Supplementary Information

Field-based rational design of p300 histone acetyltransferase inhibitor and systematic evaluation as an anti-fibrotic agent

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Contents

EXPERIMENTAL SECTION

Chemistry. The chemicals and reagents used were obtained from Aldrich Chemical Co. and TCI. All solvents used for chromatography were used directly without distillation. Melting points were measured without correction in open capillaries with a Barnstead Electrothermal melting point apparatus, Manual MELTEMP (Model No: 1202D). Chromatographic separations were monitored by thin-layer chromatography using a commercially available pre-coated Merck Kieselgel 60 F254 plate (0.25 mm) and detected by visualization under UV at 254 and 365 nm. Silica gel column chromatography was carried out with Merck Kieselgel 60 (0.040–0.063 mm). The purity was assessed by HPLC (Shimadzu LC-20AD) analysis under the following conditions: column, SunFire C18 (4.6 mm × 150 mm, 5 um); mobile phase, isocratic A: acetonitrile 85%, B: water 15% over 15 min; flow rate, 1.0 mL/min; detection, UV detector (Shimadzu Spd-M20A diode array detector). The purity of each compound is described as a percentage (%). NMR spectra were recorded on a Varian AS 400 (^{1}H NMR at 400 MHz and ^{13}C NMR at 100 MHz) or JEOL JNM-ECZ500R/S1 (^{1}H NMR at 500 MHz and ^{13}C NMR at 125 MHz) with tetramethylsilane as an internal standard. Chemical shift (d) values are expressed in ppm, and coupling constant *(J)* values are expressed in hertz (Hz).

General synthetic method for compounds 1–6. A mixture of substituted 4-hydroxybenzaldehyde (1 equiv.), corresponding to substituted benzyl chloride (1 equiv.) and K_2CO_3 (1 equiv.) in DMF was mixed at 80 ℃ for 1 d. The reaction mixture was cooled to room temperature and extracted with ethyl acetate. The organic solvent was washed with water, $NaHCO_3$, and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography to give *O*-benzylated compounds **1**–**6**.

3-Chloro-4-(3-chlorobenzyloxy)-5-methoxybenzaldehyde (1)

5-Chlorovanilin (1.00 g, 5.36 mmol) and 3-chlorobenzyl chloride (0.70 g, 5.36 mmol) were used to produce compound **1** as an ivory solid (1.50 g, 96.5%): R_f 0.54 (ethyl acetate: *n*-hexane = 1:3); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.95 (s, 3H), 5.13 (s, 2H), 7.30-7.32 (m, 2H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.37-7.39 (m, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.53-7.54 (m, 1H), 9.86 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) 56.5, 74.3, 109.6, 125.9, 126.4, 128.5, 128.6, 129.4, 129.9, 132.9, 134.5, 138.7, 149.4, 154.5, 190.1 ppm.

3-Bromo-4-(3-chlorobenzyloxy)-5-methoxybenzaldehyde (2)

5-Bromovanilin (1.00 g, 4.33 mmol) and 3-chlorobenzyl chloride (0.58 g, 5.36 mmol) were used to give compound **2** as an ivory solid (1.50 g, 96.5%): R_f 0.65 (ethyl acetate: *n*-hexane = 1:3); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.94 (s, 3H), 5.12 (s, 2H), 7.30-7.32 (m, 2H), 7.38 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.40 (d, *J* = 2.0 Hz, 1H), 7.54-7.56 (m, 1H), 7.66 (d, *J* = 2.0 Hz, 1H), 9.85 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) 56.5, 74.2, 110.3, 118.5, 126.5, 128.6, 129.0, 129.9, 133.5, 134.5, 138.7, 150.4, 154.4, 190.0 ppm.

4-((3-Chlorobenzyl)oxy)-3-iodo-5-methoxybenzaldehyde (3)

5-Iodovanilin (1.00 g, 3.60 mmol) and 3-chlorobenzyl chloride (0.58 g, 5.36 mmol) were used to give compound **3** as an ivory solid (1.423 g, 98.1%): R_f 0.67 (ethyl acetate: *n*-hexane = 1:3); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.94 (s, 3H), 5.10 (s, 2H), 7.31-7.33 (m, 2H), 7.41 (dd, *J* = 8.4, 1.2 Hz, 1H),.7.43 (d, *J* = 1.6 Hz, 1H), 7.57-7.58 (m, 1H), 7.87 (d, *J* = 1.6 Hz, 1H), 9.84 (s, 1H); ^{13}C-NMR ($CDCl_3$, 100 MHz) 56.4, 74.0, 92.8, 111.2, 126.6, 128.7, 128.8, 129.9, 134.4, 134.5, 135.1, 138.7, 152.9, 153.2, 189.9 ppm.

3-((2-Chloro-4-formyl-6-methoxyphenoxy)methyl)benzamide (4)

5-Chlorovanilin (0.40 g, 2.14 mmol) and 3-(chloromethyl)benzamide (0.36 g, 2.14 mmol) were used to give compound **4** as a white solid (0.32 g, 45.0%): R_f 0.10 (ethyl acetate: *n*-hexane = 1:1); ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 3.88 (s, 3H), 5.11 (s, 2H), 7.30 (d, *J* = 2.0 Hz, 1H), 7.37 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.77 (ddd, *J* = 7.6, 1.6, 1.2 Hz, 1H), 794 (dd, *J* = 1.6, 1.6 Hz, 1H), 9.78 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6) 56.4, 74.1, 110.9, 124.1, 127.2, 127.6, 127.9, 128.2, 131.1, 132.6, 134.4, 136.6, 148.2, 154.0, 167.6, 191.1 ppm.

3-((2-Bromo-4-formyl-6-methoxyphenoxy)methyl)benzamide (5)

5-Bromovanilin (0.18 g, 0.79 mmol) and 3-(chloromethyl)benzamide ((0.13 g, 0.79 mmol) were used to give compound **5** as a white solid (0.20 g, 73.2%): R_f 0.16 (ethyl acetate: *n*-hexane = 1:1); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 3.88 (s, 3H), 5.10 (s, 2H), 7.34 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.60 (d, *J* = 2.0 Hz, 1H), 7.62 (ddd, *J* = 7.6, 1.2, 1.2 Hz 1H), 7.78 (ddd, *J* = 7.6, 1.2, 1.2 Hz 1H), 7.96 (dd, *J* = 1.2, 1.2 Hz, 1H), 9.78 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6) 55.7, 73.8, 110.0, 117.7, 126.9, 127.2, 127.6, 127.9, 131.0, 132.6, 133.5, 136.3, 149.5, 153.6, 168.5, 189.3 ppm.

3-((4-Formyl-2-iodo-6-methoxyphenoxy)methyl)benzamide (6)

5-Iodovanilin (0.26 g, 0.94 mmol) and 3-(chloromethyl)benzamide ((0.16 g, 0.94 mmol) were used to give compound **6** as a white solid (0.28 g, 72.4%): R_f 0.10 (ethyl acetate: *n*-hexane = 1:1); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ 3.88 (s, 3H), 5.09 (s, 2H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.65 (ddd, *J* = 7.6, 1.6, 1.6 Hz 1H), 7.78 (ddd, *J* = 7.6, 1.2, 1.2, Hz 1H), 7.79 (d, *J* = 2.0 Hz, 1H), 7.98 (dd, *J* = 1.6, 1.6 Hz, 1H), 9.76 (s, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6) 55.6, 73.6, 92.2, 111.0, 126.9, 127.3, 127.8, 131.1, 133.5, 113.6, 133.7, 136.2,

151.9, 152.4, 168.5, 189.1 ppm.

General synthetic methods for chalcone analogues A1–24. We added 50% NaOH (2.0–5.0 equiv.) to a reaction mixture of acetophenone derivative and substituted *O*-benzylated benzaldehyde derivative in EtOH (10 mL). The reaction mixture was stirred at room temperature (24 h), and then water was added. The reaction mixture was extracted with EtOAc and then washed with H_2O and brine, successively. The organic layer was collected and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography to give the desired product.

(*E*)-3-((4-(3-(3-Aminophenyl)-3-oxoprop-1-en-1-yl)-2-chloro-6-methoxyphenoxy)methyl) benzamide (A1)

Compound **4** (200 mg, 0.63 mmol) and 3-aminoacetophenone (85 mg, 0.63 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: dichloromethane = 4:1) to give **A1** as a yellow solid (78 mg, 28.6%): R_f 0.42 (ethyl acetate: dichloromethane = 4:1); mp 68-72 ℃; HPLC: R_T 3.012 min (purity 95.19%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.95 (s, 3H), 5.11 (s, 2H), 5.36 (s, 2H), 6.86 (ddd, *J* = 7.6, 2.0, 0.8 Hz, 1H), 7.21 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.27 (dd, *J* = 2.0, 2.0 Hz, 1H), 7.37-7.39 (m, 2H), 7.47 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.56 (d, *J* = 1.6 Hz, 1H), 7.62 (d, *J* = 1.6 Hz, 1H), 7.63 (d, J = 15.6 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 15.6 Hz, 1H), 7.86 (ddd, *J* = 7.6, 1.6, 1.2 Hz, 1H), 8.00 (br s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.5, 74.0, 111.9, 112.9, 116.6, 118.7, 122.1, 123.1, 127.1, 127.5, 127.6, 128.2, 129.1, 131.1, 131.8, 134.3, 136.9, 138.3, 141.8, 144.8, 149.1, 153.8, 167.7, 189.5 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{24}H_{21}ClN_2O_4$ calcd 437.1263, found 437.1264.

(*E*)-3-((4-(3-(3-Aminophenyl)-3-oxoprop-1-en-1-yl)-2-bromo-6-methoxyphenoxy)methyl)

benzamide (A2)

Compound **5** (150 mg, 0.41 mmol) and 3-aminoacetophenone (49 mg, 0.36 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: dichloromethane = 4:1) to give **A2** as a yellow solid (35 mg, 20.1%): R_f 0.29 (ethyl acetate:dichloromethane = 4:1); mp 72-76 ℃; HPLC: R_T 3.83 min (purity 97.27%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.95 (s, 3H), 5.09 (s, 2H), 5.36 (s, 2H), 6.85 (ddd, *J* = 8.0, 2.4, 1.2 Hz, 1H), 7.21 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.26 (dd, *J* = 2.0, 2.0 Hz, 1H), 7.37-7.39 (m, 2H), 7.48 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.60 (d, *J* = 1.6 Hz, 1H), 7.62 (d, *J* = 16.0 Hz, 1H), 7.67 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 1.6 Hz, 1H), 7.82 (d, *J* = 15.6 Hz, 1H), 7.85 (ddd, *J* = 8.0, 1.2, 1.2 Hz, 1H), 8.00 (br s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) 51.7, 69.1, 107.8, 108.2, 111.8, 112.7, 114.0, 118.3, 120.2, 122.4, 122.8, 123.4, 124.4, 126.3, 127.7, 129.6, 132.1, 133.6, 137.0, 141.1, 144.4, 148.8, 162.9, 184.7 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{24}H_{21}BrN_2O_4$ calcd 481.0757, found 481.0757.

(*E*)-3-((4-(3-(3-Aminophenyl)-3-oxoprop-1-en-1-yl)-2-iodo-6-methoxyphenoxy)methyl) benzamide (A3)

Compound **6** (150 mg, 0.36 mmol) and 3-aminoacetophenone (49 mg, 0.36 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: dichloromethane = 4:1) to give **A3** as a yellow solid (13 mg, 6.8%): R_f 0.38 (ethyl acetate: dichloromethane = 4:1); mp 106-110 ℃; HPLC: R_T 3.357 min (purity 97.12%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.94 (s, 3H), 5.06 (s, 2H), 5.35 (s, 2H), 6.85 (ddd, *J* = 7.6, 2.0, 0.8 Hz, 1H), 7.21 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.26 (dd, *J* = 2.0, 2.0 Hz, 1H), 7.36-7.39 (m, 2H), 7.49 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.60 (d, *J* = 16.0 Hz, 1H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 15.6 Hz, 1H), 7.85 (ddd, *J* = 8.0, 1.6, 1.2 Hz, 1H), 7.90 (d, *J* = 1.6 Hz, 1H), 8.06 (br s, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.3, 73.6, 93.7, 112.9, 113.3, 116.5, 118.7, 122.8, 127.0, 127.6, 128.2, 129.1, 130.7, 131.1, 133.3, 134.3, 136.9, 138.3, 141.7, 148.5, 149.1, 152.4, 167.7, 189.5

ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{24}H_{21}IN_2O_4$ calcd 529.0619, found 529.0616.

(*E*)-3-(3-(4-((3-Carbamoylbenzyl)oxy)-3-chloro-5-methoxyphenyl)acryloyl)benzamide (A4)

Compound **4** (100 mg, 0.31 mmol) and 3-carbamoylacetophenone (51 mg, 0.31 mmol) were used and purified by silica gel column chromatography (eluent: methanol: dichloromethane = 1:10) to give **A4** as a weak yellow solid (60 mg, 41.3%): R_f 0.50 (methanol: dichloromethane = 1:9); mp 170-174 ℃; HPLC: R_T 2.249 min (purity 95.54%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.89 (s, 3H), 5.06 (s, 2H), 7.12 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 1.6 Hz, 1H), 7.37 (dd, J = 8.0, 7.6 Hz, 1H), 7.52 (dd, J = 8.0, 7.6 Hz, 1H), 7.57 (d, J = 16.0 Hz, 1H), 7.61 (d, J = 8.0, 1.6 Hz, 1H), 7.63 (d, J = 16.0 Hz, 1H), 7.78 (d, J = 8.0, 1.6, 1.2 Hz, 1H), 7.95 (dd, J = 2.0, 1.2 Hz, 1H), 8.09-8.13 (m, 2H), 8.55 (dd, J = 1.6, 1.6 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.5, 74.0, 112.5, 122.1, 122.6, 127.1, 127.3, 127.6, 127.7, 128.2, 128.9, 131.1, 131.2, 131.6, 132.0, 134.3, 134.9, 136.9, 137.5, 143.0, 145.0, 153.8, 167.2, 167.7, 188.8 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{25}H_{21}ClN_2O_5$ calcd 465.1212, found 465.1211.

(*E*)-3-(3-(3-Bromo-4-((3-carbamoylbenzyl)oxy)-5-methoxyphenyl)acryloyl)benzamide (A5)

Compound **5** (100 mg, 0.27 mmol) and 3-carbamoylacetophenone (45 mg, 0.31 mmol) were used and purified by silica gel column chromatography (eluent: methanol: dichloromethane = 1:10) to give **A5** as a weak yellow solid (40 mg, 28.5%): R_f 0.50 (methanol: dichloromethane = 1:9); mp 216-220 ℃; HPLC: R_T 2.302 min (purity 99.11%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.89 (s, 3H), 5.05 (s, 2H), 7.15 (d, J = 2.0 Hz, 1H), 7.38 (dd, J = 8.0, 7.6 Hz, 1H), 7.47 (d, J = 1.6 Hz, 1H), 7.52 (dd, J = 8.0, 7.6 Hz, 1H), 7.58 (d, J = 15.6 Hz, 1H), 7.61 (d, J = 8.0, 1.6 Hz, 1H), 7.63 (d, J = 15.6 Hz, 1H), 7.64 (d, J = 7.6, 2.0, 1.2 Hz, 1H), 7.78 (ddd, J = 8.0, 1.6,

1.2 Hz, 1H), 7.97 (dd, *J* = 2.0, 2.0 Hz, 1H), 8.09-8.13 (m, 2H), 8.55 (dd, *J* = 1.6, 1.6 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.5, 73.9, 113.1, 117.5, 122.6, 125.0, 127.1, 127.4, 127.6, 128.2, 128.9, 131.1, 131.2, 132.0, 132.3, 134.3, 134.9, 136.9, 137.6, 142.9, 146.1, 153.6, 167.2, 167.7, 188.8 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{25}H_{21}BrN_2O_5$ calcd 509.0707, found 509.0708.

(*E*)-3-(3-(4-((3-Carbamoylbenzyl)oxy)-3-iodo-5-methoxyphenyl)acryloyl)benzamide (A6)

Compound **6** (100 mg, 0.24 mmol) and 3-carbamoylacetophenone (40 mg, 0.24 mmol) were used and purified by silica gel column chromatography (eluent: methanol: dichloromethane = 1:10) to give **A6** as a weak yellow solid (35 mg, 25.9%): R_f 0.50 (methanol: dichloromethane = 1:9); mp 164-170 ℃; HPLC: R_T 2.411 min (purity 98.53%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.94 (s, 3H), 5.05 (s, 2H), 7.42 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 7.58 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.65 (d, *J* = 15.6 Hz, 1H), 7.67 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.82 (d, *J* = 2.0 Hz, 1H), 7.83 (ddd, *J* = 7.6, 1.6, 1.2 Hz, 1H), 7.84 (d, *J* = 15.6 Hz, 1H), 8.01 (dd, *J* = 2.0, 1.6 Hz, 1H), 8.12-8.15 (m, 1H), 8.21 (ddd, *J* = 8.0, 1.6, 1.2 Hz, 1H), 8.58 (ddd, *J* = 1.6, 1.6 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.3, 73.6, 93.7, 113.8, 122.3, 127.1, 127.3, 127.6, 128.2, 128.9, 130.8, 131.1, 131.2, 132.0, 133.1, 134.3, 134.8, 136.9, 137.6, 142.8, 148.7, 152.4, 167.2, 167.7, 188.8 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{25}H_{21}IN_2O_5$ calcd 557.0568, found 557.0568.

(*E*)-3-((2-Chloro-4-(3-(3-hydroxyphenyl)-3-oxoprop-1-en-1-yl)-6-methoxyphenoxy) methyl)benzamide (A7)

Compound **4** (200 mg, 0.63 mmol) and 1-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)ethan-1-one (138 mg, 0.63 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: dichloromethane = 4:1) to give **A7** as a yellow solid (35 mg, 12.8%): R_f 0.45 (ethyl acetate: dichloromethane = 4:1); mp 188-192 ℃; HPLC: R_T 1.752 min (purity 99.59%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.96 (s, 3H), 5.11 (s, 2H), 7.07 (ddd, *J* = 8.0, 2.4, 0.8 Hz,

1H), 7.36-7.40 (m, 2H),7.47 (dd, J = 8.0, 7.6 Hz, 1H), 7.49 (dd, J = 1.6, 1.6 Hz, 1H), 7.59 (d, J = 16.0 Hz, 1H), 7.63-7.67 (m, 4H), 7.85 (ddd, J = 8.0, 1.6, 1.2 Hz, 1H), 7.90 (d, J = 15.6 Hz, 1H), 7.98-8.01 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.5, 74.0, 112.0, 114.7, 119.7, 120.4, 122.3, 122.8, 127.1, 127.5, 127.6, 128.2, 129.8, 131.1, 131.7, 134.3, 136.9, 138.9, 142.4, 144.9, 153.8, 157.7, 167.7, 189.0 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{24}H_{20}ClNO_5$ calcd 438.1103, found 438.1103.

(*E*)-3-((2-Bromo-4-(3-(3-hydroxyphenyl)-3-oxoprop-1-en-1-yl)-6-methoxyphenoxy) methyl)benzamide (A8)

Compound **5** (100 mg, 0.27 mmol) and 1-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)ethan-1-one (60 mg, 0.27 mmol) were used and purified by silica gel column chromatography (eluent: methanol: dichloromethane = 1:10) to give **A8** as a weak yellow solid (38 mg, 28.9%): R_f 0.56 (methanol: dichloromethane = 1:9); mp 156-160 ℃; HPLC: R_T 4.850 min (purity 95.82%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.96 (s, 3H), 5.09 (s, 2H), 7.07 (ddd, J = 7.6, 2.0, 1.2 Hz, 1H), 7.38 (dd, J = 8.0, 8.0 Hz, 1H), 7.39 (br s, 1H), 7.48 (dd, J = 8.0, 7.6 Hz, 1H), 7.49 (d, J = 2.4 Hz, 1H), 7.63 (d, J = 2.0 Hz, 1H), 7.65 (d, J = 15.6 Hz, 1H), 7.67 (dd, J = 7.6, 1.6 Hz, 1H), 7.79 (d, J = 1.6 Hz, 1H), 7.85 (ddd, J = 7.6, 1.6, 1.2 Hz, 1H), 7.89 (d, J = 15.6 Hz, 1H), 8.00 (br s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.5, 73.9, 112.6, 114.7, 117.4, 119.7, 120.3, 122.8, 125.1, 127.1, 127.6, 128.2, 129.8, 131.1, 132.4, 134.3, 136.9, 138.9, 142.3, 145.9, 153.6, 157.7, 167.7, 188.9 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{24}H_{20}BrNO_5$ calcd 482.0598, found 482.06.

(*E*)-3-((4-(3-(3-Hydroxyphenyl)-3-oxoprop-1-en-1-yl)-2-iodo-6-methoxyphenoxy) methyl)benzamide (A9)

Compound **6** (200 mg, 0.49 mmol) and 1-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)ethan-1-one (107 mg, 0.49 mmol) were used and purified by silica gel column chromatography (eluent:

methanol: dichloromethane = 1:20) to give **A9** as a yellow solid (136 mg, 52.9%): R_f 0.53 (methanol: dichloromethane = 1:9); mp 186-190 ℃; HPLC: R_T 3.232 min (purity 97.54%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.87 (s, 3H), 5.02 (s, 2H), 7.00 (ddd, J = 7.6, 2.0, 1.2 Hz, 1H), 7.13 (d, J = 1.6 Hz, 1H), 7.22 (dd, J = 8.0, 8.0 Hz, 1H), 7.35-7.41 (m, 4H), 7.53 (d, J = 15.6 Hz, 1H), 7.59 (d, J = 2.0 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.78 (dd, J = 8.0, 1.6 Hz, 1H), 7.99 (dd, J = 1.6, 1.6 Hz, 1H)); ^{13}C-NMR (400 MHz, DMSO-d_6) 56.3, 73.6, 93.7, 113.3, 114.7, 118.7, 120.3, 122.5, 127.1, 127.6, 128.2, 129.8, 131.0, 131.1, 133.2, 134.4, 136.9, 138.9, 142.2, 148.6, 152.4, 157.7, 167.7, 188.9 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{24}H_{20}INO_5$ calcd 530.0459, found 530.0457.

(*E*)-3-(3-Chloro-4-((3-chlorobenzyl)oxy)-5-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl) prop-2-en-1-one (A10)

Compound **1** (100 mg, 0.32 mmol) and 3,4,5-trimethoxyacetophenone (67.4 mg, 0.32 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3) to give **A10** as an off-white solid (30 mg, 18.6%): R_f 0.19 (ethyl acetate: *n*-hexane = 1:3); mp: 93-95 ℃; HPLC: R_T 2.70 min (purity 100%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 3.95 (s, 3H), 3.96 (s, 6H), 5.07 (s, 2H), 7.04 (d, J = 2.0 Hz, 1H), 7.26 (d, J = 2.4 Hz, 2H), 7.30-7.32 (m, 2H), 7.34 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 15.6 Hz, 1H), 7.37-7.39 (m, 1H), 7.55 (dd, J = 0.8, 0.8 Hz, 1H), 7.68 (d, J = 15.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) 56.5, 56.7, 61.2, 74.4, 106.1, 106.5, 111.5, 121.9, 122.4, 126.5, 128.5, 128.6, 129.4, 129.9, 131.9, 133.5, 134.5, 139.0, 143.3, 146.0, 153.4, 154.2, 189.1 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{26}H_{24}Cl_2O_6$ calcd 503.1023, found 503.1024.

(*E*)-3-(3-Bromo-4-((3-chlorobenzyl)oxy)-5-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl) prop-2-en-1-one (A11)

Compound **2** (100 mg, 0.28 mmol) and 3,4,5-trimethoxyacetophenone (59 mg, 0.28 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3) to give **A11** as a yellow solid (55 mg, 35.8%): R_f 0.26 (ethyl acetate: *n*-hexane = 1:3); mp: 94-98 ℃; HPLC: R_T 5.77 min (purity 99.71%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.94 (s, 3H), 3.95 (s, 3H), 3.96 (s, 6H), 5.06 (s, 2H), 7.08 (d, *J* = 2.0 Hz, 1H), 7.26 (d, *J* = 2.4 Hz, 2H), 7.31-7.34 (m, 2H), 7.36 (d, *J* = 15.6 Hz, 1H), 7.41 (ddd, *J* = 8.4, 1.2, 1.2 Hz, 1H), 7.51 (d, *J* = 1.6 Hz, 1H), 7.57 (br s, 1H), 7.68 (d, *J* = 15.6 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.3, 56.5, 60.2, 73.2, 106.4, 113.4, 117.4, 122.6, 124.6, 126.7, 127.9, 128.0, 130.2, 132.4, 132.9, 139.3, 142.1, 142.3, 145.7, 152.9, 153.4, 187.9 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{26}H_{24}BrClO_6$ calcd 547.0518, found 547.0515.

(*E*)-3-(4-((3-Chlorobenzyl)oxy)-3-iodo-5-methoxyphenyl)-1-(3,4,5-trimethoxyphenyl) prop-2-en-1-one (A12)

Compound **3** (100 mg, 0.25 mmol) and 3,4,5-trimethoxyacetophenone (52 mg, 0.25 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3) to give **A12** as a weak yellow solid (57 mg, 38.7%): R_f 0.23 (ethyl acetate: *n*-hexane = 1:3); mp: 96-110 ℃; HPLC: R_T 6.152 min (purity 99.61%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 3.95 (s, 3H), 3.96 (s, 6H), 5.05 (s, 2H), 7.12 (d, *J* = 2.0 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 2H), 7.32-7.34 (m, 2H), 7.35 (d, *J* = 15.6 Hz, 1H), 7.44 (ddd, *J* = 7.2, 1.6, 1.2 Hz, 1H), 7.59 (dd, *J* = 1.2, 1.2 Hz, 1H), 7.67 (d, *J* = 15.6 Hz, 1H), 7.71 (d, *J* = 2.0 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.3, 56.4, 60.2, 72.9, 93.6, 106.4, 114.0, 122.4, 126.7, 127.9, 130.2, 130.6, 132.8, 132.9, 133.2, 139.3, 142.1, 142.2, 148.4, 152.3, 152.9, 187.9 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{26}H_{24}ClIO_6$ calcd 595.0379, found 595.0377.

(*E*)-3-((2-Chloro-6-methoxy-4-(3-oxo-3-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl)phenoxy)

methyl)benzamide (A13)

Compound **4** (170 mg, 0.53 mmol) and 3,4,5-trimethoxyacetophenone (112 mg, 0.53 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: *n*-hexane = 2:1) to give **A13** as a weak yellow solid (140 mg, 51.3%): R_f 0.13 (ethyl acetate: *n*-hexane = 2:1); mp: 170-174 ℃; HPLC: R_T 4.95 min (purity 96.24%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.84 (s, 3H), 3.87 (s, 3H), 3.88 (s, 6H), 5.05 (s, 2H), 7.06 (d, *J* = 1.6 Hz, 1H), 7.22 (s, 2H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.39 (d, *J* = 15.6 Hz, 1H), 7.58 (d, *J* = 15.6 Hz, 1H), 7.60 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.77 (ddd, *J* = 7.6, 1.6, 1.2 Hz, 1H), 7.95 (dd, *J* = 1.6, 1.2 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.0, 56.1, 60.5, 74.1, 105.9, 110.9, 121.5, 122.0, 127.1, 127.4, 128.1, 128.5, 131.2, 131.3, 133.0, 133.6, 136.8, 142.2, 142.6, 145.3, 152.8, 153.7, 168.8, 188.4 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{27}H_{26}ClNO_7$ calcd 512.1471, found 512.1472.

(*E*)-3-((2-Bromo-6-methoxy-4-(3-oxo-3-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl)phenoxy) methyl)benzamide (A14)

Compound **5** (100 mg, 0.27 mmol) and 3,4,5-trimethoxyacetophenone (58 mg, 0.27 mmol) were used to give **A14** as a weak yellow solid (100 mg, 65.4%): R_f 0.13 (ethyl acetate: *n*-hexane = 2:1); mp: 156-160 ℃; HPLC: R_T 5.26 min (purity 97.00%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.88 (s, 9H), 5.04 (s, 2H), 7.11 (d, *J* = 1.6 Hz, 1H), 7.22 (s, 2H), 7.29 (d, *J* = 2.0 Hz, 1H), 7.38 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.40 (d, *J* = 15.6 Hz, 1H), 7.44 (d, *J* =1.6 Hz, 1H), 7.58 (d, *J* = 15.6 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.78 (ddd, *J* = 7.6, 1.6, 1.2 Hz, 1H), 7.97 (dd, *J* = 1.6, 1.2 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 55.7, 55.9, 60.3, 73.8, 105.7, 111.3, 117.7, 121.8, 124.2, 126.8, 127.2, 127.8, 131.0, 131.7, 132.7, 133.4, 136.6, 141.9, 142.2, 146.1, 152.5, 153.3, 168.6, 188.1 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{27}H_{26}BrNO_7$ calcd 556.0965, found 556.0965.

(*E*)-3-((2-Iodo-6-methoxy-4-(3-oxo-3-(3,4,5-trimethoxyphenyl)prop-1-en-1-yl)phenoxy) methyl)benzamide (A15)

Compound **6** (100 mg, 0.24 mmol) and 3,4,5-trimethoxyacetophenone (51 mg, 0.24 mmol) were used to give **A15** as a weak yellow solid (75 mg, 51.2%): R_f 0.13 (ethyl acetate: *n*-hexane = 2:1); mp: 198-202 ℃; HPLC: R_T 5.76 min (purity 96.51%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 3.87 (s, 3H), 3.88 (s, 6H), 5.03 (s, 2H), 7.14 (d, *J* = 1.6 Hz, 1H), 7.21 (s, 2H), 7.38 (d, *J* = 15.2 Hz, 1H), 7.39 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.57 (d, *J* = 15.6 Hz, 1H), 7.63 (d, *J* = 1.6 Hz, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.78 (ddd, *J* = 8.0, 1.6, 1.2 Hz, 1H), 7.99 (dd, *J* = 1.6, 1.2 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 55.6, 55.9, 60.3, 73.6, 92.6, 105.7, 112.3, 121.7, 126.8, 127.3, 127.8, 130.2, 131.1, 132.6, 132.7, 133.5, 136.5, 141.9, 142.1, 148.6, 152.1, 152.5, 168.5, 188.1 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{27}H_{26}INO_7$ calcd 604.0827, found 604.0825.

(*E*)-3-(3-Chloro-4-((3-chlorobenzyl)oxy)-5-methoxyphenyl)-1-(3-hydroxyphenyl)prop-2-en-1-one (A16)

Compound **1** (100 mg, 0.32 mmol) and 1-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)ethan-1-one (70.1 mg, 0.32 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3) to give **A16** as an ivory solid (26 mg, 18.9%):. R_f 0.13 (ethyl acetate: *n*-hexane = 1:3); mp: 135-137 ℃; HPLC: R_T 6.80 min (purity 97.0%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.88 (s, 3H), 4.98 (s, 2H), 7.00 (ddd, *J* = 8.0, 1.6, 0.8 Hz, 1H), 7.06 (d, *J* = 2.0 Hz, 1H), 7.22-7.26 (m, 4H),7.30 (ddd, *J* = 8.0, 2.0, 1.6 Hz, 1H), 7.37-7.41 (m, 2H), 7.39 (d, *J* = 15.6 Hz, 1H), 7.46 (d, *J* = 2.4 Hz, 1H), 7.54 (d, *J* = 15.6 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.5, 73.3, 112.0, 114.7, 119.7, 120.4, 122.3, 122.8, 126.7, 127.5, 127.8, 128.0, 129.8, 130.2, 131.8, 132.9, 138.9, 139.3, 142.3, 144.8, 153.7, 157.7, 189.0 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{23}H_{18}Cl_2O_4$ calcd 429.0655, found 429.0655.

(*E*)-3-(3-Bromo-4-((3-chlorobenzyl)oxy)-5-methoxyphenyl)-1-(3-hydroxyphenyl)prop-2-en-1-one (A17)

Compound **2** (100 mg, 0.28 mmol) and 1-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)ethan-1-one (62 mg, 0.28 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3) to give **A17** as a yellow solid (62 mg, 46.5%): R_f 0.14 (ethyl acetate: *n*-hexane = 1:3); mp: 152-156 ℃; HPLC: R_T 3.515 min (purity 98.44%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.95 (s, 3H), 5.07 (s, 2H), 7.07 (dd, *J* = 8.0, 2.4 Hz, 1H), 7.38 (dd, *J* = 8.0, 7.6 Hz, 1H), 7.41-7.49 (m, 4H), 7.57 (br s, 1H), 7.62 (d, *J* = 2.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.65 (d, *J* = 16.0 Hz, 1H), 7.79 (dd, *J* = 2.0, 1.6 Hz, 1H), 7.90 (d, *J* = 15.6 Hz, 1H), 9.81 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.5, 73.2, 112.6, 114.7, 117.3, 119.7, 120.3, 122.8, 125.1, 126.7, 127.9, 128.0, 129.8, 130.2, 132.4, 132.9, 138.9, 139.3, 142.2, 145.8, 153.5, 157.7, 188.9 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{23}H_{18}BrClO_4$ calcd 473.015, found 473.0149.

