Integration of Borylation of Aryllithiums and Suzuki–Miyaura Coupling Using Monolithic Pd Catalyst

A. Nagaki, K. Hirose, Y. Moriwaki, K. Mitamura, K. Matsukawa, N. Ishizuka and J. Yoshida

General

GC analysis was performed on a SHIMADZU GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, CBPI; 0.25 mm x 25 m; initial oven temperature, 50 ^{o}C; rate of temperature increase, 10 ^{o}C/min; final oven temperature, 250 ^{o}C). ^{1}H and ^{13}C NMR spectra were recorded on Varian MERCURYplus-400 (^{1}H 400 MHz, ^{13}C 100 MHz) spectrometer with Me_4Si or $CDCl_3$ as a standard in $CDCl_3$ unless otherwise noted. Preparative gel permeation chromatography was performed on Japan Analytical Industry LC-918. THF was purchased from Kanto Chemical Co., Inc. as a dry solvent and used without further purification. Hexane was purchased from Wako, distilled before use, and stored over molecular sieves 4A. Bromobenzene, *p*-bromobenzonitrile, *m*-bromobenzonitrile, *o*-bromobenzonitrile, 4,4'-dibromobiphenyl, 2-bromothiophene, 2-(1-adamantyl)-4-bromoanisole, *p*-iodobenzonitrile, *m*-iodobenzonitrile, *o*-iodobenzonitrile, iodobenzene, methyl 4-iodobenzoate, 4-iodoanisole, 2-iodothiophene, trimethoxyborane and *n*-butyllithium were commercially available. Methyl 6-iodo-2-naphthoate was synthesized according to the literature.[1]

Stainless steel (SUS304) T-shaped micromixer with inner diameter of 250 and 500 μm was manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with inner diameter of 500 and 1000 μm were purchased from GL Sciences and were cut into appropriate lengths (3.5, 25, 50, 100, 300 cm). The micromixer and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW) to construct the flow microreactor in the laboratory. The flow microreactor was dipped in the bath to control the temperature. Solutions were continuously introduced to the flow microreactor using syringe pumps, Harvard PHD 2000, equipped with gastight syringes purchased from SGE or a plunger pump, shimadzu LC-20AT.

Preparation of a Flow Reactor Packed with a Polymer Monolith Containing Immobilized Pd

1,3-Bis(*N*,*N*-diglycidylaminomethyl)cyclohexane (Tetrad C, Mitsubishi Gas Chemical, Tokyo, Japan) was added to a solution of poly(ethylene glycol) (PEG, molecular mass = 200; Wako Pure Chemical Industries, Osaka, Japan) with 4,4'-Diaminodicyclohexylmethane (BACM, Wako Pure Chemical Industries, Osaka, Japan) and 6-(Phenylamino)-1,3,5-triazine-2,4-dithiol (TADT, Sankyo Chemical, Nagoya, Japan), and stirred at room temperature for 30 min. The resultant homogeneous solution was poured into a cylindrical stainless steel (an empty HPLC column, 4.6 mm ID x 150 mm length) and allowed to react at 100 ^{o}C. The reaction temperature was varied so that epoxy monolithic gels with various domain size were produced. The gelation occurred within 30 min and the cured sample was subsequently aged at same temperature for a day. The epoxy monoliths thus formed were washed with tetrahydrofuran (THF) by HPLC pump at 0.1 mL/min for an hour then 5 mL of THF solution solved with palladium acetate (0.5 wt%, Wako Pure Chemical Industries, Osaka, Japan) was injected into the column at 0.05 mL/min. The columns adsorbed with Palladium acetate was immersed in PEG (molecular mass = 300, PEG300) to be heat-treated at 100 ^{o}C for 4 hours and allowed to stand still for overnight at room temperature. The columns replaced THF by PEG300 was heat-treated again at 160 ^{o}C for 4 hours, subsequently washed with THF and water by HPLC pump at 0.1 mL/min for an hour respectively. The 5 mL of aqueous solutions of sodium borohydride (0.5 wt%, Wako Pure Chemical Industries, Osaka, Japan) were injected into the columns at 0.05 mL/min to be allowed reduction of palladium ion adsorbed on the surface of the monoliths.

Crosscoupling of Bromobenzene and *p*-Iodobenzonitrile by the Sequence of Lithiation, Borylation and Suzuki-Miyaura Coupling in a Flow

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**), and three tube pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 100 cm), **P2** (ϕ = 1000 μm, L = 50 cm), and **P3** (ϕ = 1000 μm, L = 100 cm)) was used for the formation of lithium borate. A solution of bromobenzene (0.10 M in THF) (flow rate: 6.0 mL/min) and a solution of *n*-BuLi (0.60 M in hexane) (flow rate: 1.0 mL/min) were introduced to **M1** (ϕ = 500 μm) at T^1 = 0 ^{o}C by syringe pumps. The resulting solution was passed through **R1** (ϕ = 1000 μm, L = 25 cm (t^{R1} = 1.7 s)) and was mixed with a

solution of trimethoxyborane (0.12 M in THF) (flow rate: 5.0 mL/min) in **M2** (ϕ = 500 μm) (T^1 = 0 °C). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm (t^{R2} = 2.0 s)) (T^1 = 0 °C). The resulting solution was collected in a vessel. Then, a solution of *p*-iodobenzonitrile (0.033 M in MeOH (0.67 eq)) was added and the mixing solution was passed through a flow reactor packed with a polymer monolith containing immobilized Pd at T^2 °C by a plunger pump. The reaction was carried out for various residence times (t^R) in the reactor by changing flow rates, and at various temperatures (T^2). After a steady state was reached, the product solution was collected (10 min). The reaction mixture was analyzed by GC and the results are summarized in Table S-1.

Table S-1. Crosscoupling of bromobenzene and *p*-iodobenzonitrile by the sequence of lithiation, borylation and Suzuki-Miyaura coupling in a flow

T^2 (°C)	flow rate (mL/min)	t^R (min)	yield (%)
60	0.2	9.4	37
	0.4	4.7	14
	1.0	1.9	0
	1.5	1.3	0
80	0.2	9.4	81
	0.4	4.7	81
	1.0	1.9	39
	1.5	1.3	30
100	0.2	9.4	96
	0.4	4.7	96
	1.0	1.9	81
	1.5	1.3	66
120	0.2	9.4	100
	0.4	4.7	95
	1.0	1.9	93
	1.5	1.3	96

Biphenyl-4-carbonitrile.
Synthesized in 96% yield in condition-A or 100% in condition-B (GC yield using an internal standard (tetradecane)); GC ^tR 21.4 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.66 (m, 4H), 7.61-7.57 (m, 2H), 7.52-7.39 (m, 3H); The spectral data were identical to those of reported in the literature.[2]

Crosscoupling of Aryl Bromides (Ar^1Br) and Aryl Halides (Ar^2X) by the Sequence of Lithiation, Borylation and Suzuki-Miyaura Coupling in a Flow

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**), and three tube pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 100 cm), **P2** (ϕ = 1000 μm, L = 50 cm), and **P3** (ϕ = 1000 μm, L = 100 cm)) was used for the formation of lithium borate. A solution of arylbromides (Ar^1Br) (0.10 M in THF) (flow rate: 6.0 mL/min) and a solution of *n*-BuLi (0.60 M in hexane) (flow rate: 1.0 mL/min) were introduced to **M1** (ϕ = 250 μm) (T^1 °C) by syringe pumps. The resulting solution was passed through **R1** (1.7 s (ϕ = 1000 μm, L = 25 cm) or 0.059 s (ϕ = 500 μm, L = 3.5 cm)) and was mixed with a solution of trimethoxyborane (0.12 M in THF) (flow rate: 5.0 mL/min) in **M2** (ϕ = 250 μm) (T^1 °C). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm (t^{R2} = 2.0 s)) (T^1 °C) (for the case of 2,2'-dibromobiphenyl, **R2** (ϕ = 1000 μm, L = 300 cm (t^{R2} = 11.8 s)) was used). The resulting solution was collected in a vessel. Then, a solution of arylhalides (Ar^2X) (0.033 M in MeOH (0.67 eq)) was added and the mixing solution was passed through a flow reactor packed with a polymer monolith containing immobilized Pd by a plunger pump (condition-A: t^R = 4.7 min, T^2 = 100 °C or condition-B: t^R = 9.4 min, T^2 = 120 °C). After a steady state was reached, the product solution was collected (10 min) (for the case of 2,2'-dibromobiphenyl, 100 min). The yield of product was determined by GC analysis or isolation. The results are summarized in Table 2.

Methyl 4-Phenylbenzoate.

Synthesized in 76% yield in condition-A or 87% in condition-B (GC yield using an internal standard (tetradecane)); GC ^tR 22.9 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13-8.08 (m, 2H), 7.69-7.60 (m, 4H), 7.50-7.36 (m, 3H), 3.94 (s, 3H); The spectral data were identical to those of reported in the literature.[3]

Biphenyl.

Synthesized in 6% yield in condition-A or 41% in condition-B (GC yield using an internal standard (tetradecane)); GC ^tR 17.0 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62-7.57 (m, 4H), 7.47-7.41 (m, 4H), 7.38-7.32 (m, 2H); The spectral data were identical to those of reported in the literature.[4]

4-Methoxybiphenyl.

Synthesized in 1% yield in condition-A or 29% in condition-B (GC yield using an internal standard (tetradecane)); GC ^tR 20.7 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.50 (m, 4H), 7.45-7.37 (m, 2H), 7.30 (t, J = 8.0 Hz, 1H), 6.98 (d, J = 8.8 Hz, 2H), 3.85 (s, 3H); The spectral data were identical to those of reported in the literature.[5]

2-Phenylthiophene.

Synthesized in 86% yield in condition-A or 92% in condition-B (GC yield using an internal standard (pentadecane)); GC ^tR 25.6 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64-7.58 (m, 2H), 7.41-7.35 (m, 2H), 7.33-7.26 (m, 3H), 7.08 (dd, J = 3.6 Hz, J = 4.8 Hz, 1H); The spectral data were identical to those of reported in the literature.[6]

4,4'-Dicyanobiphenyl.

Synthesized in 68% yield in condition-A or 91% in condition-B (GC yield using an internal standard (tetradecane)); GC ^tR 25.4 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81-7.76 (m, 4H), 7.72-7.67 (m, 4H); The spectral data were identical to those of reported in the literature.[7]

3,4'-Dicyanobiphenyl.

Synthesized in 17% yield in condition-A or 83% in condition-B (GC yield using an internal standard (tetradecane)); GC ^tR 25.2 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1H), 7.84-7.75 (m, 3H), 7.72 (d, J = 7.6 Hz, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 140.4, 132.9, 132.0, 131.5, 130.8, 130.0, 127.8, 118.4, 118.3, 113.5, 112.2; HRMS (ACPI) calcd. for $C_{14}H_9N_2^+$ [MH^+]: 205.0760, found: 205.0759.

2,4'-Dicyanobiphenyl.

Synthesized in 12% yield in condition-A or 91% in condition-B (GC yield using an internal standard (tetradecane)); GC ^tR 24.2 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84-7.78 (m, 3H), 7.74-7.65 (m, 3H), 7.57-7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 142.5, 134.0, 133.2, 132.5, 129.9, 129.6, 128.8, 118.4, 118.0, 112.7, 111.2; HRMS (ACPI) calcd. for $C_{14}H_9N_2^+$ [MH^+]: 205.0760, found: 205.0758.

Methyl 4-(4-Cyanophenyl)benzoate.

Synthesized in 34% yield in condition-A or 84% in condition-B (GC yield using an internal standard (tetradecane)); GC ^tR 26.5 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17-8.12 (m, 2H), 7.78-7.69 (m, 4H), 7.68-7.64 (m, 2H), 3.96 (s, 3H); The spectral data were identical to those of reported in the literature.[8]

Methyl 4-(3-Cyanophenyl)benzoate.

Synthesized in 15% yield in condition-A or 87% in condition-B (GC yield using an internal standard (tetradecane)); GC ^tR 26.3 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.0 Hz, 2H), 7.90 (s, 1H), 7.84 (d, J = 7.6 Hz, 1H), 7.68 (d, J = 7.6 Hz, 1H), 7.63 (d, J = 8.0 Hz, 2H), 7.58 (t, J = 7.6 Hz, 1H) 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 143.1, 141.3, 131.6, 131.5, 130.8, 130.4, 130.0, 129.8, 127.1, 118.6, 113.2, 52.3; HRMS (ACPI) calcd. for $C_{15}H_{11}NO_2$ [M^+]: 237.0784, found: 237.0789; The spectral data were identical to those of reported in the literature.[9]

Methyl 4-(2-Cyanophenyl)benzoate.

Synthesized in 2% yield in condition-A or 52% in condition-B (GC yield using an internal standard (tetradecane)); GC ^tR 25.6 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19-8.14 (m, 2H), 7.82-7.78 (m, 1H), 7.71-7.61 (m, 3H), 7.56-7.46 (m, 2H) 3.96 (s, 3H); The spectral data were identical to those of reported in the literature.[10]

1-Cyano-4''-bromo-4,1':4',1''-terphenylene.

