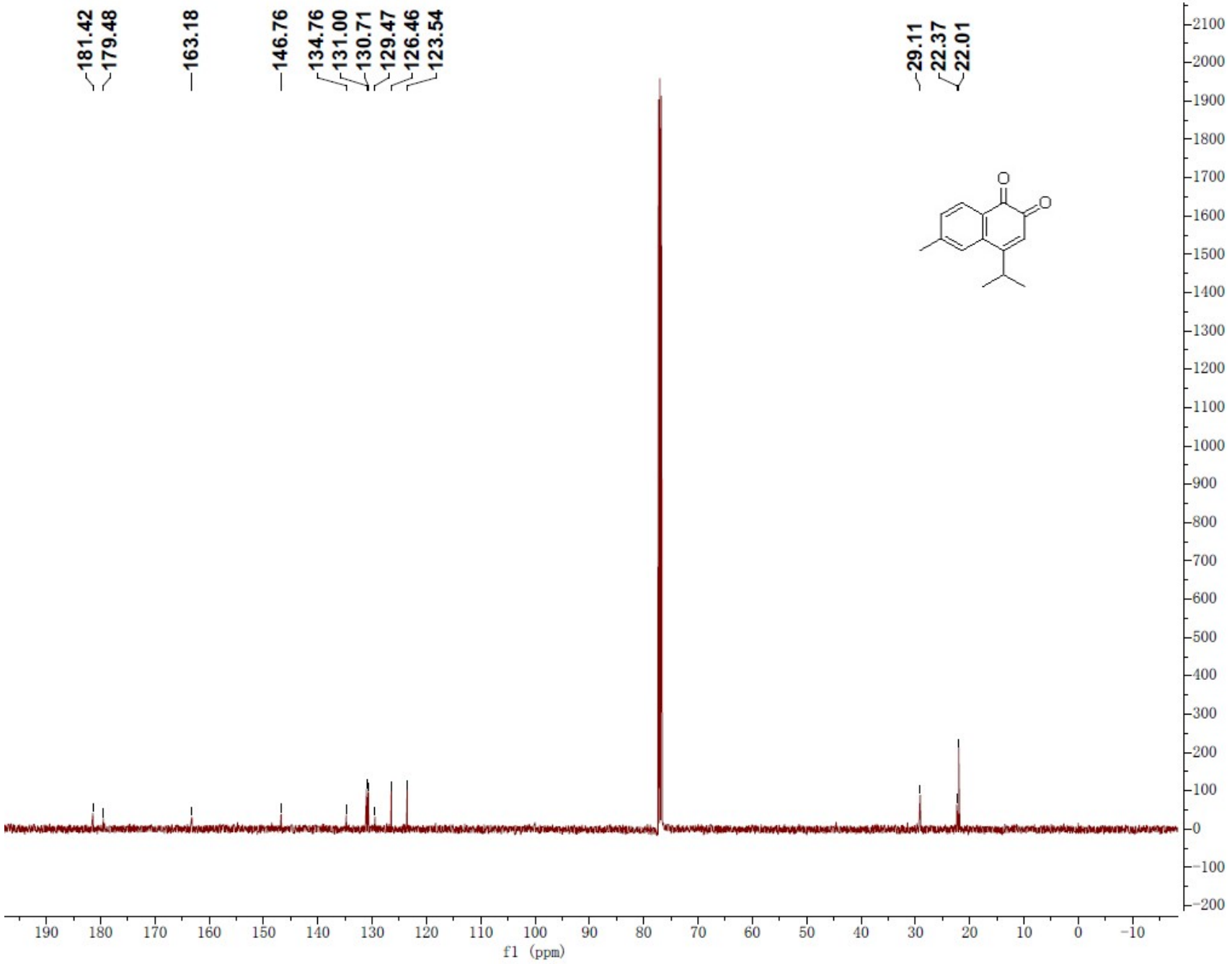
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 14



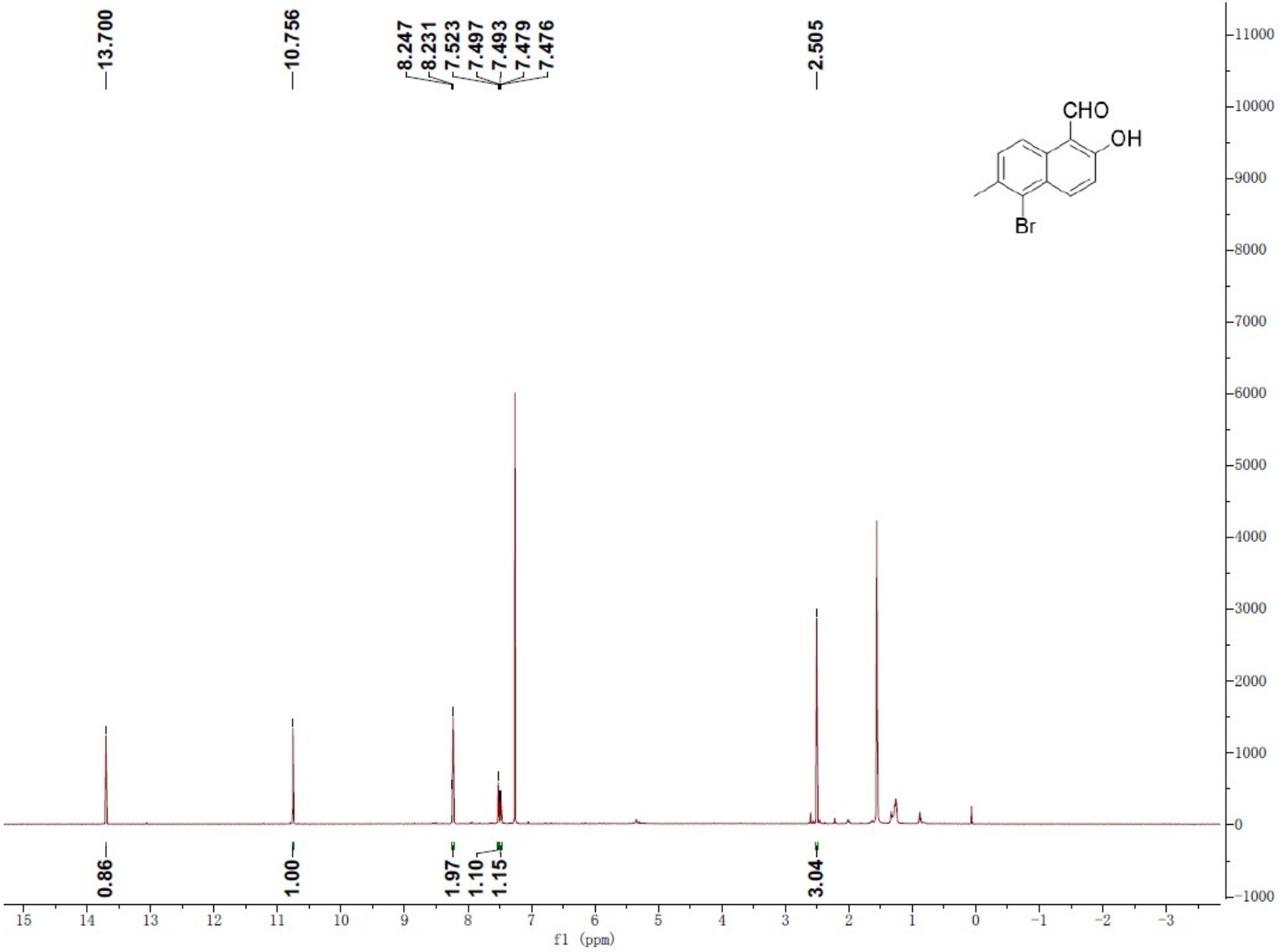
