Supporting Information

A Divergent Approach to Flavones and Aurones via Dihaloacrylic Acids. Unexpected Dependence on the Halogen Atom

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Contents

A. Experimental Details and Characterization Data.

I. General

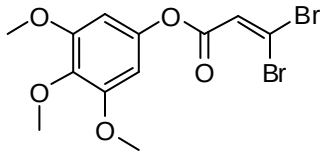
Unless otherwise noted, materials were obtained from commercial suppliers and used without purification. Tetrahydrofuran and diethyl ether were distilled from sodium and benzophenone. Dichloromethane, benzene and diisopropyl amine were distilled over calcium hydride. All experiments were performed under an argon atmosphere unless otherwise noted. Organic extracts were dried over anhydrous magnesium sulfate. Nuclear magnetic resonance experiments were performed with either a Varian 300 MHz or 400 MHz instrument. All chemical shifts are reported relative to $CDCl_3$ (7.27 ppm for ^1H and 77.23 ppm for ^{13}C), unless otherwise noted. Coupling constants (*J*) are reported in Hz with abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Low resolution and high resolution mass spectra were recorded on a Q-TOF mass spectrometer. Standard grade silica gel (60 Å, 32-63 µm) was used for flash column chromatography.

II. Synthetic Experimental Procedure

Representative procedure for steglich esterification

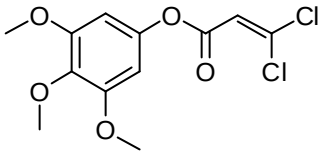
A solution of 3,4,5-trimethoxyphenol **6a** (2.30 g, 12.44 mmol), acrylic acid derivative **7b** (1.93 g, 13.69 mmol) and DMAP (0.15 g, 1.24 mmol) in 10 ml of dry CH_2Cl_2 and 2 ml of dry DMF was treated at 0 ^oC under argon with DCC (2.60 g, 12.44 mmol). The mixture was stirred for 5 min at 0 ^oC and 30 min at room temperature. After the completion of reaction, reaction mixture was filtered through celite and diluted with CH_2Cl_2 followed by washing twice with HCl (1.0 M) and twice with saturated solution of $NaHCO_3$. The organic phase was washed with brine, dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. Residue was purified by column chromatography using 12.5% EtOAc/hexanes as elutent to give pure product.

3,4,5-Trimethoxyphenyl 3,3-dibromoacrylate (9)



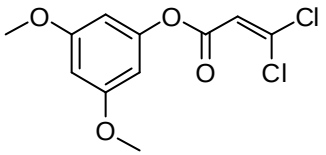
Yield = 71%; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.20 (s, 1H), 6.36 (s, 2H), 3.82 (s, 6H), 3.81 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 161.1, 153.6, 146.2, 136.1, 127.1, 109.9, 99.0, 61.1, 56.4; MS (*m/z*): 396.9113; HRMS calcd for $C_{12}H_{12}Br_2O_5$: 393.9051, found: 393.9056.

3,4,5-Trimethoxyphenyl 3,3-dichloroacrylate (13a)



Yield = 71%; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.54 (s, 1H), 6.33 (s, 2H), 3.78 (s, 9H); ^{13}C NMR (100MHz, $CDCl_3$): δ 160.7, 153.5, 146.1, 140.1, 135.9, 119.2, 119.1, 98.9, 98.9, 98.9, 60.9, 56.1; MS (*m/z*): 307.0128; HRMS calcd for $C_{12}H_{12}Cl_2O_5$: 306.0062, found: 306.0055.

3,5-Dimethoxyphenyl 3,3-dichloroacrylate (13b)

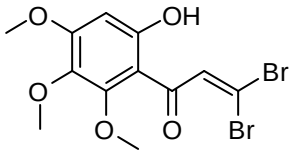


Yield = 77%; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.58 (d, J = 0.6 Hz, 1H), 6.36 (s, 1H), 6.28 – 6.32 (m, 2H), 3.77 (s, 6H); ^{13}C NMR (100MHz, $CDCl_3$): δ 161.3, 160.7, 151.7, 140.2, 119.4, 119.3, 100.2, 100.1, 98.7, 55.7; MS (*m/z*): 277.0026, 225.1957; HRMS calcd for $C_{11}H_{10}Cl_2O_4$: 275.9956, found: 275.9953.

Representative procedure for Fries rearrangement of **9** and **13a-b**

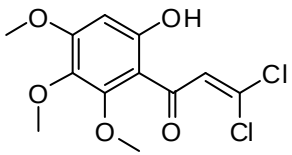
Ester **13a** (1.0 g, 3.26 mmol) was taken in dry 1,2-dichloroethane (75 ml) and added to a slurry of $AlCl_3$ (0.48 g, 3.60 mmol) in 1,2-dichloroethane (25 ml) at 0 ^{o}C under argon. Resulting dark brown solution was refluxed with monitoring. After the completion of reaction, the reaction mixture was poured over 1:1 mixture of ice and HCl (1.0 M) and stirred for 30 min. Organic phase was separated and aqueous layer was extracted with CH_2Cl_2 (3 x 100 ml). Combined organic phases were then washed with water, brine and dried over anhydrous $MgSO_4$. Solvent was evaporated under reduced pressure and crude product was purified by column chromatography using 10% EtOAc/hexanes as elutent.

3,3-Dibromo-1-(6-hydroxy-2,3,4-trimethoxyphenyl)prop-2-en-1-one (10)



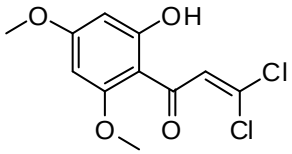
Yield: 41%; ^{1}H NMR (400MHz, $CDCl_3$) δ 12.78 (s, 1H), 7.86 (s, 1H), 6.24 (s, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.77 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 191.1, 162.9, 161.6, 154.8, 137.6, 108.2, 97.6, 96.6, 96.5, 61.9, 61.4, 56.5; MS (*m/z*): 396.9113; HRMS calcd for $C_{12}H_{12}Br_2O_5$: 393.9051, found: 393.9056.

3,3-Dichloro-1-(6-hydroxy-2,3,4-trimethoxyphenyl)prop-2-en-1-one (14a)



Yield: 40%; ^{1}H NMR (400MHz, $CDCl_3$) δ 12.90 (s, 1H), 7.40 (s, 1H), 6.25 (s, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 189.8, 162.8, 161.3, 154.7, 135.3, 131.4, 128.9, 108.4, 96.6, 61.9, 61.4, 56.4; MS (*m/z*): 307.0128; HRMS calcd for $C_{12}H_{12}Cl_2O_5$: 306.0062, found: 306.0055.

3,3-Dichloro-1-(2-hydroxy-4,6-dimethoxyphenyl)prop-2-en-1-one (14b)

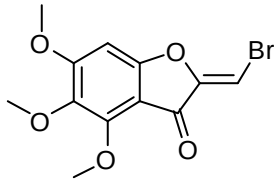


Yield: 60%; ^{1}H NMR (400MHz, $CDCl_3$) δ 13.46 (s, 1H), 7.35 (s, 1H), 6.07 (d, J = 4.0 Hz, 1H), 5.90 (d, J = 2.2 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 189.3, 168.4, 167.3, 162.3, 131.6, 129.3, 106.1, 94.0, 91.5, 56.3, 55.9; MS (*m/z*): 277.0026, 241.0263, 223.0596, 197.0805; HRMS calcd for $C_{11}H_{10}Cl_2O_4$: 275.9956, found: 275.9953.

Representative procedure for base mediated cyclization of **10** and **14a-b**

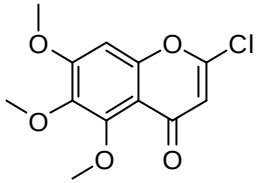
Phenol **14a** was taken in THF (5 ml) and to this, NaOH (33.0 ml, 0.02 N) solution was added at 0 ^{o}C. Resulting reaction mixture was stirred at room temperature for 3 h with monitoring. After the completion of reaction, reaction mixture was acidified by HCl (1.0 M) to a pH 5 and extracted with EtOAc (3 x 50 ml). Combined organic extracts were then washed with water and brine, dried over anhydrous $MgSO_4$, filtered and evaporated *in vacuo* to obtain crude chromone **15a**. The crude compound was then purified by column chromatography using 50% EtOAc/hexanes as elutent.

2-(Bromomethylene)-4,5,6-trimethoxybenzofuran-3(2H)-one (11b)



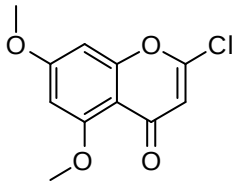
Yield: 64%; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.74 (s, 1H), 6.48 (s, 1H), 4.19 (s, 3H), 3.94 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 177.4, 164.0, 162.4, 152.3, 152.0, 136.9, 107.2, 94.8, 90.8, 62.5, 61.8, 56.9; MS (*m/z*): 314.9858; HRMS calcd for $C_{12}H_{11}BrO_5$: 314.9863, found: 314.9858.

2-Chloro-5,6,7-trimethoxy-4H-chromen-4-one (15a)



Yield: 65%; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.24 (s, 1H), 3.94 (s, 6H), 3.89 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 175.8, 158.0, 154.7, 153.9, 152.8, 141.1, 112.1, 111.8, 96.3, 62.4, 61.7, 56.5; MS (*m/z*): 271.0361, 139.9717; HRMS calcd for $C_{12}H_{11}ClO_5$: 270.0295, found: 270.0288.

2-Chloro-5,7-dimethoxy-4H-chromen-4-one (15b)

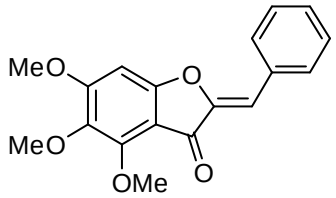


Yield: 68%; ^{1}H NMR (400MHz, $CDCl_3$) δ 6.43 (d, J = 2.1 Hz, 1H), 6.36 (d, J = 2.0 Hz, 1H), 6.22 (s, 1H), 3.91 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 176.2, 164.4, 161.1, 160.1, 153.5, 112.5, 108.4, 97.0, 92.9, 56.7, 56.1; MS (*m/z*): 241.0260, 223.0595, 197.0804; HRMS calcd for $C_{11}H_9ClO_4$: 240.0189, found: 240.0187.

Representative procedure for Suzuki coupling to prepare aurones **12a-c**

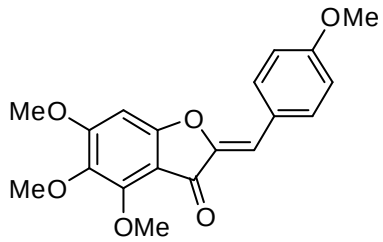
A 100 ml oven dried round bottom flask, equipped with a stir bar is charged with anhydrous dioxane (10 ml), powdered anhydrous K_2CO_3 (0.26 g, 1.90 mmol), phenylboronic acid (**8a**) (0.1161 g, 0.95 mmol) and aurone precursor **11b** (0.20 g, 0.635 mmol). Nitrogen was passed through the resulting reaction mixture for at least 20 min. To this was added the $Pd(PPh_3)_4$ (0.037g, 0.032 mmol) catalyst and resulting reaction mixture was heated to 90 ^{o}C and stirred with constant monitoring. After the completion of the reaction (6 h), reaction mixture was filtered through celite and evaporated under reduced pressure. The residue was partitioned between water and ethyl acetate and organic phase was separated. Aqueous layer was washed with ethyl acetate (2 x 30 ml) and all organic phases were mixed together, washed with brine and dried over anhydrous magnesium sulfate. Solvent was evaporated under reduced pressure to obtain crude aurone **12a** which was purified by silica gel column chromatography using 50% EtOAc:hexanes as elutent to obtain pure aurone **12a** in 85% isolated yield.

(*Z*)-2-benzylidene-4,5,6-trimethoxybenzofuran-3(2*H*)-one (12a)



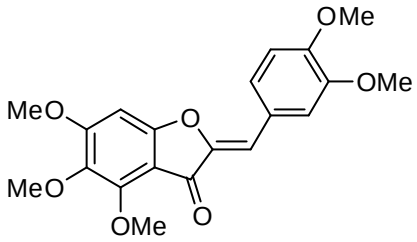
Yield: 85%; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.86 (d, J = 8.0 Hz, 2H), 7.43 (t, J = 8.0 Hz, 2H), 7.37 (d, J = 4.0 Hz, 1H), 6.76 (s, 1H), 6.54 (s, 1H), 4.25 (s, 3H), 3.97 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 181.0, 164.3, 161.9, 151.9, 147.9, 136.8, 132.7, 131.4, 129.7, 129.0, 111.4, 107.2, 90.8, 62.6, 61.9, 56.9; MS (*m/z*): 313.11, 187.08, 121.05; HRMS calcd for $C_{18}H_{16}O_5$: 313.1071, found: 313.1074.

(Z)-4,5,6-trimethoxy-2-(4-methoxybenzylidene)benzofuran-3(2H)-one (12b)



Yield: 81%; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.82 (d, J = 12.0 Hz, 2H), 6.95 (d, J = 8.0 Hz, 2H), 6.75 (s, 1H), 6.54 (s, 1H), 4.25 (s, 3H), 3.97 (s, 3H), 3.86 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 181.0, 164.0, 161.6, 160.9, 151.8, 146.8, 136.7, 133.2, 125.4, 114.6, 111.7, 107.5, 90.7, 62.7, 61.9, 56.8, 55.6; MS (*m/z*): 343.1169; HRMS calcd for $C_{19}H_{18}O_6$: 342.1103, found: 342.1096.

(Z)-2-(3,4-dimethoxybenzylidene)-4,5,6-trimethoxybenzofuran-3(2H)-one (12c)

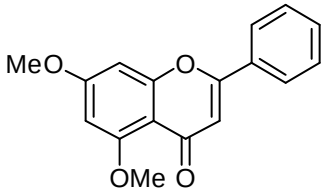


Yield: 80%; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.43 – 7.48 (m, 2H), 6.93 (d, J = 8.0 Hz, 1H), 6.74 (s, 1H), 6.51 (s, 1H), 4.26 (s, 3H), 3.99 (s, 3H), 3.97 (s, 3H), 3.94 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 180.9, 163.9, 161.6, 151.8, 150.7, 149.2, 146.8, 136.8, 125.7, 125.6, 113.7, 112.0, 111.4, 107.5, 90.7, 62.7, 61.9, 56.9, 56.2, 56.1; MS (*m/z*): 373.1287; HRMS calcd for $C_{20}H_{20}O_7$: 372.1209, found: 372.1214.

Representative procedure for Suzuki coupling to prepare flavones **1-5**

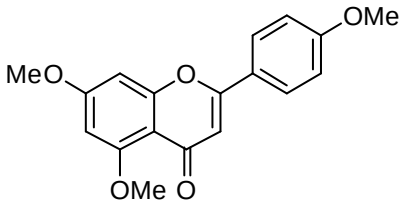
A 100 ml oven dried round bottom flask, equipped with a stir bar is charged with anhydrous dioxane (10 ml), powdered anhydrous K_2CO_3 (0.345 g, 2.49 mmol), phenylboronic acid (**8a**) (0.2030 g, 1.66 mmol) and chromone **15b** (0.20 g, 0.831 mmol). Nitrogen was passed through the resulting reaction mixture for at least 20 min. To this was added the $Pd(PPh_3)_4$ (0.048 g, 0.042 mmol) catalyst and resulting reaction mixture was refluxed with constant monitoring. After the completion of the reaction (18 h), reaction mixture was filtered through celite and evaporated under reduced pressure. The residue was partitioned between water and ethyl acetate and organic phase was separated. Aqueous layer was washed with ethyl acetate (2 x 30 ml) and all organic phases were mixed together, washed with brine and dried over anhydrous magnesium sulfate. Solvent was evaporated under reduced pressure to obtain crude flavone **1** which was purified by silica gel column chromatography using 2% MeOH:DCM as elutent to obtain pure flavone **1** in 74% isolated yield.

5,7-dimethoxy-2-phenyl-4H-chromen-4-one (1)



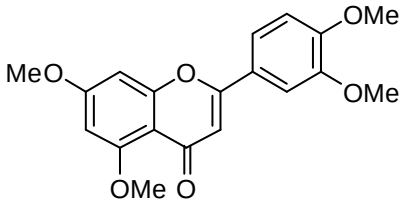
Yield: 74%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.88 (m, 2H), 7.46 – 7.52 (m, 3H), 6.68 (s, 1H), 6.57 (d, J = 2.3 Hz, 1H), 6.37 (d, J = 2.3 Hz, 1H), 3.95 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 164.2, 161.0, 160.8, 160.1, 131.7, 131.4, 129.1, 126.1, 109.3, 109.2, 96.4, 93.0, 56.7, 56.0; MS (*m/z*): 283.0963, 269.0804; HRMS calcd for $C_{17}H_{14}O_4$: 282.0892, found: 282.0890.

5,7-dimethoxy-2-(4-methoxyphenyl)-4H-chromen-4-one (2)



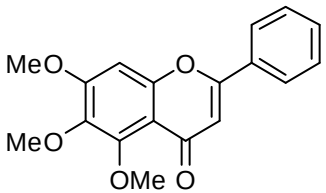
Yield: 72%; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 6.96 (d, J = 8.0 Hz, 2H), 6.56 (s, 1H), 6.51 (d, J = 4.0 Hz, 1H), 6.32 (d, J = 4.0 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.6, 163.8, 161.9, 160.7, 160.6, 159.7, 127.5, 123.7, 114.3, 109.1, 107.6, 96.0, 92.8, 56.4, 55.7, 55.4; MS (*m/z*): 313.1062; HRMS calcd for $C_{18}H_{16}O_5$: 313.0998, found: 313.0989.