Synthesized in 54% yield in condition-B (isolated yield). After extraction with EtOAc, the crude product was thoroughly washed with hexane and water to give the product as white solid (59.8 mg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.70 (m, 4H), 7.68 (s, 4H), 7.60 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H); The spectral data were identical to those of reported in the literature.[11]

2,2'-Bithiophene.

Synthesized in 83% yield in condition-A or 94% in condition-B (GC yield using an internal standard (pentadecane)); GC ^tR 25.6 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, J = 1.2 Hz, J = 5.2 Hz, 1H), 7.17 (dd, J = 1.2 Hz, J = 3.6 Hz, 1H), 7.01 (dd, J = 3.6 Hz, J = 5.2 Hz, 1H); The spectral data were identical to those of reported in the literature.[12]

4-(Thiophen-2-yl)benzonitrile.

Synthesized in 78% yield in condition-A or 87% in condition-B (GC yield using an internal standard (tetradecane)); GC ^tR 25.6 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.63 (m, 4H), 7.44-7.38 (m, 2H), 7.13 (dd, J = 3.6 Hz, J = 5.2 Hz, 1H); The spectral data were identical to those of reported in the literature.[13]

Methyl 4-(Thiophen-2-yl)benzoate.

Synthesized in 71% yield in condition-A or 86% in condition-B (GC yield using an internal standard (tetradecane)); GC ^tR 25.6 min; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07-8.02 (m, 2H), 7.70-7.65 (m, 1H), 7.42 (dd, J = 1.2 Hz, J = 3.6 Hz, 1H), 7.36 (dd, J = 1.2 Hz, J = 5.2 Hz, 1H), 7.11 (dd, J = 3.6 Hz, J = 5.2 Hz, 1H), 3.93 (s, 3H); The spectral data were identical to those of reported in the literature.[14]

Synthesis of Adapalene

A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**), and three tube pre-cooling units (**P1** (inner diameter ϕ = 1000 μm, length L = 100 cm), **P2** (ϕ = 1000 μm, L = 50 cm), and **P3** (ϕ = 1000 μm, L = 100 cm)) was used for the formation of lithium borate. A solution of 2-(1-Adamantyl)-4-bromoanisole (0.10 M in THF) (flow rate: 6.0 mL/min) and a solution of *n*-BuLi (0.60 M in hexane) (flow rate: 1.0 mL/min) were introduced to **M1** (ϕ = 500 μm) at T^1 = 0 °C by syringe pumps. The resulting solution was passed through **R1** (ϕ = 1000 μm, L = 50 cm (t^{R1} = 3.4 s)) and was mixed with a solution of trimethoxyborane (0.12 M in THF) (flow rate: 5.0 mL/min) in **M2** (ϕ = 500 μm) (T^1 = 0 °C). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm (t^{R2} = 2.0 s)) (T^1 = 0 °C). The resulting solution was collected in a vessel. Then, a solution of methyl 6-iodo-2-naphthoate (0.033 M (0.67 eq) in THF/MeOH = 1.5:1) was added and the mixing solution was passed through a flow reactor packed with a polymer monolith containing immobilized Pd at 120 °C by a plunger pump. The reaction was carried out for 9.4 minutes in the reactor. After a steady state was reached, the product solution was collected (21 hours). After evaporation of solvents, the crude product was thoroughly washed with MeOH (2 × 150 mL) to give Methyl 6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoate (1.55 g, 86%).

Methyl 6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoate (0.517 g) and 20 mL of 1,2-propanediol were placed in a flask and the mixture was heated to 190 °C. The resulting transparent solution was supplemented with 0.534 g of sodium hydroxide in two portions and mixed for 20 min. The mixture was acidified until pH 1 with 6 N HCl. The resulting suspension was mixed for 30 min and washed with hot water (2 × 50 mL). After drying for 12 h at 120 °C, the yield was 0.458 g (89%).

Methyl 6-Iodo-2-naphthoate.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.29 (s, 1H), 8.07 (dd, J = 2.0 Hz, J = 8.6 Hz, 1H), 7.79 (dd, J = 2.0 Hz, J = 8.8 Hz 1H), 7.76 (d, J = 8.4 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 3.98 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 136.7, 136.6, 135.3, 131.1, 130.9, 130.6, 127.9, 127.0, 126.2, 94.7, 52.3; HRMS (ACPI) calcd. for $C_{12}H_{10}IO_2$ [MH^+]: 312.9720, found: 312.9711; The spectral data were identical to those of reported in the literature.[1]

Methyl 6-(3-(1-Adamantyl)-4-methoxyphenyl)-2-naphthoate.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (s, 1H), 8.07 (dd, J = 1.6 Hz, J = 8.6 Hz, 1H), 8.01 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.4 Hz, 1H), 7.80 (dd, J = 2.0 Hz, J = 8.6 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 7.55 (dd, J = 2.4 Hz, J = 8.0 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 3.99 (s, 3H), 3.91 (s, 3H), 2.18 (s, 6H), 2.10 (s, 3H), 1.57 (s, 6H); The spectral data were identical to those of reported in the literature.[15]

6-(3-(1-Adamantyl)-4-methoxyphenyl)-2-naphthoic Acid (Adapalene).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.58 (s, 1H), 8.21 (s, 1H), 8.14 (d, J = 8.8 Hz, 1H), 8.06 (d, J = 9.2 Hz, 1H), 7.97 (dd, J = 1.6 Hz, J = 8.4 Hz, 1H), 7.88 (dd, J = 1.6 Hz, J = 8.6 Hz, 1H), 7.65 (dd, J = 2.4 Hz, J = 8.4 Hz, 1H), 7.57 (d, J = 2.4 Hz, 1H), 7.11 (d, J = 8.8 Hz, 1H), 3.86 (s, 3H), 2.13 (s, 6H), 2.06 (s, 3H), 1.75 (s, 6H), 13.1(s, 1H); The spectral data were identical to those of reported in the literature.[15]

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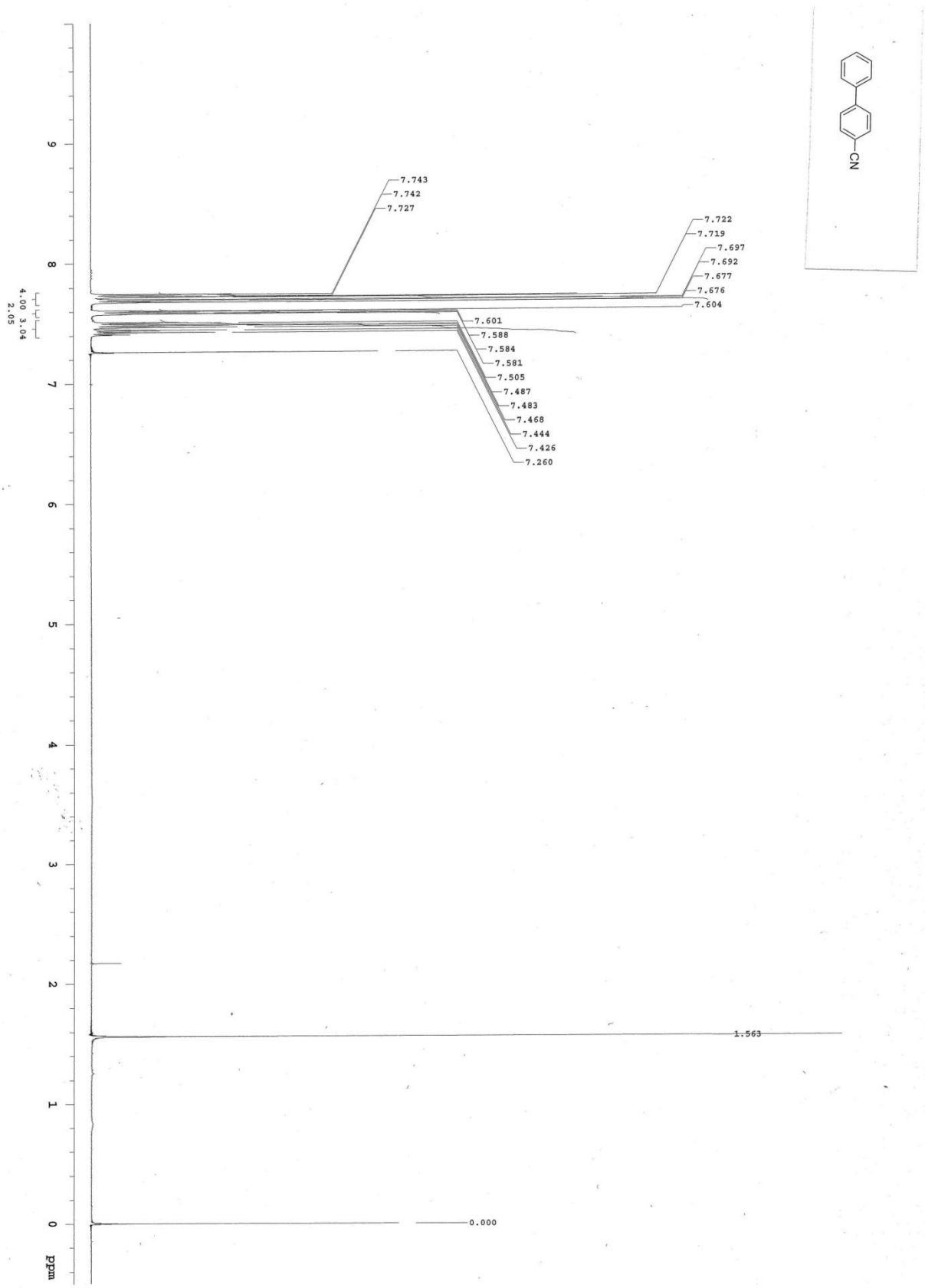
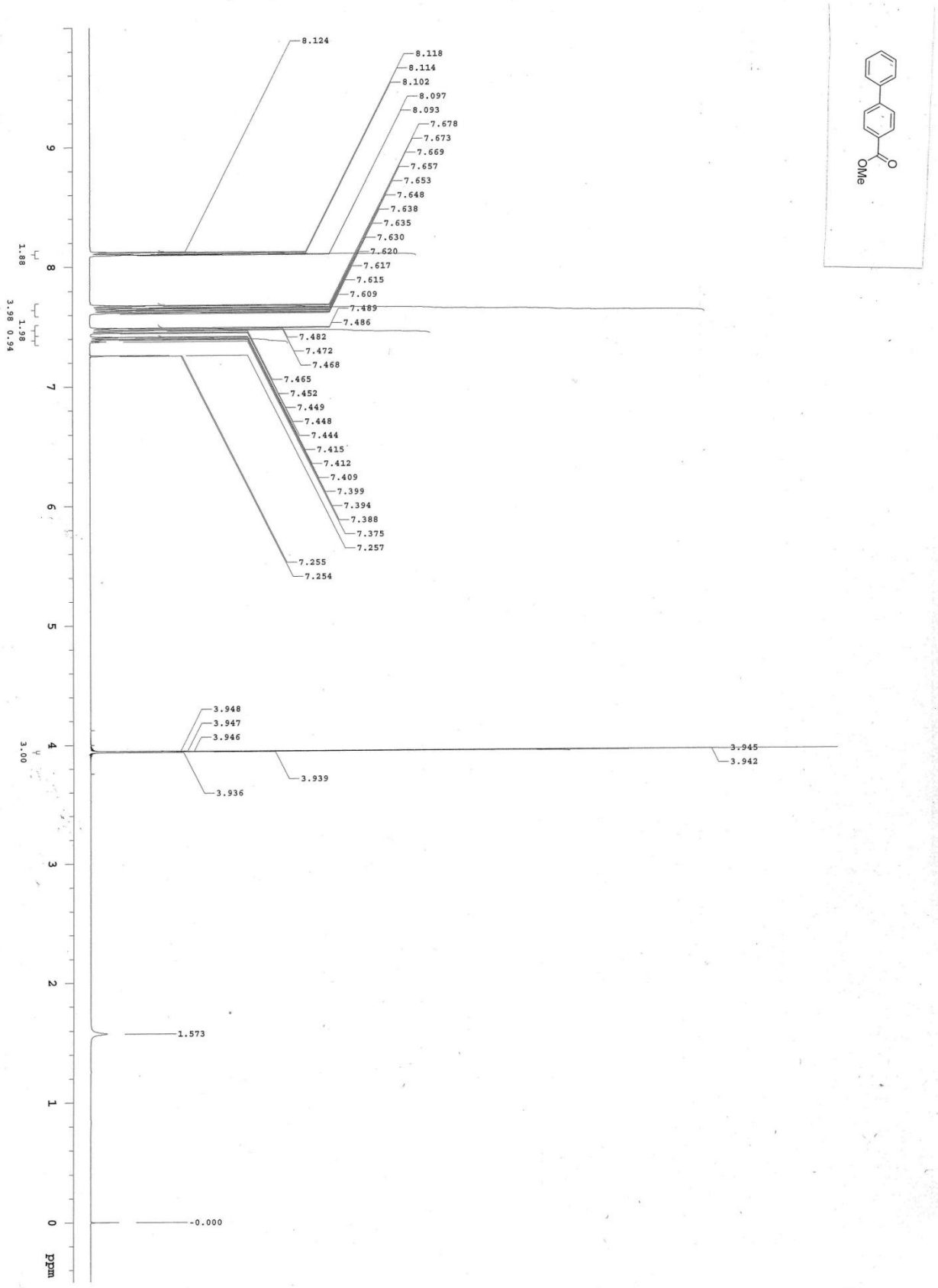
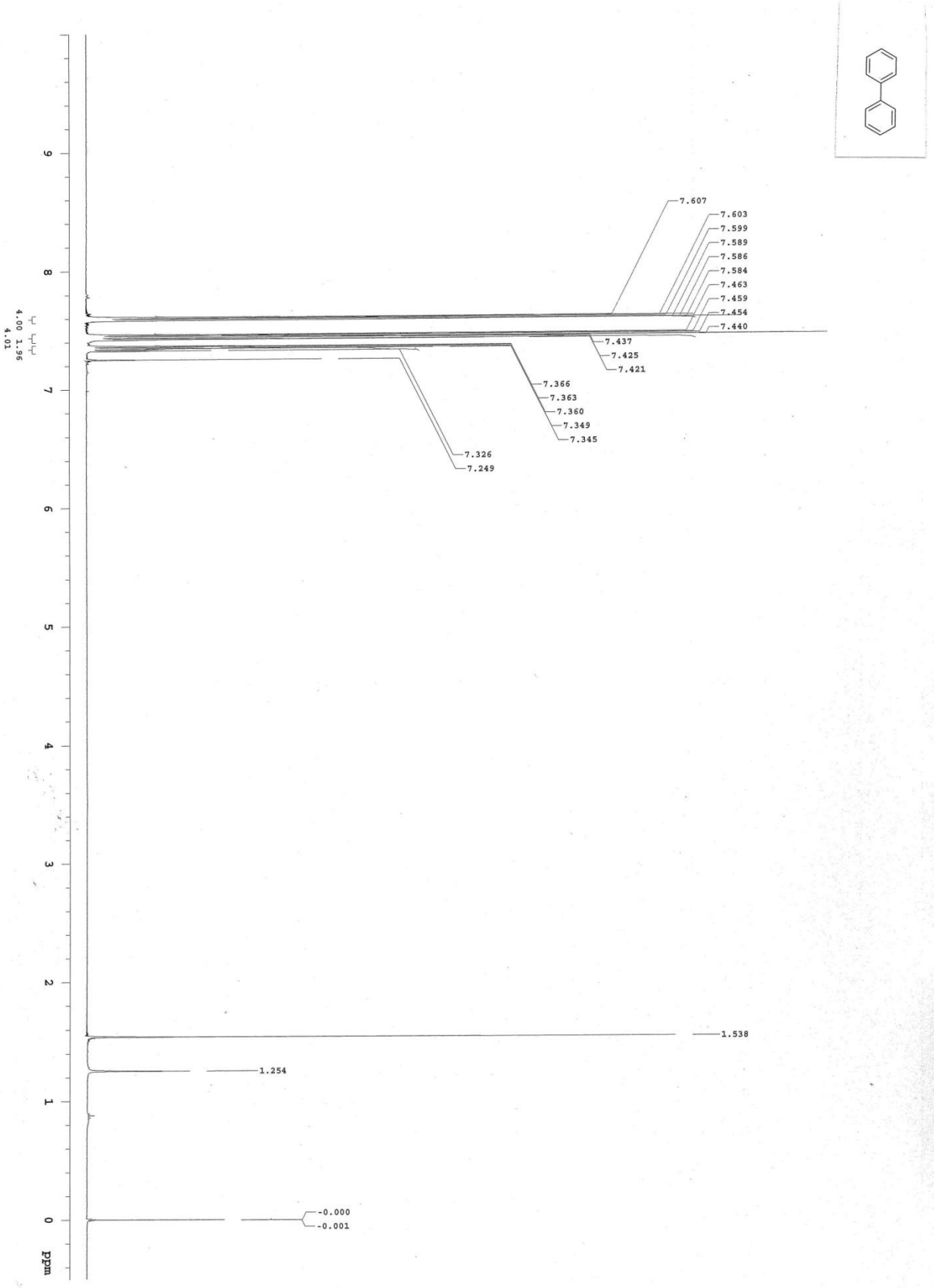


