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Cytotoxicity of novel cross-conjugated arylated cyclopentene-1,3-diones

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Experimental section

The IR spectra were recorded in CH_2Cl_2 on a Shimadzu IR Prestige-21 spectrometer. The mass spectra (electron impact, 70 eV) were obtained an LCMS-2010EV mass spectrometer (Shimadzu) (sample solution in chloroform/acetonitrile were injected by a syringe at a flow rate of 0.1 ml min^{-1}, eluent MeCN/water, 95:5) in the register mode of positive ions when the ionizing potential of the needle electrode 4.5 kV (the temperature of capillary interface is 250°C, the voltage of capillary interface is 5 V. Flow rate of atomizing gas (nitrogen) 1.5 dm^3 min^{-1} for chemical ionization at atmospheric pressure). Elemental analysis of synthesized compounds was obtained on the EURO EA-2000 CHNS analyzer. The reaction course was monitored by TLC on "Sorbphil" plates (Russia) with visualization of compounds by treatment with an alkaline solution of potassium permanganate. The products were isolated by column chromatography using Macherey-Nagel silica gel (Germany), 30–60 g per gram of substrate; freshly distilled solvents were used as eluents. Melting points were determined on a Boetius apparatus (PHMK 05 VEB Wagetechnik Rapido, Radebeul). The starting compounds **1a-d** were obtained according to the literature.[S1]

NMR spectra were recorded on a Bruker Avance-III (500.13 and 125.77 MHz) instrument with PABBO direct detection probe in 5 mm NMR tubes, at 298 K. Chemical shifts in the ^1H NMR and ^{13}C NMR spectra are expressed in parts per million (ppm) from tetramethylsilane as external standard. The ^1H NMR spectra were acquired with a spectral width of 5.6 kHz and 32k data points and 8 scans, providing a digital resolution of ca. 0.5 Hz (^1H 90° pulse width = 11.5 μs). For $^{13}C\{^1H\}$ NMR spectra, a spectral width of 29.7 kHz was used with 64k data points and required quantity of scans (^{13}C 90° pulse width = 9.7 μs).

Optimization of geometric parameters, solution of the vibrational problem in the gas phase for Z/E isomers of compounds **4a, 4b, 6a** and **6b** were performed using tight convergence criteria and Becke's three-parameter hybrid functional combined with the Lee–Yang–Parr correlation functional (B3LYP)[S2,S3] with the 6-311++G(d,p) basis set using the keyword *opt* by the Gaussian 09 program.[S4] The calculation of the magnetic shielding constants by the GIAO method was carried out in the WP04/aug-cc-pVDZ approximation according to the

recommendations from CHESHIRE web site, the calculation of the contribution of the Fermi contact to the nuclear proton-carbon spin scalar couplings was carried out in the B3LYP/6-311++G(d,p)u+1s approximation.[S5]

Gradient selected {^{1}H, ^{13}C} HSQC spectra were recorded using the standard Bruker sequence (hsqcetgp). These data were collected with 4096 × 512 data points with 2 scans for each increment. The delay d4 was set to 1.72 ms. Three-bond heteronuclear coupling constants were determined by using LR-HSQMBC experiment: the Bruker hsqcetgplrsp pulse sequence was used (AQ_mod = DQD, FnMODE = Echo-Antiecho, SW = 4.0 ppm, QSINE line broadening 0.1 Hz) with 2 scans over a 2k × 512 data point matrix with followed by 2k zero-filling in both dimensions. Gradient selected {^{1}H, ^{13}C} HMBC spectra (hmbcgpndqf) were collected with 4096 x 512 data points with 4 scans for each increment. The delay d6 was set to 71.4 ms. Spectral widths of 6.0 and 29.7 kHz were used in the *F*2 (^{1}H) and *F*1 (^{13}C) domains, respectively. {^{1}H, ^{13}C} HSQC and HMBC data were processed using a sine window in the *F*2 and *F*1 dimensions. {^{1}H, ^{1}H} gs-COSY data were collected with 4K x 512 data points with 2 scans for each increment. For the {^{1}H, ^{1}H} NOESY NMR experiments, the solution was degassed to remove any dissolved oxygen. The following parameters and procedures are commonly employed: spectral width 6.0 kHz, 4K data matrix and 256 time increments of 2 transients each, mixing time 0.5 s.

The structure of compounds **4a,b** and **6a,b** was established from the data of ^{1}H, ^{13}C NMR spectra using two-dimensional correlation {^{1}H, ^{13}C} HSQC, HMBC and LR-HSQMBC as well as {^{1}H, ^{1}H} dqCOSY and NOESY. On the basis of the spectral data obtained we have found that the reaction product is a mixture of the *E*- and *Z*-isomers of 4-chloro-2-methylene-5-arylcyclopent-4-ene-1,3-diones with a slight prevalence of the latter one. The configurational assignments of *Z* and *E* isomers of compounds **4a,b** and **6a,b** was performed based on carbon-hydrogen coupling constants from the LR-HSQMBC spectra and supported by the B3LYP/6-311++G(d,p)u+1s calculations. The LR-HSQMBC experiment developed by Williamson et al.[S6] is optimized for observing the full range of $^{n}J_{CH}$ weak long-range correlations and produces intense and well resolved cross-peaks.[S7]

In the ^{1}H NMR spectra, the signals of the exo-methylidene group H-1' are observed as singlets in the range of 7.51-7.88 ppm. The absence of homonuclear coupling for the H-1' protons leads to producing sharped doublets of the long-range cross peaks in the LR-HSQMBC spectra with vicinal carbonyl groups C1 and C3 (Figures S8 and S9, *a*).

Comparative analysis of the calculated ^{13}C chemical shifts showed that the C1-carbonyl are more deshielded than the C3 signals for both the *Z*-isomers and the *E*-isomers of the studied compounds (Table S1). The Z/E-isomers were determined from the characteristic *cis* (~6.5 Hz)

and *trans* (~10.6 Hz)[S8] experimental $^{3}J_{CH}$ coupling constants of the H-1' proton with C1 and C3 carbons (Figure S9, *b*). The observed values of the proton-carbon $^{n}J_{CH}$ constants are in good agreement with the calculated values (Table S1).

It should be noted that for the interaction of the *exo*-methylidene proton H-1' with carbons C4 and C5, it was not possible to obtain the exact value of the $^{4}J_{CH}$ coupling constants from the LR-HSQMBC spectra due to the overlap of these cross peaks with other signals. However, at a qualitative level, these cross-peaks were detected in the HMBC spectra: the H-1'/ C5 interaction is observed in the *E*-isomer, and H-1' / C4 is observed for the *Z*-isomer (Figure S9, *b*), which also agrees with the calculated $^{n}J_{CH}$ data.

Biological assays

Cell culture conditions and treatments

HEK293 (Human Embryonic Kidney 293 cells), Jurkat *(*Human leukaemic T cell lymphoblast), A-549 (Human pulmonary adenocarcinoma), MCF-7 (Human breast adenocarcinoma), HepG2 (Human hepatocellular carcinoma) and SH-SY5Y (Human neuroblastoma) cell lines were purchased from the Russian Cell Culture Collection (Institute of Cytology Russian Academy of Science, Saint Petersburg, Russia). HEK293, SH-SY5Y, MCF-7, HepG2, A-549 cells were maintained in Dulbecco's modified Eagle's medium (DMEM) (Invitrogen, USA) supplemented with 2 mM *L*-glutamine (Sigma-Aldrich, UK), 10% fetal bovine serum (FBS; Invitrogen, USA), 50 μg/mL gentamicin sulfate (Invitrogen, USA). Jurkat cells were grown in RPMI 1640 medium (Invitrogen, USA) supplemented with 10% FBS, 50 μg/mL gentamicin sulfate and 2 mM *L*-glutamine. All cells were cultured at 37°C and 5% CO_2. All compounds were dissolved in 100% DMSO (Sigma-Aldrich, UK) to 100 mM stock solutions and diluted in completed DMEM or RPMI immediately before addition to the assay plates. DMSO was maintained at a final concentration of 0.1% unless otherwise specified.

Cell viability

Cells were cultured at appropriate density in 96-well plates (3.0×10^4 cells per well for HEK293 and SH-SY5Y; 1.2×10^4 cells per well for MCF-7 and A-549; 2×10^4 cells per well for HepG2; 1×10^5 cells per well for Jurkat) in a same volume of the proper media. Cells were treated with compounds at final concentrations of 0.1 – 100 μM for 48 h and cell viability was assessed using the MTT cell viability assay.[S9]

Experiments were repeated independently two times in triplicate and data were expressed as MTT reduction relative to control (cells treated with 0.1% DMSO). Absorbance was measured within 60 min at 540 nm using the 2300 EnSpire® Multimode Plate Reader (Perkin Elmer, United States). The concentration of the compound that inhibited 50% cell viability (IC_{50} value)

was calculated using nonlinear regression analysis (GraphPad Prism v.5.02; GraphPad Software Inc., USA). The viability of control cells was set as 100%, and the viability in the experimental groups was calculated by comparing the optical density reading with the control. Data were expressed as mean ± SD calculated from two independent experiments, performed in triplicate. Differences between experimental groups were analyzed by one-way ANOVA followed by Dunnett's Post Hoc test. 5-Fluorouracil was evaluated as a positive control for MTT assay.

6,8-Dichloro-9-phenyl-1,4-dioxaspiro[4.4]non-8-ene-7-one **2a.** To a stirred suspension of **1a** (0.1 g, 0.411 mmol), $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and $PhB(OH)_2$ (50 mg, 0.41 mmol) in dioxane (10 ml), a solution of K_2CO_3 (0.132 g, 0.957 mmol) in H_2O (0.1 ml) was added. The mixture was refluxed under Ar for 5 h and then cooled to room temperature. The mixture was diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (3×25 ml). The combined organic layers were dried $MgSO_4$, filtered, and the filtrate was concentrated in vacuum. The residue was purified by column chromatography on a silica gel column (elution with petroleum ether - EtOAc, 10:1→1:4). Yield 70 mg (60%). Pale yellow, deliquescent crystals, m.p. 56-57°C. IR (ν/cm^{-1}): 685, 733, 881, 947, 1026, 1052, 1075, 1092, 1157, 1186, 1224, 1266, 1290, 1354, 1465, 1490, 1507, 1618, 1653, 1685, 1718. MS (EI) *m/z*, %: 285 $[MH]^+$ (37), 327 $[M + MeCN]^+$ (100). Found (%): C, 54.98; H, 3.43; Cl, 24.99. Calc. for $C_{13}H_{10}Cl_2O_3$ (%): C, 54.76; H, 3.54; Cl, 24.87. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.12-4.30 (m, 4H, OCH_2), 4.64 (s, 1H, CHCl), 7.47-7.48 (m, 3H, Ph), 7.59-7.61 (m, 2H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 63.79 (CHCl), 66.66 (OCH_2), 109.93 (C^5), 128.35 (C_q-Ph), 128.56 (C_m-Ph), 130.54 (C_o-Ph), 133.32 (C_p-Ph), 129.62 (C^8), 159.42 (C^9), 189.27 (C^7).

8-Chloro-9-phenyl-1,4-dioxaspiro[4.4]non-8-en-7-one **2b** was obtained similarly to compound **2a** from **1b** (0.1 g, 0.478 mmol) and phenylboronic acid (58 mg, 0.478 mmol). Yield 83 mg (69%). Colorless crystals, m.p. 108-109.5°C. IR (ν/cm^{-1}): 704, 743, 770, 832, 855, 951, 967, 1013, 1022, 1124, 1165, 1225, 1284, 1300, 1377, 1464, 1492, 1639, 1733. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 2.87 (s, 2H, H-6), 3.85-3.88 (m, 2H, OC<u>H</u>$_2$), 3.96-3.99 (m, 2H, OC<u>H</u>$_2$), 7.44 (t, 3H, *J* 3.2 Hz, H-Ph), 7.59-7.62 (m, 2H, H-Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 46.62 (C^6), 66.02 (OCH_2), 111.24 (C^5), 128.41 (C_q-Ph), 128.50 (C_m-Ph), 130.01 (C_o-Ph), 130.91 (C_p-Ph), 134.76 (C^8), 160.80 (C^9), 195.21 (C^7). MS (EI), *m/z* (%): 251 $[MH]^+$ (20), 293 $[MH + MeCN]^+$ (100). Found (%): C, 62.48; H, 4.48; Cl, 14.40. Calc. for $C_{13}H_{11}ClO_3$ (%): C, 62.29; H, 4.42; Cl, 14.14.

5-Allyl-2,5-dichloro-4,4-dimethoxy-3-phenylcyclopent-2-en-1-one **2c** was obtained similarly to the compound **2a** from **1c** (0.2 g, 0.701 mmol) and phenylboronic acid (86 mg, 0.701 mmol). Yield 30 mg (13%). Pale yellow, deliquescent crystals. IR (ν/cm^{-1}): 697, 746, 974, 1001,

1030, 1077, 1200, 1456, 1602, 1743, 2841, 2948, 2981. MS (EI) *m/z*, %: 327 $[M\text{H}]^+$ (34), 291 $[M\text{-Cl}]^+$ (20). ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 2.76 (d, 2H, H-1', *J* 7.1 Hz), 3.48 (s, 3H, OCH_3), 3.50 (s, 3H, OCH_3), 5.10-5.15 (m, 2H, $=CH_2$), 5.84-5.88 (m, 1H, =CH), 7.46-7.48 (m, 3H, H-Ph), 7.78-7.80 (m, 2H, H-Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 42.42 ($C^{1'}$), 52.09 (OCH_3), 52.62 (OCH_3), 75.04 (C^5), 105.06 (C^4), 119.58 ($=CH_2$), 126.53 (C^2), 128.38 (C_q-Ph), 129.50 (C_m-Ph), 130.56 (C_o-Ph), 131.74 (=CH), 134.27 (C_p-Ph), 158.75 (C^3), 184.82 (C^1).

2,4-Dichloro-5-phenylcyclopent-4-ene-1,3-dione **3a.** Compound **2a** (74 mg, 0.249 mmol) on stirring was added in small portions to concentrated sulfuric acid (2 ml) cooled to 0°C, and the mixture was stirred for ~1 h at 0°C, then diluted with $CHCl_3$ (10 ml). The organic phase was separated and the acidic layer was extracted with $CHCl_3$ (3×10 ml). The combined extracts were washed with 5% solution of $NaHCO_3$ (2×10 ml), and saturated solution of NaCl (2×10 ml), dried over $MgSO_4$, filtered and evaporated in vacuum. The residue was purified by column chromatography on a silica gel (elution with petroleum ether - EtOAc, 1:5). Yield 56 mg (92%). Light yellow crystals, m.p. 98-100°C. IR (ν/cm^{-1}): 691, 730, 860, 980, 1135, 1178, 1238, 1283, 1301, 1446, 1491, 1570, 1583, 1601, 1723, 1762, 2849, 2919. MS (EI) *m/z*, %: 239 (240, 241) $[M\text{-H}]^-$ (100). Found (%): C, 55.08; H, 2.45; Cl, 29.77. Calc. for $C_{11}H_7ClO_2$ (%): C, 54.80; H, 2.51; Cl, 29.41. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 4.77 (s, 1H, H-2), 7.51-7.57 (m, 3H, H-Ph), 7.87-7.89 (m, 2H, H-Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 52.01 (C^2), 126.49 (C_q-Ph), 128.82 (C_m-Ph), 130.08 (C_o-Ph), 132.21 (C_p-Ph), 149.20 (C^4), 151.39 (C^5), 187.10 (C^3), 190.02 (C^1).

