SUPPORTING INFORMATION

Multicomponent Petasis Reaction for the Synthesis of Functionalized 2-Aminothiophenes and Thienodiazepines

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CONTENTS

GENERAL CHEMISTRY INFORMATION

Solvents and chemicals

All reactions were performed in ambient atmosphere. All the solvents and reagents are purchased from Fischer Scientific, TCI Chemical, or Sigma Aldrich and used without further purification.

Thin layer chromatography (TLC)

Thin layer chromatography (TLC) was performed on silica coated aluminium plates (Merck 60 F254) and visualized under UV irradiation (254 nm), I_2 stain, or potassium permanganate stain (1.5 g $KMnO_4$, 10 g K_2CO_3, 1.25 mL of 10% aqueous NaOH solution and 200 mL of water)

Purification

Chromatographic purification of products was achieved as flash column chromatography on the automated medium pressure liquid chromatography (MPLC, Buchi Pure C-810, Buchi Pure C-835) with proper solvents or preparative chromatography (Buchi Pure C-835, Nuleodur C18 gravity VP 125/10 5 μm) with H_2O (+ 0.1% TFA) and acetonitrile (+ 0.1% TFA). Recrystallization of products from crude products was performed with indicated solvents. Purification by titration was achieved by dispersing crude products and collecting the precipitate with indicated solvent. Yields refer to pure compounds after purification by flash column chromatography, preparative chromatography, recrystallization, or titration.

LC-MS

LC-MS was performed on an Agilent 1260 II Infinity system equipped with a mass detector (column: InfinityLab Poroshell 120 EC-C18, 2.1x150, 2.7 μm). Appropriate gradient systems were applied by mixing H_2O (+ 0.1% TFA) and acetonitrile (+ 0.1% TFA).

NMR

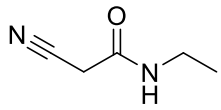
NMR spectra were obtained by Bruker AV 400 Avance III HD (^{1}H-NMR: 400 MHz, ^{13}C-NMR: 101 MHz), Bruker AV 500 BioSpin (^{1}H NMR: 500 MHz, ^{13}C NMR: 126 MHz), Bruker AV 700 Avance III HD (^{1}H NMR: 700 MHz). Data is reported in ppm with reference to the used deuterated solvent ($CDCl_3$: 7.26 ppm, 77.16 ppm; DMSO-d_6: 2.50 ppm, 39.52 ppm). Multiplicities of NMR signals are abbreviated as follows; s: singlet, d: doublet, t: triplet, q: quartet, and m: multiplet. The assignment of peaks were accomplished with 2D NMR correlation (COSY, HSQC, HMBC). Intramolecular cyclization of **7a-7h** were confirmed by HMBC.

High-resolution mass spectrometry (HRMS)

High-resolution mass spectrometry (HRMS) was acquired on an LTQ Orbitrap mass spectrometer coupled to an Accela HPLC-System (HPLC column: Hypersyl GOLD, 50 mm x 1 mm, particle size 1.9 µm, ionization method: electron spray ionization (ESI)).

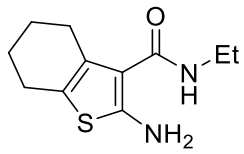
SYNTEHTIC PROCEDURES AND COMPOUND CHARACTERIZATION

2-Cyano-*N*-ethylacetamide (1a)



The compound was synthesized according to a literature procedure.[1] 70% ethylamine aqueous solution (31.2 mL, 374.8 mmol) was added dropwise to ethyl cyanoacetate (20.0 mL, 187.4 mmol) with stirring at room temperature in water bath for 15 minutes. The reaction mixture was stirred at 35 °C for 5 h. The mixture was then cooled to 0 °C overnight. The orange precipitate was filtered off and washed with cold ether to give a desired product as a white solid (17.7g, 84 %). ^{1}H NMR (400 MHz, CDCl3): δ 6.16 (s, 1H), 3.38 – 3.32 (m, 4H), 1.21 (t, J = 7.28 Hz, 3H).

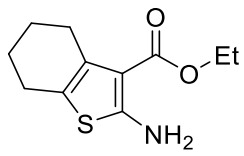
2-Amino-*N*-ethyl-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (2a)



The compound was synthesized according to a literature procedure.[2] A mixture of cyclohexanone (7.0 mL, 67.8 mmol), **1a** (7.6 g, 67.8 mol), ammonium acetate (5.2 g, 67.8 mmol) and glacial acetic acid (3.9 mL, 67.8 mmol) in cyclohexane (150 mL) was refluxed for overnight with 3Å molecular sieves (15 g). The reaction mixture was cooled, diluted with cyclohexane, and washed successively with water, 10% aqueous sodium bicarbonate solution, and dried over anhydrous magnesium sulphate. The solvent was removed under vacuum to give crude 2-cyano-2-cyclohexylidene-*N*-ethyl-acetamide (6.5 g, 50 %). To a mixture of the crude 2-cyano-2-cyclohexylidene-*N*-ethyl-acetamide (3.5 g, 18.0 mmol) and

sulphur (0.69 g, 21.6 mmol) in ethanol (18 mL) was added diethylamine (1.9 mL, 18.0 mmol) dropwise with stirring at room temperature. The mixture was stirred for 3 h at 48 ˚C, cooled to 4 ˚C overnight and the solid obtained was filtered, washed with ethanol. The crude product was recrystallized from solvent mixture (IPA:H_2O = 9:1, v/v) to give a yellow crystal (4.3 g, 56 %). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91 (s, 2H), 5.63 (s, 1H), 3.43–3.37 (m, 2H), 2.65–2.57 (m, 2H), 2.57–2.49 (m, 2H), 1.81–1.78 (m, 4H), 1.19 (t, *J* = 7.25 Hz, 3H).

Ethyl 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (2b)

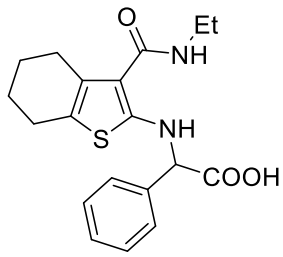


The compound was synthesized according to a literature procedure.[3] To a solution of ethyl cyanoacetate **1b** (5.0 mL, 46.9 mmol), cyclohexanone (4.9 mL, 46.9 mmol), and sulfur (1.5 g, 46.9 mmol) in absolute ethanol (310 mL) under argon was added triethylamine (7.8 mL, 56.2 mmol). The resulting mixture was allowed to be refluxed for 12 h. The suspension was filtered through a pad of celite and washed with ethanol. The combined filtrate was concentrated to dryness. The crude product was purified by recrystallization from solvent mixture (IPA:H_2O=3:2, v/v) to give the product as an orange crystal (6.2 g, 59 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (s, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 2.72–2.64 (m, 2H), 2.57–2.44 (m, 2H), 1.88–1.66 (m, 4H), 1.33 (t, *J* = 7.1 Hz, 3H).

General Procedure of the Multicomponent Petasis Reaction to Synthesize Functionalized 2-aminothiophenes 5-6

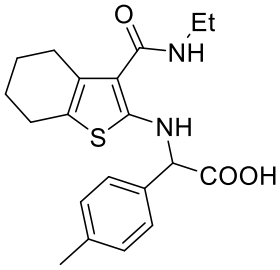
2-Aminothiophene (0.89 mmol), aldehyde (1.07 mmol, 1.2 equiv.), and boronic acid (1.07 mmol, 1.2 equiv.) were added in HFIP (5 mL, 0.18 M) with 3Å molecular sieves (0.4 g powder, 2-fold weight of 2-aminothiophene). The mixture was stirred at room temperature and monitored by LC-MS. The solvent was then evaporated under reduced pressure. The residue was subsequently redispersed in 5 mL of solvent mixture (ACN:H_2O = 6:4, v/v) and dried at lyophilizer overnight. The obtained solid was suspended in a solvent mixture (ACN:H_2O = 6:4, v/v) or Et_2O and the solid was recollected by filtration and washed with a cold mixture of 60% ACN in H_2O or Et_2O to give the product as a solid. Alternatively, the residue obtained after solvent evaporation was purified by preparative chromatography.

2-((3-(Ethylcarbamoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-phenylacetic acid (5a)



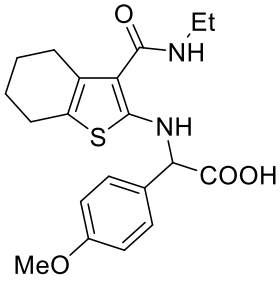
Using **2a** (1.5 g, 6.7 mmol), glyoxylic acid monohydrate **3a** (0.74 g, 8.0 mmol) and phenylboronic acid **4a** (0.98 g, 8.0 mmol) and 3Å molecular sieves (3 g) in HFIP (37.5 mL) with the reaction time of 1 h and washing with 60 % ACN in H_2O to give the desired product (1.26 g, 53 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.30 (s, 1H), 8.68 (d, J = 6.9 Hz, 1H), 7.55 – 7.21 (m, 5H), 6.81 (t, J = 5.6 Hz, 1H), 4.89 (d, J = 6.9 Hz, 1H), 3.26–3.20 (m, 2H), 2.65 – 2.53 (m, 2H), 2.46 – 2.36 (m, 2H), 1.75 – 1.57 (m, 4H), 1.08 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.0, 165.1, 156.0, 137.2, 129.8, 128.2 (2), 127.7, 126.8 (2), 117.0, 108.3, 62.3, 33.1, 25.3, 23.5, 22.2, 21.9, 14.6. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{19}H_{23}N_2O_3S$, 359.1424; found, 359.1424.

2-((3-(Ethylcarbamoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-(*p*-tolyl)acetic acid (5b)



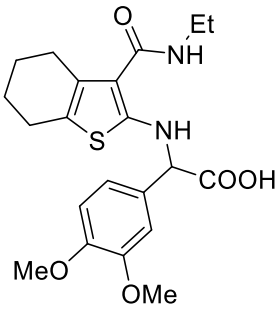
Using **2a** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.5 mg, 1.07 mmol), and 4-tolylboronic acid **4b** (145.5 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 1 h and washing with 60 % ACN to give the desired product (247.5 mg, 75 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.20 (s, 1H), 8.64 (d, J = 6.9 Hz, 1H), 7.26 (d, J = 7.5 Hz, 2H), 7.16 (d, J = 7.5 Hz, 2H), 6.78 (t, J = 5.7 Hz, 1H), 4.83 (d, J = 6.9 Hz, 1H), 3.25–3.21 (m, 2H), 2.64–2.56 (m, 2H), 2.47–2.36 (m, 2H), 2.27 (s, 3H), 1.72–1.60 (m, 4H), 1.09 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.2, 165.1, 156.1, 137.0, 134.2, 129.7, 128.8 (2), 126.7(2), 116.9, 108.3, 62.0, 33.1, 25.3, 23.5, 22.2, 21.9, 20.2, 14.6. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{20}H_{25}N_2O_3S$, 373.1580; found, 373.1581.

2-((3-(Ethylcarbamoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-(4-methoxyphenyl) acetic acid (5c)



Using **2a** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.5 mg, 1.07 mmol), and 4-methoxyphenylboronic acid **4c** (162.6 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 1 h and washing with 60 % ACN to give the desired product (264.0 mg, 76 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.20 (s, 1H), 8.63 (d, J = 6.7 Hz, 1H), 7.29 (d, J = 8.7 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 6.79 (t, J = 5.6 Hz, 1H), 4.81 (d, J = 6.7 Hz, 1H), 3.73 (s, 3H), 3.25–3.20 (m, 2H), 2.64 – 2.57 (m, 2H), 2.47 – 2.37 (m, 2H), 1.72 – 1.59 (m, 4H), 1.08 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.3, 165.1, 158.6, 156.1, 129.7, 128.9, 128.0 (2), 116.9, 113.6 (2), 108.2, 61.7, 54.6, 33.1, 25.3, 23.5, 22.2, 22.0, 14.6. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{20}H_{25}N_2O_4S$, 389.1530; found, 389.1532.

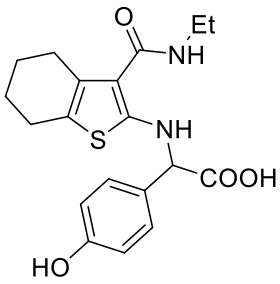
2-(3,4-Dimethoxyphenyl)-2-((3-(ethylcarbamoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)acetic acid (5d)



Using **2a** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.5 mg, 1.07 mmol), and 3,4-dimethoxyphenylboronic acid **4d** (194.7 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 1 h and washing with Et_2O to give the desired product (245.1 mg, 66 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.16 (s, 1H), 8.56 (d, J = 6.9 Hz, 1H), 7.00 – 6.87 (m, 3H), 6.81 (t, J = 5.6 Hz, 1H), 4.81 (d, J = 6.9 Hz, 1H), 3.73 (s, 3H), 3.71 (s, 3H), 3.25–3.21 (m, 2H), 2.65 – 2.55 (m, 2H), 2.47 – 2.39 (m, 2H), 1.72 – 1.61 (m, 4H), 1.08 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.3, 165.1, 156.1, 148.2, 148.2, 129.7, 129.3, 119.0, 117.2, 111.2, 110.3, 108.6, 62.1, 55.0, 55.0,

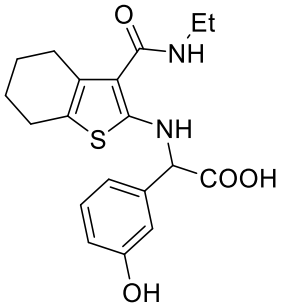
33.1, 25.3, 23.6, 22.2, 22.0, 14.6. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{21}H_{27}N_2O_5S$, 419.1635; found, 419.1635.

2-((3-(Ethylcarbamoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-(4-hydroxyphenyl) acetic acid (5e)



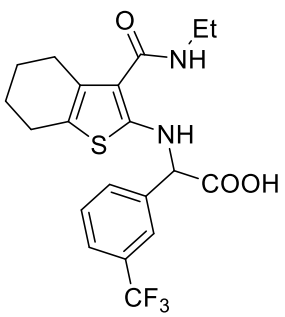
Using **2a** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.5 mg, 1.07 mmol), and 4-hydroxyphenylboronic acid **4e** (147.6 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 1 h and washing with Et_2O to give the desired product (290.9 mg, 87 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.09 (s, 1H), 9.48 (s, 1H), 8.57 (d, *J* = 6.9 Hz, 1H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.77 (t, *J* = 5.6 Hz, 1H), 6.73 (d, *J* = 8.6 Hz, 2H), 4.73 (d, *J* = 6.9 Hz, 1H), 3.24–3.20 (m, 2H), 2.65–2.56 (m, 2H), 2.47–2.40 (m, 2H), 1.73–1.59 (m, 4H), 1.08 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 171.6, 165.2, 157.0, 156.4, 129.8, 128.1 (2), 127.3, 117.0, 115.0 (2), 108.3, 62.0, 33.2, 25.5, 23.7, 22.3, 22.1, 14.7. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{19}H_{23}N_2O_4S$, 375.1373; found, 375.1374.

2-((3-(Ethylcarbamoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-(3-hydroxyphenyl) acetic acid (5f)



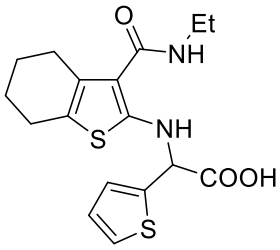
Using **2a** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.5 mg, 1.07 mmol), and 3-hydroxyphenylboronic acid **4f** (147.6 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 3 h and washing with 60 % ACN to give the desired product (52.7 mg, 16 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ 13.24 (s, 1H), 9.50 (s, 1H), 8.66 (d, J = 7.0 Hz, 1H), 7.14 (t, J = 7.8 Hz, 1H), 6.85 – 6.73 (m, 3H), 6.68 (d, J = 8.1 Hz, 1H), 4.77 (d, J = 7.0 Hz, 1H), 3.25–3.20 (m, 2H), 2.67–2.55 (m, 2H), 2.46–2.39 (m, 2H), 1.72–1.58 (m, 4H), 1.08 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.0, 165.1, 157.1, 156.2, 138.4, 129.8, 129.2, 117.7, 116.8, 114.7, 113.3, 108.0, 62.2, 33.1, 25.4, 23.5, 22.2, 22.0, 14.6. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{19}H_{23}N_2O_4S$, 375.1373; found,375.1374.

2-((3-(Ethylcarbamoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-(3-(trifluoromethyl)-phenyl)acetic acid (5g)



Using **2a** (100.0 mg, 0.45 mmol), glyoxylic acid monohydrate **3a** (49.2 mg, 0.54 mmol), and 3-(Trifluoromethyl)phenylboronic acid **4g** (101.6 mg, 0.54 mmol) and 3Å molecular sieves (0.2 g) in HFIP (2.5 mL) with the reaction time of 4 h. After evaporation of the solvent, the crude was purified by preparative chromatography to give the desired product (30.8 mg, 16 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.54 (s, 1H), 8.66 (s, 1H), 7.74 (s, 1H), 7.72 – 7.68 (m, 2H), 7.62 (t, J = 7.7 Hz, 1H), 6.87 (t, J = 5.6 Hz, 1H), 5.11 (s, 1H), 3.28 – 3.21 (m, 2H), 2.65 – 2.56 (m, 2H), 2.46 – 2.37 (m, 2H), 1.73 – 1.58 (m, 4H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 170.5, 165.1, 155.5, 139.0, 131.0, 130.0, 129.6, 129.2 and 129.1 and 128.9 and 128.7 (q, $^{2}J_{C\text{-}F}$ = 32 Hz), 126.0 and 124.5 and 122.9 and 121.4 (q, $^{1}J_{C\text{-}F}$ = 272 Hz), 124.7 and 124.7 and 124.7 and 124.7 (q, $^{3}J_{C\text{-}F}$ = 4 Hz), 123.5 and 123.4 and 123.4 and 123.4 (q, $^{3}J_{C\text{-}F}$ = 4 Hz), 117.7, 109.3, 62.0, 33.2, 25.4, 23.6, 22.3, 22.0, 14.6. LCMS-ESI (m/z): calculated for $[M+H]^+$ $C_{20}H_{22}F_3N_2O_3S$, 427.1; found, 427.2.

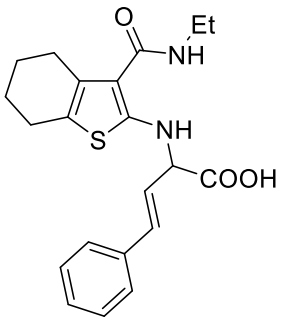
2-((3-(Ethylcarbamoyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-(thiophen-2-yl)acetic acid (5k)



Using **2a** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.5 mg, 1.07 mmol), and 2-thiopheneboronic acid **4k** (136.9 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 1 h and washing with 60 % ACN to give the desired product (244.4 mg, 75 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.48 (s, 1H), 8.53 (d, J = 6.7 Hz, 1H), 7.48 (dd, J = 5.1, 1.3 Hz, 1H), 7.15 (d, J = 3.3 Hz, 1H), 7.00 (dd, J = 5.1 and 3.3 Hz, 1H), 6.86 (t, J = 5.6 Hz, 1H), 5.18 (d, J = 6.7 Hz, 1H), 3.24–3.20 (m, 2H), 2.66 – 2.55 (m, 2H), 2.47–2.42 (m, 2H), 1.75–1.59 (m, 4H), 1.08 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.3, 165.0, 155.6, 140.4, 129.8, 126.5, 126.4, 125.8,

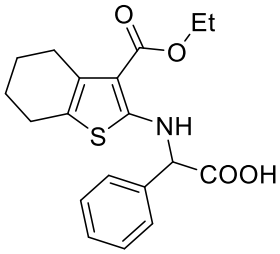
117.6, 109.2, 58.4, 33.1, 25.3, 23.5, 22.2, 21.9, 14.6. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{17}H_{21}N_2O_3S_2$, 365.0988; found, 365.0990.

(*E*)-2-((3(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-4-phenylbut-3-enoic acid (5l)



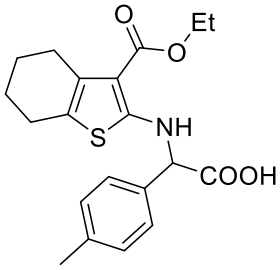
Using **2a** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.5 mg, 1.07 mmol), and *trans*-2-phenylvinylboronic acid **4l** (158.3 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 40 min and washing with 60 % ACN to give the desired product (212.9 mg, 62 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.30 (s, 1H), 8.31 (d, J = 6.9 Hz, 1H), 7.46 (d, J = 7.7 Hz, 2H), 7.33 (t, J = 7.7 Hz, 2H), 7.26 (t, J = 7.4 Hz, 1H), 6.84 (t, J = 5.7 Hz, 1H), 6.70 (d, J = 15.8 Hz, 1H), 6.31 (dd, J = 15.8 and 6.8 Hz, 1H), 4.52–4.51 (m, 1H), 3.25–3.21 (m, 2H), 2.67–2.58 (m, 2H), 2.48–2.46 (m, 2H), 1.74–1.62 (m, 4H), 1.09 (t, J = 7.2 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 171.0, 165.2, 156.4, 135.3, 132.5, 130.1, 128.3 (2), 127.7, 126.2 (2), 124.6, 117.0, 108.6, 61.1, 33.2, 25.5, 23.7, 22.3, 22.1, 14.7. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{21}H_{25}N_2O_3S$, 385.1580; found, 385.1580.

2-((3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-phenylacetic acid (6a)



Using **2b** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.1 mg, 1.07 mmol) and phenylboronic acid **4a** (129.9 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 1 h and washing with 60 % ACN to give the desired product (233.6 mg, 73 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.50 (s, 1H), 8.70 (d, J = 6.2 Hz, 1H), 7.42–7.35 (m, 4H), 7.32 (t, J = 6.7 Hz, 1H), 5.00 (d, J = 6.2 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.66–2.56 (m, 2H), 2.43–2.32 (m, 2H), 1.69–1.57 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 170.8, 164.9, 160.4, 136.6, 131.6, 128.4 (2), 128.0, 126.9 (2), 116.8, 102.9, 62.0, 58.7, 26.0, 23.5, 22.3, 21.9, 13.9. LCMS-ESI (m/z): calculated for $[M+H]^+$ $C_{19}H_{22}NO_4S$, 360.1; found, 360.0.

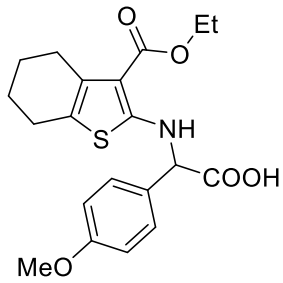
2-((3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-(*p*-tolyl)acetic acid (6b)



Using **2b** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.1 mg, 1.07 mmol) and 4-tolylboronic acid **4b** (144.8 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 1 h and washing with 60 % ACN to give the desired product (240.9 mg, 73 %). ^{1}H

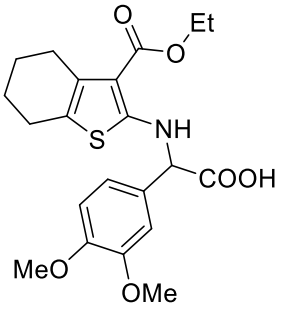
NMR (700 MHz, DMSO-d_6) δ 13.43 (s, 1H), 8.67 (d, J = 6.2 Hz, 1H), 7.27 (d, J = 7.7 Hz, 2H), 7.18 (d, J = 7.7 Hz, 2H), 4.94 (d, J = 6.2 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.66–2.55 (m, 2H), 2.43–2.33 (m, 2H), 2.28 (s, 3H), 1.70–1.55 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 171.8, 165.7, 161.3, 138.2, 134.4, 132.4, 129.8 (2), 127.6 (2), 117.6, 103.7, 62.6, 59.5, 26.8, 24.3, 23.2, 22.8, 21.2, 14.8. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{20}H_{24}NO_4S$, 374,1421; found, 374.1422.

2-((3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-(4-methoxyphenyl) acetic acid (6c)



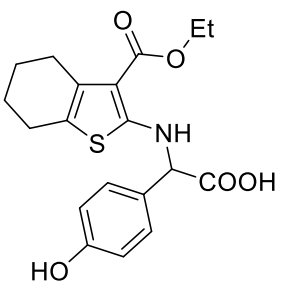
Using **2b** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.1 mg, 1.07 mmol) and 4-methoxyphenylboronic acid **4c** (161.9 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 1 h and washing with 60 % ACN to give the desired product (264.6 mg, 77 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.40 (s, 1H), 8.65 (d, J = 6.1 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 6.93 (d, J = 8.4 Hz, 2H), 4.93 (d, J = 6.1 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 2.67–2.54 (m, 2H), 2.44–2.33 (m, 2H), 1.71–1.55 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 171.1, 164.9, 160.4, 158.9, 131.6, 128.3, 128.1 (2), 116.8, 113.8 (2), 102.8, 61.4, 58.7, 54.8, 26.0, 23.5, 22.3, 21.9, 13.9. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{20}H_{24}NO_5S$, 390.1370; found, 390.1371.

2-(3,4-Dimethoxyphenyl)-2-((3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino) acetic acid (6d)



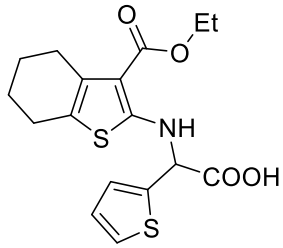
Using **2b** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.1 mg, 1.07 mmol) and 3,4-dimethoxyphenylboronic acid **4d** (193.8 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 3 h and washing with 60 % ACN to give the desired product (306.2 mg, 82 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.37 (s, 1H), 8.63 (d, J = 6.1 Hz, 1H), 6.98–6.88 (m, 3H), 4.91 (d, J = 6.1 Hz, 1H), 4.20 (q, J = 7.1 Hz, 2H), 3.73 (s, 3H), 3.72 (s, 3H), 2.65–2.57 (m, 2H), 2.42–2.35 (m, 2H), 1.68–1.58 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 171.0, 164.9, 160.6, 148.5, 148.4, 131.5, 128.7, 119.1, 116.9, 111.5, 110.6, 103.0, 61.7, 58.7, 55.2, 55.1, 26.0, 23.5, 22.3, 21.9, 13.9. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{21}H_{26}NO_6S$, 420.1475; found, 420.1474.

2-((3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-(4-hydroxyphenyl) acetic acid (6e)



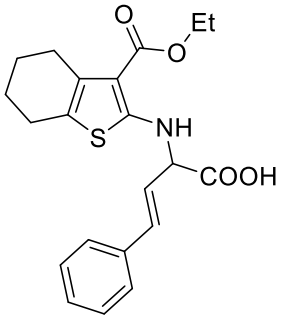
Using **2b** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.1 mg, 1.07 mmol) and 4-hydroxyphenylboronic acid **4e** (146.9 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 1.5 h and washing with 60 % ACN to give the desired product (282.5 mg, 85 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.32 (s, 1H), 9.54 (s, 1H), 8.63 (d, *J* = 6.1 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.76 (d, *J* = 8.3 Hz, 2H), 4.86 (d, *J* = 6.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.68–2.57 (m, 2H), 2.45–2.35 (m, 2H), 1.71–1.59 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 171.2, 164.9, 160.6, 157.1, 131.5, 128.1 (2), 126.5, 116.7, 115.2 (2), 102.7, 61.5, 58.7, 26.0, 23.5, 22.3, 21.9, 13.9. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{19}H_{22}NO_5S$, 376.1213; found, 376.1214.

2-((3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-(thiophen-2-yl)acetic acid (6k)



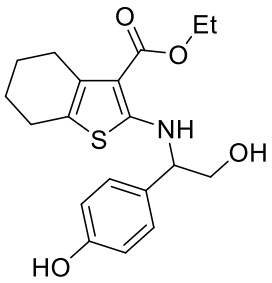
Using **2b** (100.0 mg, 0.44 mmol), glyoxylic acid monohydrate **3a** (49.0 mg, 0.53 mmol) and 2-thiopheneboronic acid **4k** (68.2 mg, 0.53 mmol) and 3Å molecular sieves (0.2 g) in HFIP (2.5 mL) with the reaction time of 1 h. Upon evaporation of solvent, the crude was purified by preparative chromatography to give the desired product (104.7 mg, 65 %). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.71 (s, 1H), 8.61 (d, *J* = 6.0 Hz, 1H), 7.50 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.19 (d, *J* = 3.5 Hz, 1H), 7.01 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.32 (d, *J* = 6.0 Hz, 1H), 4.19 (q, *J* = 7.1 Hz, 2H), 2.65 – 2.58 (m, 2H), 2.45 – 2.39 (m, 2H), 1.70 – 1.60 (m, 4H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 170.0, 164.8, 160.2, 139.7, 131.6, 127.0, 126.7, 126.1, 117.3, 103.5, 58.8, 58.1, 26.0, 23.5, 22.3, 21.9, 13.9. LCMS-ESI (m/z): calculated for $[M+H]^+$ $C_{17}H_{20}NO_4S_2$, 366.1; found, 366.0.

(*E*)-2-((3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-4-phenylbut-3-enoic acid (6l)



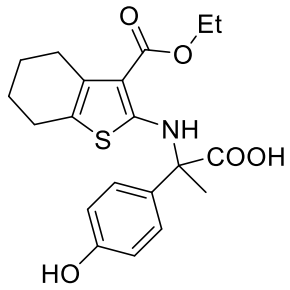
Using **2b** (200.0 mg, 0.89 mmol), glyoxylic acid monohydrate **3a** (98.1 mg, 1.07 mmol) and *trans*-2-phenylvinylboronic acid **4l** (157.6 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 40 min and washing with 60 % ACN to give the desired product (110.6 mg, 32 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 13.53 (s, 1H), 8.40 (d, J = 6.3 Hz, 1H), 7.48 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.27 (t, J = 7.6 Hz, 1H), 6.73 (d, J = 15.8 Hz, 1H), 6.32 (dd, J = 15.8 and 7.0 Hz, 1H), 4.64–4.63 (m, 1H), 4.20 (q, J = 7.1 Hz, 2H), 2.68–2.60 (m, 2H), 2.47–2.41 (m, 2H), 1.71–1.59 (m, 4H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 170.6, 164.9, 160.9, 135.2, 133.1, 131.7, 128.3 (2), 127.8, 126.3 (2), 123.8, 116.7, 102.9, 60.7, 58.7, 26.1, 23.6, 22.4, 22.0, 13.9. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{21}H_{24}NO_4S$, 386.1421; found, 386.1423.

Ethyl 2-((2-hydroxy-1-(4-hydroxyphenyl)ethyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (6m)



Using **2b** (100.0 mg, 0.44 mmol), glycoaldehyde dimer **3b** (64.0 mg, 0.53 mmol) and 4-hydroxyphenylboronic acid **4e** (73.5 mg, 0.53 mmol) and 3Å molecular sieves (0.2 g) in HFIP (2.5 mL) with the reaction time of 5 h. The residuce after solvent evaporation was purified by preparative chromatography to give the desired product (104.2 mg, 65 %). ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.34 (s, 1H), 8.34 (d, J = 5.6 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 6.70 (d, J = 8.5 Hz, 2H), 5.20 (t, J = 5.2 Hz, 1H), 4.19–4.16 (m, 3H), 3.68–3.45 (m, 2H), 2.64–2.55 (m, 2H), 2.39–2.31 (m, 2H), 1.66–1.56 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 164.9, 162.9, 156.4, 131.2, 129.0, 127.7 (2), 116.1, 114.8 (2), 102.0, 65.2, 62.0, 58.4, 26.0, 23.5, 22.3, 21.9, 13.9. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{19}H_{24}NO_4S$, 362.1421; found, 362.1422.

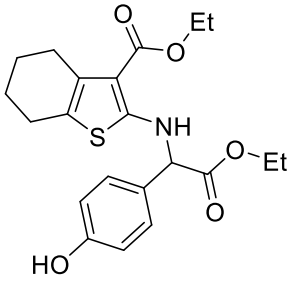
2-((3-(Ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-yl)amino)-2-(4-hydroxyphenyl) propanoic acid (6n)



Using **2b** (100.0 mg, 0.44 mmol), pyruvic acid **3c** (37.5 µl, 0.53 mmol) and 4-hydroxyphenylboronic acid **4e** (73.5 mg, 0.53 mmol) and 3Å molecular sieves (0.2 g) in HFIP (2.5 mL) with the reaction time of 2 h. The residue after solvent evaporation was purified by preparative chromatography to give the desired product (80.4 mg, 47 %). ^{1}H NMR (600 MHz, DMSO-d_6) δ 13.35 (s, 1H), 9.53 (s, 1H), 9.33 (s, 1H), 7.20 (d, J = 8.7 Hz, 2H), 6.73 (d, J = 8.7 Hz, 2H), 4.19 (q, J = 7.1 Hz, 2H), 2.63–2.54 (m, 2H), 2.35–2.23 (m, 2H), 1.88 (s, 3H), 1.65–1.55 (m, 4H), 1.27 (t, J = 7.1 Hz, 3H). ^{13}C NMR (151 MHz, DMSO-d_6) δ 174.2, 164.9, 158.5, 156.7, 130.5, 128.7, 127.9 (2), 117.2, 115.0 (2), 103.6, 62.7, 58.6,

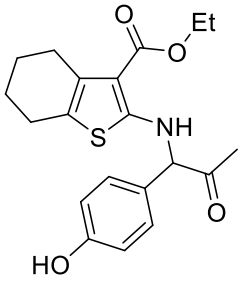
26.0, 23.3, 22.3, 22.0, 20.5, 13.9. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{20}H_{24}NO_5S$, 390.1370; found, 390.1370.

Ethyl 2-((2-ethoxy-1-(4-hydroxyphenyl)-2-oxoethyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (6o)



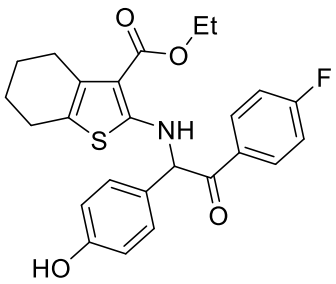
Using **2b** (200.0 mg, 0.89 mmol), ethyl glyoxalate solution **3d** (50% in toluene, 0.21 mL, 1.07 mmol) and 4-hydroxyphenylboronic acid **4e** (146.9 mg, 1.07 mmol) and 3Å molecular sieves (0.4 g) in HFIP (5 mL) with the reaction time of 12 h. The residue after solvent evaporation was purified by preparative chromatography to give the desired product (78.5 mg, 22 %). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.60 (s, 1H), 8.55 (d, J = 6.5 Hz, 1H), 7.18 (d, J = 8.6 Hz, 2H), 6.75 (d, J = 8.5 Hz, 2H), 4.96 (d, J = 6.5 Hz, 1H), 4.30–3.94 (m, 4H), 2.70–2.55 (m, 2H), 2.45–2.31 (m, 2H), 1.74–1.51 (m, 4H), 1.26 (t, J = 7.1 Hz, 3H), 1.11 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.8, 164.8, 160.3, 157.2, 131.5, 128.0 (2), 125.8, 116.9, 115.2 (2), 102.9, 61.4, 61.1, 58.7, 25.9, 23.4, 22.2, 21.8, 13.8, 13.4. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{21}H_{26}NO_5S$, 404.1526; found, 404.1525.

Ethyl 2-((1-(4-hydroxyphenyl)-2-oxopropyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (6p)



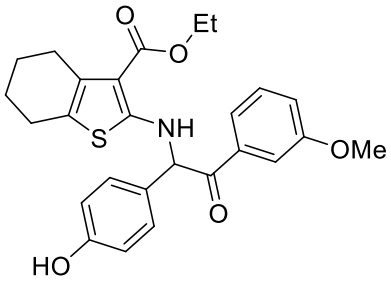
Using **2b** (100.0 mg, 0.44 mmol), pyruvic aldehyde **3e** (91.4 µl, 0.53 mmol) and 4-hydroxyphenylboronic acid **4e** (73.5 mg, 0.53 mmol) and 3Å molecular sieves (0.2 g) in HFIP (2.5 mL) with the reaction time of 14 h. The residue after solvent evaporation was purified by preparative chromatography to give the desired product (14.0 mg, 8 %). ^{1}H NMR (500 MHz, Methanol-d_4) δ 8.77 (d, J = 8.6 Hz, 2H), 8.35 (d, J = 8.6 Hz, 2H), 6.60 (s, 1H), 5.81 (q, J = 7.1 Hz, 2H), 4.28–4.15 (m, 2H), 4.03–3.93 (m, 2H), 3.63 (s, 3H), 3.26 (m, 4H), 2.93 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, Methanol-d_4) δ 203.7, 167.1, 162.6, 158.7, 133.1, 130.1 (2), 127.5, 118.3, 116.4 (2), 104.0, 70.0, 60.0, 27.4, 25.9, 24.8, 23.8, 23.5, 14.3. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{20}H_{24}NO_4S$, 374.1421; found, 374.1421.

Ethyl 2-((2-(4-fluorophenyl)-1-(4-hydroxyphenyl)-2-oxoethyl)amino)-4,5,6,7-tetrahydrobenzo[*b*] thiophene-3-carboxylate (6q)



Using **2b** (100.0 mg, 0.44 mmol), (4-fluorophenyl)(oxo)acetaldehyde monohydrate **3f** (92.1 mg, 0.53 mmol) and 4-hydroxyphenylboronic acid **4e** (73.5 mg, 0.53 mmol) and 3Å molecular sieves (0.2 g) in HFIP (2.5 mL) with the reaction time of 2 h. The residue after solvent evaporation was purified by preparative chromatography to give the desired product (59.3 mg, 29 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.92 (d, *J* = 6.5 Hz, 1H), 8.18–8.16 (m, 2H), 7.32–7.30 (m, 2H), 7.24 (d, *J* = 8.0 Hz, 2H), 6.68 (d, *J* = 8.0 Hz, 2H), 6.13 (d, *J* = 6.5 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 2.66 – 2.55 (m, 2H), 2.45 – 2.36 (m, 2H), 1.71 – 1.56 (m, 4H), 1.29 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 193.5, 165.6 and 164.1 (d, $^{1}J_{C\text{-}F}$ = 252 Hz), 164.8, 160.6, 157.2, 131.7 and 131.7 (d, $^{3}J_{C\text{-}F}$ = 10 Hz) (2), 131.6, 130.3 and 130.3 (d, $^{4}J_{C\text{-}F}$ = 2 Hz), 129.3 (2), 125.8, 116.6, 115.6 and 115.5 (d, $^{2}J_{C\text{-}F}$ = 22 Hz) (2), 115.4 (2), 102.8, 63.5, 58.7, 26.0, 23.6, 22.4, 21.9, 14.0. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{25}H_{25}FNO_4S$, 454.1483; found, 454.1480.

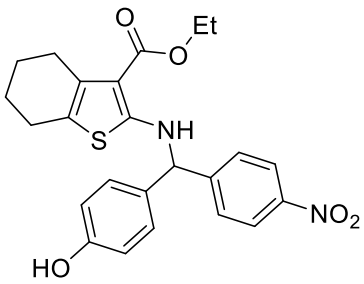
Ethyl 2-((1-(4-hydroxyphenyl)-2-(3-methoxyphenyl)-2-oxoethyl)amino)-4,5,6,7-tetrahydrobenzo-[*b*]thiophene-3-carboxylate (6r)



Using **2b** (100.0 mg, 0.44 mmol), 2-(3-methoxyphenyl)-2-oxoacetaldehyde monohydrate **3g** (97.0 mg, 0.53 mmol) and 4-hydroxyphenylboronic acid **4e** (73.5 mg, 0.53 mmol) and 3Å molecular sieves (0.2 g) in HFIP (2.5 mL) with the reaction time of 3 h. The residue after solvent evaporation was purified by preparative chromatography to give the desired product (36.4 mg, 18 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 9.56 (s, 1H), 8.92 (d, *J* = 6.5 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.53 (s, 1H), 7.41 (t, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 1H), 6.69 (d, *J* = 8.3 Hz, 2H), 6.14 (d, *J* = 6.5

Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.80 (s, 3H), 2.69–2.57 (m, 2H), 2.47–2.38 (m, 2H), 1.72–1.56 (m, 4H), 1.31 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 194.7, 164.8, 160.6, 159.0, 157.1, 135.0, 131.6, 129.6, 129.3 (2), 125.8, 121.0, 119.4, 116.6, 115.4 (2), 113.1, 102.8, 63.6, 58.7, 55.0, 26.0, 23.6, 22.4, 21.9, 14.0. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{26}H_{28}NO_5S$, 466.1683; found, 466.1679.