2-(3,4-dimethoxyphenyl)-5,7-dimethoxy-4H-chromen-4-one (3)



Yield: 69%; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.46 (d, J = 8.0 Hz, 1H), 6.92 (d, J = 8.0 Hz, 1H), 6.57 (s, 1H), 6.52 (s, 1H), 6.33 (s, 1H), 3.94 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.8, 164.1, 161.0, 160.8, 160.0, 151.8, 149.3, 124.1, 119.6, 111.2, 109.3, 108.6, 108.1, 108.0, 96.3, 93.0, 56.6, 56.3, 56.0; MS (*m/z*): 343.1177, 329.1014; HRMS calcd for $C_{19}H_{18}O_6$: 342.1103, found: 342.1104.

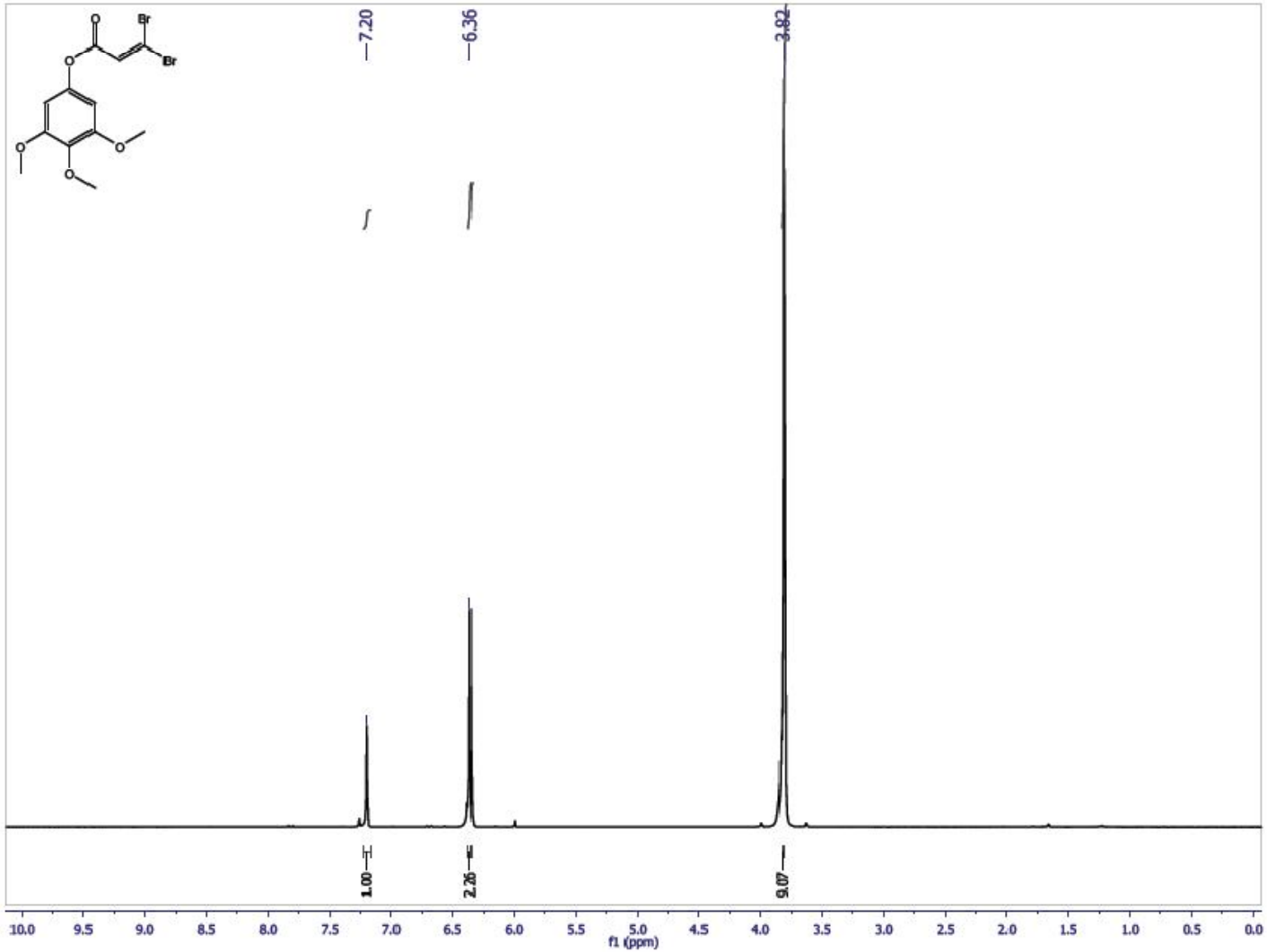
5,6,7-Trimethoxy-2-phenyl-4H-chromen-4-one (4)



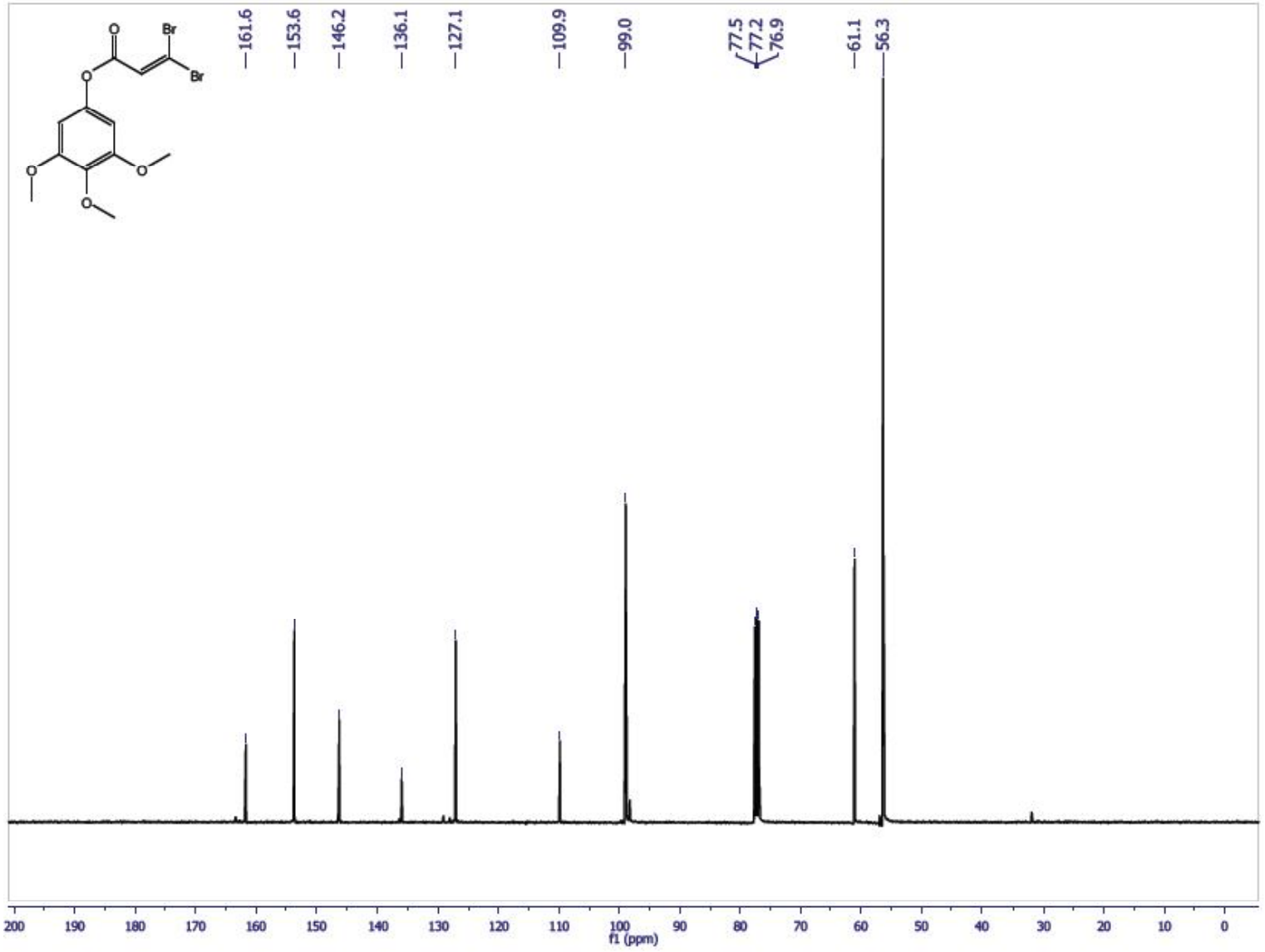
Yield: 67%; ^{1}H NMR (400MHz, $CDCl_3$) δ 7.84 – 7.88 (m, 2H), 7.50 (d, J = 2.0 Hz, 2H), 7.48 (d, J = 2.0 Hz, 1H), 6.80 (s, 1H), 6.66 (s, 1H), 3.98 (s, 3H), 3.97 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 177.4, 161.3, 157.9, 154.7, 152.7, 140.5, 131.7, 131.5, 129.1, 126.1, 113.1, 108.6, 96.5, 62.4, 61.7, 56.5.