4-Chloro-5-phenylcyclopent-4-ene-1,3-dione **3b.** was obtained similarly to compound **3a** from compound **2b** (0.2 g, 0.798 mmol) and conc. H_2SO_4 (5 ml). Yield 0.147 g (89%). Light yellow crystals, m.p. 97-99°C. IR (ν/cm^{-1}): 692, 697, 733, 757, 848, 927, 967, 1013, 1032, 1078, 1138, 1149, 1178, 1229, 1259, 1279, 1298, 1334, 1347, 1372, 1443, 1464, 1489, 1569, 1589, 1599, 1699, 1714, 1733, 1753, 2911, 2952, 3056. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.23 (s, 2H, H-2), 7.52-7.53 (m, 3H, H-Ph), 7.80-7.82 (m, 2H, H-Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 42.01 (C^2), 127.04 (C_q-Ph), 128.51 (C_m-Ph), 128.85 (C_o-Ph), 131.34 (C_p-Ph), 149.44 (C^4), 152.36 (C^5), 191.85 (C^3), 195.02 (C^1). MS (EI), *m/z* (%): 205 $[M\text{-H}]^-$ (38), 411 $[2M\text{-H}]^-$ (100). Found (%): C, 63.67; H, 3.43; Cl, 17.35. Calc. for $C_{11}H_7ClO_2$ (%): C, 63.94; H, 3.41; Cl, 17.12.

(2E,Z)-4-Chloro-2-(2-furylmethylidene)-5-phenylcyclopent-4-ene-1,3-dione **4a.** Butyllithium (2.65 M solution in hexane, 0.35 ml, 0.94 mmol) was added dropwise under argon to a solution of Pr^i_2NH (0.12 mL, 0.87 mmol) in anhydrous THF (20 ml) cooled to –60°C. The mixture was stirred for 15-20 min followed by a dropwise addition of a solution of **3b** (0.15 g, 0.73 mmol) in THF (3 ml). The mixture was cooled to –78°C followed by dropwise addition of furfural (0.06 m, 0.73 mmol) solution in THF (3 ml). The mixture was stirred for 1 h at –20°C and for 30-40 min at room temperature. Then, saturated solution of NH_4Cl (2-3 ml) was added

with stirring continued for 10 min. THF was evaporated, and the residue was extracted with $CHCl_3$ (3×10 ml). The combined organic layers were washed with, saturated solution of NaCl (2×10 ml), dried with $MgSO_4$, and concentrated. The residue was chromatographed in a column with SiO_2 using EtOAc–petroleum ether (1:10→1:5) as the eluent. Yield 81 mg (42%), a mixture of isomers in a ratio of ~1:1 (^{1}H NMR) with a slight prevalence of the *Z*-isomer. Sand-coloured powder, m.p. 106-108°C. IR (ν/cm^{-1}): 699, 756, 796, 929, 941, 1015, 1087, 1158, 1212, 1281, 1349, 1411, 1466, 1496, 1601, 1607, 1633, 1674, 1713, 3311, 3446. MS (EI) *m/z*, %: 285 [*M*H]$^+$ (100). Found (%): C, 67.77; H, 3.23; Cl, 12.66. Calc. for $C_{16}H_9ClO_3$ (%): C, 67.50; H, 3.19; Cl, 12.45.

Z-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 6.70 (dd, 1H, $^3J_{4"-3"}$ 3.8 Hz, $^3J_{4"-5"}$ 1.6 Hz, H-4$_{furyl}$); 7.51-7.54 (m, 3H, H$_m$-Ph, H$_p$-Ph); 7.57 (s, 1H, H-1'); 7.76 (d, 1H, $^3J_{5"-4"}$ 1.6 Hz, H-5$_{furyl}$); 7.92 (d, 2H, ^3J 6.8 Hz, H$_o$-Ph); 8.42 (d, 1H, $^3J_{3"-4"}$ 3.8 Hz, H-3$_{furyl}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 114.59 (C$^4_{furyl}$), 119.28 (C^2), 124.17 (C$^3_{furyl}$), 126.91 (C$^{1'}$), 127.61 (C$_q$-Ph), 128.53 (C$_m$-Ph), 130.08 (C$_o$-Ph), 131.00 (C$_p$-Ph), 146.34 (C^5), 148.93 (C$^5_{furyl}$), 149.17 (C^4), 150.72 (C$^2_{furyl}$), 184.06 (C^3); 188.96 (C^1).

E-Isomer. ^{1}H NMR ((500 MHz, $CDCl_3$) δ: 6.69 (dd, 1H, $^3J_{4"-3"}$ 3.8 Hz, $^3J_{4"-5"}$ 1.6 Hz, H-4$_{furyl}$); 7.51-7.54 (m, 3H, H$_m$-Ph, H$_p$-Ph); 7.60 (s, 1H, H-1'); 7.76 (d, 1H, $^3J_{5"-4"}$ 1.6 Hz, H-5$_{furyl}$); 7.87 (d, 2H, ^3J 6.8 Hz, H$_o$-Ph); 8.38 (d, 1H, $^3J_{3"-4"}$ 3.8 Hz, H-3$_{furyl}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 114.59 (C$^4_{furyl}$), 119.56 (C^2), 124.44 (C$^3_{furyl}$), 127.02 (C$^{1'}$), 127.61 (C$_q$-Ph), 128.48 (C$_m$-Ph), 130.00 (C$_o$-Ph), 131.03 (C$_p$-Ph), 146.38 (C^4), 149.02 (C$^5_{furyl}$), 149.44 (C^5), 150.52 (C$^2_{furyl}$), 185.91 (C^3), 187.58 (C^1).

(2E)-4-Chloro-5-phenyl-2-(2-thienylmethylidene)cyclopent-4-ene-1,3-dione **4b** was obtained similarly to compound **4a** from dione **3b** (0.29 g, 1.40 mmol) and thiophene-2-carbaldehyde (0.157 g, 1.40 mmol). Yield 0.194 g (46%), a mixture of *Z,E*-isomers in a ratio of ~3:2. Light yellow crystals, m.p. 157-158°C. IR (ν/cm^{-1}): 1713, 1684, 1653, 1610, 1602, 1560, 1490, 1485, 1457, 1415, 1395, 1377, 1280, 1152, 1081, 1045, 869, 781, 731, 689. MS (EI) *m/z*, %: 301 (302, 303) [*M*+H]$^+$ (12). Found (%): C, 63.63; H, 3.14; Cl, 11.45; S, 10.94. Calc. for $C_{16}H_9ClO_2S$ (%): C, 63.90; H, 3.02; Cl, 11.79; S, 10.66%.

Z-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.23 (dd, 1H, $^3J_{4"-5"}$ 4.9 Hz, $^3J_{4"-3"}$ 3.7 Hz, H-4$_{thienyl}$), 7.52 (t, 1H, ^3J 6.8 Hz, H$_p$-Ph), 7.53 (t, 2H, ^3J 6.8 Hz, ^3J 6.8 Hz, H$_m$-Ph), 7.83 (s, 1H, H-1'), 7.85 (dd, 1H, $^3J_{5"-4"}$ 4.9 Hz, $^4J_{5"-3"}$ 1.2 Hz, H-5$_{thienyl}$), 7.92 (d, 2H, ^3J 6.8 Hz, H$_o$-Ph), 8.05 (dd, 1H, $^3J_{3"-4"}$ 3.7 Hz, $^4J_{3"-5"}$ 1.2 Hz, H-3$_{thienyl}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 119.52 (C^2), 127.59 (C$_q$-Ph), 128.51 (C$_m$-Ph), 128.70 (C$^4_{thienyl}$), 130.10 (C$_o$-Ph), 131.00 (C$_p$-Ph), 133.72 (C$^{1'}$), 136.88 (C$^2_{thienyl}$), 137.87 (C$^5_{thienyl}$), 141.10 (C$^3_{thienyl}$), 146.37 (C^5), 148.95 (C^4), 184.48 (C^3), 189.23 (C^1).

E-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.22 (dd, 1H, $^3J_{4''\text{-}5''}$ 4.9 Hz, $^3J_{4''\text{-}3''}$ 3.7 Hz, H-$4_{thienyl}$), 7.52 (t, 1H, ^3J 6.8 Hz, H_p-Ph), 7.53 (t, 2H, ^3J 6.8 Hz, ^3J = 6.8, H_m-Ph), 7.84 (dd, 1H, $^3J_{5''\text{-}4''}$ 4.9 Hz, $^4J_{5''\text{-}3''}$ 1.2 Hz, H-$5_{thienyl}$), 7.88 (s, 1H, H-1'), 7.91 (d, 2H, ^3J 6.8 Hz, H_o-Ph), 7.99 (dd, 1H, $^3J_{3''\text{-}4''}$ 3.7 Hz, $^4J_{3''\text{-}5''}$ 1.2 Hz, H-$3_{thienyl}$).^{13}C NMR (125 MHz, $CDCl_3$) δ: 119.65 (C^2), 127.68 (C_q-Ph), 128.55 (C_m-Ph), 128.63 ($C^4{}_{thienyl}$), 130.05 (C_o-Ph), 131.05 (C_p-Ph), 133.93 ($C^{1'}$), 136.57 ($C^2{}_{thienyl}$), 138.14 ($C^5{}_{thienyl}$), 141.60 ($C^3{}_{thienyl}$), 146.32 (C^4), 149.17 (C^5), 186.13 (C^3), 188.14 (C^1).

(2E,Z)-4-Chloro-5-phenyl-2-(3,4,5-trimethoxybenzylidene)cyclopent-4-ene-1,3-dione **4c** was obtained similarly to the compound **4a** from dione **3b** (0.345 g, 1.67 mmol) and 3,4,5-trimethoxybenzaldehyde (0.32 g, 1.67 mmol). Yield 0.35 g (55%), a mixture of *Z,E*-isomers in a ratio of ~1:1 with a slight prevalence of the *Z*-isomer. Light yellow crystals, m.p. 162-165°C. IR (ν/cm^{-1}): 2954, 2922, 2850, 1686, 1614, 1574, 1503, 1465, 1426, 1376, 1341, 1314, 1246, 1126, 1003, 788, 735, 694. MS (EI) *m/z*, %: 385 (386, 387) $[MH]^+$ (37), 197 (100). Found (%): C, 65.82; H, 4.50; Cl, 9.44. Calc. for $C_{21}H_9ClO_3$ r(%): C, 65.55; H, 4.45; Cl, 9.21%.

Z-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.94 (s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 7.34-7.43 (m, 3H, H-Ph), 7.52 (br.s, 2H, H-Ar), 7.79-7.85 (m, 2H, H-Ph), 7.92 (s, 1H, H-1'). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 56.35 (OCH_3), 61.07 (OCH_3), 111.86 ($C^2{}_{Ar}$, $C^6{}_{Ar}$), 122.20 (C^2), 127.55 ($C^1{}_{Ar}$), 128.46 (C_q-Ph), 129.65 (C_m-Ph), 130.09 (C_o-Ph), 131.11 (C_p-Ph), 143.08 (C^4), 144.70 ($C^{1'}$), 145.96 ($C^4{}_{Ar}$), 149.71 (C^5), 152.90 ($C^5{}_{Ar}$, $C^3{}_{Ar}$), 184.68 (C^3), 189.45 (C^1).

E-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.93 (3H, s, OCH_3), 3.95 (6H, s, OCH_3), 7.34-7.43 (3H, m, Ar), 7.61 c (1H, s, H-Ar), 7.63 c (1H, s, H-Ar), 7.79-7.85 (2H, m, Ph), 7.93 (1H, s, CH=). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 56.33 (OCH_3), 61.12 (OCH_3), 111.52 ($C^2{}_{Ar}$, $C^6{}_{Ar}$), 122.68 (C^2), 127.62 ($C^1{}_{Ar}$), 128.42 (C_q-Ph), 129.30 (C_m-Ph),130.06 (C_o-Ph), 131.07 (C_p-Ph), 143.01 (C^4), 144.76 ($C^{1'}$), 146.28 ($C^4{}_{Ar}$), 150.27 (C^5), 152.33 ($C^5{}_{Ar}$, $C^3{}_{Ar}$), 186.56 (C^3), 187.81 (C^1).

(2E,Z)-4-Chloro-2-(4-methoxybenzylidene)-5-phenylcyclopent-4-ene-1,3-dione **4d** was obtained similarly to compound **4a** from dione **3b** (0.237 g, 1.15 mmol) and 4-methoxybenzaldehyde (0.139 g, 1.15 mmol). Yield 0.186 g (50%), a mixture of *Z,E*-isomers in a ratio of ~3:2 (as determined by ^{1}H NMR). Light yellow crystals, m.p. 145-147°C. IR (ν/cm^{-1}): 1689, 1619, 1587, 1564, 1511, 1464, 1455, 1377, 1314, 1267, 1257, 1179, 1145, 1095, 1048, 1021, 867, 830, 782, 688. MS (EI) *m/z*, %: 325 (326, 327) $[MH]^+$ (100).

Z-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.89 (s, 3H, OCH_3), 6.99 (d, 2H, *J* 8.8, H-Ar), 7.49-7.54 (m, 3H, H-Ph), 7.65 (s, 1H, H-1'), 7.83-7.86 (m, 1H, H-Ph), 7.92 (d, 1H, *J* 7.9 Hz, H-Ph), 8.43 (d, 2H, *J* 8.8 Hz, H-Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.62 (OCH_3), 114.45 ($C^3{}_{Ar}$, $C^5{}_{Ar}$), 120.97 ($C^1{}_{Ar}$), 125.86 (C^2), 127.75, 128.52, 130.12, 130.91 (C_{Ph}), 136.83 ($C^2{}_{Ar}$, $C^6{}_{Ar}$), 144.11 ($C^{1'}$), 145.66 (C^4), 149.34 (C^5), 164.02 ($C^4{}_{Ar}$), 184.58 (C^1), 189.79 (C^3).

E-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.88 (s, 3H, OCH_3), 6.98 (d, 2H, *J* 8.7 Hz, H-Ar), 7.49-7.54 (m, 3H, H-Ph), 7.69 (s, 1H, H-1'), 7.83-7.86 (m, 1H, H-Ph), 7.91 (d, 1H, ^3J 7.2 Hz, H-Ph), 8.40 (d, 2H, *J* 8.8 Hz, H-Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.62 (OCH_3), 114.32 (C^3_{Ar}, C^5_{Ar}), 121.97 (C^1_{Ar}), 125.58 (C^2), 127.75 (C-Ph), 128.43, 130.06, 130.91 (C-Ph), 137.02 (C^2_{Ar}, C^6_{Ar}), 144.29 ($C^{1'}$), 145.90 (C^4), 149.55 (C^5), 163.99 (C^4_{Ar}), 186.78 (C^1), 188.05 (C^3).

4-Chloro-5-(2,4,6-trimethoxyphenyl)cyclopent-4-ene-1,3-dione **5.** A solution of 1,3,5-trimethoxybenzene (0.46 g, 2.73 mmol) in dichloroethane (10 mi) and tin(IV) chloride (0.51 ml) were sequentially added to a stirred solution of compound **1b** (0.36 g, 2.18 mmol) in dichloroethane (30 ml). The reaction mixture was refluxed for 5 h and then cooled to room temperature. Then distilled water (20 ml) was added, and the mixture was diluted with $CHCl_3$ (30 ml). The organic layer was separated, washed with a saturated $NaHCO_3$ solution (2×15 ml), and dried with $MgSO_4$. The solvent was evaporated, and the residue was purified by column chromatography on a silica gel column (elution with petroleum ether - EtOAc, 10:1). Yield 0.478 g (75%). Dark yellow crystals, m.p. 138-140°C. IR (ν/cm^{-1}): 2952, 2854, 1755, 1716, 1620, 1586, 1496, 1467, 1455, 1440, 1416, 1375, 1343, 1282, 1233, 1209, 1163, 1138, 1125, 1055, 1028, 967, 953, 814, 499. Found (%): C, 56.99; H, 4.51; Cl, 11.64. Calc. for $C_{14}H_{13}ClO_5$ (%): C, 56.67; H, 4.42; Cl, 11.95. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.16 (s, 2H, H-2), 3.76 (s, 6H, OCH_3), 3.84 (s, 3H, OCH_3), 6.18 (s, 2H, H-Ar). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 42.13 (C^2), 55.50 (OCH_3), 55.84 (OCH_3), 90.94 (C^3_{Ar}, C^5_{Ar}), 98.32 (C^1_{Ar}), 153.11 (C^4), 153.55 (C^5), 158.83 (C^2_{Ar}, C^6_{Ar}), 163.99 (C^4_{Ar}), 192.35 (C^3), 194.16 (C^1).