Ethyl 2-(((4-hydroxyphenyl)(4-nitrophenyl)methyl)amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophene -3-carboxylate (6t)

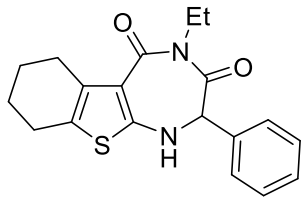


Using **2b** (100.0 mg, 0.44 mmol), 4-nitrobenzaldehyde **3i** (80.5 mg, 0.53 mmol) and 4-hydroxyphenylboronic acid **4e** (73.5 mg, 0.53 mmol) and 3Å molecular sieves (0.2 g) in HFIP (2.5 mL) with the reaction time of 2 h under reflux. The residue after solvent evaporation was purified by preparative chromatography to give the desired product (26.8 mg, 13 %). ^{1}H NMR (700 MHz, DMSO-d_6) δ 9.55 (s, 1H), 8.37 (d, *J* = 6.0 Hz, 1H), 8.22 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.3 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.75 (d, *J* = 8.1 Hz, 2H), 5.65 (d, *J* = 6.0 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.67–2.60 (m, 2H), 2.42–2.34 (m, 2H), 1.72–1.57 (m, 4H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (176 MHz, DMSO-d_6) δ 165.3, 161.5, 156.9, 149.2, 146.4, 131.5, 130.5, 127.9 (2), 127.6 (2), 123.7 (2), 117.2, 115.4 (2), 103.0, 62.9, 58.9, 26.0, 23.5, 22.3, 21.9, 13.9. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{24}H_{25}N_2O_5S$, 453.1479; found, 453.1476.

General Procedure for the Synthesis of Thieno[1,4]diazepine-3,5(4*H*)-diones 7

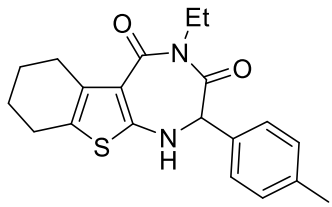
The 2-aminothiophene **5** (100.0 mg) was dissolved in THF (150 mL) to give a clear reaction mixture. To the reaction mixture, EDC·HCl (1.2 equiv.) was added and stirred at room temperature overnight. The solvent was evaporated under vacuo and the resuling solid was redissolved in ethyl acetate. The excessive EDC and urea were removed by washing with H_2O. The organic phase was collected and dried with $MgSO_4$. The crude after solvent evaporation was purified by flash chromatography.

4-Ethyl-2-(4-hydroxyphenyl)-1,2,6,7,8,9-hexahydro-3*H*-benzo[4,5]thieno[2,3-*e*][1,4]diazepine-3,5(4*H*)-dione (7a)



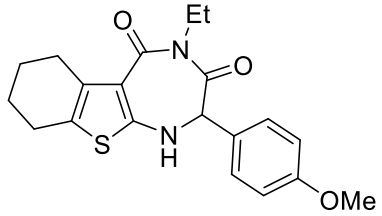
Using **5a** (100.0 mg, 0.28 mmol) and EDC·HCl (64.2 mg, 0.34 mmol) in THF (150 mL) to give the desired product (78.0 mg, 75 %). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.44–7.36 (m, 3H), 7.34–7.30 (m, 2H), 5.20 (d, *J* = 3.3 Hz, 1H), 4.84 (d, *J* = 3.3 Hz, 1H), 4.01–3.96 (m, 1H), 3.92–3.87 (m, 1H), 2.90–2.78 (m, 2H), 2.61–2.47 (m, 2H), 1.86–1.65 (m, 4H), 1.24 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 167.9, 163.9, 157.5, 136.0, 134.8, 128.9, 128.9 (2), 128.0 (2), 121.7, 114.4, 66.4, 40.9, 27.8, 24.8, 22.8, 22.6, 13.7. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{19}H_{21}N_2O_2S$, 341.1318; found, 341.1319.

4-Ethyl-2-(*p*-tolyl)-1,2,6,7,8,9-hexahydro-3*H*-benzo[4,5]thieno[2,3-*e*][1,4]diazepine-3,5(4*H*)-dione (7b)



Using **5b** (50.0 mg, 0.13 mmol) and EDC·HCl (30.9 mg, 0.16 mmol) in THF (150 mL) to give the desired product (35.6 mg, 75 %). ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.21 (s, 4H), 5.18 (d, *J* = 3.2 Hz, 1H), 4.79 (d, *J* = 3.2 Hz, 1H), 4.00–3.93 (m, 1H), 3.91–3.86 (m, 1H), 2.91–2.81 (m, 2H), 2.58–2.47 (m, 2H), 2.36 (s, 3H), 1.85–1.65 (m, 4H), 1.23 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 168.0, 164.1, 157.6, 138.9, 136.0, 131.8, 129.6 (2), 128.0 (2), 121.6, 114.3, 66.2, 40.9, 27.8, 24.8, 22.9, 22.6, 21.2, 13.8. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{20}H_{23}N_2O_2S$, 355.1475; found, 355.1476.

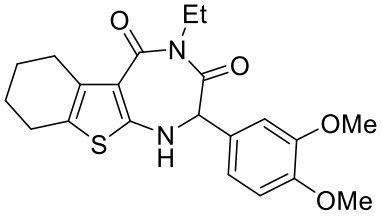
4-Ethyl-2-(4-methoxyphenyl)-1,2,6,7,8,9-hexahydro-3*H*-benzo[4,5]thieno[2,3-*e*][1,4]diazepine-3,5(4*H*)-dione (7c)



Using **5c** (100.0 mg, 0.26 mmol) and EDC·HCl (59.2 mg, 0.31 mmol) in THF (150 mL) to give the desired product (84.2 mg, 88 %). ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.25 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 5.13 (d, *J* = 2.2 Hz, 1H), 4.75 (d, *J* = 2.2 Hz, 1H), 4.00–3.93 (m, 1H), 3.90–3.85 (m, 1H), 3.81 (s, 3H), 2.91 – 2.81 (m, 2H), 2.59 – 2.46 (m, 2H), 1.85 – 1.66 (m, 4H), 1.23 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 168.0, 164.1, 160.0, 157.6, 136.0, 129.5 (2), 126.9,

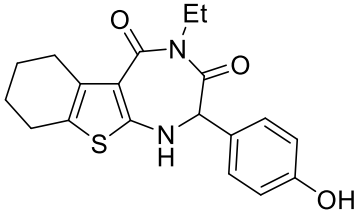
121.6, 114.3 (3), 65.9, 55.3, 40.9, 27.8, 24.8, 22.9, 22.6, 13.8. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{20}H_{23}N_2O_3S$, 371.1424; found, 371.1425.

2-(3,4-Dimethoxyphenyl)-4-ethyl-1,2,6,7,8,9-hexahydro-3*H*-benzo[4,5]thieno[2,3-*e*][1,4]diazepine-3,5(4*H*)-dione (7d)



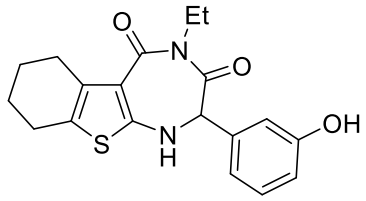
Using **5d** (100.0 mg, 0.24 mmol) and EDC·HCl (55.0 mg, 0.29 mmol) in THF (150 mL) to give the desired product (53.9 mg, 56 %). ^{1}H NMR (700 MHz, Chloroform-*d*) δ 6.87–6.85 (m, 3H), 5.21 (d, *J* = 3.2 Hz, 1H), 4.80 (d, *J* = 3.2 Hz, 1H), 4.01–3.95 (m, 1H), 3.99–3.89 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.91 – 2.80 (m, 2H), 2.59 – 2.46 (m, 2H), 1.84–1.67 (m, 4H), 1.24 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 168.1, 164.0, 157.4, 149.4, 149.2, 136.0, 127.1, 121.7, 120.7, 114.5, 111.2, 111.0, 66.1, 55.9 (2), 40.9, 27.8, 24.8, 22.9, 22.6, 13.8. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{21}H_{25}N_2O_4S$, 401.1530; found, 401.1528.

4-Ethyl-2-(4-hydroxyphenyl)-1,2,6,7,8,9-hexahydro-3*H*-benzo[4,5]thieno[2,3-*e*][1,4]diazepine-3,5(4*H*)-dione (7e)



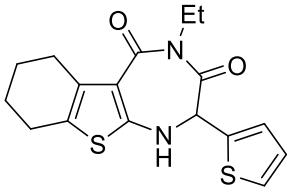
Using **5e** (100.0 mg, 0.27 mmol) and EDC·HCl (61.4 mg, 0.32 mmol) in THF (150 mL) to give the desired product (81.3 mg, 85 %). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.16 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 5.56 (s, 1H), 5.19 (s, 1H), 4.75 (s, 1H), 4.02–3.96 (m, 1H), 3.91–3.86 (m, 1H), 2.91–2.79 (m, 2H), 2.59–2.47 (m, 2H), 1.86–1.66 (m, 4H), 1.24 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.2, 164.2, 157.8, 156.3, 135.8, 129.5 (2), 126.6, 121.7, 115.9 (2), 114.2, 65.8, 41.0, 27.7, 24.8, 22.8, 22.6, 13.8. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{19}H_{21}N_2O_3S$, 357.1267; found, 357.1268.

4-Ethyl-2-(3-hydroxyphenyl)-1,2,6,7,8,9-hexahydro-3*H*-benzo[4,5]thieno[2,3-*e*][1,4]diazepine-3,5(4*H*)-dione (7f)



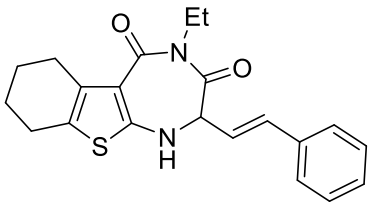
Using **5f** (30.0 mg, 0.08 mmol) and EDC·HCl (18.4 mg, 0.10 mmol) in THF (45 mL) to give the desired product (17.4 mg, 61 %). ^{1}H NMR (600 MHz, Chloroform-*d*) δ 7.23 (t, *J* = 7.7 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.82–6.77 (m, 2H), 5.35 (s, 1H), 4.80 (s, 1H), 4.00–3.95 (m, 1H), 3.92–3.87 (m, 1H), 2.88 – 2.78 (m, 2H), 2.59 – 2.46 (m, 2H), 1.84 – 1.67 (m, 4H), 1.24 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (151 MHz, Chloroform-*d*) δ 168.1, 164.0, 157.6, 156.2, 136.1, 135.9, 130.1, 121.8, 120.1, 116.2, 114.8, 114.3, 66.0, 41.0, 27.7, 24.8, 22.8, 22.6, 13.7. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{19}H_{21}N_2O_3S$, 357.1267; found, 357.1268.

4-Ethyl-2-(thiophen-2-yl)-1,2,6,7,8,9-hexahydro-3*H*-benzo[4,5]thieno[2,3-*e*][1,4]diazepine-3,5(4*H*)-dione (7g)



Using **5k** (100.0 mg, 0.27 mmol) and EDC·HCl (63.1 mg, 0.33 mmol) in THF (150 mL) to give the desired product (67.6 mg, 71 %). ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.39 (d, *J* = 5.0 Hz, 1H), 7.09 (d, *J* = 3.5 Hz, 1H), 7.01 (dd, *J* = 5.0 and 3.5 Hz, 1H), 5.19 (s, 1H), 5.18 (s, 1H), 4.03–3.98 (m, 1H), 3.93–3.88 (m, 1H), 2.92 – 2.80 (m, 2H), 2.60 – 2.47 (m, 2H), 1.84 – 1.68 (m, 4H), 1.25 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (176 MHz, Chloroform-*d*) δ 166.9, 163.8, 156.6, 136.1, 136.0, 128.2, 127.5, 126.6, 122.1, 114.7, 61.8, 41.0, 27.8, 24.8, 22.9, 22.6, 13.8. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{17}H_{19}N_2O_2S_2$, 347.0883; found, 347.0884.

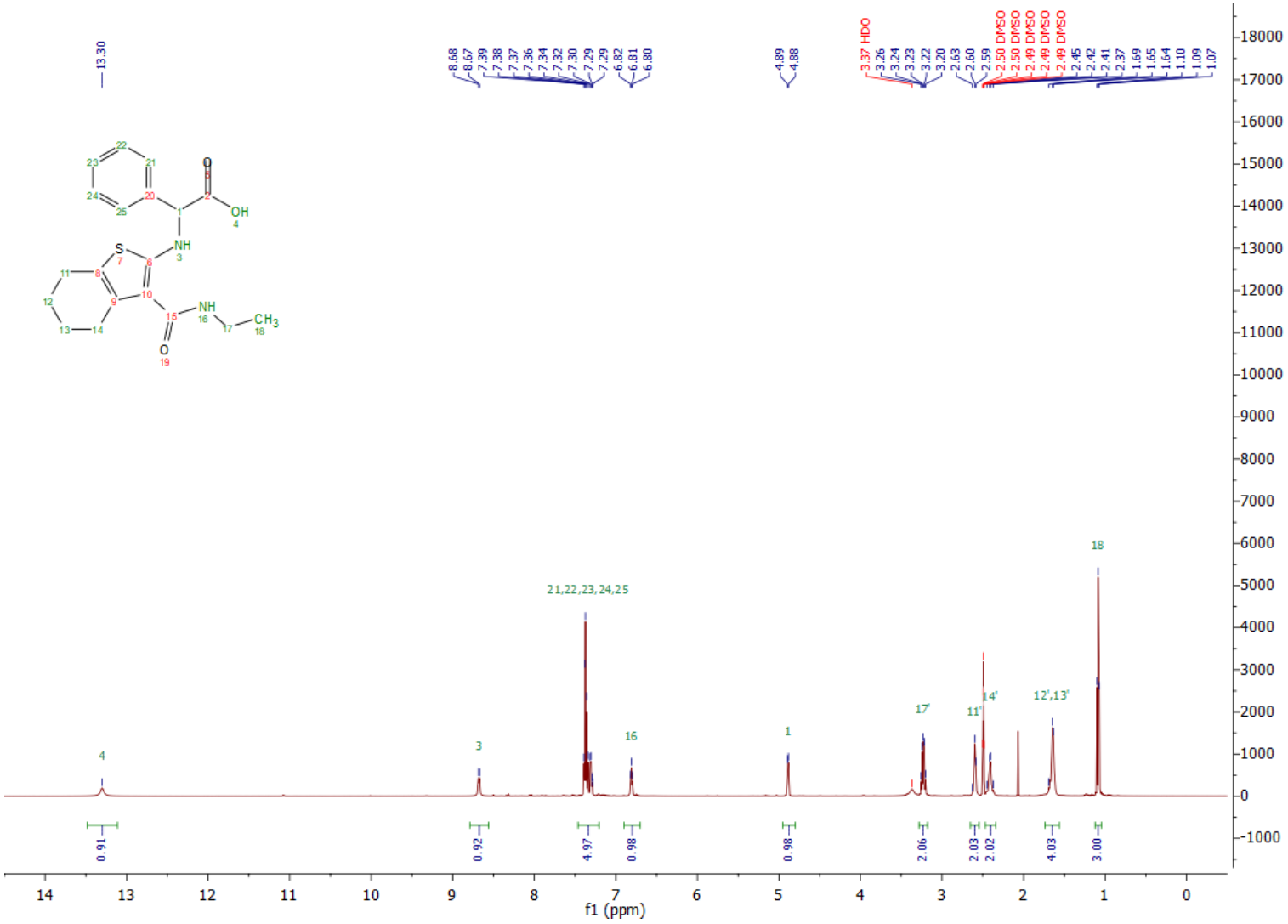
(*E*)-4-Ethyl-2-styryl-1,2,6,7,8,9-hexahydro-3*H*-benzo[4,5]thieno[2,3-*e*][1,4]diazepine-3,5(4*H*)-dione (7h)



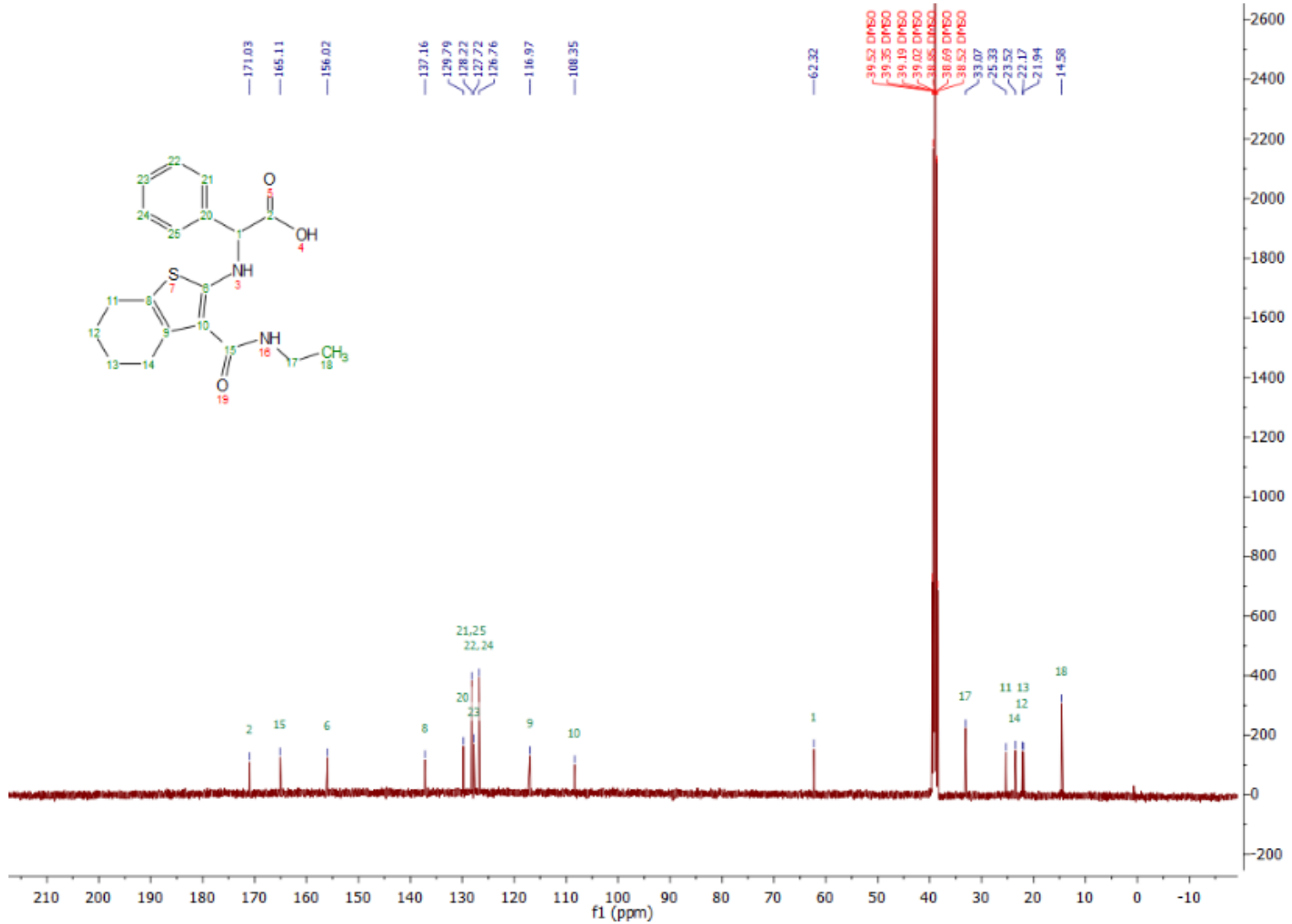
Using **5l** (100.0 mg, 0.26 mmol) and EDC·HCl (59.8 mg, 0.31 mmol) in THF (150 mL) to give the desired product (67.8 mg, 71 %). ^{1}H NMR (700 MHz, Chloroform-*d*) δ 7.41 (d, *J* = 7.4 Hz, 2H), 7.34 (t, *J* = 7.4 Hz, 2H), 7.29 (t, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 16.1 Hz, 1H), 6.60 (dd, *J* = 16.1, 7.3 Hz, 1H), 4.99 (d, *J* = 2.5 Hz, 1H), 4.42 (dd, *J* = 7.3 and 2.5 Hz, 1H), 4.02–3.97 (m, 1H), 3.89–3.84 (m, 1H), 2.92 – 2.85 (m, 2H), 2.60 – 2.48 (m, 2H), 1.87 – 1.69 (m, 4H), 1.23 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (176 MHz,

Chloroform-*d*) δ 168.0, 164.0, 157.2, 136.5, 136.1, 135.5, 128.7 (2), 128.6, 126.8 (2), 122.0, 121.7, 114.3, 63.9, 40.5, 27.9, 24.8, 22.9, 22.7, 13.8. HRMS-ESI (m/z): calculated for $[M+H]^+$ $C_{21}H_{23}N_2O_2S$, 367.1475; found, 367.1475.

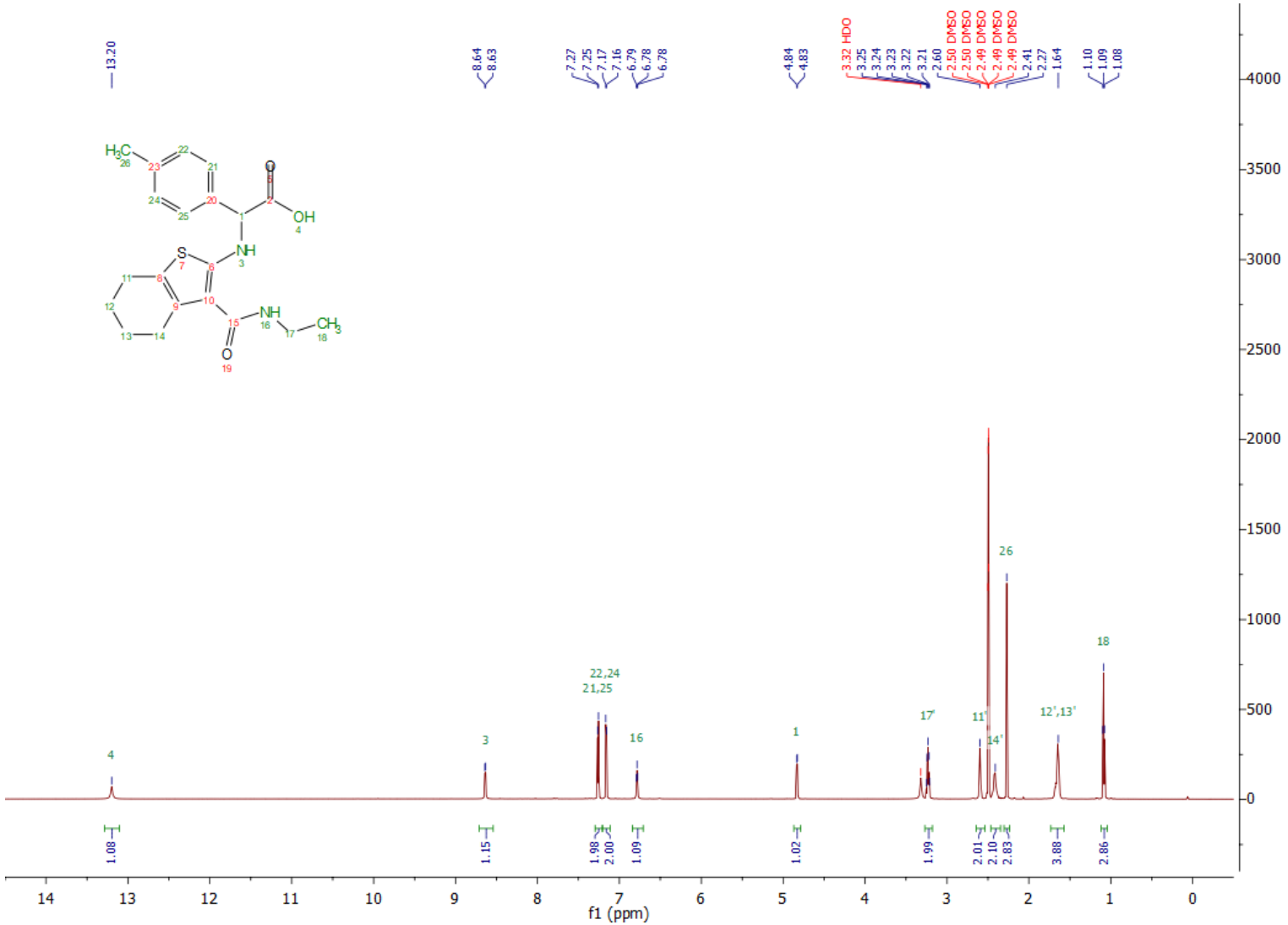
NMR SPECTRA — ^{1}H NMR of **5a** (500 MHz, DMSO-d_6)



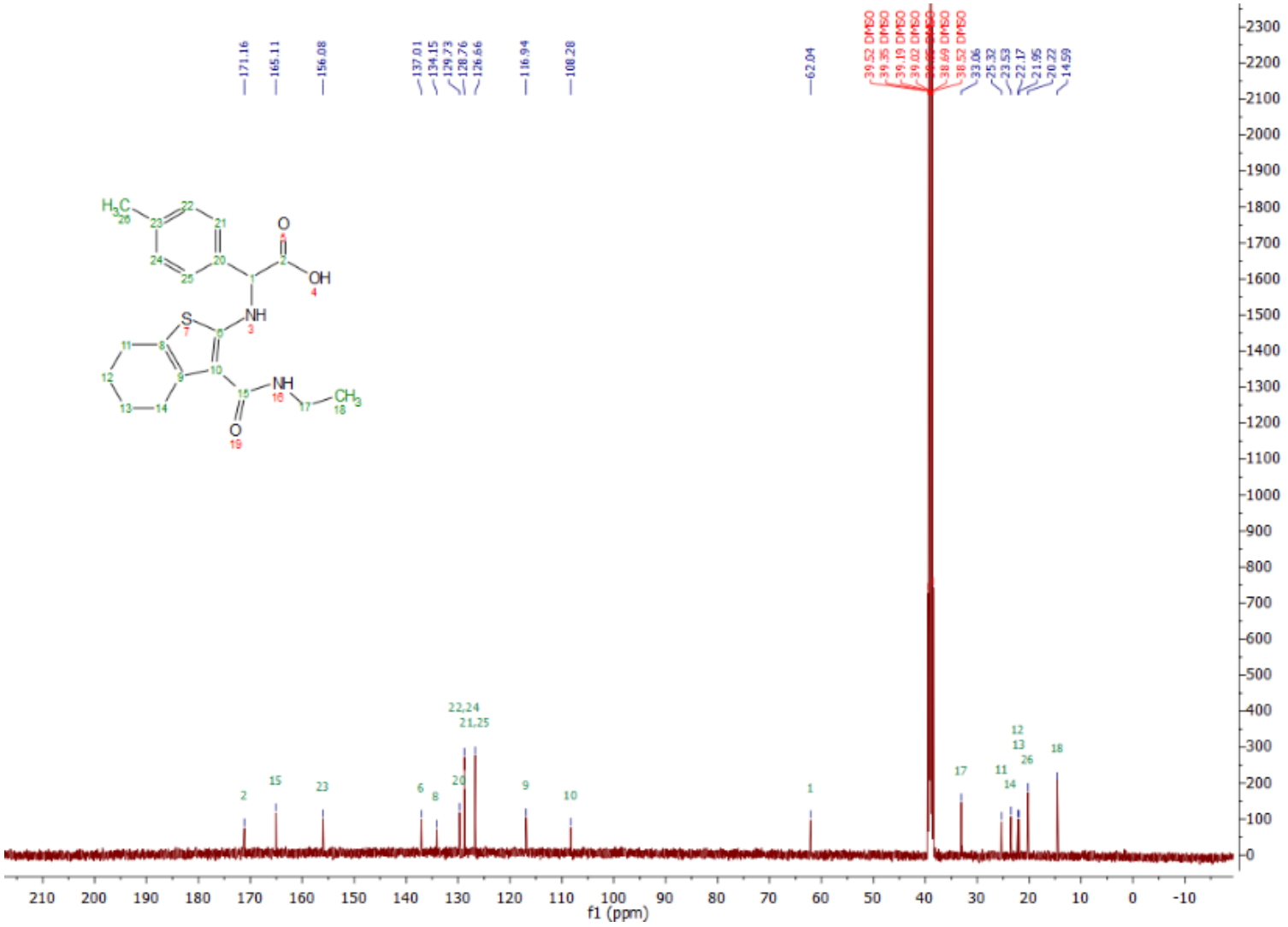
^{13}C NMR of **5a** (126 MHz, DMSO-d_6)



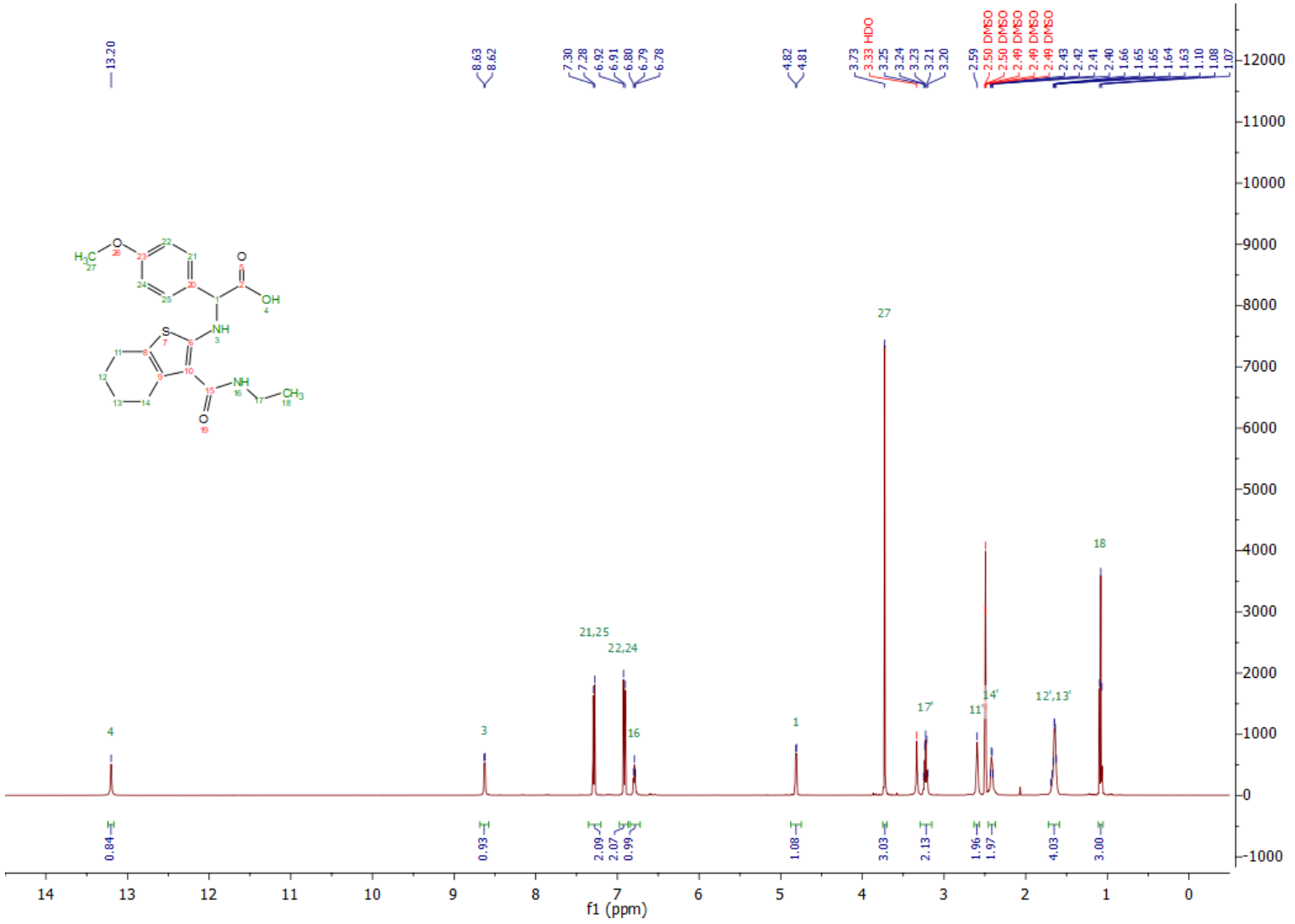
[1]H-NMR of **5b** (700 MHz, DMSO-d_6)



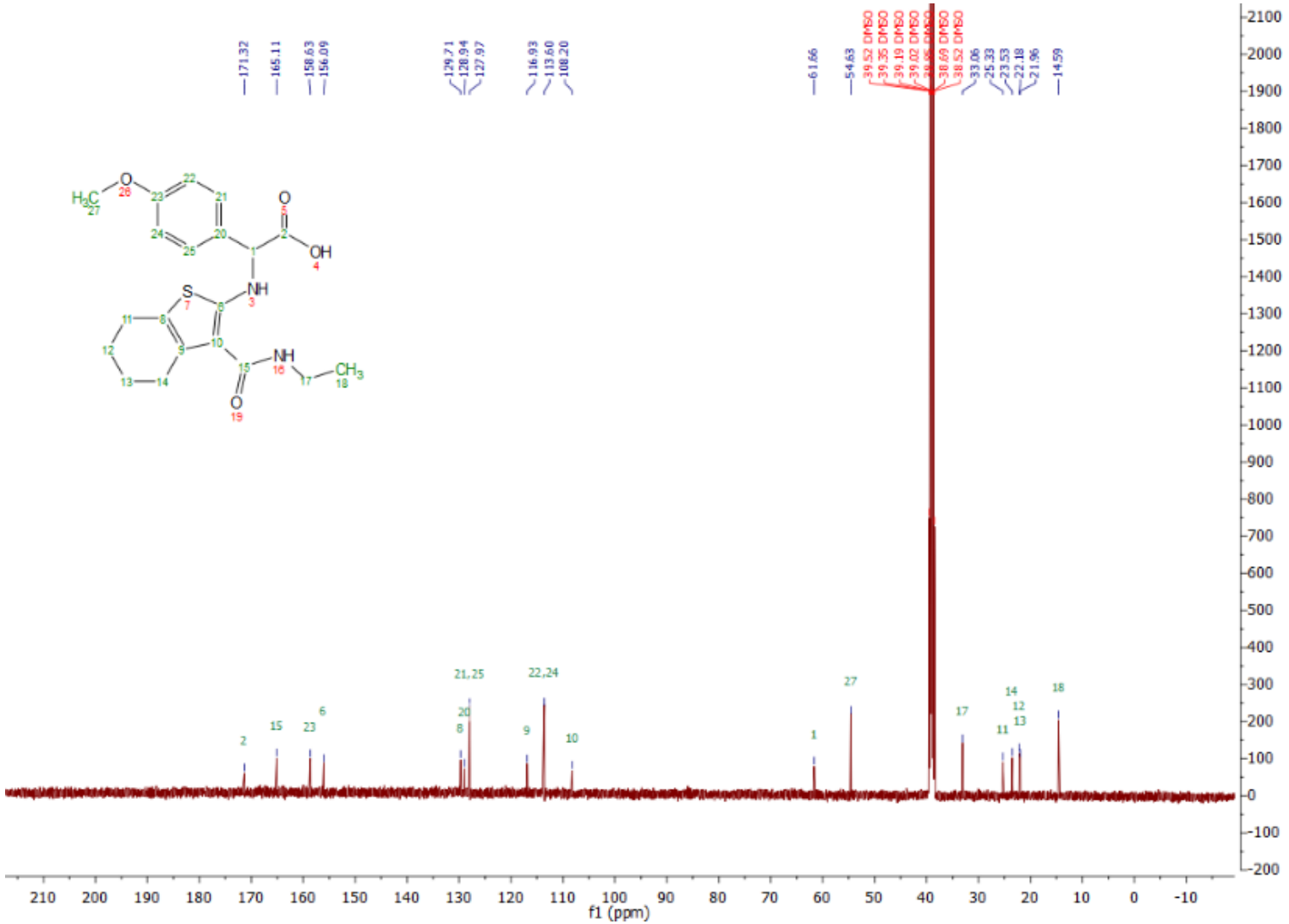
^{13}C-NMR of **5b** (126 MHz, DMSO-d_6)



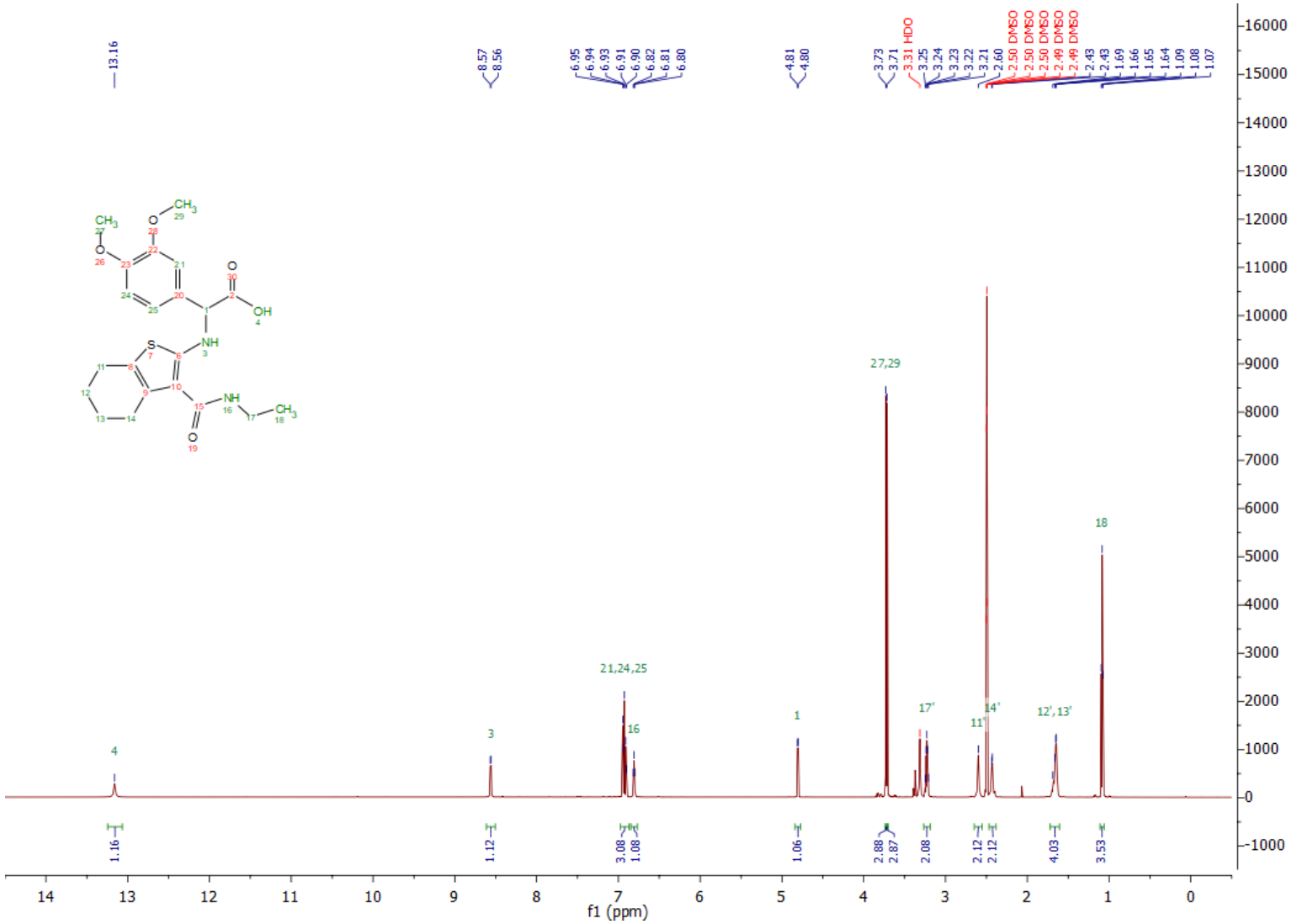
[1]H-NMR of **5c** (500 MHz, DMSO-d_6)