(*E*)-3-(4-((3-Chlorobenzyl)oxy)-3-iodo-5-methoxyphenyl)-1-(3-hydroxyphenyl)prop-2-en-1-one (A18)

Compound **3** (100 mg, 0.25 mmol) and 1-(3-((tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)ethan-1-one (55 mg, 0.25 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3) to give **A18** as a yellow solid (57 mg, 43.8%): R_f 0.15 (ethyl acetate: *n*-hexane = 1:3); mp: 154-154 ℃; HPLC: R_T 3.854 min (purity 98.36%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3H), 4.94 (s, 2H), 7.00 (ddd, *J* = 8.0, 2.0, 1.2 Hz, 1H), 7.05 (d, *J* = 1.6 Hz, 1H), 7.22-7.26 (m, 3H), 7.31 (d, *J* = 15.6 Hz, 1H), 7.33-7.36 (m, 1H), 7.38-7.41 (m, 2H), 7.50 (br s, 1H), 7.53 (d, *J* = 16.0 Hz, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 9.02 (s, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.3, 72.9, 93.6, 113.3, 114.7, 119.7, 120.3, 122.6, 126.7, 127.9, 128.0, 129.8, 130.2, 131.0, 132.9, 133.2, 138.9, 139.3, 142.2, 148.4, 152.3, 157.7, 188.9 ppm; HRMS-ESI

(m/z) $[M+H]^+$ $C_{23}H_{18}ClIO_4$ calcd 521.0011, found 521.0008.

(*E*)-1-(3-Aminophenyl)-3-(3-chloro-4-((3-chlorobenzyl)oxy)-5-methoxyphenyl)prop-2-en-1-one (A19)

Compound **1** (230 mg, 0.74 mmol) and 3-aminoacetophenone (100 mg, 0.74 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3) to give **A19** as an orange solid (60 mg, 18.9%): R_f 0.06 (ethyl acetate: *n*-hexane = 1:3); mp: 105-107 ℃; HPLC: R_T 3.57 min (purity 98.1%); ^{1}H-NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ 3.72 (s, 3H), 4.82 (s, 2H), 5.36 (s, 2H), 6.91 (d, *J* = 2.0 Hz, 1H), 6.91-6.93 (m, 1H), 7.07-7.14 (m, 5H), 7.22 (d, *J* = 15.6 Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.30 (br s, 1H), 7.33 (dd, J = 1.6, 1.6 Hz, 1H), 7.39 (d, *J* = 15.6 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$+DMSO-d_6) 55.7, 73.4, 110.2, 116.3, 120.3, 121.2, 121.5, 122.1, 125.7, 127.6, 127.7, 128.2, 129.0, 129.1, 131.1, 133.4, 138.3, 139.3, 144.7, 149.1, 149.2, 153.7, 189.5 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{23}H_{19}Cl_2NO_3$ calcd 428.0815, found 428.0815.

(*E*)-1-(3-Aminophenyl)-3-(3-bromo-4-((3-chlorobenzyl)oxy)-5-methoxyphenyl)prop-2-en-1-one (A20)

Compound **2** (100 mg, 0.28 mmol) and 3-aminoacetophenone (38 mg, 0.28 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3) to give **A20** as an orange solid (57 mg, 42.9%). R_f 0.07 (ethyl acetate: *n*-hexane = 1:3); mp: 114-118 ℃; HPLC: R_T 7.183 min (purity 97.59%); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 5.05 (s, 2H), 6.91 (ddd, *J* = 8.0, 1.6, 0.8 Hz, 1H), 7.08 (d, *J* = 1,6 Hz, 1H), 7.29 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.31-7.33 (m, 3H), 7.38 (d, *J* = 15.6 Hz, 1H), 7.37 (dd, *J* = 1.6, 1.2 Hz, 1H), 7.40-7.42 (m, 1H), 7.47 (d, *J* = 1,6 Hz, 1H), 7.57 (br s, 1H), 7.65 (d, *J* = 16.0 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.5, 73.2, 112.5, 112.9, 116.6, 117.3, 118.7, 123.1, 124.9, 126.7, 127.9, 128.0,

129.1, 130.2, 132.5, 132.9, 138.3, 139.3, 141.7, 145.7, 149.1, 153.5, 189.5 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{23}H_{19}BrClNO_3$ calcd 472.031, found 472.0312.

(*E*)-1-(3-Aminophenyl)-3-(4-((3-chlorobenzyl)oxy)-3-iodo-5-methoxyphenyl)prop-2-en-1-one (A21)

Compound **3** (200 mg, 0.50 mmol) and 3-aminoacetophenone (67 mg, 0.50 mmol) were used and purified by silica gel column chromatography (eluent: ethyl acetate: *n*-hexane = 1:3) to give **A21** as a yellow solid (64 mg, 42.9%): R_f 0.08 (ethyl acetate: *n*-hexane = 1:3); mp: 90-94 ℃; HPLC: R_T 4.245 min (purity 99.61%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.93 (s, 3H), 5.03 (s, 2H), 5.34 (s, 2H), 6.85 (ddd, J = 8.0, 2.8, 0.8, 1H), 7.21 (dd, J = 8.0, 7.6 Hz, 1H), 7.26 (dd, J = 2.0, 2.0 Hz, 1H), 7.37 (ddd, J = 7.6, 1.6, 1.2 Hz, 1H), 7.42-7.46 (m, 2H), 7.48 (ddd, J = 7.6, 1.6, 1.2 Hz, 1H), 7.58-7.62 (m, 3H), 7.80 (d, J = 16.0 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.3, 72.9, 93.6, 112.9, 113.3, 116.5, 118.7, 122.9, 126.7, 127.8, 127.9, 129.1, 130.2, 130.7, 132.9, 133.3, 138.3, 139.3, 141.6, 148.3, 149.1, 152.3, 189.4 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{23}H_{19}ClINO_3$ calcd 520.0171, found 520.0171.

(*E*)-3-(3-(3-Chloro-4-((3-chlorobenzyl)oxy)-5-methoxyphenyl)acryloyl)benzamide (A22)

Compound **1** (100 mg, 0.32 mmol) and 3-carbamoylacetophenone (52 mg, 0.32 mmol) were used and purified by silica gel column chromatography (eluent: methanol: dichloromethane = 1:10) to give **A22** as a weak yellow solid (41 mg, 28.2%): R_f 0.72 (methanol: dichloromethane = 1:9); mp: 170-174 ℃; HPLC: R_T 5.842 min (purity 95.46%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.95 (s, 3H), 5.10 (s, 2H), 7.41-7.46 (m, 3H), 7.56 (br s, 2H), 7.61 (d, J = 1.6 Hz, 1H), 7.67 (dd, J = 8.0, 7.6 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.73 (d, J = 15.6 Hz, 1H), 7.99 (d, J = 15.6 Hz, 1H), 8.15 (ddd, J = 7.6, 1.6, 1.2 Hz, 1H), 8.19 (br s, 1H), 8.31 (ddd, J = 7.6, 1.6, 1.2 Hz, 1H), 8,57 (dd, J = 1.6, 1.6 Hz, 1H); ^{13}C-NMR (400 MHz, DMSO-d_6) 56.5, 73.3, 112.5, 122.1,

122.6, 126.7, 127.3, 127.6, 127.9, 128.0, 128.9, 130.2, 131.2, 131.7, 132.0, 132.9, 134.9, 137.5, 139.3, 142.9, 144.9, 153.6, 167.2, 188.8 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{24}H_{19}Cl_2NO_4$ calcd 456.0764, found 456.0764.

(*E*)-3-(3-(3-Bromo-4-((3-chlorobenzyl)oxy)-5-methoxyphenyl)acryloyl)benzamide (A23)

Compound **2** (100 mg, 0.28 mmol) and 3-carbamoylacetophenone (46 mg, 0.28 mmol) were used and purified by silica gel column chromatography (eluent: methanol: dichloromethane = 1:10) to give **A23** as a weak yellow solid (59 mg, 41.8%): R_f 0.68 (methanol: dichloromethane = 1:9); mp: 154-158 ℃; HPLC: R_T 11.607 min (purity 99.70%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.95 (s, 3H), 5.08 (s, 2H), 7.41-7.43 (m, 2H), 7.45-7.47 (m, 1H), 7.56-7.58 (m, 2H), 7.64 (d, J = 1.6 Hz, 1H), 7.67 (dd, J = 8.0, 7.6 Hz, 1H), 7.73 (d, J =15.6 Hz, 1H), 7.84 (d, J = 1,6 Hz, 1H), 7.98 (d, J = 16.0 Hz, 1H), 8.16 (ddd, J = 7.6, 1.6, 0.8 Hz, 1H), 8.20 (br s, 1H), 8.32 (ddd, J = 7.6, 1.6, 0.8 Hz, 1H), 8.57 (dd, J = 1.6, 1.6 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.5, 73.2, 113.1, 117.4, 122.6, 124.9, 126.7, 127.4, 127.9, 128.0, 128.9, 130.2, 131.2, 132.0, 132.3, 132.9, 134.9, 137.5, 139.3, 142.8, 145.9, 153.5, 167.2, 188.8 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{24}H_{19}BrClNO_4$ calcd 500.0259, found 500.0259.

(*E*)-3-(3-(4-((3-Chlorobenzyl)oxy)-3-iodo-5-methoxyphenyl)acryloyl)benzamide (A24)

Compound **3** (100 mg, 0.25 mmol) and 3-carbamoylacetophenone (41 mg, 0.25 mmol) were used and purified by silica gel column chromatography (eluent: methanol: dichloromethane = 1:10) to give **A24** as a weak yellow solid (51 mg, 37.1%): R_f 0.53 (methanol: dichloromethane = 1:9); mp: 160-164 ℃; HPLC: R_T 6.711 min (purity 95.46%); ^{1}H-NMR (400 MHz, DMSO-d_6) δ 3.94 (s, 3H), 5.05 (s, 2H), 7.42-7.44 (m, 2H), 7.48 (ddd, J = 7.6, 0.8 Hz, 1H), 7.56 (br s, 1H), 7.61 (br s, 1H), 7.64 (d, J = 2.0 Hz, 1H), 7.66 (d, J = 7.6 Hz, 1H), 7.71 (d, J =15.2 Hz, 1H), 7.96 (d, J = 15.2 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 8.15 (ddd, J = 8.0, 1.2, 1.2 Hz, 1H), 8.20

(br s, 1H), 8.32 (ddd, J = 7.6, 1.2, 1.2 Hz, 1H), 8.57 (dd, J = 2.0, 1.6 Hz, 1H); ^{13}C-NMR (100 MHz, DMSO-d_6) 56.3, 72.9, 93.6, 113.8, 122.4, 126.7, 127.3, 127.9, 128.0, 128.8, 130.2, 130.8, 131.2, 132.0, 132.9, 133.1, 134.8, 137.6, 139.3, 142.8, 148.5, 152.3, 167.2, 188.8 ppm; HRMS-ESI (m/z) $[M+H]^+$ $C_{24}H_{19}ClINO_4$ calcd 548.012, found 548.0118.

***In silico* qualitative SAR study**

For the qualitative SAR analysis, all the compounds were imported into Cresset's Forge v10.4.2 software and subjected to field-based alignment to generate conformations and molecular fields for each compound. The molecule with the highest potency throughout the series was then selected as the reference molecule for the alignment. To understand the SAR of the HAT series molecules, the aligned structures were initially compared side-by-side with respect to the reference molecule, HAT-12, to assess the effects of each functional group on the p300 inhibitory activity of the compounds. Qualitative Activity Atlas model was additionally constructed using the recommended default settings[1] to visualize the activity cliff summary of these findings in 3D plots, describing the electrostatic and hydrophobic fields. An additional field-based activity atlas model was built for the 24 new compounds with the same settings we used for the HAT compounds.

***In silico* docking study**

The 3D co-crystal structure of the p300 HAT domain and its bi-substrate inhibitor Lys-CoA was retrieved from PDB ID 3BIY and prepared through Sybyl-X 2.1.1. software (Tripos Associates Inc.). Water was removed, and the hydrogen atoms were added to the original crystal structure. 3D structure files for HAT-12 and **A6** were also generated through Sybyl-X 2.1.1 and minimized energetically using the Tripos force field with Gasteiger-Huckel charges. Docking was carried out with simulations using the Lamarckian Genetic Algorithm. Default search

parameters were used except for a population size of 270,000 and 50 docking runs. The accuracy and reliability of the docking model were validated by evaluating the RMSD value of re-docked Lys-CoA with respect to its original crystallographic orientation.

In vitro HAT assay

HAT assay was performed using the HAT Activity Fluorometric Assay Kit (BioVision, Milpitas, CA, USA) according to the manufacturer's instructions. 100ng of p300, PCAF, or GCN5 recombinant protein (Enzo Life Science, Farmingdale, NJ, USA) was used as an enzyme source and Histone-H3 peptide was used as a substrate. Enzyme reaction was monitored by measuring fluorescence (Ex/Em = 535/587 nm) using a Varioskan Flash 3001 reader (Thermo Fisher Scientific, Finland) in kinetic mode for 60 minutes at 25ºC.

Cell culture, reagents, RNA isolation and quantitative RT-PCR

Mouse lung fibroblast cell line Mlg was purchased from Korean Cell Line Bank (Seoul, Korea). Cells were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% (v/v) fetal bovine serum (FBS), 1% antibiotic/antimycotic solution (Corning, Manassas, VA, USA) at 37°C under 5% CO2. C646 was purchased from Sigma-Aldrich (St. Louis, MO, USA) and TGF-β1 was purchased from ProSpec (East Brunswick, NJ, USA). To knock down EP300 expression, siRNA was used with Lipofectamine RNAiMAX reagent (Thermo Scientific, Carlsbad, CA, USA). Negative control (NC) 5'-CCUCGUGCCGUUCCAUCAGGUAGUU-3' and 5'-CUACCUGAUGGAACGGCACGAGGUU-3'; siEP300#1 5'-CCUGUUUGCCUUUGAAGAAUU-3' and 5'- UUCUUCAAAGGCAAACAGGUU-3'; siEP300#2 5'-GCAAAUGCAGCAAGGAAAUUU-3' and 5'-AUUUCCUUGCUGCAUUUGCUU -3'. Total RNA from cells was prepared using Ribospin

II (GeneAll Biotech, Korea), and cDNA was synthesized using CellScript (CellSafe, Korea), both following to the manufacturer's protocol. The following PCR primer sequences for mouse were used for qRT-PCR: COL1A1 5'-ATGGATTCCCGTTCGAGTACG-3' and 5'-TCAGCTGGATAGCGACATCG-3', COL1A2 5'-TGCAGTAACTTCGTGCCTAGC-3' and 5'- ACGTGGTCCTCTGTCTCCA-3', ACTA2 5'-GTGACTCACAACGTGCCTATC-3' and 5'- CTCGGCAGTAGTCACGAAGG-3', FN 5'-AAGACCATACCTGCCGAATG-3' and 5'-GAACATGACCGATTTGGACC-3', SNAI1 5'-TCTGAAGATGCACATCCGAAGCCA-3' and 5'- AGGAGAATGGCTTCTCACCAGTGT-3', SNAI2 5'-AGATGCACATTCGAACCCAC -3' and 5'- GTCTGCAGATGAGCCCTCAG-3', TUBA1A 5'-GTGCATCTCCATCCATGTTG-3' and 5'- GTGGGTTCCAGGTCTACGAA -3', EP300 5'- CTGTGAACAACATGAGTGCTAGTCC-3' and 5'- TGAGCTGCTGTTGGCAAAGG-3'. The cDNA concentration was normalized using mouse TUBA1A. Quantitative RT-PCR analysis was performed using SYBR Green PCR master mix reagents and an ABI Prism 7700 sequence detection system (Applied Biosystems, Carlsbad, CA, USA).

Western blotting

A6, C646, or TSA (Trichostatin A, Sigma-Aldrich) treated cells were lysed in lysis buffer (20 mM Tris-Cl, 150 mM NaCl, 1% Triton X-100, 1.5% MgCl2, 1 mM ethylenediaminetetraacetate, 1 mM Na2VO4, 1 mM phenylmethylsulfonyl fluoride, and protease inhibitor cocktail at pH 7.5. Equal amounts of protein extracts were subjected to electrophoresis on sodium dodecyl sulfate-polyacrylamide gels and transferred to nitrocellulose transfer membranes (Whatman, Dassel, Germany). The membranes were blocked in Tris-buffer (pH 7.4) containing 0.1% (v/v) Tween 20 (Sigma-Aldrich) and 5% (w/v) nonfat Difco skim milk (BD Biosciences, San Jose, CA, USA), then probed with primary antibodies including

anti-Histone H3, anti-acetyl-Histone H3 (Lys9) (Cell Signaling, Danvers, MA, USA), and anti-□-actin (Sigma–Aldrich). To visualize bound antibodies, membranes were incubated with appropriate secondary anti-rabbit or anti-mouse horseradish peroxidase-conjugated antibody (Thermo Scientific, Rockford, IL, USA) for 1 hour, and then detected using the Fusion solo S (Vilber Lourmat, Collegien, France) with an enhanced chemiluminescence detection reagent (Thermo Fisher Scientific).

MTT assay

The cytotoxicity of A6 was measured with the MTT assay. Mlg mouse fibroblast cells were seeded in the 24 well plate. Next day, A6 was added and incubated for 24 h. 15 μM concentration of MTT solution (Sigma-Aldrich) was added to cells and incubated for 90 minutes at 37°C, and then media was removed, formation of formazan was dissolved in DMSO for 30 minutes with shaking at room temperature. The absorbance was measured at 570 nm using a microplate reader.

Animal studies

All animal experiments were approved by the Institutional Animal Care and Use Committee of the Yonsei University College of Medicine (IACUC no. 2018-0087). 8-week-old male mice were injected with saline (vehicle control) or 4 mg/kg bleomycin (Santa Cruz Biotechnology, Santa Cruz, CA, USA) intratracheally. Mice were sacrificed 10 days after receiving bleomycin, and lung tissues were harvested. TGF-β_1 transgenic mice (*Ccsp-rtTA-tTS-TGF-β_1*) and littermate controls were randomized to normal water or water containing 0.5 mg/ml of doxycycline (Sigma-Aldrich) for 28 days, as described previously.[2] To test the effect of **A6** in

bleomycin-induced fibrosis, the mice were treated with **A6** (0.15 mg/kg or 0.5 mg/kg) or C646 (0.15 mg/kg) through daily intraperitoneal injection beginning the day after bleomycin treatment. The mice were then sacrificed on day 9 after bleomycin or saline treatment, and the BALF and lung tissues were harvested.

Soluble collagen assay

The collagen content in the mouse lungs was assessed using a Sircol Collagen Assay Kit (Biocolor, Carrickfergus, UK) according to the manufacturer's instructions.

ELISA analysis

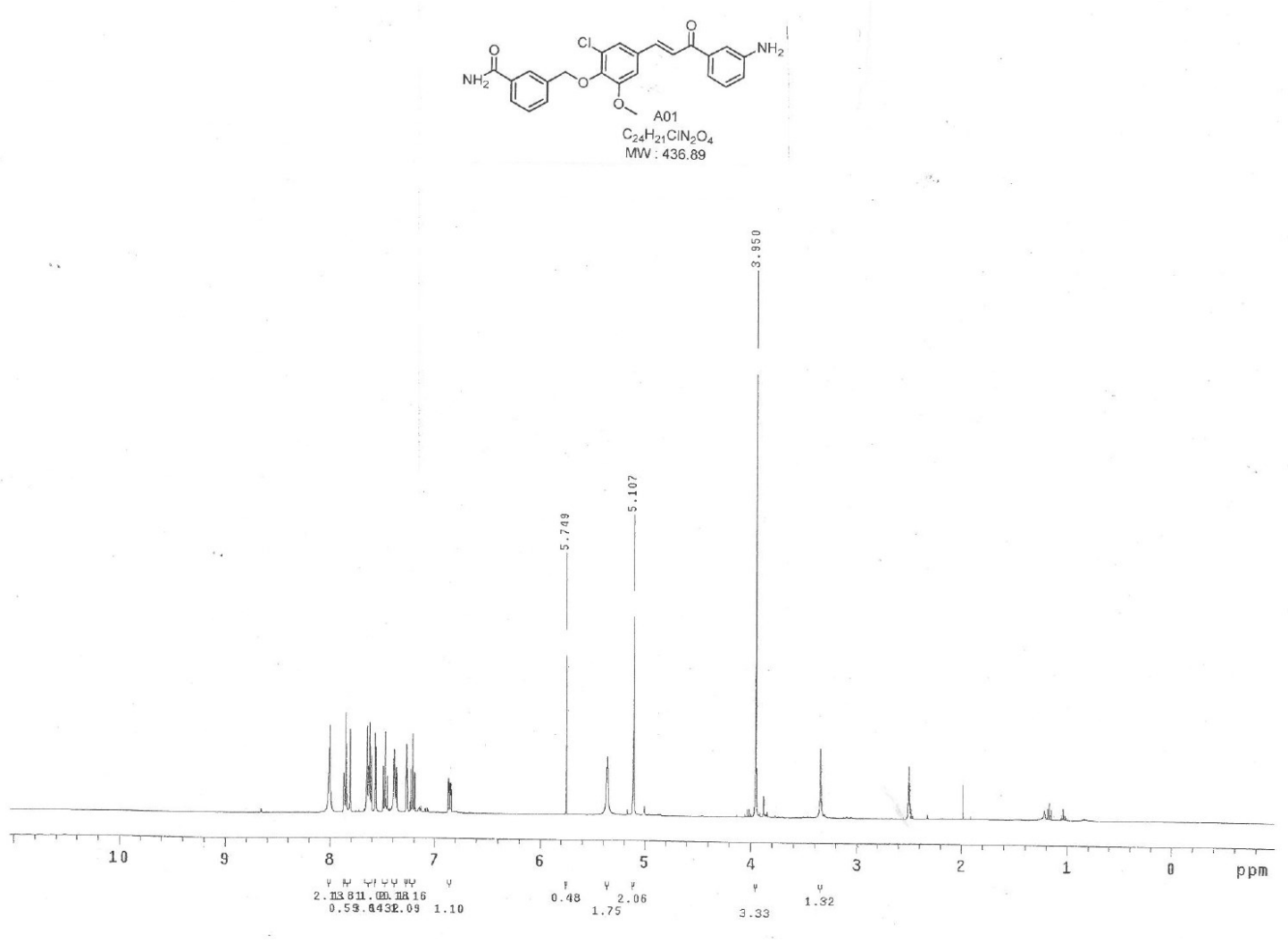
The concentrations of activated TGF-β1 (*R&D Systems*, MN, *USA*) in BALF were detected using ELISA kits according to the manufacturer's protocols.

Immunohistochemistry (IHC) and Masson's trichrome staining (MTS)

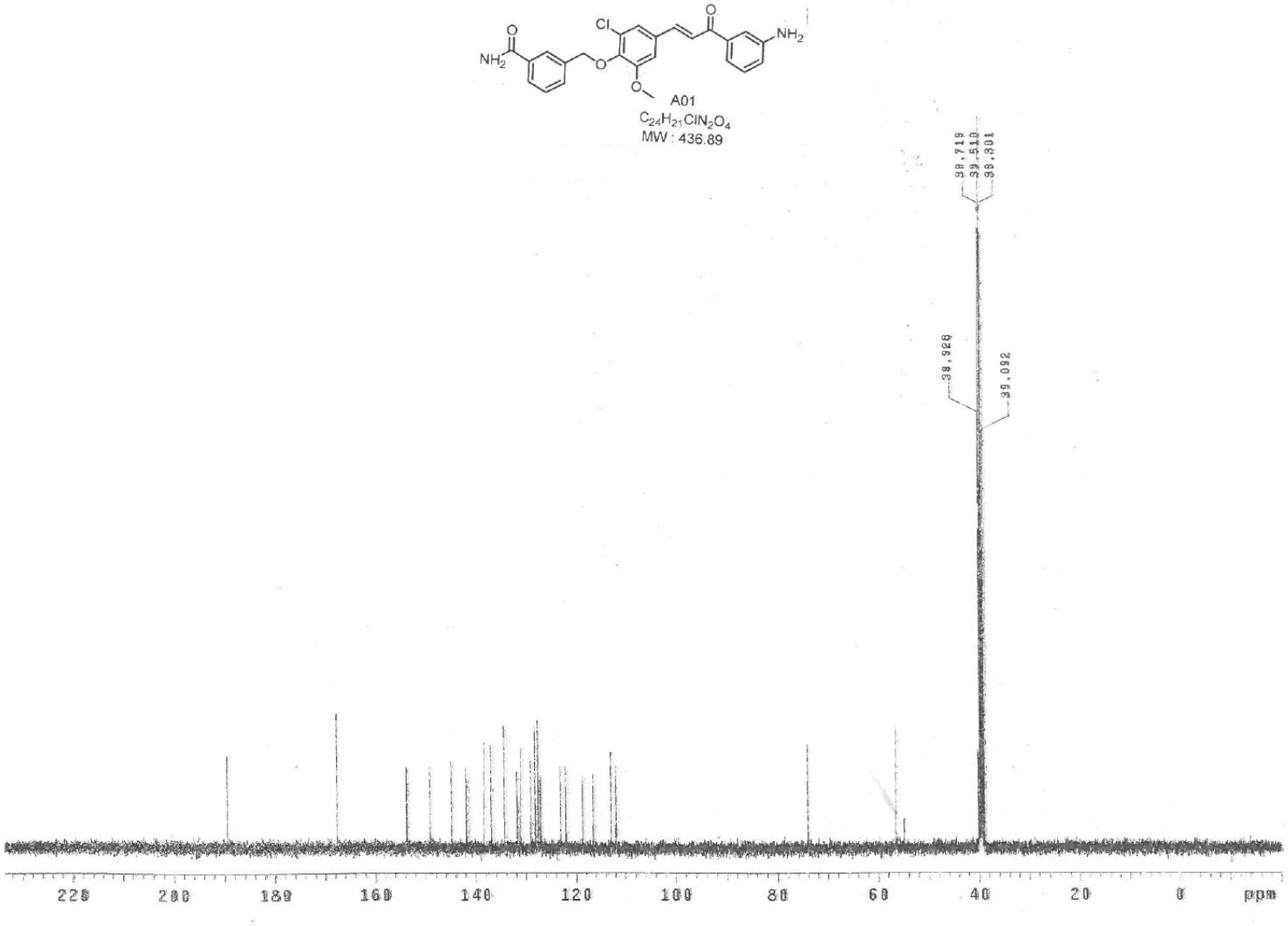
Mouse lung tissues from each group were fixed in formaldehyde (10% w/v) for 48 hours at room temperature and embedded in paraffin. Tissue sections were processed for IHC and MTS. Immunohistochemical staining was performed as previously described[3]. P300 antibody was purchased from Abcam (Cambridge, MA, USA). To visualize bound antibodies, an Immunostaining-DAKO Envision Plus Kit (DAKO, Santa Cruz, CA, USA) was used. MTS was performed using Weigert's Iron Hematoxylin Set (Sigma-Aldrich) and Masson's Trichrome Staining Kit (Sigma-Aldrich) according to the manufacturer's manual.

^{1}H NMR and ^{13}C NMR Spectra of all the compounds (A1-A24)