(2E,Z)-4-Chloro-2-(2-furylmethylidene)-5-(2,4,6-trimethoxyphenyl)cyclopent-4-ene-1,3-dione **6a.** Obtained similarly to the compound **4a** from dione **5** (0.2 g, 0.674 mmol) and furfural (0.06 ml, 0.73 mmol). Yield 0.154 g (61%), a mixture of *Z*,*E*-isomers in a ratio of ~5:4. Bright yellow crystals, m.p. 136-138°C. IR (ν/cm^{-1}): 766, 882, 910, 950, 1023, 1093, 1128, 1163, 1171, 1210, 1232, 1259, 1343, 1349, 1377, 1418, 1443, 1464, 1583, 1629, 1692. MS (EI) *m/z*, %: 375 (376, 377) $[M\text{H}]^+$ (100).

Z-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.78 (s, 6H, OCH_3), 3.86 (s, 3H, OCH_3), 6.20 (s, 2H, H-3*Ar*, H-5*Ar*), 6.68 (dd, 1H, $^3J_{4''\text{-}3''}$ 3.7 Hz, $^3J_{4''\text{-}5''}$ 1.8 Hz, H-4$_{furyl}$), 7.51 (s, 1H, H-1'), 7.72 (d, 1H, $^3J_{5''\text{-}4''}$ 1.8 Hz, H-5$_{furyl}$), 8.37 (d, 1H, $^3J_{3''\text{-}4''}$ 3.7 Hz, H-3$_{furyl}$). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.50 (OCH_3), 55.91 (OCH_3), 90.98 (C^3_{Ar}, C^5_{Ar}), 98.71 (C^1_{Ar}), 114.24 (C^4_{furyl}), 120.32 (C^2), 123.18 (C^3_{furyl}), 125.75 ($C^{1'}$), 147.97 (C^5), 148.25 (C^5_{furyl}), 150.80 (C^2_{furyl}), 153.19 (C^4), 159.11 (C^2_{Ar},C^6_{Ar}), 163.80 (C^4_{Ar}), 184.39 (C^3), 188.27 (C^1).

E-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.78 (s, 6H, OCH_3), 3.87 (s, 3H, OCH_3), 6.21 (s, 2H, H-3$_{Ar}$, H-5$_{Ar}$), 6.64 (dd, 1H, $^3J_{4''\text{-}3''}$ 3.7 Hz, $^3J_{4''\text{-}5''}$ 1.8 Hz, H-4$_{furyl}$), 7.54 (s, 1H, H-1'), 7.71

(d, 1H, $^{3}J_{5"\text{-}4"}$ 1.8 Hz, H-5_{Ar}), 8.35 (d, 1H, $^{3}J_{3"\text{-}4"}$ 3.7 Hz, H-3_{Ar}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.50 (OCH_3), 55.89 (OCH_3), 90.98 (C^3_{Ar}, C^5_{Ar}), 98.71 (C^1_{Ar}), 114.29 (C^4_{furyl}), 120.64 (C^2), 123.39 (C^3_{furyl}), 125.70 ($C^{1'}$), 148.25 (C^5_{furyl}), 150.33 (C^4), 150.68 (C^2_{furyl}), 151.04 (C^5), 159.04 (C^2_{Ar}, C^6_{Ar}), 163.80 (C^4_{Ar}), 186.20 (C^3), 186.89 (C^1).

(2E,Z)-4-Chloro-2-(3,4,5-trimethoxybenzylidene)-5-(2,4,6-trimethoxyphenyl)-cyclopent-4-ene-1,3-dione **6b** was obtained similarly to compound **4a** from dione **5** (0.1 g, 0.33 mmol) and 3,4,5-trimethoxybenzaldehyde (66 mg, 0.33 mmol). Yield 80 mg (51%), a mixture of *Z,E*-isomers in a ratio of ~3:2 (as determined by ^{1}H NMR). Bright yellow crystals, m.p. 168-170°C. IR (ν/cm^{-1}): 615, 734, 812, 884, 911, 920, 950, 995, 1007, 1031, 1052, 1101, 1127, 1162, 1188, 1208, 1229, 1276, 1313, 1339, 1379, 1429, 1455, 1464, 1471, 1505, 1579, 1615, 1684, 1690, 1730, 2841, 2944, 3013, 3104. MS (EI) *m/z*, %: 475 (476, 477) [*M*H]$^+$ (100).

Z-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.78 (s, 6H, OCH_3), 3.87 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.97 (s, 6H, OCH_3), 6.20 (s, 2H, H-3'$_{Ar,}$ H-5'$_{Ar}$), 7.55 (s, 1H, H-1'), 7.81 (s, 2H, H-$2_{Ar,}$ H-6_{Ar}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.49 (OCH_3), 55.87 (OCH_3), 56.33 (OCH_3), 61.04 (OCH_3), 91.03 ($C^{3'}_{Ar}$, $C^{5'}_{Ar}$), 98.75 ($C^{1'}_{Ar}$), 111.54 (C^2_{Ar}, C^6_{Ar}), 123.20 (C^2), 128.04 (C^1_{Ar}), 142.98 ($C^{1'}$), 142.47 (C^4), 147.67 (C^4_{Ar}), 150.06 (C^5), 152.84 (C^3_{Ar}, C^5_{Ar}), 158.95 ($C^{2'}_{Ar}$, $C^{6'}_{Ar}$), 163.87 ($C^{4'}_{Ar}$), 184.94 (C^3), 188.72 (C^1).

E-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.77 (s, 6H, OCH_3), 3.88 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 3.97 (s, 6H, OCH_3), 6.21 (s, 2H, H-3'$_{Ar,}$ H-5'$_{Ar}$), 7.58 (s, 1H, H-1'), 7.82 (s, 2H, H-$2_{Ar,}$ H-6_{Ar}). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.46 (OCH_3), 55.79 (OCH_3), 56.29 (OCH_3), 91.00 ($C^{3'}_{Ar}$, $C^{5'}_{Ar}$), 98.65 ($C^{1'}_{Ar}$), 111.39 (C^2_{Ar}, C^6_{Ar}), 123.75 (C^2), 127.99 (C^1_{Ar}), 143.17 ($C^{1'}$), 142.53 (C^4), 147.67 (C^4_{Ar}), 151.72 (C^5), 153.66 (C^3_{Ar}, C^5_{Ar}), 159.08 ($C^{2'}_{Ar}$, $C^{6'}_{Ar}$), 163.87 ($C^{4'}_{Ar}$), 186.75 (C^3), 187.20 (C^1).

(2E,Z)-4-Chloro-2-(3,4-dimethoxybenzylidene)-5-(2,4,6-trimethoxyphenyl)cyclopent-4-ene-1,3-dione **6c** was obtained similarly to compound **4a** from dione **5** (0.2 g, 0.675 mmol) and 3,4-dimethoxybenzaldehyde (0.11 g, 0.675 mmol). Yield 0.168 g (56%), a mixture of *Z,E*-isomers in a ratio of ~4:3 (as determined by ^{1}H NMR). Bright yellow crystals, m.p. 215-217°C. IR (ν/cm^{-1}): 513, 574, 616, 636, 704, 735, 768, 792, 815, 889, 923, 951, 1022, 1034, 1098, 1130, 1148, 1165, 1185, 1207, 1228, 1252, 1275, 1340, 1387, 1419, 1456, 1516, 1584, 1615, 1683, 1714, 2840, 2964, 3006, 3099. MS (EI) *m/z*, %: 445 (446, 447) [*M*H]$^+$ (100).

Z-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.75 (s, 6H, OCH_3), 3.82 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.02 (s, 3H, OCH_3), 6.18 (s, 2H, H-3''', H-5'''), 6.91 (d, 1H, $^{3}J_{5"\text{-}6"}$ 8.4 Hz, H-5''), 7.56 (s, 1H, H-1'), 7.56 (dd, 1H, $^{3}J_{6"\text{-}5"}$ 8.4 Hz, $^{4}J_{6"\text{-}2"}$ 1.8 Hz, H-6''), 8.69 (d, 1H, $^{4}J_{2"\text{-}6"}$ 1.8 Hz, H-2''). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.38 (OCH_3), 55.78 (OCH_3), 55.95 (OCH_3), 56.04 (OCH_3),

90.93 ($C^{3'''}$, $C^{5'''}$), 98.78 ($C^{1'''}$), 110.53 ($C^{5''}$), 114.78 ($C^{2''}$), 121.69 (C^{2}), 126.36 ($C^{1''}$), 130.53 ($C^{6''}$), 143.11 ($C^{1'}$), 147.19 (C^{5}), 148.70 ($C^{3''}$), 153.10 (C^{4}), 153.36 ($C^{4''}$), 159.02 ($C^{2'''}$, $C^{6'''}$), 163.68 ($C^{4'''}$), 185.06 (C^{3}), 188.91 (C^{1}).

E-Isomer. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.75 (s, 6H, OCH_3), 3.82 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 6.19 (s, 2H, H-3''', H-5'''), 6.90 (d, 1H, $^{3}J_{5''\text{-}6''}$ 8.4 Hz, H-5''), 7.58 (s, 1H, H-1'), 7.62 (dd, 1H, $^{3}J_{6''\text{-}5''}$ 8.4 Hz, $^{4}J_{6''\text{-}2''}$ 1.8 Hz, H-6''), 8.59 (d, 1H, $^{4}J_{2''\text{-}6''}$ 1.8 Hz, H-2''). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 55.38 (OCH_3), 55.78 (OCH_3), 55.95 (OCH_3), 56.02 (OCH_3), 90.91 ($C^{3'''}$, $C^{5'''}$), 98.69 ($C^{1'''}$), 110.53 ($C^{5''}$), 115.13 ($C^{2''}$), 122.28 (C^{2}), 126.16 ($C^{1''}$), 130.50 ($C^{6''}$), 142.93 ($C^{1'}$), 148.76 ($C^{3''}$), 149.63 (C^{4}), 151.05 (C^{5}), 153.29 ($C^{4''}$) 158.91 ($C^{2'''}$, $C^{6'''}$), 163.82 ($C^{4'''}$), 186.85 (C^{3}), 187.41 (C^{1}).

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NMR and correlation spectra of some compounds

