Supplementary content

Low cytotoxic quinoline-4-carboxylic acids derived from vanillin precursors as potential human dihydroorotate dehydrogenase inhibitors

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1. Experimental section

1.1. Physical measurements and methods

Melting points were determined on a Mel-Temp capillary melting points apparatus, model 1001, and are uncorrected. Elemental (C, H, N, S) analysis of the samples was carried out in the Center for Instrumental Analysis, Faculty of Chemistry, Belgrade. IR spectra were obtained on a Perkin Elmer Spectrum One FT-IR spectrometer with a KBr disc. ^{1}H and ^{13}C-NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer. UV–Vis spectra were recorded on a double beam UV–Vis spectrophotometer model Cary 300 (Agilent Technologies, Santa Clara, USA) with 1.0 cm quartz cells.

1.2. General procedure for the synthesis of 4a-t

To the aqueous solution of NaOH (21.887 mmol, 3.8 mL of distilled H_2O) monochloroacetic acid (10.94 mmol, 1033.83mg) and vanillin (9.48 mmol, 1442.38 mg) were added, and the reaction mixture was refluxed for 100 minutes. Afterwards, the mixture in the flask was cooled to room temperature, 15 mL of distilled H_2O was added and the solution was acidified with 2M HCl to pH 2, whereby a beige precipitate was formed. The suspension was cooled in the refrigerator for 2 h, the precipitate was filtrated, washed with a small amount of cold water and dried over anhydrous $CaCl_2$. The crude product was purified by dissolving in hot distilled water. After cooling in a refrigerator for 2 h, brown-yellow crystals were formed. The compound was filtered off, dried over anhydrous $CaCl_2$ and used for further synthesis. In the next step, the compound **2** (2.857 mmol, 600.49 mg) was measured into a 50 mL flask, followed by the addition of dry, freshly distilled CH_2Cl_2 (14.28 mL), $SOCl_2$ (28.57 mmol, 2.07 mL) and 4 drops of DMF. After 12 h of stirring at room temperature, the solvent was evaporated under reduced pressure, and the excess of $SOCl_2$ was removed by azeotropic distillation with toluene. Then, a corresponding amine (2.857 mmol), $NaHCO_3$ (5.714 mmol, 479.85 mg) and dry CH_2Cl_2 (14.28 mL) were added to the formed acid chloride, without its previous isolation, and the reaction mixture was further stirred at room temperature for additional 4.5 h. After completion, CH_2Cl_2 was evaporated under reduced pressure, 28.60 mL of distilled water was added to the residue, and the pH was adjusted to 10 by addition of solid Na_2CO_3. In the case of compounds

4b, **4i** and **4t** this suspension was left overnight at room temperature, vigorously stirred for 20 minutes the next day and then filtered. In all other cases after pH adjustment, the suspension was stirred for 20 minutes and filtered. With exception of **4o**, which was obtained with satisfactory purity and used for further synthesis without purification, all other **4a-t** derivatives were purified by dissolving in an appropriate solution of hot aqueous ethanol, and left overnight in the refrigerator. Compounds **4a-g**, **4j**, **4l**, **4n**, **4r** and **4s-t** were recrystallized from 50% aqueous solution of EtOH, **4i** from 55%, **4m** and **4p** from 60% EtOH, while **4h** and **4k** were purified by recrystallization from 65% EtOH. Derivatives **4a-t** were obtained in satisfactory yields ranging from 42 to 78%.

1.3. General procedure for the synthesis of quinoline-4-cabroxylic acids 5a-t

A mixture of the corresponding derivatives **4a-t** (1 mmol) and freshly distilled pyruvic acid (1.5 mmol, 0.132 g) in absolute ethanol (5.8 mL, except **5h**) was refluxed for 15 min. In the case of compound **5h**, 10.4 mL of solvent was added due to poor solubility of the starting substrate **4h** in absolute ethanol. After cooling the flask, the solution of aniline (1 mmol, 0.093 g) in absolute ethanol (1 mL) was added, and the mixture was refluxed for 3 h (10 h for **5h**). Afterwards, the flask was allowed to stand at 4 ° C overnight, and the formed precipitate of the corresponding compounds **5a-t** was then filtered and dried over $CaCl_2$. In order to achieve high purity of compounds, all derivatives **5a-t** (except **5p**) were purified by dissolving in a small amount of ethanol with mild heating and left in the refrigerator overnight. The compound **5p** was recrystallized from THF, while derivatives **5a**, **5s** and **5t** after recrystallization from ethanol were treated with THF in order to remove ethanol which incorporated into the structure of the compounds and then dried at room temperature for 3-5 days after which the amount of ethanol was significantly reduced. The final quinoline-4-carboxylic acids were obtained in yields ranging from 28% to 58%.

1.4. Determination of lipophilicity

In a volumetric flask 0.5 mg of the corresponding compound was weighed, dissolved in 100μL of DMF, and diluted to 25 mL with *n*-octanol (**5h**, **5i**, **5j**, **5k**, **5l**, **5m**, **5n**, **5p**, **5q**, **5r**, **5s** and **5t**). From this solution 5 mL (**5b**, **5c**, **5d**, **5e**, **5f** и **5g**), or 4 mL (**5a**) was measured and diluted with *n*-octanol to 10mL. Due to the good solubility in water, in the case of compound **5o**, for stock solution was weighed 1 mg, dissolved in 100μL of DMF, and diluted with *n*-octanol to 25 mL in order to obtain a solution of higher concentration so that the concentration after treatment would not be too low and deviate from Lambert-Beer's law. The absorbance of tested compounds in these *n*-octanol solutions was measured by UV-Vis spectrophotometry. Afterwards, 4 mL of each *n*-octanol solution and 8 mL of phosphate buffer was shaken on mechanical shaker for 30 minutes. After phase separation, *n*-octanol layer was dried over anhydrous sodium sulphate and absorbance of this layer was measured. The concentrations of each compound before and after treatment on mechanical shaker are shown in **Table 1**. $LogD_{7.4}$ value was determined using equation: $logD_{7.4} = log(y/x-y)$ where x represents concentration of compound in *n*-octanol phase before shaking and y represents concentration of compound in *n*-octanol phase after the treatment on mechanical shaker. For each compound, five independent measurements were performed.

Table 1. The concentrations of tested compounds before and after the treatment.

compd.	C_1(M)	λ(nm)	C_2(M)
5a	1.8672×10^{-5}	348	1.5660×10^{-5}
5b	2.2601×10^{-5}	346	1.9768×10^{-5}
5c	2.2601×10^{-5}	348	2.1973×10^{-5}
5d	2.1716×10^{-5}	348	2.0319×10^{-5}
5e	2.1121×10^{-5}	346	1.8627×10^{-5}
5f	2.1957×10^{-5}	347	2.1412×10^{-5}
5g	2.1957×10^{-5}	348	2.0296×10^{-5}
5h	4.2383×10^{-5}	348	4.1333×10^{-5}
5i	4.2383×10^{-5}	344	4.2184×10^{-5}
5j	4.2383×10^{-5}	348	4.1146×10^{-5}
5k	3.9569×10^{-5}	352	3.7700×10^{-5}
5l	3.9569×10^{-5}	348	3.7885×10^{-5}
5m	3.8207×10^{-5}	348	3.7348×10^{-5}
5n	4.5202×10^{-5}	348	3.3434×10^{-5}
5o	8.6679×10^{-5}	350	1.1823×10^{-5}
5p	4.4400×10^{-5}	348	1.4208×10^{-5}
5q	4.3714×10^{-5}	348	2.1677×10^{-5}
5r	4.5819×10^{-5}	349	4.1726×10^{-5}
5s	4.6032×10^{-5}	347	3.9603×10^{-5}
5t	3.9637×10^{-5}	339	3.6328×10^{-5}

C_1 - concentration of tested compound in *n*-octanol phase before distribution (mol L^{-1});
λ - wavelength at the absorption maximum (nm);
C_2 - concentration of tested compound in *n*-octanol phase after distribution (mol L^{-1}).

1.5. Characterisation data for 4a-t and 5a-5t derivatives

1.5.1. 2-(4-Formyl-2-methoxyphenoxy)-N-phenylacetamide × 0.5H_2O (**4a**): Beige powder; yield: 0.619g (76%); mp 148-149 ºC; IR (KBr, cm^{-1}): 3437, 1680, 1601, 1561, 1278, 1135, 751; ^{1}H NMR (200 MHz, DMSO-d_6): 3.88 (*s*, 3H, OCH_3), 4.86 (*s*, 2H, CH_2), 7.04-7.14 (*m*, 2H, Ar-H), 7.29-7.36 (*m*, 2H, Ar-H,), 7.45 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 7.52-7.63 (*m*, 3H, Ar-H), 9.85 (*s*, 1H, CHO), 10.20 (*s*, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): 55.82, 67.88, 110.30, 112.95, 119.54 (2C), 123.80, 125.67, 128.90 (2C), 130.42, 138.45, 149.42, 152.88, 165.88, 191.39; Anal. Calcd. For $C_{16}H_{15}NO_4 \times 0.5H_2O$ (294.29 g/mol): C, 65.30; H, 5.48; N, 4.76; Found: C, 65.54; H, 5.39; N, 4.78.

1.5.2 2-(4-Formyl-2-methoxyphenoxy)-N-(o-tolyl)acetamide (**4b**): Light beige powder; yield: 0.632g (74%); mp 133-134 ºC; IR (KBr, cm^{-1}): 3438, 3396, 1685, 1596, 1507, 1278, 1135, 762; ^{1}H NMR (200 MHz, DMSO-d_6): 2.22 (*s*, 3H, CH_3), 3.89 (*s*, 3H, O$\underline{CH_3}$), 4.90 (*s*, 2H, CH_2), 7.05-7.26 (*m*, 4H, Ar-H), 7.46 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 7.55-7.60 (*m*, 2H, Ar-H), 9.44 (*s*, 1H, NH), 9.87 (*s*, 1H, CHO); ^{13}C NMR (50 MHz, DMSO-d_6): 17.66, 55.86, 67.75, 110.30, 113.04, 124.06, 125.34, 125.60, 126.20, 130.44, 130.51, 130.92, 135.57, 149.43, 152.57, 165.87, 191.49; Anal. Calcd. For $C_{17}H_{17}NO_4$ (299.32 g/mol): C, 68.21; H, 5.72; N, 4.68; Found: C, 66.83; H, 5.46; N, 4.61.

*1.5.3 2-(4-Formyl-2-methoxyphenoxy)-N-(m-tolyl)*acetamide (**4c**): Beige powder; yield: 0.538g (63%); mp 108-109 ºC; IR (KBr, cm^{-1}): 3436, 3380, 1682, 1507, 1276, 1134, 1031, 733; ^{1}H NMR (200 MHz, DMSO-d_6): 2.27 (*s*, 3H, CH_3), 3.88 (*s*, 3H, OCH_3), 4.85 (*s*, 2H, CH_2), 6.89 (*d*, 1H, Ar-H, *J* = 7.4 Hz), 7.09-7.24 (*m*, 2H, Ar-H), 7.37-7.45 (*m*, 3H, Ar-H), 7.54 (*dd*, 1H, Ar-H, *J* = 8.3 Hz and *J* =1.9 Hz), 9.85 (*s*, 1H, CHO), 10.12 (*s*, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): 21.33, 55.82, 67.90, 110.34, 112.97, 116.72, 120.05, 124.48, 125.64, 128.71, 130.42, 138.10, 138.36, 149.42, 152.89, 165.79, 191.34; Anal. Calcd. For $C_{17}H_{17}NO_4$ (299.32 g/mol): C, 68.21; H, 5.72; N, 4.68; Found: C, 67.89; H, 5.54; N, 4.64.

1.5.4. 2-(4-Formyl-2-methoxyphenoxy)-N-(p-tolyl)acetamide (**4d**): Light brown powder; yield: 0.572g (67%); mp 129-130 ºC; IR (KBr, cm^{-1}): 3437, 3241, 1667, 1509, 1282, 1141, 1027, 813; ^{1}H NMR (200 MHz, DMSO-d_6): 2.25 (*s*, 3H, CH_3), 3.87 (*s*, 3H, OCH_3), 4.83 (*s*, 2H, CH_2), 7.12 (*m*, 3H, Ar-H), 7.44-7.56 (*m*, 4H, Ar-H), 9.84 (*s*, 1H, CHO), 10.10 (*s*, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): 20.45, 55.78, 67.91, 110.31, 112.97, 119.51 (2C), 125.58, 129.20 (2C), 130.38, 132.71, 135.88, 149.39, 152.86, 165.56, 191.30; Anal. Calcd. For $C_{17}H_{17}NO_4$ (299.32 g/mol): C, 68.22; H, 5.72; N, 4.68; Found: C, 67.81; H, 5.53; N, 4.68.

1.5.5. N-(2-Fluorophenyl)-2-(4-formyl-2-methoxyphenoxy)acetamide × *0.5H_2O* (**4e**): Beige powder; yield: 0.528g (61%); mp 130-131 ºC; IR (KBr, cm^{-1}): 3381, 1701, 1657, 1545, 1278, 1134, 762; ^{1}H NMR (200 MHz, DMSO-d_6): 3.88 (*s*, 3H, OCH_3), 4.94 (*s*, 2H, CH_2), 7.13-7.85 (*m*, 4H, Ar-H), 7.45 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 7.55 (*dd*, 1H, *J* = 8.2 Hz and *J* = 1.8 Hz), 7.90-

7.98 (*m*, 1H, Ar-H), 9.86 (*s*, 1H, CHO), 9.91 (*s*, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): 55.86, 67.68, 110.36, 113.42, 115.58 (J_{CF} = 19.15 Hz), 123.76 (C-F), 124.55 (J_{CF} = 3.55 Hz), 125.40 (C-F), 125.57 (C-F), 125.76, 130.53, 149.42, 152.63, 153.53 (J_{CF} = 243.40 Hz), 166.32, 191.11; Anal. Calcd. For $C_{16}H_{14}FNO_4 \times 0.5H_2O$ (312.28 g/mol): C, 61.54; H, 4.84; N, 4.49; Found: C, 61.70; H, 4.75; N, 4.53.

1.5.6. N-(3-Fluorophenyl)-2-(4-formyl-2-methoxyphenoxy)acetamide × 0,5H₂O (**4f**): Light brown powder; yield: 0.641g (74%); mp 135-136 ºC; IR (KBr, cm^{-1}): 3382, 3154, 1682, 1615, 1508, 1268, 1134, 853, 735; ^{1}H NMR (200 MHz, DMSO-d_6): 3.89 (*s*, 3H, OCH_3), 4.89 (*s*, 2H, CH_2), 6.87-6.98 (*m*, 1H, Ar-H), 7.13 (*d*, 1H, Ar-H, *J* = 8.4 Hz), 7.35-7.40 (*m*, 2H, Ar-H), 7.44-7.46 (*m*, 1H, Ar-H), 7.53-7.65 (*m*, 2H, Ar-H), 9.86 (*s*, 1H, CHO), 10.46 (*s*, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): 55.81, 67.83, 106.37 (J_{CF} = 26.05 Hz), 110.03 (C-F), 110.40, 113.05, 115.29 (J_{CF} = 2.20 Hz), 125.57, 130.48, 130.51 (J_{CF} = 9.35 Hz), 140.14 (J_{CF} = 11.10 Hz), 149.43, 152.79, 162.16 (J_{CF} = 239.95 Hz), 166.29, 191.33; Anal. Calcd. For $C_{16}H_{14}FNO_4 \times 0.5H_2O$ (312.28 g/mol): C, 61.54; H, 4.84; N, 4.49; Found: C, 61.73; H, 4.76; N, 4.54.

1.5.7. N-(4-Fluorophenyl)-2-(4-formyl-2-methoxyphenoxy)acetamide × 0.5H₂O (**4g**): Light beige powder; yield: 0.606g (70%); mp 139-140 ºC; IR (KBr, cm^{-1}): 3346, 1686, 1508, 1285, 1031, 819; ^{1}H NMR (200 MHz, DMSO-d_6): 3.88 (*s*, 3H, OCH_3), 4.85 (*s*, 2H, CH_2), 7.10-7.21 (*m*, 3H, Ar-H), 7.44 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 7.54 (*dd*, 1H, Ar-H, *J* = 8.3 Hz and *J* = 1.9 Hz), 7.60-7.67 (*m*, 2H, Ar-H), 9.85 (*s*, 1H, CHO), 10.28 (*s*, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): 55.78, 67.82, 110.29, 112.97, 115.43 (J_{CF} = 22.15 Hz), 121.35 (J_{CF} = 7.75 Hz), 125.61 (2C), 130.41, 134.81 (J_{CF} = 2.55 Hz), 149.40, 152.61, 152.83, 158.27 (J_{CF} = 238.50 Hz), 165.81, 191.35; Anal. Calcd. For $C_{16}H_{14}FNO_4 \times 0.5H_2O$ (312.28 g/mol): C, 61.54; H, 4.84; N, 4.49; Found: C, 61.50; H, 4.74; N, 4.50.

1.5.8. N-(2-Chlorophenyl)-2-(4-formyl-2-methoxyphenoxy)acetamide × 0.5H₂O (**4h**): Light pink powder; yield: 0.638g (70%); mp 164-165 ºC; IR (KBr, cm^{-1}): 3361, 1698, 1536, 1434, 1265, 1135, 1032, 733; ^{1}H NMR (200 MHz, DMSO-d_6): 3.90 (*s*, 3H, CH_3), 4.94 (*s*, 2H, CH_2), 7.17-7.25 (*m*, 2H, Ar-H), 7.33-7.42 (*m*, 1H, Ar-H), 7.47 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 7.52-7.60 (*m*, 2H, Ar-H), 8.02 (*dd*, 1H, Ar-H, *J* = 8.2 Hz and *J* = 1.6 Hz), 9.64 (*s*, 1H, NH), 9.88 (*s*, 1H, CHO); ^{13}C

NMR (50 MHz, DMSO-d_6): 55.90, 67.66, 110.28, 113.24, 123.87, 124.83, 125.57, 126.15, 127.81, 129.54, 130.69, 134.08, 149.41, 152.12, 166.19, 191.41; Anal. Calcd. For $C_{16}H_{14}ClNO_4 \times 0.5H_2O$ (328.74 g/mol): C, 58.46; H, 4.60; N, 4.26; Found: C, 58.79; H, 4.46; N, 4.31.

1.5.9. N-(3-Chlorophenyl)-2-(4-formyl-2-methoxyphenoxy)acetamide × 0.5H₂O (**4i**): Yellow powder; yield: 0.710g (78%); mp 113-114 ºC; IR (KBr, cm^{-1}): 3366, 1679, 1596, 1508, 1279, 1139, 1031, 676; ^{1}H NMR (200 MHz, DMSO-d_6): 3.88 (*s*, 3H, CH_3), 4.89 (*s*, 2H, CH_2), 7.11-7.18 (*m*, 2H, Ar-H), 7.36 (*m*, 1H, Ar-H), 7.45-7.57 (*m*, 3H, Ar-H), 7.83 (*t*, 1H, Ar-H, *J* = 2.0 Hz), 9.86 (*s*, 1H, CHO), 10.43 (*s*, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): 55.79, 67.78, 110.37, 113.04, 117.91, 119.02, 123.44, 125.54, 130.46, 130.51, 133.16, 139.84, 149.40, 152.76, 166.30, 191.29; Anal. Calcd. For $C_{16}H_{14}ClNO_4 \times 0.5H_2O$ (328.74 g/mol): C, 58.46; H, 4.60; N, 4.26; Found: C, 58.79; H, 4.53; N, 4.37.

1.5.10. N-(4-Chlorophenyl)-2-(4-formyl-2-methoxyphenoxy)acetamide × 0.5H₂O (**4j**): Light beige powder; yield: 0.628g (69%); mp 135-136 ºC; IR (KBr, cm^{-1}): 3389, 1683, 1589, 1507, 1277, 1137, 1028, 803; ^{1}H NMR (200 MHz, DMSO-d_6): 3.88 (*s*, 3H, CH_3), 4.87 (*s*, 2H, CH_2), 7.12 (*d*, 1H, Ar-H, *J* = 8.4 Hz), 7.36-7.46 (*m*, 3H, Ar-H), 7.54 (*dd*, 1H, Ar-H, *J* = 8.2 Hz and *J* = 1.8 Hz), 7.61-7.69 (*m*, 2H, Ar-H), 9.85 (*s*, 1H, CHO), 10.36 (*s*, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): 55.78, 67.82, 110.31, 112.98, 121.07 (2C), 125.59, 127.35, 128.76 (2C), 130.42, 137.38, 149.39, 152.79, 166.05, 191.33; Anal. Calcd. For $C_{16}H_{14}ClNO_4 \times 0.5H_2O$ (328.74 g/mol): C, 58.46; H, 4.60; N, 4.26; Found: C, 58.29; H, 4.44; N, 4.30.

1.5.11. 2-(4-Formyl-2-methoxyphenoxy)-N-(2-(trifluoromethyl)phenyl)acetamide × 0.5H₂O (**4k**): White powder; yield: 0.735g (73%); mp 155-156 ºC; IR (KBr, cm^{-1}): 3392, 3252, 1676, 1589, 1318, 1117, 770; ^{1}H NMR (200 MHz, DMSO-d_6): 3.88 (*s*, 3H, OCH_3), 4.91 (*s*, 2H, CH_2), 7.17 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 7.41-7.49 (*m*, 2H, Ar-H), 7.57 (*dd*, 1H, Ar-H, *J* = 8.2 Hz and *J* = 1.8 Hz), 7.67-7.84 (*m*, 3H, Ar-H), 9.63 (*s*, 1H, NH), 9.87 (*s*, 1H, CHO); ^{13}C NMR (50 MHz, DMSO-d_6): 55.83, 67.49, 110.25, 113.12, 123.75 (J_{CF} = 271.00 Hz), 122.69 (J_{CF} = 28.95 Hz), 125.52, 126.36 (C-F), 126.46 (C-F), 127.59 (C-F), 133.31 (C-F), 130.70, 134.56 (C-F), 149.42, 152.15, 166.77, 191.43; Anal. Calcd. For $C_{17}H_{14}F_3NO_4 \times 0.5H_2O$ (362.29 g/mol): C, 56.36; H, 4.17; N, 3.87; Found: C, 56.04; H, 4.02; N, 3.90.

1.5.12. 2-(4-Formyl-2-methoxyphenoxy)-N-(3-(trifluoromethyl)phenyl)acetamide × 0.5H_2O (**4l**): Light yellow powder; yield: 0.766g (76%); mp 120-121 ºC; IR (KBr, cm^{-1}): 3387, 1690, 1590, 1545, 1338, 1271, 1117, 695; ^{1}H NMR (200 MHz, DMSO-d_6): 3.88 (*s*, 3H, OCH_3), 4.91 (*s*, 2H, CH_2), 7.13 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 7.41-7.45 (*m*, 2H, Ar-H), 7.51-7.61 (*m*, 2H, Ar-H), 7.81 (*d*, 1H, Ar-H, *J* = 8 Hz), 8.11 (*s*, 1H, Ar-H), 9.85 (*s*, 1H, CHO), 10.60 (*s*, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): 55.80, 67.74, 110.37, 113.05, 115.61 (J_{CF} = 4.05 Hz), 120.05 (J_{CF} = 3.55 Hz), 123.08 (C-F), 124.09 (J_{CF} = 270.15 Hz), 125.56, 129.57 (J_{CF} = 31.45 Hz), 130.08, 130.47 (C-F), 139.21 (C-F), 149.41, 152.77, 166.57, 191.32; Anal. Calcd. For $C_{17}H_{14}F_3NO_4 \times 0.5H_2O$ (362.29 g/mol): C, 56.36; H, 4.17; N, 3.87; Found: C, 56.40; H, 4.10; N, 3.93.

1.5.13. 2-(4-Formyl-2-methoxyphenoxy)-N-(4-(trifluoromethyl)phenyl)acetamide (**4m**): White powder; yield: 0.736g (73%); mp 154-155 ºC; IR (KBr, cm^{-1}): 3257, 1675, 1542, 1325, 1140, 1067, 841; ^{1}H NMR (200 MHz, DMSO-d_6): 3.88 (*s*, 3H, OCH_3), 4.91 (*s*, 2H, CH_2), 7.13 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 7.45 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 7.54 (*dd*, 1H, Ar-H, *J* = 8.3 Hz and *J* =1.9 Hz), 7.69 (*d*, 2H, Ar-H, *J* = 8.8 Hz), 7.83 (*d*, 2H, Ar-H, *J* = 8.6 Hz), 9.85 (*s*, 1H, CHO), 10.60 (*s*, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): 55.80, 67.77, 110.37, 113.02, 119.42 (2C, C-F), 123.15 (J_{CF} = 31.70 Hz), 124.36 (J_{CF} = 269.60 Hz), 125.56 (2C), 126.16 (J_{CF} = 3.47 Hz), 130.46, 142.01 (C-F), 149.40, 152.76, 166.57, 191.33; Anal. Calcd. For $C_{17}H_{14}F_3NO_4$ (353.29 g/mol): C, 57.79; H, 3.99; N, 3.96; Found: C, 38.50; H, 2.67; N, 2.67.

1.5.14. N-Benzyl-2-(4-formyl-2-methoxyphenoxy)acetamide (**4n**): Beige powder; yield: 0.512g (60%); mp 105-106 ºC; IR (KBr, cm^{-1}): 3423, 1678, 1590, 1514, 1274, 1123, 1028, 782; ^{1}H NMR (200 MHz, DMSO-d_6): 3.85 (*s*, 3H, CH_3), 4.35 (*d*, 2H, NH$\underline{CH_2}$, *J* = 6.0 Hz), 4.72 (*s*, 2H, CH_2), 7.09 (*d*, 1H, Ar-H, *J* = 8.4 Hz), 7.19-7.37 (*m*, 5H, Ar-H), 7.44 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 7.53 (*dd*, 1H, Ar-H, *J* = 8.2 Hz and *J* = 1.8 Hz), 8.56 (*t*, 1H, NH, *J* = 6.0 Hz), 9.86 (*s*, 1H, CHO); ^{13}C NMR (50 MHz, DMSO-d_6): 42.11, 55.76, 67.87, 110.23, 113.15, 125.55, 126.91, 127.34 (2C), 128.32 (2C), 130.47, 139.13, 149.47, 152.74, 167.17, 191.38; Anal. Calcd. For $C_{17}H_{17}NO_4$ (299.32 g/mol): C, 68.21; H, 5.72; N, 4.68; Found: C, 67.57; H, 5.32; N, 4.55.

1.5.15. 2-(4-Formyl-2-methoxyphenoxy)-N-(pyridin-3-ylmethyl)acetamide (**4o**): White powder; yield: 0.583g (68%); mp 75-76 ºC; IR (KBr, cm^{-1}): 3488, 3387, 3200, 1656, 1508, 1265, 1138, 732; ^{1}H NMR (200 MHz, DMSO-d_6): 3.85 (*s*, 3H, CH_3), 4.35 (*d*, 2H, NH$\underline{CH_2}$, *J* = 6.0 Hz), 4.72 (*s*, 2H, CH_2), 7.08 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 7.31-7.38 (*m*, 1H, Py-H), 7.44 (*d*, 1H, Ar-H, *J* = 1.6 Hz), 7.52 (*dd*, 1H, Ar-H, *J* = 8.2 Hz and *J* =1.8 Hz), 7.64-7.68 (*m*, 1H, Py-H), 8.44-8.50 (*m*, 2H, Py-H), 8.68 (*t*, 1H, NH, *J* = 6.0 Hz), 9.86 (*s*, 1H, CHO); ^{13}C NMR (50 MHz, DMSO-d_6): 39.91, 55.81, 67.86, 110.25, 113.14, 123.54, 125.63, 130.52, 134.75, 135.24, 148.23, 148.89, 149.50, 152.74, 167.52, 191.49; Anal. Calcd. For $C_{16}H_{16}N_2O_4$ (300.31 g/mol): C, 63.99; H, 5.37; N, 9.33; Found: C, 54.48; H, 5.53; N, 7.87.

1.5.16. 2-(4-Formyl-2-methoxyphenoxy)-N-(furan-2-ylmethyl)acetamide (**4p**): Light brown powder; yield: 0.347g (42%); mp 80-81 ºC; IR (KBr, cm^{-1}): 3272, 1682, 1654, 1508, 1263, 1136, 1030, 735; ^{1}H NMR (200 MHz, DMSO-d_6): 3.86 (*s*, 3H, CH_3), 4.34 (*d*, 2H, NH$\underline{CH_2}$, *J* = 5.8 Hz), 4.68 (*s*, 2H, CH_2), 6.25 (*dd*, 1H, Fur-H, *J* = 3.2 Hz and *J* = 0.8 Hz), 6.40 (*m*, 1H, Fur-H), 7.07 (*d*, 1H, Ar-H, *J* = 8.4), 7.43 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 7.53 (*dd*, 1H, Ar-H, *J* = 8.2 Hz and *J* = 1.8 Hz), 7.59 (*m*, 1H, Fur-H), 8.52 (*t*, 1H, NH, *J* = 5.8 Hz), 9.85 (*s*, 1H, CHO); ^{13}C NMR (50 MHz, DMSO-d_6): 35.51, 55.77, 67.75, 107.03, 110.29, 110.52, 113.16, 125.50, 130.47, 142.16, 149.45, 151.90, 152.73, 167.04, 191.34; Anal. Calcd. For $C_{15}H_{15}NO_5$ (289.28 g/mol): C, 62.28; H, 5.23; N, 4.84; Found: C, 62.19; H, 5.25; N, 4.79.

1.5.17. 2-(4-Formyl-2-methoxyphenoxy)-N-(thiophen-2-ylmethyl)acetamide × 0.5H_2O (**4q**): White powder; yield: 0.636g (73%); mp 123-124 ºC; IR (KBr, cm^{-1}): 3274, 1660, 1506, 1257, 1136, 1026, 704; ^{1}H NMR (200 MHz, DMSO-d_6): 3.85 (*s*, 3H, CH_3), 4.50 (*d*, 2H, NH$\underline{CH_2}$, *J* = 6.0 Hz), 4.69 (*s*, 2H, CH_2), 6.93-6.99 (*m*, 2H, Thio-H), 7.06 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 7.39-7.44 (*m*, 2H, Ar-H, Thio-H), 7.52 (*dd*, 1H, Ar-H, *J* = 8.2 Hz and *J* = 1.8 Hz), 8.68 (*t*, 1H, NH, *J* = 6.0 Hz), 9.85 (*s*, 1H, CHO); ^{13}C NMR (50 MHz, DMSO-d_6): 37.22, 55.78, 67.72, 110.20, 113.10, 125.24, 125.60, 125.73, 126.74, 130.46, 141.99, 149.45, 152.72, 167.06, 191.43; Anal. Calcd. For $C_{15}H_{15}NO_4S \times 0.5H_2O$ (314.35 g/mol): C, 57.31; H, 5.13; N, 4.46; S, 10.20; Found: C, 56.87; H, 5.39; N, 4.47; S, 10.47.

1.5.18. 2-(4-Formyl-2-methoxyphenoxy)-N-hexylacetamide (**4r**): White powder; yield: 0.485g (58%); mp 76-77 ºC; IR (KBr, cm^{-1}): 3291, 2934, 1653, 1549, 1284, 1140, 1027, 737; ^{1}H NMR (200 MHz, DMSO-d_6): 0.85 (*t*, 3H, CH_3, J = 6.5 Hz), 1.23-1.44 (*m*, 8H, CH_2), 3.12 (*q*, 2H, -NH-$\underline{CH_2}$-CH_2-, *J* = 6.4 Hz), 3.86 (*s*, 3H, O$\underline{CH_3}$), 4.61 (*s*, 2H, -O$\underline{CH_2}$-CO-), 7.05 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 7.43 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 7.53 (*dd*, 1H, Ar-H, *J* = 8.3 Hz and *J* = 1.9 Hz), 7.99 (*t*, 1H, NH, *J* = 5.5 Hz), 9.85 (*s*, 1H, CHO); ^{13}C NMR (50 MHz, DMSO-d_6): 13.99, 22.16, 26.10, 29.07, 31.06, 38.46, 55.76, 67.91, 110.27, 113.08, 125.47, 130.42, 149.43, 152.75, 166.79, 191.28; Anal. Calcd. For $C_{16}H_{23}NO_4$ (293.36 g/mol): C, 65.51; H, 7.90; N, 4.77; Found: C, 65.07; H, 7.63; N, 4.73.

1.5.19. N-Cyclohexyl-2-(4-formyl-2-methoxyphenoxy)acetamide (**4s**): White powder; yield: 0.482g (58%); mp 137-138 ºC; IR (KBr, cm^{-1}): 3418, 2933, 1683, 1508, 1265, 1148, 1034, 810; ^{1}H NMR (200 MHz, DMSO-d_6): 1.02-1.75 (*m*, 10H, cyclohexyl), 3.57 (*m*, 1H, cyclohexyl), 3.86 (*s*, 3H, CH_3), 4.60 (*s*, 2H, -O$\underline{CH_2}$-), 7.05 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 7.43 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 7.53 (*dd*, 1H, Ar-H, *J* = 8.3 Hz and *J* = 1.9 Hz), 7.88 (*d*, 1H, NH, *J* = 8 Hz), 9.85 (*s*, 1H, CHO); ^{13}C NMR (50 MHz, DMSO-d_6): 24.53 (2C), 25.25, 32.31 (2C), 47.50, 55.77, 67.89, 110.27, 113.16, 125.50, 130.37, 149.40, 152.83, 165.89, 191.28; Anal. Calcd. For $C_{16}H_{21}NO_4$ (291.34 g/mol): C, 65.96; H, 7.27; N, 4.81; Found: C, 62.64; H, 6.76; N, 4.43.

1.5.20. N-((1s,3s)-Adamantan-1-yl)-2-(4-formyl-2-methoxyphenoxy)acetamide (**4t**): Light yellow powder; yield: 0.470g (48%); mp 137-138 ºC; IR (KBr, cm^{-1}): 3382, 2912, 1683, 1590, 1276, 1164, 1039, 810; ^{1}H NMR (200 MHz, DMSO-d_6): 1.62 (*s*, 6H, Ad), 1.95-2.02 (*m*, 9H, Ad), 3.86 (*s*, 3H, CH_3), 4.55 (*s*, 2H, CH_2), 7.07 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 7.41-7.43 (*m*, 2H, Ar-H, NH), 7.54 (*dd*, 1H, Ar-H, *J* = 8.2 Hz and *J* = 1.8 Hz), 9.85 (*s*, 1H, CHO); ^{13}C NMR (50 MHz, DMSO-d_6): 28.94 (3C), 36.04 (3C), 41.06 (3C), 51.10, 55.82, 67.86, 110.25, 113.13, 125.57, 130.34, 149.35, 152.76, 165.88, 191.29; Anal. Calcd. For $C_{20}H_{25}NO_4$ (343.42 g/mol): C, 69.95; H, 7.34; N, 4.08; Found: C, 67.56; H, 6.81; N, 3.88.

1.5.21. 2-(3-Methoxy-4-(2-oxo-2-(phenylamino)ethoxy)phenyl)quinoline-4-carboxylic acid (**5a**): Light yellow powder; yield: 0.146g (34%); mp 205-206 ºC; IR (KBr, cm^{-1}): 3299, 2959, 1707, 1657, 1596, 1424, 1211, 1034, 866, 761; ^{1}H NMR (200 MHz, DMSO-d_6): 3.98 (*s*, 3H, CH_3),

4.81 (*s*, 2H, CH_2), 7.05-7.15 (*m*, 2H, Ar-H), 7.30-7.38 (*m*, 2H, Ar-H), 7.62-7.72 (*m*, 3H, Ar-H), 7.80-7.90 (*m*, 2H, Ar-H), 7.96 (*d*, 1H, *J* = 2 Hz), 8.17 (*dd* , 1H, Ar-H, *J* = 8.4 Hz and *J* = 0.6 Hz), 8.45 (*s*, 1H, Ar-H), 8.60 (*dd*, 1H, Ar-H, *J* = 8.4 Hz and *J* = 1 Hz), 10.17 (*s*, 1H, NH); ^{13}C NMR (50 MHz, DMSO-d_6): 56.05, 68.52, 111.08, 114.32, 118.89, 119.64 (2C), 120.34, 123.24, 123.76, 125.41, 127.44, 128.84 (2C), 129.69, 130.15, 131.90, 137.71, 138.45, 148.36, 149.41, 149.60, 155.45, 166.40, 167.72; Anal. Calcd. For $C_{25}H_{20}N_2O_5$ (428.44 g/mol): C, 70.08; H, 4.71; N, 6.54; Found: C, 70.39; H, 4.72; N, 6.56.

1.5.22. 2-(3-Methoxy-4-(2-oxo-2-(o-tolylamino)ethoxy)phenyl)quinoline-4-carboxylic acid (**5b**): Beige powder; yield: 0.126g (28%); mp 246-247 ºC; IR (KBr, cm^{-1}): 3446, 3372, 2921, 1719, 1644, 1598, 1519, 1245, 756; ^{1}H NMR (200 MHz, DMSO-d_6): 2.24 (*s*, 3H, CH_3), 3.98 (*s*, 3H, O$\underline{CH_3}$), 4.84 (*s*, 2H, CH_2), 7.05-7.25 (*m*, 4H, Ar-H), 7.57-7.71 (*m*, 2H, Ar-H), 7.79-7.91 (*m*, 2H, Ar-H), 7.97 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 8.15 (*d*, 1H, Ar-H, *J* = 8.0 Hz), 8.46 (*s*, 1H, Ar-H), 8.59 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 9.42 (*s*, 1H, NH), 14.03 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 17.57, 56.03, 68.22, 110.96, 114.16, 118.83, 120.27, 123.21, 123.91, 125.24, 125.37, 126.18, 127.41, 129.65, 130.12, 130.39, 130.75, 131.91, 135.60, 137.71, 148.32, 149.09, 149.51, 155.38, 166.31, 167.68; Anal. Calcd. For $C_{26}H_{22}N_2O_5$ (442.46 g/mol): C, 70.58; H, 5.01; N, 6.33; Found: C, 70.42; H, 5.01; N, 6.35.

1.5.23. 2-(3-Methoxy-4-(2-oxo-2-(m-tolylamino)ethoxy)phenyl)quinoline-4-carboxylic acid (**5c**): Beige yellow powder; yield: 0.133g (30%); mp 225-226 ºC; IR (KBr, cm^{-1}): 3384, 2921, 2599, 1717, 1643, 1561, 1520, 1421, 1237, 776; ^{1}H NMR (200 MHz, DMSO-d_6): 2.28 (*s*, 3H, CH_3), 3.98 (*s*, 3H, O$\underline{CH_3}$), 4.80 (*s*, 2H, CH_2), 6.90 (*d*, 1H, Ar-H, *J* = 7.4 Hz), 7.11 (*d*, 1H, Ar-H, *J* = 8.6 Hz), 7.21 (*t*, 1H, Ar-H, *J* = 7.8 Hz), 7.40-7.48 (*m*, 2H, Ar-H), 7.62-7.71 (*m*, 1H, Ar-H), 7.78-7.88 (*m*, 2H, Ar-H), 7.96 (*d*, 1H, Ar-H, *J* = 2 Hz), 8.14 (*dd*, 1H, Ar-H, *J* = 8.2 Hz and *J* = 0.6 Hz), 8.45 (*s*, 1H, Ar-H), 8.59 (*dd*, 1H, Ar-H, *J* = 8.5 Hz and *J* = 1.0 Hz), 10.08 (*s*, 1H, NH), 13.99 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 21.25, 55.99, 68.45, 111.02, 114.23, 116.74, 118.82, 120.08, 120.27, 123.18, 124.39, 125.34, 127.37, 128.61, 129.62, 130.07, 131.81, 137.63, 138.00, 138.29, 148.29, 149.35, 149.53, 155.38, 166.25, 167.65; Anal. Calcd. For $C_{26}H_{22}N_2O_5$ (442.46 g/mol): C, 70.58; H, 5.01; N, 6.33; Found: C, 70.25; H, 4.94; N, 6.37.

1.5.24. 2-(3-Methoxy-4-(2-oxo-2-(p-tolylamino)ethoxy)phenyl)quinoline-4-carboxylic acid × 1H₂O (**5d**): Beige powder; yield: 0.150g (34%); mp 224-225 ºC; IR (KBr, cm^{-1}): 3372, 2921, 2511, 1707, 1640, 1549, 1349, 1269, 1127, 1036, 808; ^{1}H NMR (200 MHz, DMSO-d_6): 2.26 (*s*, 3H, CH_3), 3.97 (*s*, 3H, O$\underline{CH_3}$), 4.78 (*s*, 2H, CH_2), 7.13 (*m*, 3H, Ar-H), 7.52 (*d*, 2H, Ar-H, *J* = 8.2 Hz), 7.62-7.71 (*m*, 1H, Ar-H), 7.78-7.88 (*m*, 2H, Ar-H), 7.96 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 8.14 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 8.44 (*s*, 1H, Ar-H), 8.59 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 10.06 (*s*, 1H, NH), 14.00 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 20.53, 55.97, 68.49, 110.99, 114.27, 118.80, 119.58 (2C), 120.26, 123.18, 125.34, 127.35, 129.14 (2C), 129.61, 130.06, 131.82, 132.66, 135.84, 137.67, 148.29, 149.35, 149.53, 155.37, 166.07, 167.65; Anal. Calcd. For $C_{26}H_{22}N_2O_5 \times 1H_2O$ (460.48 g/mol): C, 67.82; H, 5.25; N, 6.08; Found: C, 68.18; H, 5.20; N, 6.15.

1.5.25. 2-(4-(2-((2-Fluorophenyl)amino)-2-oxoethoxy)-3-methoxyphenyl)quinoline-4-carboxylic acid × 1.5H₂O (**5e**): Beige powder; yield: 0.192g (43%); mp 248-249 ºC; IR (KBr, cm^{-1}): 3372, 2922, 1714, 1622, 1556, 1519, 1266, 1207, 1036, 749; ^{1}H NMR (200 MHz, DMSO-d_6): 3.98 (*s*, 3H, CH_3), 4.89 (*s*, 2H, CH_2), 7.13-7.36 (*m*, 4H, Ar-H), 7.63-7.71 (*m*, 1H, Ar-H), 7.79-7.90 (*m*, 2H, Ar-H), 7.93-8.02 (*m*, 2H, Ar-H), 8.14 (*d*, 1H, Ar-H, *J* = 7.8 Hz), 8.46 (*s*, 1H, Ar-H), 8.60 (*d*, 1H, Ar-H, *J* = 7.8 Hz), 9.86 (*s*, 1H, NH), 13.74 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 56.05, 68.33, 111.05, 114.48, 115.51 (J_{CF} = 19.15 Hz), 118.88, 120.30, 123.26, 123.69 (C-F), 124.51 (J_{CF} = 3.45 Hz), 125.41 (J_{CF} = 1.2 Hz), 125.52 (C-F), 125.66, 127.38, 129.65, 130.07, 132.09, 137.69, 148.35, 149.14, 149.58, 153.51 (J_{CF} = 243.15 Hz), 155.38, 166.78, 167.70; Anal. Calcd. For $C_{25}H_{19}FN_2O_5 \times 1.5H_2O$ (473.46 g/mol): C, 63.42; H, 4.68; N, 5.92; Found: C, 63.21; H, 4.57; N, 5.91.

1.5.26. 2-(4-(2-((3-Fluorophenyl)amino)-2-oxoethoxy)-3-methoxyphenyl)quinoline-4-carboxylic acid × 0.5H₂O (**5f**): Light orange powder; yield: 0.134g (30%); mp 237-238 ºC; IR (KBr, cm^{-1}): 3437, 3394, 1699, 1605, 1548, 1425, 1262, 773, 680; ^{1}H NMR (200 MHz, DMSO-d_6): 3.98 (*s*, 3H, CH_3), 4.83 (*s*, 2H, CH_2), 6.88-6.98 (*m*, 1H, Ar-H), 7.13 (*d*, 1H, Ar-H, *J* = 8.4 Hz), 7.36-7.41 (*m*, 2H, Ar-H), 7.60-7.72 (*m*, 2H, Ar-H), 7.80-7.89 (*m*, 2H, Ar-H), 7.97 (*d*, 1H, Ar-H, *J* = 2 Hz), 8.15 (*dd*, 1H, Ar-H, *J* = 8.2 Hz and *J* = 0.6 Hz), 8.45 (*s*, 1H, Ar-H), 8.60 (*dd*, 1H, Ar-H, *J* = 8.4 Hz and *J* = 1 Hz), 10.40 (*s*, 1H, NH), 13.99 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6):

56.00, 68.47, 106.46 (J_{CF} = 26.05 Hz), 110.21 (J_{CF} = 20.95 Hz), 111.09, 114.37, 115.37 (J_{CF} = 1.75 Hz), 118.86, 120.29, 123.26, 125.41, 127.37, 129.65, 130.08, 130.44 (J_{CF} = 9.4 Hz), 131.99, 137.77, 140.14 (J_{CF} = 10.95 Hz), 148.34, 149.29, 149.59, 155.40, 162.15 (J_{CF} = 239.9 Hz), 166.82, 167.72; Anal. Calcd. For $C_{25}H_{19}FN_2O_5 \times 0.5H_2O$ (455.44 g/mol): C, 65.93; H, 4.43; N, 6.15; Found: C, 65.71; H, 4.35; N, 6.15.

1.5.27. 2-(4-(2-((4-Fluorophenyl)amino)-2-oxoethoxy)-3-methoxyphenyl)quinoline-4-carboxylic acid × 0.5H₂O (**5g**): Light yellow powder; yield: 0.174g (39%); mp 212-213 ºC; IR (KBr, cm^{-1}): 3065, 2600, 1705, 1663, 1548, 1508, 1424, 1209, 813; ^{1}H NMR (200 MHz, DMSO-d_6): 3.99 (*s*, 3H, CH_3), 4.81 (*s*, 2H, CH_2), 7.12-7.25 (*m*, 3H, Ar-H), 7.65-7.72 (*m*, 3H, Ar-H), 7.80-7.90 (*m*, 2H, Ar-H), 7.98 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 8.15 (*d*, 1H, Ar-H, *J* = 8 Hz), 8.46 (*s*, 1H, Ar-H), 8.61 (*d*, 1H, Ar-H, *J* = 7.8 Hz), 10.24 (*s*, 1H, NH), 14.00 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 55.98, 68.51, 111.07, 114.39, 115.31 (J_{CF} = 22.15 Hz), 118.81, 120.26, 121.46 (J_{CF} = 7.8 Hz), 123.19, 125.34 (2C), 127.33, 129.60, 130.03 (2C), 131.93, 134.73 (J_{CF} = 2.55 Hz), 137.65, 148.29, 149.31, 149.58, 155.36, 158.27 (J_{CF} = 238.8 Hz), 166.31, 167.63; Anal. Calcd. For $C_{25}H_{19}FN_2O_5 \times 0.5H_2O$ (455.44 g/mol): C, 65.93; H, 4.43; N, 6.15; Found: C, 66.10; H, 4.40; N, 6.18.

1.5.28. 2-(4-(2-((2-Chlorophenyl)amino)-2-oxoethoxy)-3-methoxyphenyl)quinoline-4-carboxylic acid × 0.5H₂O (**5h**): Light orange powder; yield: 0.264g (57%); mp 226-227 ºC; IR (KBr, cm^{-1}): 3455, 3361, 1700, 1595, 1540, 1518, 1271, 1032, 750; ^{1}H NMR (200 MHz, DMSO-d_6): 4.00 (*s*, 3H, CH_3), 4.90 (*s*, 2H, CH_2), 7.17-7.26 (*m*, 2H, Ar-H), 7.39 (*td*, 1H, Ar-H, *J* = 7.7 Hz and *J* = 1.4 Hz), 7.56 (*dd*, 1H, Ar-H, *J* = 7.9 Hz and *J* = 1.5 Hz), 7.64-7.72 (*m*, 1H, Ar-H), 7.80-7.92 (*m*, 2H, Ar-H), 7.99 (*d*, 1H, Ar-H, *J* = 2 Hz), 8.08 (*dd*, 1H, Ar-H, *J* = 8.1 Hz and *J* = 1.5 Hz), 8.16 (*d*, 1H, Ar-H, *J* = 7.8 Hz) 8.48 (*s*, 1H, Ar-H), 8.61 (*dd*, 1H, Ar-H, *J* = 8.4 Hz and *J* = 0.8 Hz), 9.63 (*s*, 1H, NH), 14.00 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 56.02, 68.11, 110.87, 114.27, 118.87, 120.24, 123.27, 123.46, 124.50, 125.41, 125.94, 127.40, 127.79, 129.47, 129.66, 130.08, 132.17, 134.11, 137.74, 148.33, 148.64, 149.48, 155.33, 166.59, 167.73; Anal. Calcd. For $C_{25}H_{19}ClN_2O_5 \times 0.5H_2O$ (471.89 g/mol): C, 63.63; H, 4.27; N, 5.94; Found: C, 63.39; H, 4.42; N, 5.93.

1.5.29. 2-(4-(2-((3-Chlorophenyl)amino)-2-oxoethoxy)-3-methoxyphenyl)quinoline-4-carboxylic acid × 0.5H_2O (**5i**): Light brown powder; yield: 0.148g (32%); mp 248-249 ºC; IR (KBr, cm^{-1}): 3391, 1699, 1594, 1519, 1422, 1252, 774; ^{1}H NMR (200 MHz, DMSO-d_6): 3.99 (*s*, 3H, CH_3), 4.85 (*s*, 2H, CH_2), 7.11-7.18 (*m*, 2H, Ar-H), 7.38 (*t*, 1H, Ar-H, *J* = 8 Hz), 7.55 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 7.68 (*t*, 1H, Ar-H, *J* = 7.4 Hz), 7.81-7.88 (*m*, 3H, Ar-H), 7.98 (*d*, 1H, Ar-H, *J* = 1.4 Hz), 8.16 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 8.47 (*s*, 1H, Ar-H), 8.62 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 10.41 (*s*, 1H, NH), 14.06 (*bs*, 1H, COOH). ^{13}C NMR (50 MHz, DMSO-d_6): 55.99, 68.45, 111.10, 114.39, 118.00, 118.82, 119.13, 120.26, 123.22, 123.42, 125.37, 127.34, 129.62, 130.04, 130.43, 131.97, 133.14, 137.71, 139.84, 148.31, 149.27, 149.58, 155.37, 166.82, 167.67; Anal. Calcd. For $C_{25}H_{19}ClN_2O_5 \times 0.5H_2O$ (471.89 g/mol): C, 63.63; H, 4.27; N, 5.94; Found: C, 63.62; H, 4.26; N, 5.96.

1.5.30. 2-(4-(2-((4-Chlorophenyl)amino)-2-oxoethoxy)-3-methoxyphenyl)quinoline-4-carboxylic acid × 0.5H_2O (**5j**): Beige powder; yield: 0.167g (36%); mp 229-230 ºC; IR (KBr, cm^{-1}): 3300, 3065, 1707, 1668, 1595, 1539, 1211, 802; ^{1}H NMR (200 MHz, DMSO-d_6): 3.99 (*s*, 3H, CH_3), 4.83 (*s*, 2H, CH_2), 7.14 (*d*, 1H, Ar-H, *J* = 8.4 Hz), 7.39-7.45 (*m*, 2H, Ar-H), 7.64-7.73 (*m*, 3H, Ar-H), 7.80-7.90 (*m*, 2H, Ar-H), 7.98 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 8.16 (*d*, 1H, Ar-H, *J* = 7.8 Hz), 8.47 (*s*, 1H, Ar-H), 8.60 (*dd*, 1H, Ar-H, *J* = 8.4 Hz and *J* = 0.8 Hz), 10.35 (*s*, 1H, NH), 13.96 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 55.98, 68.47, 111.03, 114.31, 118.90, 120.28, 121.19 (2C), 123.25, 125.40, 127.39 (2C), 128.71 (2C), 129.65, 130.09, 131.93, 137.38, 137.63, 148.34, 149.31, 149.57, 155.40, 166.60, 167.70; Anal. Calcd. For $C_{25}H_{19}ClN_2O_5 \times 0.5H_2O$ (471.89 g/mol): C, 63.63; H, 4.27; N, 5.94; Found: C, 63.68; H, 4.30; N, 5.96.

1.5.31. 2-(3-Methoxy-4-(2-oxo-2-((2-(trifluoromethyl)phenyl)amino)ethoxy)phenyl)quinoline-4-carboxylic acid × 0.5H_2O (**5k**): Yellow powder; yield: 0.149g (30%); mp 227-228 ºC; IR (KBr, cm^{-1}): 3465, 3405, 2917, 1693, 1594, 1517, 1293, 1178, 1035, 757; ^{1}H NMR (200 MHz, DMSO-d_6): 3.98 (*s*, 3H, CH_3), 4.87 (*s*, 2H, CH_2), 7.17 (*d*, 1H, Ar-H, *J* = 8.6 Hz), 7.45 (*t*, 1H, Ar-H, *J* = 7.6 Hz), 7.63-7.68 (*m*, 1H, Ar-H), 7.71-7.84 (*m*, 3H, Ar-H), 7.87-7.91 (*m*, 2H, Ar-H), 7.98 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 8.15 (*d*, 1H, Ar-H, *J* = 7.8 Hz), 8.47 (*s*, 1H, Ar-H), 8.60 (*dd*, 1H, Ar-H, *J* = 8.2 Hz and *J* = 0.8 Hz), 9.60 (*s*, 1H, NH), 13.99 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 55.95, 67.91, 110.82, 114.13, 118.91, 120.192, 122.83 (J_{CF} = 29.02 Hz), 123.28, 124.61 (J_{CF}

= 271.25 Hz), 125.42, 126.11(C-F), 126.38 (J_{CF} = 3.2 Hz), 127.09 (C-F), 127.43, 129.69, 130.11, 132.12, 133.28 (C-F), 134.65 (J_{CF} = 1.7 Hz), 137.70, 148.35, 148.68, 149.49, 155.36, 167.15, 167.75; Anal. Calcd. For $C_{26}H_{19}F_3N_2O_5 \times 0.5H_2O$ (505.45 g/mol): C, 61.78; H, 3.99; N, 5.54; Found: C, 61.68; H, 3.98; N, 5.57.

1.5.32. 2-(3-Methoxy-4-(2-oxo-2-((3-(trifluoromethyl)phenyl)amino)ethoxy)phenyl)quinoline-4-carboxylic acid × 0.5H₂O (**5l**): Yellow powder; yield: 0.208g (42%); mp > 250 ºC; IR (KBr, cm^{-1}): 3379, 2939, 2624, 1702, 1549, 1335, 1251, 1117, 799; ^{1}H NMR (200 MHz, DMSO-d_6): 3.98 (*s*, 3H, CH_3), 4.85 (*s*, 2H, CH_2), 7.13 (*d*, 1H, Ar-H, *J* = 8.4 Hz), 7.42-7.46 (*m*, 1H, Ar-H), 7.55-7.71 (*m*, 2H, Ar-H), 7.79-7.88 (*m*, 3H, Ar-H), 7.96 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 8.12-8.16 (*m*, 2H, Ar-H), 8.45 (*s*, 1H, Ar-H), 8.60 (*d*, 1H, Ar-H, *J* = 8.2 Hz), 10.55 (*s*, 1H, Ar-H), 14.00 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 55.85, 68.41, 111.10, 114.40, 115.71 (J_{CF} = 3.40 Hz), 118.78, 119.97 (J_{CF} = 3.25 Hz), 120.25, 123.19 (2C, C-F), 124.05 (J_{CF} = 270.05 Hz), 125.34, 127.33, 129.55 (J_{CF} = 31.32 Hz), 129.60, 129.99 (2C, C-F),131.97, 137.71, 139.17 (C-F), 148.29, 149.26, 149.58, 155.35, 167.04, 167.64; Anal. Calcd. For $C_{26}H_{19}F_3N_2O_5 \times 0.5H_2O$ (505.45 g/mol): C, 61.78; H, 3.99; N, 5.54; Found: C, 61.54; H, 3.95; N, 5.50.

1.5.33. 2-(3-Methoxy-4-(2-oxo-2-((4-(trifluoromethyl)phenyl)amino)ethoxy)phenyl)quinoline-4-carboxylic acid × 1.5H₂O (**5m**): Beige powder; yield: 0.169g (34%); mp 211-212 ºC; IR (KBr, cm^{-1}): 3393, 2499, 1701, 1603, 1543, 1523, 1331, 1272, 1113, 841; ^{1}H NMR (200 MHz, DMSO-d_6): 3.98 (*s*, 3H, CH_3), 4.86 (*s*, 2H, CH_2), 7.12 (*d*, 1H, Ar-H, *J* = 8.4 Hz), 7.63-7.73(*m*, 3H, Ar-H), 7.79-7.89 (*m*, 4H, Ar-H), 7.96 (*d*, 1H, Ar-H, *J* = 2 Hz), 8.14 (*dd*, 1H, Ar-H, *J* = 8.4 Hz and *J* = 0.6 Hz), 8.44 (*s*, 1H, Ar-H), 8.60 (*dd*, 1H, Ar-H, *J* = 8.5 Hz and *J* = 0.9 Hz), 10.56 (*s*, 1H, NH), 13.79 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 56.00, 68.47, 111.13, 114.41, 118.86, 119.54 (2C, C-F), 120.28, 123.25, 123.84 (J_{CF} = 31.72 Hz), 124.35 (J_{CF} = 269.65 Hz), 125.40 (2C), 126.08 (J_{CF} = 3.32 Hz), 127.36, 129.64, 130.06, 132.02, 137.71, 142.00 (C-F), 148.34, 149.28, 149.60, 155.39, 167.10, 167.70; Anal. Calcd. For $C_{26}H_{19}F_3N_2O_5 \times 1.5H_2O$ (523.47 g/mol): C, 59.66; H, 4.24; N, 5.35; Found: C, 59.97; H, 4.27; N, 5.36.

1.5.34. 2-(4-(2-(Benzylamino)-2-oxoethoxy)-3-methoxyphenyl)quinoline-4-carboxylic acid (**5n**): Beige powder; yield: 0.150g (34%); mp 199-200 ºC; IR (KBr, cm^{-1}): 3390, 2923, 1703, 1636,

1518, 1422, 1245, 1214, 1031, 809; ^{1}H NMR (200 MHz, DMSO-d_6): 3.95 (*s*, 3H, CH_3), 4.38 (*d*, 2H, -NH$\underline{CH_2}$, *J* = 6.0 Hz), 4.69 (*s*, 2H, CH_2), 7.42 (*d*, 1H, Ar-H, *J* = 8.6 Hz), 7.24-7.35 (*m*, 5H, Ar-H), 7.64-7.73 (*m*, 1H, Ar-H), 7.81-7.88 (*m*, 2H, Ar-H), 7.96 (*d*, 1H, Ar-H, *J* = 2 Hz), 8.16 (*dd*, 1H, Ar-H, *J* = 8.3 Hz and *J* = 0.5 Hz), 8.47 (*s*, 1H, Ar-H), 8.58 (*t*, 1H, NH, *J* = 6.0 Hz), 8.62 (*dd*, 1H, Ar-H, *J* = 8.5 Hz and *J* = 0.9 Hz) 13.98 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 42.13, 55.96, 68.54, 111.04, 114.64, 118.87, 120.25, 123.23, 125.38, 126.87 (2C), 127.34 (2C), 127.42, 128.30 (2C), 129.66, 130.12, 132.01, 137.69, 139.16, 148.34, 149.29, 149.65, 155.42, 167.70; Anal. Calcd. For $C_{26}H_{22}N_2O_5$ (442.46 g/mol): C, 70.58; H, 5.01; N, 6.33; Found: C, 70.37; H, 5.00; N, 6.29.

1.5.35. 2-(3-Methoxy-4-(2-oxo-2-((pyridin-3-ylmethyl)amino)ethoxy)phenyl)quinoline-4-carboxylic acid × 1H_2O (**5o**): Light brown powder; yield: 0.226g (51%); mp 215-216 ºC; IR (KBr, cm^{-1}): 3357, 2930, 1680, 1588, 1516, 1424, 1250, 1172, 1029, 797; ^{1}H NMR (200 MHz, DMSO-d_6): 3.95 (*s*, 3H, CH_3), 4.41 (*d*, 2H, NH$\underline{CH_2}$, *J* = 5.8 Hz), 4.69 (*s*, 2H, CH_2), 7.10 (*d*, 1H, Ar-H, *J* = 8.4 Hz), 7.34-7.40 (*m*, 1H, Py-H), 7.65-7.72 (*m*, 2H, Ar-H, Py-H), 7.81-7.88 (*m*, 2H, Ar-H), 7.96 (*d*, 1H, Ar-H, *J* = 1.4 Hz), 8.16 (*d*, 1H, Ar-H, *J* = 8 Hz), 8.46 (*s*, 1H, Ar-H), 8.53-8.71 (*m*, 4H, NH, Ar-H, 2 Py-H); ^{13}C NMR (50 MHz, DMSO-d_6): 39.88, 55.96, 68.52, 111.06, 114.63, 118.83, 120.23, 123.24 (2C), 125.40, 127.40, 129.65, 130.11, 132.06, 135.25 (2C), 137.83, 148.04, 148.33, 148.76, 149.23, 149.65, 155.40, 167.73, 167.98; Anal. Calcd. For $C_{25}H_{21}N_3O_5 \times 1H_2O$ (461.47 g/mol): C, 65.07; H, 5.02; N, 9.11; Found: C, 65.44; H, 4.85; N, 9.05.

1.5.36. 2-(4-(2-((Furan-2-ylmethyl)amino)-2-oxoethoxy)-3-methoxyphenyl)quinoline-4-carboxylic acid × 1H_2O (**5p**): Beige powder; yield: 0.238g (55%); mp 229-230 ºC; IR (KBr, cm^{-1}): 3444, 2936, 1705, 1630, 1590, 1517, 1427, 1256, 1150, 780; ^{1}H NMR (200 MHz, DMSO-d_6): 3.94 (*s*, 3H, CH_3), 4.36 (*d*, 2H, NH$\underline{CH_2}$, *J* = 5.8 Hz), 4.64 (*s*, 2H, CH_2), 6.26 (*d*, 1H, Fur-H, *J* = 2.8 Hz), 6.40 (*dd*, 1H, Fur-H, *J* = 3.1 Hz and *J* = 1.9 Hz), 7.08 (*d*, 1H, Ar-H, *J* = 8.4 Hz), 7.59-7.71 (*m*, 2H, Ar-H, Fur-H), 7.81-7.87 (*m*, 2H, Ar-H), 7.94 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 8.14 (*d*, 1H, Ar-H, *J* = 8 Hz), 8.44 (*s*, 1H, Ar-H), 8.49 (*t*, 1H, NH, *J* = 5.8 Hz), 8.59 (*d*, 1H, Ar-H, *J* = 8 Hz), 13.87 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 35.49, 55.95, 68.36, 106.95, 110.48, 110.99, 114.56, 118.81, 120.22, 123.18, 125.34, 127.38, 129.62, 130.09, 131.95, 137.69, 142.09,

148.29, 149.25, 149.59, 151.94, 155.38, 167.53, 167.65; Anal. Calcd. For $C_{24}H_{20}N_2O_6 \times 1H_2O$ (450.45 g/mol): C, 64.47; H, 4.81; N, 6.18; Found: C, 63.99; H, 4.92; N, 6.22.

1.5.37. 2-(3-Methoxy-4-(2-oxo-2-((thiophen-2-ylmethyl)amino)ethoxy)phenyl)quinoline-4-carboxylic acid × *0.5H₂O* (**5q**): Brown powder; yield: 0.233 (52%); mp 206-207 ºC; IR (KBr, cm^{-1}): 3346, 2935, 1700, 1632, 1587, 1516, 1255, 1212, 1146, 696; ^{1}H NMR (200 MHz, DMSO-d_6): 3.95 (*s*, 3H, CH_3), 4.54 (*d*, 2H, NH$\underline{CH_2}$, *J* = 5.8 Hz), 4.65 (*s*, 2H, CH_2), 6.95-7.02 (*m*, 2H, Thio-H), 7.08 (*d*, 1H, Ar-H, *J* = 8.6 Hz), 7.41 (*dd*, 1H, Thio-H, *J* = 4.9 Hz and *J* = 1.5 Hz), 7.64-7.72 (*m*, 1H, Ar-H), 7.82-7.87 (*m*, 2H, Ar-H), 7.95 (*d*, 1H, Ar-H, *J* = 2 Hz), 8.15 (*d*, 1H, Ar-H, *J* = 7.8 Hz), 8.46 (*s*, 1H, Ar-H), 8.61 (*dd*, 1H, Ar-H, *J* = 8.4 Hz and *J* = 0.8 Hz), 8.67 (*t*, 1H, NH, *J* = 5.8 Hz), 14.00 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 37.17, 55.91, 68.38, 110.98, 114.55, 118.82, 120.19, 123.21, 125.06, 125.37, 125.60, 126.65, 127.36, 129.62, 130.05, 131.97, 137.70, 141.98, 148.30, 149.23, 149.59, 155.36, 167.51, 167.68; Anal. Calcd. For $C_{24}H_{20}N_2O_5S \times 0.5H_2O$ (457.50 g/mol): C, 63.01; H, 4.63; N, 6.12; S, 7.01; Found: C, 63.31; H, 4.61; N, 6.11; S, 7.13.

1.5.38. 2-(4-(2-(Hexylamino)-2-oxoethoxy)-3-methoxyphenyl)quinoline-4-carboxylic acid (**5r**): White powder; yield: 0.157g (36%); mp 179-180 ºC; IR (KBr, cm^{-1}): 3422, 2931, 1712, 1647, 1549, 1519, 1247, 1036, 798; ^{1}H NMR (200 MHz, DMSO-d_6): 0.84 (*t*, 3H, CH_3, J = 6.3 Hz), 1.23-1.46 (*m*, 8H, CH_2), 3.14 (*q*, 2H, -NH-$\underline{CH_2}$-CH_2-, *J* = 6.5 Hz), 3.97 (*s*, 3H, O$\underline{CH_3}$), 4.58 (*s*, 2H, -O$\underline{CH2}$-CO-), 7.08 (*d*, 1H, Ar-H, *J* = 8.6 Hz), 7.67-7.72 (*m*, 1H, Ar-H), 7.83-7.88 (*m*, 2H, Ar-H), 7.96 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 7.99 (*t*, 1H, NH, *J* = 6.0 Hz), 8.15 (*d*, 1H, Ar-H, *J* = 7.8 Hz), 8.46 (*s*, 1H, Ar-H), 8.61 (*d*, 1H, Ar-H, *J* = 7.8 Hz), 14.01 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 13.92, 22.13, 26.10, 29.10, 31.06, 38.45, 55.93, 68.50, 110.95, 114.44, 118.82, 120.20, 123.22, 125.36, 127.33, 129.61, 130.02, 131.90, 137.59, 148.32, 149.27, 149.58, 155.35, 167.31, 167.65; Anal. Calcd. For $C_{25}H_{28}N_2O_5$ (436.50 g/mol): C, 68.79; H, 6.47; N, 6.42; Found: C, 69.08; H, 6.46; N, 6.51.

1.5.39. 2-(4-(2-(Cyclohexylamino)-2-oxoethoxy)-3-methoxyphenyl)quinoline-4-carboxylic acid (**5s**): Yellow powder; yield: 0.252g (58%); mp 230-231 ºC; IR (KBr, cm^{-1}): 3443, 3267, 2934, 1704, 1655, 1518, 1252, 774; ^{1}H NMR (200 MHz, DMSO-d_6): 1.19-1.76 (*m*, 10H, cyclohexyl),

3.59 (*m*, 1H, cyclohexyl), 3.96 (*s*, 3H, CH_3), 4.56 (*s*, 2H, -O$\underline{CH_2}$-), 7.07 (*d*, 1H, Ar-H, *J* = 8.6 Hz), 7.62-7.70 (*m*, 1H, Ar-H), 7.78-7.86 (*m*, 3H, Ar-H), 7.94 (*d*, 1H, NH, *J* = 1.8 Hz), 8.14 (*d*, 1H, Ar-H, *J* = 8 Hz), 8.44 (*s*, 1H, Ar-H), 8.59 (*d*, 1H, Ar-H, *J* = 8 Hz), 13.09 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 24.59 (2C), 25.28, 32.37 (2C), 47.47, 55.95, 68.51, 110.87, 114.51, 118.81, 120.26, 123.23, 125.41, 127.38, 129.64, 130.10, 131.86, 137.85, 148.31, 149.35, 149.55, 155.38, 166.46, 167.75; Anal. Calcd. For $C_{25}H_{26}N_2O_5$ (434.48 g/mol): C, 69.11; H, 6.03; N, 6.45; Found: C, 72.42; H, 6.25; N, 6.67.

1.5.40. 2-(4-(2-((1s,3s)-Adamantan-1-ylamino)-2-oxoethoxy)-3-methoxyphenyl)quinoline-4-carboxylic acid × 1H_2O (**5t**): White powder; yield: 0.180g (37%); mp 226-227 ºC; IR (KBr, cm^{-1}): 3443, 3389, 2908, 1625, 1549, 1515, 1255, 1143, 778; ^{1}H NMR (200 MHz, DMSO-d_6): 1.63 (*s*, 6H, Ad), 1.97-2.02 (*m*, 9H, Ad), 3.96 (*s*, 3H, CH_3), 4.51 (*s*, 2H, CH_2), 7.09 (*d*, 1H, Ar-H, *J* = 8.6 Hz), 7.35 (*s*, 1H, NH), 7.63-7.71(*m*, 1H, Ar-H), 7.79-7.88 (*m*, 2H, Ar-H), 7.94 (*d*, 1H, Ar-H, *J* = 1.8 Hz), 8.14 (*d*, 1H, Ar-H, *J* = 8 Hz), 8.45 (*s*, 1H, Ar-H), 8.59 (*dd*, 1H, Ar-H, *J* = 8.4 Hz and *J* =1 Hz), 13.98 (*bs*, 1H, COOH); ^{13}C NMR (50 MHz, DMSO-d_6): 28.98 (3C), 36.06 (3C), 41.13 (3C), 51.06, 56.00, 68.50, 110.87, 114.44, 118.86, 120.31, 123.25, 125.41, 127.39, 129.65, 130.10, 131.82, 137.73, 148.34, 149.28, 149.47, 155.39, 166.47, 167.73; Anal. Calcd. For $C_{29}H_{30}N_2O_5 \times 1H_2O$ (504.58 g/mol): C, 69.03; H, 6.39; N, 5.55; Found: C, 69.60; H, 6.24; N, 5.56.

