Supporting Information

An Oxidation of Benzyl Methyl Ethers with NBS that Selectively Affords Either Aromatic Aldehydes or Aromatic Methyl Esters

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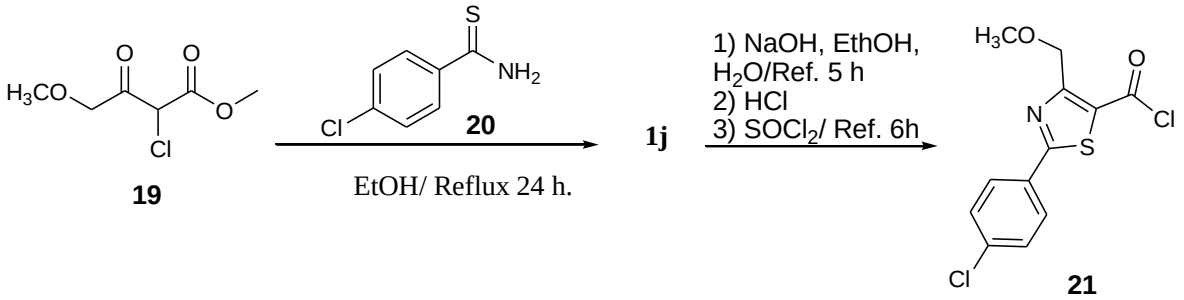
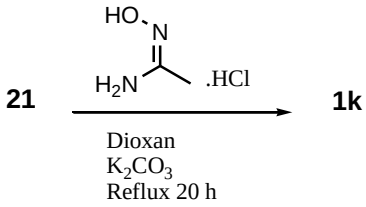
Preparation of Phenylthiazole Derivatives

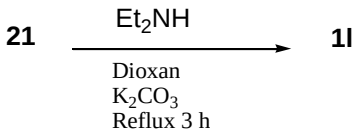
Scheme 1S



Scheme 2S



Scheme 3S



Experimental

General, ^{1}H NMR spectra were determined at 300 MHz and ^{13}C spectra were obtained at 75.46 MHz in deuterated chloroform ($CDCl_3$). Chemical shifts are given in parts per million (ppm) on the delta (δ) scale. Chemical shifts were related to that of the solvent. Mass spectra were recorded at 70 eV. Ethers **1a-c** and **1e** are commercially available. Other known, non-commercially available, benzyl ether derivatives were prepared from the corresponding bromomethyl analogues using Williamson's method. NMR data and comparison with authentic commercial samples confirmed the structures and purities of compounds **2a-f** and **3a-h**. The full scheme for preparation of phenylthiazoles **1j-l** and their antiviral activity will publish separately.

Methyl 2-(4-Chlorophenyl)-4-(methoxymethyl)thiazole-5-carboxylate (1j). 4-Chloro-thiobenzamide (**20**, 3.420 g, 20 mmol) and α-chlorodiketo derivative **19** (5.00 g, 27.7 mmol) were added to absolute ethanol (50 mL). The reaction mixture was heated to reflux for 24 h. After removal of solvent under reduced pressure, the residue was

purified by silica gel chromatography (hexanes-ethyl acetate 3:2) to provide the desired compound as an off-white solid (43.420 g, 74.4 %): mp 100-101 ^{o}C. ^{1}H NMR ($CDCl_3$) δ 7.82 (d, *J* = 7 Hz, 2 H), 7.31 (d, *J* = 7 Hz, 2 H), 4.84 (s, 2 H), 3.82 (s, 3 H), 3.45 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.2, 161.4, 160.0, 137.1, 130.9, 129.0, 128.0, 124.0, 67.9, 58.8, 52.3; MS (*m/z*, rel intensity) 300 (MH^+, 18), 298 (MH^+, 60); HRMS (EI), *m/z* M^+ 297.0227 calcd for $C_{13}H_{12}ClNO_3S$ 297.0226.

2-(4-Chlorophenyl)-4-(methoxymethyl)thiazole-5-carbonyl Chloride (21). NaOH (4.00 g, 100 mmol) was added to a solution of methyl ester **1j** (6.237 g, 21 mmol) in ethanol (40 mL) and water (5 mL). The reaction mixture was heated under reflux for 5 h, and then allowed to cool to room temperature. The reaction mixture was filtered and the pH of the liquid phase was adjusted to 2 with hydrochloride acid. The solid was filtered and dried to provide 2-(4-chlorophenyl)-4-(methoxymethyl)thiazole-5-carboxylic acid as a white solid (4.98 g, 83.7 %): mp 197-199 ^{o}C (dec.). ^{1}H NMR (DMSO) δ 3.33 (s, 3 H), 4.76 (s, 2 H), 5.8 (brs, 1 H), 7.50 (d, *J* = 7.5 Hz, 2 H), 7.91, (d, *J* = 7.5 Hz, 2 H); ^{13}C NMR (DMSO) δ 168.4, 163.0, 159.6, 136.8, 131.8, 130.2, 129.0, 127.4, 67.7, 58.8; MS (*m/z*, rel intensity) 286 (MH^+, 39), 284 (MH^+, 100). The crude carboxylic acid derivative (4.88 g, 17.24 mmol) was heated under reflux with thionyl chloride (25 mL) for 6 h. The solvent was evaporated under reduced pressure. The brown residue was collected and purified by silica gel flash chromatography, using hexane: ethyl acetate (7:3), to yield a brownish white solid (2.507 g, 96 %): mp 91 ^{o}C. IR (film) 2976, 1742, 1593 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.96 (d, *J* = 7.2 Hz, 2 H), 7.43 (d, *J* = 7.2 Hz, 2 H), 4.80 (s, 2 H), 3.52 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 172.9, 162.7, 157.6, 138.2, 130.3, 129.4, 128.3, 68.7, 59.3; MS (*m/z*, rel intensity) 308 (MH^+, 18), 306 (MH^+, 31), 304 (MH^+, 12), 302 (MH^+, 17); HRMS (CI), *m/z* M^+ 301.9806, calcd for $C_{12}H_9Cl_2NO_2S$ 301.9809.

5-(2-(4-Chlorophenyl)-4-(methoxymethyl)thiazol-5-yl)-3-methyl-1,2,4-oxadiazole (1k). Acetamide oxime hydrochloride (49 mg, 0.66 mmol) and potassium carbonate (91 mg, 0.66 mmol) were added to a stirred solution of the acid chloride **21** (100 mg, 0.33 mmol) in dioxane (5 mL). The reaction mixture was heated under reflux for 20 h. The solvent was taken off under reduced pressure and the solid residue was partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was separated and dried over anhydrous magnesium sulfate. The obtained solid product was purified by silica gel flash chromatography using hexane: ethyl acetate (9:1) to afford a yellowish-white solid (99 mg, 93 %): mp 89 ^{o}C. ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3 H), 3.53 (s, 3 H), 4.96 (s, 2 H), 7.42 (d, *J* = 7.5 Hz, 2 H), 7.93 (d, *J* = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 169.6, 169.2, 167.6, 157.6, 137.4, 130.6,

129.2, 128.1, 118.0, 68.0, 59.0, 11.5; MS (*m/z*, rel intensity) 324 (MH^+, 14.4), 322 (MH^+, 41.5), 292 (39), 294 (100); HRMS (ESI), *m/z* MH^+ 322.0417 calcd for $C_{14}H_{13}ClN_3O_2S$ 322.0415.

2-(4-Chlorophenyl)-*N,N*-diethyl-4-(methoxymethyl)thiazole-5-carboxamide (1l). Diethylamine (29 mg, 0.66 mmol) and potassium carbonate (91 mg, 0.66 mmol) were added to a stirred solution of the acid chloride 2**1** (100 mg, 0.33 mmol) in dioxane (5 mL). The reaction mixture was heated under reflux for 3 h. The solvent was taken off under reduced pressure and the solid residue was partitioned between ethyl acetate (10 mL) and water (10 mL). The organic layer was separated and dried over anhydrous magnesium sulfate. The obtained solid product was purified by crystallization from ethanol to afford the titled compound as colorless crystals (90 %): mp 112-113 ^oC. ^1H NMR ($CDCl_3$) δ 7.86 (d, *J* = 8.7 Hz, 2 H), 7.40 (d, *J* = 8.7 Hz, 2 H), 4.57 (s, 2 H), 3.45 (s, 7 H), 1.20 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 165.9, 162.0, 151.9, 136.4, 131.2, 129.1, 127.8, 68.7, 58.8, 43.2, 39.7, 12.7; MS (*m/z*, rel intensity) 363 (MNa^+, 12), 361 (MNa^+, 26.8), 309 (M^+- Et, 39), 307 (M^+- Et, 100); HRMS (ESI), *m/z* MNa^+ 361.0753 calcd for $C_{16}H_{19}ClN_2O_2SNa$ 361.0755.

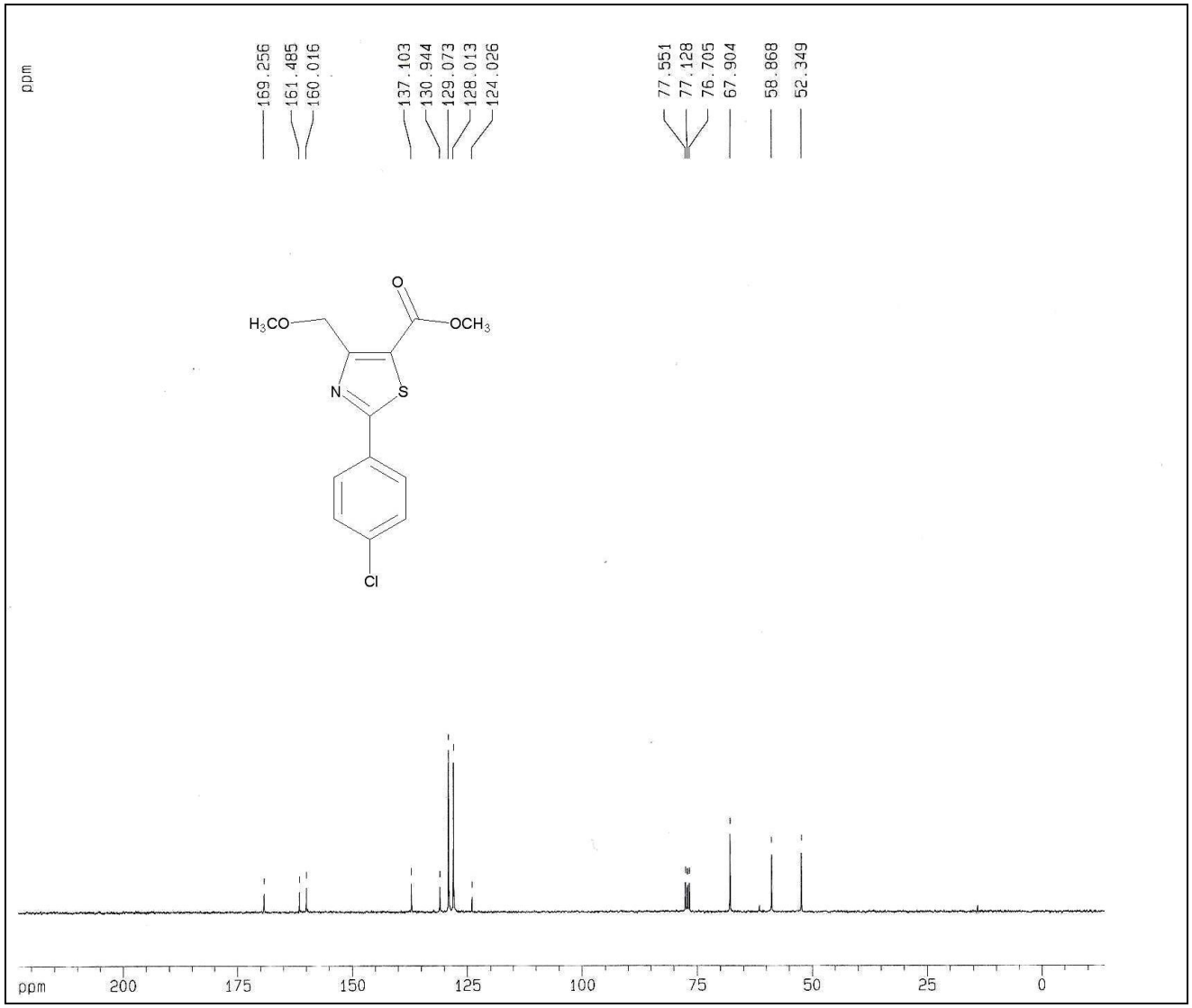
2-(4-Chlorophenyl)-5-(3-methyl-1,2,4-oxadiazol-5-yl)thiazole-4-carbaldehyde (2h). White solid (55%): mp 153-155 ^oC. ^1H NMR ($CDCl_3$) δ 10.69 (s, 1 H), 8.00 (d, *J* = 8.4 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 2 H), 2.52 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 183.3, 170.1, 168.3, 153.7, 138.4, 129.8, 129.5, 128.5, 11.5; MS (*m/z*, rel intensity) 307 (M^+, 34), 305 (M^+, 100); HRMS (ESI), *m/z* MH^+ 305.0027 calcd for $C_{13}H_8ClN_3O_2S$ 305.0025; HPLC (98.75 %).

Methyl 2-(4-Chlorophenyl)-5-(3-methyl-1,2,4-oxadiazol-5-yl)thiazole-4-carboxylate (3j). White solid (71%): mp 119-120 ^oC. ^1H NMR ($CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 4.01 (s, 2 H), 2.49 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.6, 167.8, 163.2, 159.3, 147.8, 138.0, 130.0, 129.4, 128.2, 118.2, 53.1, 11.5; HRMS (ESI), *m/z* (M^+-OCH_3) 303.9947, calcd for $C_{13}H_7ClN_3O_2S$ 303.9948.

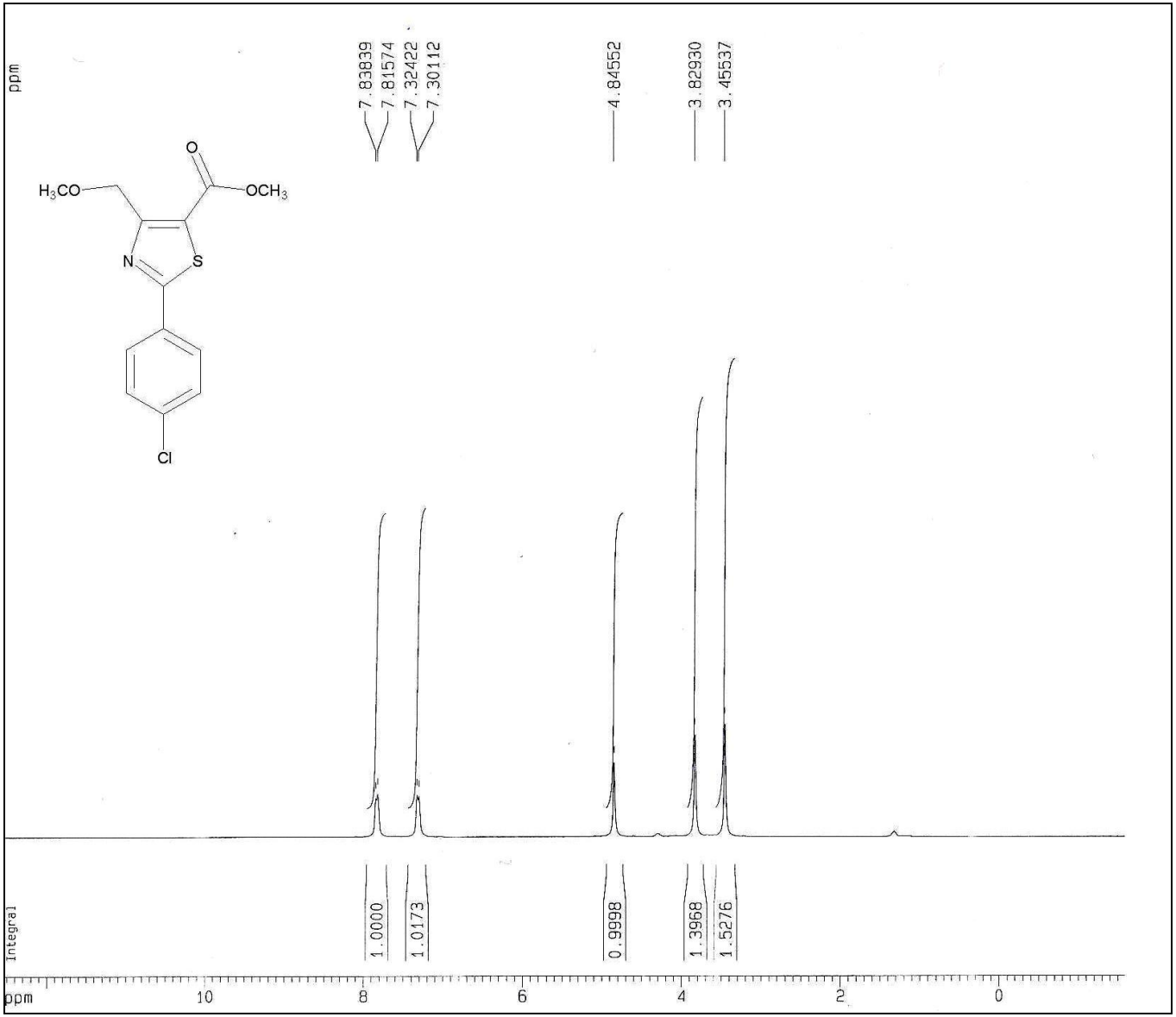
2-(4-Chlorophenyl)-*N,N*-diethyl-4-formylthiazole-5-carboxamide (2i). Colorless solid (57 %): mp 145-147 ^oC. ^1H NMR ($CDCl_3$) δ 10.09 (s, 1 H), 7.91 (d, *J* = 8.4 Hz, 2 H), 7.46 (d, *J* = 8.4 Hz, 2 H), 3.61 (q, *J* = 6.0 Hz, 2 H), 3.28 (q, *J* = 6.0 Hz, 2 H), 1.32 (t, *J* = 6.0 Hz, 3 H), 1.12 (t, *J* = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 184.2, 166.5, 160.3, 150.0, 138.4, 137.3, 130.3, 129.4, 128.0, 43.2, 39.8, 13.9, 12.3; HRMS (ESI), *m/z* MNa^+ 345.0443, calcd for $C_{15}H_{15}ClN_2O_2SNa$ 345.0440.