B. ^{1}H and ^{13}C NMR spectra

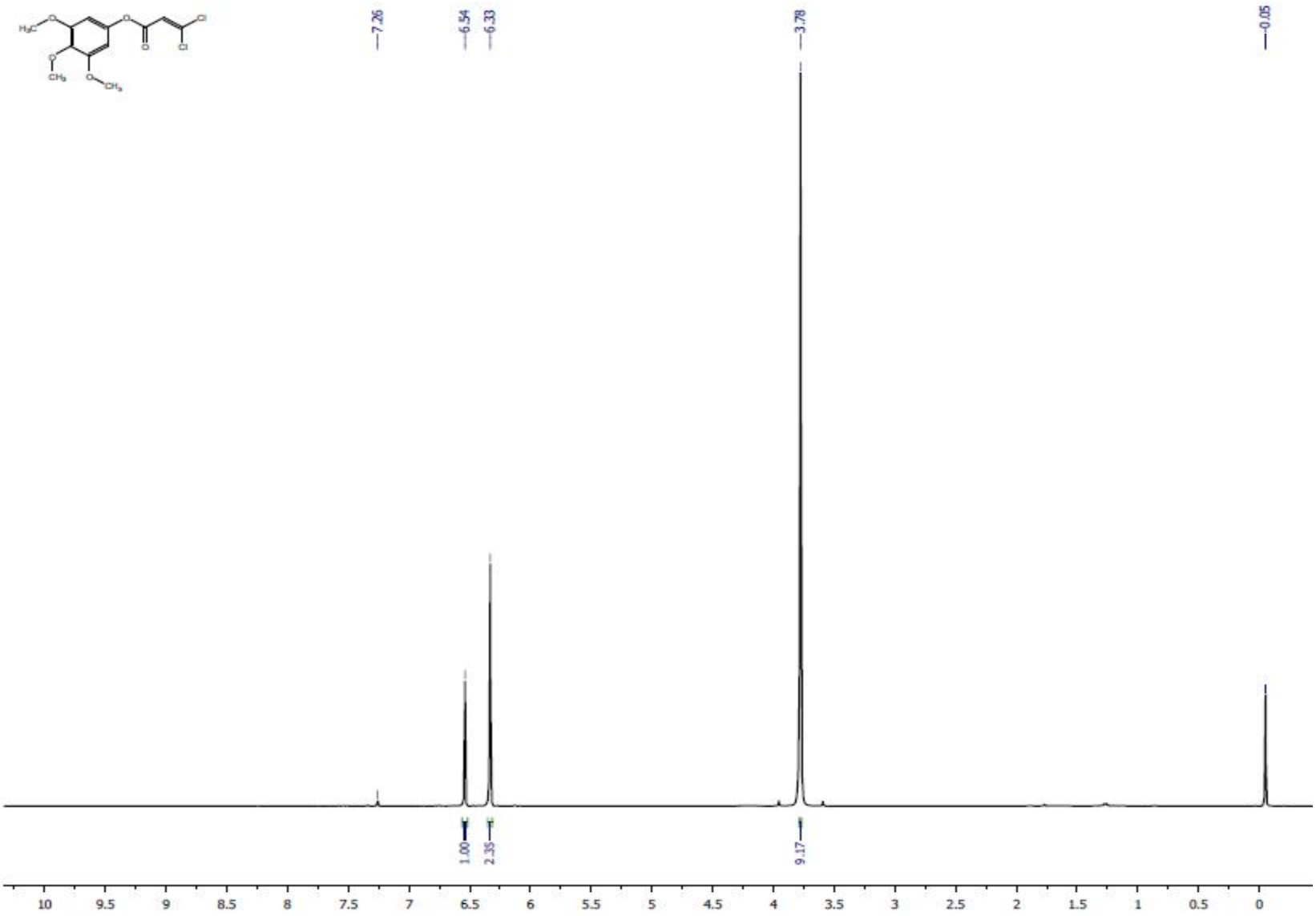
Compound 9 – ^{1}H-NMR



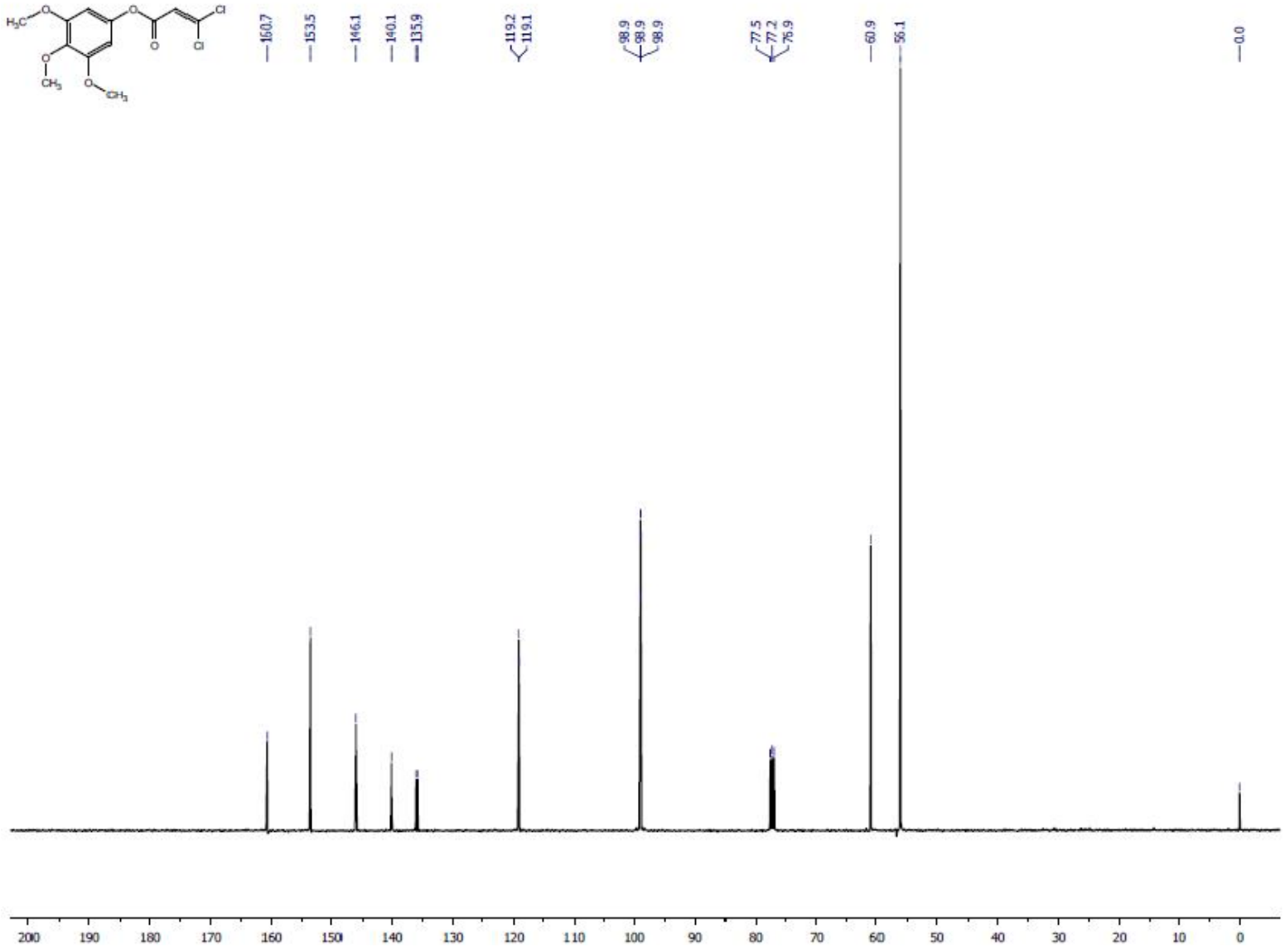
Compound 9 – ^{13}C-NMR



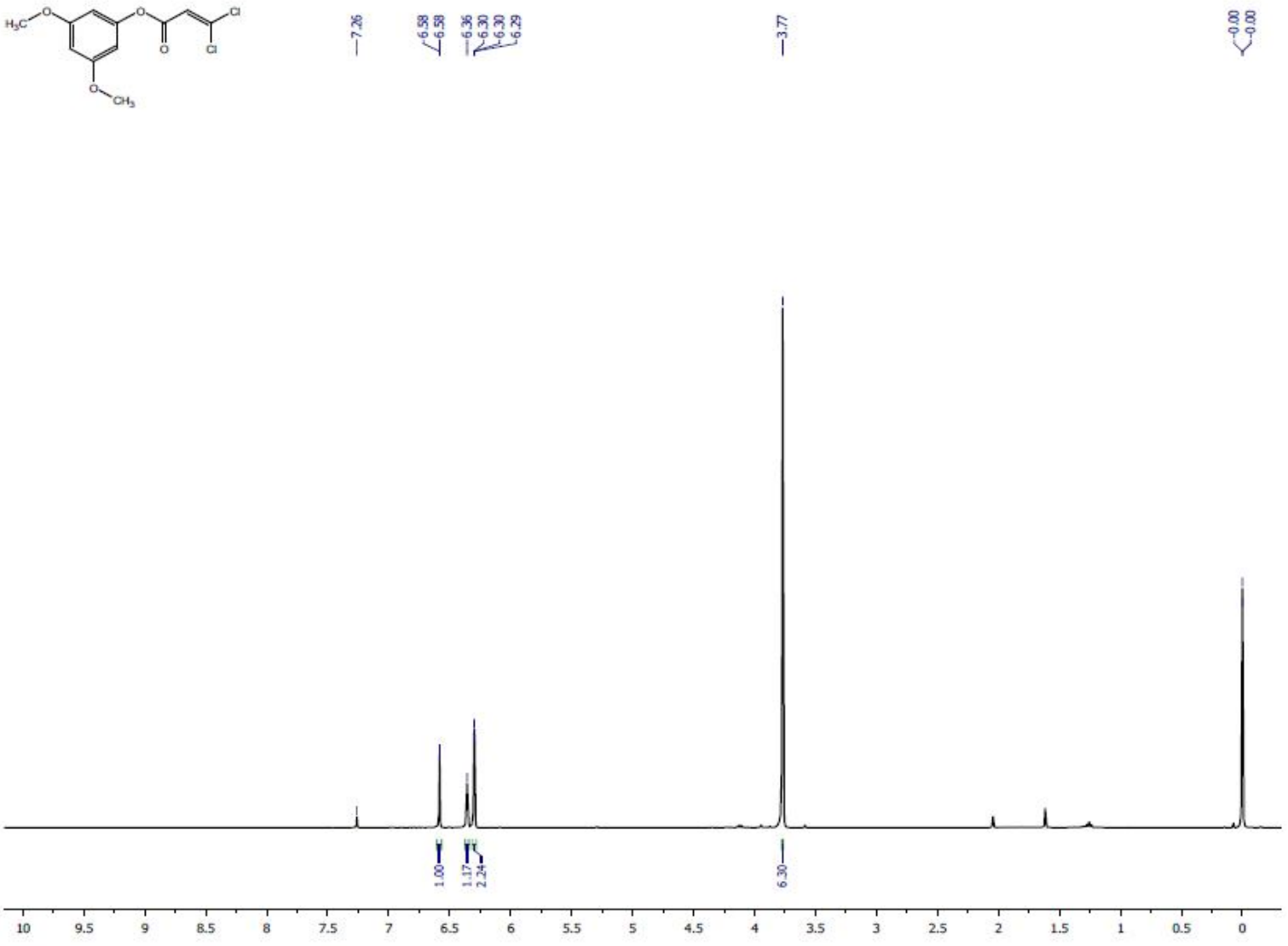
Compound 13a – ^{1}H-NMR



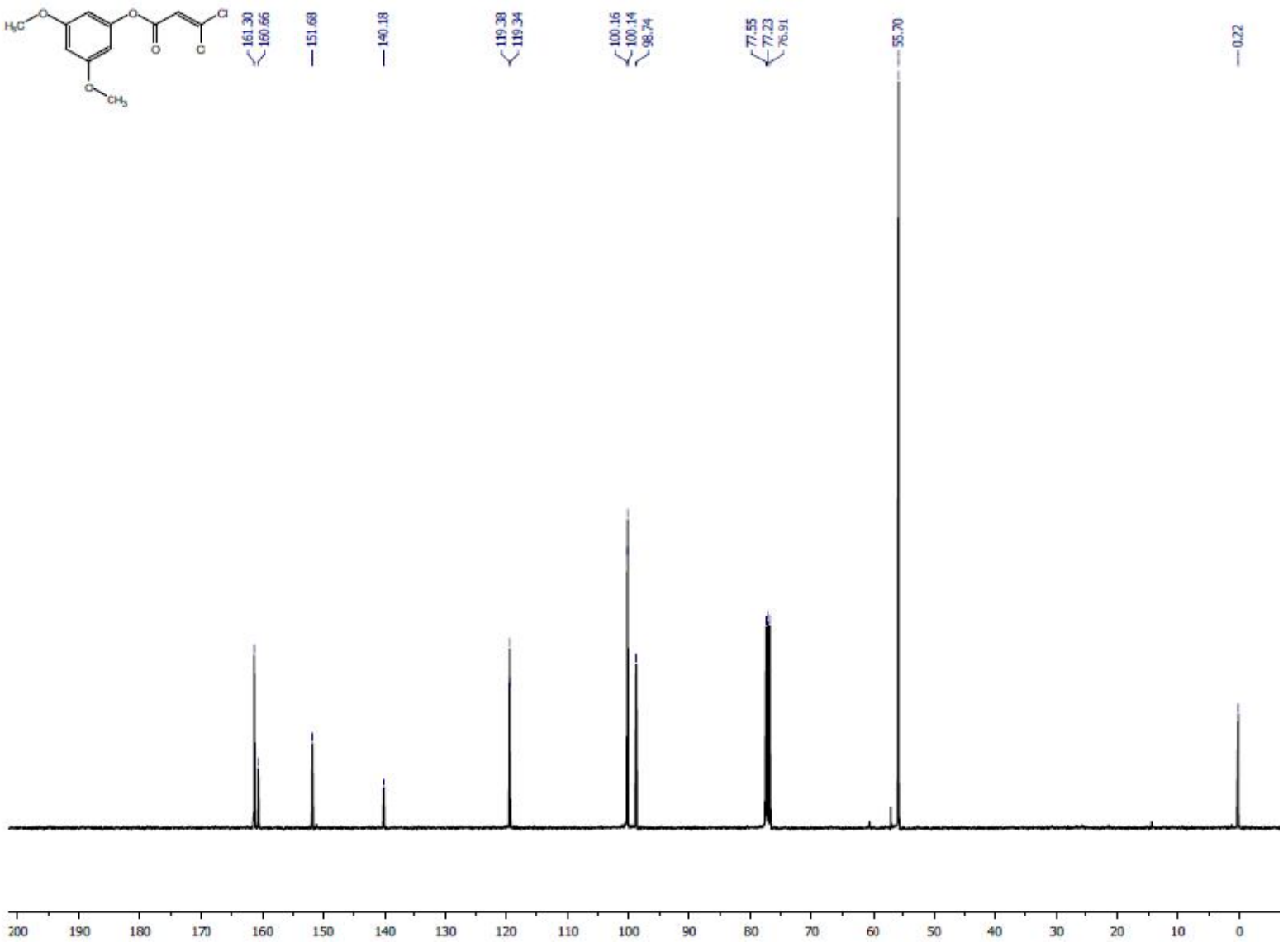
Compound 13a – ^{13}C-NMR



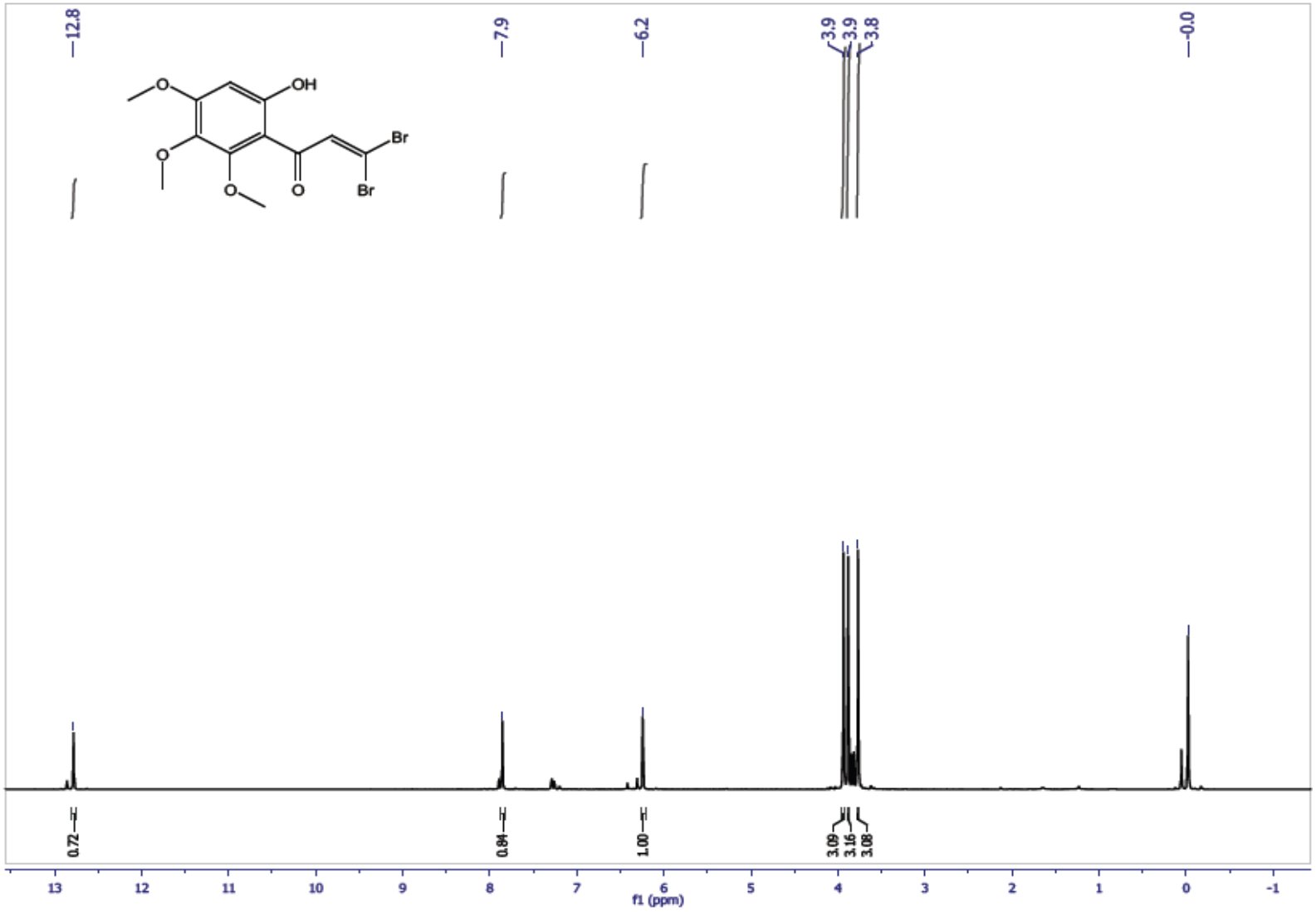