2. The bioactive conformations of 5a-5t as *h*DHODH inhibitors

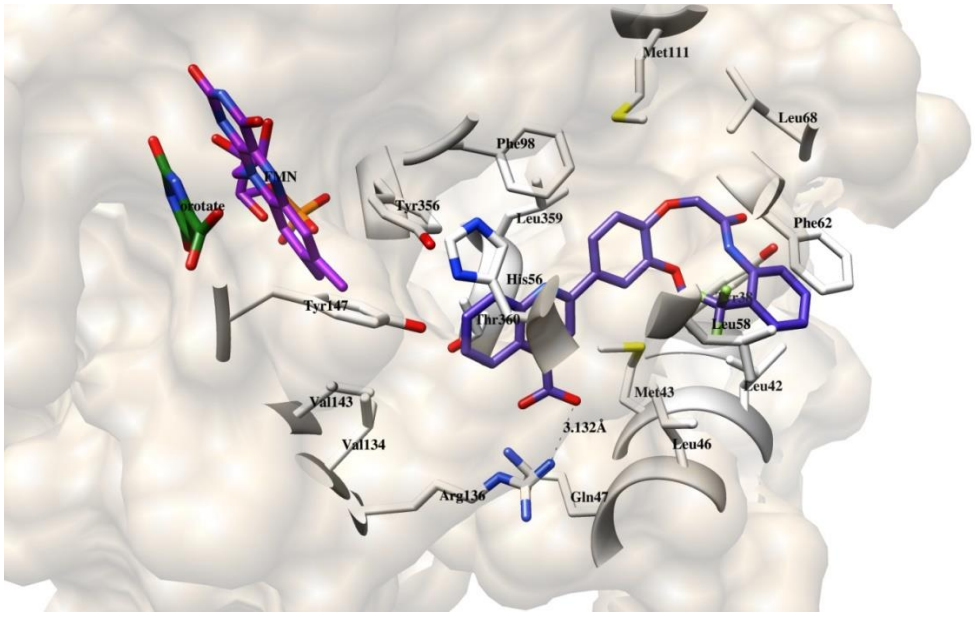

Fig. S1. The bioactive conformation of **5k** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

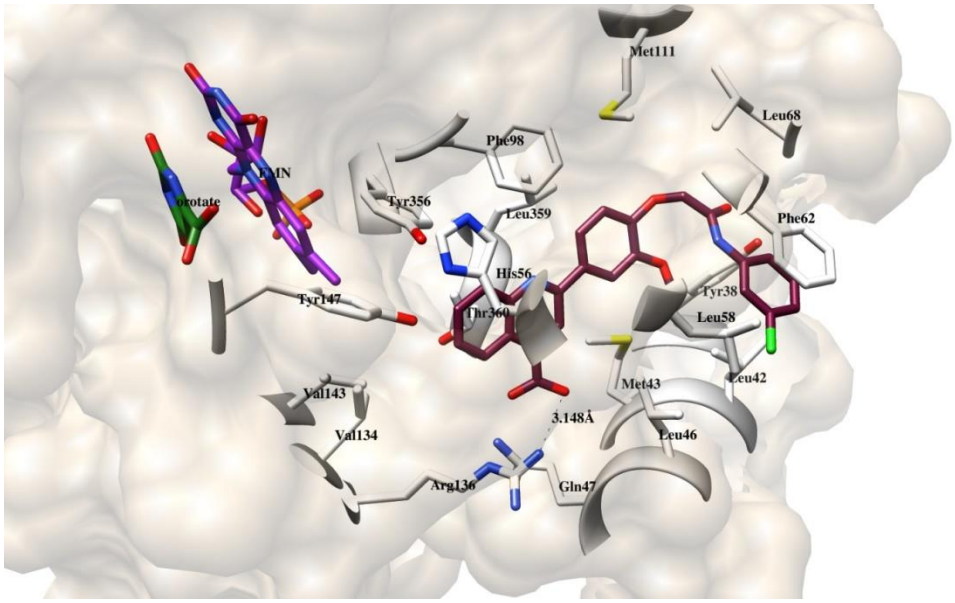

Fig. S2. The bioactive conformation of **5i** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

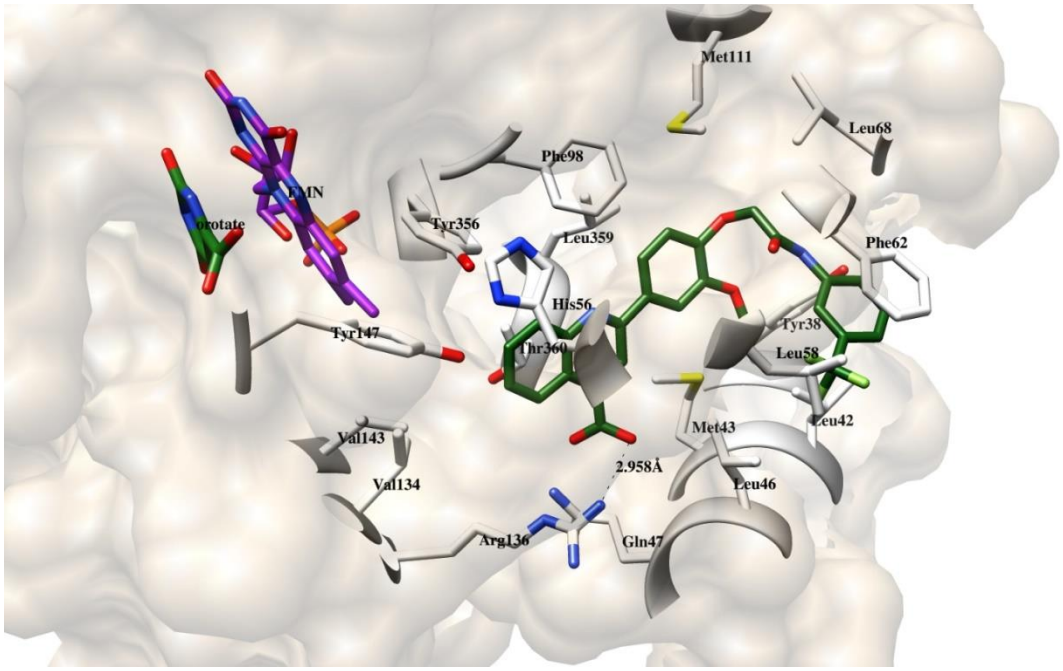

Fig. S3. The bioactive conformation of **5l** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

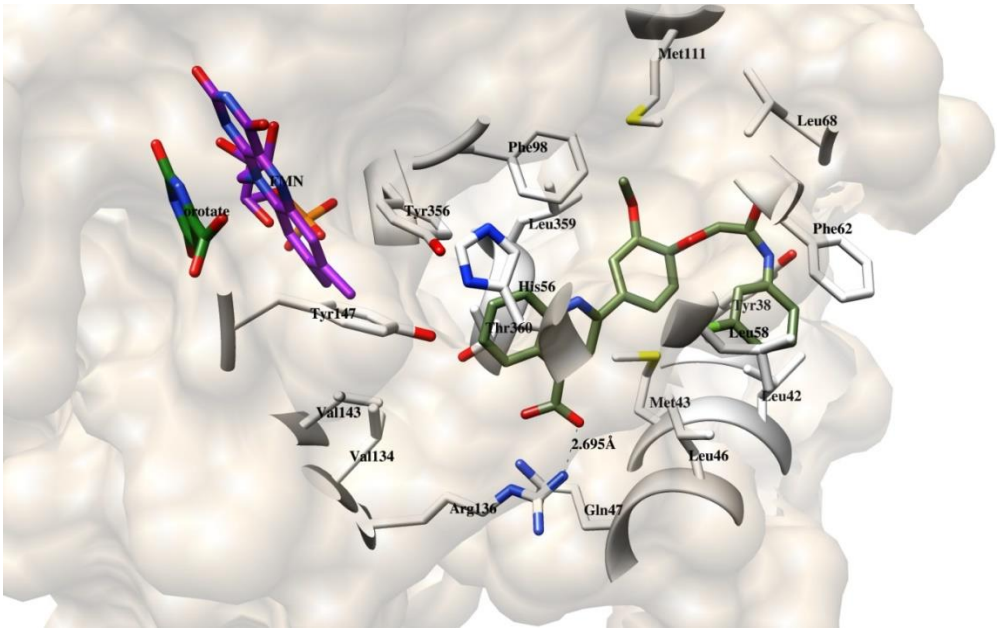

Fig. S4. The bioactive conformation of **5e** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

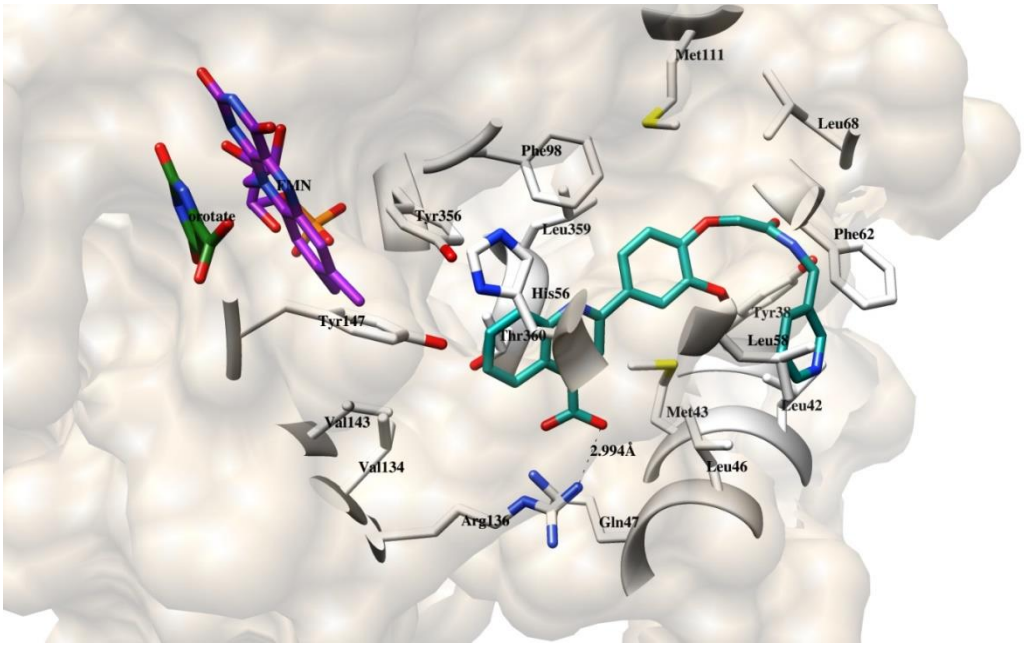

Fig. S5. The bioactive conformation of **5o** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

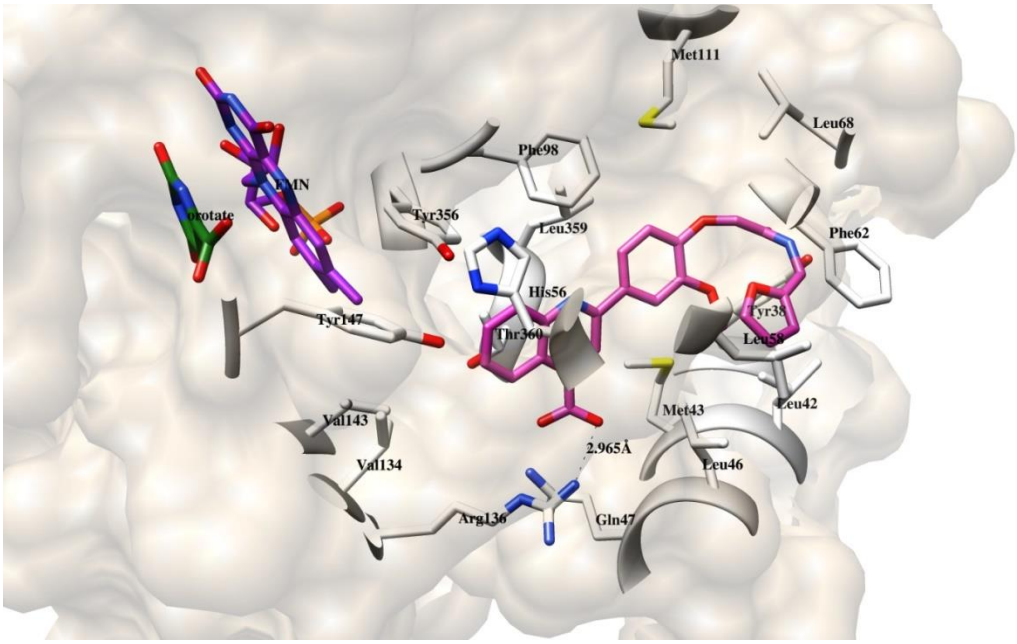

Fig. S6. The bioactive conformation of **5p** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

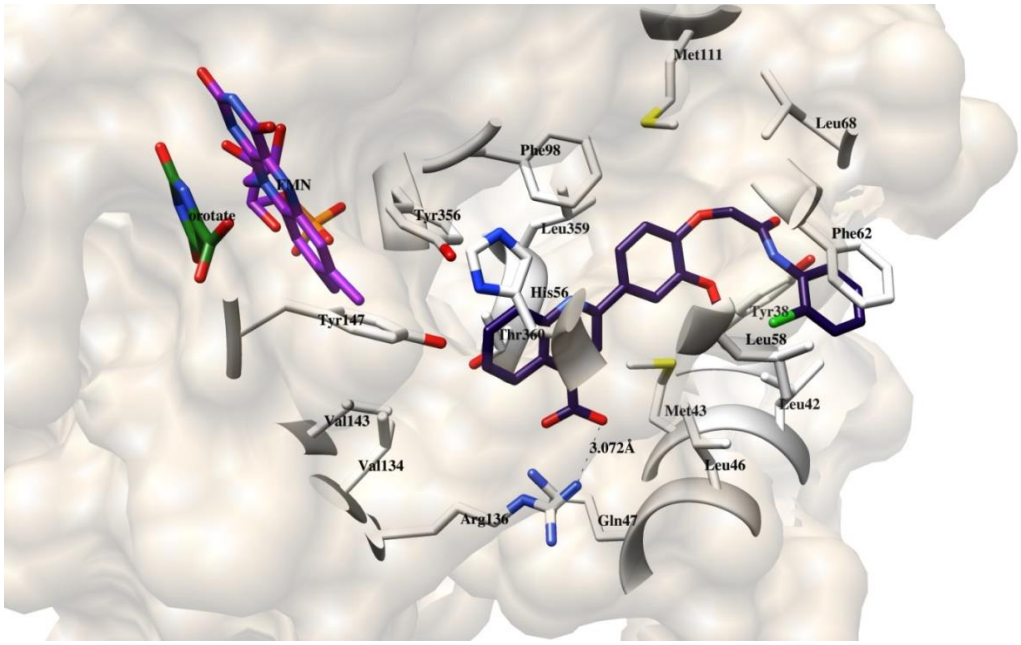

Fig. S7. The bioactive conformation of **5h** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

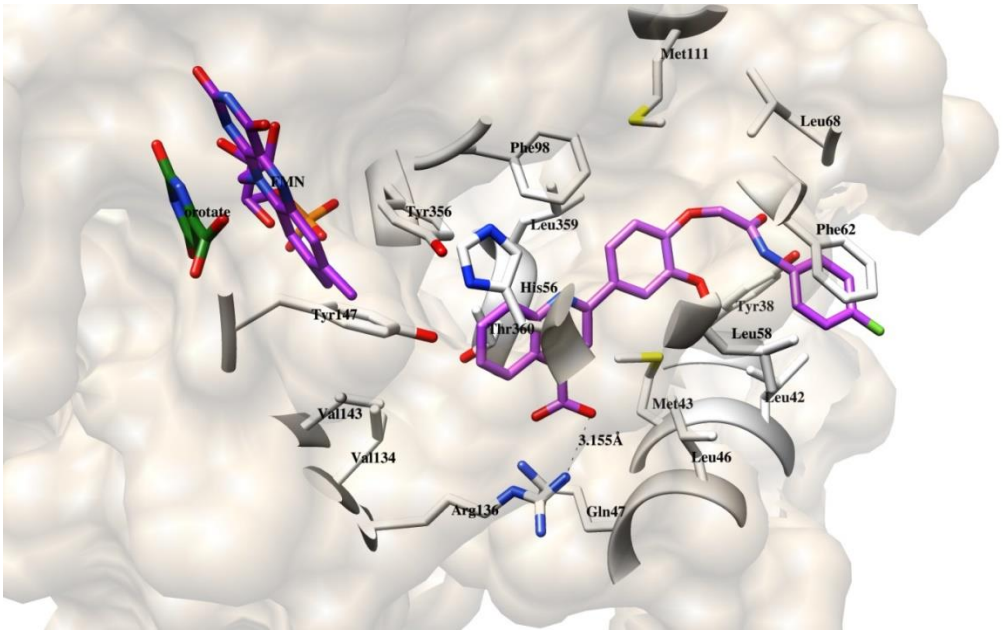

Fig. S8. The bioactive conformation of **5g** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

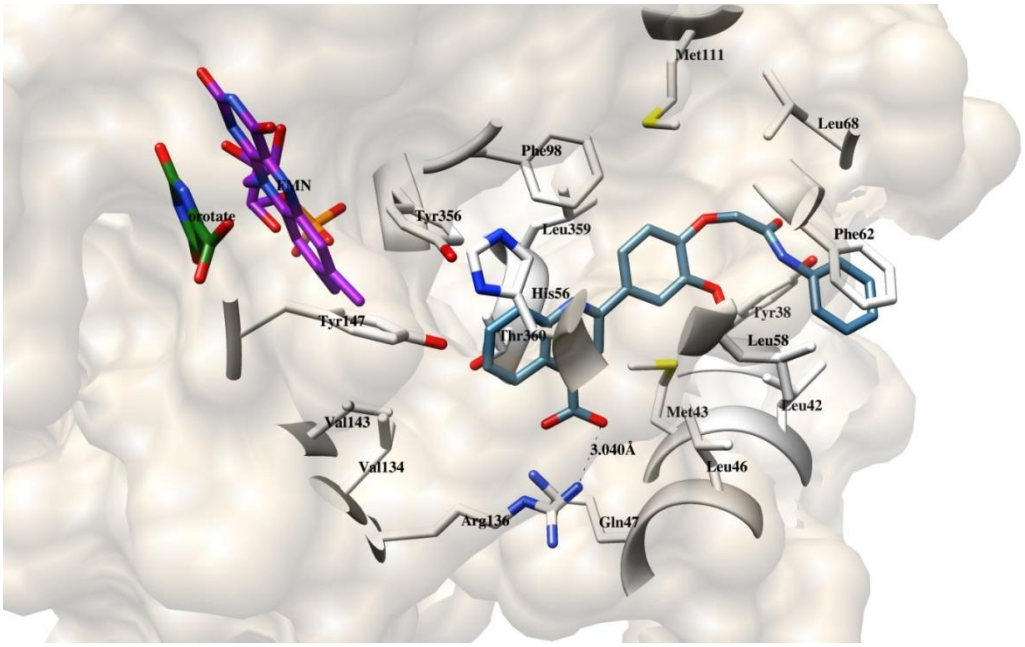

Fig. S9. The bioactive conformation of **5s** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

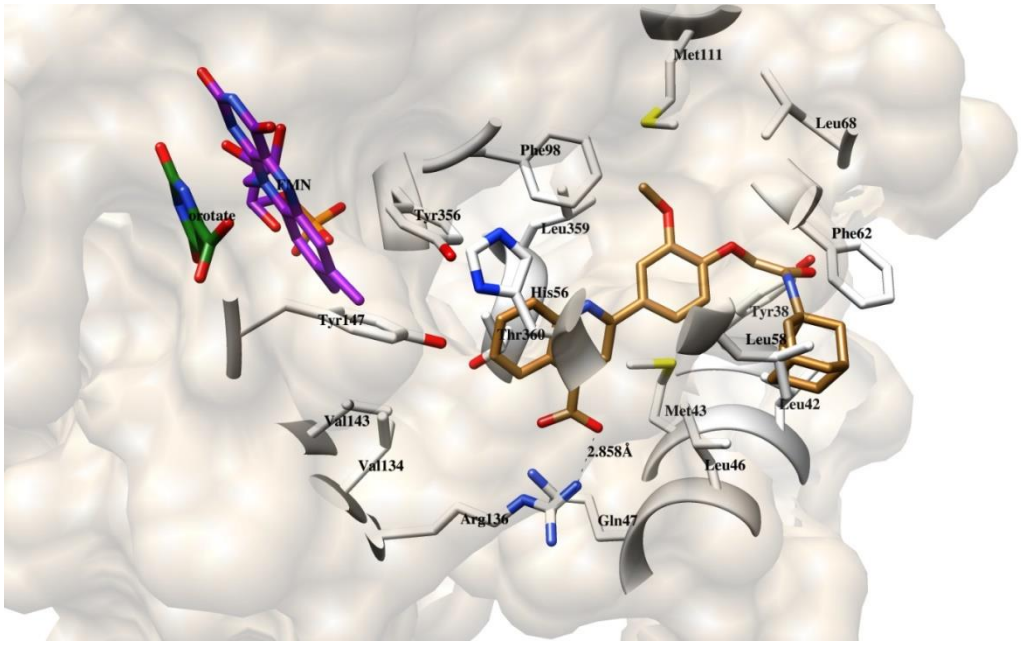

Fig. S10. The bioactive conformation of **5t** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

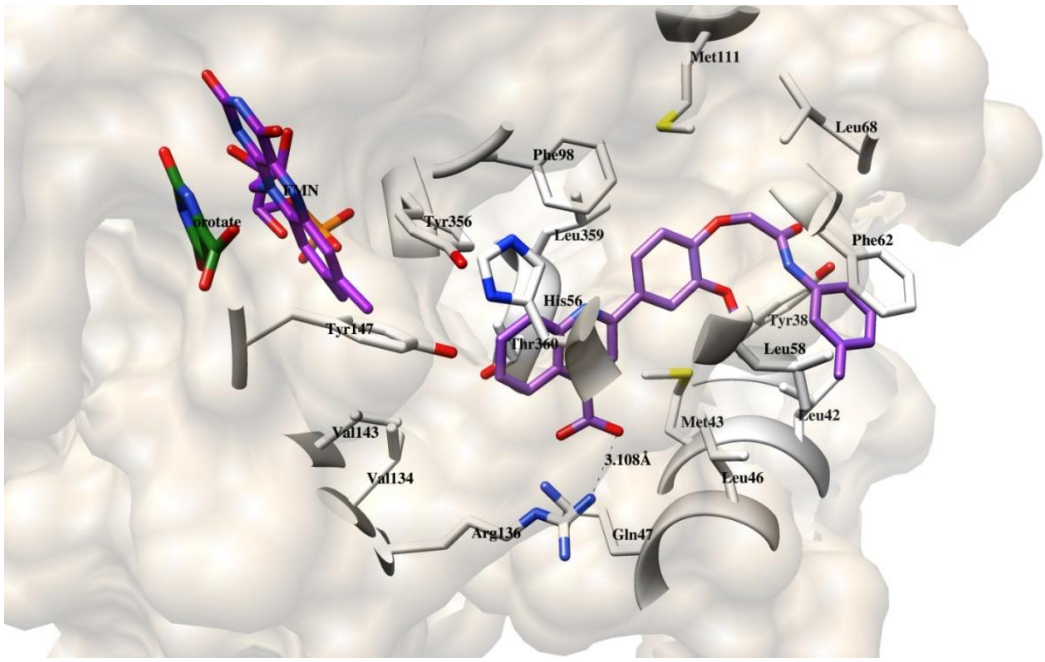

Fig. S11. The bioactive conformation of **5c** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

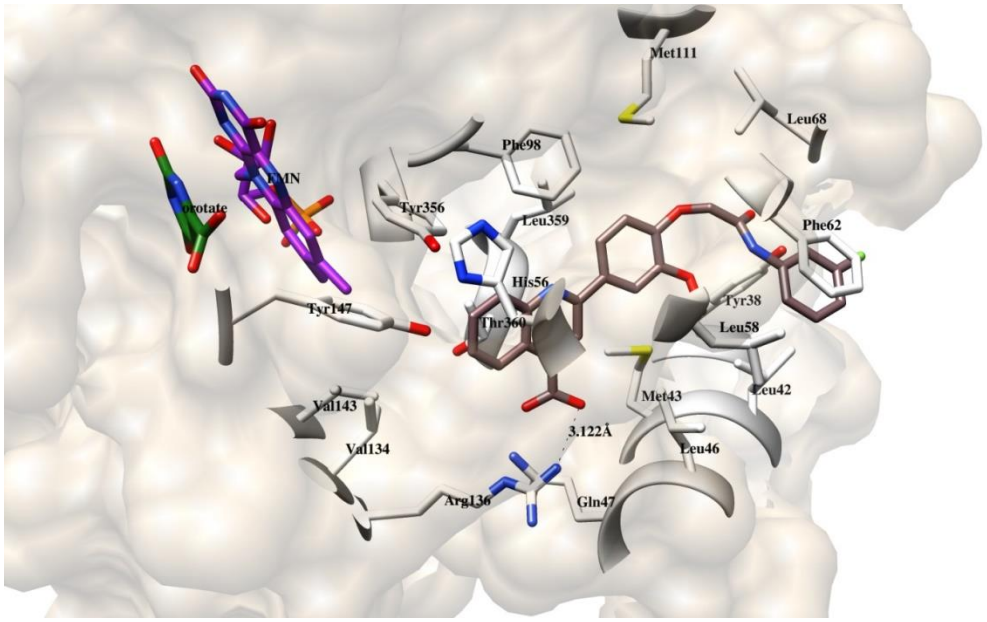

Fig. S12. The bioactive conformation of **5f** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

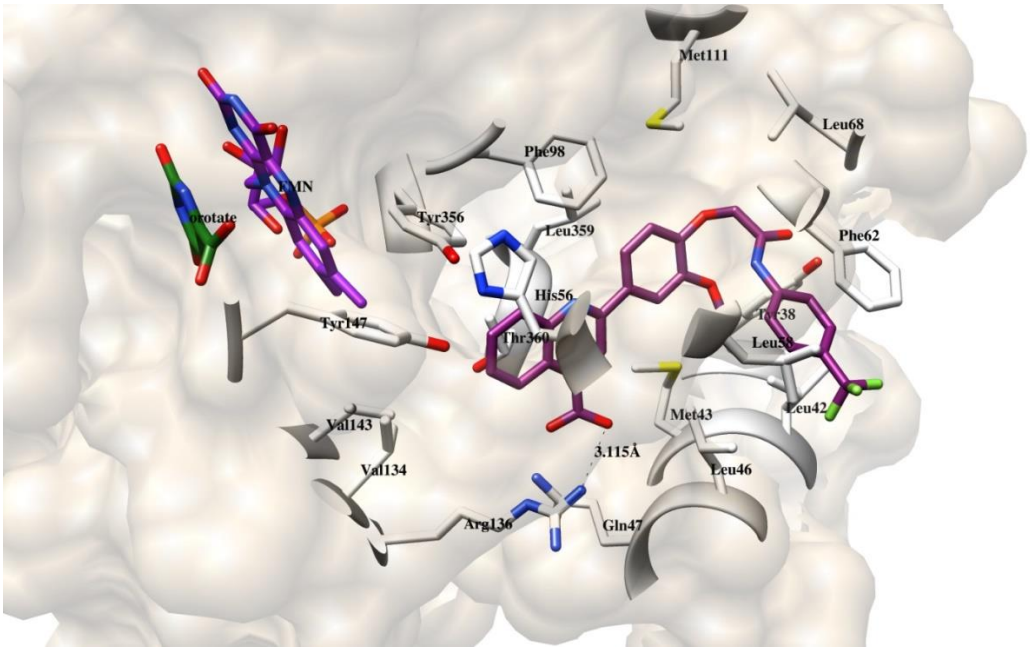

Fig. S13. The bioactive conformation of **5m** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

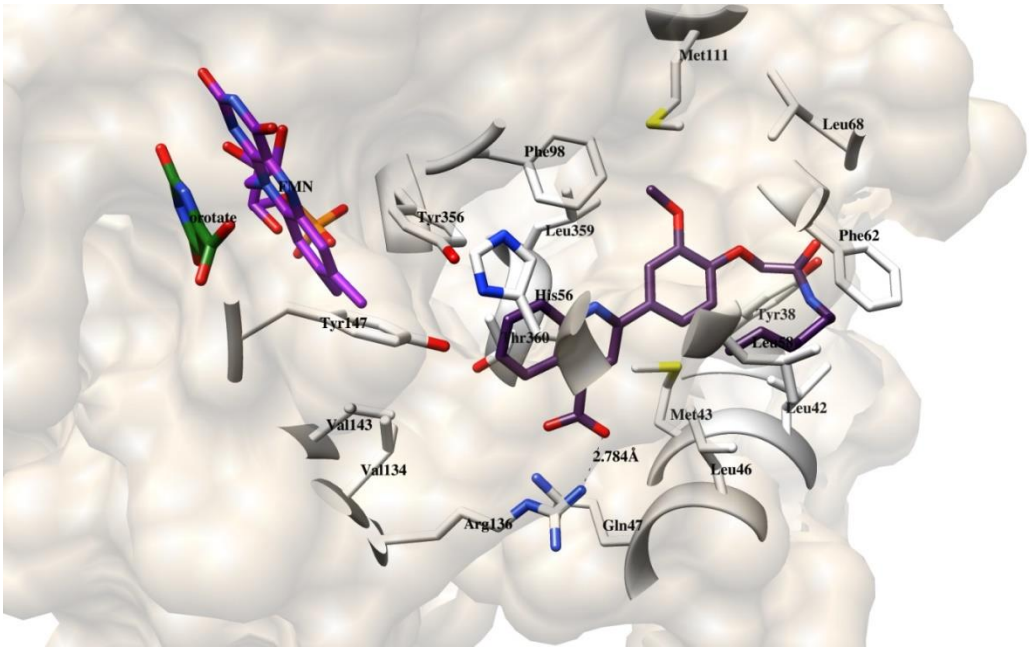

Fig. S14. The bioactive conformation of **5r** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

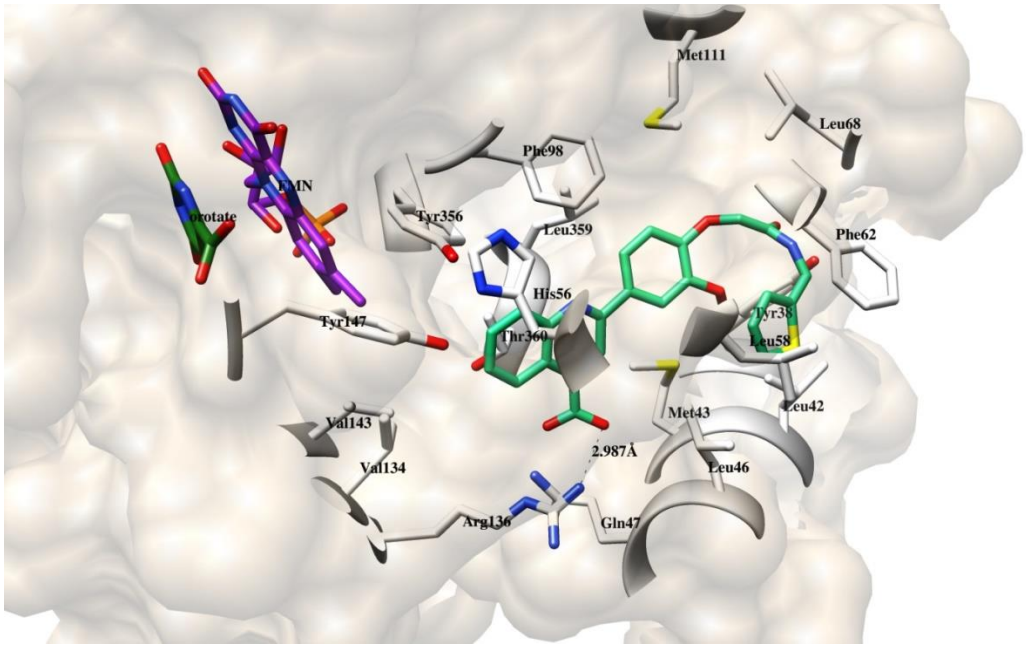

Fig. S15. The bioactive conformation of **5q** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

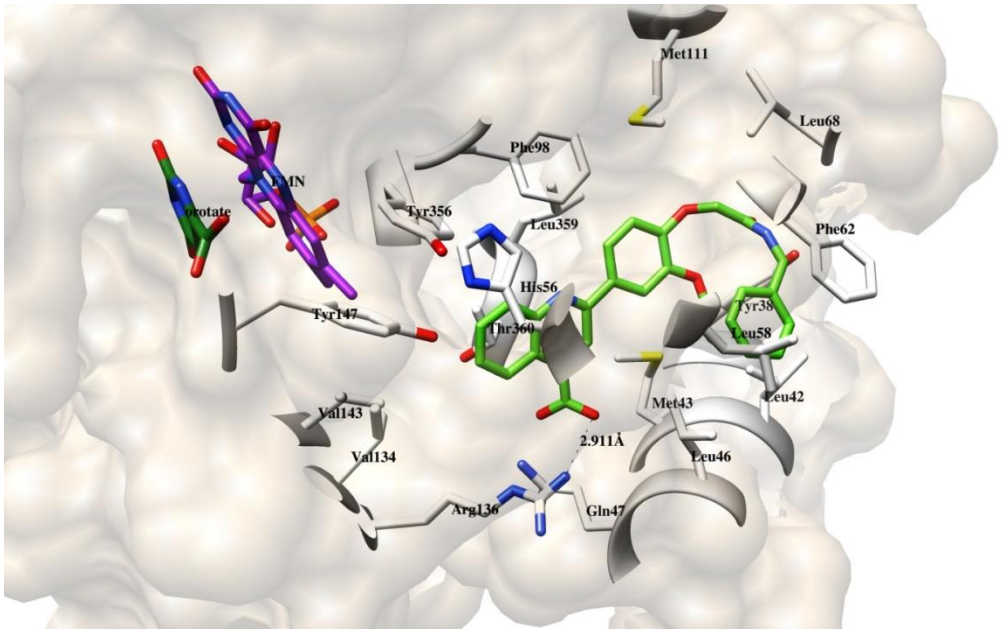

Fig. S16. The bioactive conformation of **5n** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

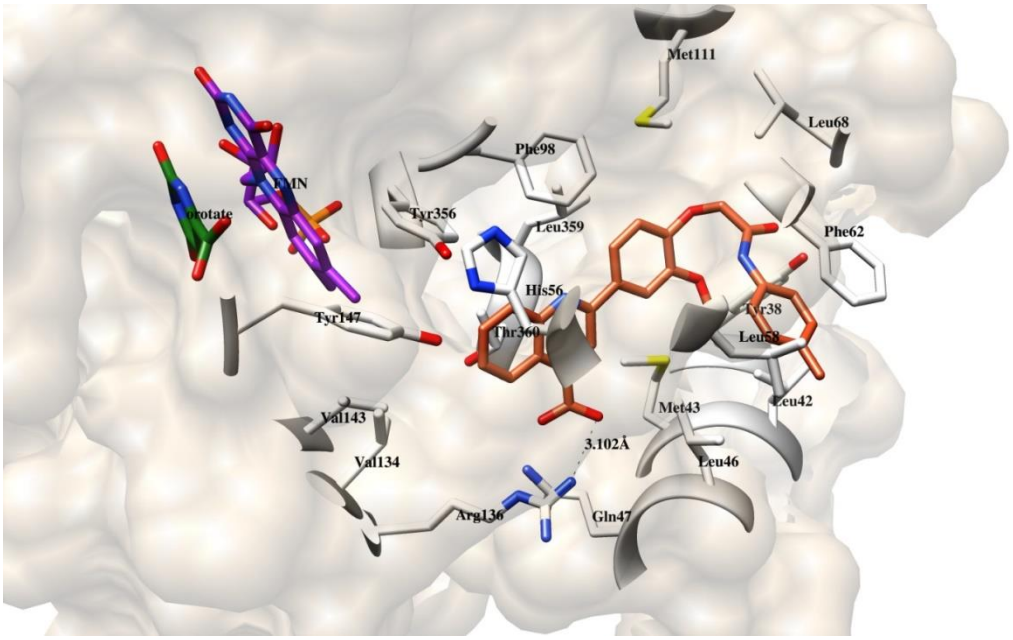

Fig. S17. The bioactive conformation of **5d** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

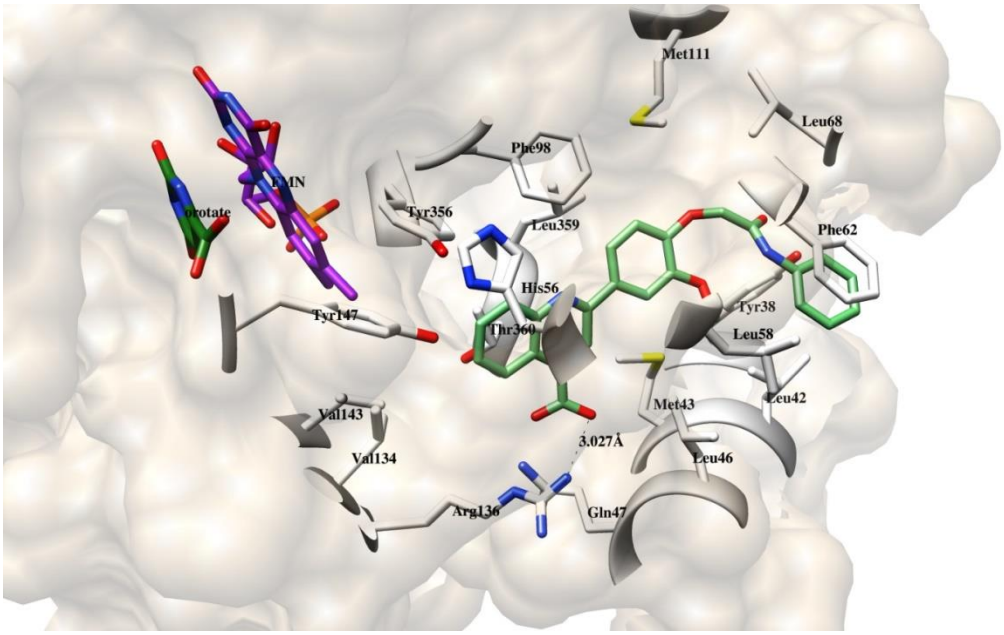

Fig. S18. The bioactive conformation of **5a** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

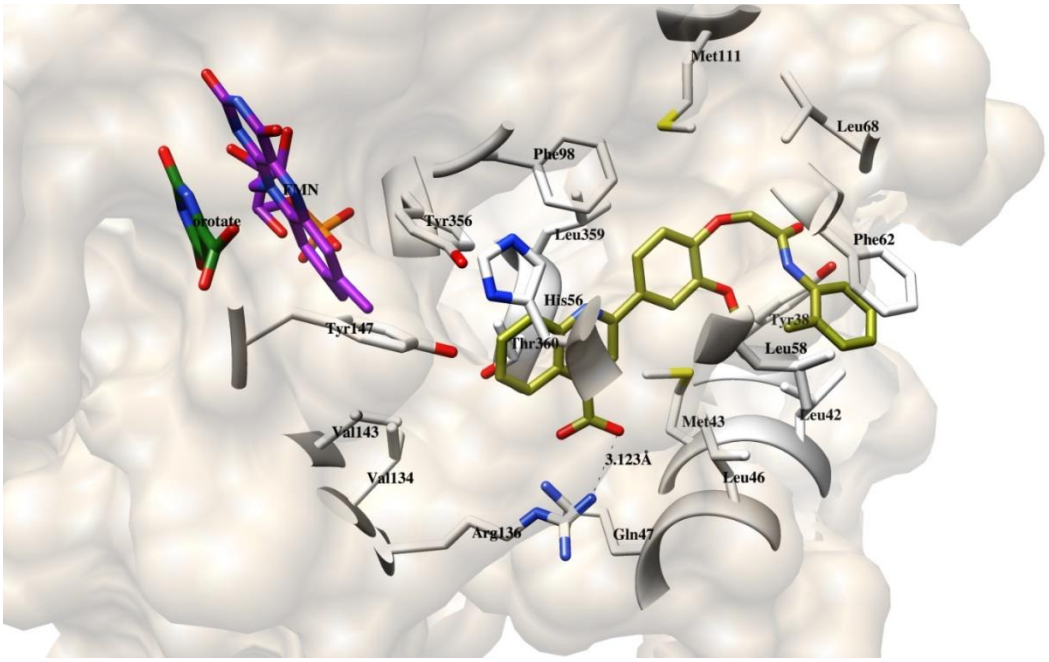

Fig. S19. The bioactive conformation of **5b** as *h*DHODH inhibitor. For the clarity of presentation, the hydrogens were omitted, the N-terminal amino acids, orotate as *h*DHODH substrate, and FMN as *h*DHODH coenzyme were depicted, whereas the remaining of the enzyme is illustrated with the surface. The established hydrogen bonds are presented with black lines.

Copies of ^{1}H and ^{13}C NMR spectra for 4a-4t

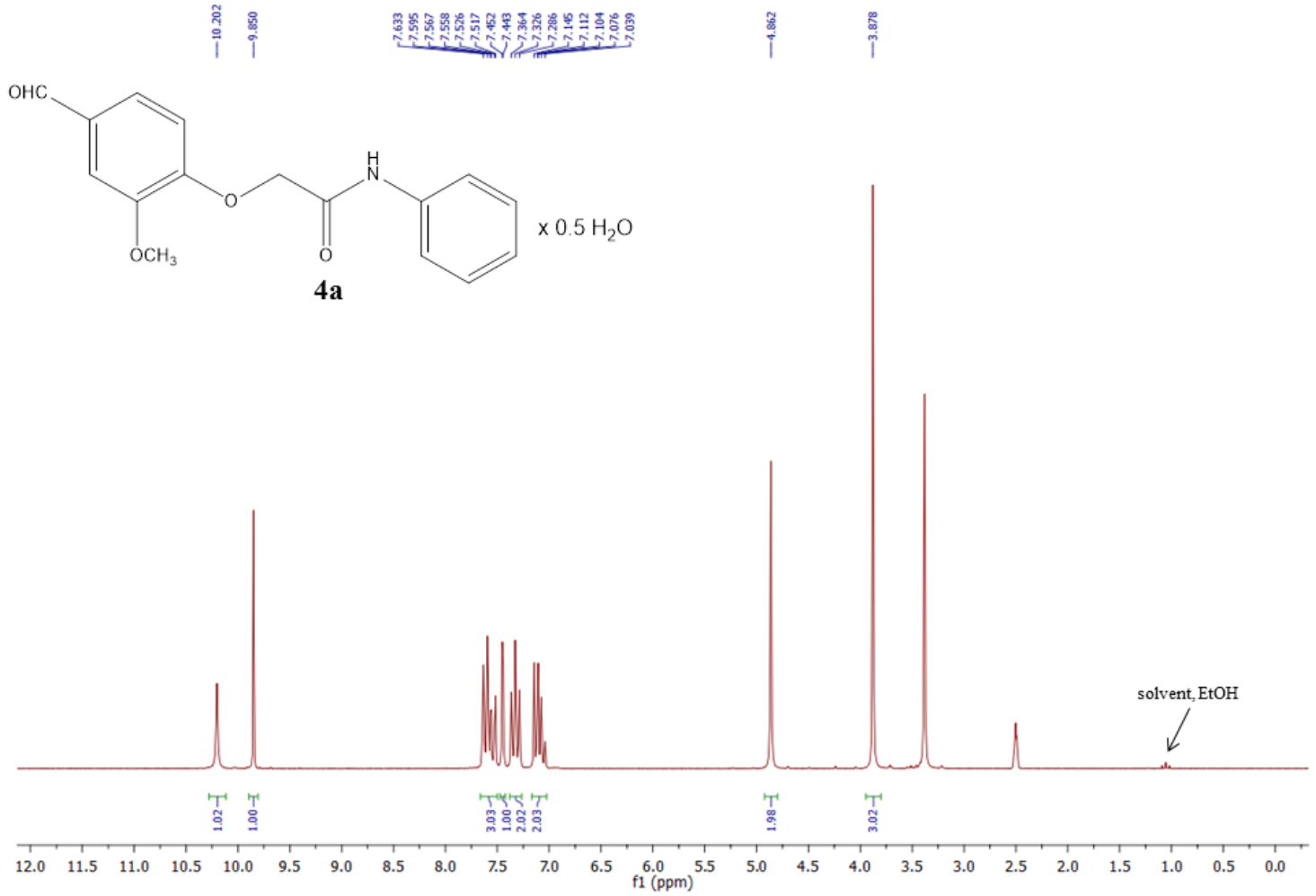

Figure S20. ^{1}H NMR spectrum of **4a** in DMSO-d_6 (200 MHz).

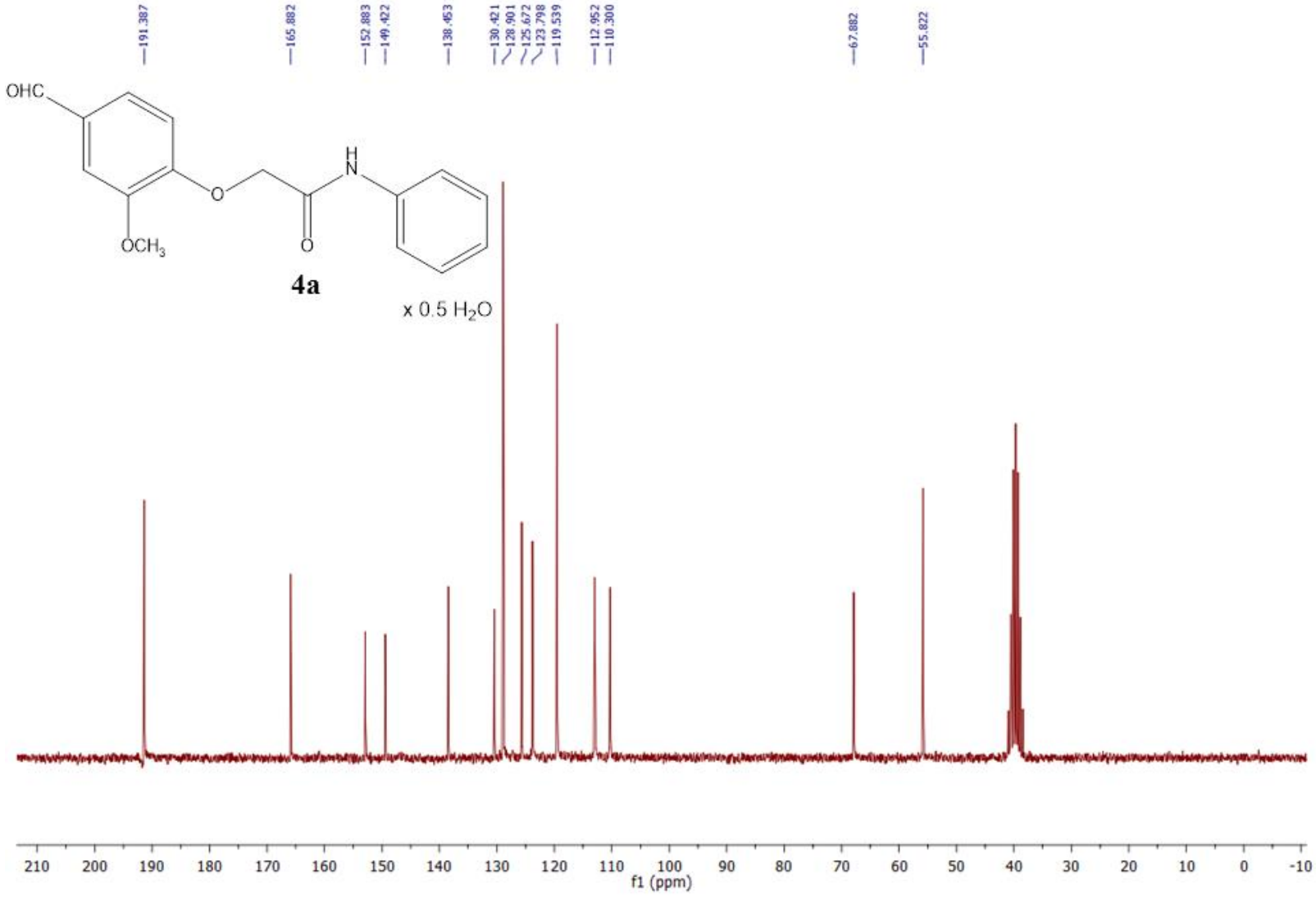

Figure S21. ^{13}C NMR spectrum of **4a** in DMSO-d_6 (50 MHz).

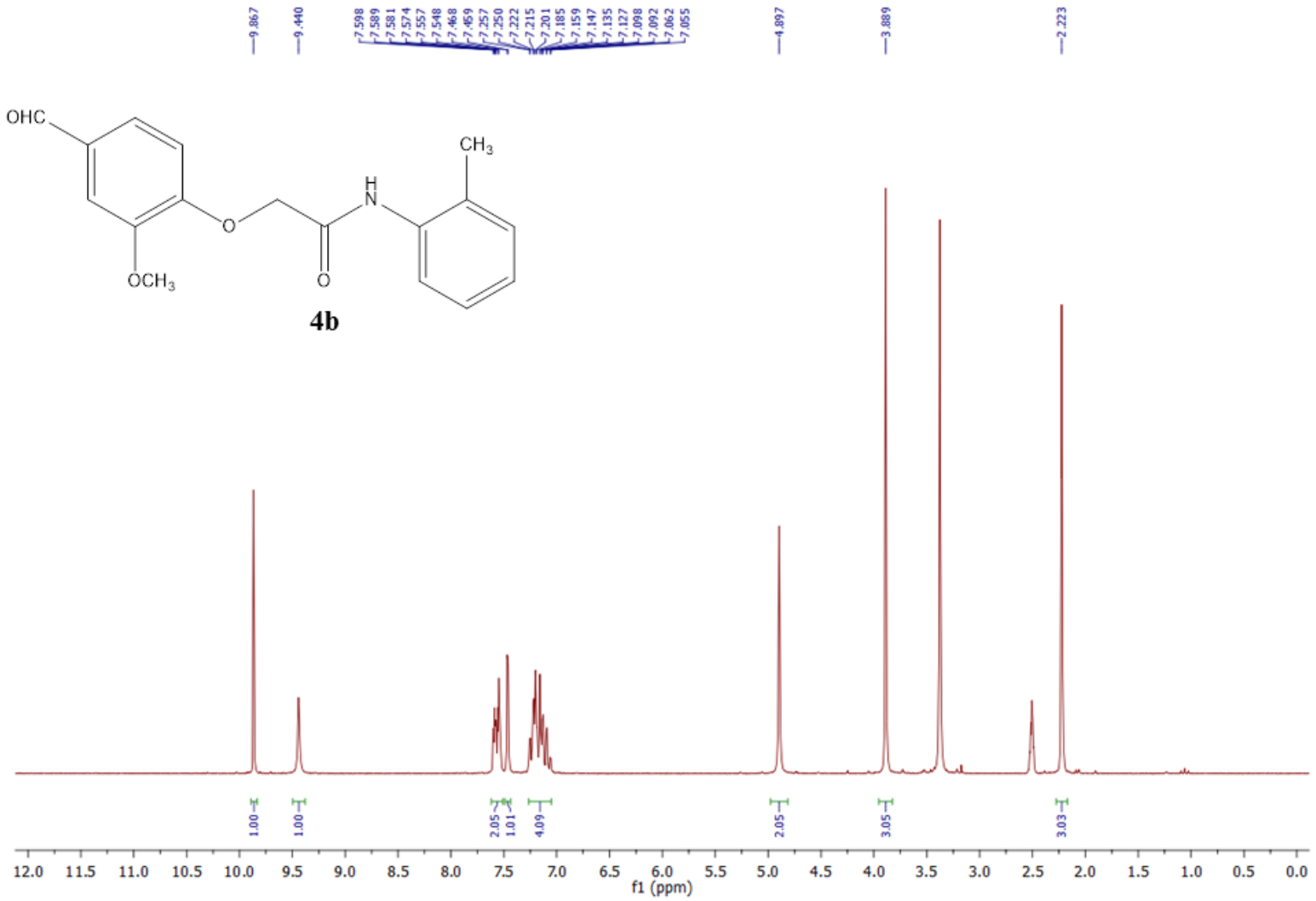

Figure S22. ^{1}H NMR spectrum of **4b** in DMSO-d_6 (200 MHz).

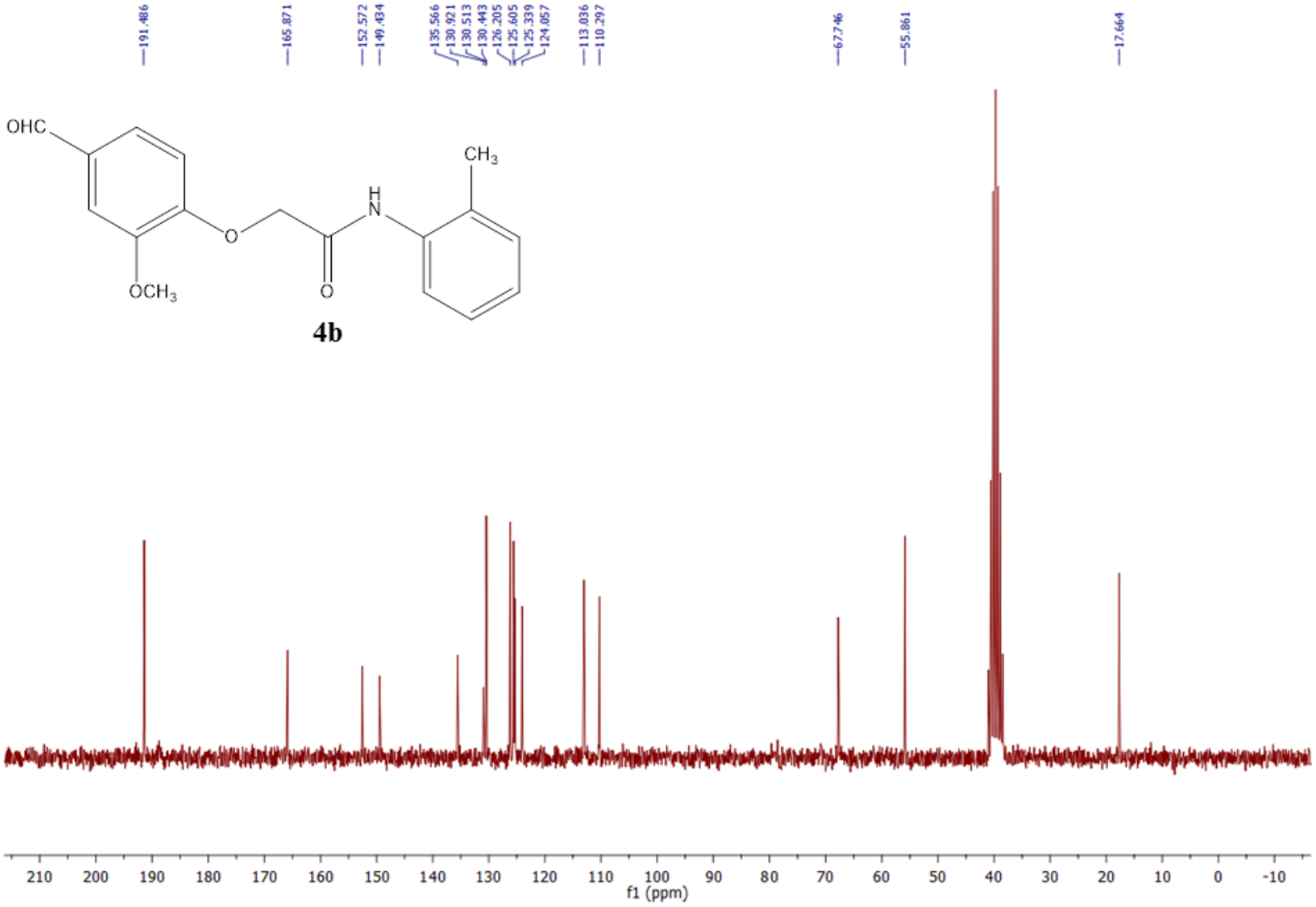

Figure S23. ^{13}C NMR spectrum of **4b** in DMSO-d_6 (50 MHz).

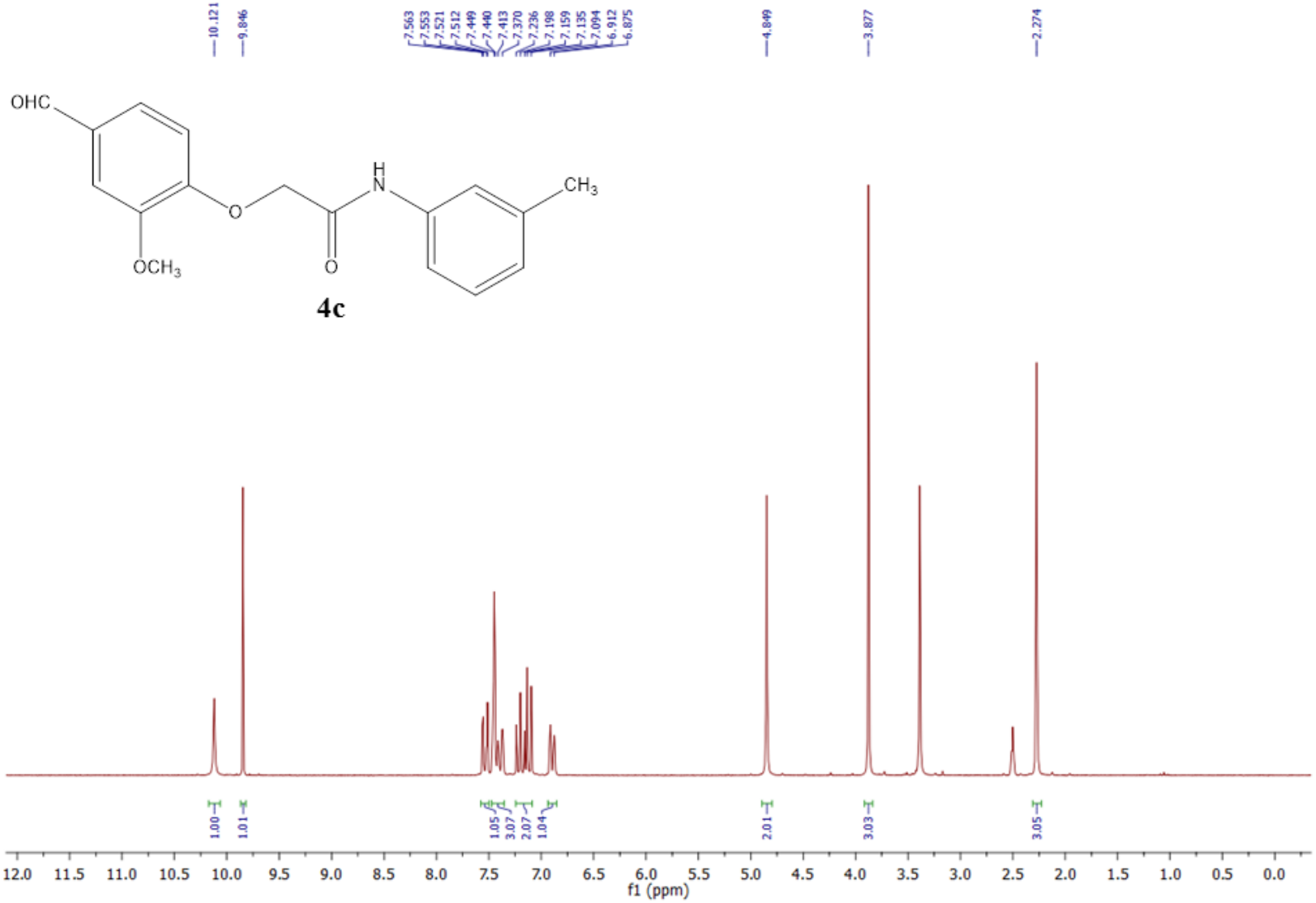

Figure S24. ^{1}H NMR spectrum of **4c** in DMSO-d_6 (200 MHz).

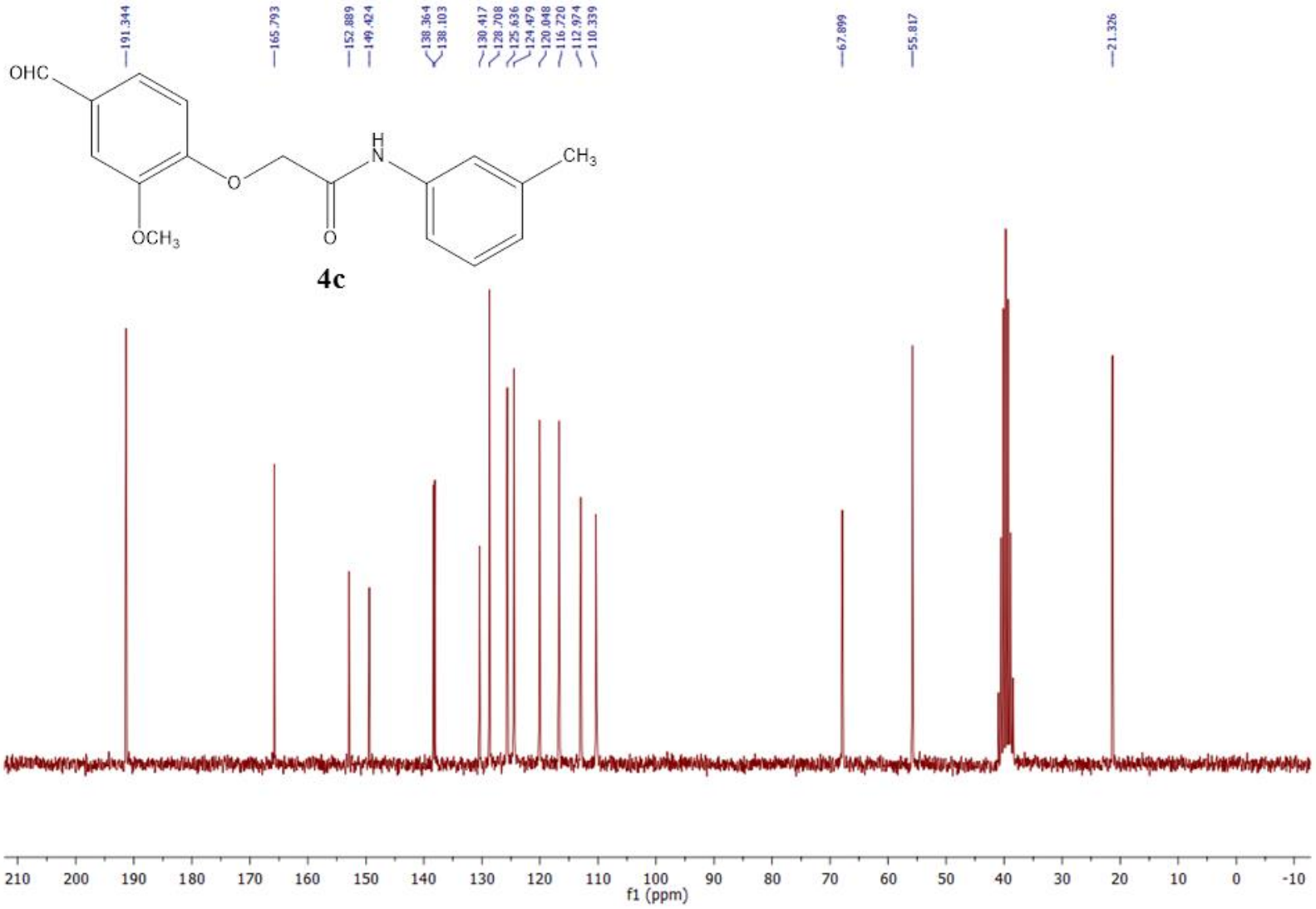

Figure S25. ^{13}C NMR spectrum of **4c** in DMSO-d_6 (50 MHz).

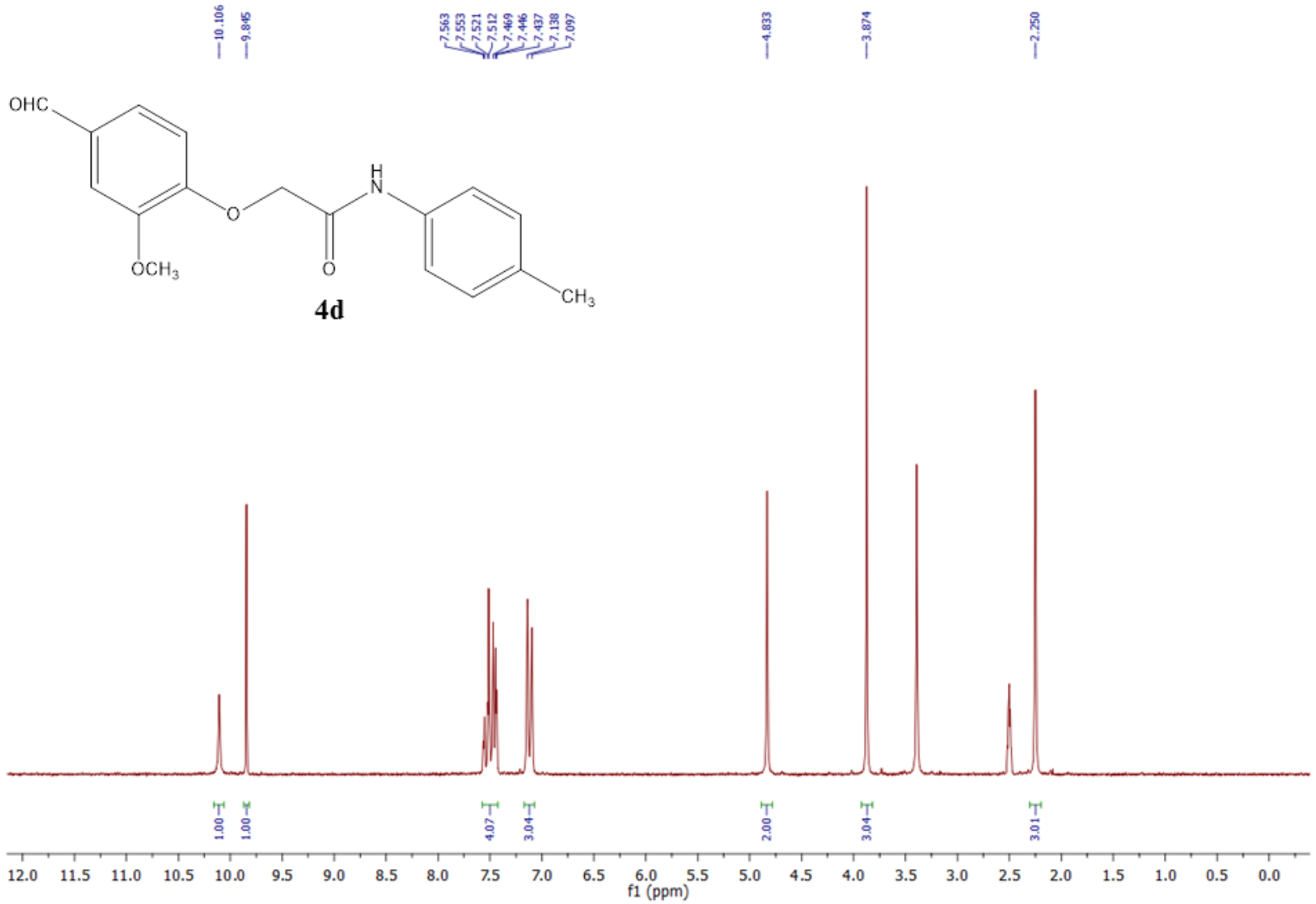

Figure S26. ^{1}H NMR spectrum of **4d** in DMSO-d_6 (200 MHz).

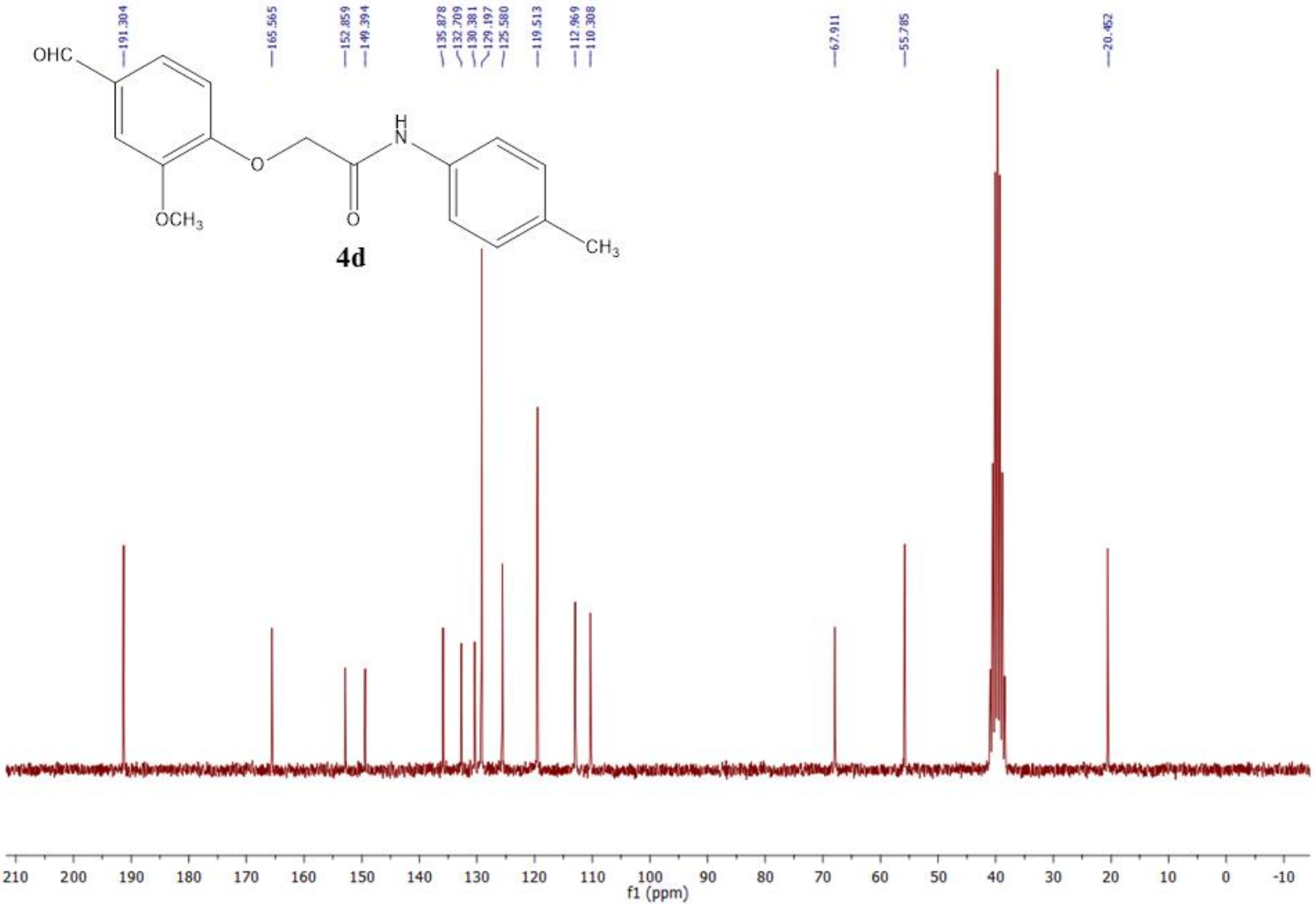

Figure S27. ^{13}C NMR spectrum of **4d** in DMSO-d_6 (50 MHz).