Methyl 2-(4-Chlorophenyl)-5-(diethylcarbamoyl)thiazole-4-carboxylate (3k). Colorless solid (65 %): mp 85-86 ^oC. ^1H NMR ($CDCl_3$) δ 7.90 (d, *J* = 8.7 Hz, 2 H), 7.44 (d, *J* = 8.7 Hz, 2 H), 3.93 (s, 3 H), 3.58 (q, *J* = 6.0 Hz, 2 H), 3.43 (q, *J* = 6.0 Hz, 2 H), 1.32 (t, *J* = 6.0 Hz, 3 H), 1.11 (t, *J* = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.9,

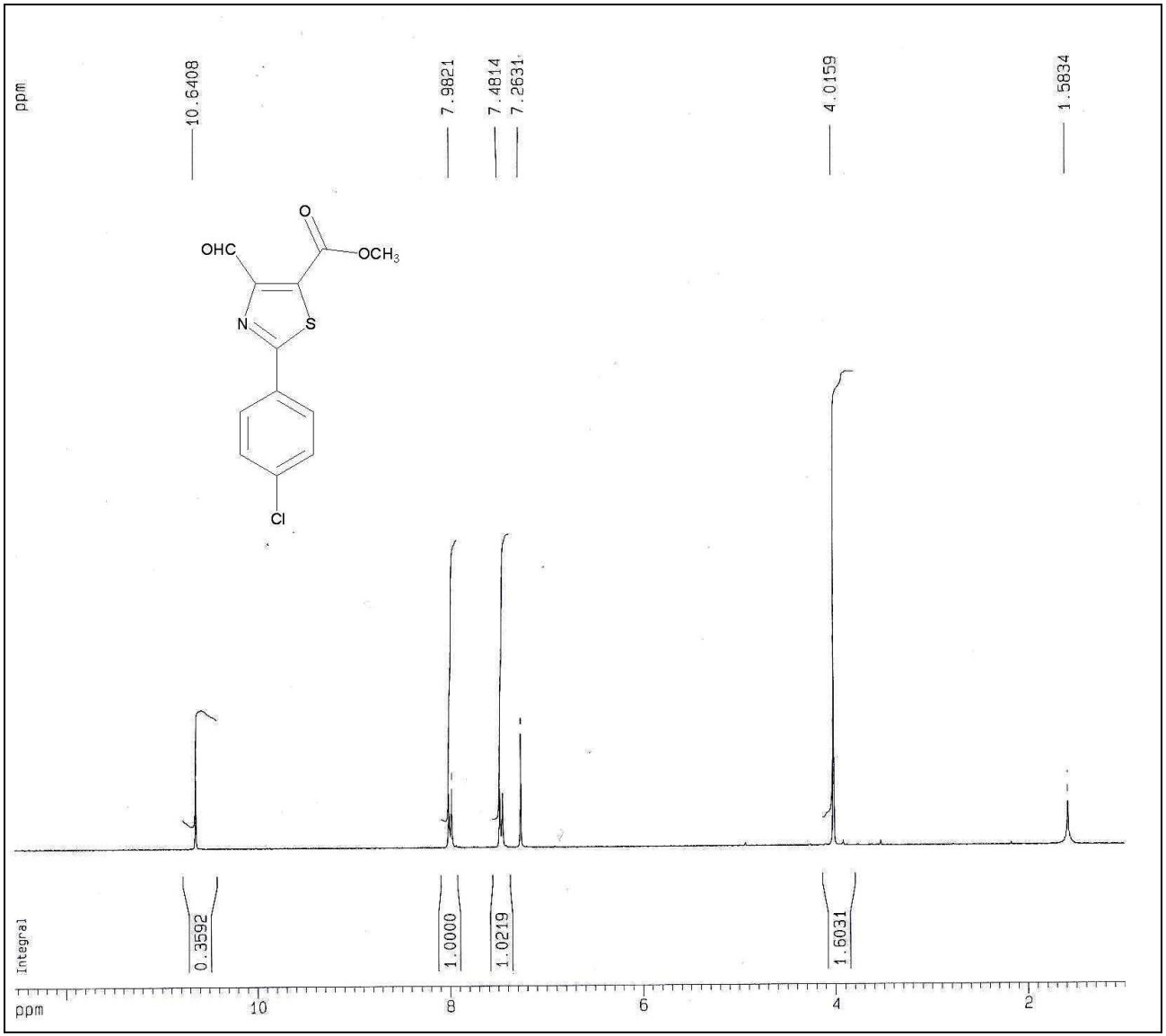
161.1, 160.9, 137.2, 130.5, 129.3, 129.1, 128.1, 127.9, 52.6, 43.2, 39.65, 29.6; HRMS (ESI), *m/z* MNa^+ 375.0545, calcd for $C_{16}H_{17}ClN_2O_3SNa$ 375.0546; HPLC (96.38 %).



^{13}C NMR spectrum of compound **1j.**



^{1}H NMR spectrum of compound **1j.**



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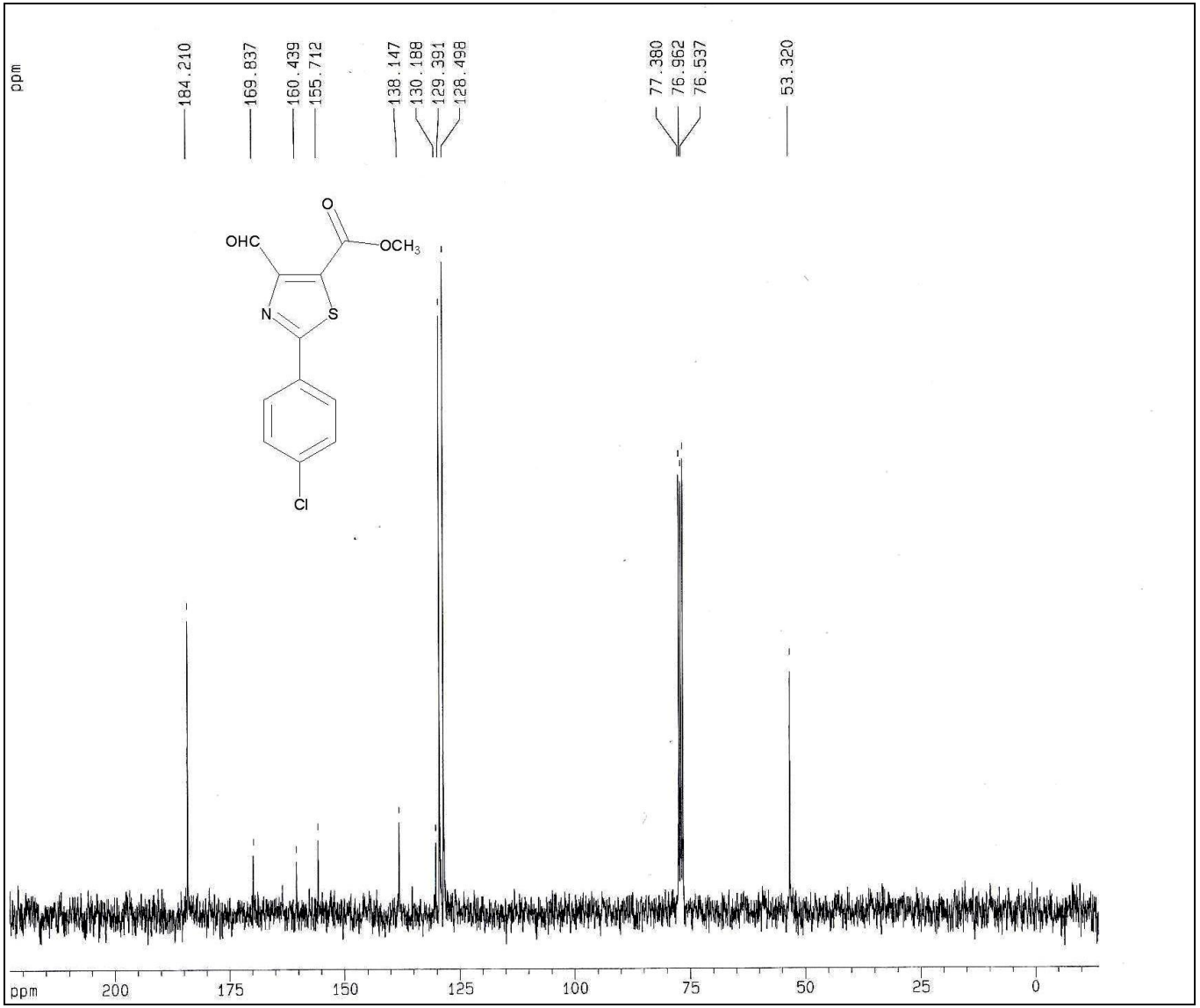
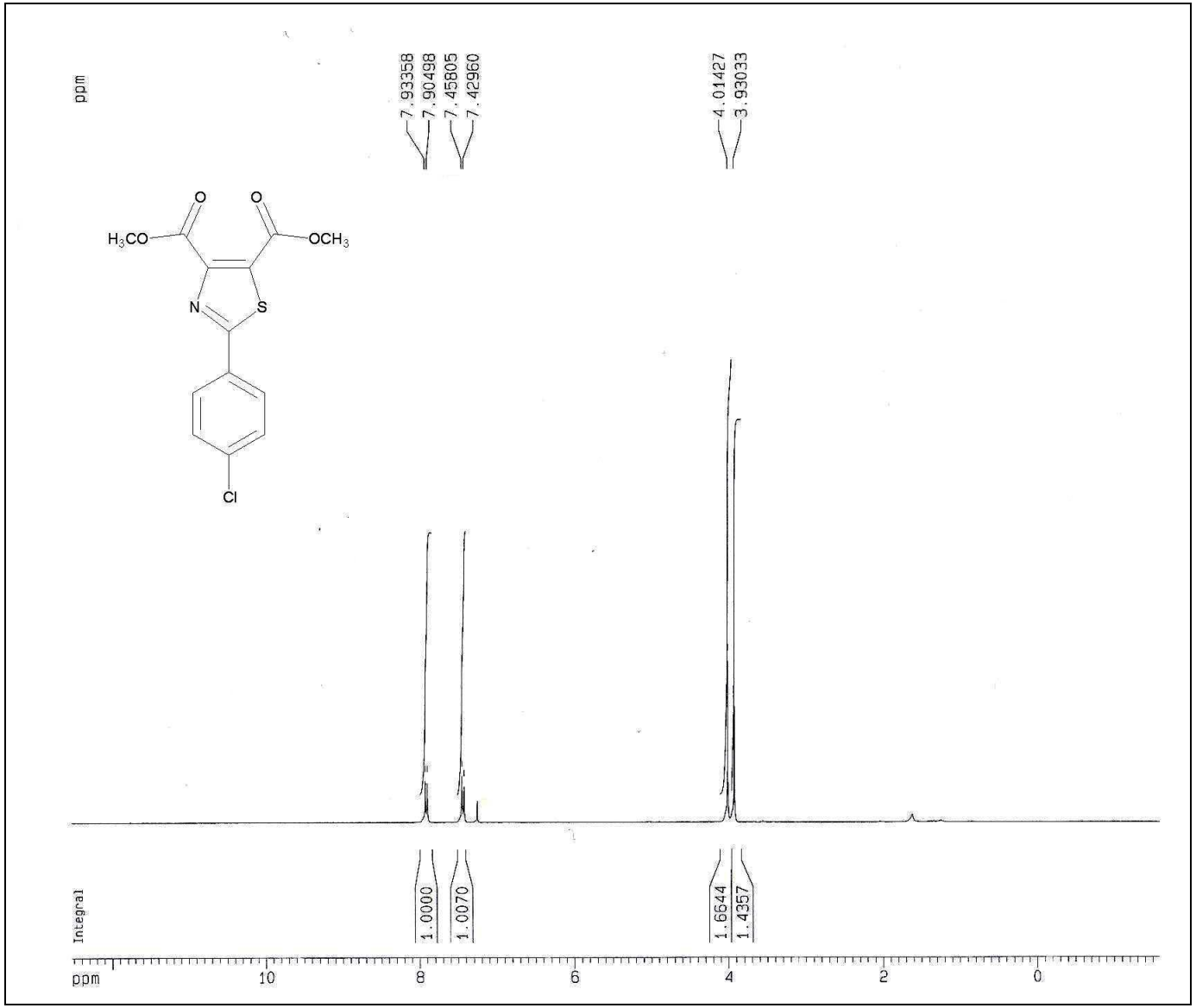
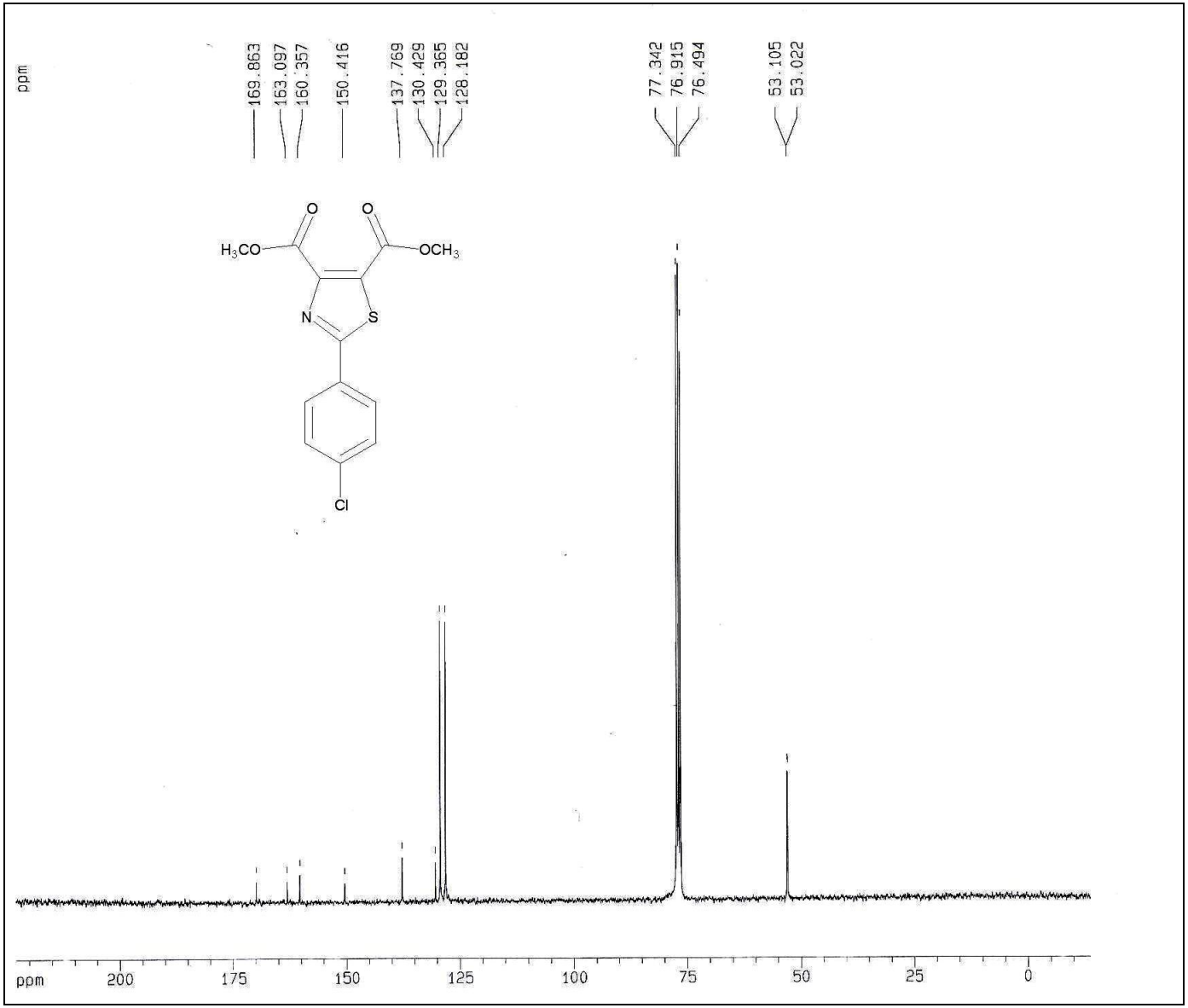