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 16



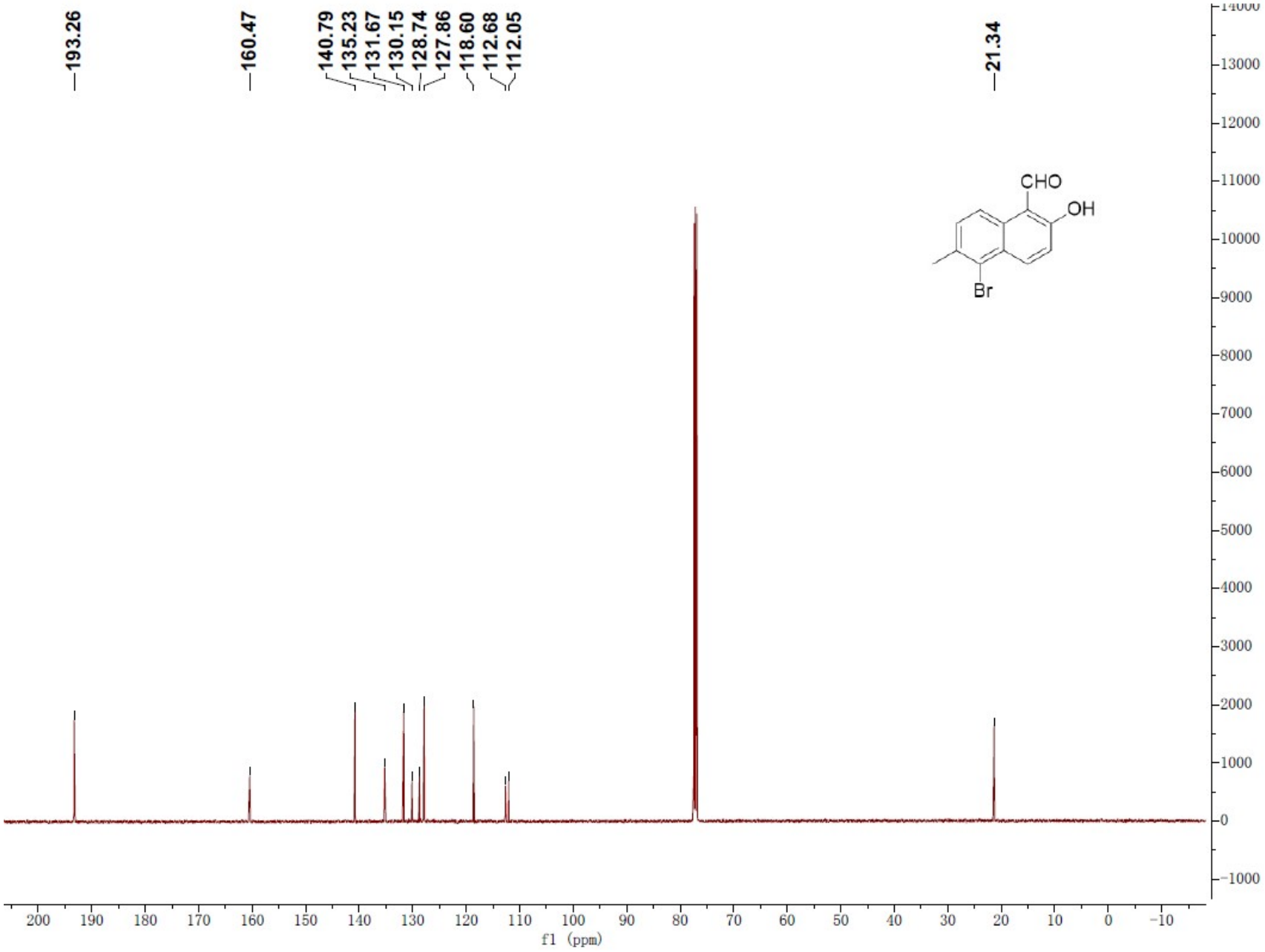