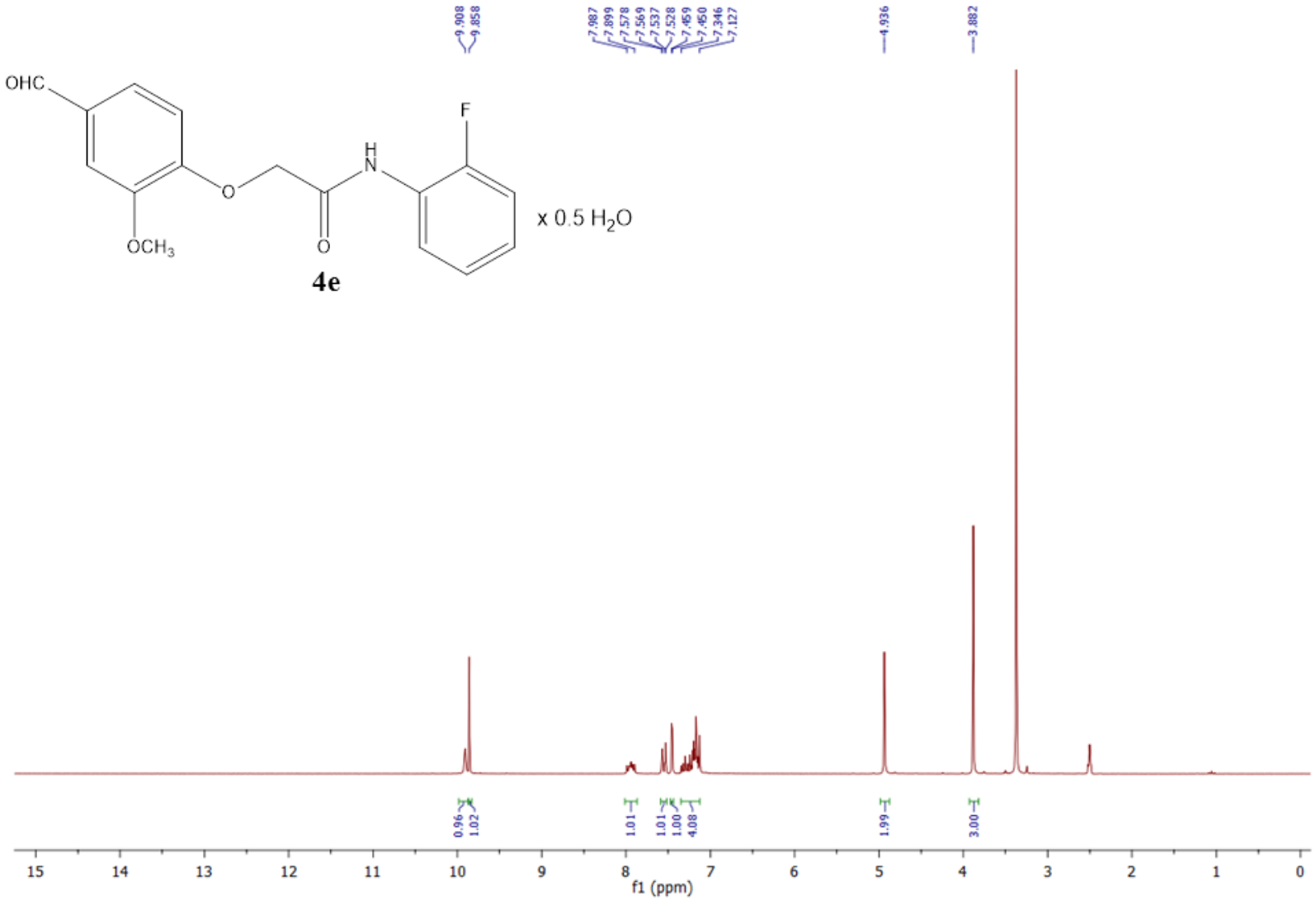

Figure S28. ^{1}H NMR spectrum of **4e** in DMSO-d_6 (200 MHz).

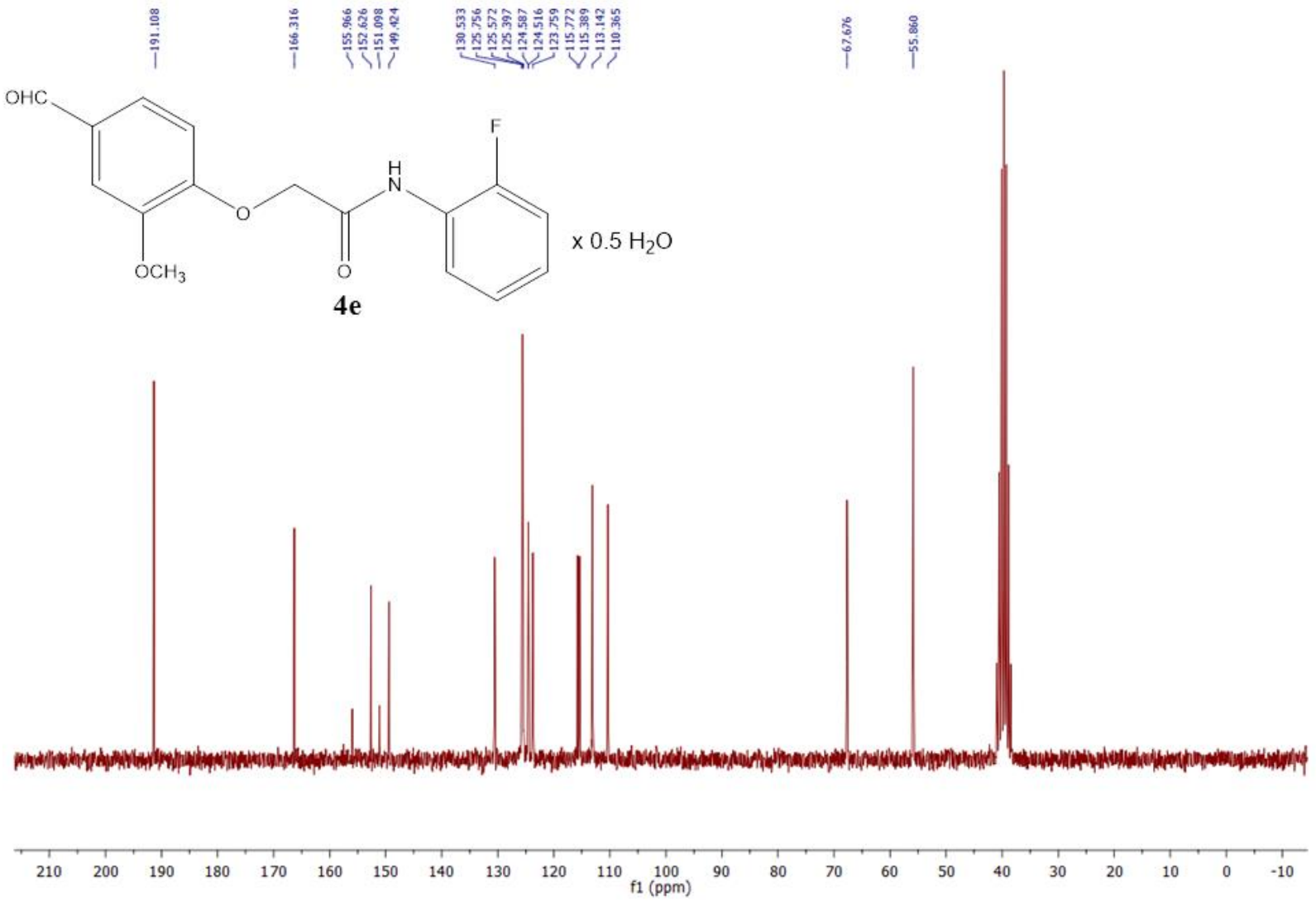

Figure S29. ^{13}H NMR spectrum of **4e** in DMSO-d_6 (50 MHz).

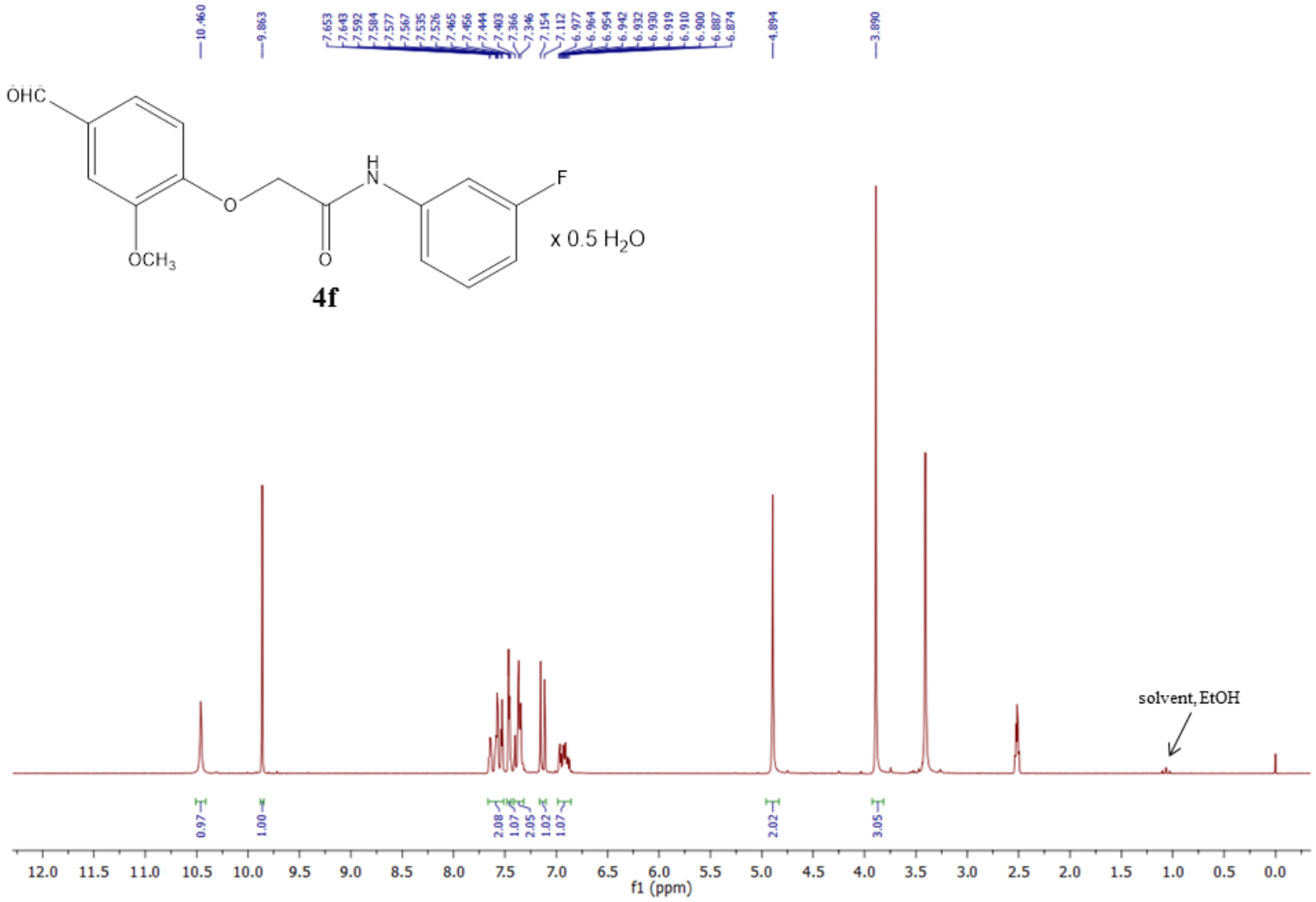

Figure S30. ^{1}H NMR spectrum of **4f** in DMSO-d_6 (200 MHz).

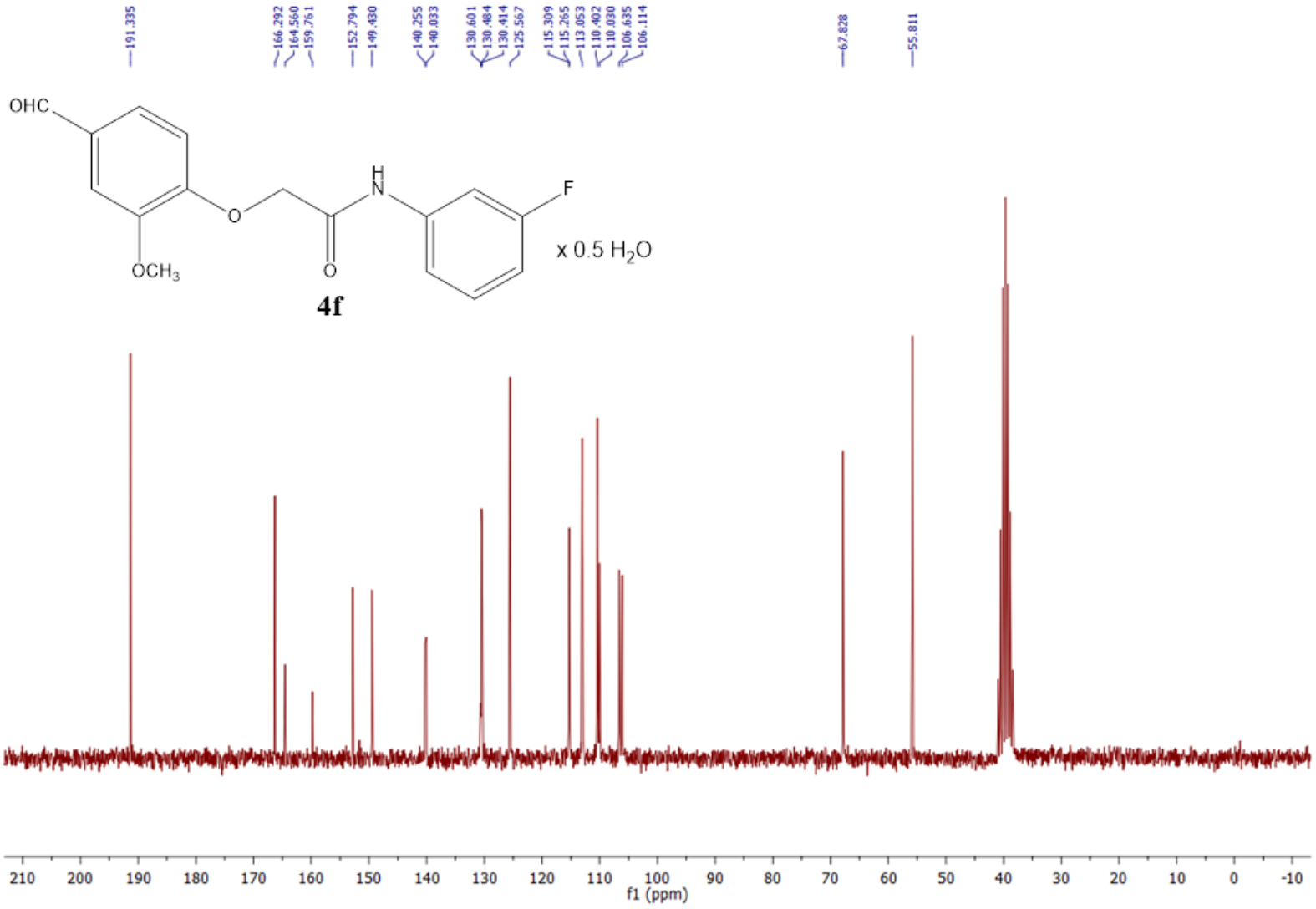

Figure S31. ^{13}C NMR spectrum of **4f** in DMSO-d_6 (50 MHz).

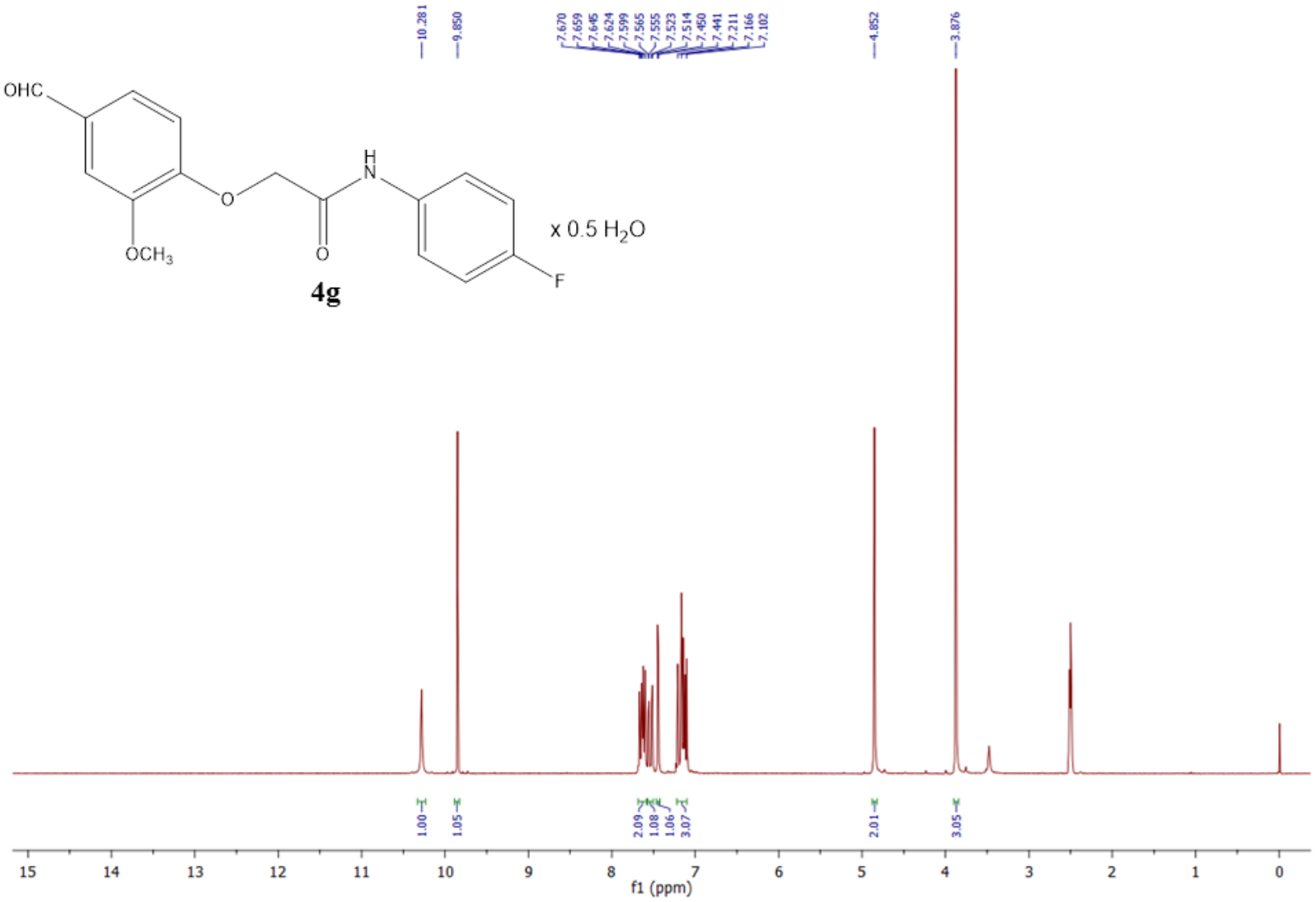

Figure S32. ^{1}H NMR spectrum of **4g** in DMSO-d_6 (200 MHz).

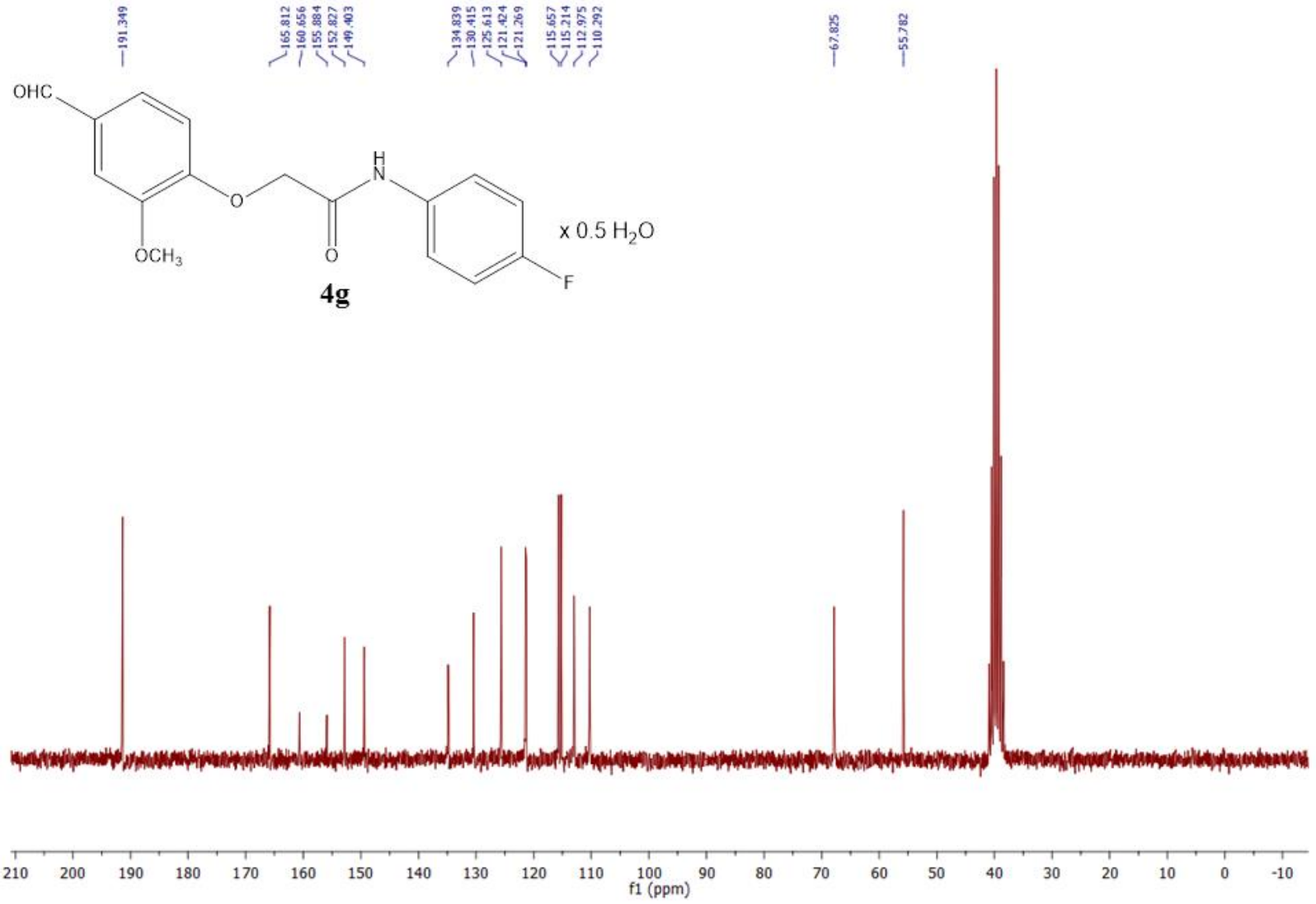

Figure S33. ^{13}C NMR spectrum of **4g** in DMSO-d_6 (50 MHz).

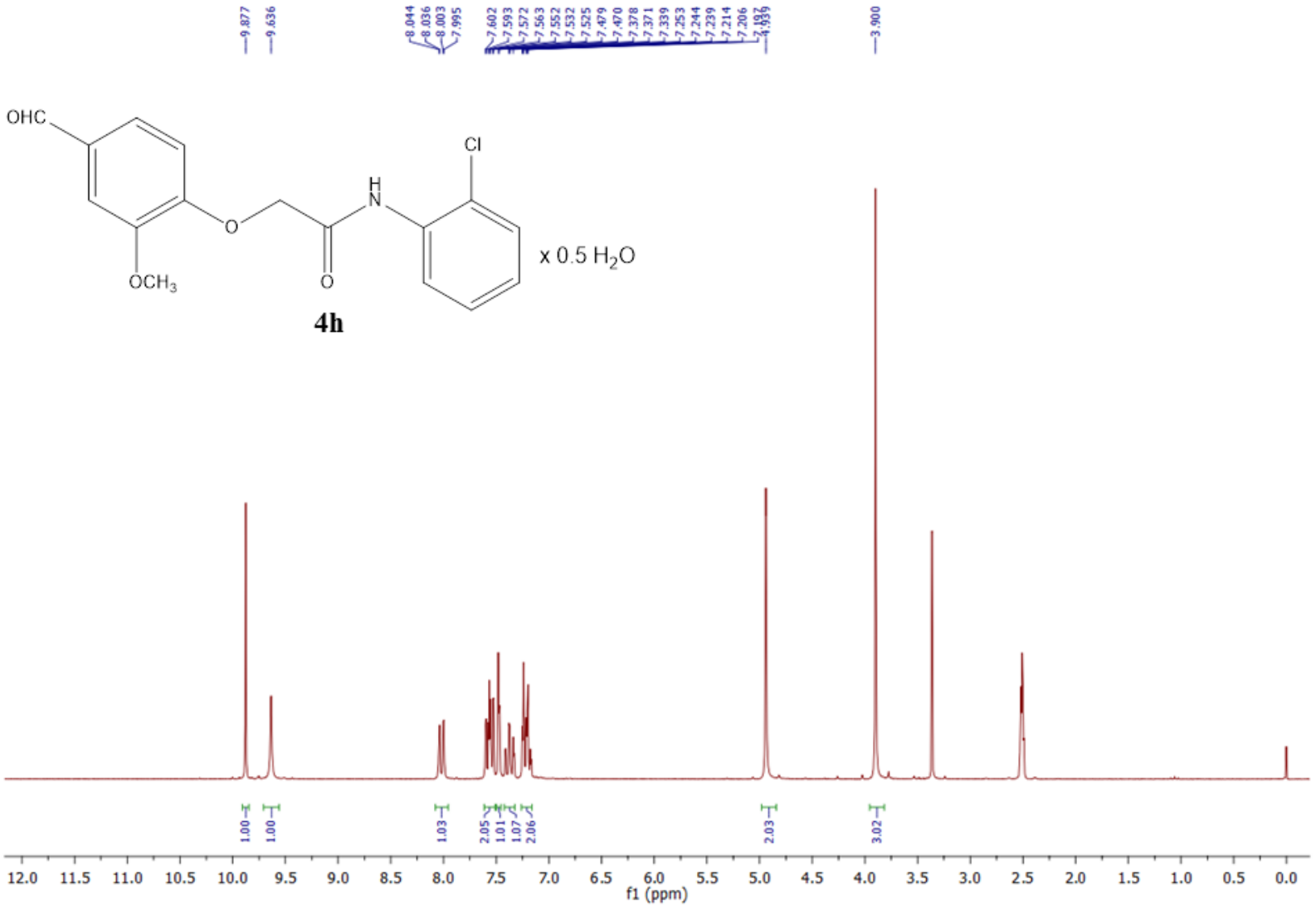

Figure S34. ^{1}H NMR spectrum of **4h** in DMSO-d_6 (200 MHz).

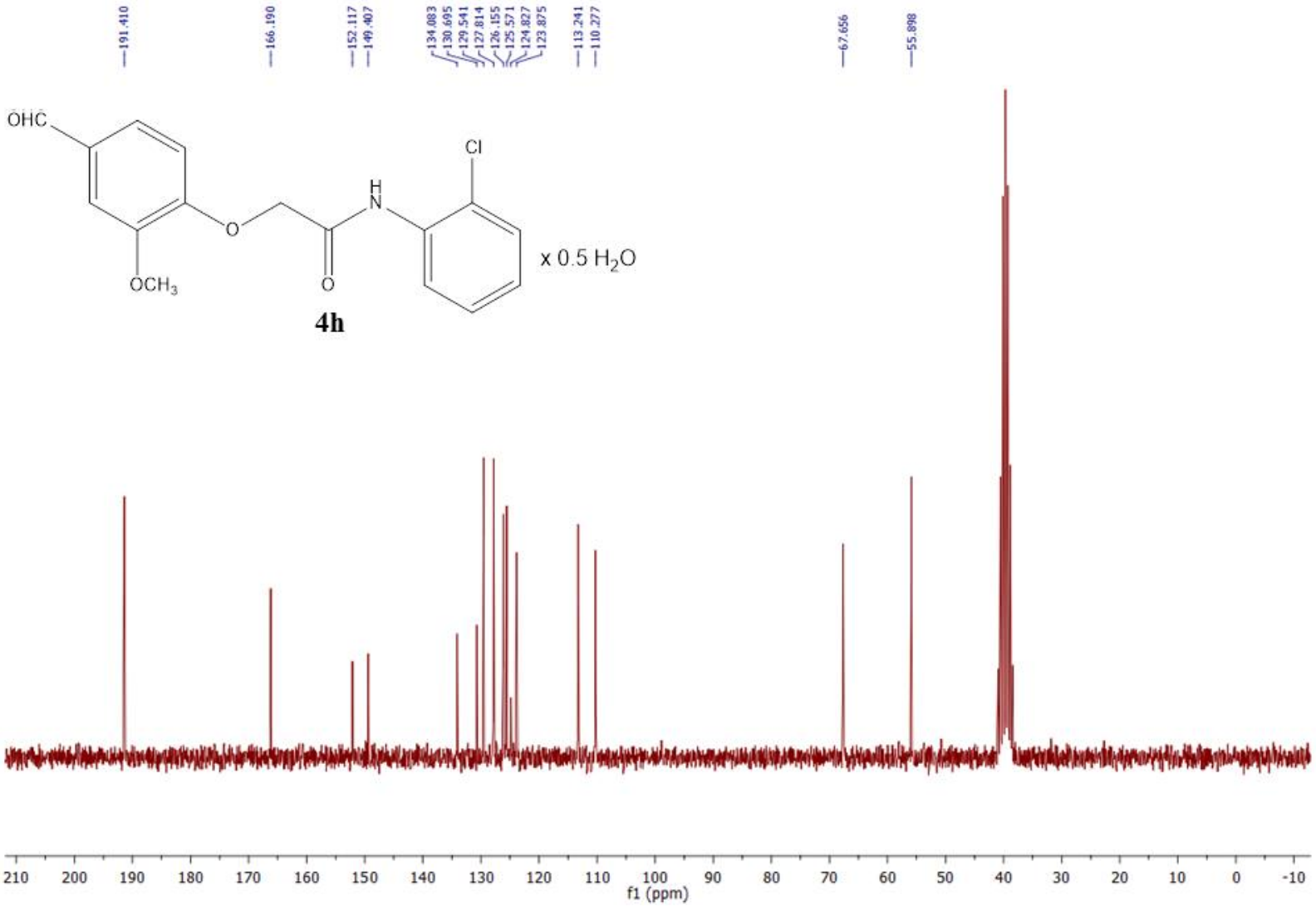

Figure S35. ^{13}C NMR spectrum of **4h** in DMSO-d_6 (50 MHz).

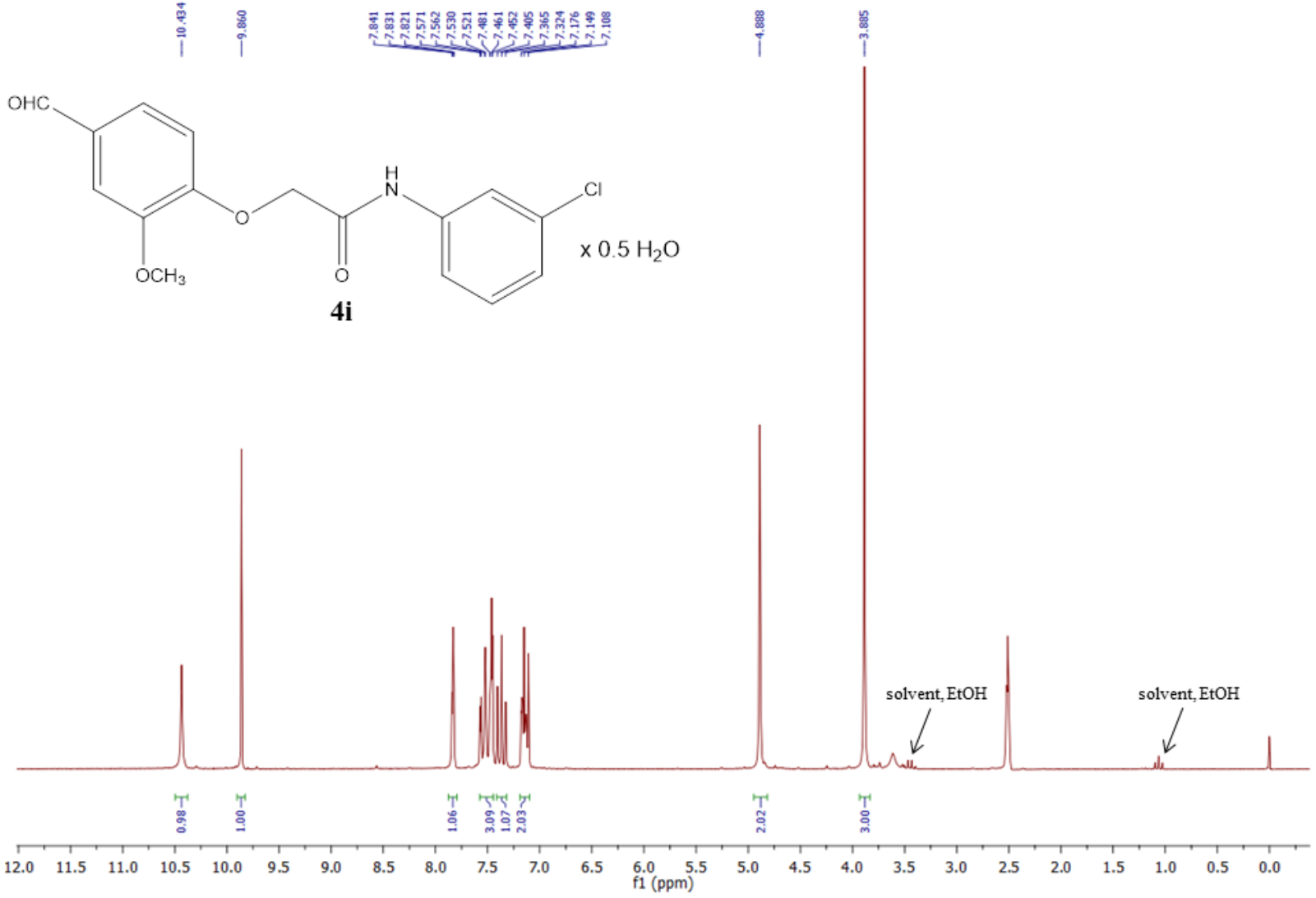

Figure S36. ^{1}H NMR spectrum of **4i** in DMSO-d_6 (200 MHz).

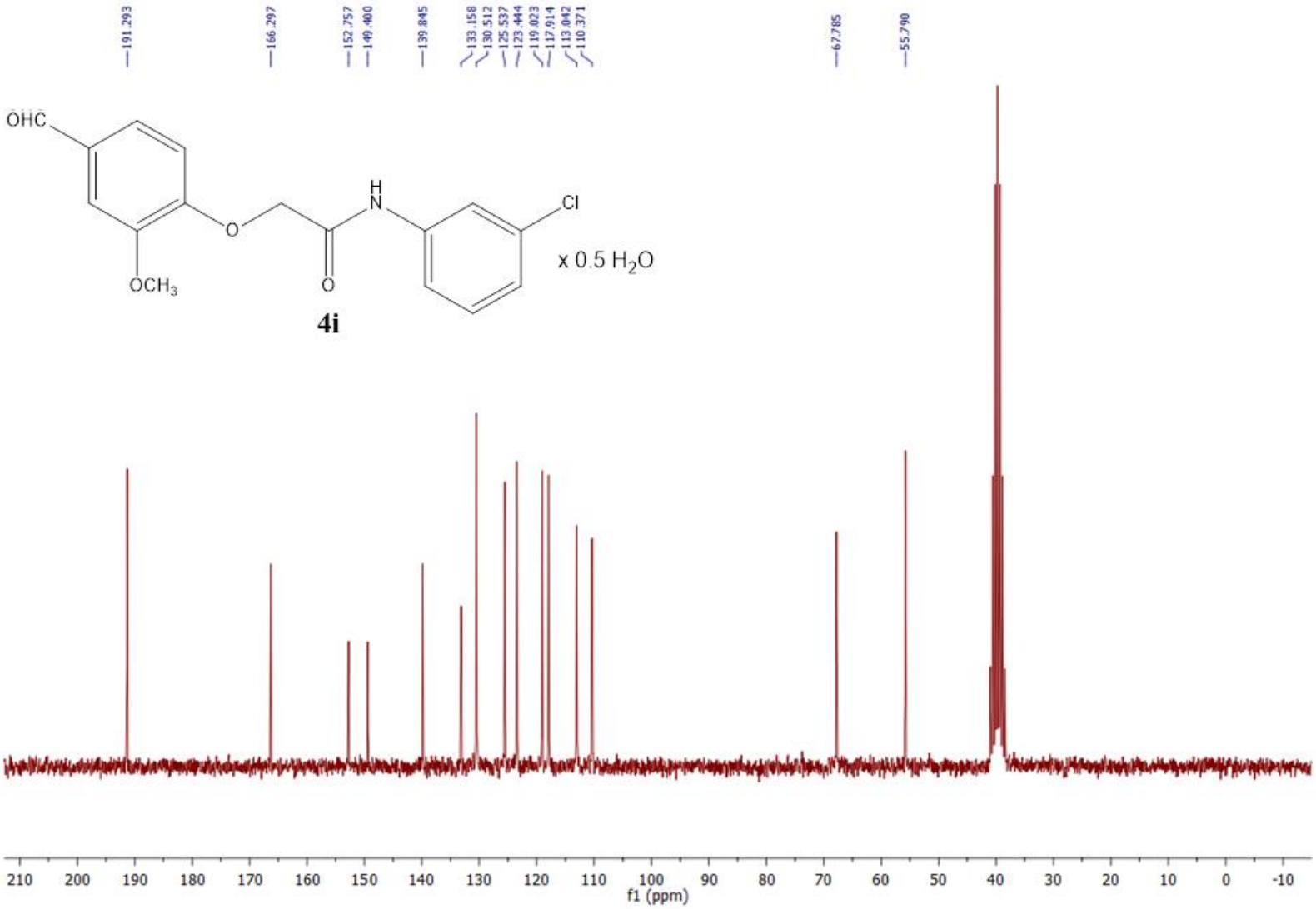

Figure S37. ^{13}C NMR spectrum of **4i** in DMSO-d_6 (50 MHz).

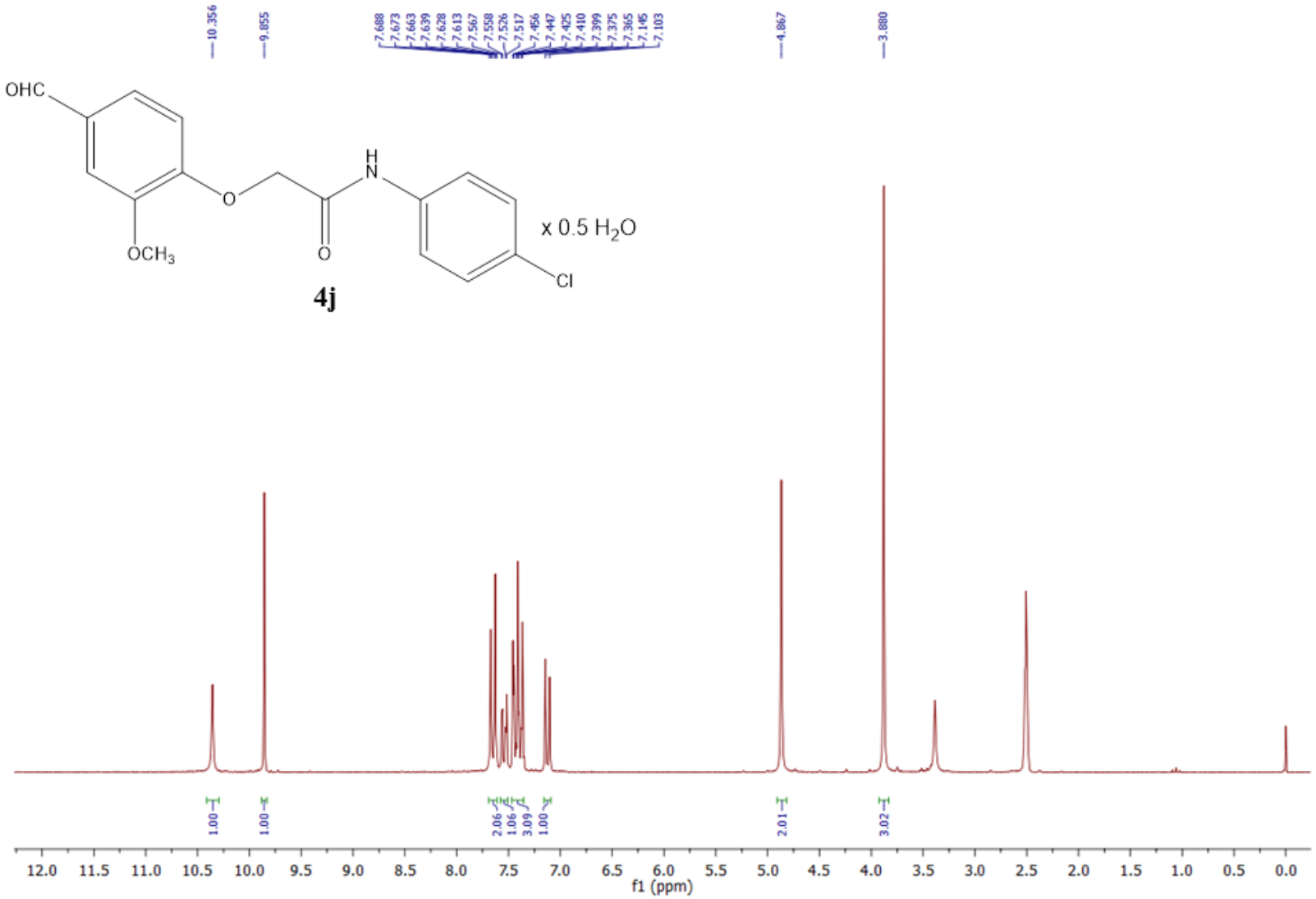

Figure S38. ^{1}H NMR spectrum of **4j** in DMSO-d_6 (200 MHz).

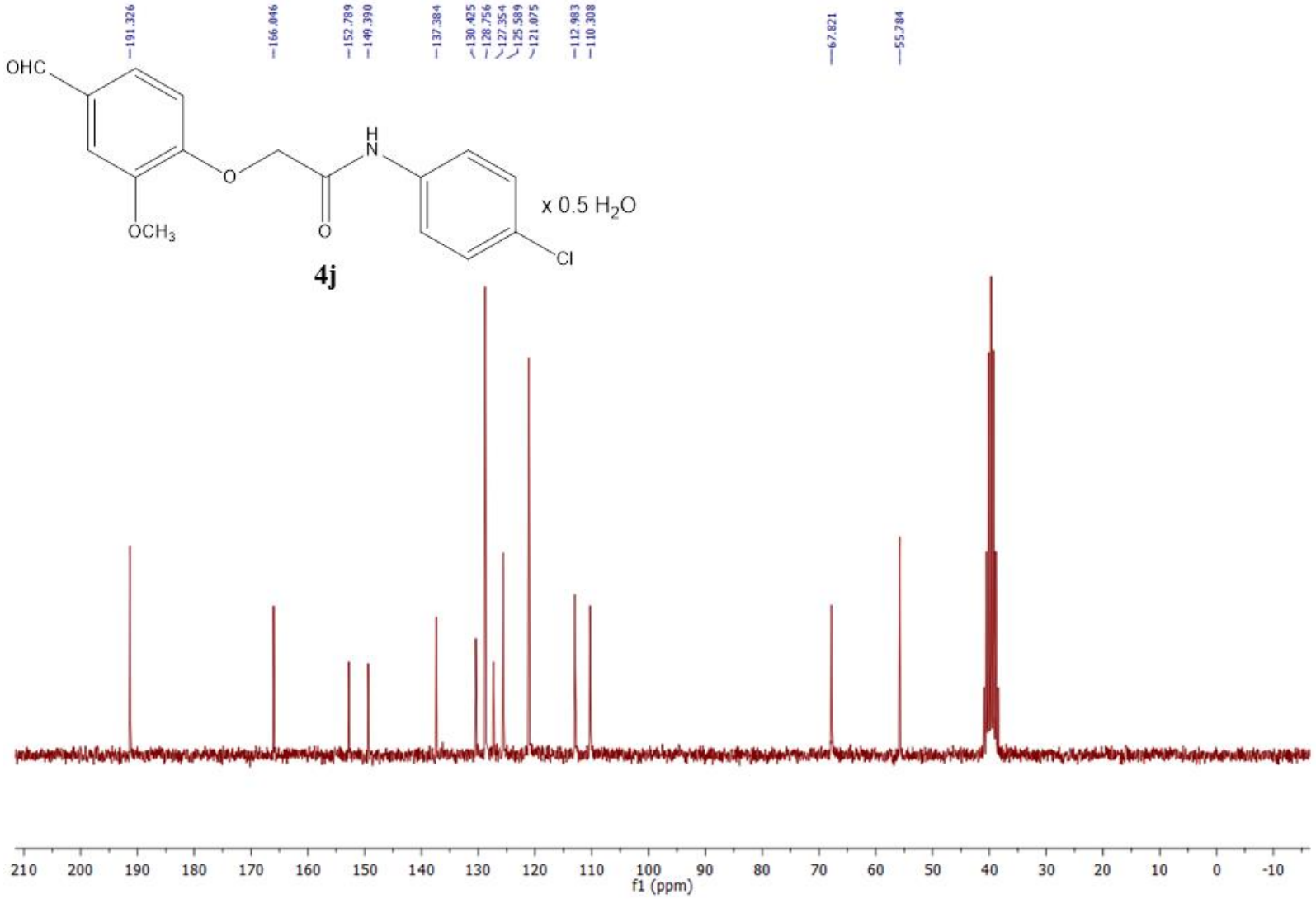

Figure S39. ^{13}C NMR spectrum of **4j** in DMSO-d_6 (50 MHz).

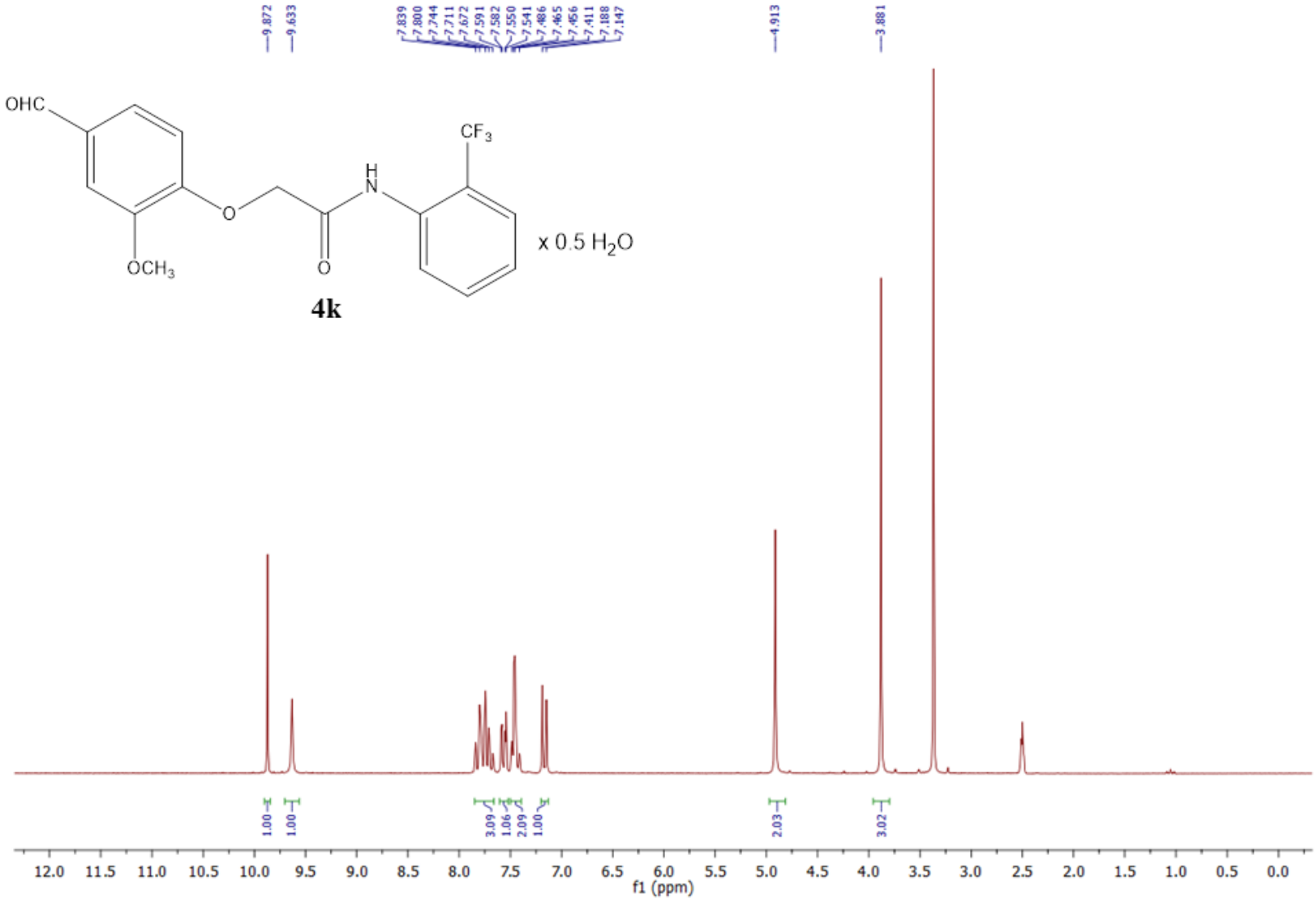

Figure S40. ^{1}H NMR spectrum of **4k** in DMSO-d_6 (200 MHz).

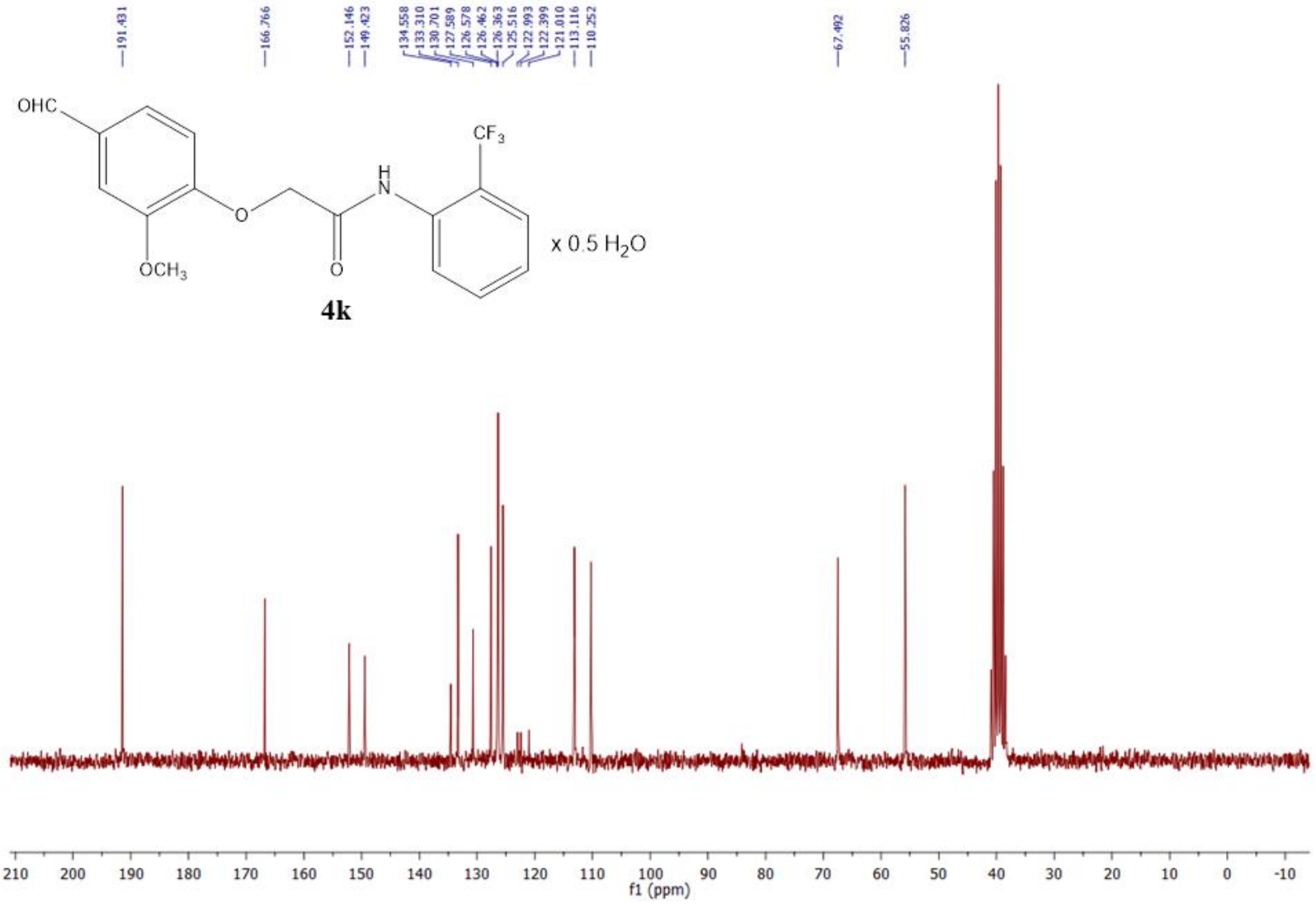

Figure S41. ^{13}C NMR spectrum of **4k** in DMSO-d_6 (50 MHz).

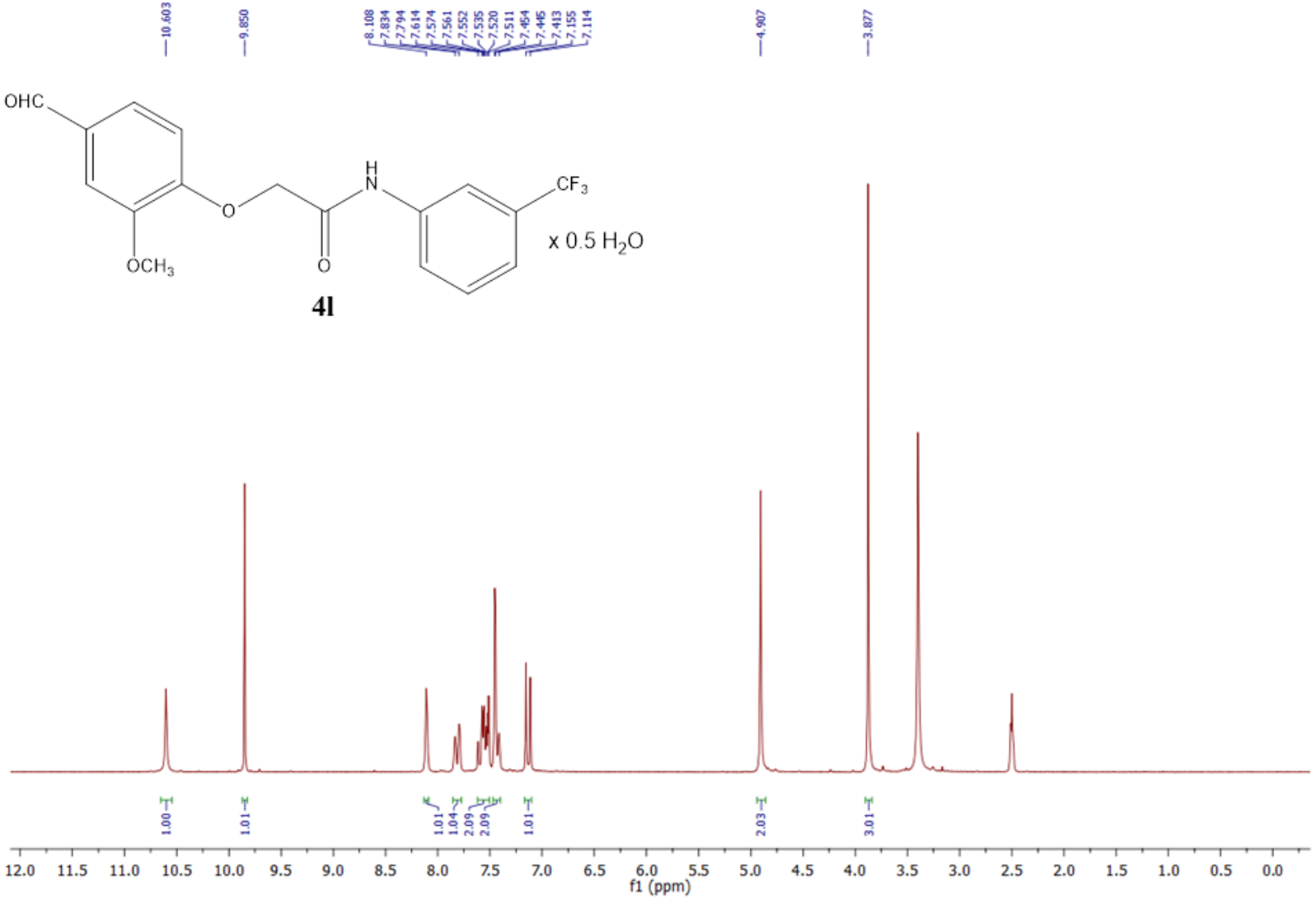

Figure S42. ^{1}H NMR spectrum of **4l** in DMSO-d_6 (200 MHz).

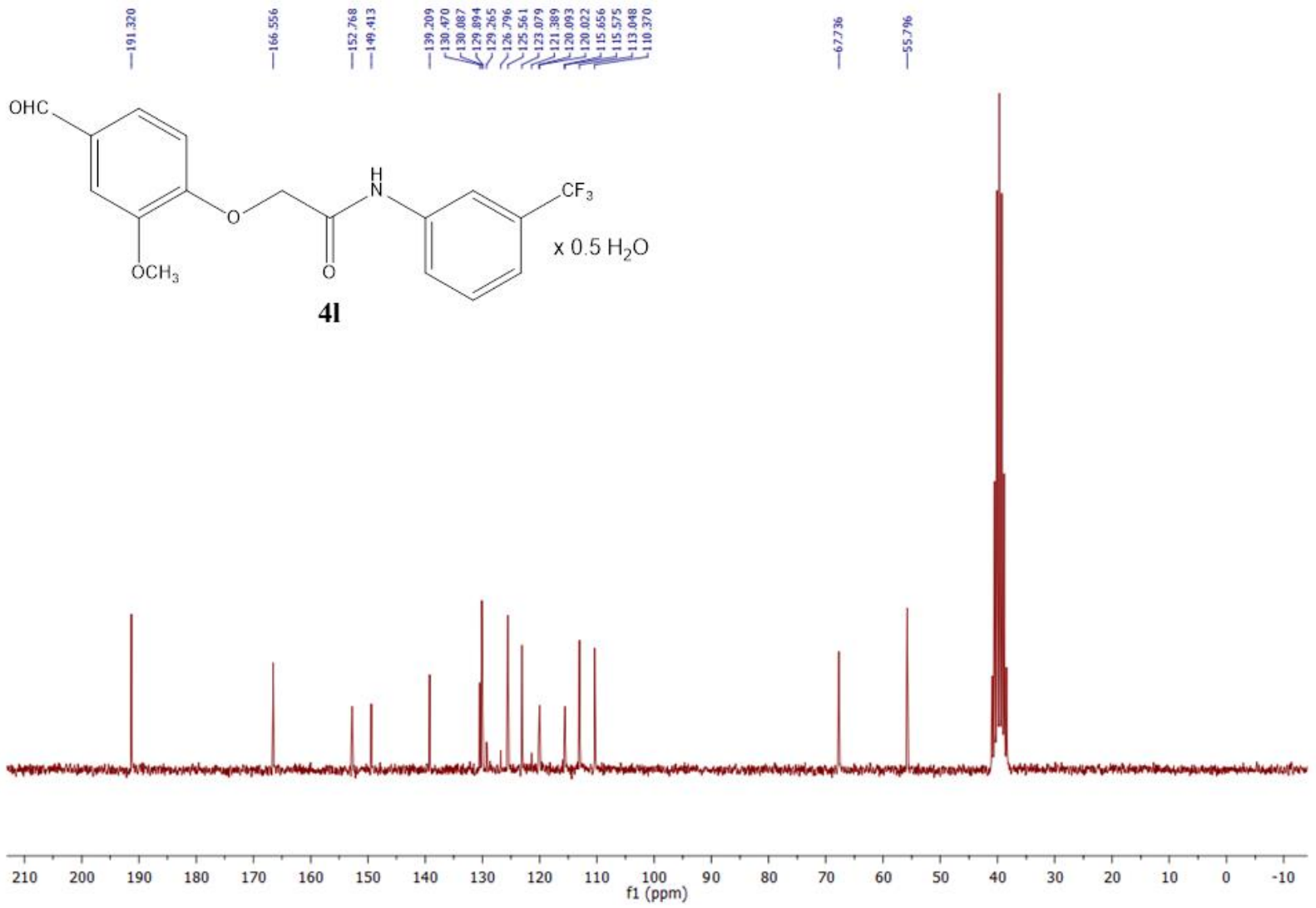

Figure S43. ^{13}C NMR spectrum of **4l** in DMSO-d_6 (50 MHz).

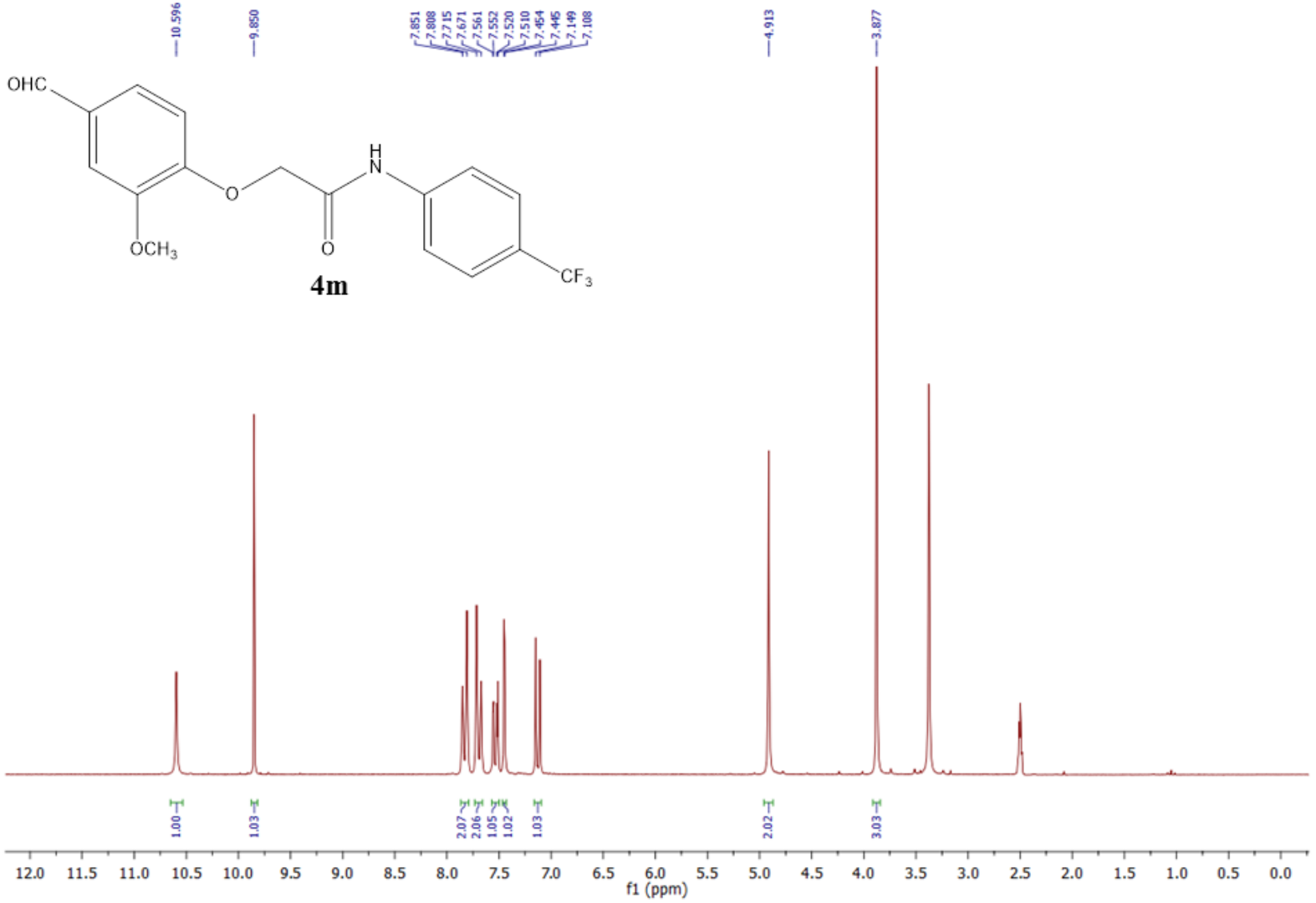

Figure S44. ^{1}H NMR spectrum of **4m** in DMSO-d_6 (200 MHz).

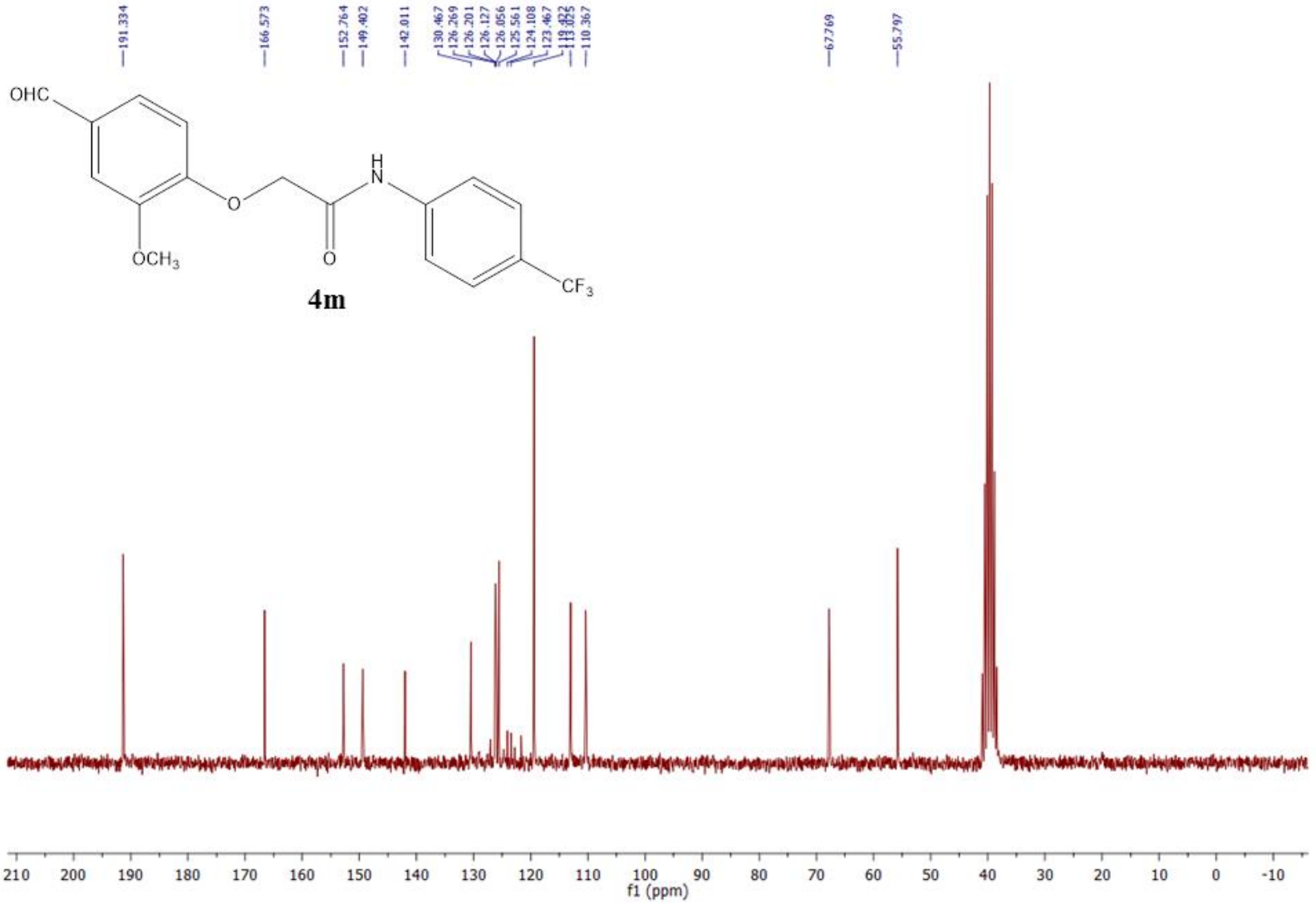

Figure S45. ^{13}C NMR spectrum of **4m** in DMSO-d_6 (50 MHz).

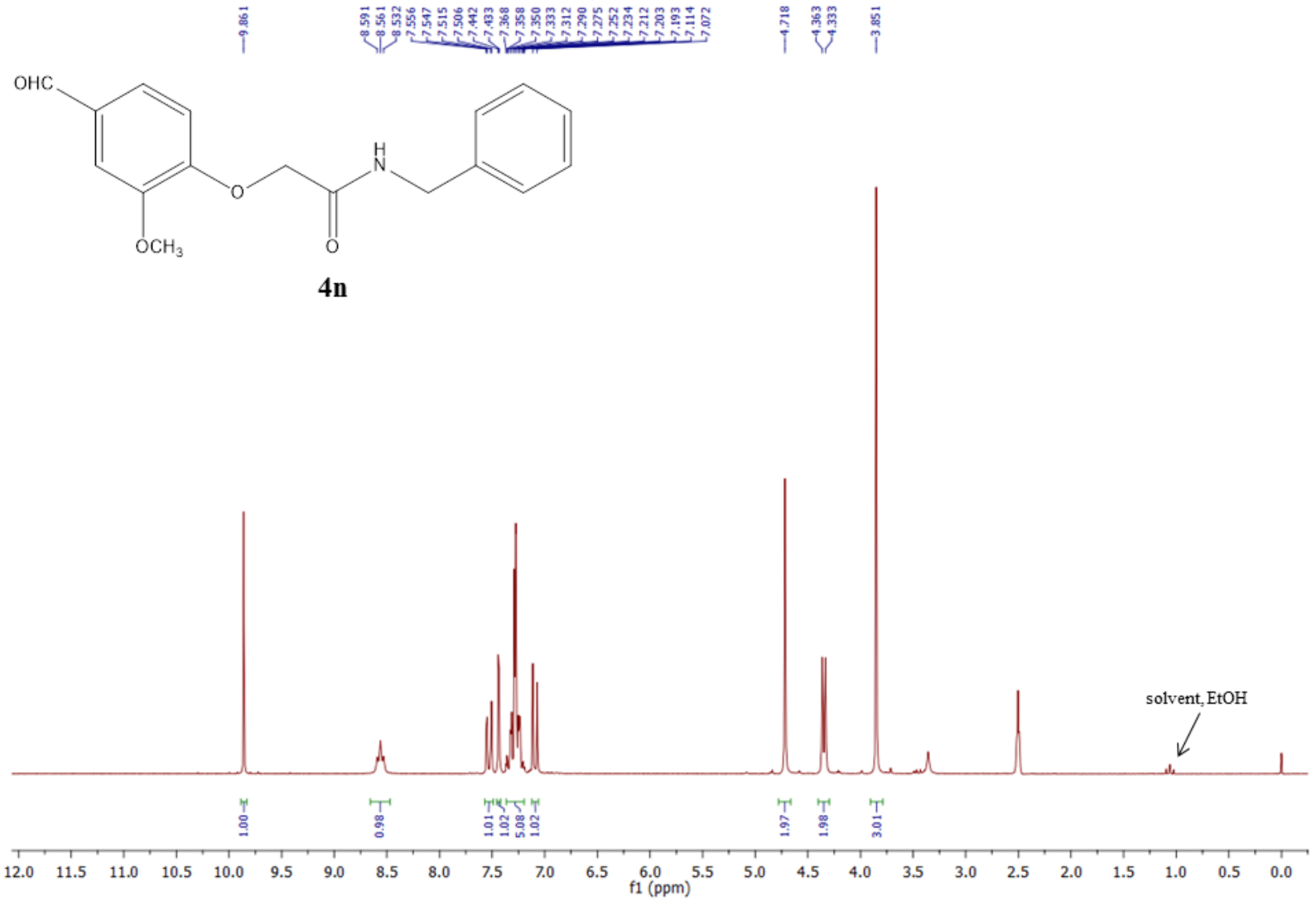

Figure S46. ^{1}H NMR spectrum of **4n** in DMSO-d_6 (200 MHz).