Compound 13b – ^{1}H-NMR



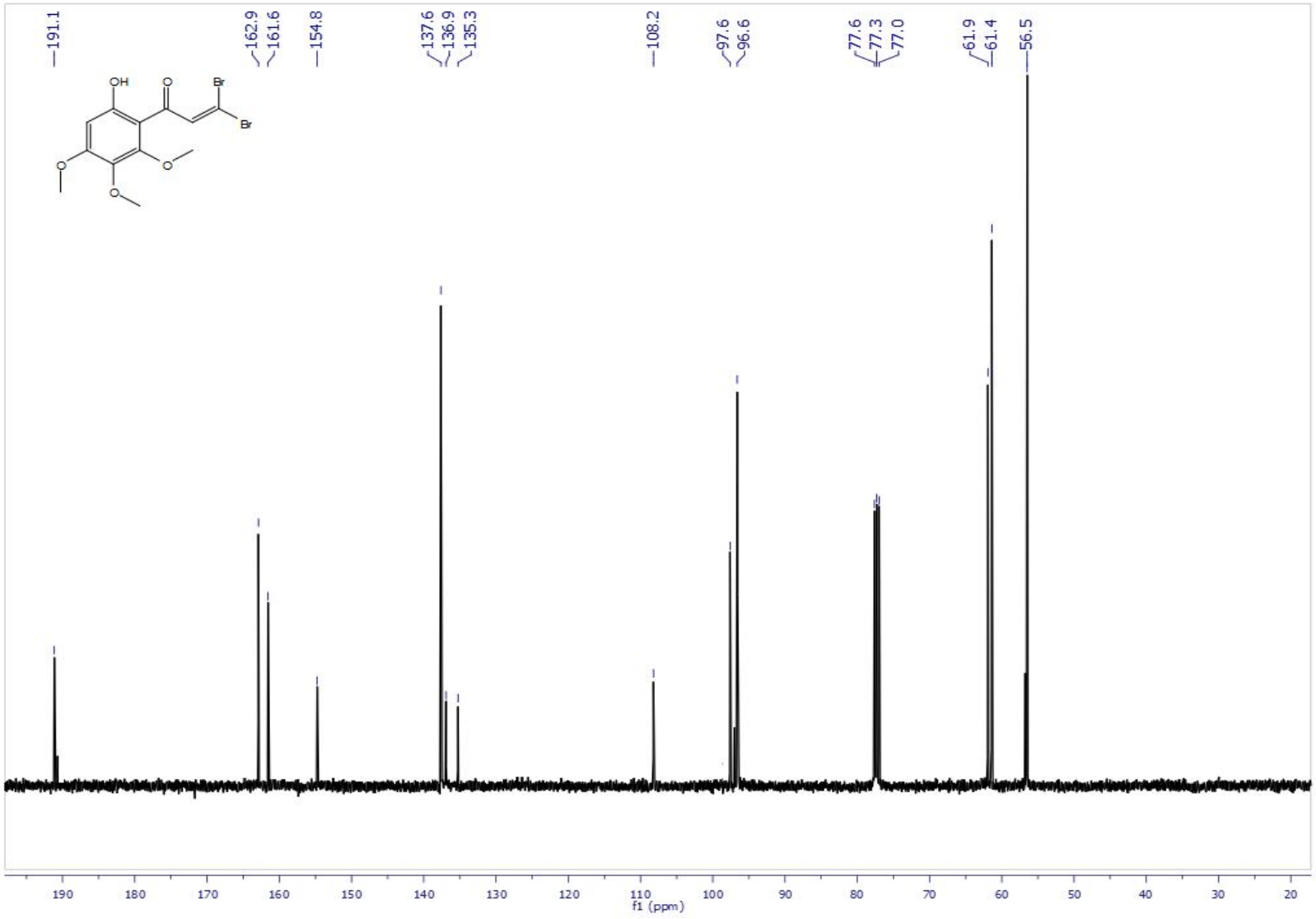
Compound 13b – ^{13}C-NMR



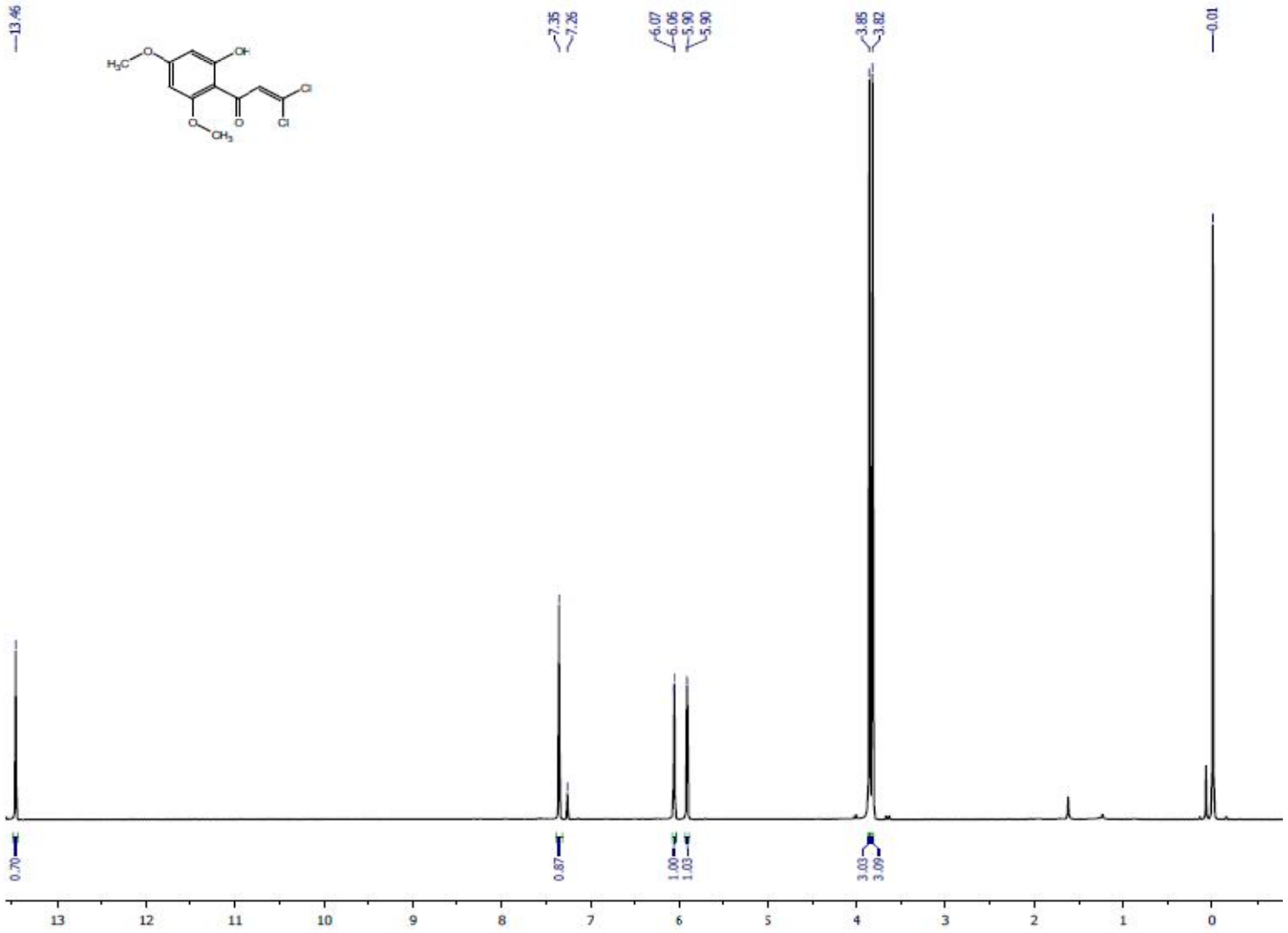
Compound 10 – ^{1}H-NMR



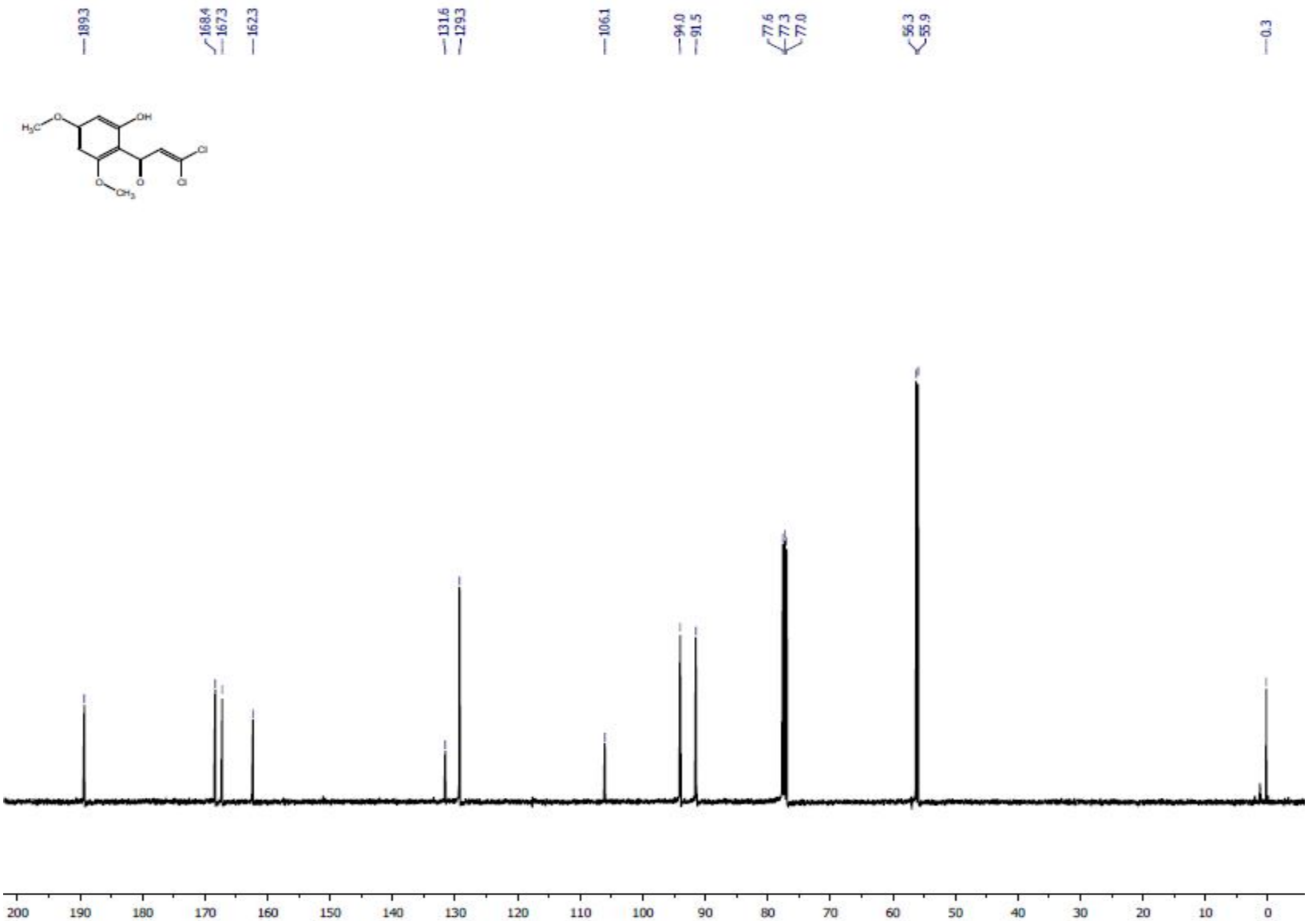
Compound 10 – ^{13}C-NMR



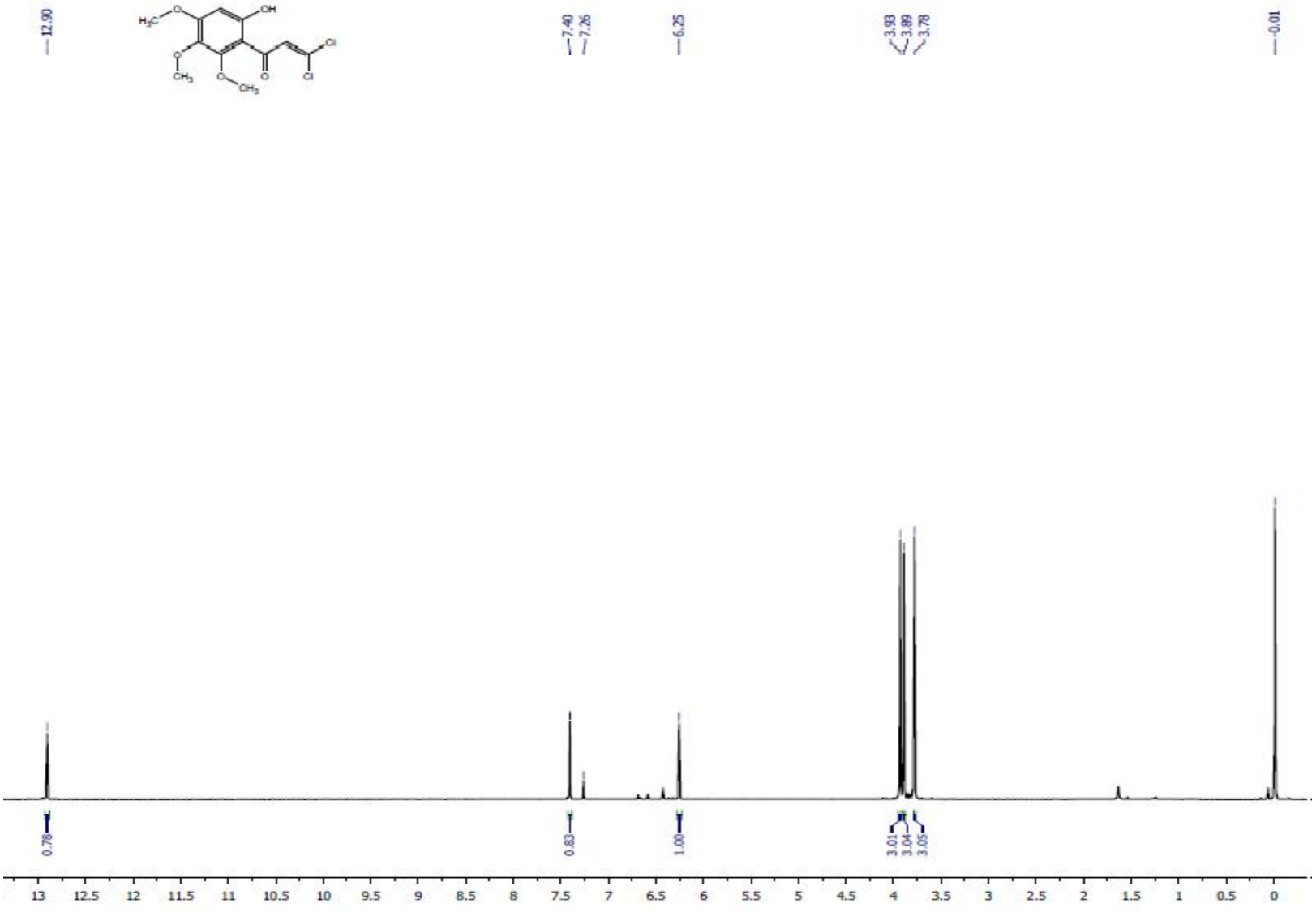
Compound 14b – ^{1}H-NMR



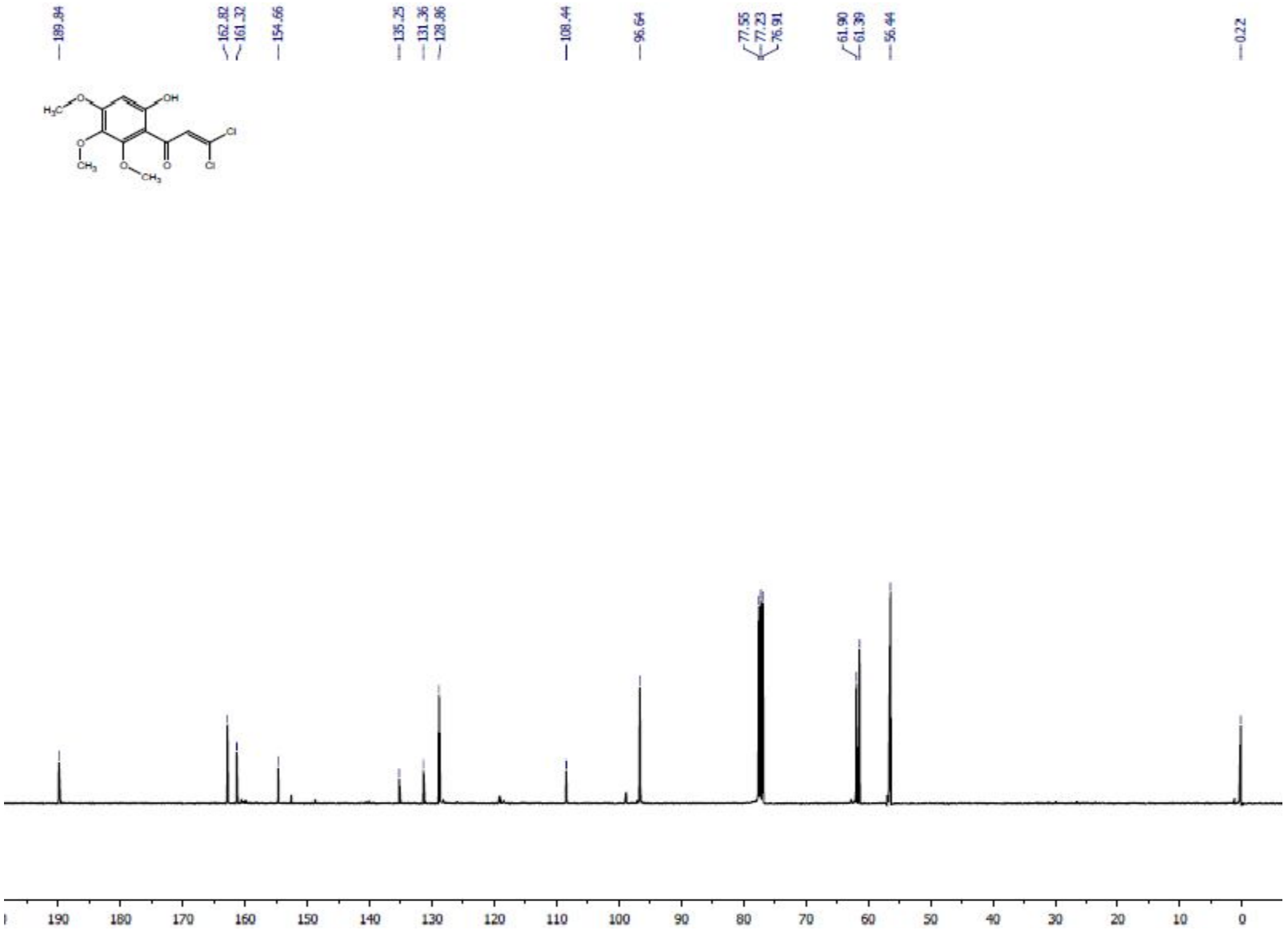