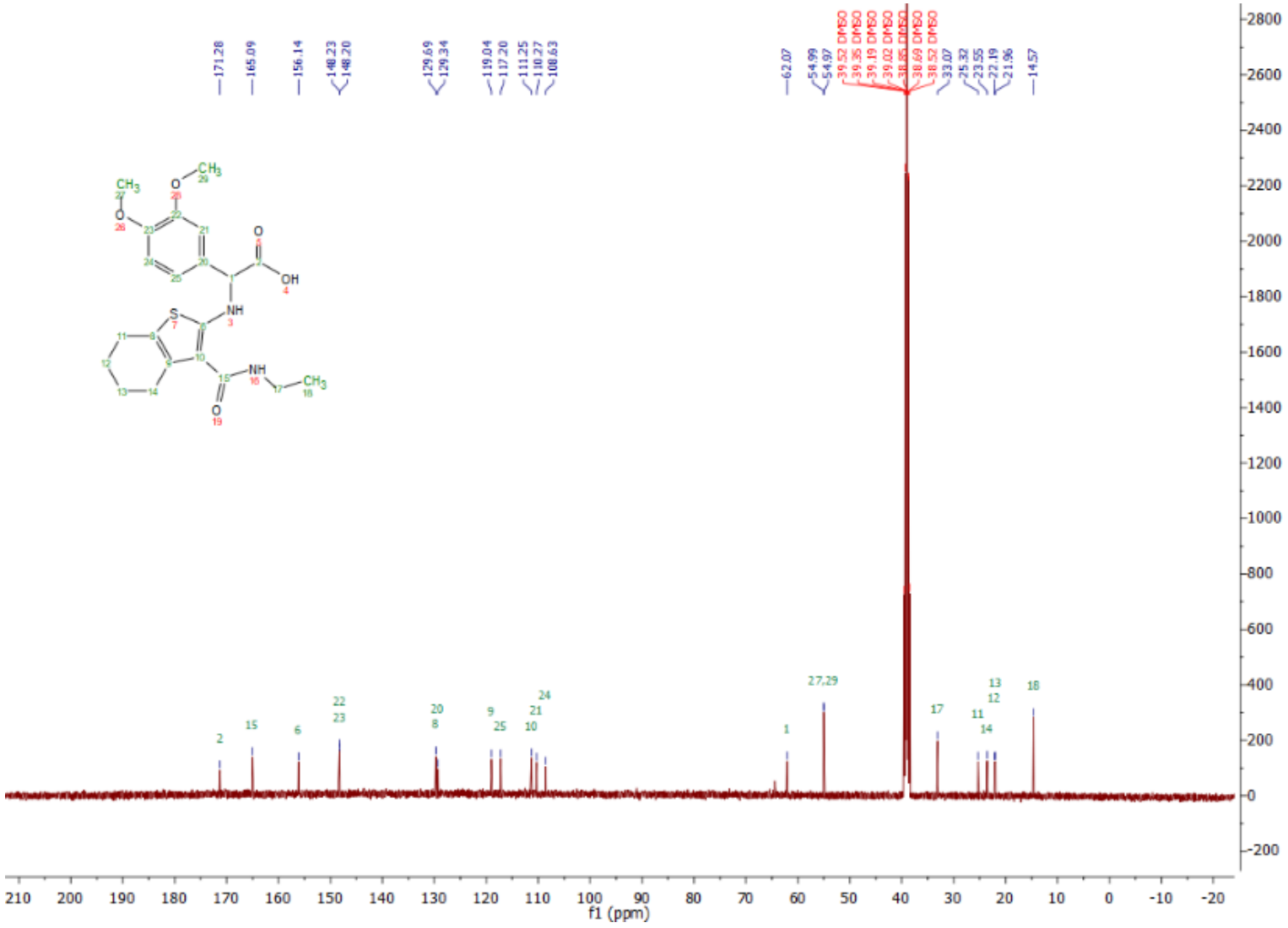
^{13}C-NMR of **5c** (126 MHz, DMSO-d_6)



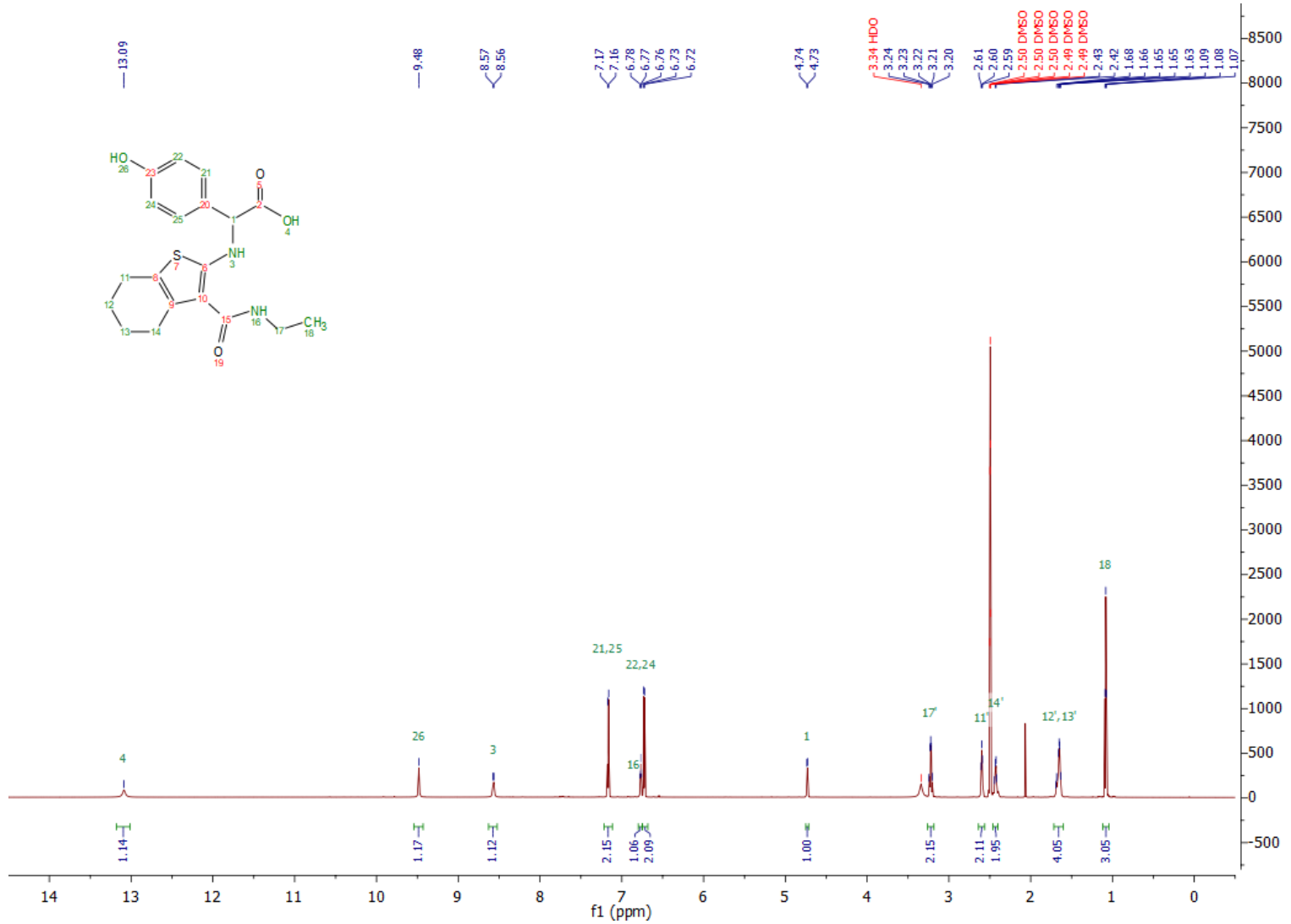
[1]H-NMR of **5d** (700 MHz, DMSO-d_6)



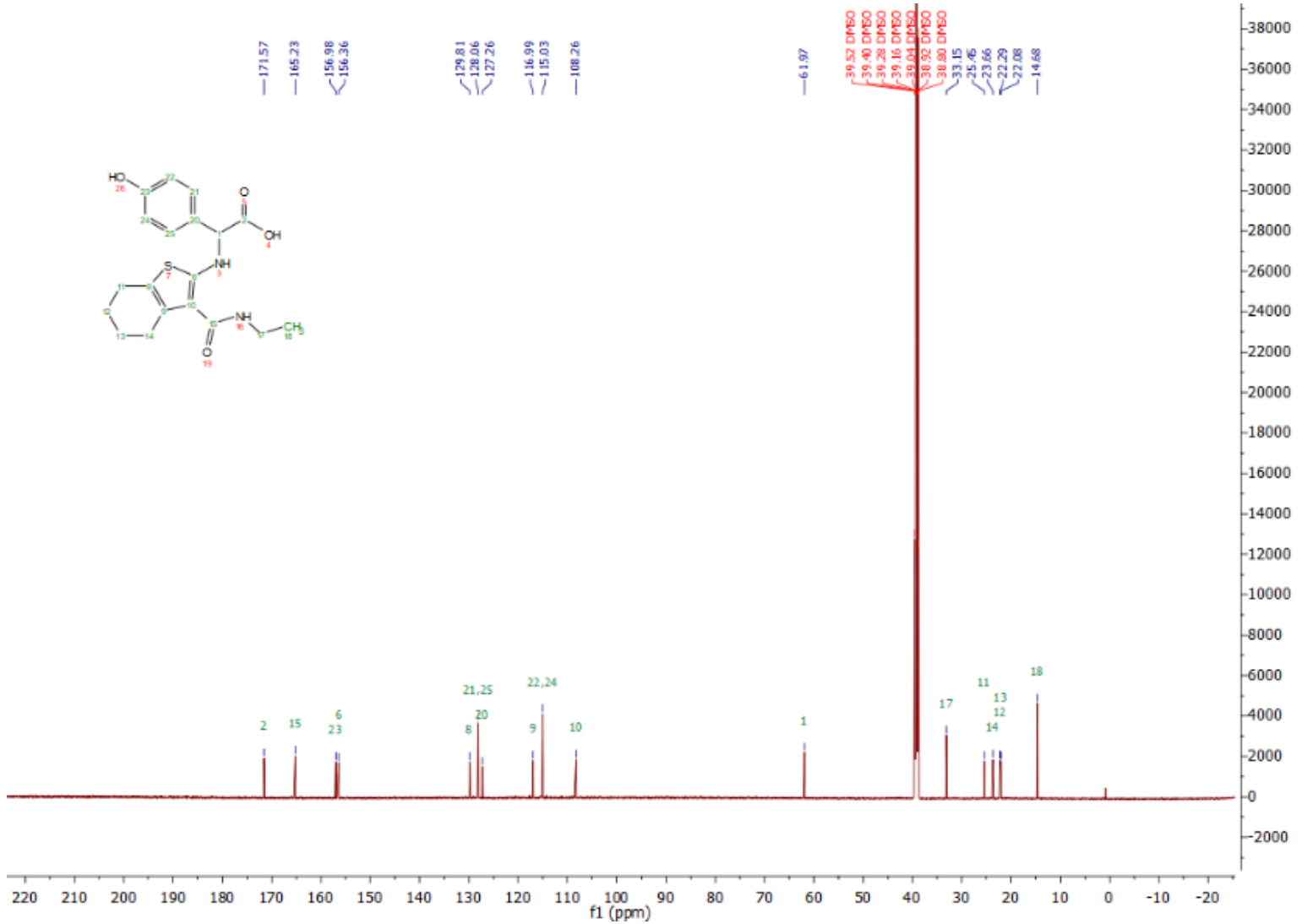
^{13}C-NMR of **5d** (126 MHz, DMSO-d_6)



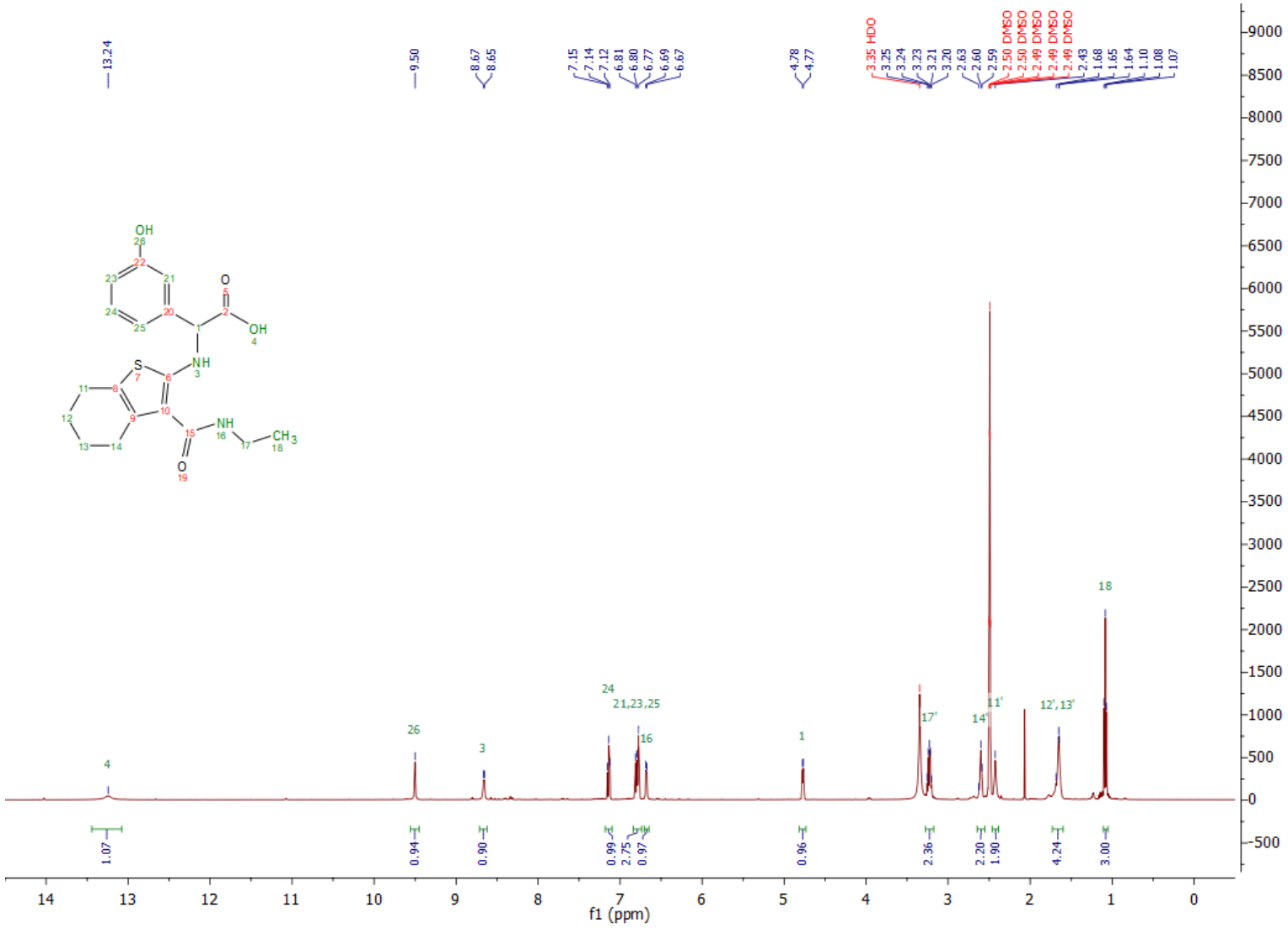
[1]H-NMR of **5e** (700 MHz, DMSO-d_6)



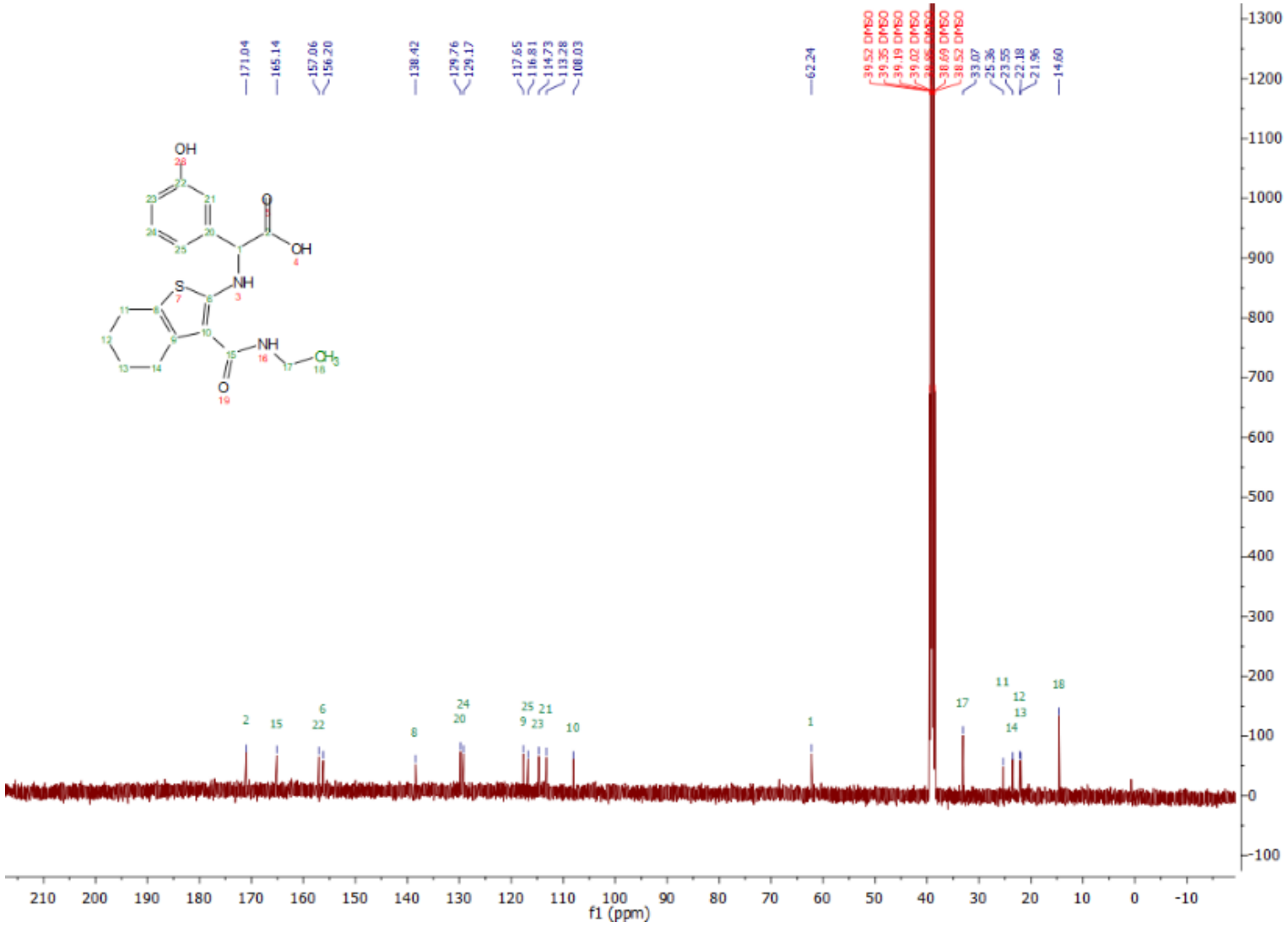
^{13}C-NMR of **5e** (176 MHz, DMSO-d_6)



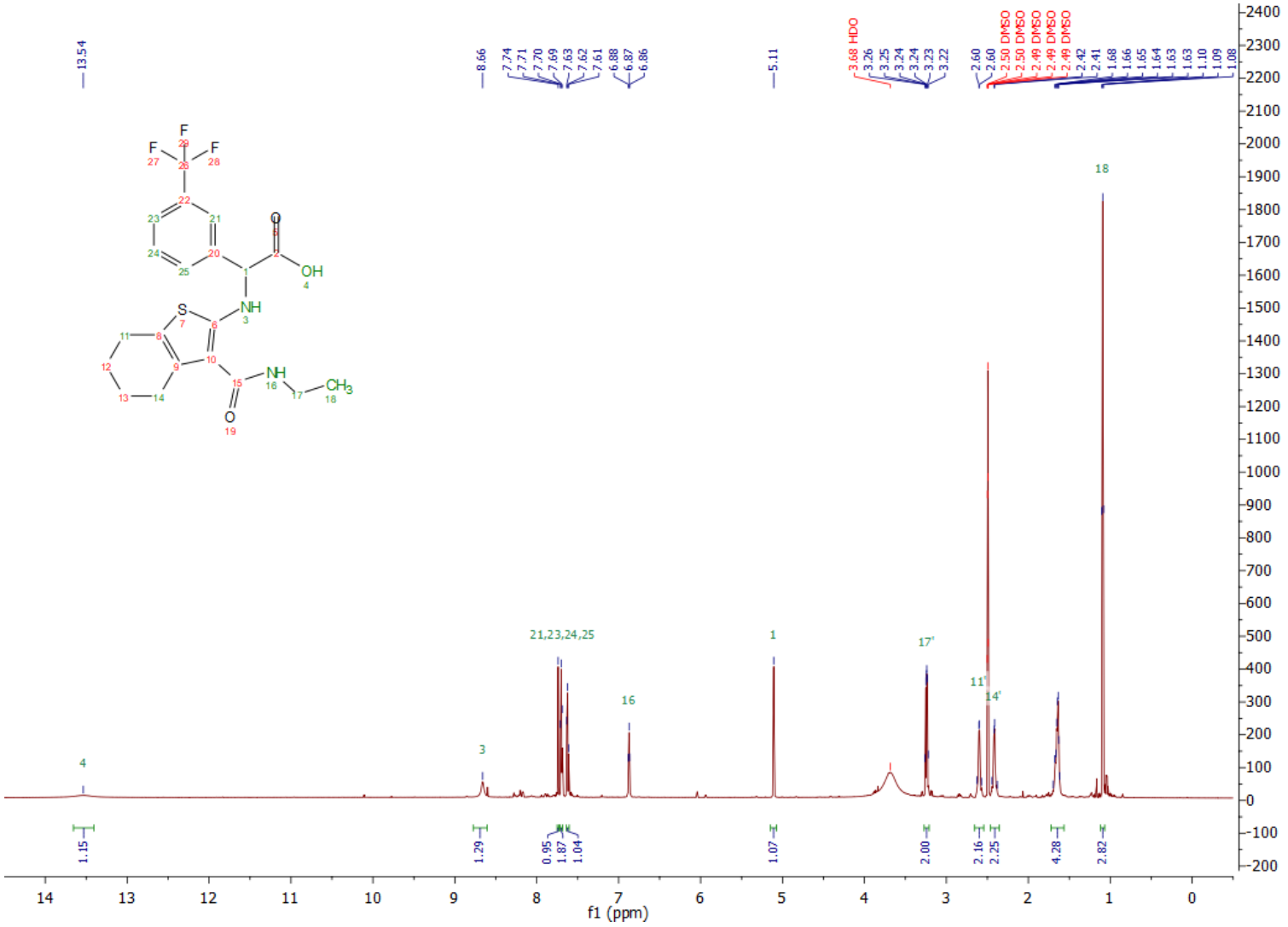
^{1}H-NMR of **5f** (500 MHz, DMSO-d_6)



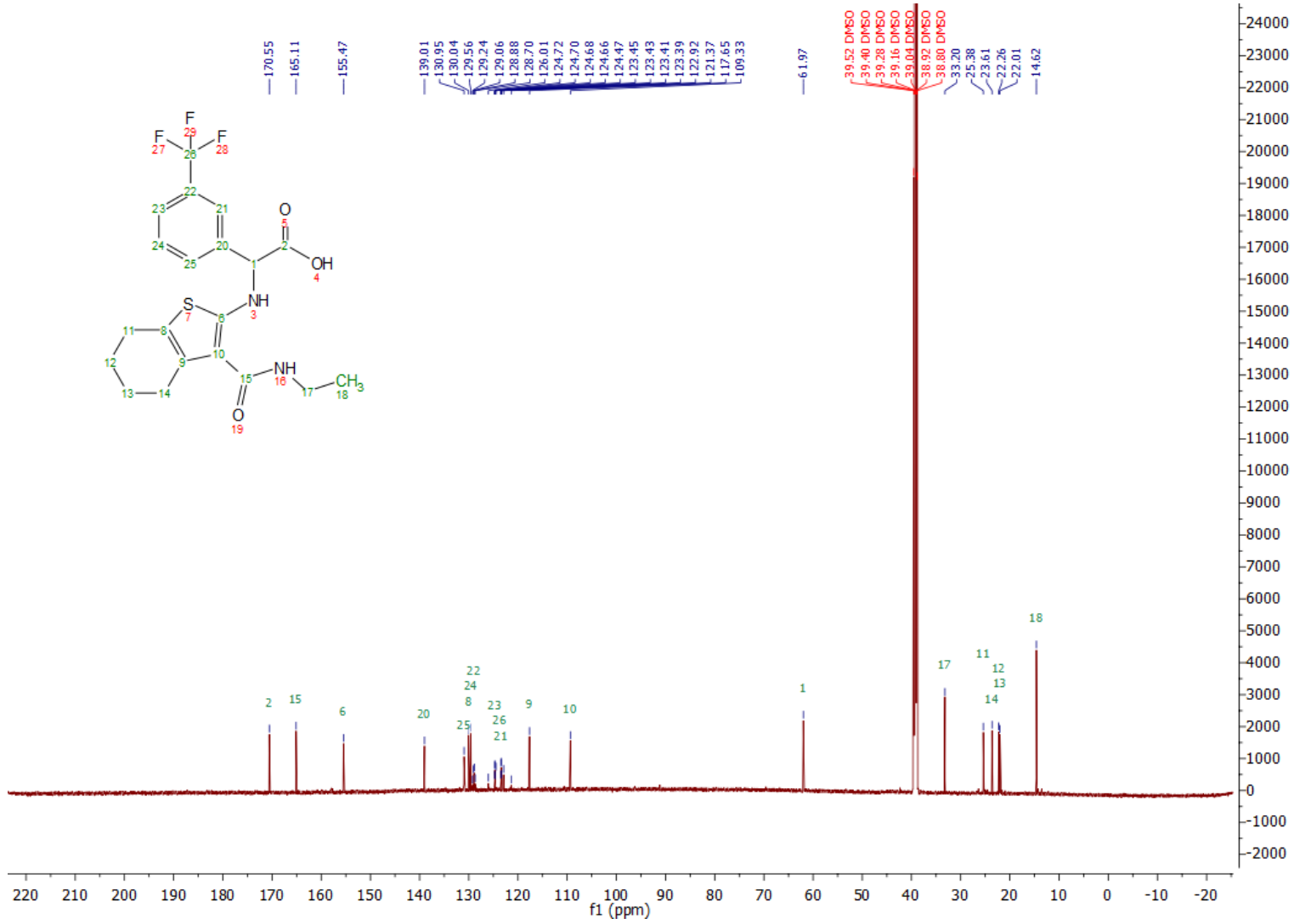
^{13}C-NMR of **5f** (126 MHz, DMSO-d_6)



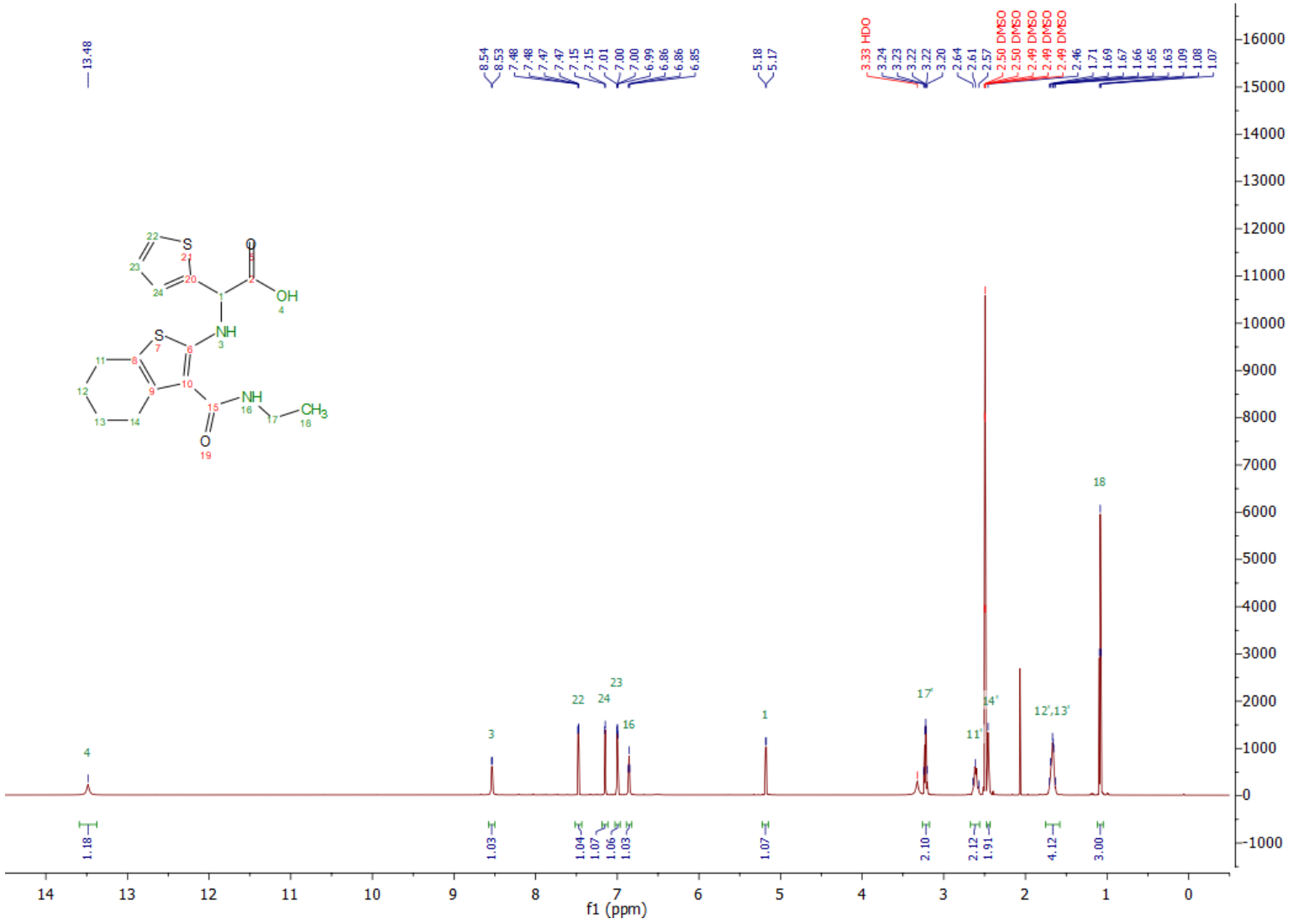
^{1}H-NMR of **5g** (700 MHz, DMSO-d_6)



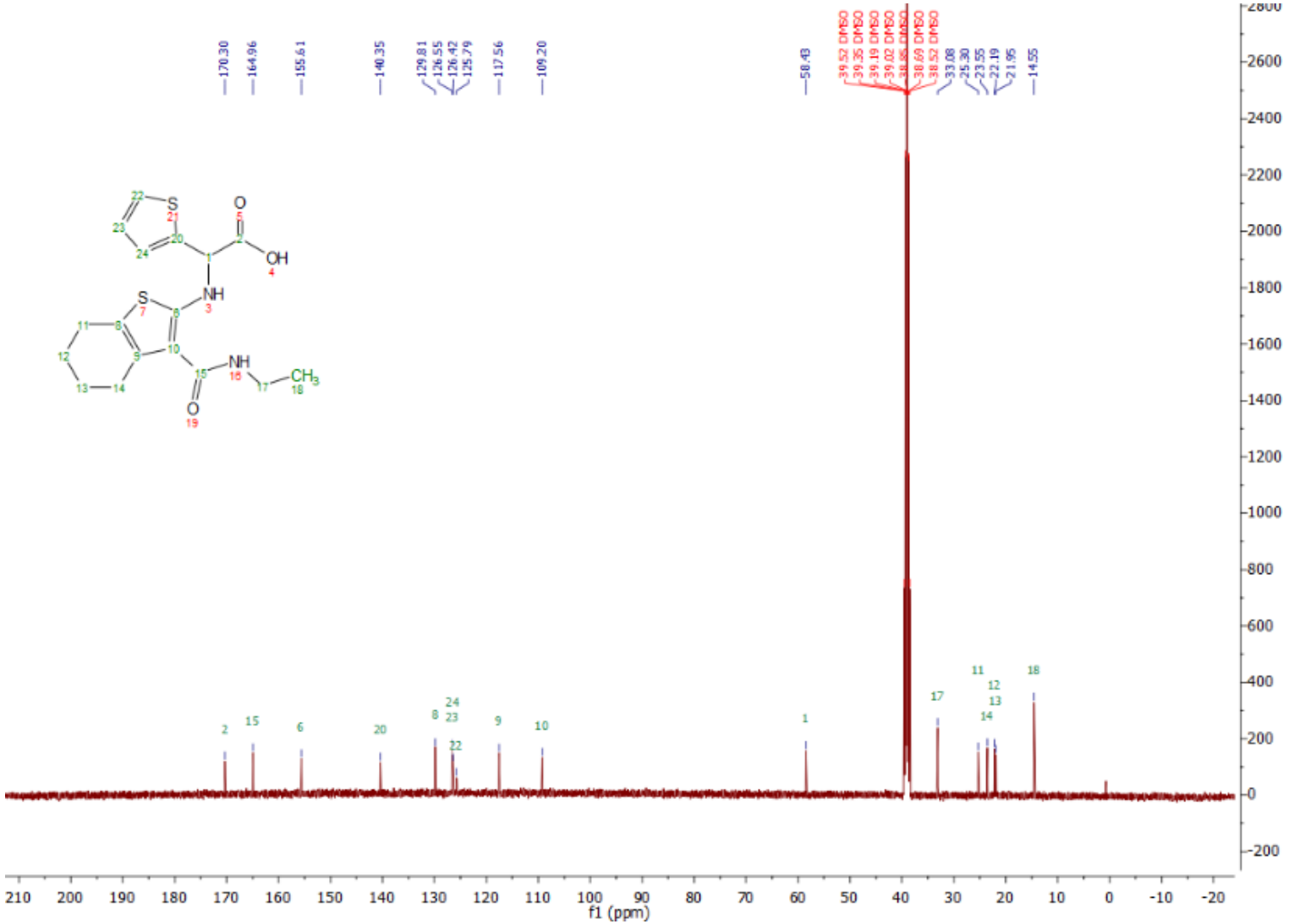
^{13}C-NMR of **5g** (176 MHz, DMSO-d_6)



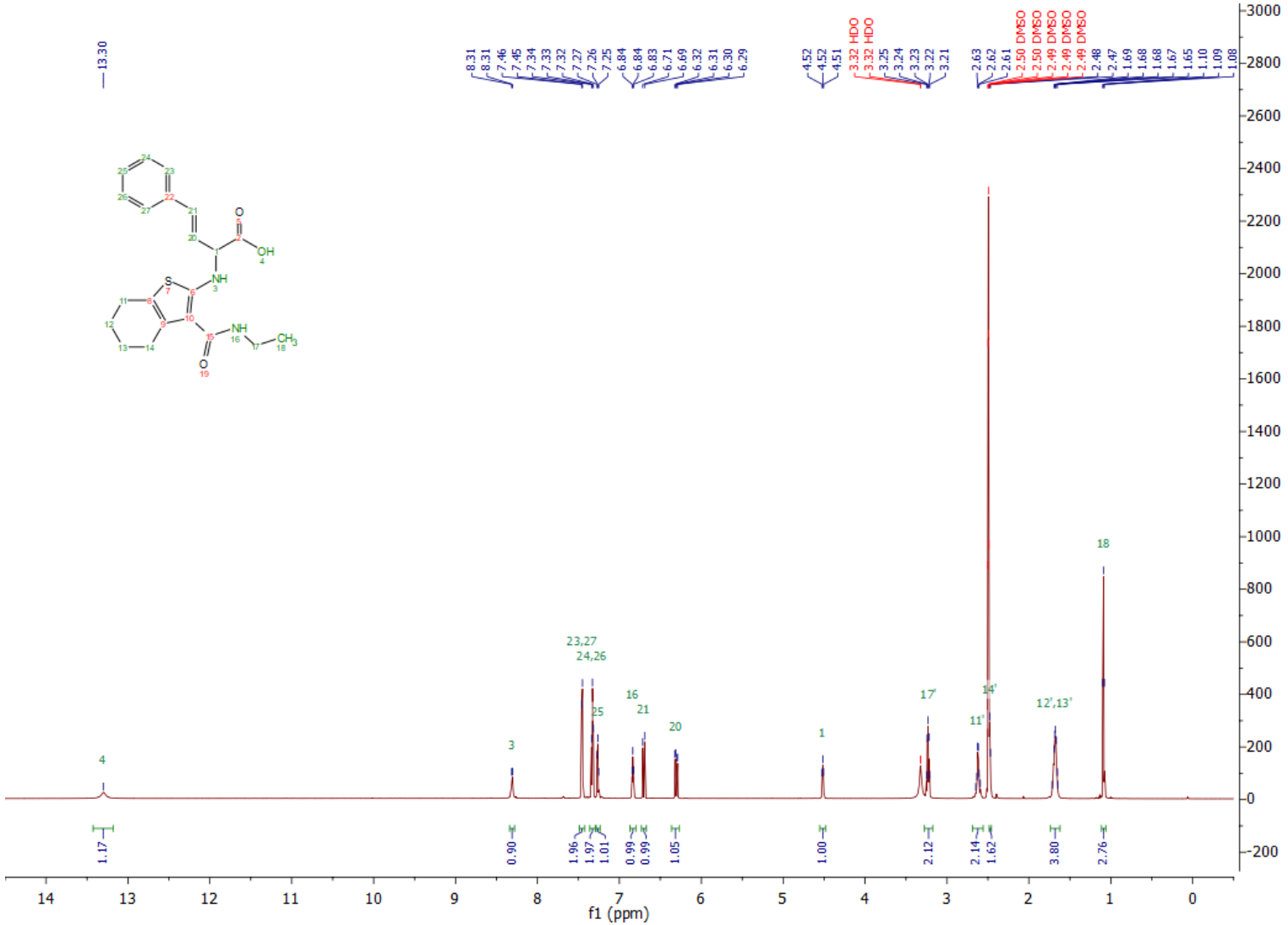
[1]H-NMR of **5k** (700 MHz, DMSO-d_6)



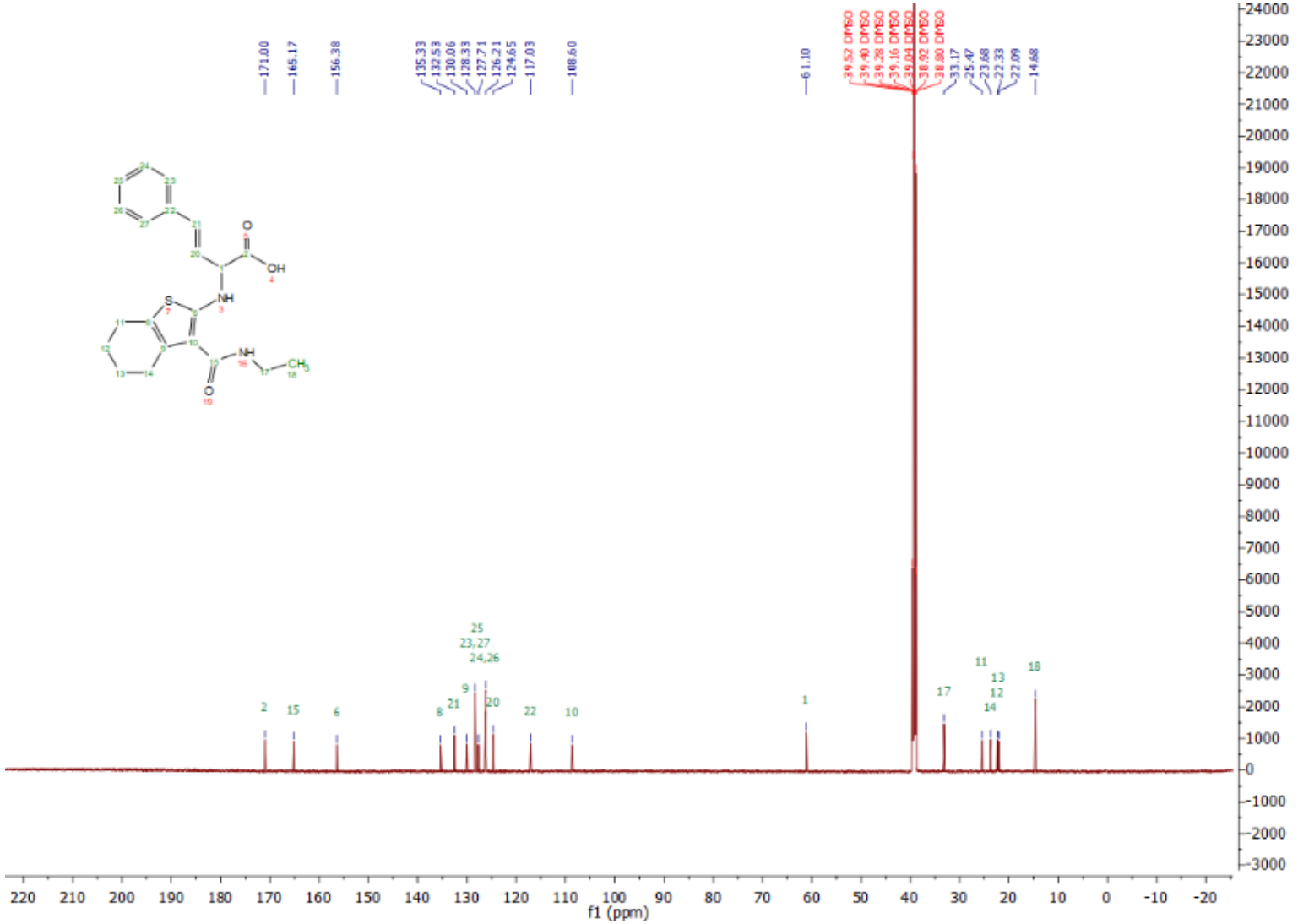
^{13}C-NMR of **5k** (126 MHz, DMSO-d_6)



