Supporting Information

PROTACs bearing piperazine-containing linkers: which effect on their protonation state?

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(1) Equal contribution

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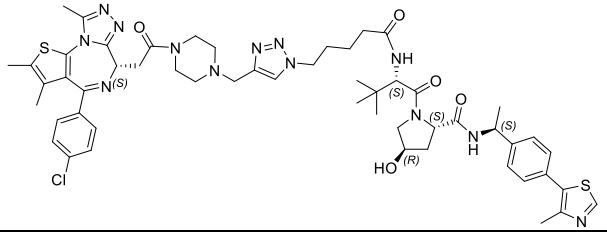
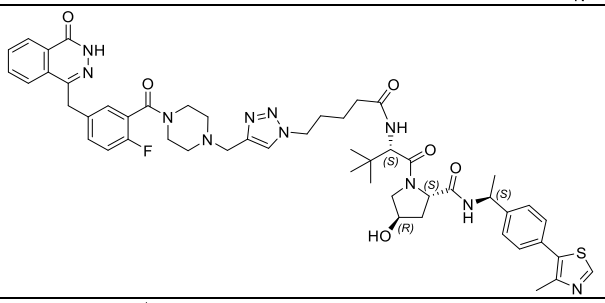
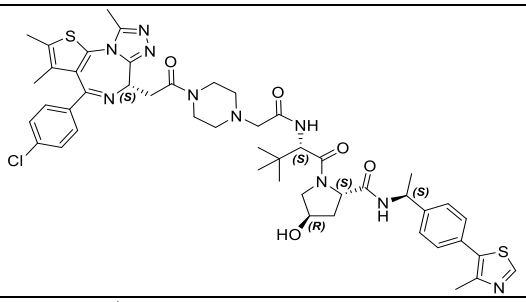
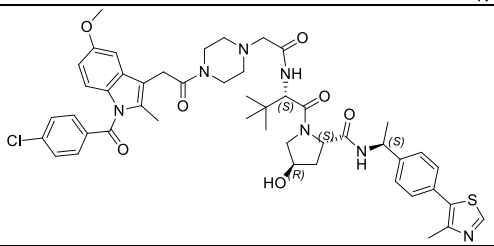
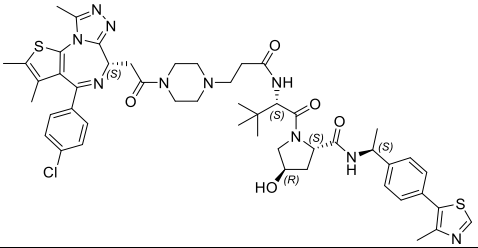
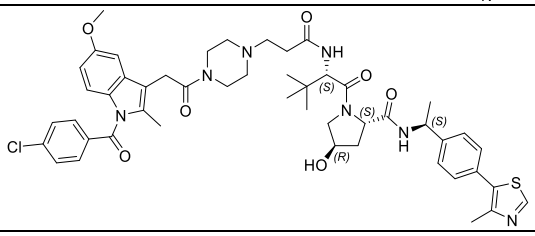
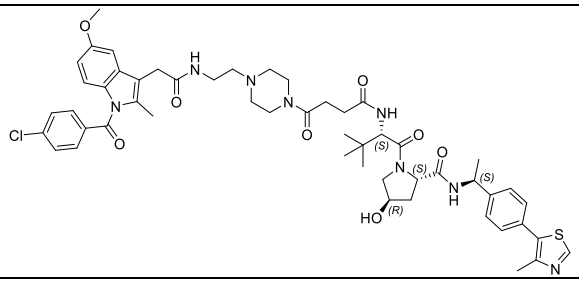
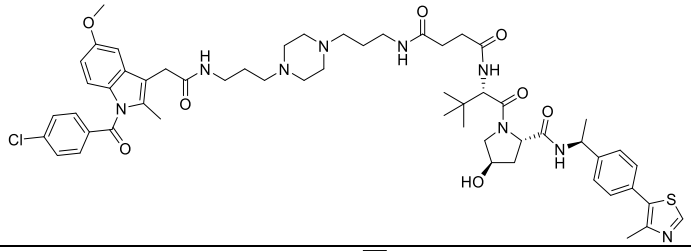
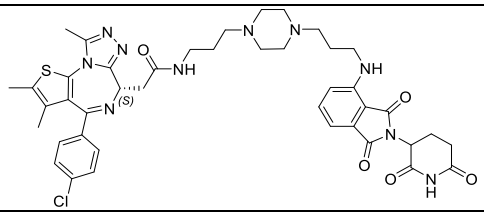
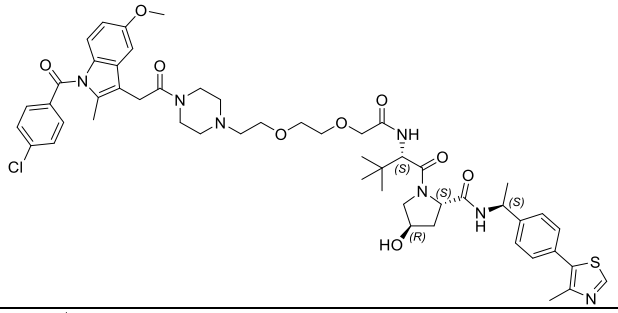
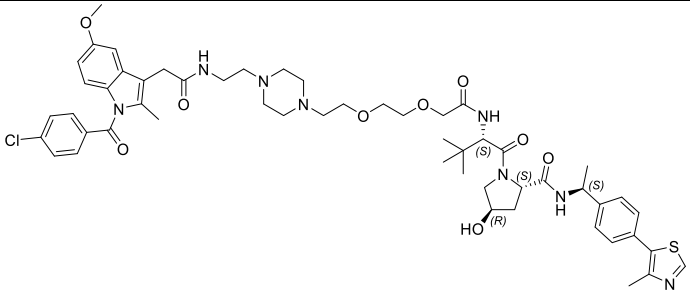
Contents

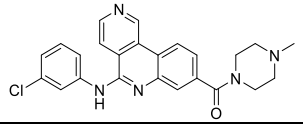
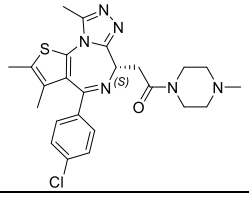
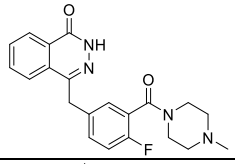
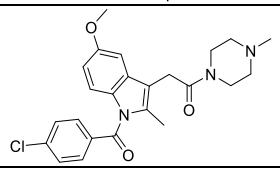
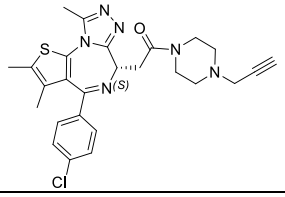
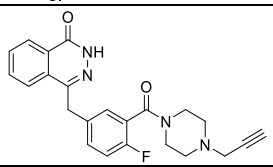
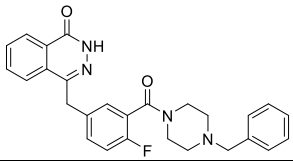
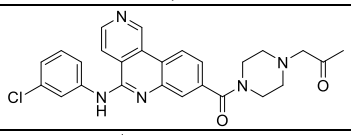
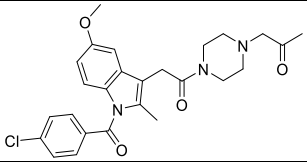
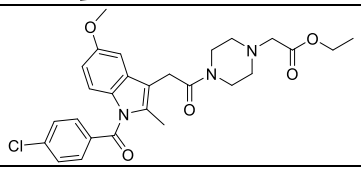
Supplementary Table S1

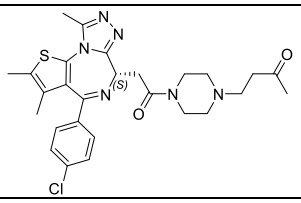
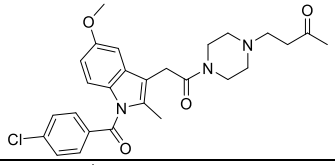
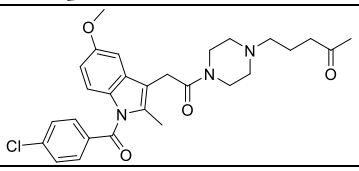
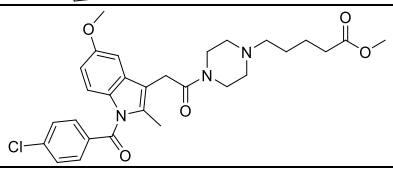
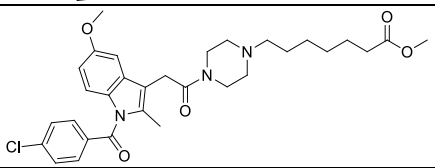
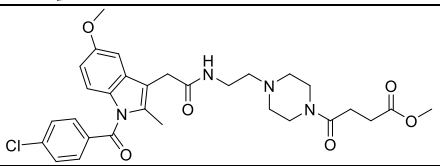
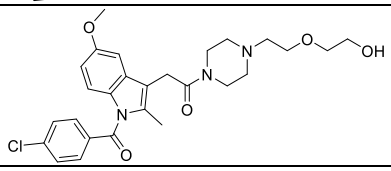
Compound	Structure	Predicted pKa[a]
PROTAC-1		4.81
PROTAC-2		2.65 4.55
PROTAC-3		2.64 5.09
PROTAC-4		4.99
PROTAC-5		2.53 7.14
PROTAC-6		2.65 7.18

PROTAC-7		2.65 6.24
PROTAC-8		2.23 7.87
PROTAC-9		2.33 8.02
PROTAC-10		2.65 6.73
PROTAC-11		2.68 7.47

[a] Ionization constant predicted using Marvin plugins *[Calculator Plugins were used for structure property prediction and calculation, Marvin v20.11, 2020, ChemAxon (http://www.chemaxon.com)]*

Supplementary Table S1

Compound	Structure	Predicted pKa [a]
1		1.57 6.85
2		7.06
3		6.70
4		7.05
5		6.25
6		5.89
7		6.71
8		1.57 5.22
9		5.40
10		4.79

11		6.70
12		6.69
13		6.80
14		7.37
15		7.67
16		6.21
17		6.73

[a] Ionization constant predicted using Marvin plugins *[Calculator Plugins were used for structure property prediction and calculation, Marvin v20.11, 2020, ChemAxon (http://www.chemaxon.com)]*

Supplementary Synthetic Chemistry Methods

General

Unless otherwise noted, starting materials, reagents, and solvents were purchased from commercial suppliers and were used as received without further purification.

Among the four POI ligands, compounds **silmitasertib** and **indomethacin** were purchased by Fluorochem, **JQ1 carboxylic acid** (**JQ1 c.a.**) derivative was purchased by Ambeed, while intermediate **18** was prepared as reported in the literature.[1] Regarding precursors and PROTACs tested in this work, **PROTAC-2**, **PROTAC-5**, **PROTAC-7**, and **PROTAC-9** were synthesized as already reported in the literature[2], while for compound **3**[1] a slightly different synthetic procedure than those already present in the literature was applied and thus herein described. Concerning intermediates required for the preparation of tested compounds, compounds **S38**[3], **S39**[4], and **S40**[5] were synthesized as already reported in the literature. For compounds **S25**, **S27**, **S35**, **S36**, and **S37** different synthetic procedures than those already reported in the literature were applied and thus herein described.

Reactions were routinely monitored by thin-layer chromatography (TLC) performed on silica gel 60 F254 (layer 0.2 mm) pre-coated aluminium foil (with fluorescent indicator UV254) (Sigma-Aldrich). Developed plates were air-dried and visualized by UV detector (λ: 254/365 nm) and/or by staining and warming with potassium permanganate or ninhydrin. Flash column chromatography was performed on Merck silica gel 60 (mesh 230-400). Automated flash chromatographic purifications were performed using Biotage® Selekt (Cartridge: Sfär Silica HC Duo 5g or 10g). Preparative TLC purification was performed on Merck silica gel 60 F_{254} (0.5 mm) pre-coated glass plates (20x20 cm) (Sigma-Aldrich). ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature at 400 and 101 MHz, respectively, on a Bruker Avance 400 spectrometer in the indicated solvent by using TMS or residual solvent peak as internal standard. Chemical shifts are reported in ppm (δ) and the coupling constants (*J*) are given in Hertz (Hz). Peak multiplicities are abbreviated as follows: s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), dt

(double triplet), q (quartet), p (pentet), and m (multiplet). High-Resolution Mass Spectroscopy (HRMS) analyses were carried out on Agilent Technologies 6540 UHD Accurate Mass Q-TOF LC-MS system. The purity of all synthesized compounds was confirmed to be >95% by UPLC-MS. The analyses were carried out according to the method listed below. The mobile phase was a mixture of water (solvent A) and acetonitrile (solvent B), both containing formic acid at 0.1%. Method: Acquity UPLC BEH C18 1.7 µm (C18, 150 x 2.1 mm) column at 40° C using a flow rate of 0.65 mL/min in a 10 min gradient elution. Gradient elution was as follows: 99.5:0.5 (A/B) to 5:95 (A/B) over 8 min, 5:95 (A/B) for 2 min, and then reversion back to 99.5:0.5 (A/B) over 0.1 min. The UV detection is an averaged signal from a wavelength of 190 nm to 640 nm and mass spectra are recorded on a mass spectrometer using positive mode electro spray ionization.

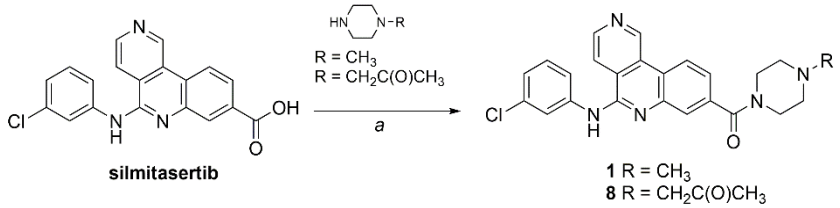
General procedure A: HATU-mediated amidation.

Under nitrogen atmosphere, to a stirred solution of the appropriate carboxylic acid (1.0 equiv), suitable amine (1.0 equiv) and DIPEA (4.0 equiv) in dry DMF was added HATU (1.25 eq) and the reaction mixture was stirred at room temperature. The mixture was poured in ice-water yielding a precipitate collected by filtration. When no precipitate formed, the mixture was extracted with EA (x3) and the reunited organic phases were washed with water (x3), brine (x3), dried over Na_2SO_4, and evaporated to dryness. The crude was purified as described below.

General procedure B: Amine Boc-deprotection.

A solution of 4.0 N HCl in dioxane was added to the appropriate Boc-protected amine and the resulting solution was stirred at room temperature for 2-3 h. The solvent was evaporated to dryness and the residue was tritured with DEE, collected by filtration, and dried *under vacuo*.

Synthesis of silmitasertib-based derivatives:



Reagents and conditions: (a) HATU, DIPEA, dry DMF, rt.