Compound 14b – ^{13}C-NMR



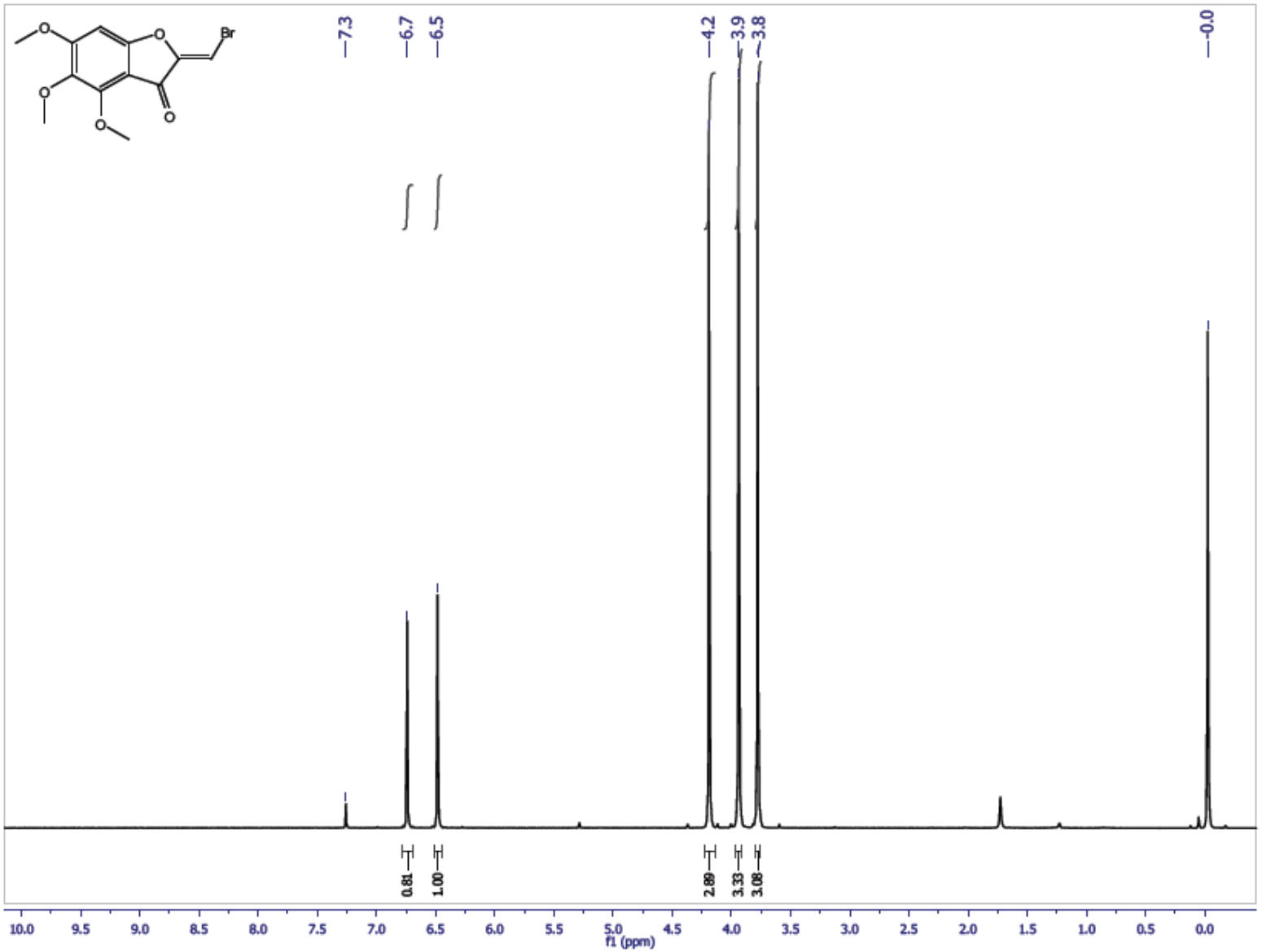
Compound 14a – ^{1}H-NMR



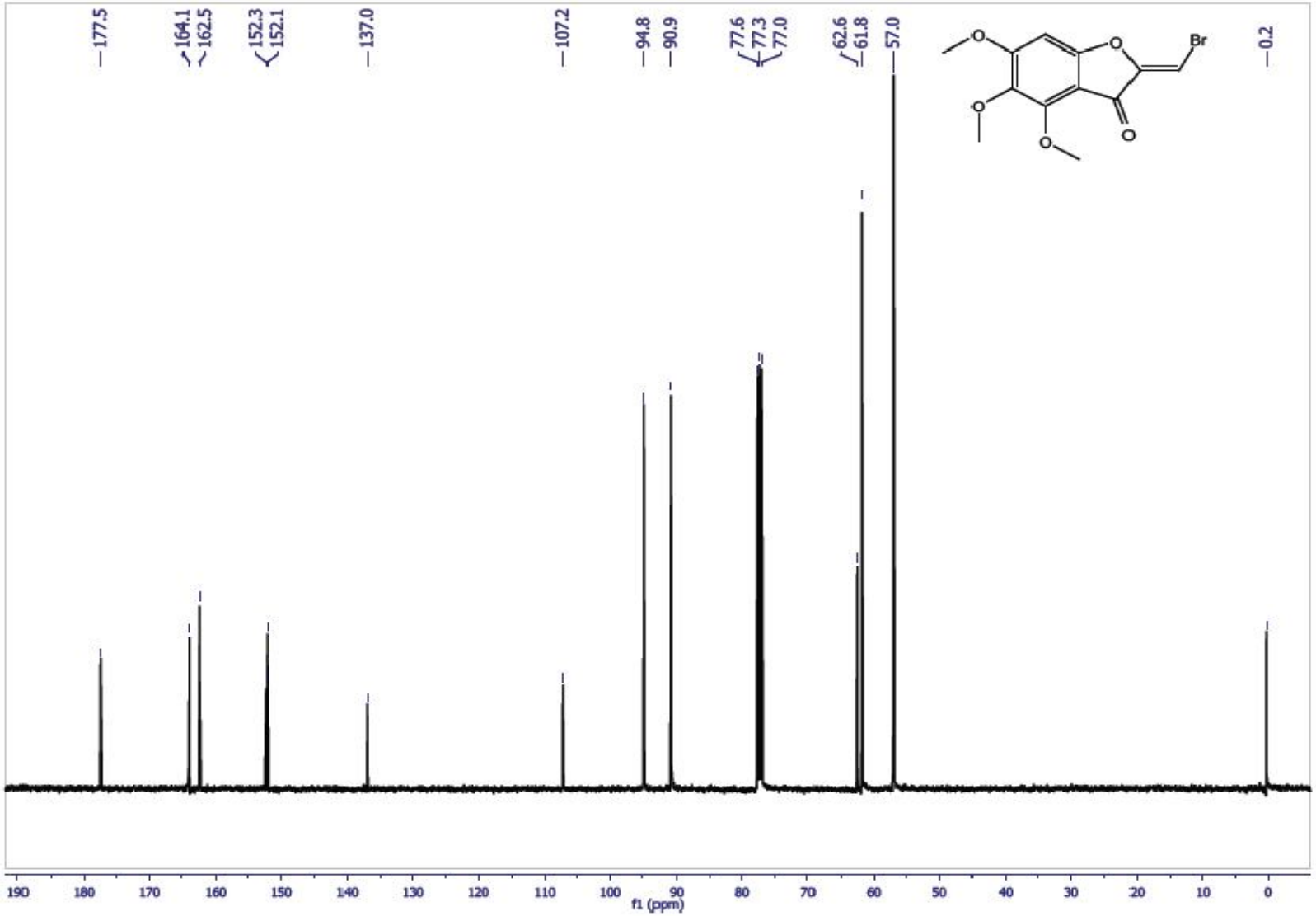
Compound 14a – ^{13}C-NMR



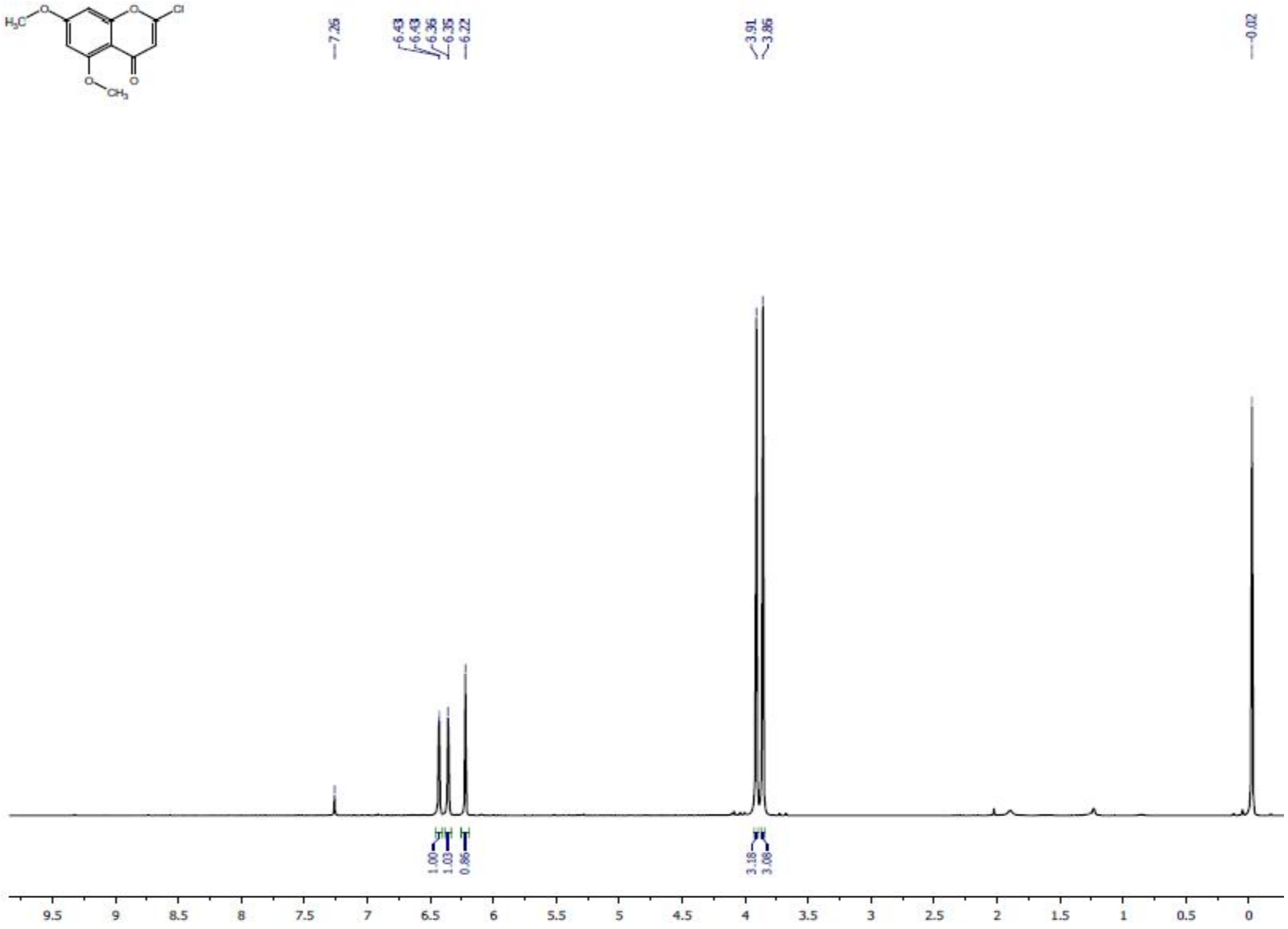
Compound 11b – ^{1}H-NMR



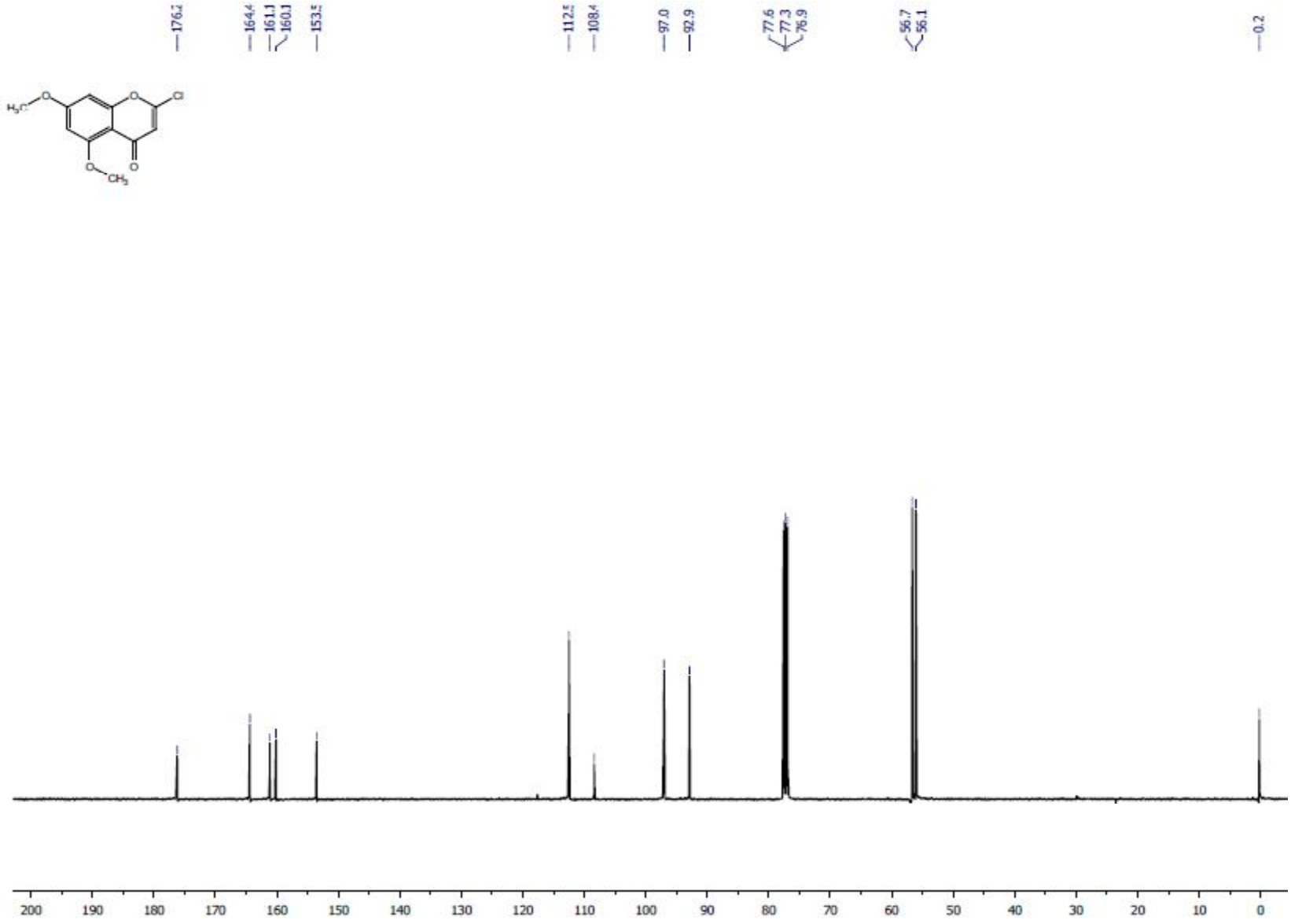
Compound 11b – ^{13}C-NMR



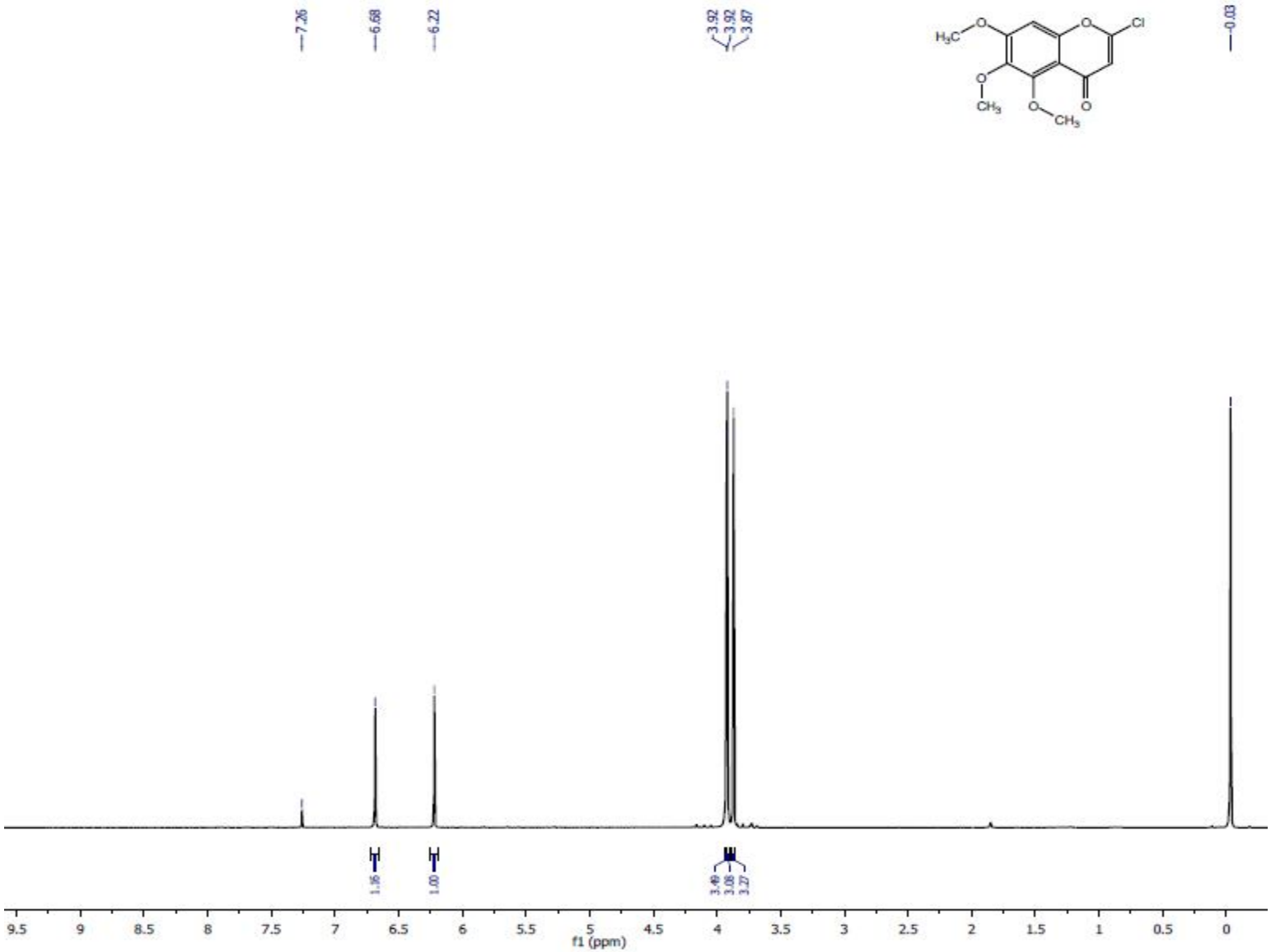