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 16



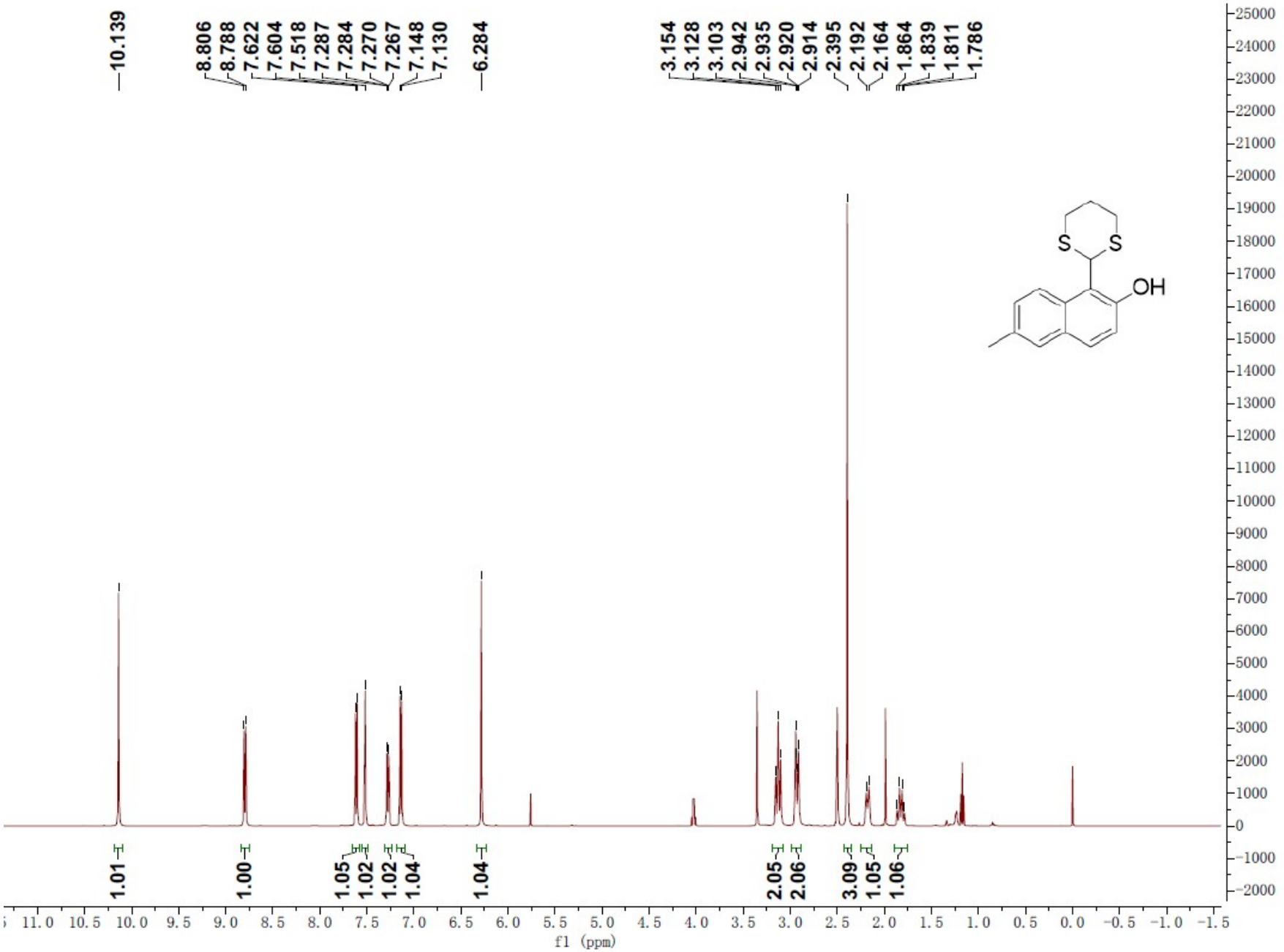
^{1}H NMR spectrum ($CDCl_3$, 500 MHz) of compound 19