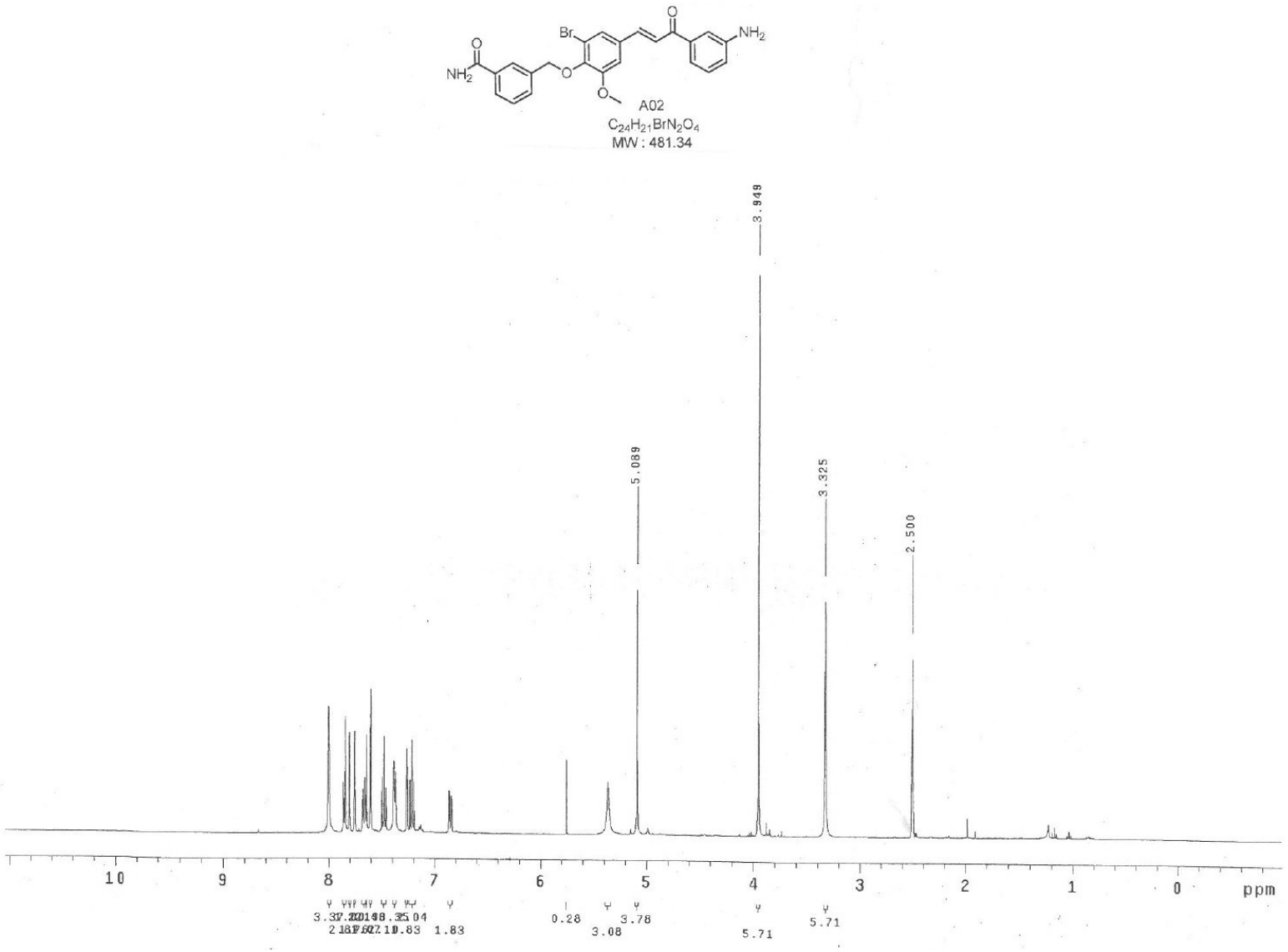
^{1}H NMR spectrum of **A1**



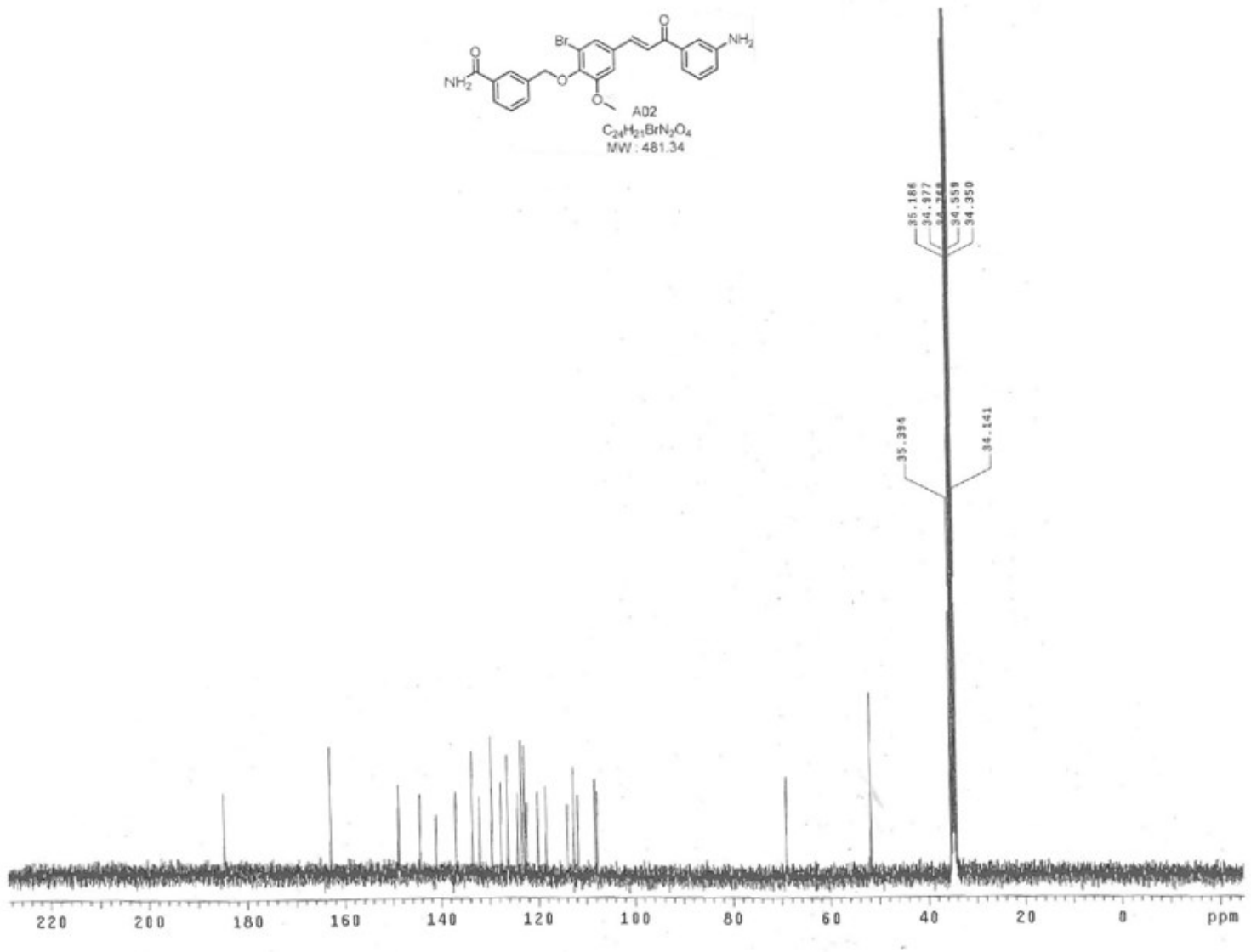
^{13}C NMR spectrum of **A1**



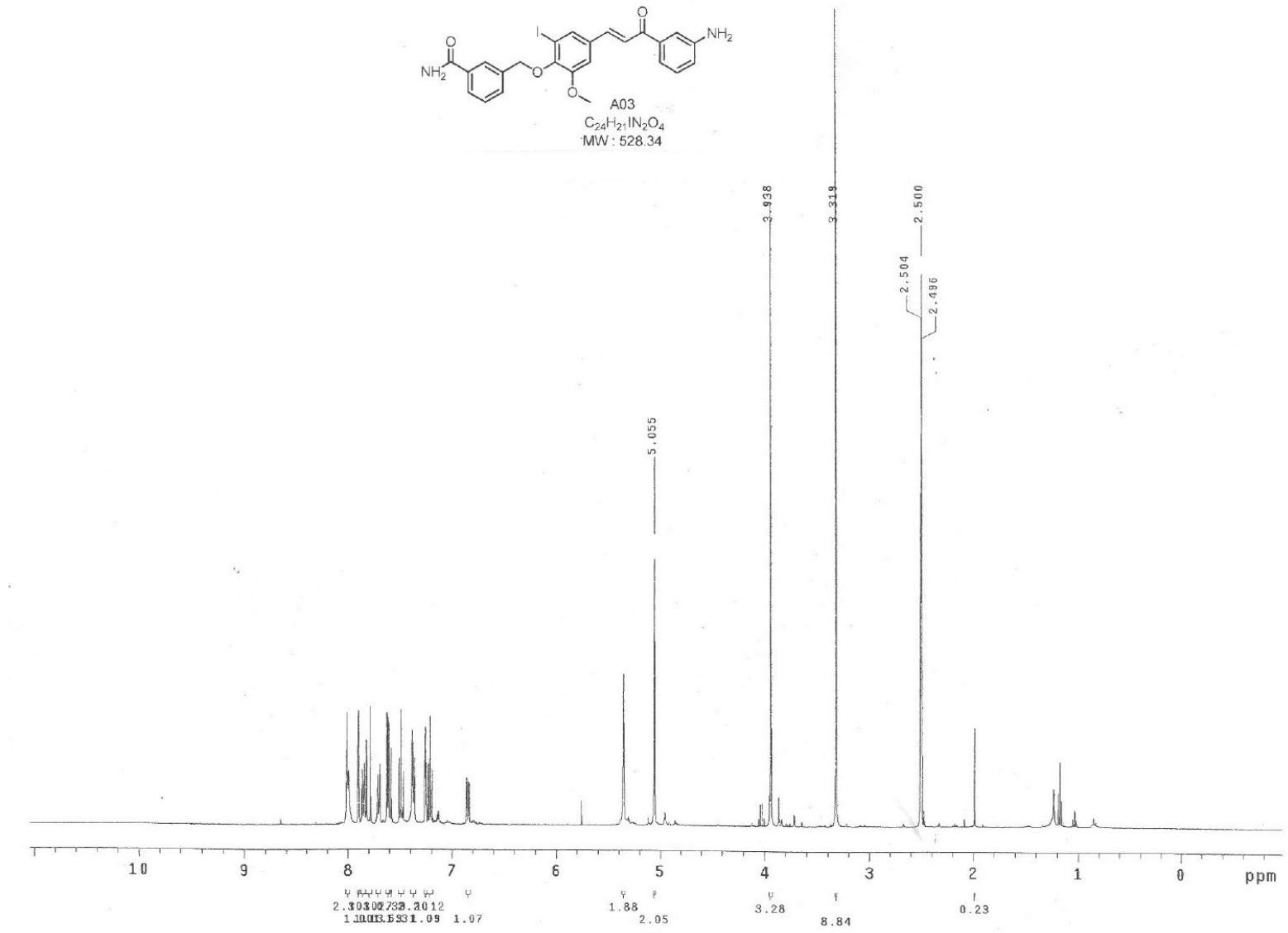
^{1}H NMR spectrum of **A2**



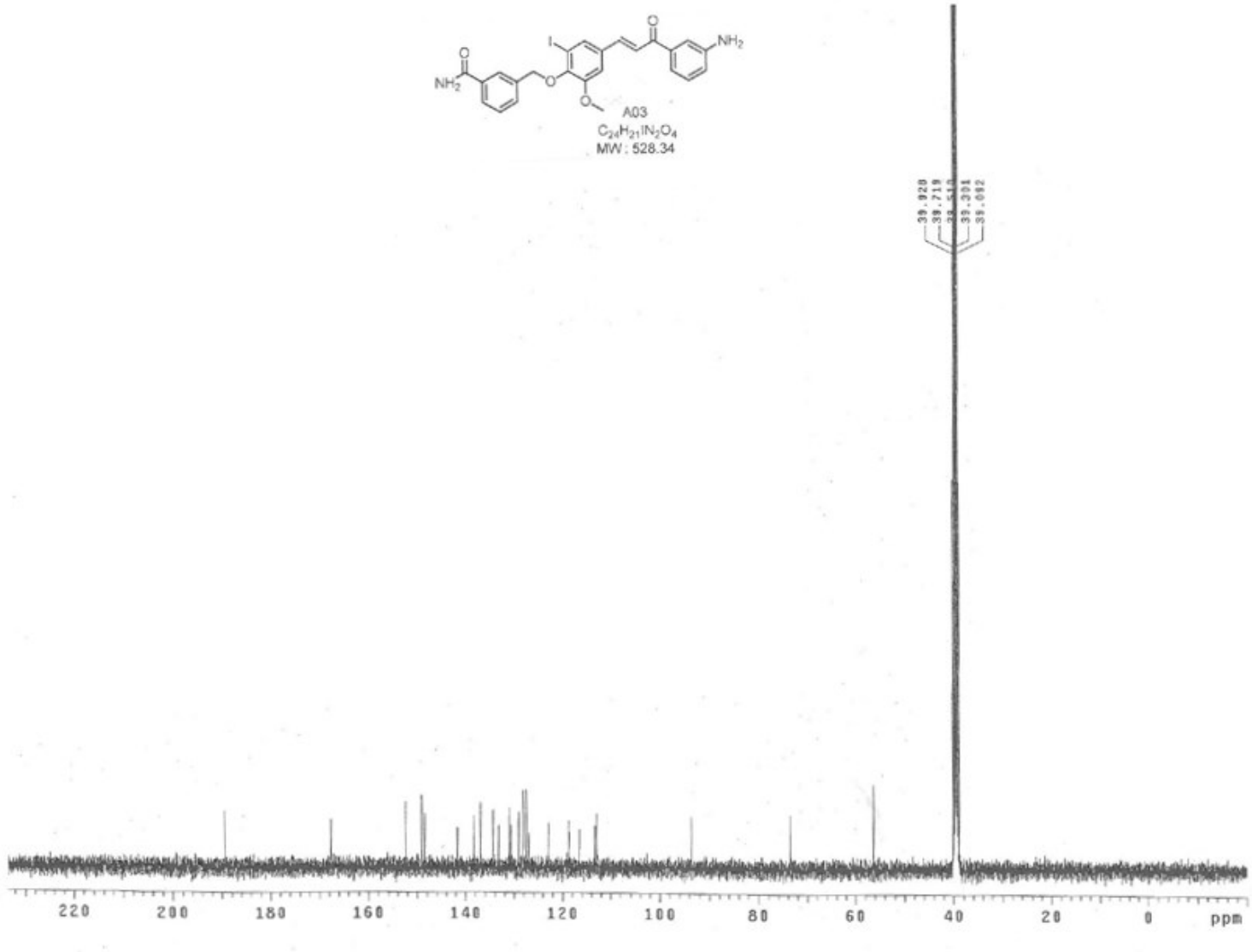
^{13}C NMR spectrum of **A2**



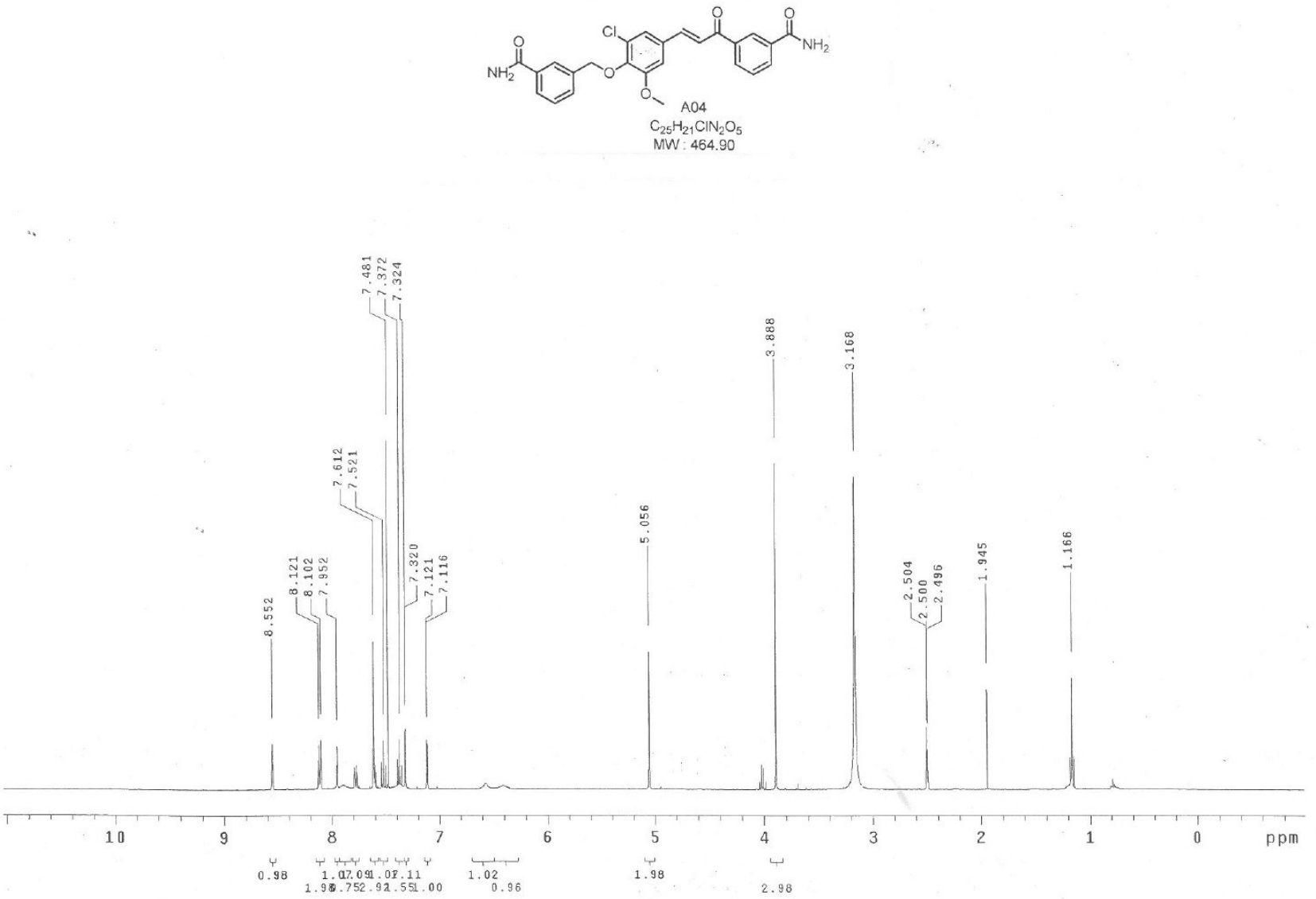
^{1}H NMR spectrum of **A3**



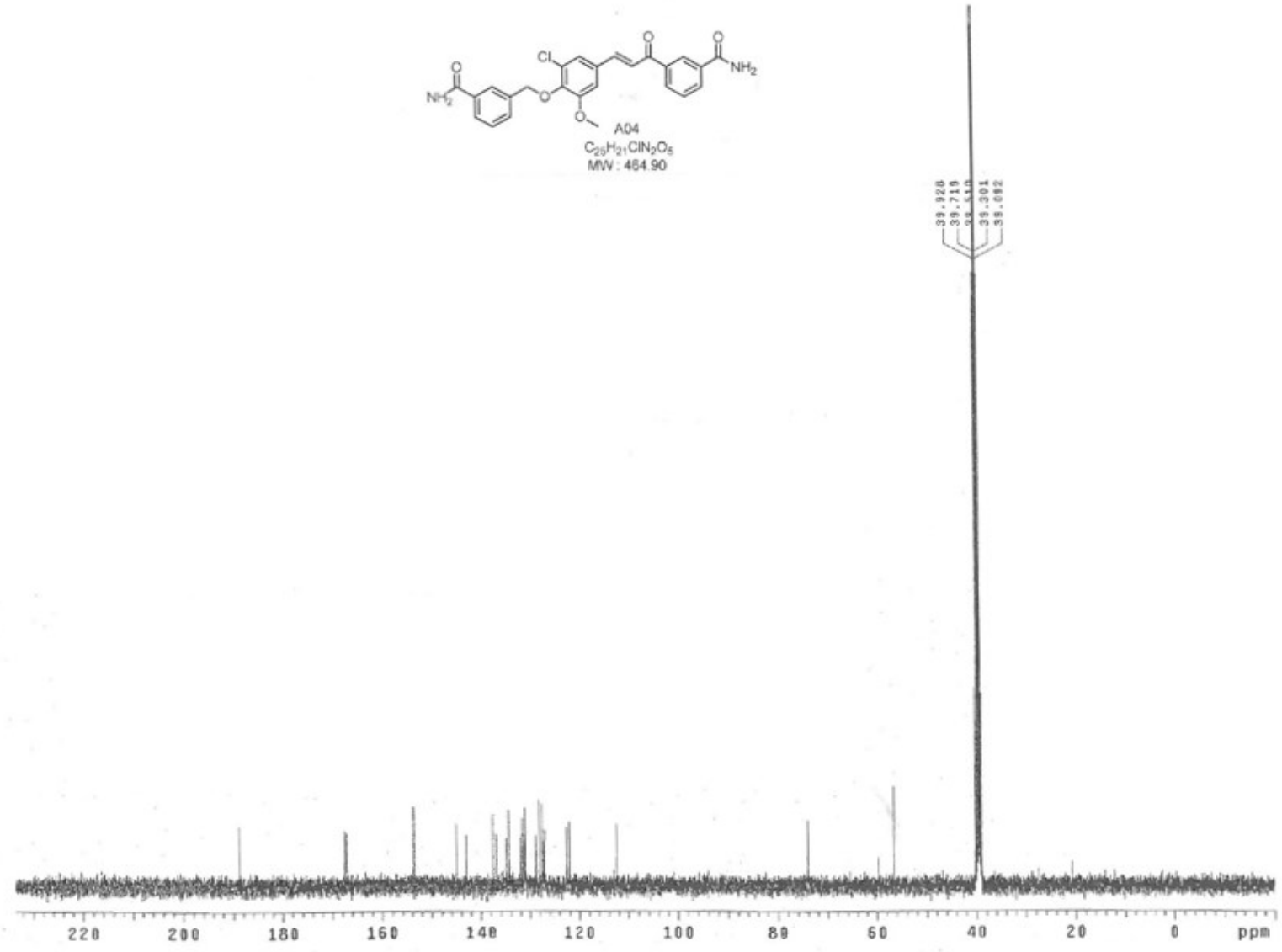
^{13}C NMR spectrum of **A3**



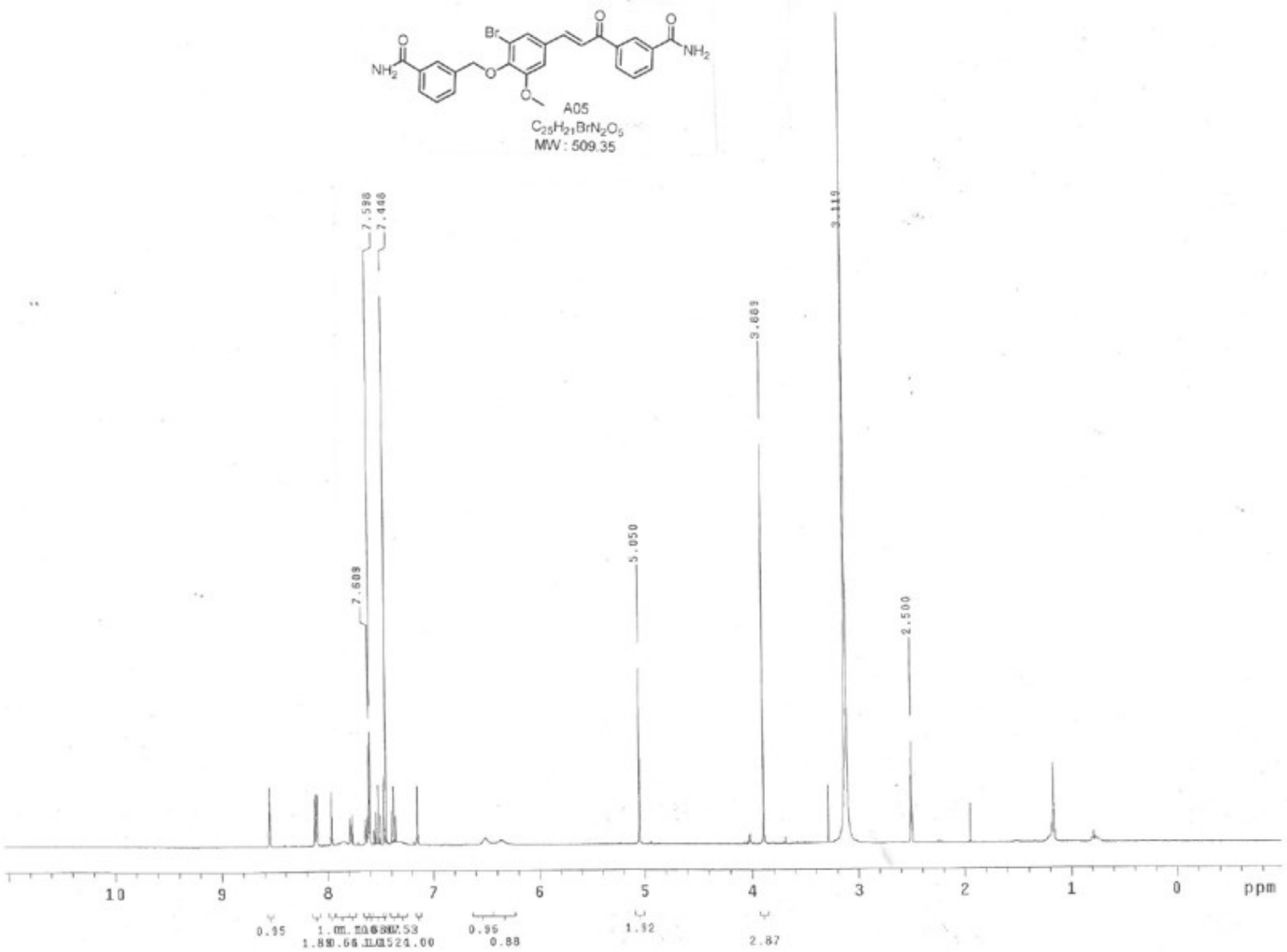
^{1}H NMR spectrum of **A4**



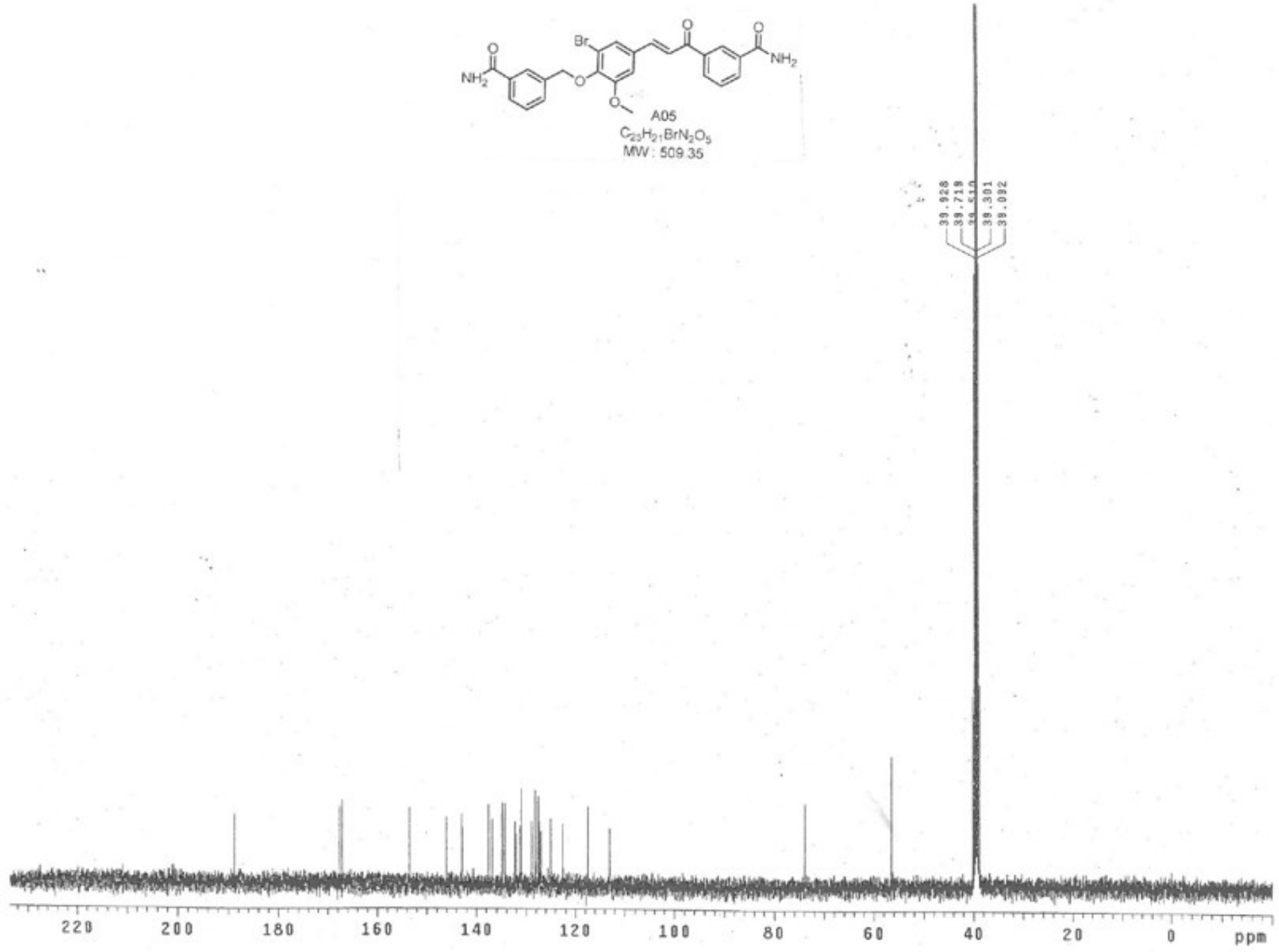
^{13}C NMR spectrum of **A4**



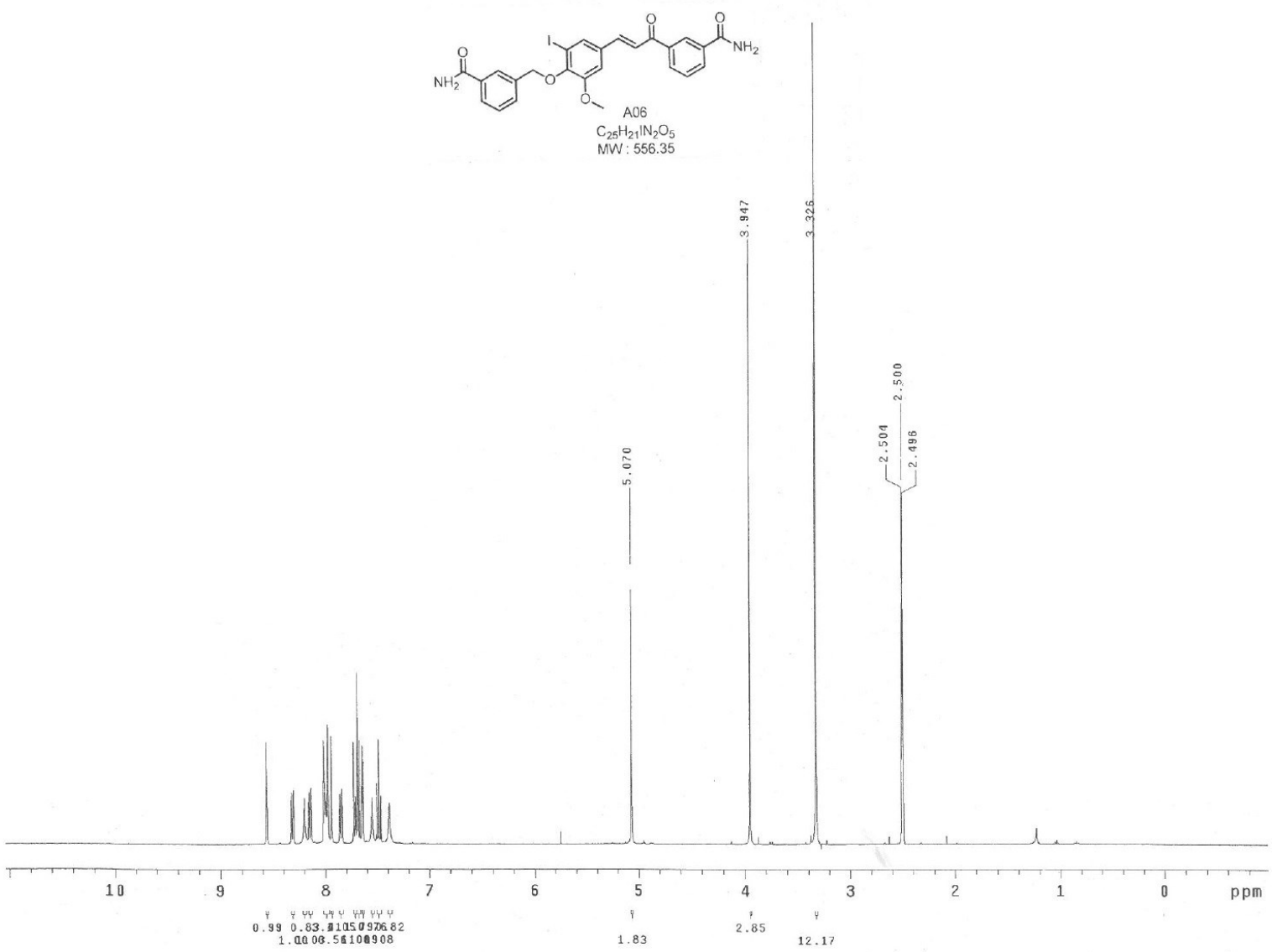
^{1}H NMR spectrum of **A5**



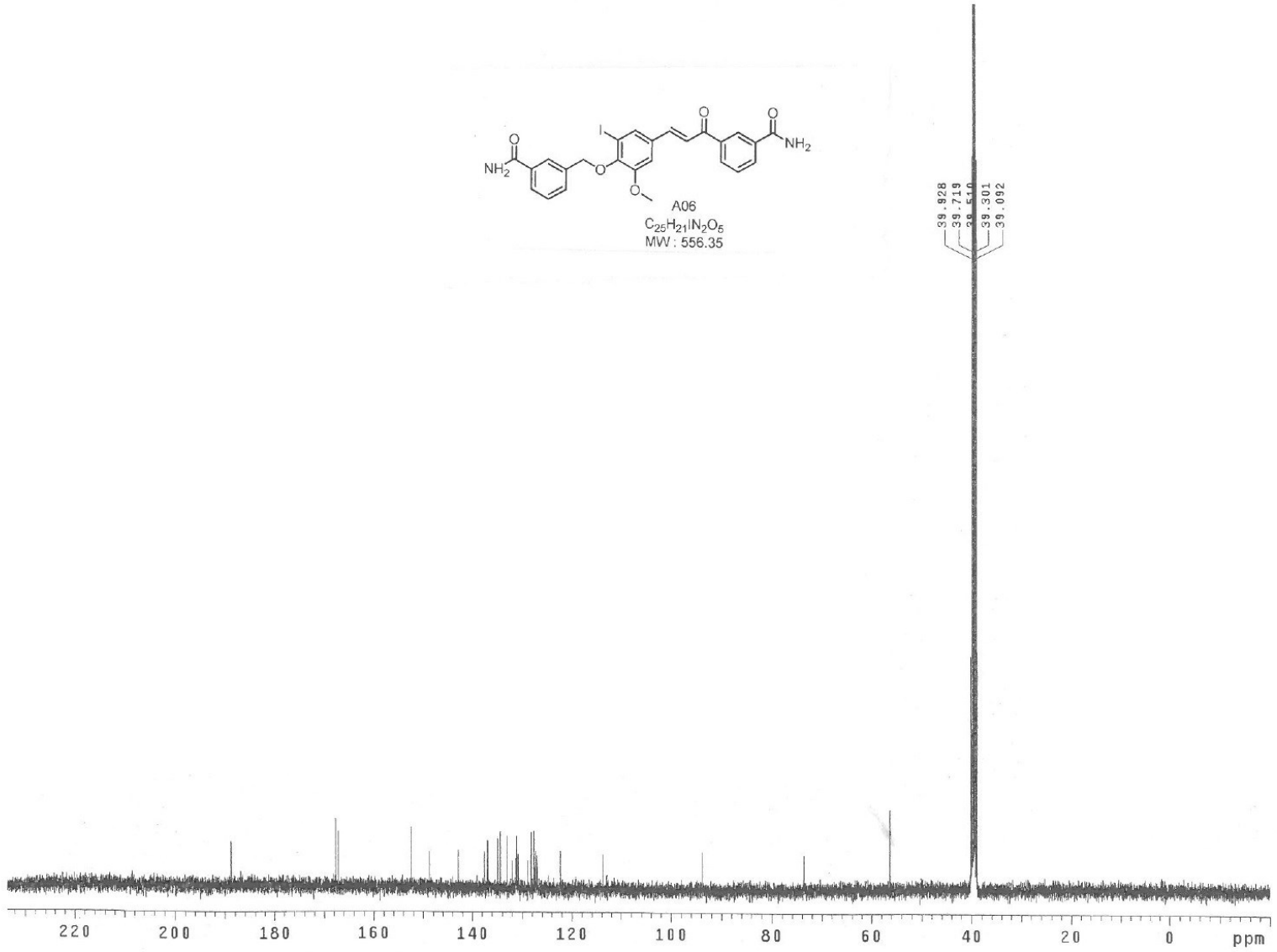