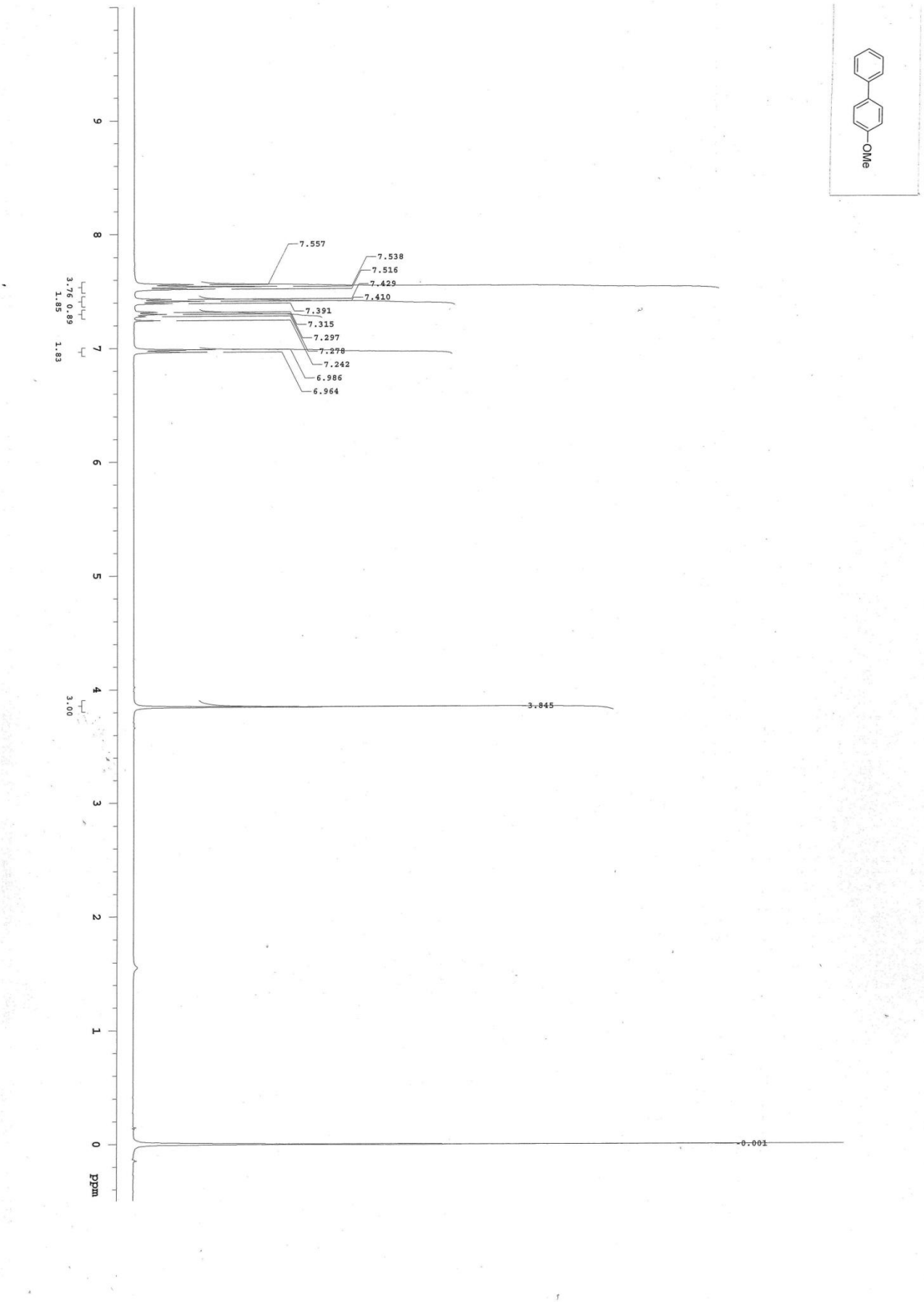
[1]H NMR spectrum of biphenyl-4-carbonitrile



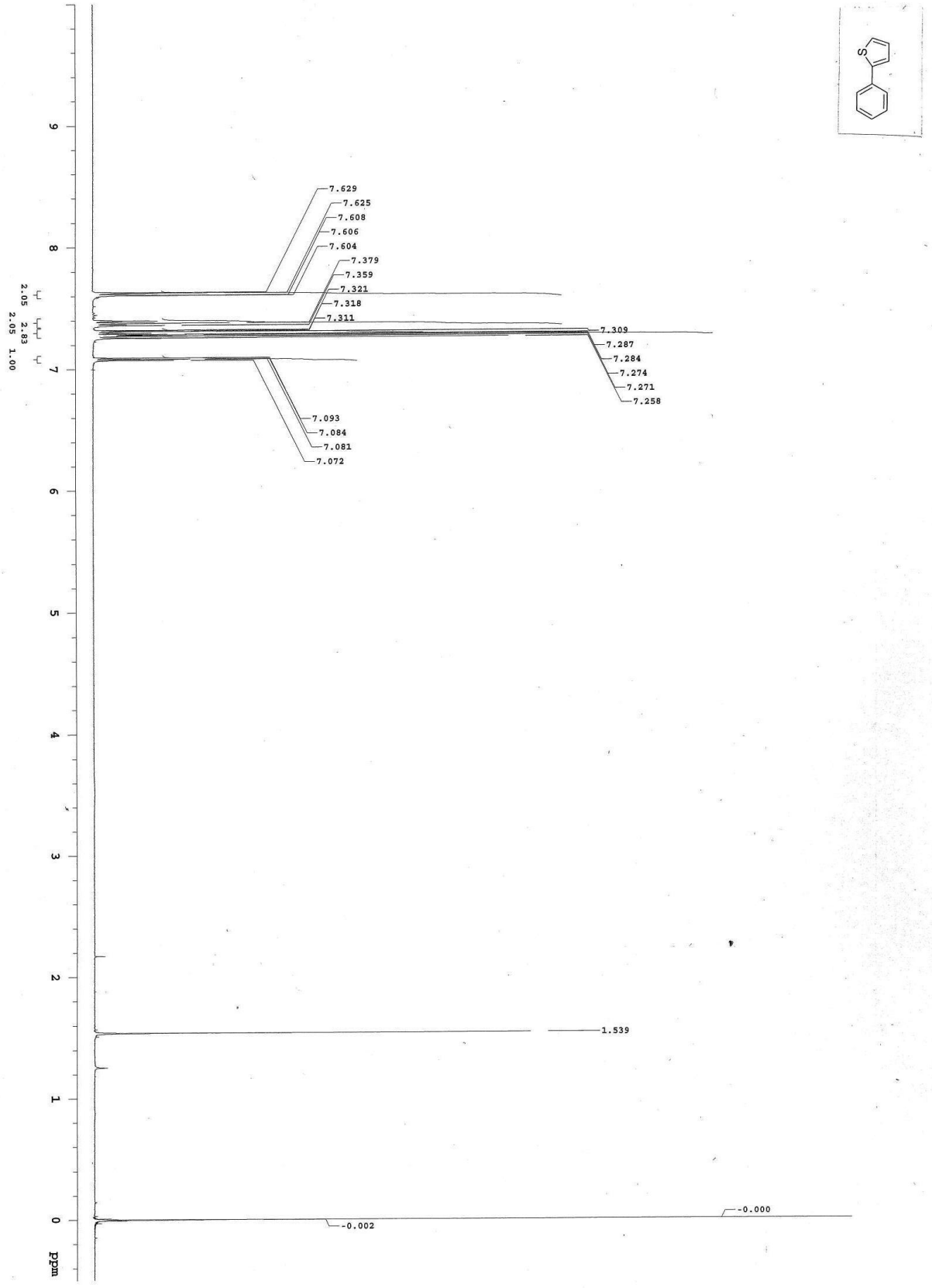
[1]H NMR spectrum of methyl 4-phenylbenzoate