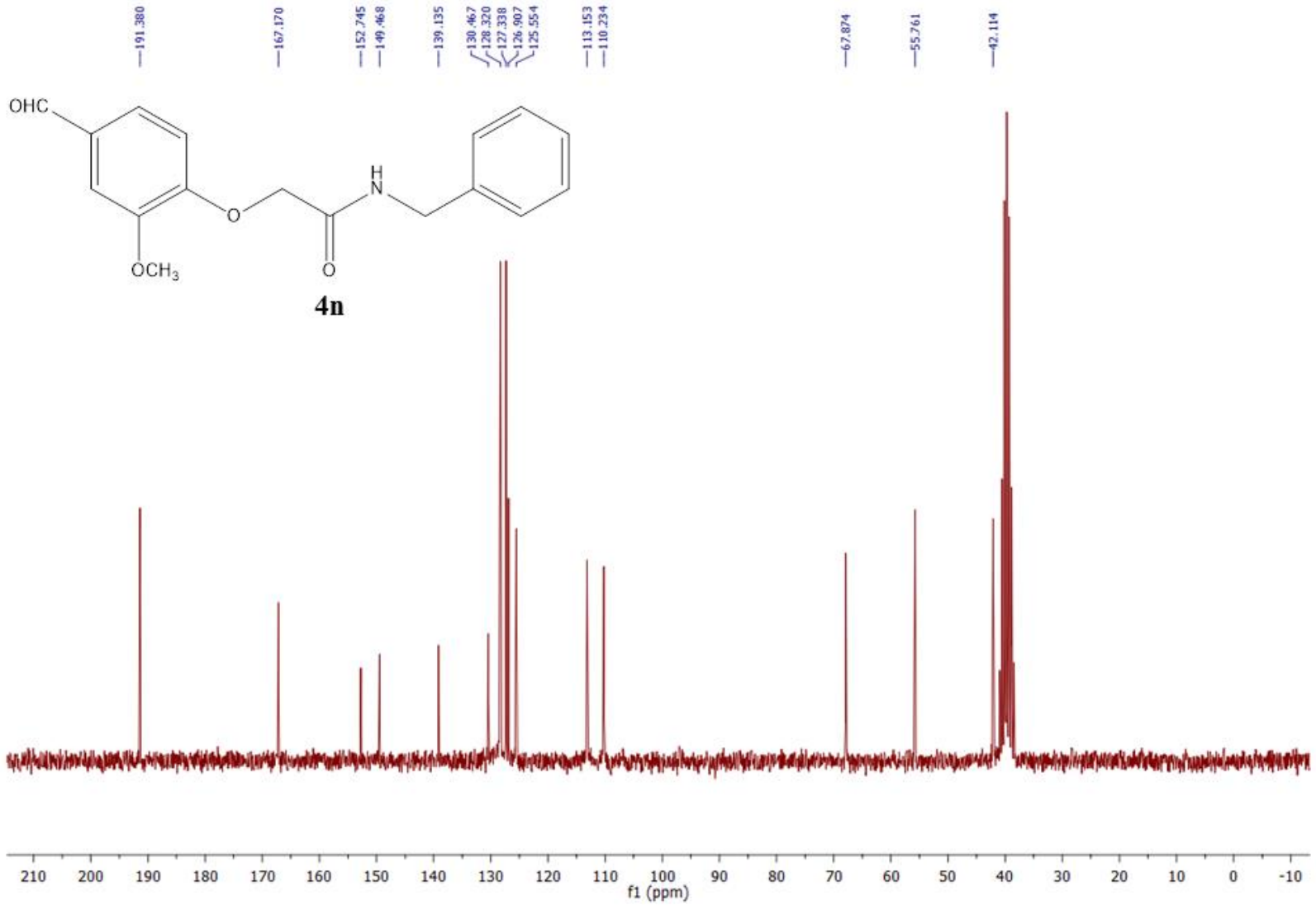

Figure S47. ^{13}H NMR spectrum of **4n** in DMSO-d_6 (50 MHz).

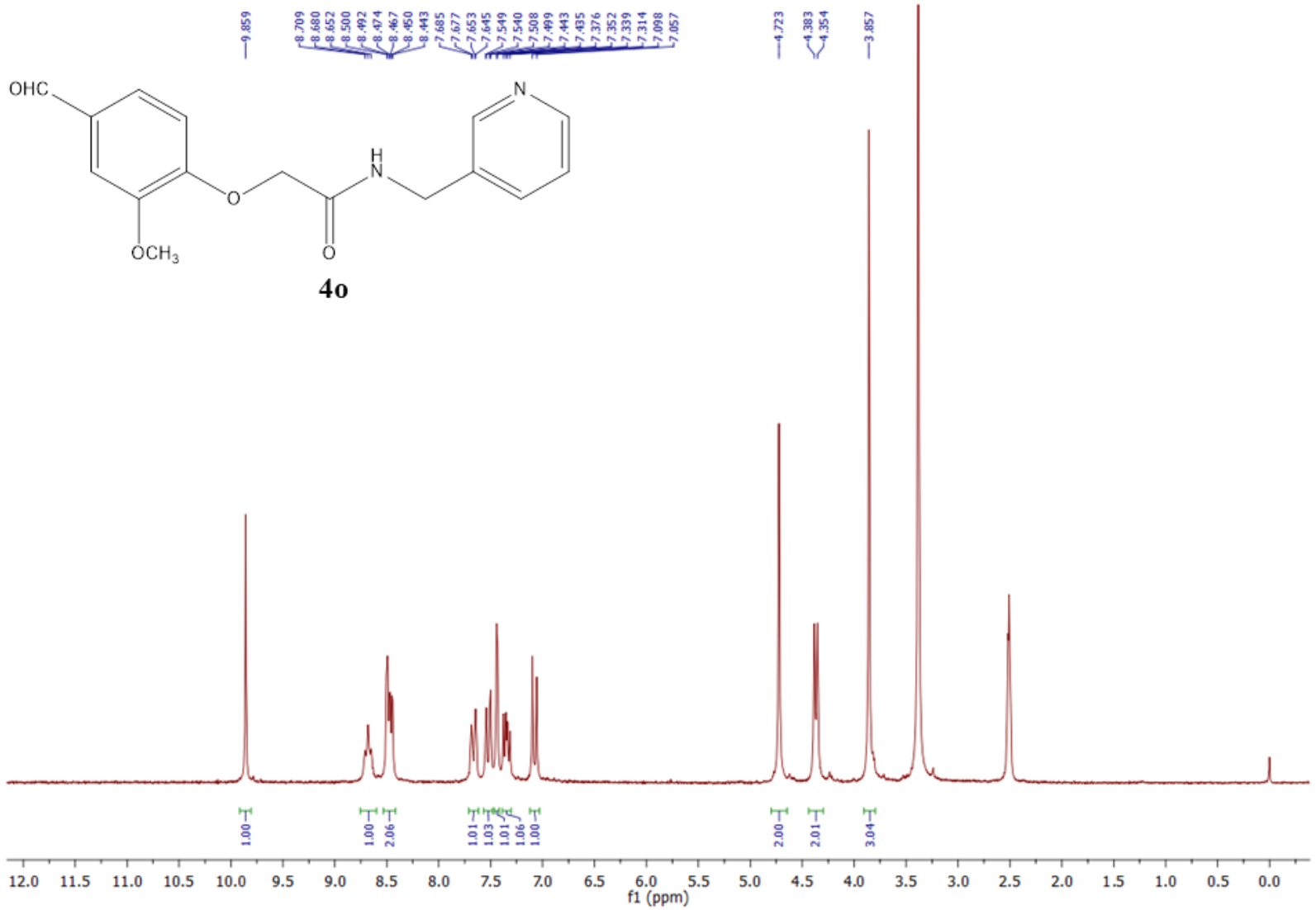

Figure S48. ^{1}H NMR spectrum of **4o** in DMSO-d_6 (200 MHz).

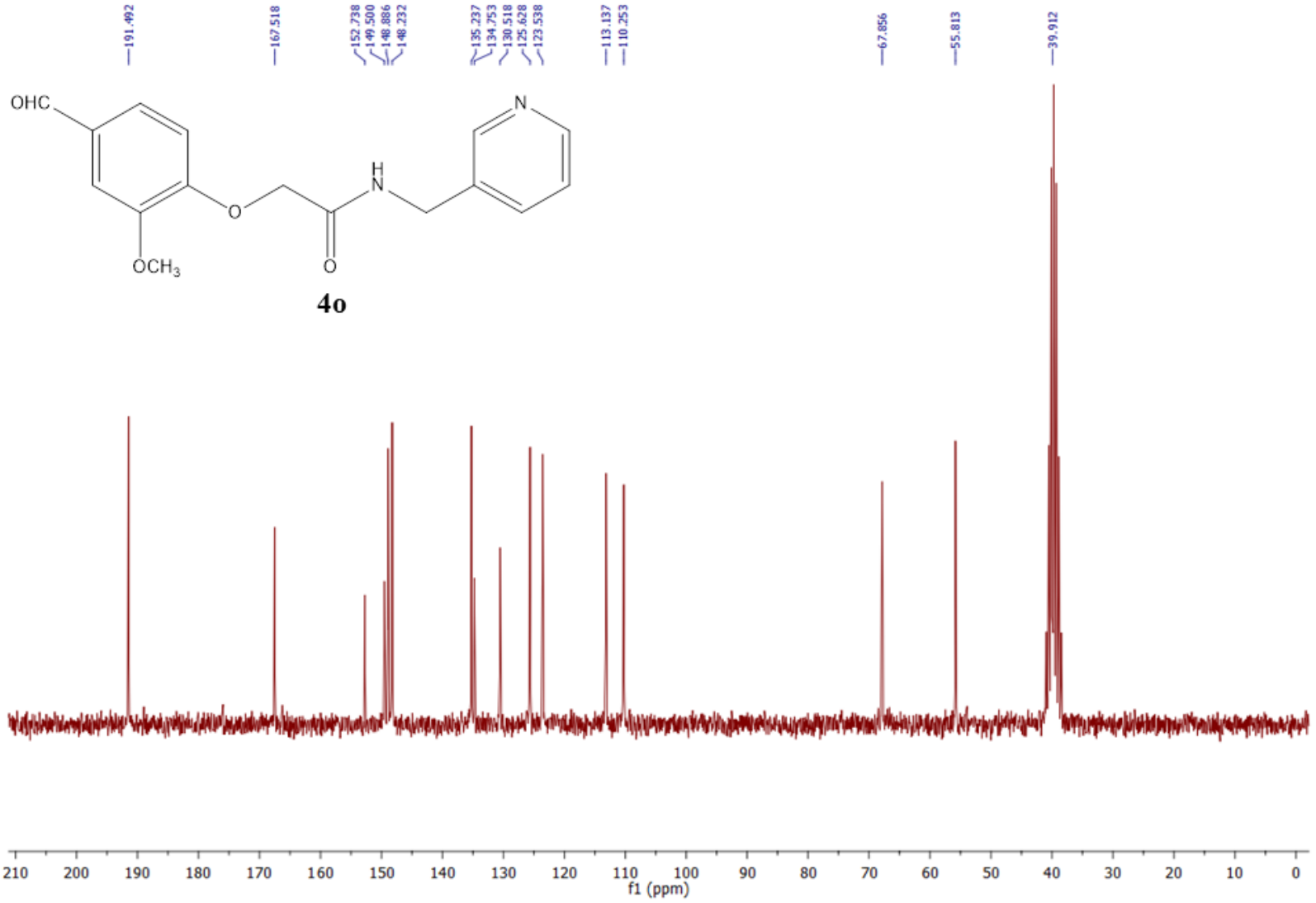

Figure S49. ^{13}C NMR spectrum of **4o** in DMSO-d_6 (50 MHz).

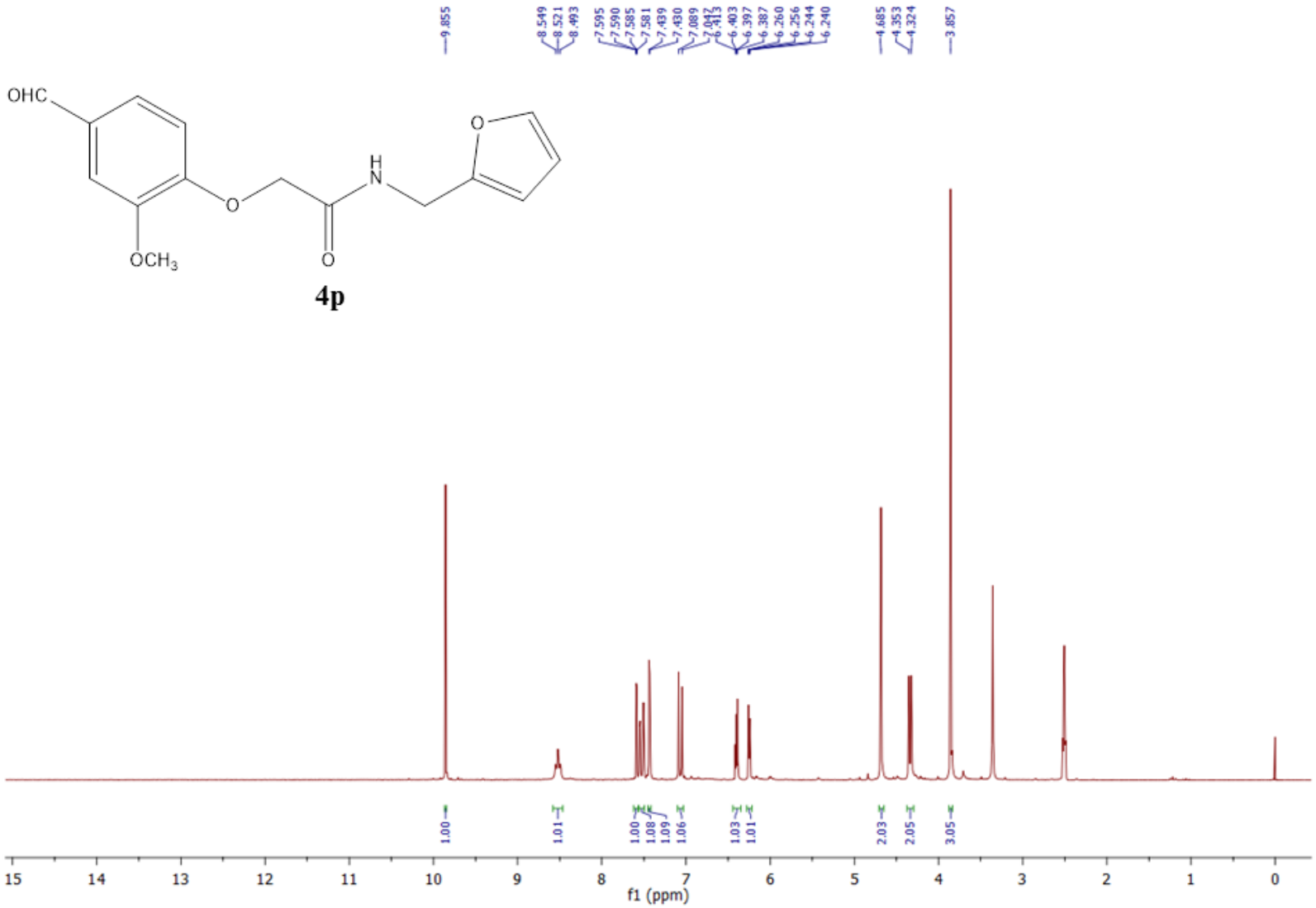

Figure S50. ^{1}H NMR spectrum of **4p** in DMSO-d_6 (200 MHz).

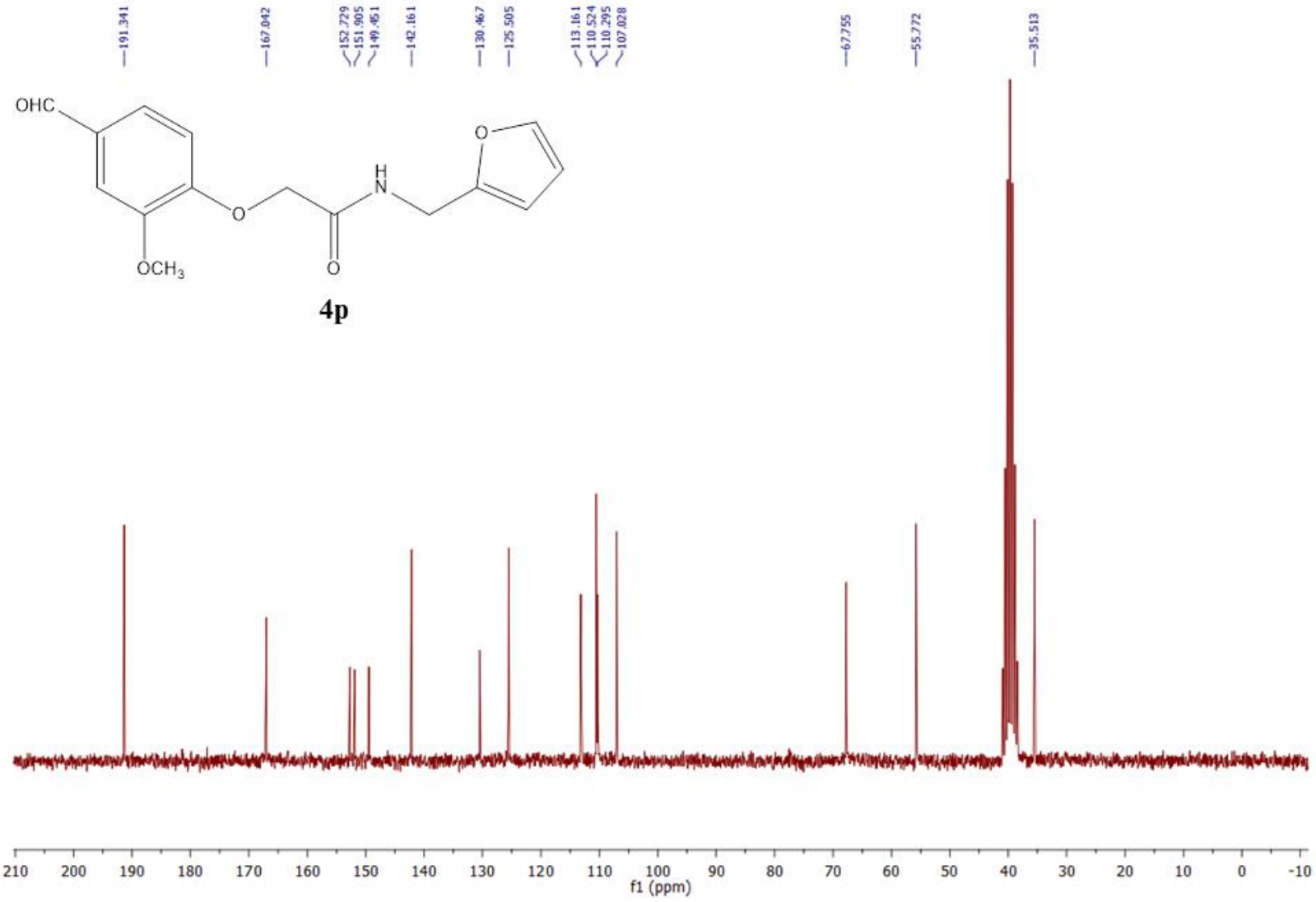

Figure S51. ^{13}C NMR spectrum of **4p** in DMSO-d_6 (50 MHz).

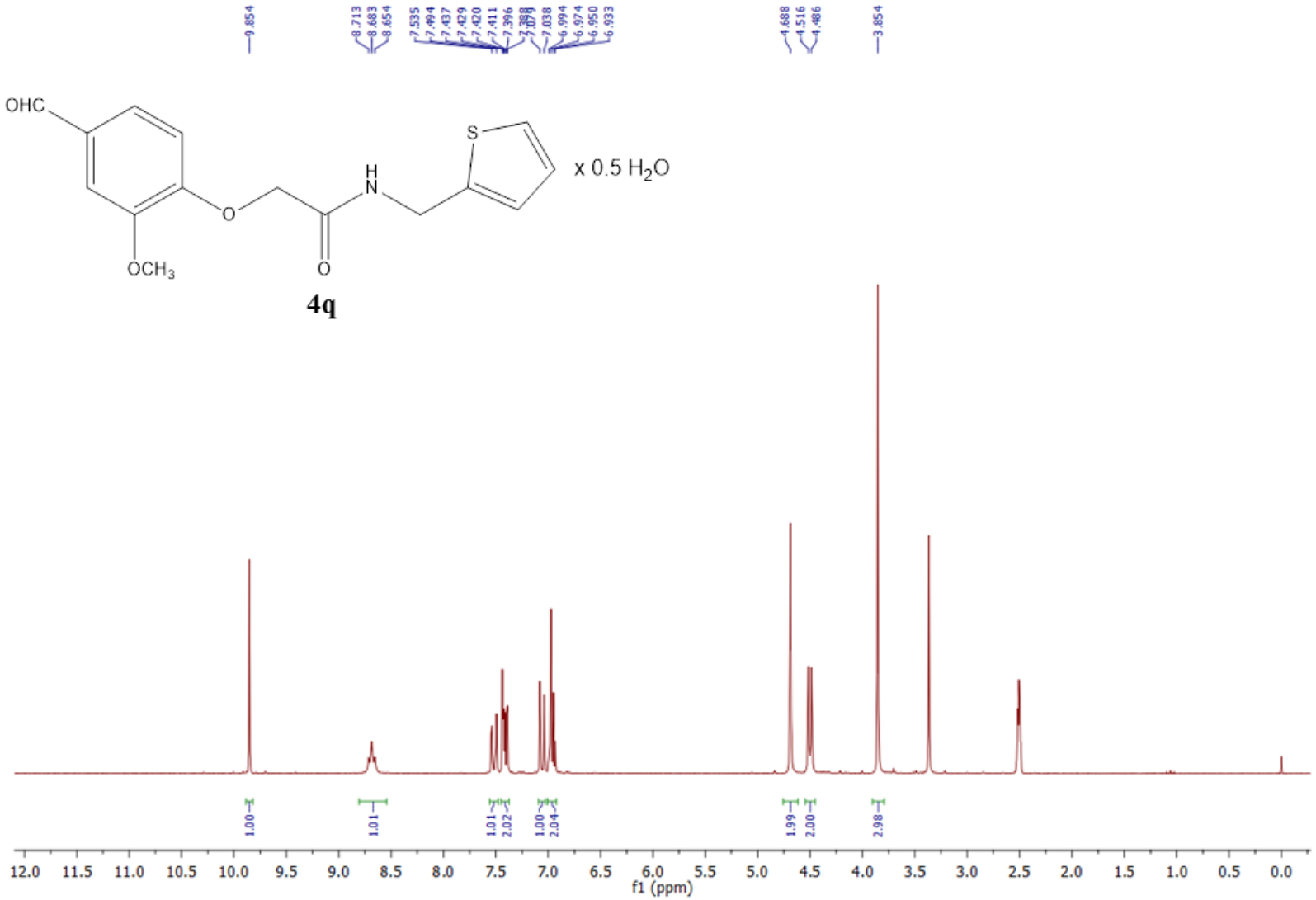

Figure S52. ^{1}H NMR spectrum of **4q** in DMSO-d_6 (200 MHz).

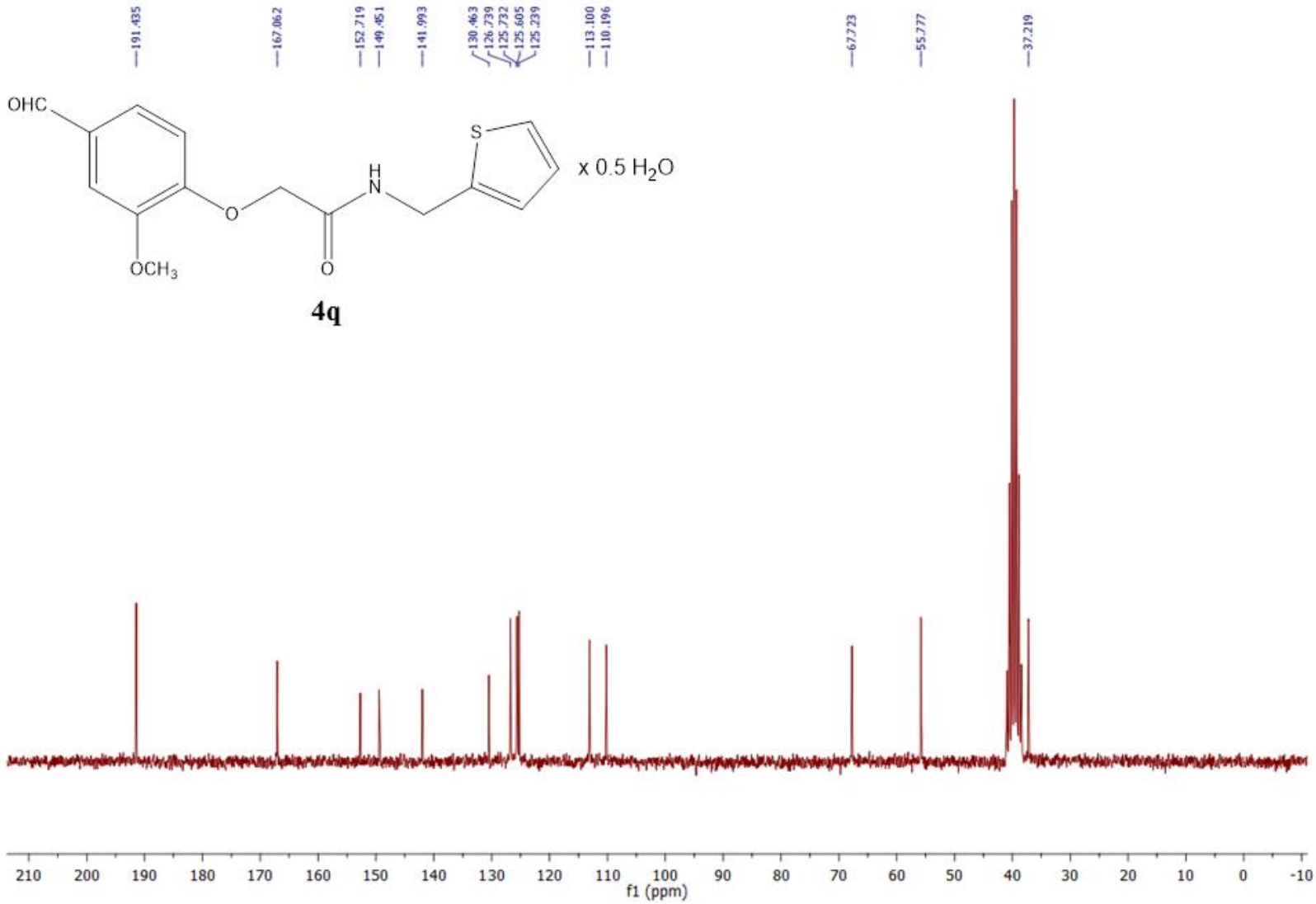

Figure S53. ^{13}C NMR spectrum of **4q** in DMSO-d_6 (50 MHz).

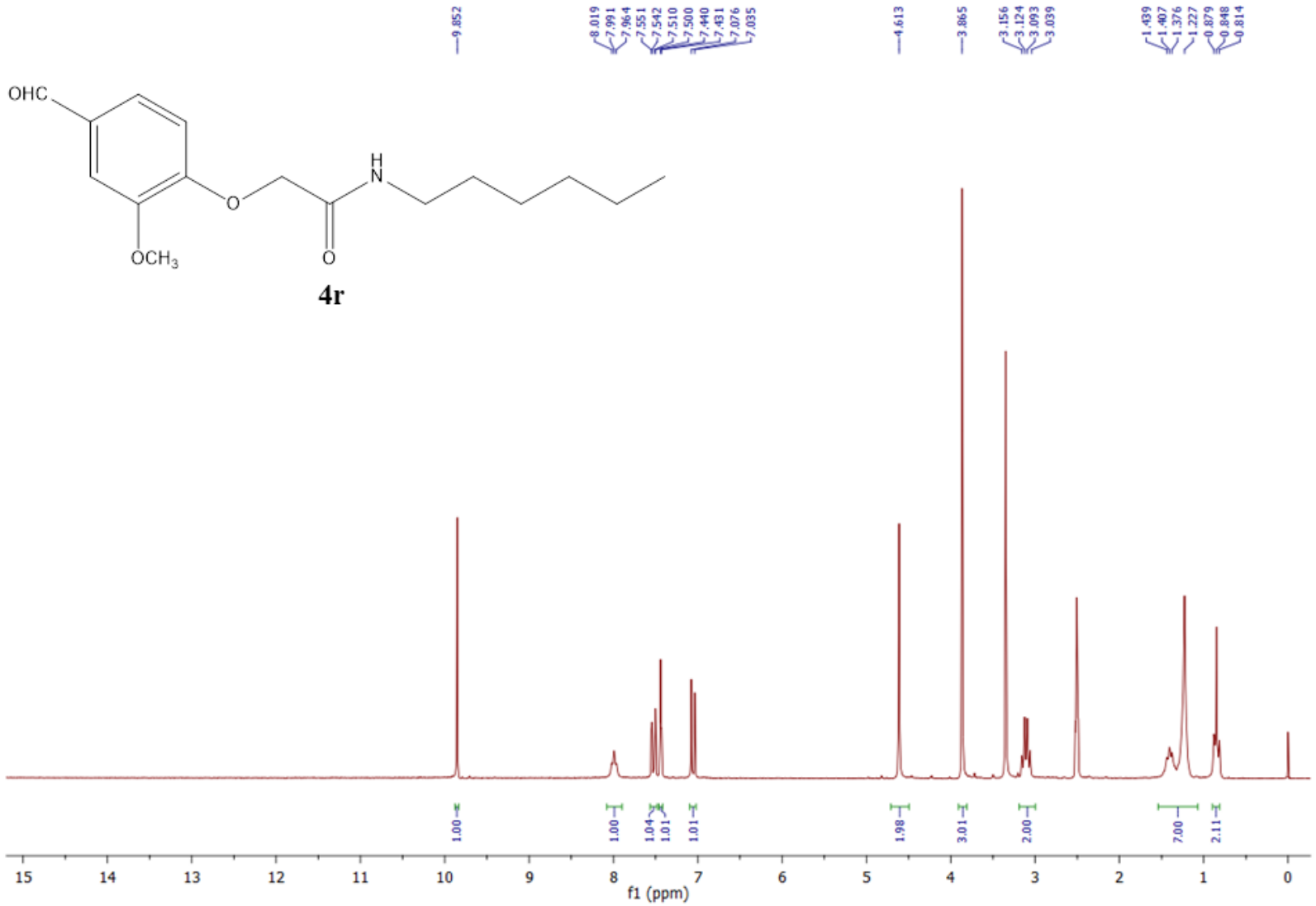

Figure S54. ^{1}H NMR spectrum of **4r** in DMSO-d_6 (200 MHz).

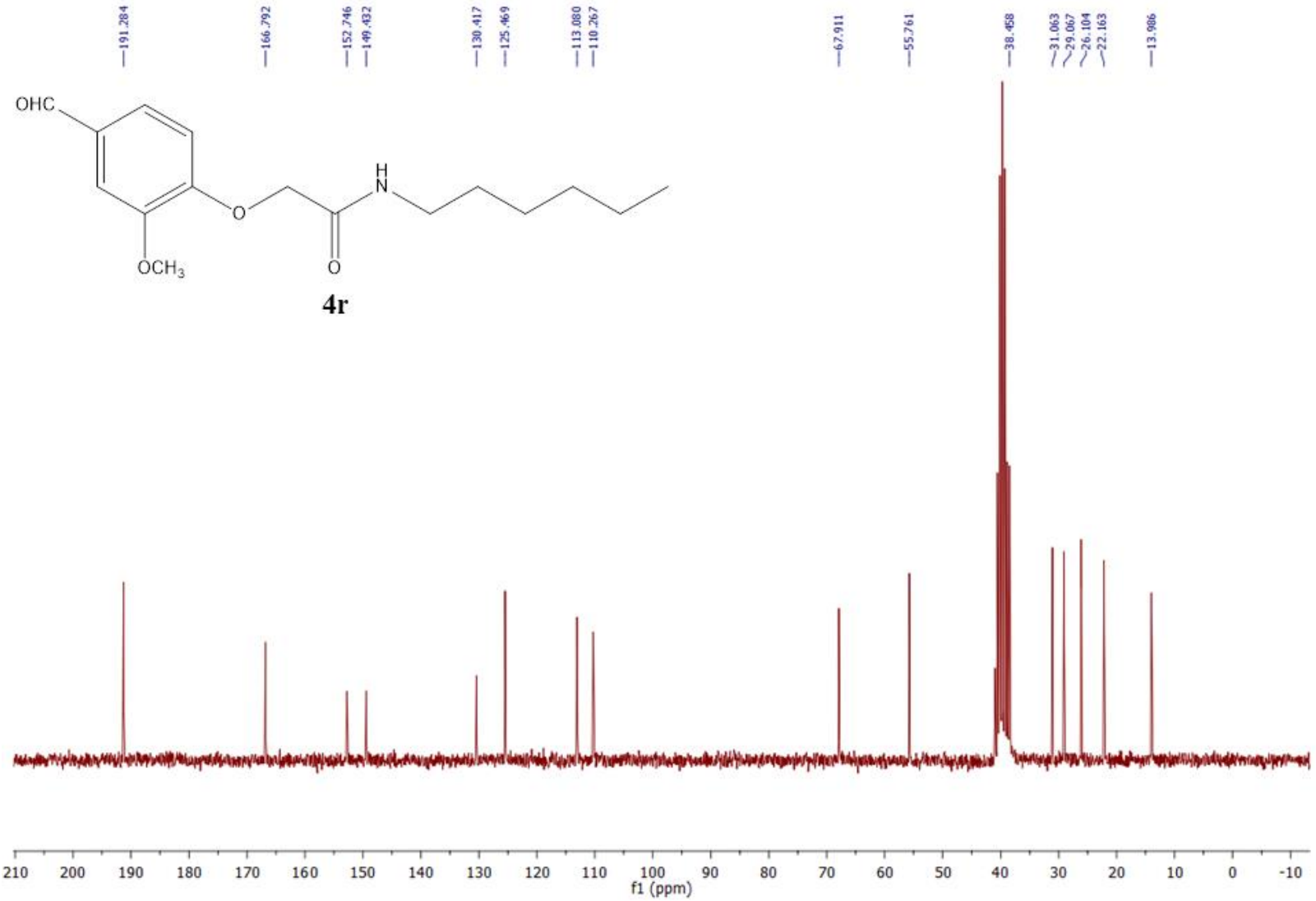

Figure S55. ^{13}C NMR spectrum of **4r** in DMSO-d_6 (50 MHz).

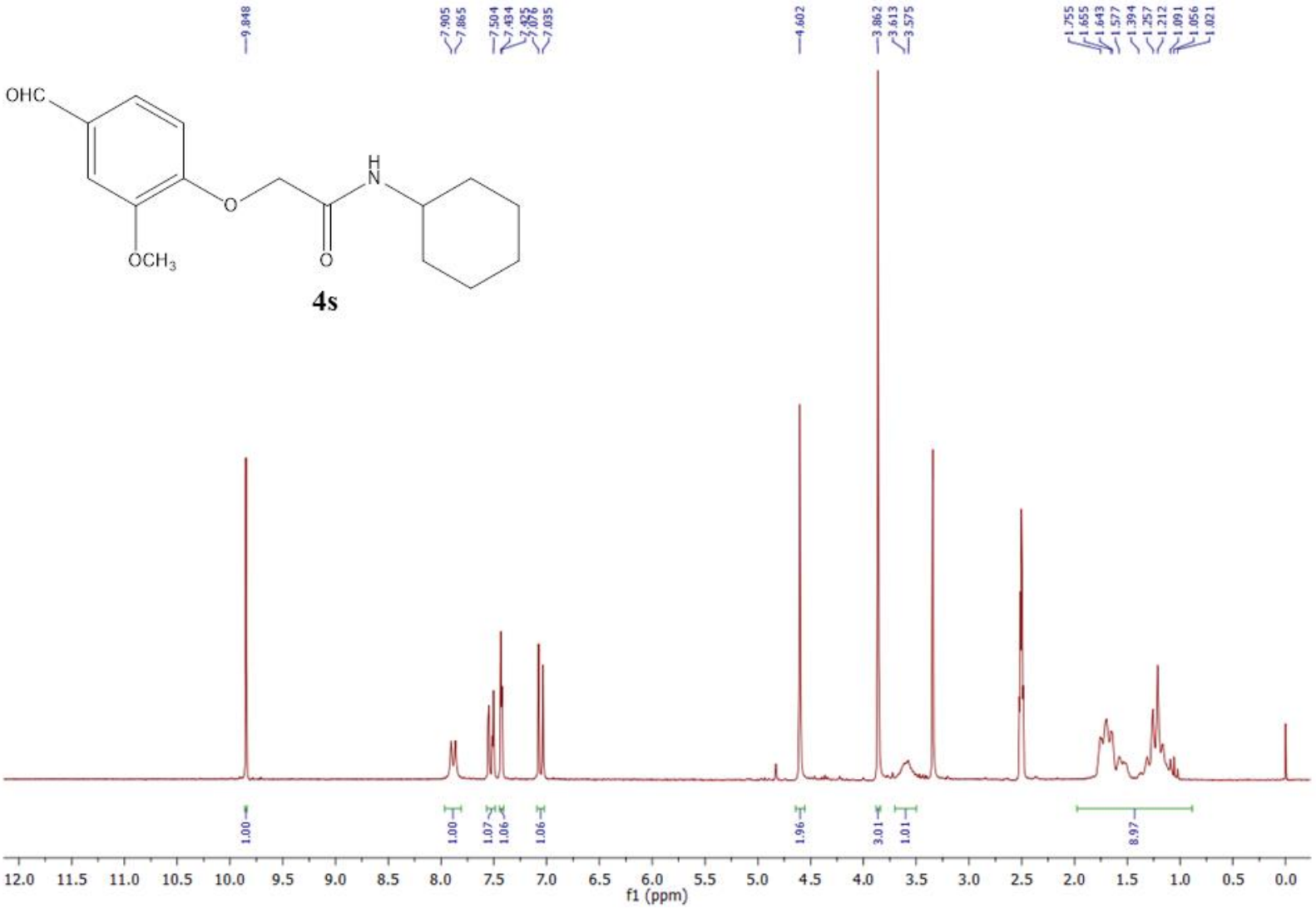

Figure S56. ^{1}H NMR spectrum of **4s** in DMSO-d_6 (200 MHz).

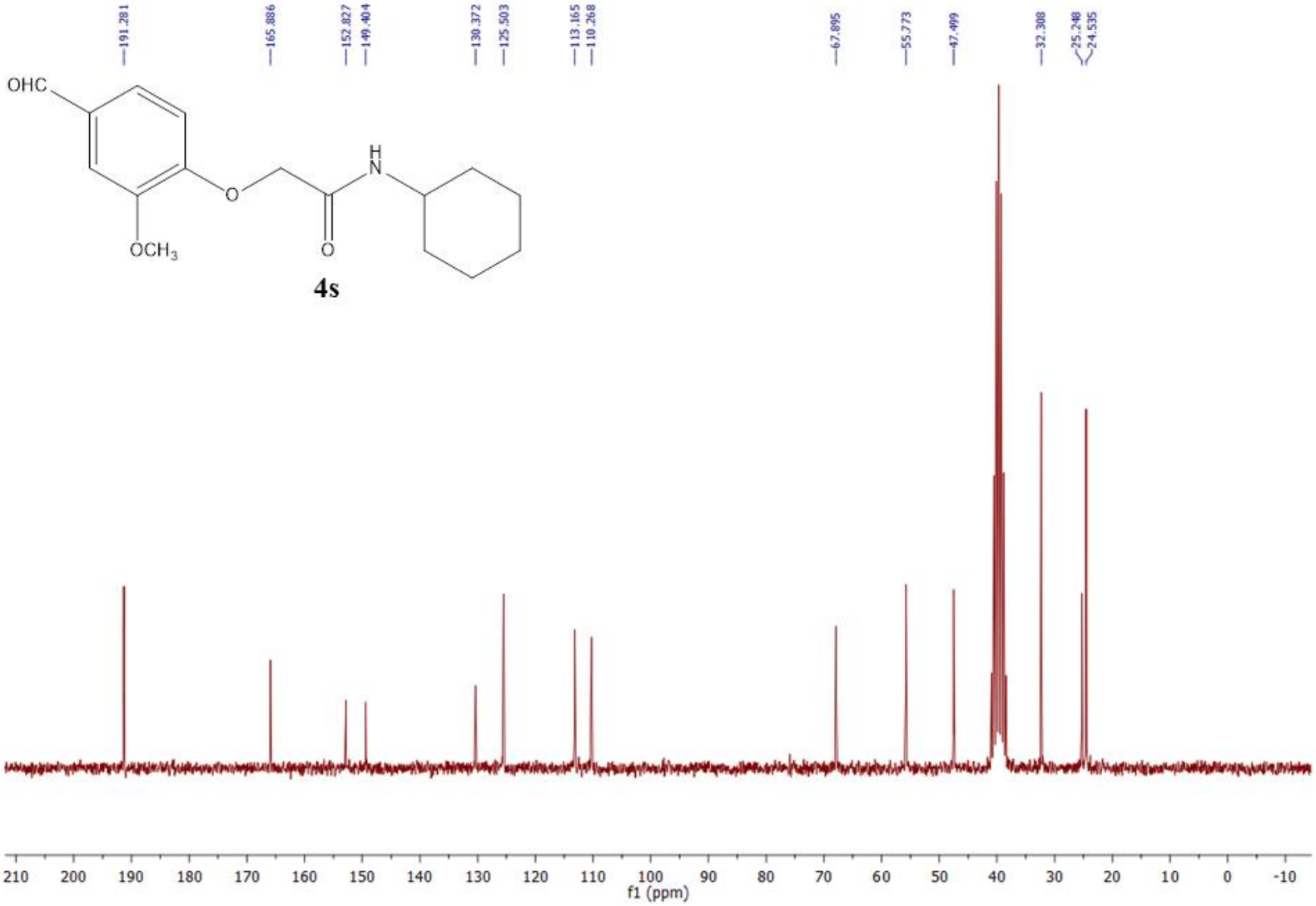

Figure S57. ^{13}C NMR spectrum of **4s** in DMSO-d_6 (50 MHz).

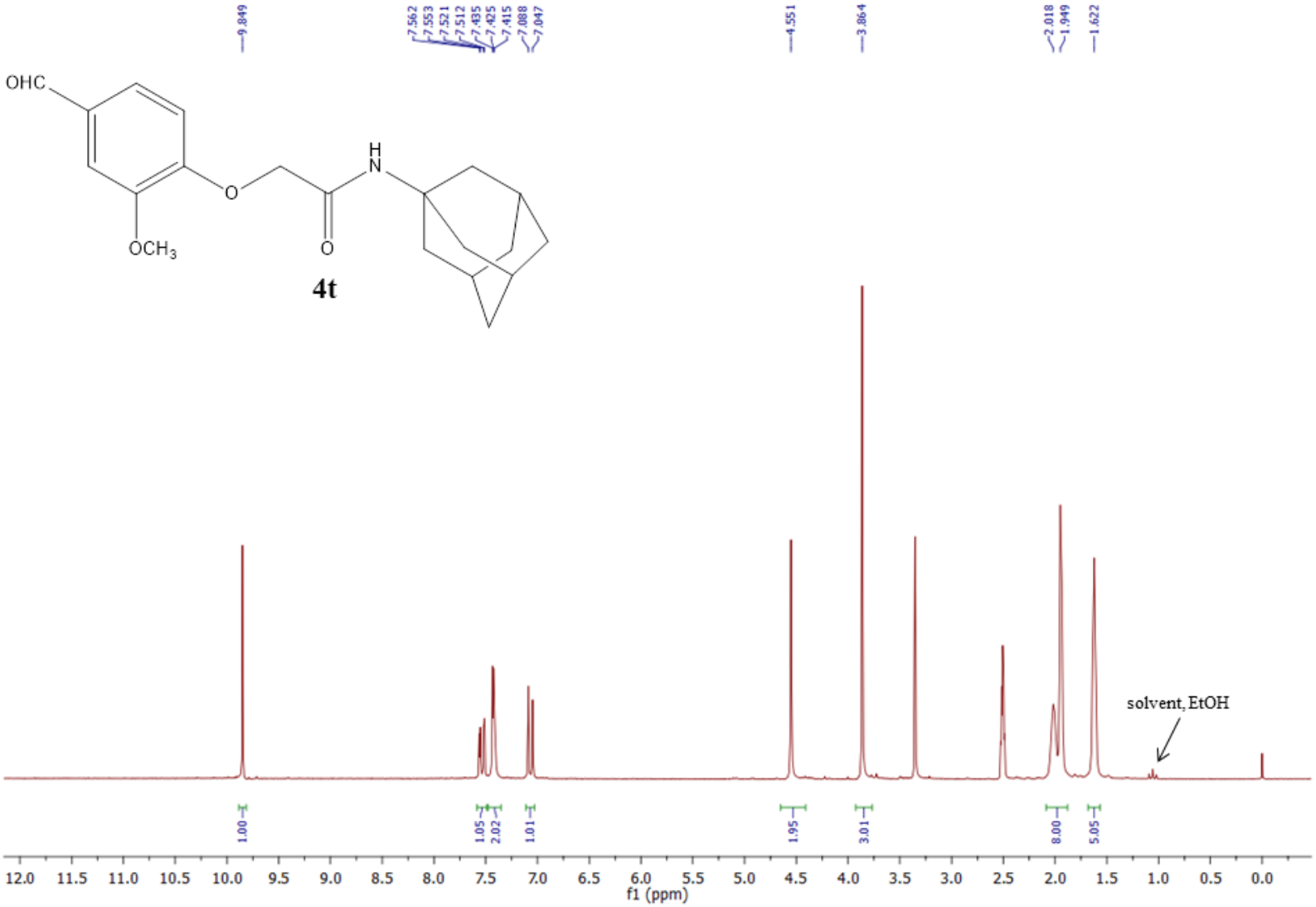

Figure S58. ^{1}H NMR spectrum of **4t** in DMSO-d_6 (200 MHz).

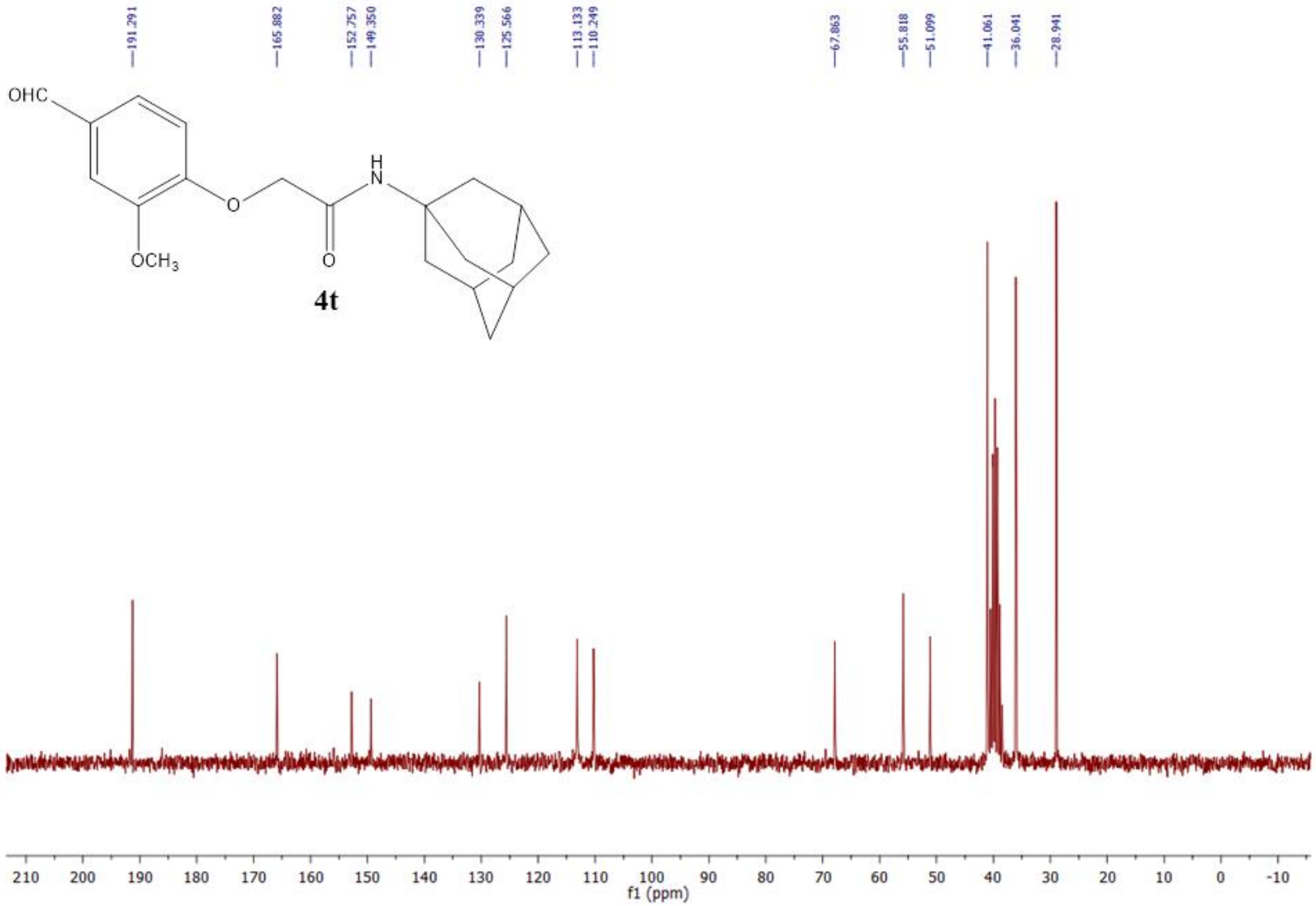

Figure S59. ^{13}C NMR spectrum of **4t** in DMSO-d_6 (50 MHz).

Copies of ^{1}H and ^{13}C NMR spectra for 5a-5t

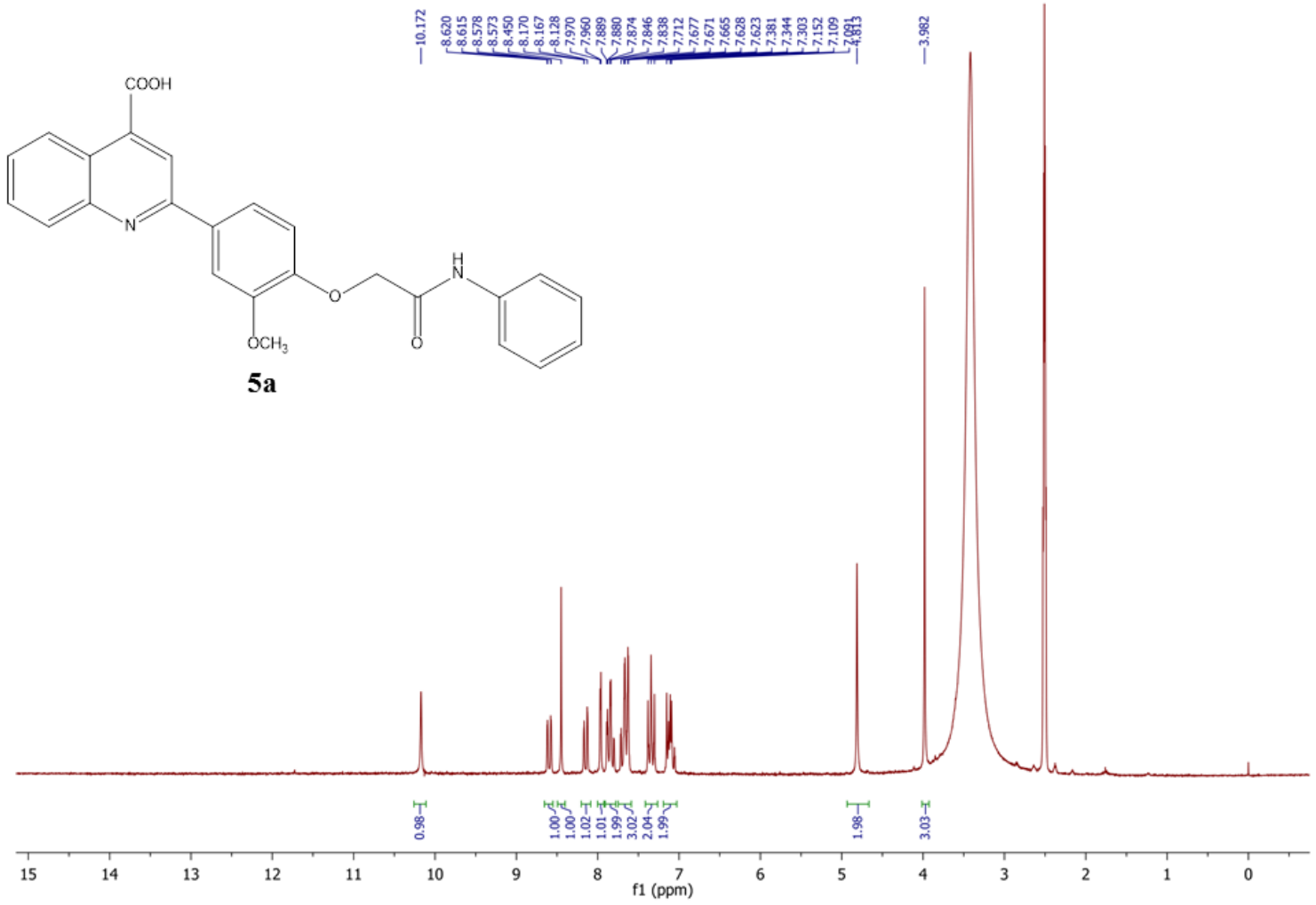

Figure S60. ^{1}H NMR spectrum of **5a** in DMSO-d_6 (200 MHz).

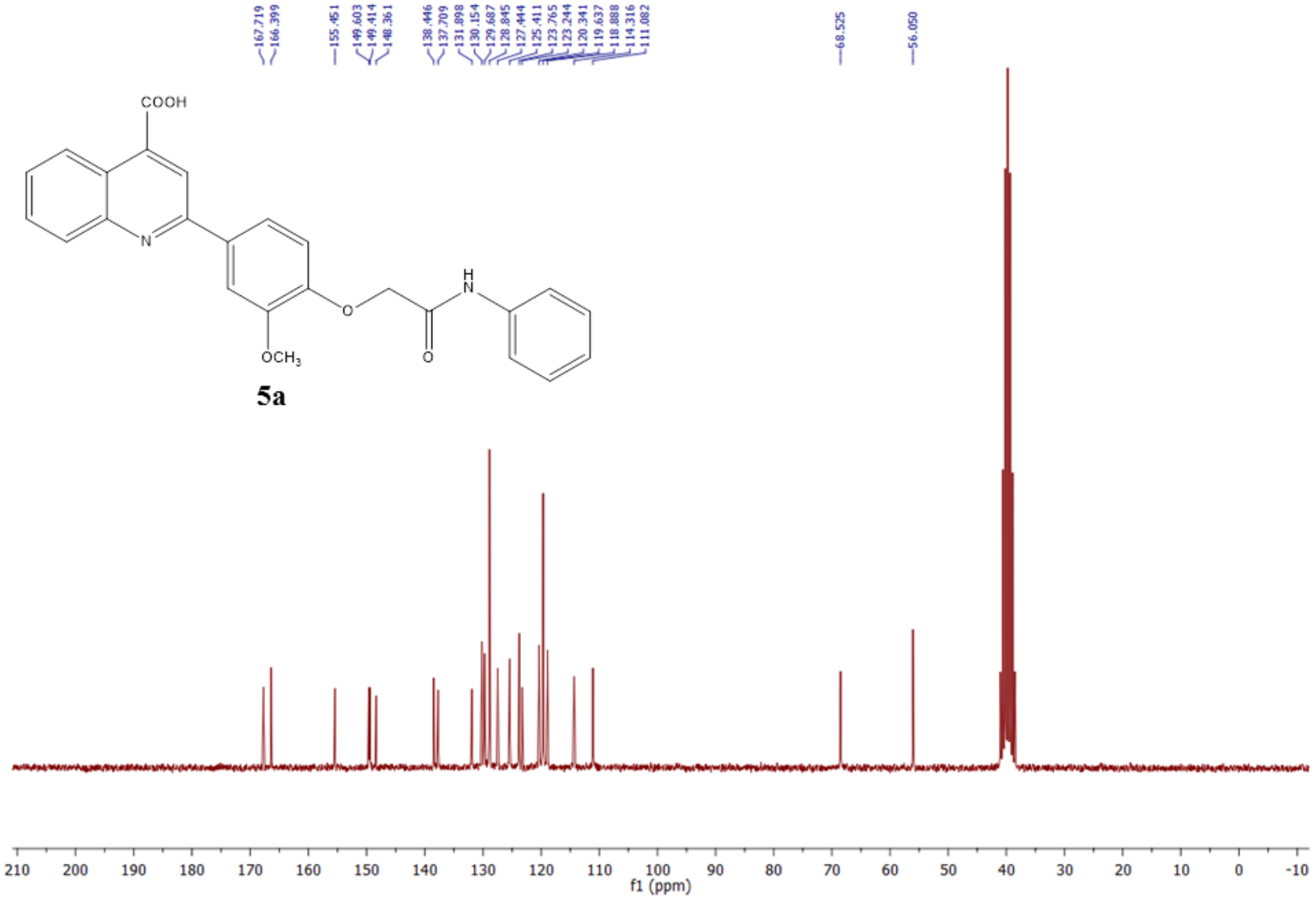

Figure S61. ^{13}C NMR spectrum of **5a** in DMSO-d_6 (50 MHz).

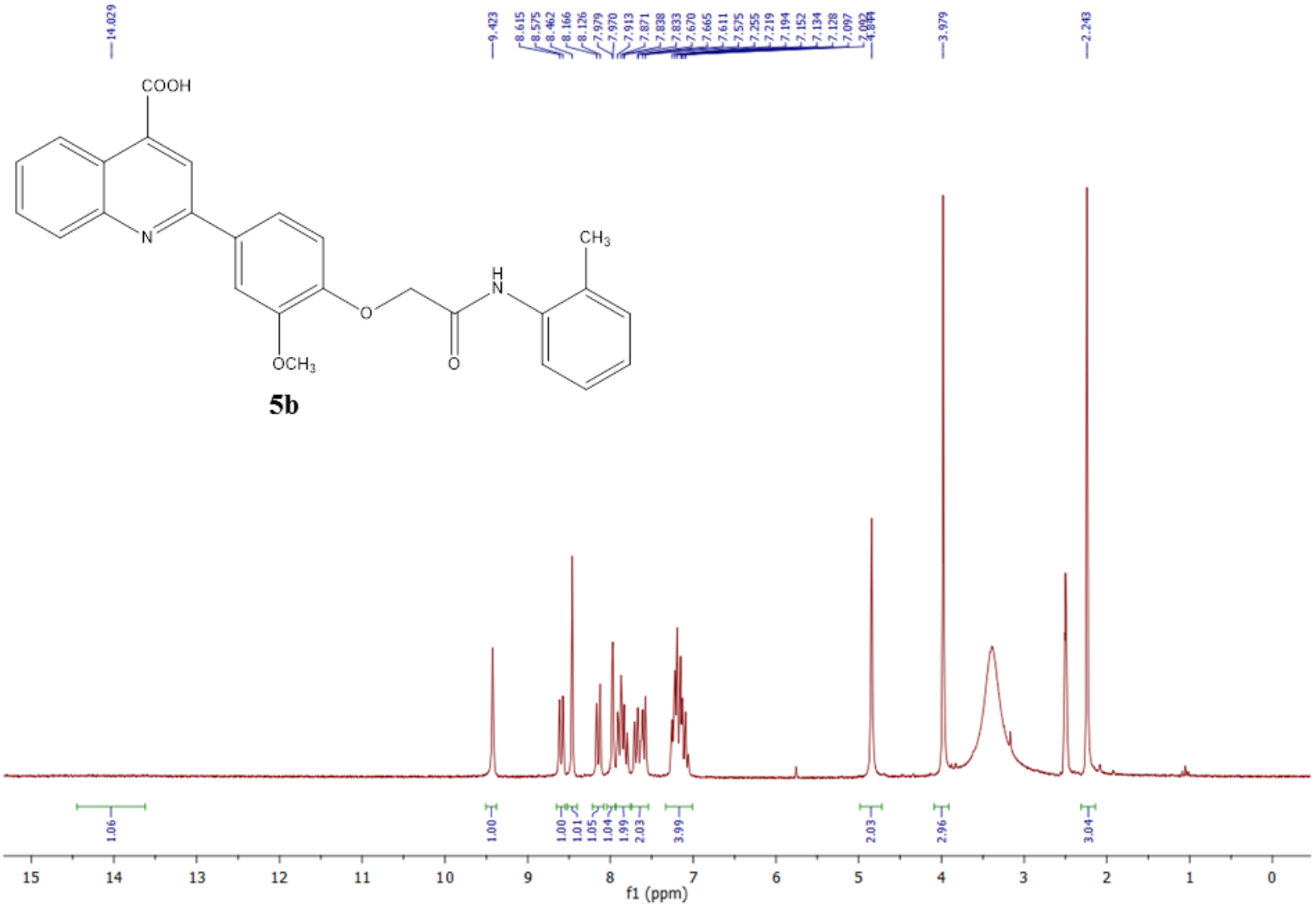

Figure S62. ^{1}H NMR spectrum of **5b** in DMSO-d_6 (200 MHz).

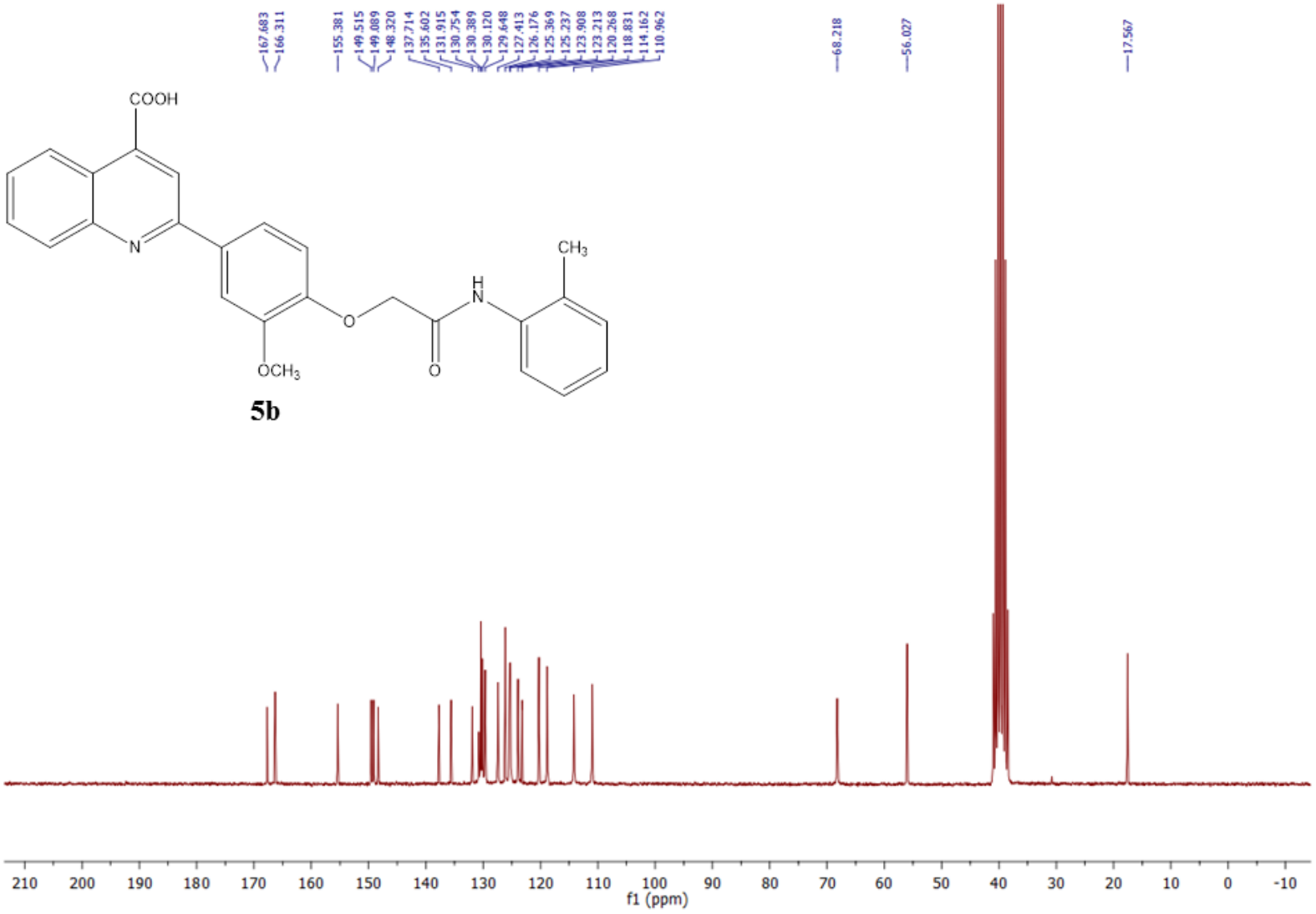

Figure S63. ^{13}C NMR spectrum of **5b** in DMSO-d_6 (50 MHz).

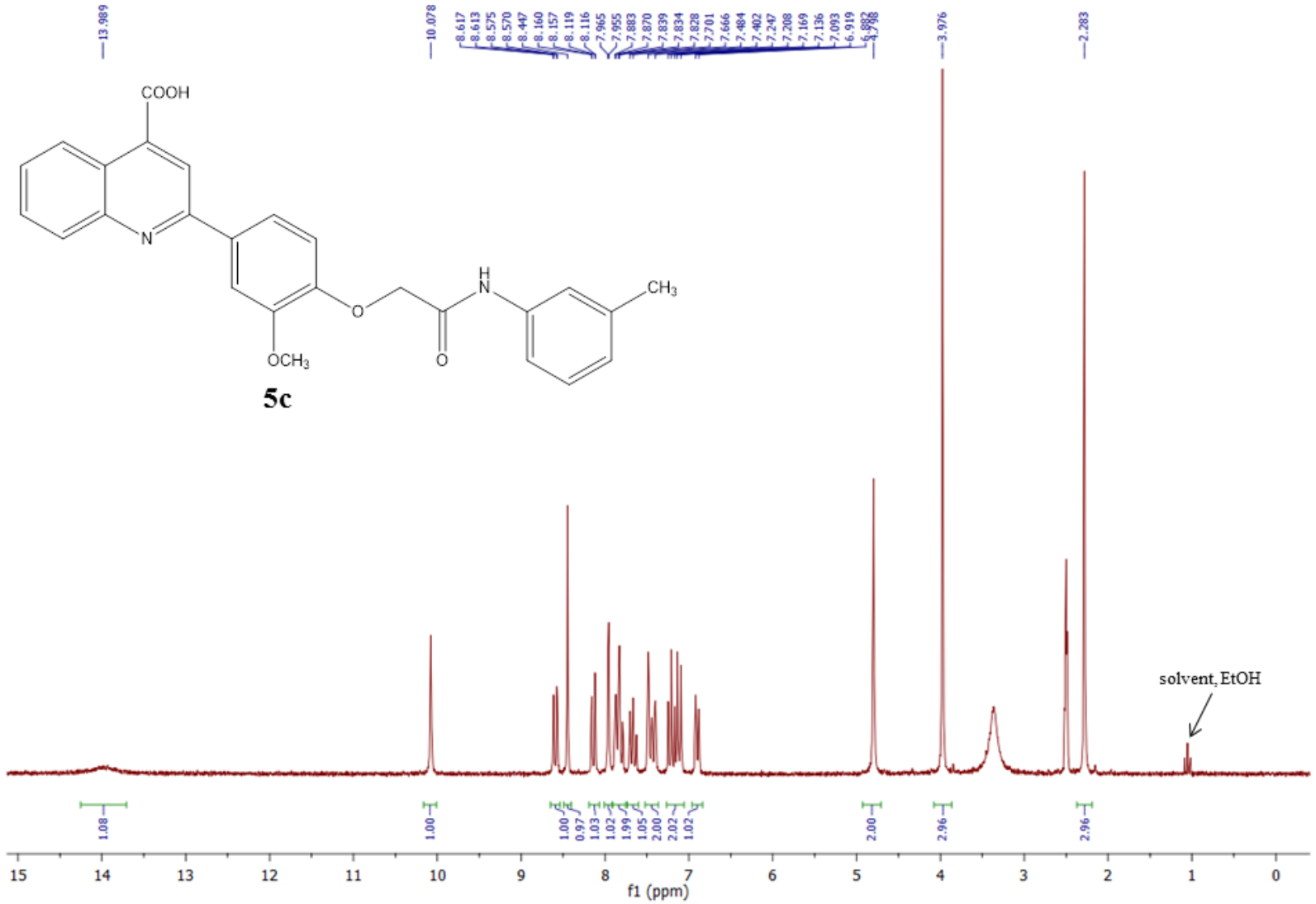

Figure S64. ^{1}H NMR spectrum of **5c** in DMSO-d_6 (200 MHz).