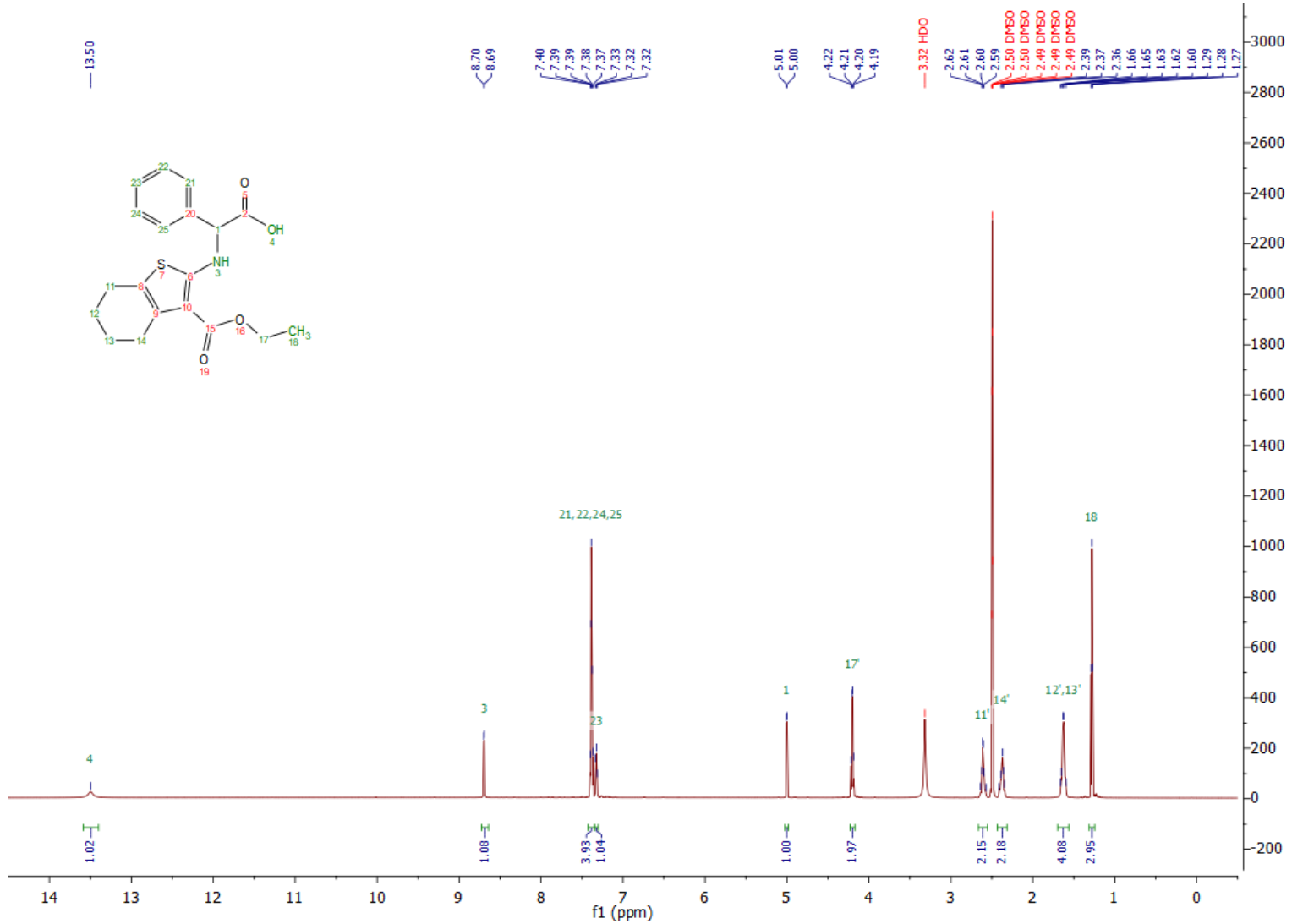
^{1}H-NMR of **5l** (700 MHz, DMSO-d_6)



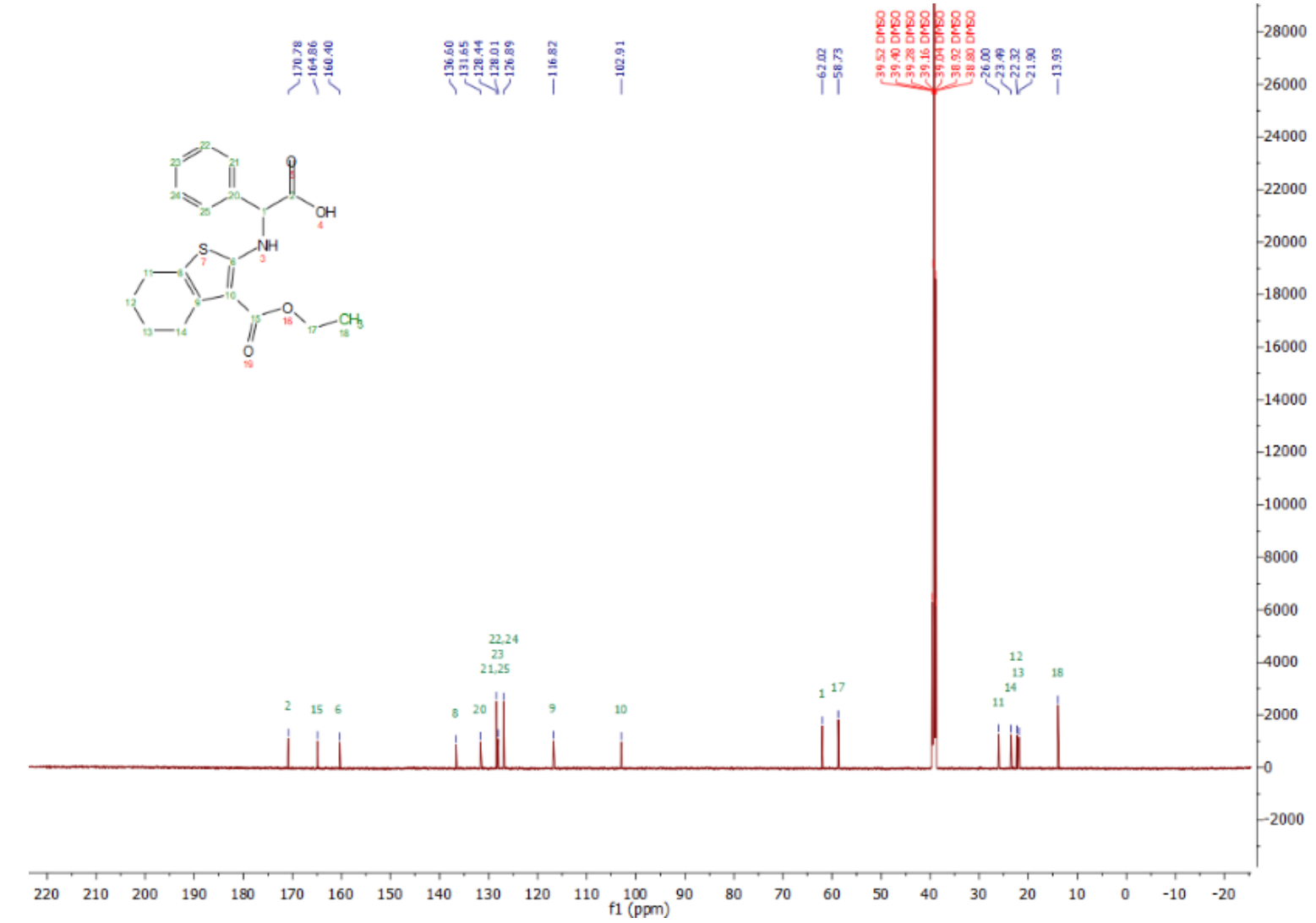
^{13}C-NMR of **5l** (176 MHz, DMSO-d_6)



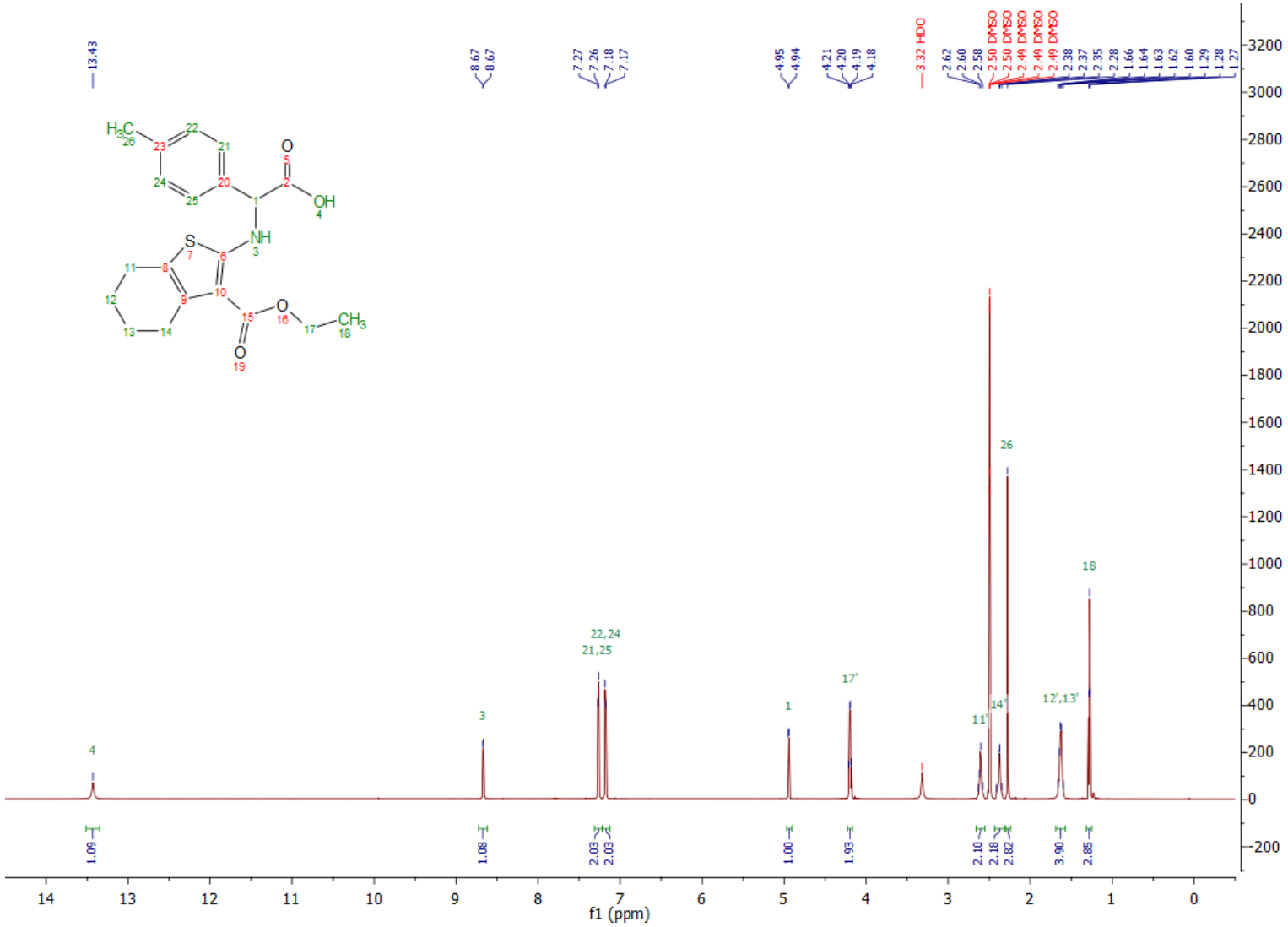
[1]H-NMR of **6a** (700 MHz, DMSO-d_6)



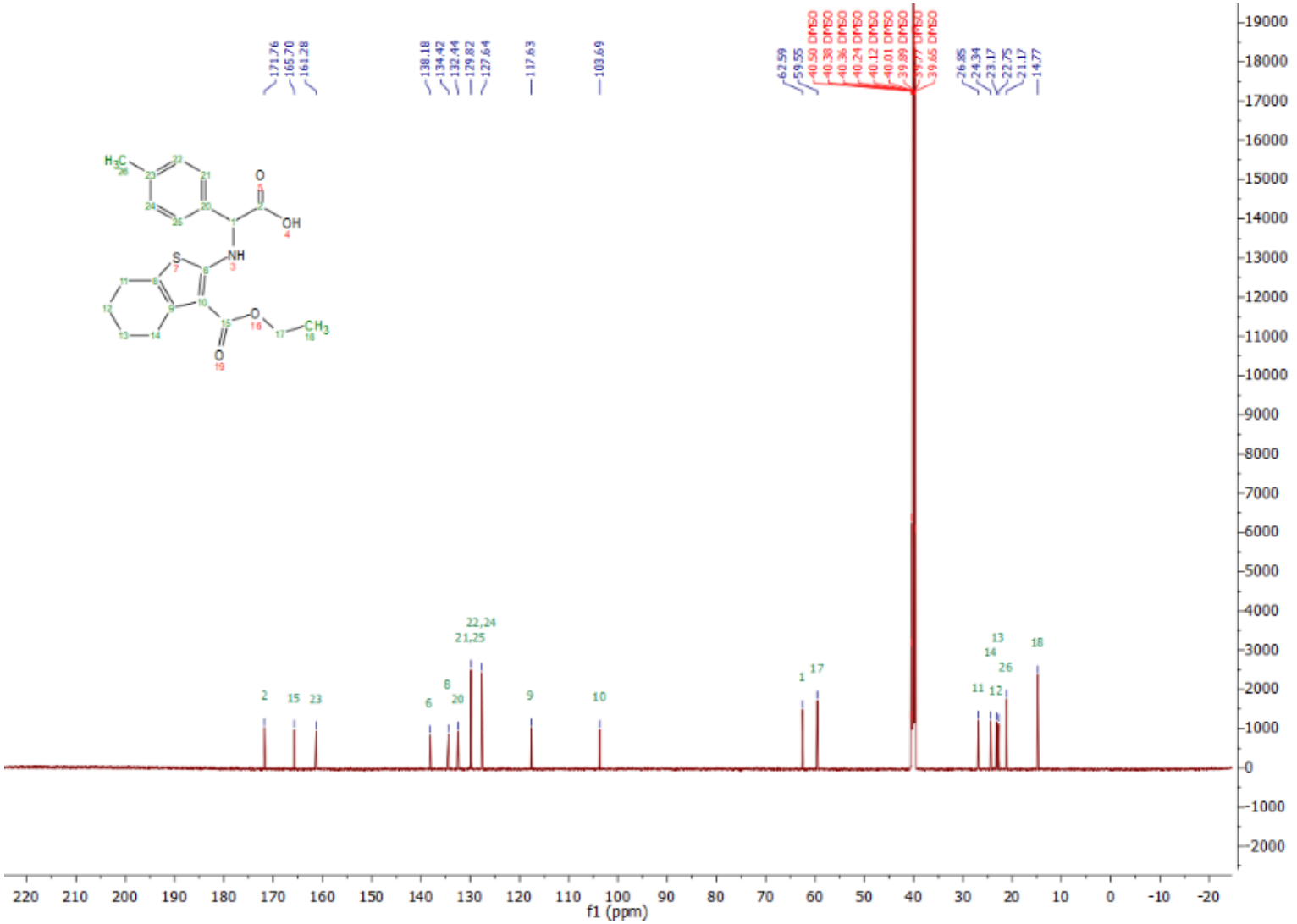
^{13}C-NMR of **6a** (176 MHz, DMSO-d_6)



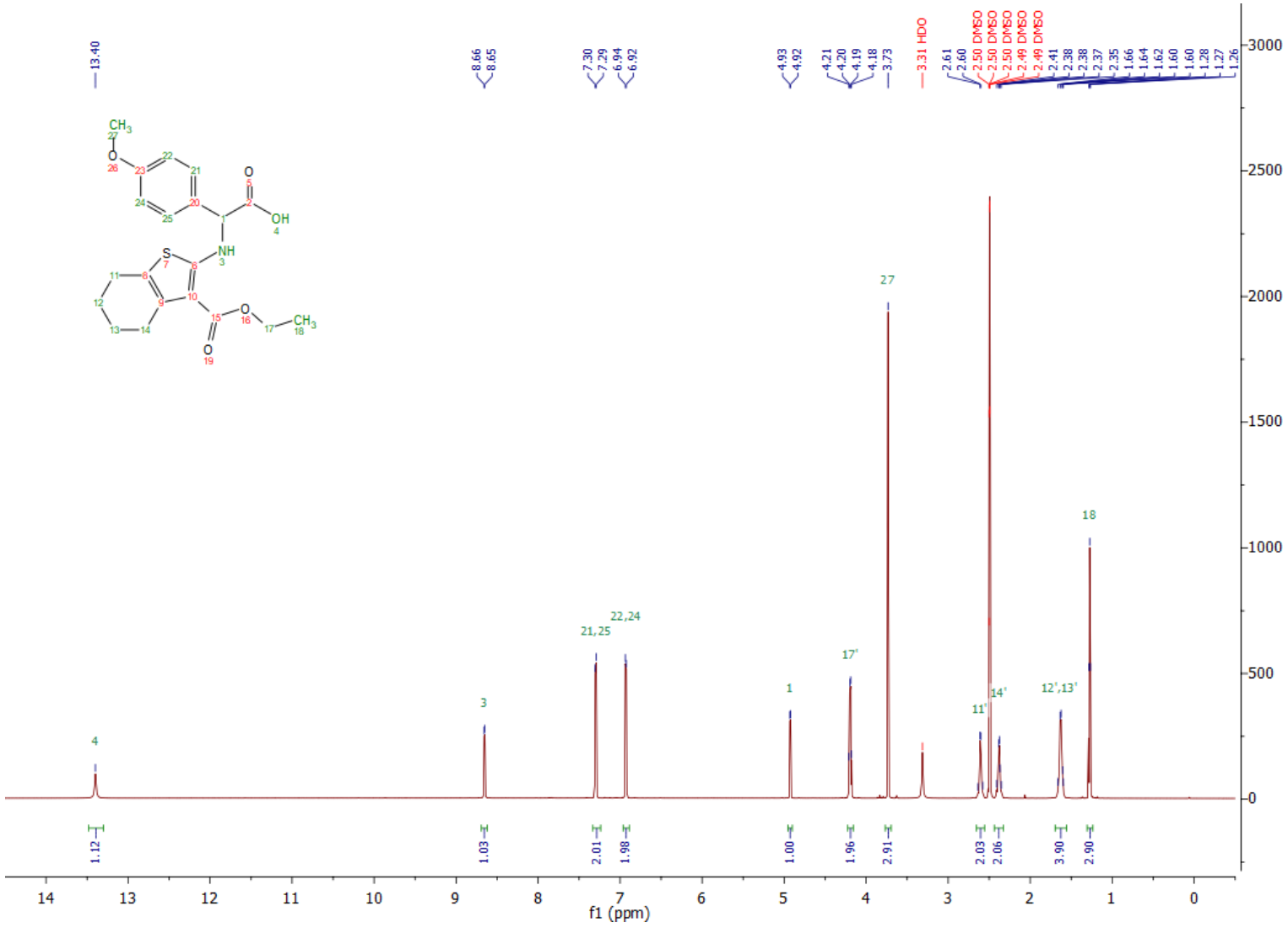
[1]H-NMR of **6b** (700 MHz, DMSO-d_6)



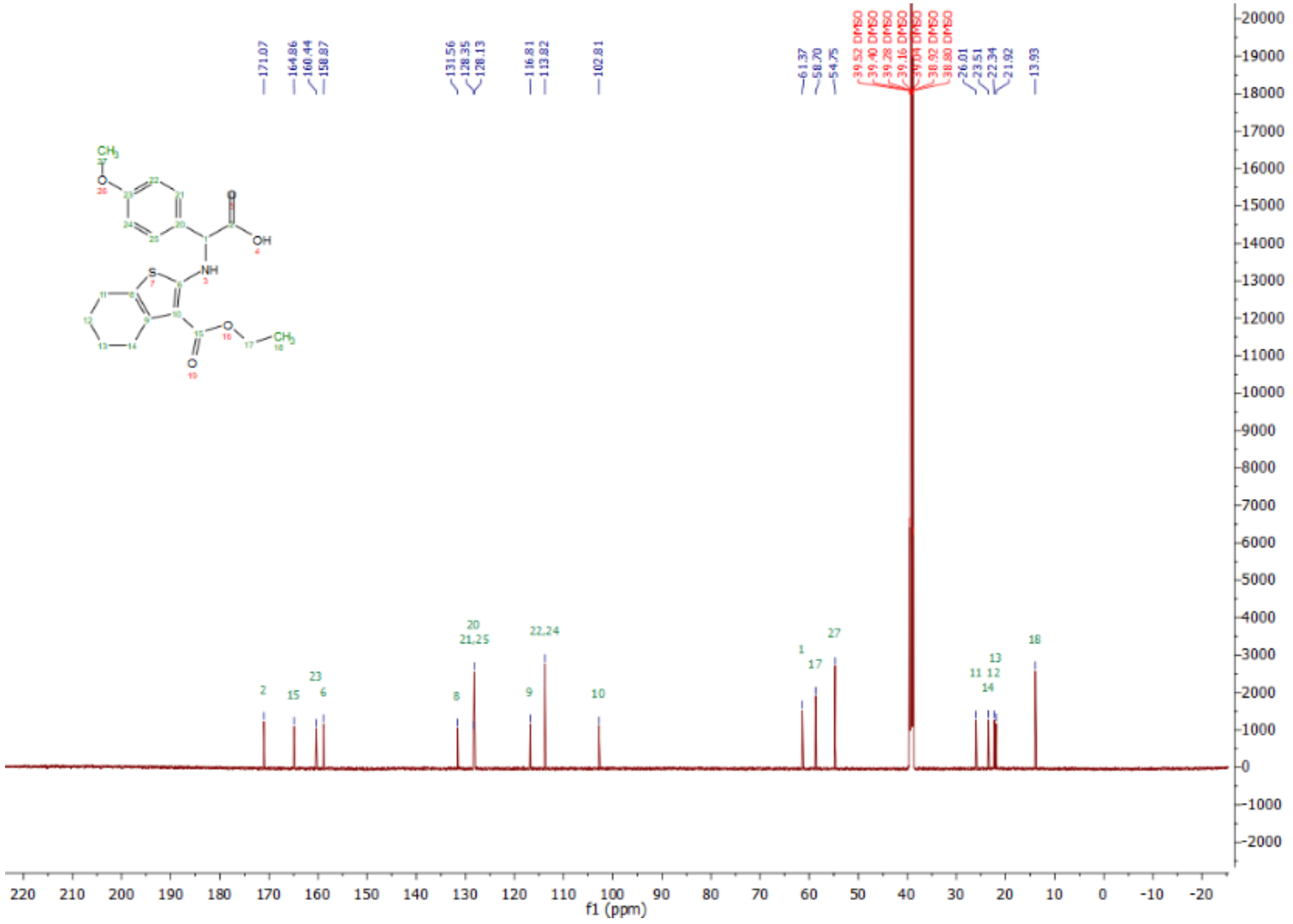
^{13}C-NMR of **6b** (176 MHz, DMSO-d_6)



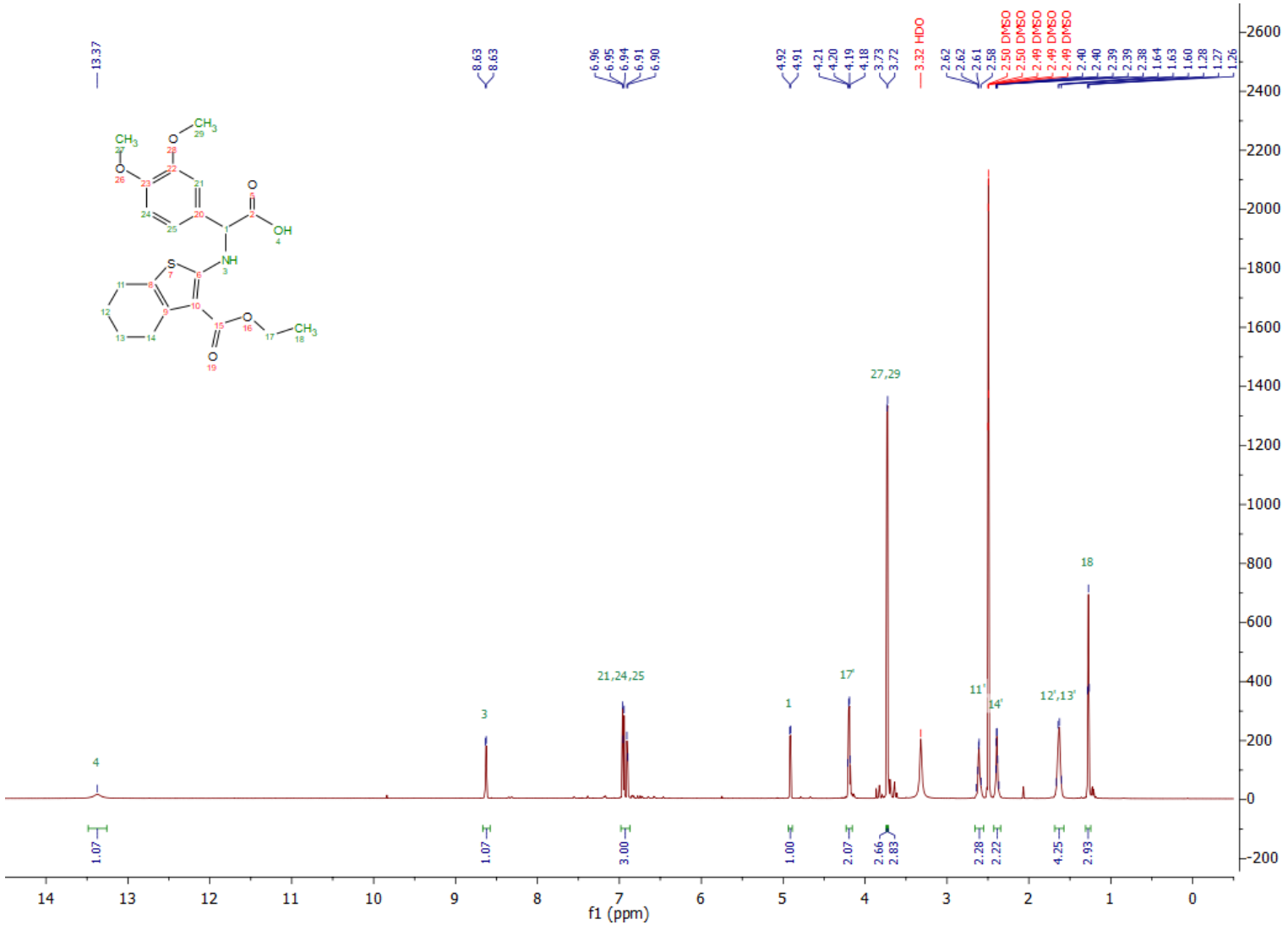
[1]H-NMR of **6c** (700 MHz, DMSO-d_6)



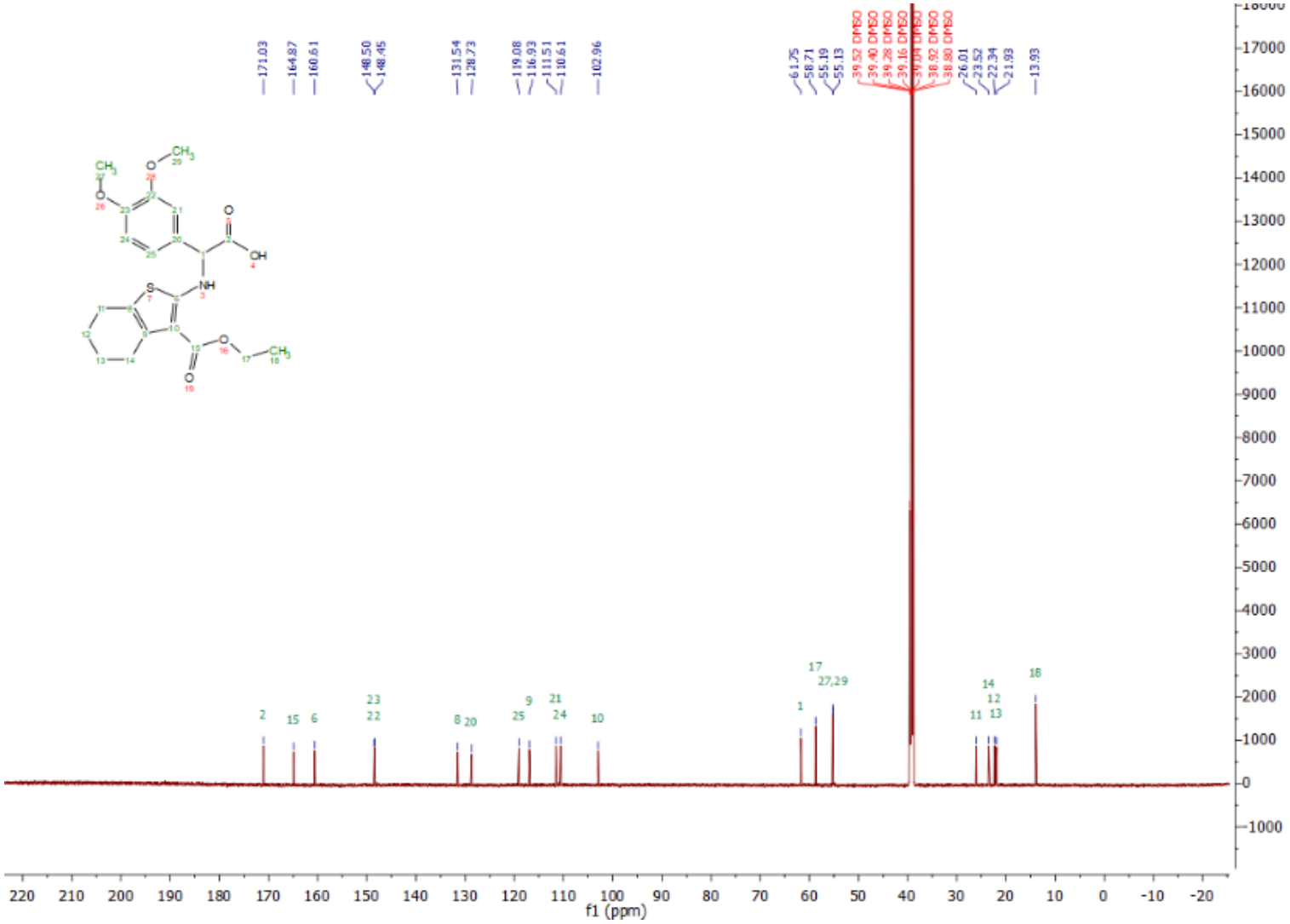
^{13}C-NMR of **6c** (176 MHz, DMSO-d_6)



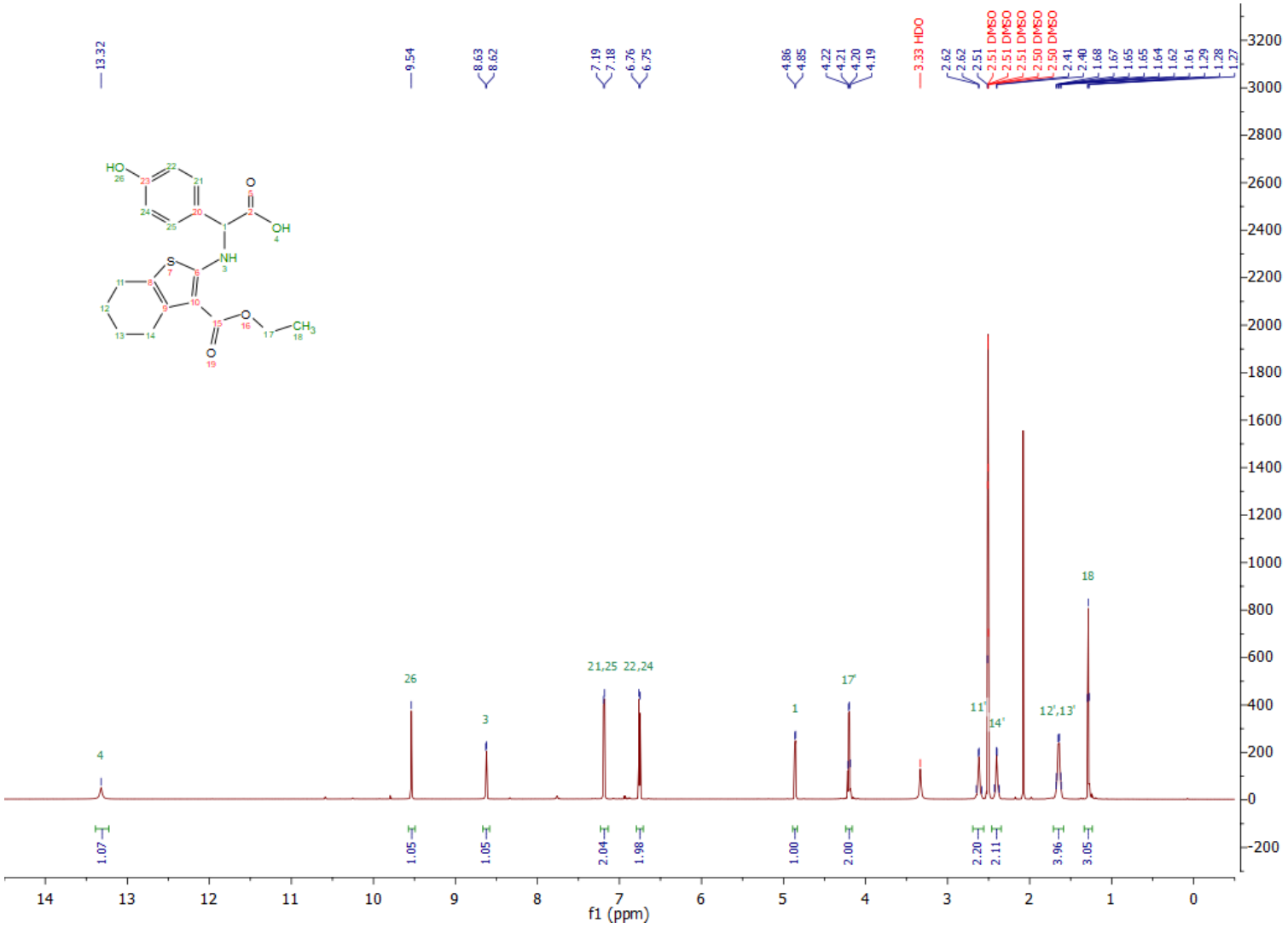
^{1}H-NMR of **6d** (700 MHz, DMSO-d_6)



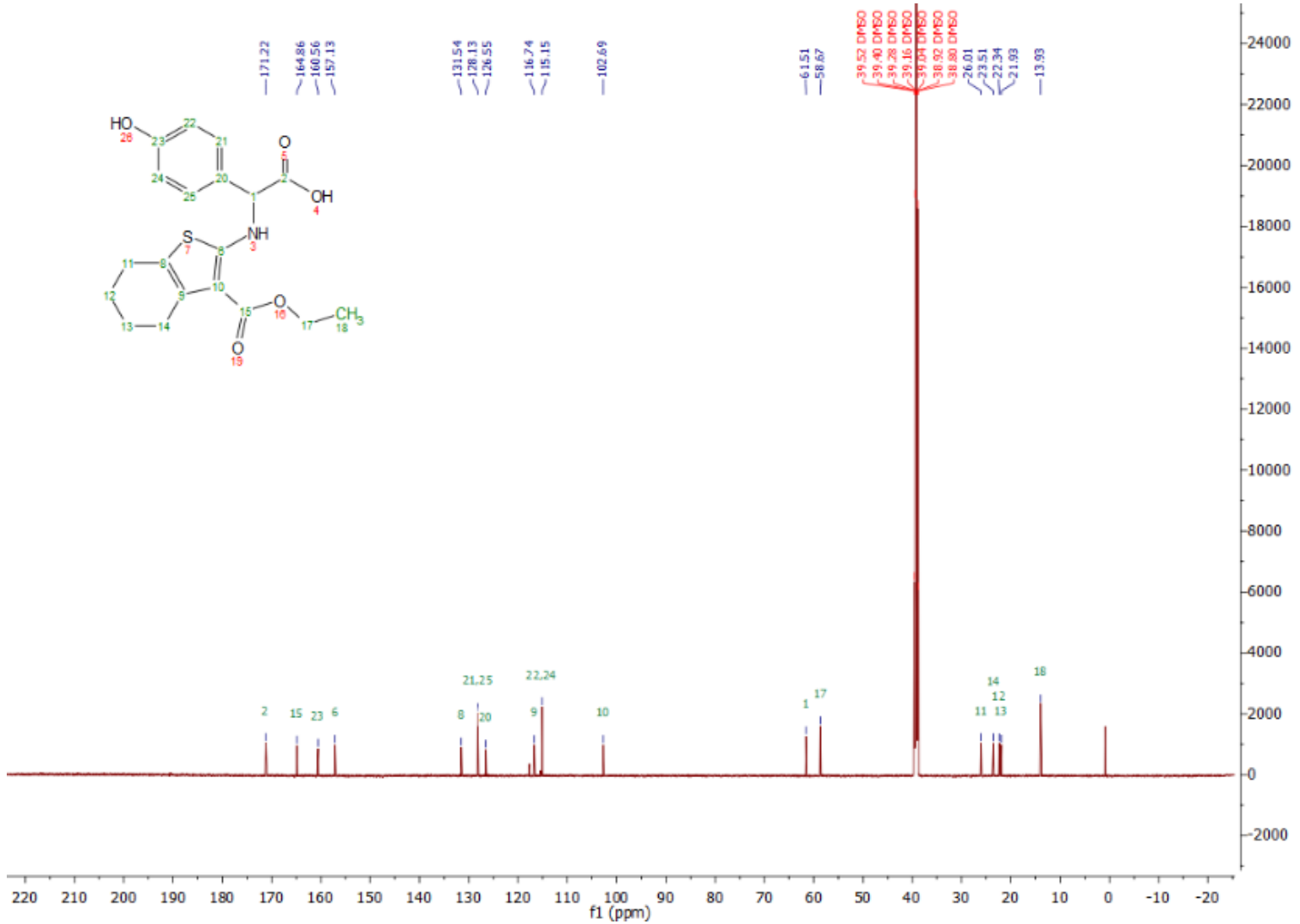
^{13}C-NMR of **6d** (176 MHz, DMSO-d_6)