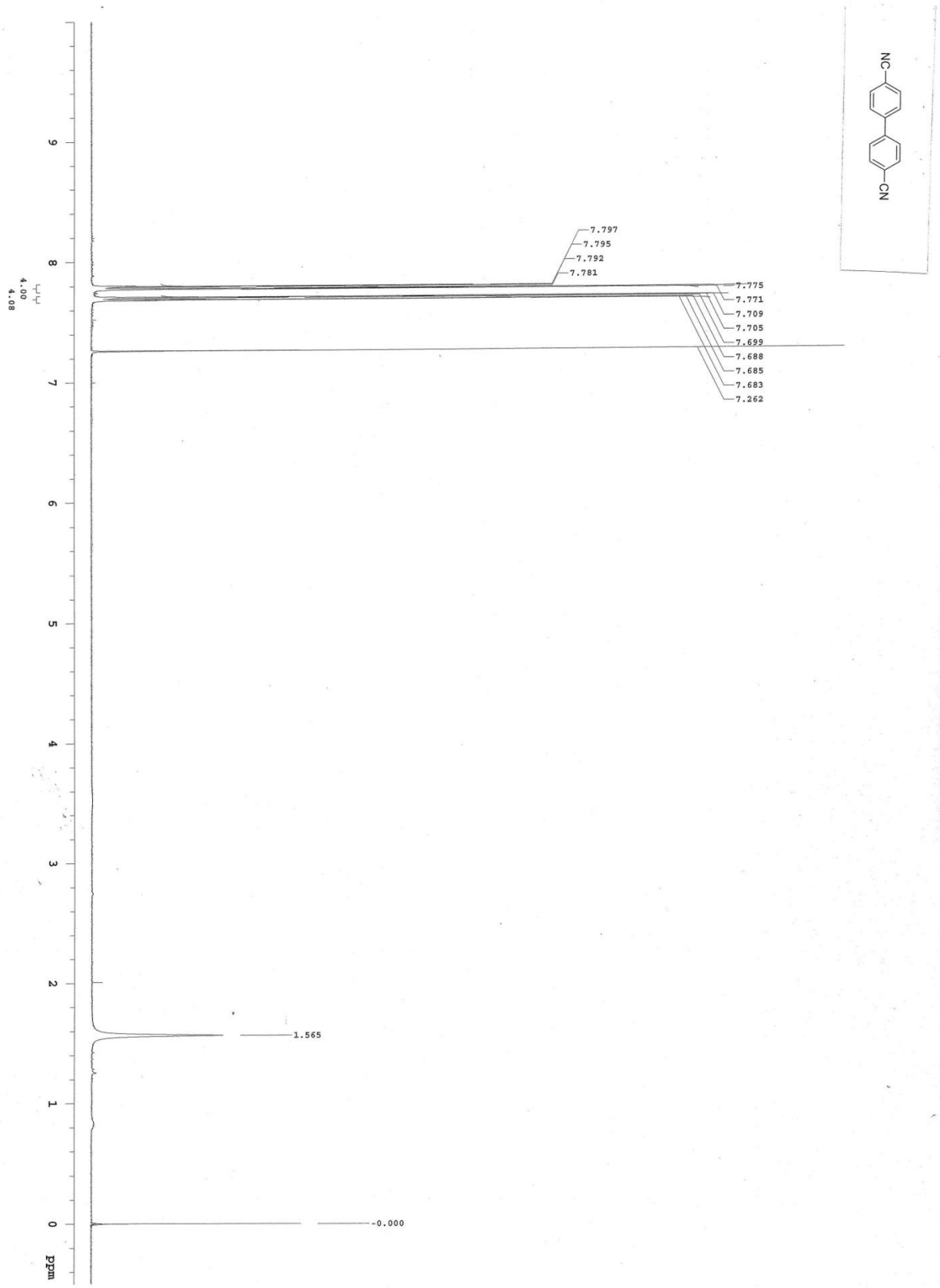
[1]H NMR spectrum of biphenyl



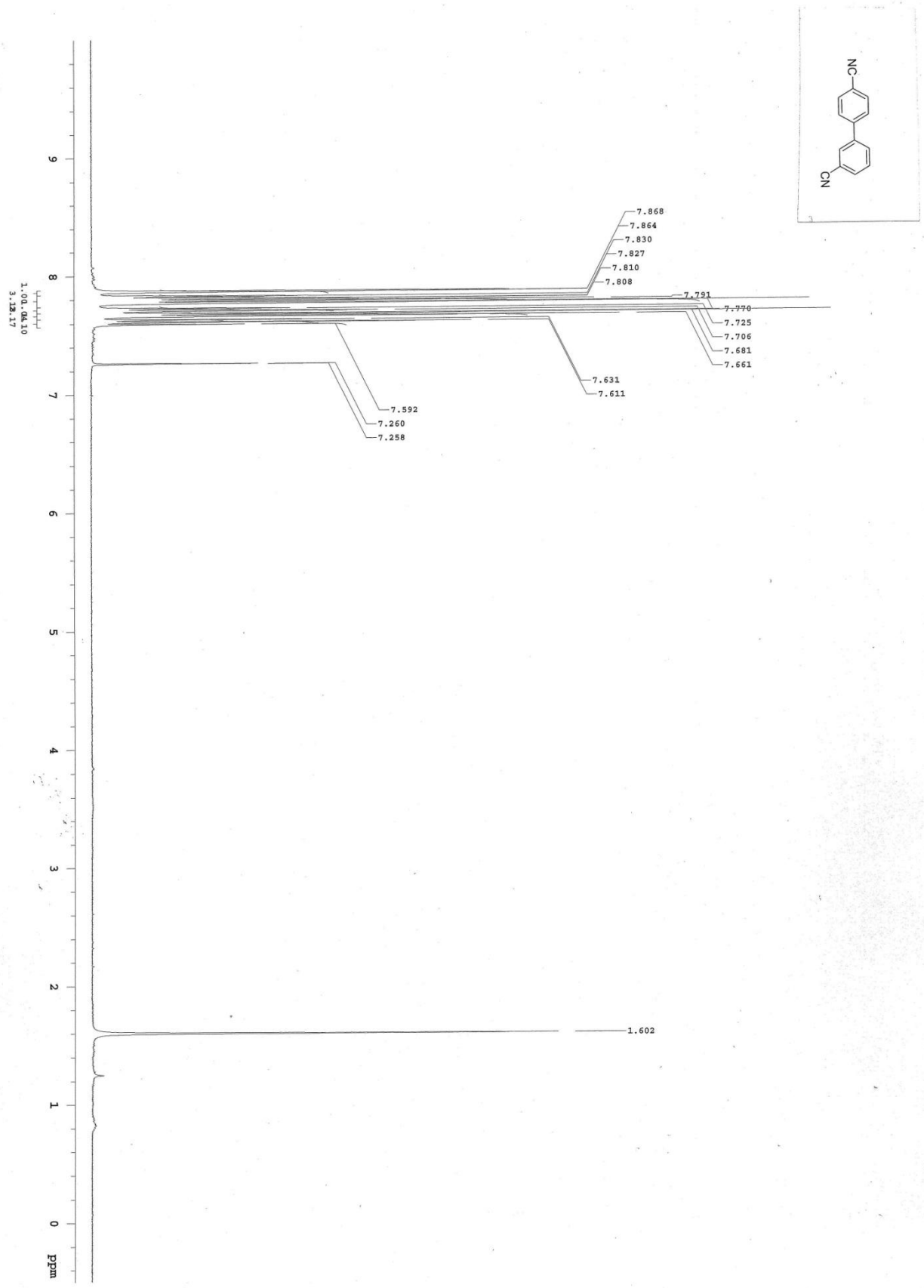
^{1}H NMR spectrum of 4-methoxybiphenyl



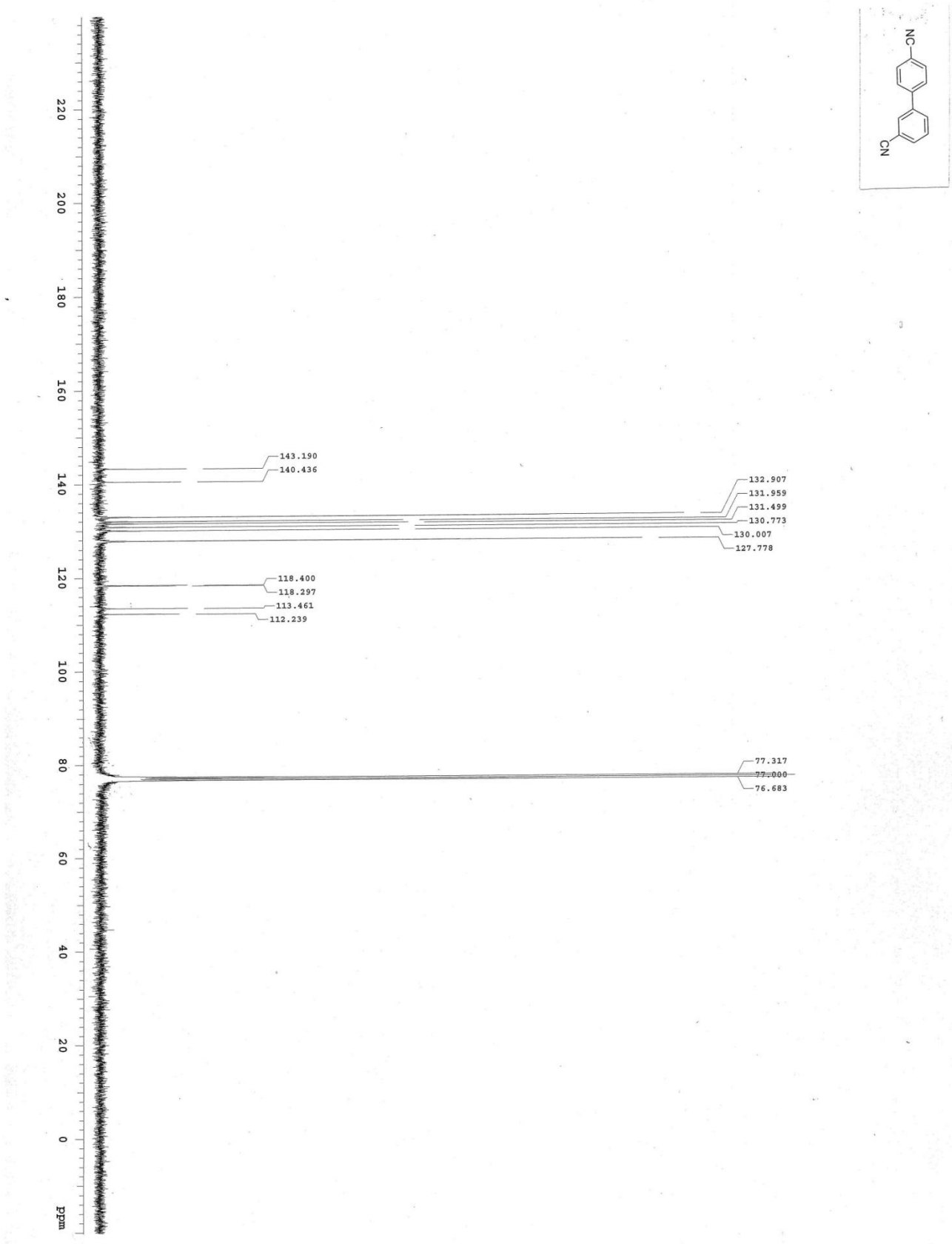
^{1}H NMR spectrum of 2-phenylthiophene



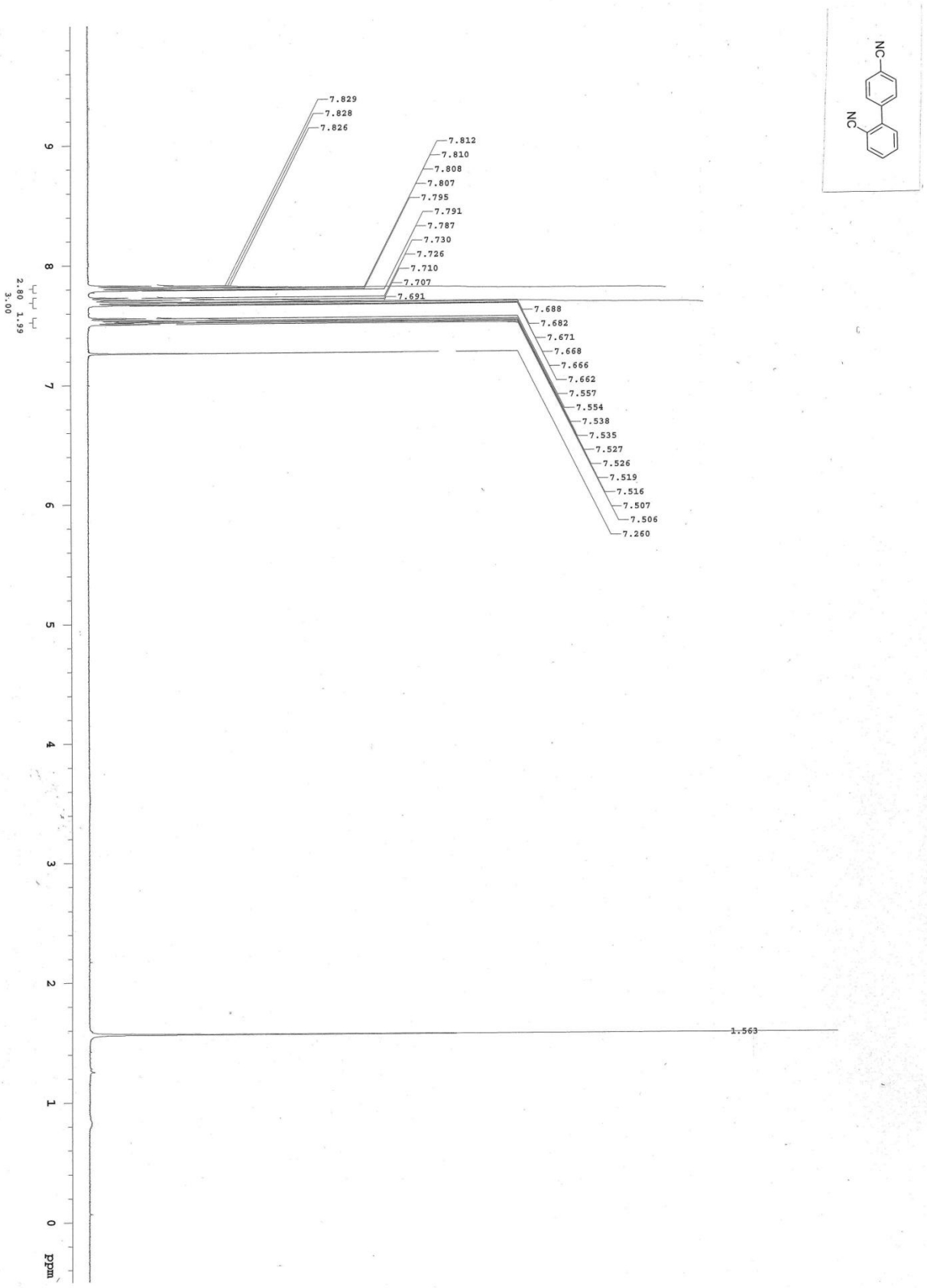
^{1}H NMR spectrum of 4,4'-dicyanobiphenyl