(5-((3-Chlorophenyl)amino)benzo[*c*][2,6]naphthyridin-8-yl)(4-methylpiperazin-1-yl)methanone (1).[6]

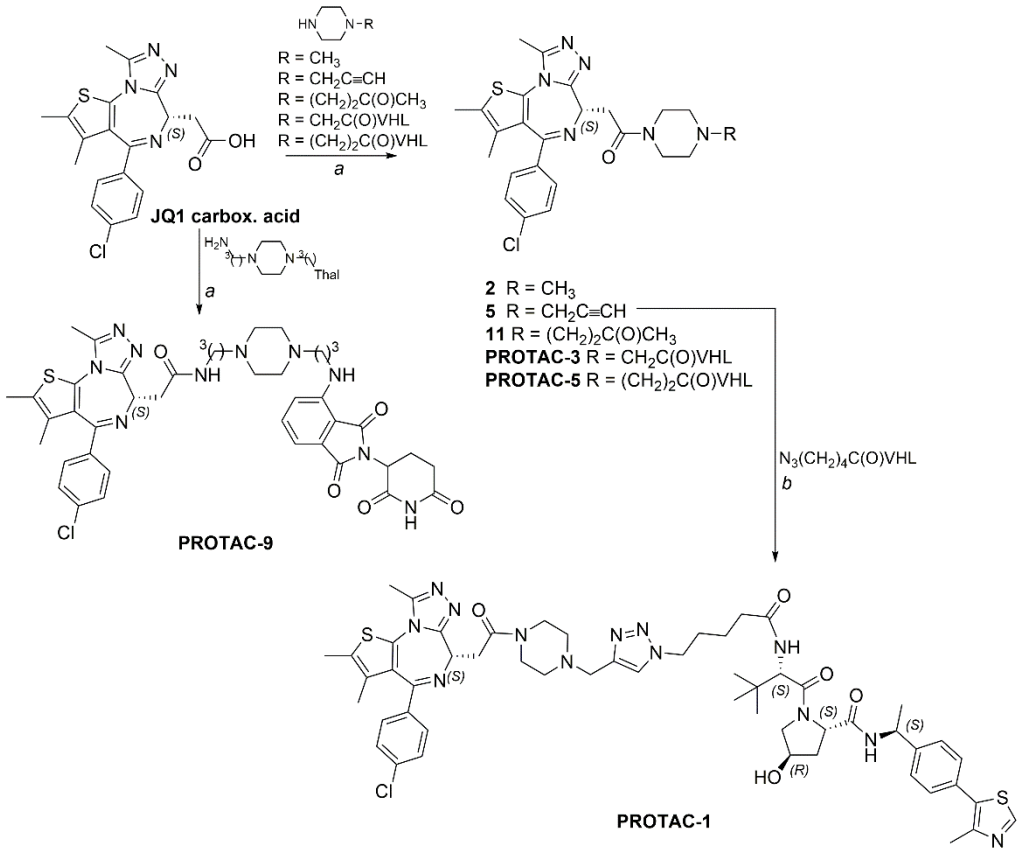
General Procedure A (3 h) was followed by using **silmitasertib** (CX-4945) (0.060 g, 0.171 mmol) and 1-methylpiperazine (0.023 mL, 0.205 mmol) to afford the titled compound as white solid (0.026 g, 35% yield) after purification by flash column chromatography on SiO_2 (DCM/MeOH, 96:4). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.17 (s, 1H), 9.67 (s, 1H), 8.98 (d, *J* = 5.6 Hz, 1H), 8.83 (d, *J* = 8.4 Hz, 1H), 8.58 (d, *J* = 5.6 Hz, 1H), 8.30 (t, *J* = 2.1 Hz, 1H), 8.15 – 8.07 (m, 1H), 7.70 (d, *J* = 1.6 Hz, 1H), 7.47 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.43 (t, *J* = 8.1 Hz, 1H), 7.13 (ddd, *J* = 8.0, 2.1, 0.8 Hz, 1H), 3.80 – 3.36 (m, 4H), 2.47 – 2.23 (m, 4H), 2.20 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.88, 150.54, 148.01, 147.55, 143.78, 142.33, 137.78, 133.21, 130.58, 127.57, 125.66, 124.03, 123.05 (2C), 122.61, 120.55, 120.15, 119.58, 116.78, 55.22, 54.63, 47.62, 46.07, 41.94. HRMS (ESI) *m/z* [M+H]+ calcd for $C_{24}H_{22}ClN_5O$ 432.15856, found 432.15847. UPLC retention time: 3.377 min.

1-(4-(5-((3-Chlorophenyl)amino)benzo[*c*][2,6]naphthyridine-8-carbonyl)piperazin-1-yl)propan-2-one (8).

General Procedure A (2 h) was followed by using **silmitasertib** (CX-4945) (0.060 g, 0.171 mmol) and **26** (0.030 g, 0.171 mmol) to afford the titled compound as white solid (0.026 g, 32% yield) after purification by flash column chromatography on SiO_2 (DCM/MeOH, 96:4). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.18 (s, 1H), 9.67 (s, 1H), 8.98 (d, *J* = 5.6 Hz, 1H), 8.83 (d, *J* = 8.3 Hz, 1H), 8.58 (d, *J* = 5.5 Hz, 1H), 8.30 (t, *J* = 2.1 Hz, 1H), 8.10 (ddd, *J* = 8.3, 2.1, 0.8 Hz, 1H), 7.71 (d, *J* = 1.6 Hz, 1H), 7.47 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.43 (t, *J* = 8.1 Hz, 1H), 7.14 (ddd, *J* = 8.0, 2.1, 0.8 Hz, 1H), 3.80 – 3.62 (m, 2H), 3.51 – 3.36 (m, 2H), 3.25 (s, 2H), 2.62 – 2.51 (m, 2H), 2.47 – 2.35 (m,

2H), 2.08 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 207.03, 168.87, 150.56, 148.03, 147.58, 143.79, 142.34, 137.72, 133.23, 130.59, 127.58, 125.71, 124.05, 123.09, 123.06, 122.63, 120.56, 120.18, 119.59, 116.79, 67.43, 53.24, 52.70, 47.68, 42.02, 28.07. HRMS (ESI) *m/z* [M+H]+ calcd for $C_{26}H_{24}ClN_5O_2$ 474.16913, found 474.16951. UPLC retention time: 3.481 min.

Synthesis of JQ1-based derivatives:



Reagents and conditions: (a) HATU, DIPEA, dry DMF, rt; (b) $CuSO_4$, sodium ascorbate, DMF/*t*BuOH/H_2O (1:1:1), rt. VHL: VHL ligand; Thal: thalidomide.

(*S*)-2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-1-(4-methylpiperazin-1-yl)ethan-1-one (2).

General Procedure A (3 h) was followed by using **JQ1 c.a.** (0.040 g, 0.099 mmol) and 1-methylpiperazine (0.011 mL, 0.099 mmol) to afford the titled compound as white solid (0.020 g, 41% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH, 93:7). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.33 (d, *J* = 8.3 Hz, 2H), 4.79 (t, *J* =

6.8 Hz, 1H), 4.10 – 3.40 (m, 6H), 2.95 – 2.27 (m, 13H), 1.68 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.09, 163.81, 155.85, 149.89, 136.75, 136.73, 132.18, 130.95, 130.71, 130.53, 129.83 (2C), 128.72 (2C), 54.56, 54.34, 45.46, 45.13, 41.08, 35.07, 29.70, 14.39, 13.09, 11.85. HRMS (ESI) *m/z* [M+H]+ calcd for $C_{24}H_{27}ClN_6OS$ 483.17283, found 483.17309. UPLC retention time: 3.657 min.

(*S*)-2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)-1-(4-(prop-2-yn-1-yl)piperazin-1-yl)ethan-1-one (5).

General Procedure A (overnight) was followed by using **JQ1 c.a.** (0.050 g, 0.125 mmol) and **S30** (0.024 mg, 0.125 mmol) to afford the titled compound as white solid (0.052 g, 82% yield) after purification by flash column chromatography on SiO_2 (DCM/MeOH, 95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 8.6 Hz, 2H), 4.79 (t, *J* = 6.5 Hz, 1H), 3.93 – 3.57 (m, 6H), 3.40 (s, 2H), 2.80 – 2.52 (m, 7H), 2.40 (s, 3H), 2.31 (s, 1H), 1.67 (s, 3H). HRMS (ESI) *m/z* [M+H]+ calcd for $C_{26}H_{27}ClN_6OS$ 507.17338, found 507.17365. UPLC retention time: 4.175 min

(*S*)-4-(4-(2-(4-(4-Chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)butan-2-one (11).

General Procedure A (3 h) was followed by using **JQ1 c.a.** (0.040 g, 0.099 mmol) and **S28** (0.019 g, 0.099 mmol) to afford the titled compound as white solid (0.018 g, 35% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH, 94:6). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 7.6 Hz, 2H), 7.33 (d, *J* = 7.6 Hz, 2H), 4.84 – 4.72 (m, 1H), 4.20 – 3.35 (m, 7H), 3.21 – 2.30 (m, *J* = 92.6 Hz, 13H), 2.21 (s, 3H), 1.67 (s, 3H). HRMS (ESI) *m/z* [M+Na]+ calcd for $C_{27}H_{31}ClN_6O_2S$ 561.18099, found 561.18112. UPLC retention time: 3.762 min.

(2*S*,4*R*)-1-((*S*)-2-(2-(4-(2-((*S*)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)acetamido)-3,3 dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (PROTAC-3).

General Procedure A (3 h) was followed by using **JQ1 c.a.** (0.037 g, 0.061 mmol) and (2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(2-(piperazin-1-yl)acetamido)-butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-

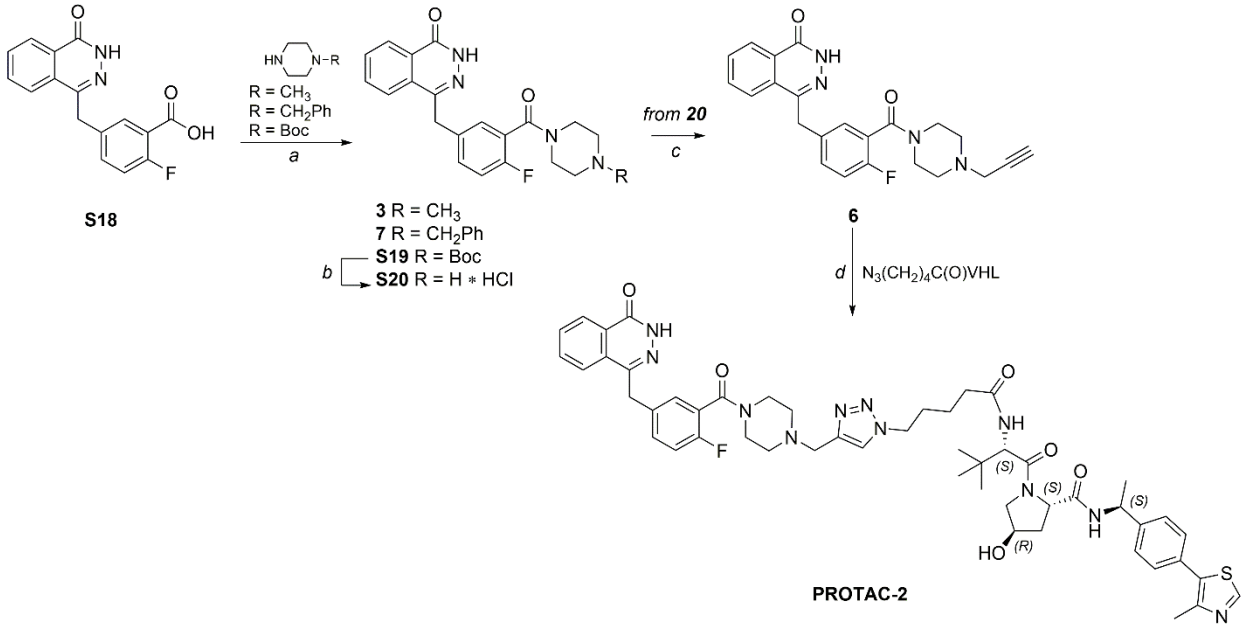
methylthiazol-5-yl)phenyl)-ethyl)pyrrolidine-2-carboxamide hydrochloride[2] (0.024 mg, 0.061 mmol) to afford the titled compound as white solid (0.020 g, 36% yield) after purification by automated flash column chromatography on SiO_2 (DCM/MeOH, 95:5). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.44 (d, *J* = 7.6 Hz, 1H), 7.78 (d, *J* = 9.6 Hz, 1H), 7.60 – 7.24 (m, 8H), 5.13 (d, *J* = 3.4 Hz, 1H), 4.95 – 4.86 (m, 1H), 4.61 – 4.50 (m, 2H), 4.45 (t, *J* = 8.2 Hz, 1H), 4.29 (bs, 1H), 3.81 – 3.36 (m, 10H), 3.19 – 2.96 (m, 3H), 2.60 (s, 4H), 2.48 – 2.39 (m, 6H), 2.11 – 2.00 (m, 1H), 1.82 – 1.73 (m, 1H), 1.63 (s, 3H), 1.38 (d, *J* = 7.1 Hz, 3H), 0.96 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.94, 169.66, 168.93, 168.77, 163.33, 155.72, 150.24, 148.22, 145.26, 137.23, 135.66, 132.68, 131.58, 131.15, 130.64 (2C), 130.35, 130.15, 130.10, 129.36, 129.30 (2C), 128.96 (2C), 126.78 (2C), 69.23, 60.93, 59.00, 56.98, 56.34, 54.62, 53.44, 53.04, 48.24, 45.56, 41.77, 38.22, 36.18, 35.20, 26.79 (3C), 22.98, 16.46, 14.50, 13.16, 11.75. HRMS (ESI) *m/z* [M+H]+ calcd for $C_{48}H_{57}ClN_{10}O_5S_2$ 953.37161, found 953.37249 UPLC retention time: 4.69 min

(2*S*,4*R*)-1-((*S*)-2-(5-(4-((4-(2-((*S*)-4-(4-Chlorophenyl)-2,3,9-trimethyl-6*H*-thieno[3,2-*f*][1,2,4]triazolo[4,3-*a*][1,4]diazepin-6-yl)acetyl)piperazin-1-yl)methyl)-1*H*-1,2,3-triazol-1-yl)pentanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (PROTAC-1).