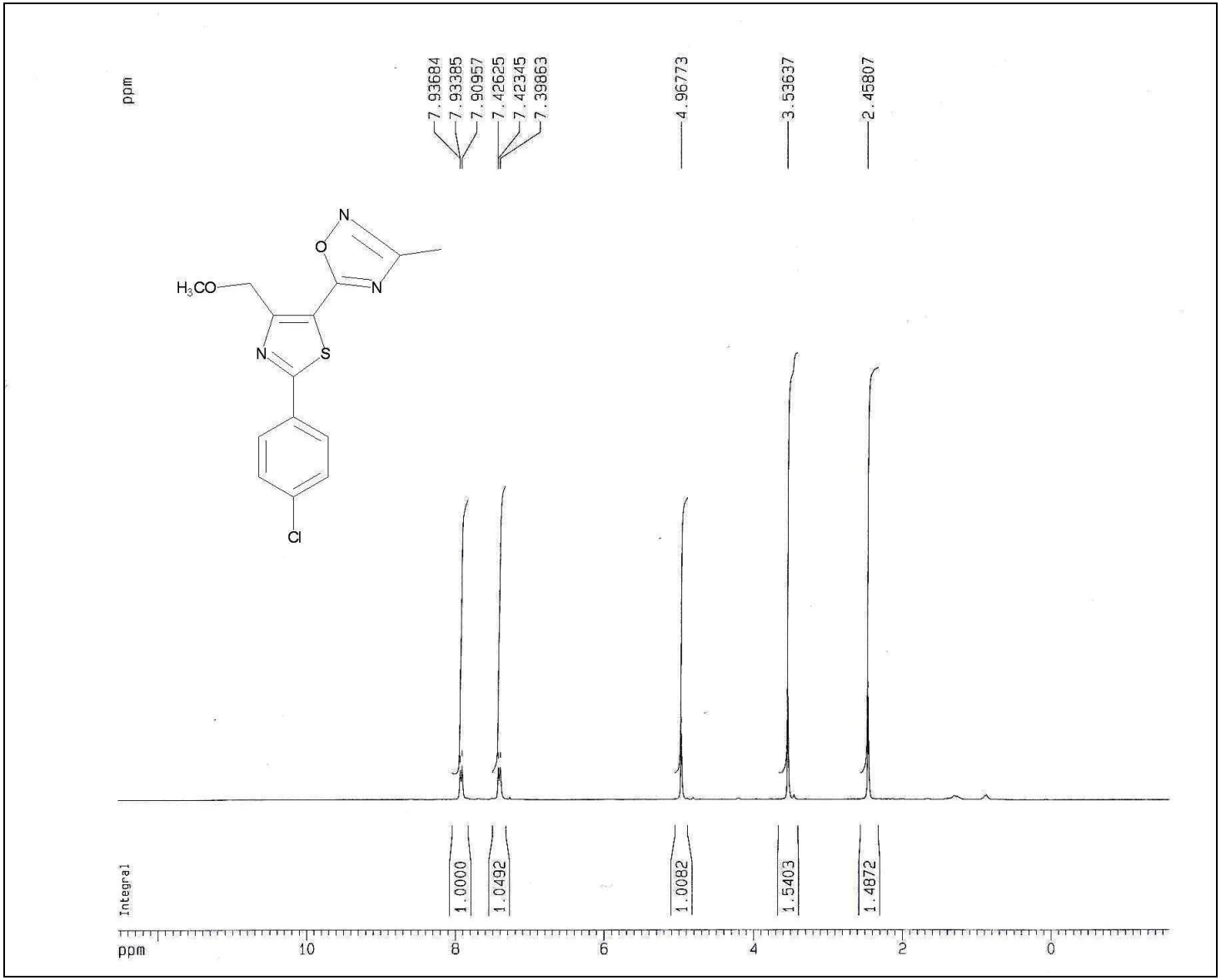
^{13}C NMR spectrum of compound **2g.**



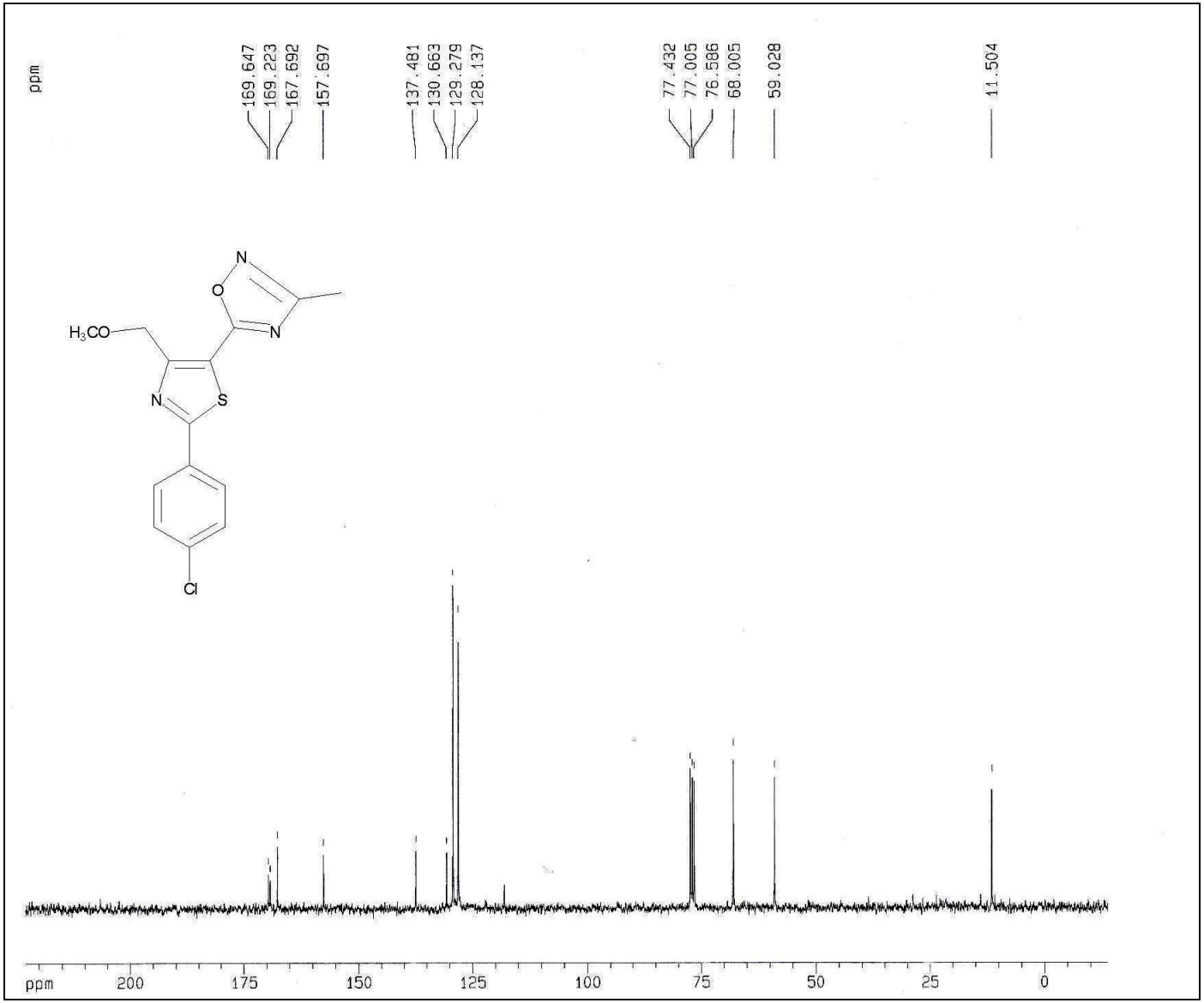
^{1}H NMR spectrum of compound **3i.**



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



[1]H NMR spectrum of compound **1k**.



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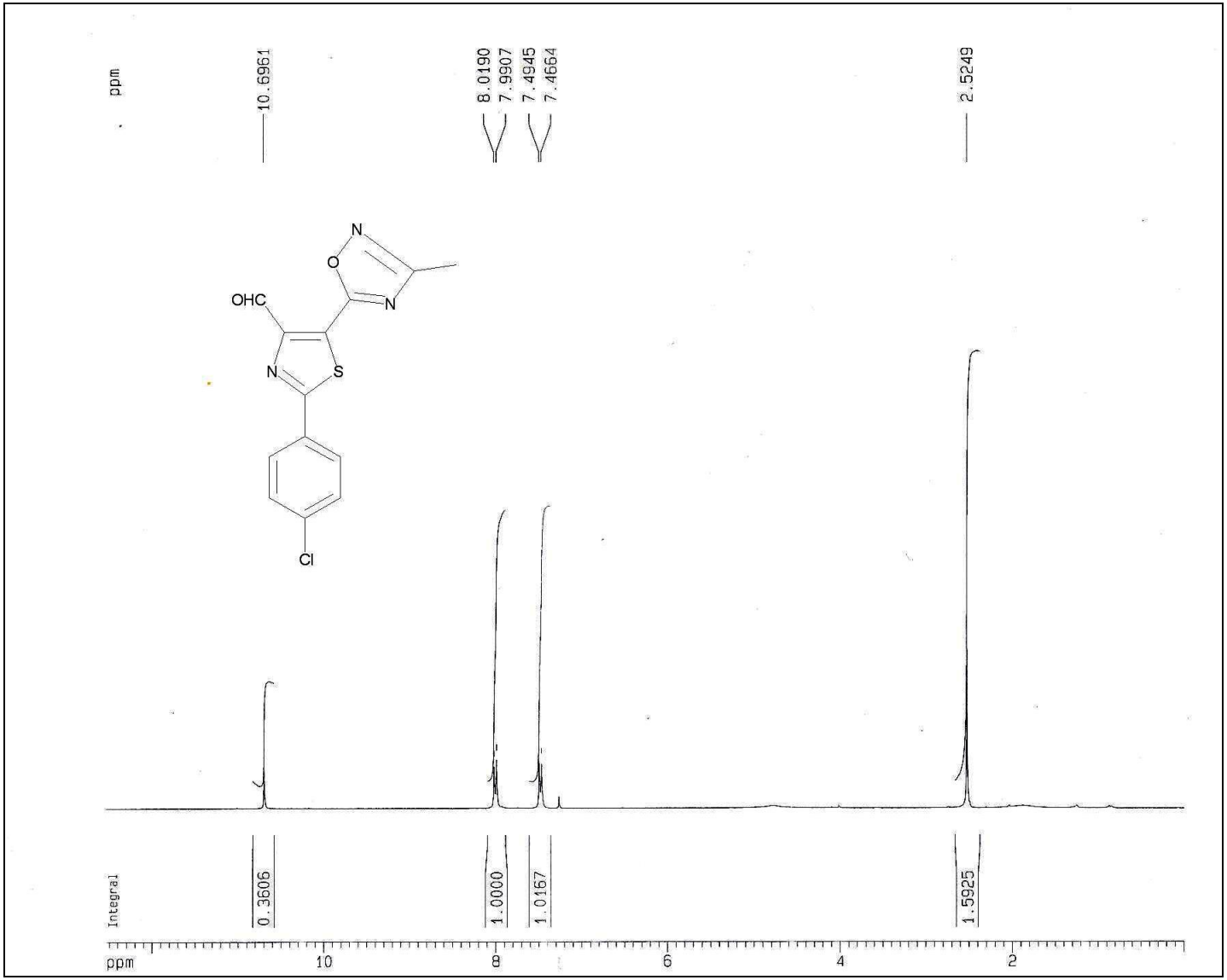

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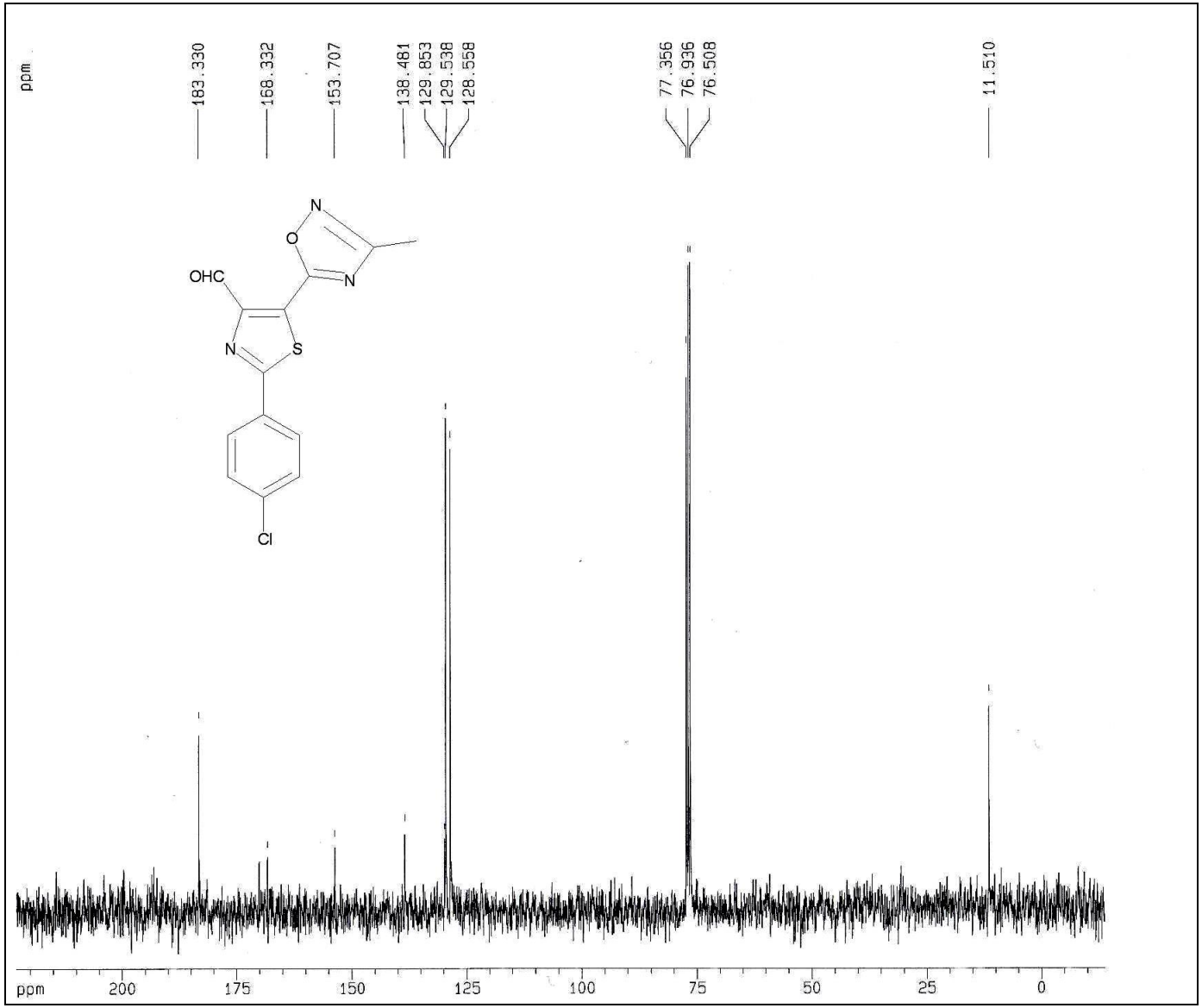

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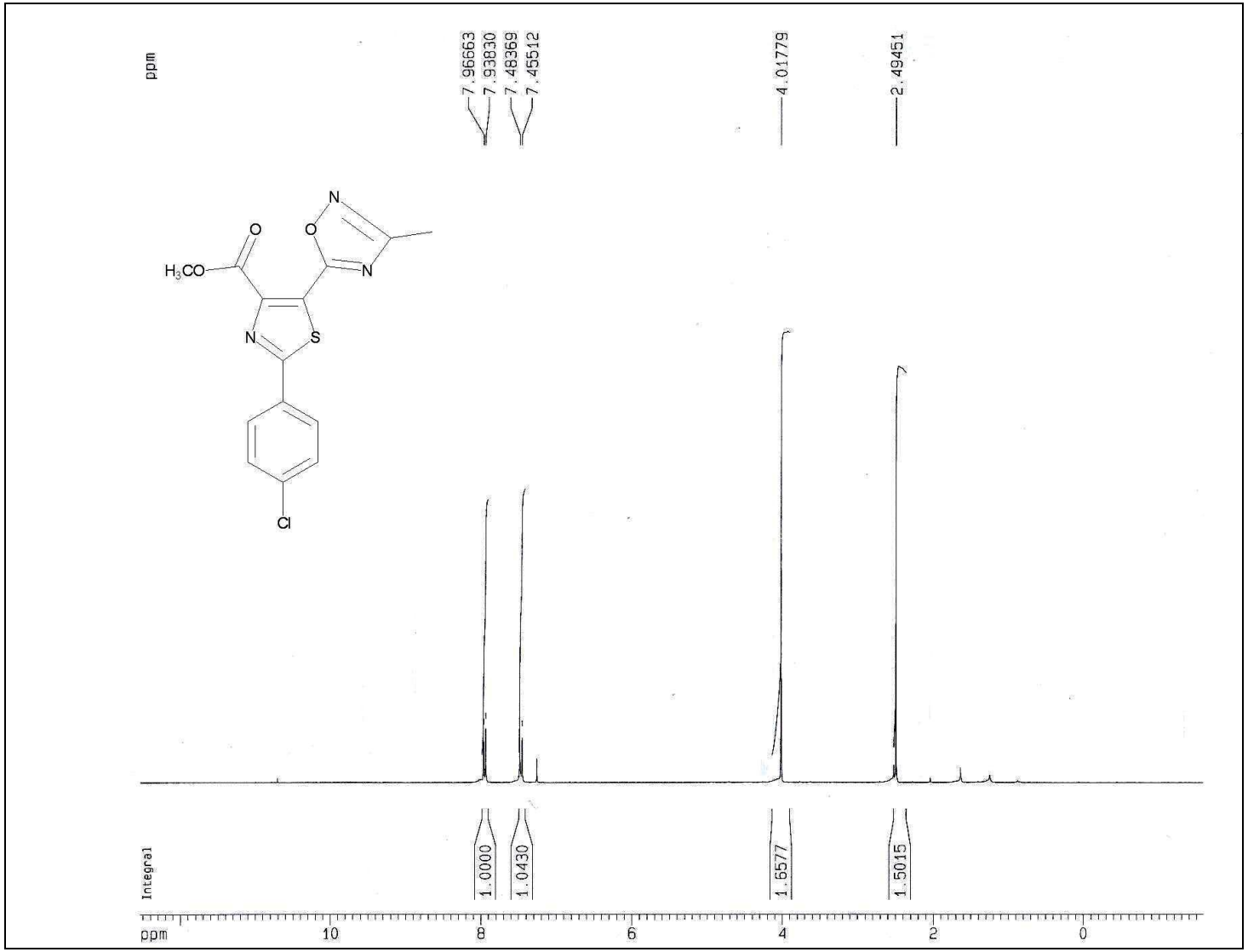

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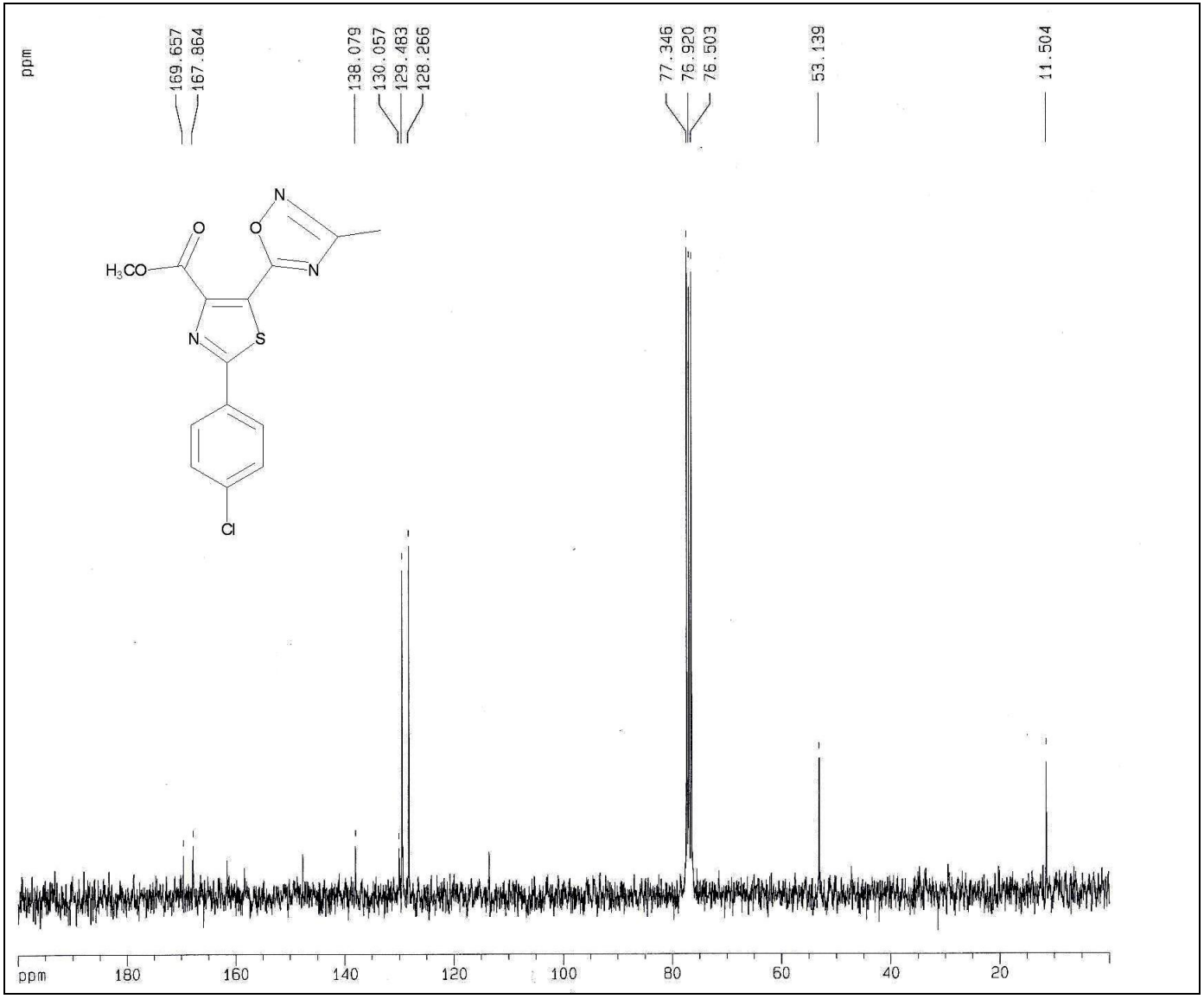