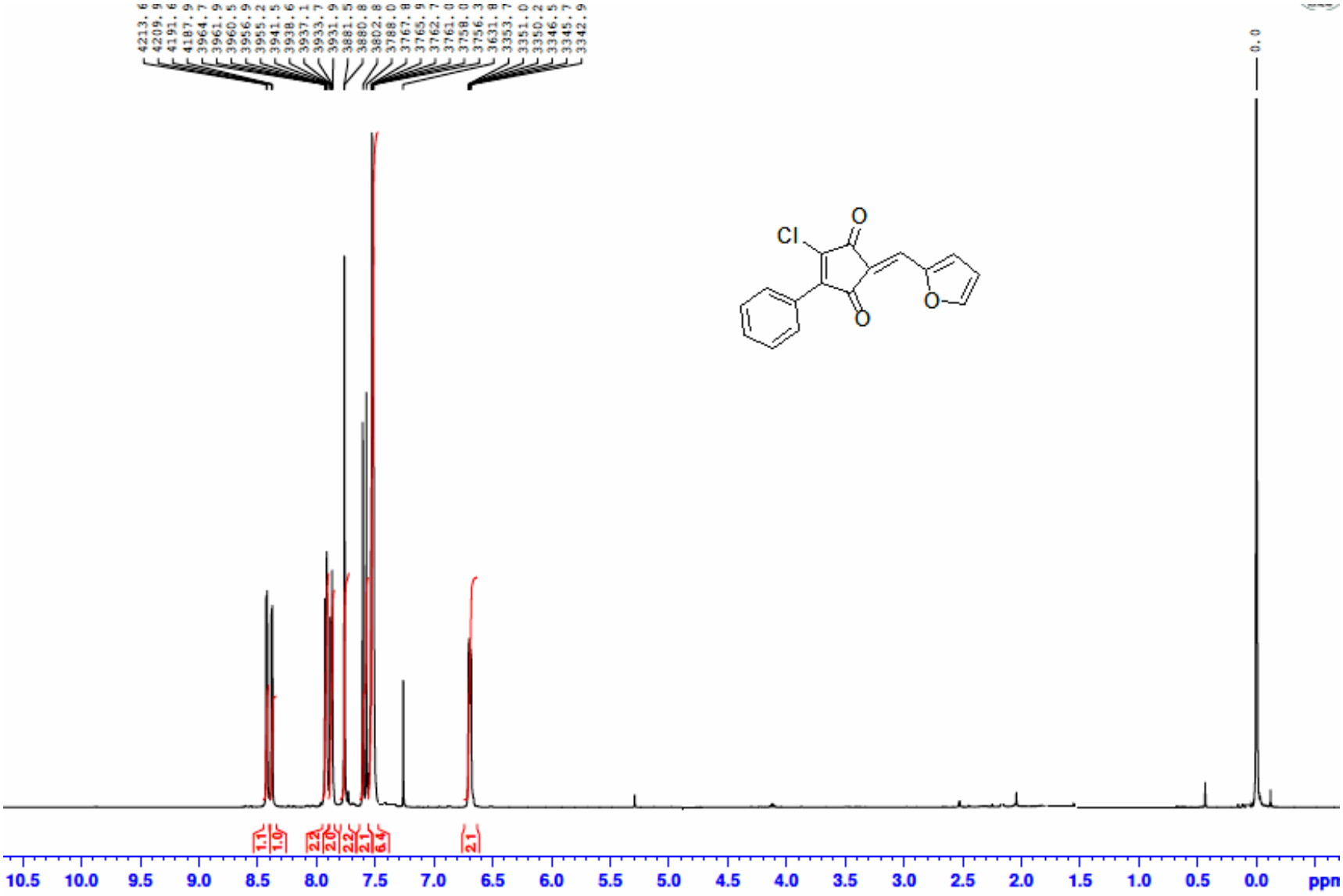

Figure S1. Complete ^{1}H NMR spectrum of compound **4a** in $CDCl_3$, 500MHz

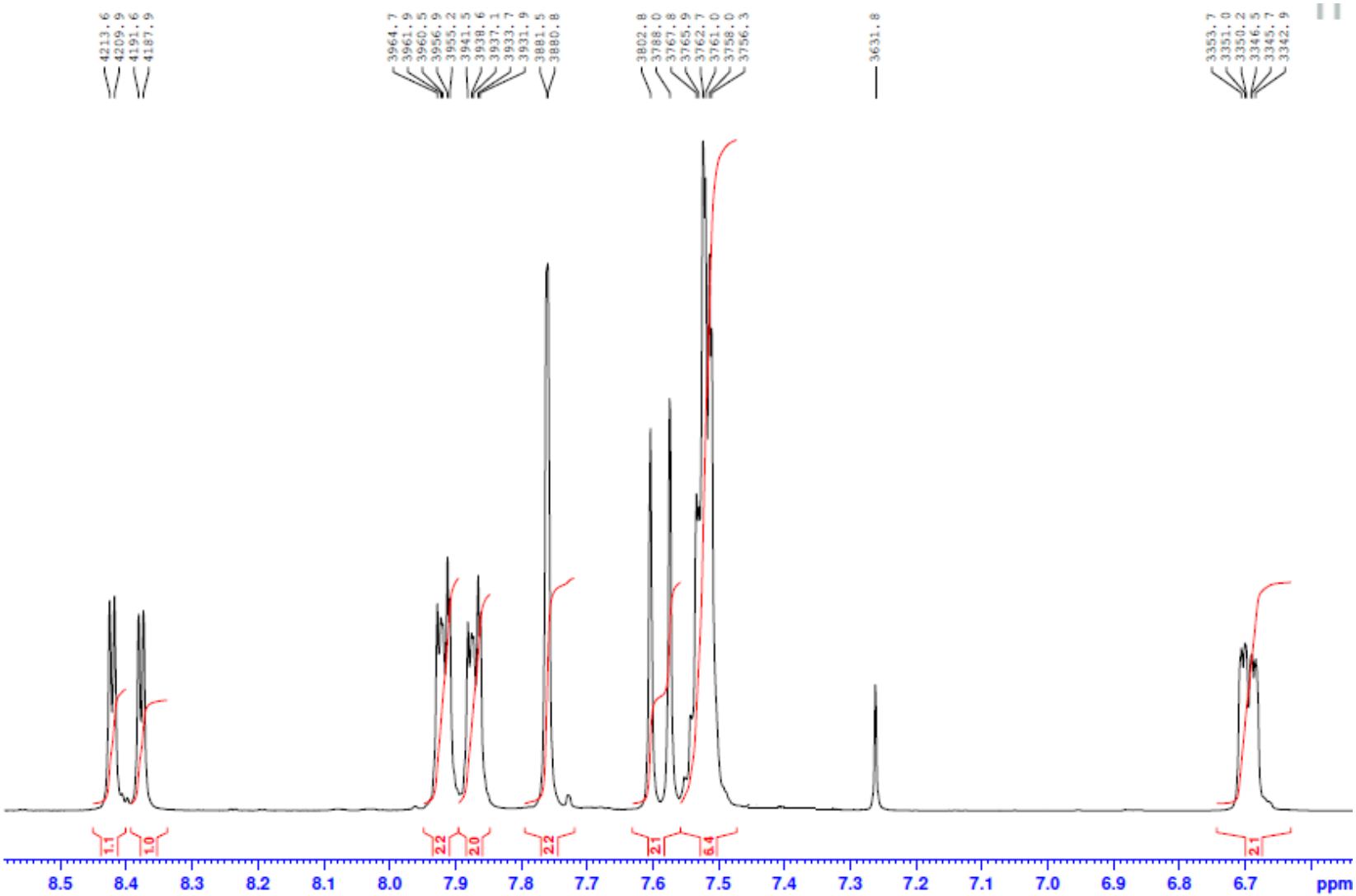

Figure S2. Expanded ^{1}H NMR spectrum of compound **4a** in $CDCl_3$, 500MHz

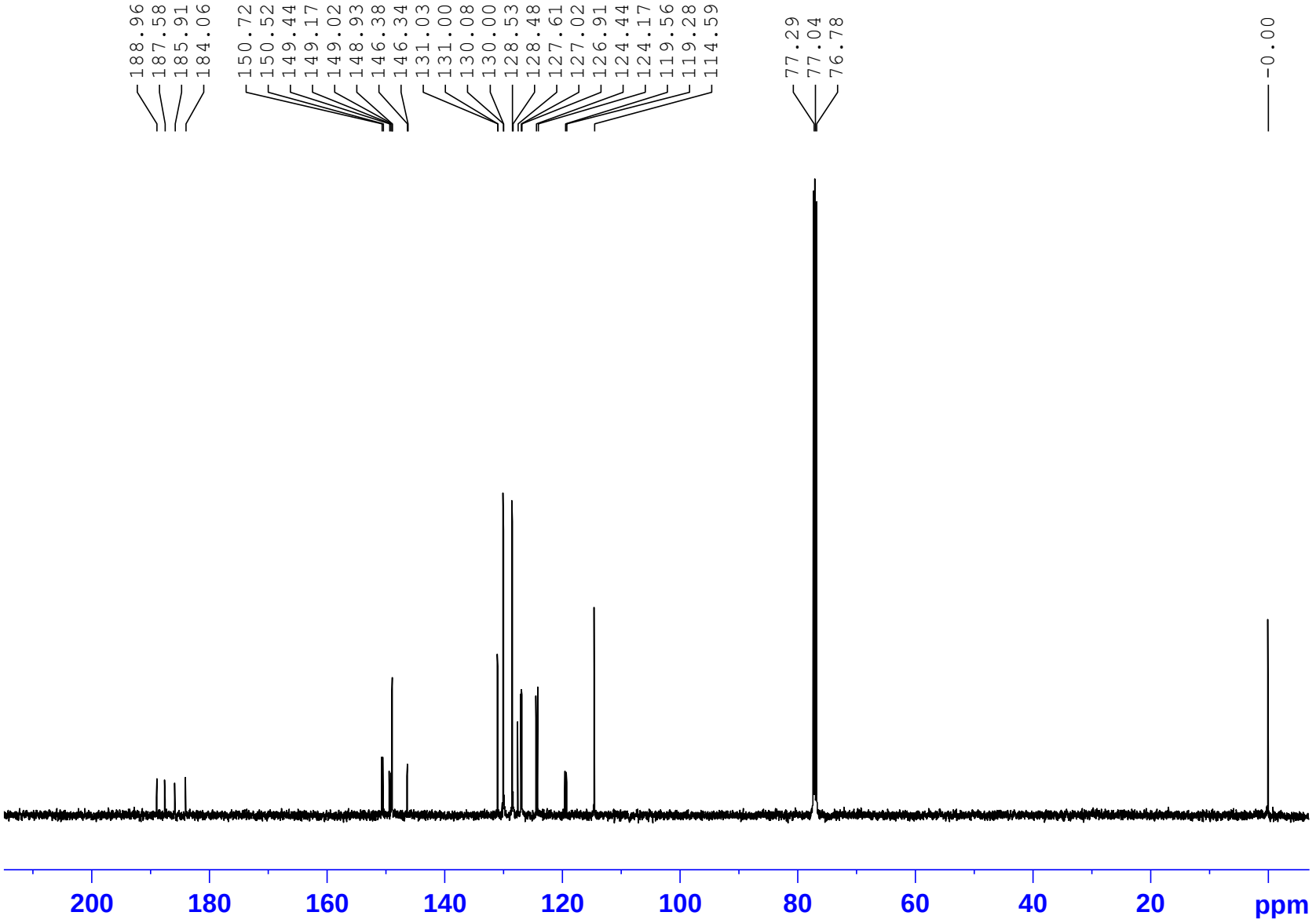

Figure S3. Complete $^{13}C\{^{1}H\}$ spectrum of compound **4a** in $CDCl_3$, 125 MHz

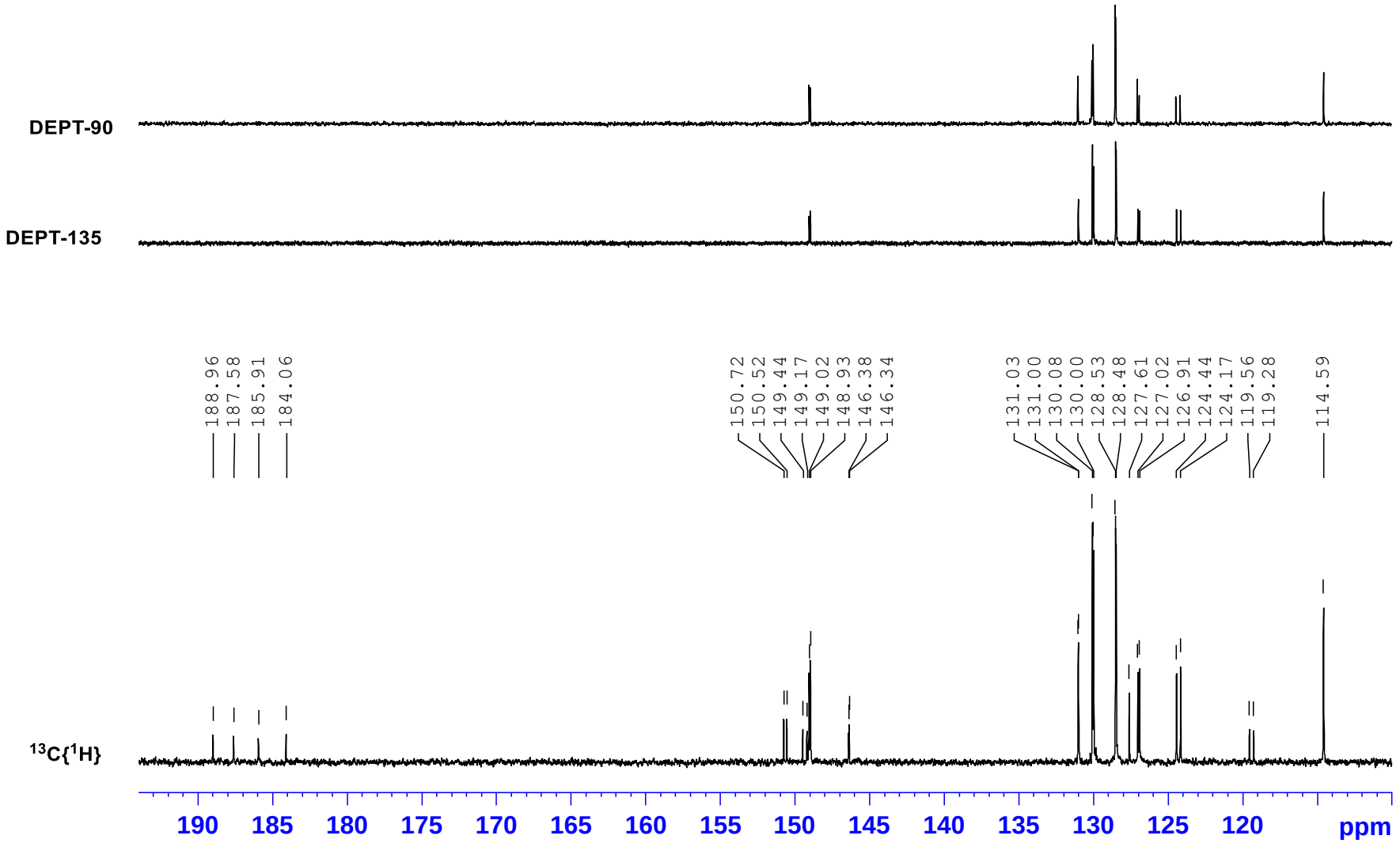

Figure S4. $^{13}C\{^{1}H\}$ and DEPT-135, DEPT-90 spectra of compound **4a** in $CDCl_3$, 125 MHz