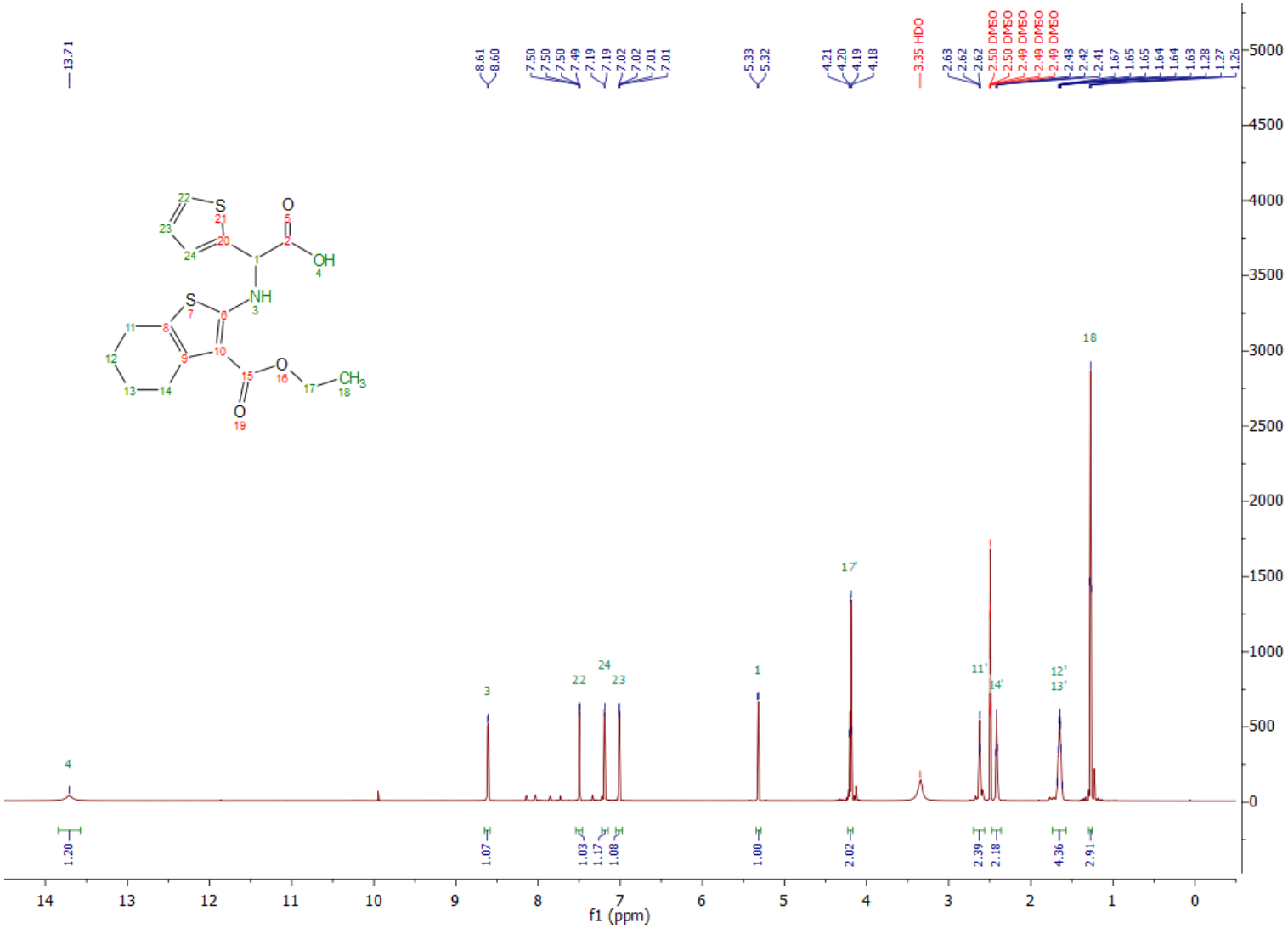
^{1}H-NMR of **6e** (700 MHz, DMSO-d_6)



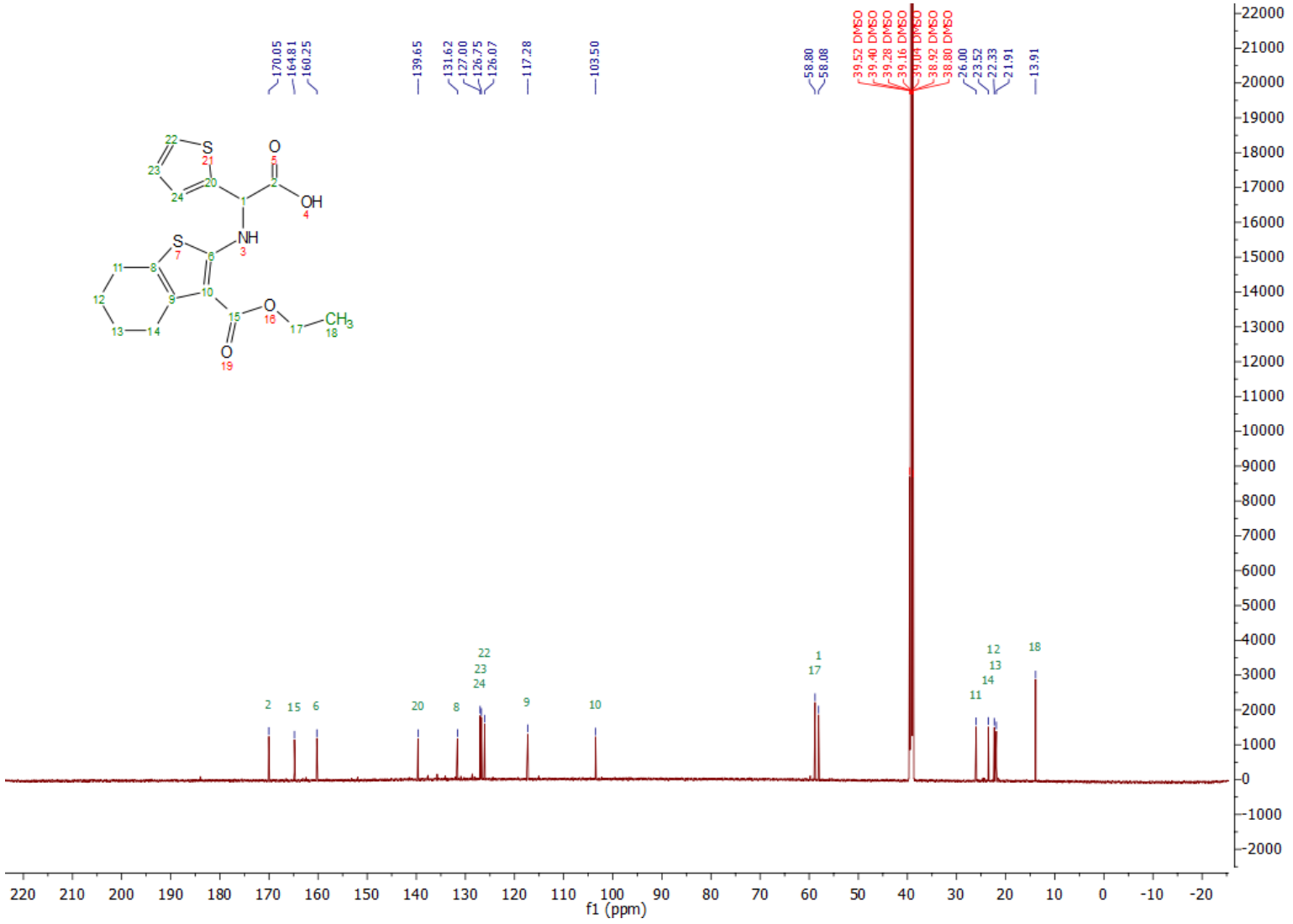
^{13}C-NMR of **6e** (176 MHz, DMSO-d_6)



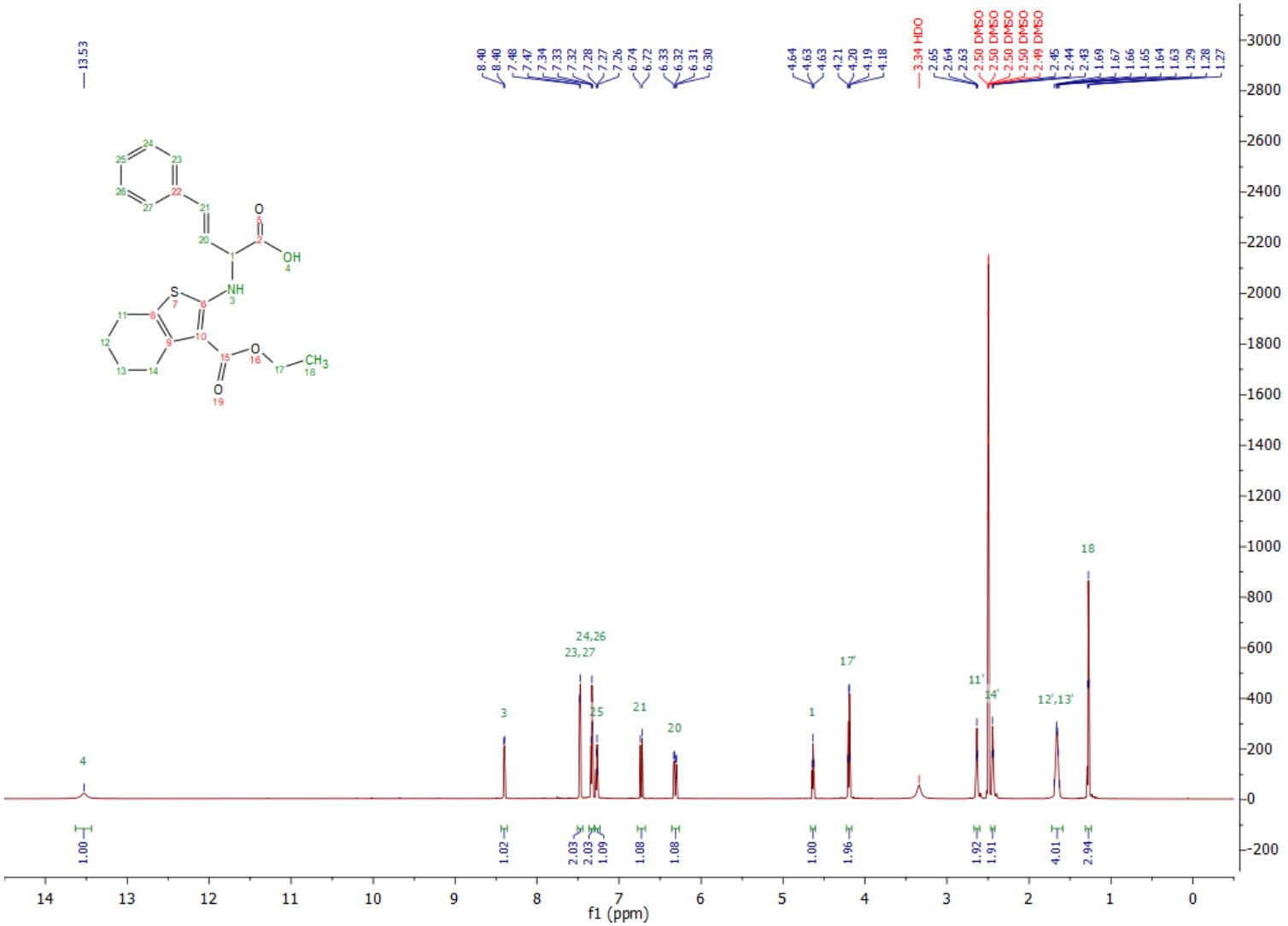
^{1}H-NMR of **6k** (700 MHz, DMSO-d_6)



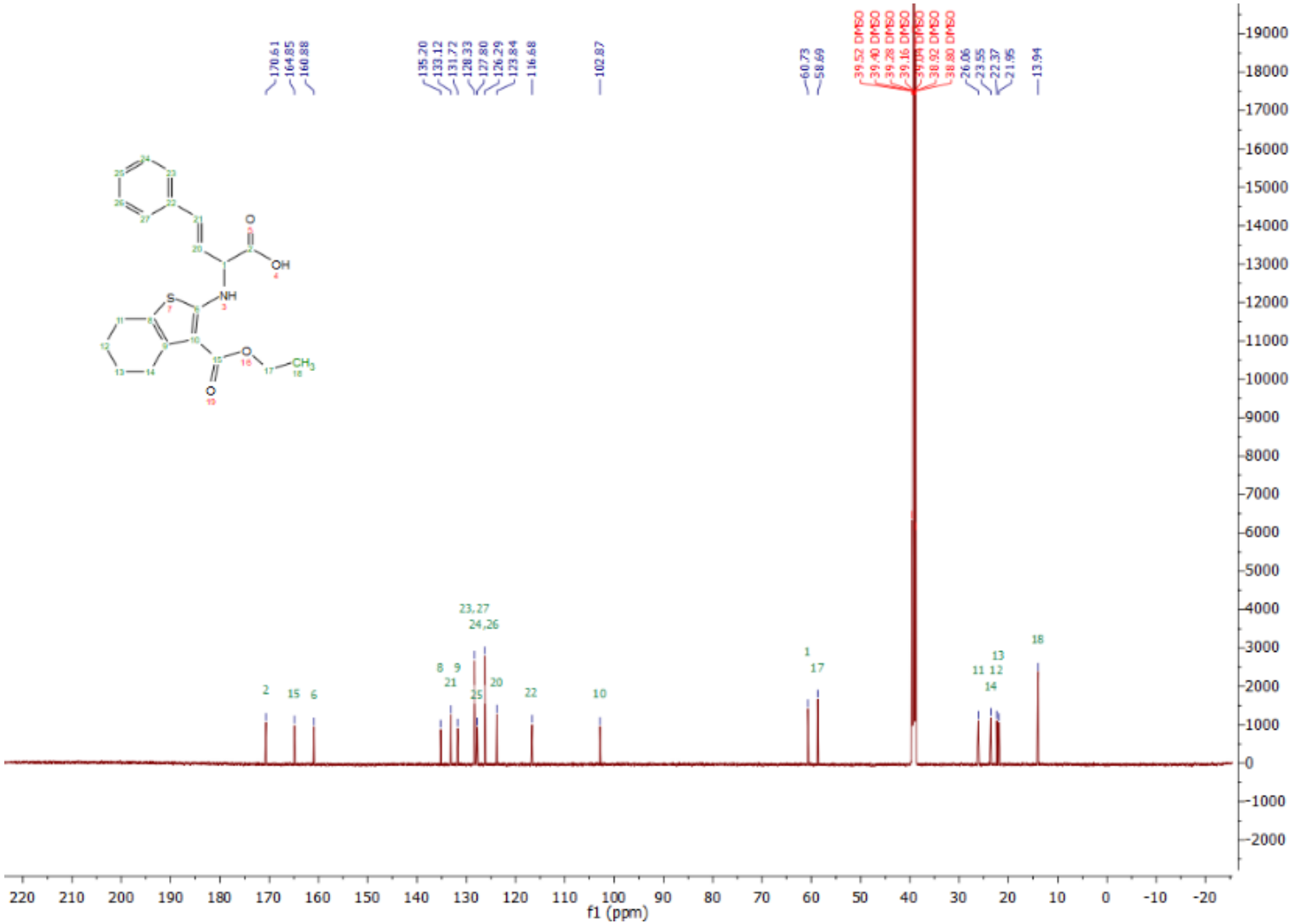
^{13}C-NMR of **6k** (176 MHz, DMSO-d_6)



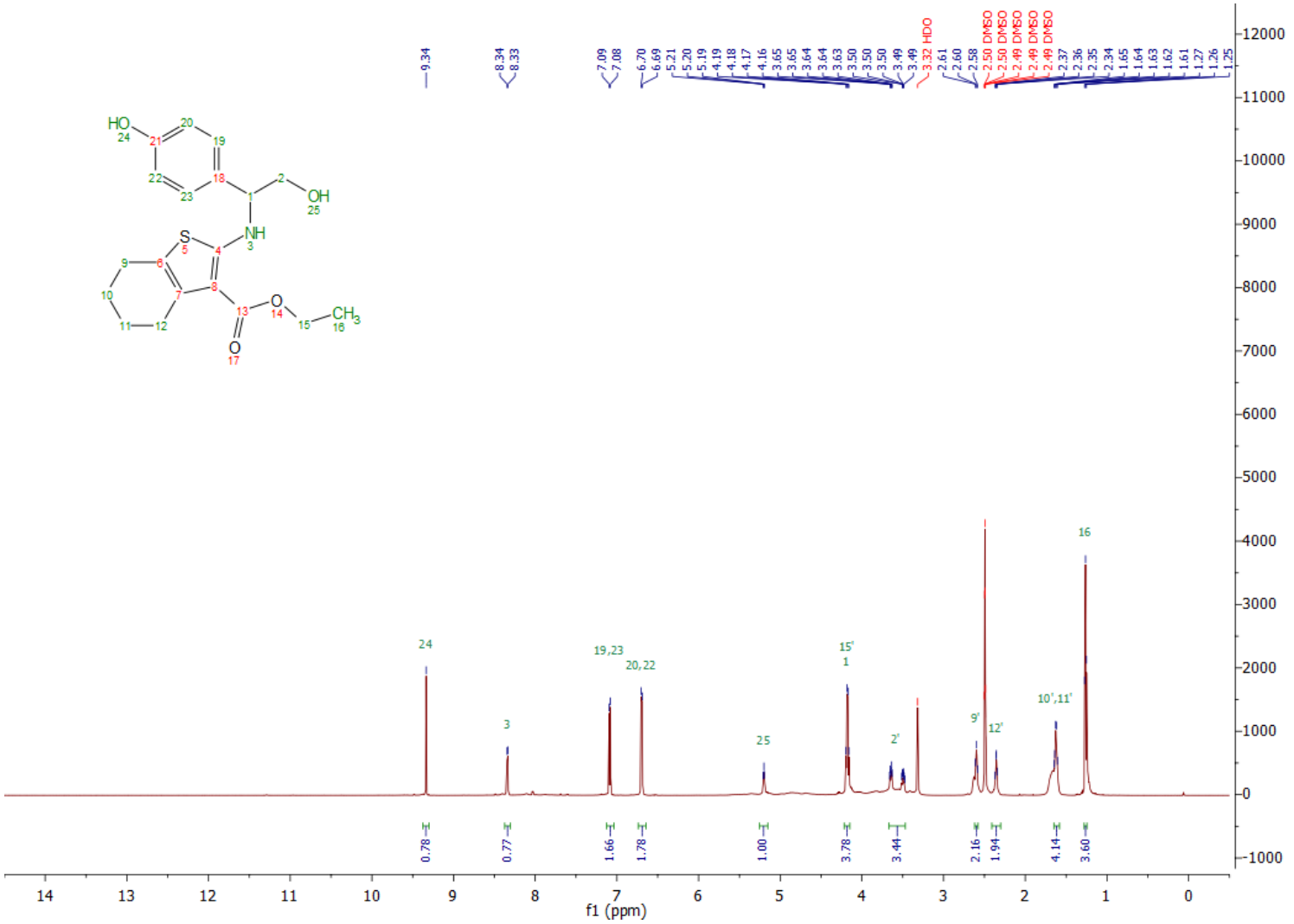
^{1}H-NMR of **6l** (700 MHz, DMSO-d_6)



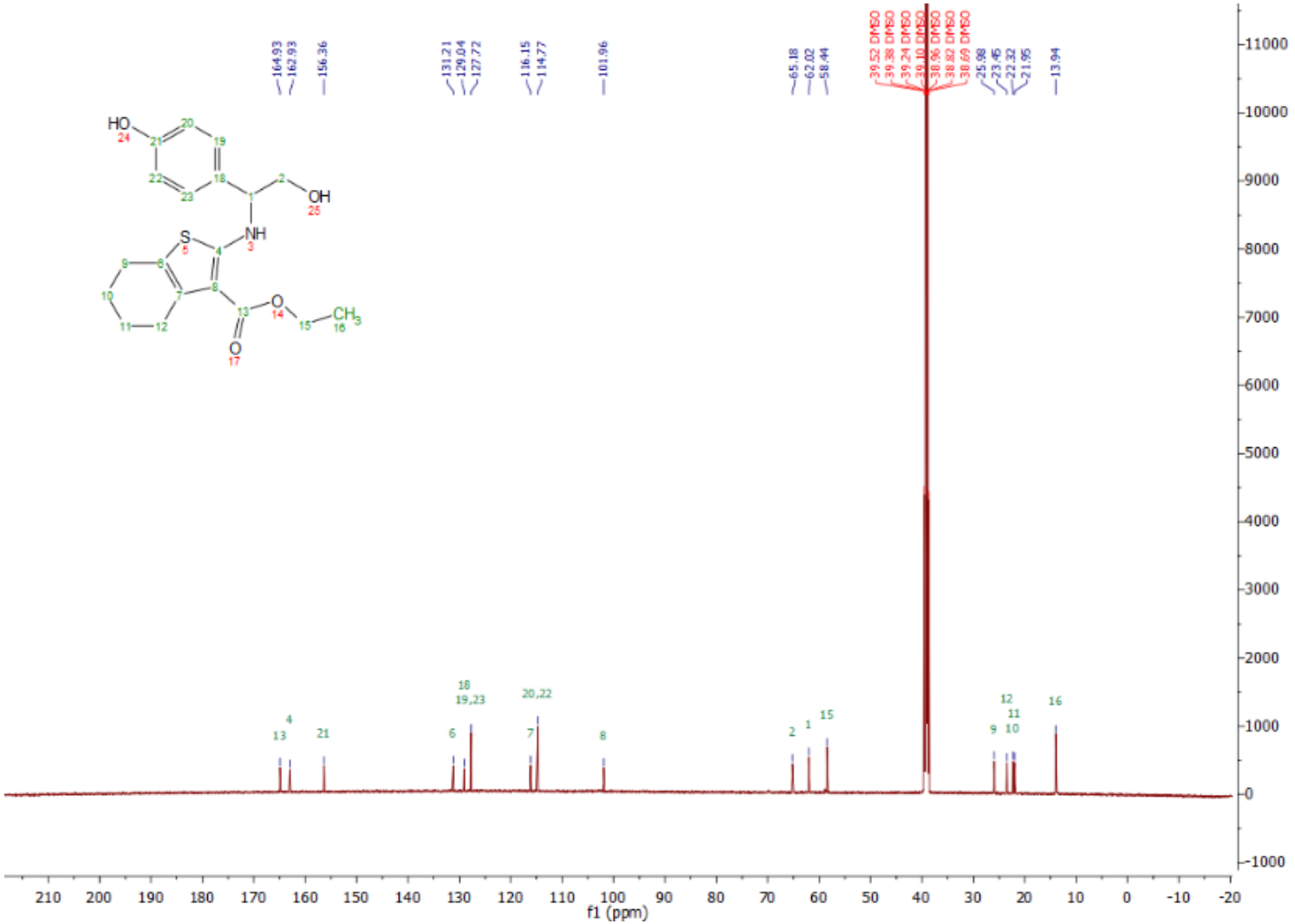
^{13}C-NMR of **6l** (176 MHz, DMSO-d_6)



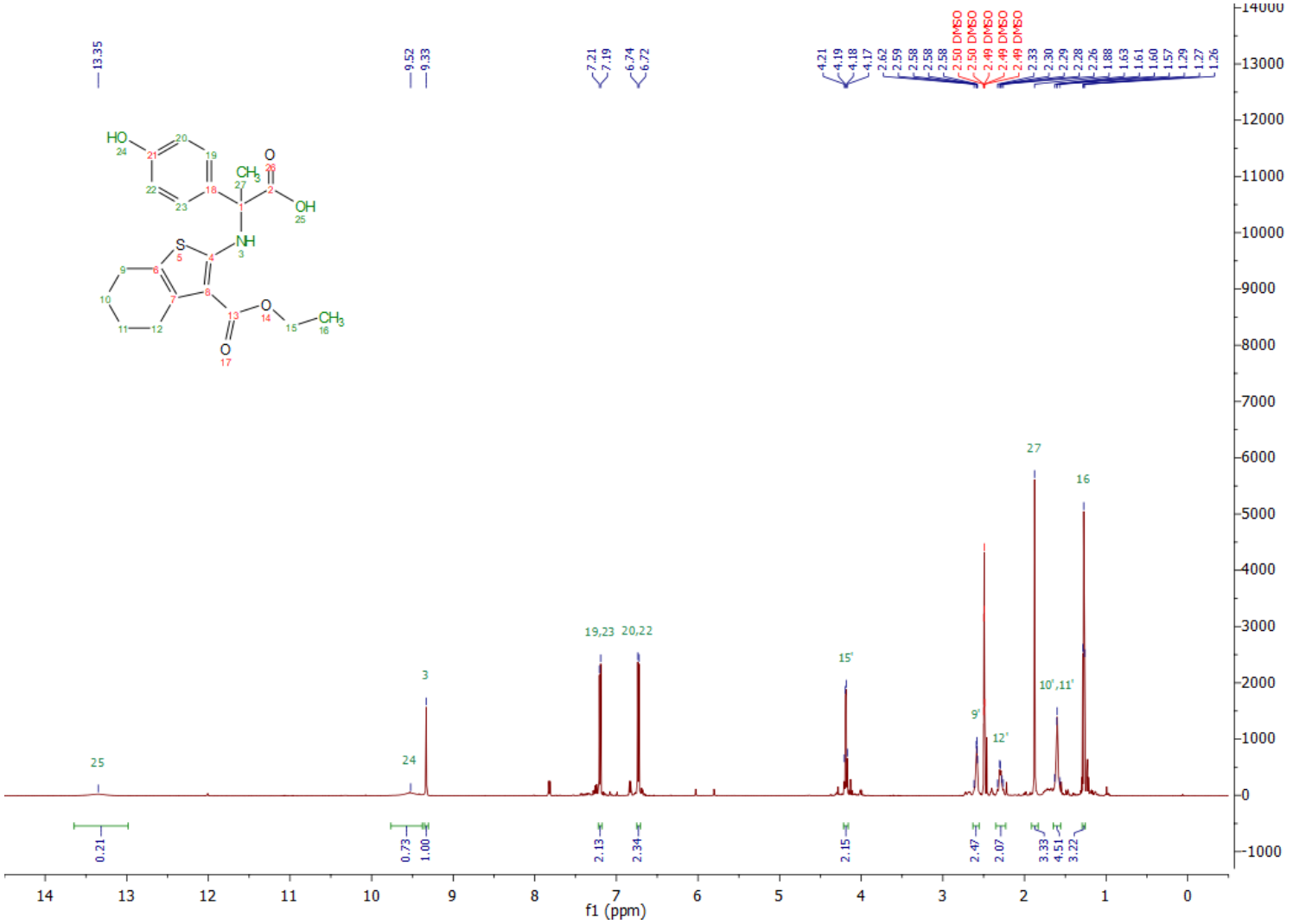
^{1}H-NMR of **6m** (600 MHz, DMSO-d_6)



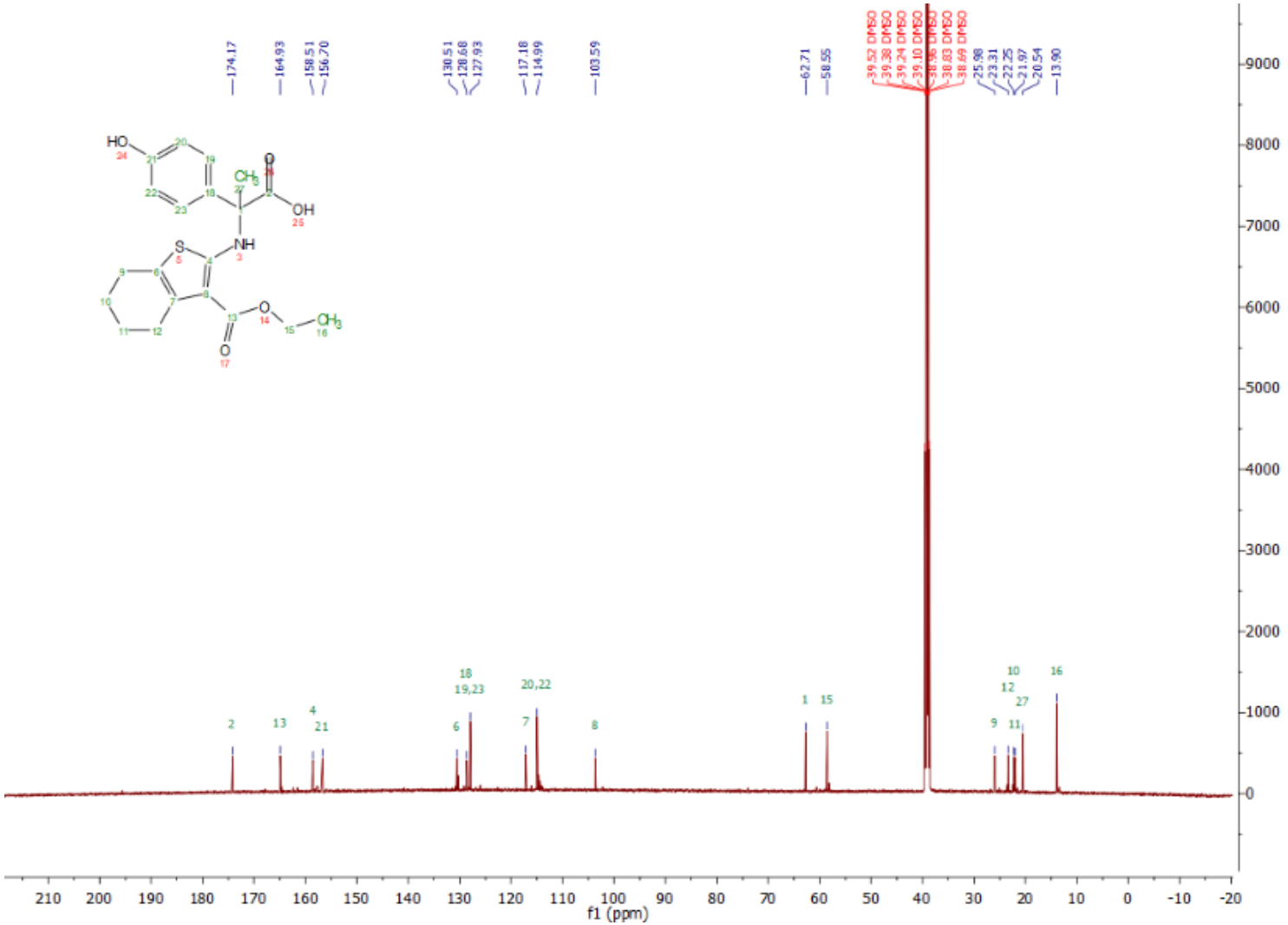
^{13}C-NMR of **6m** (151 MHz, DMSO-d_6)



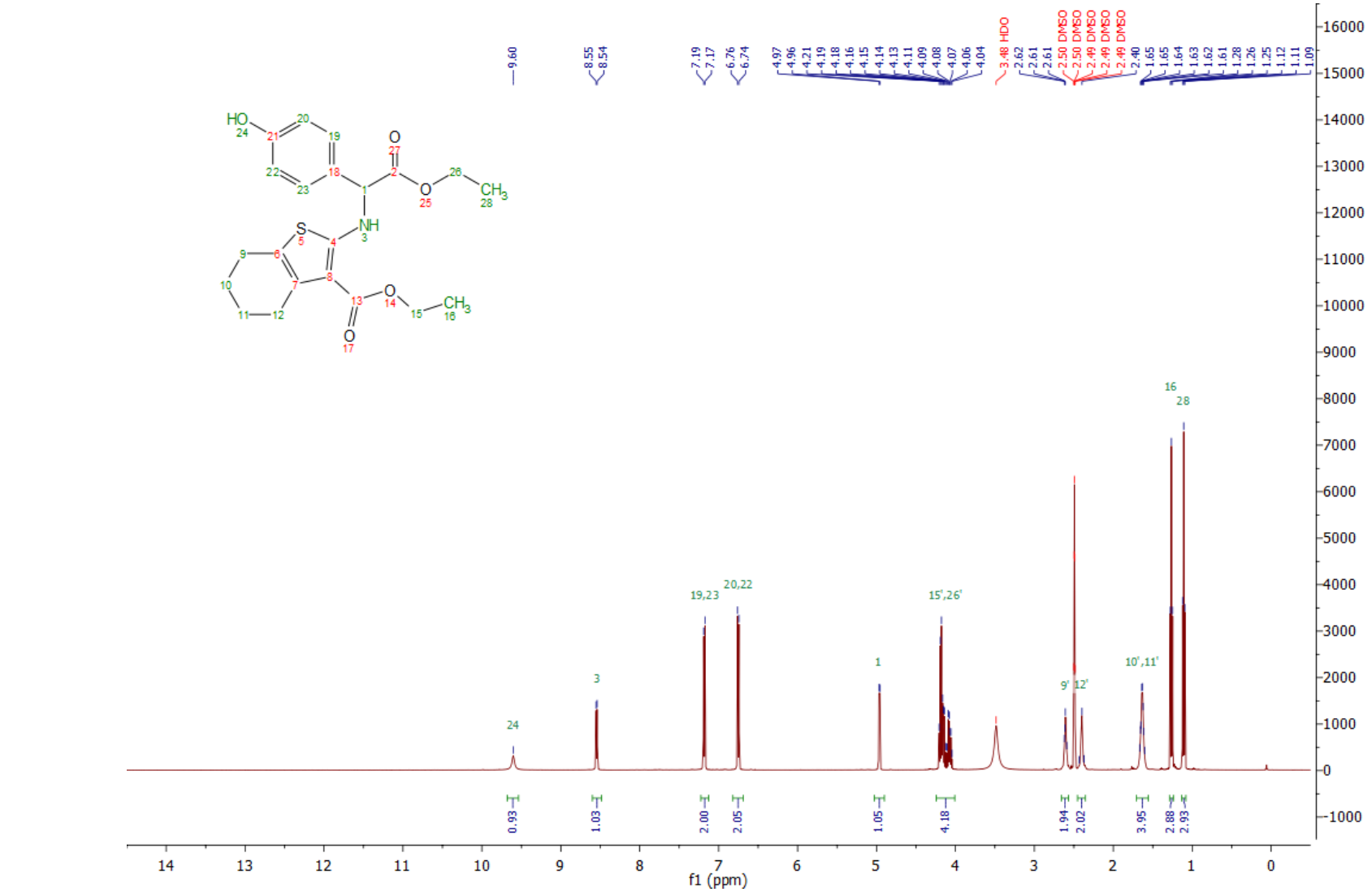
^{1}H-NMR of **6n** (600 MHz, DMSO-d_6)



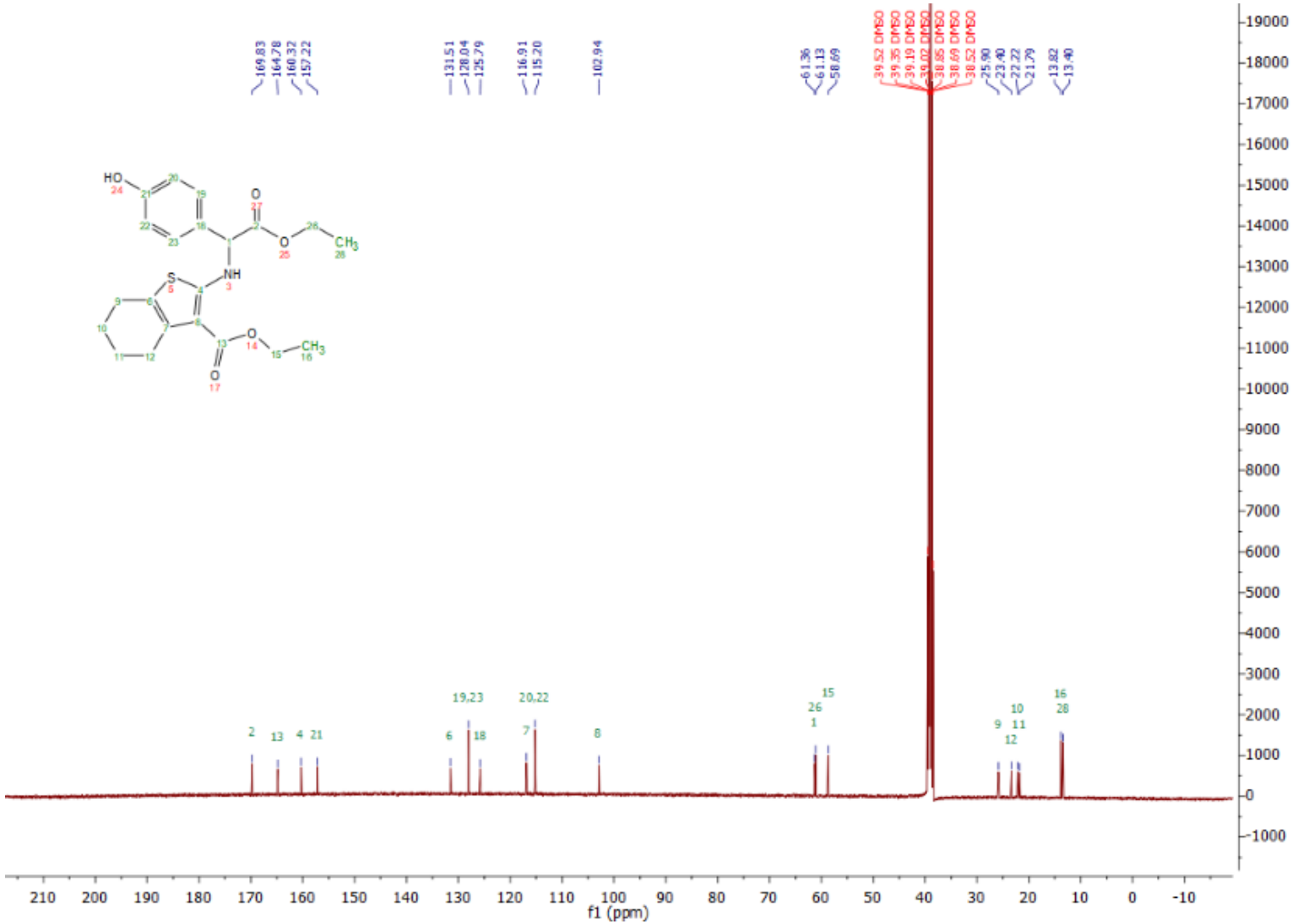
^{13}C-NMR of **6n** (151 MHz, DMSO-d_6)