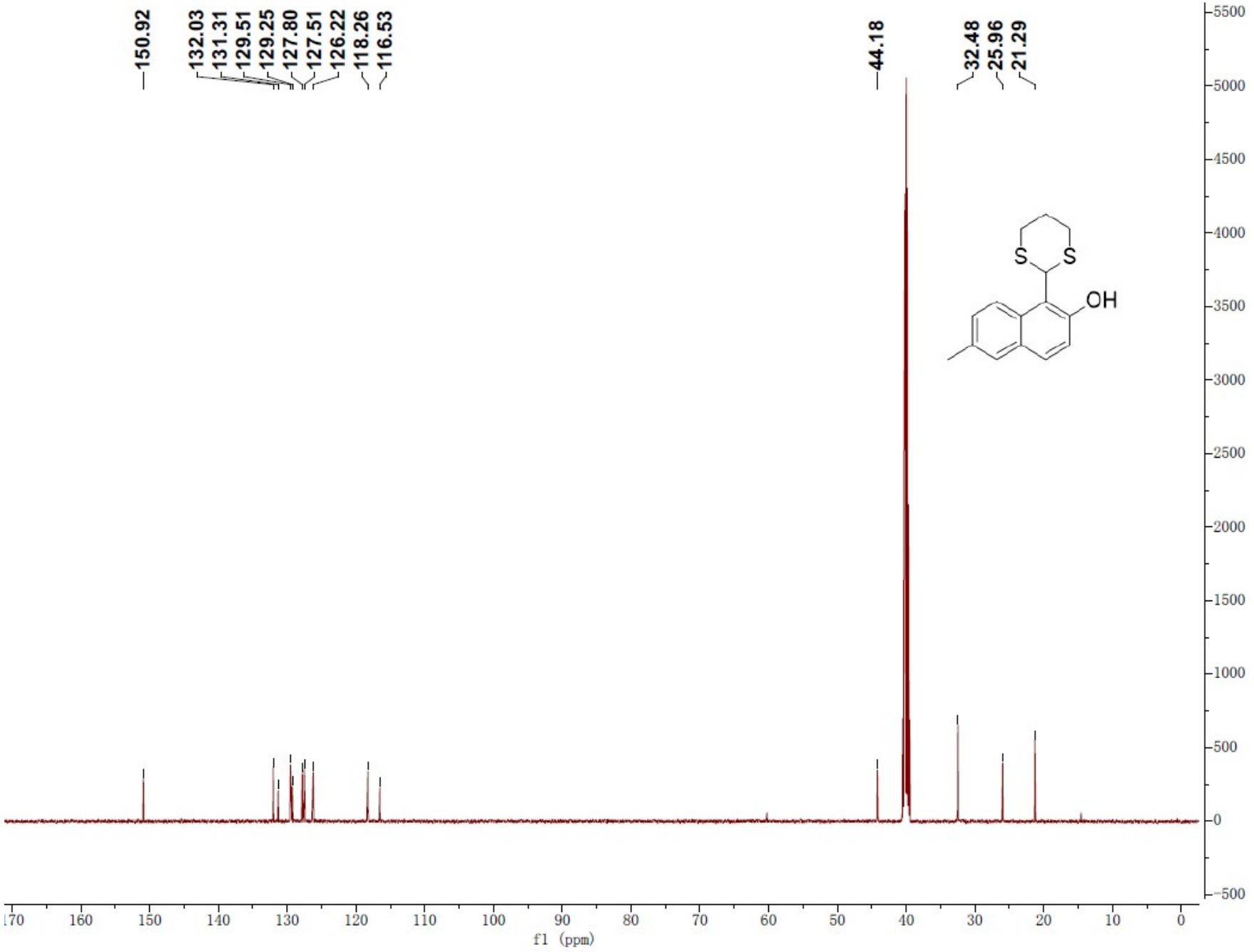
^{13}C NMR spectrum ($CDCl_3$, 125 MHz) of compound 19