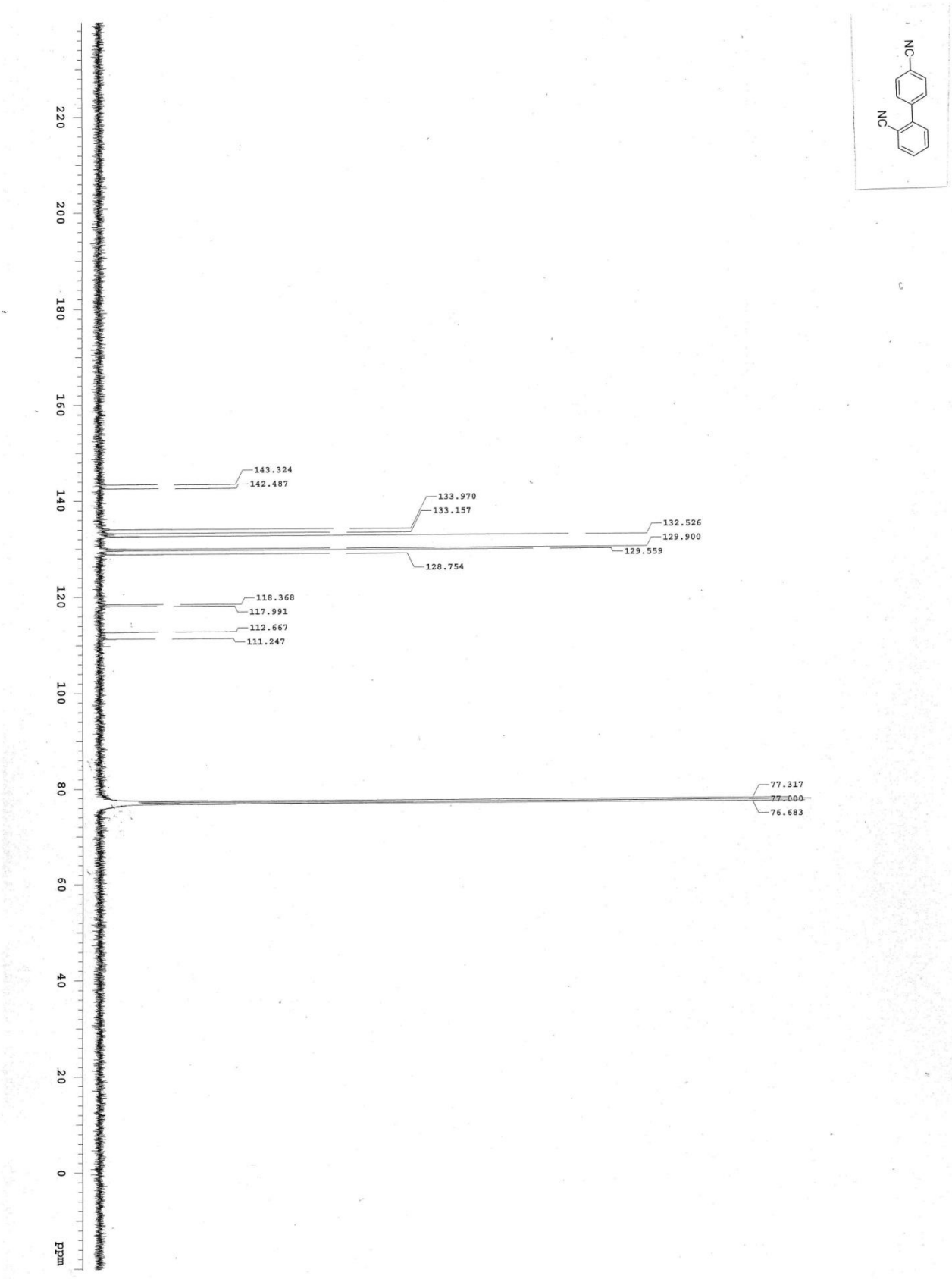
^{1}H NMR spectrum of 3,4'-dicyanobiphenyl



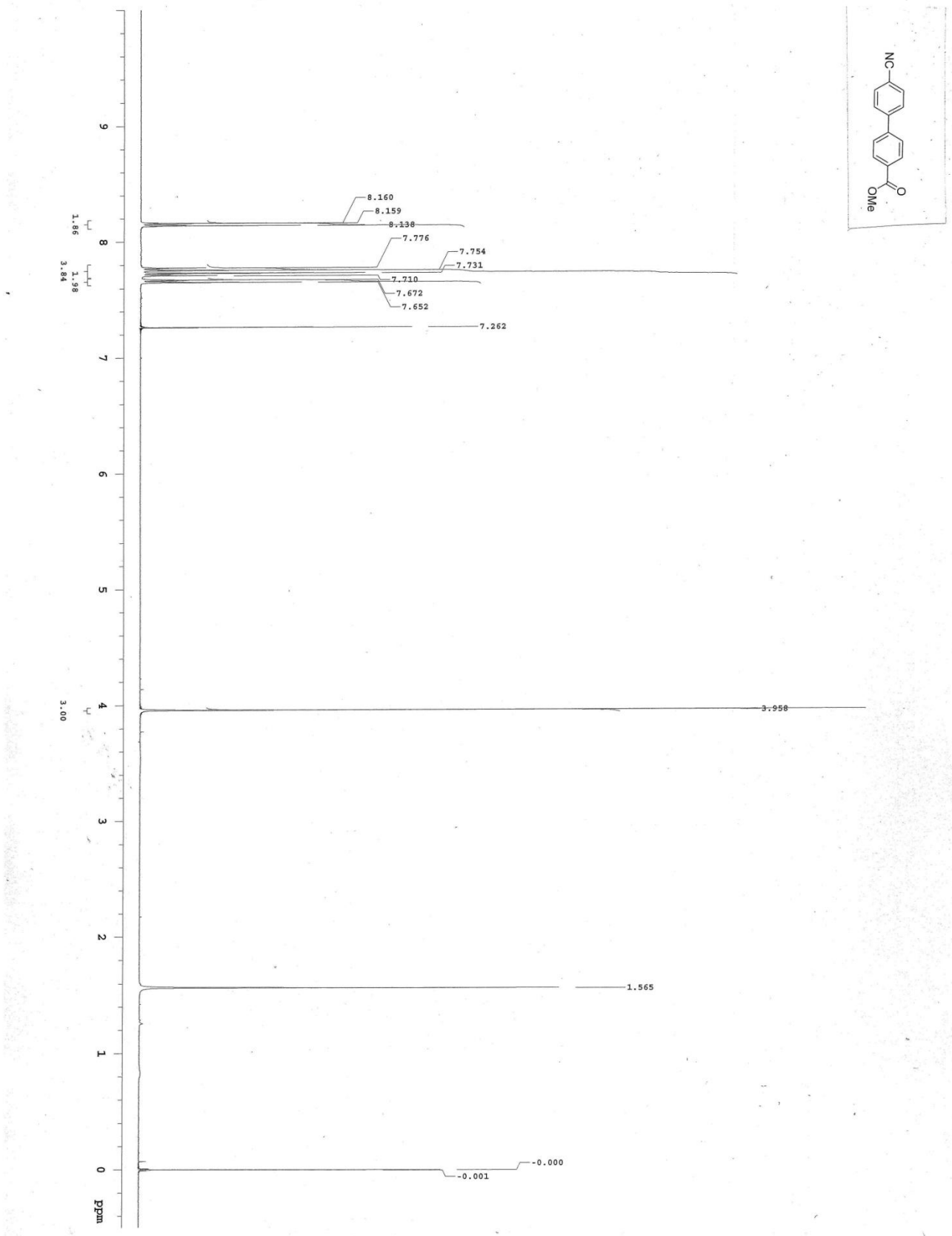
^{13}C NMR spectrum of 3,4'-dicyanobiphenyl



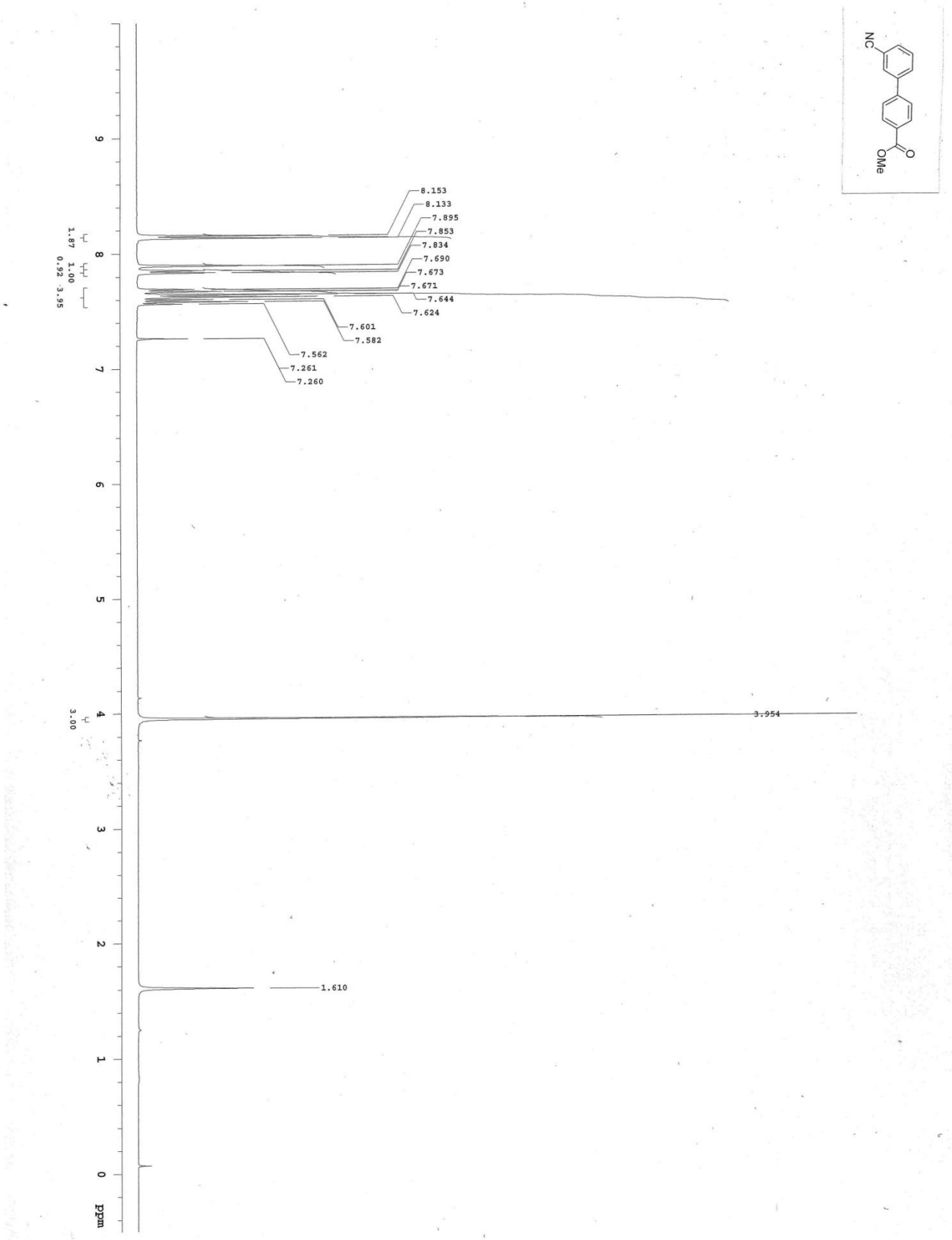
^{1}H NMR spectrum of 2,4'-dicyanobiphenyl