To the solution of **5** (0.044 g, 0.079 mmol) and (2*S*,4*R*)-1-((*S*)-2-(2-azidoacetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide[2] (0.040 g, 0.079 mmol) in a mixture of DMF/*t*BuOH/H_2O (1:1:1) (3.0 mL), $CuSO_4$ (0.010 g, 0.039 mmol) and sodium ascorbate (0.047 g, 0.237 mmol) were added and the reaction mixture was stirred at room temperature for 3 h. Then, the reaction mixture was poured in ice-water yielding a white precipitate which was collected by filtration and purified by flash column chromatography on SiO_2 (DCM/MeOH, 93:7 to 90:10) to give the titled compound (0.030 g, 35% yiled) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.37 (d, *J* = 7.7 Hz, 1H), 8.01 (s, 1H), 7.86 (d, *J* = 9.1 Hz, 1H), 7.56 – 7.34 (m, 8H), 5.10 (d, *J* = 3.1 Hz, 1H), 4.95 – 4.88 (m, 1H), 4.60 – 4.48 (m, 2H), 4.42 (t, *J* = 7.9 Hz, 1H), 4.34 (t, *J* = 6.6 Hz, 2H), 4.27 (bs, 1H), 3.73 – 3.36 (m,

9H), 2.59 (s, 3H), 2.49– 2.08 (m, 12H), 2.04 – 1.94 (m, 1H), 1.88 – 1.72 (m, 3H), 1.62 (s, 3H), 1.53 – 1.31 (m, 5H), 0.92 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 172.10, 171.07, 170.02, 168.54, 163.32, 155.72, 150.22, 148.22, 145.12, 143.46, 137.22, 135.65, 132.66, 131.58, 131.13, 130.62 (2C), 130.34, 130.15, 130.09, 129.29 (2C), 128.94 (2C), 126.84 (2C), 126.71, 124.19, 69.22, 59.00, 56.87, 56.75, 54.62, 52.96(2C), 52.50, 49.41, 48.15, 45.41, 41.60, 38.19, 35.64, 35.20, 34.55, 29.79, 26.90 (3C), 22.91, 22.81, 16.45, 14.49, 13.16, 11.75. HRMS (ESI) *m/z* [M+H]+ calcd for $C_{54}H_{66}ClN_{13}O_5S_2$ 1076.45126, found 1076.45214. UPLC retention time: 4.831 min.

Synthesis of olaparib-based derivatives:



Reagents and conditions: (a) HATU, DIPEA, dry DMF, rt; (b) HCl 4N in dioxane, rt; (c) 3-bromoprop-1-yne, K_2CO_3, KI, ACN, reflux; (c) $CuSO_4$, sodium ascorbate, DMF/*t*BuOH/H_2O (1:1:1), rt. VHL: VHL ligand.

4-(4-Fluoro-3-(4-methylpiperazine-1-carbonyl)benzyl)phthalazin-1(2*H*)-one (3).[1]

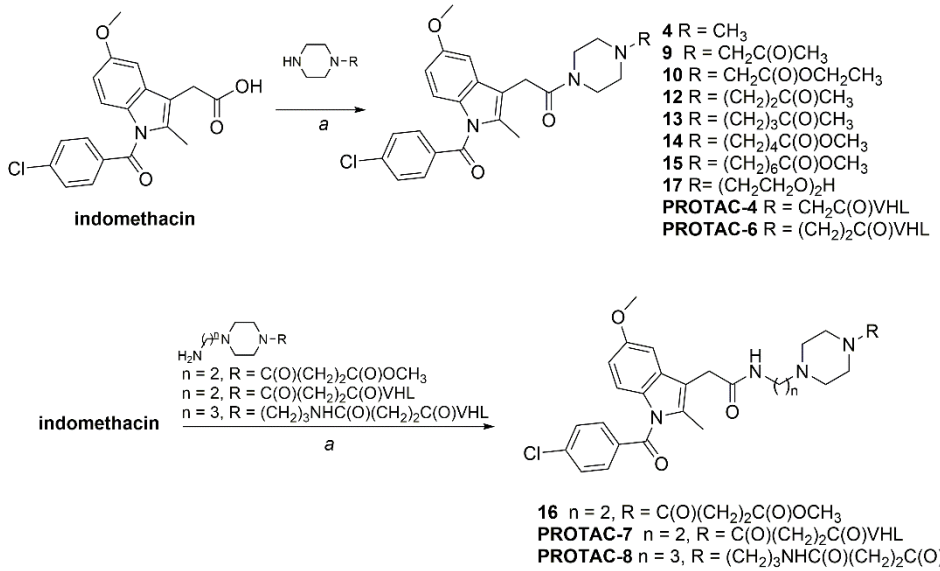
In particular, General Procedure A (18 h) was followed by using **S18**[1] (0.070 g, 0.234 mmol) and 1-methylpiperazine (0.031 mL, 0.281 mmol) to afford the titled compound as white solid (0.037 g, 42% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH, 94:6). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.59 (s, 1H), 8.26 (d, *J* = 7.7 Hz, 1H), 7.96 (d, *J* = 8.2 Hz,

1H), 7.88 (t, *J* = 7.6 Hz, 1H), 7.83 (t, *J* = 7.5 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.33 – 7.29 (m, 1H), 7.21 (t, *J* = 9.0 Hz, 1H), 4.32 (s, 2H), 3.64 – 3.54 (m, 2H), 3.15 – 3.11 (m, 2H), 2.34-2.28 (m, 2H), 2.19 – 2.13 (m, 5H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.21, 159.84, 156.77 (d, *J* = 244.4 Hz), 145.37, 135.28 (d, *J* = 3.3 Hz), 133.96, 132.05, 131.95, 129.53, 129.19 (d, *J* = 3.9 Hz), 128.36, 126.54, 125.95, 124.33 (d, *J* = 18.5 Hz), 116.35 (d, *J* = 21.7 Hz), 55.05, 54.62, 46.90, 46.01, 41.65, 36.85. HRMS m/z [M+H]+ calcd for $C_{21}H_{21}FN_4O_2$ 381.17213, found 381.17254. UPLC retention time: 2.371 min.

4-(3-(4-Benzylpiperazine-1-carbonyl)-4-fluorobenzyl)phthalazin-1(2*H*)-one (7).

General Procedure A (3 h) was followed by using 2-fluoro-5-((4-oxo-3,4-dihydrophthalazin-1-yl)methyl)benzoic acid[1] (0.078 g, 0.263 mmol) and **S32** (0.056 g, 0.263 mmol) to afford the titled compound as white solid (0.040 g, 33% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH, 95:5). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.60 (s, 1H), 8.26 (d, *J* = 7.8 Hz, 1H), 7.96 (d, *J* = 7.8 Hz, 1H), 7.88 (t, *J* = 7.5 Hz, 1H), 7.81 (t, *J* = 7.5 Hz, 1H), 7.46 – 7.38 (m, 1H), 7.38 – 7.16 (m, 7H), 4.33 (s, 2H), 3.68 – 3.55 (m, 2H), 3.48 (s, 2H), 3.19 – 3.11 (m, 2H), 2.45 – 2.35 (m, 2H), 2.29 – 2.19 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 164.18, 159.83, 156.79 (d, *J* = 244.5 Hz), 145.35, 138.17, 135.26 (d, *J* = 3.2 Hz), 133.94, 132.02, 131.97, 129.53, 129.38 (2C), 129.20 (d, *J* = 3.8 Hz), 128.69 (2C), 128.36, 127.53, 126.54, 125.95, 124.29 (d, *J* = 18.5 Hz), 116.36 (d, *J* = 21.6 Hz), 62.24, 53.13, 52.58, 47.02, 41.80, 36.86. HRMS m/z [M+H]+ calcd for $C_{27}H_{25}FN_4O_2$ 457.20343, found 457.20332. UPLC retention time: 3.107 min.

Synthesis of indomethacin-based derivatives:



Reagents and conditions: (a) HATU, DIPEA, dry DMF, rt. VHL: VHL ligand.

2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-1-(4-methylpiperazin-1-yl)ethan-1-one (4).

General Procedure A (4 h) was followed by using **indomethacin** (0.040 g, 0.112 mmol) and *N*-methyl piperazine (0.012 mL, 0.112 mmol) to afford the titled compound as yellow powder (0.021 g, 59% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM:MeOH, 97:3 to 95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.66 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.89 – 3.57 (m, 9H), 2.61 – 2.27 (m, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.65, 168.29, 156.03, 139.29, 135.20, 133.91, 131.21 (2C), 130.85, 130.70, 129.13 (2C), 114.89, 113.31, 111.54, 101.52, 55.75, 54.95, 54.69, 45.94, 45.72, 41.86, 30.20, 13.47. HRMS (ESI) m/z [M+H]+ calculated for $C_{24}H_{26}ClN_3O_3$ 440.17355, found 440.17403. UPLC retention time: 4.068 min.

1-(4-(2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl)piperazin-1-yl)propan-2-one (9).

General Procedure A (4 h) was followed by using **indomethacin** (0.100 g, 0.280 mmol) and **S26** (0.050 g, 0.280 mmol) to afford the titled compound as yellow powder (0.021 g, 16% yield) after purification by automated reverse-phase flash chromatography on C18 silica gel cartridge

(H_2O:ACN, from 50:50 to 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 2.3 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 9.0, 2.4 Hz, 1H), 3.91 – 3.68 (m, 7H), 3.68 – 3.56 (m, 2H), 3.28 (s, 2H), 2.68 – 2.43 (m, 4H), 2.37 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.46, 168.66, 168.27, 156.05, 139.35, 135.24, 133.81, 131.21 (2C), 130.82, 130.51, 129.15 (2C), 114.94, 112.94, 111.61, 101.41, 63.01, 55.76, 52.56 (2C), 45.06, 41.21, 30.30, 27.99, 13.47. HRMS (ESI) m/z [M + H]+ calcd for $C_{26}H_{28}ClN_3O_4$ 482.18411, found 482.18376. UPLC retention time: 4.22 min.

Ethyl 2-(4-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl)piperazin-1-yl)acetate (10).

General Procedure A (3 h) was followed by using **indomethacin** (0.50 g, 0.139 mmol) and **S38** (0.030 g, 0.139 mmol) to afford the titled compound as white solid (0.033 g, 46% yield) after purification by flash column chromatography on SiO_2 (DCM:MeOH, 98:2) followed by preparative TLC eluting with DCM:MeOH 95:5. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.3 Hz, 2H), 7.46 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.64 (dd, *J* = 9.0, 2.4 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 3.75 – 3.65 (m, 4H), 3.63 – 3.52 (m, 2H), 3.19 (s, 2H), 2.63 – 2.41 (m, 4H), 2.36 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.72, 168.63, 168.26, 156.02, 139.25, 135.15, 133.89, 131.19 (2C), 130.83, 130.62, 129.12 (2C), 114.90, 113.21, 111.56, 101.45, 60.85, 58.90, 55.73, 52.61, 52.47, 45.65, 41.76, 30.26, 14.21, 13.47. HRMS m/z [M+H]+ calcd for $C_{27}H_{30}ClN_3O_5$ 512.19468, found 512.19445. UPLC retention time: 4.821min.

4-(4-(2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl)piperazin-1-yl)butan-2-one (12).

General Procedure A (4 h) was followed by using **indomethacin** (0.111 g, 0.311 mmol) and **S28** (0.060 g, 0.311 mmol) to afford the titled compound as white solid (0.025 g, 16% yield) after purification by flash column chromatography on SiO_2 (DCM/Acetone/MeOH, 88:10:2).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.5 Hz, 2H), 7.46 (d, *J* = 8.5 Hz, 2H), 6.96 (d, *J* = 2.4 Hz, 1H),

6.81 (d, *J* = 9.0 Hz, 1H), 6.64 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.81 (s, 3H), 3.69 (s, 2H), 3.67 – 3.60 (m, 2H), 3.56 – 3.44 (m, 2H), 2.73 – 2.52 (m, 4H), 2.45 – 2.27 (m, 7H), 2.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.37, 168.59, 168.25, 156.00, 139.27, 135.15, 133.89, 131.19 (2C), 130.82, 130.65, 129.12 (2C), 114.87, 113.27, 111.51, 101.52, 55.73, 53.08, 52.72, 52.44, 45.80, 41.90, 41.07, 30.25, 30.12, 13.46. HRMS m/z [M+H]+ calcd for $C_{27}H_{30}ClN_3O_4$ 496.19976, found 496.19972. UPLC retention time: 4.18 min.

5-(4-(2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl)piperazin-1-yl)pentan-2-one (13).

General Procedure A (16 h) was followed by using **indomethacin** (0.219 g, 0.612 mmol) and **S34** (0.118 g, 0.612 mmol) to afford the titled compound as yellowish solid (0.075 g, 24% yield) after purification by automated flash column chromatography on SiO_2 cartridge (DCM:MeOH, from 99:1 to 90:10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.62 (m, 2H), 7.50 – 7.43 (m, 2H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.82 (s, 3H), 3.70 (s, 2H), 3.67 – 3.60 (m, 2H), 3.55 – 3.45 (m, 2H), 2.46 (t, *J* = 7.1 Hz, 2H), 2.43 – 2.26 (m, 9H), 2.15 (s, 3H), 1.81 – 1.71 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.41, 168.62, 168.28, 156.02, 139.28, 135.17, 133.92, 131.21 (2C), 130.85, 130.69, 129.13 (2C), 114.89, 113.31, 111.54, 101.51, 57.42, 55.75, 52.92, 52.86, 45.78, 41.91, 41.15, 30.24, 30.22, 20.70, 13.48. HRMS m/z [M+H]+ calcd for $C_{28}H_{32}ClN_3O_4$ 510.21541, found 510.21543. UPLC retention time: 4.21 min.

Methyl 5-(4-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl)piperazin-1-yl)pentanoate (14).

General Procedure A (3 h) was followed by using **indomethacin** (0.50 g, 0.139 mmol) and **S39** (0.038 g, 0.139 mmol) to afford the titled compound as white solid (0.037 g, 49% yield) after purification by flash column chromatography on SiO_2 (DCM:MeOH, 98:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.63 (m, 2H), 7.49 – 7.44 (m, 2H), 6.98 (d, *J* = 2.5 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 2H), 3.69 – 3.59 (m, 5H), 3.54 – 3.48 (m, 2H), 2.44 – 2.24 (m, 11H), 1.69 – 1.61 (m, 2H), 1.52 – 1.45 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$)

δ 173.93, 168.58, 168.25, 156.00, 139.24, 135.13, 133.93, 131.19 (2C), 130.83, 130.70, 129.11(2C), 114.87, 113.37, 111.52, 101.51, 57.88, 55.73, 53.18, 52.85, 51.53, 45.90, 42.00, 33.80, 30.21, 26.16, 22.74, 13.48. HRMS m/z [M+Na]+ calcd for $C_{29}H_{34}ClN_3O_5$ 562.20792, found 562.20841. UPLC retention time: 4.479 min.

Methyl 7-(4-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl)piperazin-1-yl)heptanoate (15).