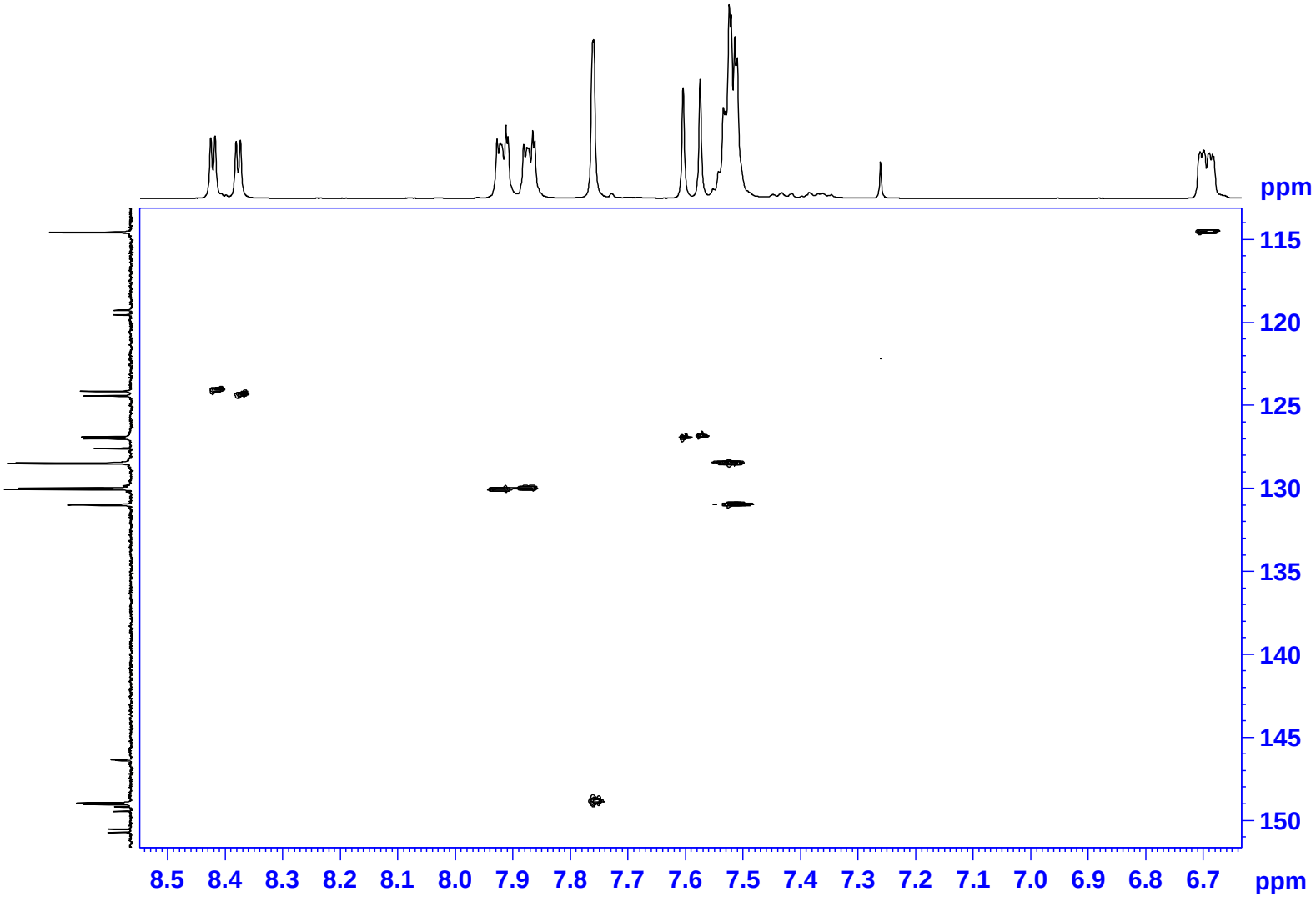

Figure S5. {^{1}H, ^{13}C} HSQC spectrum of compound **4a** in $CDCl_3$, 500 MHz

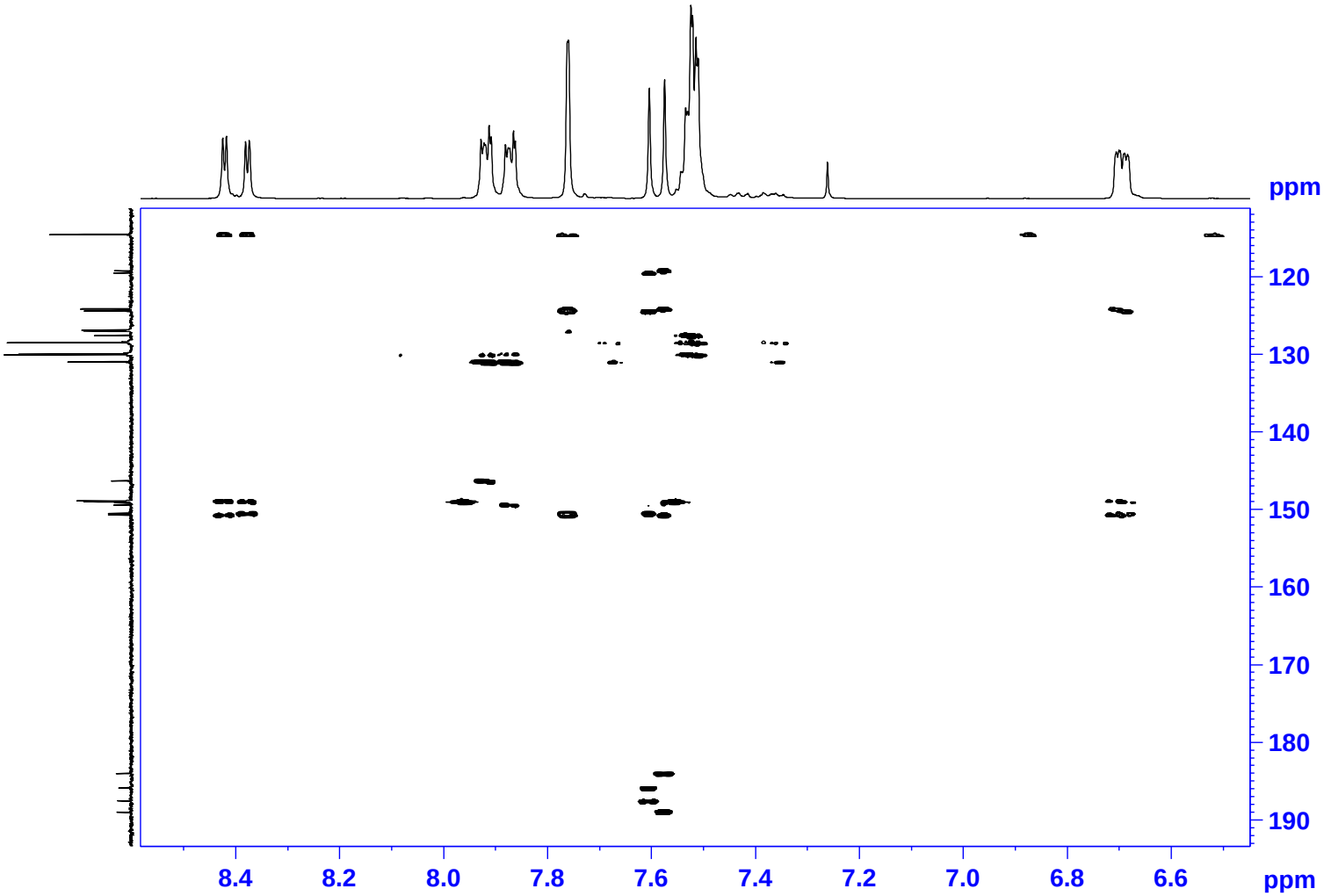

Figure S6. {^{1}H, ^{13}C} HMBC spectrum of compound **4a** in $CDCl_3$, 500 MHz

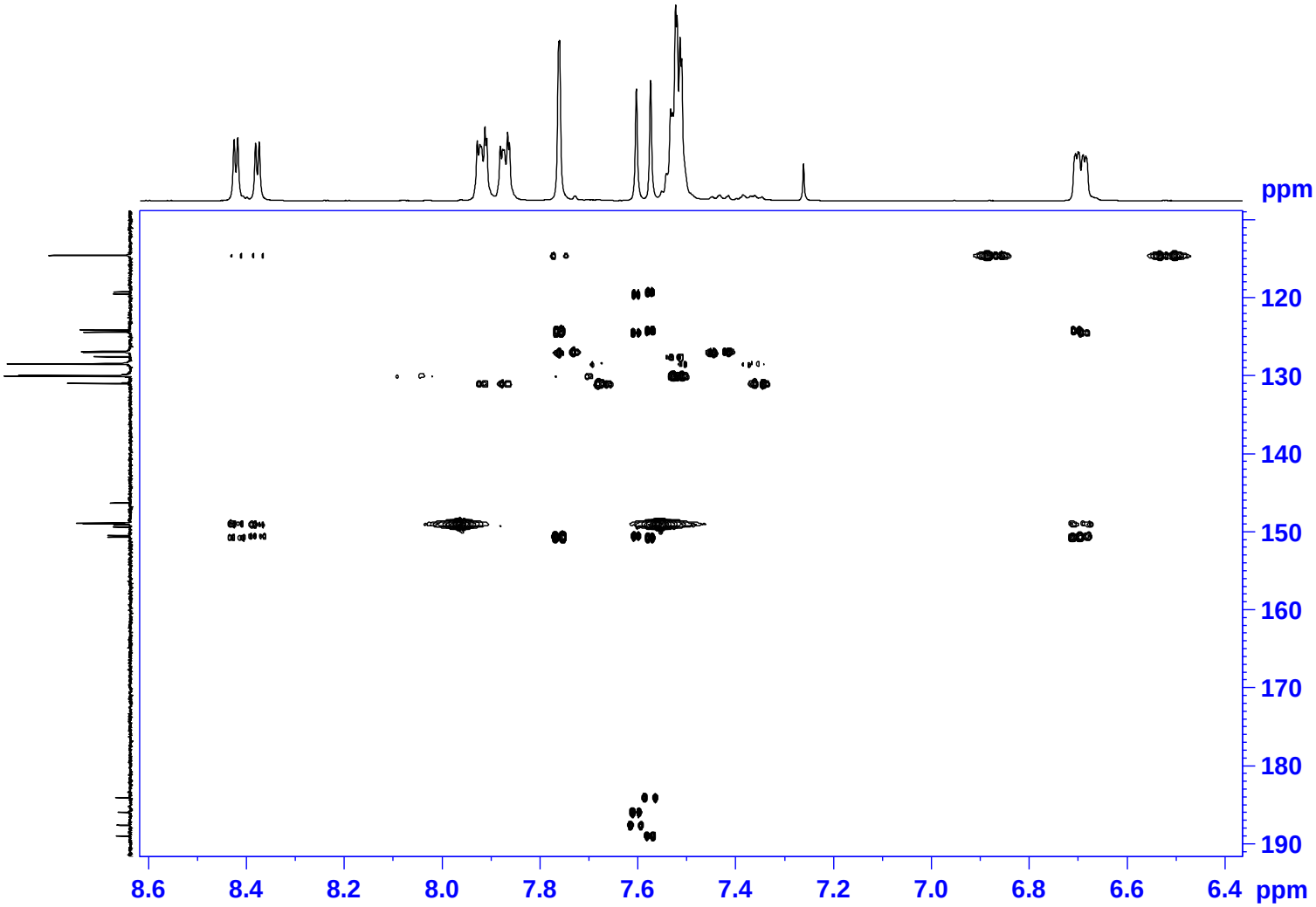

Figure S7. {^{1}H, ^{13}C} LR-HSQMBC spectrum of compound **4a** in $CDCl_3$, 500 MHz

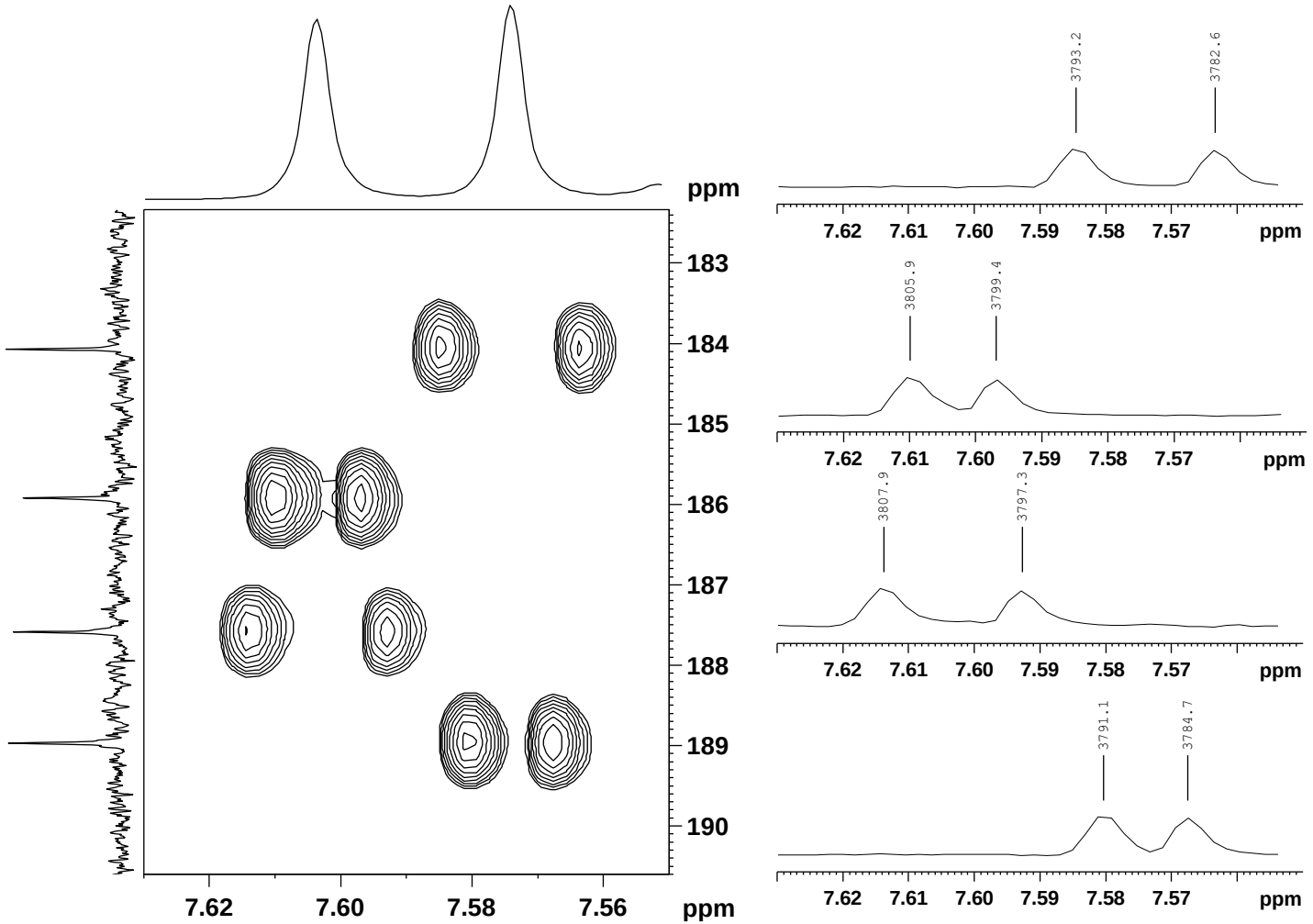

Figure S8. Expanded {^{1}H, ^{13}C} LR-HSQMBC spectrum of compound **4a** in $CDCl_3$, 500 MHz

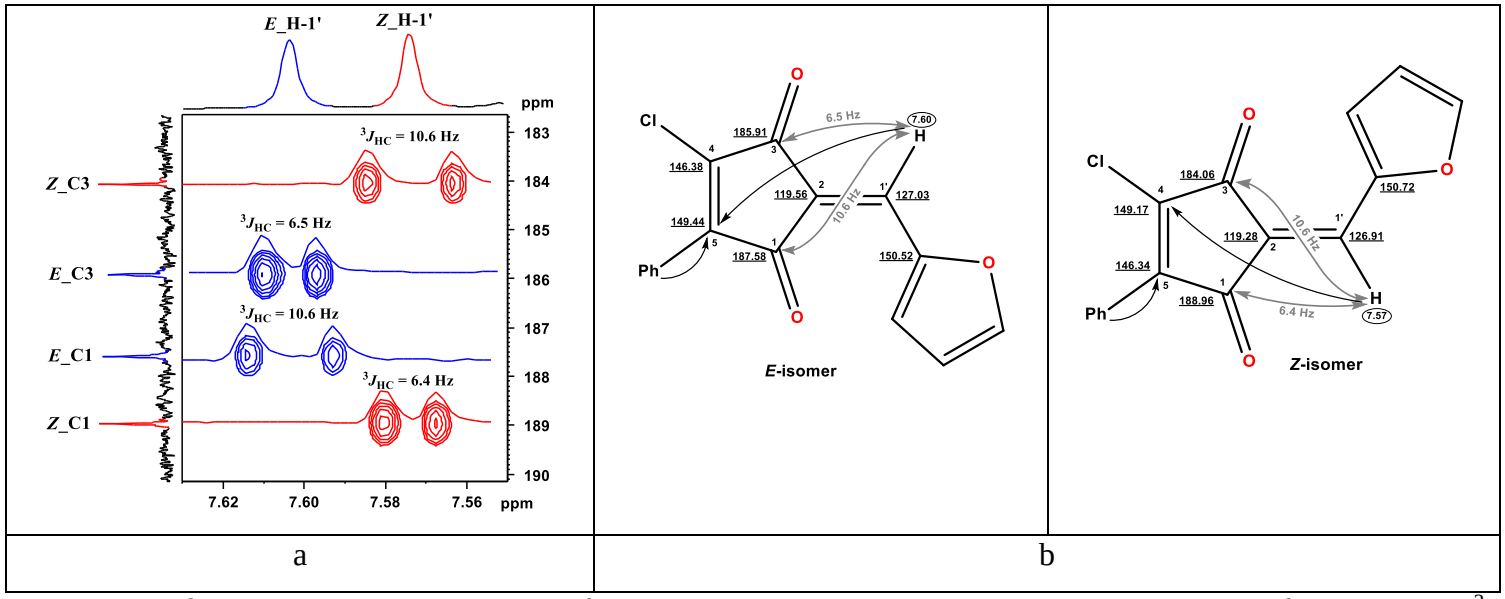

Figure S9. Fragment of LR-HSQMBC (a) spectrum of compound **4a** in $CDCl_3$ solution and representation of experimental $^3J_{CH}$ values with signals assignments of its Z/E isomers (b).

Table S1. Calculated ^{13}C NMR chemical shifts data (in ppm)* and calculated $^nJ_{CH}$ values (in Hz)** for exomethylene H-1' with the corresponding carbon (in parentheses)

^{13}C	**4a**		**4b**		**6a**		**6b**	
	Z	***E***	***Z***	***E***	***Z***	***E***	***Z***	***E***
C1	187.27 (6.8)	186.22 (10.3)	186.51 (6.8)	185.68 (10.1)	187.75 (6.9)	185.99 (10.2)	187.62 (7.3)	186.11 (10.5)
C2	120.25 (-1.8)	120.50 (-1.9)	121.70 (-1.8)	121.97 (-2.0)	121.58 (-1.7)	121.84 (-1.8)	123.47 (-1.3)	123.92 (-1.4)
C3	181.52 (10.1)	182.68 (6.8)	181.54 (10.2)	182.65 (6.9)	181.38 (10.0)	183.15 (6.9)	181.88 (10.6)	183.94 (7.4)
C4	158.99 (2.0)	156.52 (0.5)	162.67 (2.1)	160.33 (0.6)	159.28 (2.0)	156.13 (0.6)	163.02 (2.1)	159.29 (0.7)
C5	147.80 (0.2)	150.83 (1.1)	150.36 (0.3)	153.17 (1.2)	147.35 (0.2)	151.20 (1.1)	148.89 (0.3)	153.19 (1.2)
C1'	124.92 (156.5)	124.86 (156.5)	123.22 (156.3)	123.33 (156.3)	131.24 (154.1)	131.08 (154.1)	141.21 (149.6)	141.25 (149.6)

* calculated by GIAO in WP04/aug-cc-pVDZ basis set. Referenced to TMS with ^{13}C chemical shielding 188.59 ppm.
** calculated in B3LYP/6-311++G(d,p)u+1s approximation.

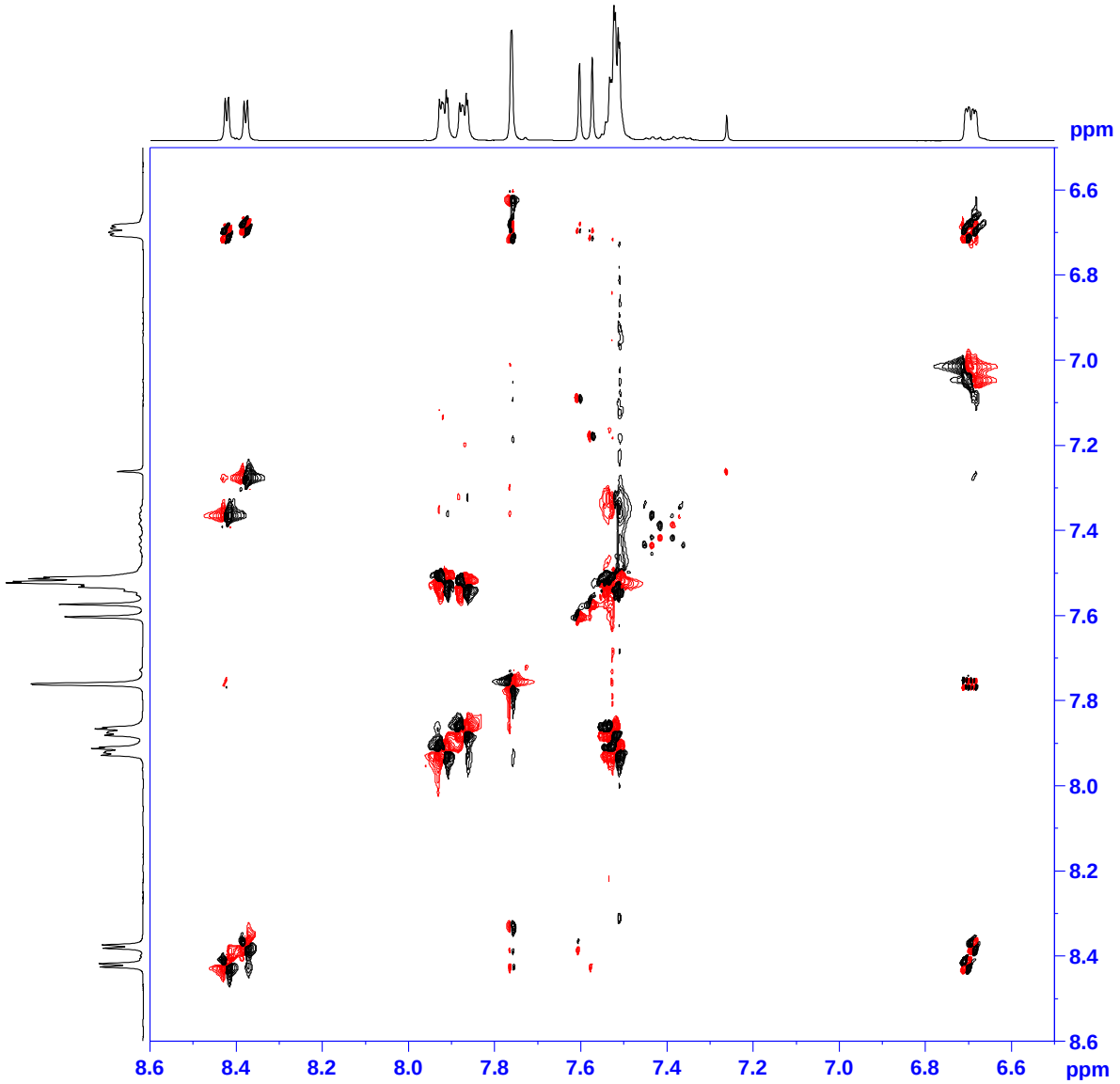

Figure S10. {^{1}H, ^{1}H} dqCOSY spectrum of compound **4a** in $CDCl_3$, 500 MHz