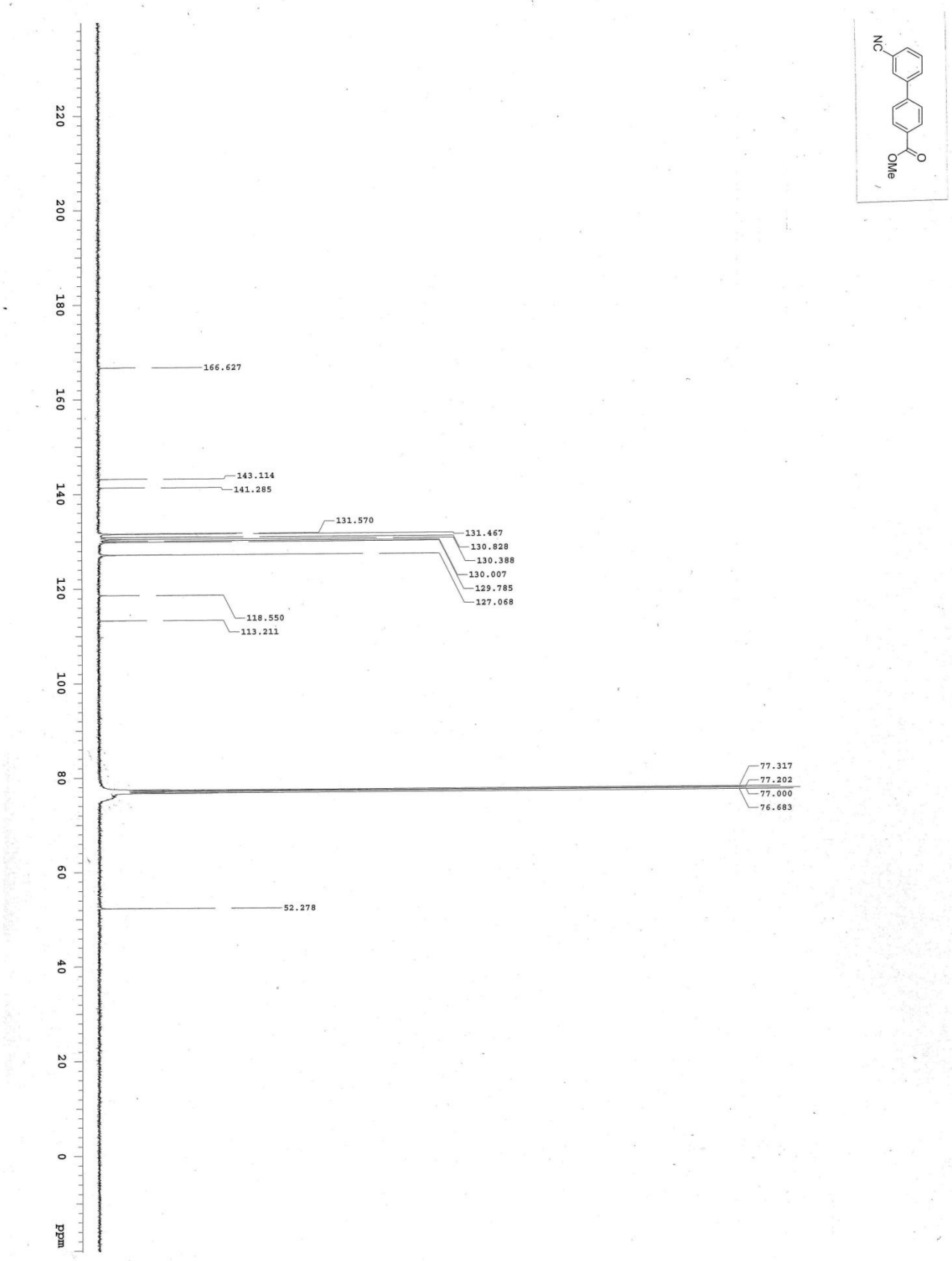
^{13}C NMR spectrum of 2,4'-dicyanobiphenyl



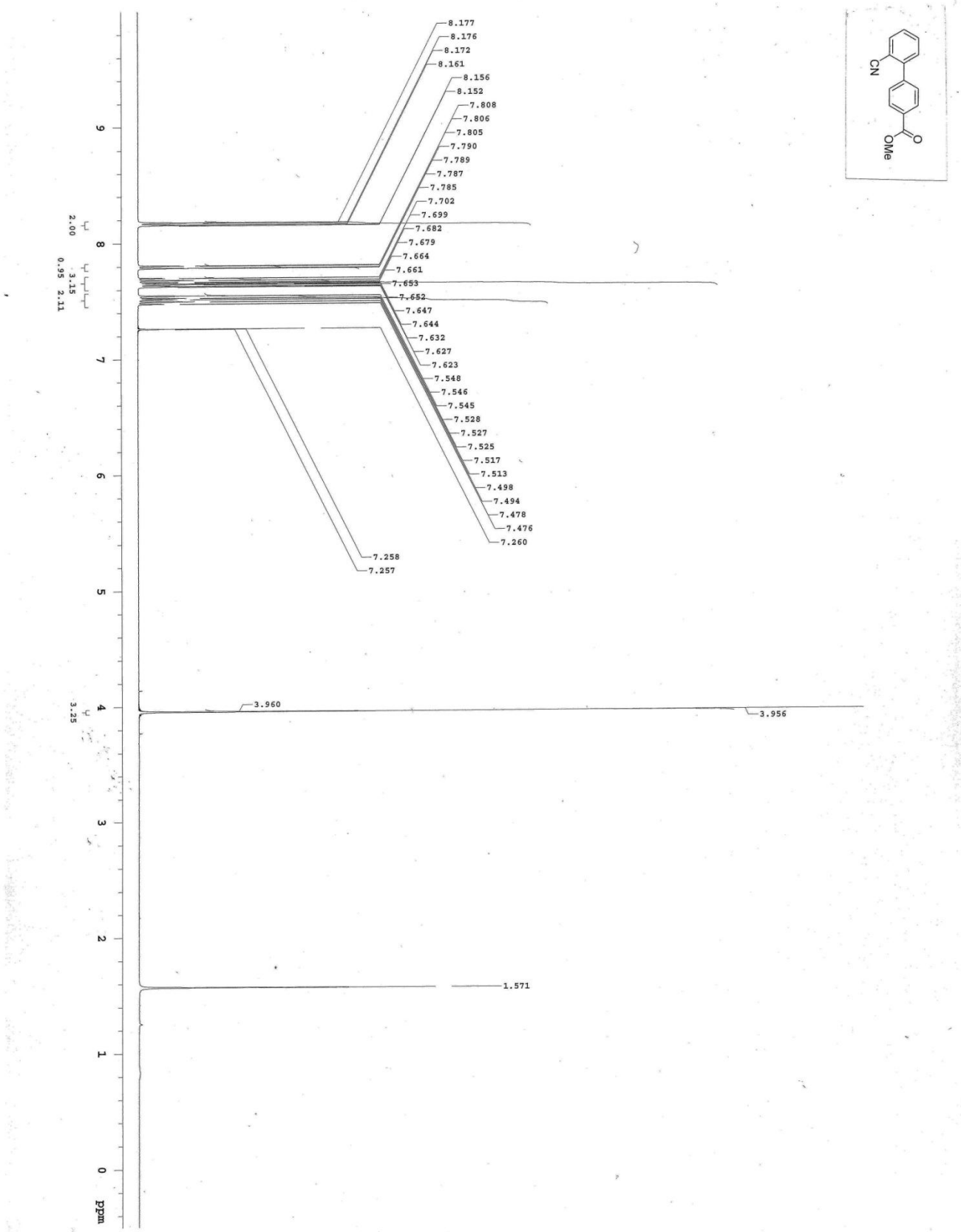
^{1}H NMR spectrum of methyl 4-(4-cyanophenyl)benzoate



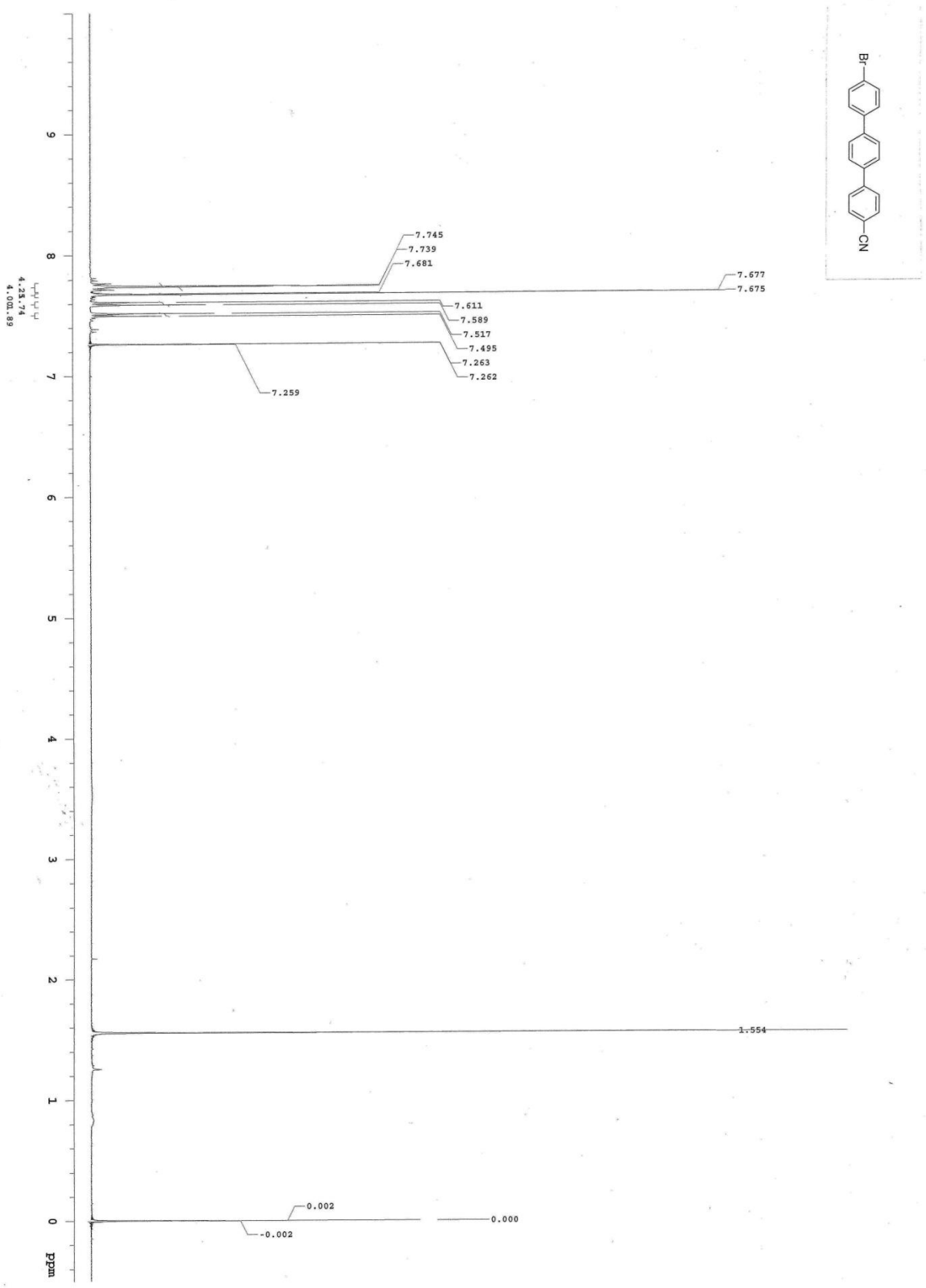
^{1}H NMR spectrum of methyl 4-(3-cyanophenyl)benzoate