Compound 15b – ^{1}H-NMR



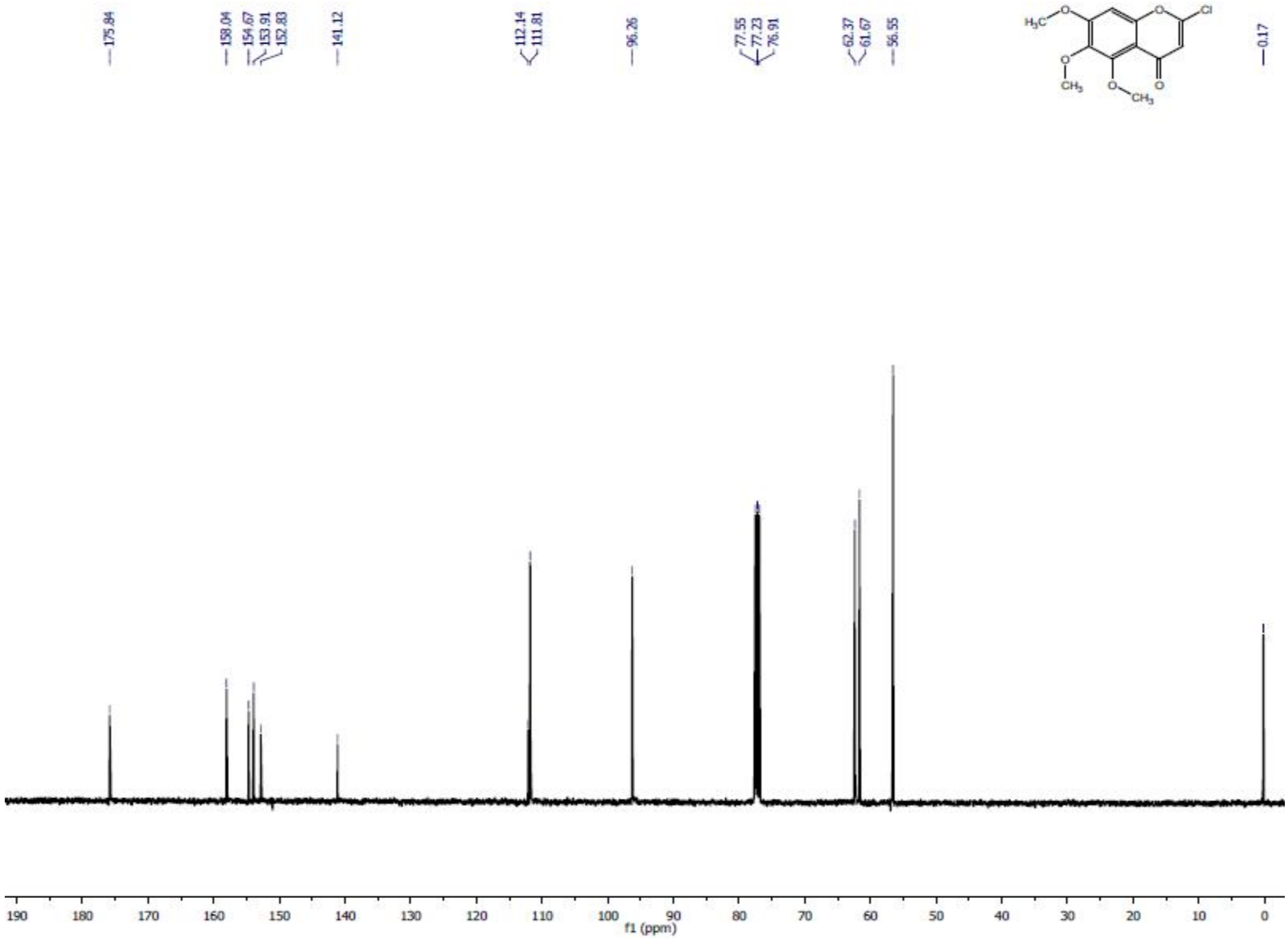
Compound 15b – ^{13}C-NMR



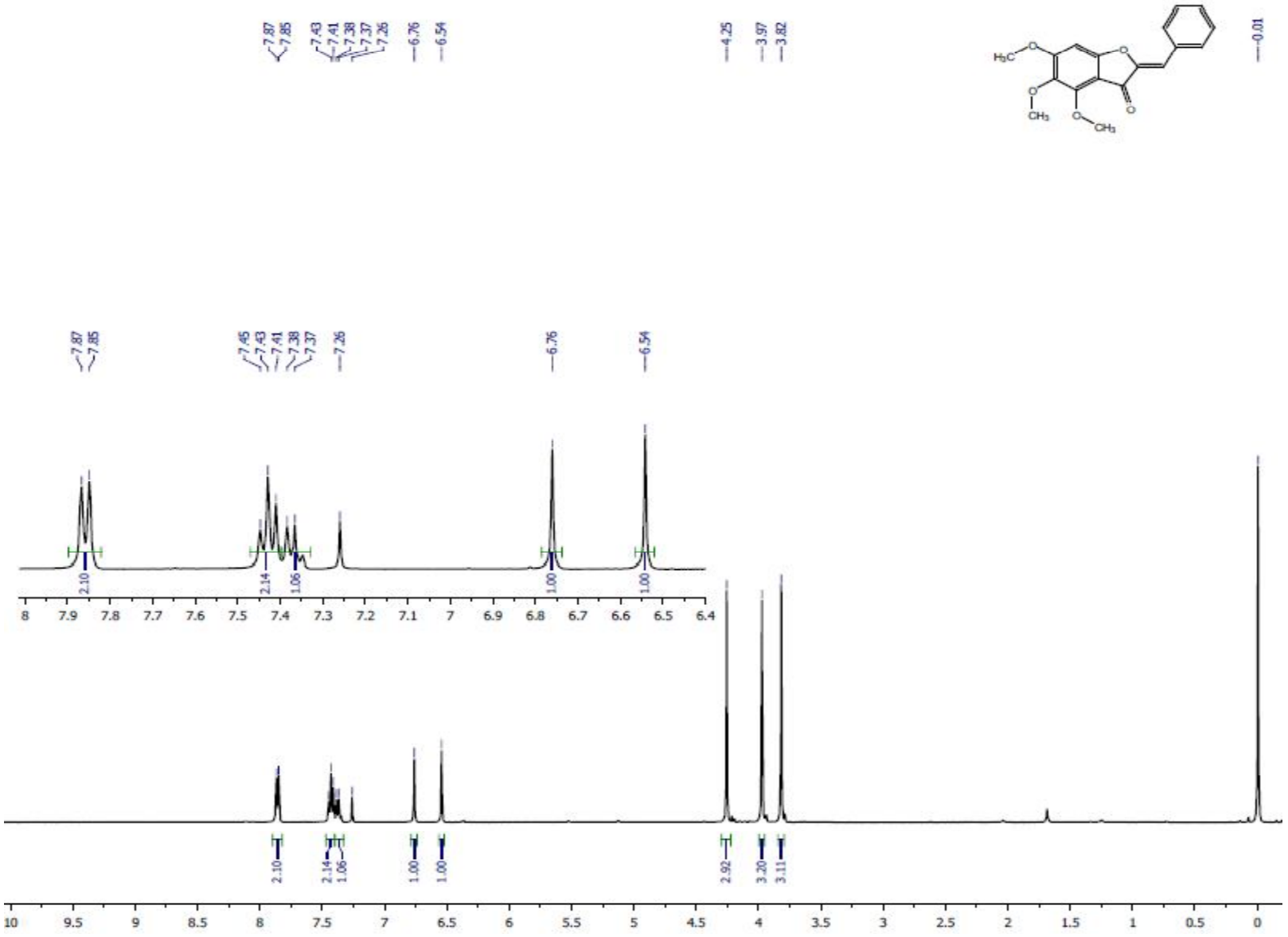
Compound 15a – ^{1}H-NMR



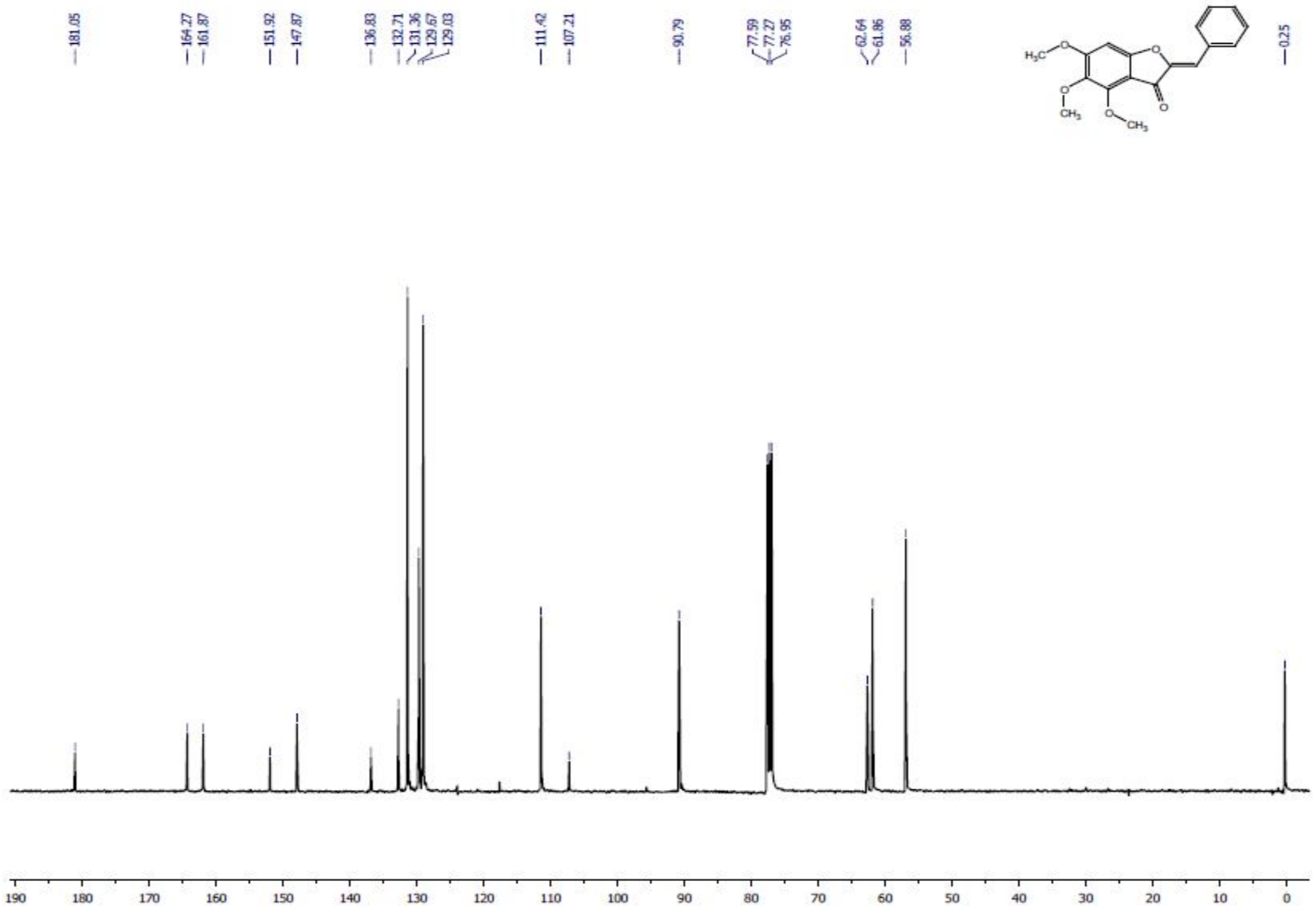
Compound 15a – ^{13}C-NMR



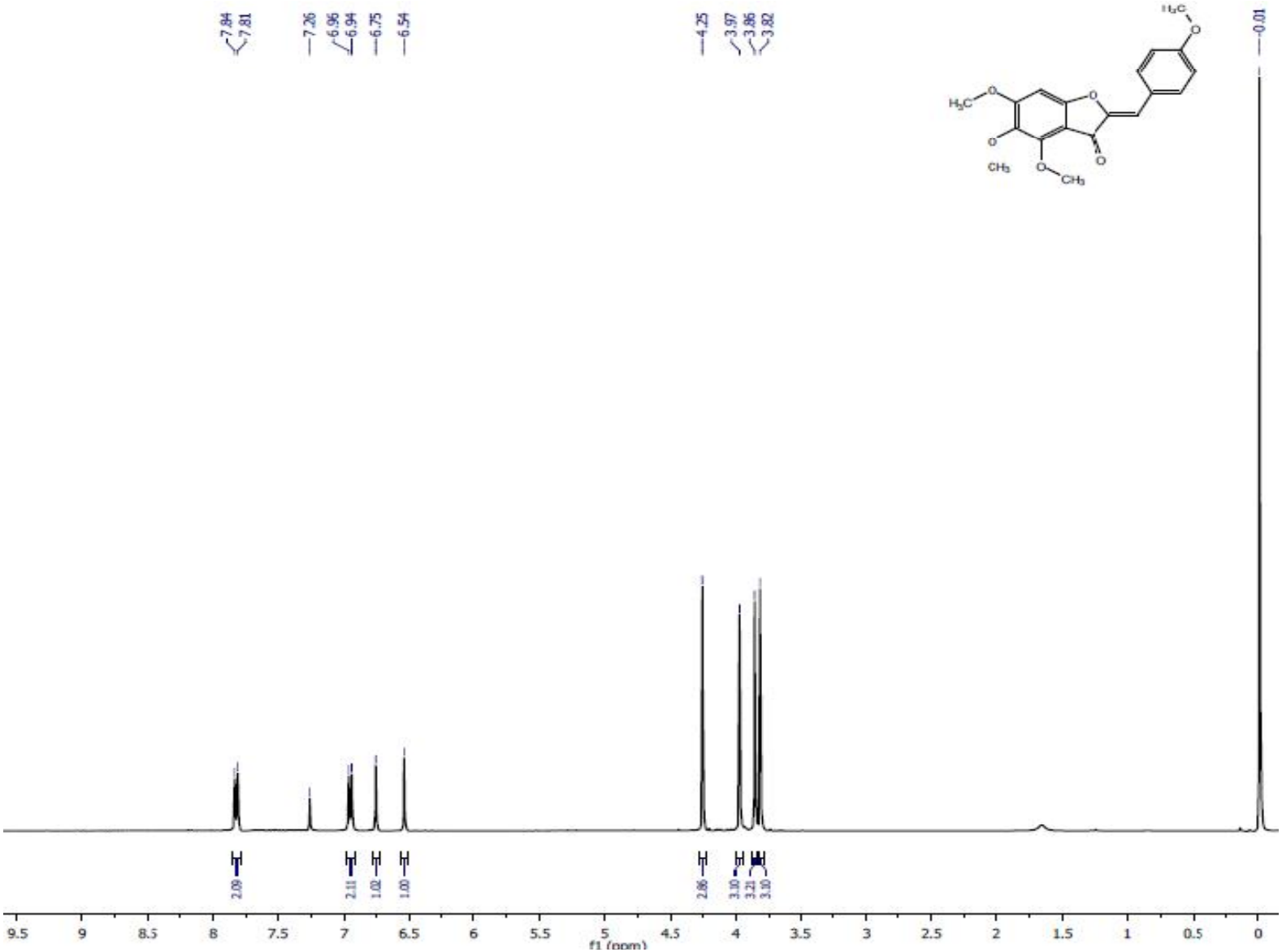
Compound 12a – ^{1}H-NMR



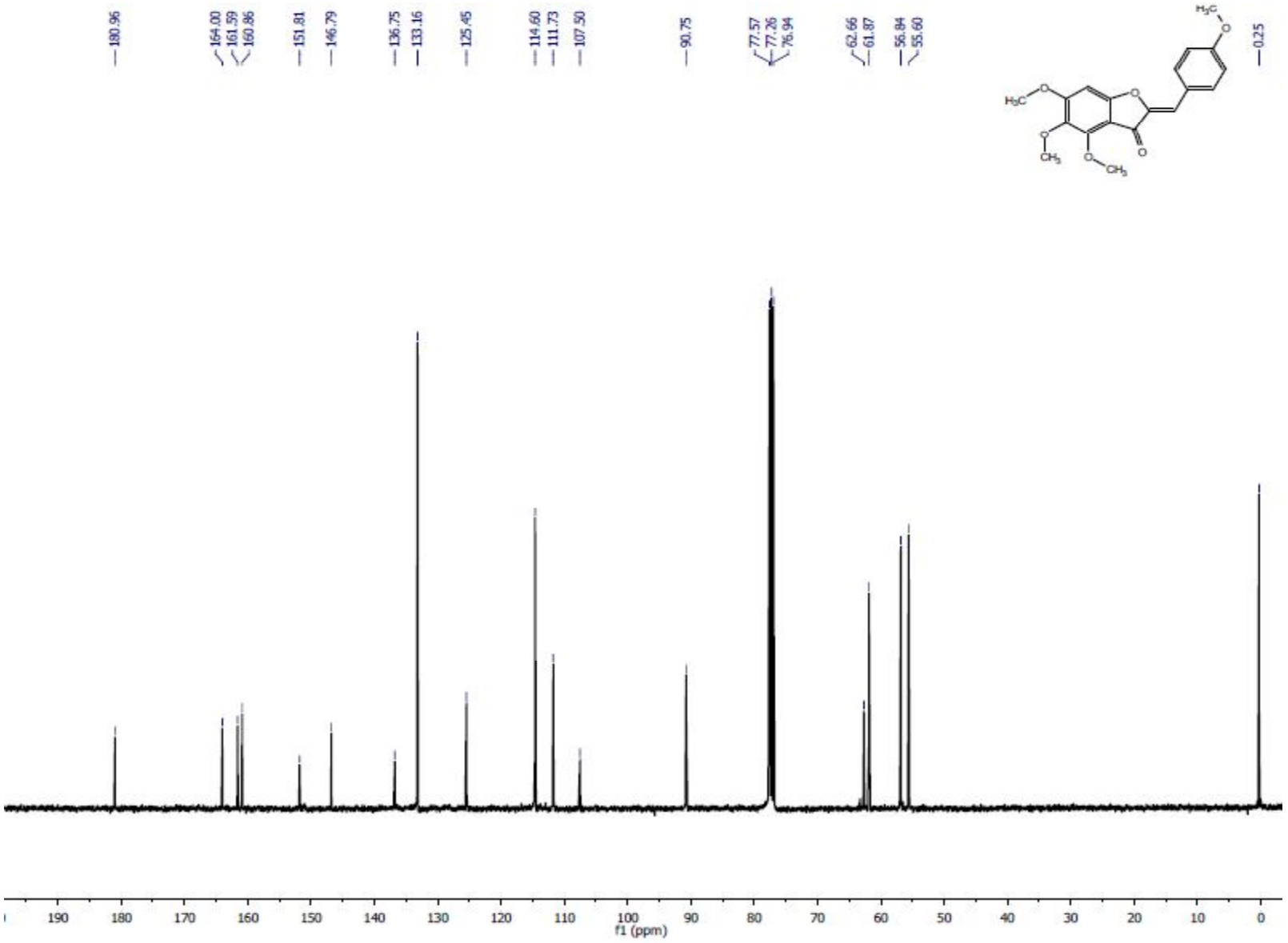
Compound 12a – ^{13}C-NMR