^{13}C NMR spectrum of **A5**



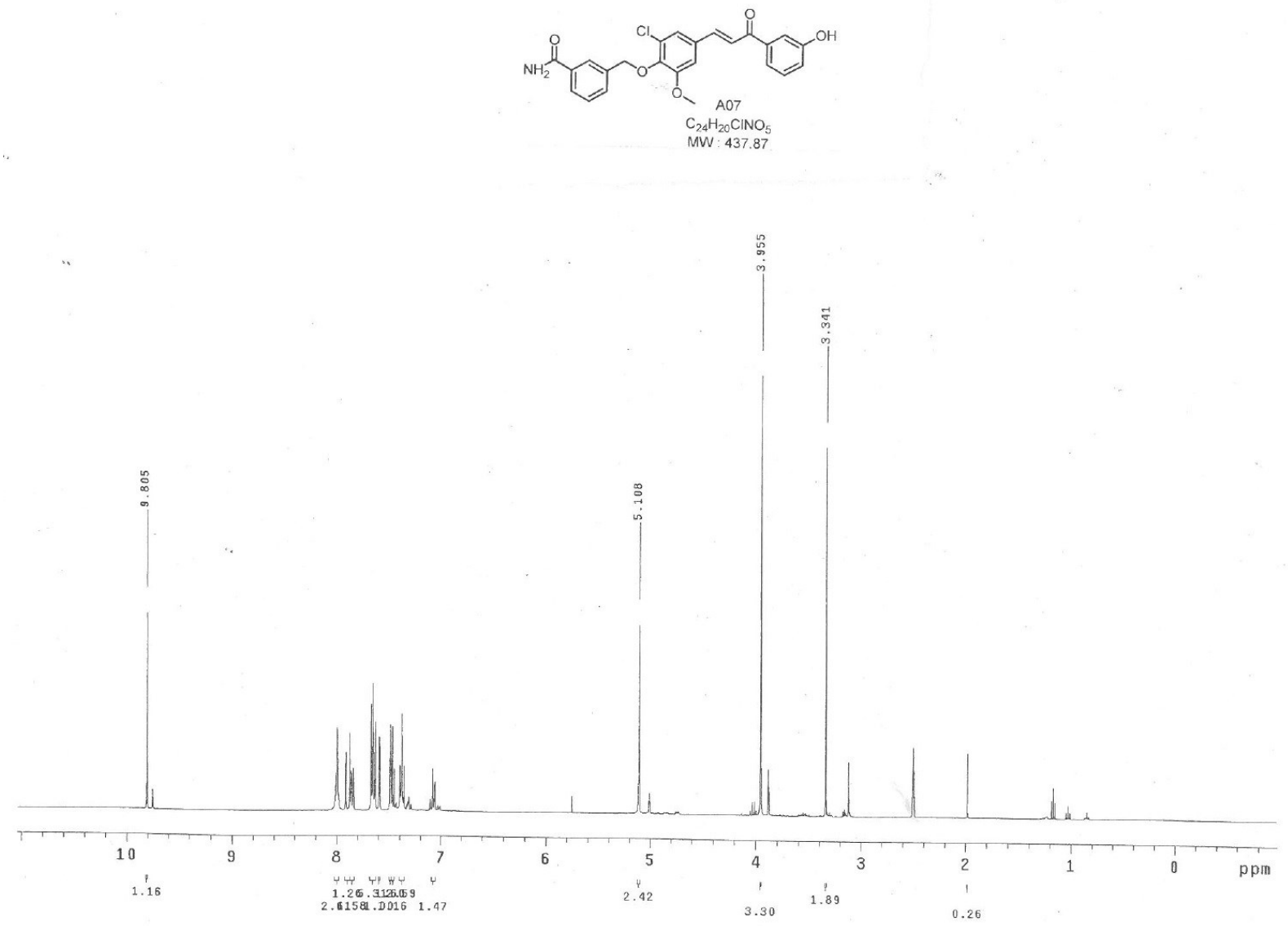
^{1}H NMR spectrum of **A6**



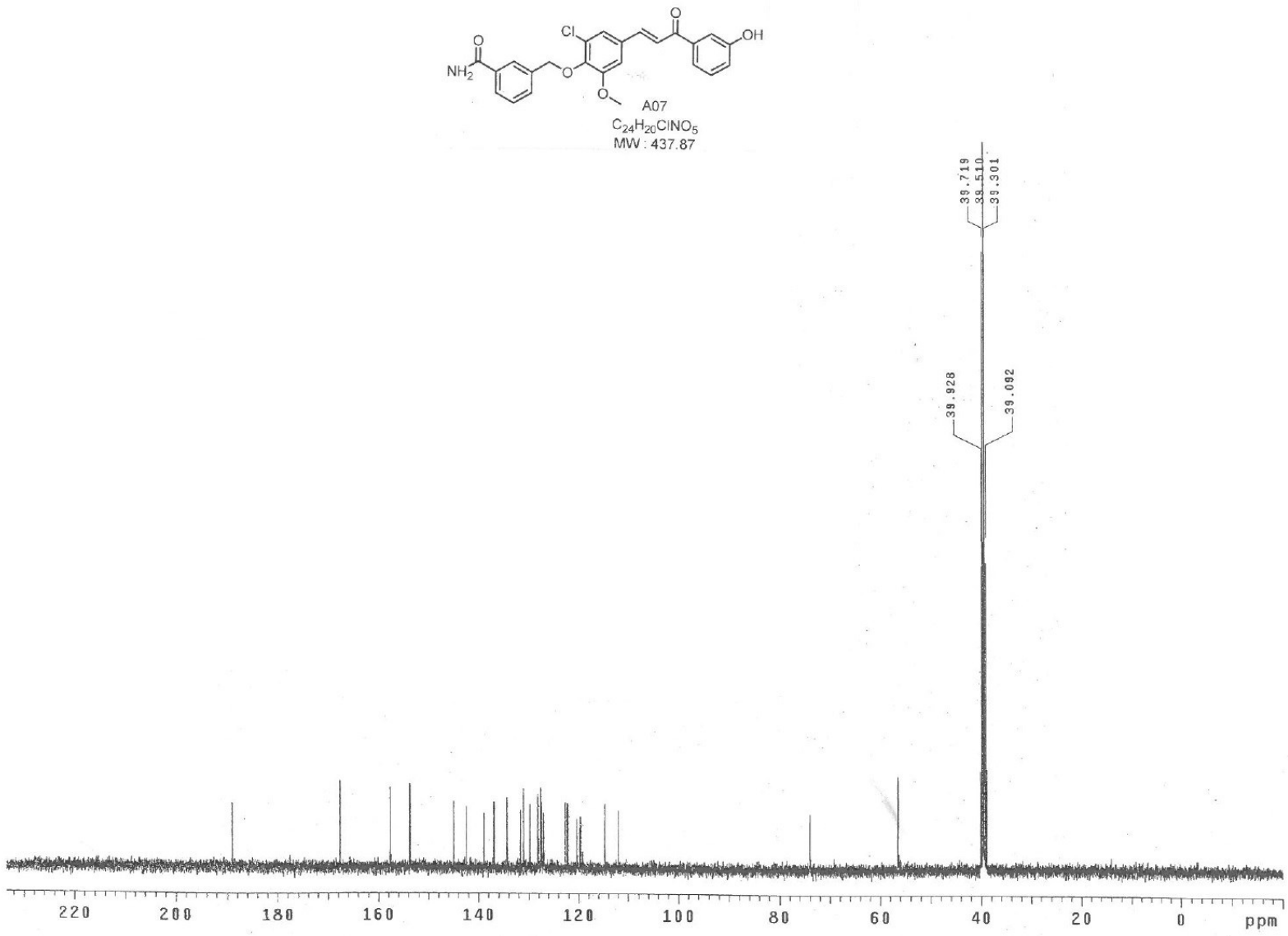
^{13}C NMR spectrum of **A6**



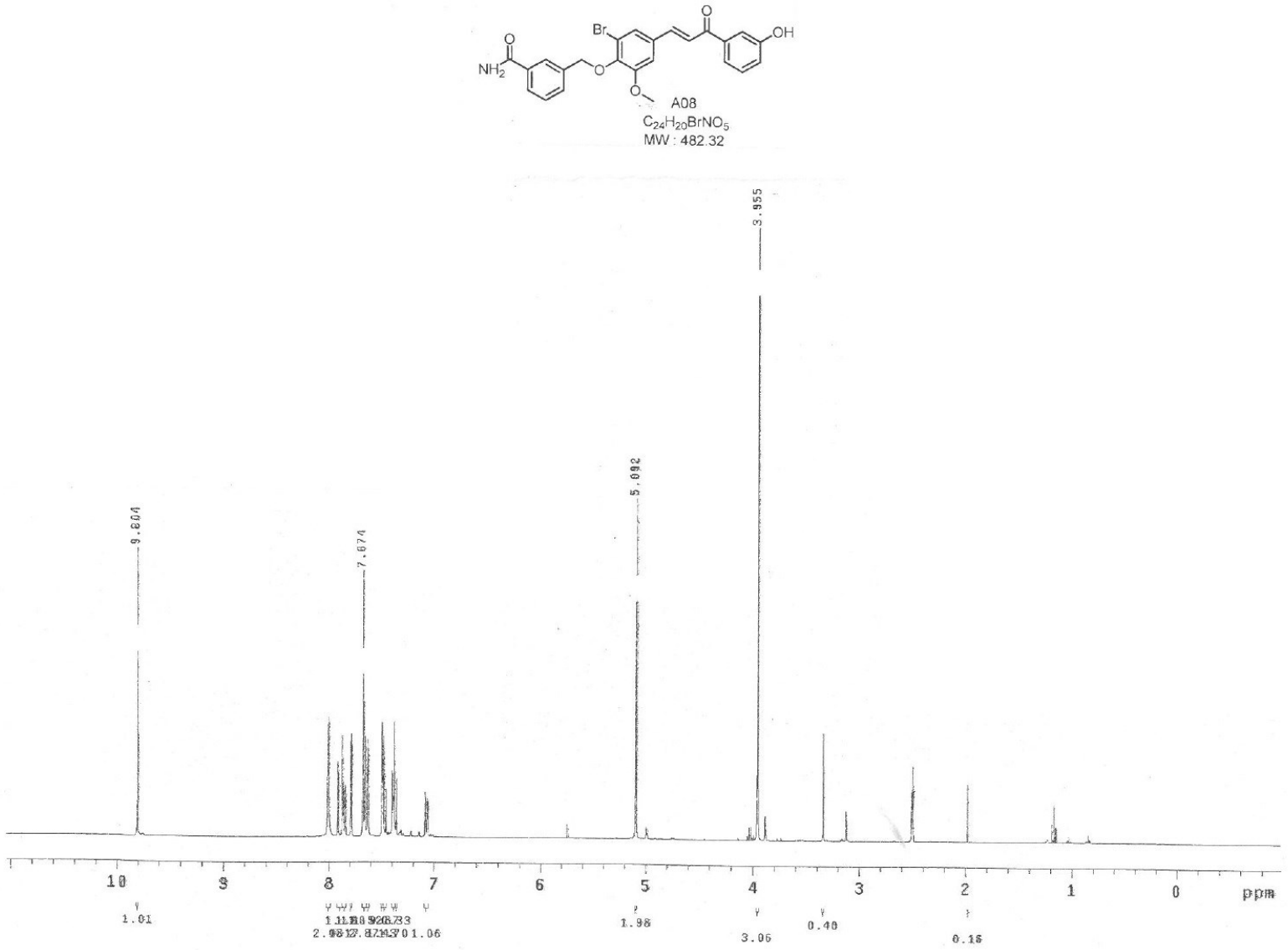
^{1}H NMR spectrum of **A7**



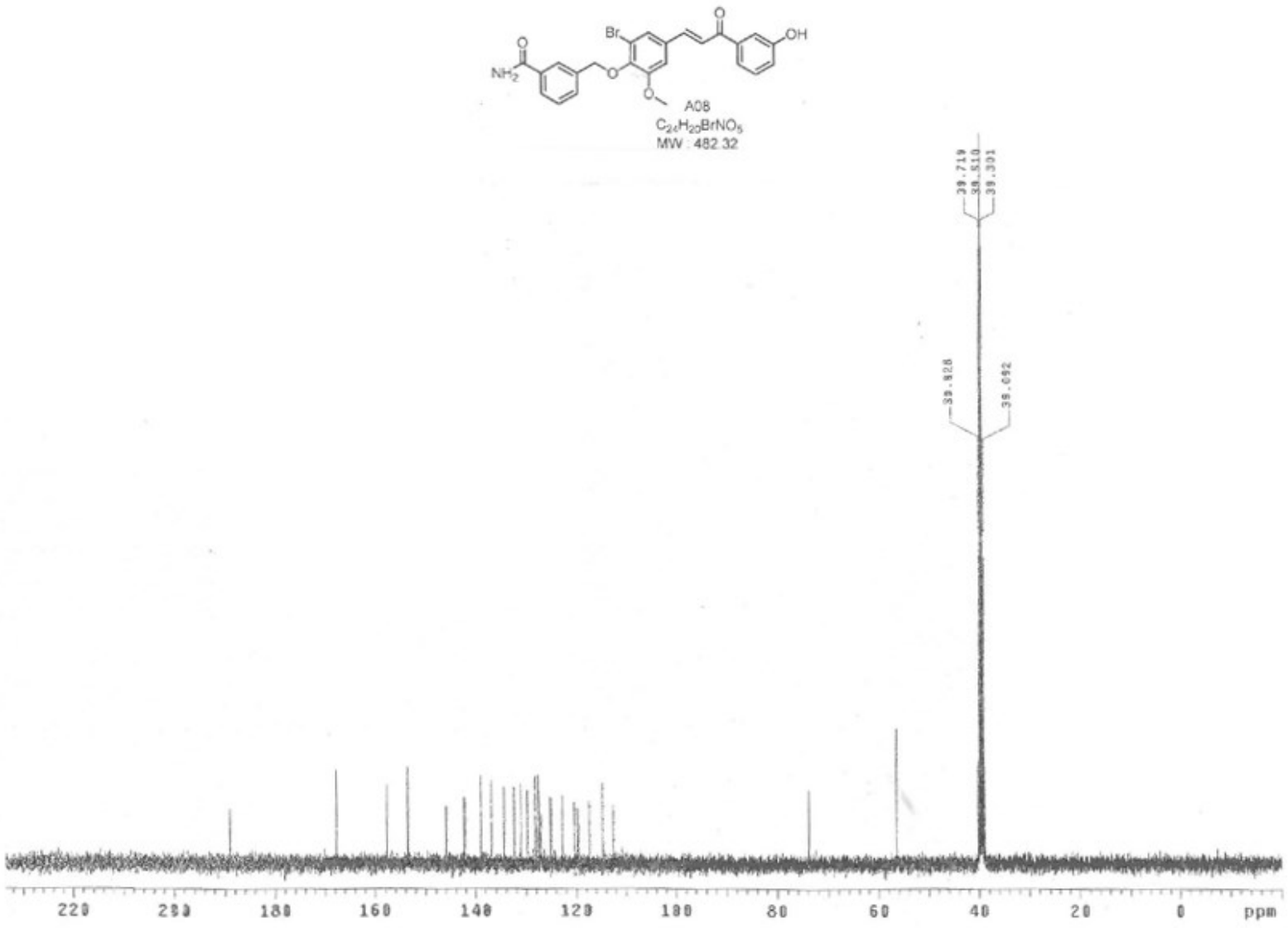
^{13}C NMR spectrum of **A7**



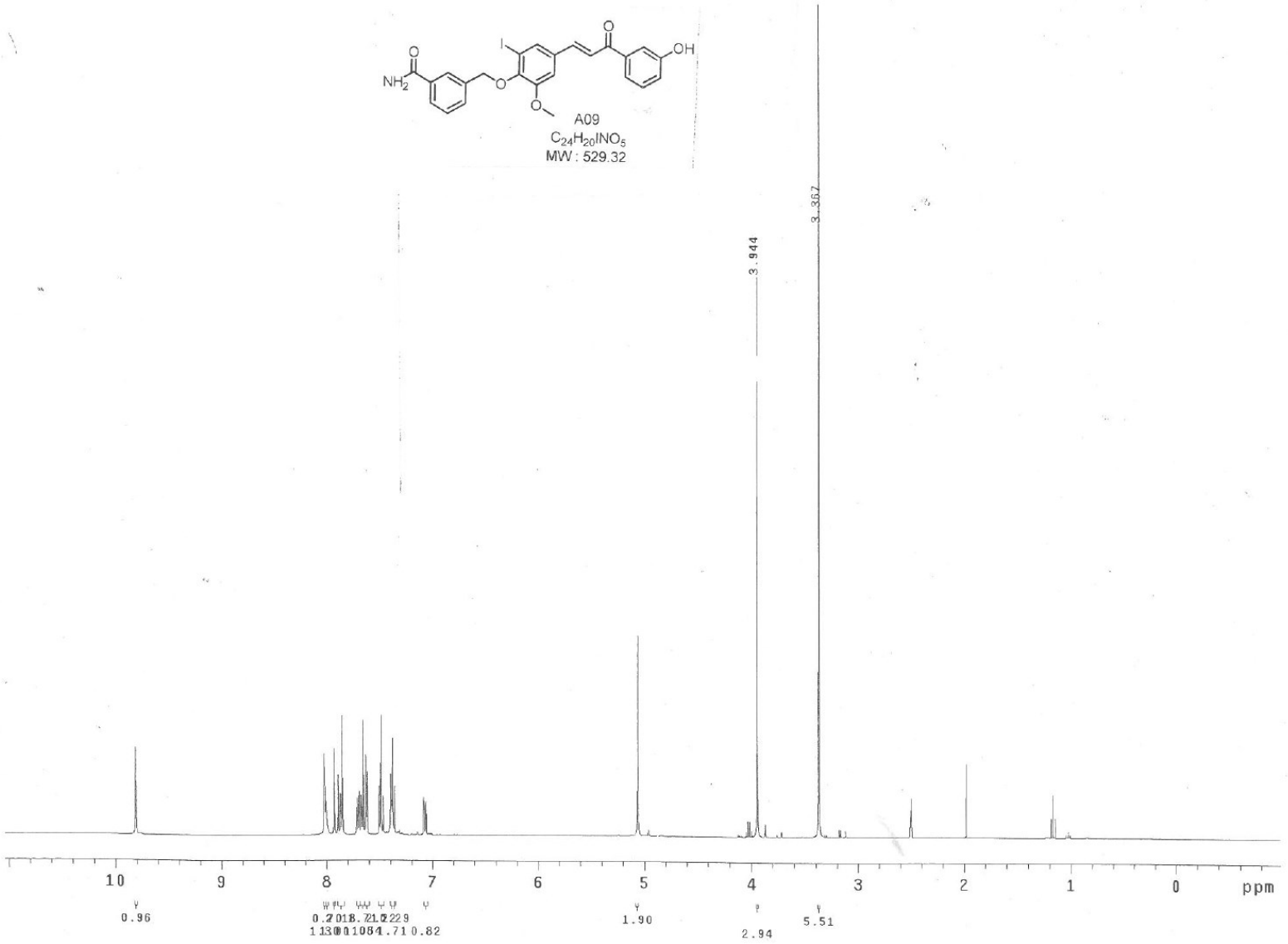
^{1}H NMR spectrum of **A8**



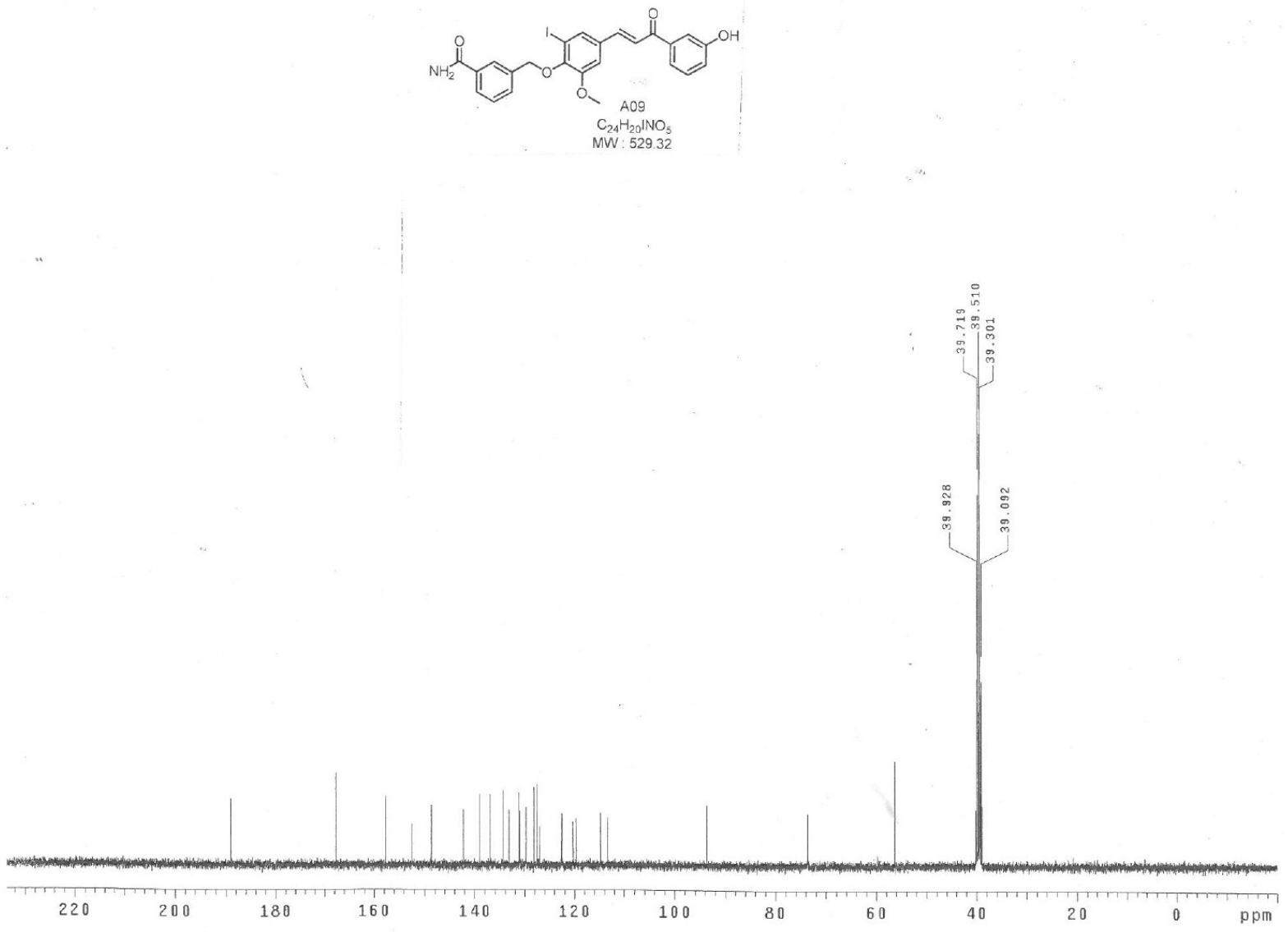
^{13}C NMR spectrum of **A8**



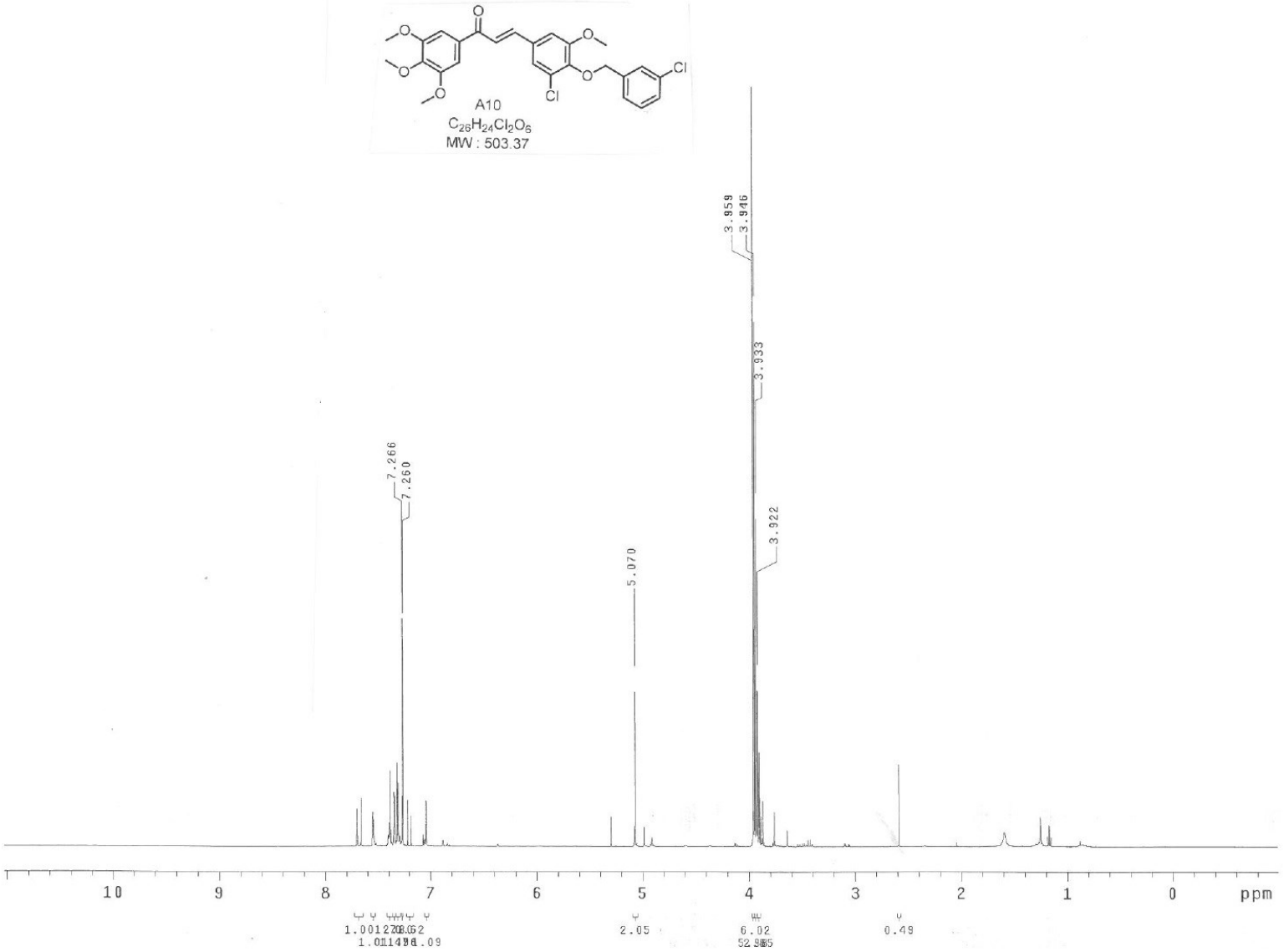
^{1}H NMR spectrum of **A9**



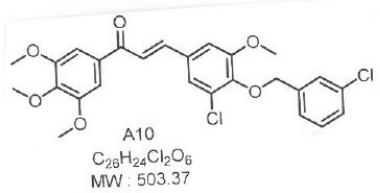
^{13}C NMR spectrum of **A9**

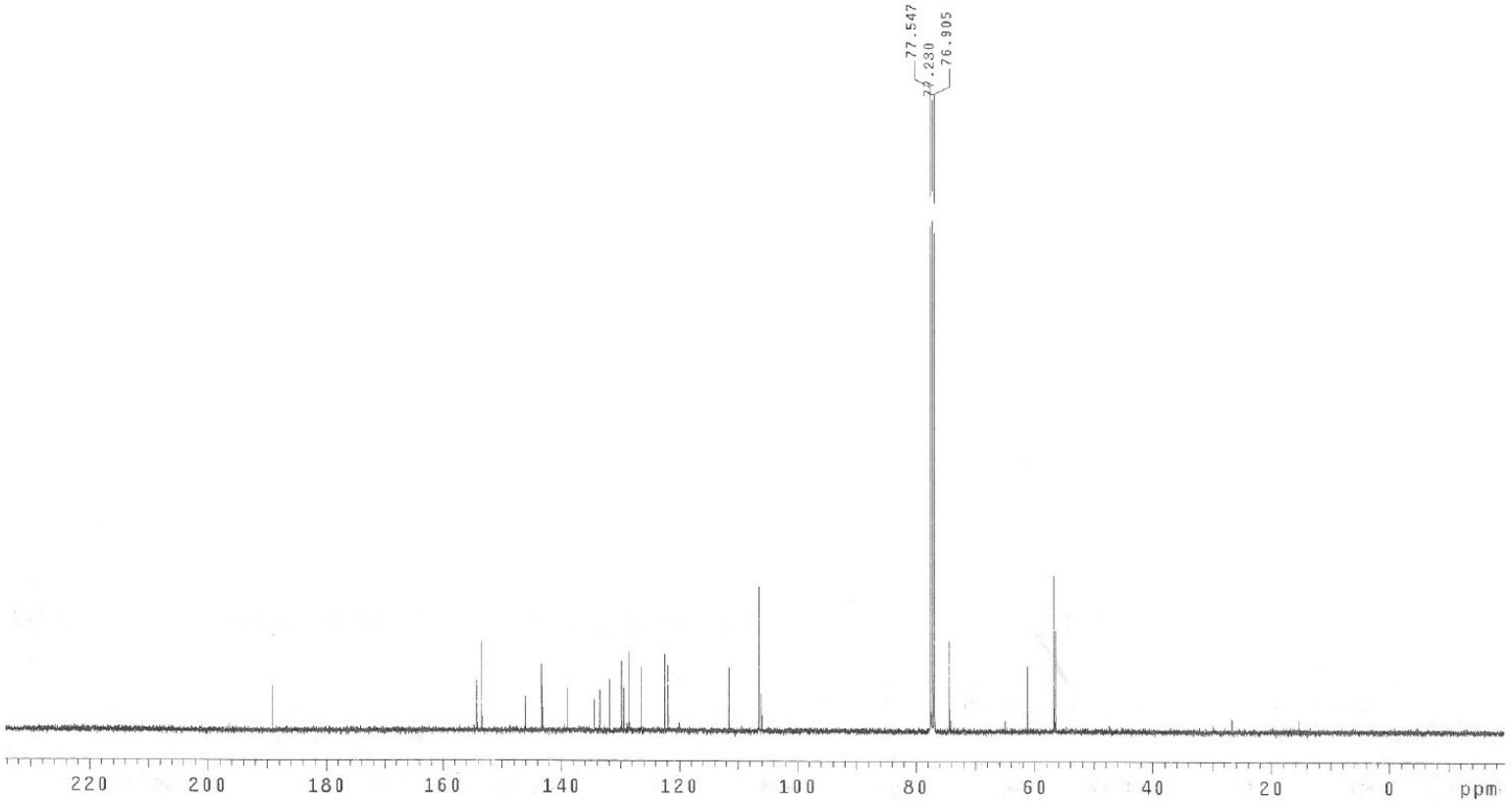


^{1}H NMR spectrum of **A10**