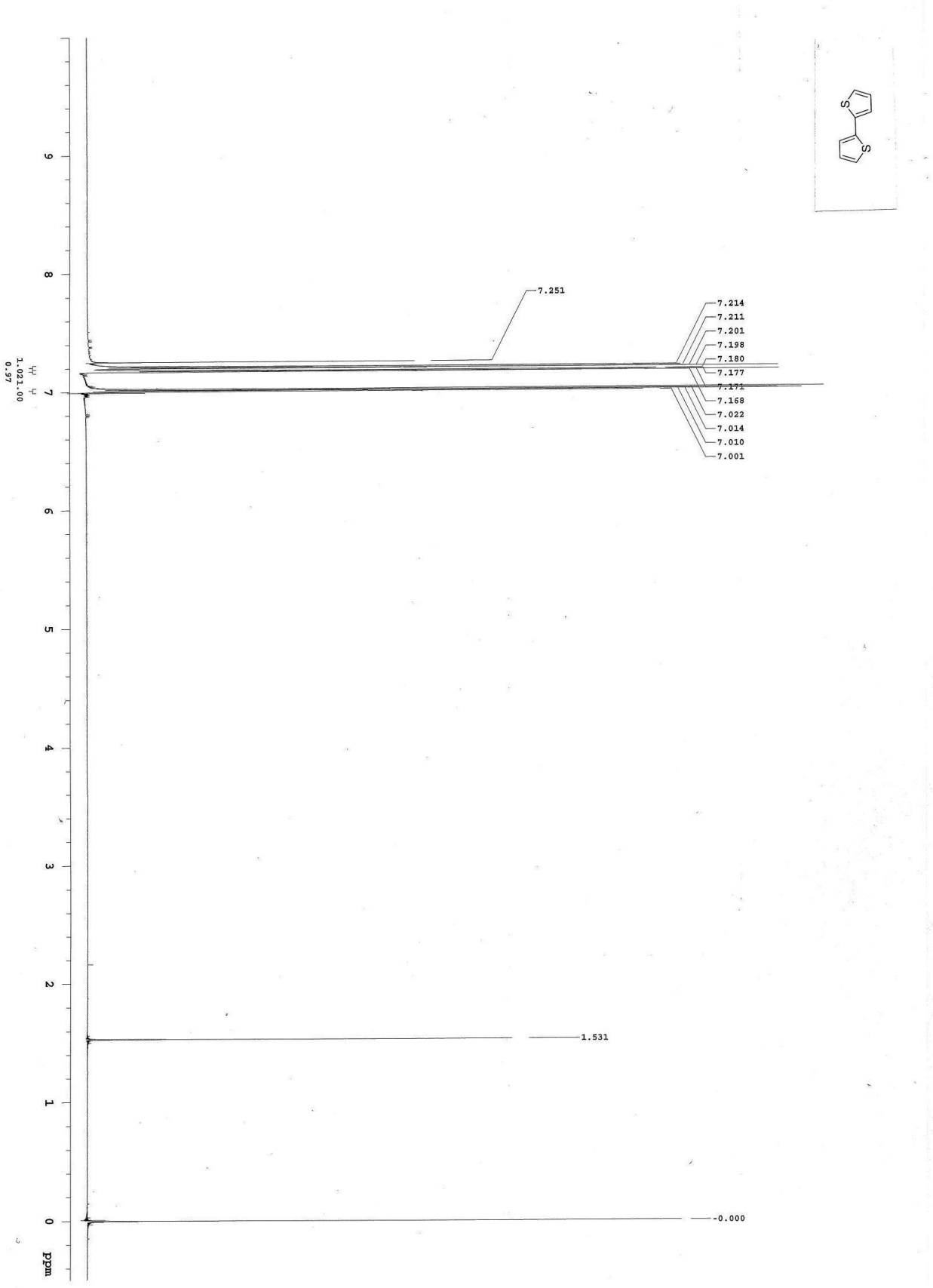
^{13}C NMR spectrum of methyl 4-(3-cyanophenyl)benzoate



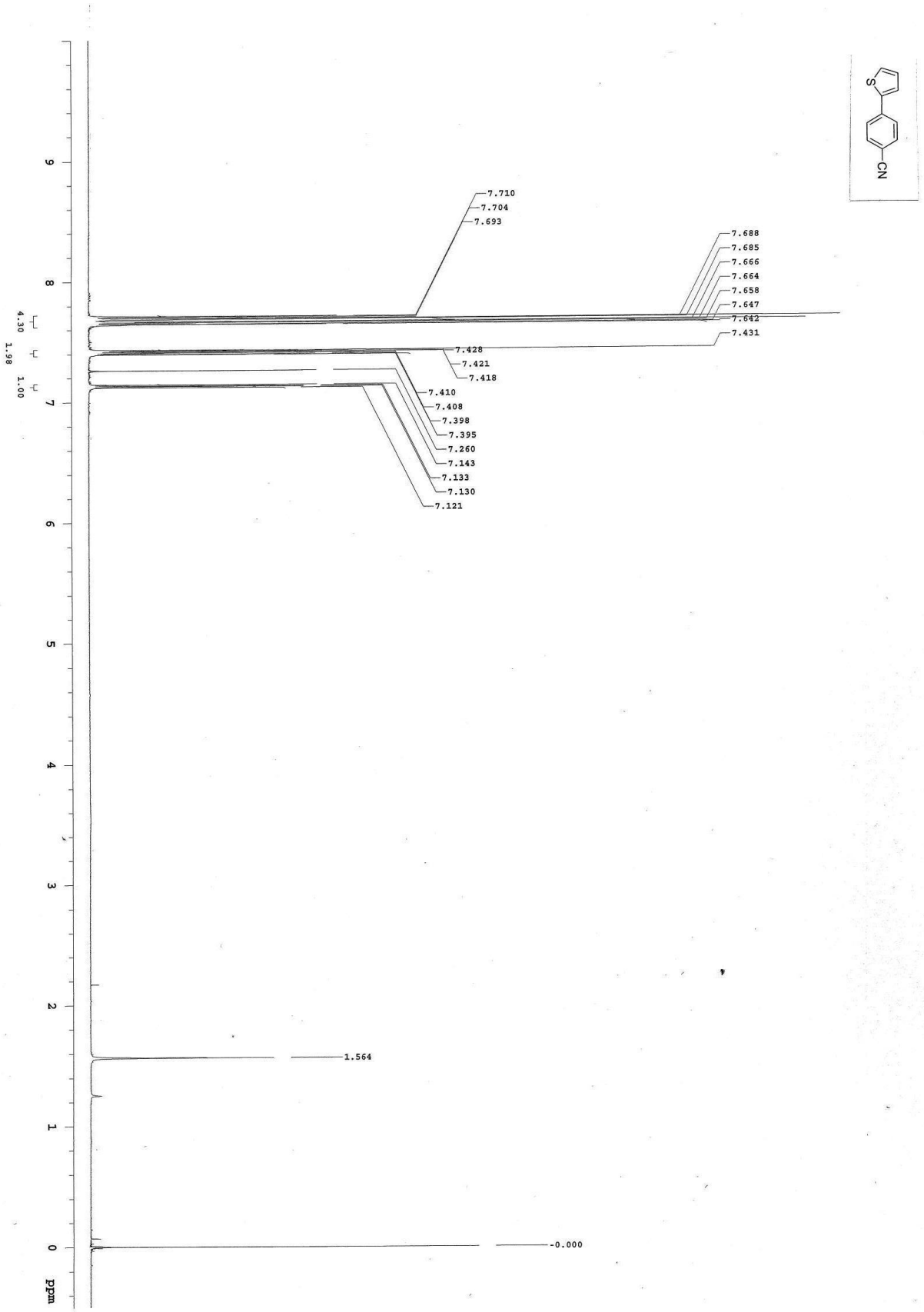
^{1}H NMR spectrum of methyl 4-(2-cyanophenyl)benzoate



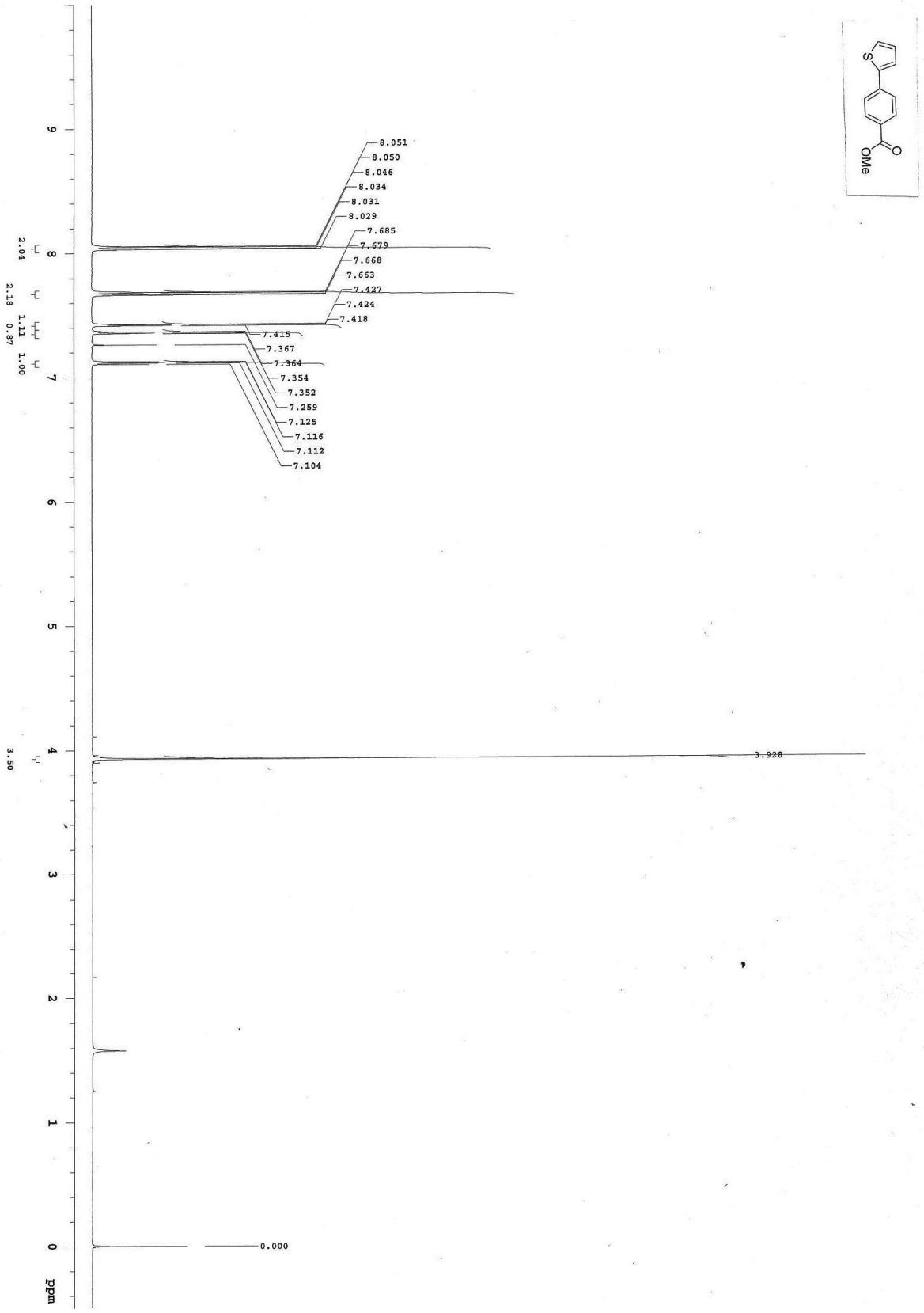
^{1}H NMR spectrum of 1-cyano-4''-bromo-4,1':4',1''-terphenylene