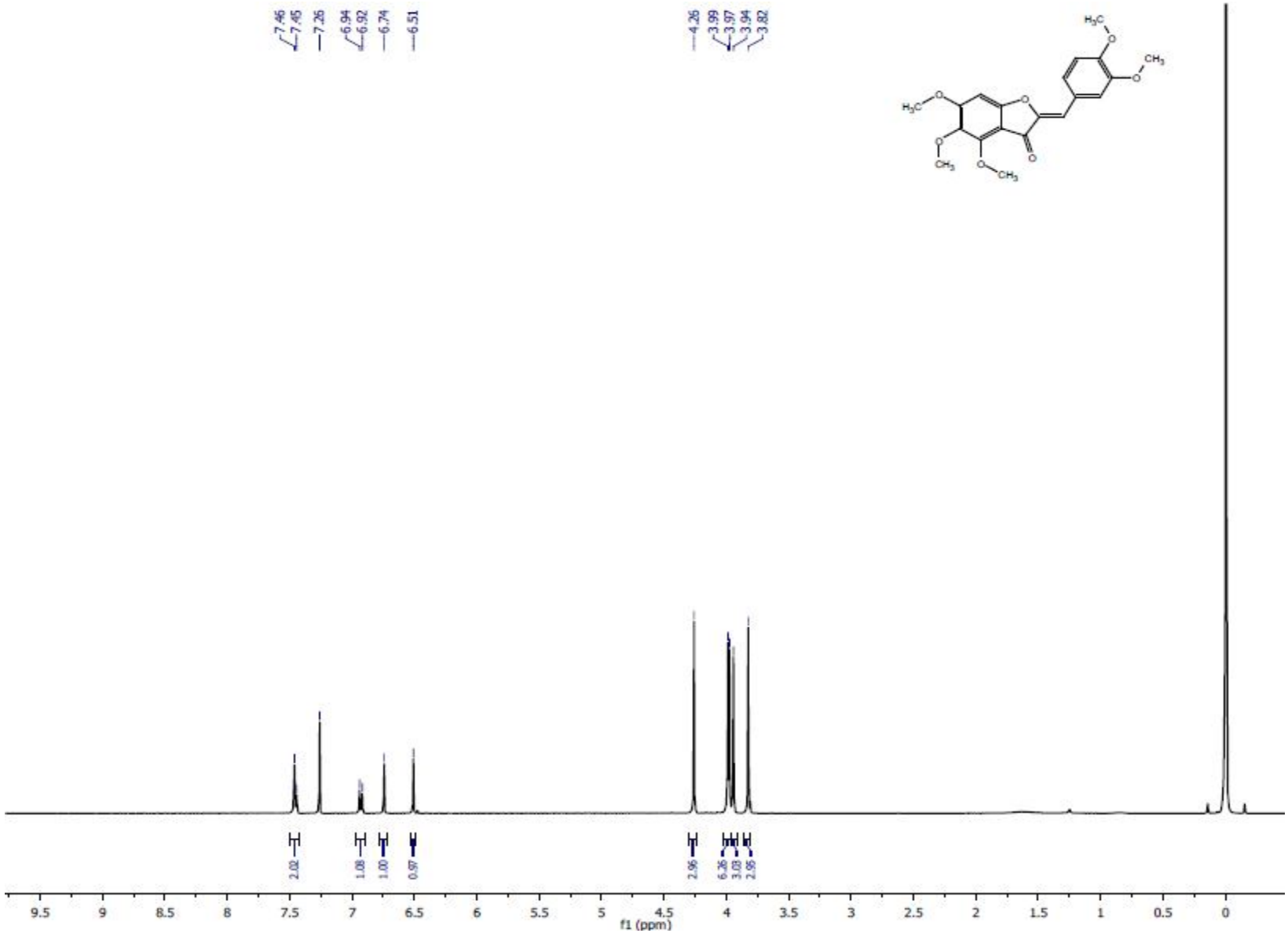
Compound 12b – ^{1}H-NMR



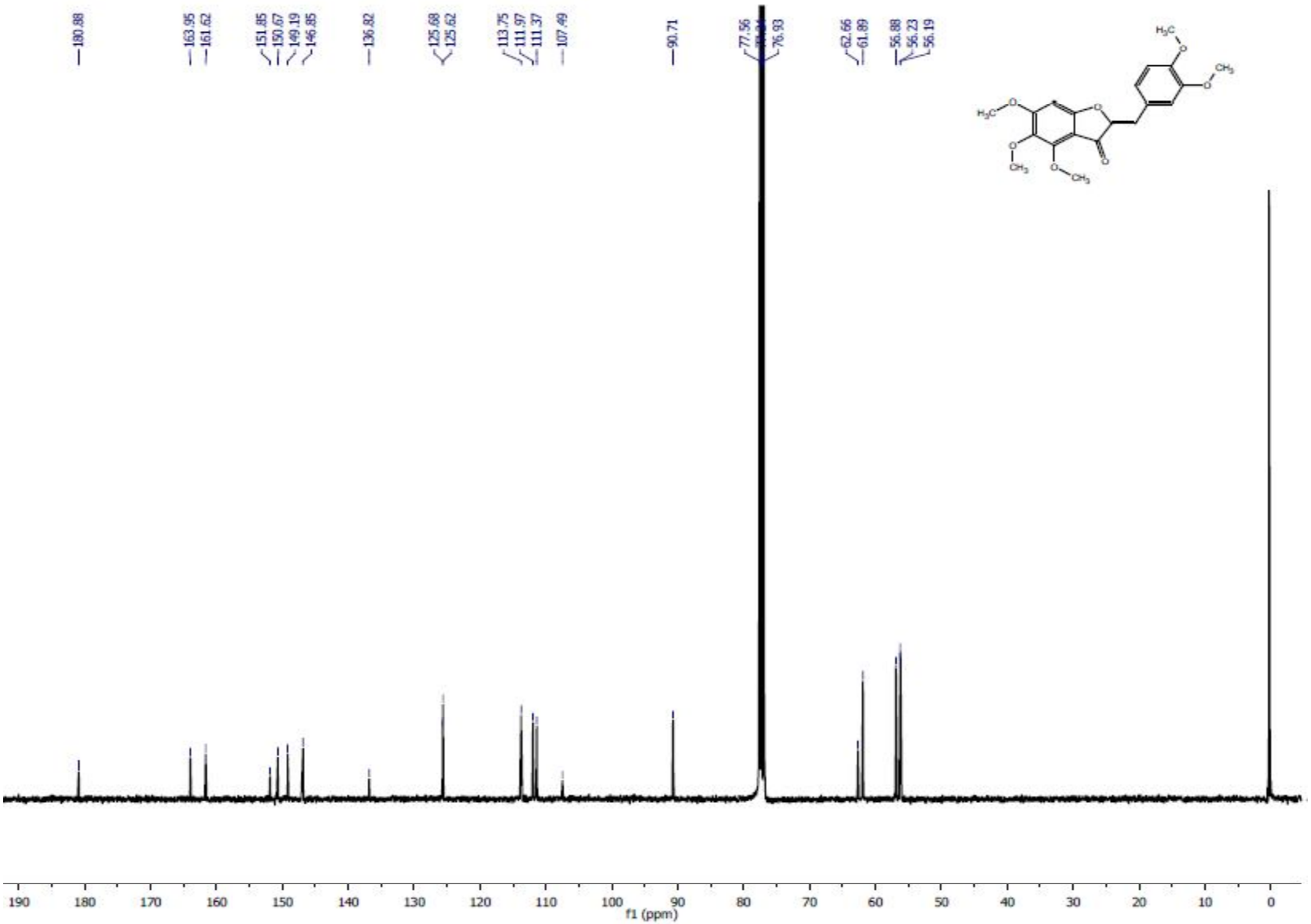
Compound 12b – ^{13}C-NMR



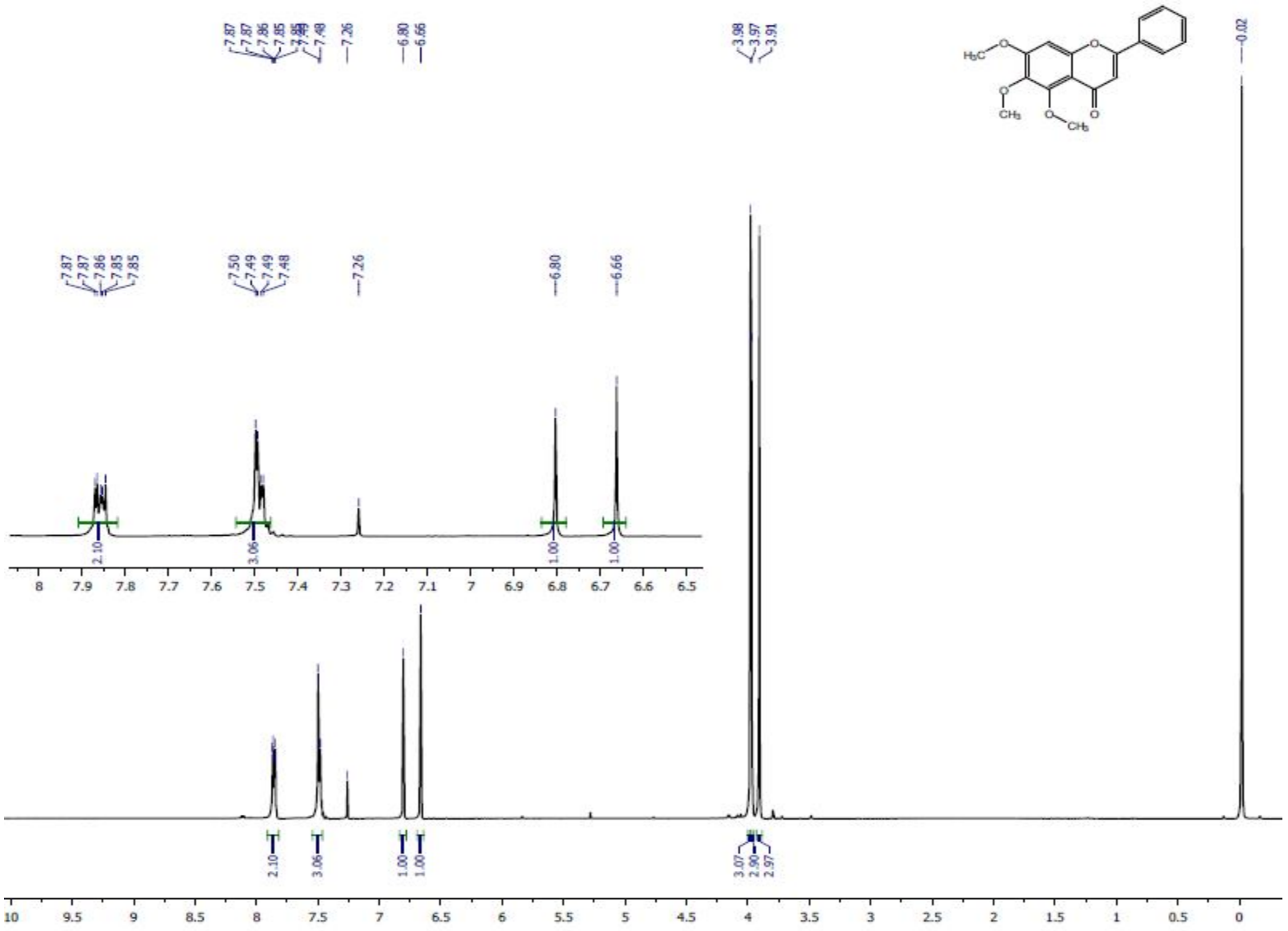
Compound 12c – ^{1}H-NMR



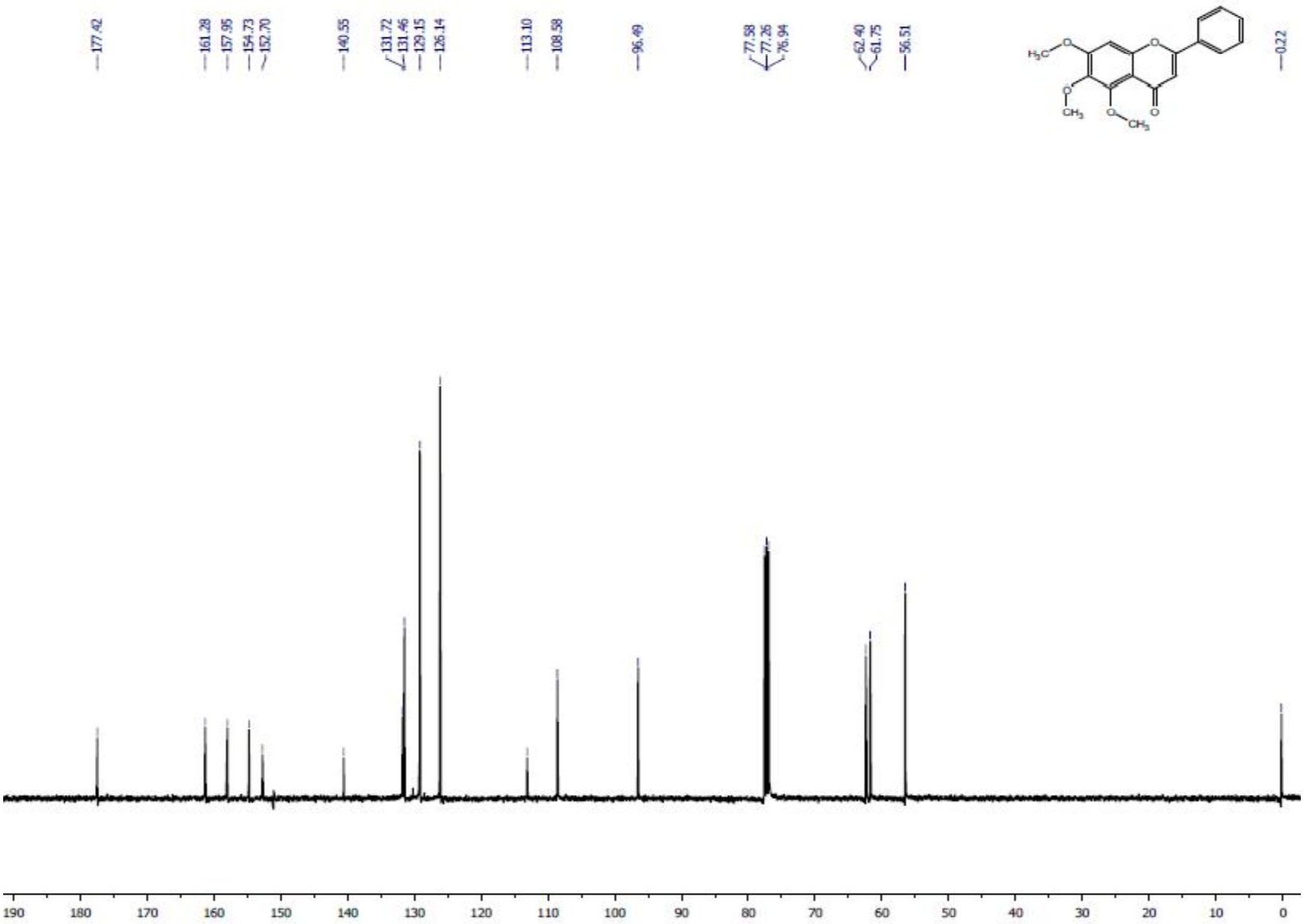
Compound 12c – ^{13}C-NMR



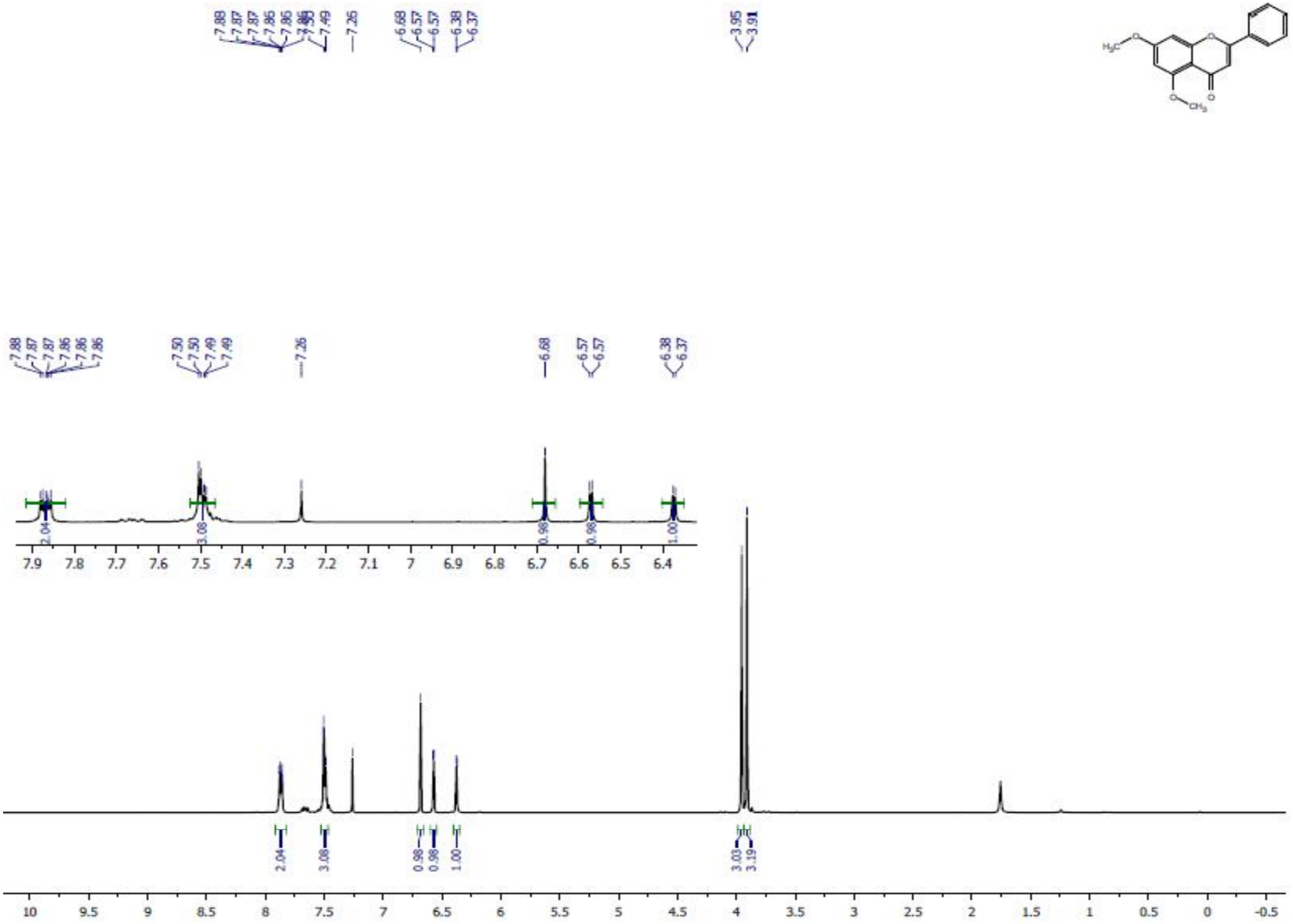
Compound 4 – ^{1}H-NMR