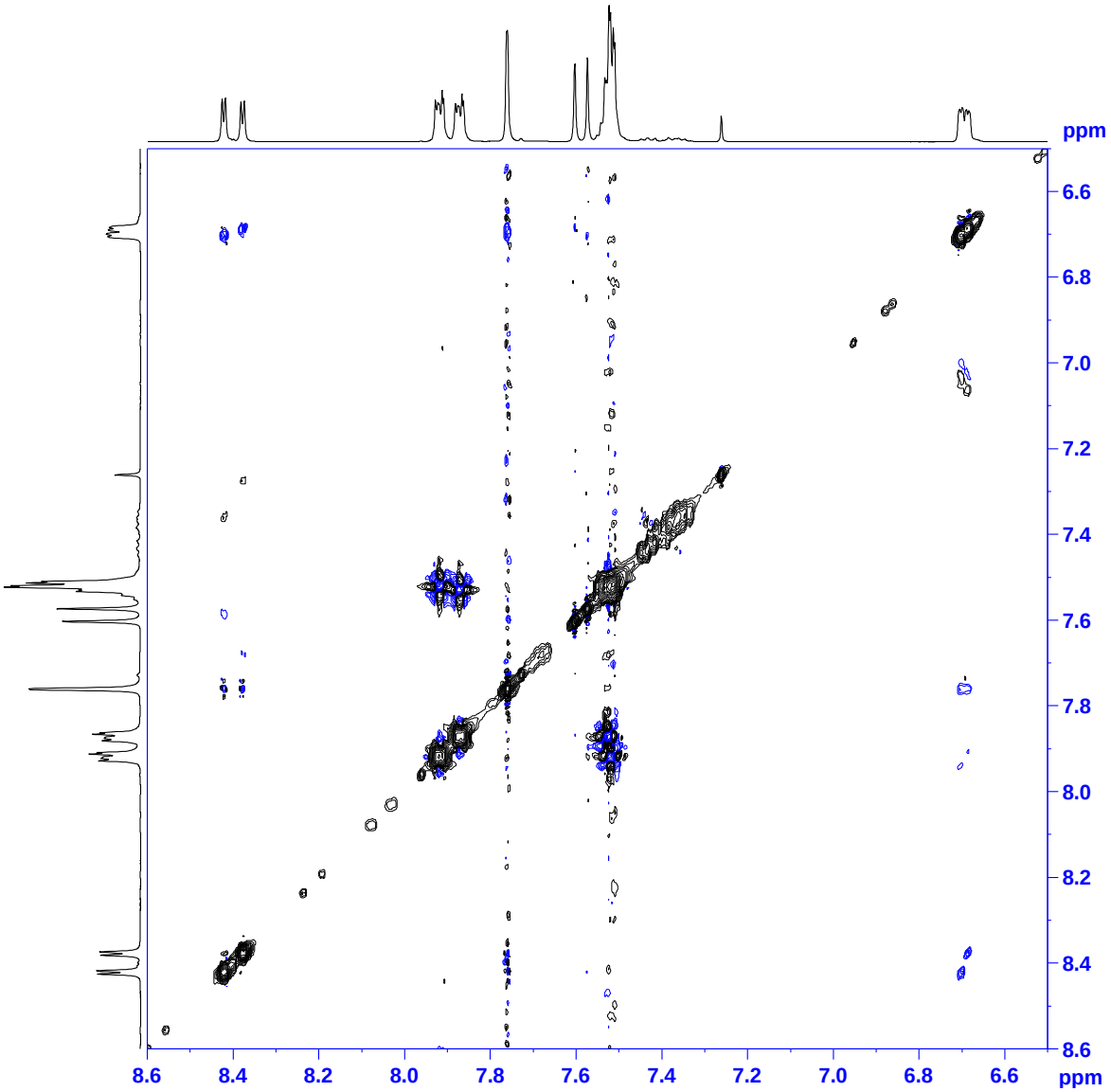

Figure S11. {^{1}H, ^{1}H} NOESY spectrum of compound **4a** in $CDCl_3$, 500 MHz