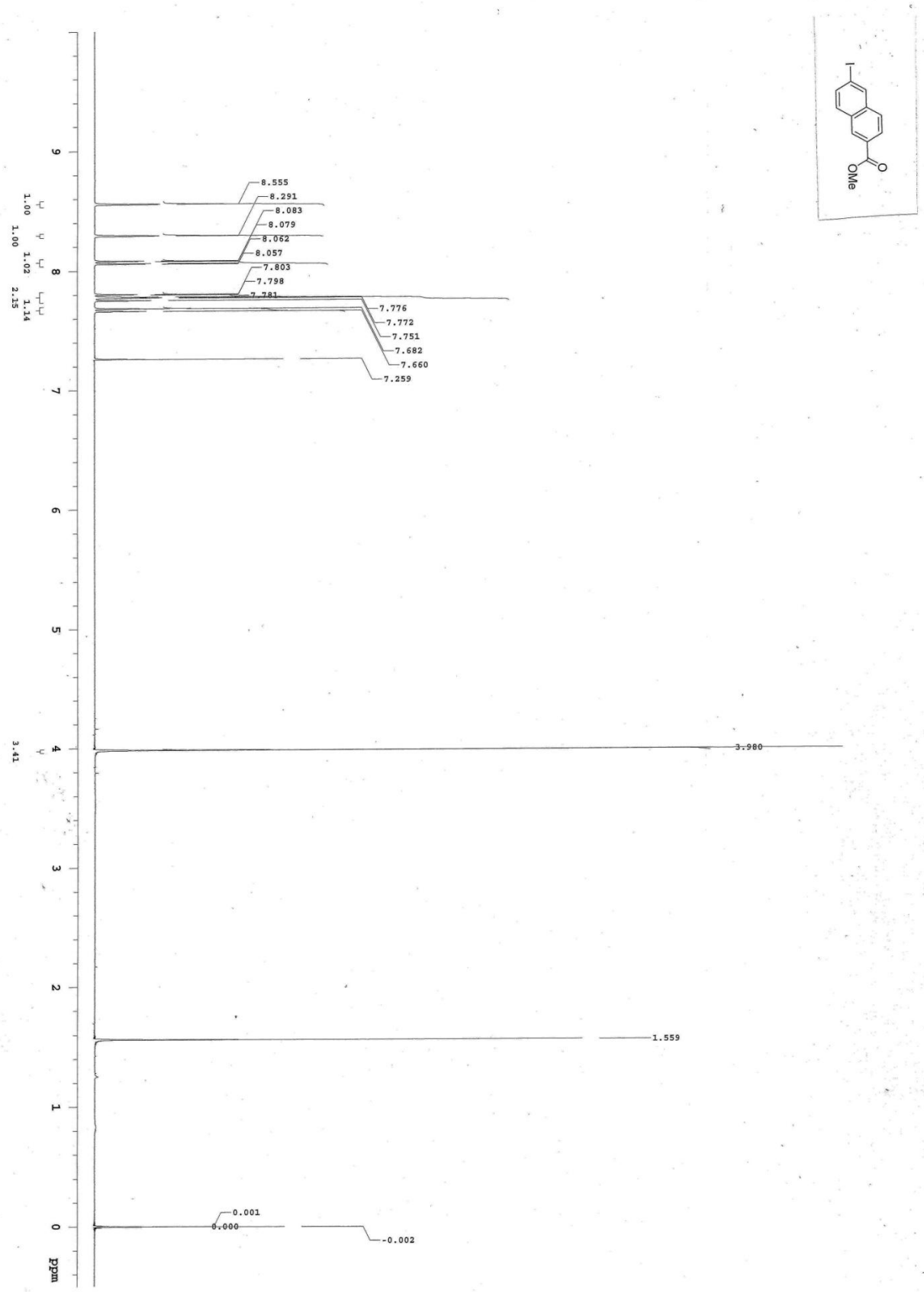
^{1}H NMR spectrum of 2,2'-bithiophene



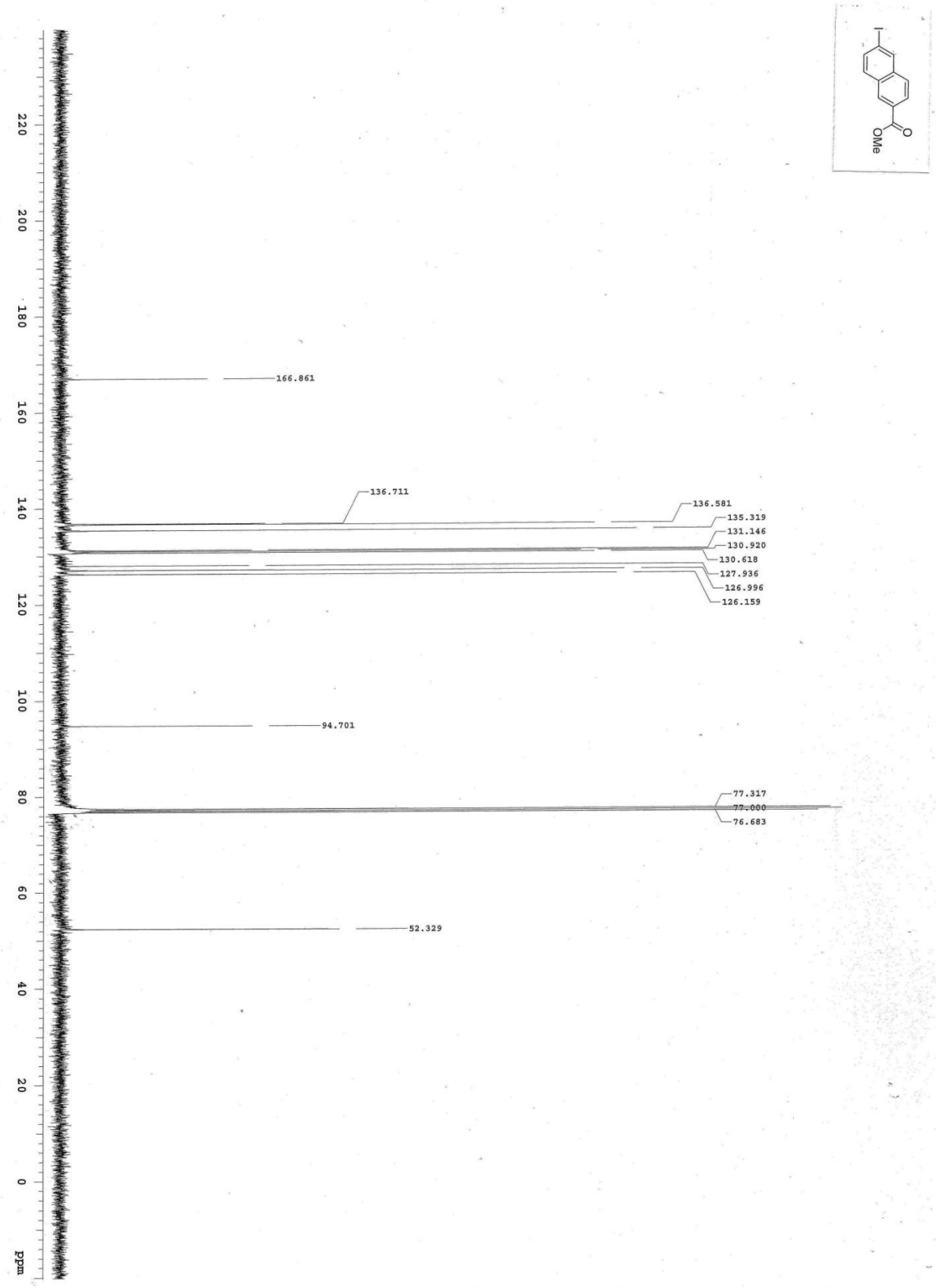
^{1}H NMR spectrum of 4-(thiophen-2-yl)benzonitrile



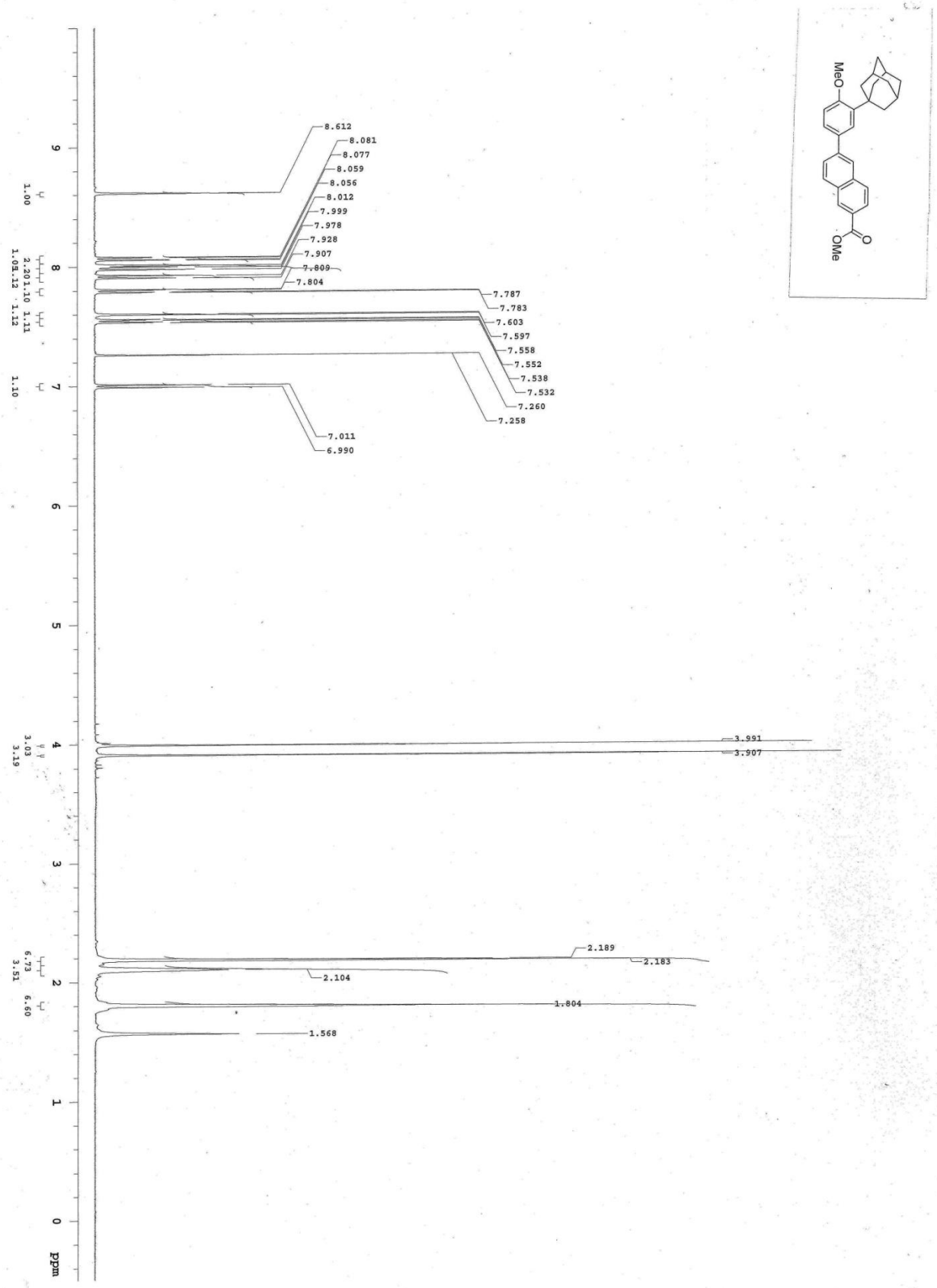
^{1}H NMR spectrum of methyl 4-(thiophen-2-yl)benzoate



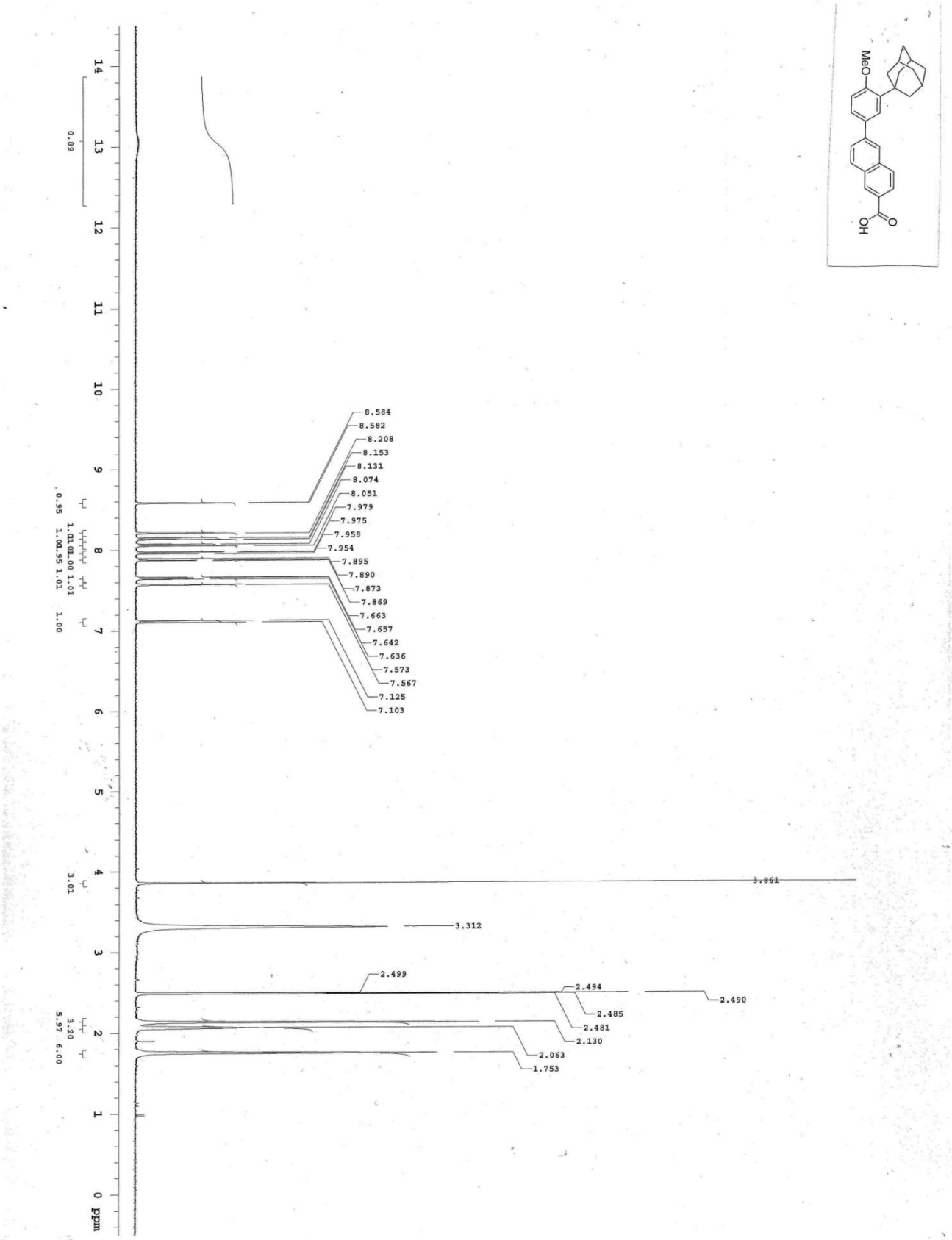
^{1}H NMR spectrum of methyl 6-iodo-2-naphthoate



^{13}C NMR spectrum of methyl 6-iodo-2-naphthoate



[1]H NMR spectrum of methyl 6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoate



[1]H NMR spectrum of 6-(3-(1-adamantyl)-4-methoxyphenyl)-2-naphthoic acid (Adapalene)