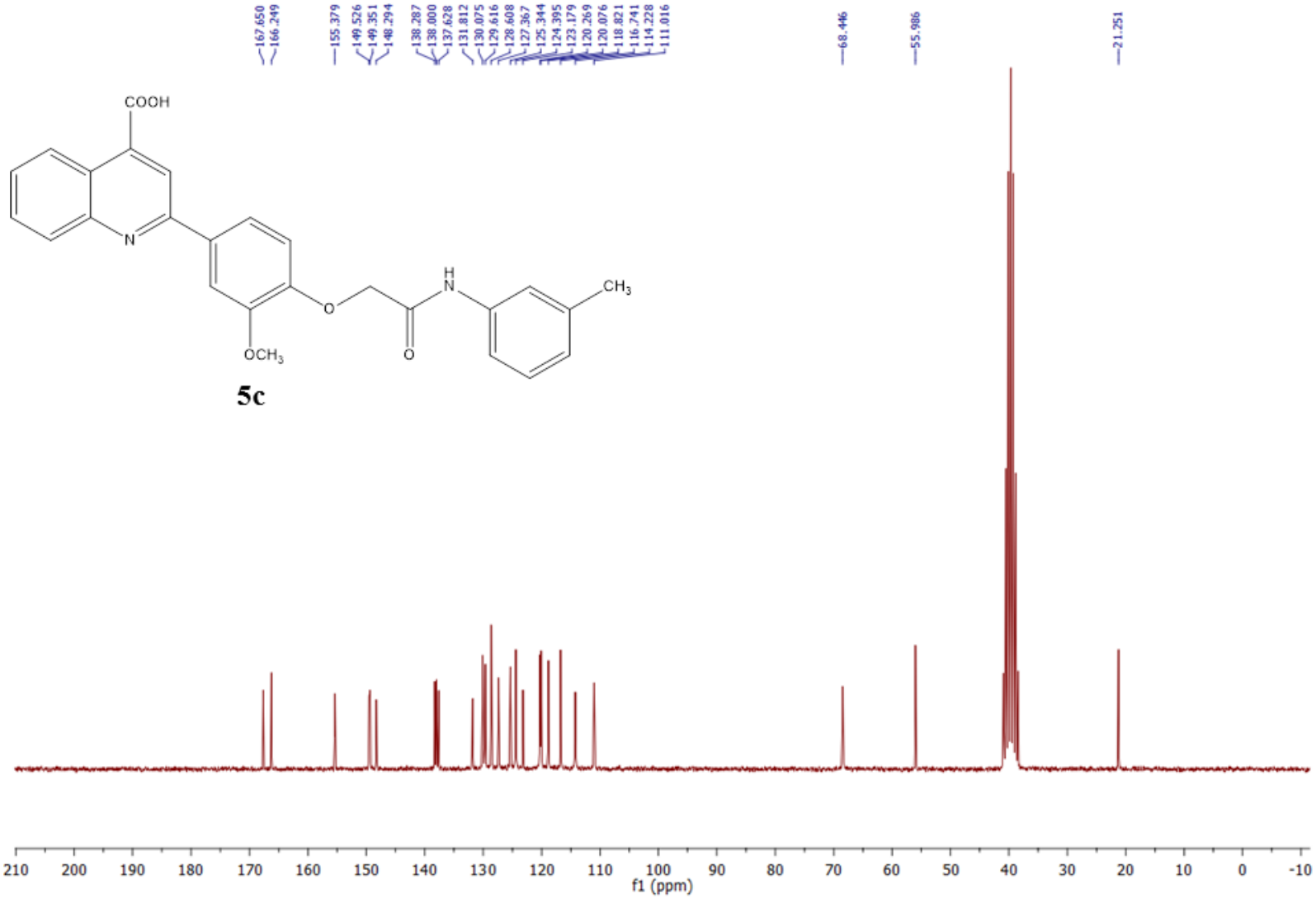

Figure S65. ^{13}C NMR spectrum of **5c** in DMSO-d_6 (50 MHz).

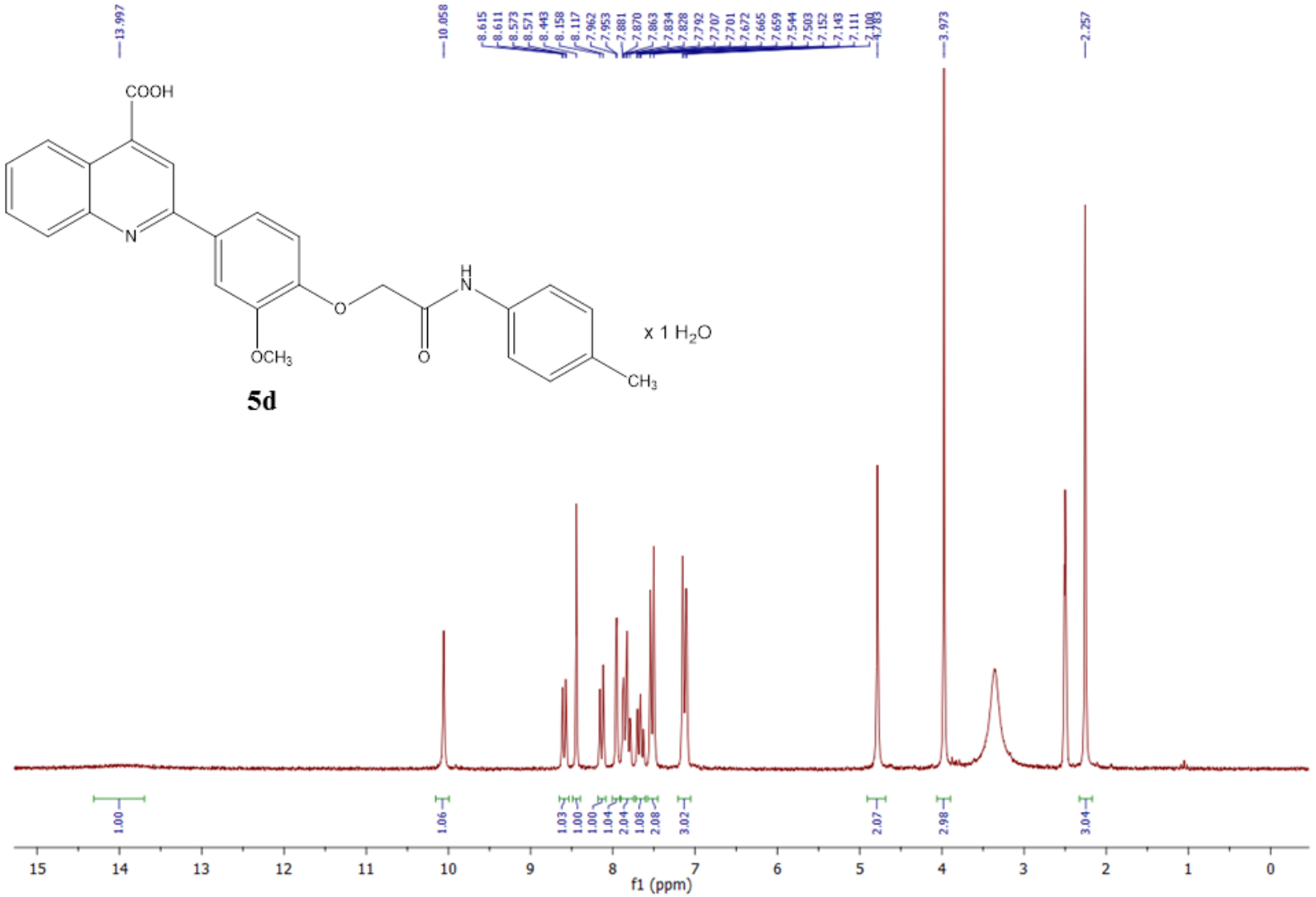

Figure S66. ^{1}H NMR spectrum of **5d** in DMSO-d_6 (200 MHz).

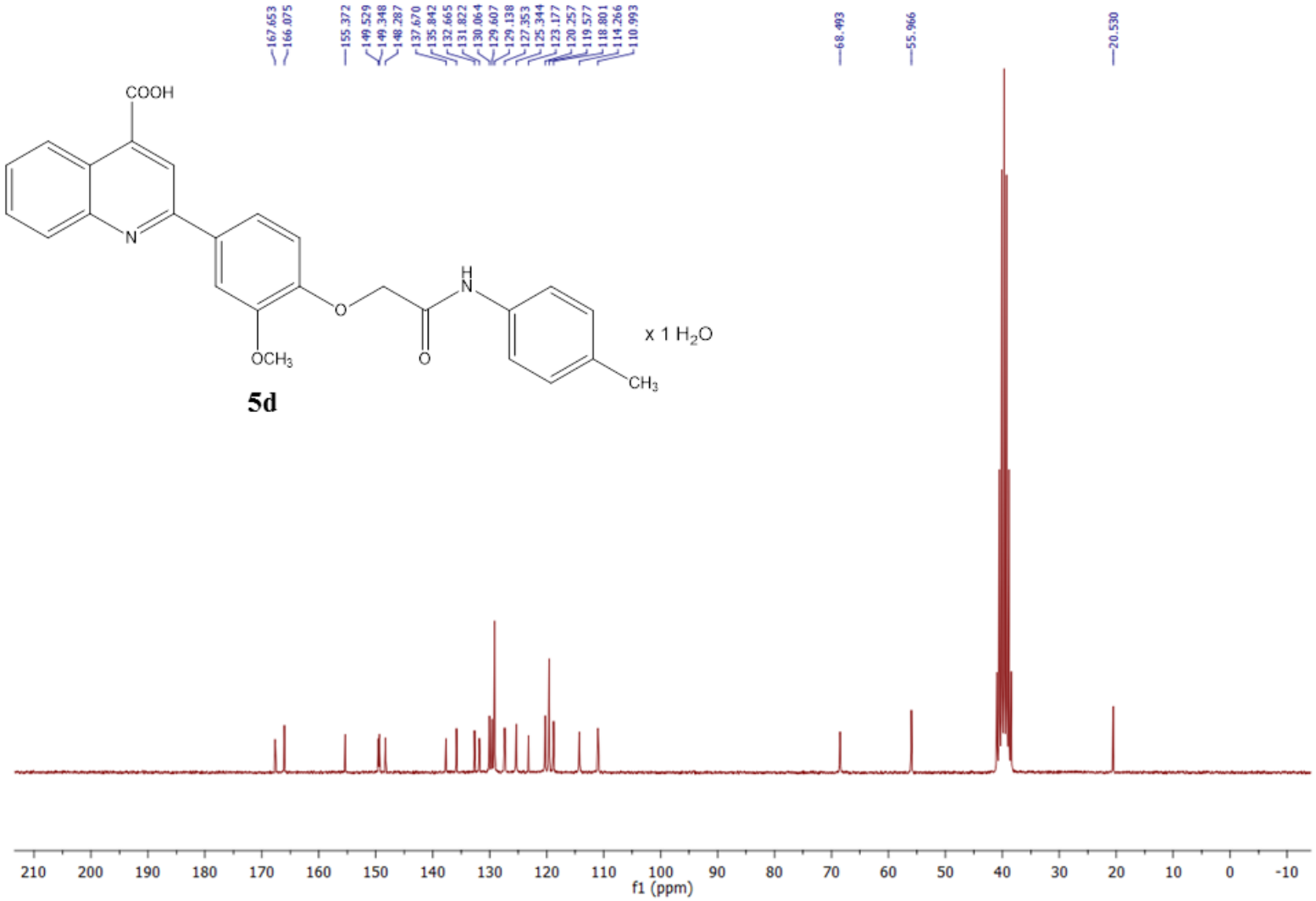

Figure S67. ^{13}C NMR spectrum of **5d** in DMSO-d_6 (50 MHz).

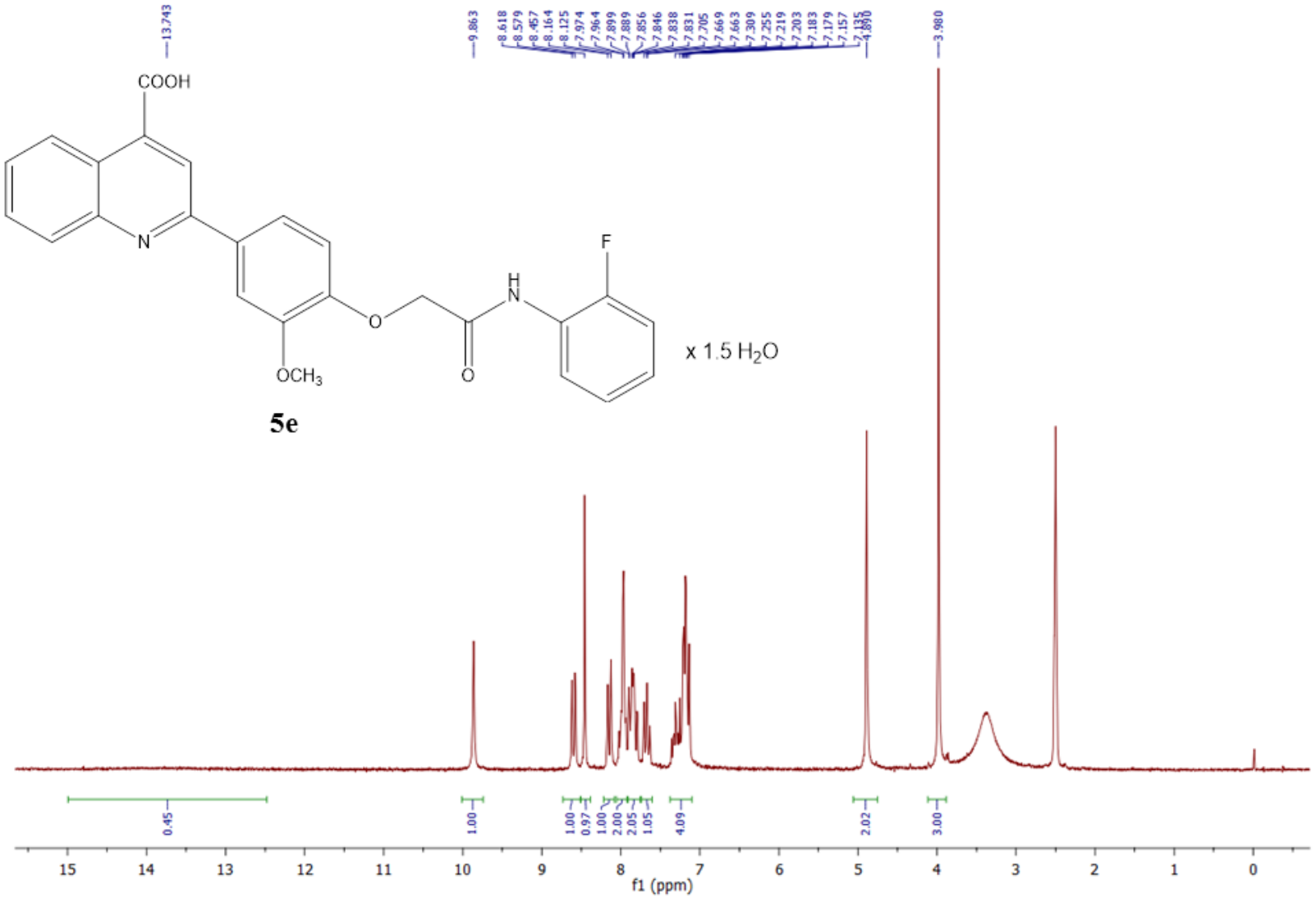

Figure S68. ^{1}H NMR spectrum of **5e** in DMSO-d_6 (200 MHz).

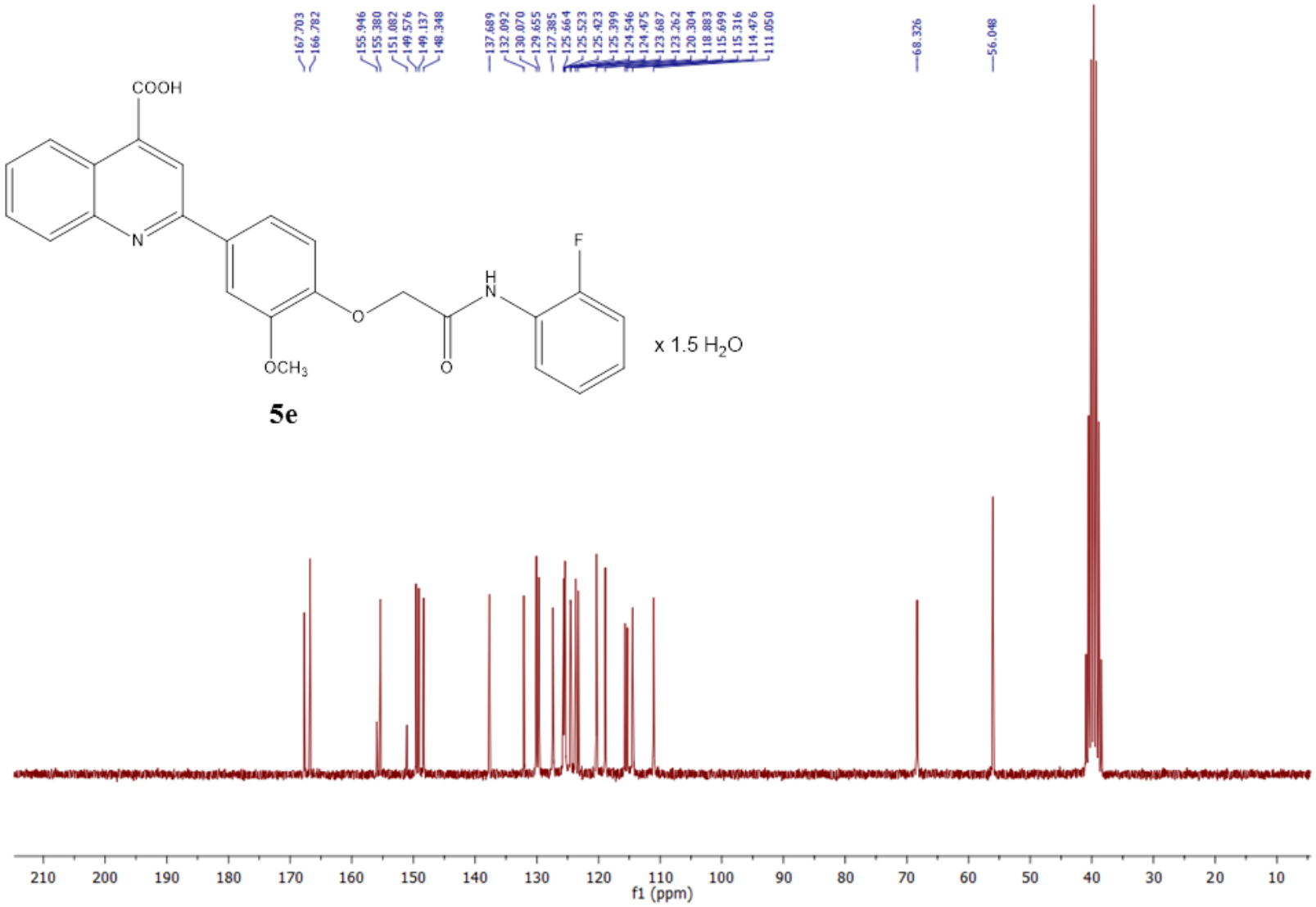

Figure S69. ^{13}C NMR spectrum of **5e** in DMSO-d_6 (50 MHz).

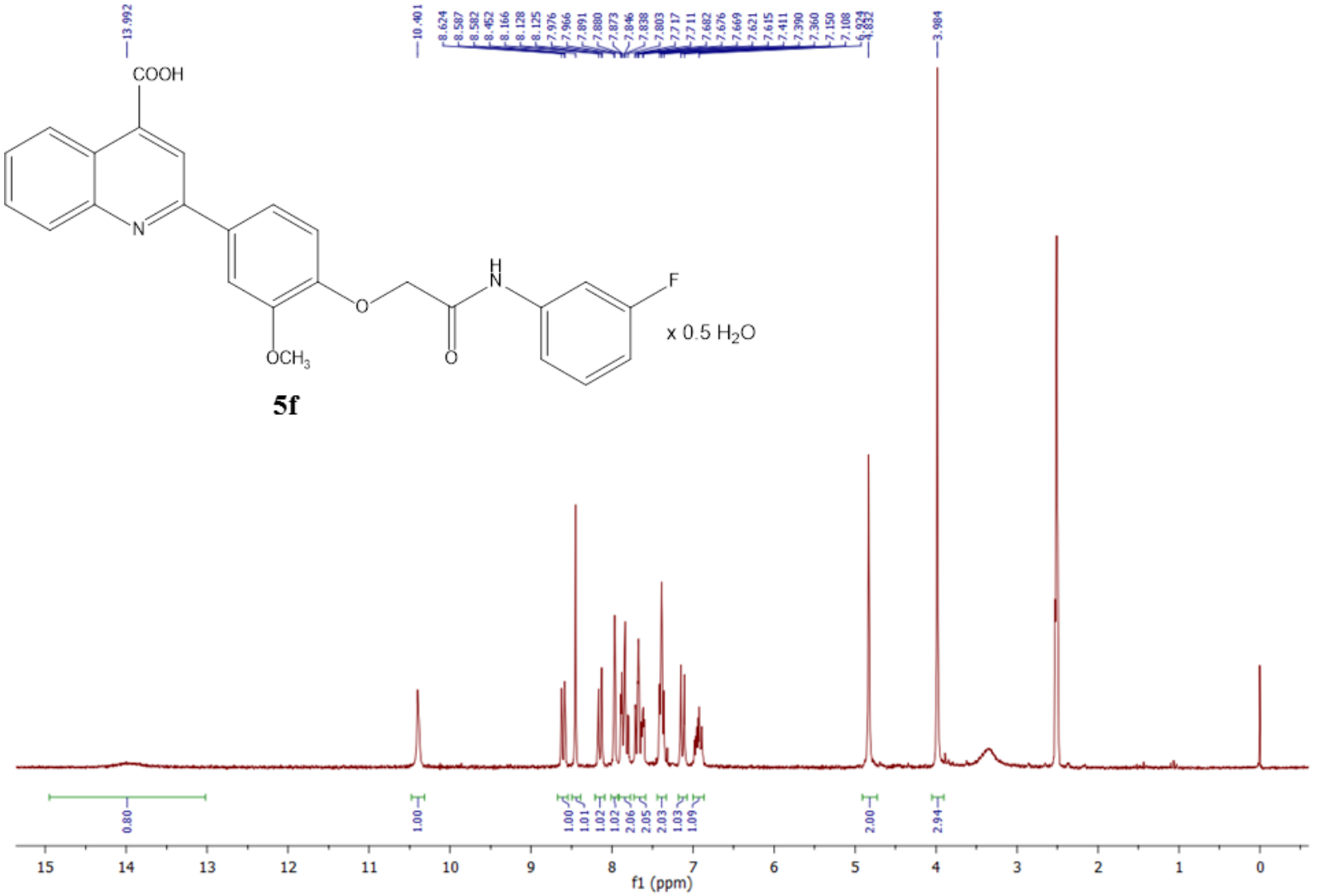

Figure S70. ^{1}H NMR spectrum of **5f** in DMSO-d_6 (200 MHz).

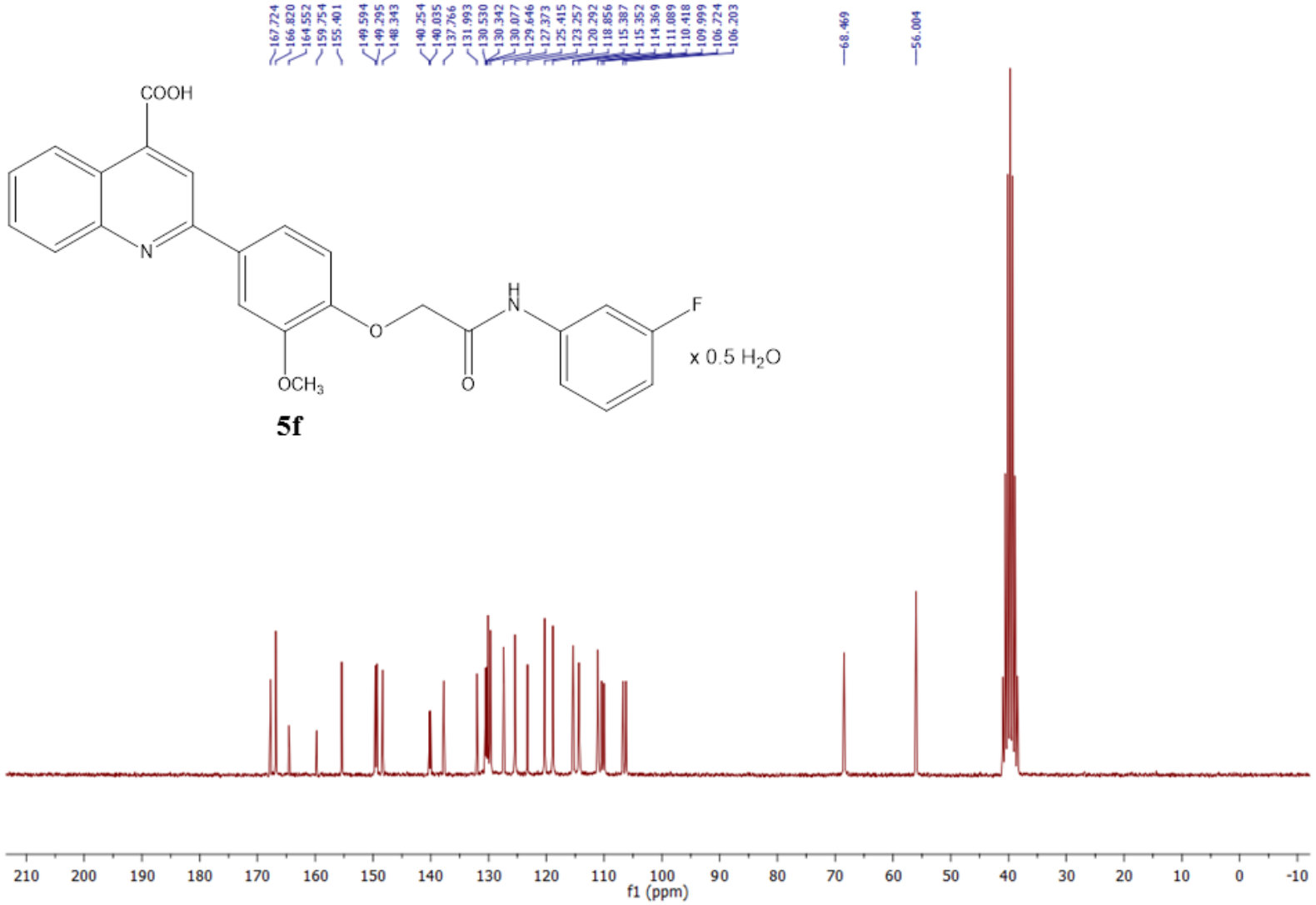

Figure S71. ^{13}C NMR spectrum of **5f** in DMSO-d_6 (50 MHz).

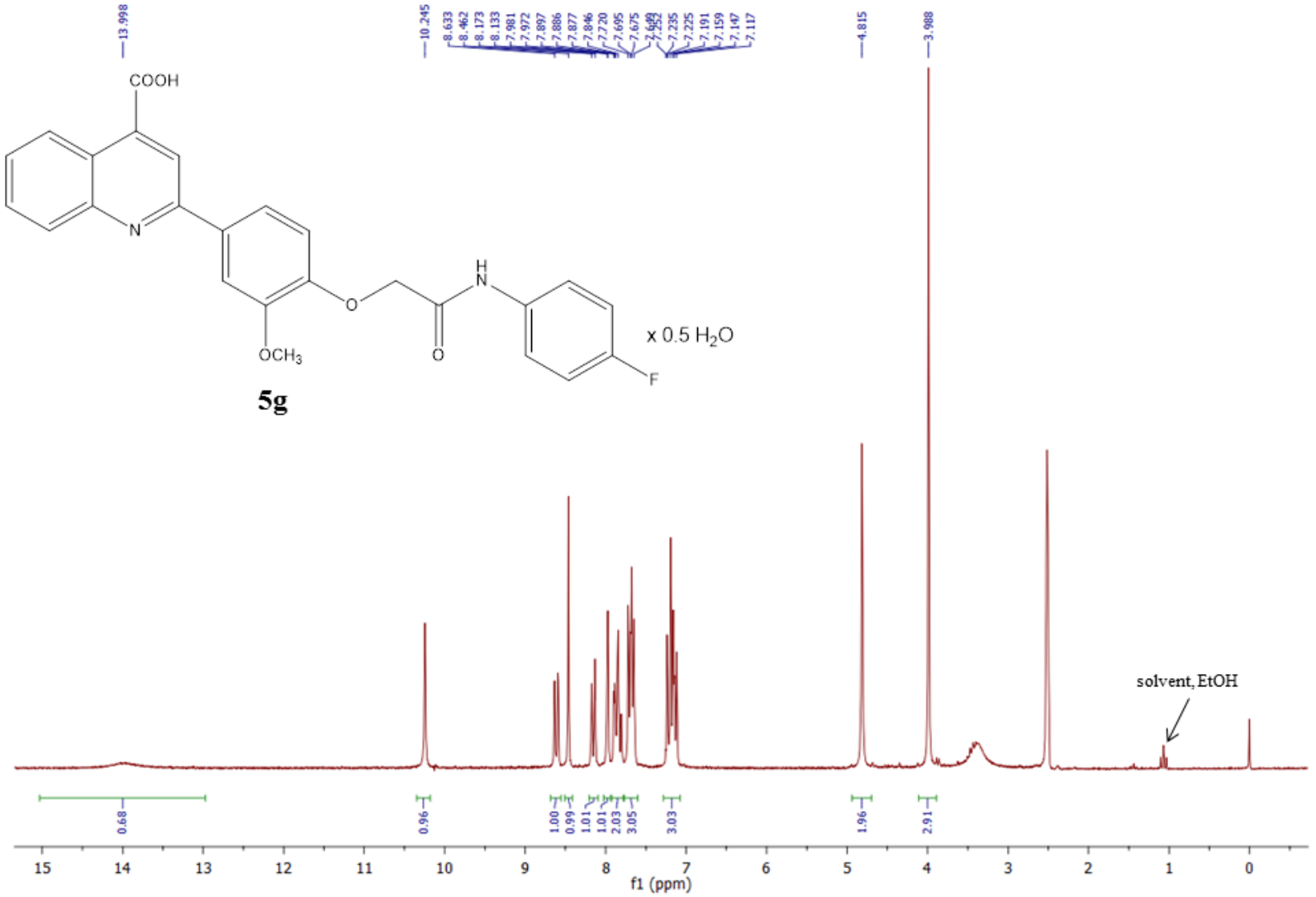

Figure S72. ^{1}H NMR spectrum of **5g** in DMSO-d_6 (200 MHz).

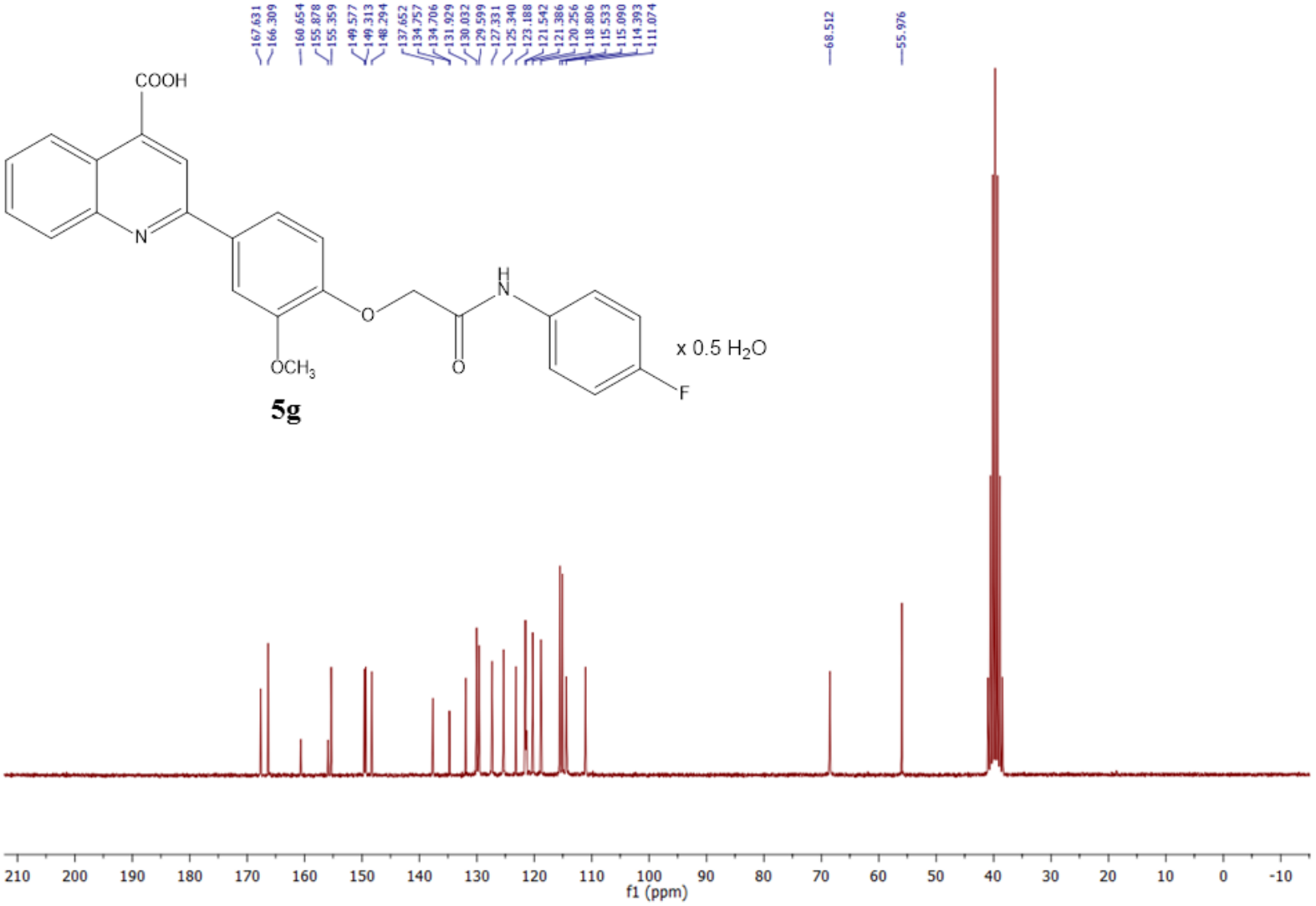

Figure S73. ^{13}C NMR spectrum of **5g** in DMSO-d_6 (50 MHz).

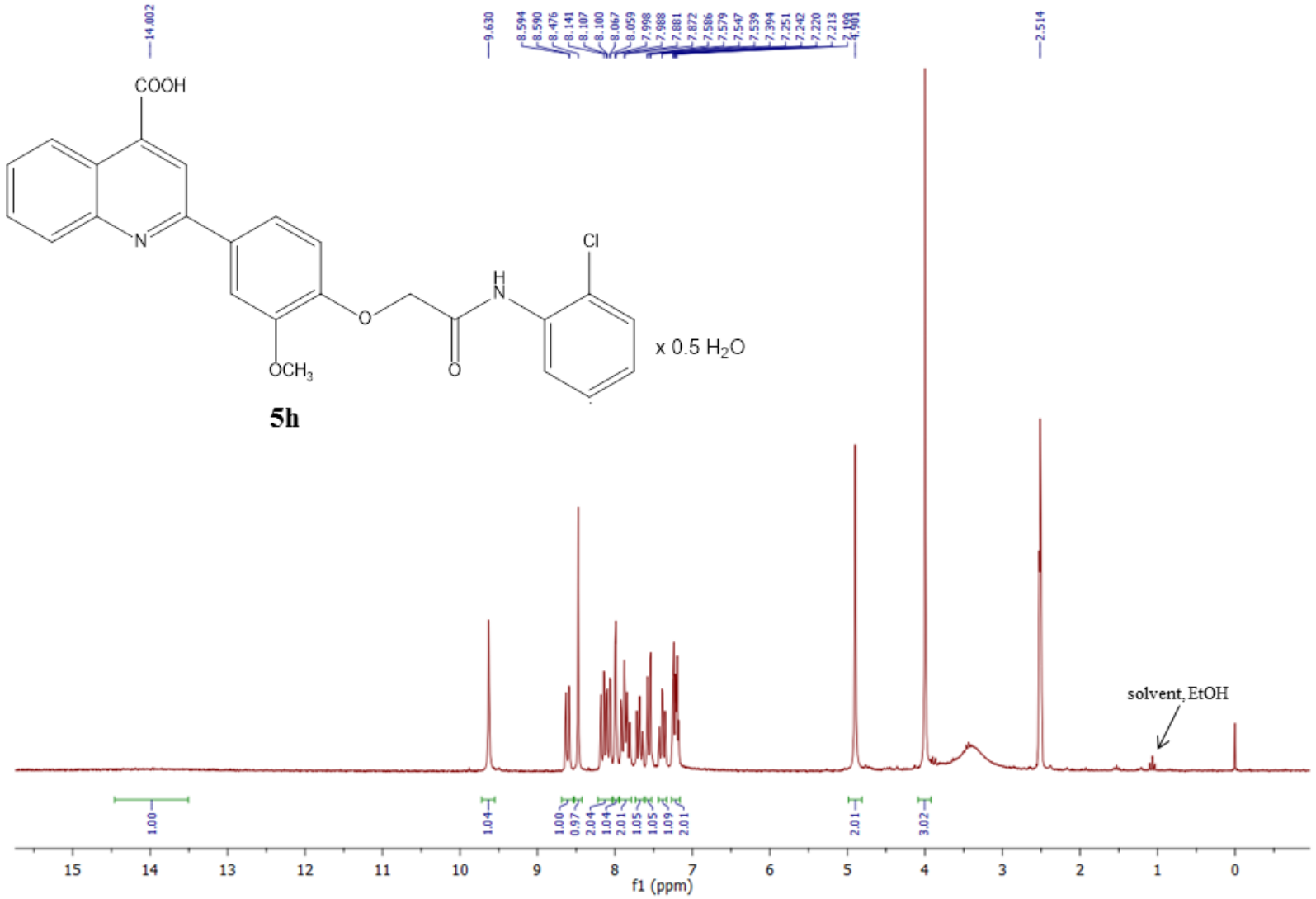

Figure S74. ^{1}H NMR spectrum of **5h** in DMSO-d_6 (200 MHz).

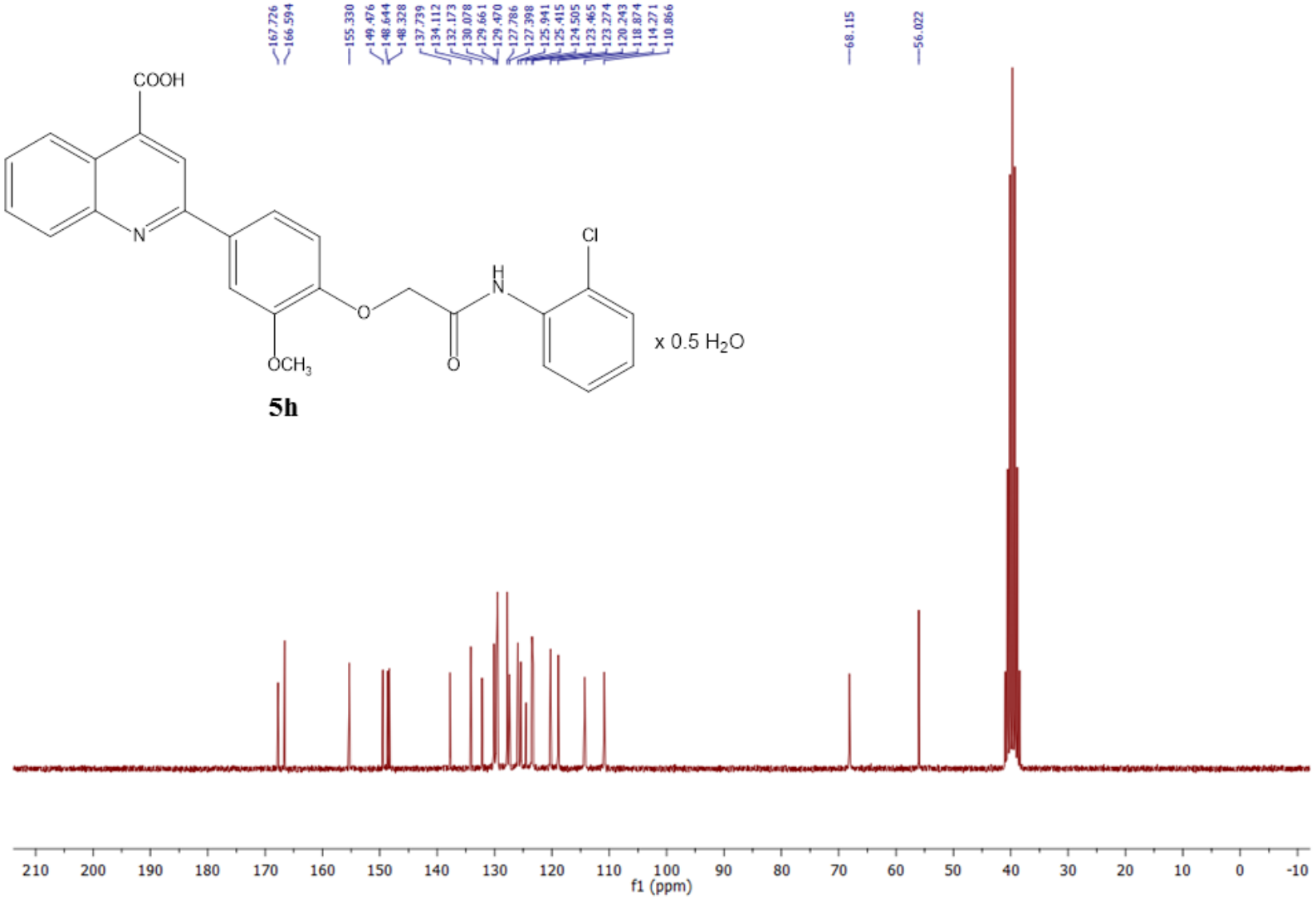

Figure S75. ^{13}C NMR spectrum of **5h** in DMSO-d_6 (50 MHz).

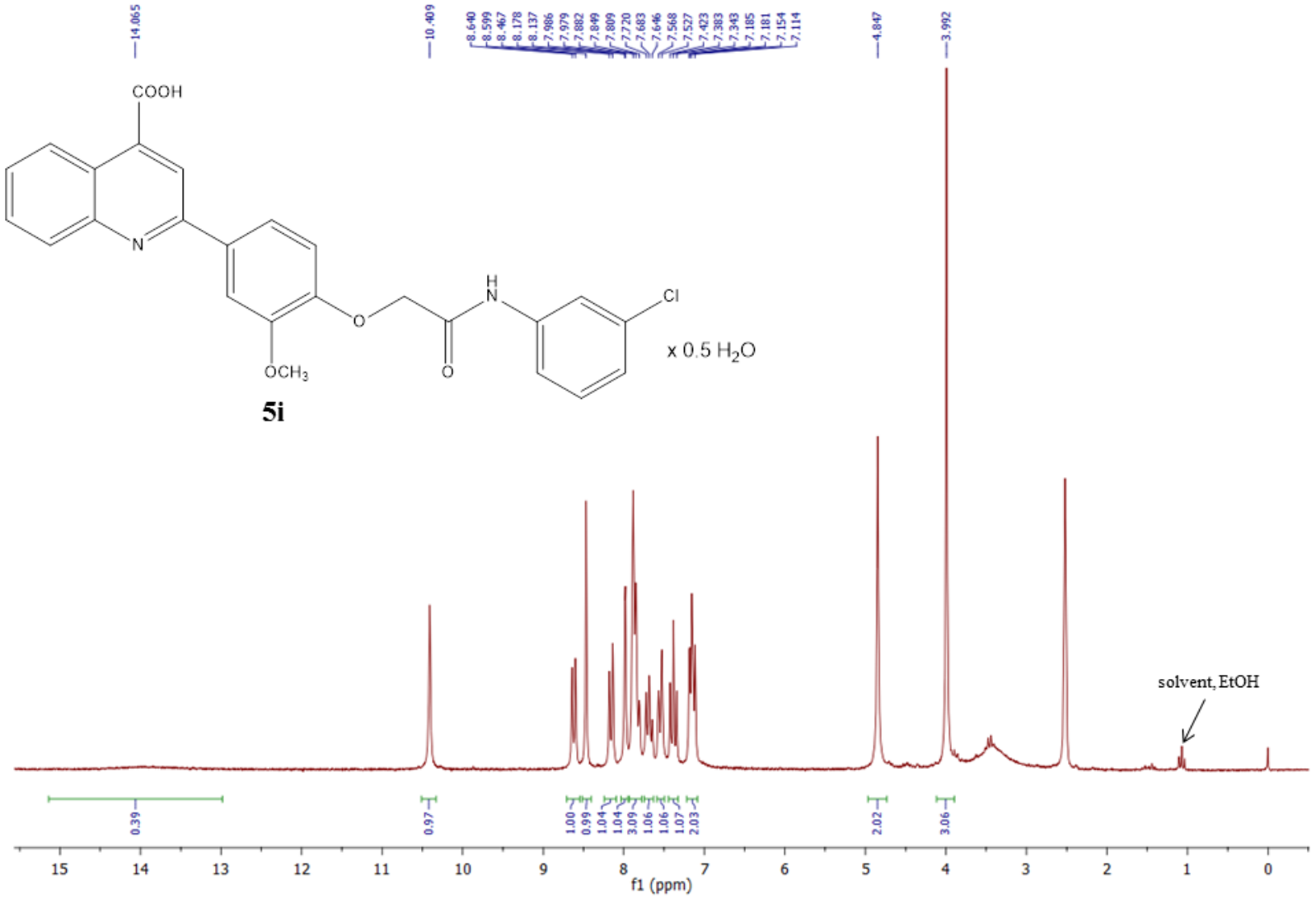

Figure S76. ^{1}H NMR spectrum of **5i** in DMSO-d_6 (200 MHz).

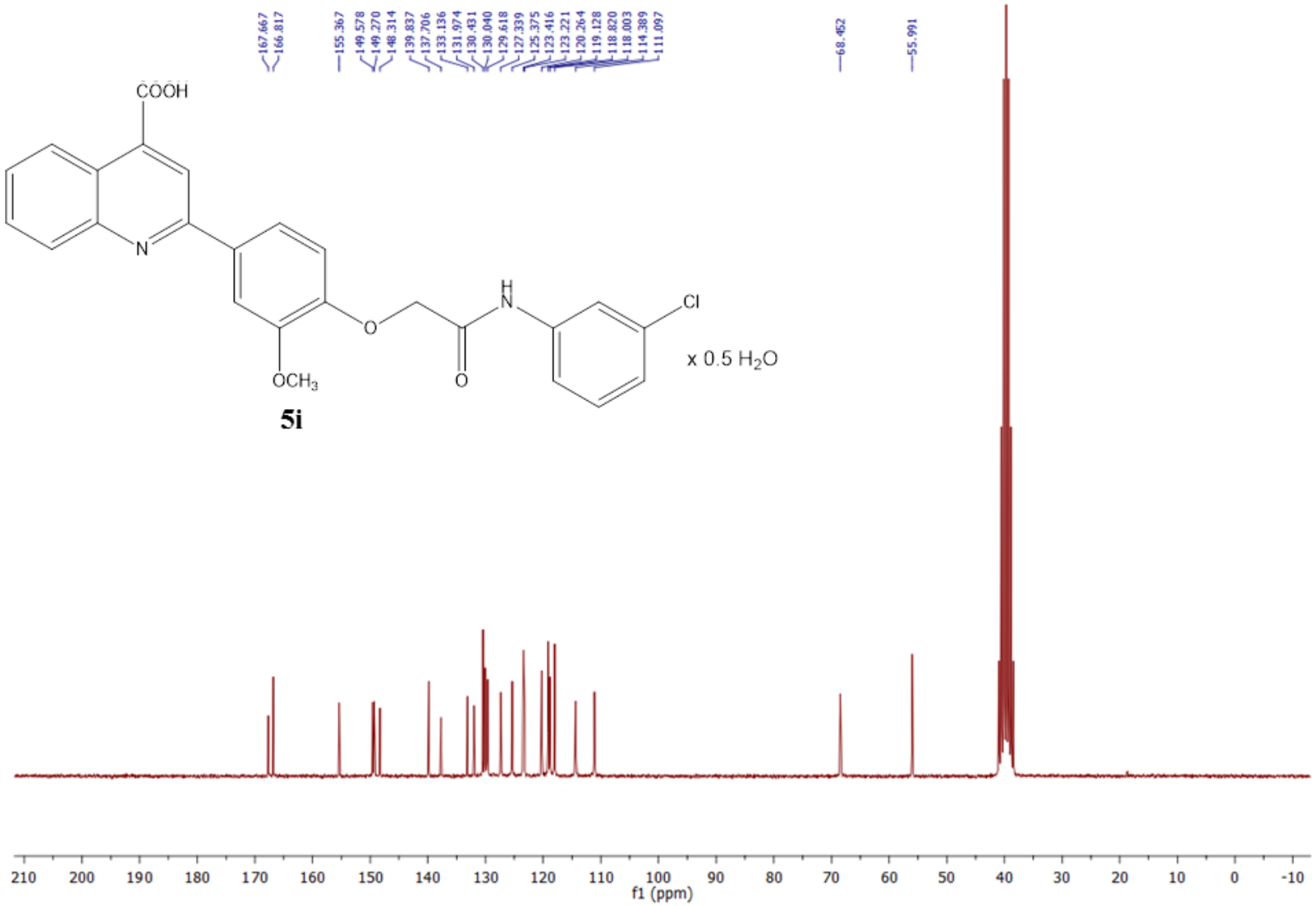

Figure S77. ^{13}C NMR spectrum of **5i** in DMSO-d_6 (50 MHz).

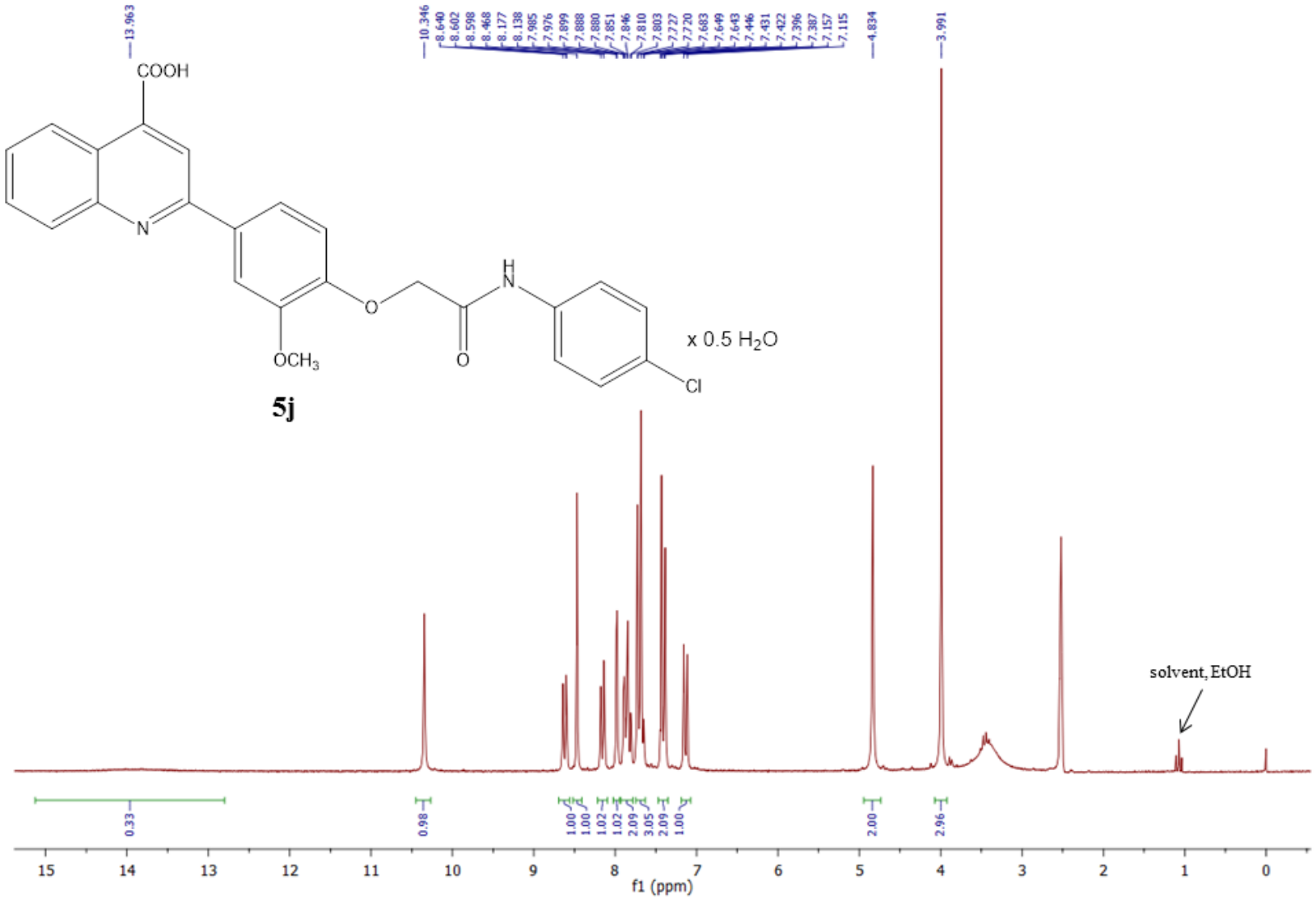

Figure S78. ^{1}H NMR spectrum of **5j** in DMSO-d_6 (200 MHz).

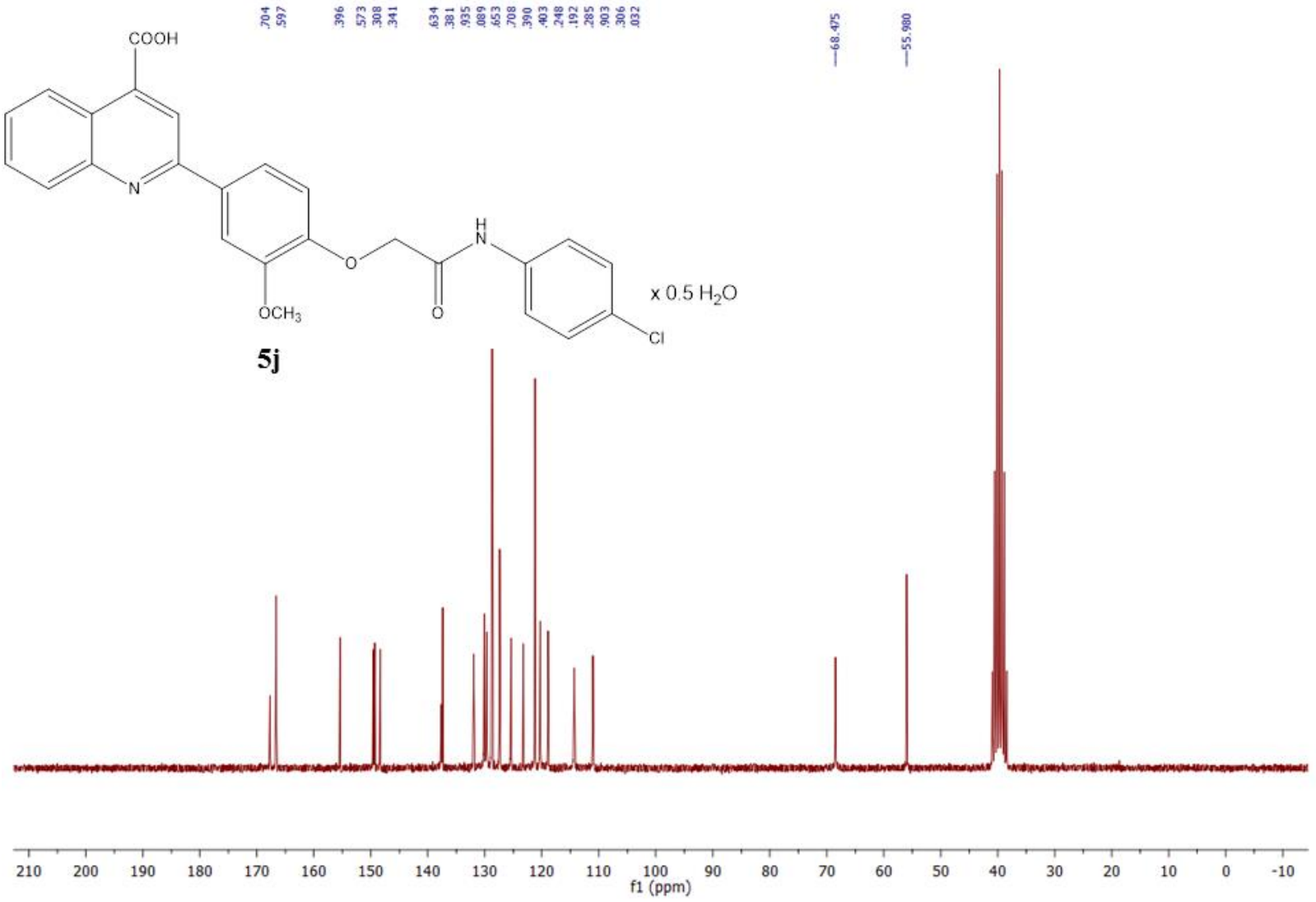

Figure S79. ^{13}C NMR spectrum of **5j** in DMSO-d_6 (50 MHz).

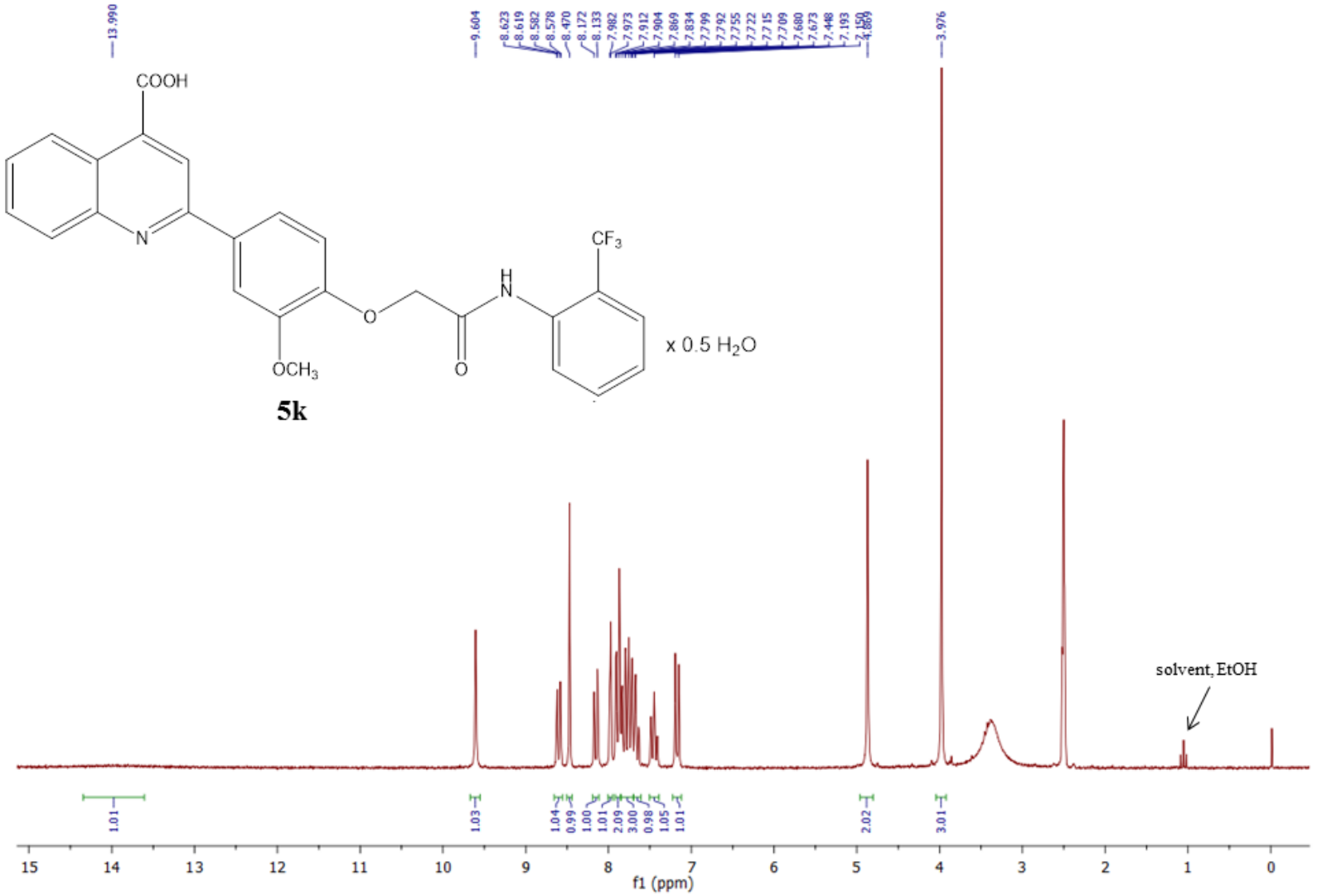

Figure S80. ^{1}H NMR spectrum of **5k** in DMSO-d_6 (200 MHz).

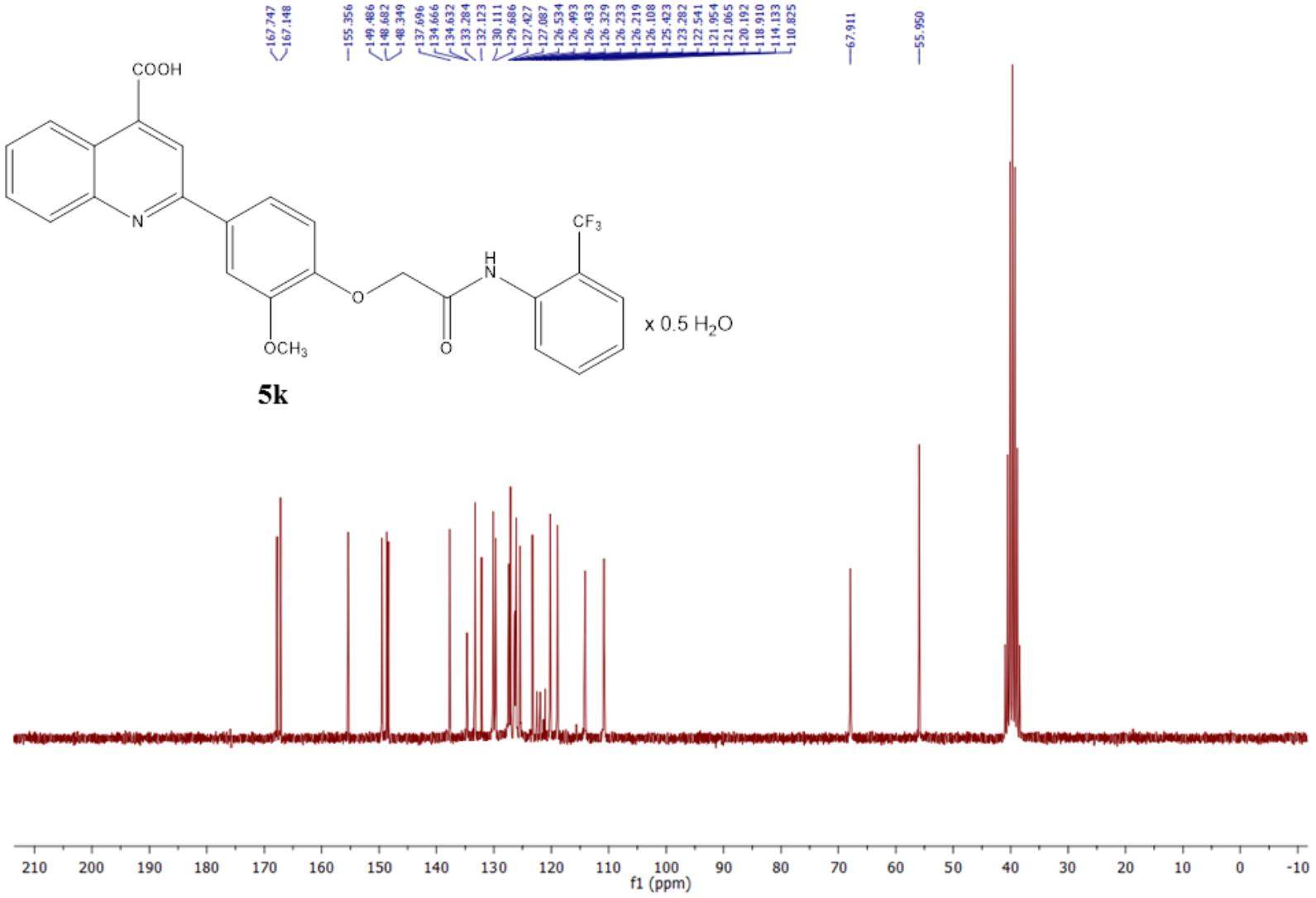

Figure S81. ^{13}C NMR spectrum of **5k** in DMSO-d_6 (50 MHz).

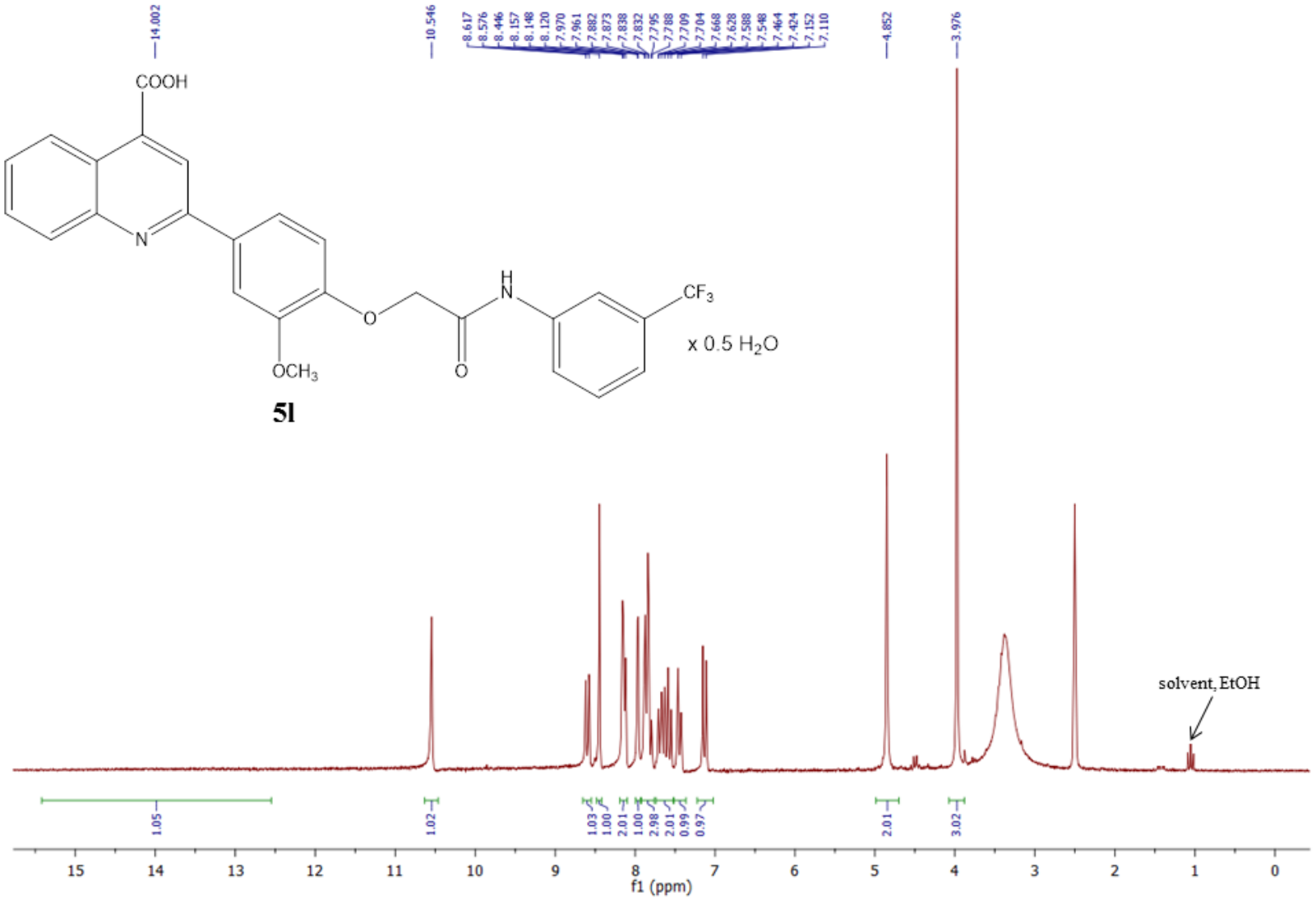

Figure S82. ^{1}H NMR spectrum of **5l** in DMSO-d_6 (200 MHz).

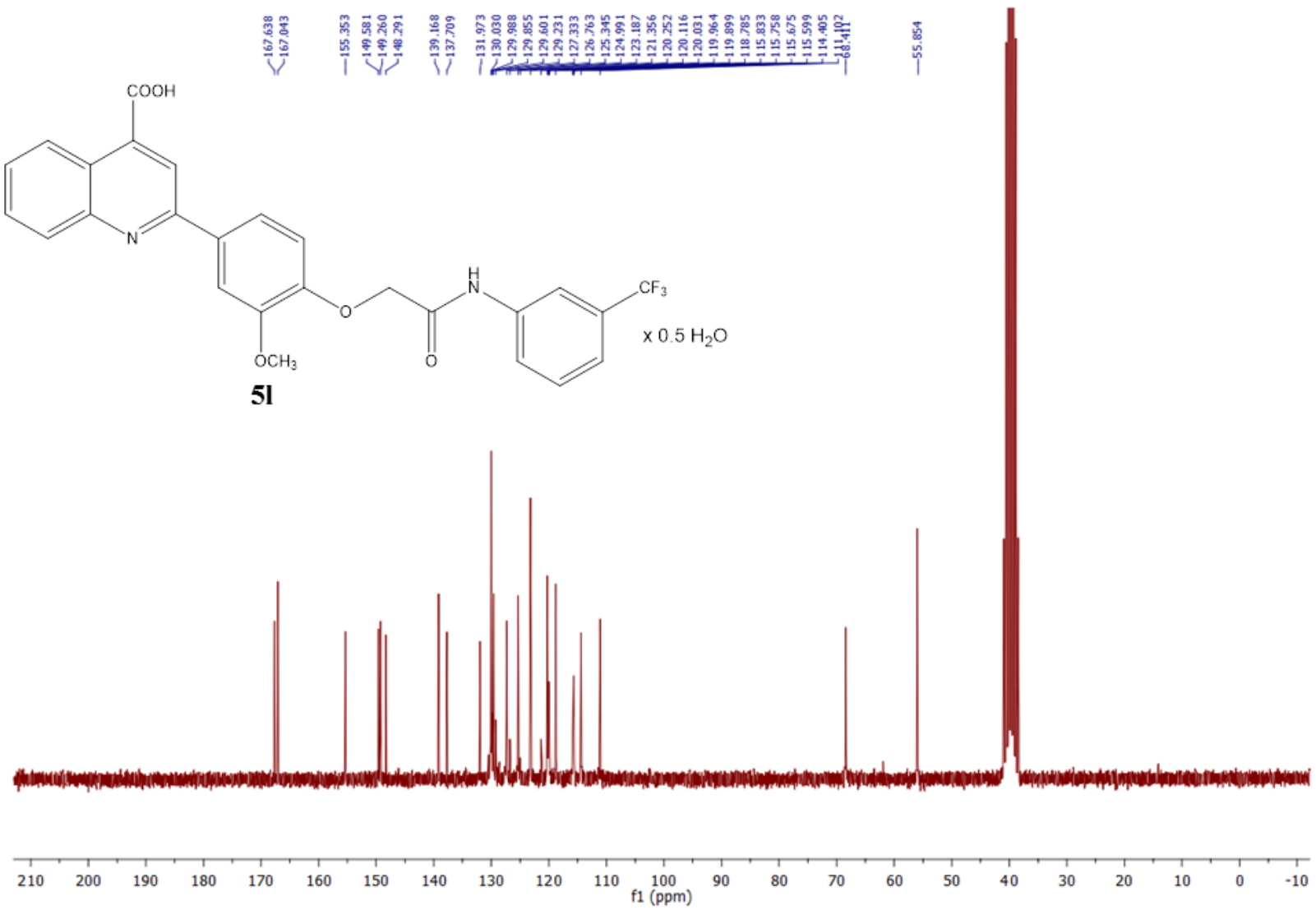

Figure S83. ^{13}C NMR spectrum of **5l** in DMSO-d_6 (50 MHz).