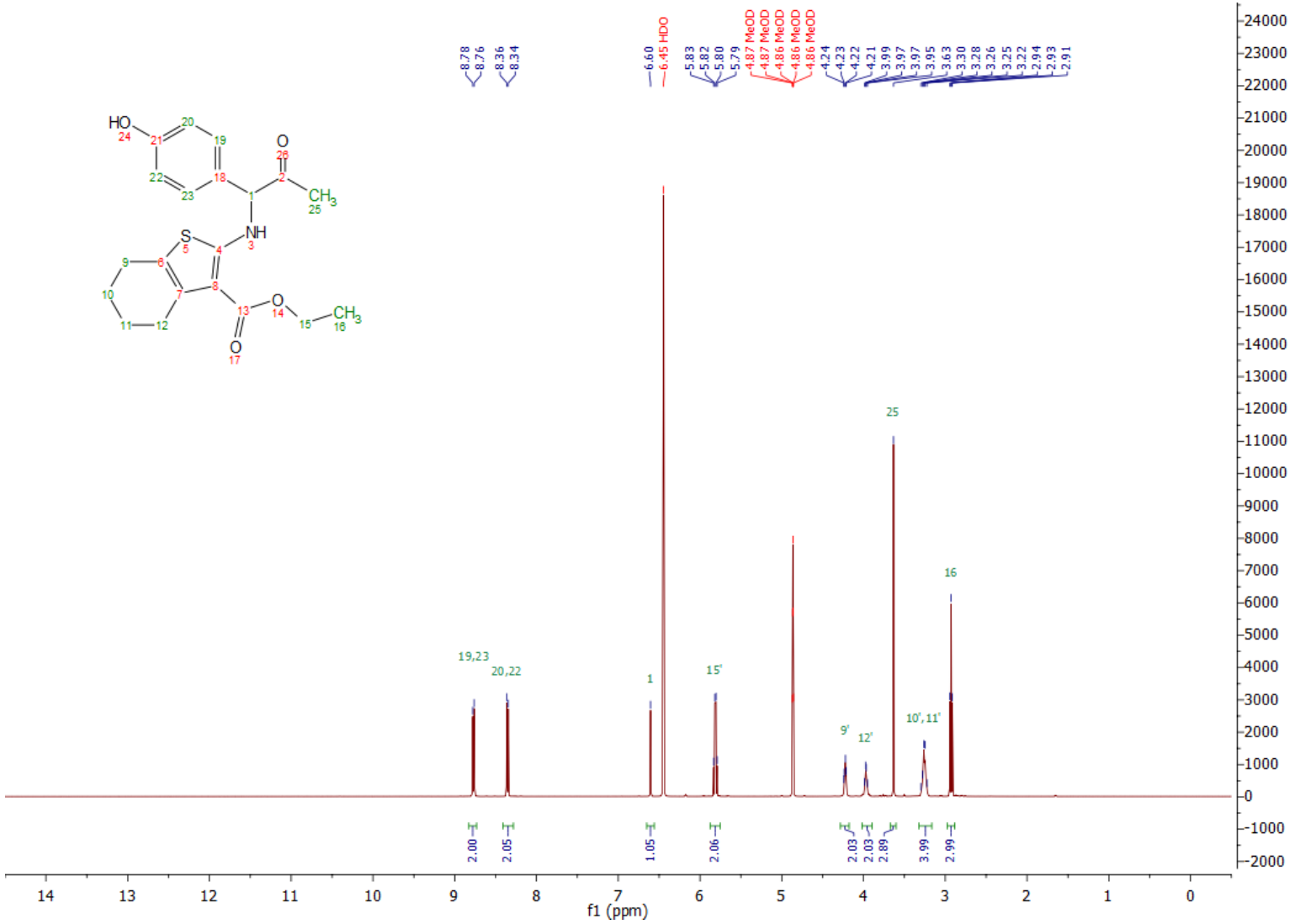
^{1}H-NMR of **6o** (500 MHz, DMSO-d_6)



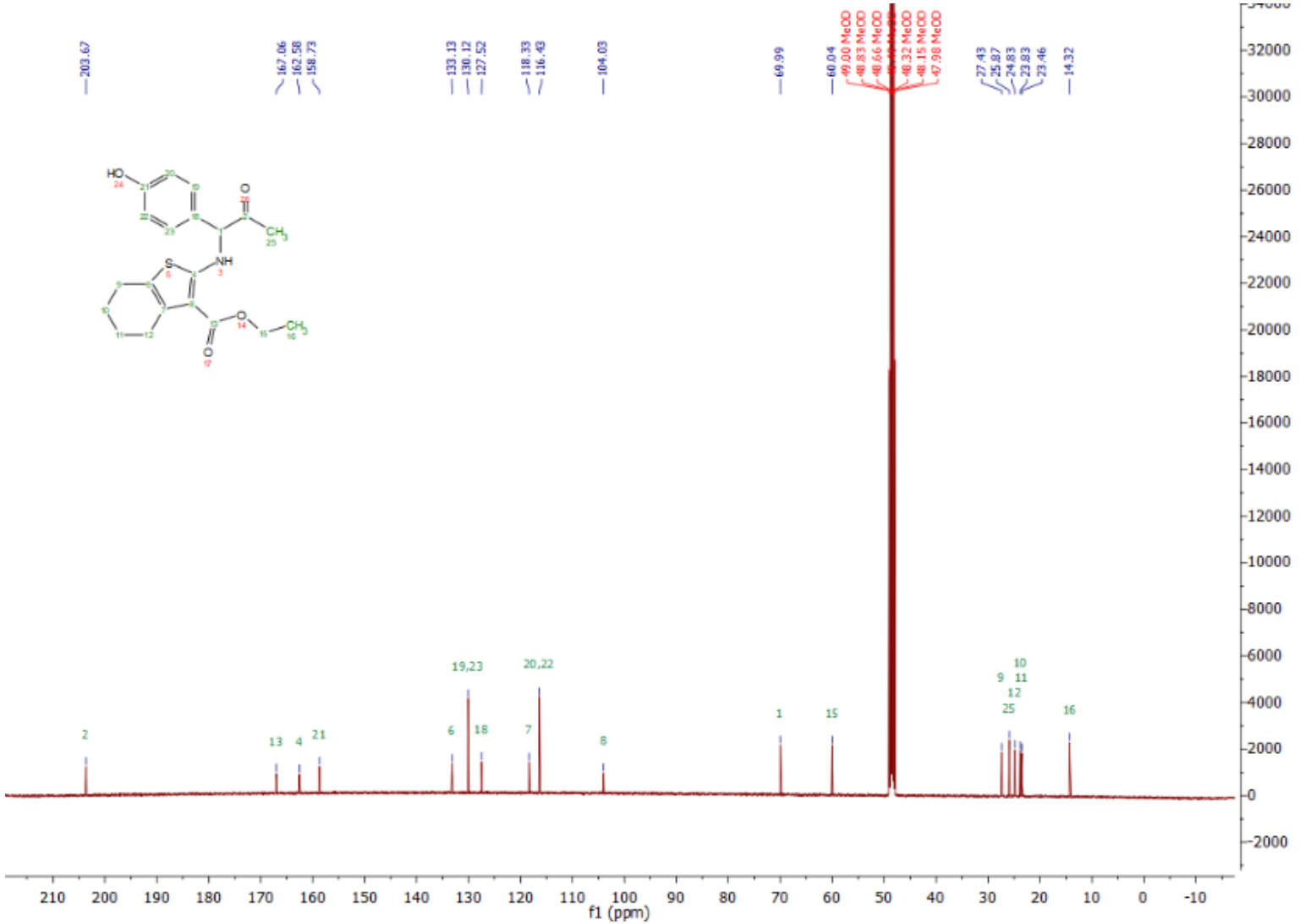
^{13}C-NMR of **6o** (126 MHz, DMSO-d_6)



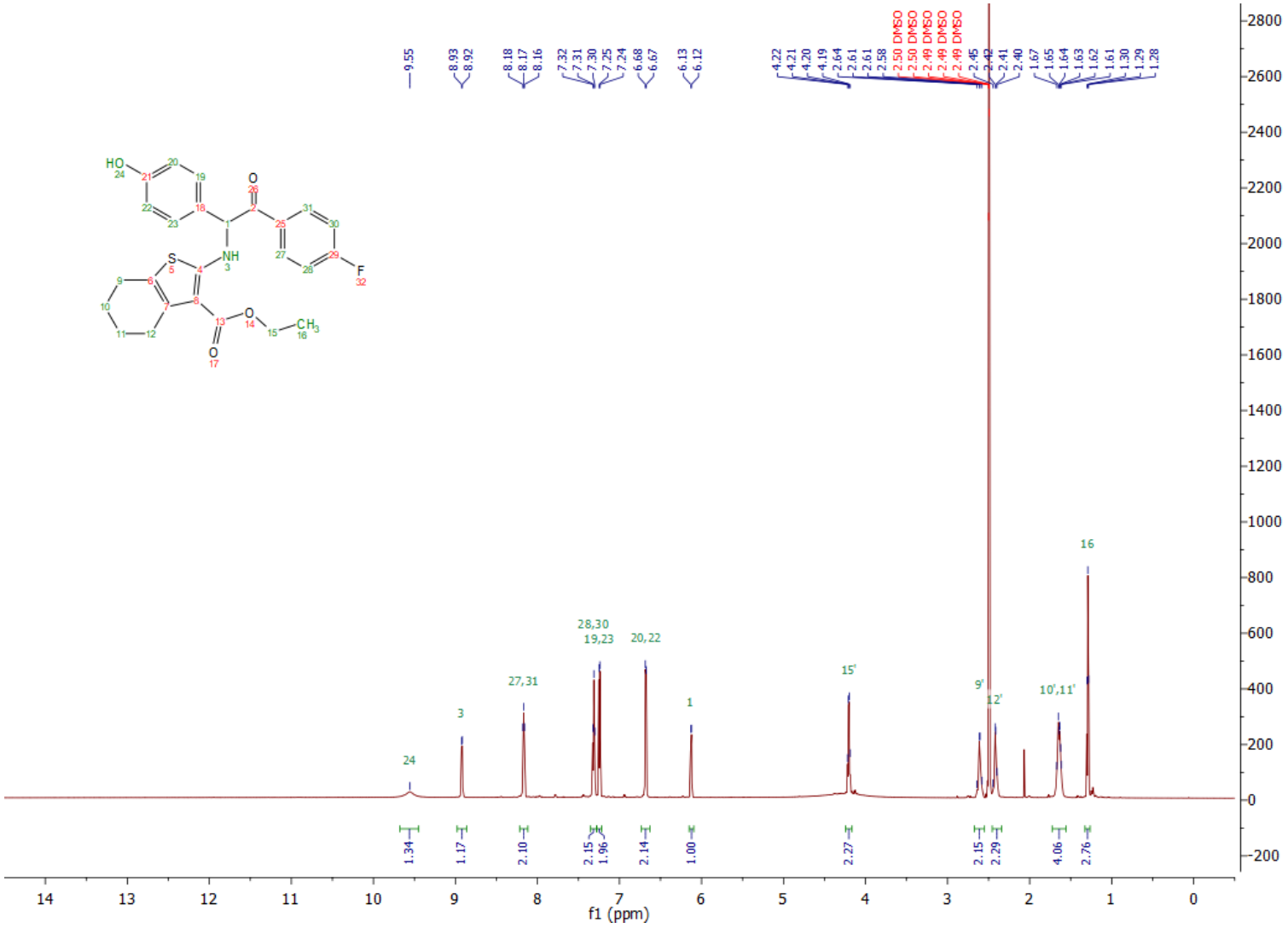
^{1}H-NMR of **6p** (500 MHz, Methanol-d_4)



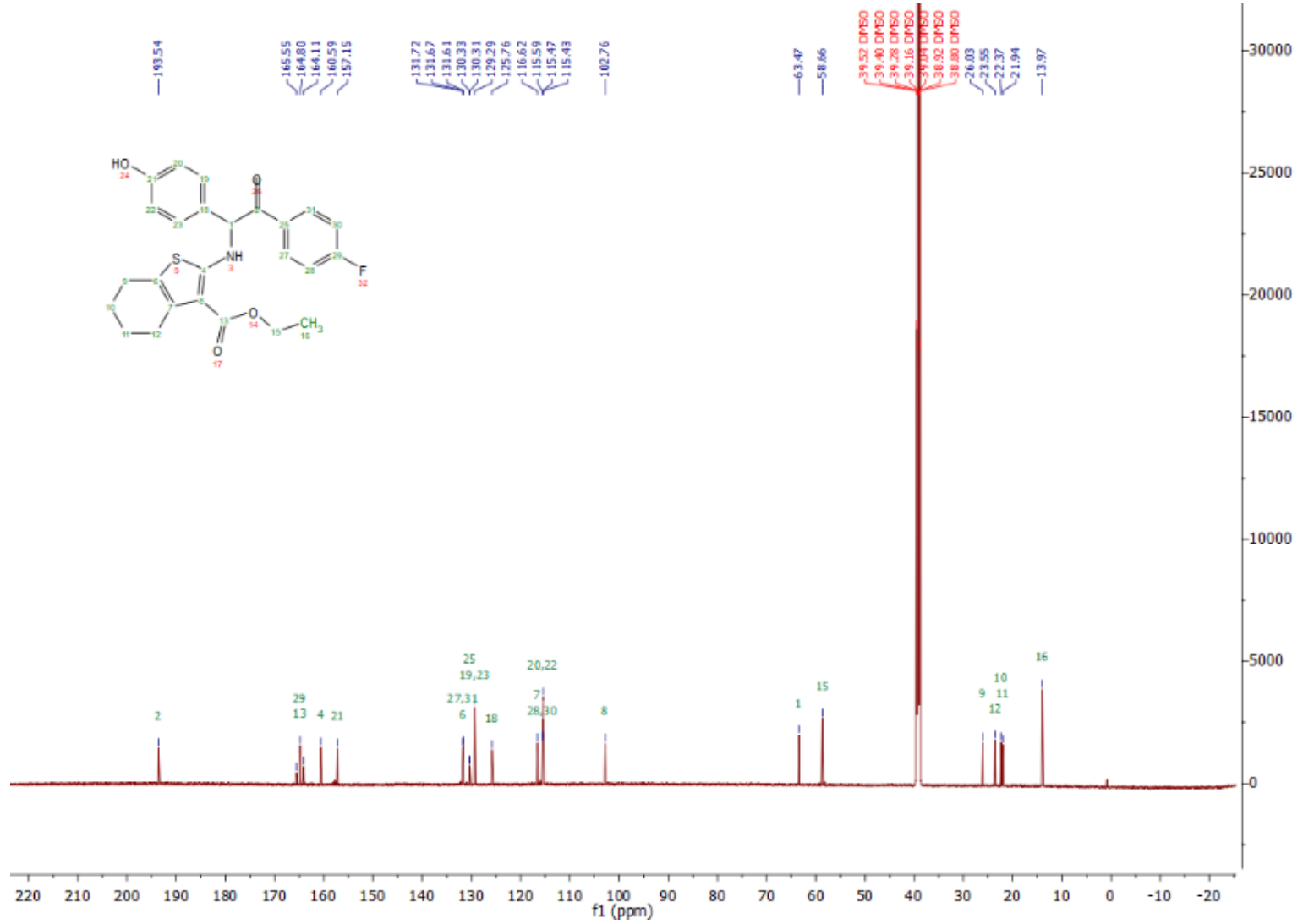
^{13}C-NMR of **6p** (126 MHz, Methanol-d_4)



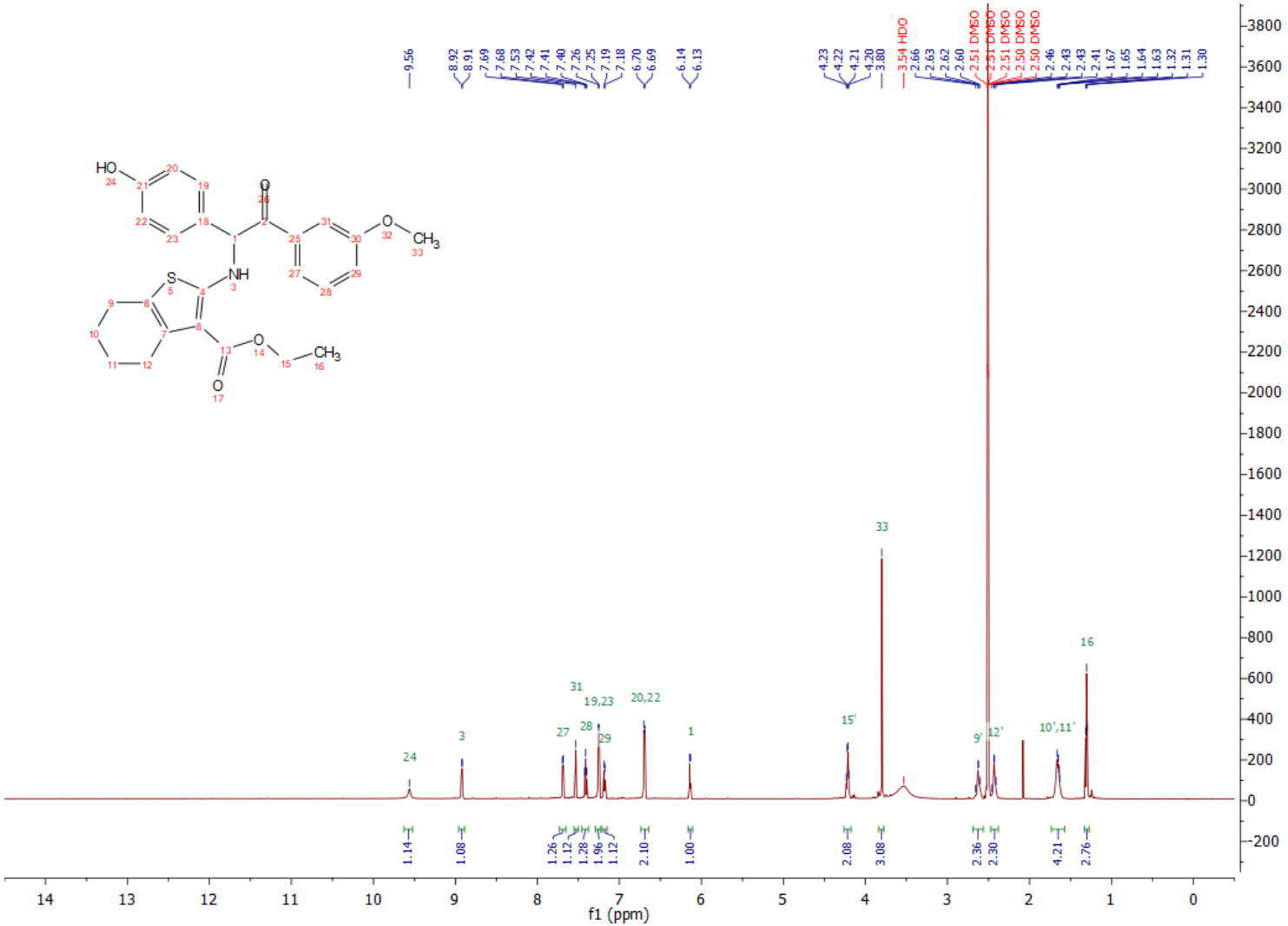
^{1}H-NMR of **6q** (700 MHz, DMSO-d_6)



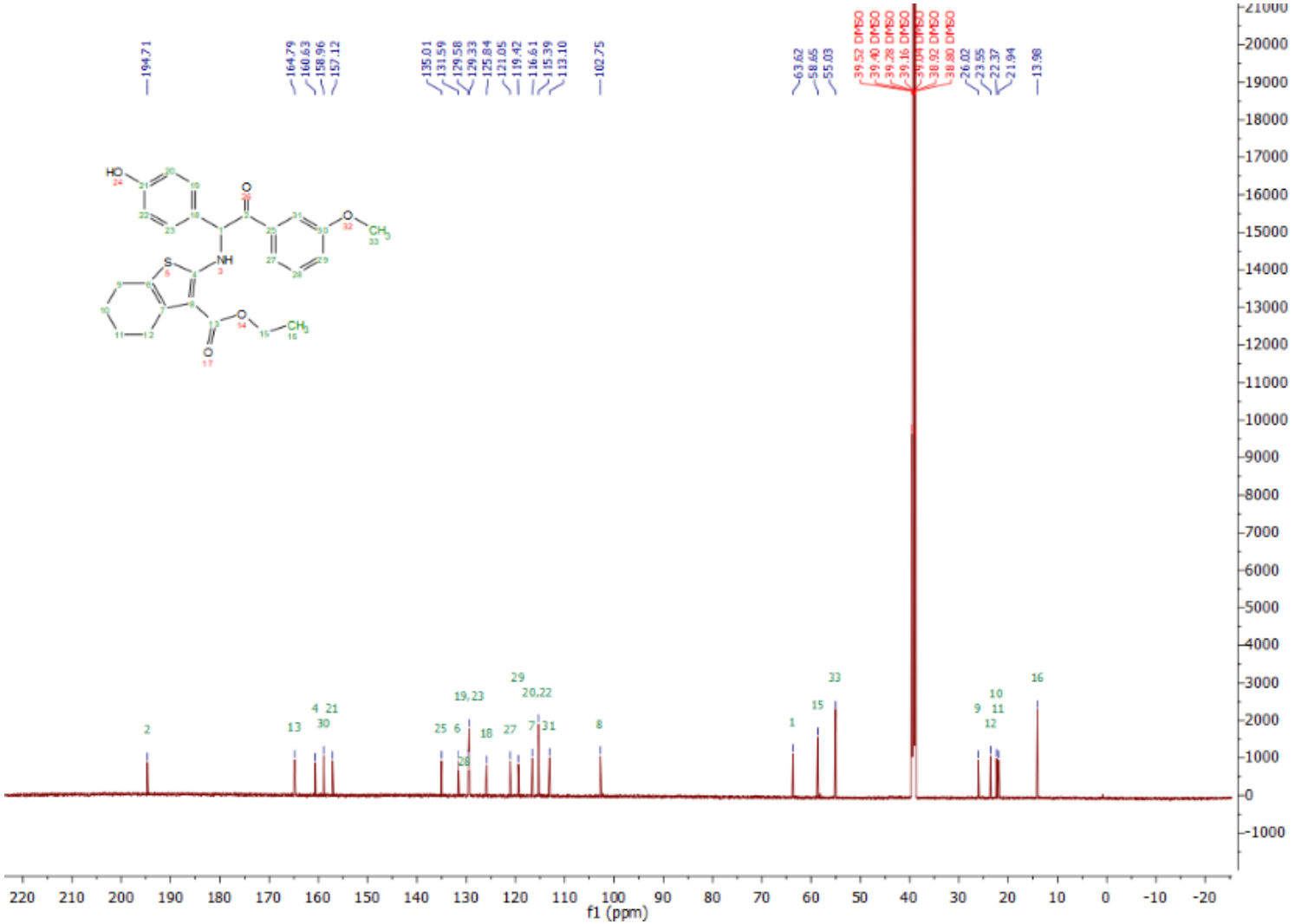
^{13}C-NMR of **6q** (176 MHz, DMSO-d_6)



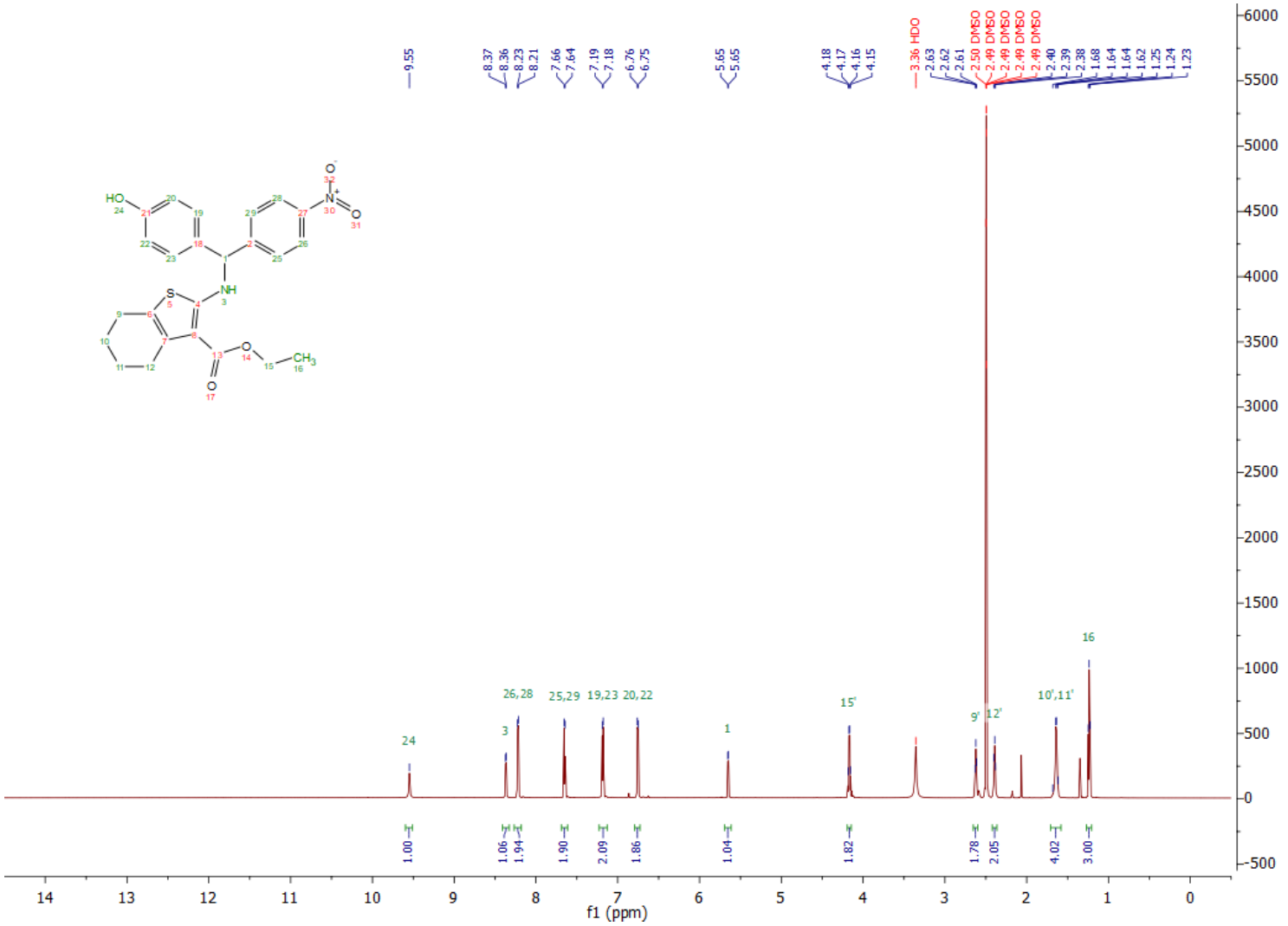
^{1}H-NMR of **6r** (700 MHz, DMSO-d_6)



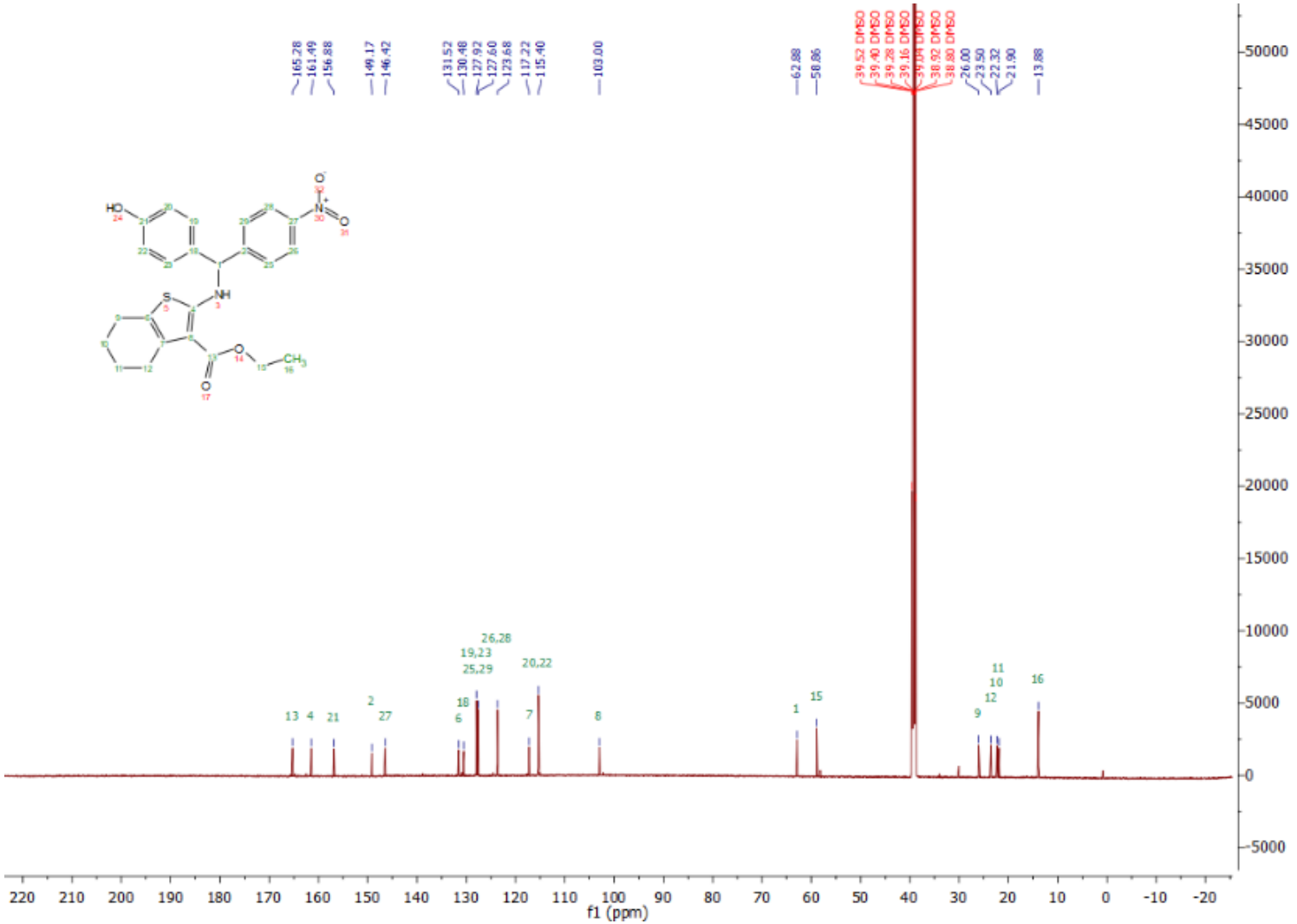
^{13}C-NMR of **6r** (176 MHz, DMSO-d_6)



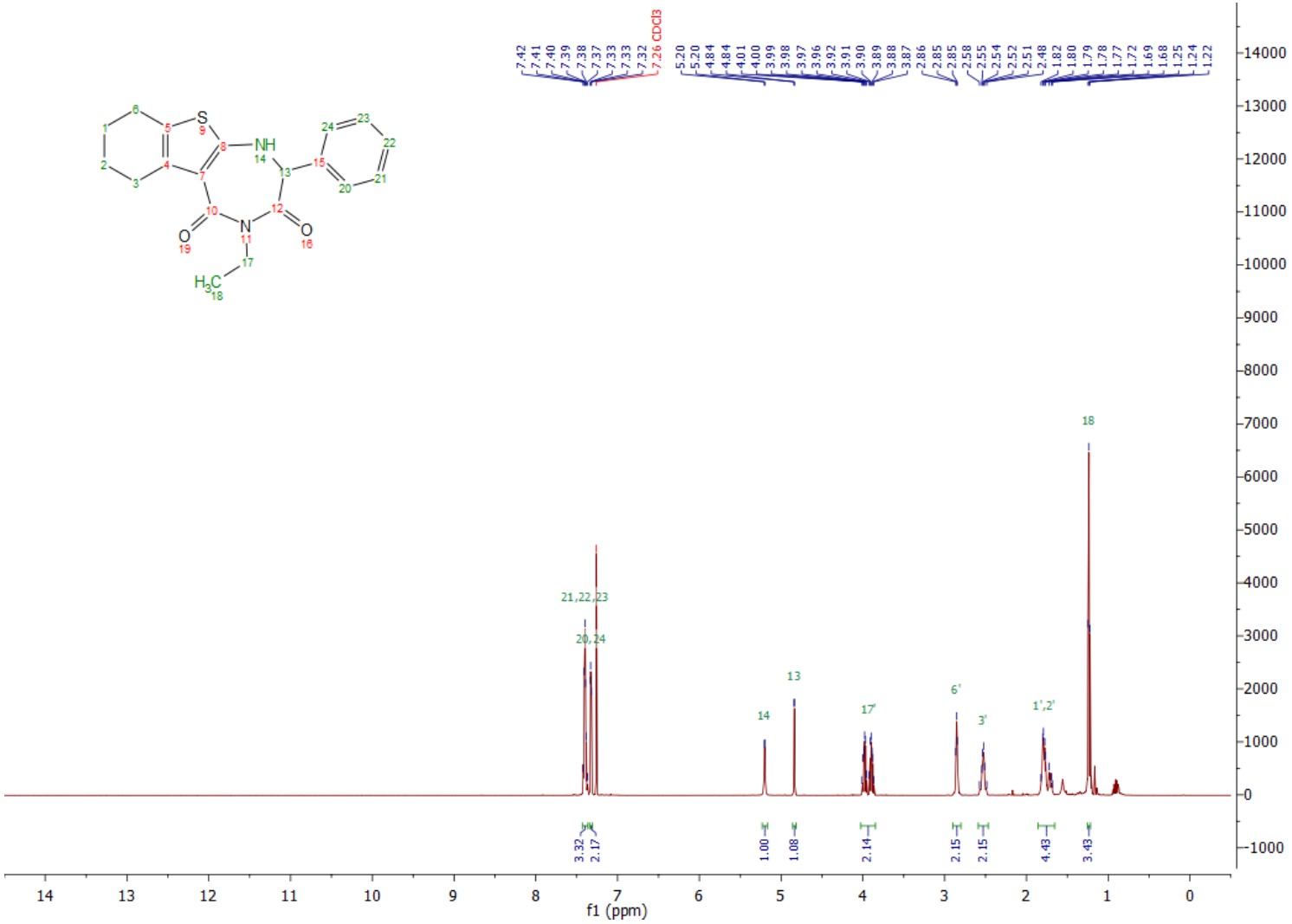
^{1}H-NMR of **6t** (700 MHz, DMSO-d_6)



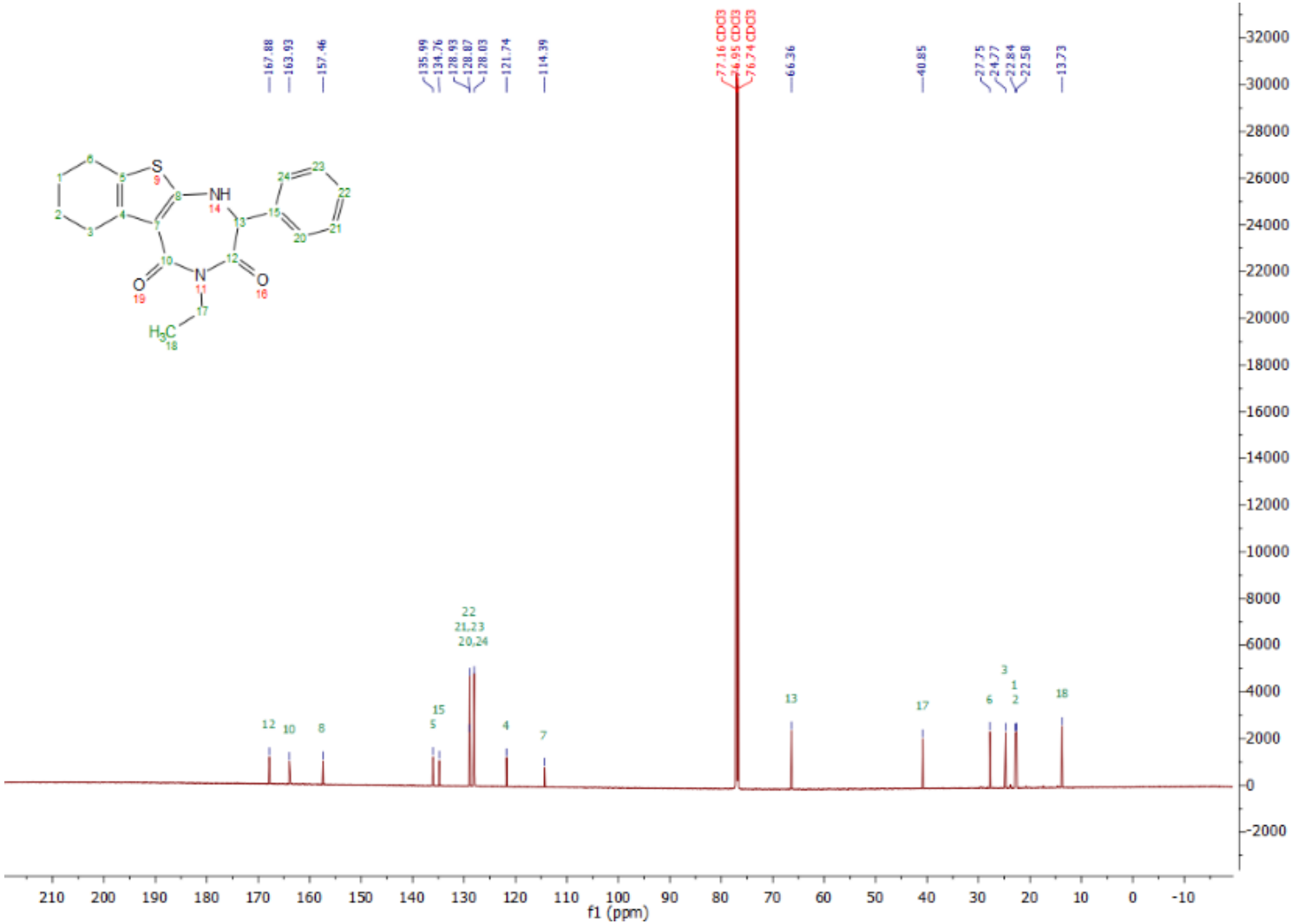
^{13}C-NMR of **6t** (176 MHz, DMSO-d_6)



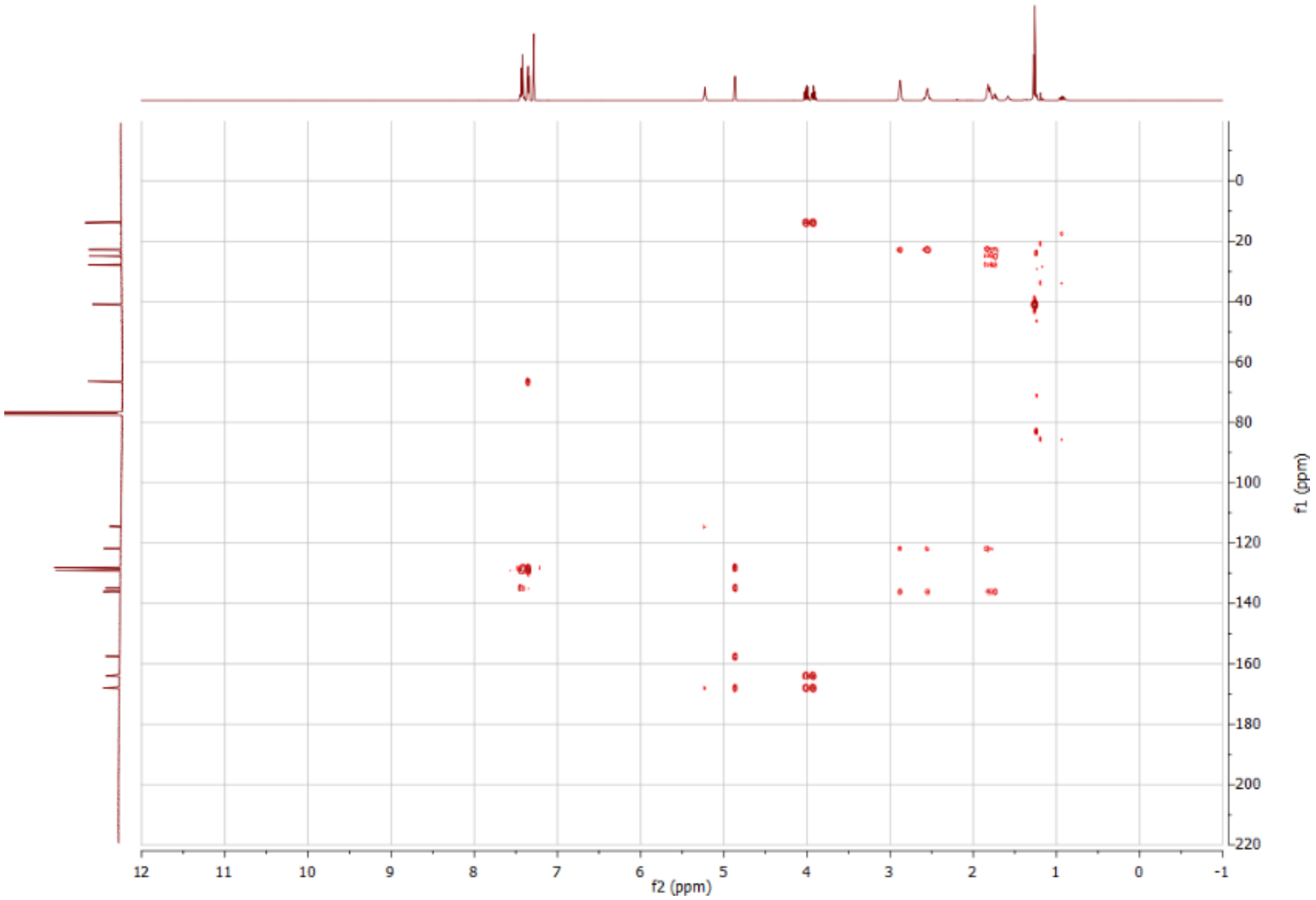
[1]H-NMR of **7a** (600 MHz, Chloroform-*d*)