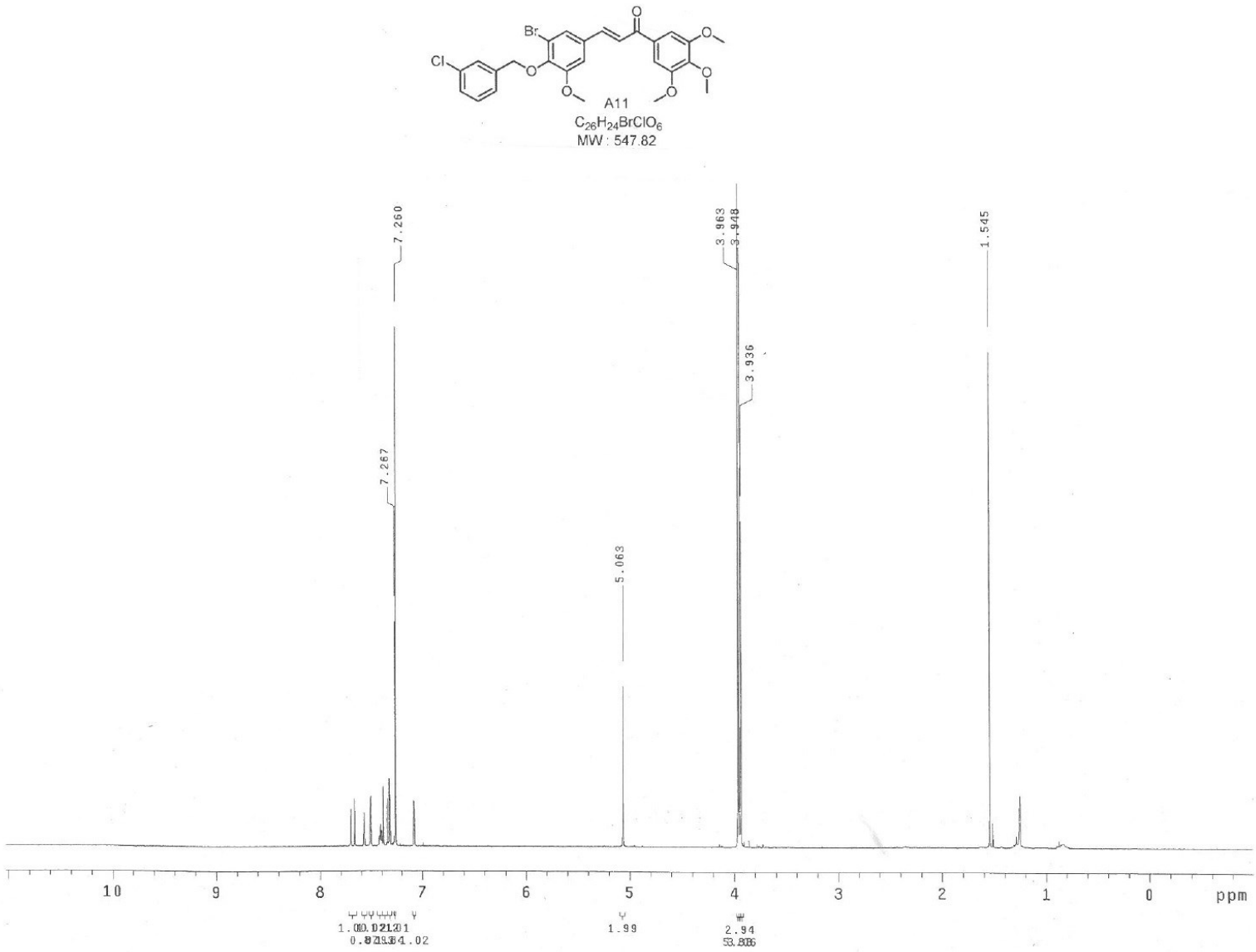


^{13}C NMR spectrum of **A10**

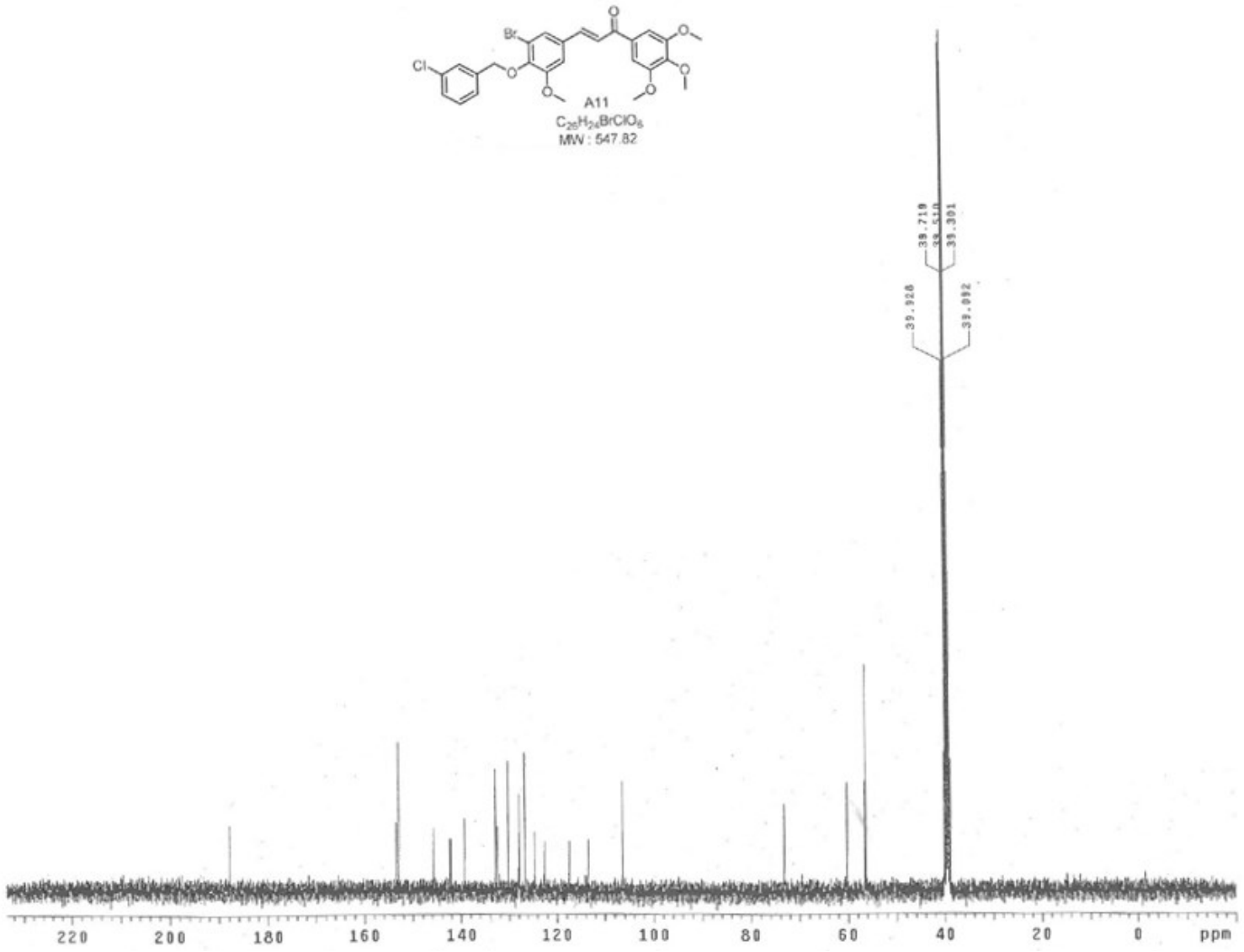




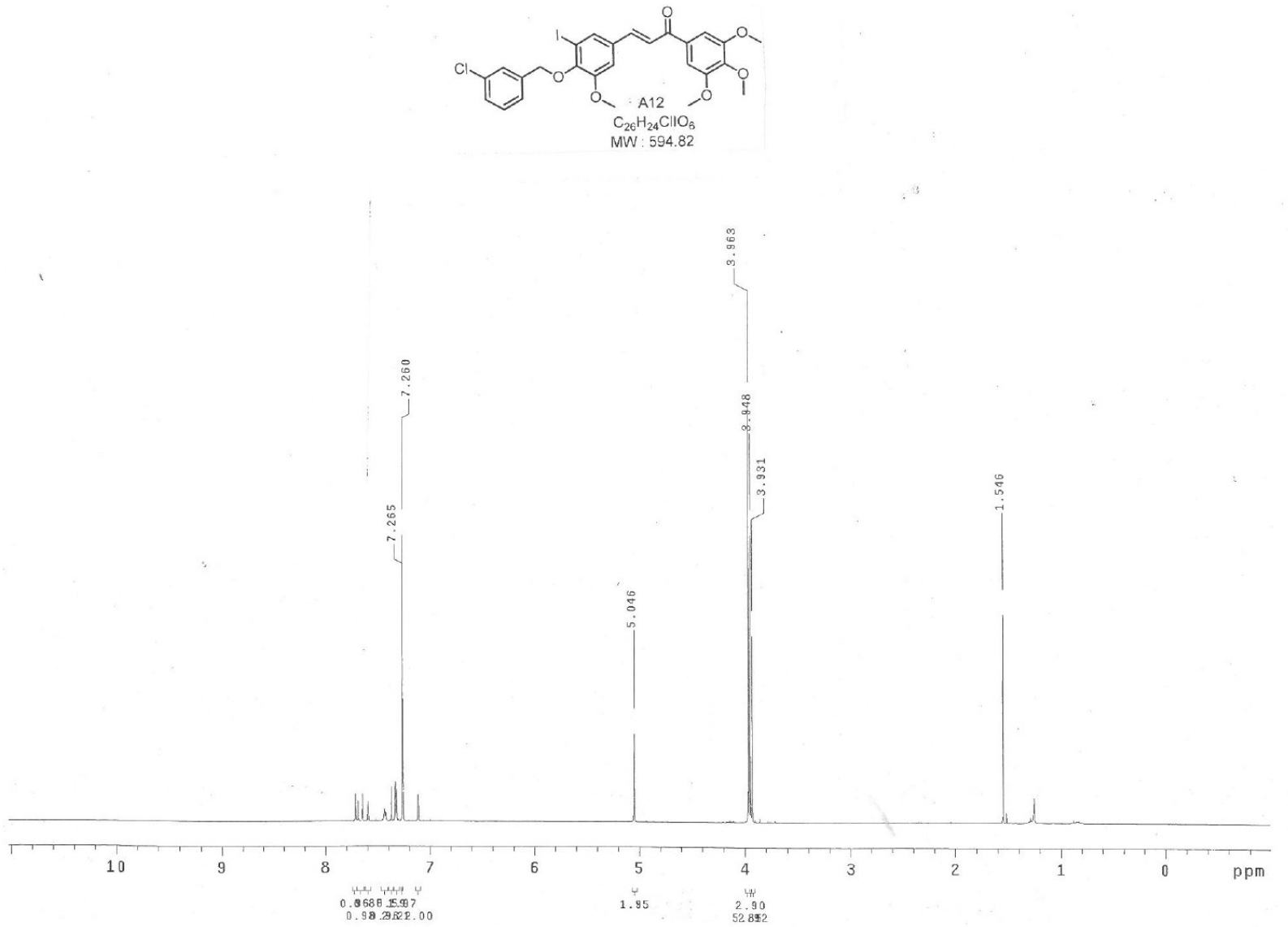
^{1}H NMR spectrum of **A11**



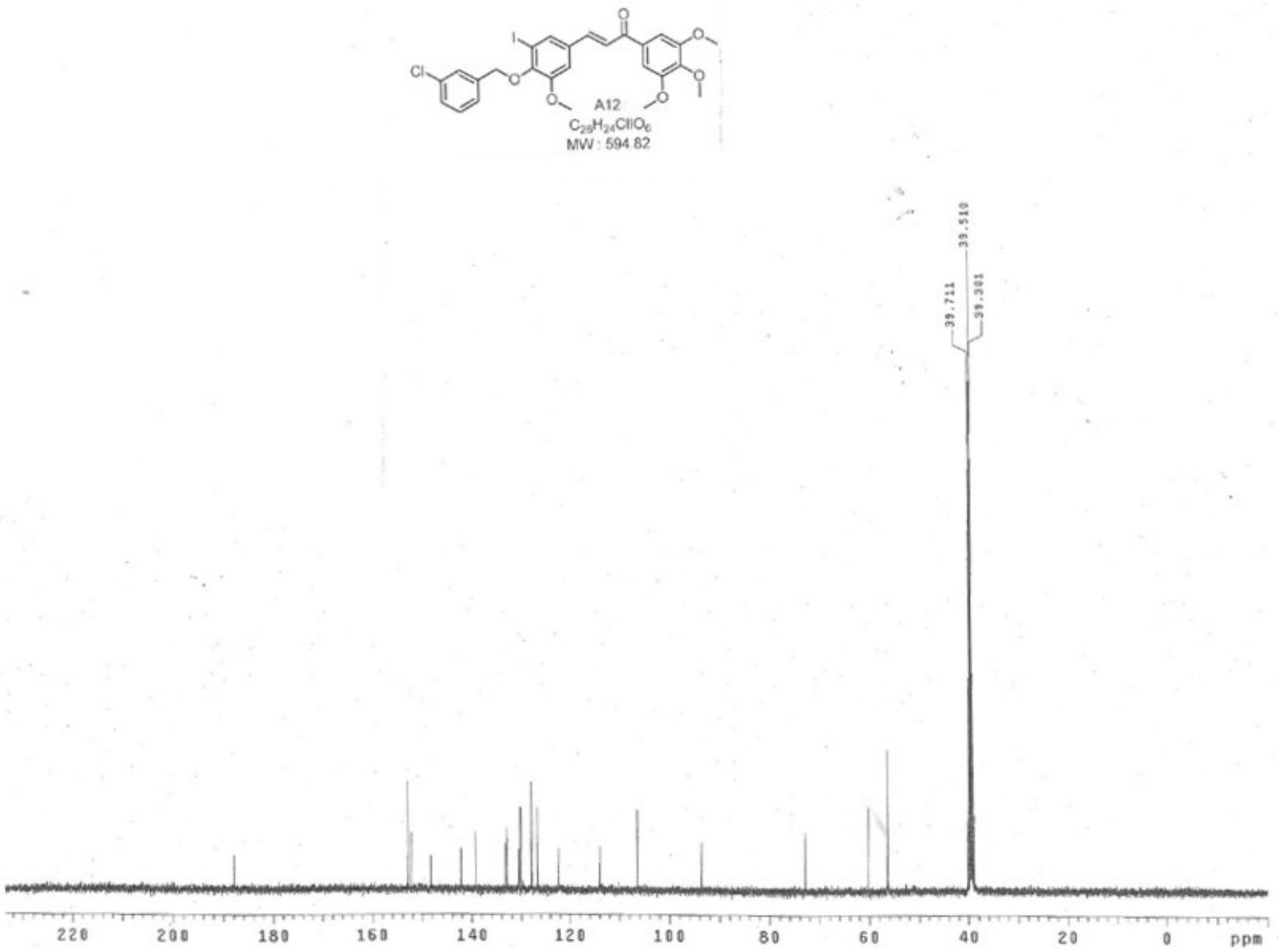
^{13}C NMR spectrum of **A11**



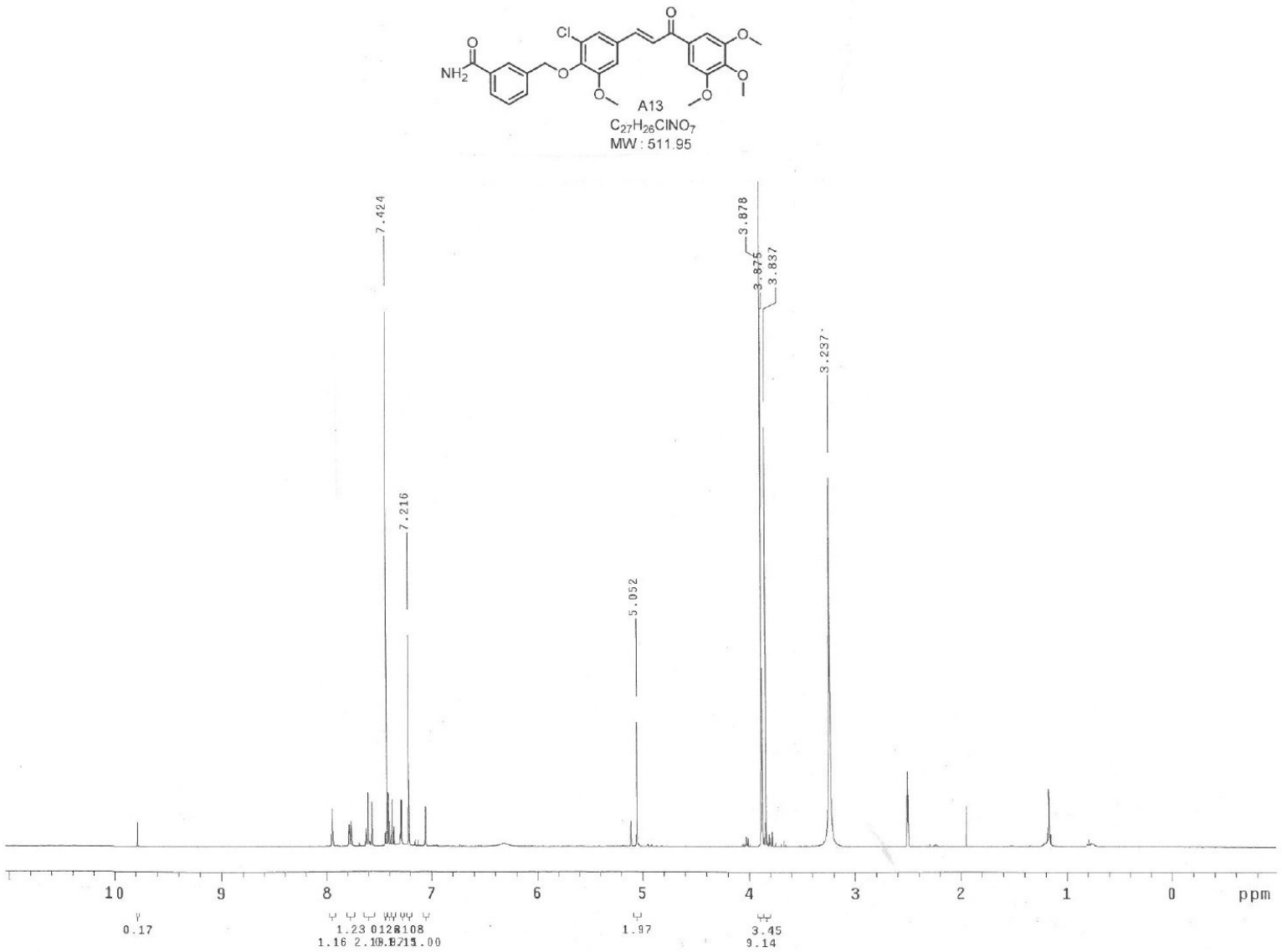
^{1}H NMR spectrum of **A12**



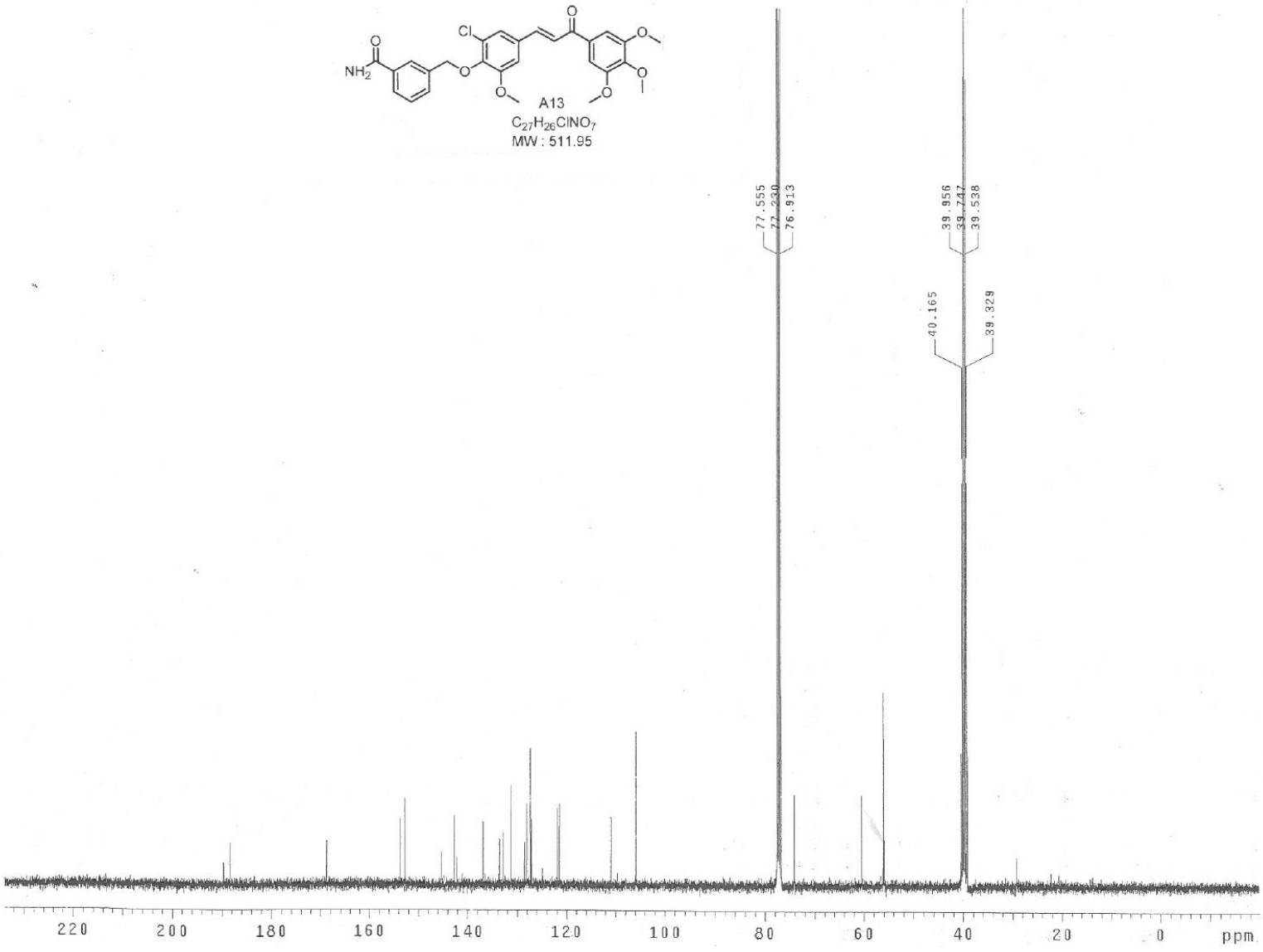
^{13}C NMR spectrum of **A12**



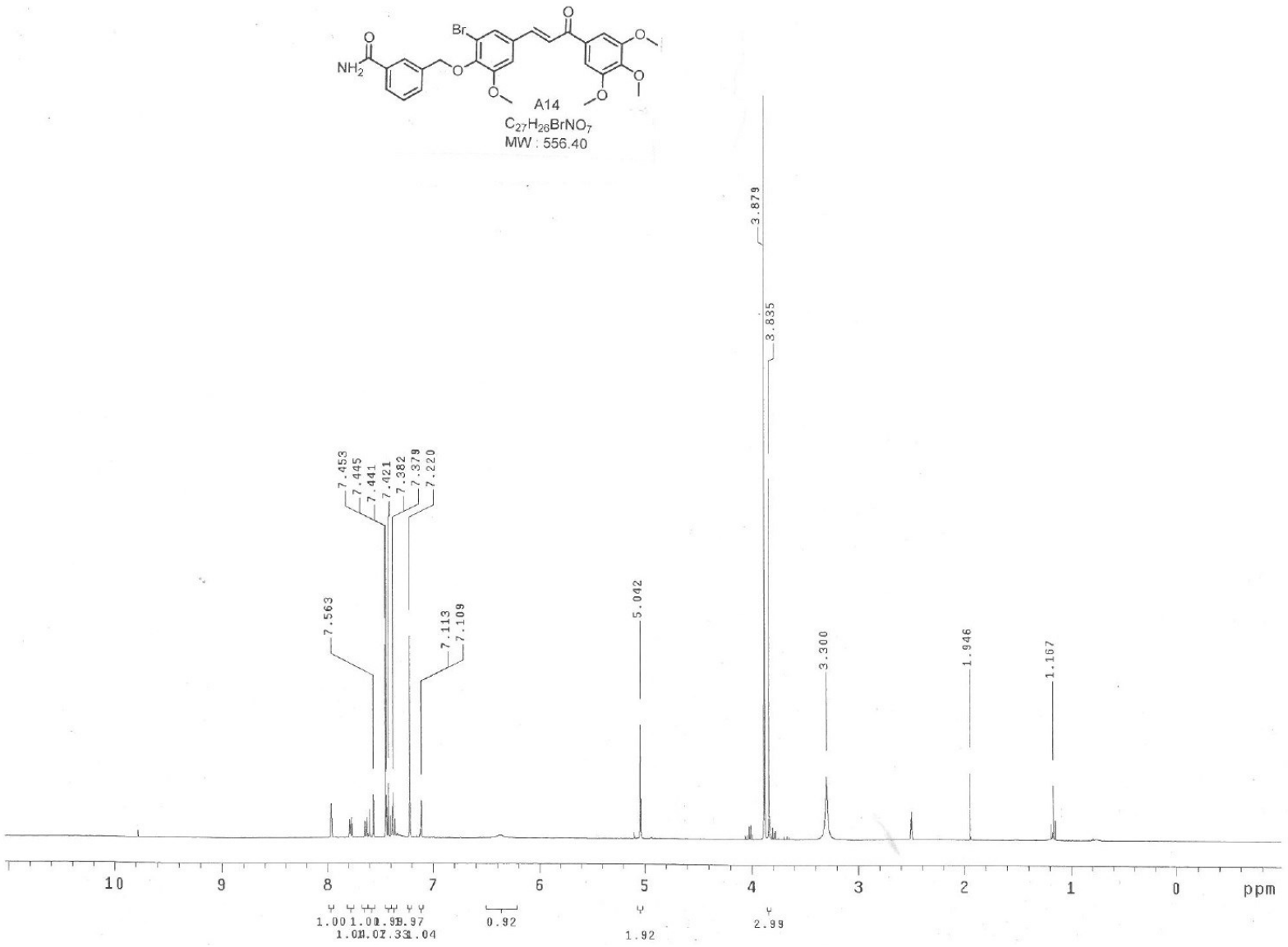
^{1}H NMR spectrum of **A13**



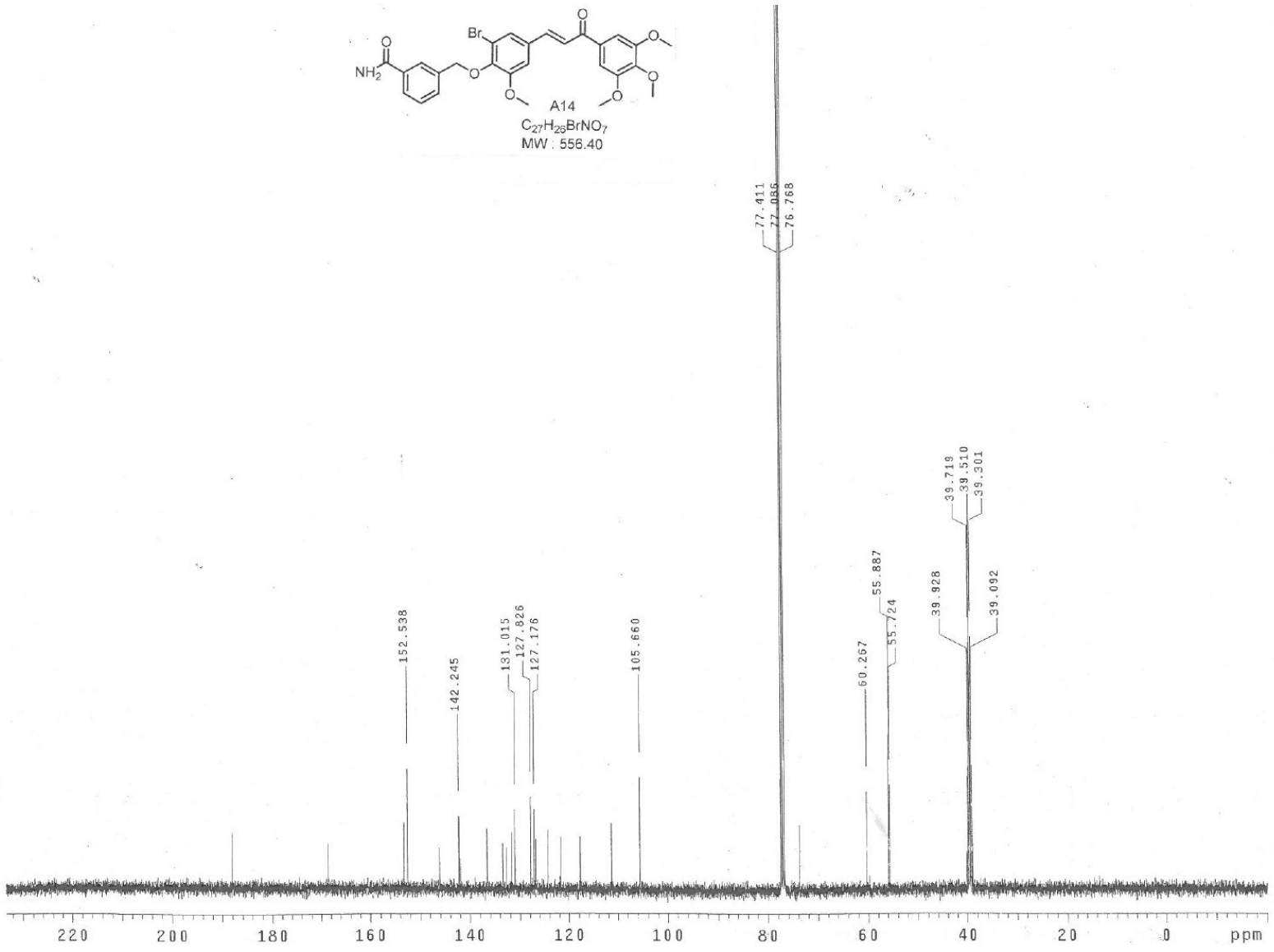
^{13}C NMR spectrum of **A13**



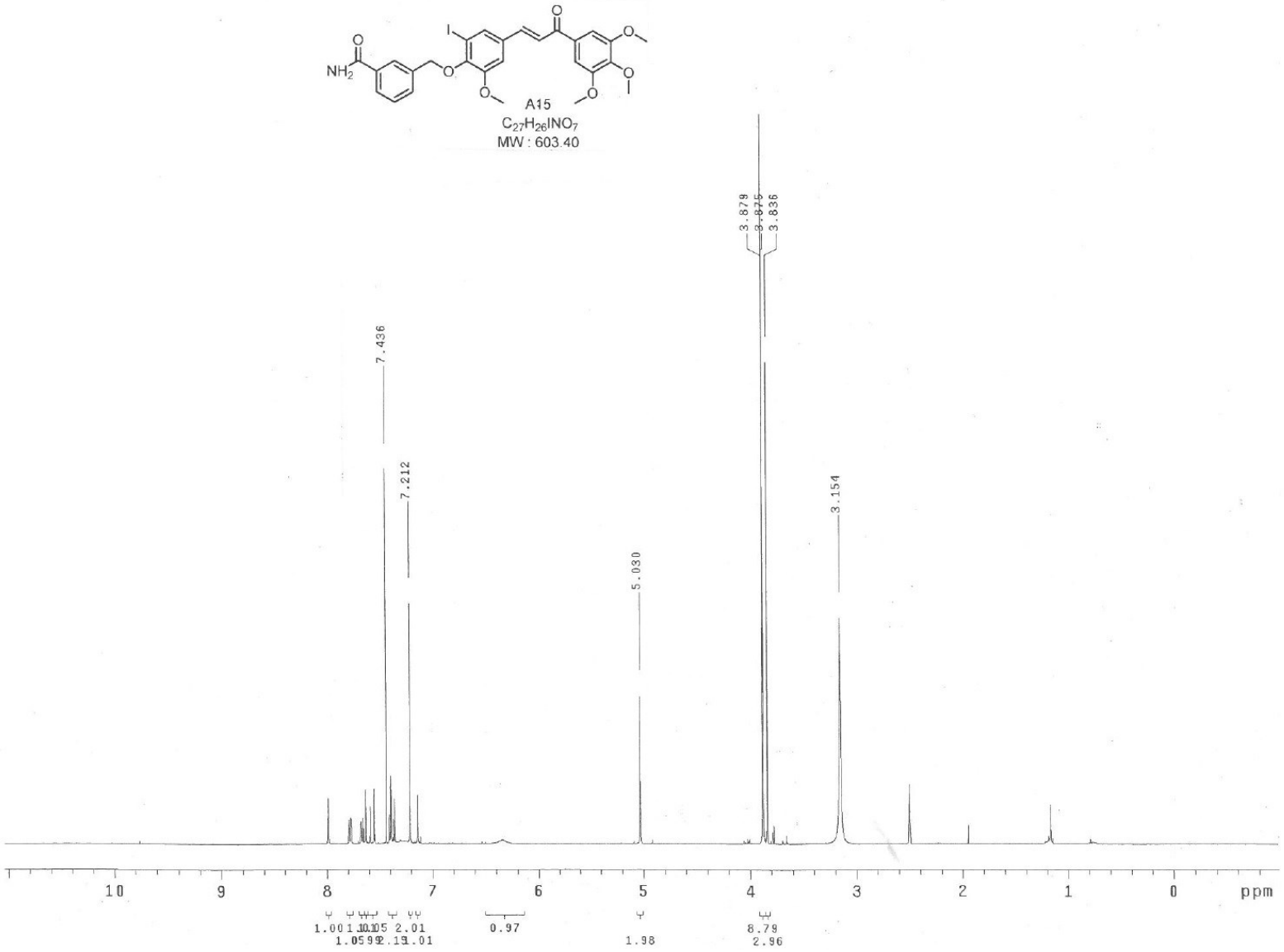
^{1}H NMR spectrum of **A14**



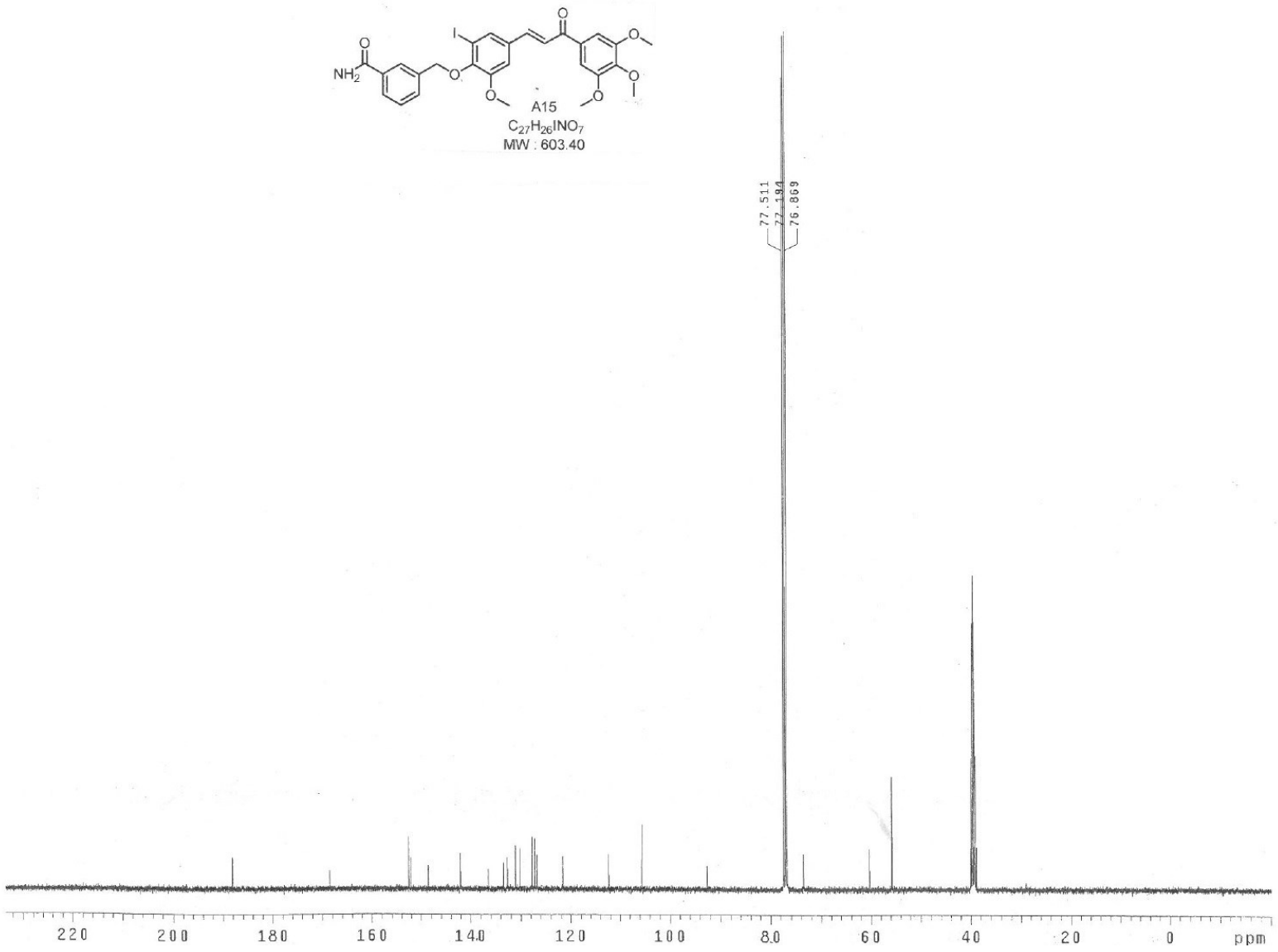
^{13}C NMR spectrum of **A14**