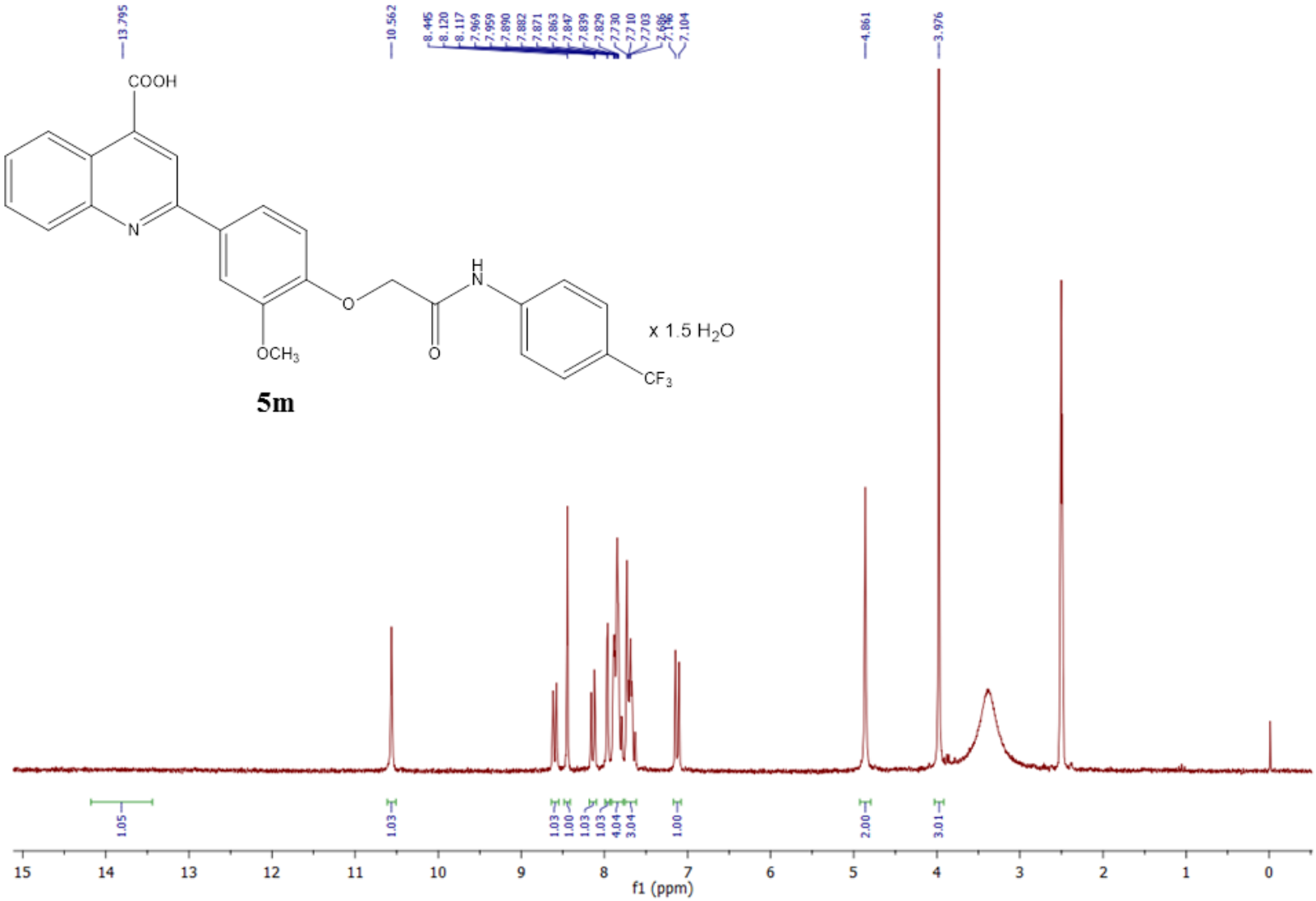

Figure S84. ^{1}H NMR spectrum of **5m** in DMSO-d_6 (200 MHz).

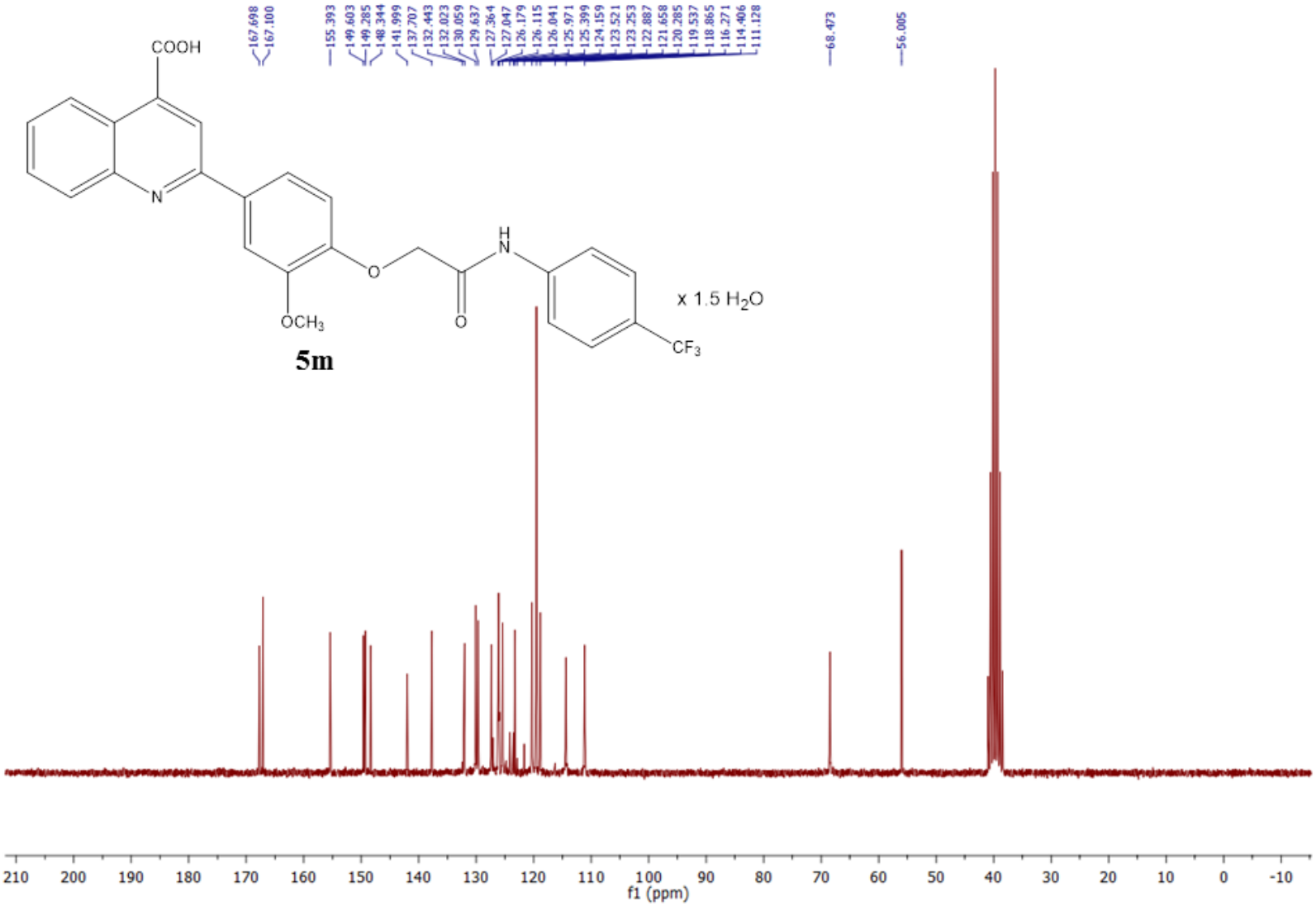

Figure S85. ^{13}C NMR spectrum of **5m** in DMSO-d_6 (50 MHz).

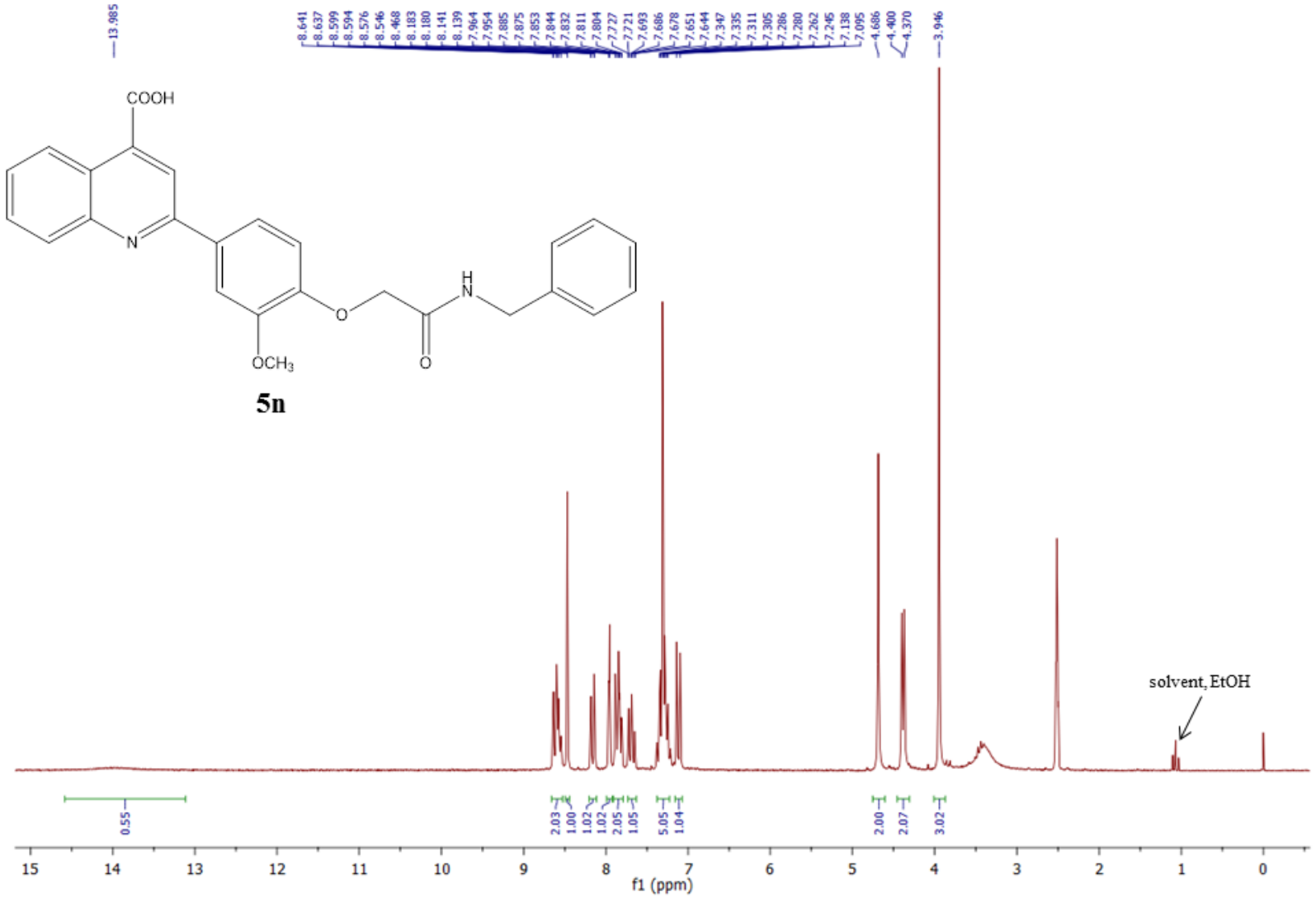

Figure S86. ^{1}H NMR spectrum of **5n** in DMSO-d_6 (200 MHz).

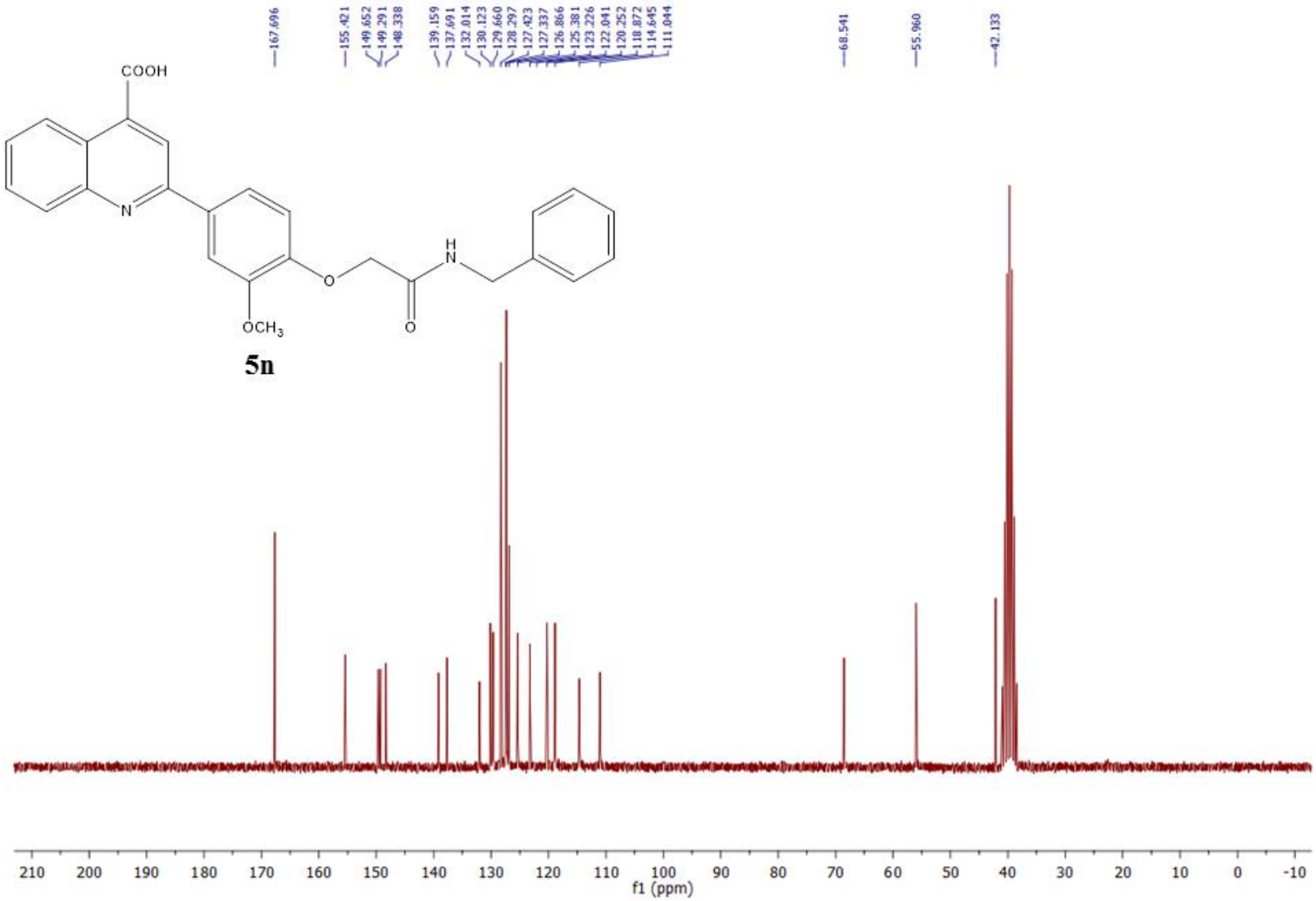

Figure S87. ^{13}C NMR spectrum of **5n** in DMSO-d_6 (50 MHz).

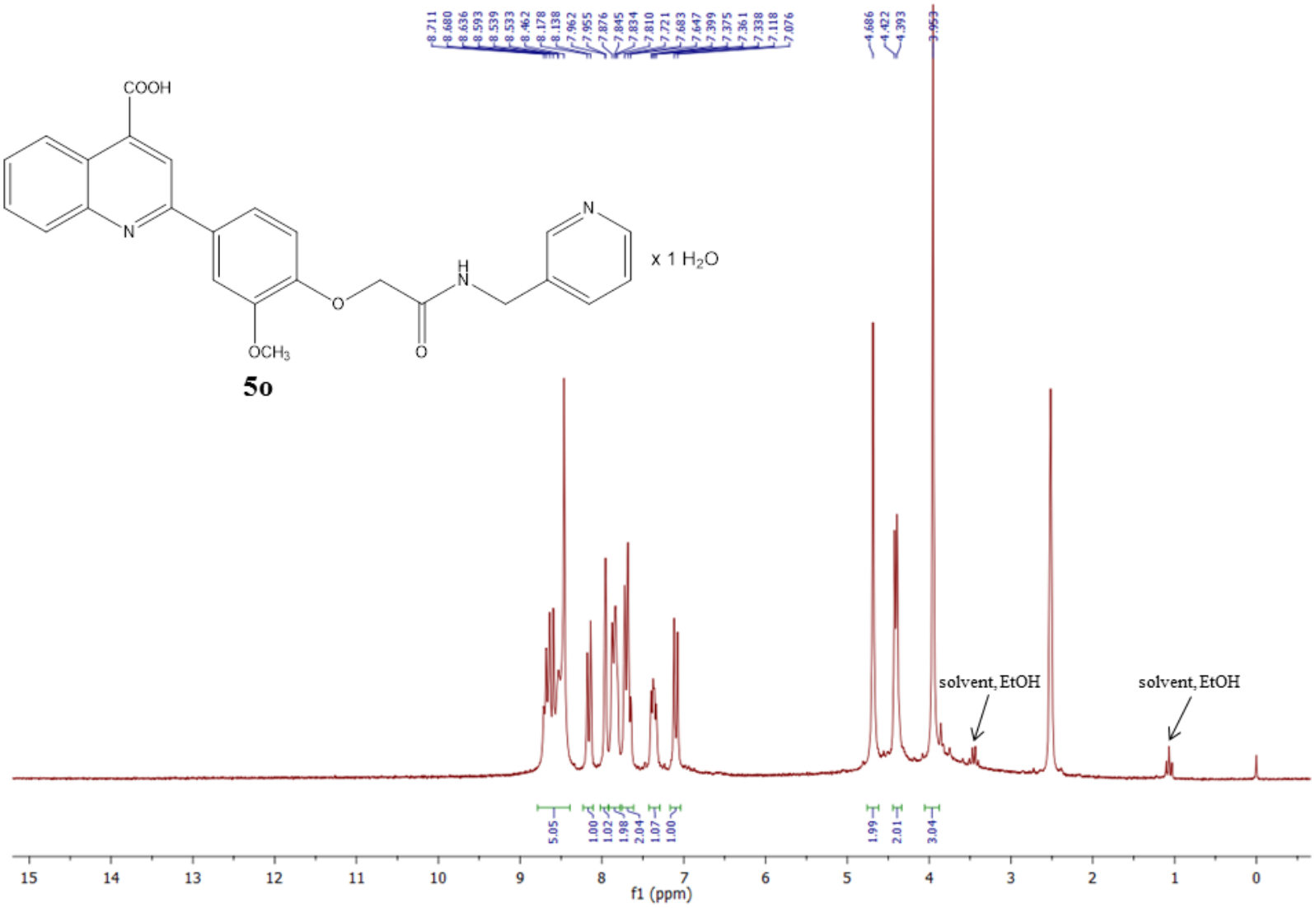

Figure S88. ^{1}H NMR spectrum of **5o** in DMSO-d_6 (200 MHz).

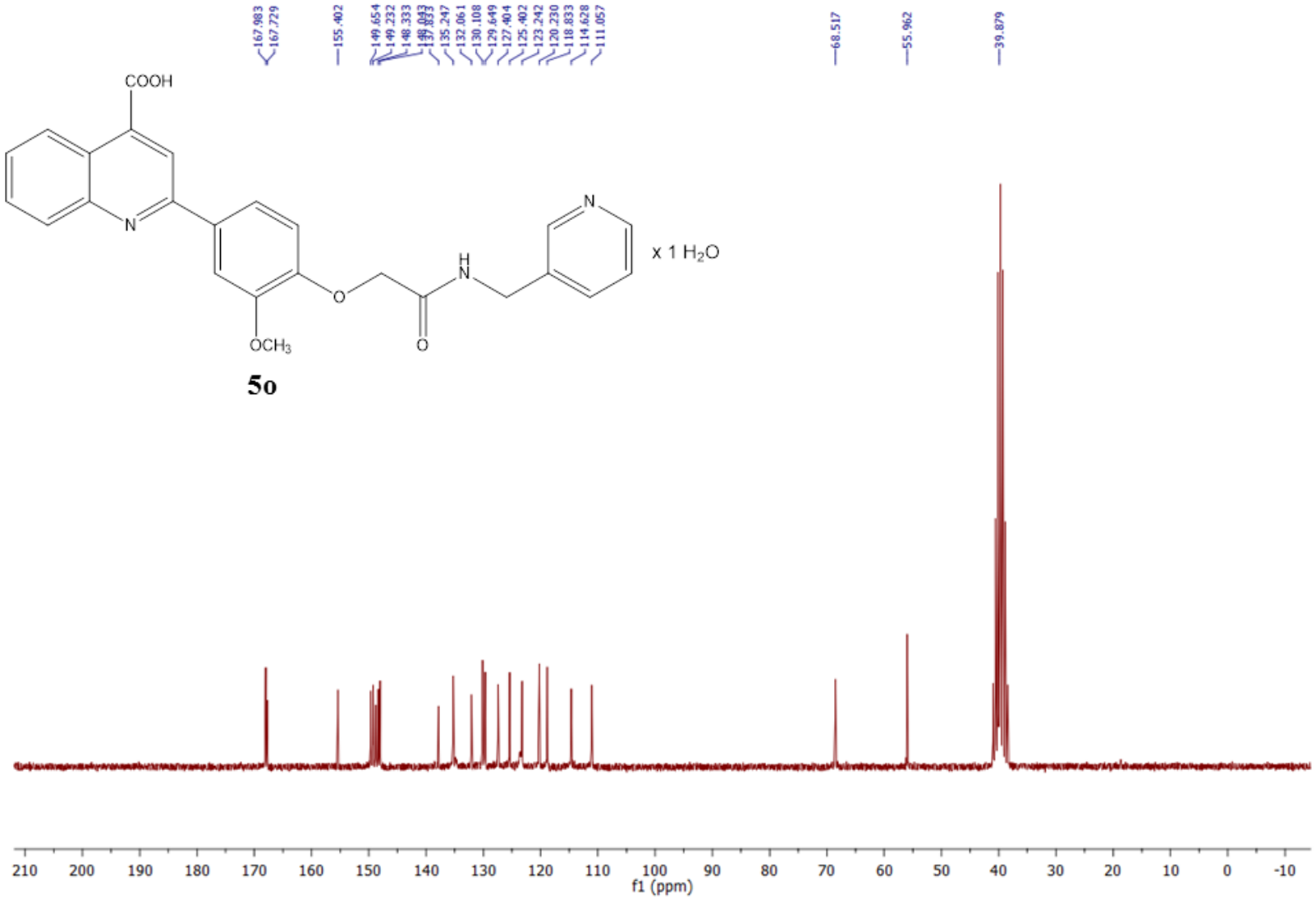

Figure S89. ^{13}C NMR spectrum of **5o** in DMSO-d_6 (50 MHz).

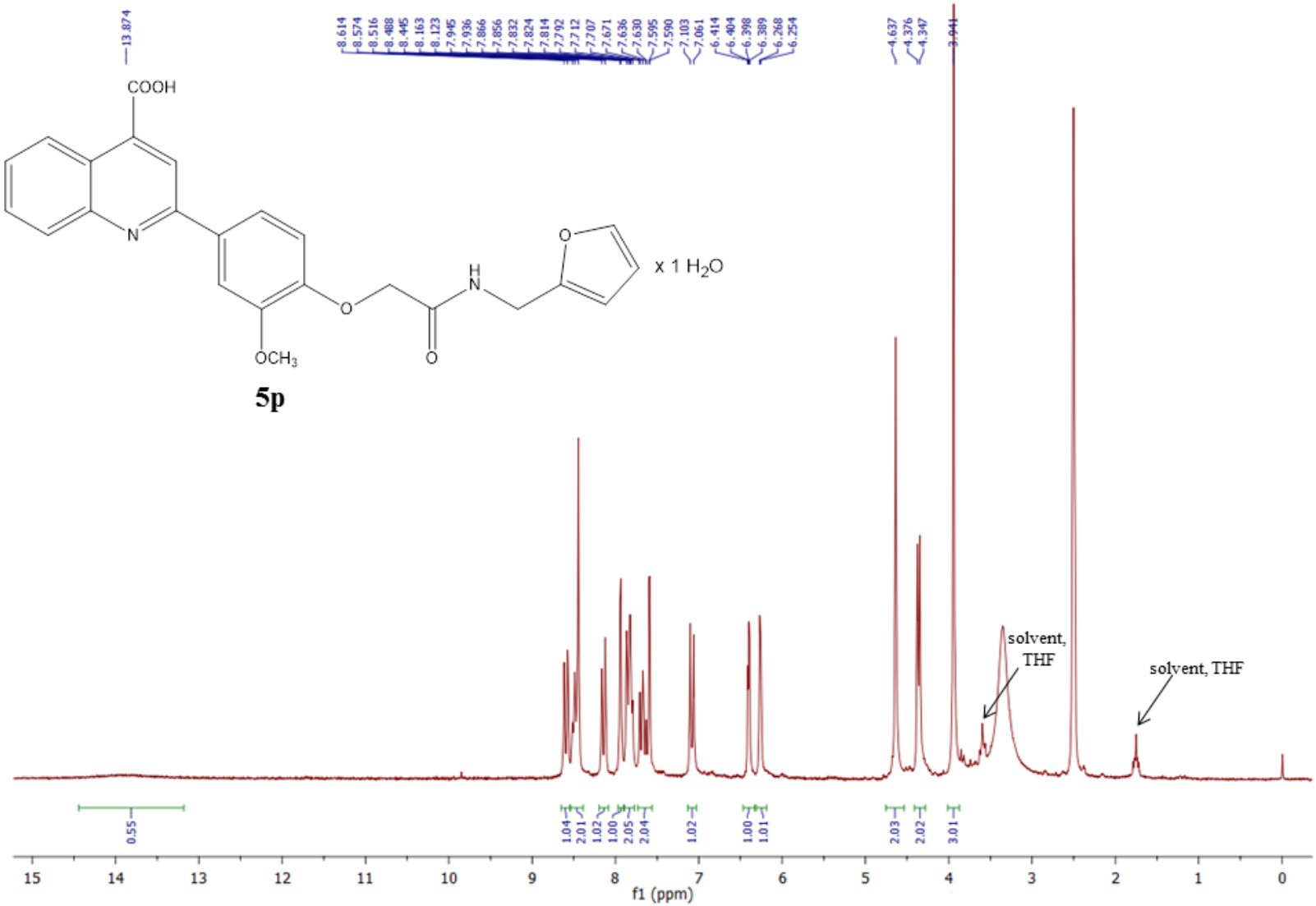

Figure S90. ^{1}H NMR spectrum of **5p** in DMSO-d_6 (200 MHz).

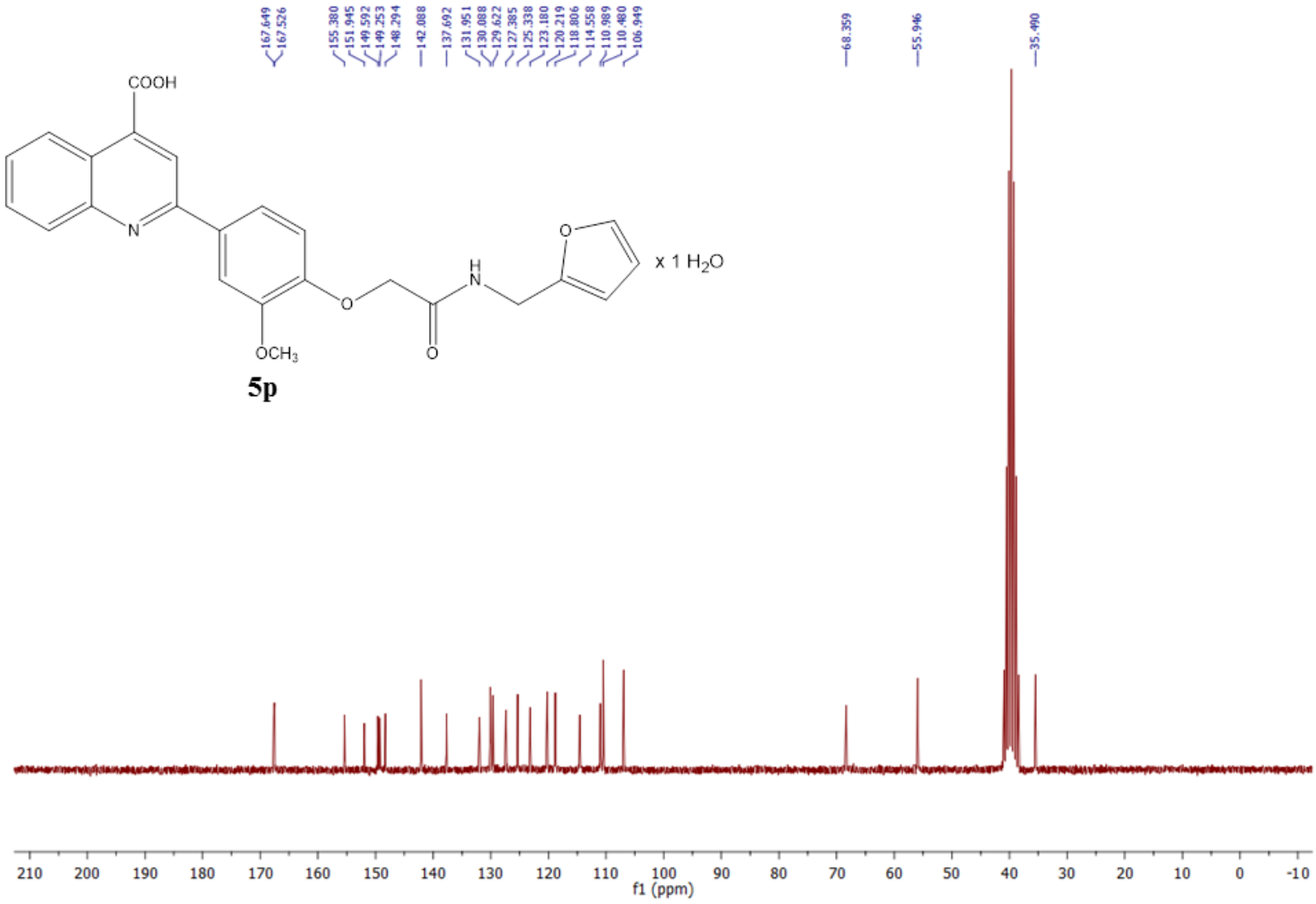

Figure S91. ^{13}C NMR spectrum of **5p** in DMSO-d_6 (50 MHz).

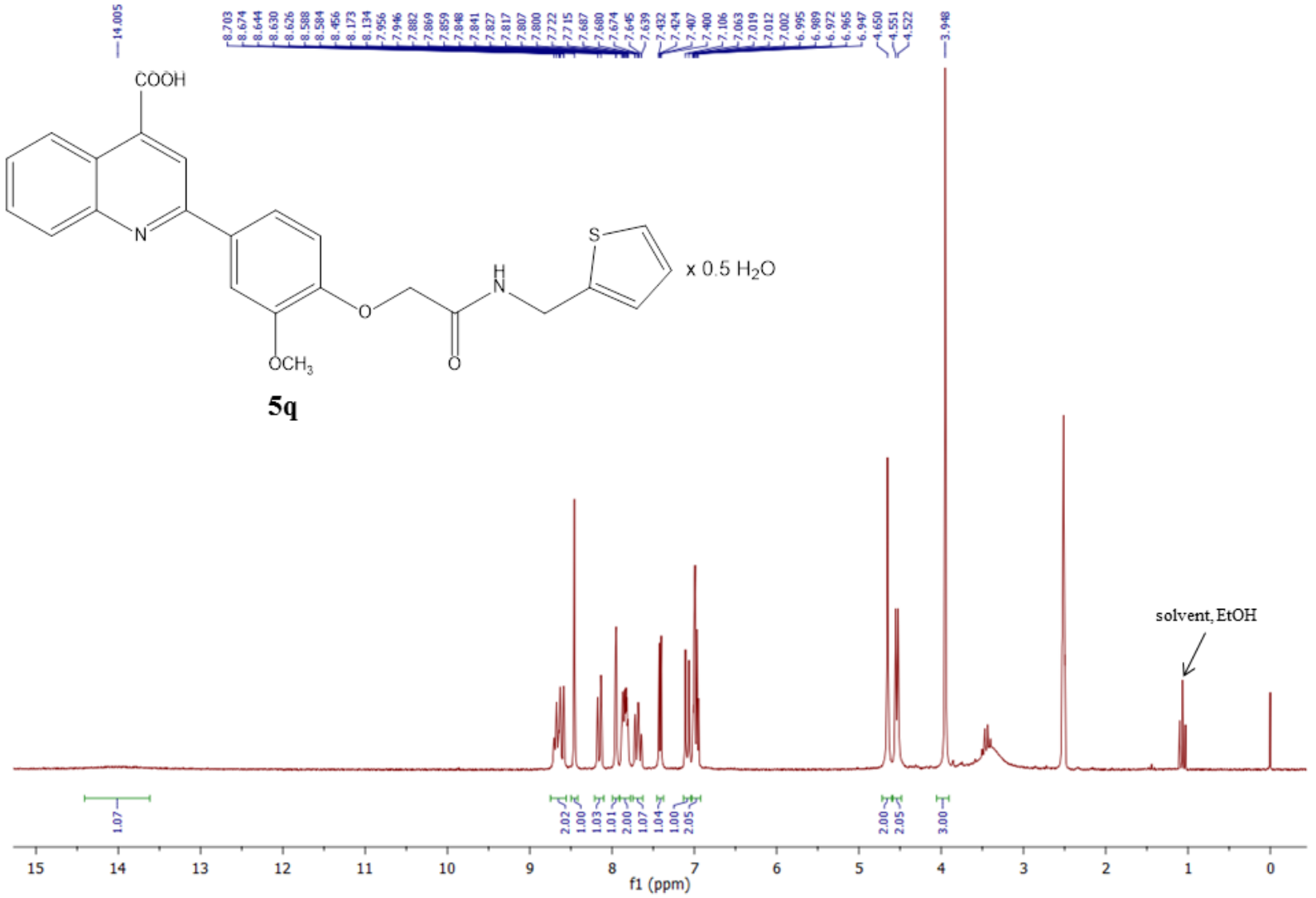

Figure S92. ^{1}H NMR spectrum of **5q** in DMSO-d_6 (200 MHz).

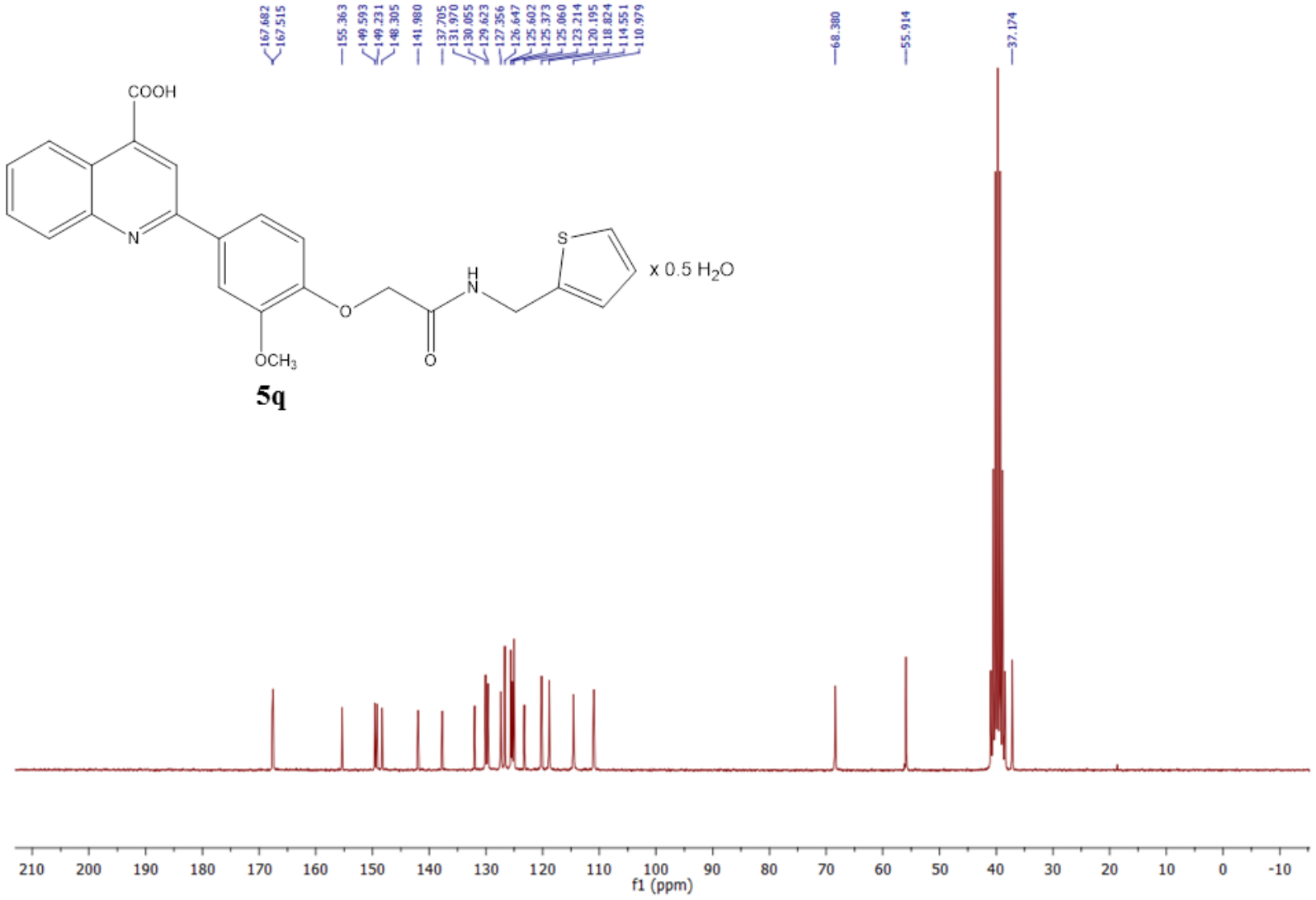

Figure S93. ^{13}C NMR spectrum of **5q** in DMSO-d_6 (50 MHz).

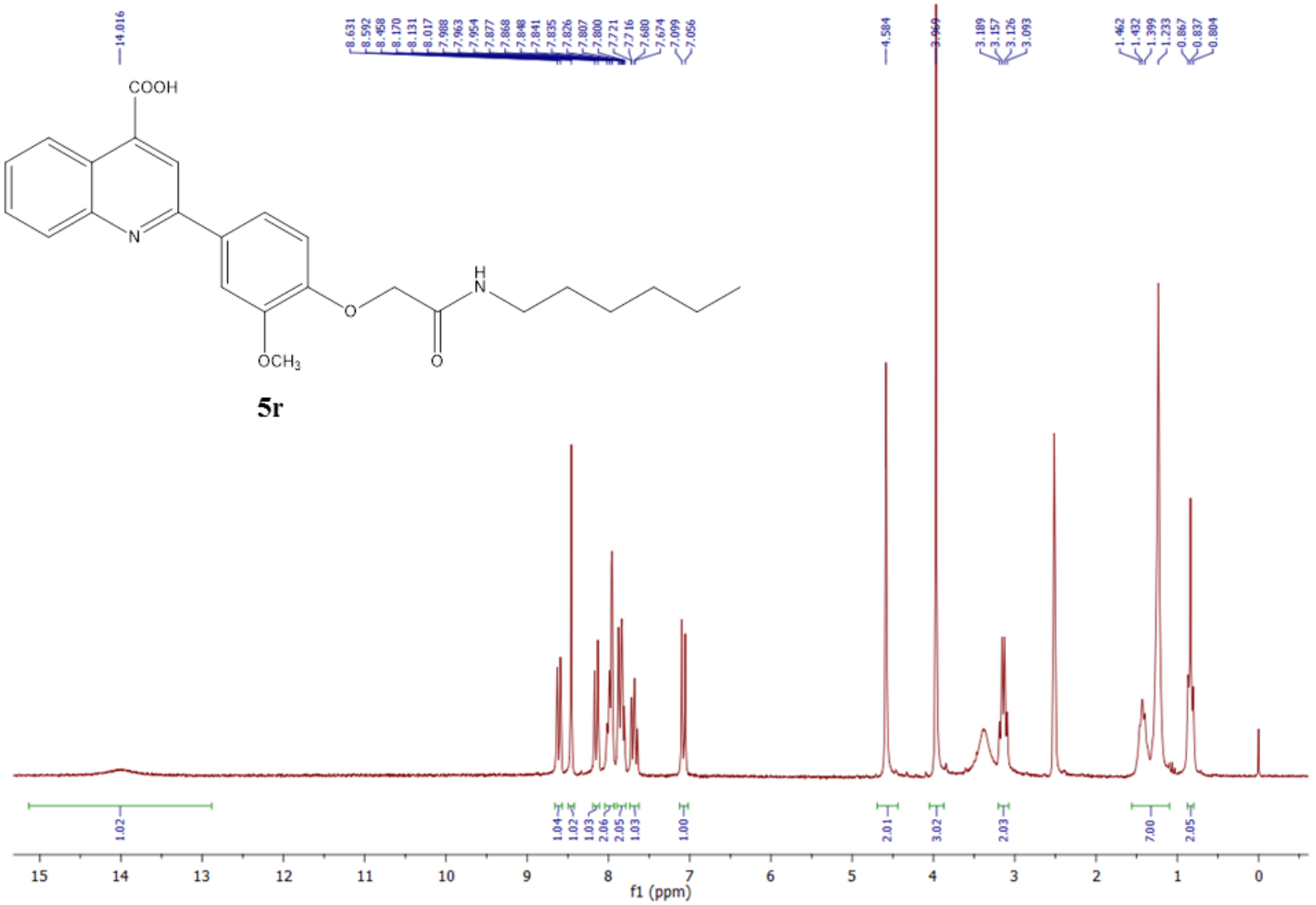

Figure S94. ^{1}H NMR spectrum of **5r** in DMSO-d_6 (200 MHz).

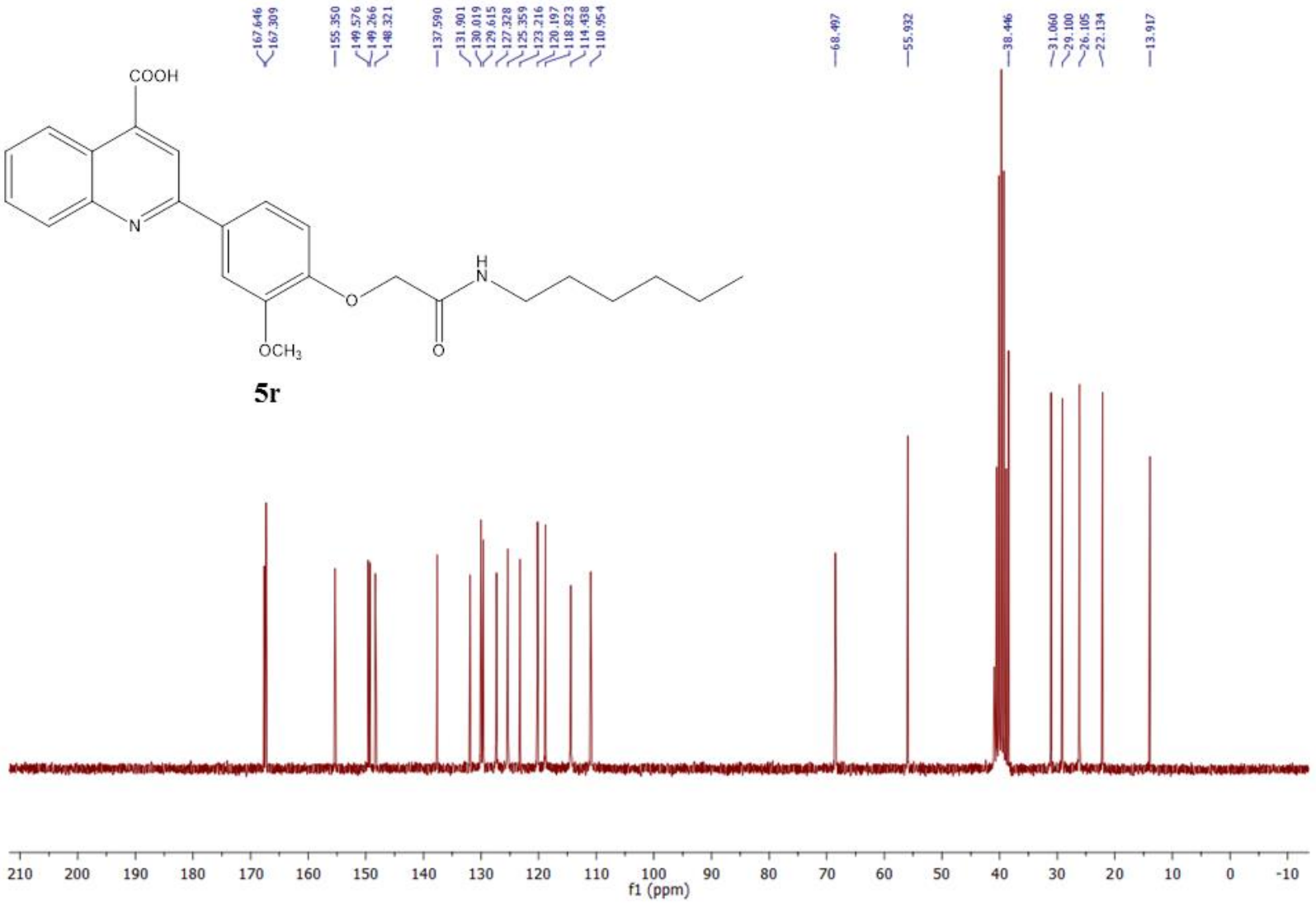

Figure S95. ^{13}C NMR spectrum of **5r** in DMSO-d_6 (50 MHz).

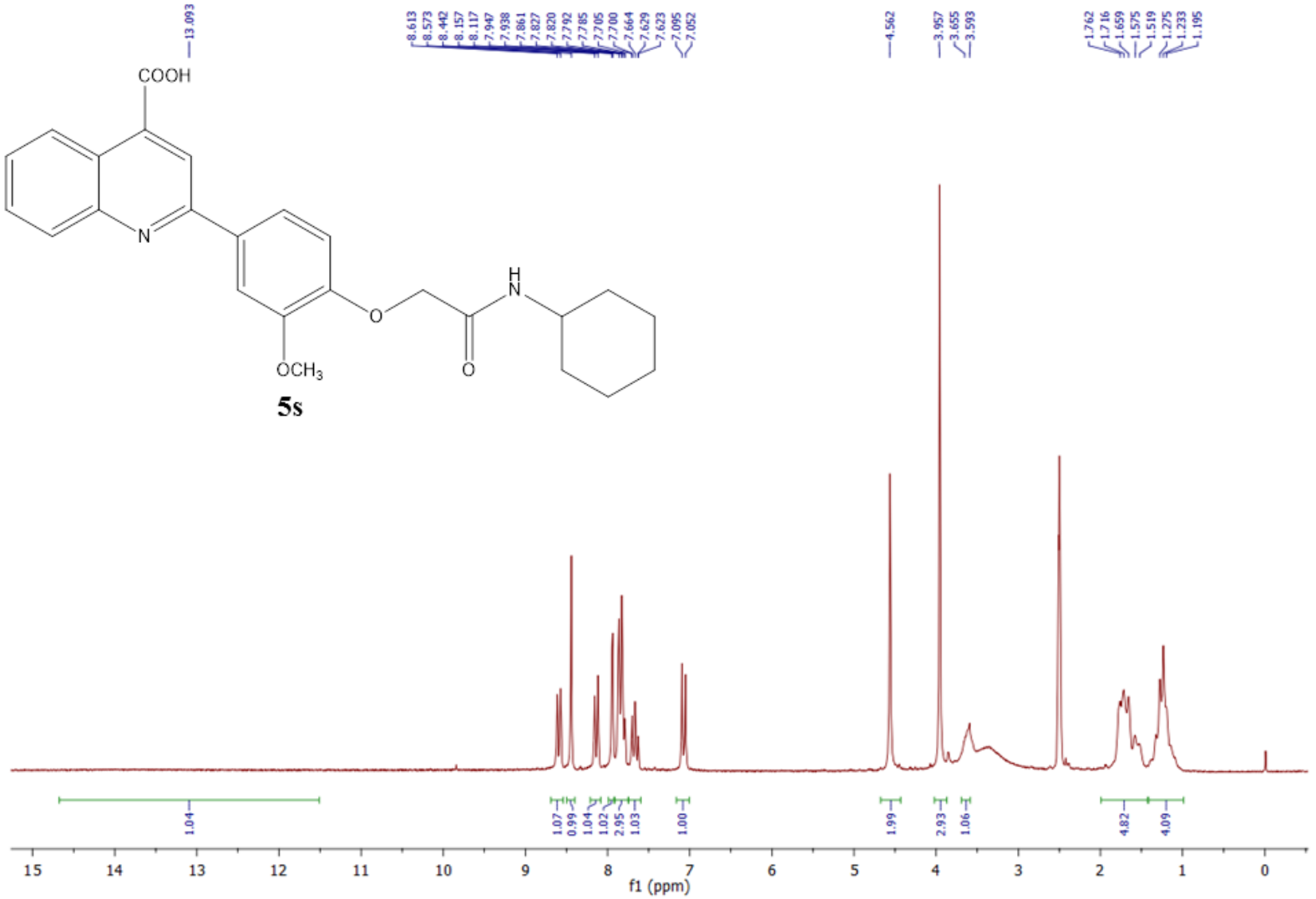

Figure S96. ^{1}H NMR spectrum of **5s** in DMSO-d_6 (200 MHz).

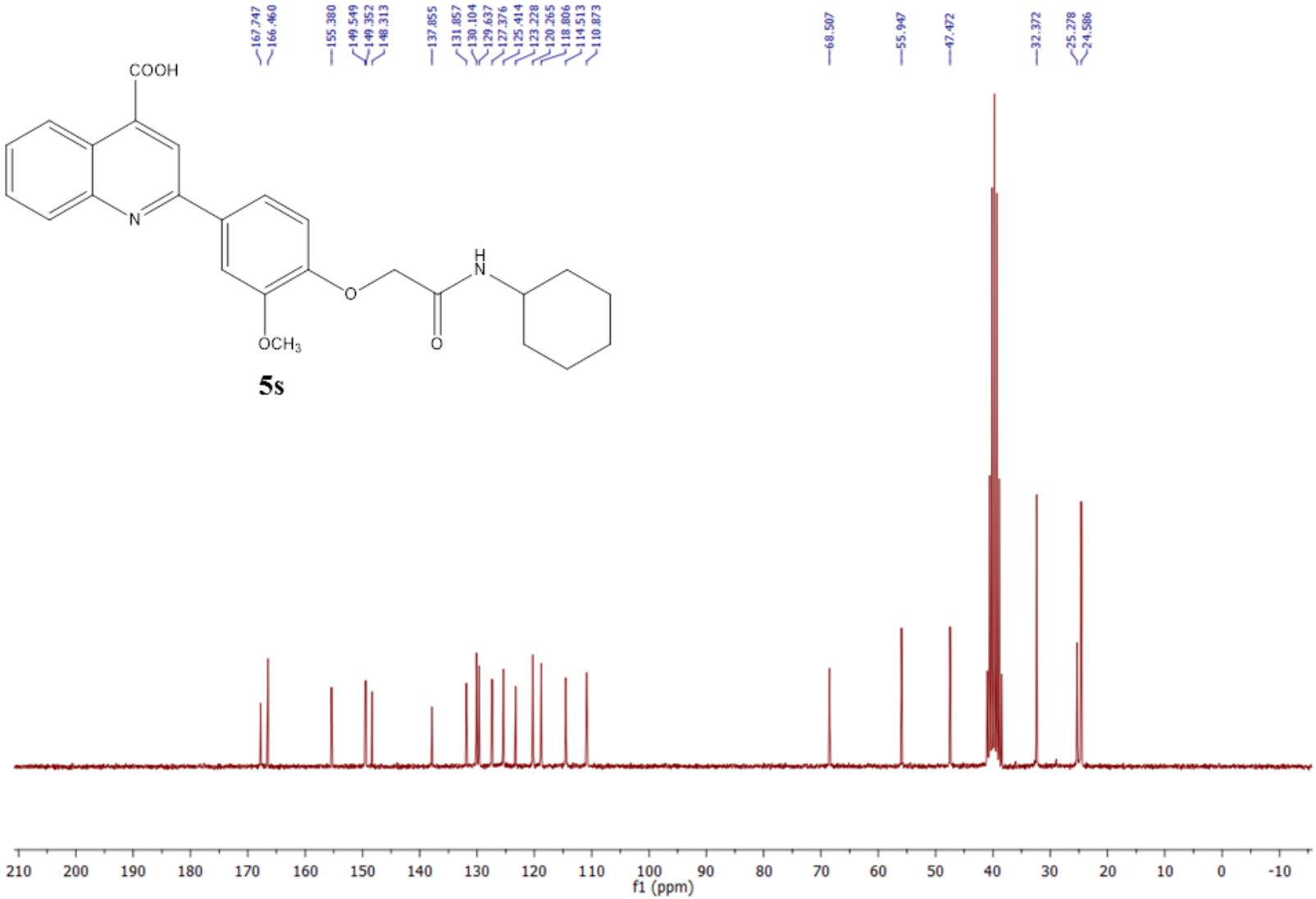

Figure S97. ^{13}C NMR spectrum of **5s** in DMSO-d_6 (50 MHz).

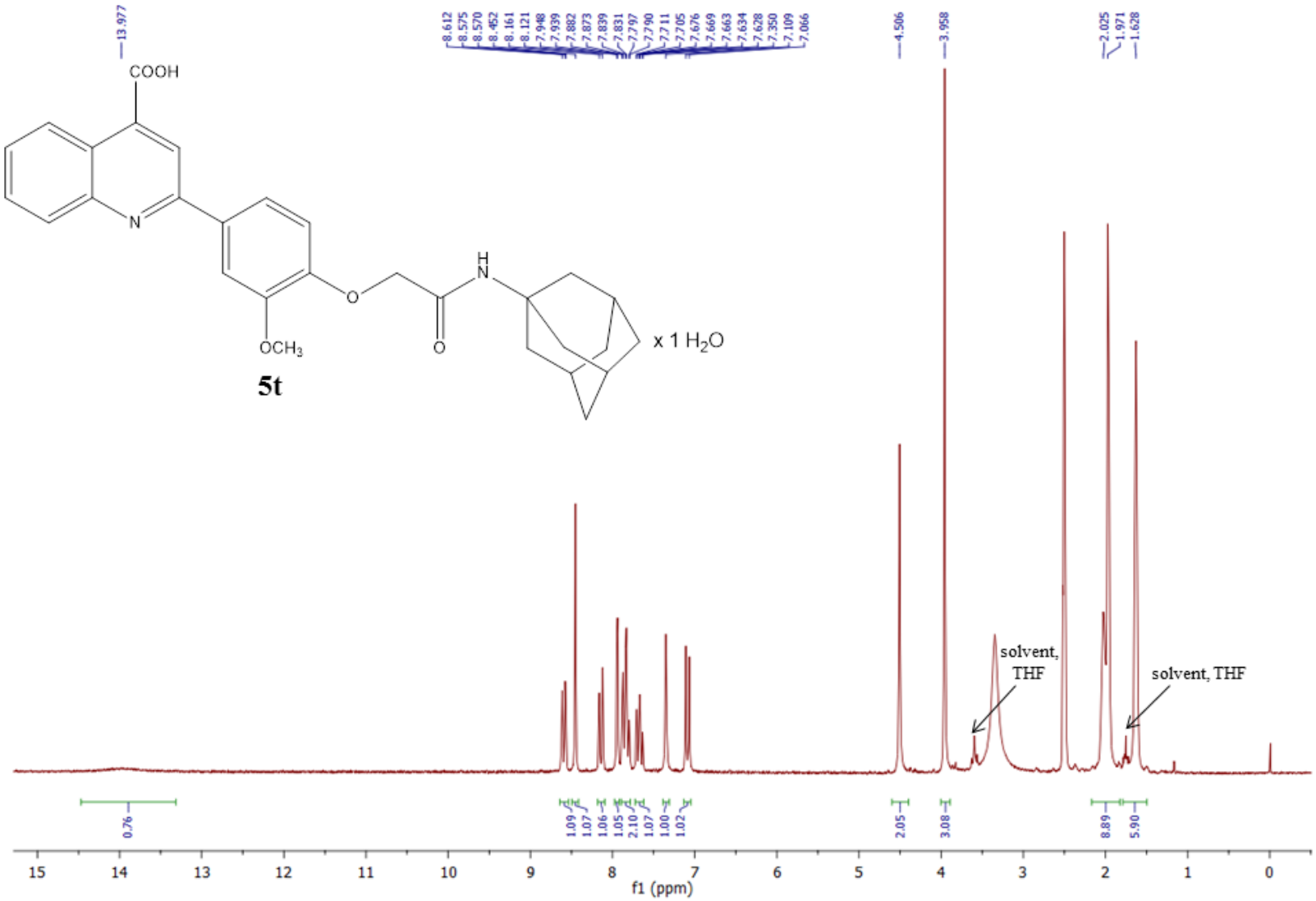

Figure S98. ^{1}H NMR spectrum of **5t** in DMSO-d_6 (200 MHz).

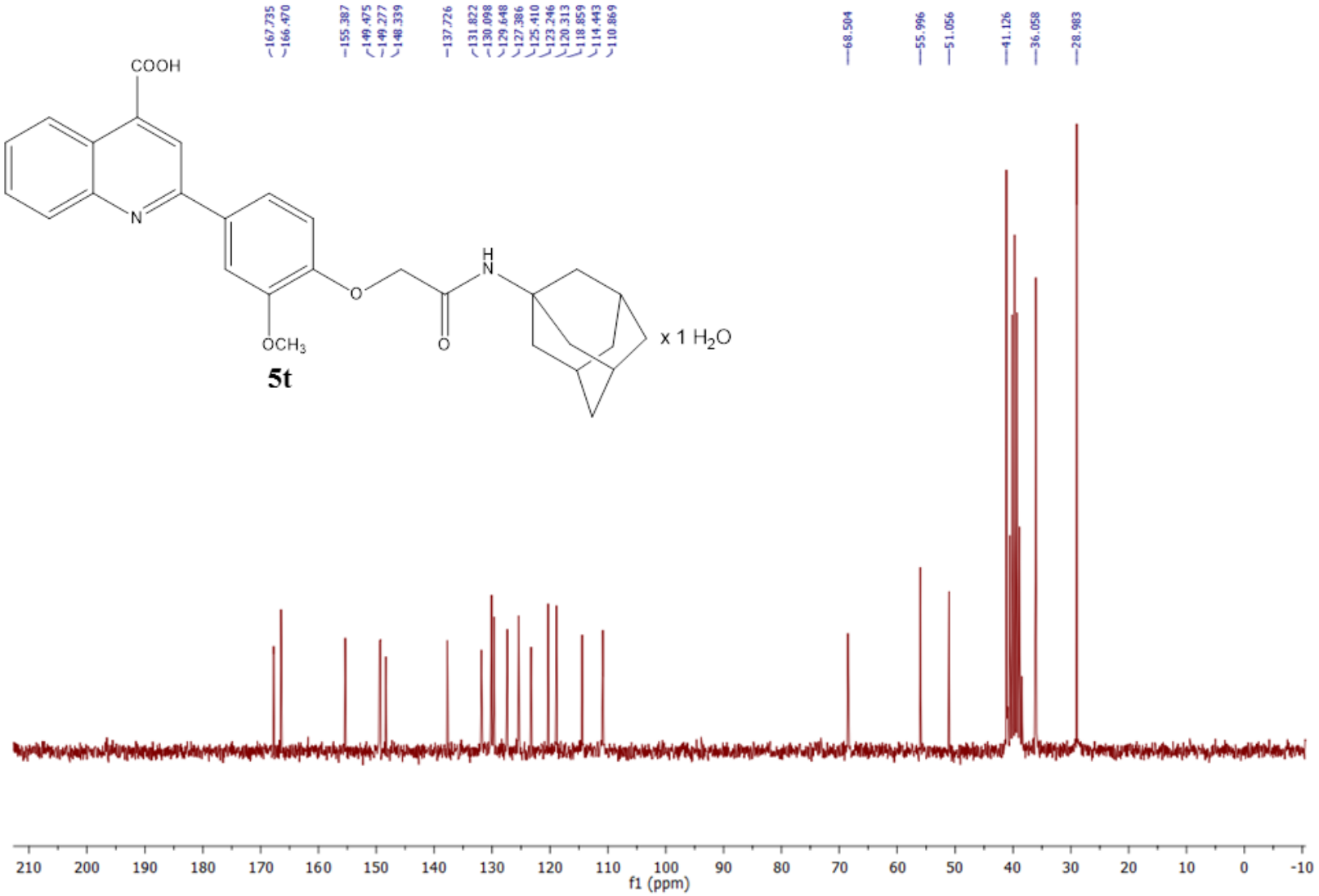

Figure S99. ^{13}C NMR spectrum of **5t** in DMSO-d_6 (50 MHz).