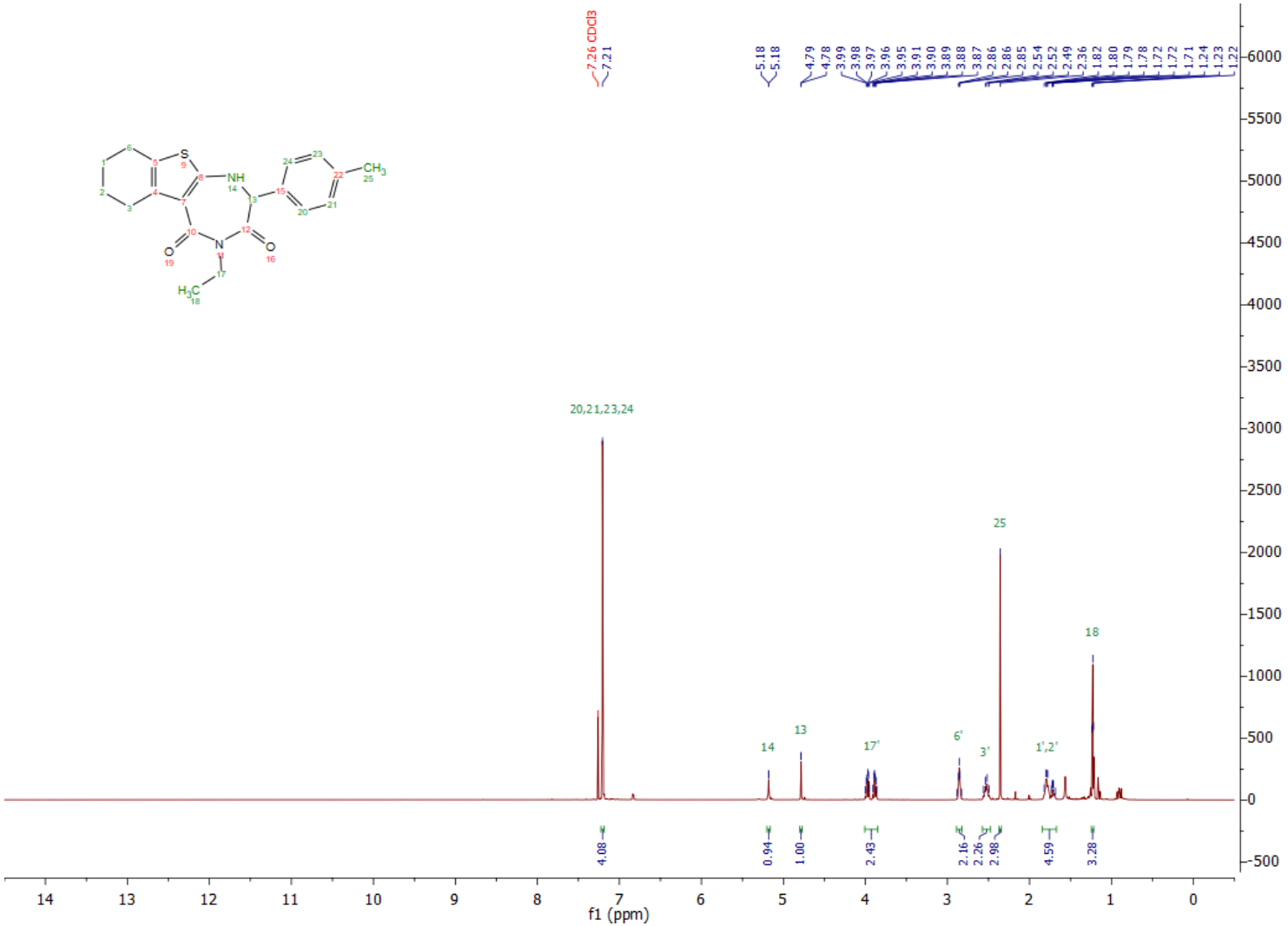
^{13}C-NMR of **7a** (151 MHz, Chloroform-*d*)



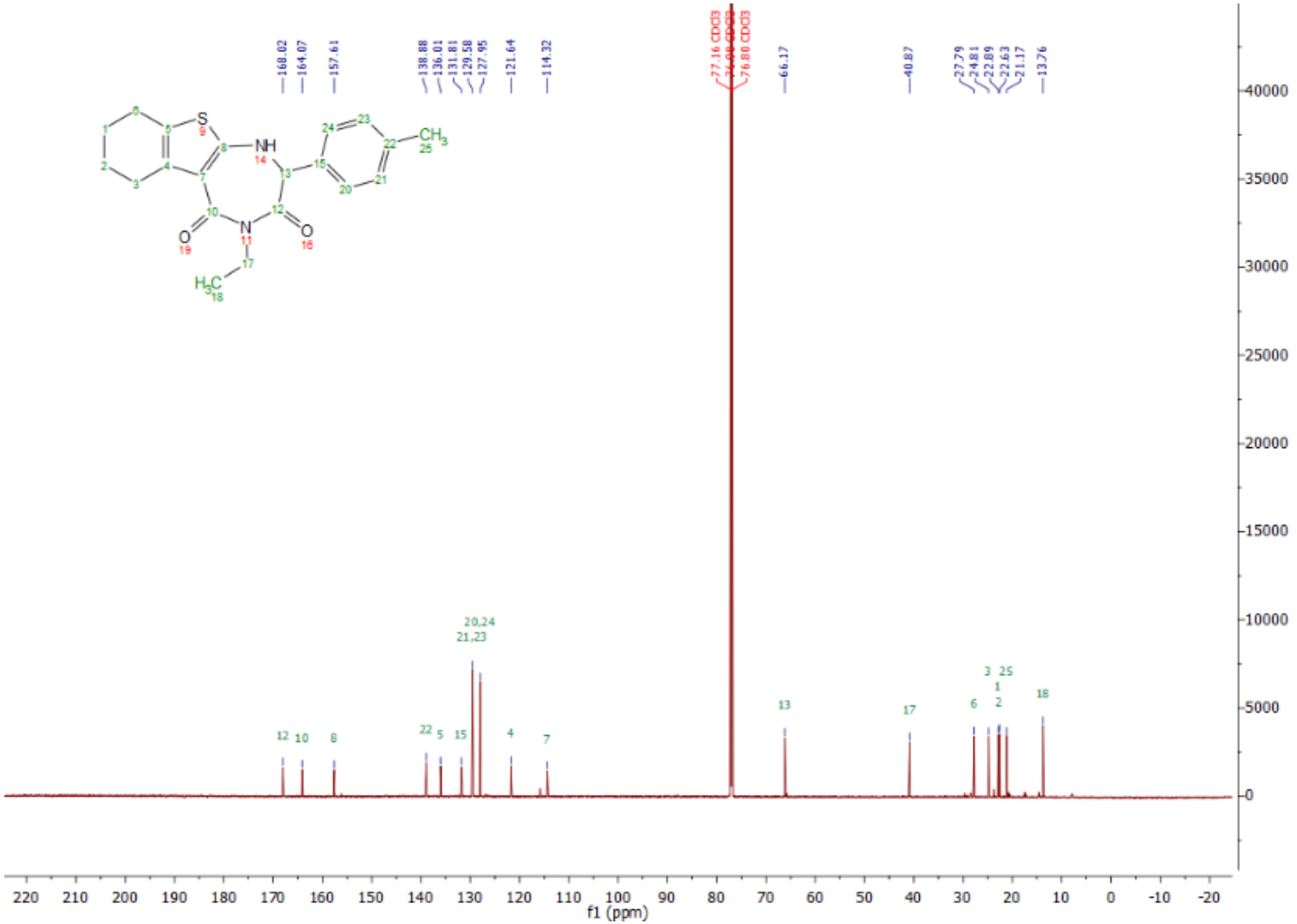
HMBC of **7a** (600 MHz, Chloroform-*d*)



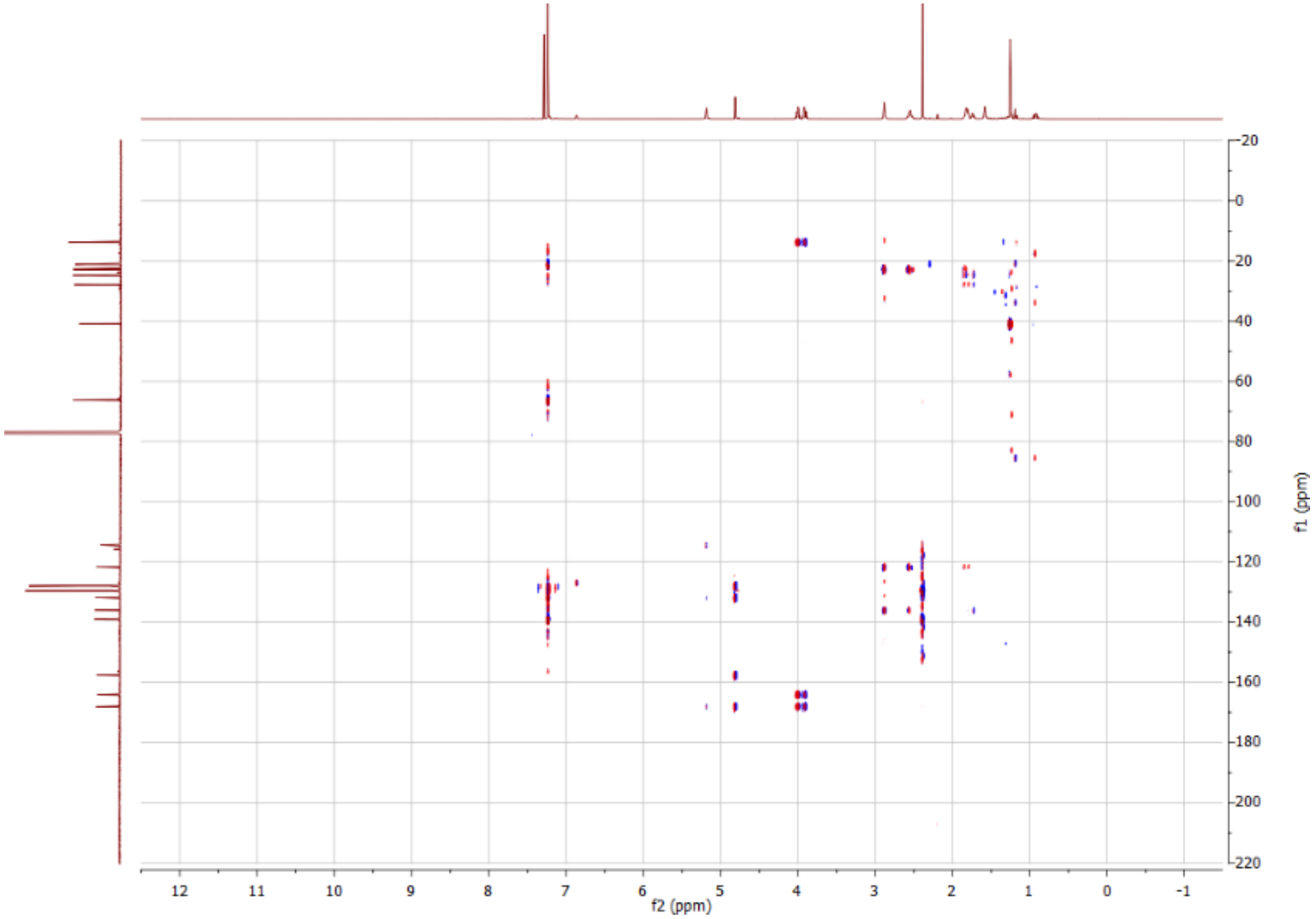
[1]H-NMR of **7b** (700 MHz, Chloroform-*d*)



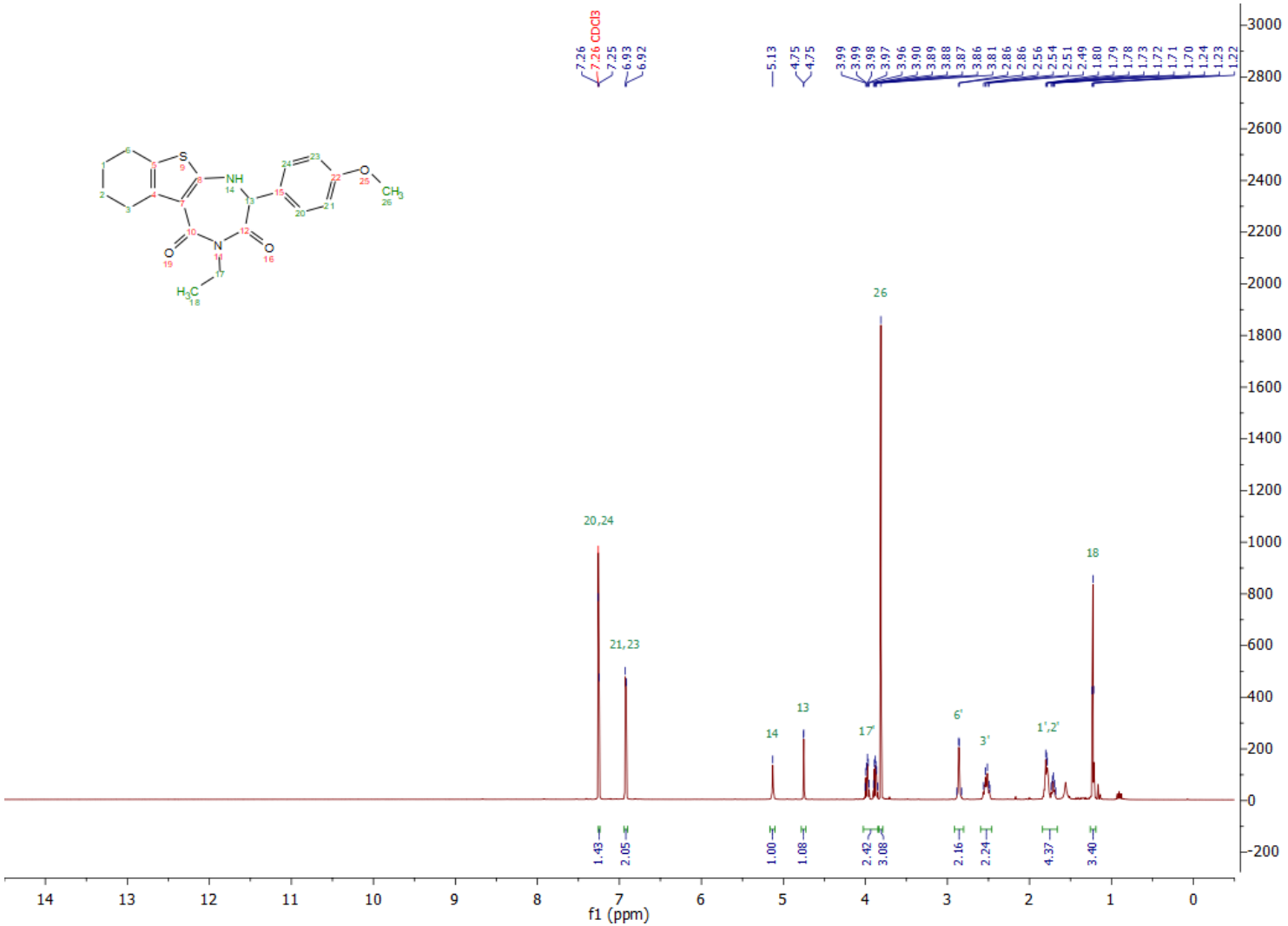
^{13}C-NMR of **7b** (176 MHz, Chloroform-*d*)



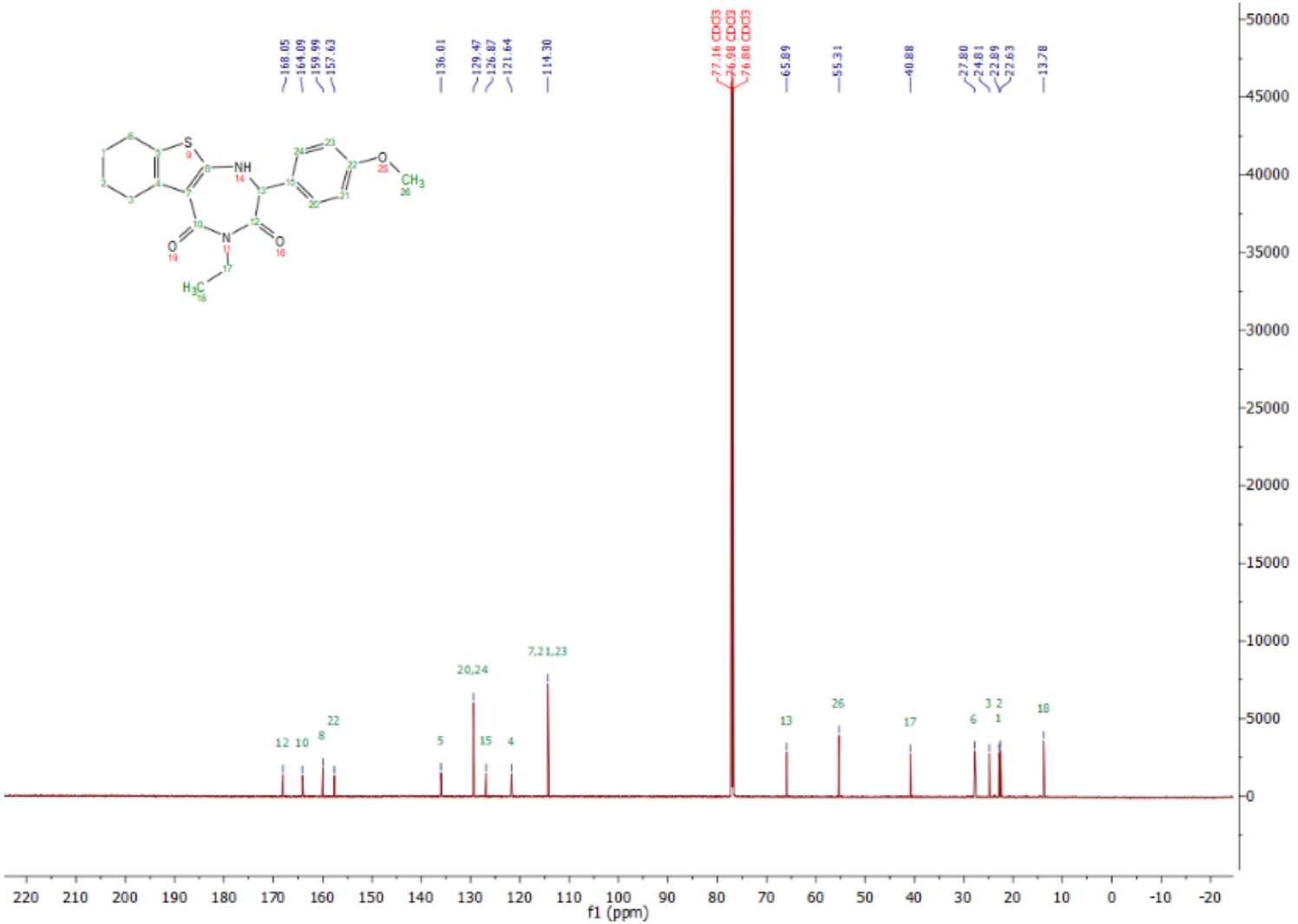
HMBC of **7b** (700 MHz, Chloroform-*d*)



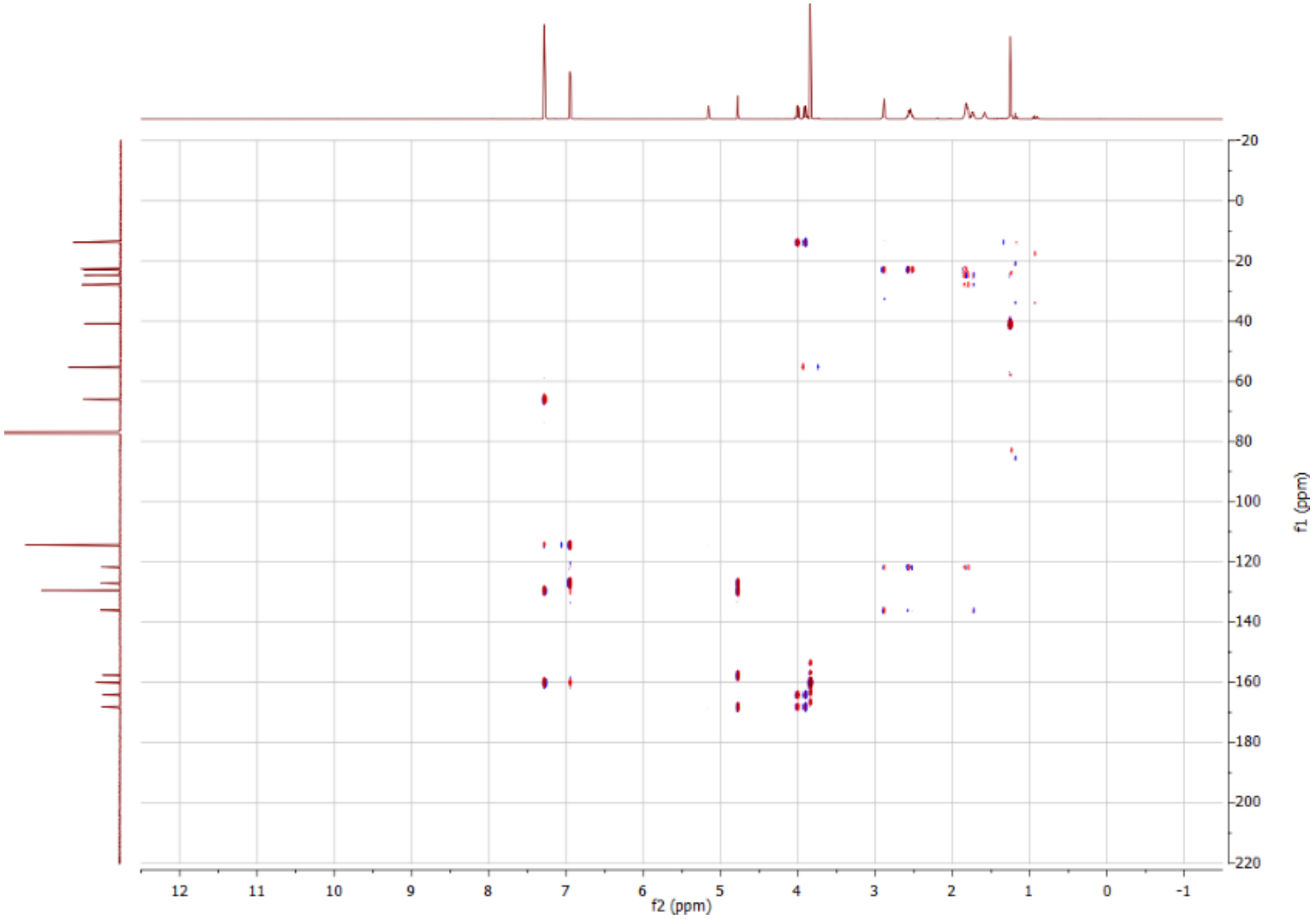
[1]H-NMR of **7c** (700 MHz, Chloroform-*d*)



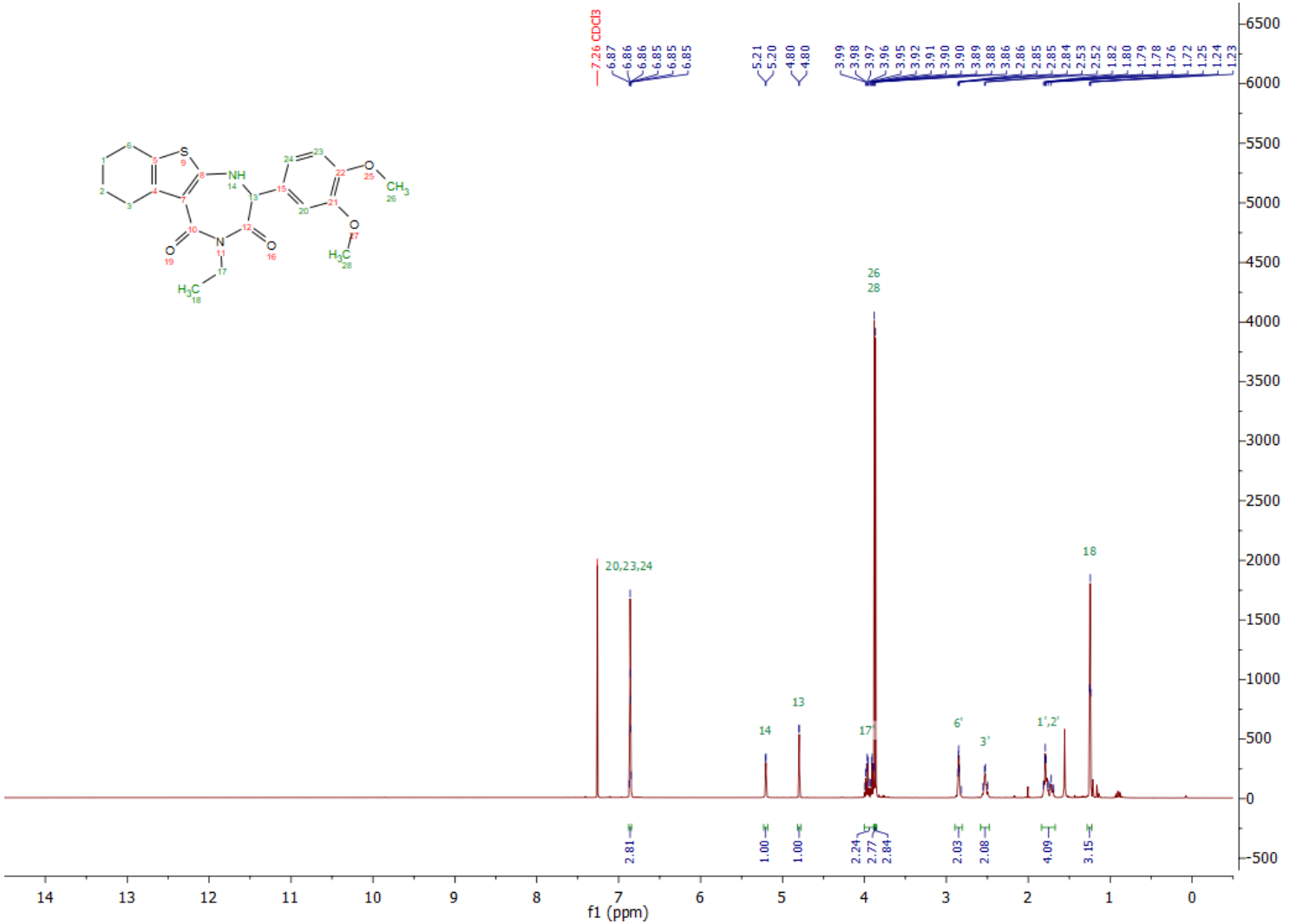
^{13}C-NMR of **7c** (176 MHz, Chloroform-*d*)



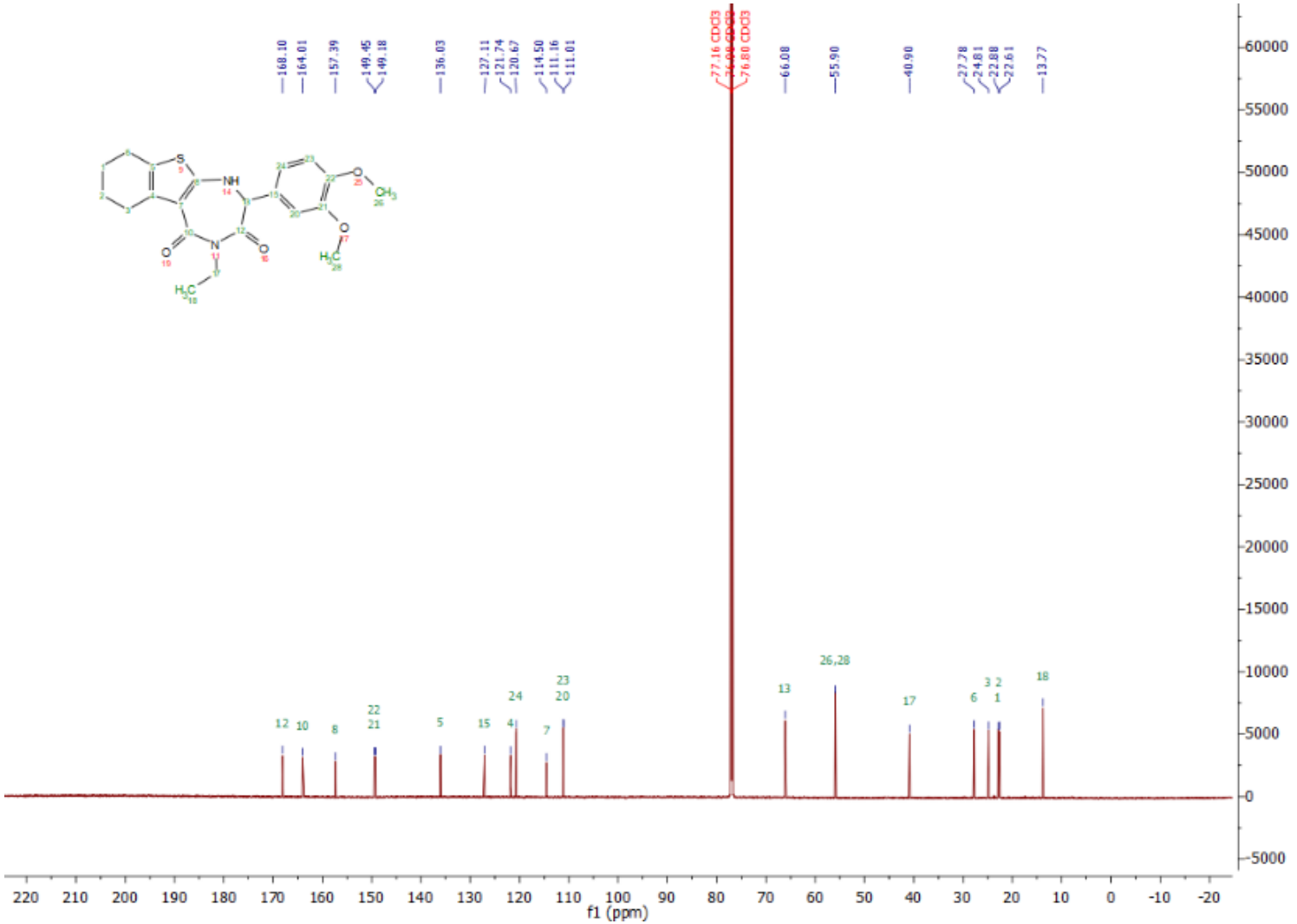
HMBC of **7c** (700 MHz, Chloroform-*d*)



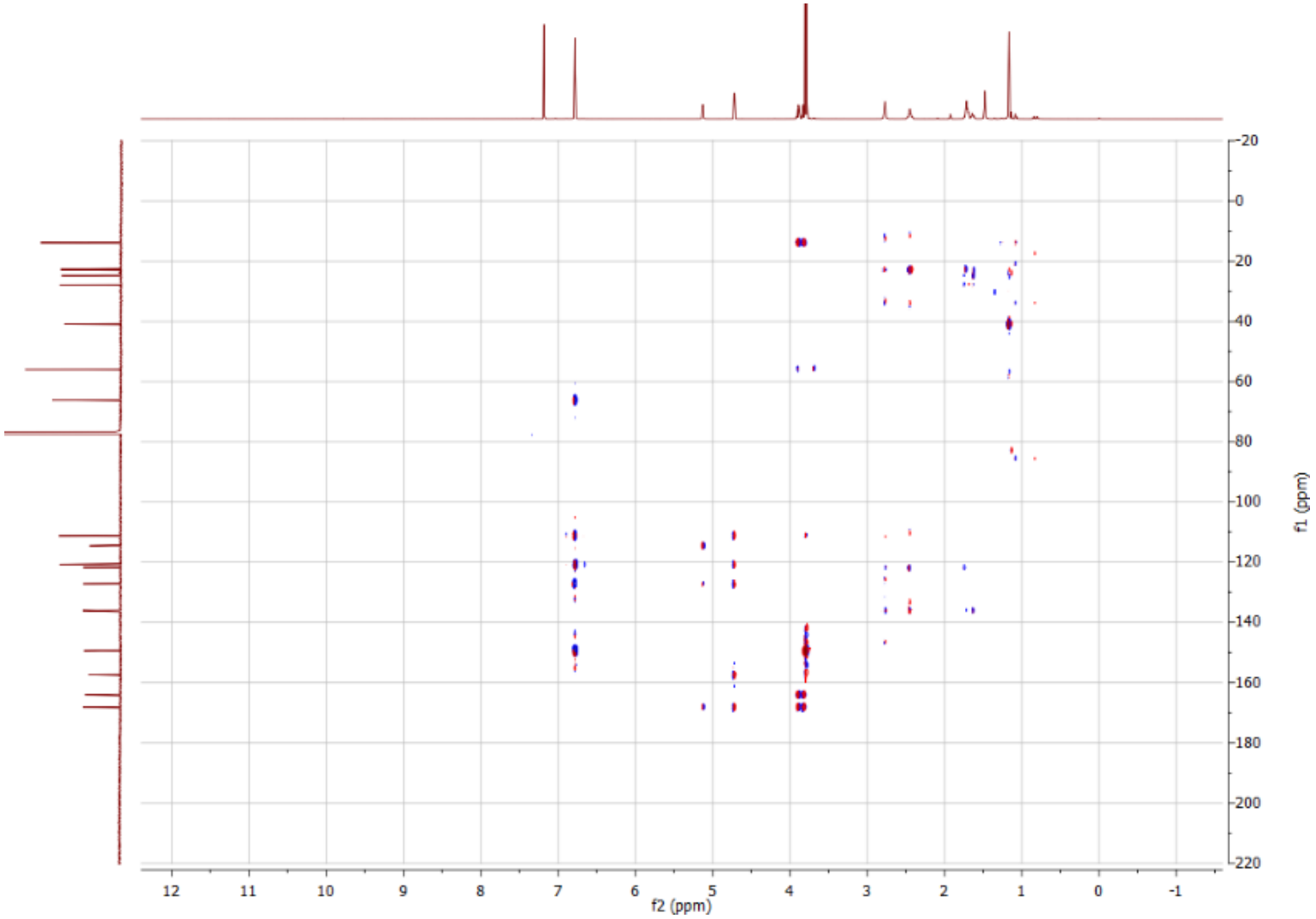
[1]H-NMR of **7d** (700 MHz, Chloroform-*d*)



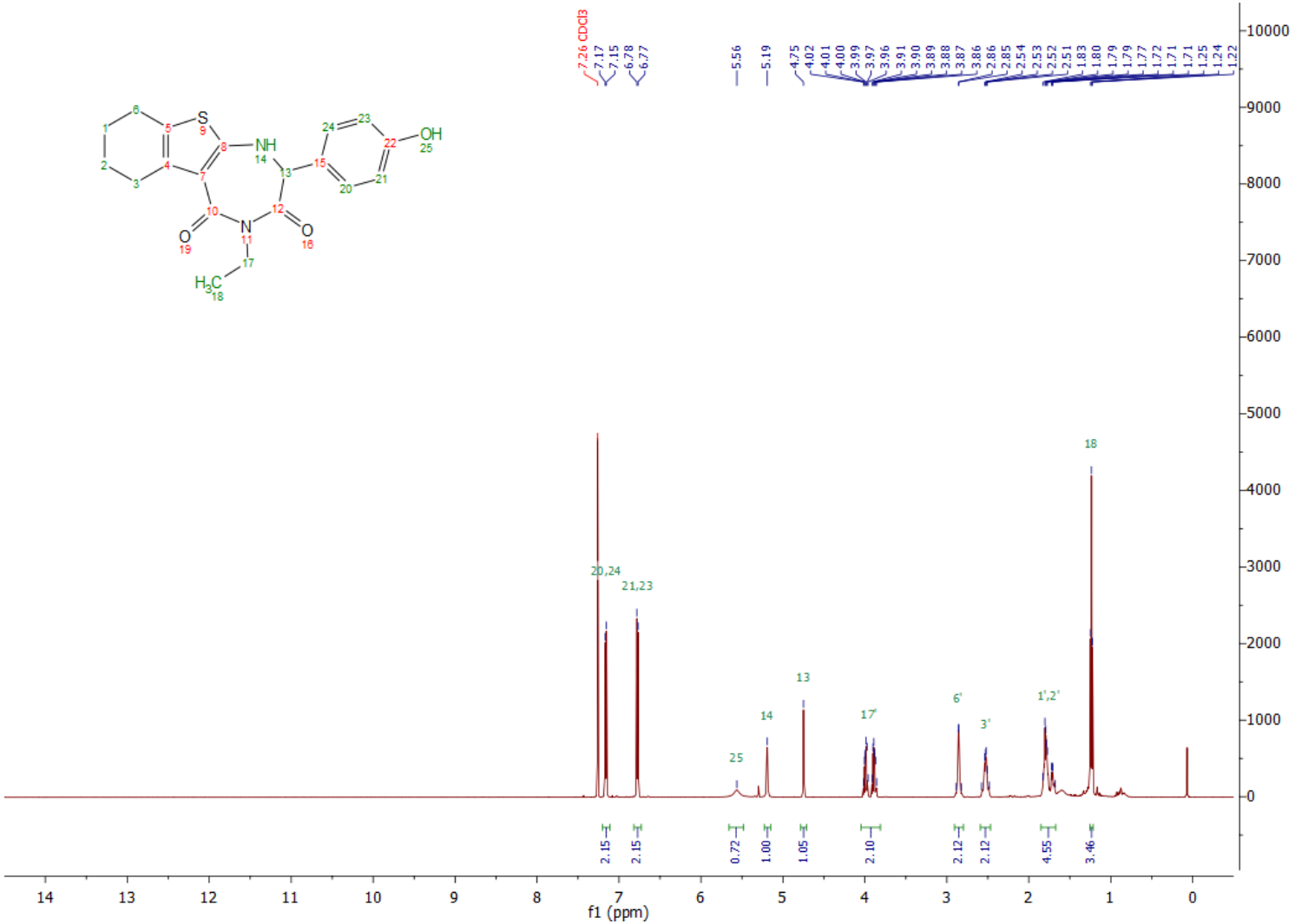
^{13}C-NMR of **7d** (176 MHz, Chloroform-*d*)