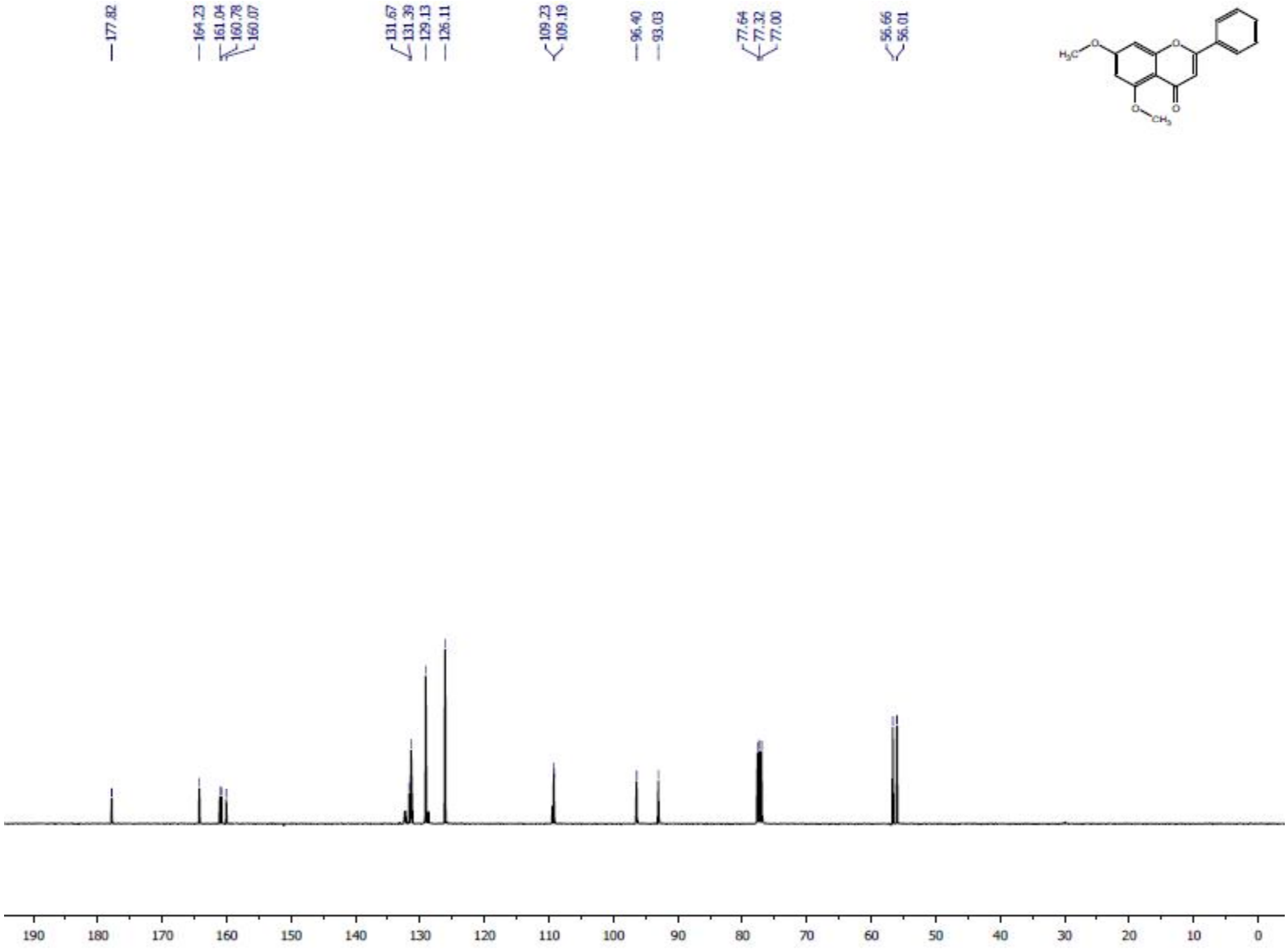
Compound 4 – ^{13}C-NMR



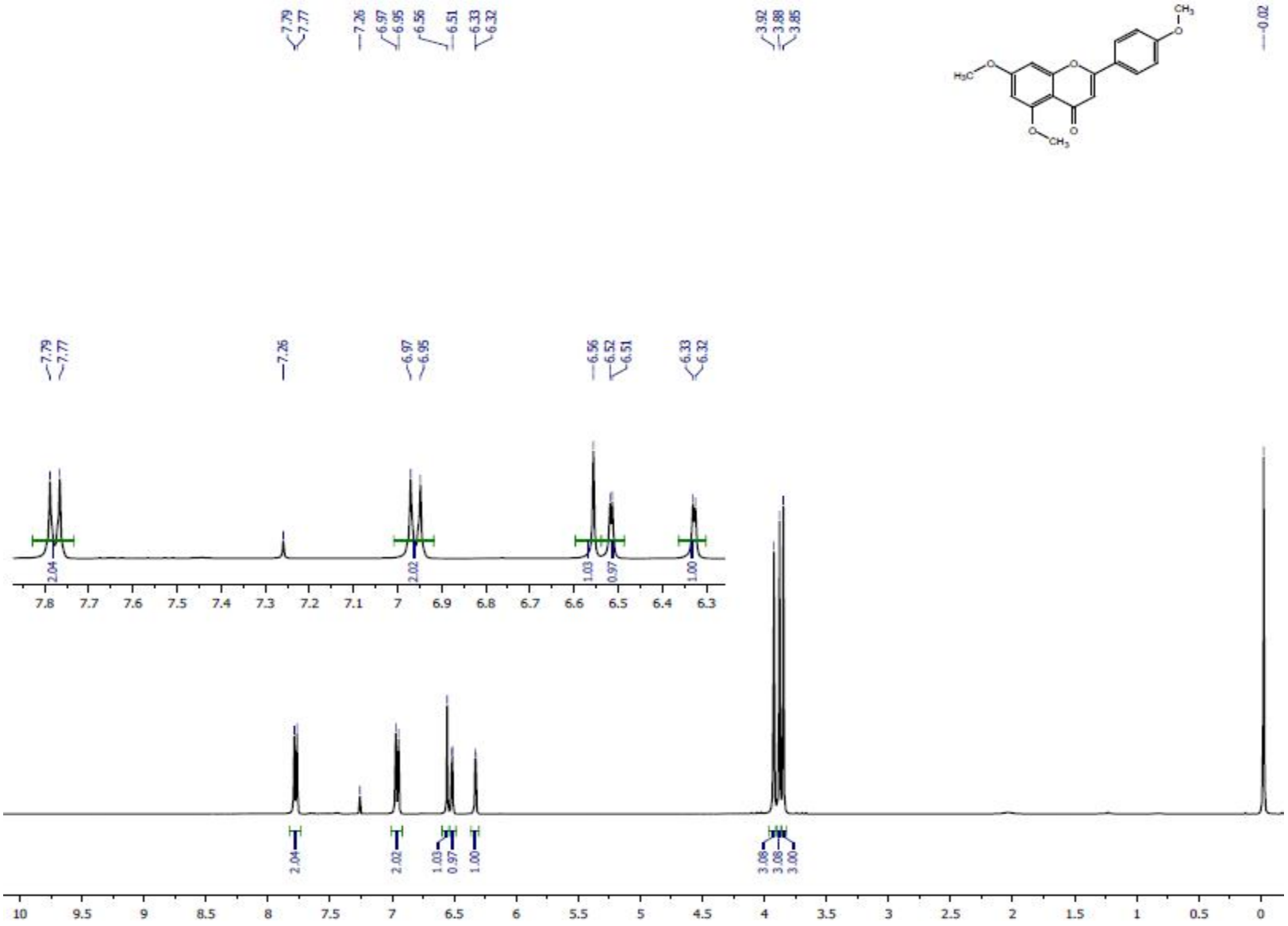
Compound 1 – ^{1}H-NMR



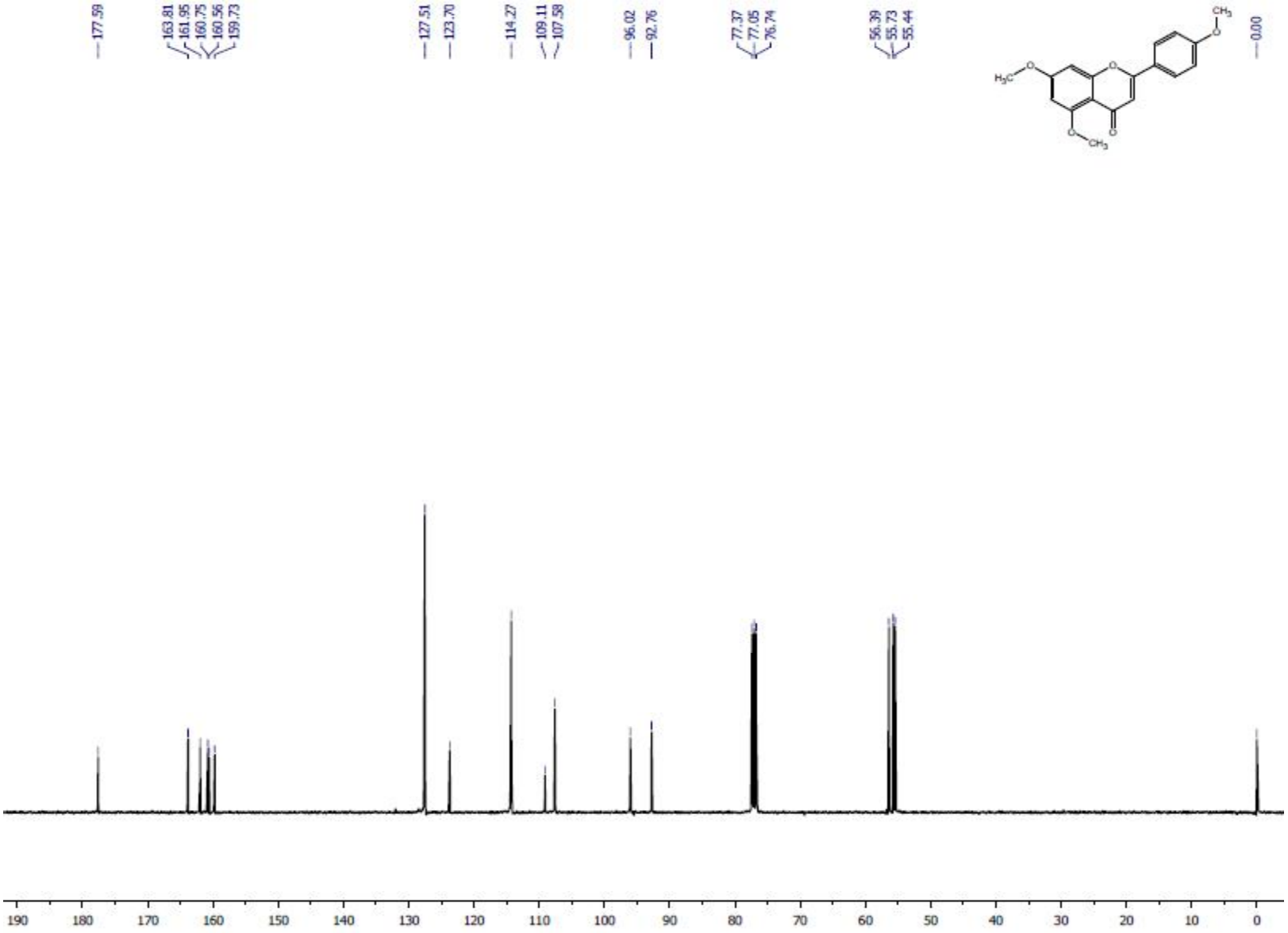
Compound 1 – ^{13}C-NMR



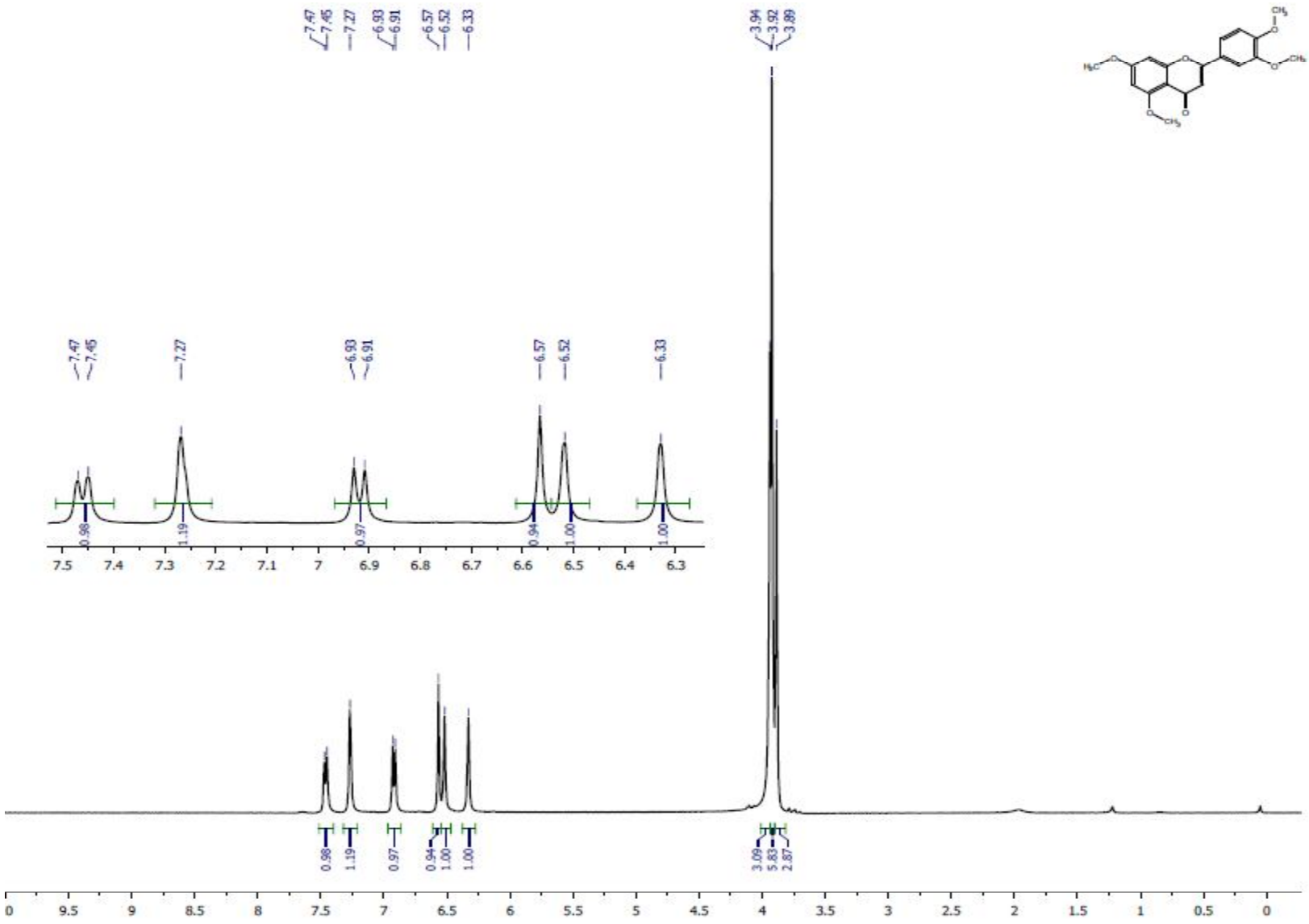
Compound 2 – ^{1}H-NMR



Compound 2 – ^{13}C-NMR



Compound 3 – ^{1}H-NMR



Compound 3 – ^{13}C-NMR