General Procedure A (3 h) was followed by using **indomethacin** (0.50 g, 0.139 mmol) and **S40** (0.042 g, 0.139 mmol) to afford the titled compound as white solid (0.047 g, 59% yield) after purification by flash column chromatography on SiO_2 (DCM:MeOH, 98:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.64 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.81 (s, 3H), 3.77 – 3.58 (m, 7H), 3.56 – 3.45 (m, 2H), 2.46 – 2.19 (m, 11H), 1.68 – 1.55 (m, 2H), 1.53 – 1.39 (m, 2H), 1.37 – 1.24 (m, 4H). ^{13}C NMR (101 MHz, CDCl3) δ 174.18, 168.57, 168.26, 156.00, 139.24, 135.14, 133.93, 131.19 (2C), 130.84, 130.71, 129.11 (2C), 114.87, 113.39, 111.52, 101.51, 58.40, 55.74, 53.26, 52.91, 51.48, 45.93, 42.02, 33.99, 30.22, 29.00, 27.08, 26.58, 24.84, 13.48. HRMS m/z [M+H]+ calcd for $C_{31}H_{38}ClN_3O_5$ 568.25728, found 568.25706. UPLC retention time: 4.780 min.

2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-1-(4-(2-(2-hydroxyethoxy)ethyl)piperazin-1-yl)ethan-1-one (17).

General Procedure A (3 h) was followed by using **indomethacin** (0.060 g, 0.168 mmol) and 2-(2-(piperazin-1-yl)ethoxy)ethan-1-ol (0.029 g, 0.168 mmol) to afford the titled compound as clear yellow oil (0.043 g, 50% yield) after purification by flash column chromatography on SiO_2 (DCM/MeOH, 97:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.60 (m, 2H), 7.53 – 7.41 (m, 2H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.64 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.81 (s, 3H), 3.73 – 3.52 (m, 12H), 2.57 (t, *J* = 5.3 Hz, 2H), 2.54 – 2.47 (m, 2H), 2.46 – 2.39 (m, 2H), 2.36 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.61, 168.28, 156.03, 139.29, 135.18, 133.89, 131.21 (2C), 130.84, 130.66, 129.13 (2C), 114.88, 113.24, 111.58, 101.50, 72.36, 67.56, 61.95, 57.70, 55.75, 53.27, 52.97, 45.54, 41.65,

30.22, 13.46. HRMS m/z $[M+H]^+$ calcd for $C_{27}H_{32}ClN_3O_5$ 514.21033, found 514. 20989. UPLC retention time: 4.013 min.

(2*S*,4*R*)-1-((*S*)-2-(2-(4-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl)piperazin-1-yl)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(thiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (PROTAC-4).

General Procedure A (18 h) was followed by using **indomethacin** (0.041 g, 0.115 mmol) and (2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(2-(piperazin-1-yl)acetamido)butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide hydrochloride [2] (0.045 g, 0.070 mmol) to afford the titled compound as yellow solid (0.020 g, 19 % yield) after purification by flash column chromatography on SiO_2 (DCM/Acetone/MeOH, 76:20:4). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.72 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.3 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 7.43 – 7.31 (m, 5H), 6.96 (d, *J* = 2.1 Hz, 1H), 6.79 (d, *J* = 9.0 Hz, 1H), 6.68 – 6.62 (m, 1H), 5.12 – 5.04 (m, 1H), 4.73 (t, *J* = 7.8 Hz, 1H), 4.55 – 4.43 (m, 2H), 4.13 (d, *J* = 11.7 Hz, 1H), 3.90 – 3.76 (m, 4H), 3.71 (s, 2H), 3.65 – 3.50 (m, 4H), 3.01 (s, 2H), 2.61 – 2.43 (m, 7H), 2.43 – 2.32 (m, 4H), 2.11 – 2.00 (m, 1H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.76, 169.47, 168.77 (2C), 168.31, 156.02, 150.31, 148.52, 143.07, 139.40, 135.31, 133.79, 131.54, 131.24 (2C), 130.95, 130.84, 130.60, 129.58 (2C), 129.17 (2C), 126.44 (2C), 114.92, 113.00, 111.47, 101.61, 70.11, 58.13 (2C), 56.62, 55.77, 53.79, 53.15 (2C), 48.86, 35.32, 34.70, 31.93, 30.25, 29.71, 26.58 (3C), 22.22, 16.11, 13.44. HRMS (ESI) m/z [M + H]+ calcd for $C_{48}H_{56}ClN_7O_7S$ 910.37232, found 910.37300. UPLC retention time: 5.27.

(2*S*,4*R*)-1-((*S*)-2-(3-(4-(2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl)piperazin-1-yl)propanamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (PROTAC-6).

General Procedure A (4 h) was followed by using **indomethacin** (0.034 g, 0.097 mmol) and (2*S*,4*R*)-1-((*S*)-3,3-dimethyl-2-(3-(piperazin-1-yl)propanamido)butanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide hydrochloride [2] (0.060 g, 0.097 mmol)

to afford the titled compound as yellow solid (0.029 g, 32% yield) after purification by flash column chromatography on SiO_2 (DCM/ MeOH, 97:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.78 (d, *J* = 7.7 Hz, 1H), 8.66 (s, 1H), 7.70 – 7.62 (m, 2H), 7.51 – 7.43 (m, 3H), 7.42 – 7.33 (m, 4H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.80 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 9.0, 2.5 Hz, 1H), 5.12 – 5.03 (m, 1H), 4.76 (t, *J* = 7.9 Hz, 1H), 4.49 (s, 1H), 4.41 (d, *J* = 7.7 Hz, 1H), 4.21 (d, *J* = 11.6 Hz, 1H), 3.91 – 3.79 (m, 4H), 3.72 (s, 2H), 3.69-3.51 (m, 4H), 3.54 (dd, *J* = 11.6, 3.5 Hz, 1H), 2.65 – 2.28 (m, 15H), 2.11 – 2.02 (m, 1H), 1.46 (d, *J* = 7.0 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.85, 172.18, 169.58, 168.72, 168.26, 155.99, 150.27, 148.51, 143.13, 139.38, 135.26, 133.78, 131.55, 131.22 (2C), 130.90, 130.84, 130.60, 129.55 (2C), 129.15 (2C), 126.42 (2C), 114.88, 113.07, 111.38, 101.64, 70.08, 58.10, 57.94, 56.45, 55.75, 53.79, 52.43 (2C), 48.82, 45.64, 41.78, 35.18, 34.48, 31.64, 30.27, 26.76 (3C), 22.25, 16.11, 13.45. HRMS (ESI) *m/z* [M + Na]+ calcd for $C_{49}H_{58}ClN_7O_7S$ 946.36992, found 946.37011. UPLC retention time: 5.021 min.

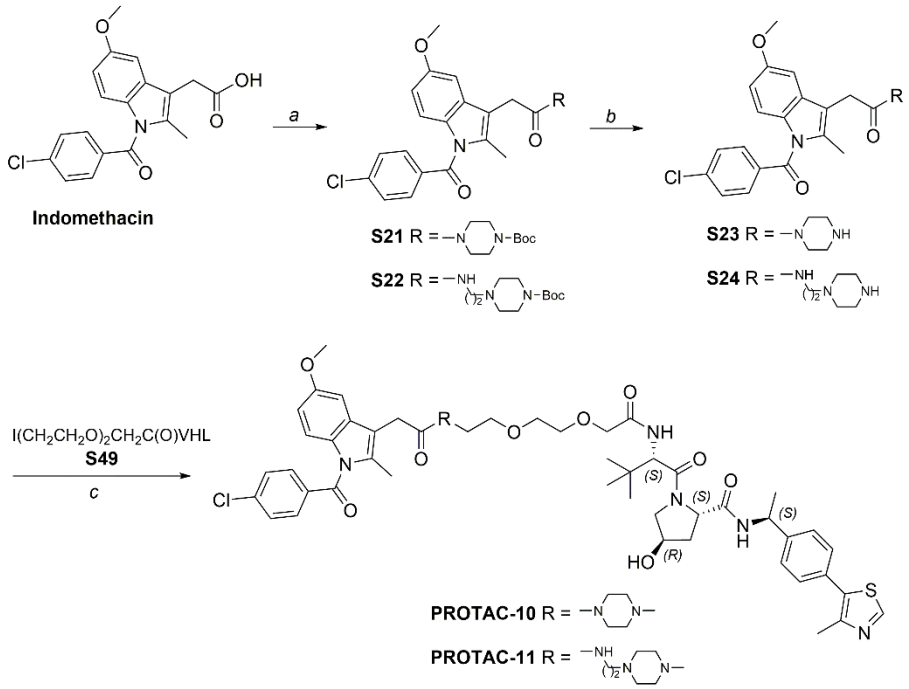
Methyl 4-(4-(2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetamido)ethyl)piperazin-1-yl)-4-oxobutanoate (16).

General Procedure A (4 h) was followed by using **indomethacin** (0.090 g, 0.250 mmol) and **S42** (0.072 g, 0.250 mmol) to afford the titled compound as yellow oil (0.041 g, 16% yield) after purification by flash column chromatography on SiO_2 (DCM/Acetone/MeOH, 88:10:2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 – 7.61 (m, 2H), 7.51 – 7.43 (m, 2H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.67 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.20 (t, *J* = 4.6 Hz, 1H), 3.79 (s, 3H), 3.67 (s, 3H), 3.63 (s, 2H), 3.31 – 3.22 (m, 4H), 3.19 – 3.10 (m, 2H), 2.68 – 2.59 (m, 2H), 2.59 – 2.50 (m, 2H), 2.39 (s, 3H), 2.35 (t, *J* = 6.0 Hz, 2H), 2.27 – 2.15 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.56, 169.73, 169.47, 168.28, 156.18, 139.71, 136.32, 133.42, 131.22 (2C), 130.92, 130.34, 129.26 (2C), 14.96, 112.98, 111.80, 101.24, 56.08, 55.77, 52.51, 52.28, 51.78, 44.91, 41.51, 35.84, 32.17, 28.99, 27.85, 13.24. HRMS m/z $[M+H]^+$ calcd for $C_{30}H_{35}ClN_4O_6$ 583.23179, found 583.23176. UPLC retention time: 4.22 min.

***N*1-(3-(4-(3-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetamido)propyl)piperazin-1-yl)propyl)-*N*4-((S)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide (PROTAC-8).**

The solution of **S46** (0.095 g, 0.115 mmol) (see Supplementary Information) in 4.0N HCl dioxane (1.0 mL) was stirred at room temperature for 3 h. The solvent was evaporated to dryness and the solid was tritured with DEE and collected by filtration, yielding *N1*-(3-(4-(3-aminopropyl)piperazin-1-yl)propyl)-*N4*-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide hydrochloride (**S47**) (0.83 g, 94% yield) as a white solid, which was directly used in the successive step without further purification.

Thus, general Procedure A (3 h) was followed by using **indomethacin** (0.021 g, 0.059 mmol) and **S47** (0.045 g, 0.059 mmol) to afford the titled compound as yellow solid (0.018 g, 28% yield) after purification by flash column chromatography on SiO_2 (DCM/MeOH, 90:10 to 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (s, 1H), 8.00 (bs, 1H), 7.85 (bs, 1H), 7.64 (d, *J* = 8.4 Hz, 2H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.41 – 7.31 (m, 4H), 6.91 (d, *J* = 1.8 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 9.1, 2.0 Hz, 1H), 6.36 (bs, 1H), 5.14 – 5.01 (m, 1H), 4.87 – 4.78 (m, 1H), 4.63 – 4.53 (m, 1H), 4.48 – 4.41 (m, 1H), 4.11 – 4.01 (m, 1H), 3.79 (s, 3H), 3.64 – 3.51 (m, 3H), 3.45 (s, 2H), 3.42 – 3.16 (m, 4H), 2.87 – 2.19 (m, 22H), 1.85 – 1.54 (m, 4H), 1.47 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H). HRMS (ESI) m/z [M + Na]+ calcd for $C_{56}H_{72}ClN_9O_8S$ 1088.48053, found 1088.48075. UPLC retention time: 4.724 min.



Reagents and conditions: (a) HATU, DIPEA, dry DMF, rt; (b) HCl 4N in dioxane, rt; (c) DIPEA, dry DMF/dry DMSO (1:1), 80°C. VHL: VHL ligand.

***Tert*-butyl 4-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl)piperazine-1-carboxylate (S21).**

General Procedure A (3 h) was followed by using **indomethacin** (0.100 g, 0.279 mmol) and *tert*-butyl piperazine-1-carboxylate (0.052 g, 0.279 mmol) to afford the titled compound as yellow solid (0.115 g, 79% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/MeOH, 99:1 to 97:3). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.62 (m, 2H), 7.51 – 7.44 (m, 2H), 6.98 (d, *J* = 2.3 Hz, 1H), 6.80 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 9.1, 2.5 Hz, 1H), 3.82 (s, 3H), 3.73 (s, 2H), 3.65 – 3.59 (m, 2H), 3.49 – 3.44 (m, 2H), 3.41 – 3.36 (m, 2H), 3.33 – 3.27 (m, 2H), 2.39 (s, 3H), 1.45 (s, 9H).

***Tert*-butyl 4-(2-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetamido)ethyl)piperazine-1-carboxylate (S22).**

General Procedure A (3 h) was followed by using **indomethacin** (0.130 g, 0.363 mmol) and *tert*-butyl 4-(2-aminoethyl)piperazine-1-carboxylate (0.083 g, 0. 363 mmol) to afford the titled compound as yellow solid (0.176 g, 85% yield) after purification by automated flash chromatography on SiO_2 cartridge (DCM/ MeOH, 99:1 to 95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.68 (d, *J* = 8.5 Hz, 2H), 7.50 – 7.45 (m, 2H), 6.92 (d, *J* = 2.1 Hz, 1H), 6.83 (d, *J* = 9.0 Hz, 1H), 6.67 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.81 (s, 3H), 3.65 (s, 2H), 3.46 – 3.07 (m, 6H), 2.55 – 2.17 (m, 9H), 1.44 (s, 9H).

2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-1-(piperazin-1-yl)ethan-1-one (S23).

The solution of **S21** (0.100 g, 0.205 mmol) in 4.0N HCl in dioxane (1.0 mL) was stirred at room temperature for 6 h. The solvent was evaporated to dryness, the crude was diluted with $NaHCO_3$ sat. solution, and then extracted with EA (x3). The reunited organic phases were washed with brine, dried over Na_2SO_4, and evaporated to dryness yielding the titled compound as a yellow solid (0.087 g, 98% yield). ^{1} H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 8.5 Hz, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 1H), 6.65 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.82 (s, 3H), 3.71 (s, 2H), 3.69 – 3.63 (m, 2H), 3.59 – 3.48 (m, 2H), 2.91 – 2.81 (m, 2H), 2.81 – 2.71 (m, 2H), 2.38 (s, 3H).

2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)-*N*-(2-(piperazin-1-yl)ethyl)acetamide (S24).

The solution of **S22** (0.170 g, 0.298 mmol) in 4.0N HCl in dioxane (2.0 mL) was stirred at room temperature for 3 h. The solvent was evaporated to dryness, the crude was diluted with $NaHCO_3$ sat. solution, and then extracted with EA (×3). The reunited organic phases were washed with brine, dried over Na_2SO_4, and evaporated to dryness yielding the titled compound as a yellow semi-solid (0.135 g, 96% yield). ^{1}H NMR (400 MHz, CDCl3) δ 7.77 – 7.60 (d, *J* = 8.5 Hz, 2H), 7.56 – 7.45 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 2.3 Hz, 1H), 6.86 (d, *J* = 9.0 Hz, 1H), 6.69 (dd, *J* = 9.0, 2.4 Hz, 1H), 6.31-6.23 (m, 1H), 3.81 (s, 3H), 3.64 (s, 2H), 3.33 – 3.22 (m, 2H), 2.66 – 2.49 (m, 4H), 2.40 (s, 3H), 2.34 (t, *J* = 6.0 Hz, 2H), 2.30 – 2.21 (m, 4H).