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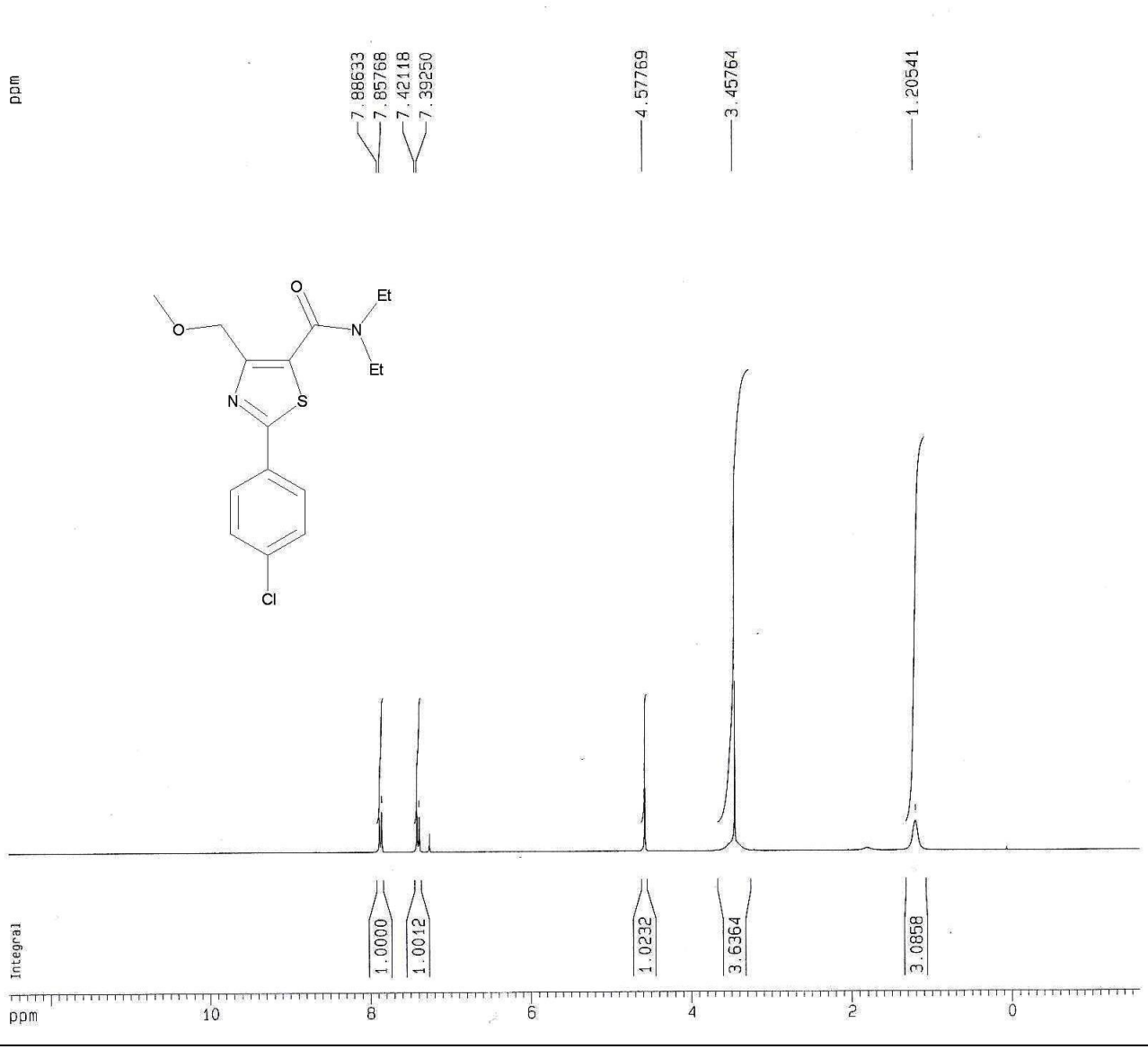
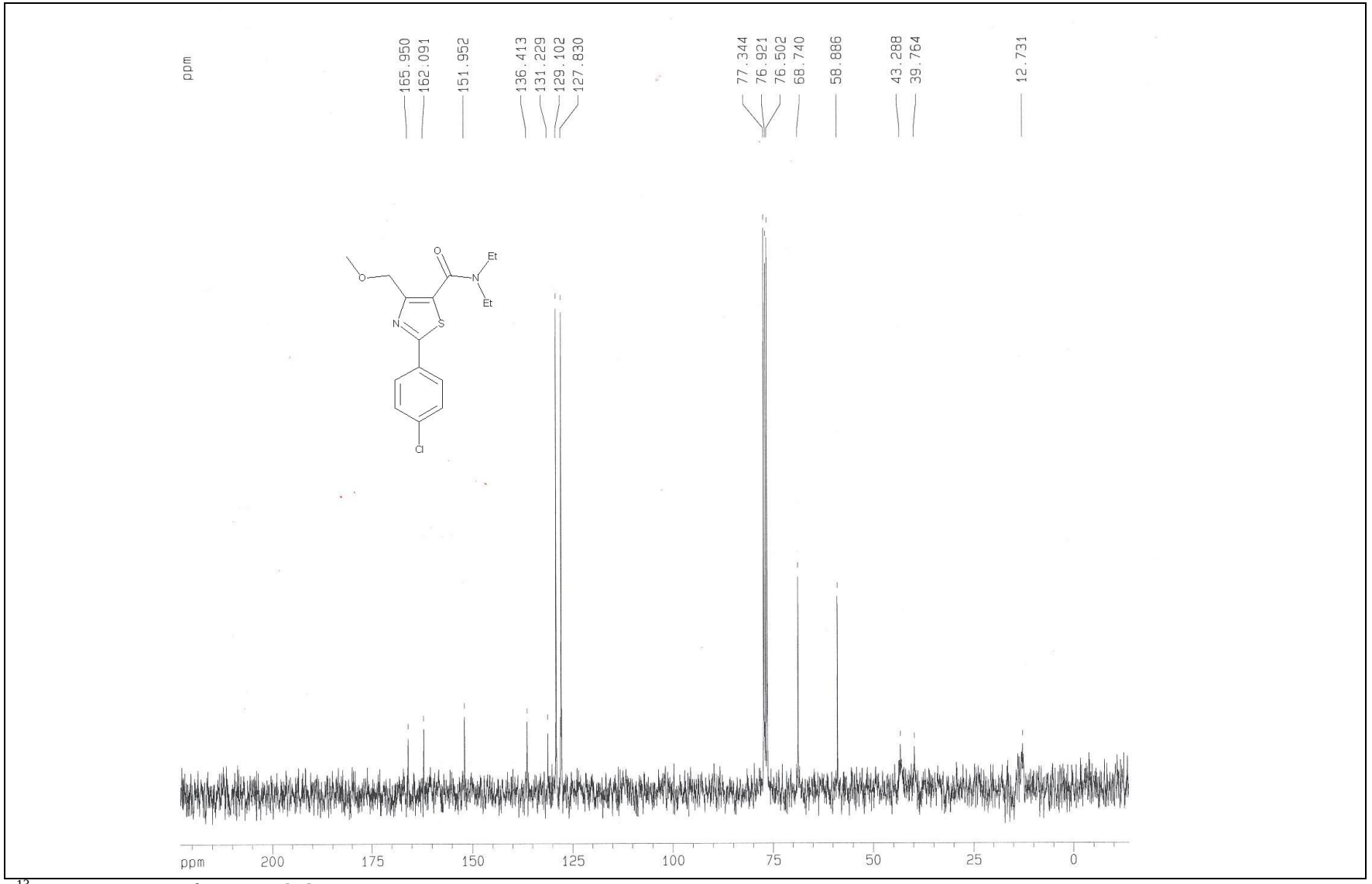
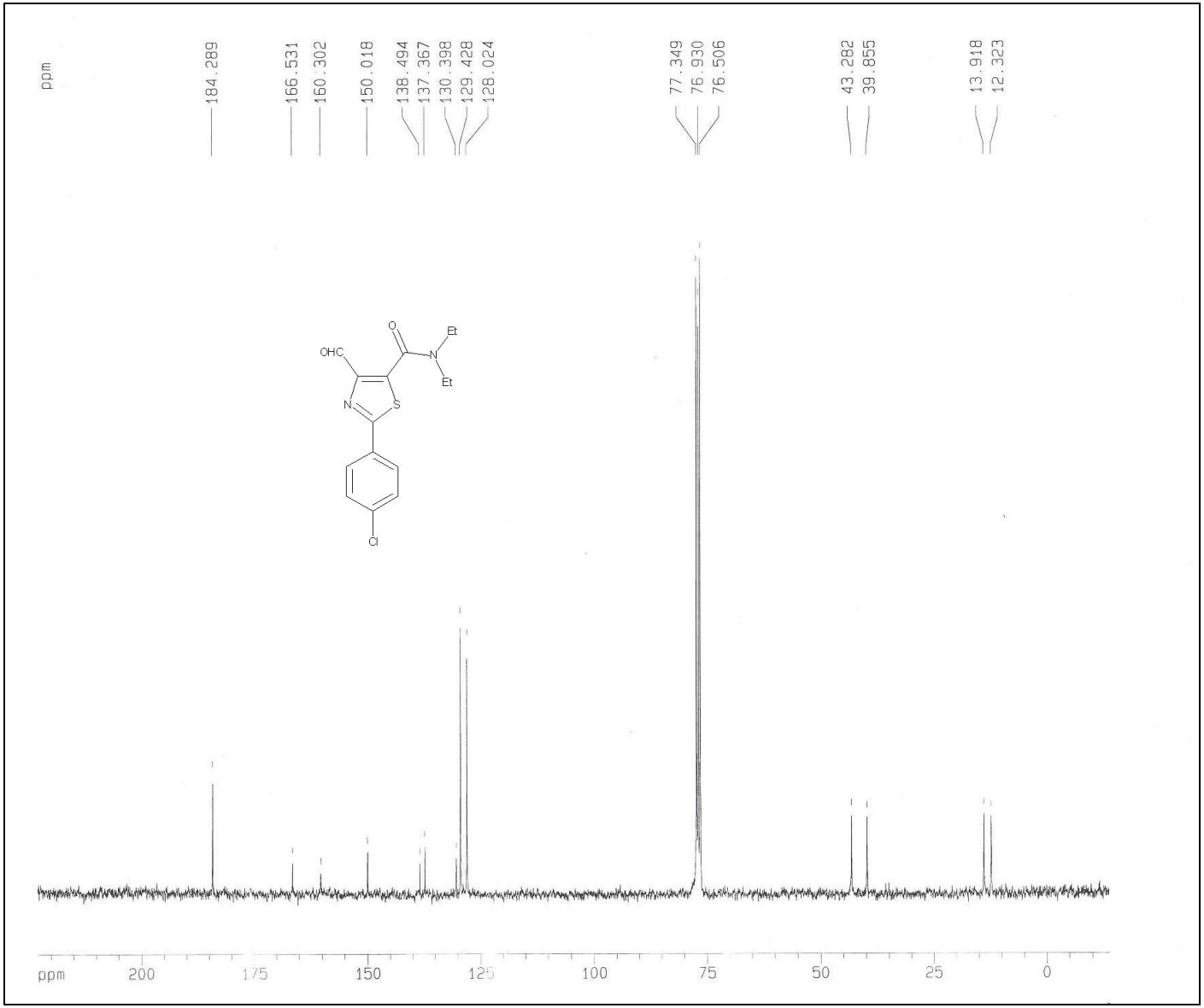