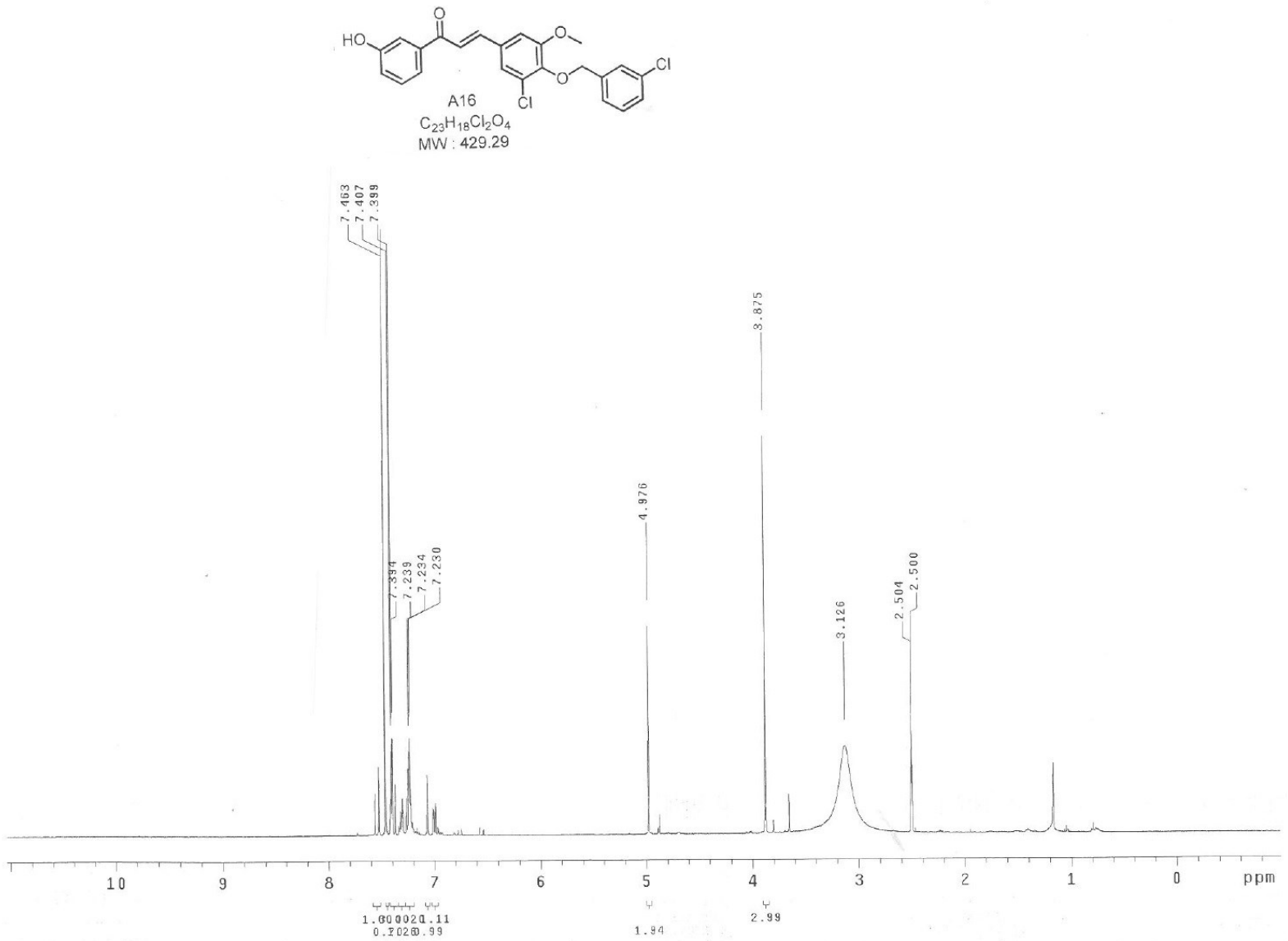
^{1}H NMR spectrum of **A15**



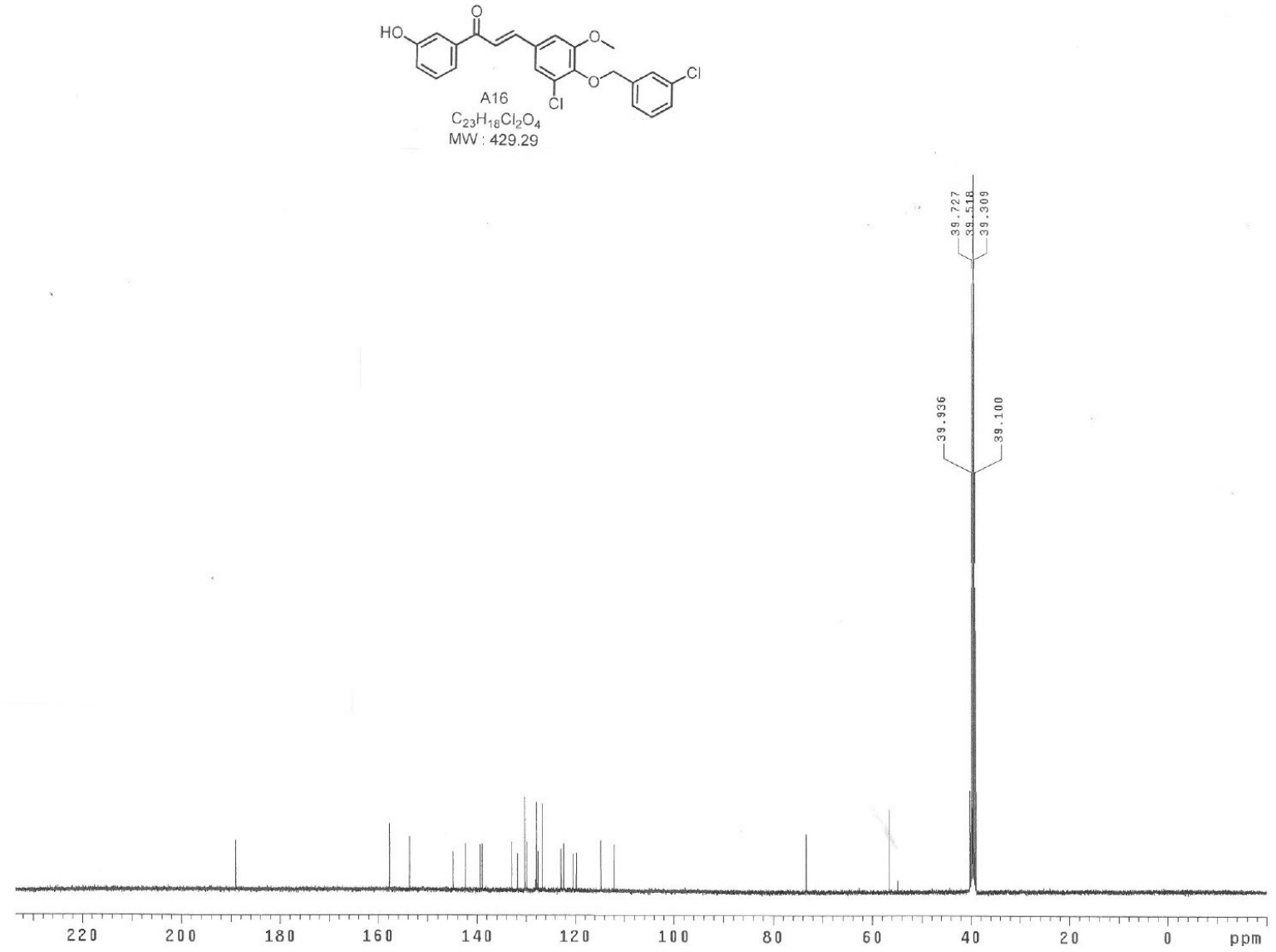
^{13}C NMR spectrum of **A15**



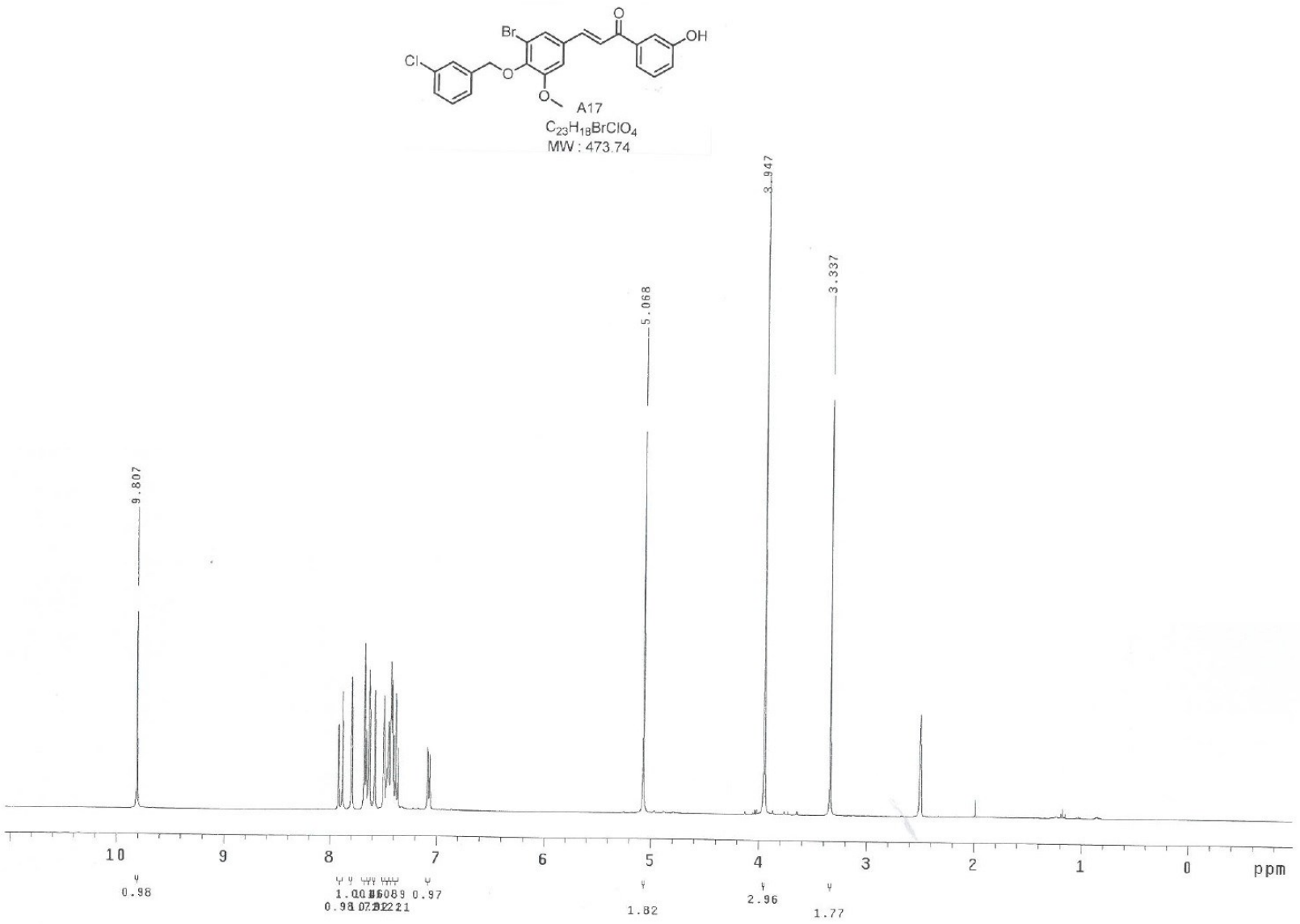
^{1}H NMR spectrum of **A16**



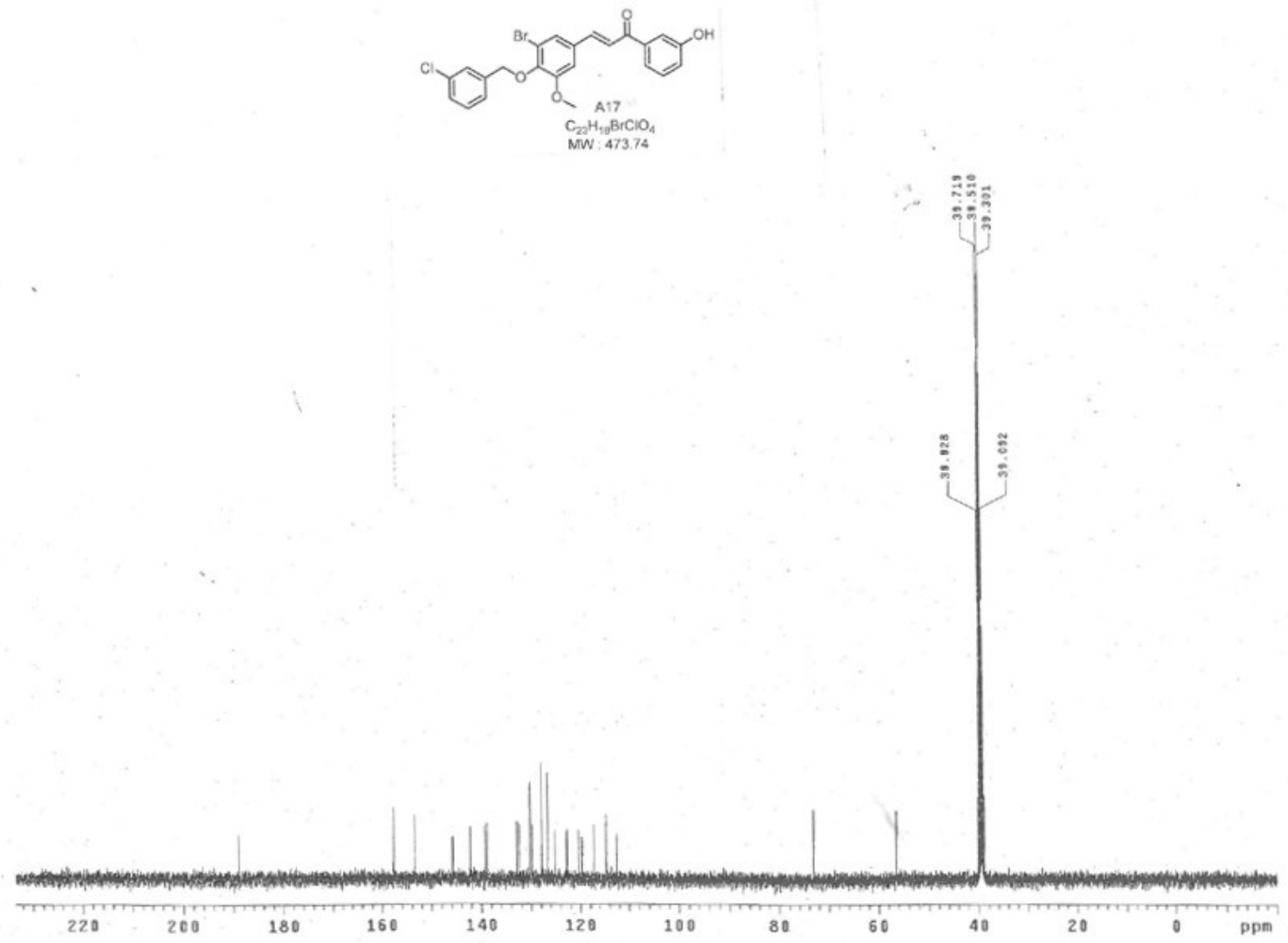
^{13}C NMR spectrum of **A16**



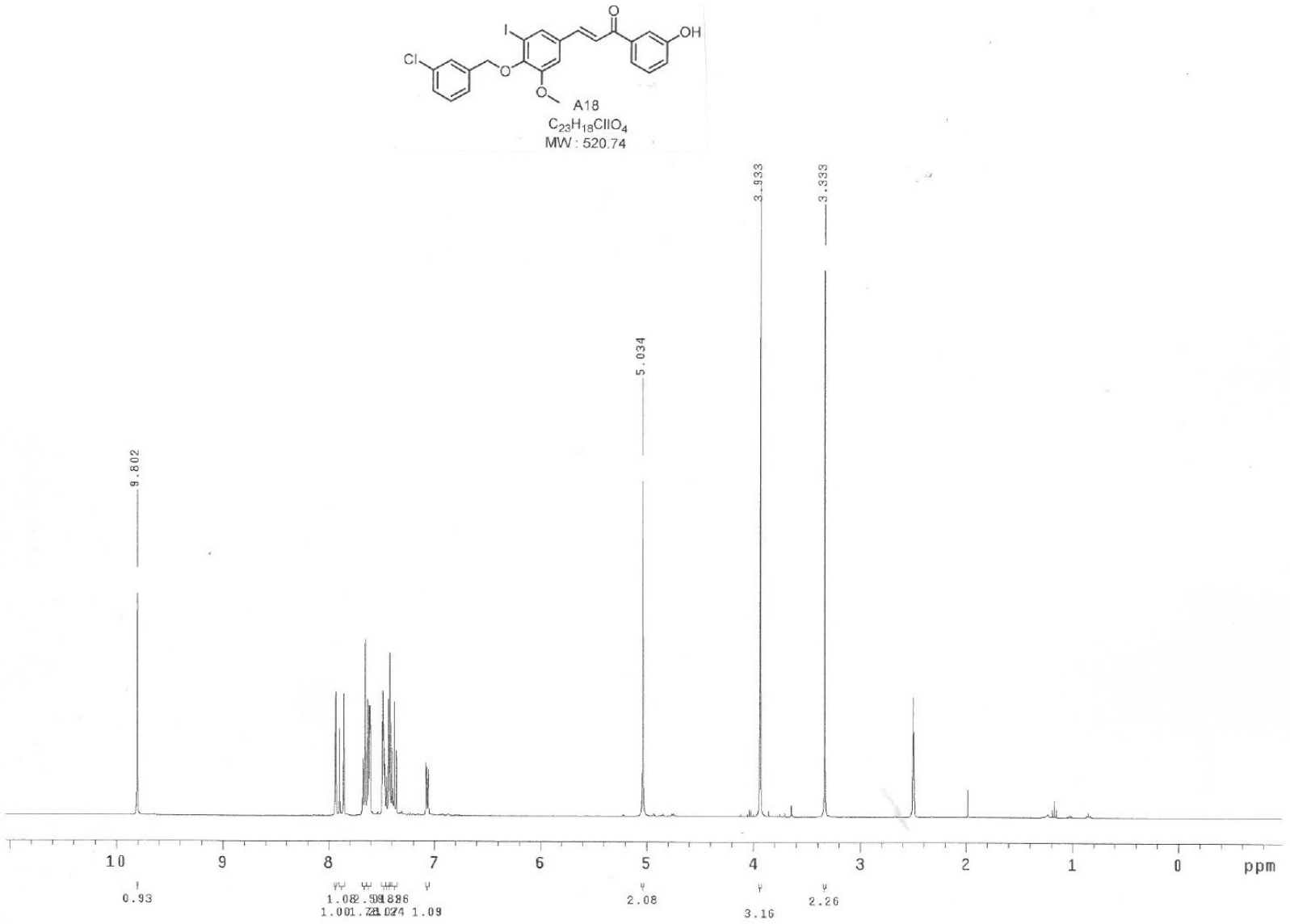
^{1}H NMR spectrum of **A17**



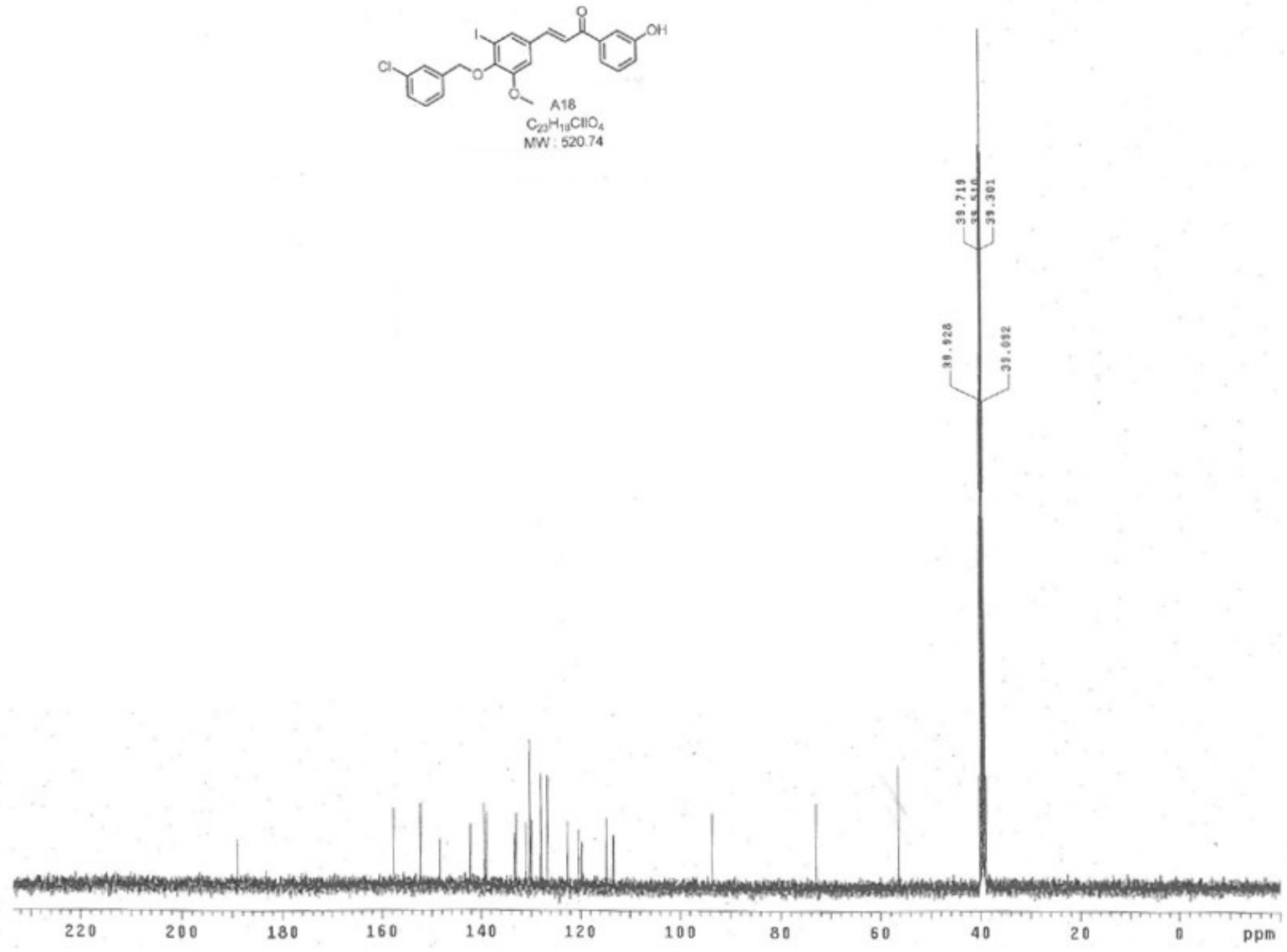
^{13}C NMR spectrum of **A17**



^{1}H NMR spectrum of **A18**



^{13}C NMR spectrum of **A18**



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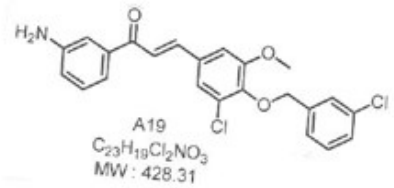
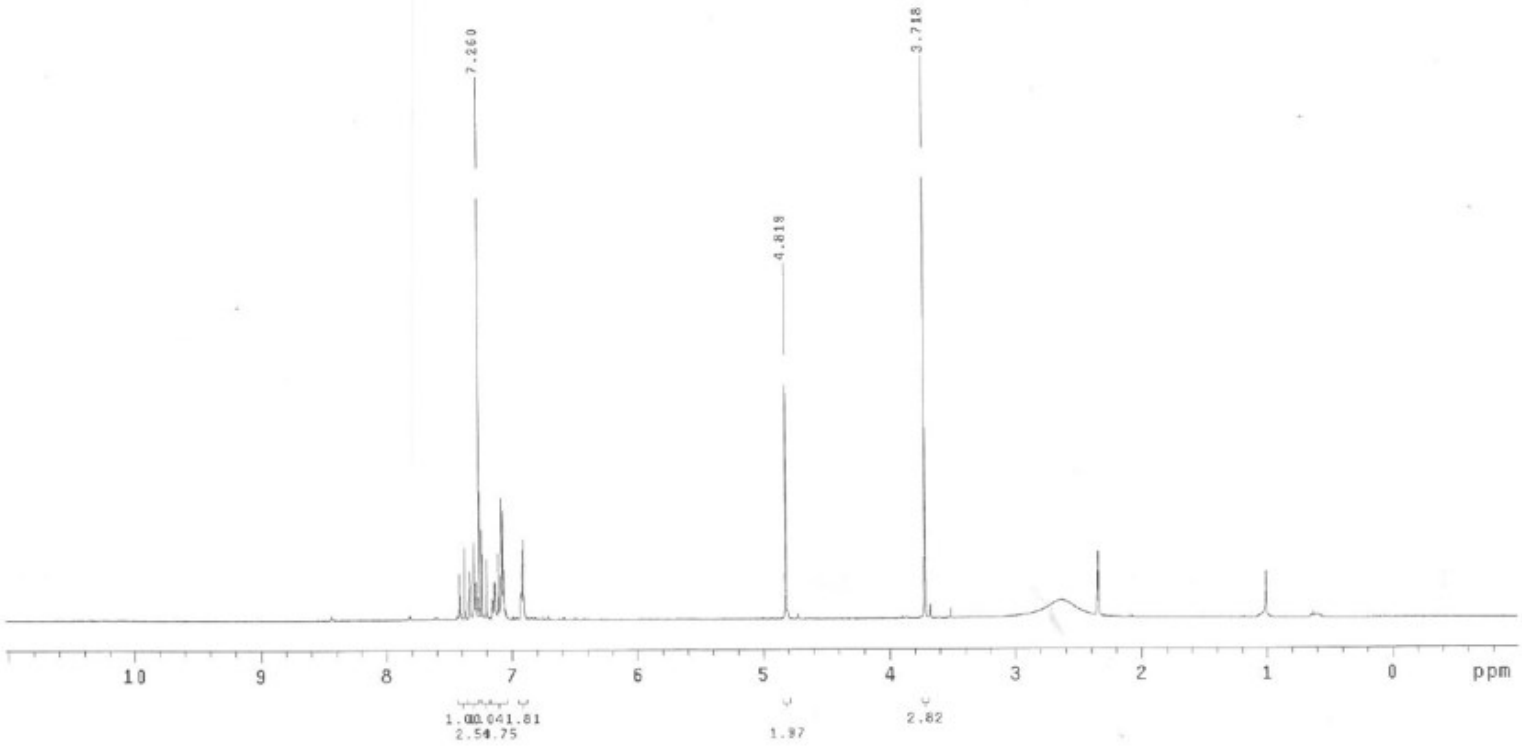
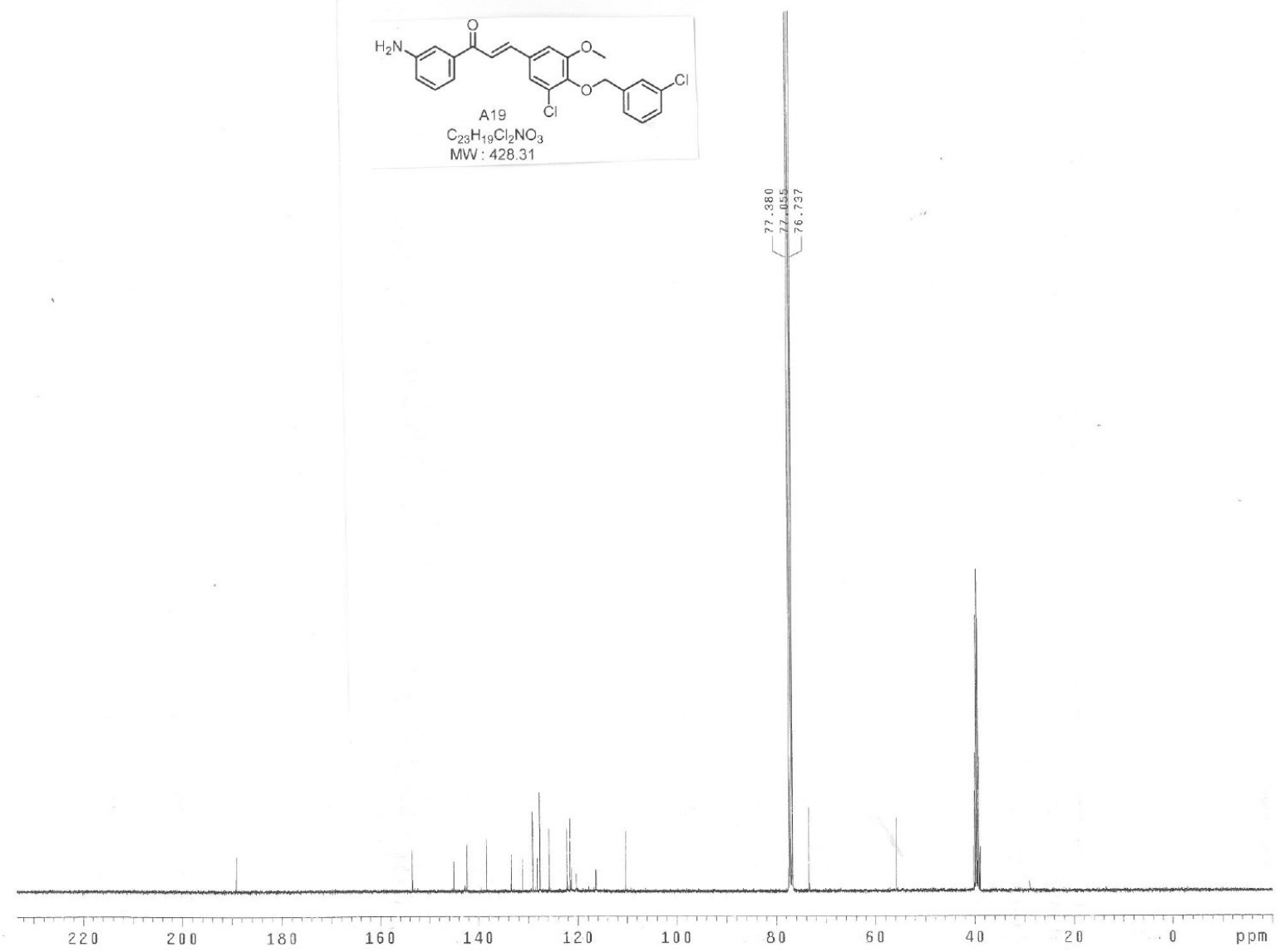