Copies of IR spectra for 4a-4t

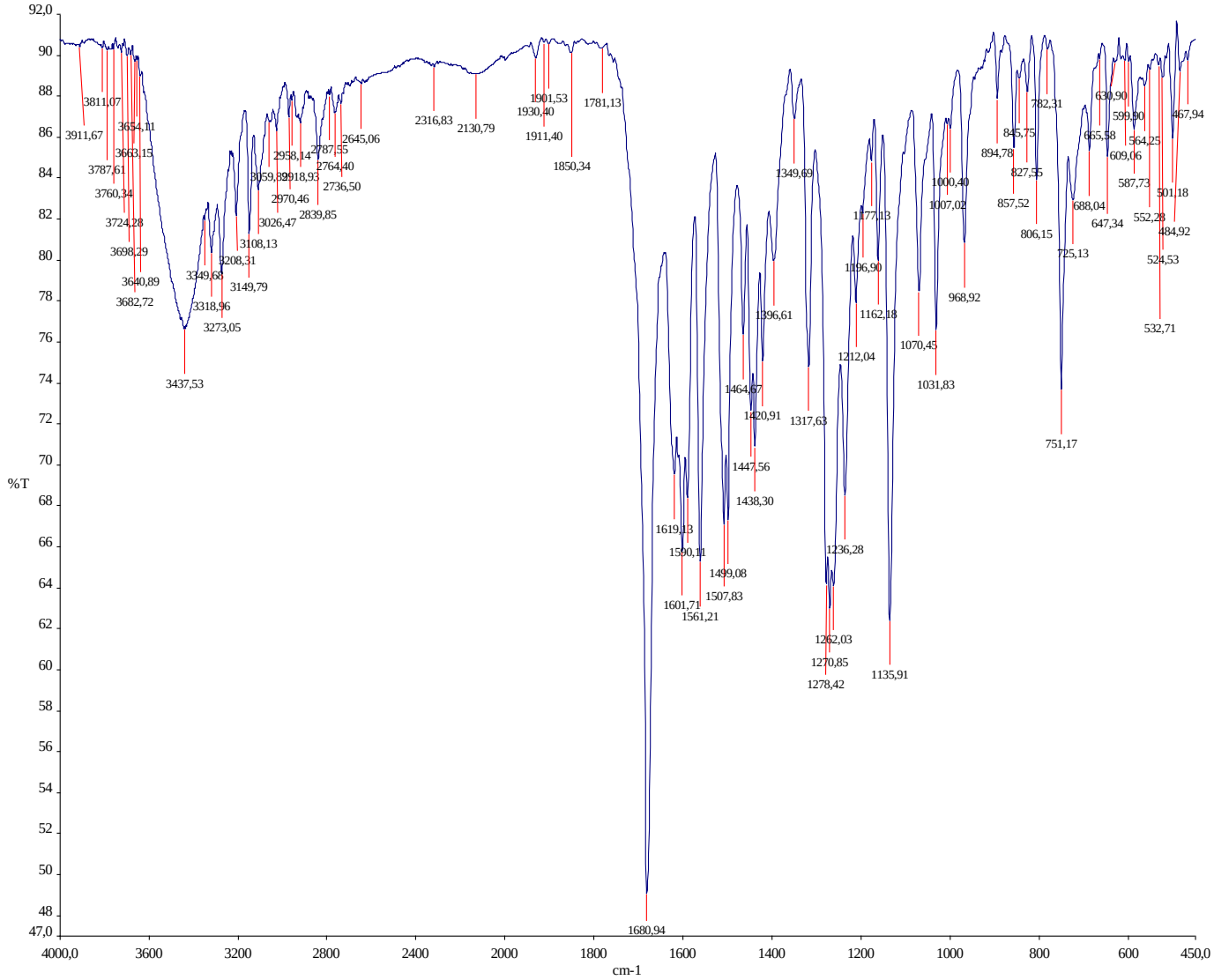

Figure S100. IR spectrum of **4a.**

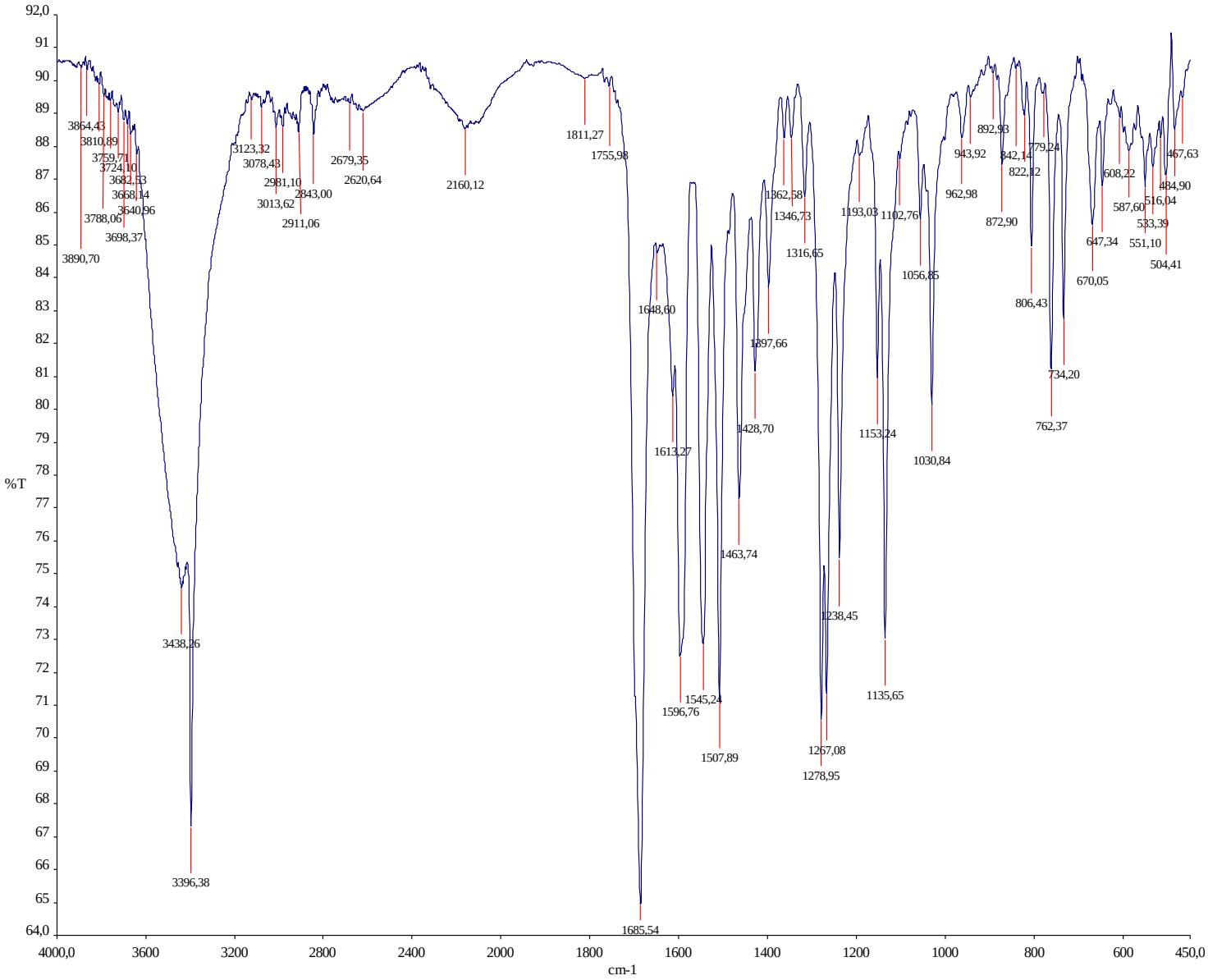

Figure S101. IR spectrum of **4b.**

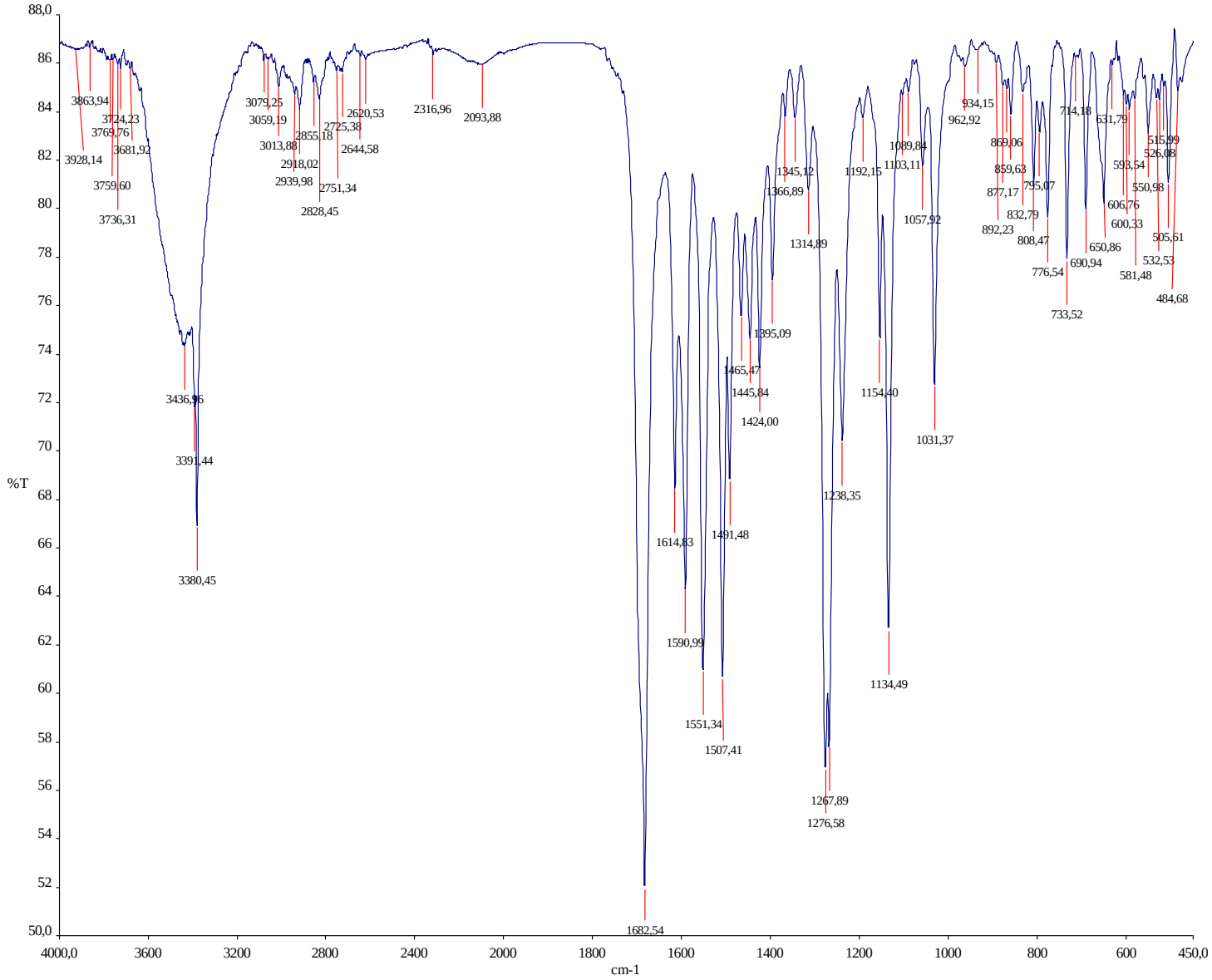

Figure S102. IR spectrum of **4c.**

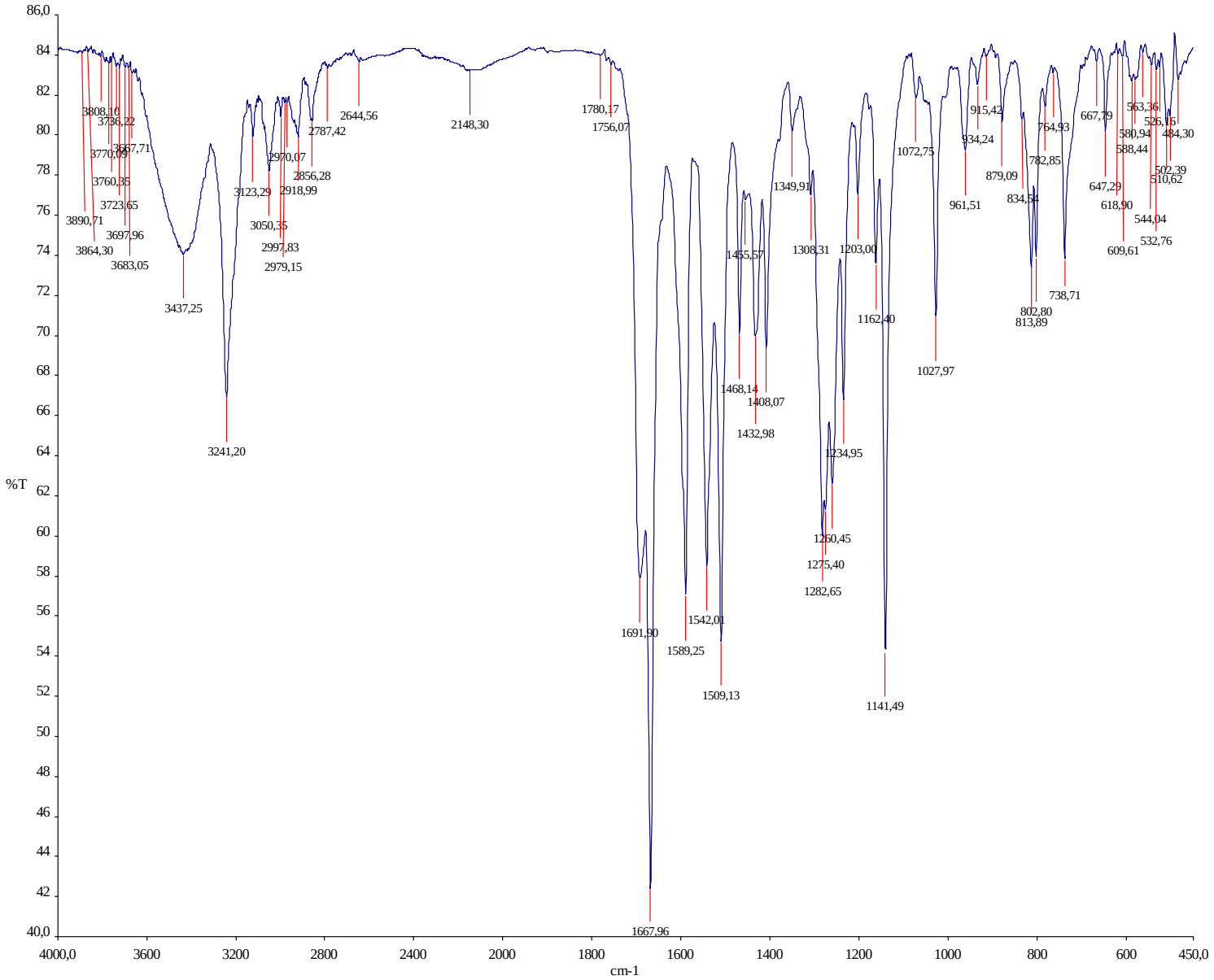

Figure S103. IR spectrum of **4d.**

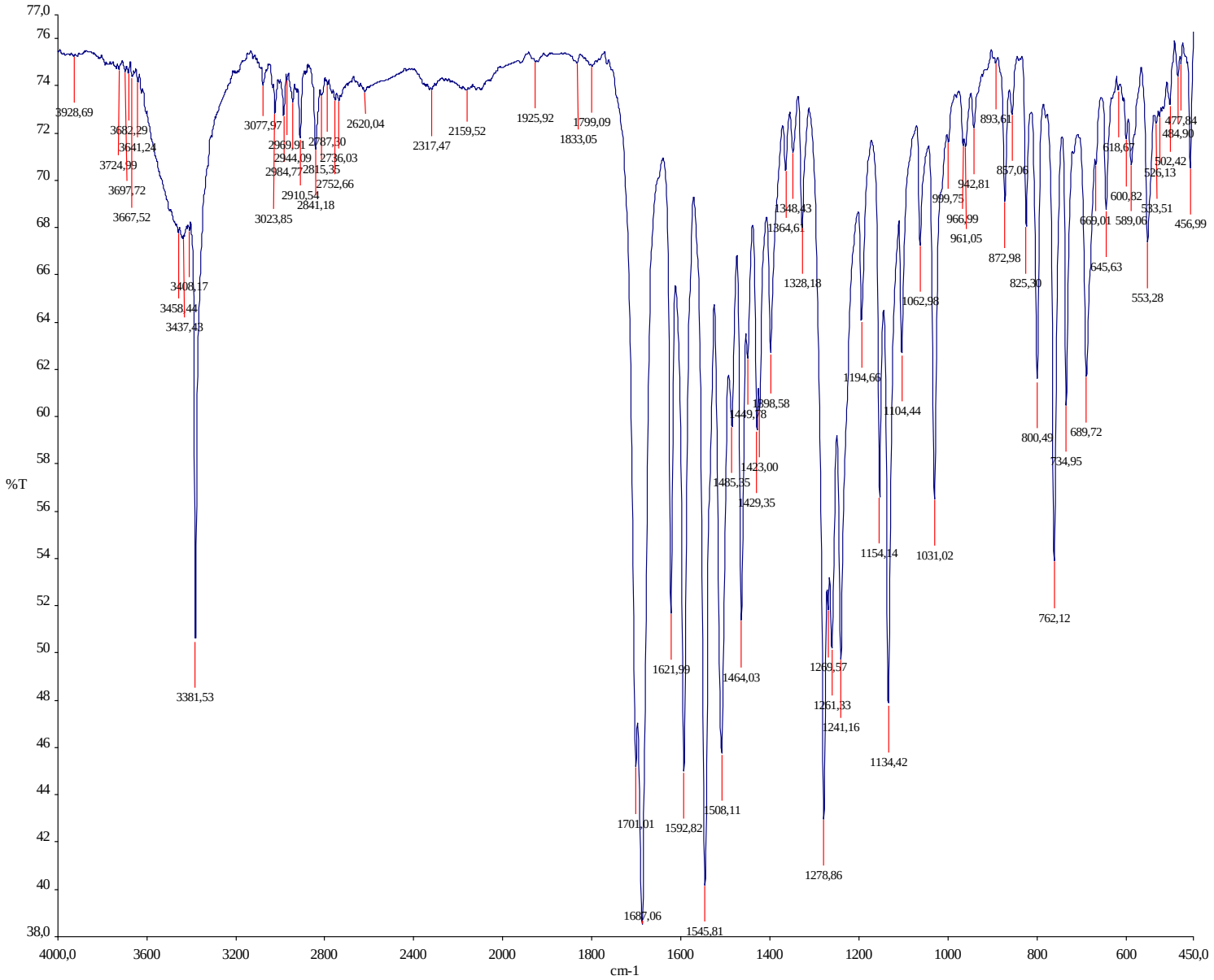

Figure S104. IR spectrum of **4e.**

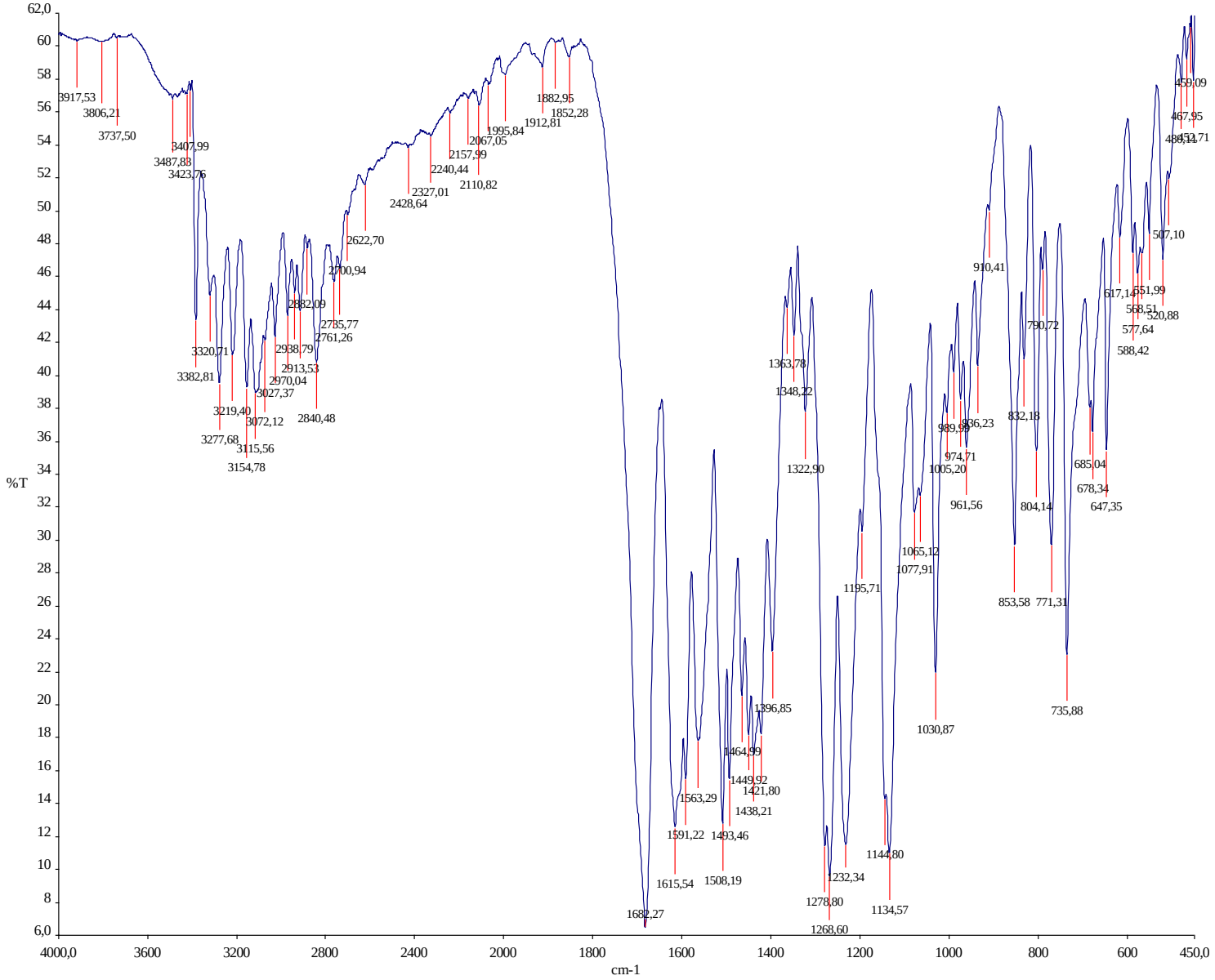

Figure S105. IR spectrum of **4f.**

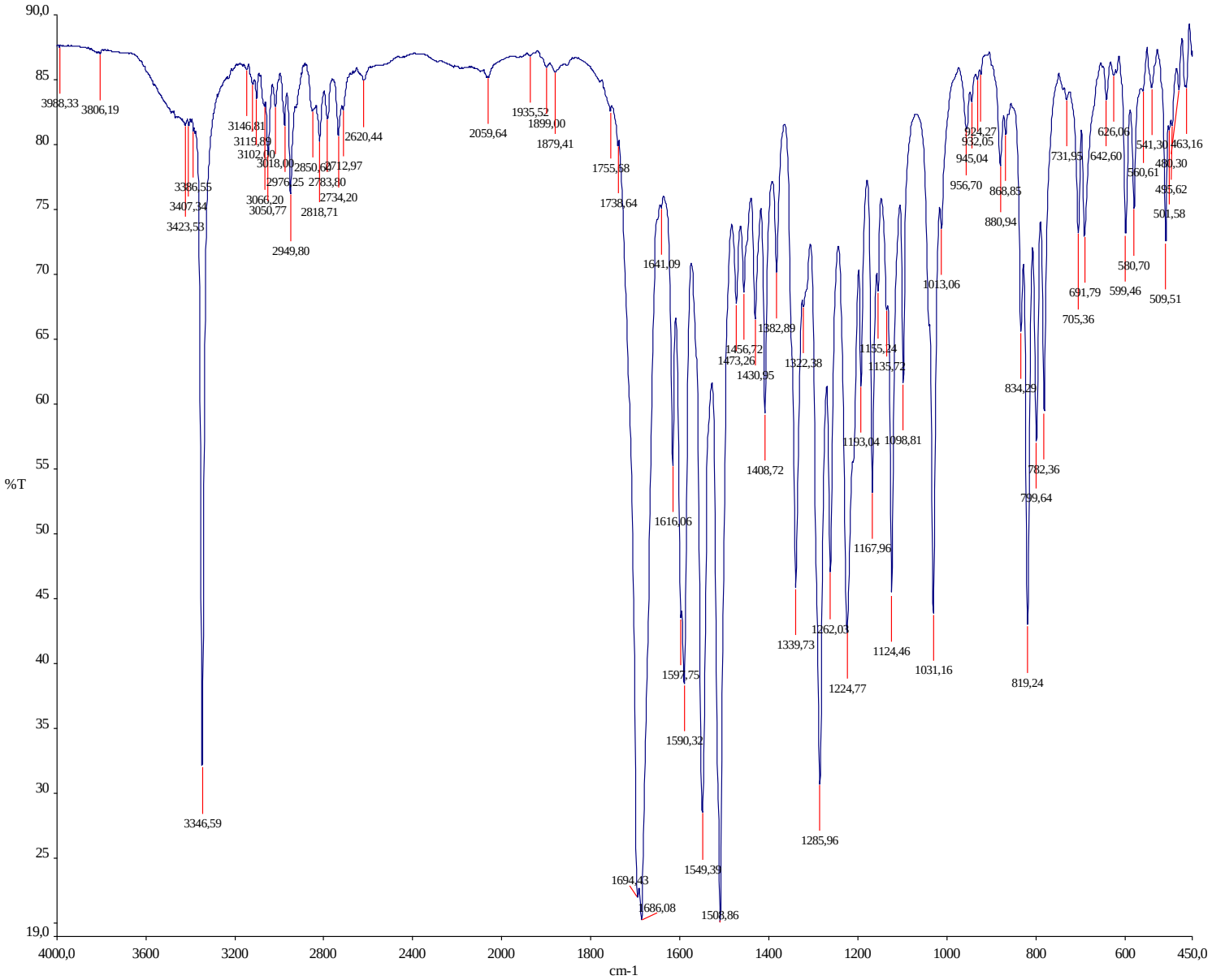

Figure S106. IR spectrum of **4g.**

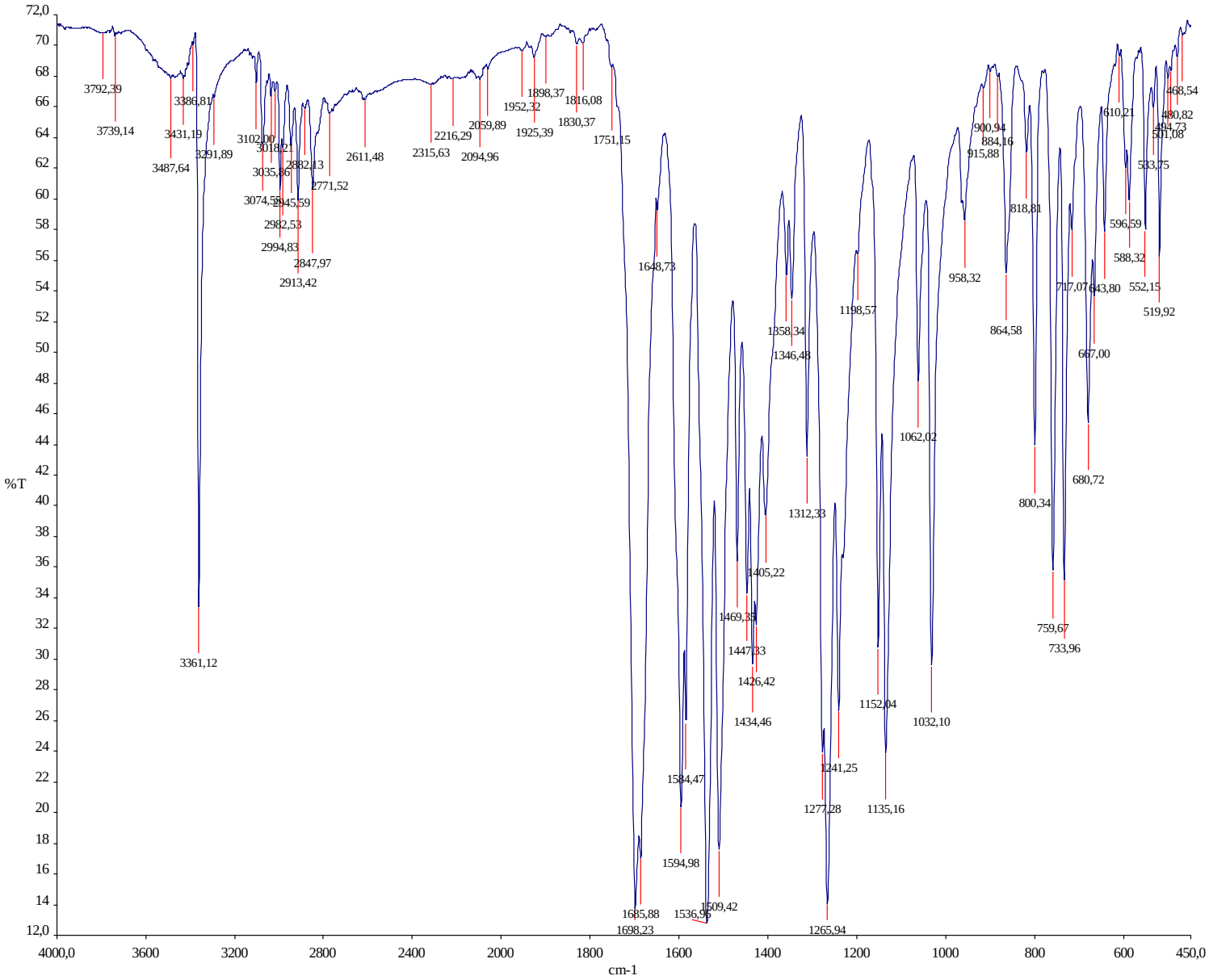

Figure S107. IR spectrum of **4h.**

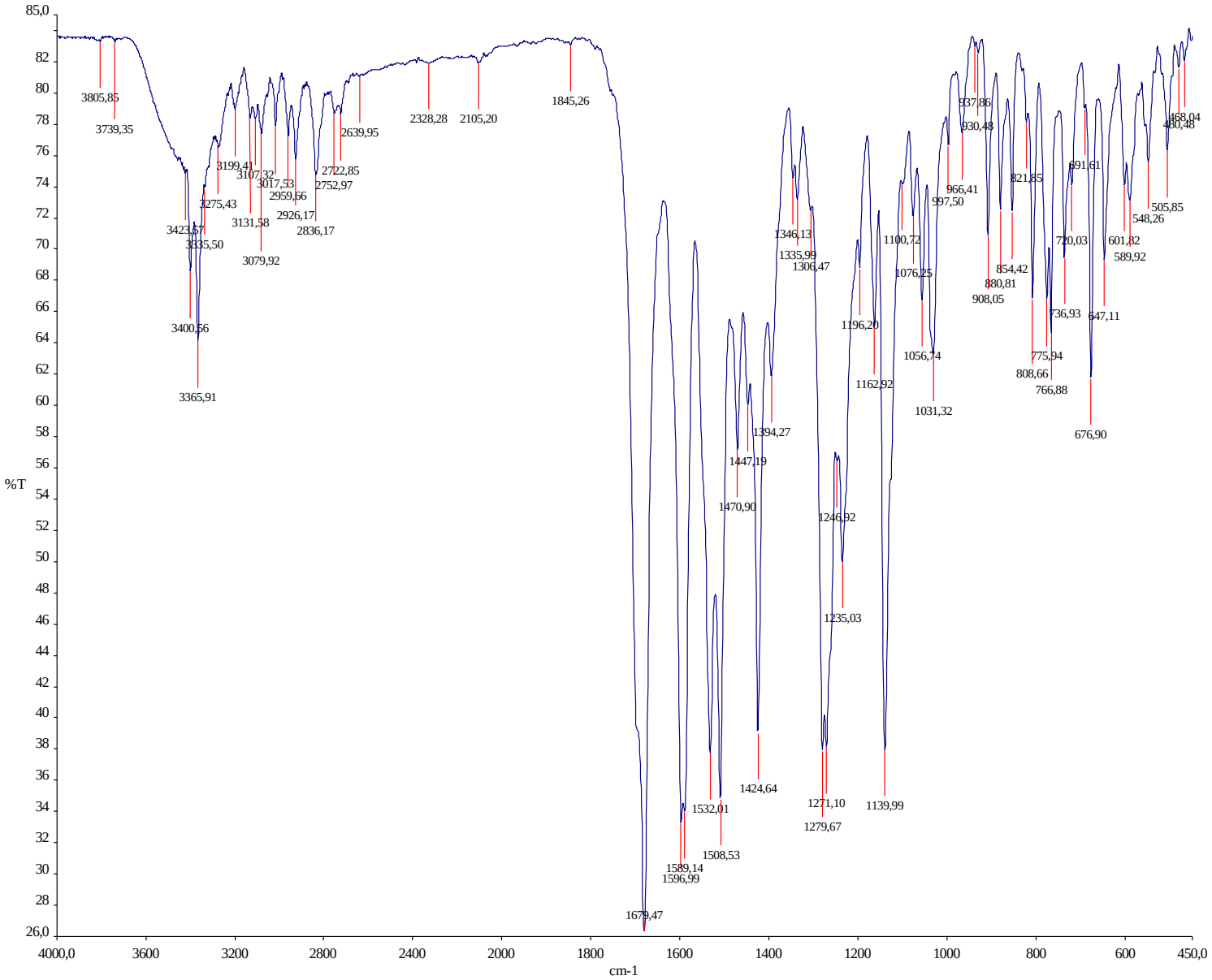

Figure S108. IR spectrum of **4i.**

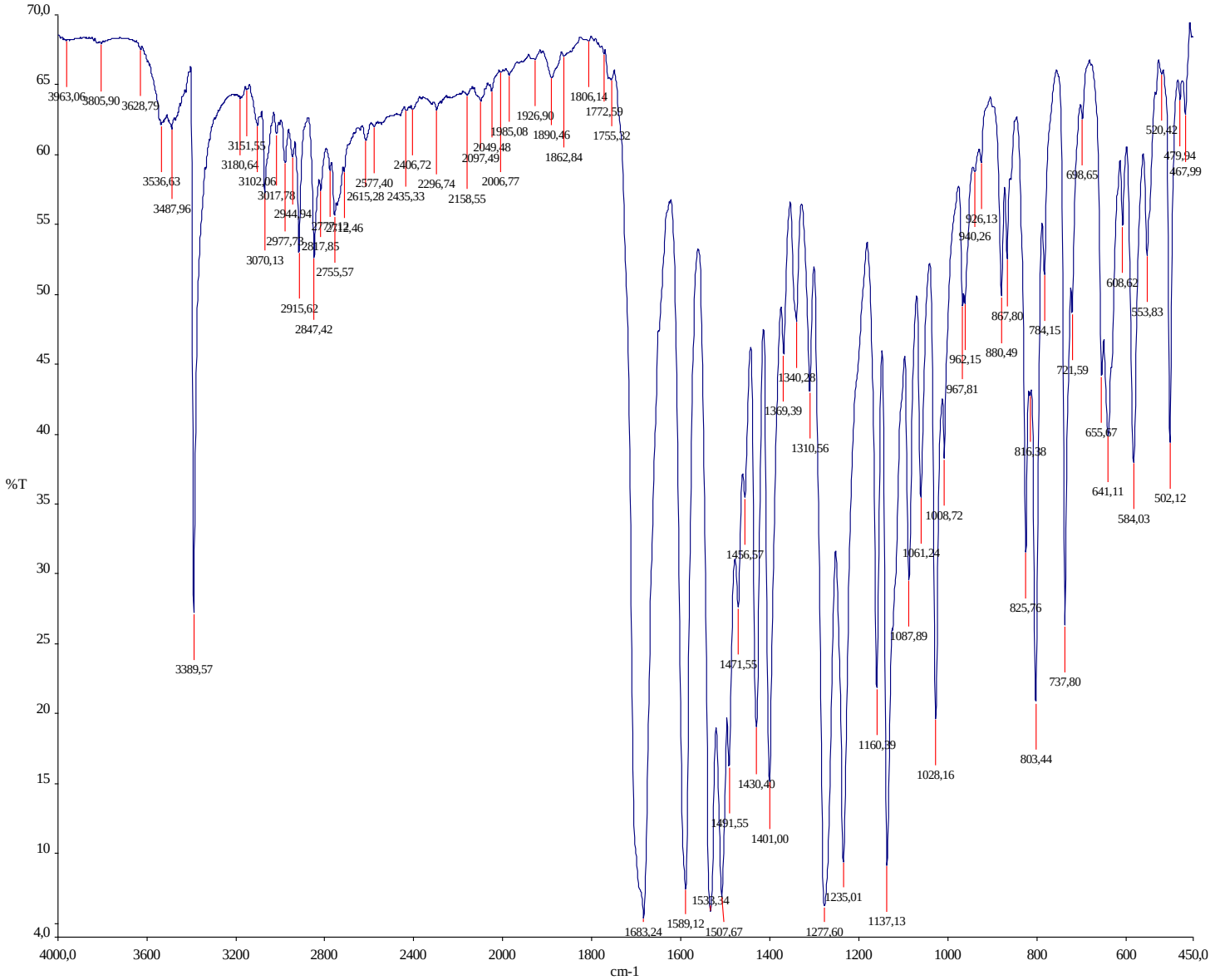

Figure S109. IR spectrum of **4j.**

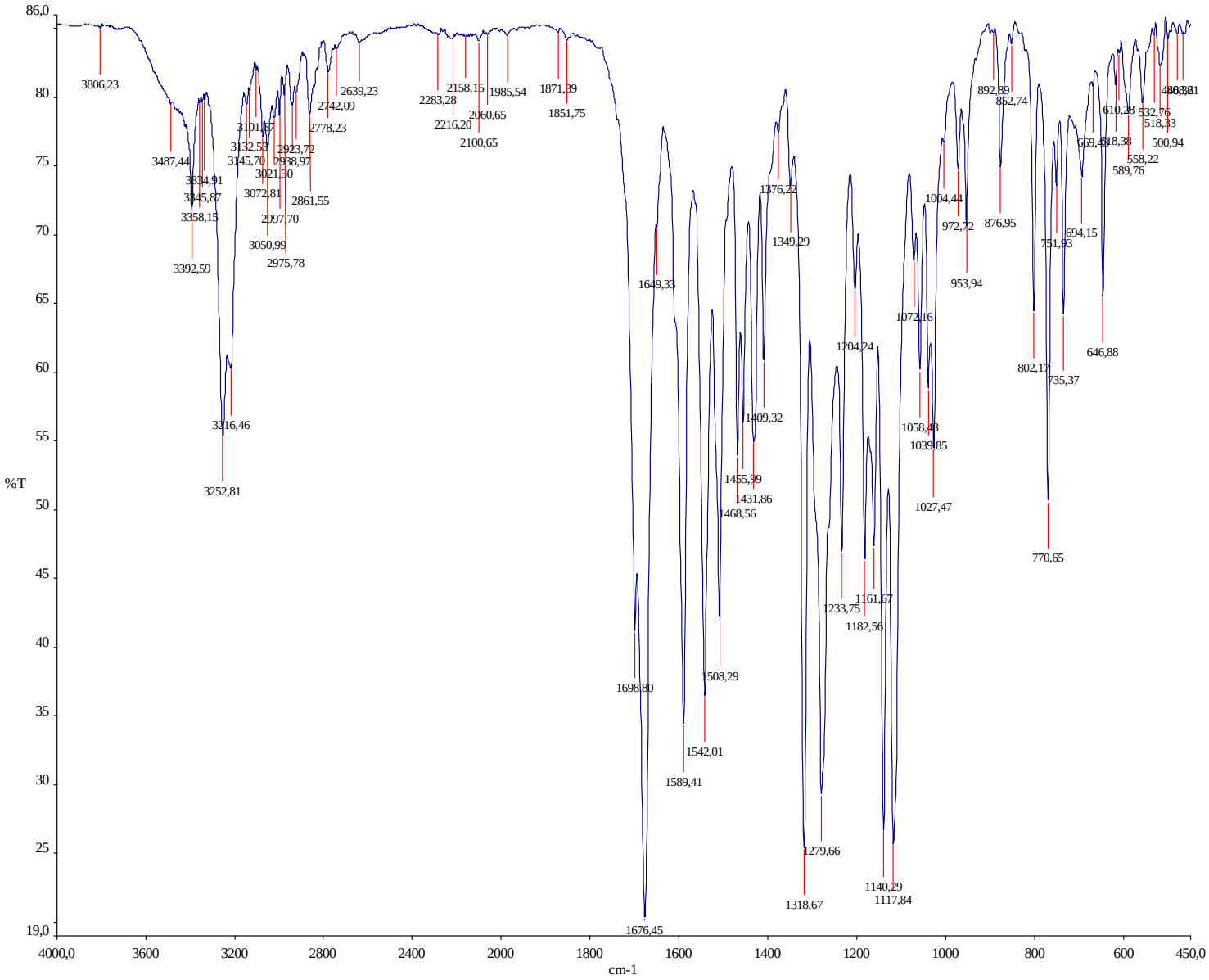

Figure S110. IR spectrum of **4k.**

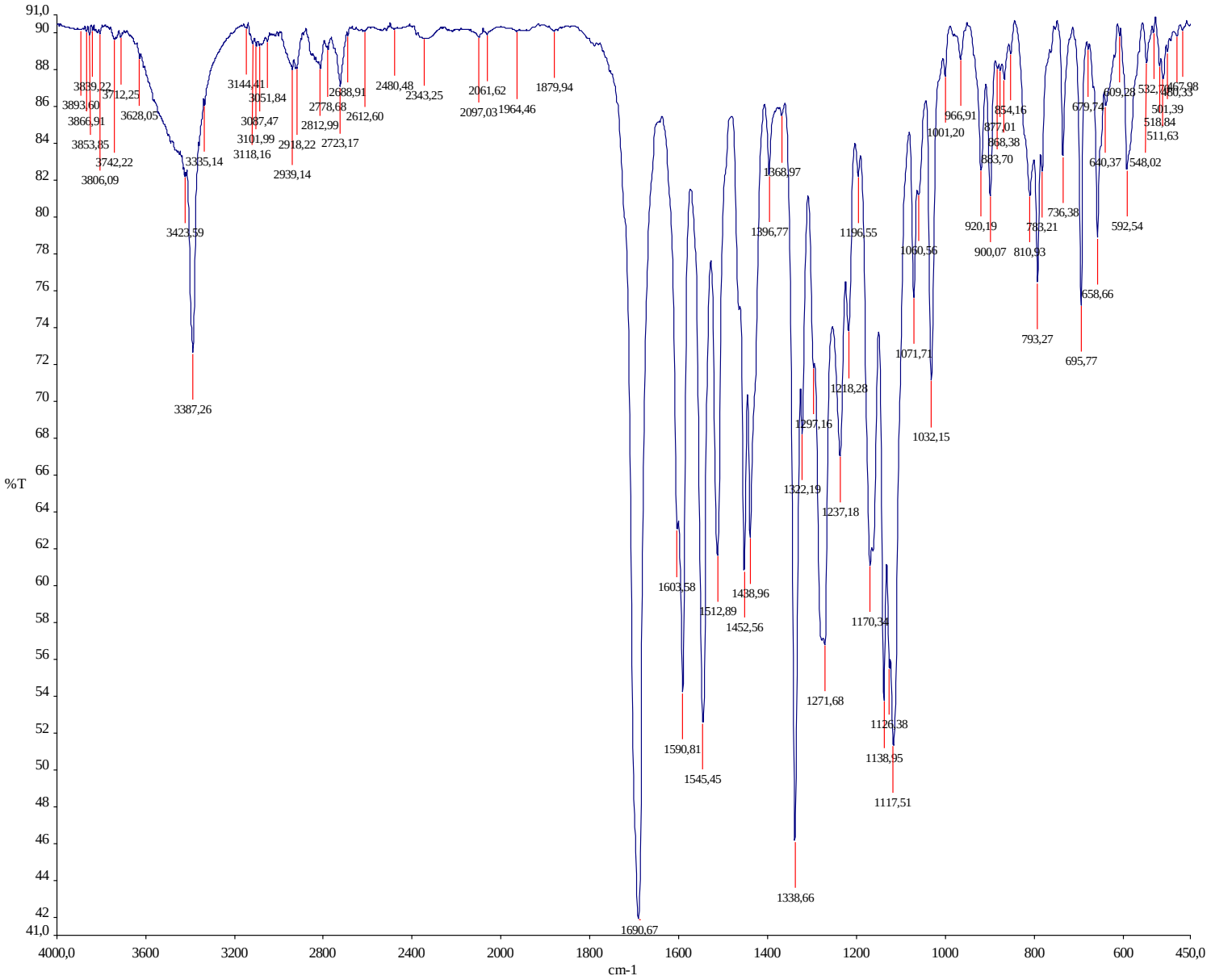

Figure S111. IR spectrum of **4l.**

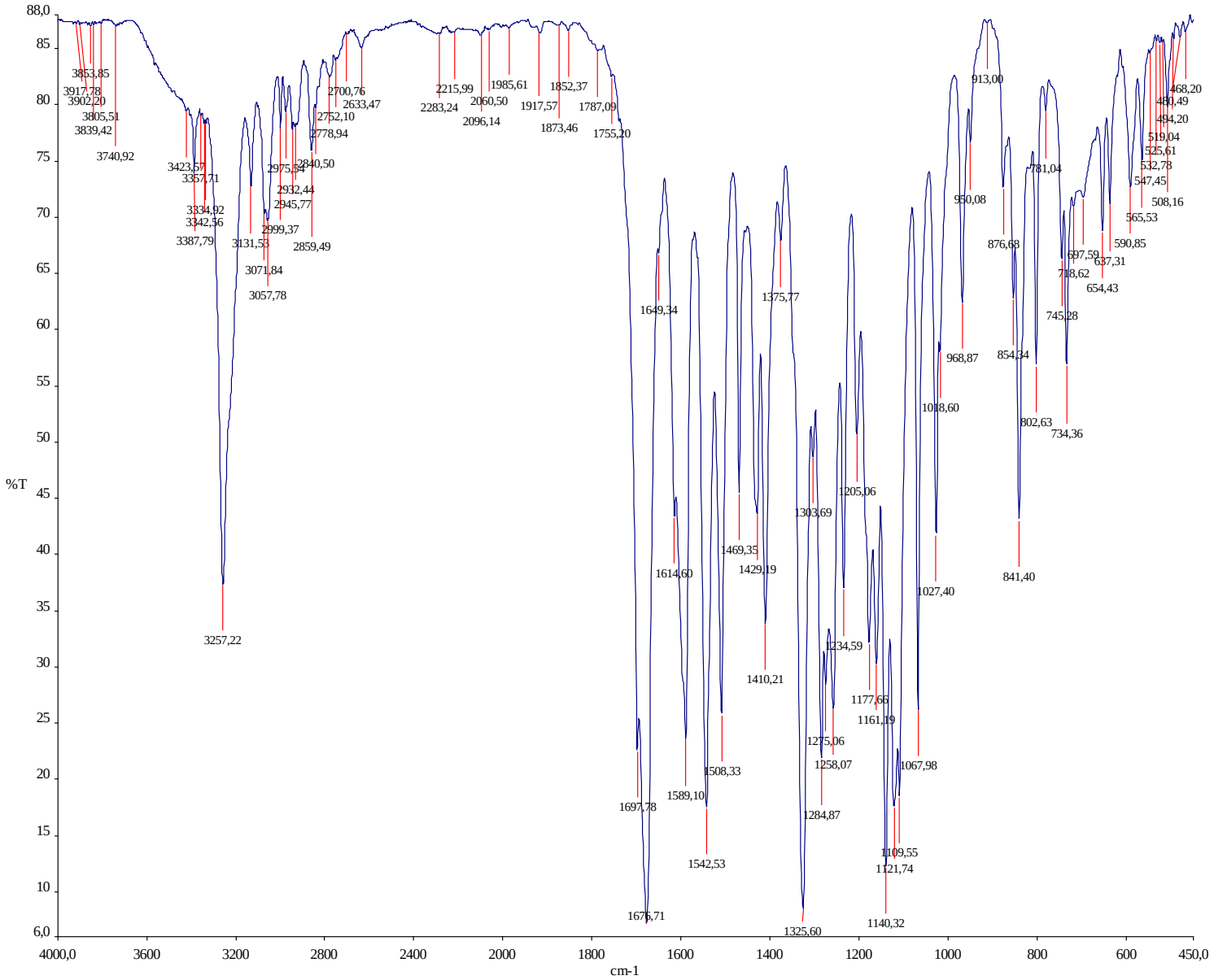

Figure S112. IR spectrum of **4m.**

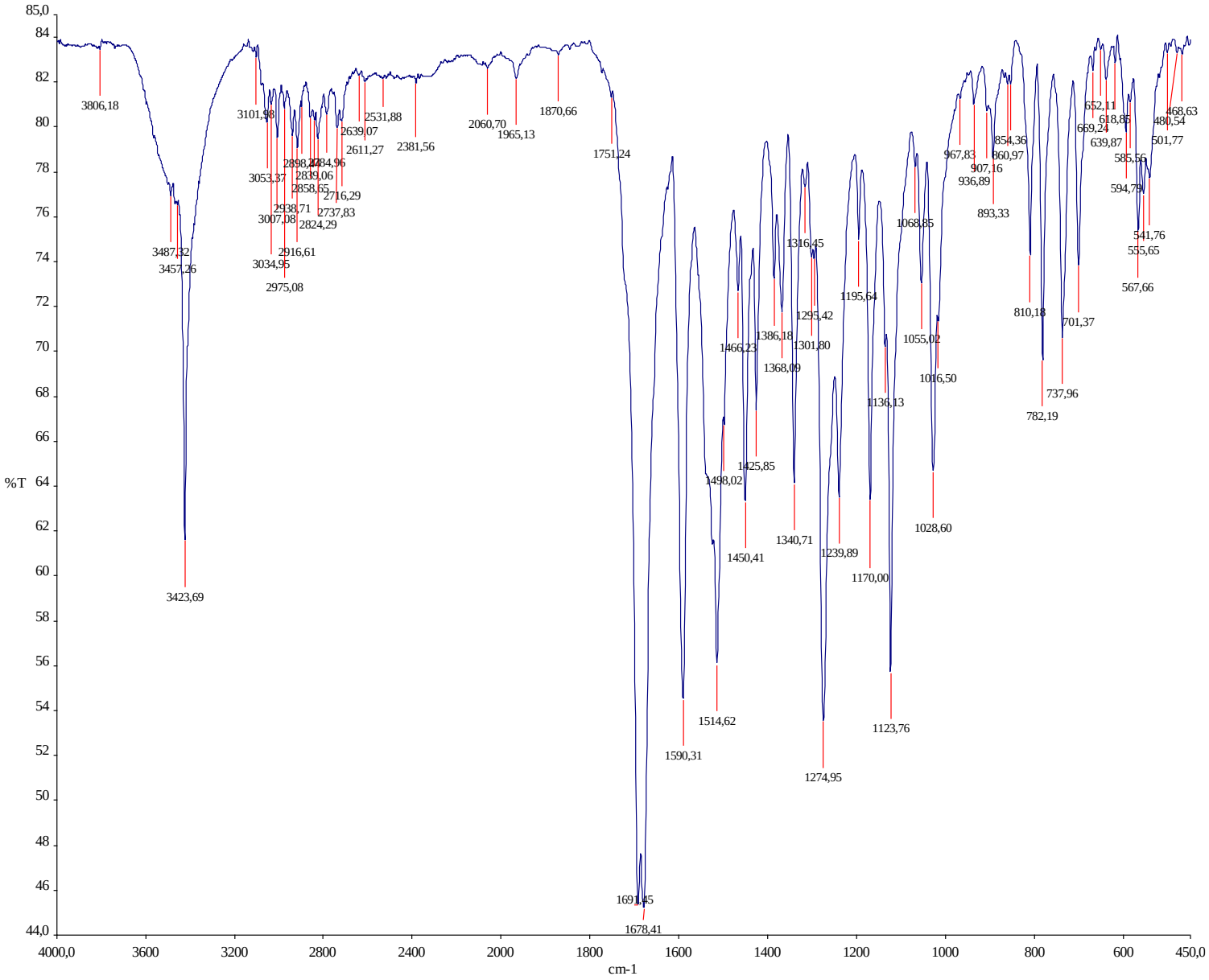

Figure S113. IR spectrum of **4n.**

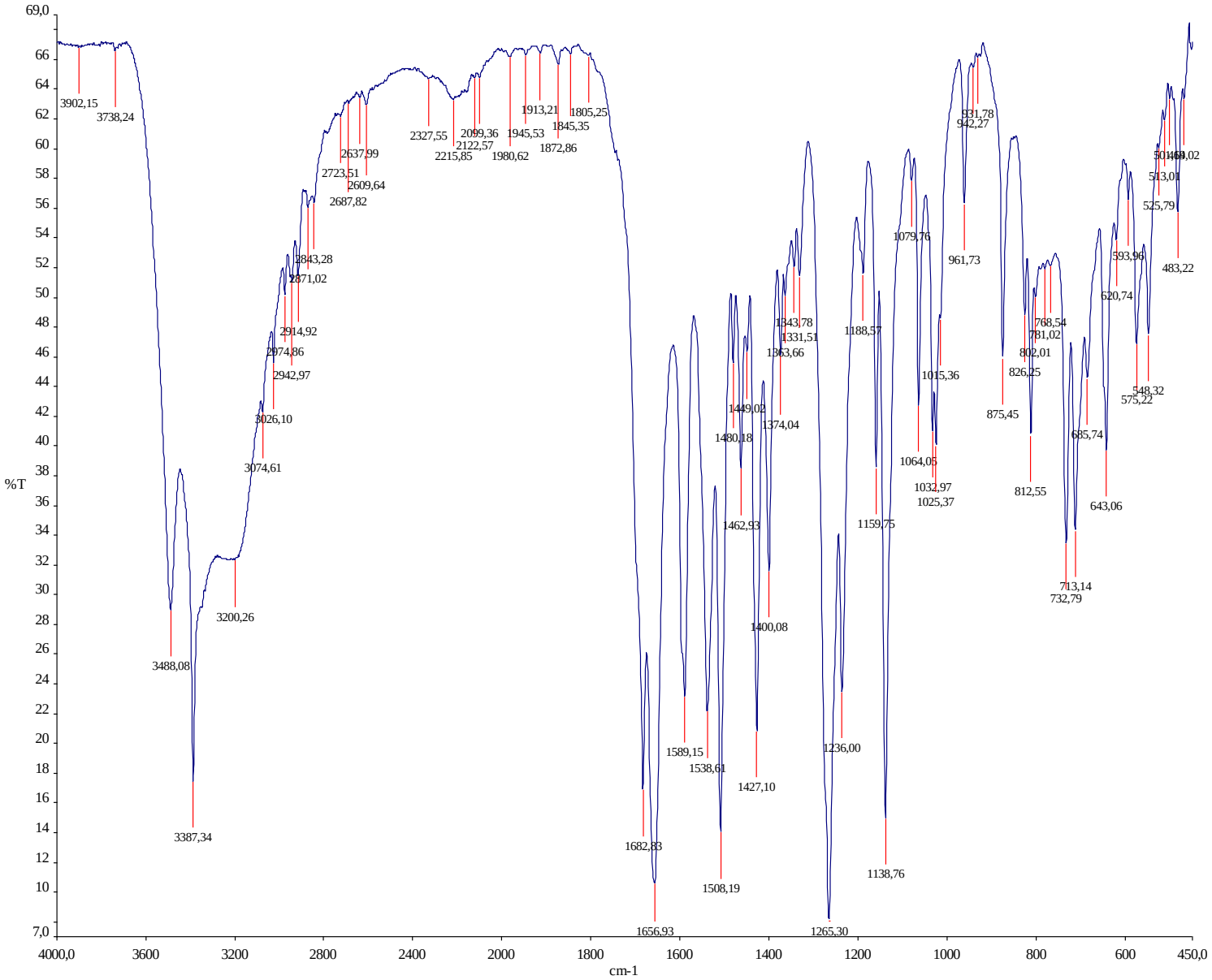

Figure S114. IR spectrum of **4o.**

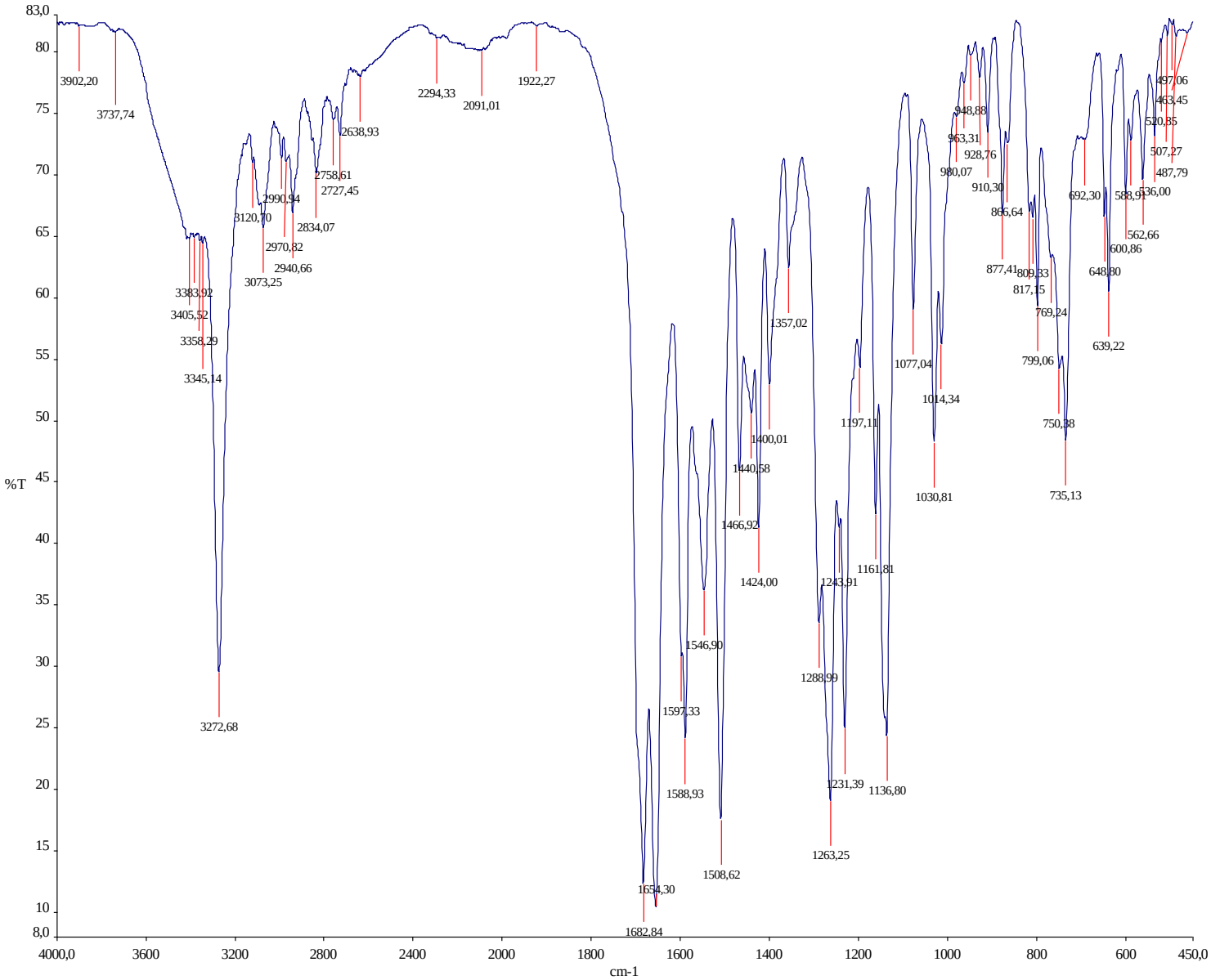

Figure S115. IR spectrum of **4p.**

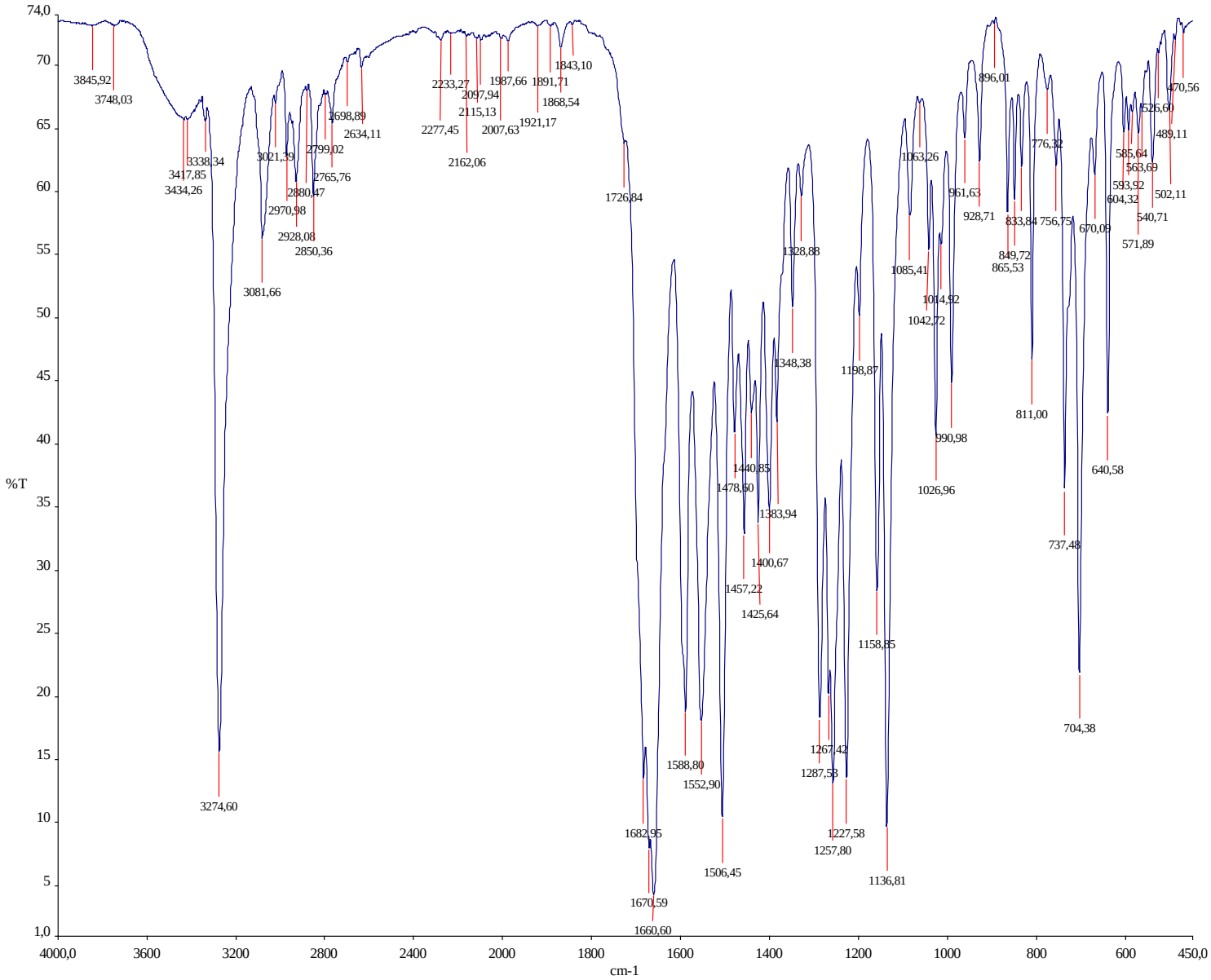

Figure S116. IR spectrum of **4q.**

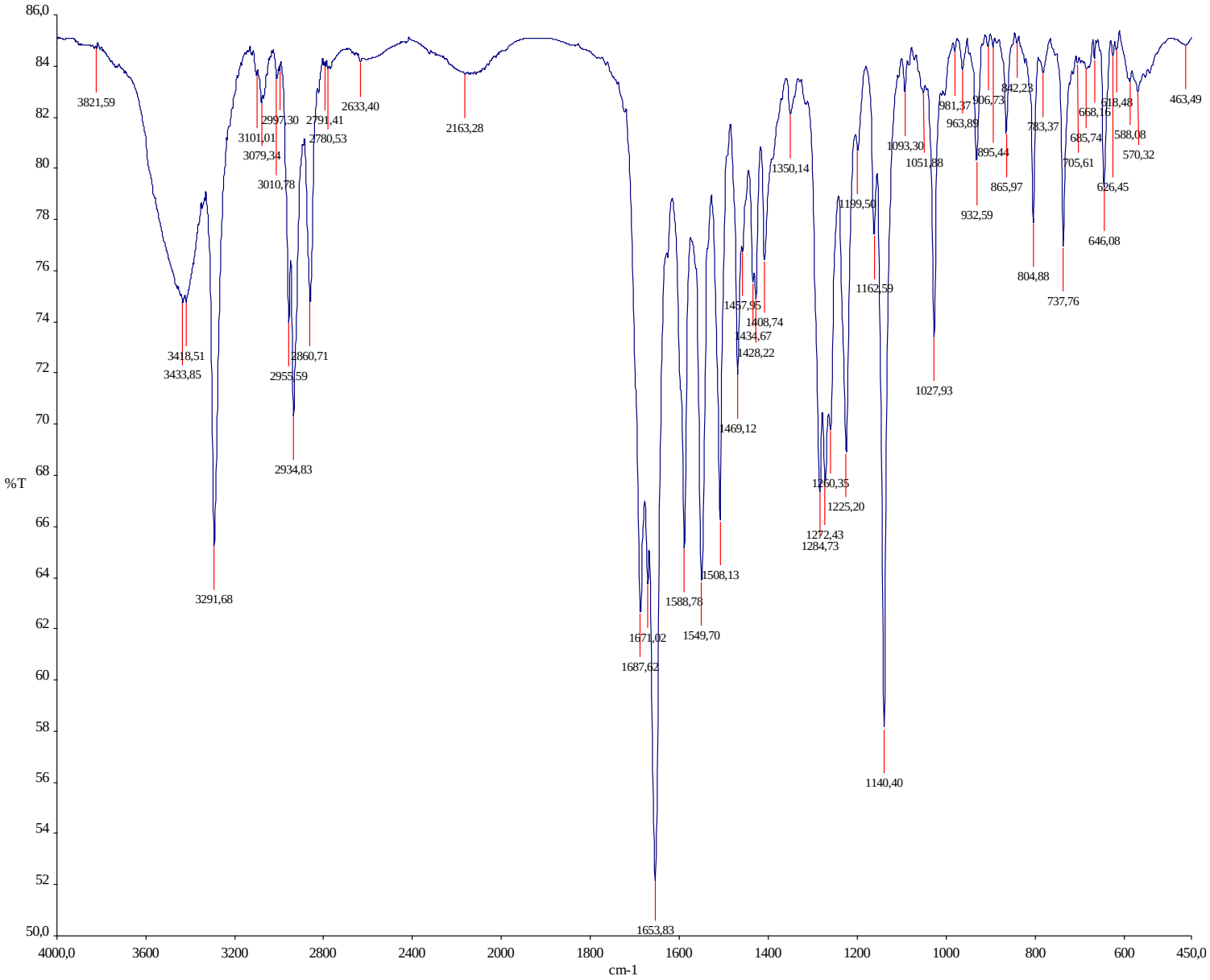

Figure S117. IR spectrum of **4r.**

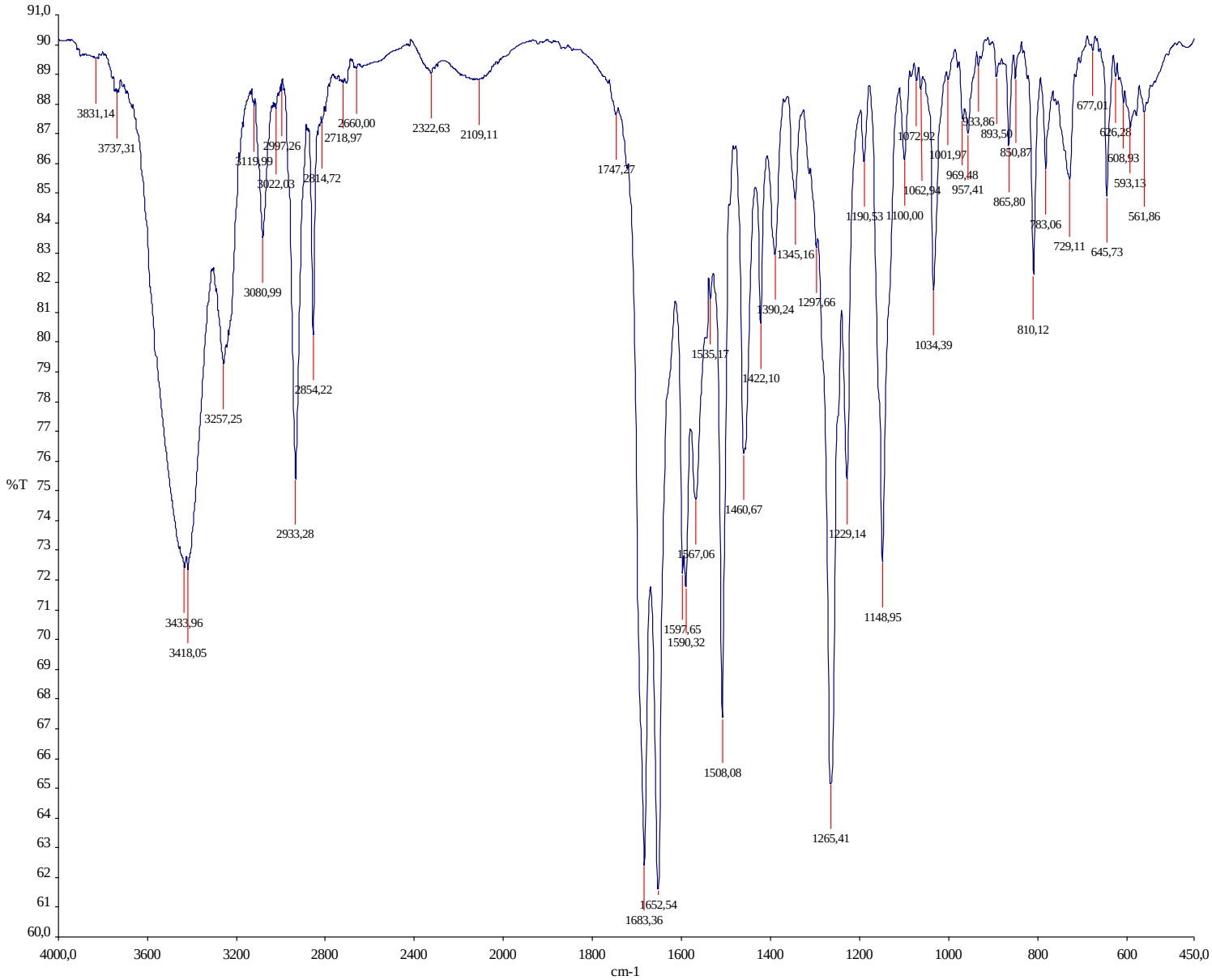

Figure S118. IR spectrum of **4s.**

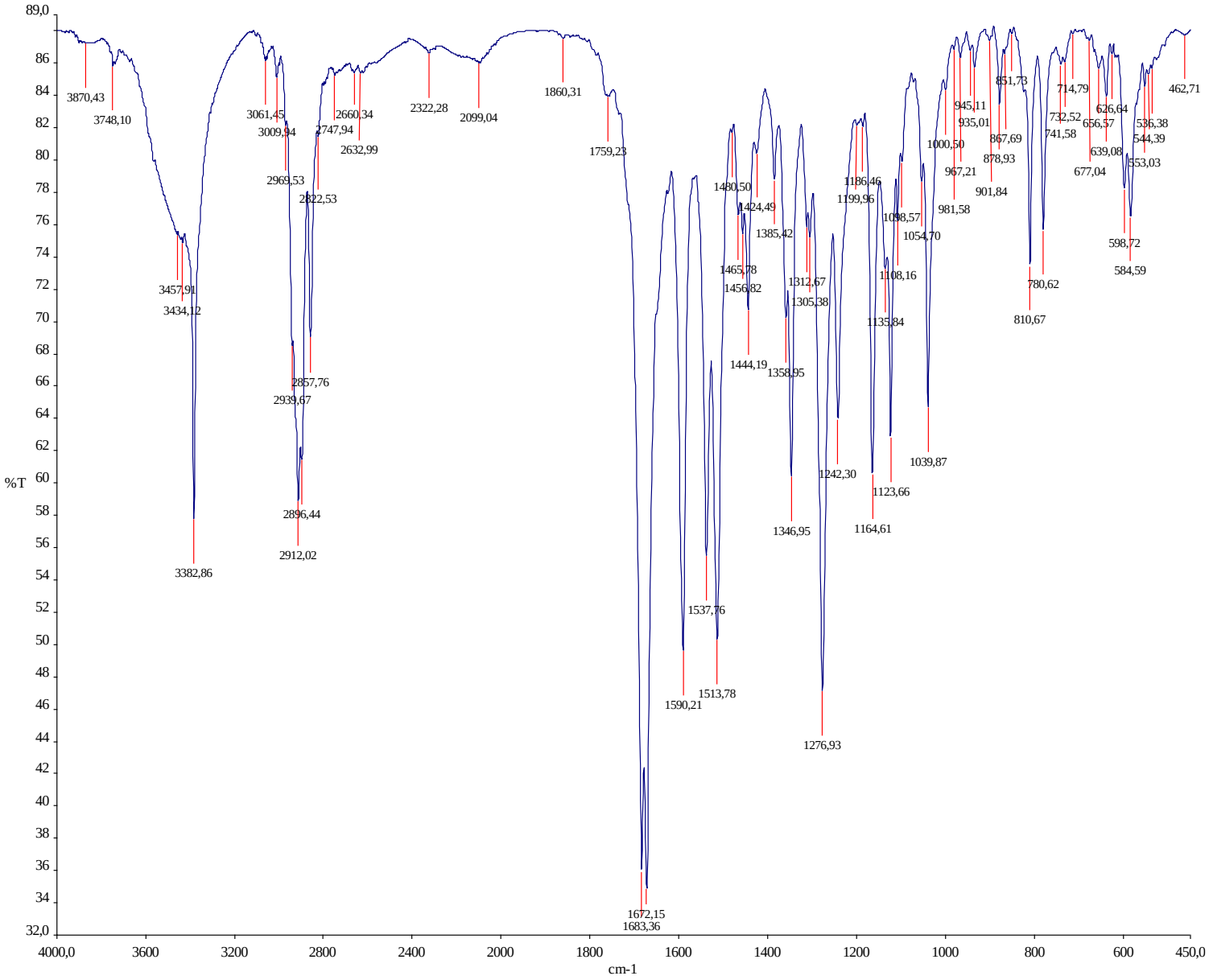

Figure S119. IR spectrum of **4t.**

Copies of IR spectra for 5a-5t

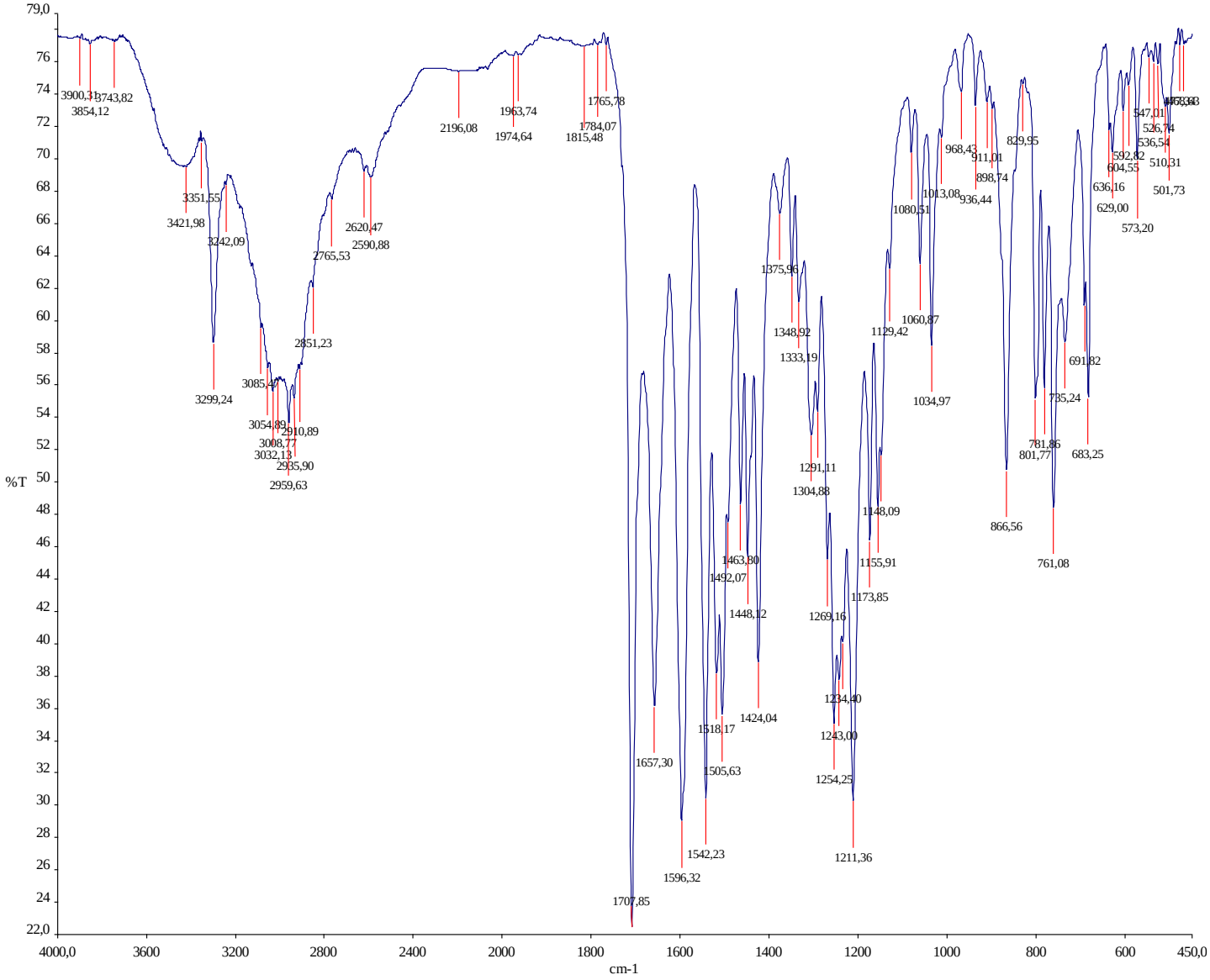

Figure S120. IR spectrum of **5a.**

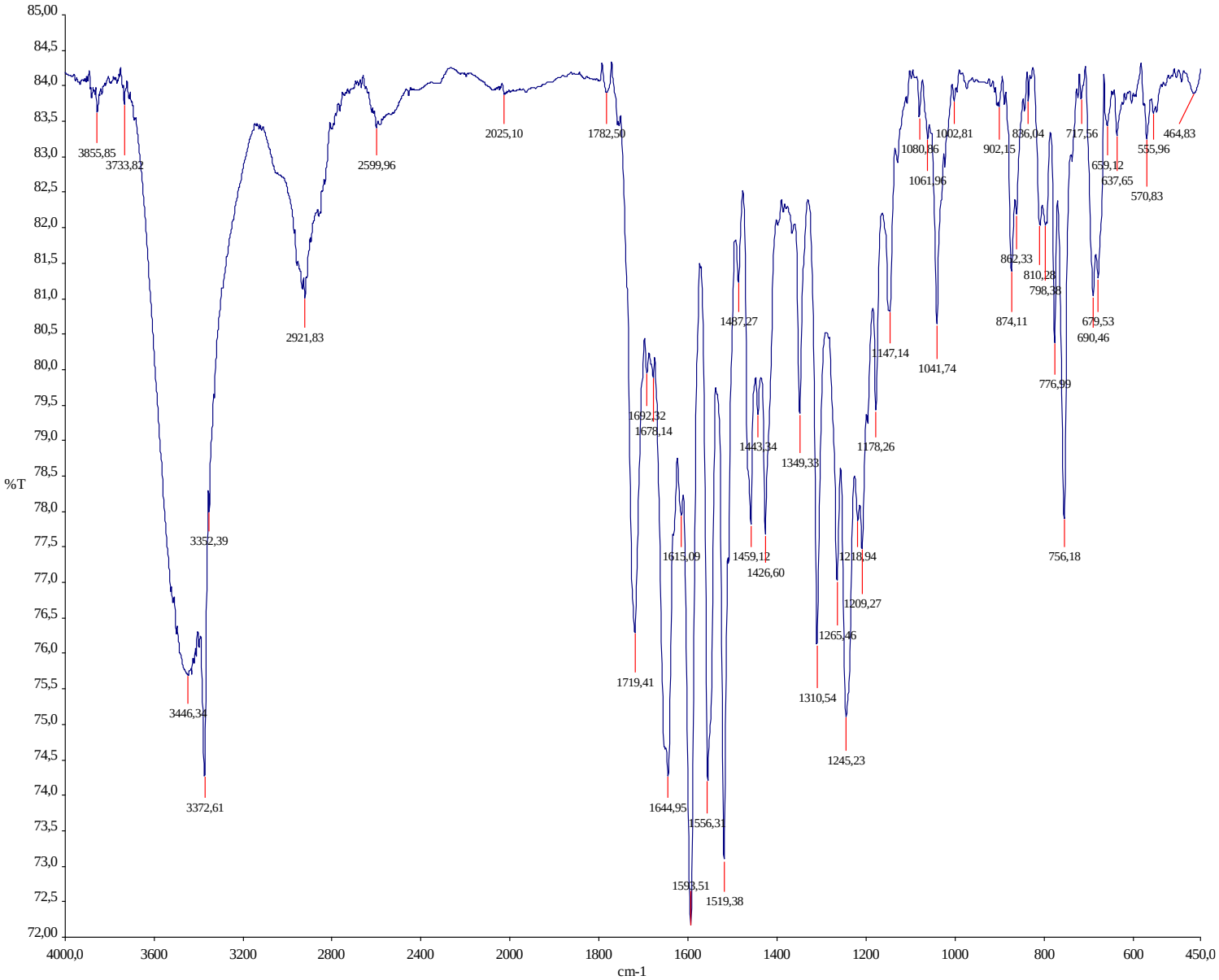

Figure S121. IR spectrum of **5b.**

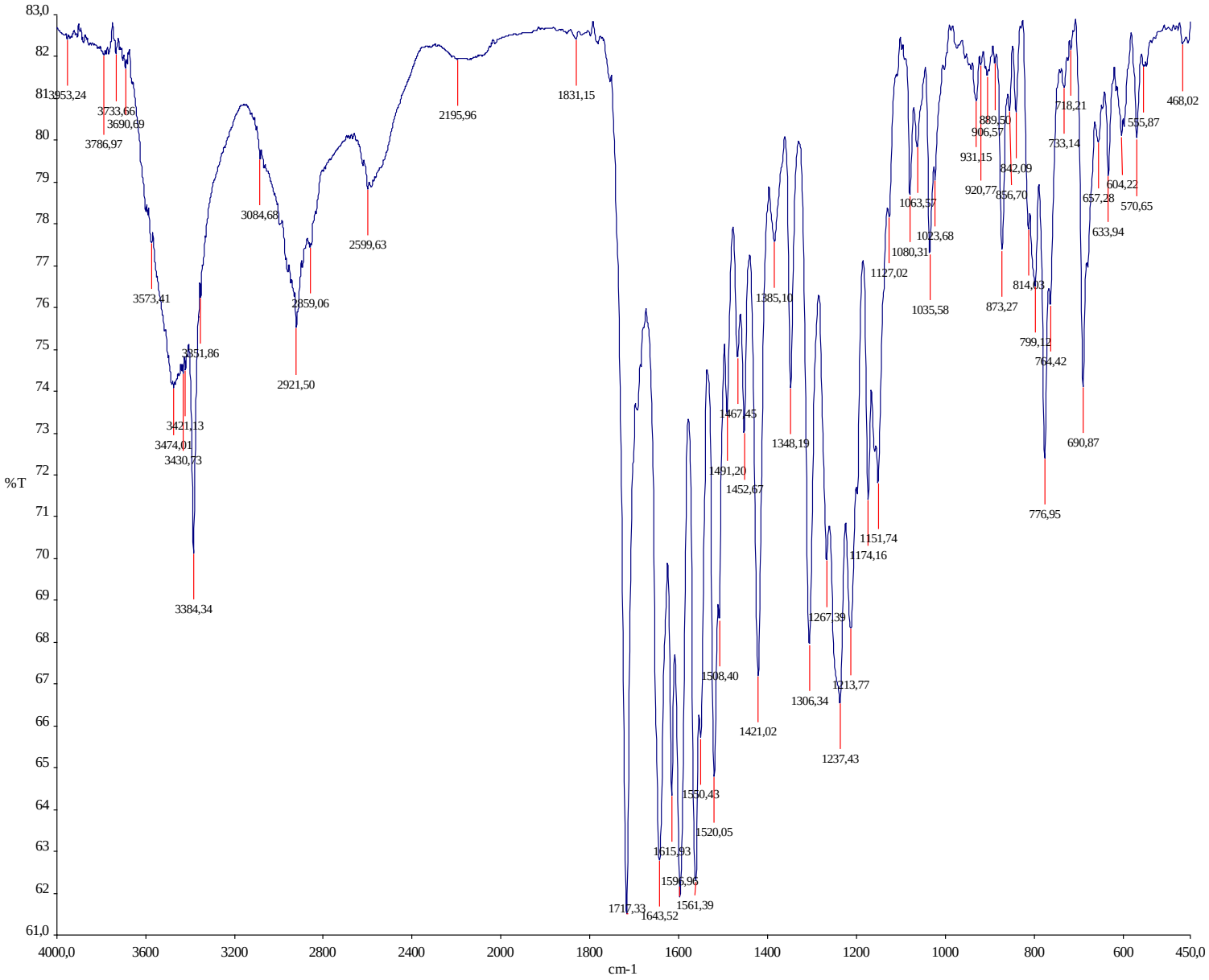

Figure S122. IR spectrum of **5c.**

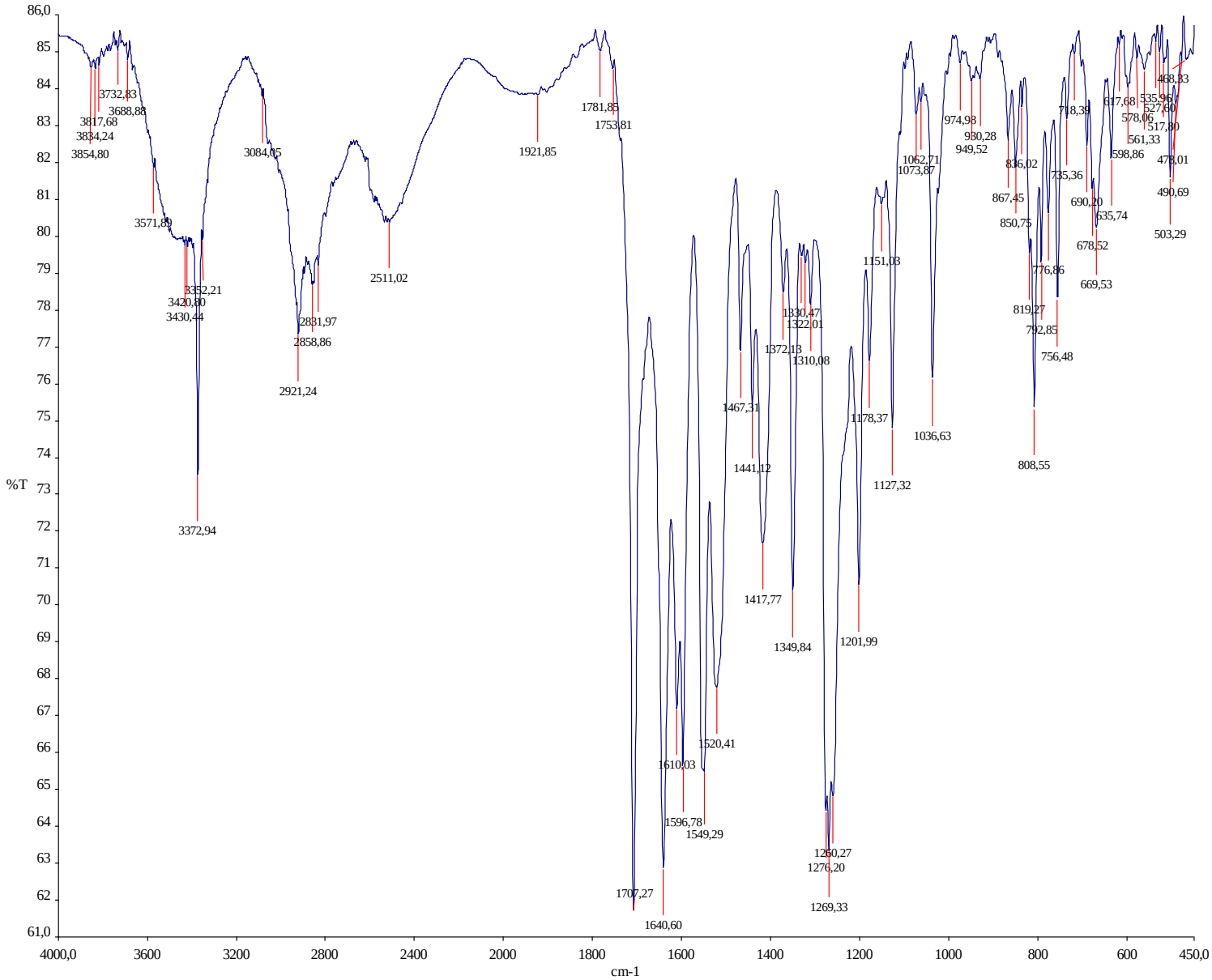

Figure S123. IR spectrum of **5d.**

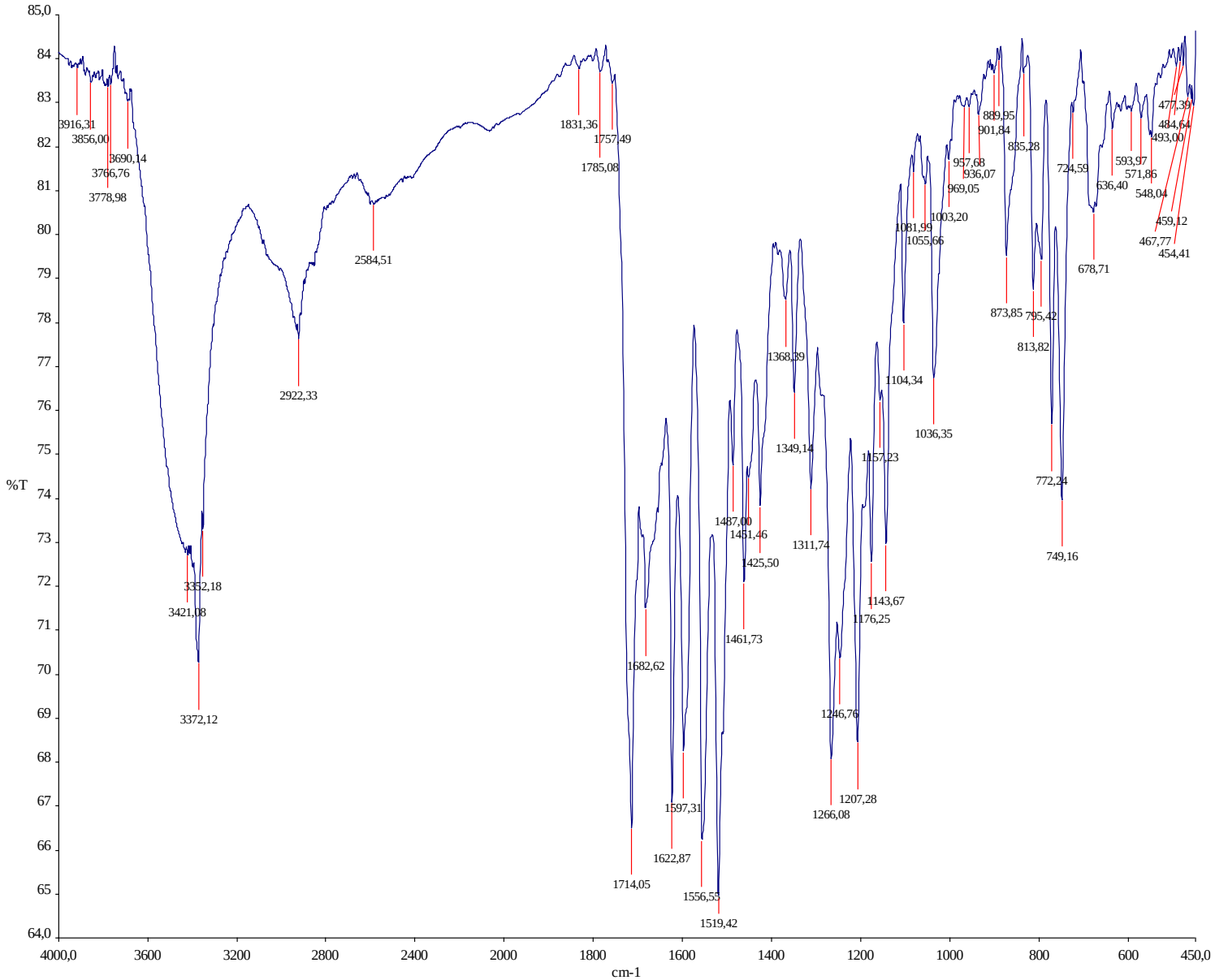