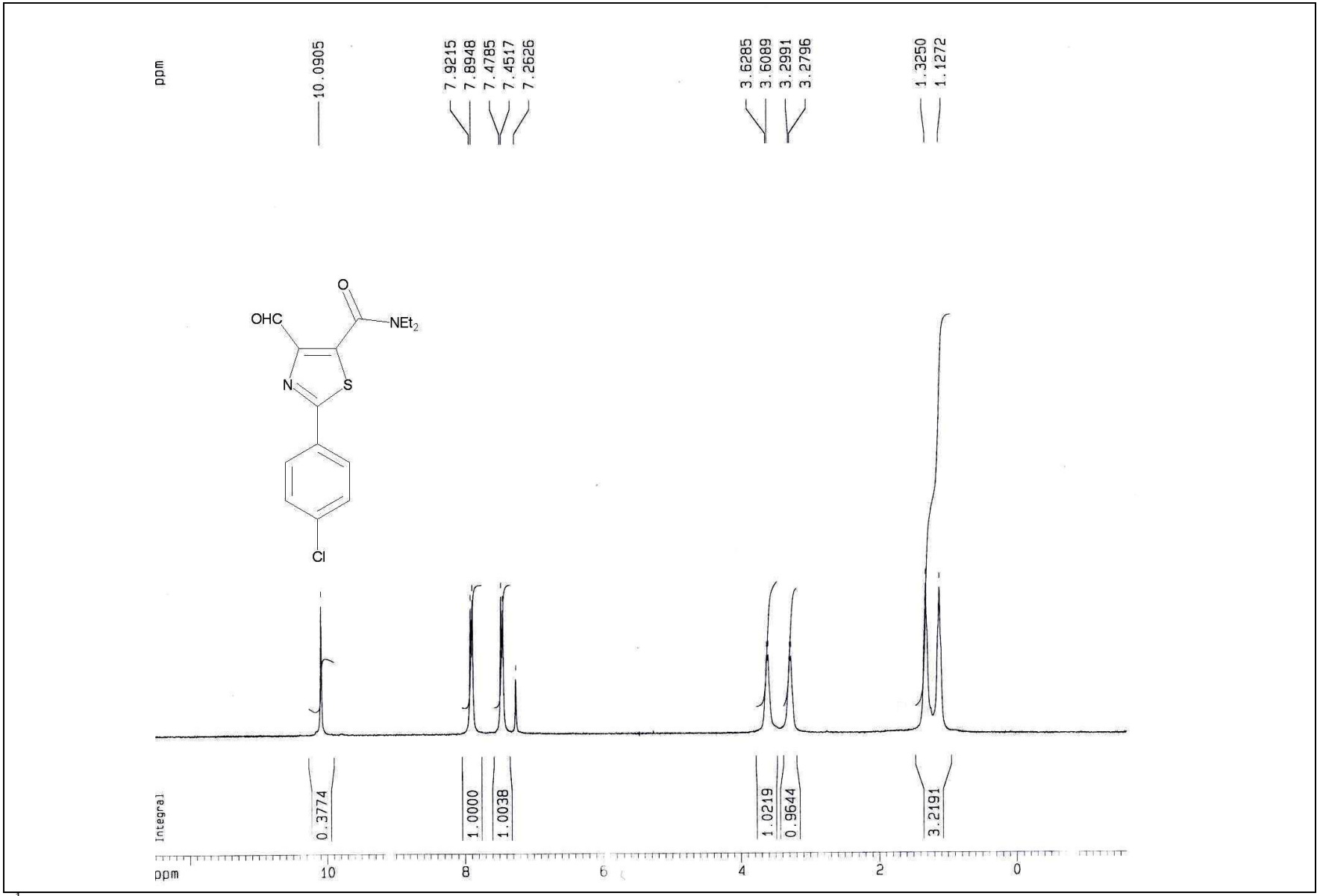
[1]H NMR spectrum of compound **1l.**



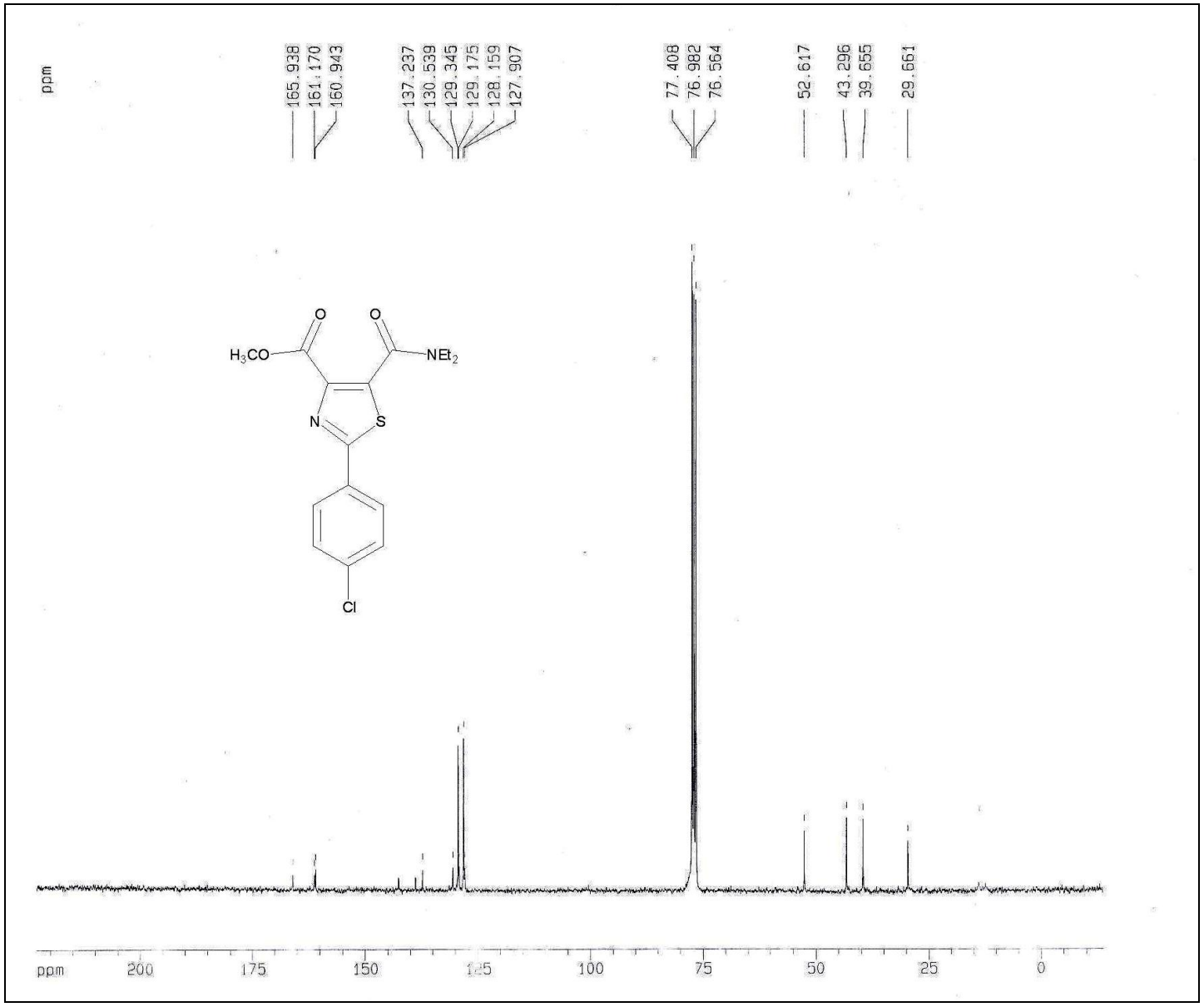
^{13}C NMR spectrum of compound **1l.**



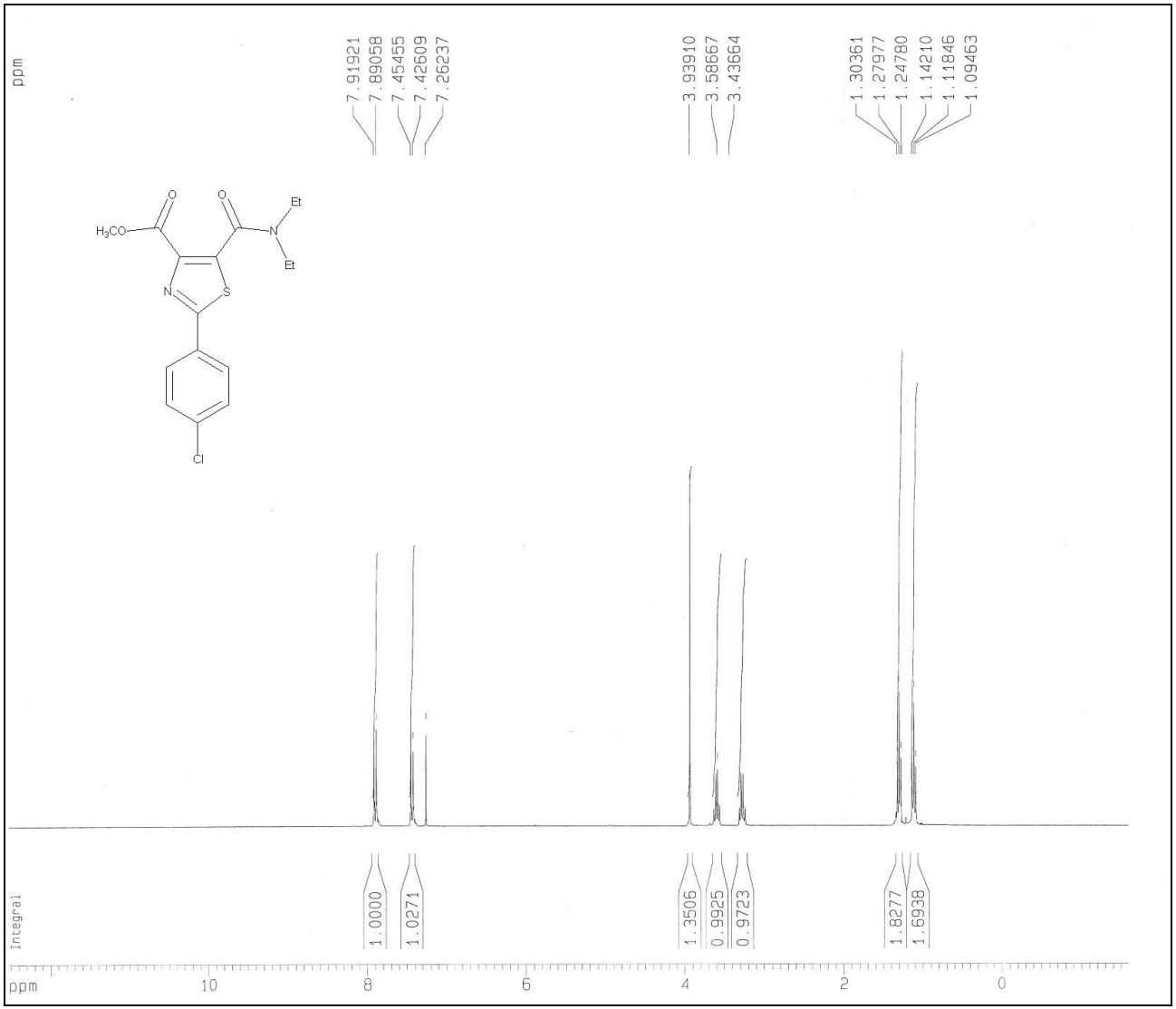
^{13}C NMR spectrum of compound **2i.**



^{1}H NMR spectrum of compound **2i.**



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



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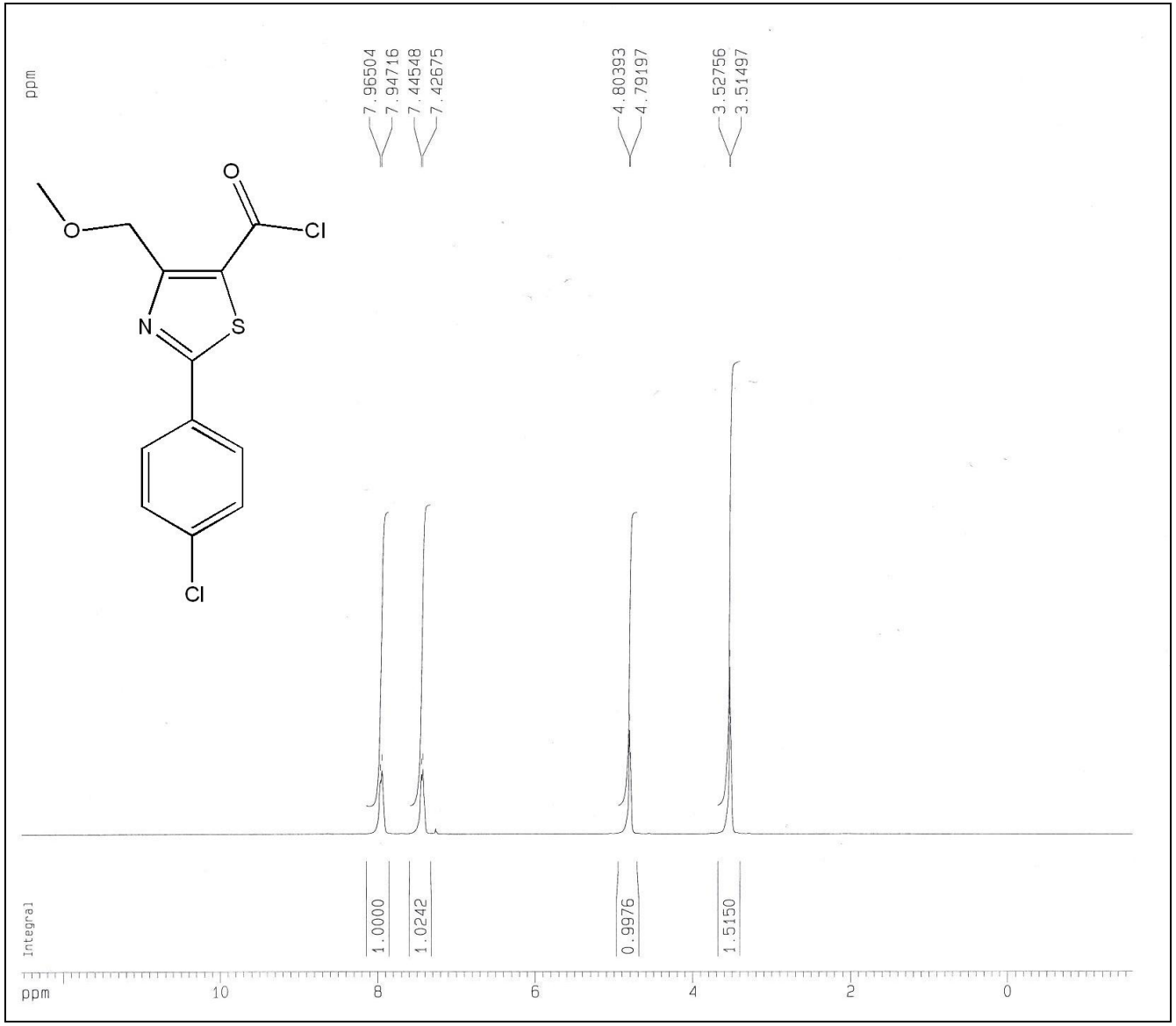
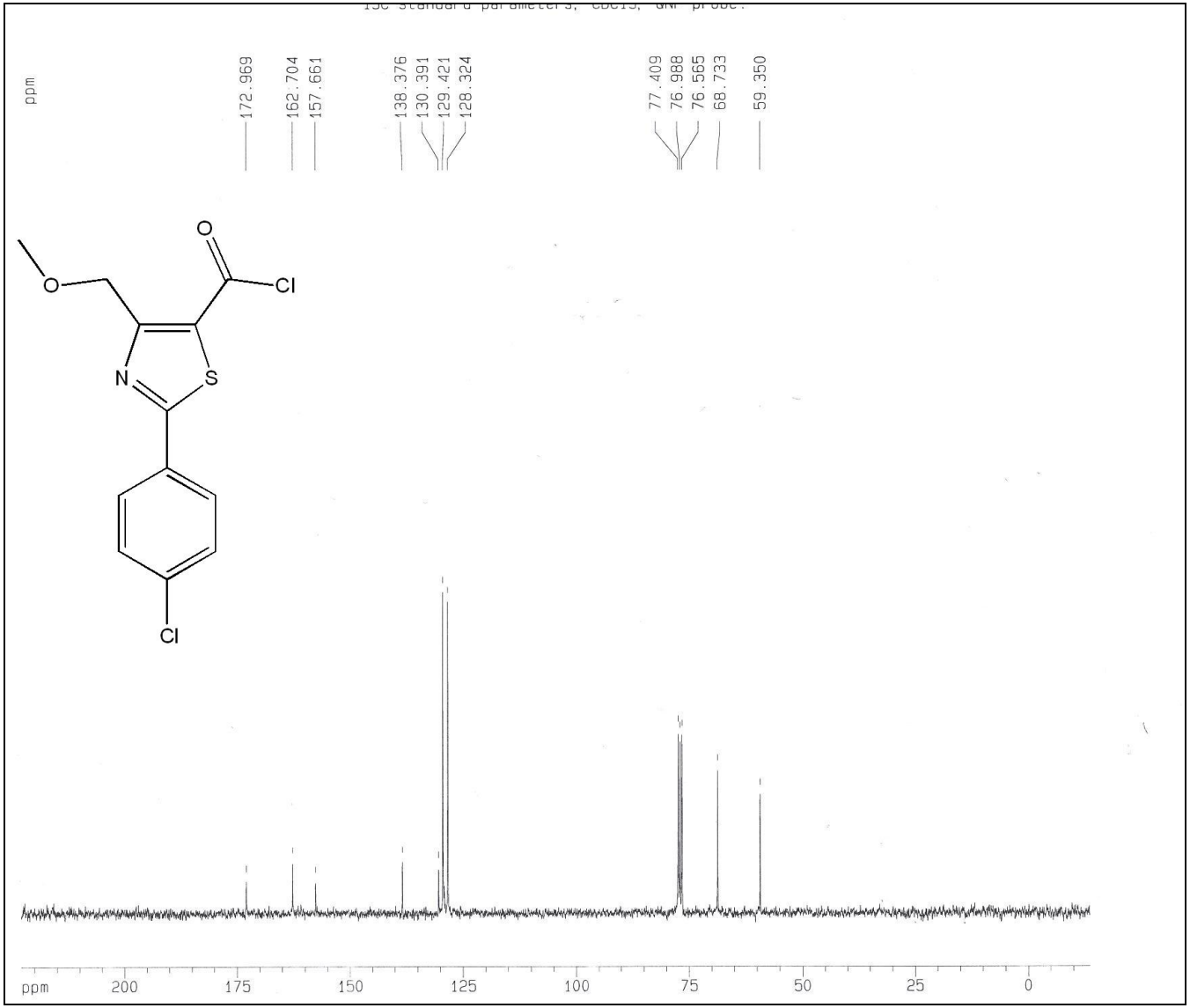


^{1}H NMR spectrum of compound **21**.



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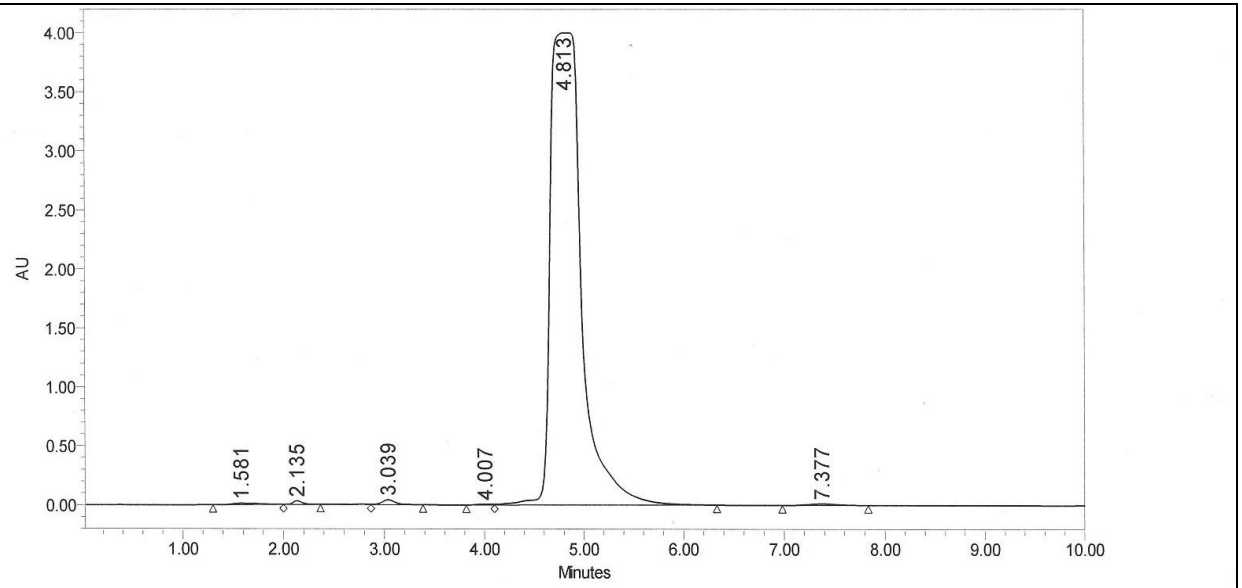
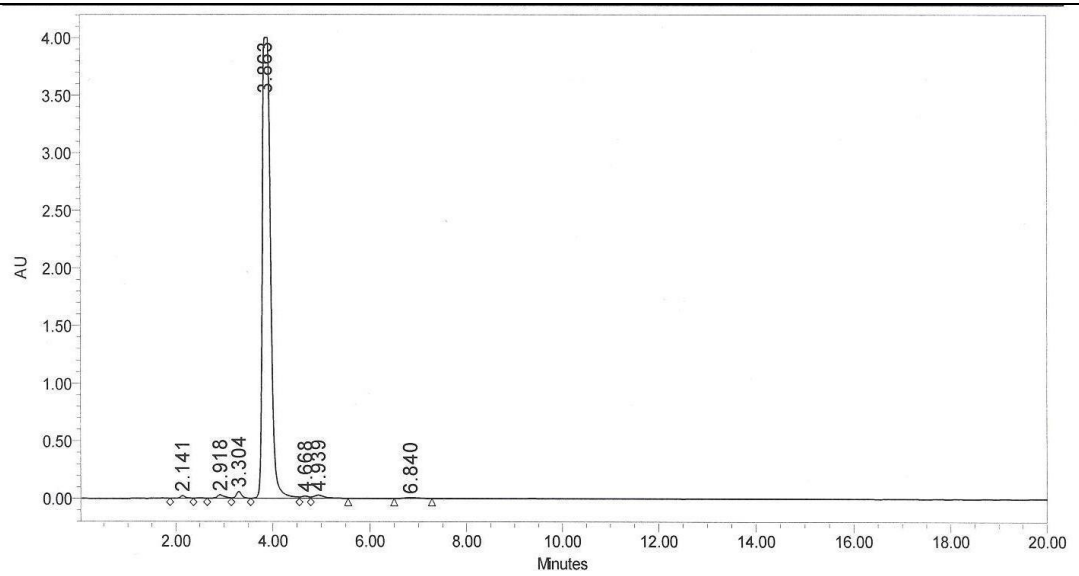


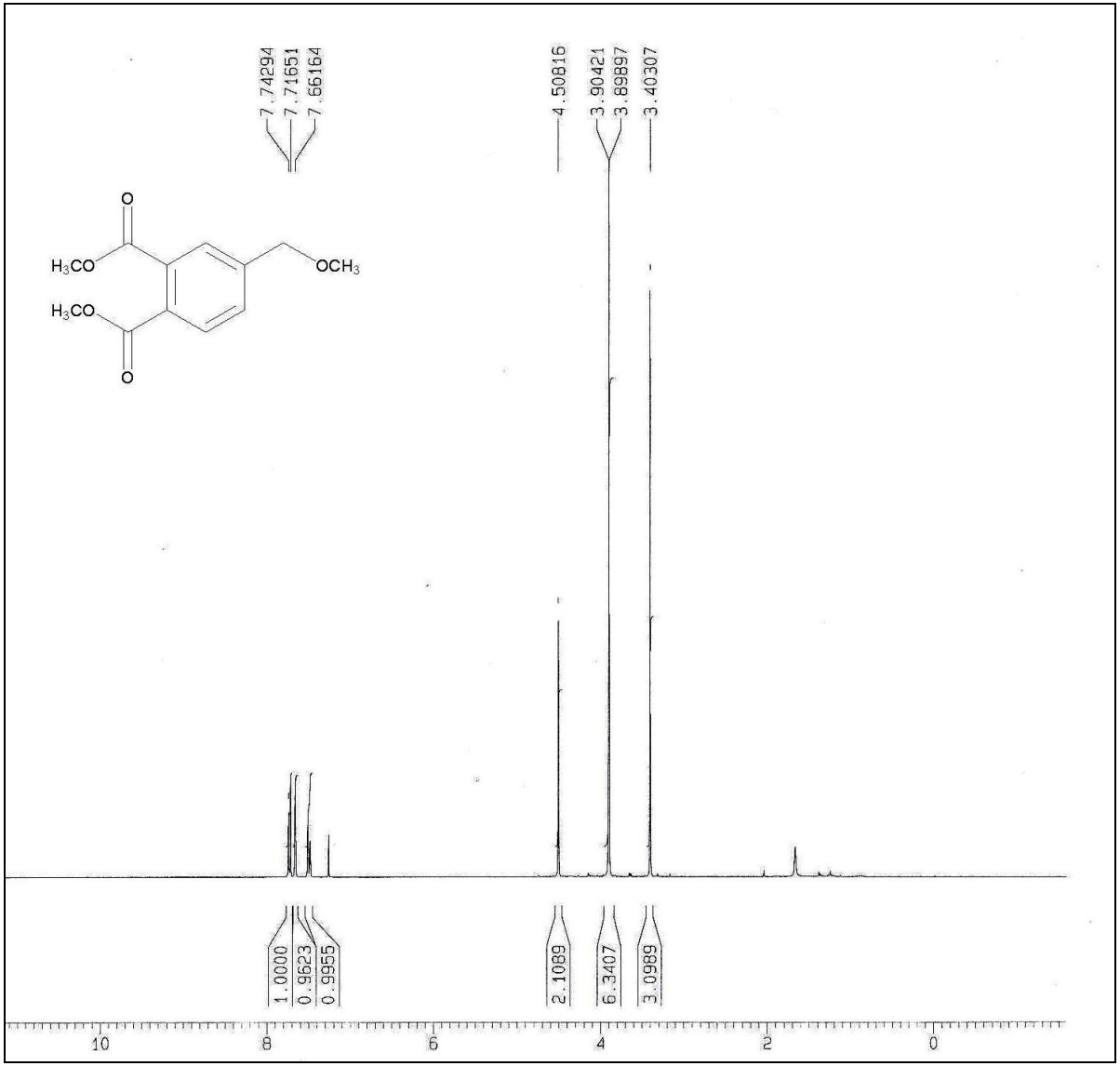
	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	1.581	222580	0.25	12369	0.30
2	2.135	205804	0.23	32247	0.79
3	3.039	350562	0.40	40542	0.99
4	4.007	78098	0.09	7274	0.18
5	4.813	87238441	98.75	3999304	97.43
6	7.377	244874	0.28	12927	0.31

HPLC Chart of compound **2h**.