^{13}C NMR spectrum of **A19**



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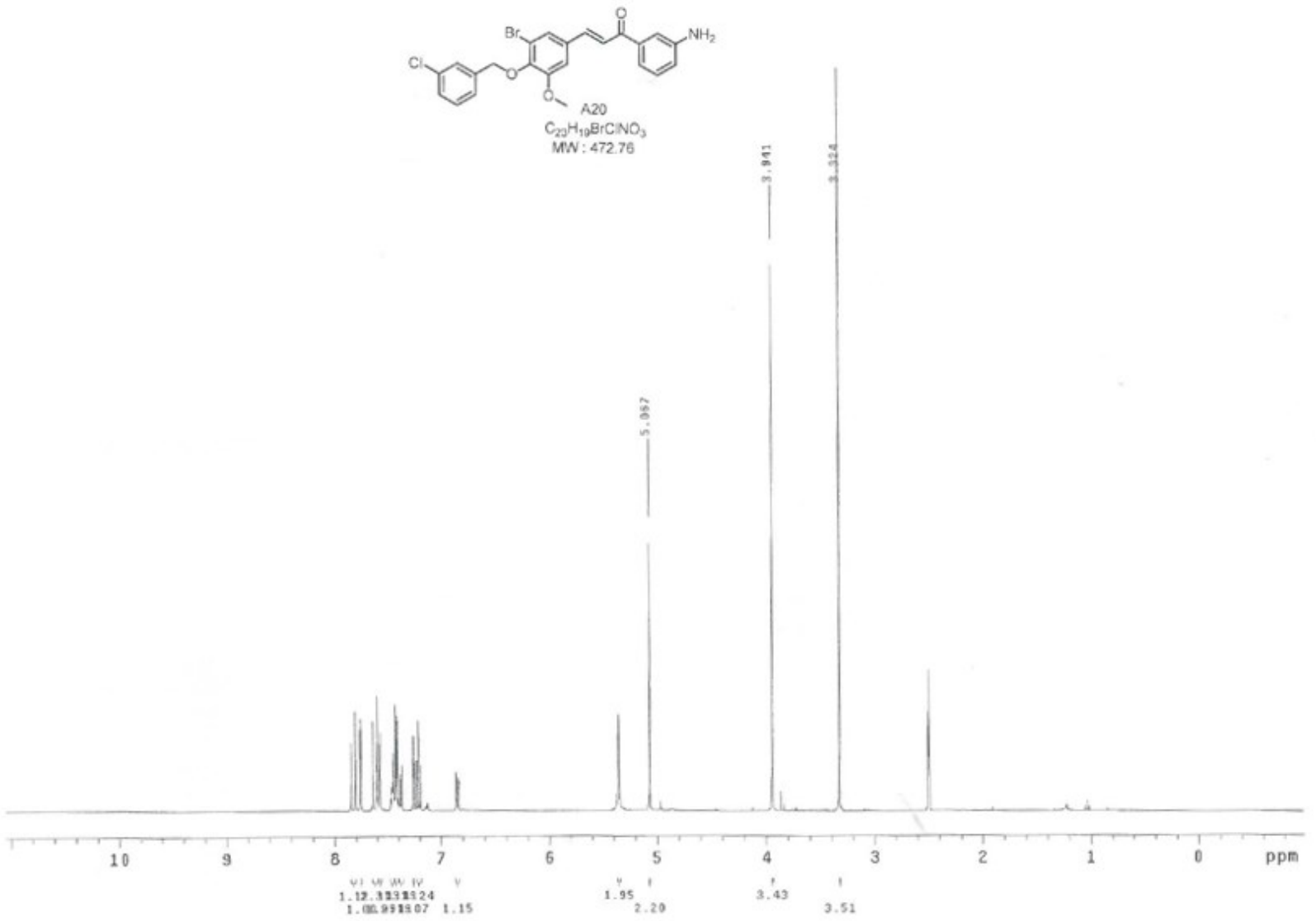

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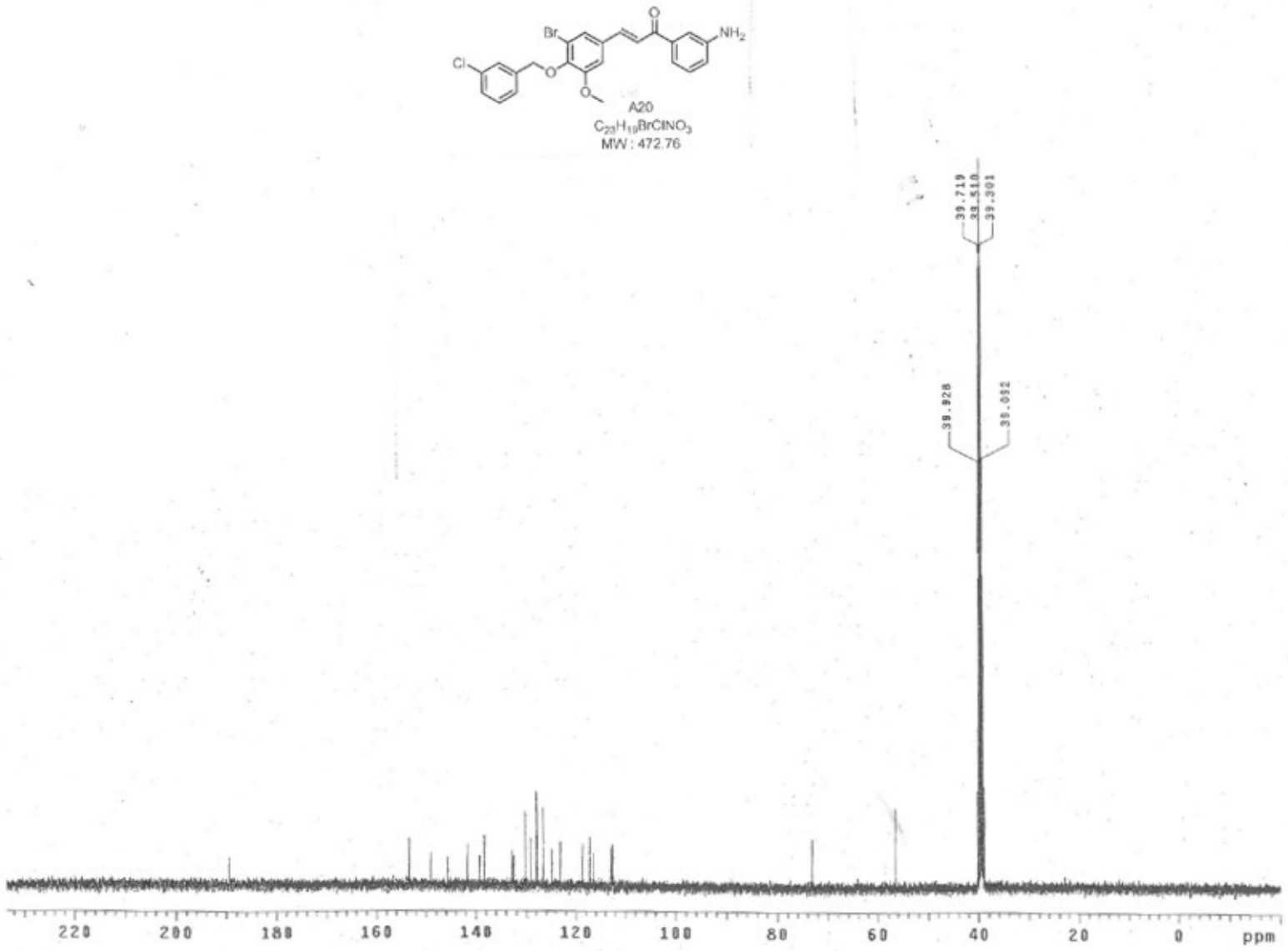

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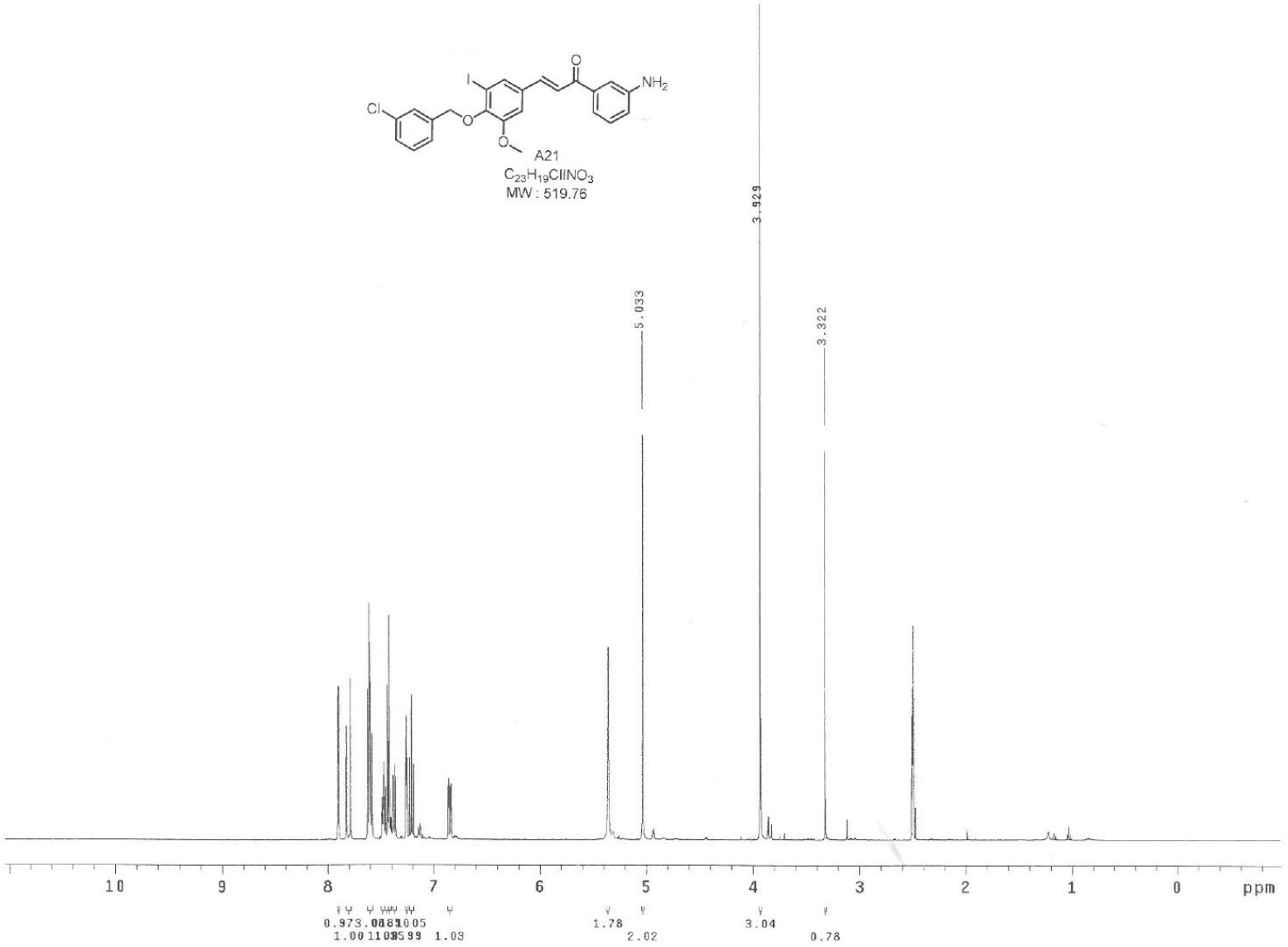
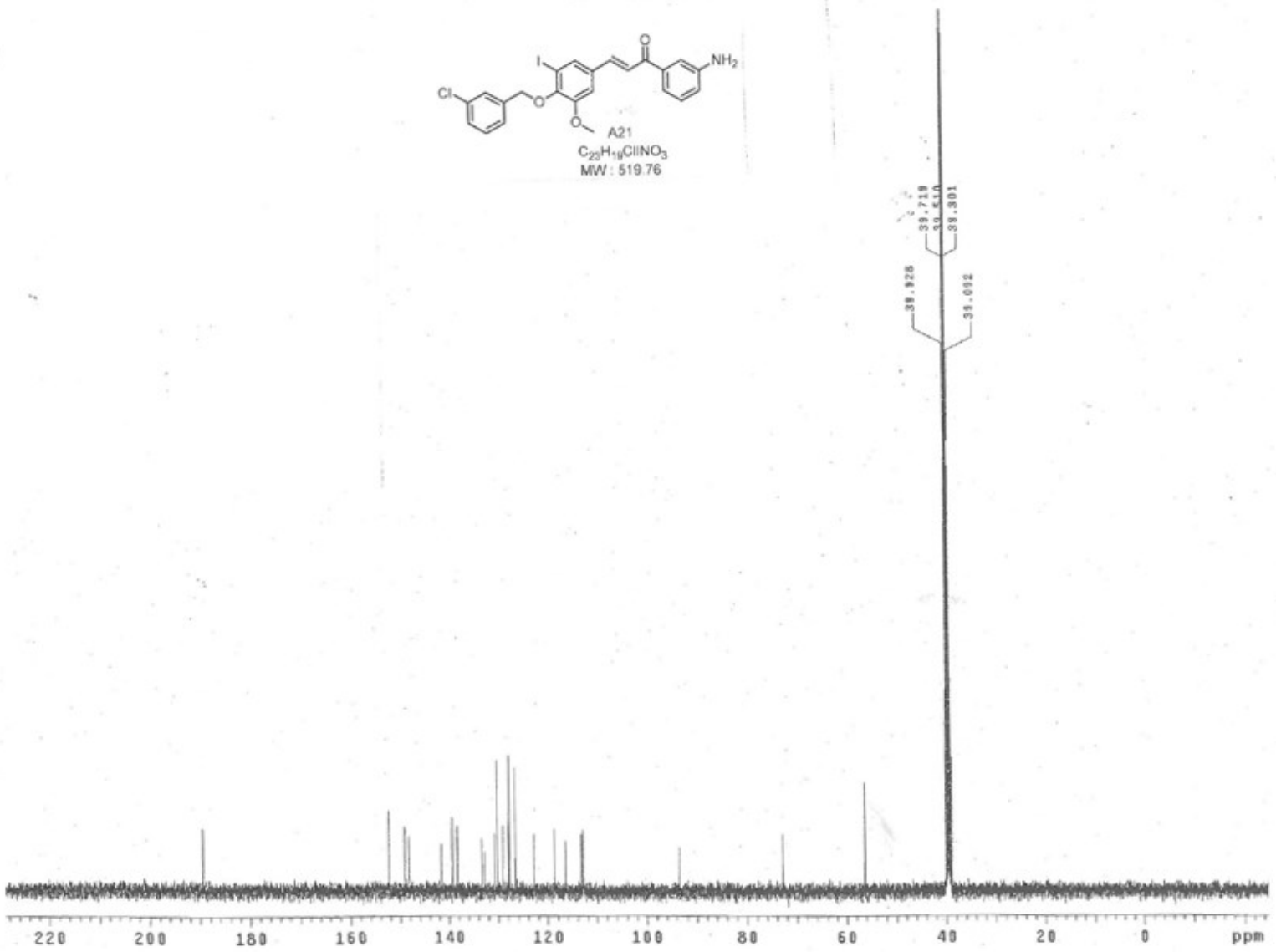
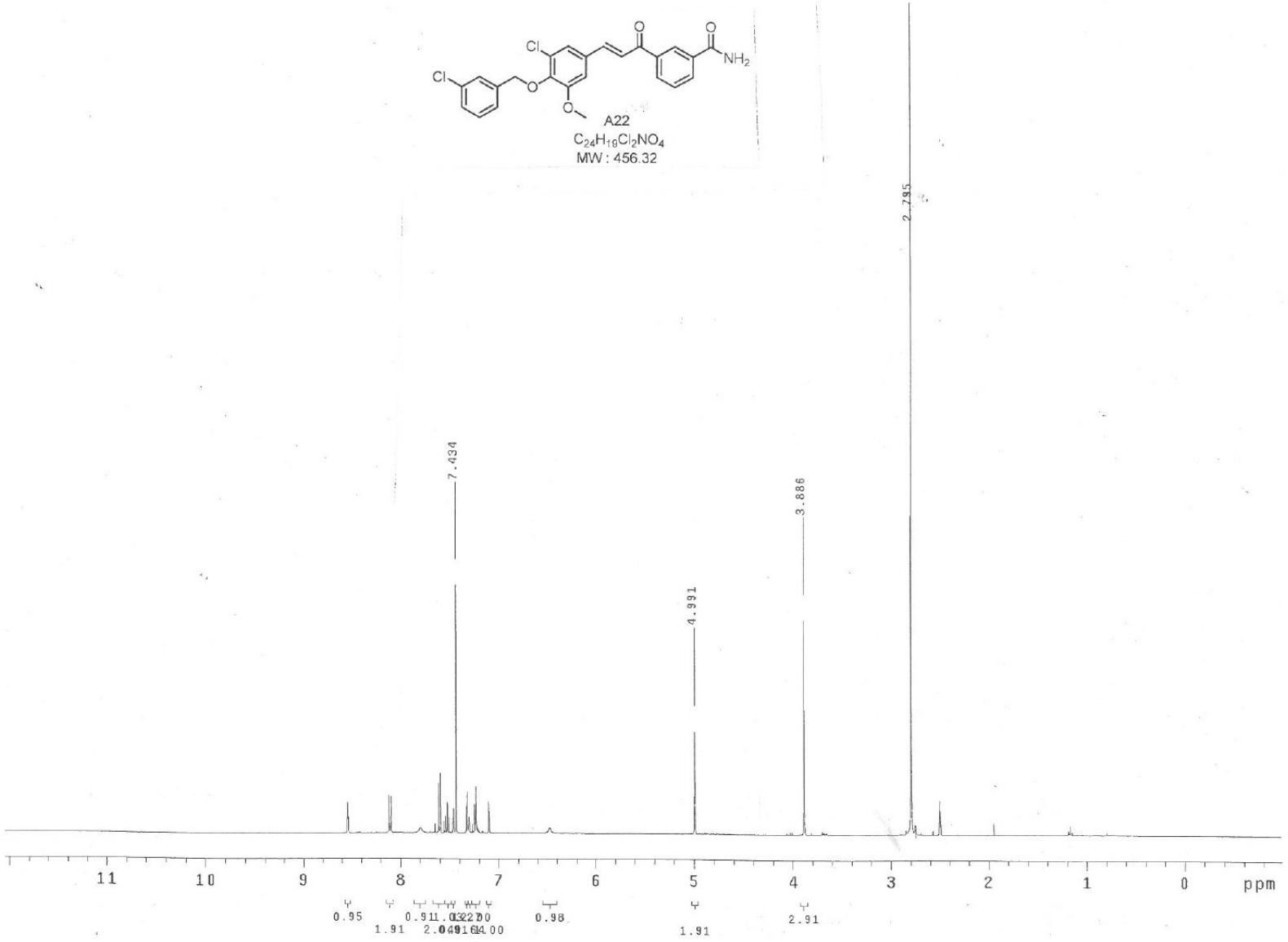