Figure S124. IR spectrum of **5e.**

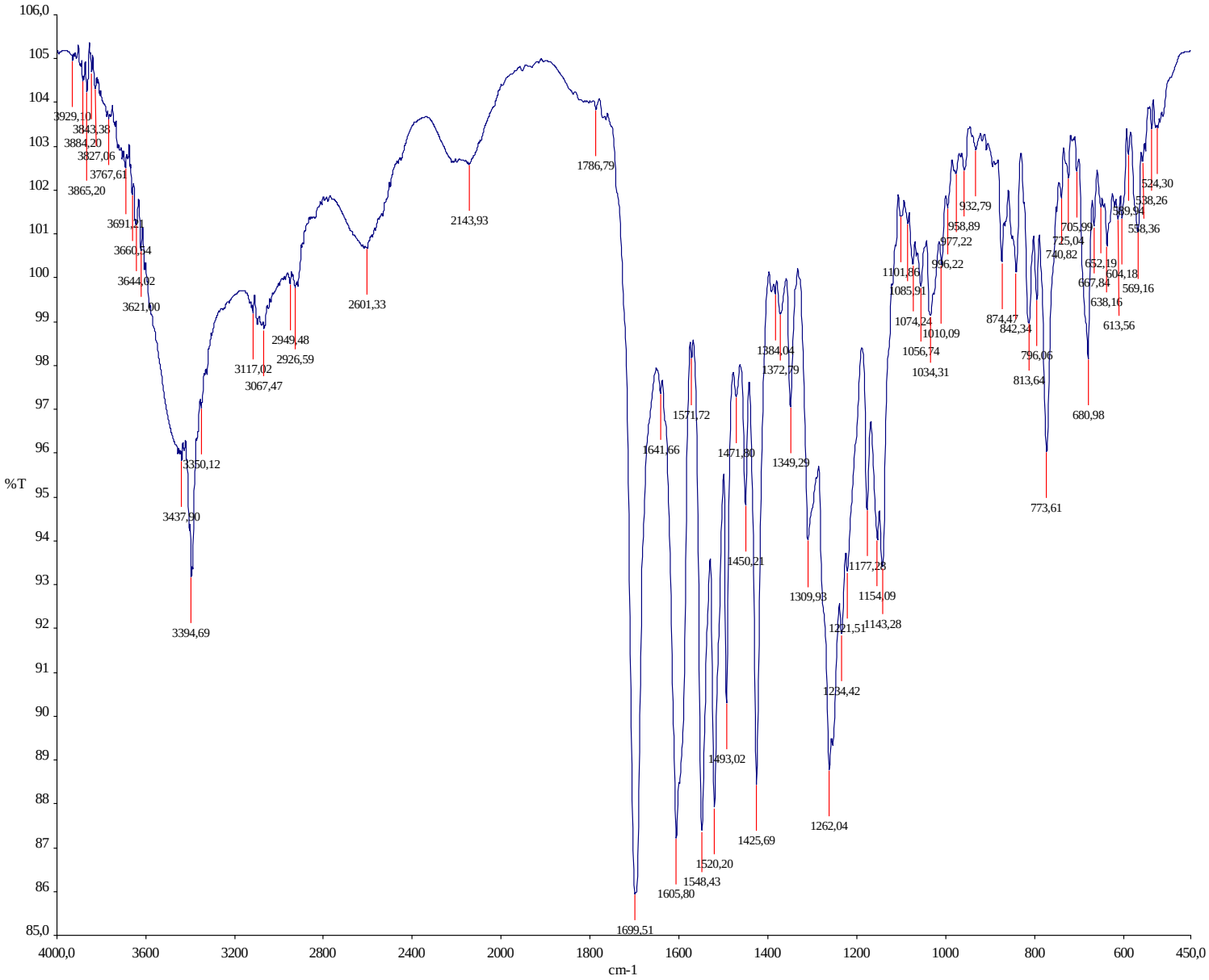

Figure S125. IR spectrum of **5f.**

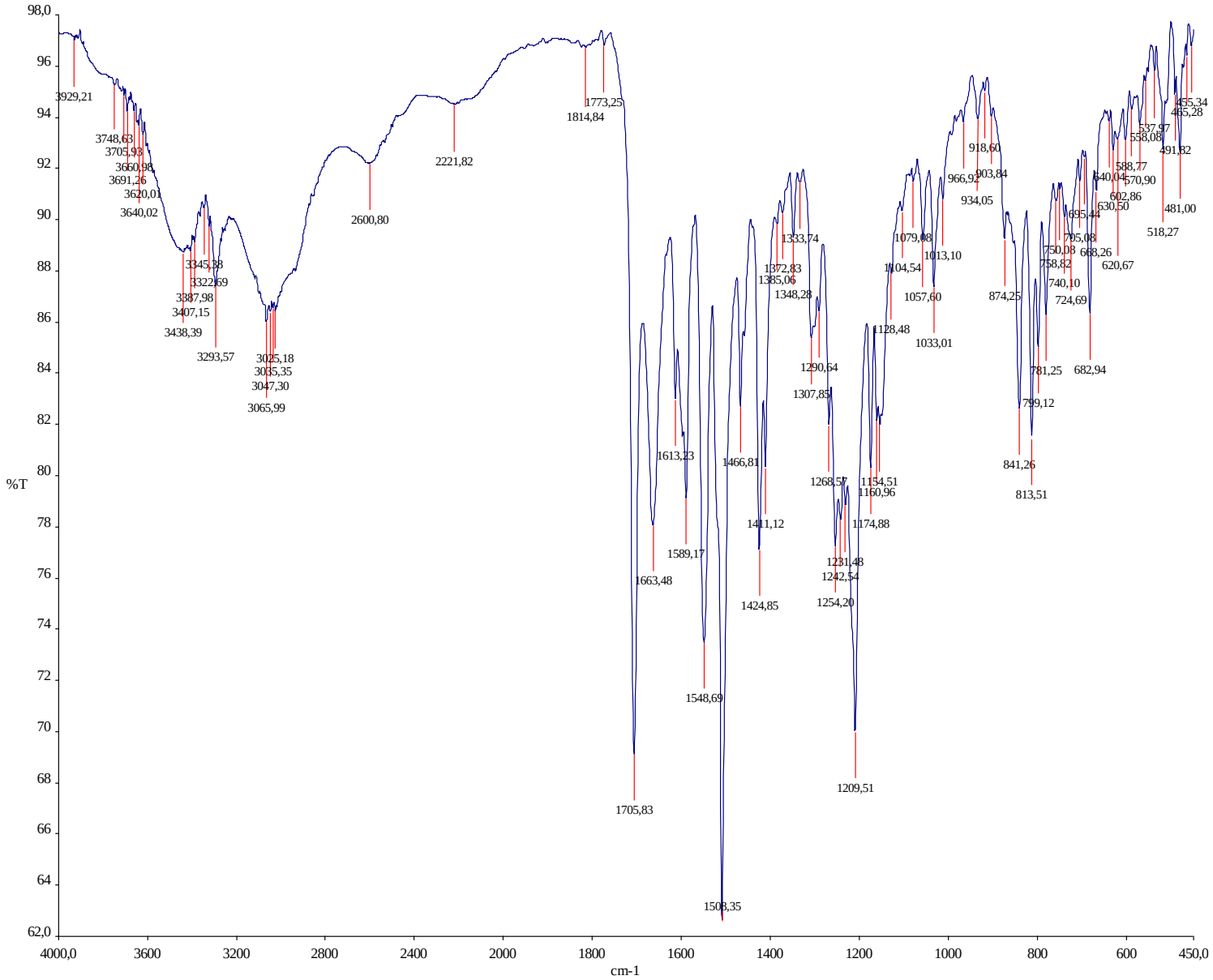

Figure S126. IR spectrum of **5g.**

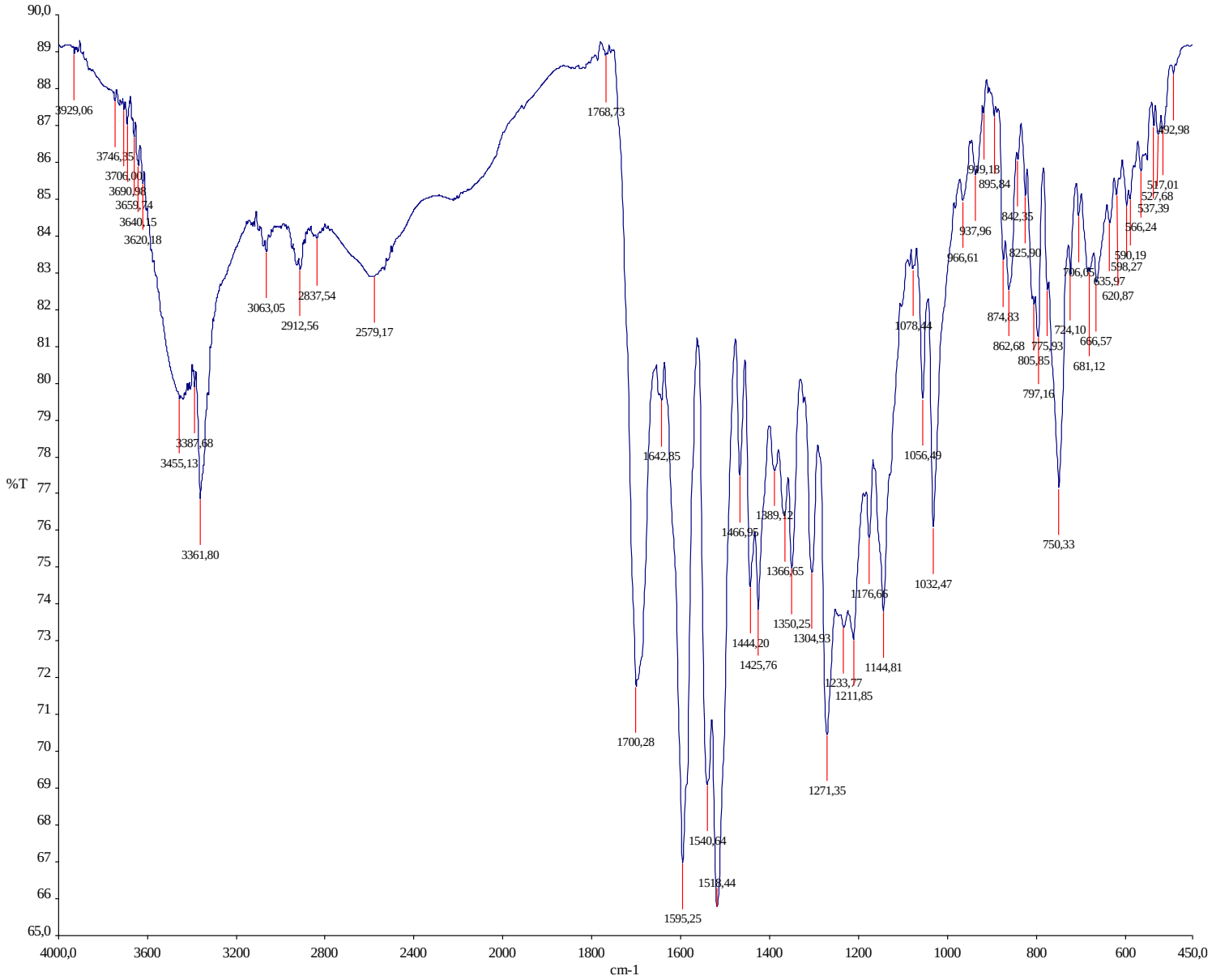

Figure S127. IR spectrum of **5h.**

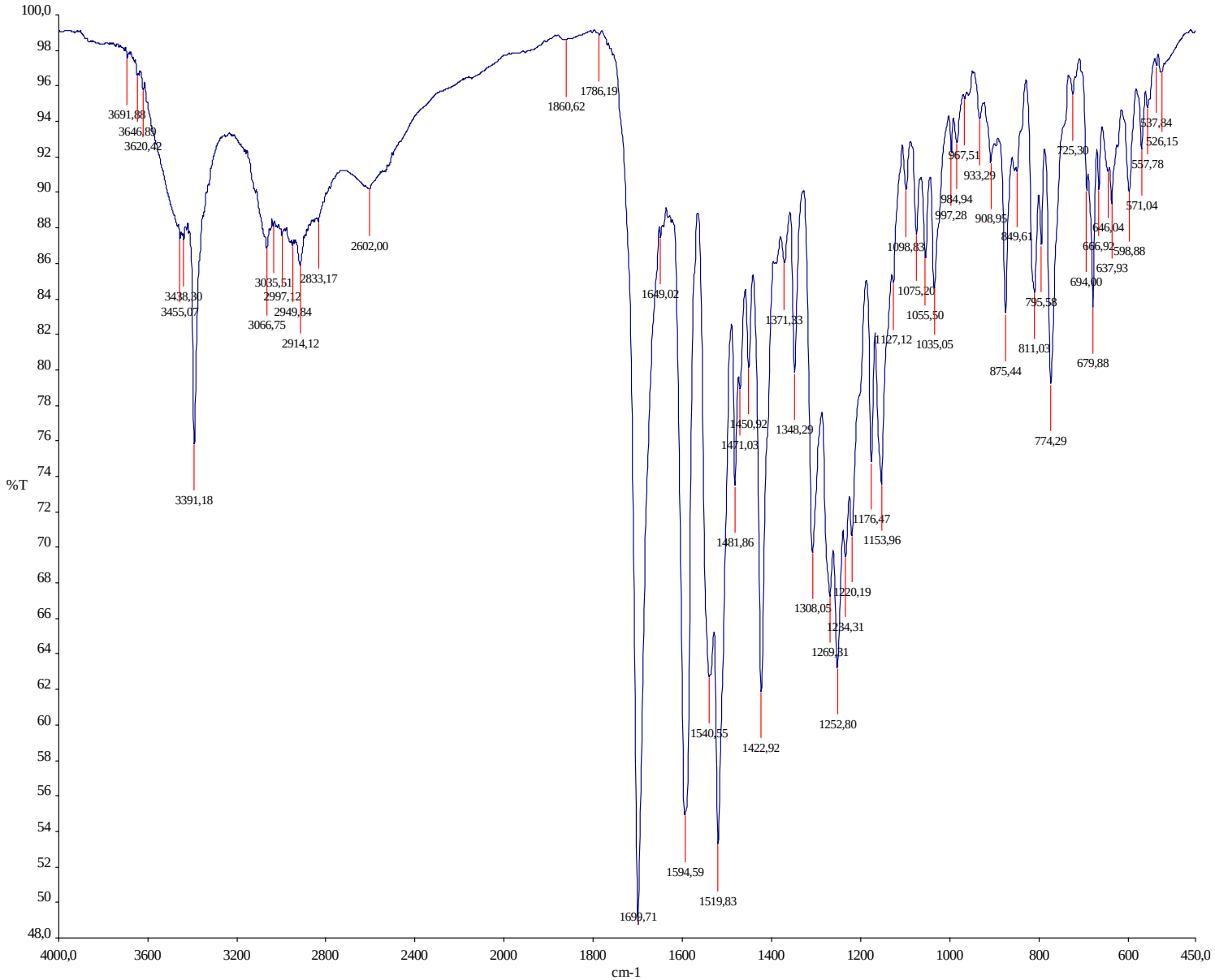

Figure S128. IR spectrum of **5i.**

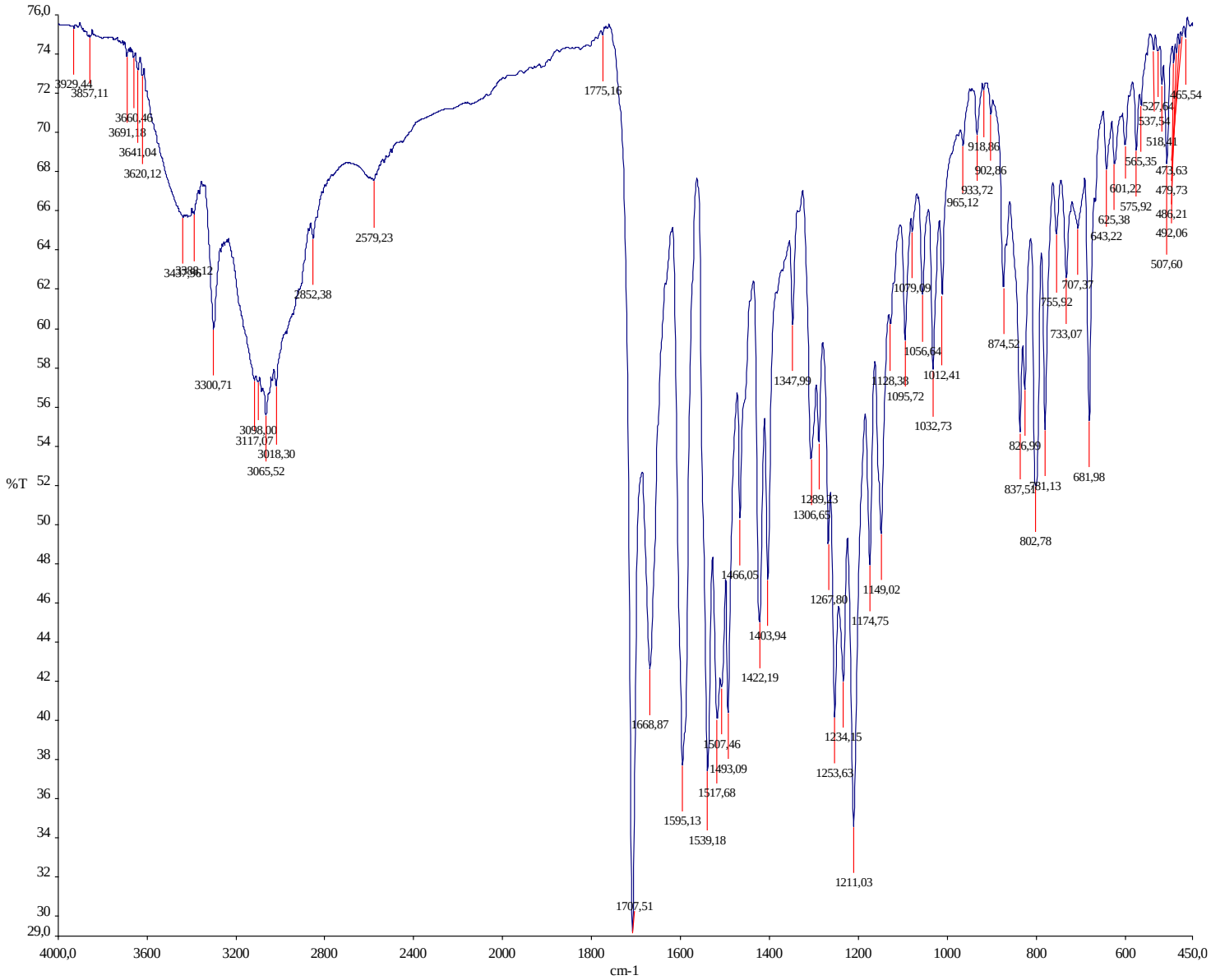

Figure S129. IR spectrum of **5j.**

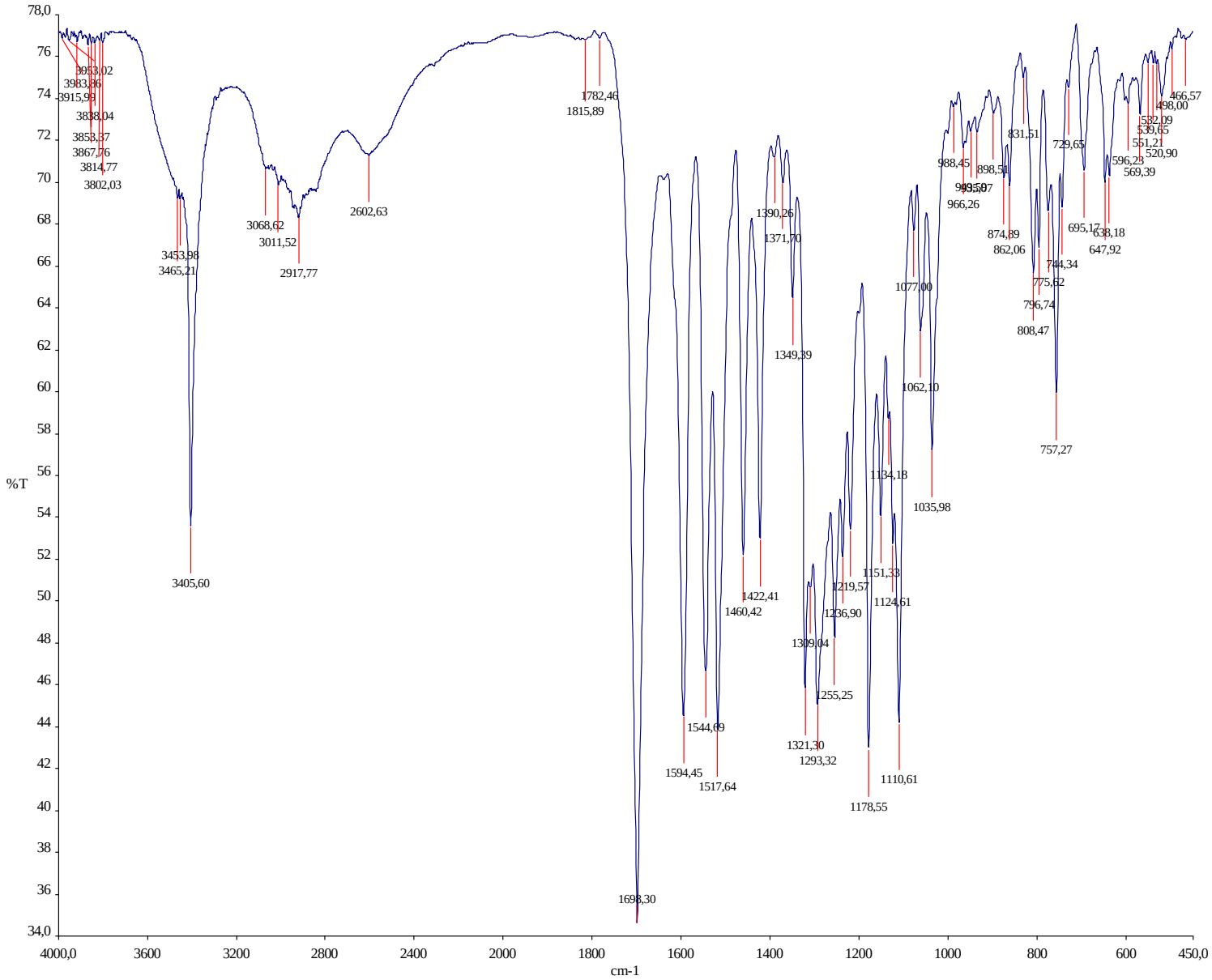

Figure S130. IR spectrum of **5k.**

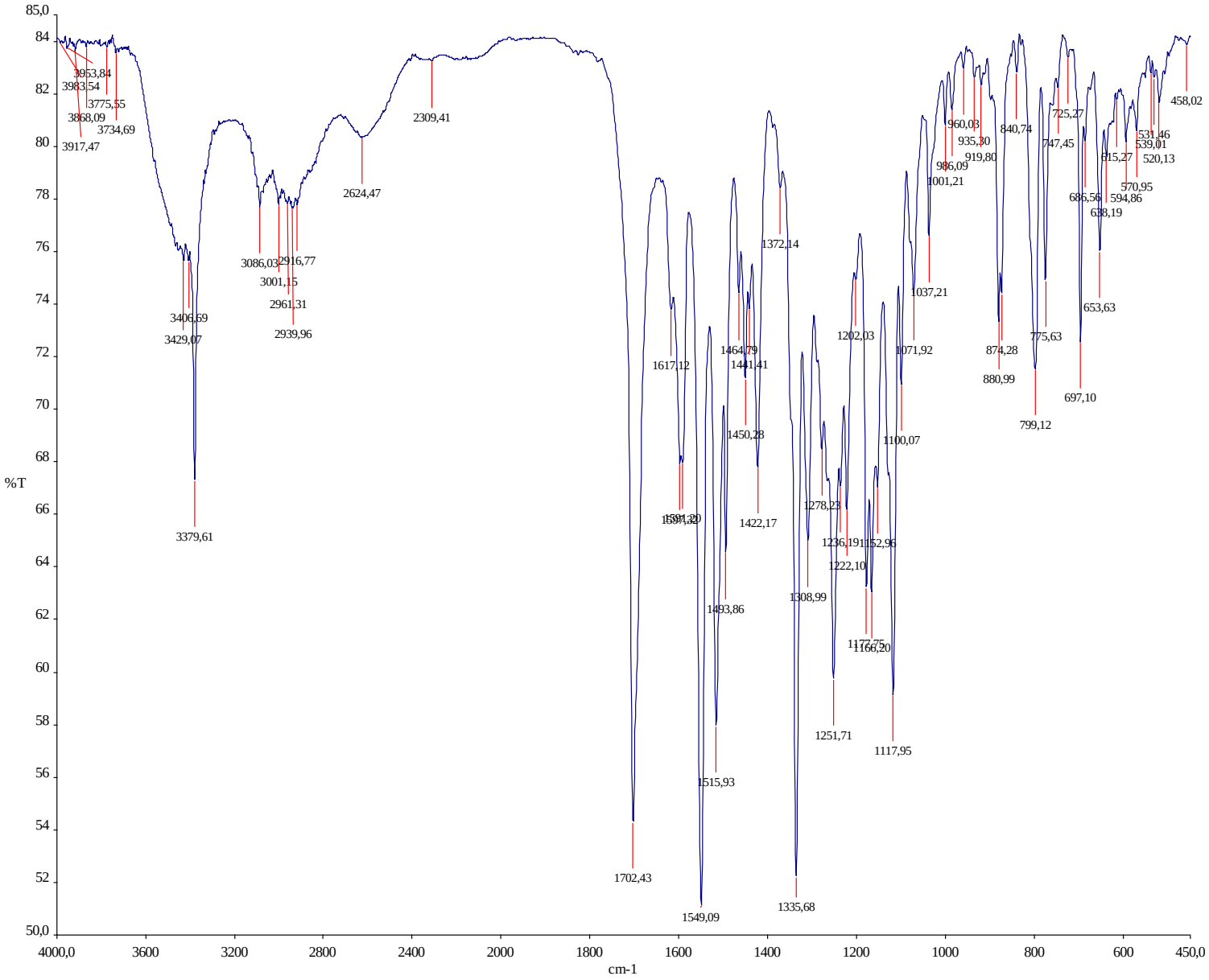

Figure S131. IR spectrum of **5l.**

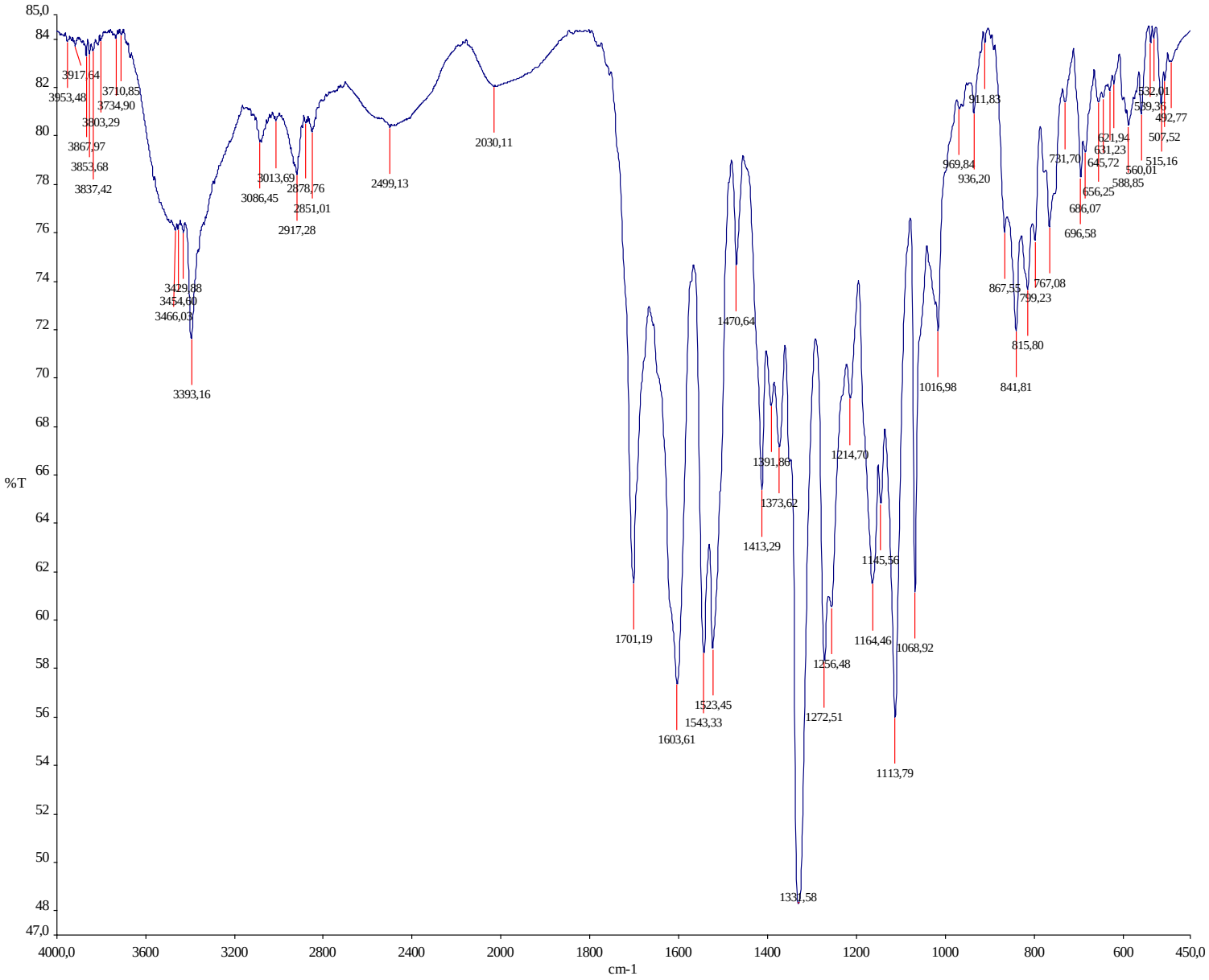

Figure S132. IR spectrum of **5m.**

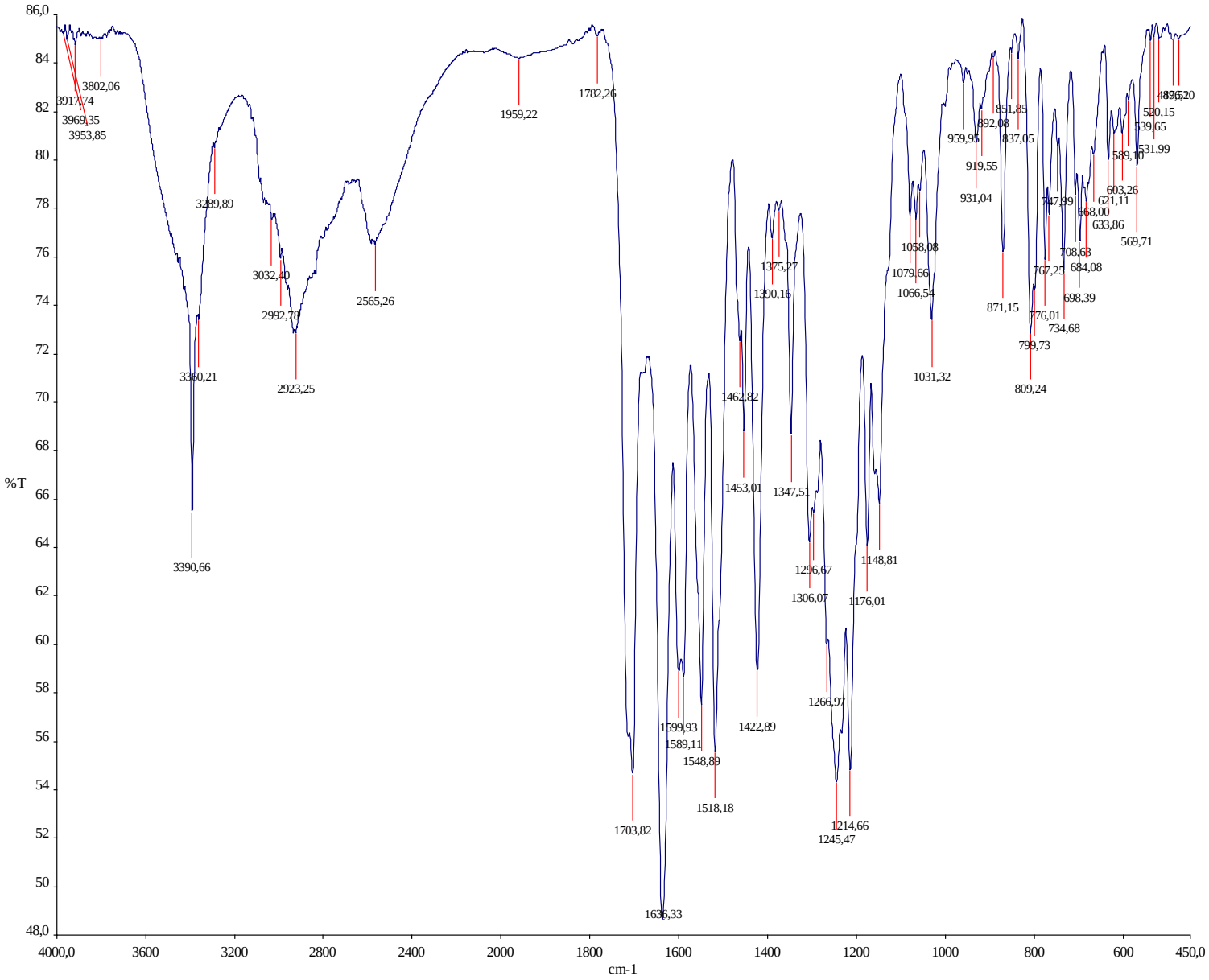

Figure S133. IR spectrum of **5n.**

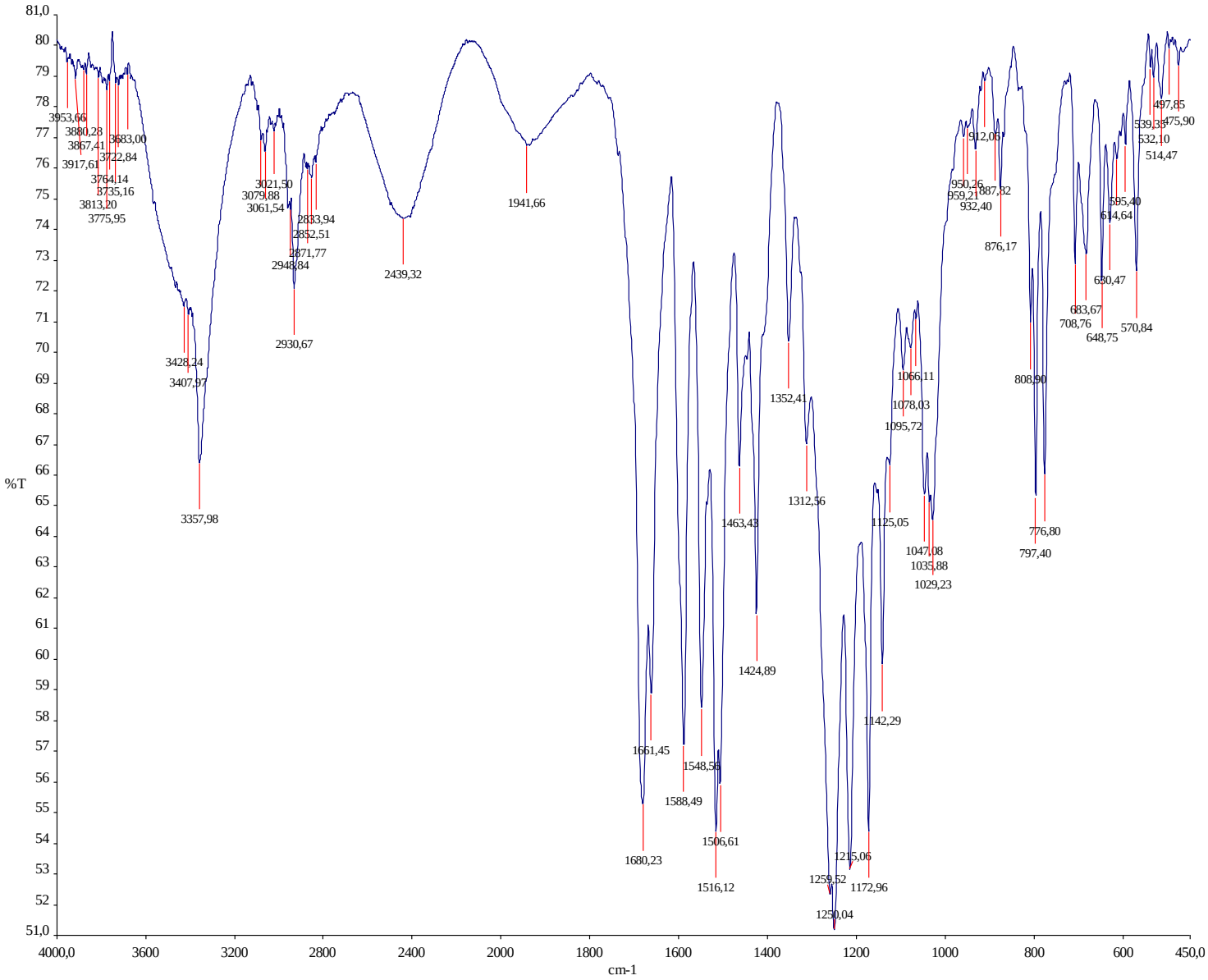

Figure S134. IR spectrum of **5o.**

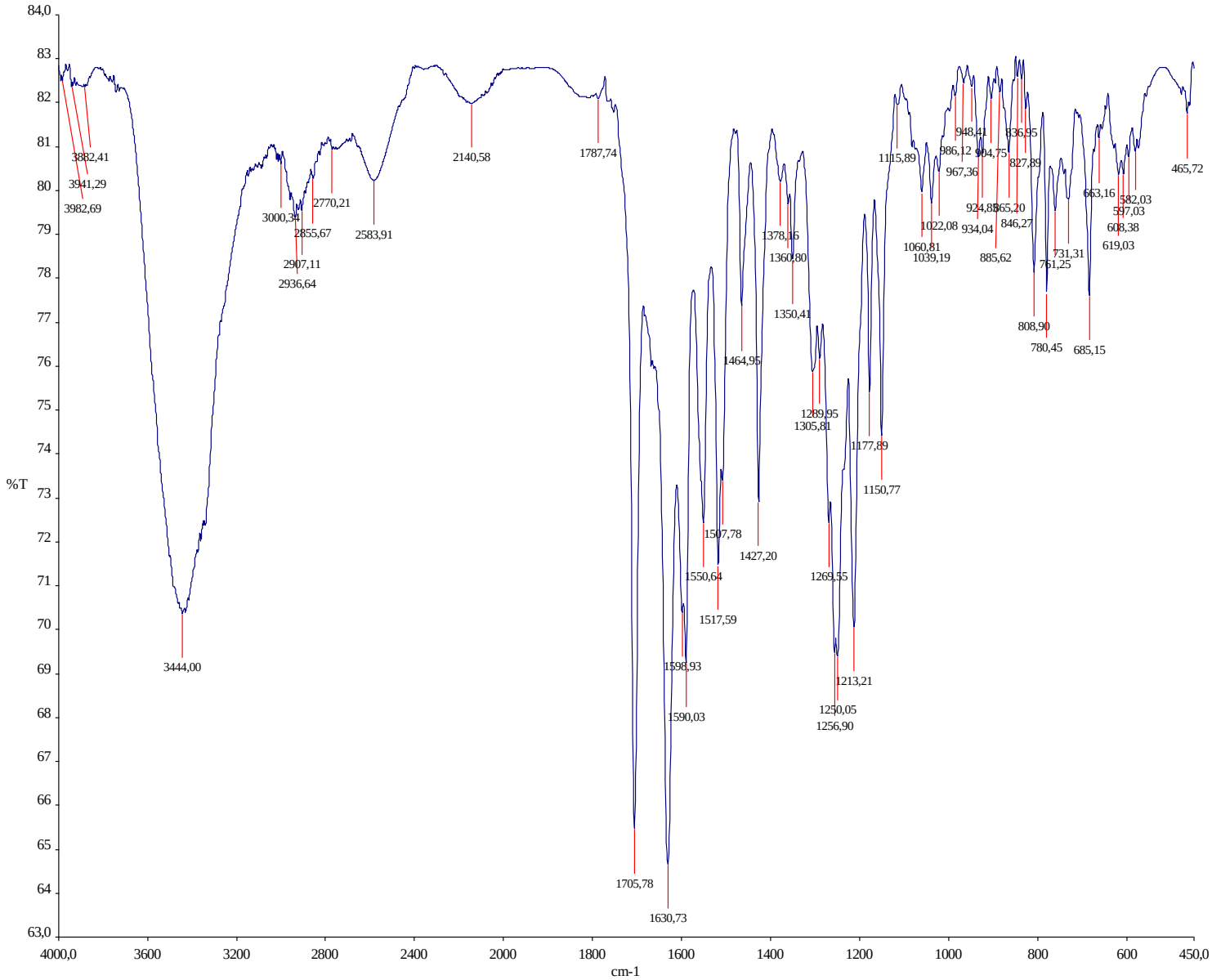

Figure S135. IR spectrum of **5p.**

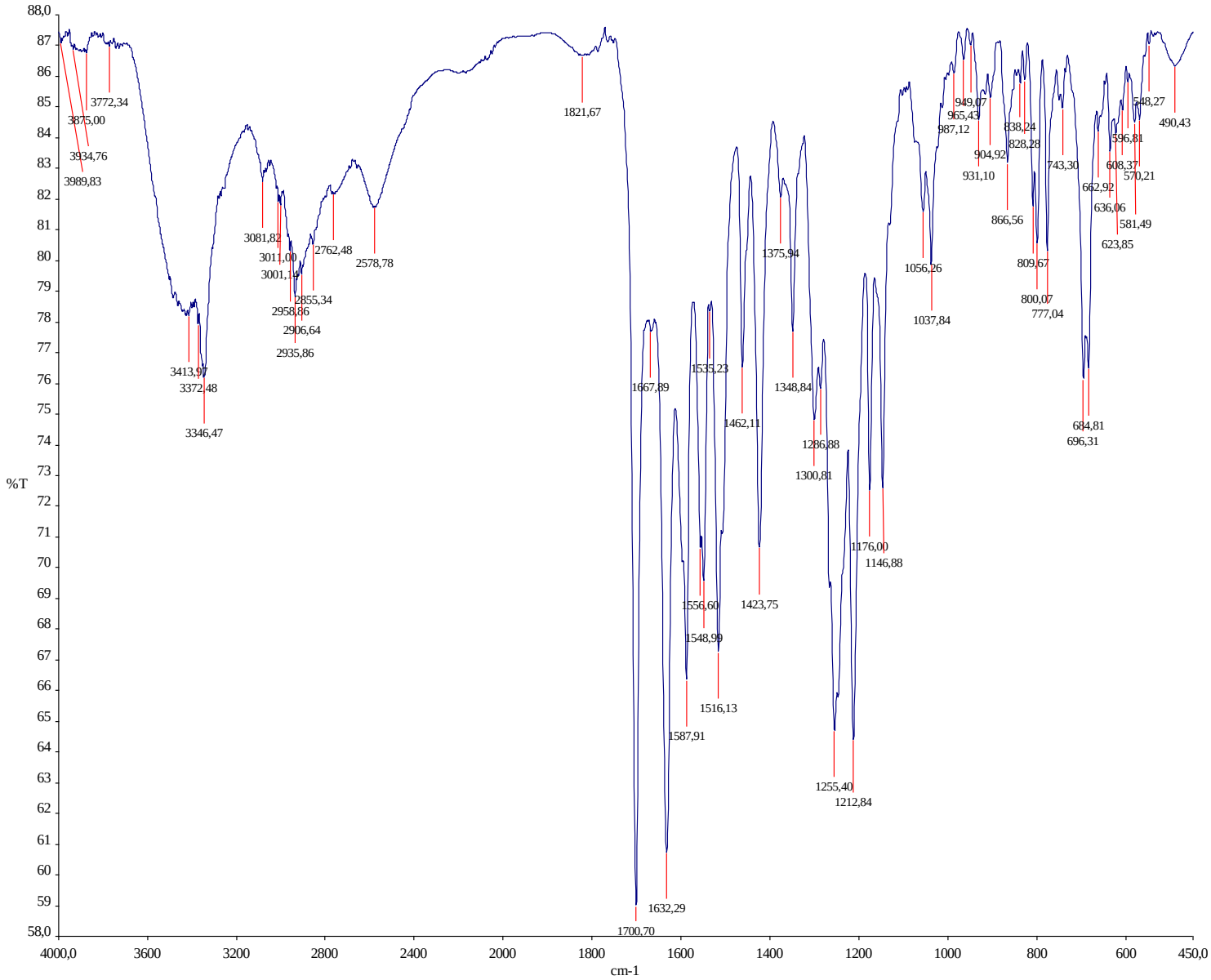

Figure S136. IR spectrum of **5q.**

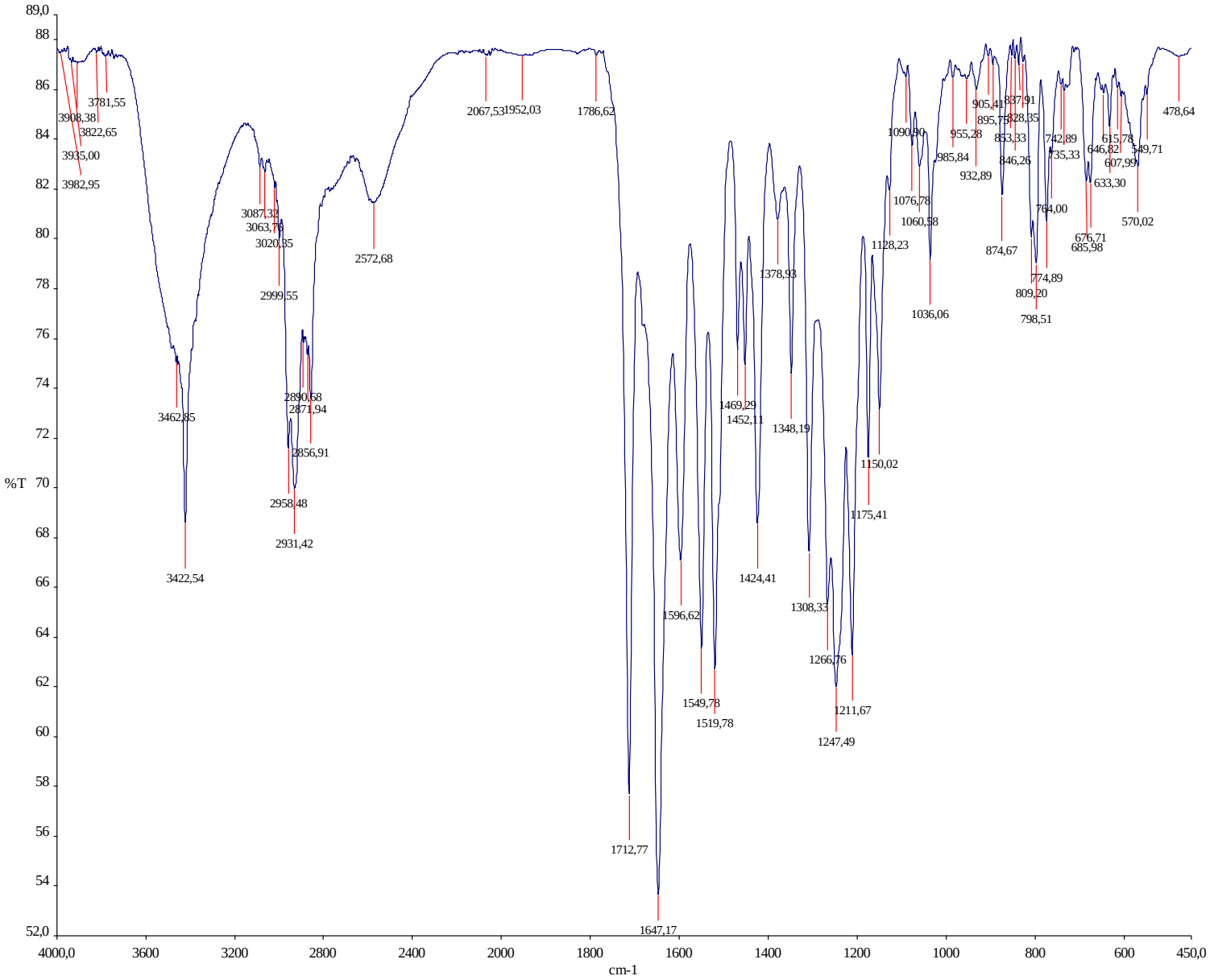

Figure S137. IR spectrum of **5r.**

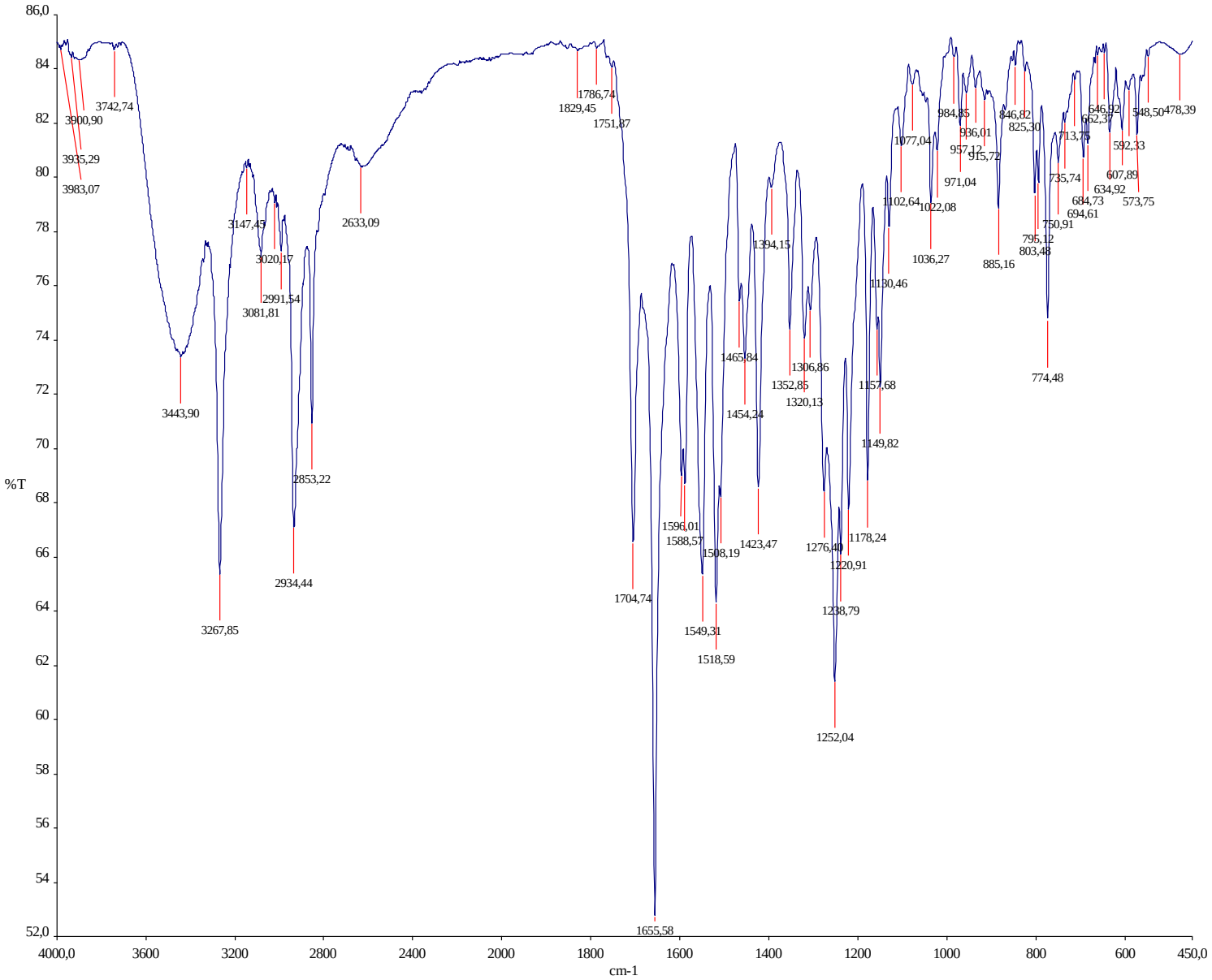

Figure S138. IR spectrum of **5s.**

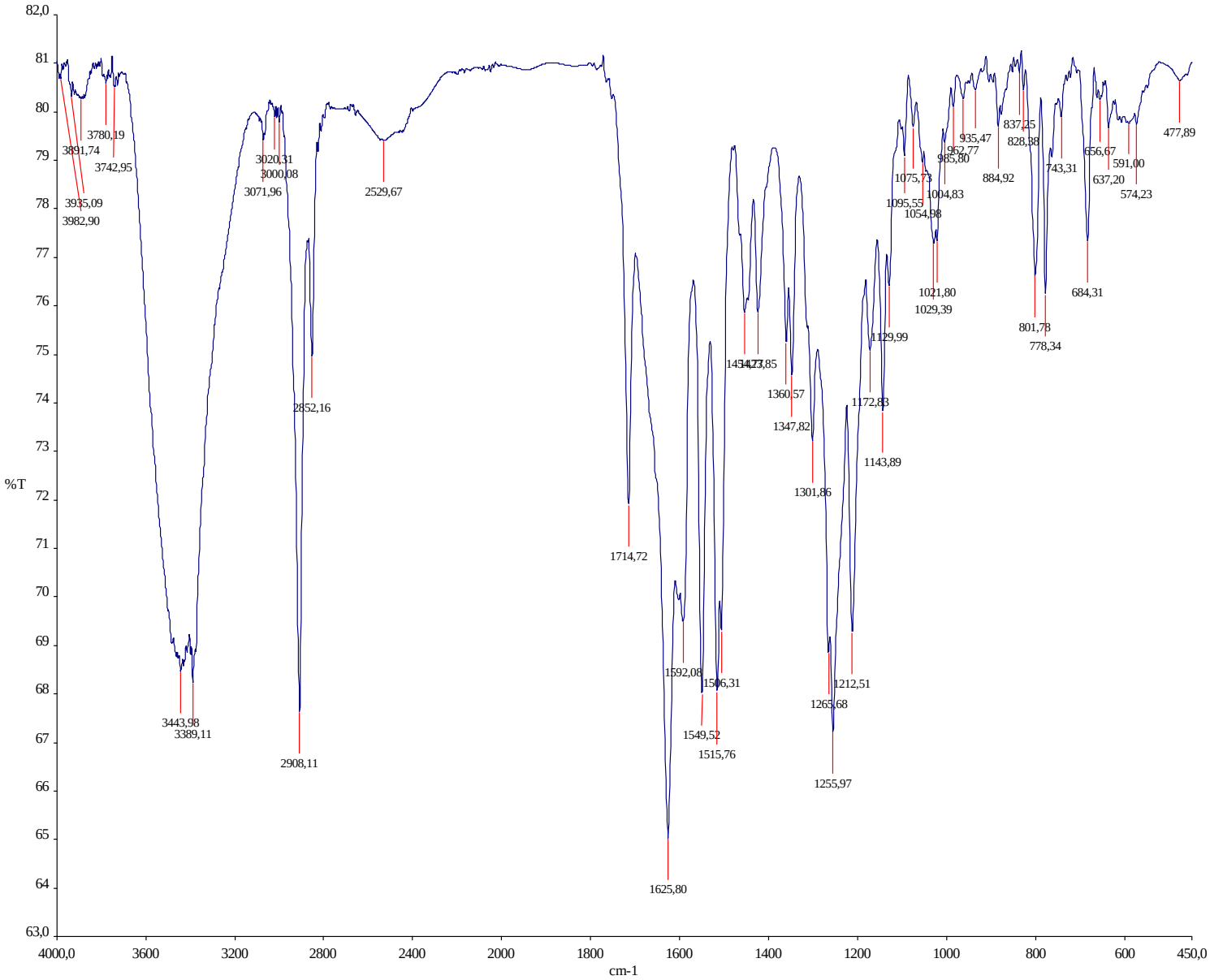

Figure S139. IR spectrum of **5t.**

3. Inhibition of *h*DHODH and cytotoxicity

The inhibiton of human dihydroorotate dehydrogenase (*h*DHODH) activity by synthesized compounds (**5a-5t**) as well as cytotoxicity against HaCat cell line were determined according to previosly reported procedure [1].

4. Docking studies

All the *in silico* experimental work followed the guidelines as described elsewhere [1].

References

[1] Petrović MM, Roschger C, Chaudary S, Zierer A, Mladenović M, Jakovljević K, Marković V, Botta B, Joksović M D. Potent human dihydroorotate dehydrogenase inhibitory activity of new quinoline-4-carboxylic acids derived from phenolic aldehydes: Synthesis, cytotoxicity, lipophilicity and molecular docking studies. *Bioorg. Chem*. 2020;105;104373. https://doi.org/10.1016/j.bioorg.2020.104373.