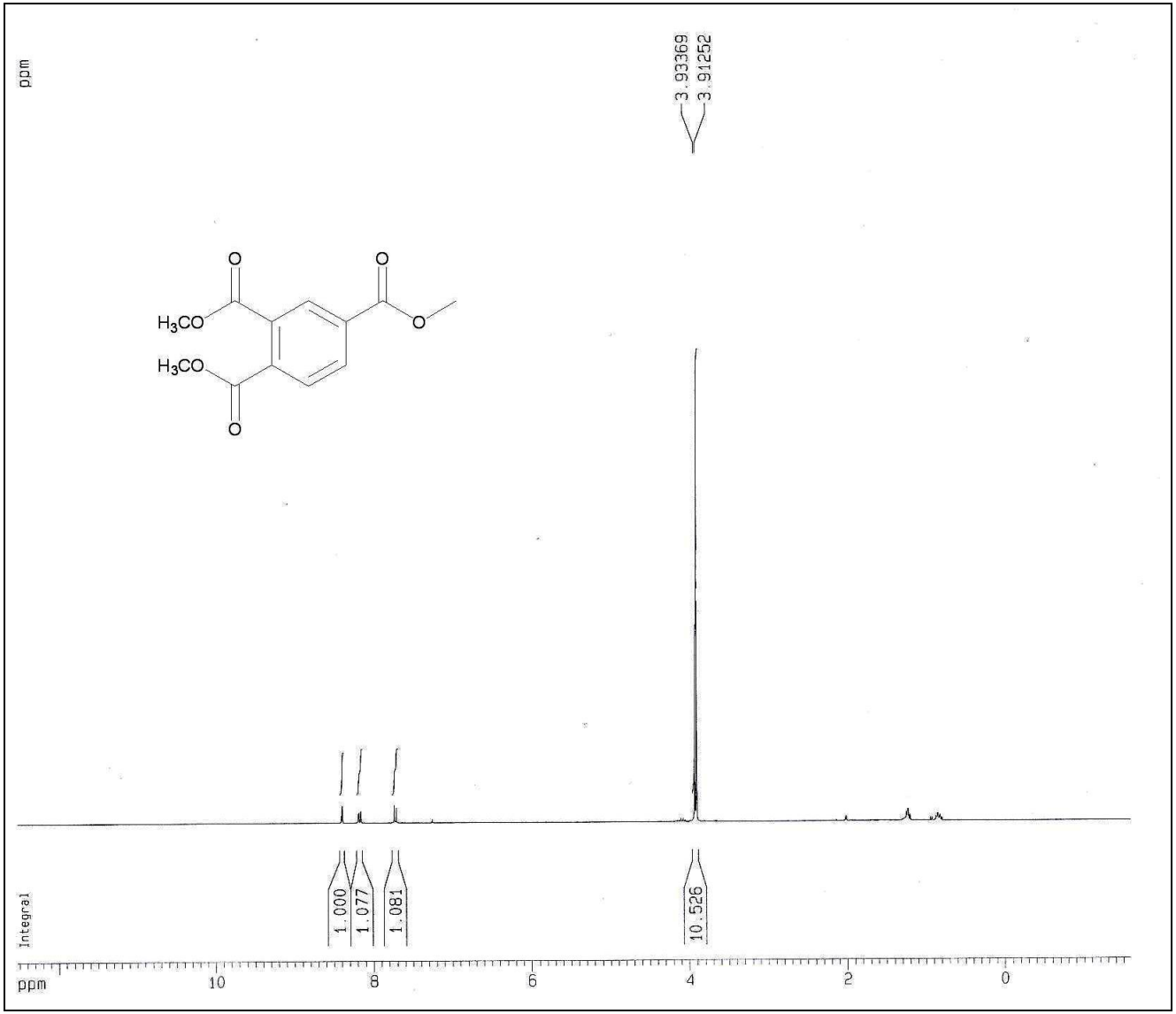


	RT (min)	Area (μV*sec)	% Area	Height (μV)	% Height
1	2.141	184166	0.38	23707	0.56
2	2.918	329590	0.68	31280	0.73
3	3.304	450754	0.93	58816	1.38
4	3.863	46602769	96.38	4102647	96.05
5	4.668	211369	0.44	20158	0.47
6	4.939	429006	0.89	27432	0.64
7	6.840	143920	0.30	7122	0.17

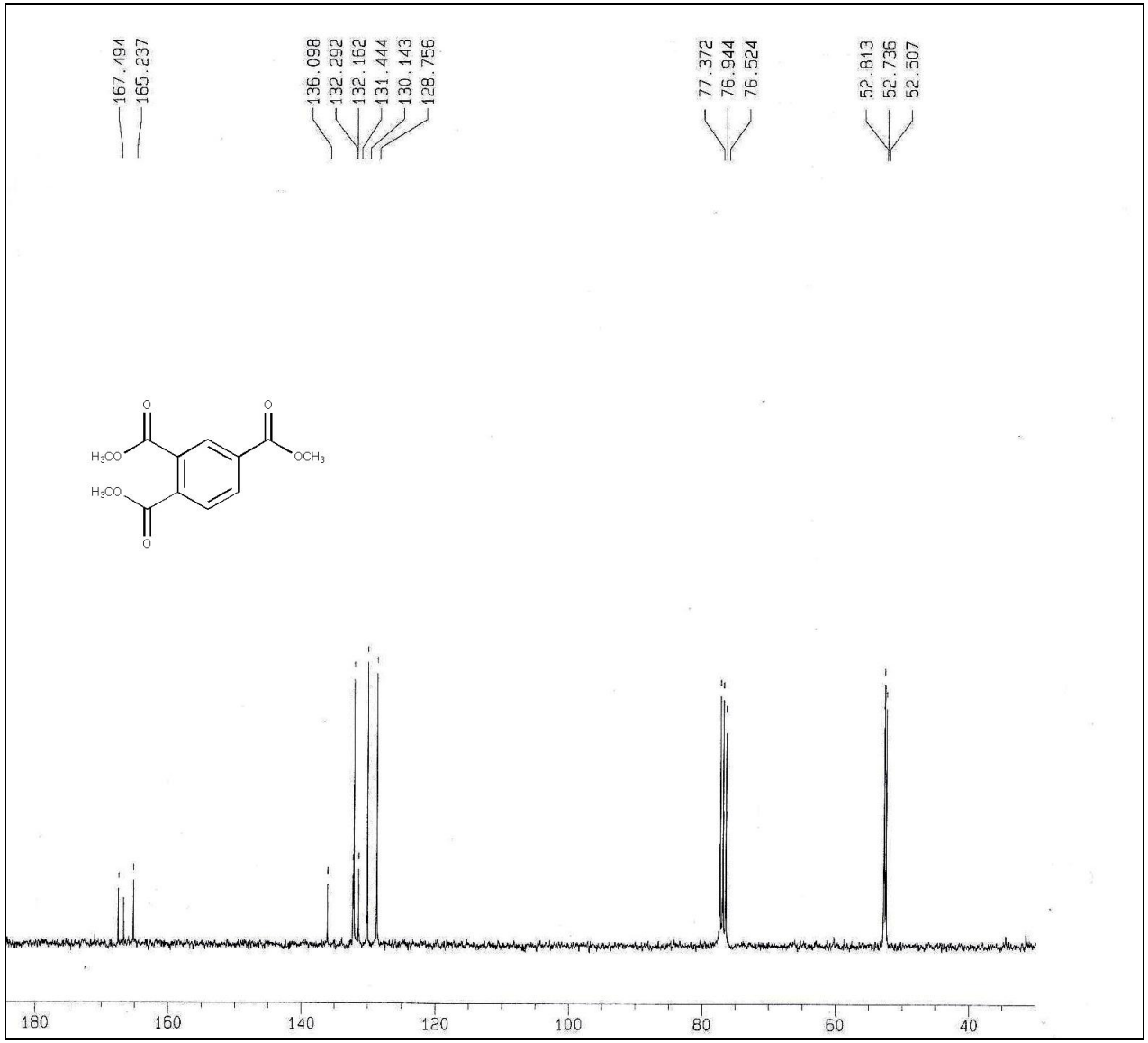
HPLC Chart of **3k**.



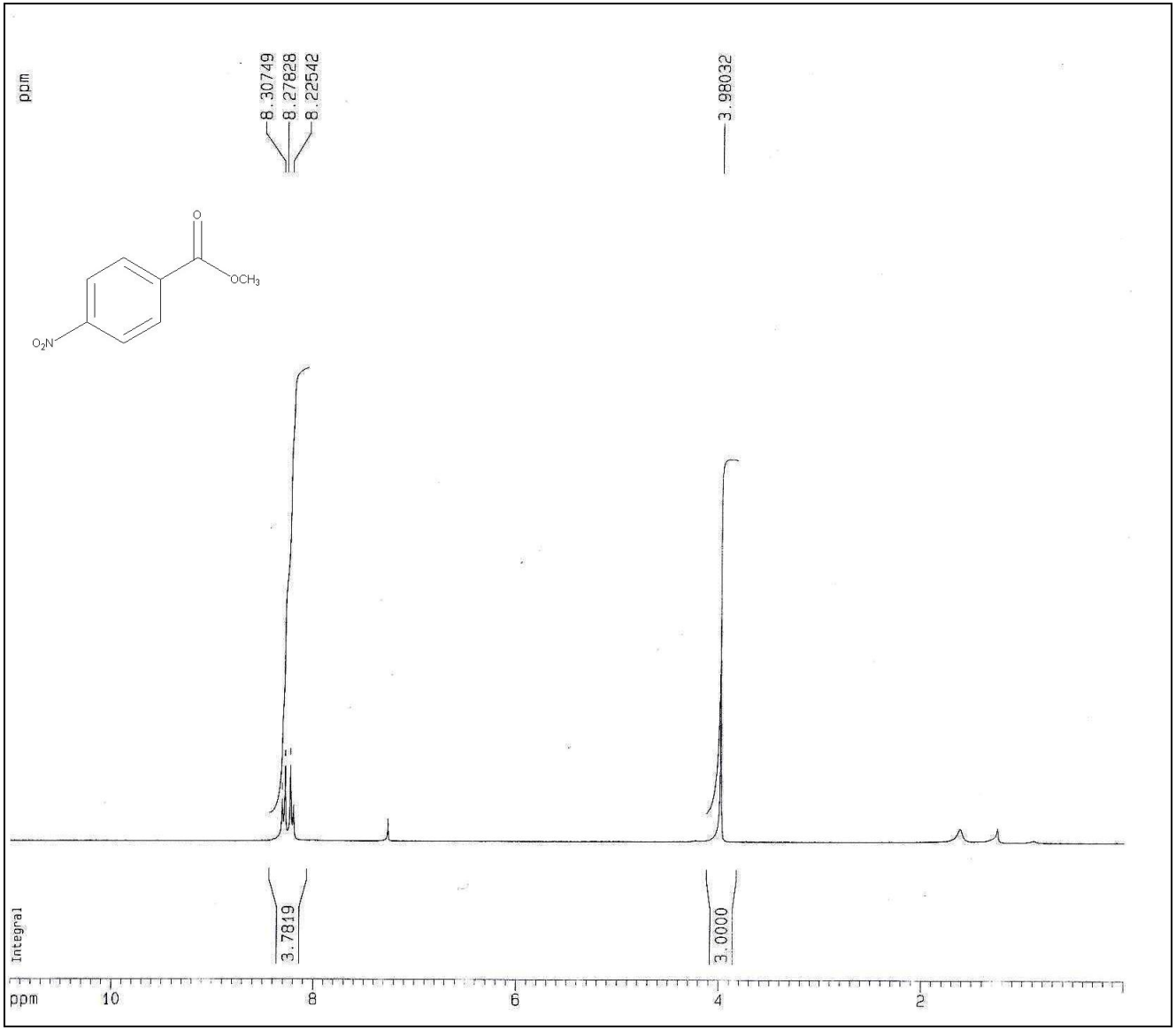
[1]H NMR spectrum of compound **1h**.



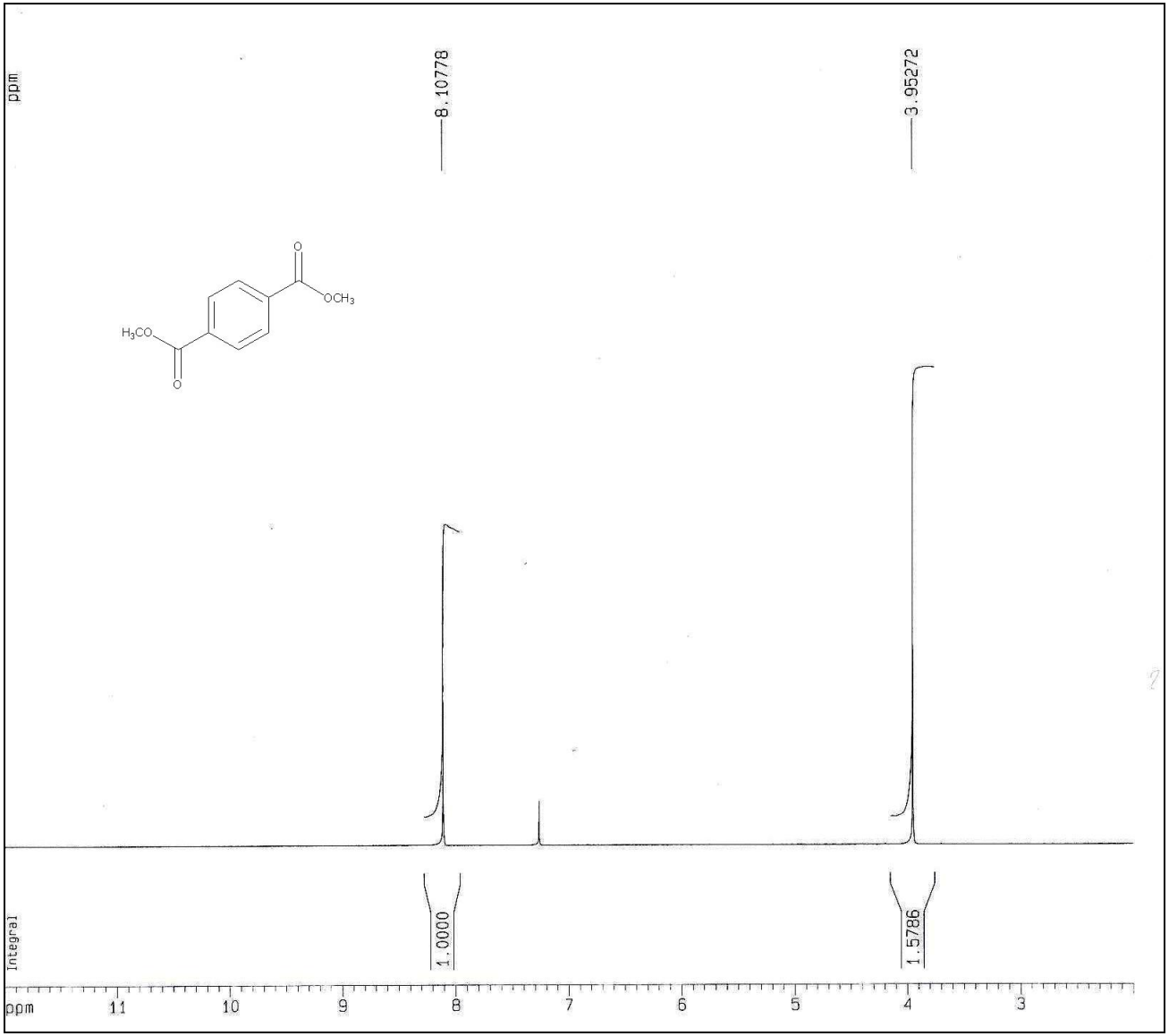
^{1}H NMR spectrum of compound **3g**.