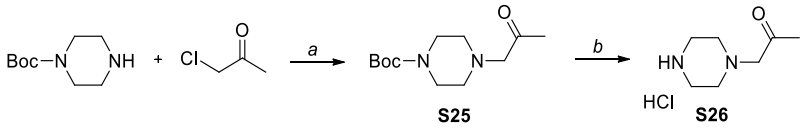
(2*S*,4*R*)-1-((*S*)-2-(2-(2-(2-(4-(2-(1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetyl)piperazin-1-yl)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (PROTAC-10).

Under nitrogen atmosphere, to the solution of **S49** (0.045 g, 0.064 mmol) in a mixture of dry DMSO and dry DMF 1:1 (2.0 ml), DIPEA (0.034 mL, 0.192 mmol) and **S23** (0.027 g, 0.064 mmol) were added. The yellow suspension was stirred at 80 °C for 18 h. After cooling, the yellow solution was diluted with EA (50 mL) and washed with $NaHCO_3$ saturated solution (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. The crude was purified by flash column chromatography on SiO_2 (DCM/MeOH, 97:3 to 95:5) to afford the titled compound as clear yellow solid (0.016 g, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (s, 1H)-, .67 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.3 Hz, 3H), 7.44-7.33 (m, 4H), 7.28 – 7.23 (m, 1H), 7.04 – 6.95 (m, 1H), 6.84 (d, *J* = 9.0 Hz, 1H), 6.67 (dd, *J* = 9.1, 1.9, 1H), 5.13 – 5.05 (m, 1H), 4.75 (t, *J* = 7.8 Hz, 1H), 4.57 (d, *J* = 8.6 Hz, 1H), 4.51 (bs, 2H), 4.16 – 4.02 (m, 3H), 3.83 (s, 3H), 3.80 – 3.51 (m, 13H), 2.73 – 2.27 (m, 13H), 2.11 – 2.00 (m, 1H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.53, 170.25, 169.65, 168.74, 168.29, 155.97, 150.26, 148.52, 143.23, 139.30, 135.25, 133.88, 131.59, 131.22 (2C), 130.88, 130.86, 130.74, 129.56 (2C), 129.13 (2C), 126.41 (2C), 114.87, 113.31, 111.39, 101.71, 70.91, 70.50, 70.43, 70.08, 68.89, 58.30, 57.44, 57.09, 56.66, 55.77, 53.72, 52.92, 48.84, 45.85, 42.02, 35.50, 35.16, 30.13, 26.52 (3C), 22.27, 16.12, 13.47. HRMS (ESI) *m/z* [M + H]+ calcd for $C_{52}H_{64}ClN_7O_9S$ 998.42475, found 998.42541. UPLC retention time: 5.087 min.

(2*S*,4*R*)-1-((*S*)-2-(2-(2-(2-(4-(2-(2-(1-(4-Chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indol-3-yl)acetamido)ethyl)piperazin-1-yl)ethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (PROTAC-11).

Under nitrogen atmosphere, to the solution of **S49** (0.108 g, 0.154 mmol) in a mixture of dry DMSO and dry DMF 1:1 (2.0 ml), DIPEA (0.081 mL, 0.462 mmol) and **S24** (0.072 g, 0.154 mmol) were added. The yellow suspension was stirred at 80 °C for 18 h. After cooling, the yellow solution was diluted with EA (50 mL) and washed with $NaHCO_3$ saturated solution (30 mL) and brine (30 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to dryness. The crude was

purified by flash column chromatography on SiO_2 (DCM/MeOH, 98:2) to afford the titled compound as clear yellow solid (0.019 g, 12% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.43 (d, *J* = 7.0 Hz, 1H), 7.90 – 7.77 (m, 1H), 7.74 – 7.59 (m, 4H), 7.51 – 7.28 (m, 5H), 7.11 (s, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 6.71 (d, *J* = 8.2 Hz, 1H), 5.13 (s, 1H), 4.96 – 4.82 (m, 1H), 4.54 (d, *J* = 9.2 Hz, 1H), 4.44 (t, *J* = 7.3 Hz, 1H), 4.28 (bs, 1H), 3.96 (s, 2H), 3.76 (s, 3H), 3.69 – 3.43 (m, 10H), 3.21 – 3.06 (m, 2H), 2.47 – 2.13 (m, 18H), 2.12 – 1.98 (m, 1H), 1.83 – 1.69 (m, 1H), 1.36 (d, *J* = 6.2 Hz, 3H), 0.94 (s, 9H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 170.89, 169.68, 169.44, 168.94, 168.29, 156.01, 151.93, 148.20, 145.17, 138.01, 135.60, 134.71, 131.59 (2C), 131.56, 131.32, 130.75, 130.14, 129.50 (2C), 129.28 (2C), 126.77 (2C), 114.98, 114.79, 111.66, 102.41, 70.90, 70.07, 69.91, 69.23, 68.77, 65.38, 59.01, 57.60, 57.34, 56.98, 56.13, 55.90, 53.52 (2C), 53.15, 48.21, 38.19, 36.74, 36.21, 31.65, 26.71 (3C), 22.95, 16.45, 13.85. HRMS (ESI) *m/z* [M + H]+ calcd for $C_{54}H_{69}ClN_8O_9S$ 1063.44890, found 1063.45014. UPLC retention time: 4.993 min.



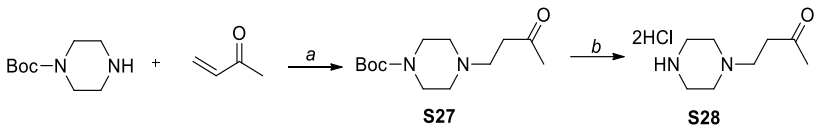
Reagents and conditions: (a) K_2CO_3, ACN, rt; (b) HCl 4.0N in dioxane, rt.

***Tert*-butyl 4-(2-oxopropyl)piperazine-1-carboxylate (S25).**[7]

To a stirring solution of *tert*-butyl piperazine-1-carboxylate (0.100 g, 0.537 mmol) in ACN (3.0 mL) was added K_2CO_3 (0.297 g, 2.147 mmol) and 1-chloropropan-2-one (0.055 mL, 0.698 mmol) and the mixture was stirred at room temperature for 20 h. The reaction was diluted with water (30 mL) and extracted with EA (× 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness to afford a yellow oil (0.116 g, 89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.53 – 3.43 (m, 4H), 3.21 (s, 2H), 2.50 – 2.39 (m, 4H), 2.15 (s, 3H), 1.45 (s, 9H).

1-(Piperazin-1-yl)propan-2-one hydrochloride (S26).

General Procedure B (2 h) was followed by using **S25** (0.110 g, 0.454 mmol) and 4.0 N HCl in dioxane (1.10 mL) to afford the titled compound as grey solid (0.080 g, 99% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.83 (bs, 2H), 4.33 (s, 2H), 3.56 – 3.22 (m, 8H), 2.16 (s, 3H).



S27 S28

Reagents and conditions: (a) K_2CO_3, ACN, rt; (b) HCl 4.0N in dioxane, rt.

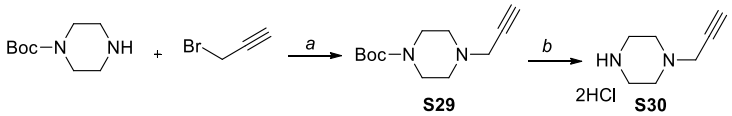
***Tert*-butyl 4-(3-oxobutyl)piperazine-1-carboxylate (S27).**[7]

To a stirring solution of *tert*-butyl piperazine-1-carboxylate (0.100 g, 0.537 mmol) in ACN (3.0 mL) was added K_2CO_3 (0.126 g, 0.913 mmol) and but-3-en-2-one (0.055 mL, 0.698 mmol) and the mixture was stirred at room temperature for 4 h. The reaction was filtered and the filtrate diluted with water (30 mL) and extracted with EA (× 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness to afford a yellow oil (0.137 g, 100% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.46 – 3.37 (m, 4H), 2.71 – 2.58 (m, 4H), 2.43 – 2.34 (m, 4H), 2.17 (s, 3H), 1.45 (s, 9H).

4-(Piperazin-1-yl)butan-2-one hydrochloride (S28).

General Procedure B (2 h) was followed by using **S27** (0.130 g, 0.507 mmol) and 4.0 N HCl in dioxane (1.30 mL) to afford the titled compound as grey solid (0.101 g, 87% yield).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.98 (bs, 1H), 9.84 (s, 2H), 3.69 – 3.23 (m, 10H), 3.06 (t, J = 6.9 Hz, 2H), 2.15 (s, 3H).

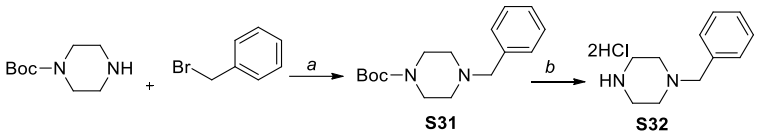


S29 S30

Reagents and conditions: (a) K_2CO_3, ACN, rt; (b) HCl 4.0N in dioxane, rt.

1-(Prop-2-yn-1-yl)piperazine dihydrochloride (S30).[8]

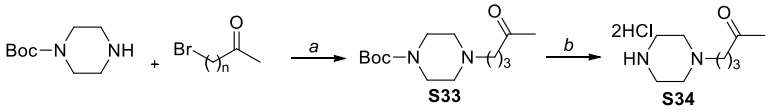
General Procedure B (overnight) was followed by using *tert*-butyl 4-(prop-2-yn-1-yl)piperazine-1-carboxylate **S29**[9] (0.228 g, 1.016 mmol) and 4.0 N HCl in dioxane (0.5 mL) to afford the titled compound as light-yellow solid (0.187 g, 94% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.59 (bs, 3H), 3.96 (s, 2H), 3.73 (s, 1H), 3.48 – 2.88 (m, 8H).



Reagents and conditions: (a) K_2CO_3, ACN, rt; (b) HCl 4.0N in dioxane, rt.

1-Benzylpiperazine dihydrochloride (S32).

General Procedure B (3 h) was followed by using *tert*-butyl 4-benzylpiperazine-1-carboxylate **S31**[10] (0.078 g, 0.282 mmol) and 4.0 N HCl in dioxane (1.0 mL) to afford the titled compound as white solid (0.062 g, 88% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.19 (bs, 1H), 9.73 (s, 2H), 7.75 – 7.32 (m, 5H), 4.36 (s, 2H), 3.65 – 3.44 (m, 6H), 3.32 – 3.08 (m, 2H).



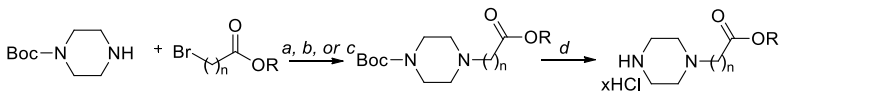
Reagents and conditions: (a) DIPEA, KI, ACN, 90°C; (b) HCl 4.0N in dioxane, rt.

***Tert*-butyl 4-(4-oxopentyl)piperazine-1-carboxylate (S33).**

To a stirring solution of *tert*-butyl piperazine-1-carboxylate (0.200 g, 1.074 mmol) in ACN (3.0 mL) were added DIPEA (0.281 mL, 1.611 mmol), 5-chloropentan-2-one (0.184 mL, 1.611 mmol), KI (0.180 g, 0. 1.074 mmol) and the mixture was refluxed for 48 h. The crude mixture was diluted with EA (20 mL), washed with water (× 2), brine, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The titled compound was afforded as a brown oil (0.185 g, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 – 3.36 (m, 4H), 2.46 (t, *J* = 7.1 Hz, 2H), 2.40 – 2.28 (m, 6H), 2.15 (s, 3H), 1.81 – 1.72 (m, *J* = 7.3 Hz, 2H), 1.45 (s, 9H).

5-(Piperazin-1-yl)pentan-2-one hydrochloride (S34).

General Procedure B (2 h) was followed by using **S33** (0.185 g, 0.684 mmol) and 4.0 N HCl in dioxane (2.0 mL) to afford the titled compound as brownish oil (0.123 g, 74% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (bs, 1H), 9.75 (bs, 2H), 3.77 – 3.57 (m, *J* = 30.0 Hz, 2H), 3.54 – 3.44 (m, 4H), 3.32 – 3.18 (m, 2H), 3.09 – 3.01 (m, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 2.10 (s, 3H), 1.90 – 1.81 (m, 2H).



S35 n = 1, R = CH_2CH_3
S36 n = 4, R = CH_3
S37 n = 6, R = CH_3

S38 n = 1, R = CH_2CH_3 * HCl
S39 n = 4, R = CH_3 * 2HCl
S40 n = 6, R = CH_3 * 2HCl

Reagents and conditions: (a) DIPEA, dry THF, rt; (b) K_2CO_3, KI, dry THF, 60°C; (c) K_2CO_3, dry THF, 60°C; (d) HCl 4.0N in dioxane, rt.

***Tert*-butyl 4-(2-ethoxy-2-oxoethyl)piperazine-1-carboxylate (S35).**[3]

To a stirring solution of *tert*-butyl piperazine-1-carboxylate (0.100 g, 0.537 mmol) in dry THF (2.0 mL) were added DIPEA (0.18 mL, 1.074 mmol) and ethyl 2-bromoacetate (0.12 mL, 0.564 mmol) and the mixture was stirred at room temperature for 18 h. The reaction was evaporated to dryness, the crude was diluted with water (30 mL) and extracted with EA (× 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness to afford a yellow oil (0.140 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.19 (q, *J* = 7.1 Hz, 2H), 3.56 – 3.41 (m, 4H), 3.23 (s, 2H), 2.67 – 2.45 (m, 4H), 1.45 (s, 9H), 1.27 (t, *J* = 7.2 Hz, 3H).

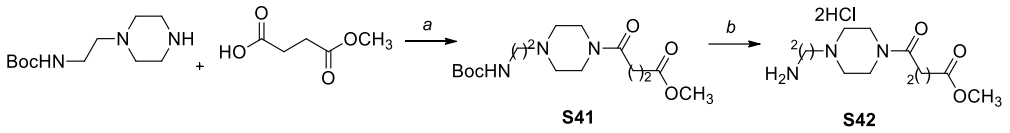
***Tert*-butyl 4-(5-methoxy-5-oxopentyl)piperazine-1-carboxylate (S36).**[4]

To a stirring solution of *tert*-butyl piperazine-1-carboxylate (0.100 g, 0.537 mmol) in dry THF (2.0 mL) were added K_2CO_3 (0.150 g, 1.074 mmol) and methyl 5-bromopentanoate (0.081 mL, 0.564 mmol) and the mixture was stirred at 60°C for 18 h. The reaction was evaporated to dryness, the crude was diluted with water (30 mL) and extracted with EA (× 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The crude was purified by flash column chromatography on SiO_2 (DCM/MeOH, 98:2) to afford the titled compound as a colourless oil (0.112 g, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.47 – 3.38 (m, 4H), 2.48 – 2.24 (m, 8H), 1.70 – 1.59 (m, *J* = 15.1, 7.6 Hz, 2H), 1.57 – 1.42 (m, 11H).