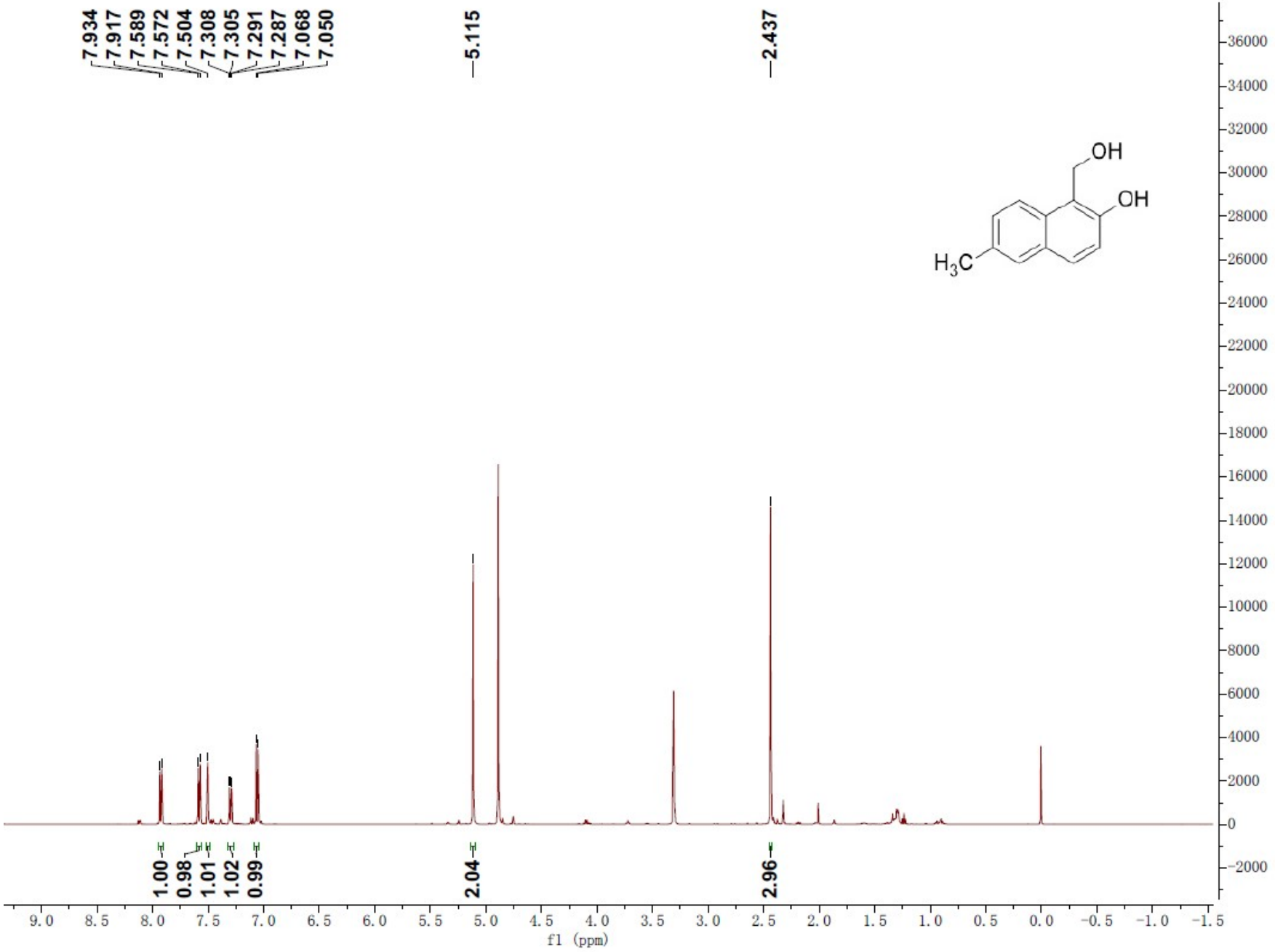
^{1}H NMR spectrum (DMSO-d_6, 500 MHz) of compound 20



^{13}C NMR spectrum (DMSO-d_6, 125 MHz) of compound 20



^{1}H NMR spectrum (Methanol-d_4, 500 MHz) of compound 22



^{13}C NMR spectrum (Methanol-d_4, 125 MHz) of compound 22