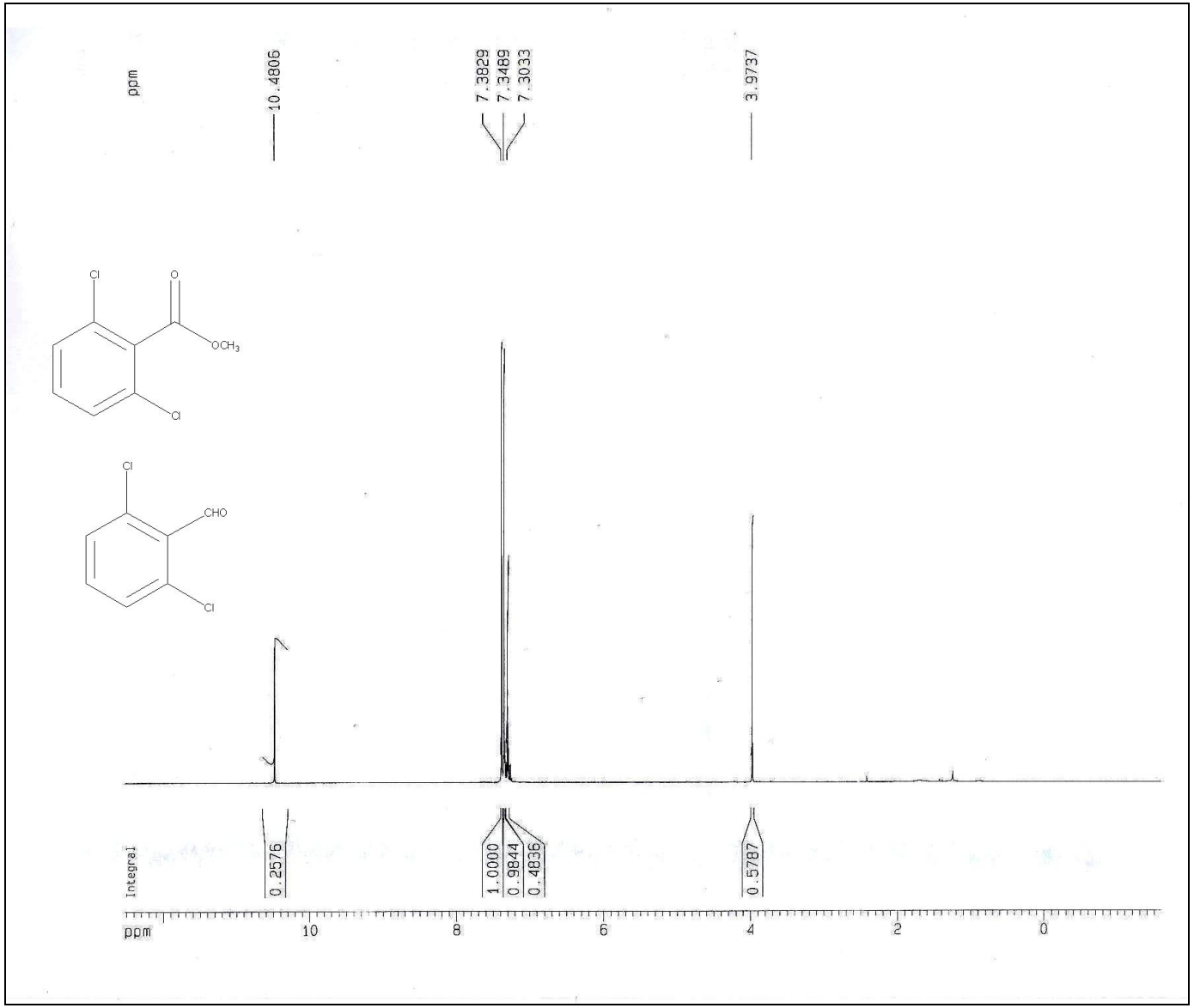
^{13}C NMR spectrum of compound **3g**.



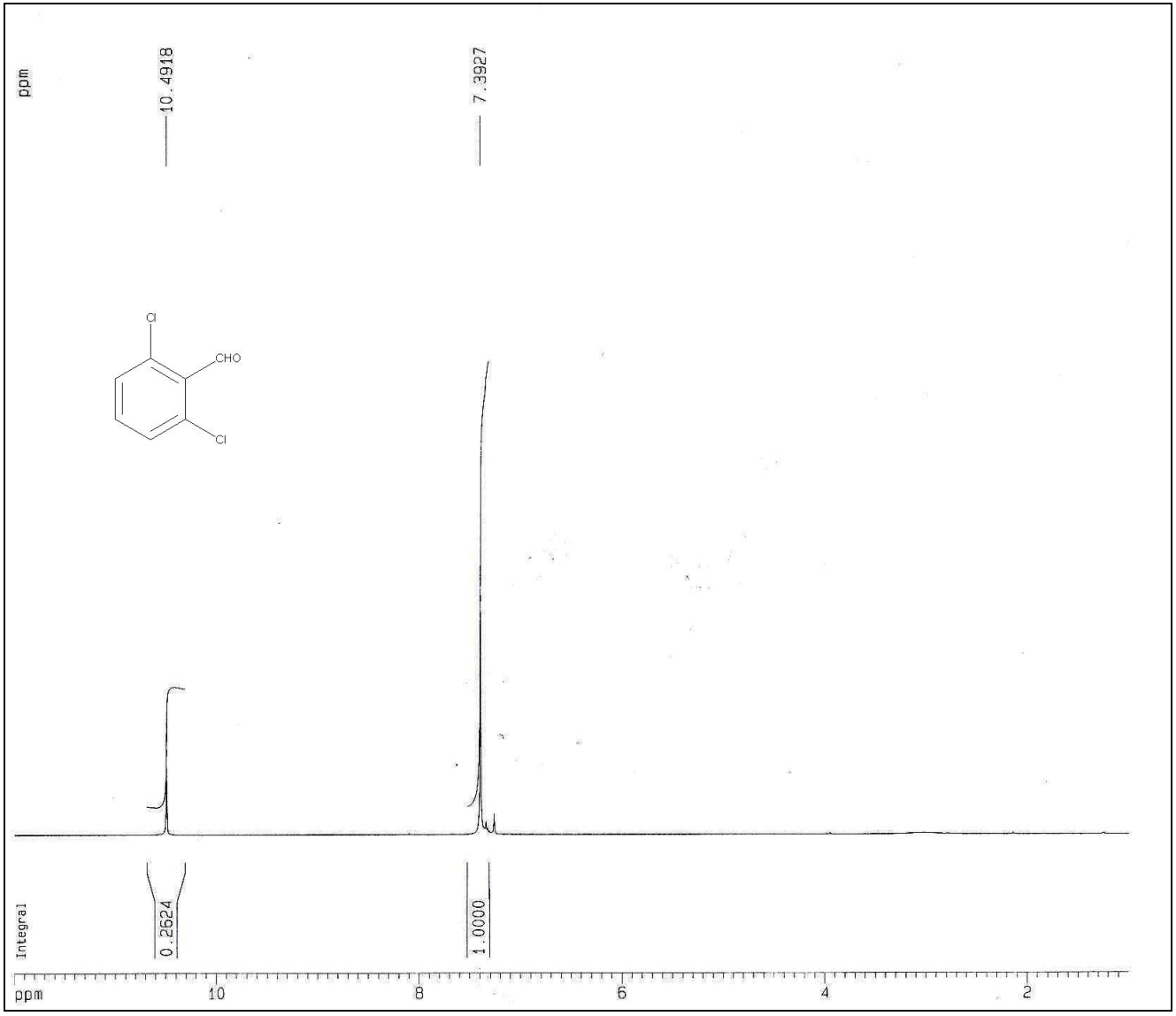
^{1}H NMR spectrum of methyl 4-nitrobenzoate **3f**.



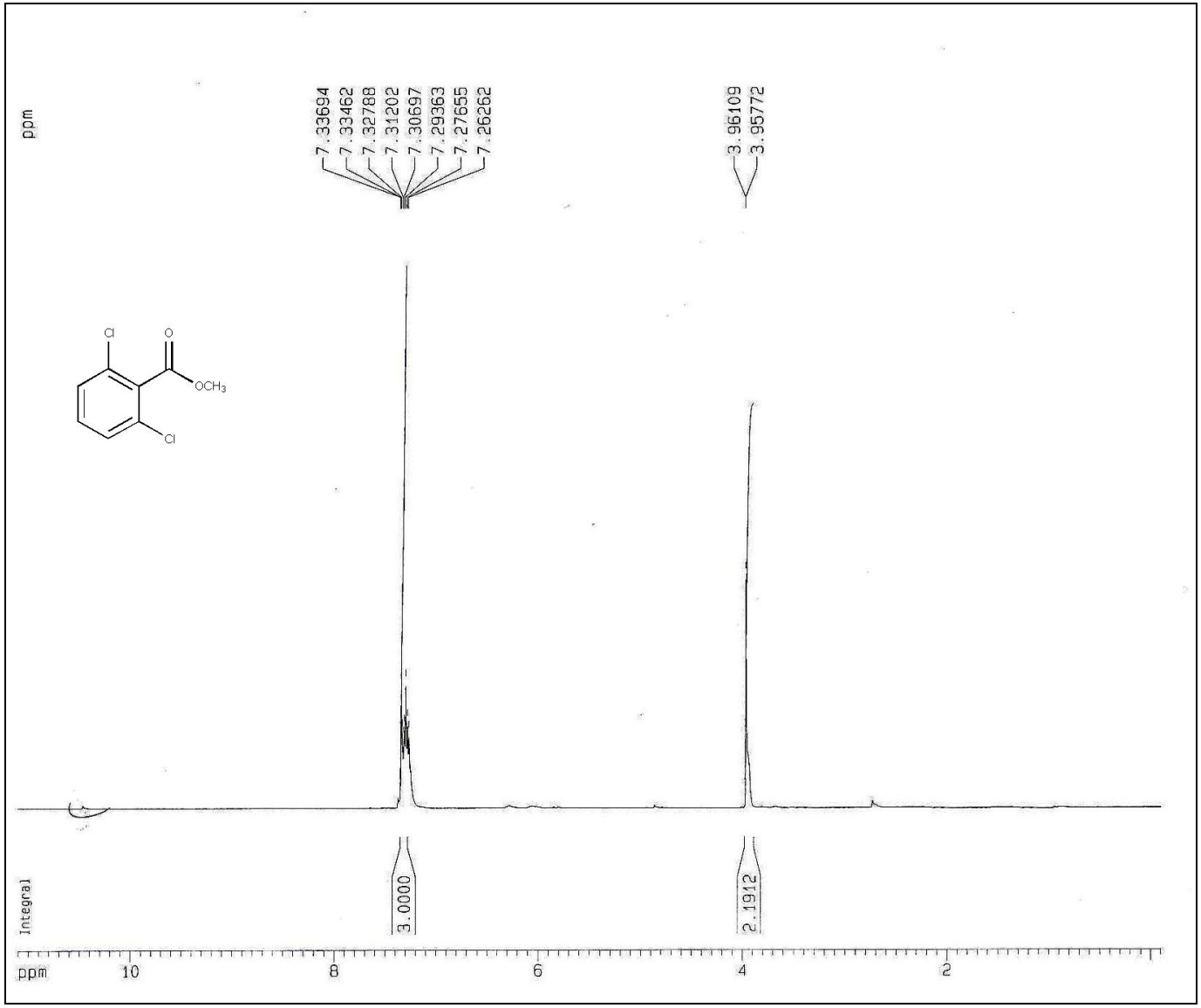
[1]H NMR spectrum of dimethyl terephthalate **3e**.



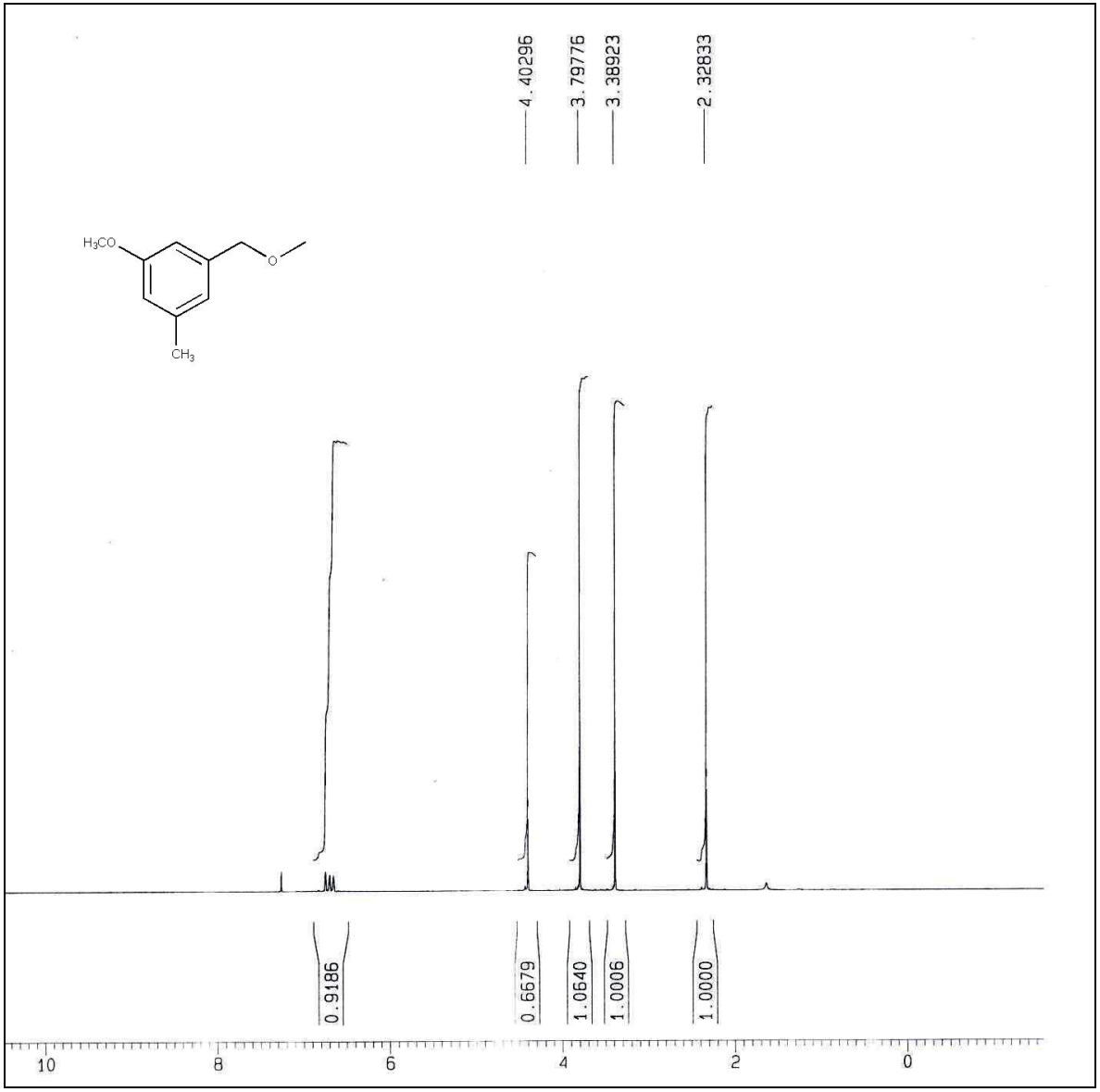
[1]H NMR spectrum of entry 5.



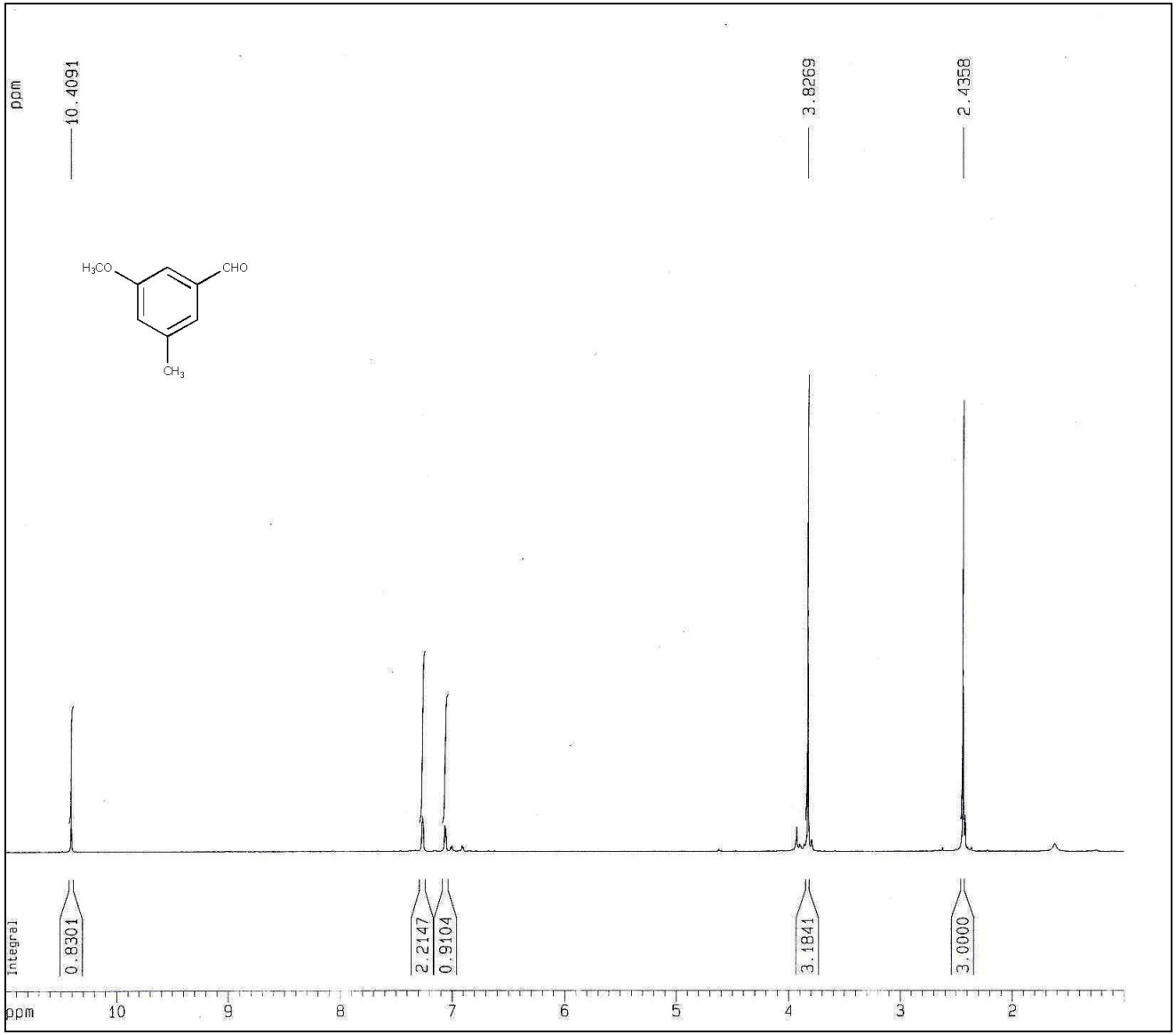
[1]H NMR spectrum of 2,6-dichlorobenzaldehyde (**2b**).