***Tert*-butyl 4-(7-methoxy-7-oxoheptyl)piperazine-1-carboxylate (S37).**[5]

To a stirring solution of *tert*-butyl piperazine-1-carboxylate (0.100 g, 0.537 mmol) in dry THF (2.0 mL) were added K_2CO_3 (0.150 g, 1.074 mmol), methyl 7-bromoheptanoate (0.11 mL, 0.644 mmol), and KI (0.009 g, 0.054 mmol) and the mixture was stirred at 60°C for 18 h. The reaction was evaporated to dryness, the crude was diluted with water (30 mL) and extracted with EA (× 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and

evaporated to dryness. The crude was purified by flash column chromatography on SiO_2 (DCM/MeOH, 98:2) to afford the titled compound as a colourless oil (0.184 g, 97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.47 – 3.36 (m, 4H), 2.41 – 2.28 (m, 6H), 1.95 – 1.77 (m, 2H), 1.68 – 1.57 (m, 3H), 1.54 – 1.27 (m, 14H).

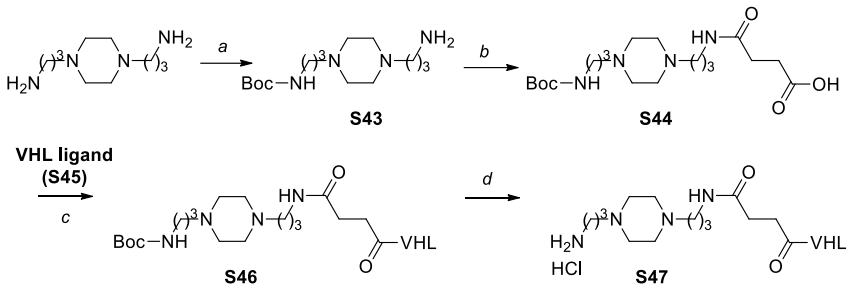


Reagents and conditions: (e) HATU, DIPEA, rt; (b) HCl 4.0N in dioxane, rt.

Methyl 3-(4-(((*tert*-butoxycarbonyl)amino)methyl)piperazin-1-yl)-3-oxopropanoate (S41).

Under nitrogen atmosphere, to a stirred solution of 4-methoxy-4-oxobutanoic acid (0.100 mg, 0.757 mmol), *tert*-butyl (2-(piperazin-1-yl)ethyl)carbamate (0.174 mg, 0.757 mmol) and DIPEA (0.396 mL, 2.271 mmol) in dry DMF (1.0 mL) was added HATU (0.360 mg, 0.964 mmol) and the reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with water, extracted with EA (x3) and the reunited organic phases were washed with water (x3), brine (x3), dried over Na_2SO_4, and evaporated to dryness. The crude was purified by flash column chromatography on SiO_2 (DCM/MeOH, 98:2) to afford the titled compound as a colourless oil (0.125 g, 48% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.03 (bs, 1H), 3.79 – 3.62 (m, 5H), 3.62 – 3.50 (m, 2H), 3.37 – 3.20 (m, 2H), 2.76 – 2.35 (m, 10H), 1.45 (s, 9H).

Methyl 3-(4-(aminomethyl)piperazin-1-yl)-3-oxopropanoate dihydrochloride (S42). General General Procedure B (4 h) was followed by using methyl **S41** (0.118 g, 0.343 mmol) and 4.0 N HCl in dioxane (1.18 mL) to afford the titled compound as white solid (0.070 g, 71% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (bs, 1H), 8.59 (s, 2H), 4.77 – 3.98 (m, 4H), 3.43 – 2.89 (m, 11H), 2.74 – 2.55 (m, 4H).



Reagents and conditions: (a) Boc_2O, dry MeOH, rt; (b) succinic anhydride, dry DCM, rt; (c) HATU, DIPEA, dry DMF, rt; (d) HCl 4.0N in dioxane, rt.

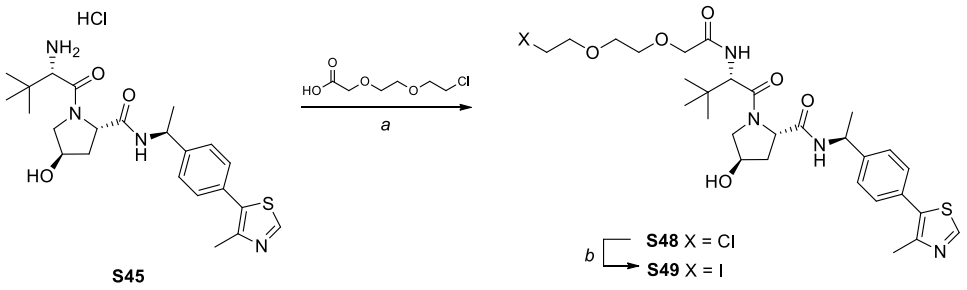
***Tert*-butyl (3-(4-(3-(4-(((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)amino)-4-oxobutanamido)propyl)piperazin-1-yl)propyl)carbamate (S46).**

Under a nitrogen atmosphere, a solution of **S43**[11] (0.150 g, 0.499 mmol) and dihydrofuran-2,5-dione (0.124 g, 0.458 mmol) in dry DCM (2.0 mL) was stirred at room temperature for 4 h. Then, the reaction mixture was evaporated to dryness to give **S44** (0.190 g, 95% yield) as a colorless oil, which was used in the successive step without further purification.

Thus, general Procedure A (18 h) was followed by using **S44** (0.190 g, 0.474 mmol) and **S45**[12] (0.228 g, 0.474 mmol) to afford the titled compound as colourless oil (0.095 g, 24% yield) after purification by flash column chromatography on SiO_2 (DCM/MeOH, 90:5 to 80:20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (s, 1H), 7.69 – 7.59 (m, 1H), 7.49 (bs, 1H), 7.43 – 7.32 (m, 4H), 7.06 (bs, 1H), 5.19 (bs, 1H), 5.15 – 5.04 (m, 1H), 4.75 (t, *J* = 8.0 Hz, 1H), 4.56 (d, *J* = 8.6 Hz, 1H), 4.47 (s, 1H), 4.01 (d, *J* = 11.2 Hz, 1H), 3.59 (dd, *J* = 11.2, 3.1 Hz, 1H), 3.44 – 3.11 (m, 4H), 3.10 – 2.20 (m, 20H), 2.16 – 2.06 (m, 1H), 1.82 – 1.61 (m, 4H), 1.57 – 1.27 (m, 12H), 1.05 (s, 9H). HRMS (ESI) m/z [M + H]+ calcd for $C_{42}H_{66}N_8O_7S$ 827.48479, found 827.48713. UPLC retention time: 3.777 min.

***N1*-(3-(4-(3-aminopropyl)piperazin-1-yl)propyl)-*N4*-((*S*)-1-((2*S*,4*R*)-4-hydroxy-2-(((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)carbamoyl)pyrrolidin-1-yl)-3,3-dimethyl-1-oxobutan-2-yl)succinamide hydrochloride (S47**).

The solution of **S46** (0.095 g, 0.115 mmol) in 4.0N HCl in dioxane (1.0 mL) was stirred at room temperature for 3 h. The solvent was evaporated to dryness, and the solid was tritured with DEE and collected by filtration, yielding the titled compound (0.83 g, 94% yield) as a white solid, which was directly used in the successive step without further purification.



Reagents and conditions: (a) HATU, DIPEA, dry DMF, rt; (b) NaI, dry acetone, reflux, 48h.

(2*S*,4*R*)-1-((*S*)-2-(2-(2-(2-chloroethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-4-hydroxy-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (S48).

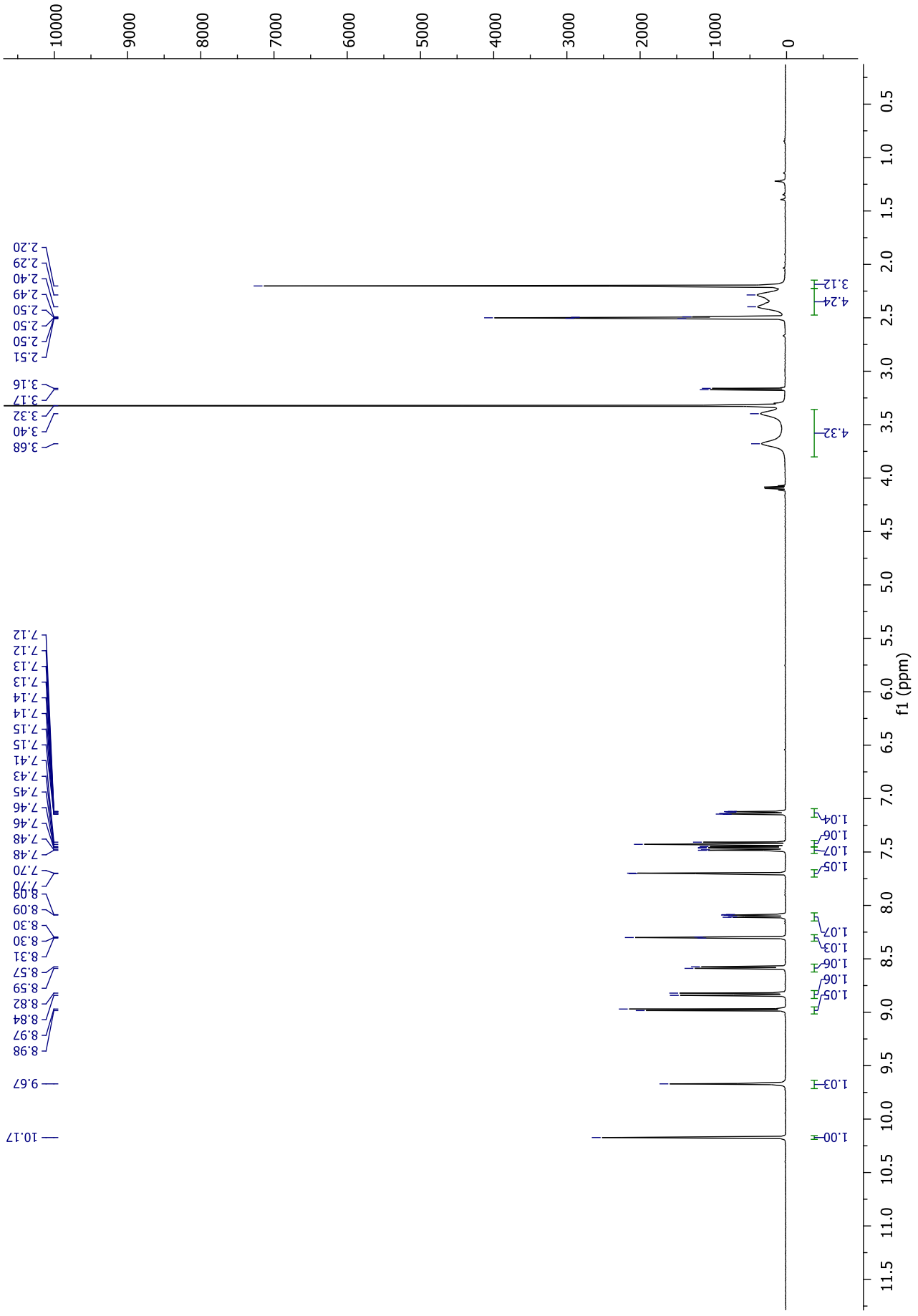
General Procedure A (5 h) was followed by using **S45** (0.250 g, 0.519 mmol) and 2-(2-(2-chloroethoxy)ethoxy)acetic acid[13] (0.095 g, 0.519 mmol) to afford the titled compound as a colorless oil (0.115 g, 36% yield) after purification by flash column chromatography on SiO_2 (DCM/MeOH, 95:5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.40 – 7.32 (m, 5H), 5.10 – 5.01 (m, 1H), 4.69 (t, *J* = 7.8 Hz, 1H), 4.56 (d, *J* = 8.9 Hz, 1H), 4.47 (bs, 1H), 4.03 – 3.95 (m, 3H), 3.78 – 3.71 (m, 2H), 3.70 – 3.64 (m, 4H), 3.64 – 3.57 (m, 3H), 2.50 (s, 3H), 2.46 – 2.36 (m, 1H), 2.09 – 1.97 (m, 1H), 1.46 (d, *J* = 6.9 Hz, 3H), 1.04 (s, 9H).

(2*S*,4*R*)-4-Hydroxy-1-((*S*)-2-(2-(2-(2-iodoethoxy)ethoxy)acetamido)-3,3-dimethylbutanoyl)-*N*-((*S*)-1-(4-(4-methylthiazol-5-yl)phenyl)ethyl)pyrrolidine-2-carboxamide (S49).