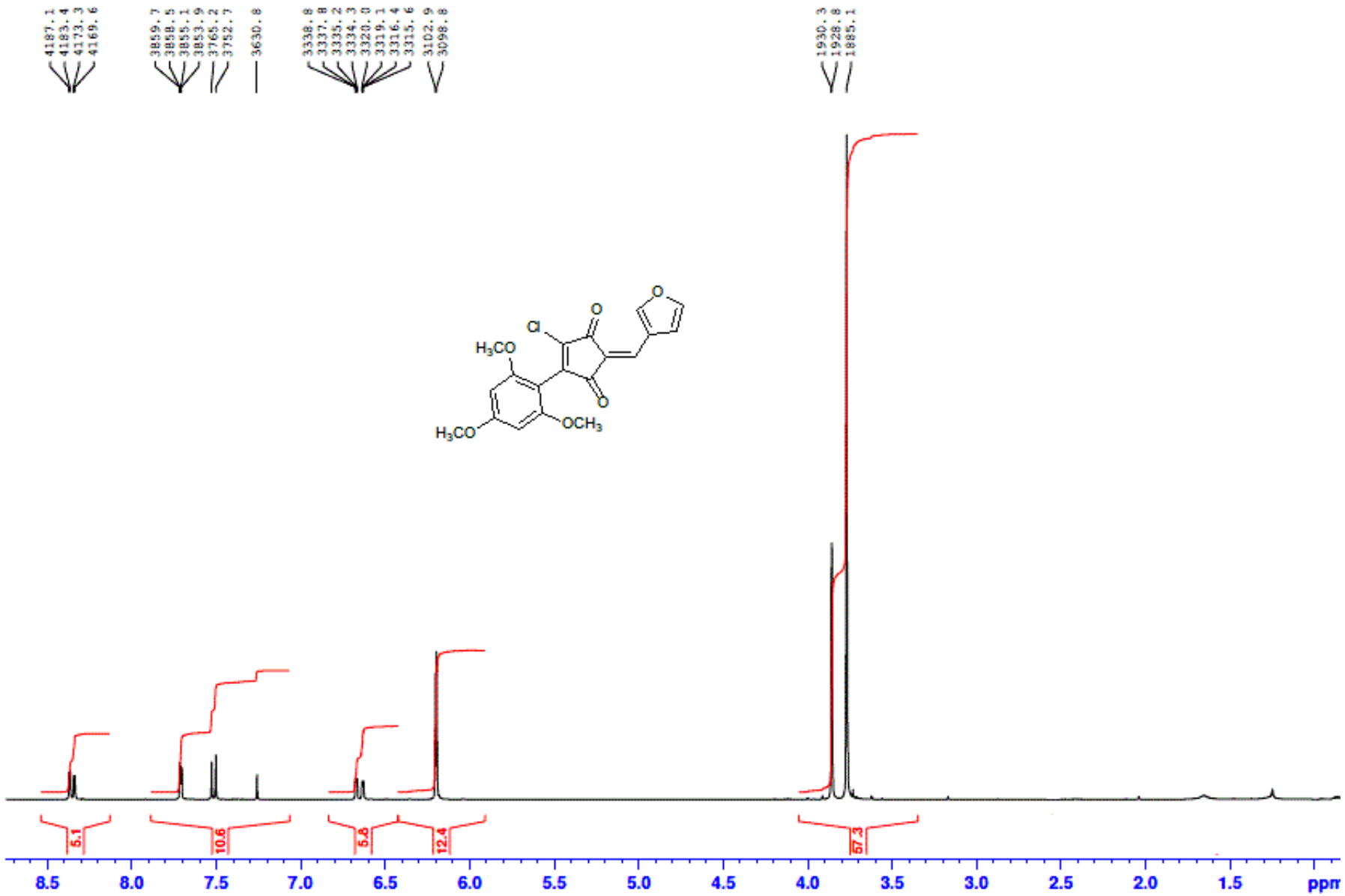

Figure S12. Complete NMR ^{1}H spectrum of compound **6a** in $CDCl_3$, 500 MHz

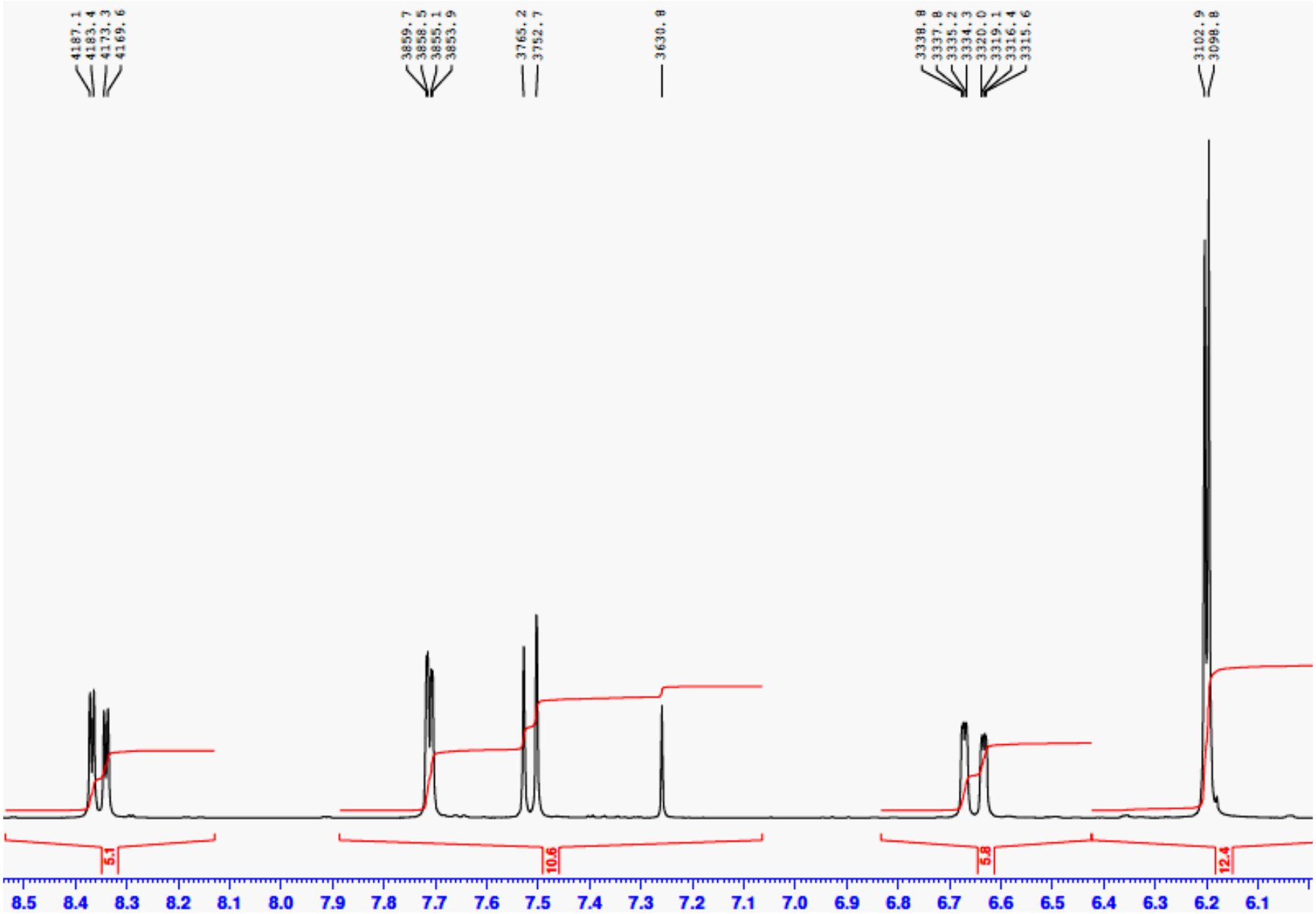

Figure S13. Expanded ^{1}H NMR spectrum of compound **6a** in $CDCl_3$, 500 MHz

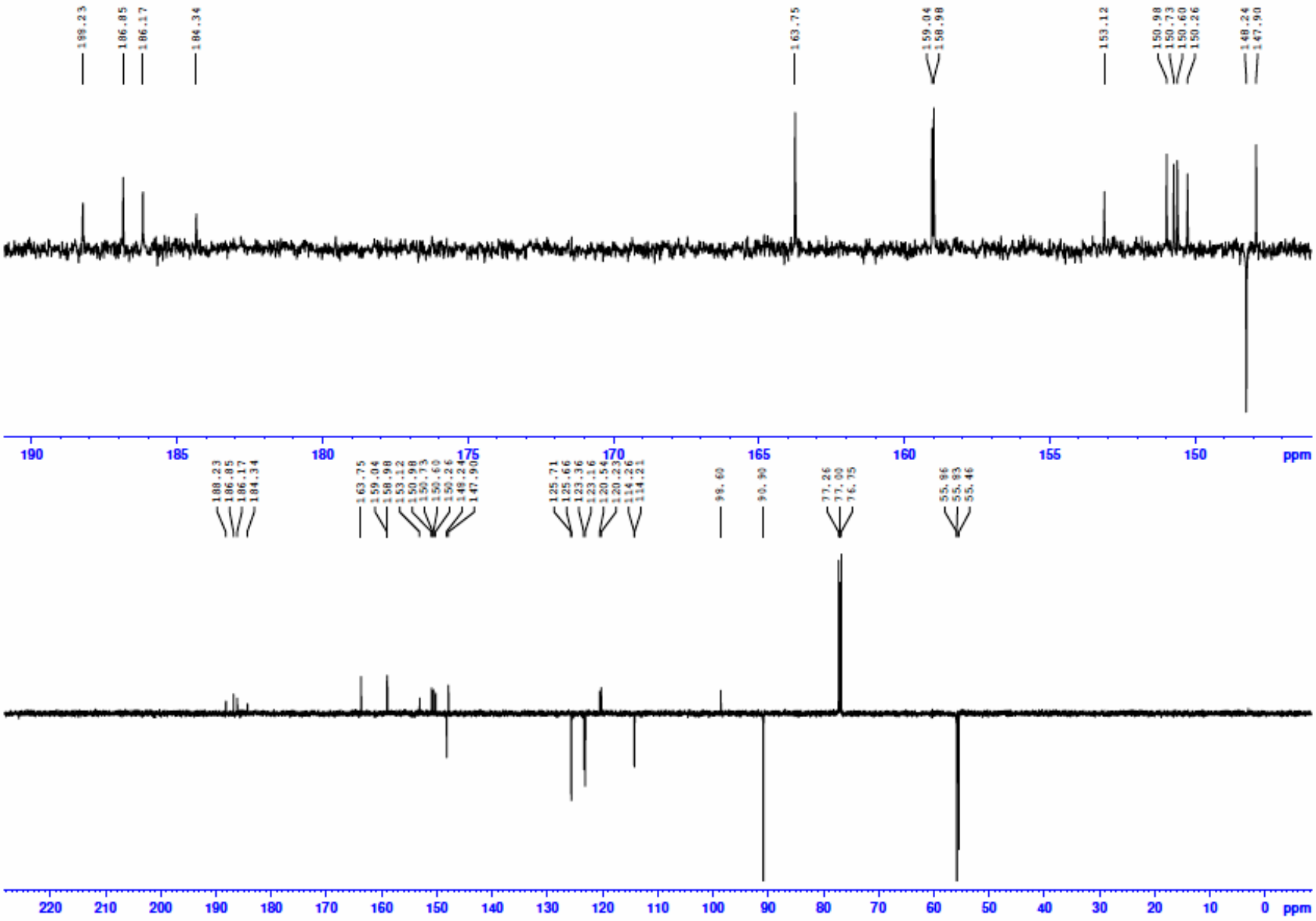

Figure S14. ^{13}C NMR spectrum of compound **6a** in $CDCl_3$, 125 MHz

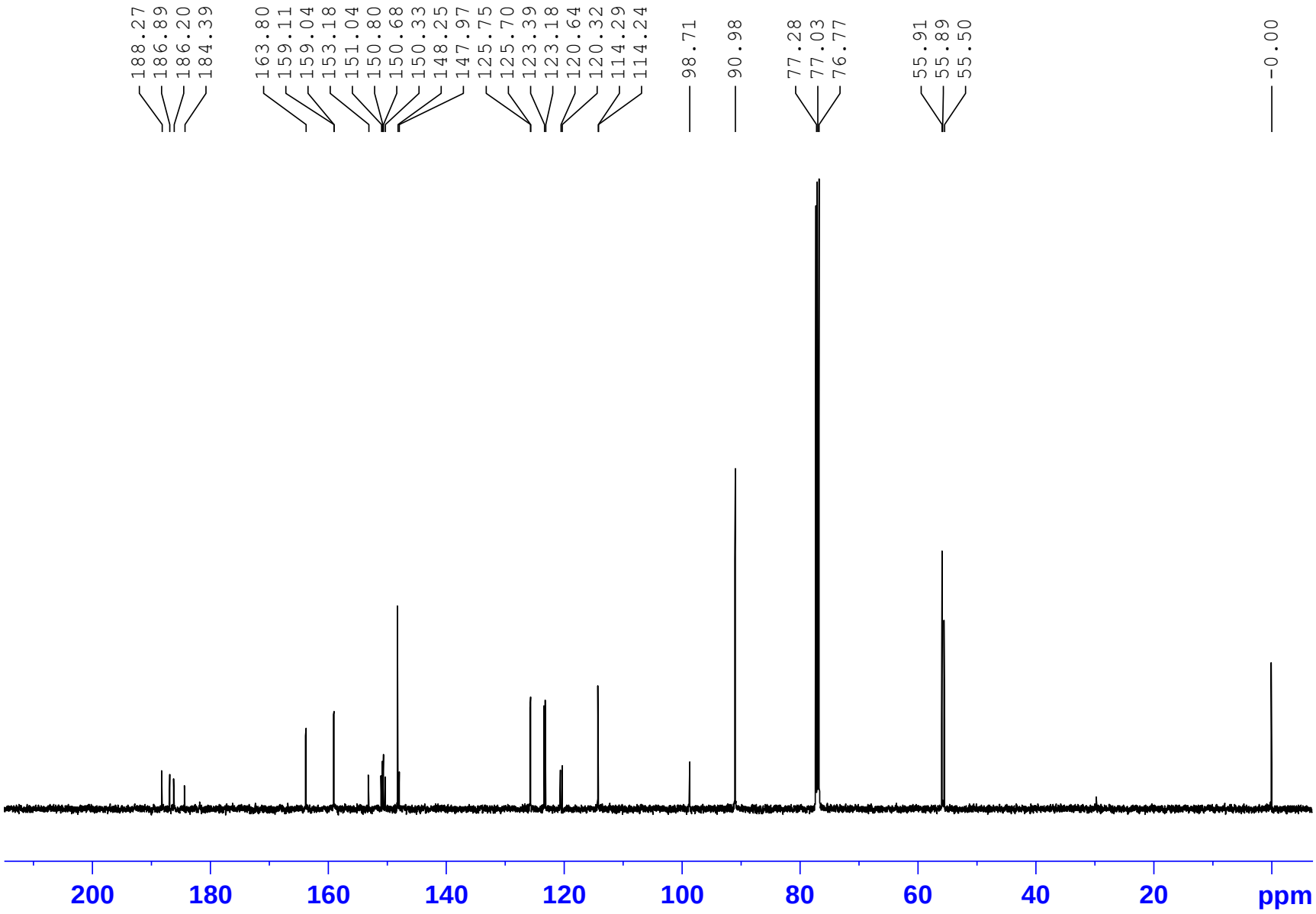

Figure S15. Complete $^{13}C\{^{1}H\}$ spectrum of compound **6a** in $CDCl_3$, 125 MHz

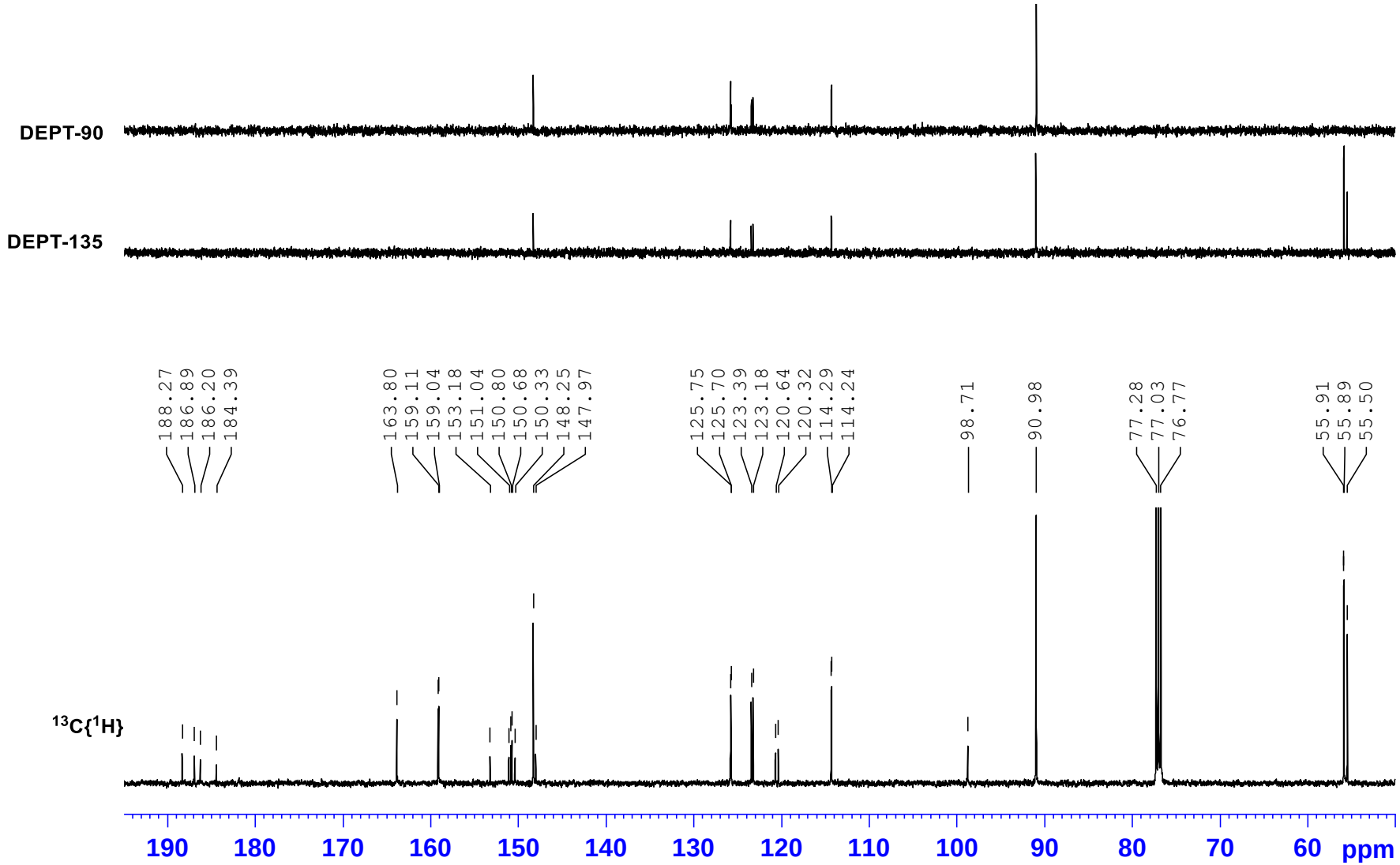

Figure S16. $^{13}C\{^{1}H\}$ and DEPT-135, DEPT-90 spectra of compound **6a** in $CDCl_3$, 125 MHz

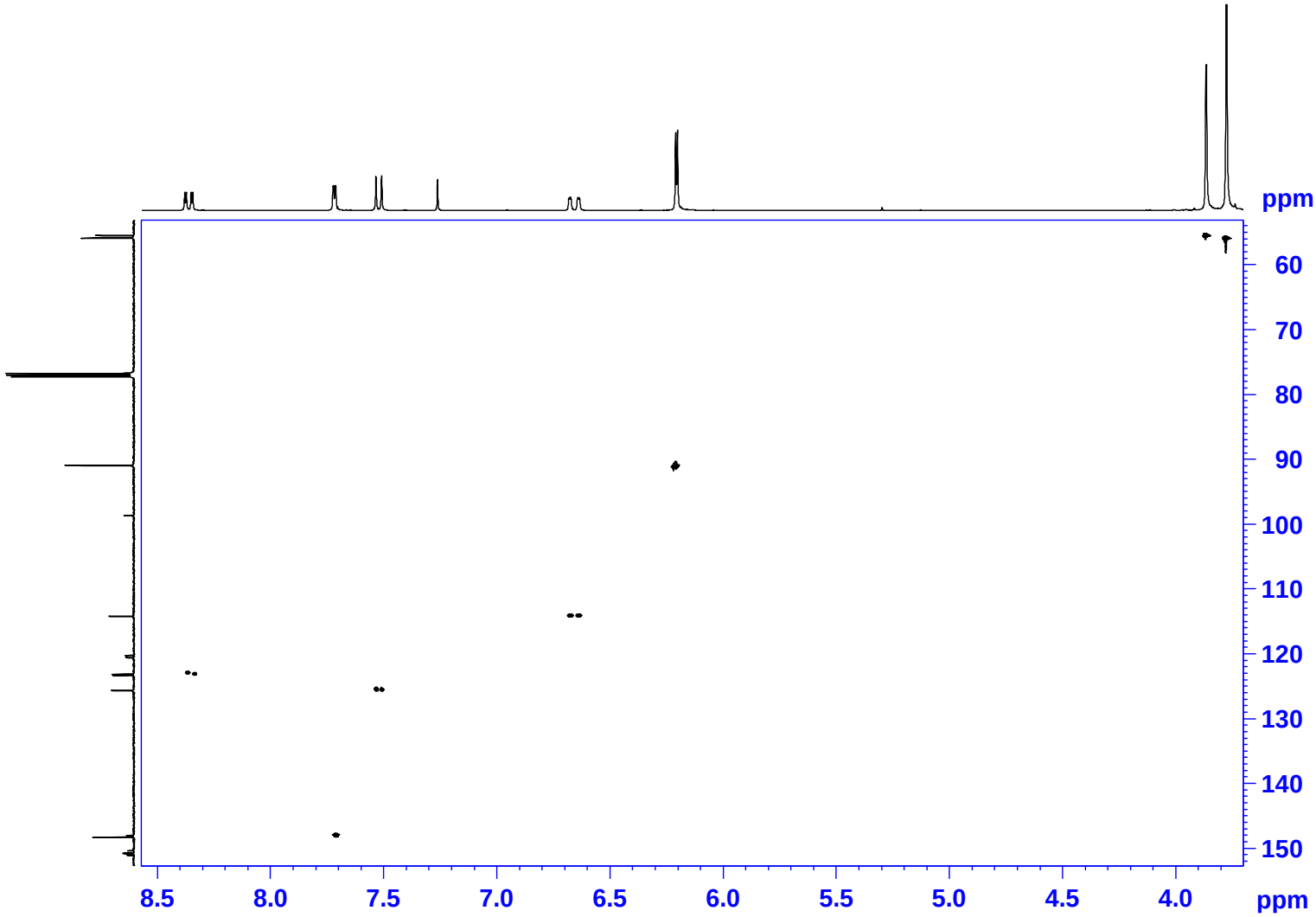

Figure S17. {^{1}H, ^{13}C} HSQC spectrum of compound **6a** in $CDCl_3$, 500 MHz

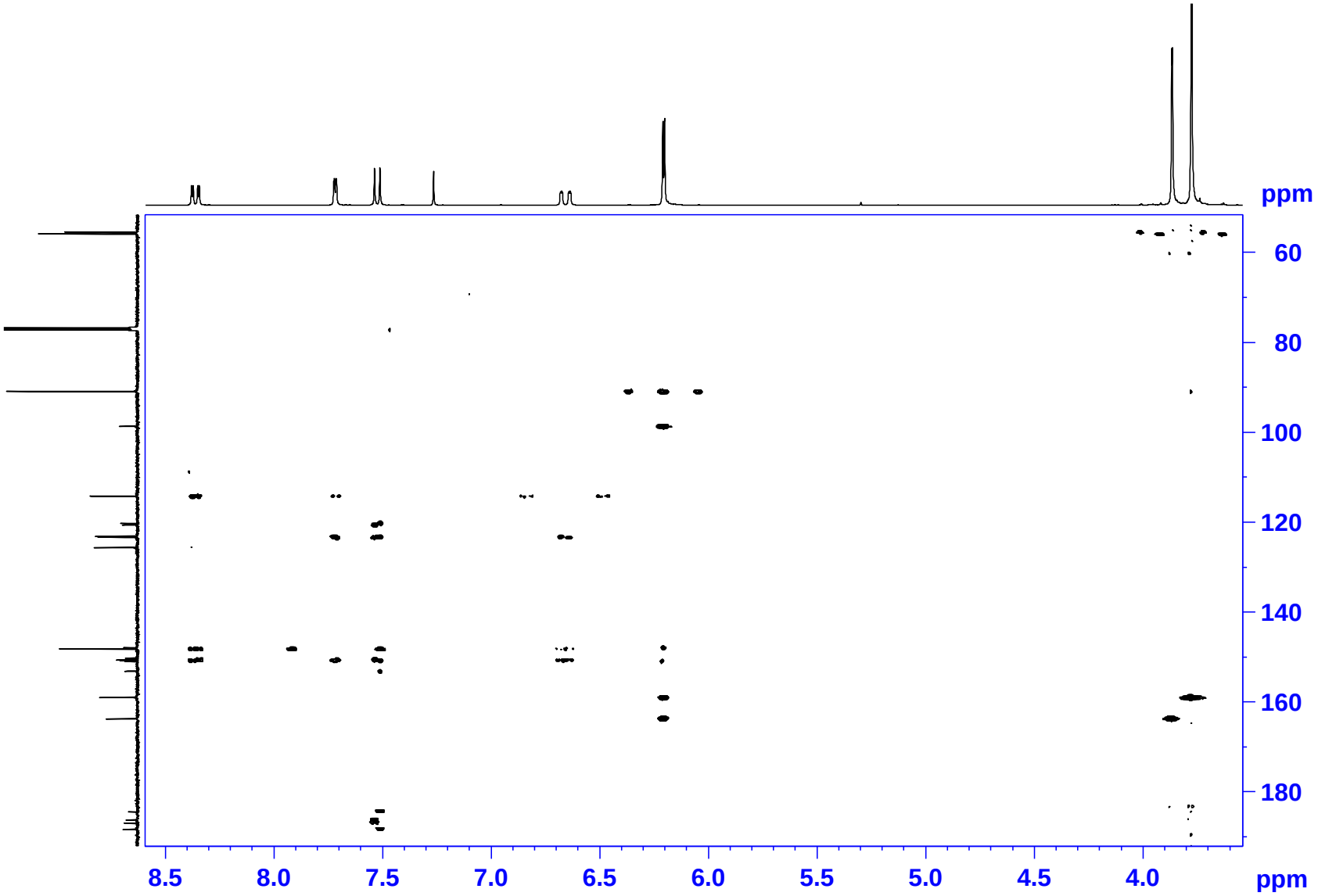

Figure S18. {^{1}H, ^{13}C} HMBC spectrum of compound **6a** in $CDCl_3$, 500 MHz