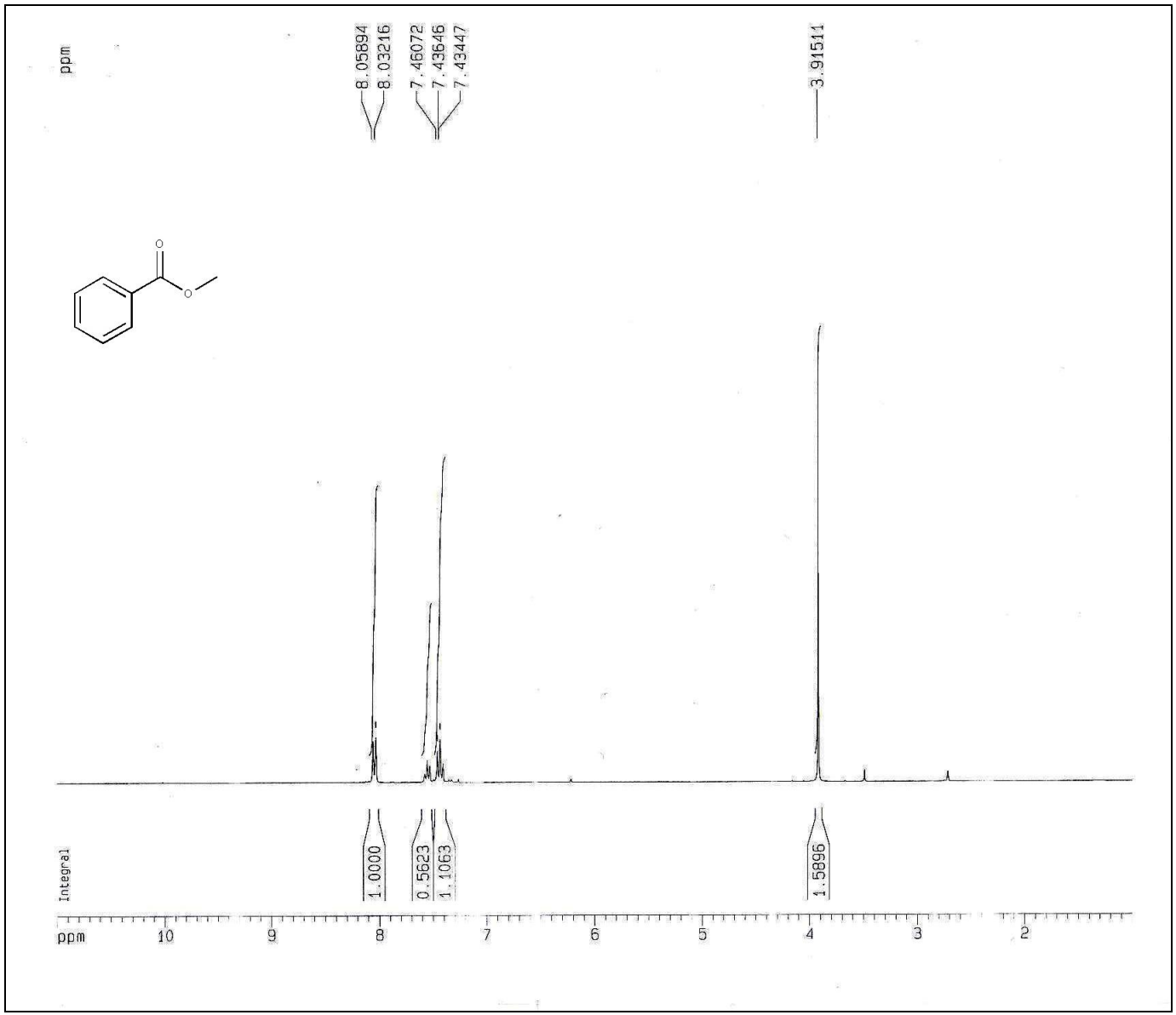
[1]H NMR spectrum of methyl 2,6-dichlorobenzoate (**3b**).



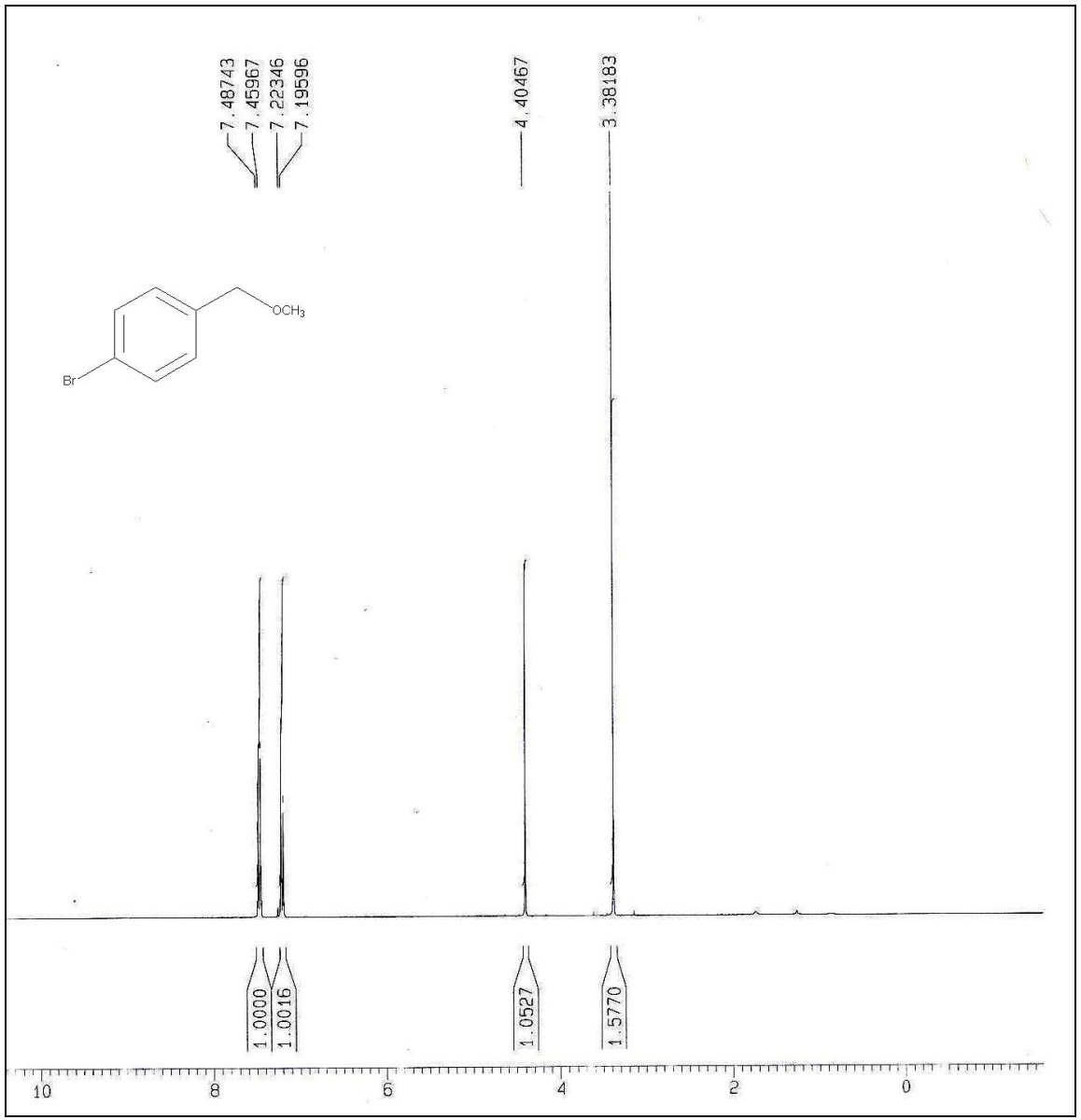
[1]H NMR spectrum of 1-methoxy-3-(methoxymethyl)-5-methylbenzene (**1f**).



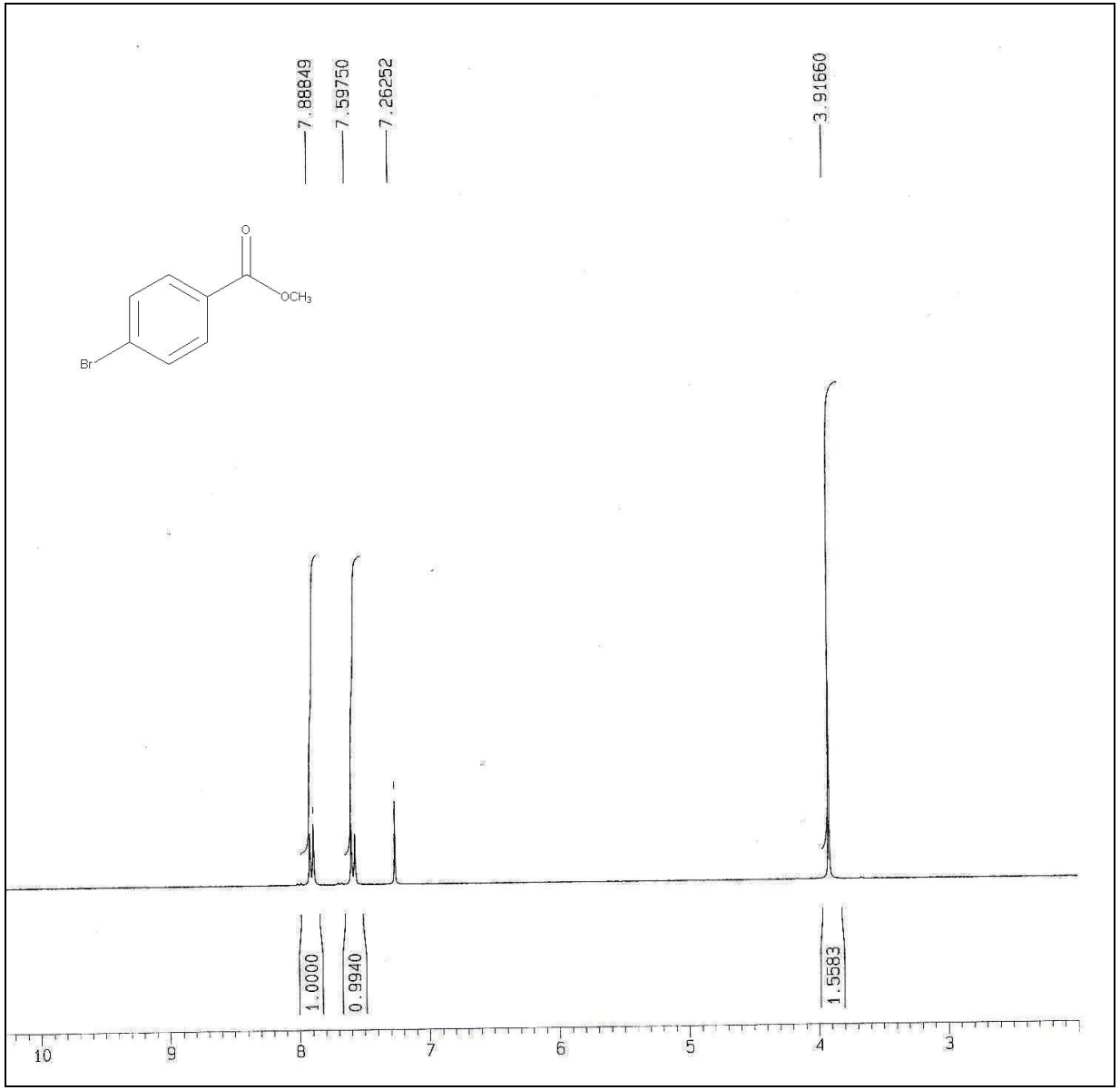
^{1}H NMR spectrum of 3-methoxy-5-methylbenzaldehyde (**2e**).



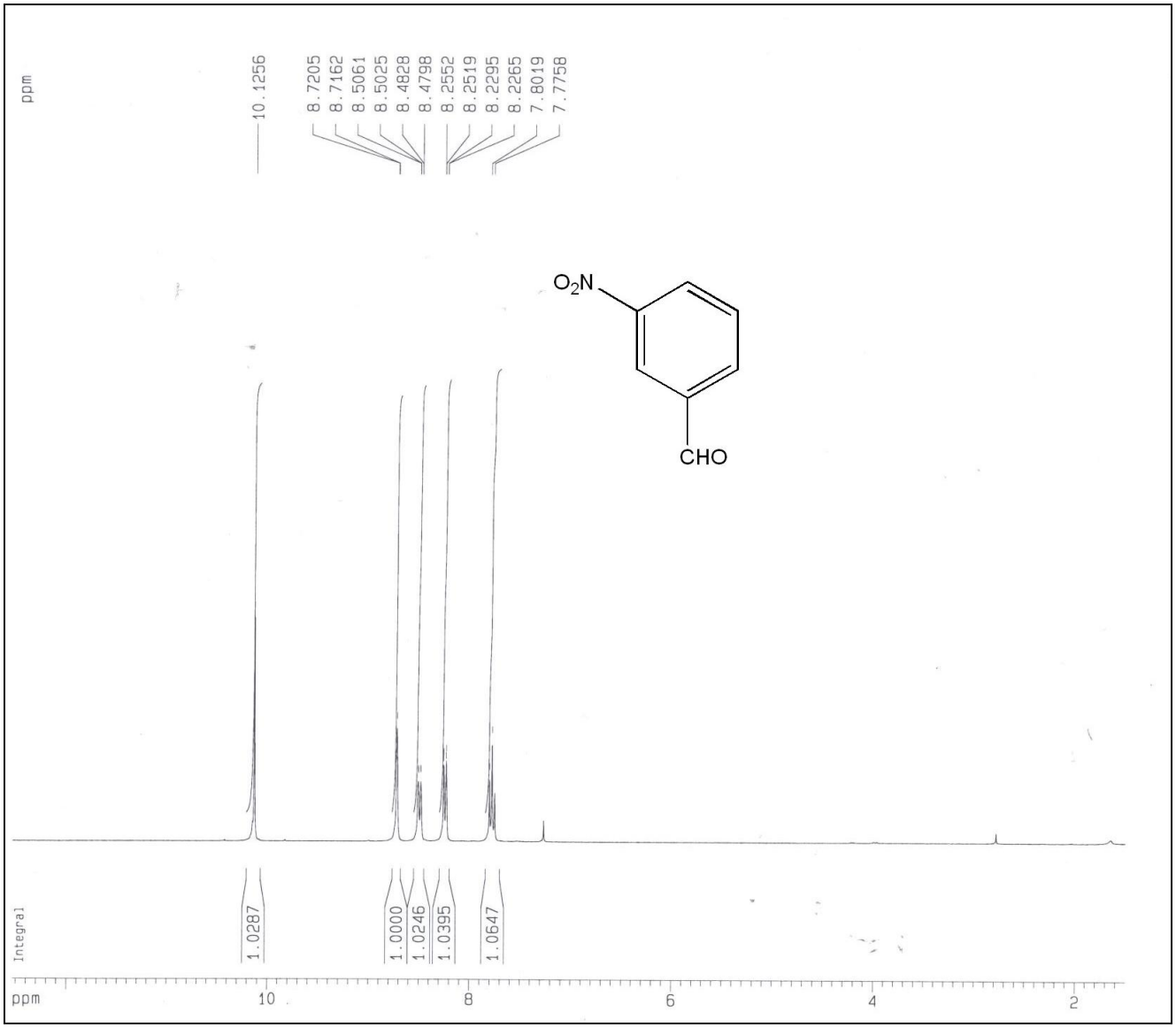
[1]H NMR spectrum of methyl benzoate (**3a**).



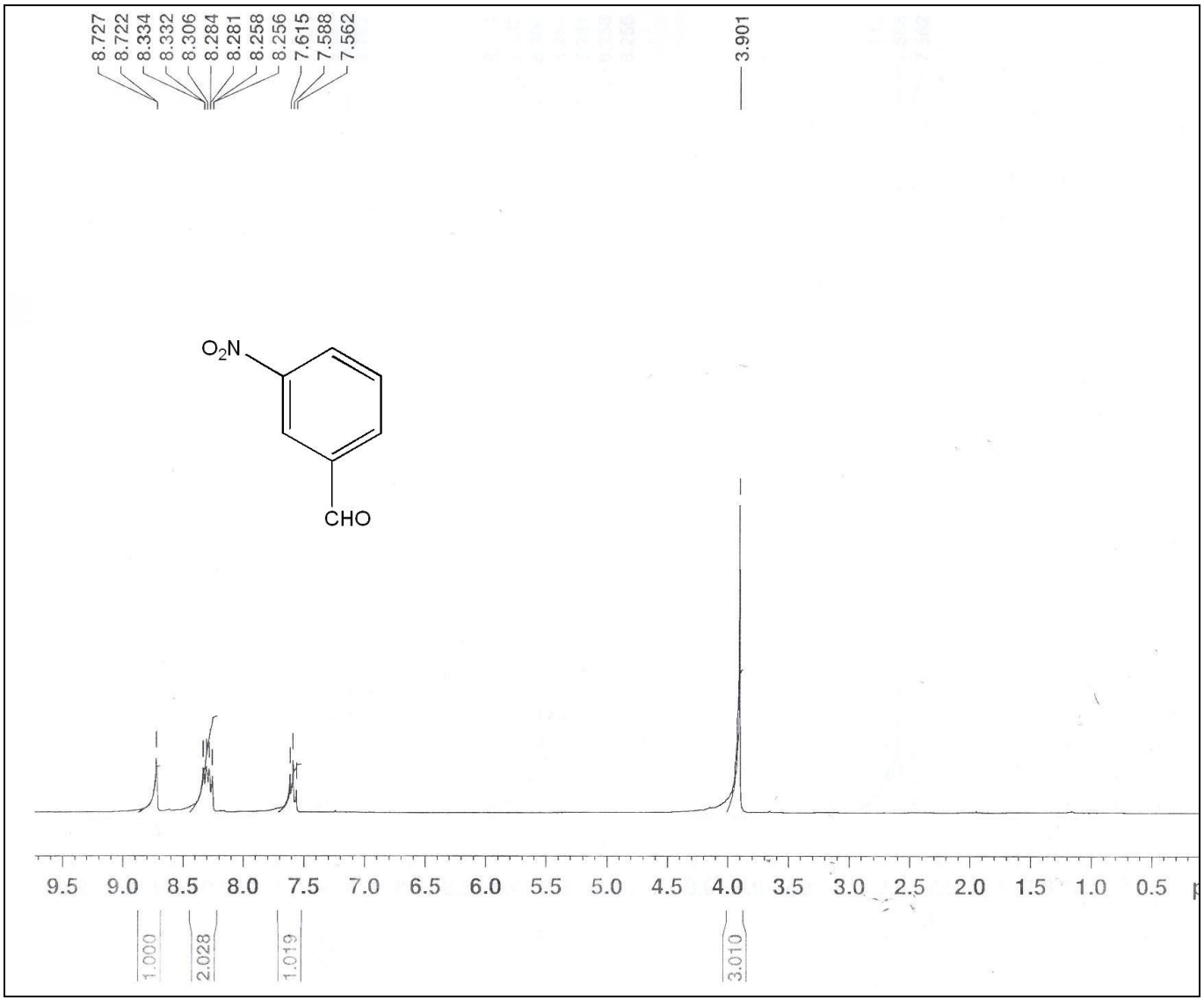
[1]H NMR spectrum of 1-(methoxymethyl)-4-bromobenzene (**1d**).



^{1}H NMR spectrum of methyl 4-bromobenzoate (**3d**).



[1]H NMR spectrum of m-nitrobenzaldehyde (**2f**).



^{1}H NMR spectrum of m-nitrobenzaldehyde (**3h**).