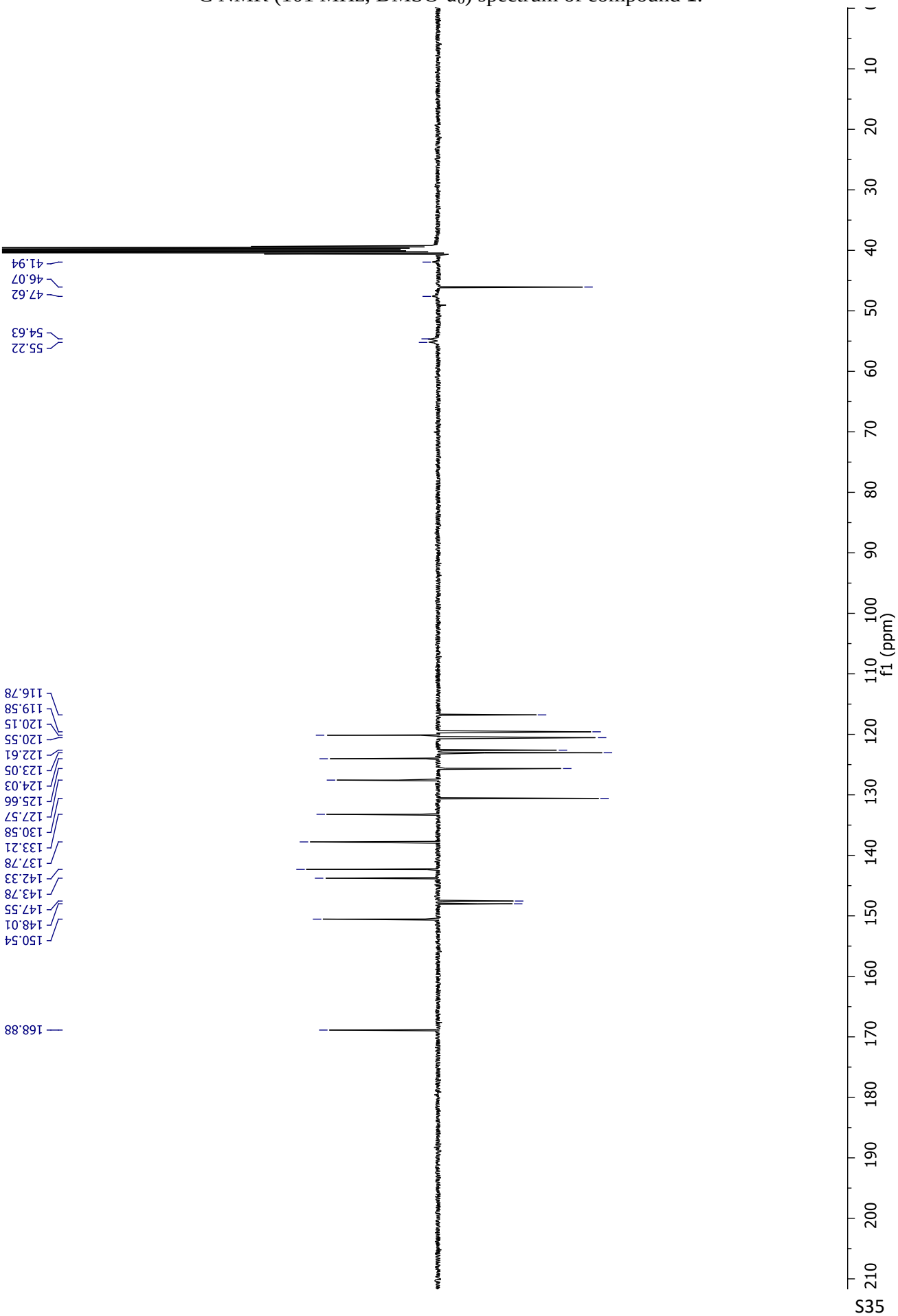
The solution of **S48** (0.045 g, 0.074 mmol) and sodium iodide (111 mg, 0.739 mmol) in dry acetone (2.5 mL) was refluxed for 48 h. After cooling, the yellow suspension was diluted with EA (15 mL) and it was washed with 10% Na_2SO_3 solution (5 mL), H_2O and brine (each 10 mL), dried over Na_2SO_4, filtered and concentrated to dryness to afford the titled compound (0.048 g, 92% yield) as

an orange semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (s, 1H), 7.51 (d, *J* = 7.9 Hz, 1H), 7.45 – 7.37 (m, 4H), 7.35 (d, *J* = 8.4 Hz, 1H), 5.13 – 5.04 (m, 1H), 4.76 (t, *J* = 7.7 Hz, 1H), 4.58 – 4.49 (m, 2H), 4.17 – 3.97 (m, 3H), 3.82 – 3.64 (m, 6H), 3.60 (dd, *J* = 11.4, 3.6 Hz, 1H), 3.29 (t, *J* = 6.9 Hz, 2H), 2.61 – 2.54 (m, 4H), 2.11 – 2.01 (m, 1H), 1.48 (d, *J* = 6.9 Hz, 3H), 1.07 (s, 9H).

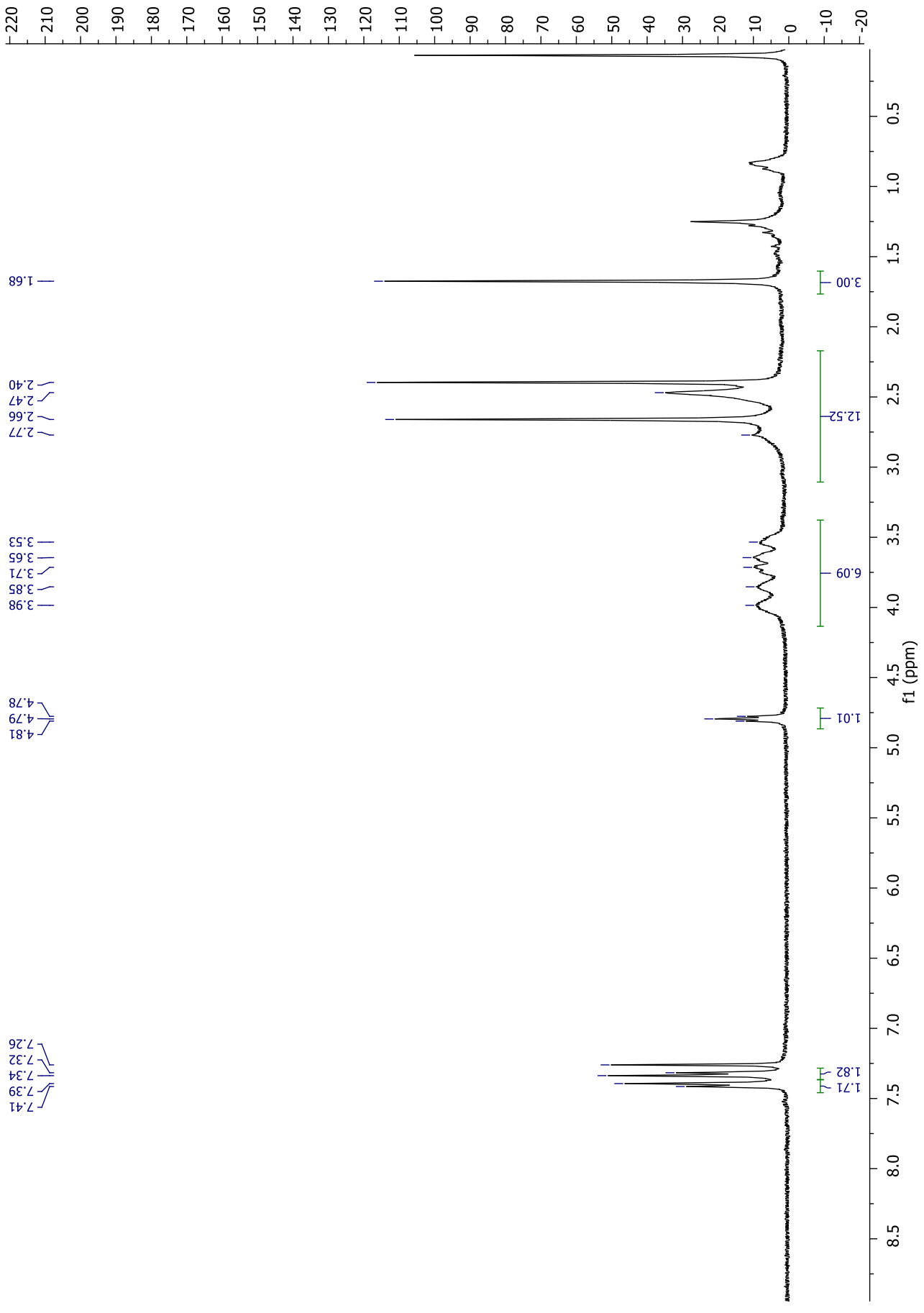
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound **1**.



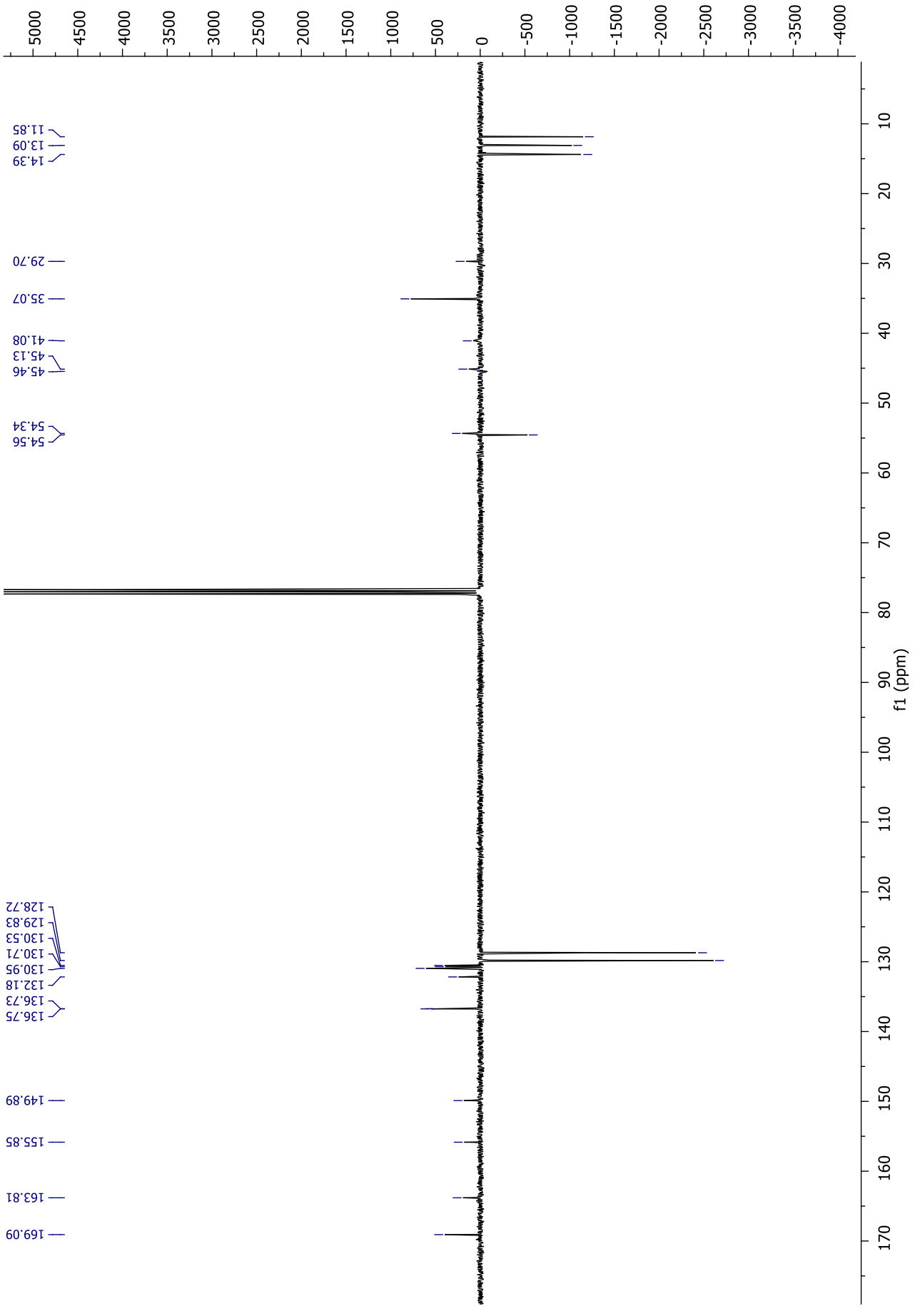
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of compound **1**.



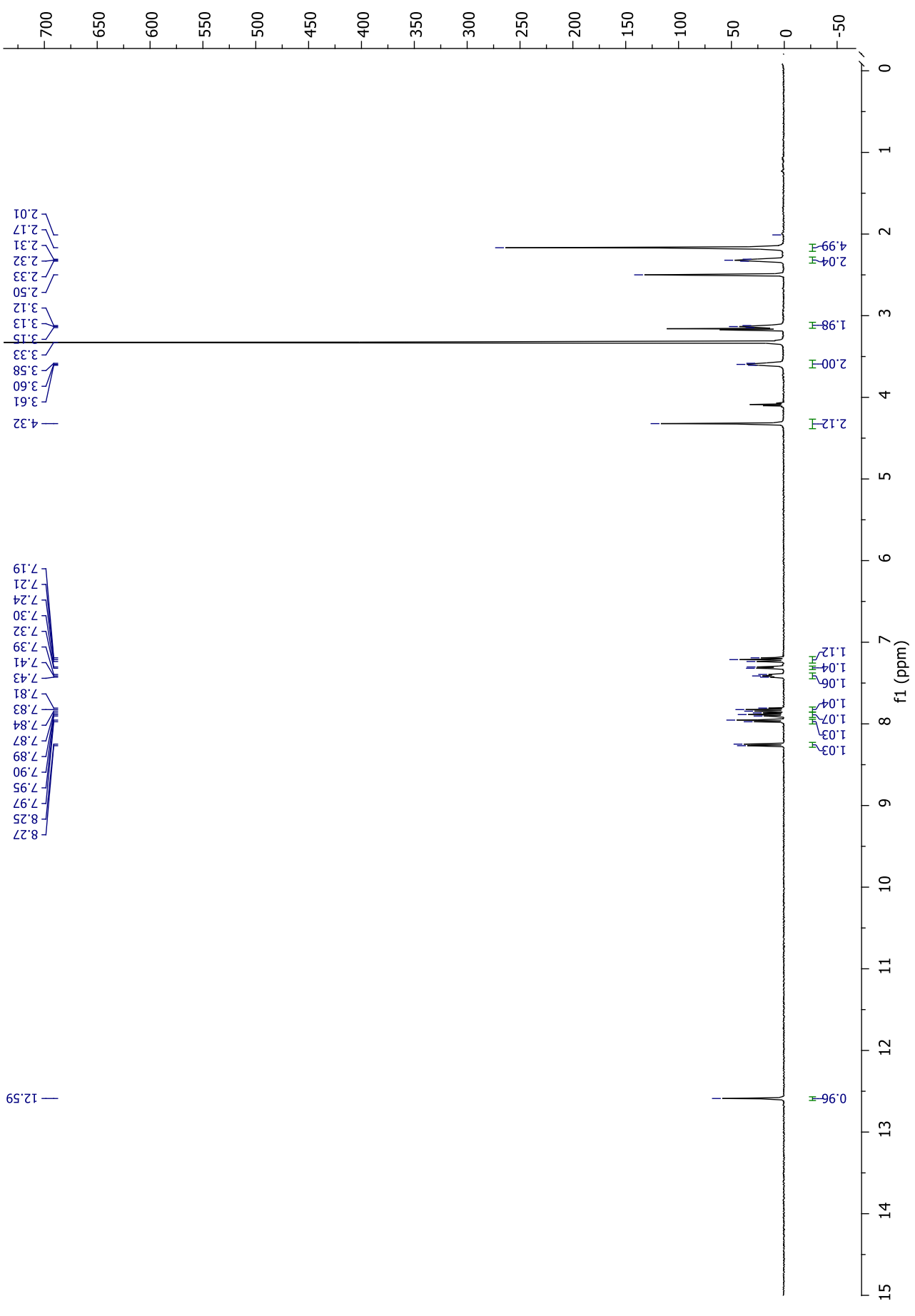
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **2**.