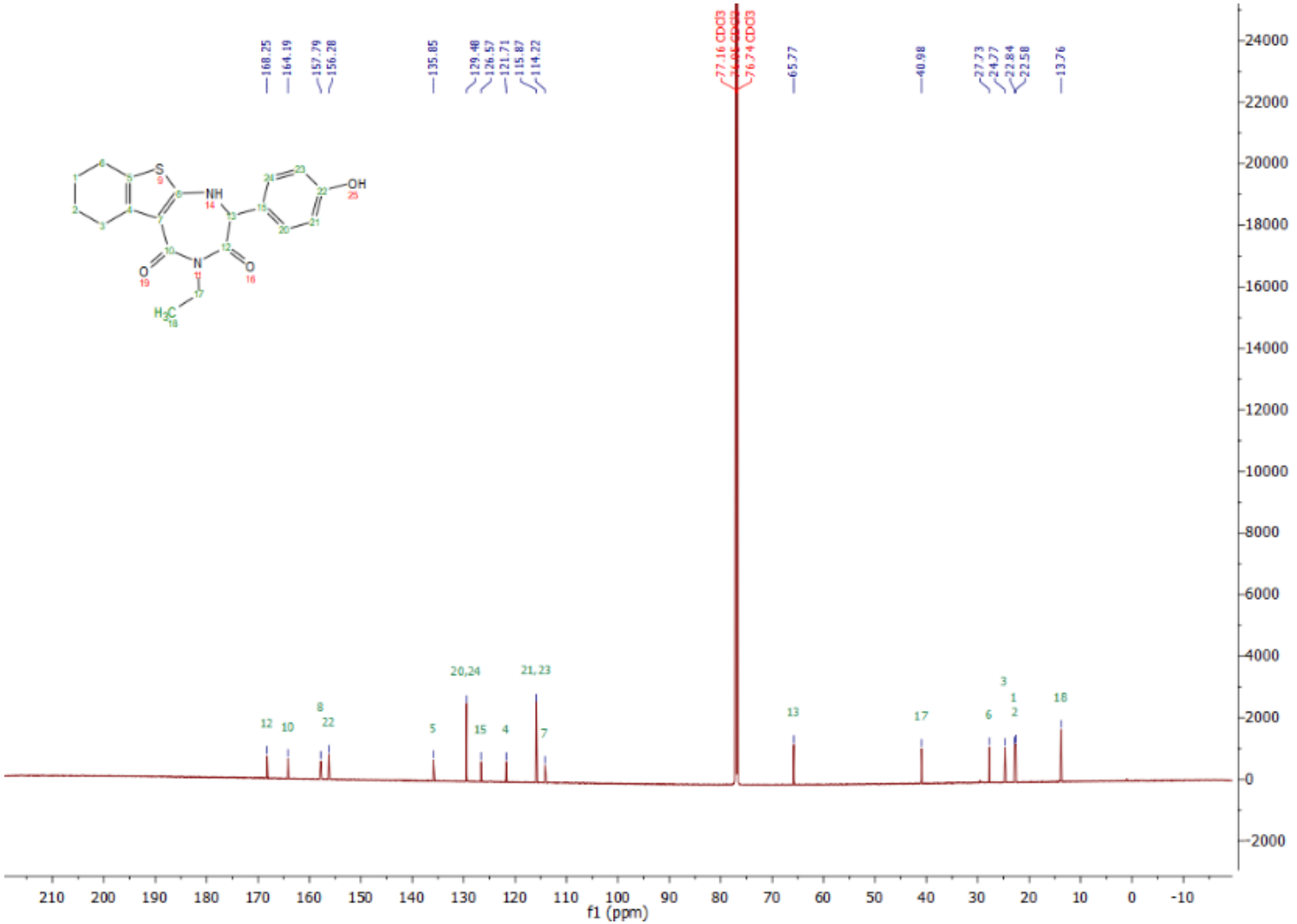
HMBC of **7d** (700 MHz, Chloroform-*d*)



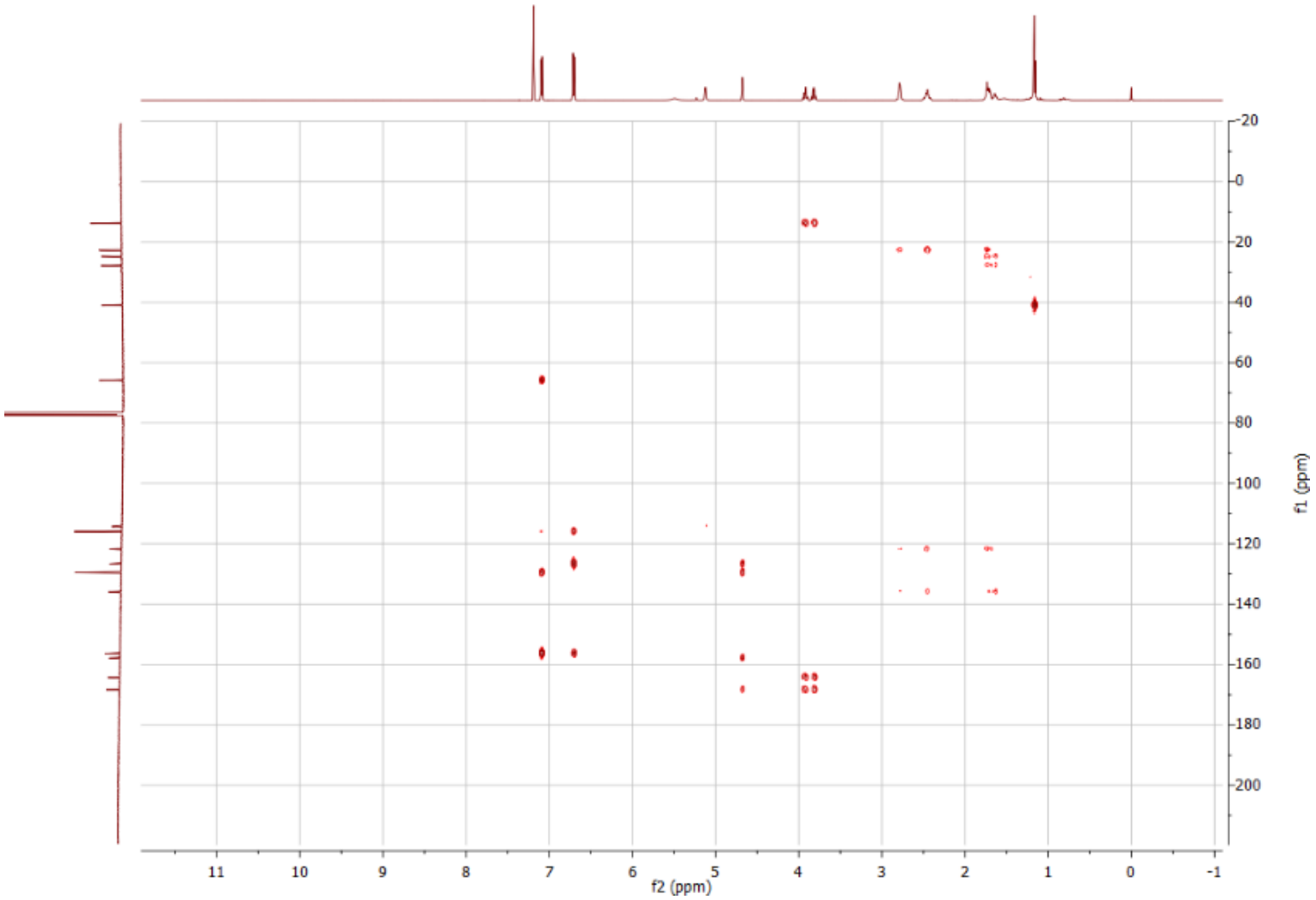
[1]H-NMR of **7e** (600 MHz, Chloroform-*d*)



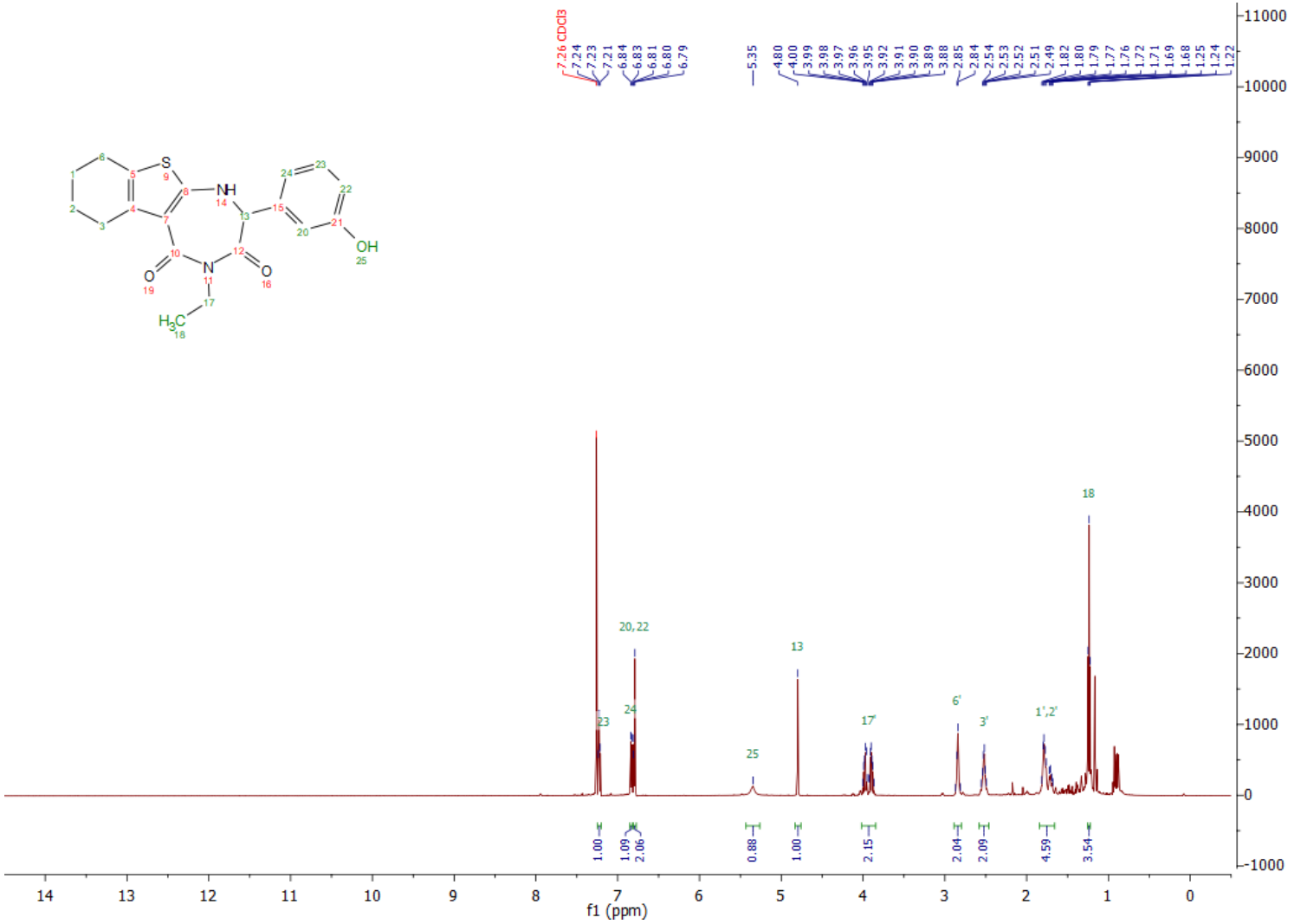
^{13}C-NMR of **7e** (151 MHz, Chloroform-*d*)



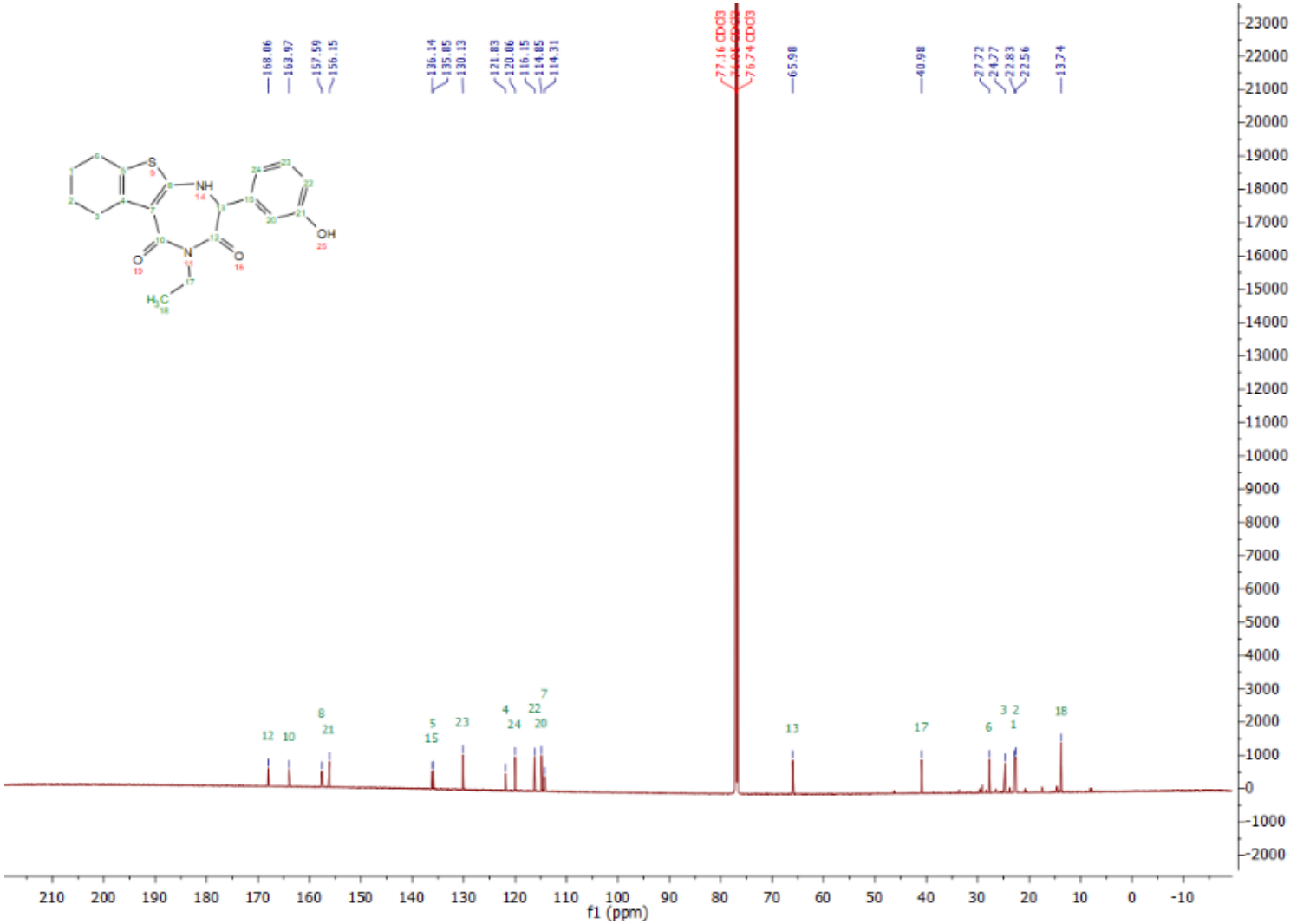
HMBC of **7e** (600 MHz, Chloroform-*d*)



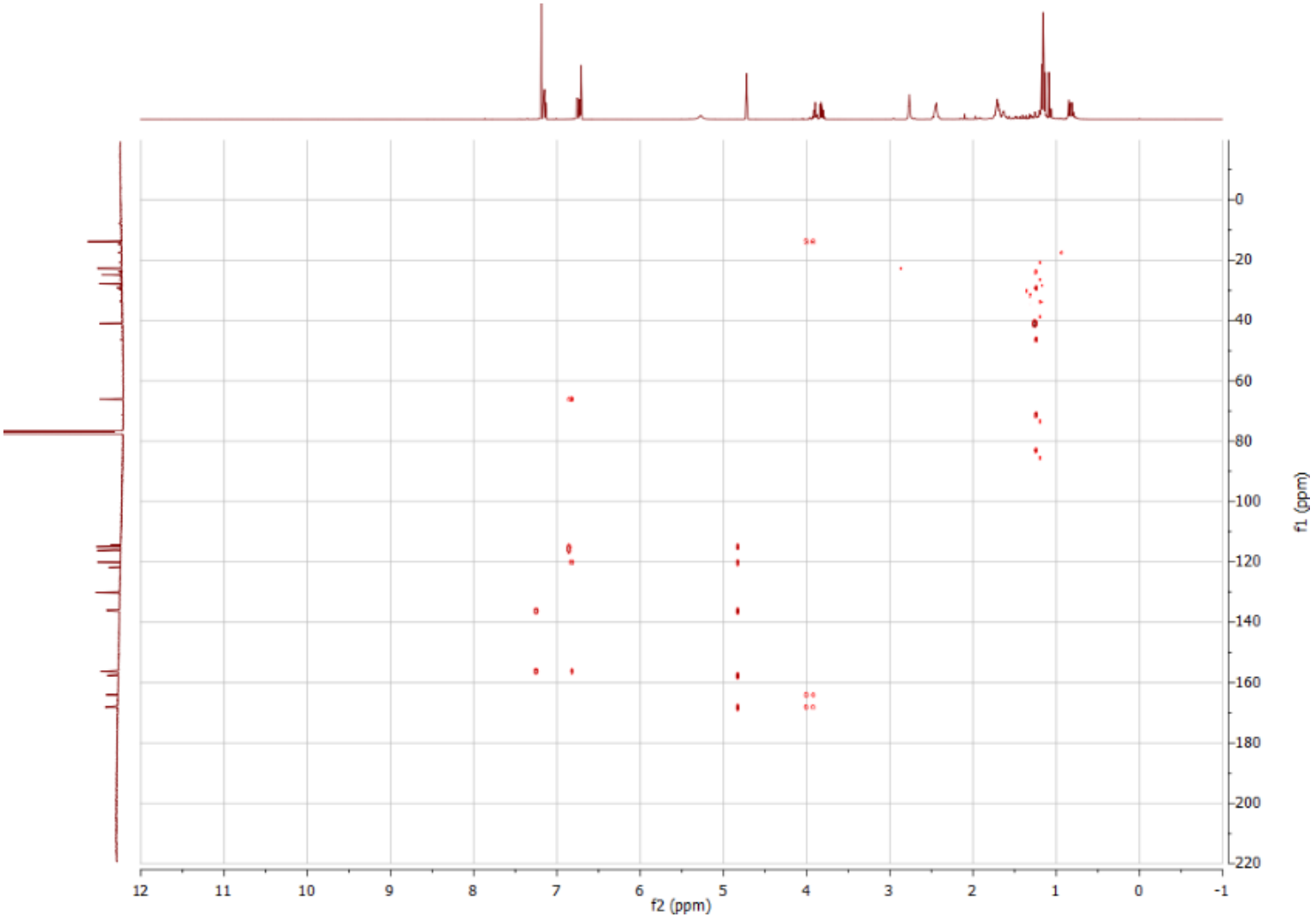
^{1}H-NMR of **7f** (600 MHz, Chloroform-*d*)



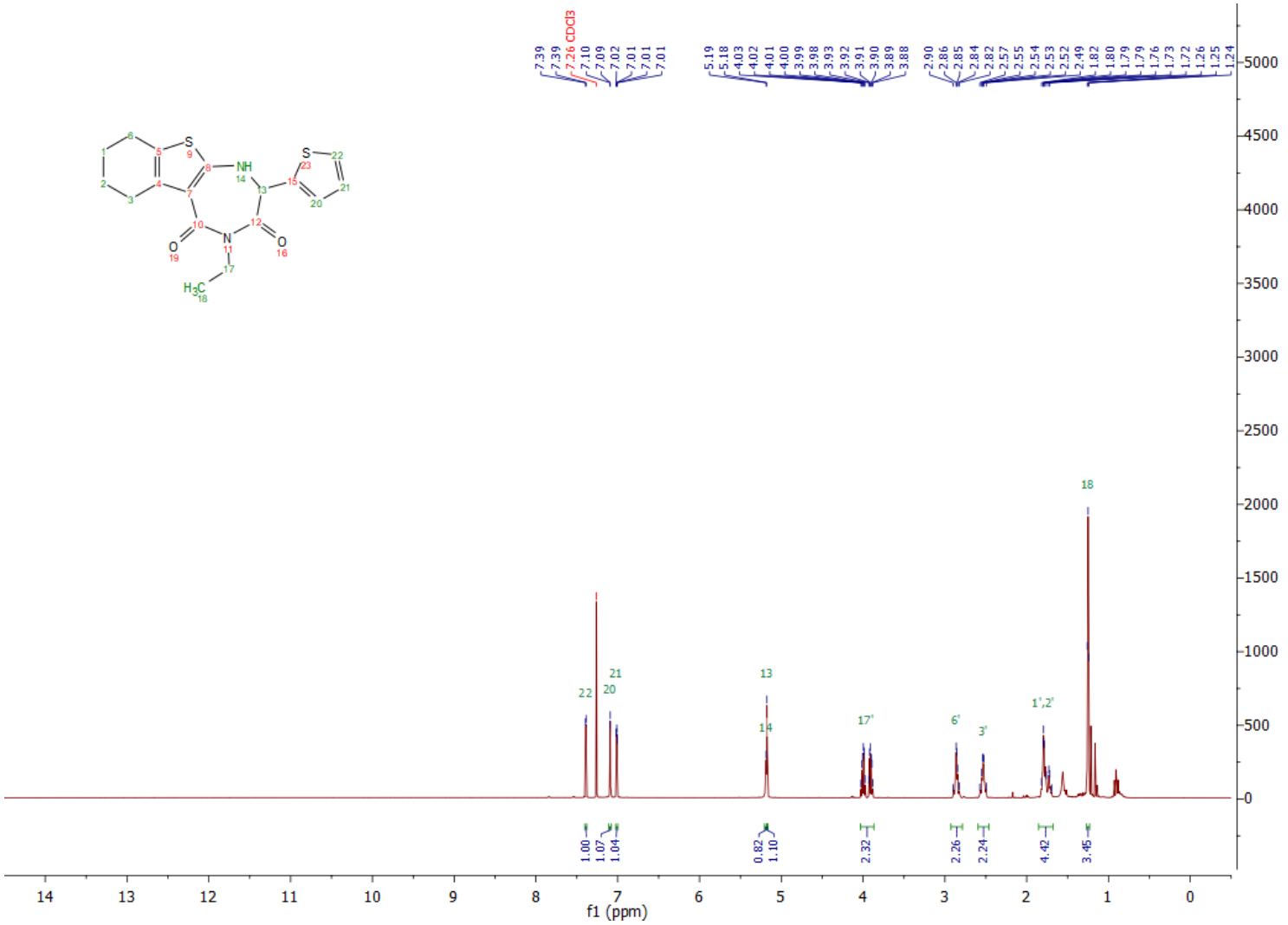
^{13}C-NMR of **7f** (151 MHz, Chloroform-*d*)



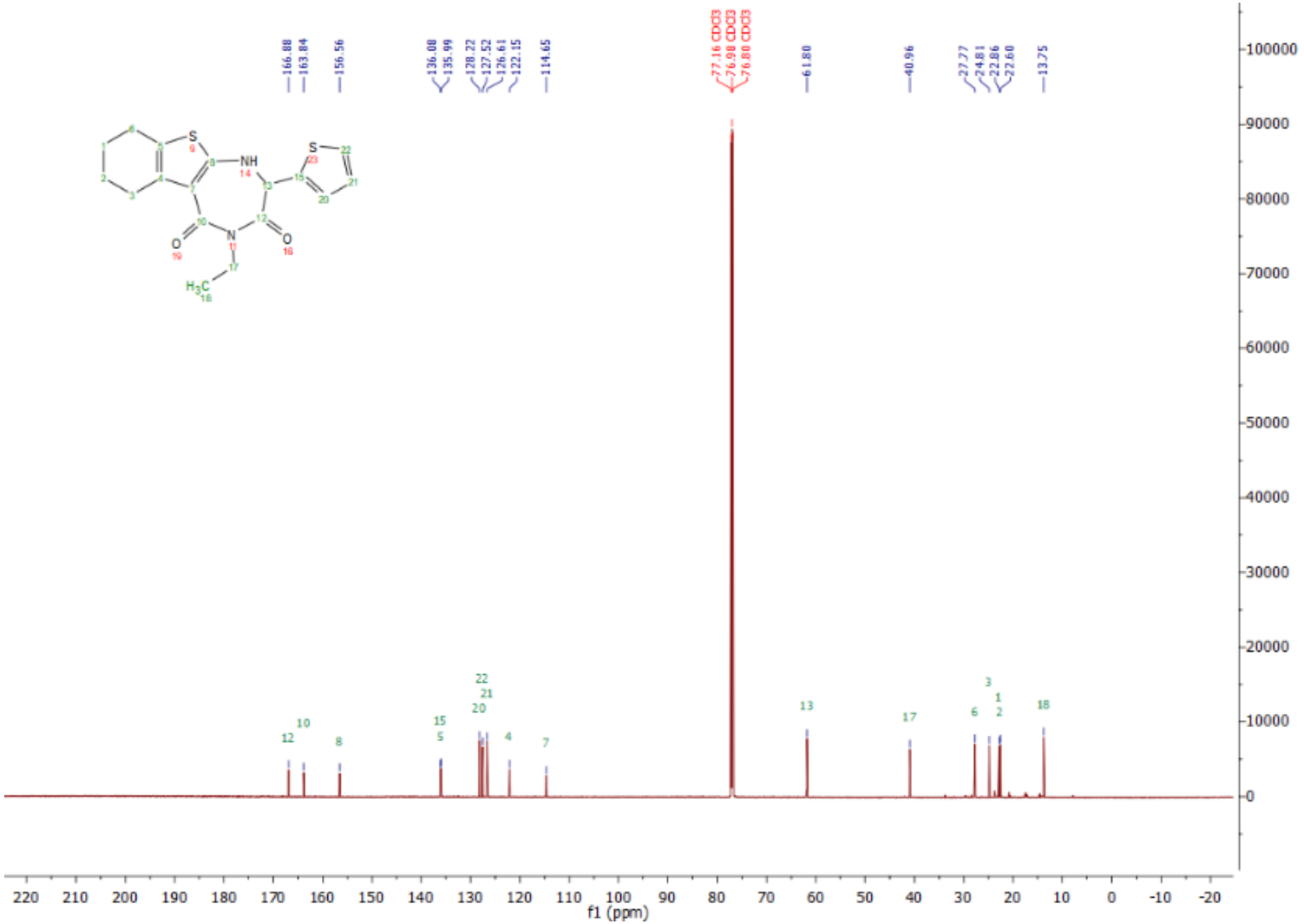
HMBC of **7f** (600 MHz, Chloroform-*d*)



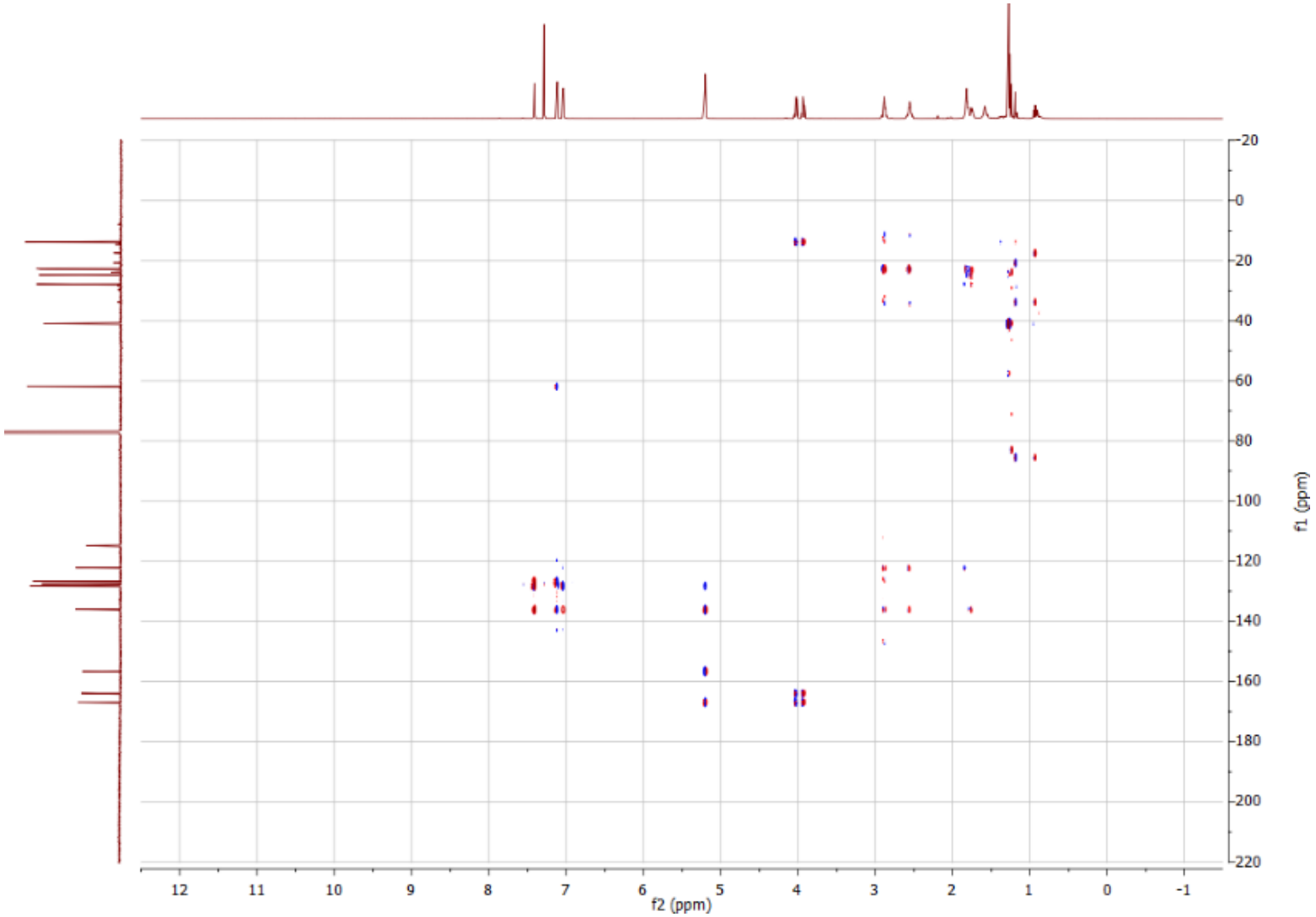
[1]H-NMR of **7g** (700 MHz, Chloroform-*d*)



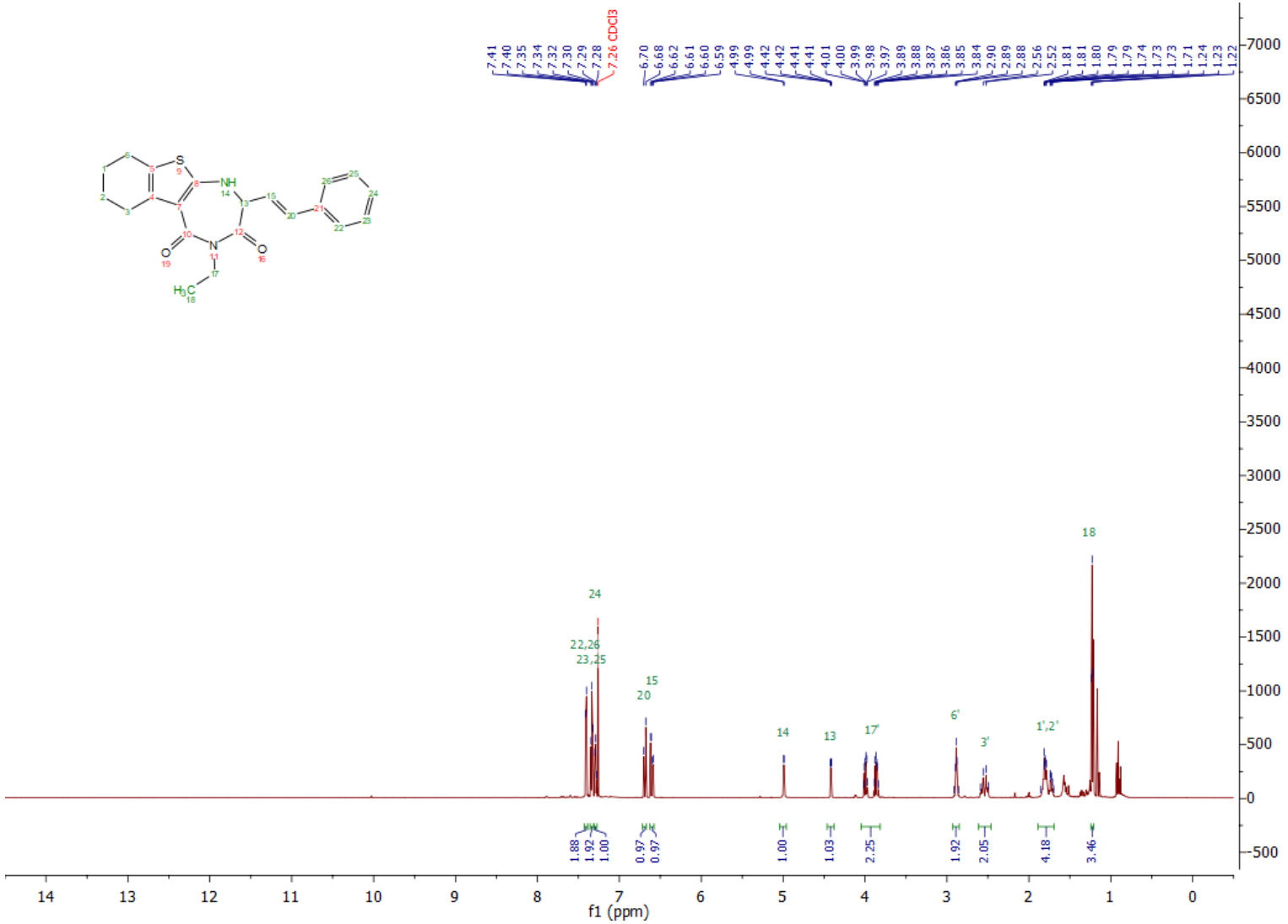
^{13}C-NMR of **7g** (176 MHz, Chloroform-*d*)



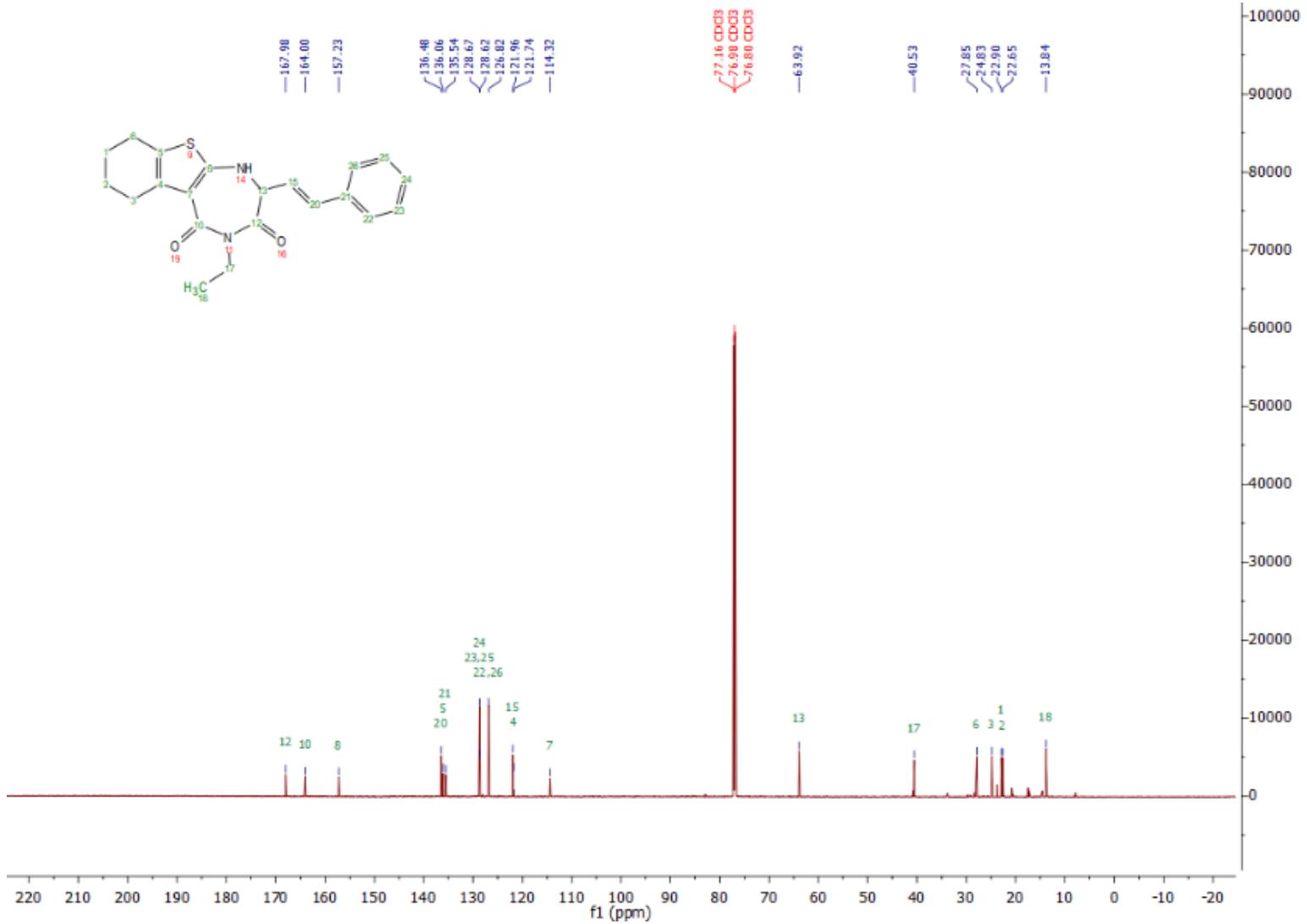
HMBC of **7g** (700 MHz, Chloroform-*d*)



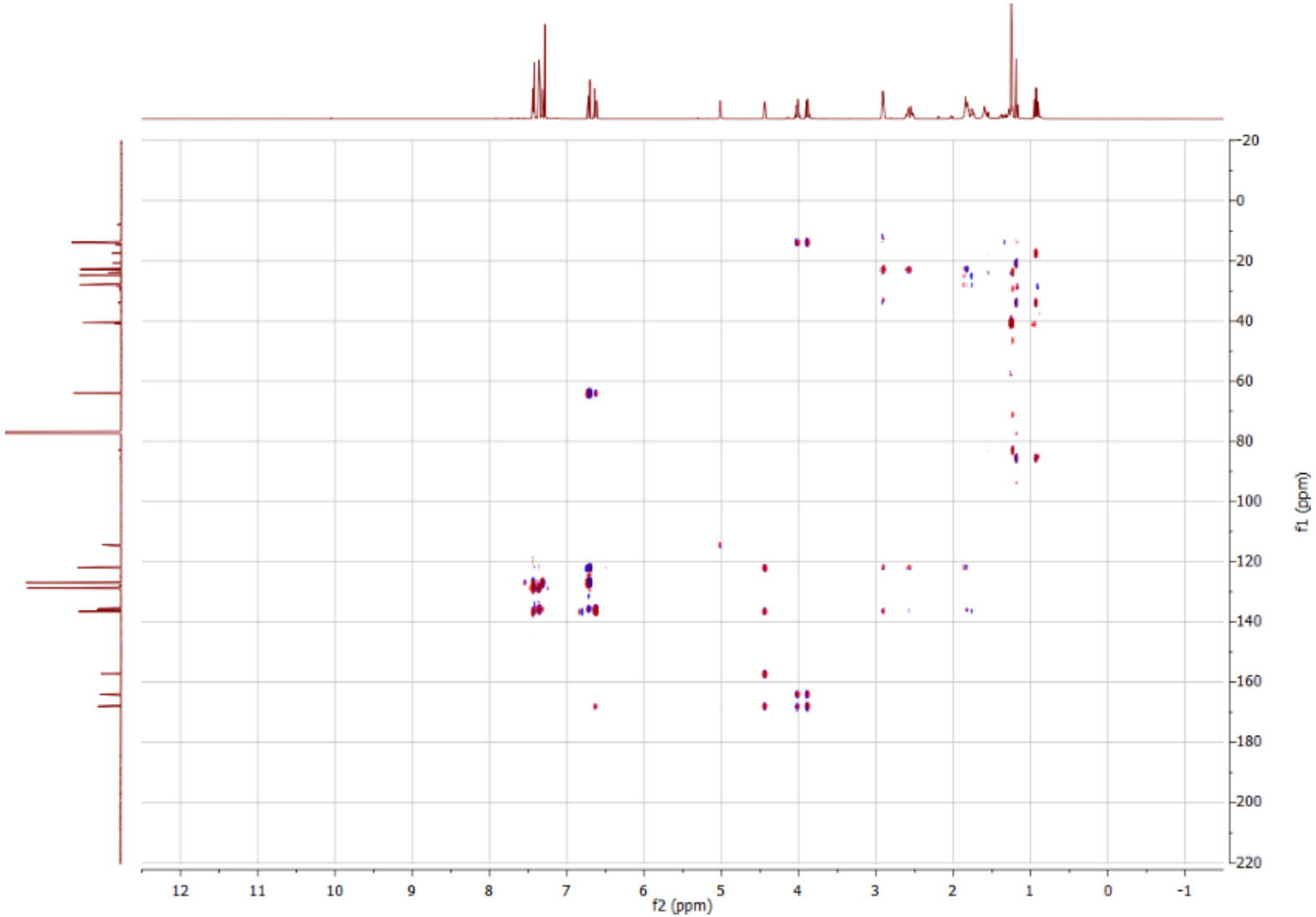
^{1}H-NMR of **7h** (700 MHz, Chloroform-*d*)



^{13}C-NMR of **7h** (176 MHz, Chloroform-*d*)



HMBC of **7h** (700 MHz, Chloroform-*d*)



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