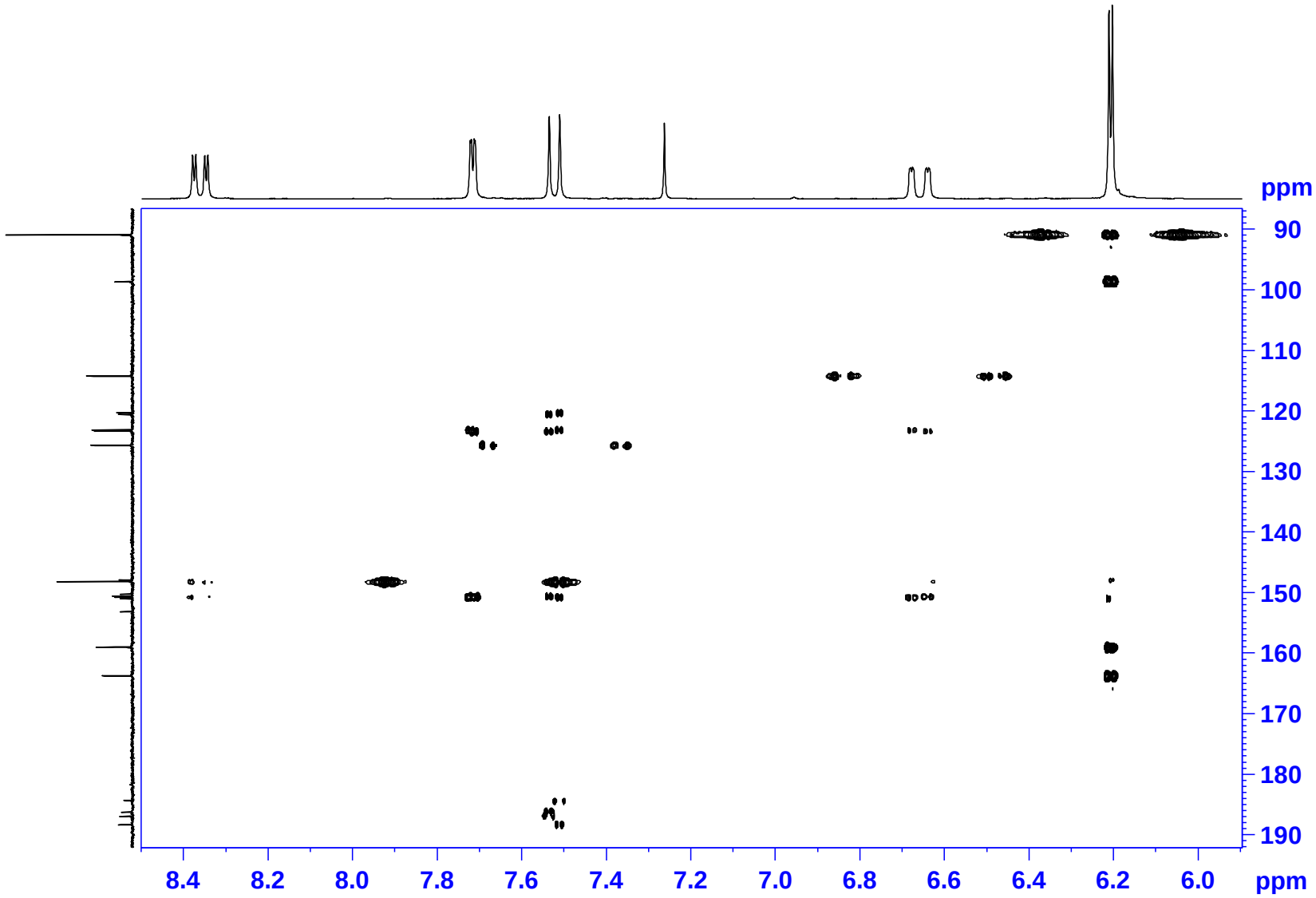

Figure S19. {^{1}H, ^{13}C} LR-HSQMBC spectrum of compound **6a** in $CDCl_3$, 500 MHz

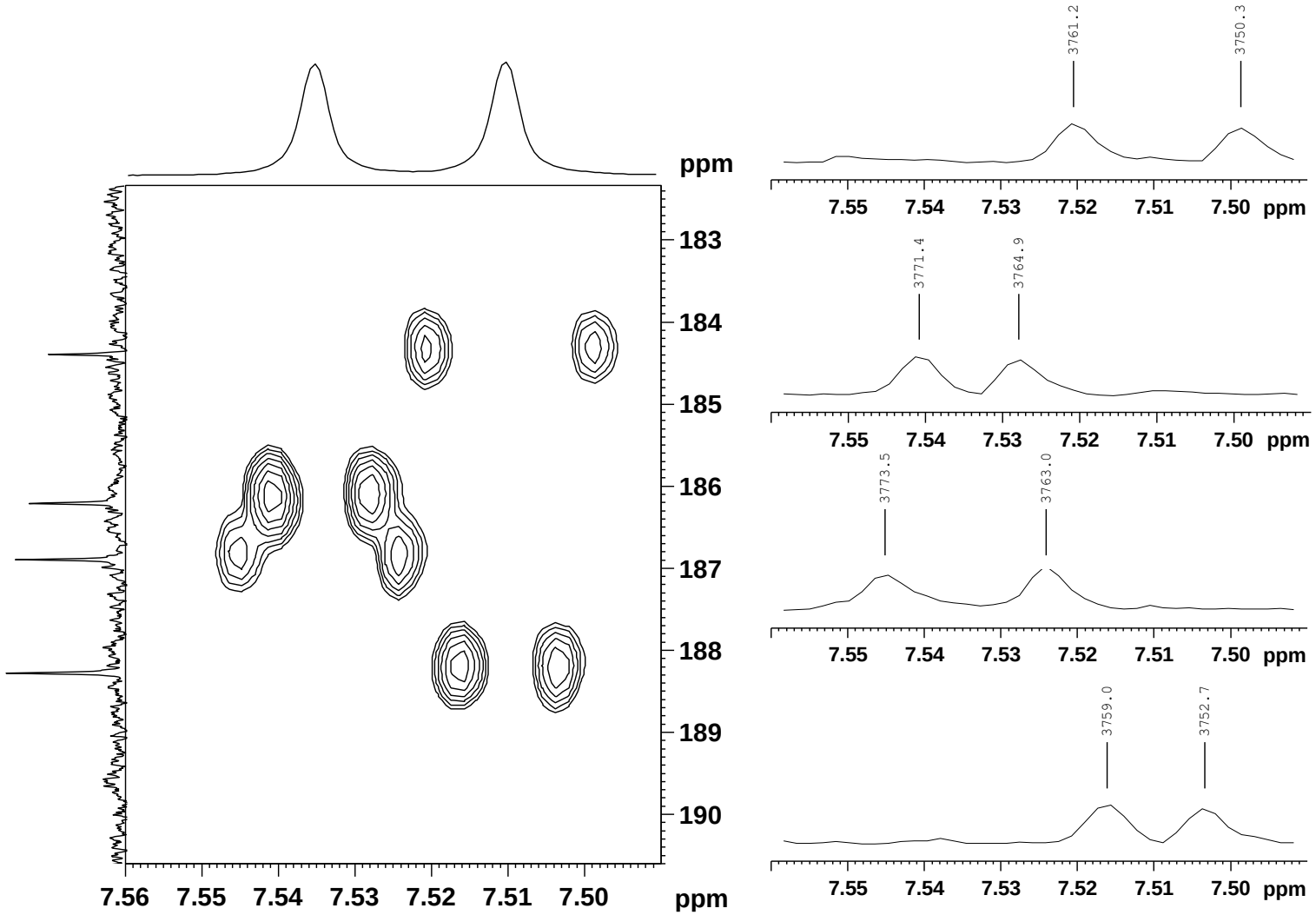

Figure 20. Expanded {^{1}H, ^{13}C} LR-HSQMBC spectrum of compound **6a** in $CDCl_3$, 500 MHz

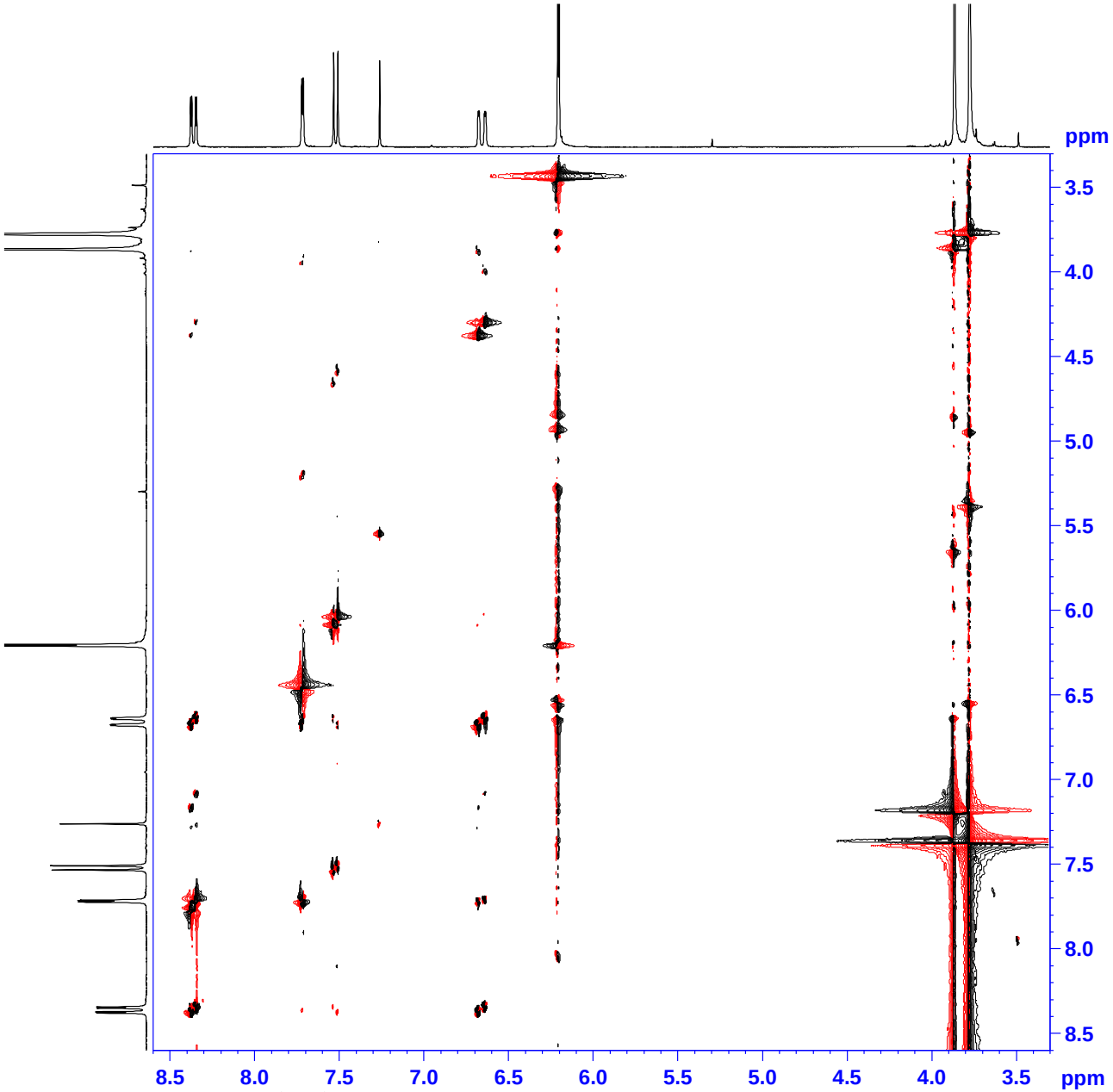

Figure S21. {^{1}H, ^{1}H} dqCOSY spectrum of compound **6a** in $CDCl_3$, 500 MHz

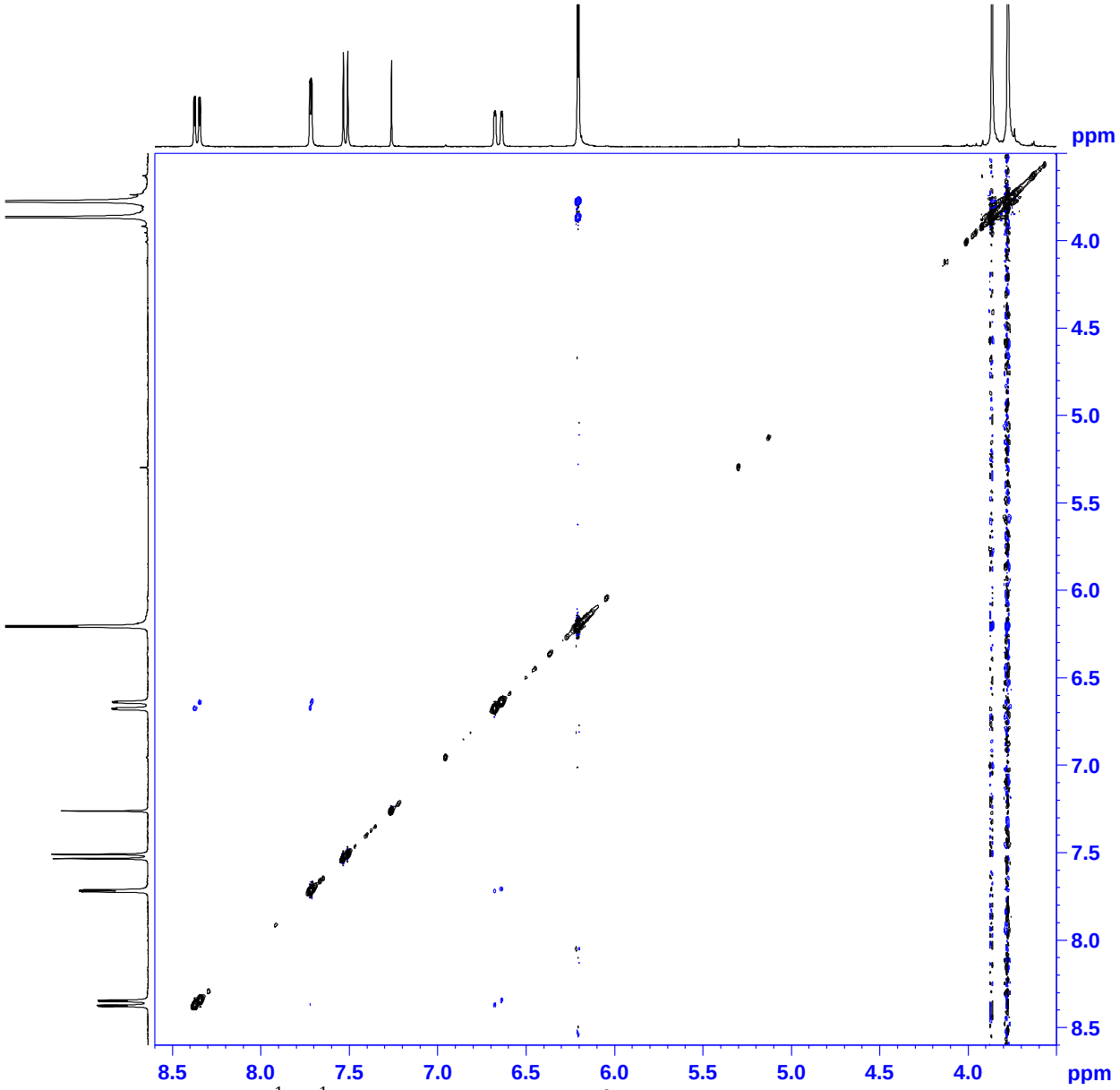

Figure S22. {^{1}H, ^{1}H} NOESY spectrum of compound **6a** in $CDCl_3$, 500 MHz