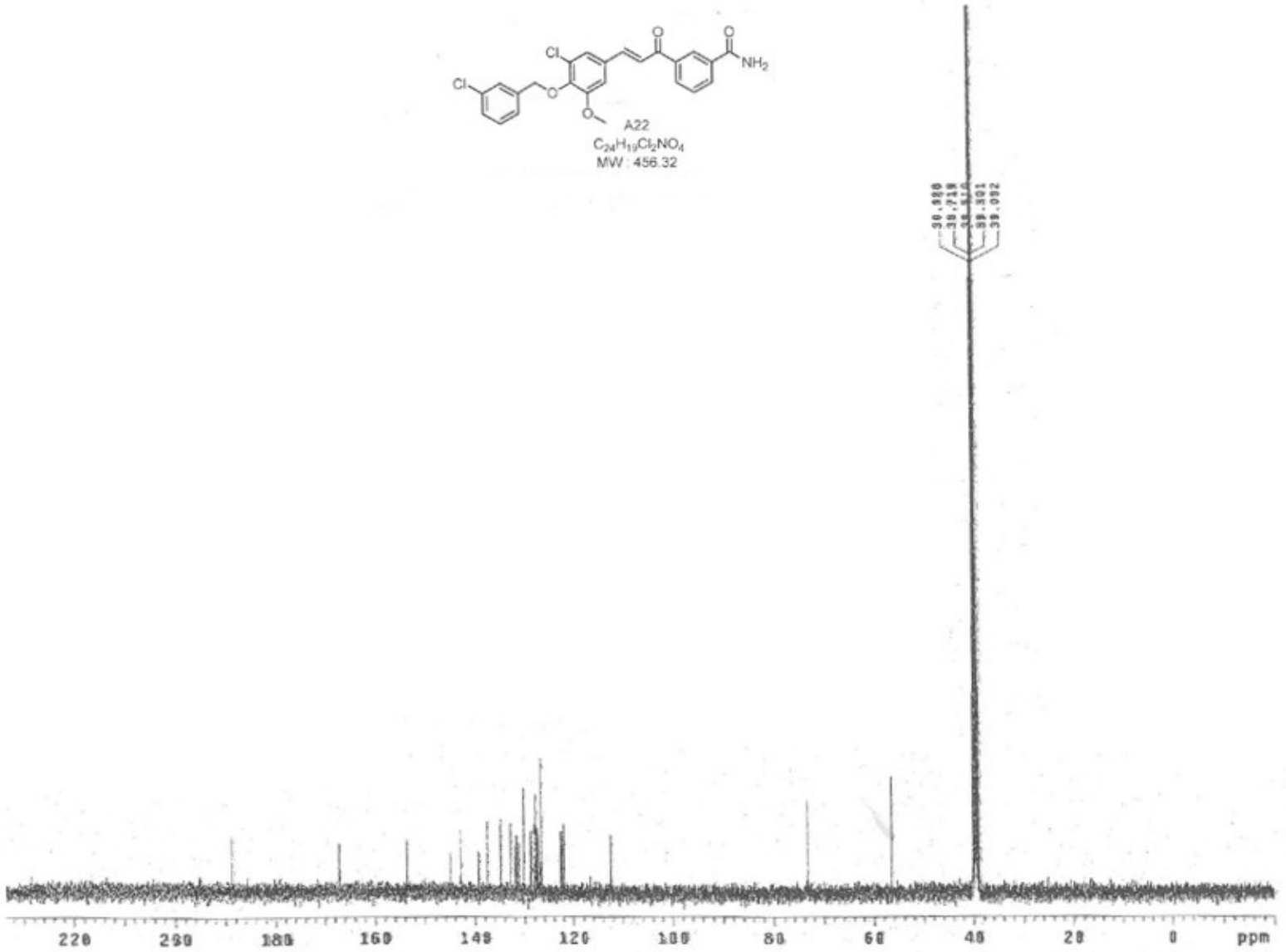
^{13}C NMR spectrum of **A21**



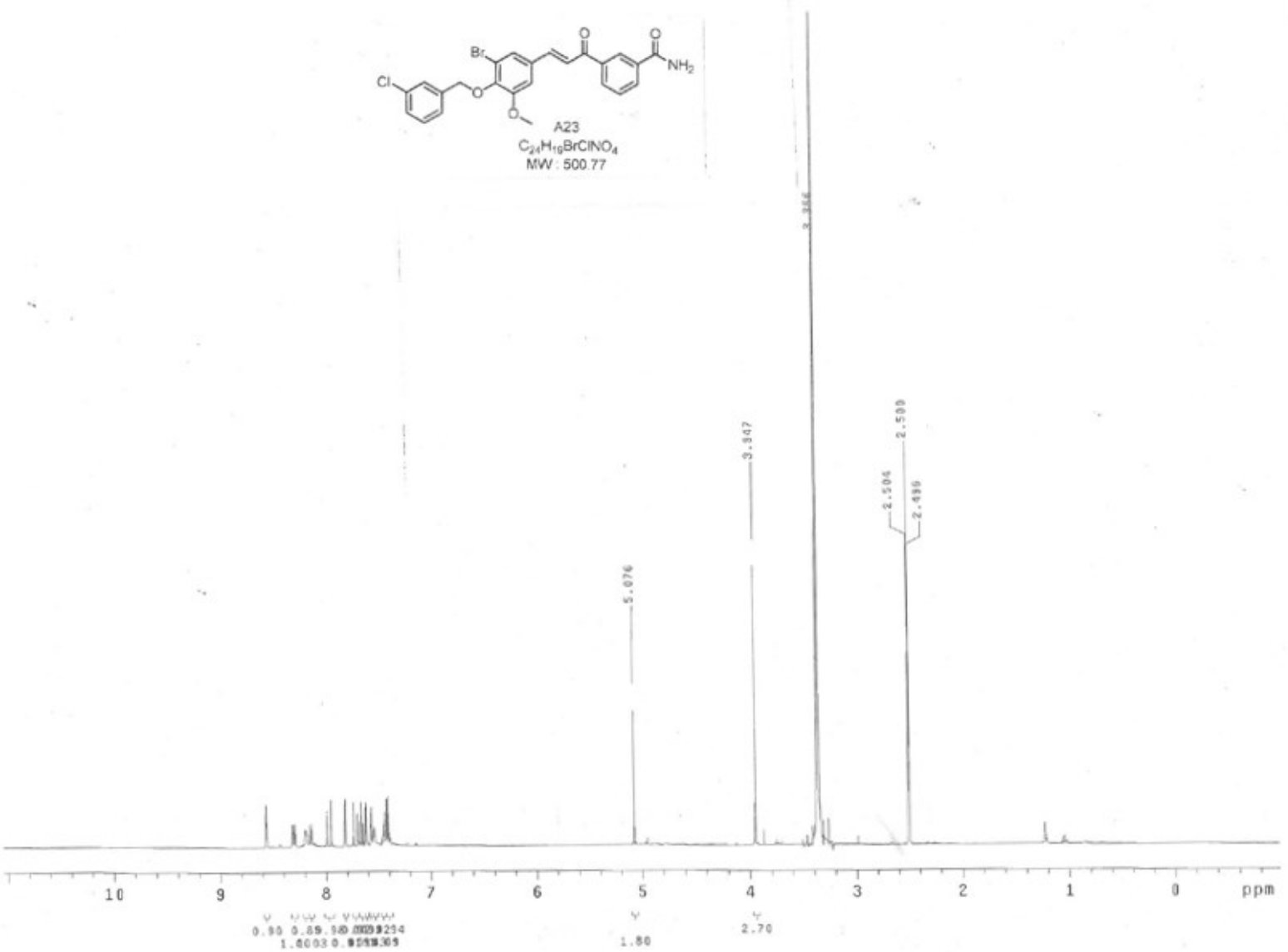
[1]H NMR spectrum of **A22**



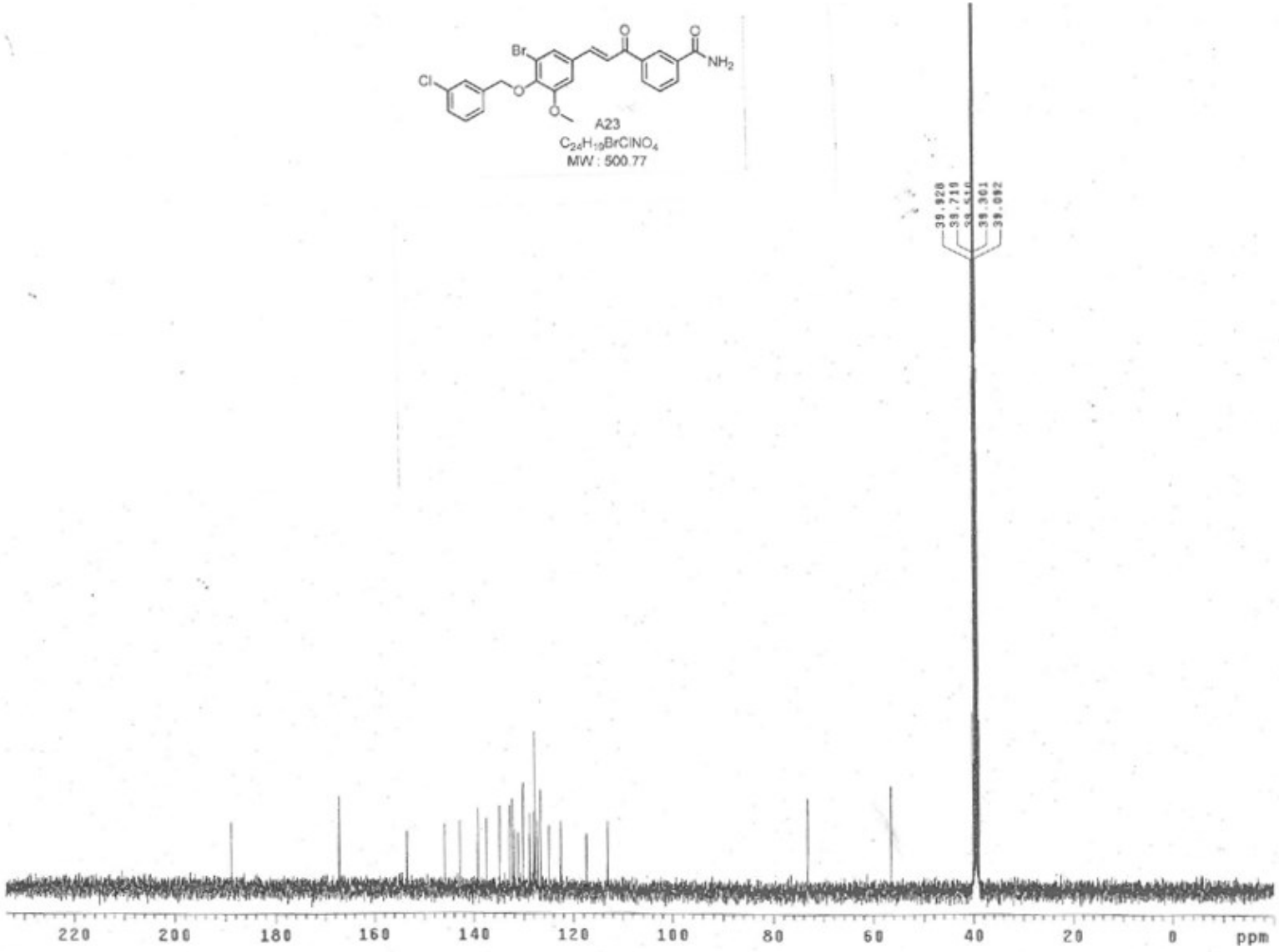
^{13}C NMR spectrum of **A22**



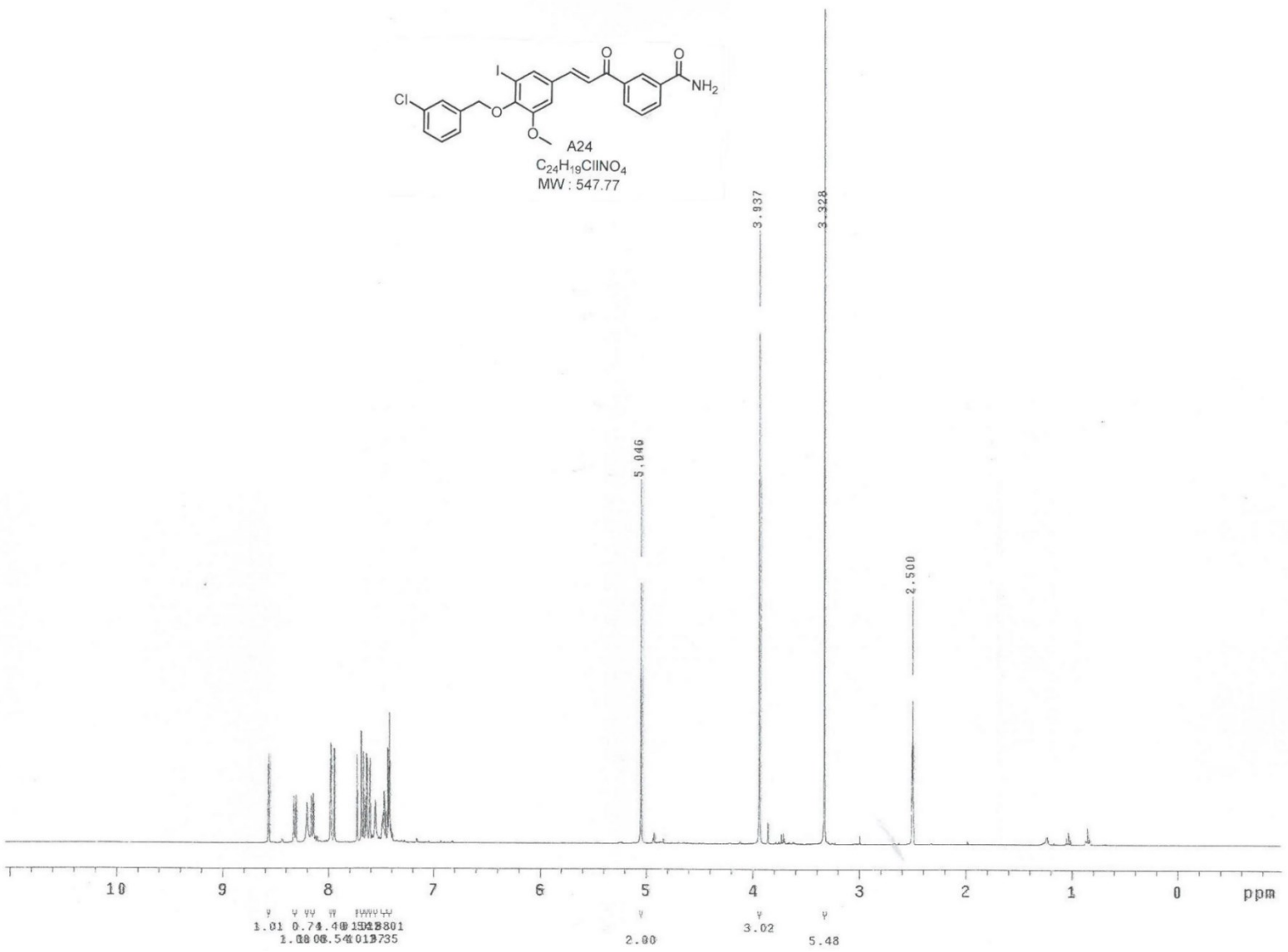
^{1}H NMR spectrum of **A23**



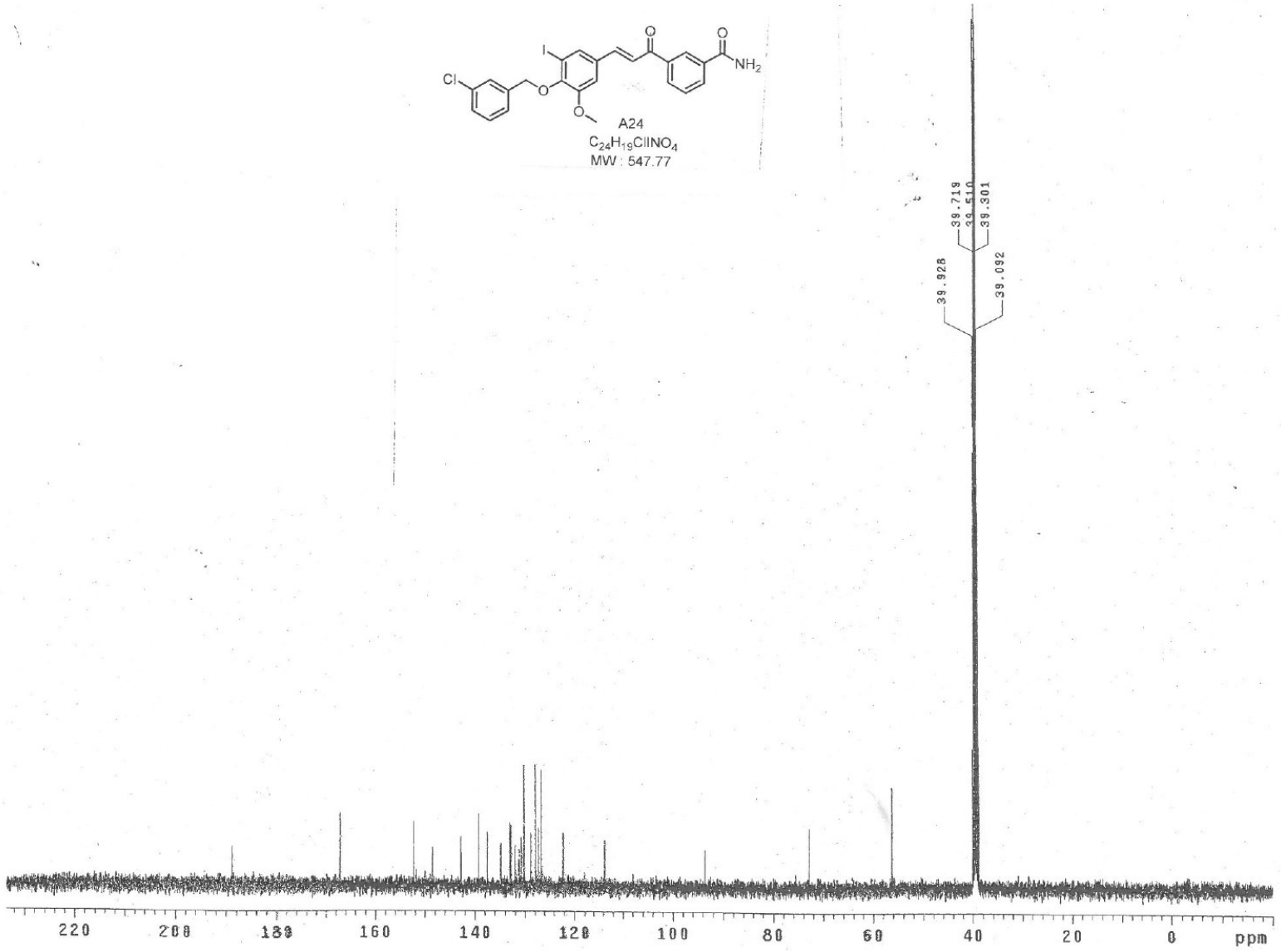
^{13}C NMR spectrum of **A23**



^{1}H NMR spectrum of **A24**



^{13}C NMR spectrum of **A24**



2. Supplementary Figures

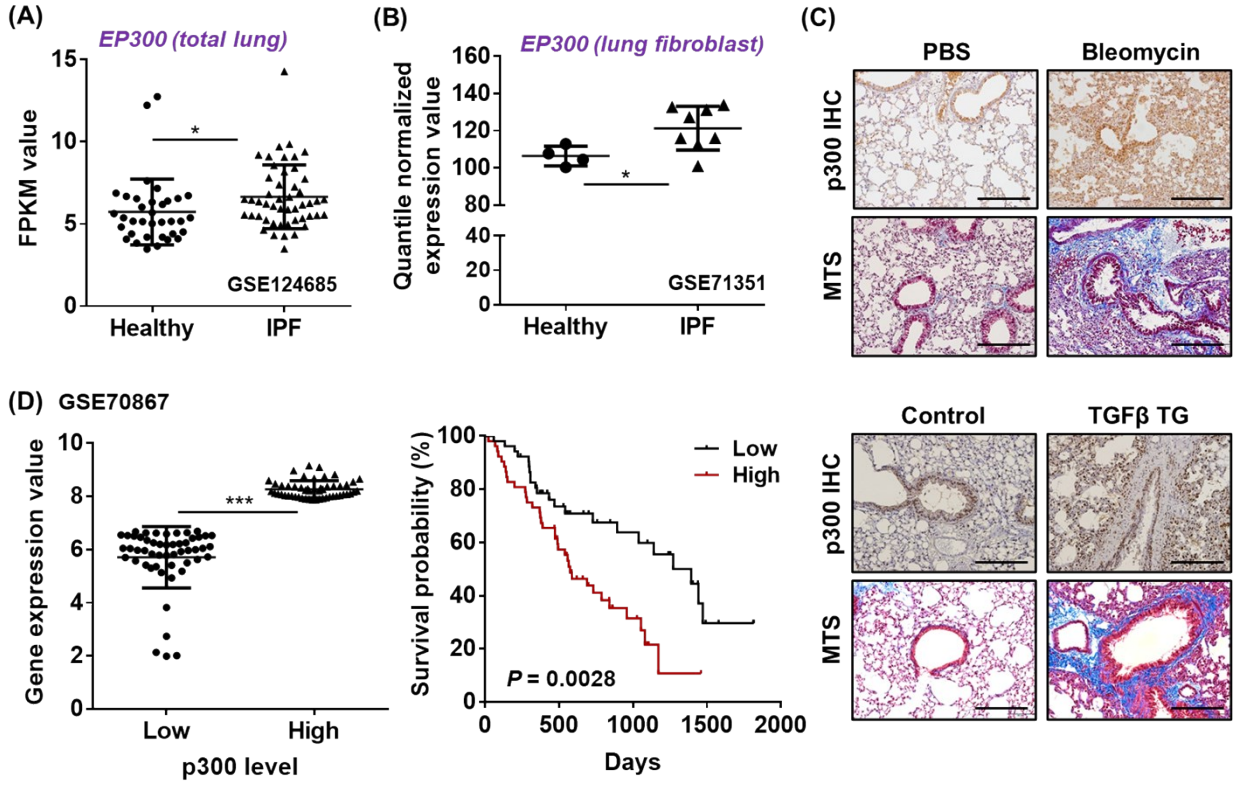
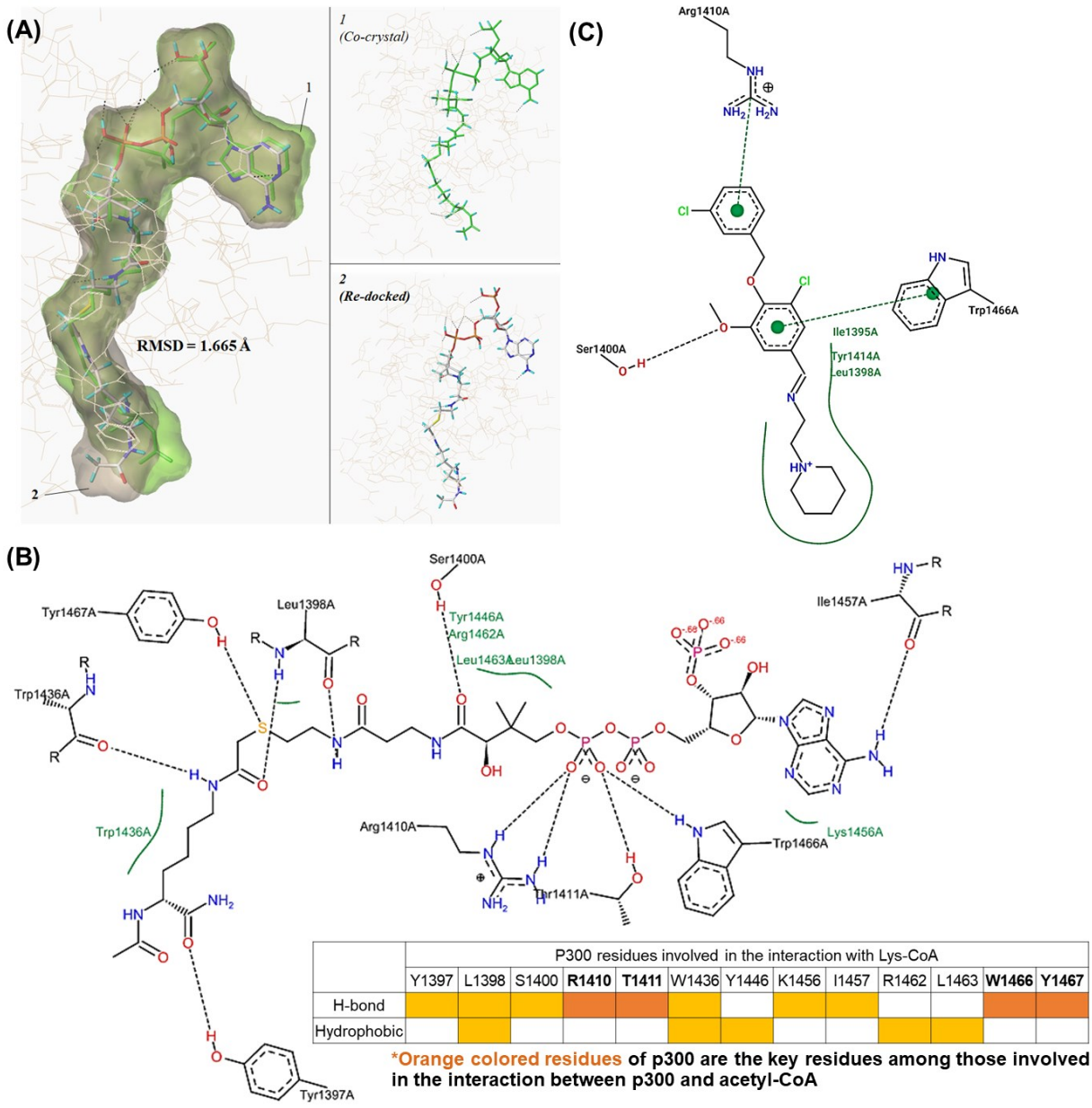


Fig. S1 p300 is highly upregulated in lung fibrosis and is associated with low survival probability of IPF patients. (A) Fragments Per Kilobase of transcript per Million mapped reads (FPKM) of EP300 in the total lung tissue from healthy volunteers (n=35) and IPF patients (n=49) in GSE124685 were compared. *p<0.05 (B) Quantile normalized expression values of EP300 in lung fibroblasts from healthy volunteers (n=4) and IPF patients (n=8) in GSE71351 were assessed. *p<0.05 (C) p300 expression level in lung tissues from both bleomycin-induced mice and inducible TGF-β transgenic mice was evaluated (Scale bars=200 μm). (D) Patients from GSE70867 with normalized expression value of EP300 in the top 30% (n=50) were assigned to $p300^{High}$ group, and those in the bottom 30% (n=50) were placed in the $p300^{Low}$ group. ***p<0.001. The overall survival rate was compared between the $p300^{High}$ and $p300^{Low}$ subgroups. **p<0.01



	P300 residues involved in the interaction with Lys-CoA												
	Y1397	L1398	S1400	**R1410**	**T1411**	W1436	Y1446	K1456	I1457	R1462	L1463	**W1466**	**Y1467**
H-bond													
Hydrophobic													

***Orange colored residues** **of p300 are the key residues among those involved in the interaction between p300 and acetyl-CoA**

Fig. S2 *In silico*-based structural evaluation on the binding mode of Lys-CoA and HAT-12 (A) Lys-CoA (internal ligand within the crystal structure) was redocked to the HAT domain structure (PDB: 3BIY) to validate the final docking method. RMSD value of the redocked Lys-CoA with respect to its original crystallographic orientation was used as the evaluation standard to assess the accuracy and reliability of the method. Calculated RMSD below 2.0 Å[4,5] generally indicates successful prediction. **(B)** 2D interaction diagram of the re-docked model of Lys-CoA from (A) generated through PoseView (https://proteins.plus). Residues of p300 that make hydrogen bonds (H-bonds) or hydrophobic interactions with Lys-CoA are as summarized above. The orange colored residues are the key amino acids generally involved in the interaction with acetyl-CoA during the acetyl group transfer mechanism. **(C)** The binding module of HAT-12 to the p300 HAT domain is demonstrated above. No H-bonds were predicted between this compound and the key four residues, R1410, T1411, W1466, and Y1467.

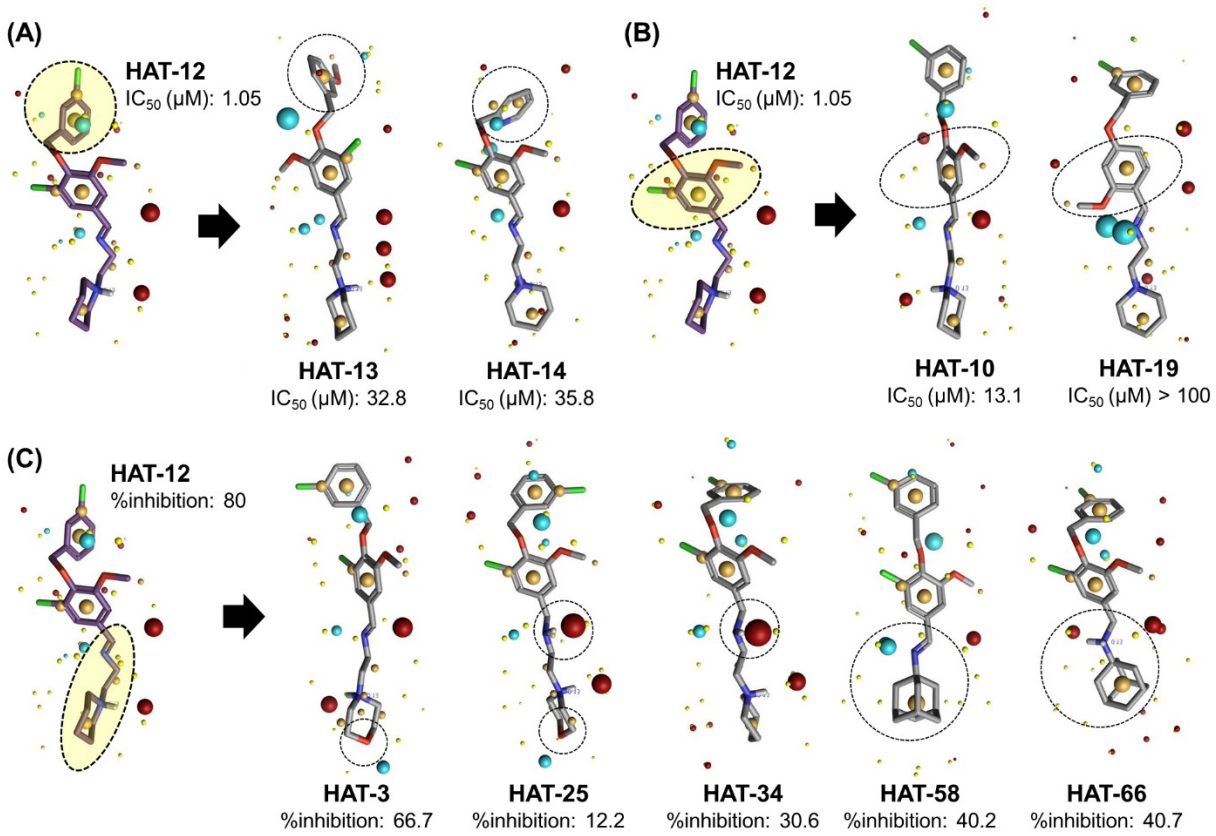


Fig. S3 Qualitative structure and activity relationship landscape of the HAT compounds. (A), (B), and (C) The effects of diverse structural modifications on the p300 inhibitory activity of the compounds were assessed qualitatively with respect to HAT-12. Activity Miner™ software was used for this analysis. Prior to the assessment, field-based alignments were made using HAT-12 as the reference molecule. (A) Replacing the chlorophenyl group with methoxyphenyl (HAT-13) or pyridine (HAT-14) made them much less active (IC_{50} values: HAT-13 = 32.84 μM, HAT-14 = 35.82 μM), which was accompanied by being more distant from the R1410, T1411, and W1466 residues of p300 in the 3D conformation. (B) The absence of the chlorine halogen atom in the *meta* position of the methoxybenzylidene group reduced the potency by 13-fold (HAT-10 IC_{50} = 13.12 μM), suggesting that chlorine is required at this position for potency. Noticeably, the methoxy group on benzylidene at the *meta*-position was found to be especially crucial for compounds to demonstrate inhibitory activity against p300, as its change to the *ortho*-position induced a dramatic loss of effect [IC_{50} (μM) of HAT-10 vs. HAT-19: 13.12 vs. >100]. (C) The inhibitory activities of compounds were also significantly diminished when the benzylidene group was reduced to benzyl [% inhibition at 100 μM of HAT-12 vs. HAT-34: 80 vs. 30.6; HAT-3 vs. HAT-25: 66.7 vs. 12.2]. This can be interpreted as the consequence of rigidity loss in the structure, which leads to conformational changes in the compounds that are relatively unfavorable for interactions with the active site of the p300 protein. Replacing the piperidinoethyl group with morpholinoethyl [% inhibition at 100 μM of HAT-12 vs. HAT-3: 80 vs. 66.7; HAT-34 vs. HAT-25: 30.6 vs. 12.2] or adamantyl [% inhibition at 100 μM of HAT-12 vs. HAT-58 vs. HAT-66: 80 vs. 40.2 vs. 40.7] also generated relatively less-potent molecules against p300 because those changes induced the loss of additional H-bonds formed by the nitrogen atom, binding the compounds less strongly to the active site.

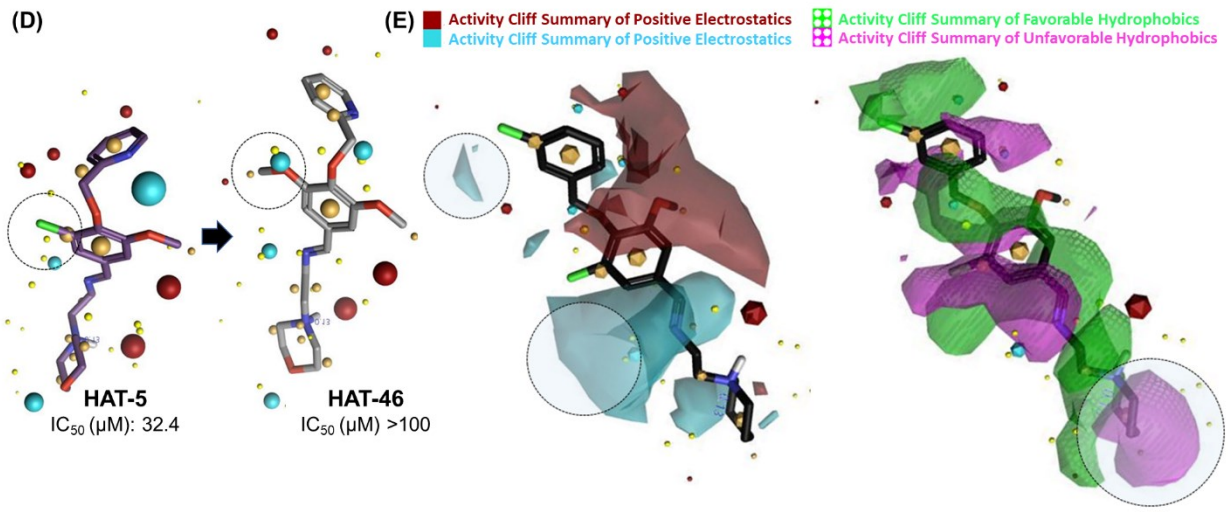


Fig. S3(Cont.). Qualitative structure and activity relationship landscape of the HAT compounds. (D) Qualitative structure and activity relationship (SAR) landscape of HAT compounds. Impact of *m*-chlorine substituent on the p300 inhibitory activity of compound was representatively demonstrated by comparing HAT-5 and HAT-46. Comparing HAT-5 and HAT-46, replacing the m-chlorine on methoxybenzylidene with a methoxy group decreased the activity by at least 3-fold [IC_{50} (μM) of HAT-5 vs. HAT-46: 32.4 vs. >100], again confirming the importance of the halogen atom at this location (E) Activity cliff summary plots for HAT-12 regarding the contributions of the electrostatic (left) and hydrophobic (right) fields. The field point pattern of HAT-12 is depicted as icosahedrons (Red, positive electrostatics; Cyan, negative electrostatics; Yellow brown, hydrophobic fields; Yellow, surface field points).

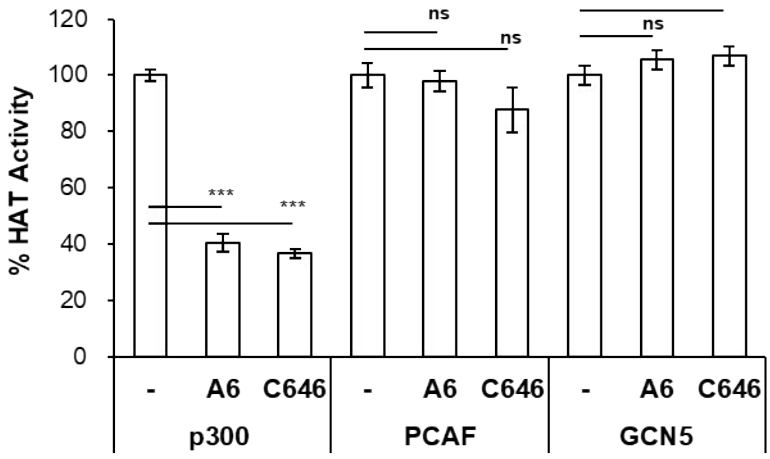


Fig. S4. P300 selective inhibitory effect of A6 on HAT activity. *In vitro* HAT assay was performed in the presence of 100ng of p300, PCAF, or GCN5 with or without 1 μM of indicating compounds. HAT activity was calculated as 100% in each control. ** $p<0.01$; N.S., not significant vs. control.

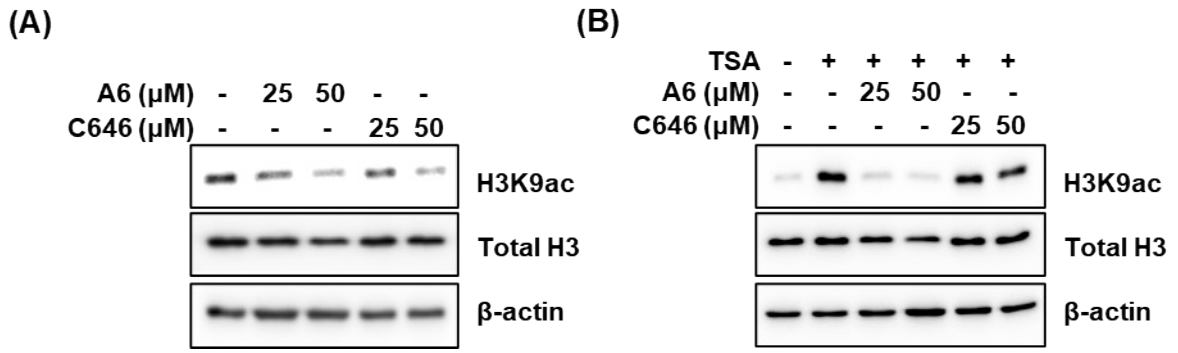


Fig. S5. Inhibitory effect of A6 on histone acetylation. (A) Mlg cells were treated with A6 or C646 for 1 h. (B) Cells were pretreated with A6 or C646 for 1 hour and then incubated with 500 nM trichostatin A (TSA) for 0.5 hour. Immunoblotting with the indicated antibodies.

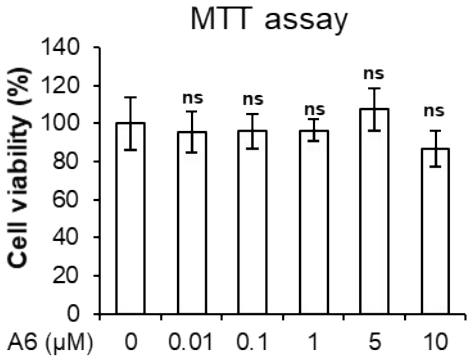


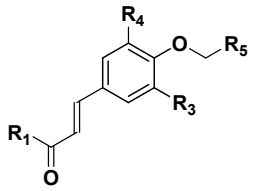
Fig. S6. Cytotoxicity of A6 in fibroblast cells. Mlg cells were treated with indicating dose of A6. Cell viability was measured by MTT assay. ns=non-significant vs. without A6.

3. Supplementary table

Table S1. *O*-benzylated benzaldehyde compounds **1-6**

Comp.	R	R_1	R_2
1	3-chlorophenyl	OCH_3	Cl
2	3-chlorophenyl	OCH_3	Br
3	3-chlorophenyl	OCH_3	I
4	3-carbamoylphenyl	OCH_3	Cl
5	3-carbamoylphenyl	OCH_3	Br
6	3-carbamoylphenyl	OCH_3	I

Table S2. Synthesized chalcone compounds A1–A24 and their *in vitro* p300 inhibitory activity



Comp.	R_1	R_3	R_4	R_5	IC_{50} (μM)[a]
C646	-	-	-	-	0.36
A1	3-aminophenyl	OCH_3	Cl	3-carbamoylphenyl	36.54
A2	3-aminophenyl	OCH_3	Br	3-carbamoylphenyl	24.64
A3	3-aminophenyl	OCH_3	I	3-carbamoylphenyl	46.68
A4	3-carbamoylphenyl	OCH_3	Cl	3-carbamoylphenyl	6.71
A5	3-carbamoylphenyl	OCH_3	Br	3-carbamoylphenyl	22.94
A6	3-carbamoylphenyl	OCH_3	I	3-carbamoylphenyl	0.87
A7	3-hydroxylphenyl	OCH_3	Cl	3-carbamoylphenyl	5.84
A8	3-hydroxylphenyl	OCH_3	Br	3-carbamoylphenyl	1.06
A9	3-hydroxylphenyl	OCH_3	I	3-carbamoylphenyl	10.93
A10	3,4,5-trimethoxyphenyl	OCH_3	Cl	3-chlorophenyl	> 50
A11	3,4,5-trimethoxyphenyl	OCH_3	Br	3-chlorophenyl	> 50
A12	3,4,5-trimethoxyphenyl	OCH_3	I	3-chlorophenyl	> 50
A13	3,4,5-trimethoxyphenyl	OCH_3	Cl	3-carbamoylphenyl	> 50
A14	3,4,5-trimethoxyphenyl	OCH_3	Br	3-carbamoylphenyl	> 50
A15	3,4,5-trimethoxyphenyl	OCH_3	I	3-carbamoylphenyl	1.82
A16	3-hydroxylphenyl	OCH_3	Cl	3-chlorophenyl	> 50
A17	3-hydroxylphenyl	OCH_3	Br	3-chlorophenyl	40.51
A18	3-hydroxylphenyl	OCH_3	I	3-chlorophenyl	43.3
A19	3-aminophenyl	OCH_3	Cl	3-chlorophenyl	> 50
A20	3-aminophenyl	OCH_3	Br	3-chlorophenyl	> 50
A21	3-aminophenyl	OCH_3	I	3-chlorophenyl	> 50
A22	3-carbamoylphenyl	OCH_3	Cl	3-chlorophenyl	> 50
A23	3-carbamoylphenyl	OCH_3	Br	3-chlorophenyl	> 50
A24	3-carbamoylphenyl	OCH_3	I	3-chlorophenyl	22.68

Table S3. The physical properties of **A6**

MW (g/mol)	Solubility (pH 7.0)	Log P	pKa
556.36	364.7 ± 1.3 μM (202.9 ± 1.0 μg/ml)	5.43	4.91/12.12

Table S4. Genotoxicity of **A6** as measured by the Ames test

Tester strain	Compound	Dose (μg/plate)	Revertant colonies/plate[a] (Mean ± S.D.) [Factor][#]	
			Without S-9 mix	With S-9 mix
TA98	Vehicle	0	15±2	25±3
	A6	8	15±2 [1.0]	26±1 [1.0]
TA100	Vehicle	0	98±9	125±7
	A6	8	110±3 [1.1]	137±5 [1.1]

[a]**Ames test**: evaluating the number of revertant colonies on a compound treated plate. The test was conducted with the maximum concentration at which the compound was soluble and nontoxic to the *S. typhimurium* tester strains.
[#]No. of revertant colonies on treated plate/No. of revertant colonies on vehicle control plate

Table S5. Cardiotoxicity of **A6** measured by hERG channel ligand binding assay

Treatment	Concentration (μM)	% Inhibition of hERG ligand binding[a]	IC_{50} (μM)[a]
E-4031	10	88.1±13.3	-
A6	10	14.8±10.6	91.1

[a]**hERG channel binding assay:** measuring the inhibitory activity against the hERG channel and its ligand using a red fluorescent hERG channel ligand tracer. Final activity was assessed as the decrease in the degree of fluorescence polarization. E-4031 is used as a control as well-known experimental antiarrhythmic drug that blocks potassium channels of hERG.[6]

Table S6. Acute toxicity of **A6**

Species	Sex	Dose (mg/kg)[b]	**Lethality (%)**
Mouse[a]	Male (n=3)	1000	**0 (0/3)**
	Female (n=3)	1000	**0 (0/3)**

[a] 9-week-old ICR mice were used.
[b]A dose of 1000 mg/kg in a formulation of 10% DMSO in corn oil was administered orally using a feeding needle.

Table S7. Pharmacokinetic properties of **A6**

	C646		**A6**	
Parameters	IV, 2 mg/kg	PO, 5 mg/kg	IV, 2 mg/kg	PO, 5 mg/kg
T_{max} (h)	NA	0.83 ± 0.29	NA	0.50 ± 0.00
C_{max} (μg/mL)	NA	0.04 ± 0.02	NA	0.15 ± 0.03
$T_{1/2}$ (h)	0.12 ± 0.00	1.22 ± 0.47	3.99 ± 0.08	3.51 ± 1.21
AUC_{last} (μg·h/ml)	0.15 ± 0.06	0.05 ± 0.02	0.46 ± 0.04	0.15 ± 0.04
AUC_{∞} (μg·h/ml)	0.15 ± 0.06	0.50 ± 0.18	0.47 ± 0.04	0.17 ± 0.05
CL (L/h/kg)	14.87 ± 5.44	NA	4.23 ± 0.34	NA
V_{ss} (L/kg)	1.29 ± 0.60	NA	13.87 ± 1.16	NA
F_t (%)	NA	13.5	NA	13.37

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