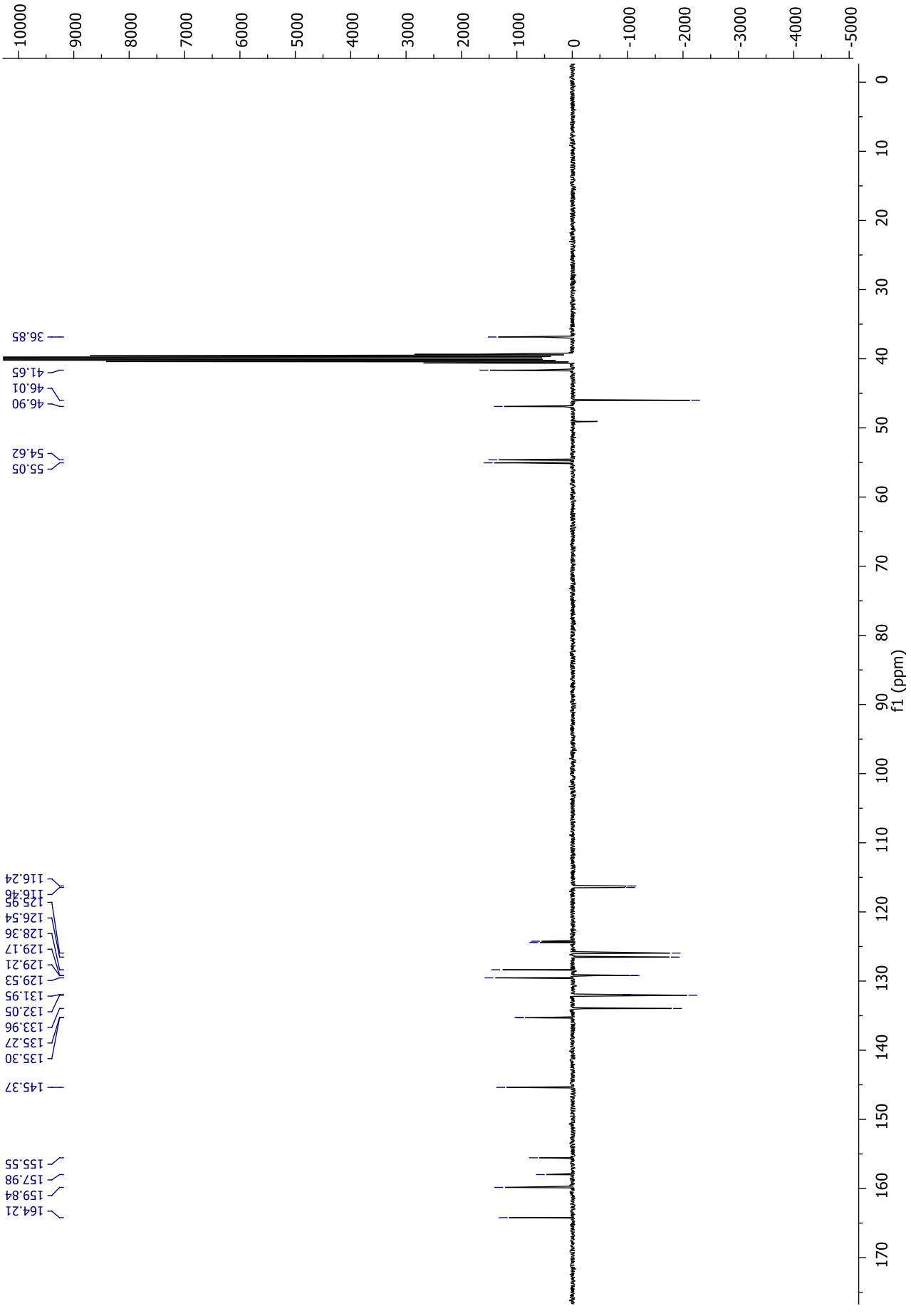
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **2**.



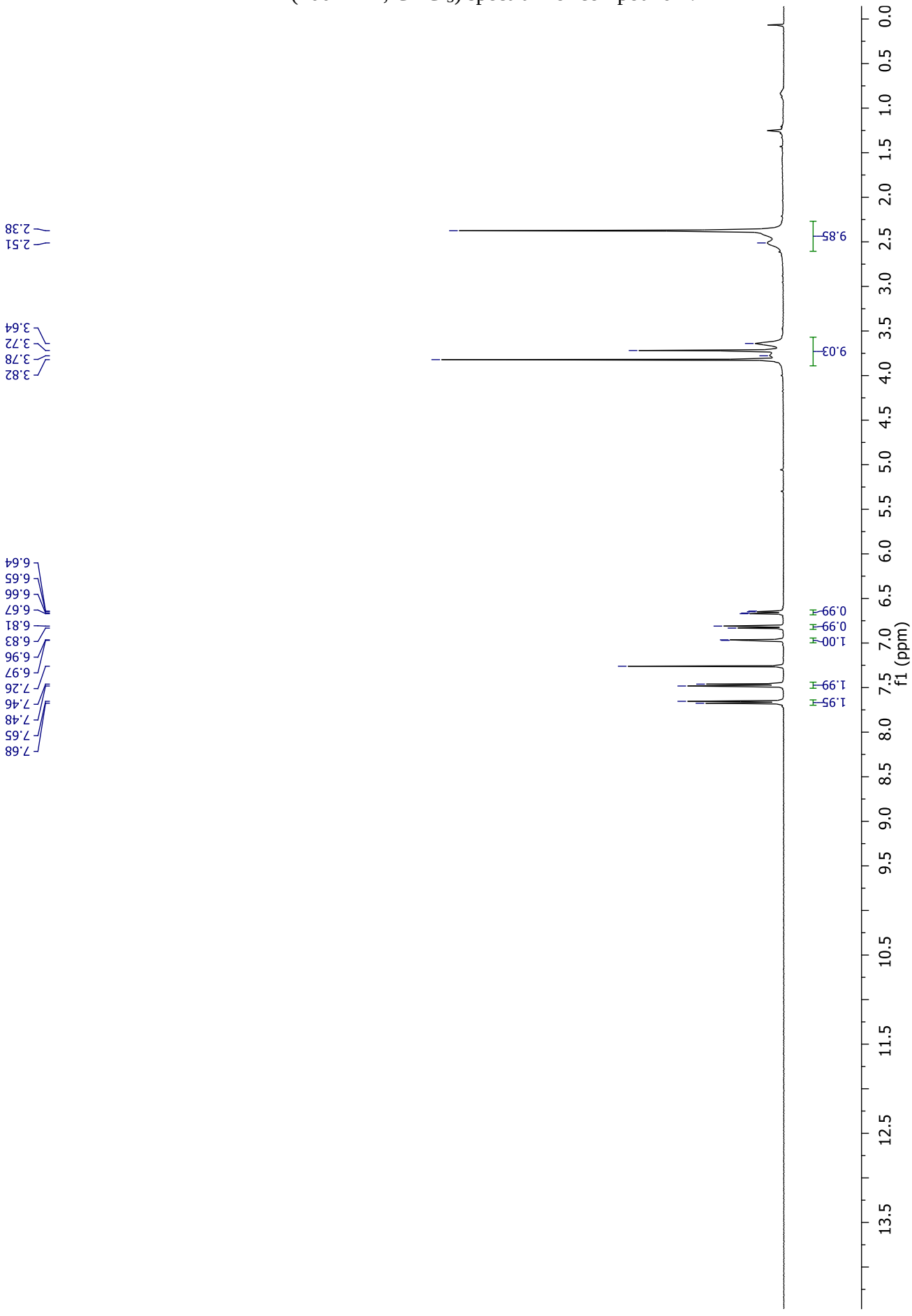
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound **3**.



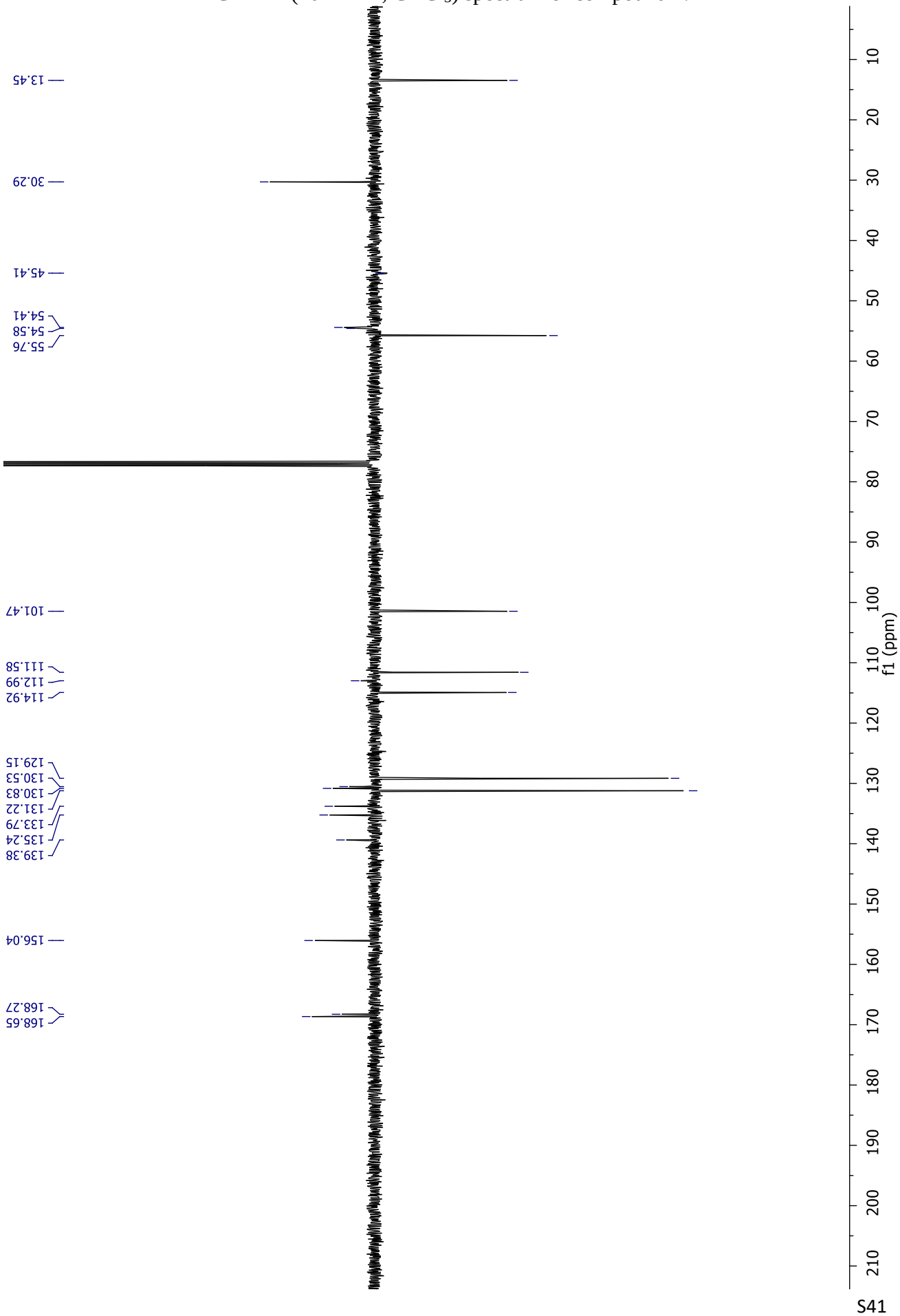
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of compound **3**.



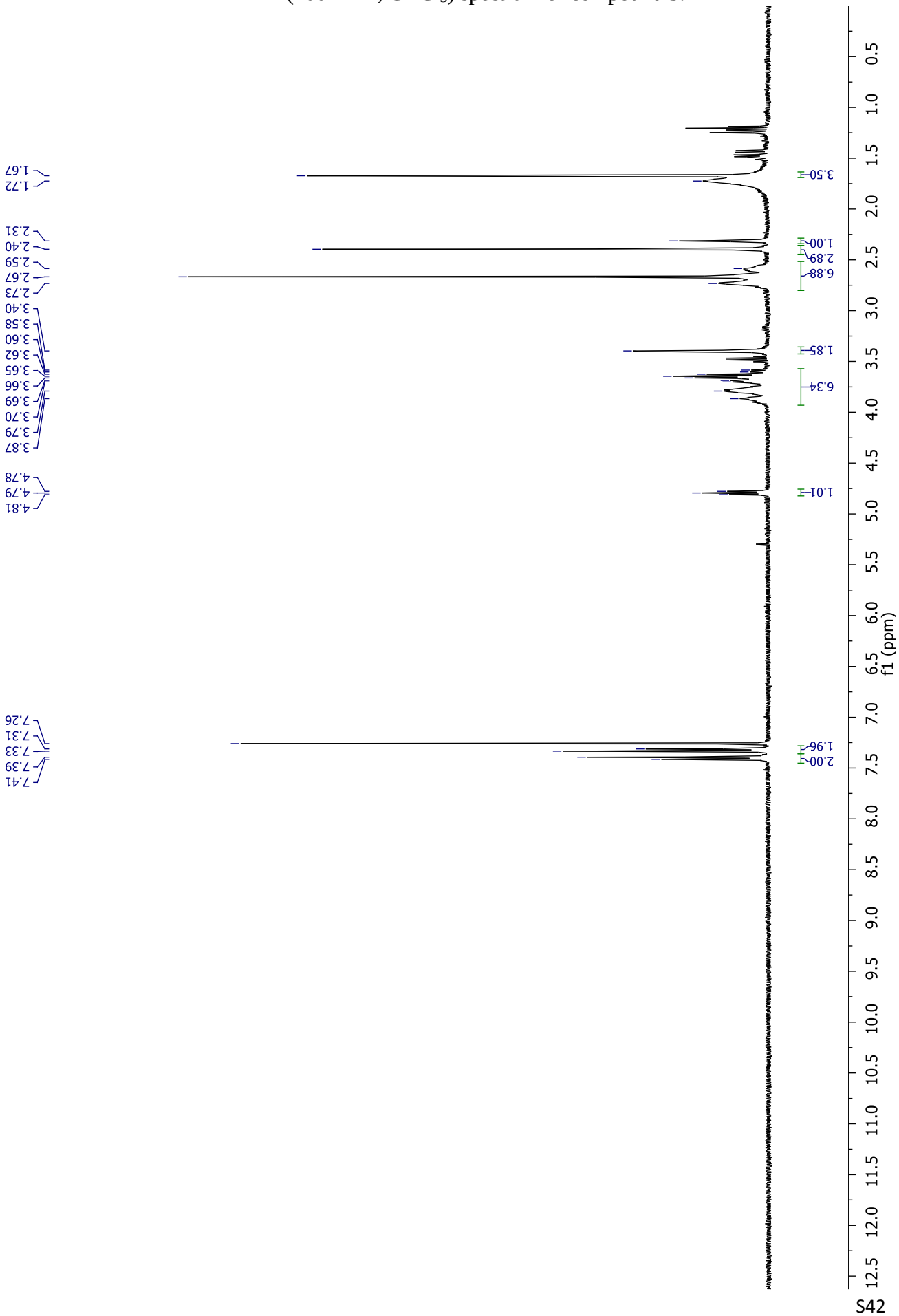
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **4**.



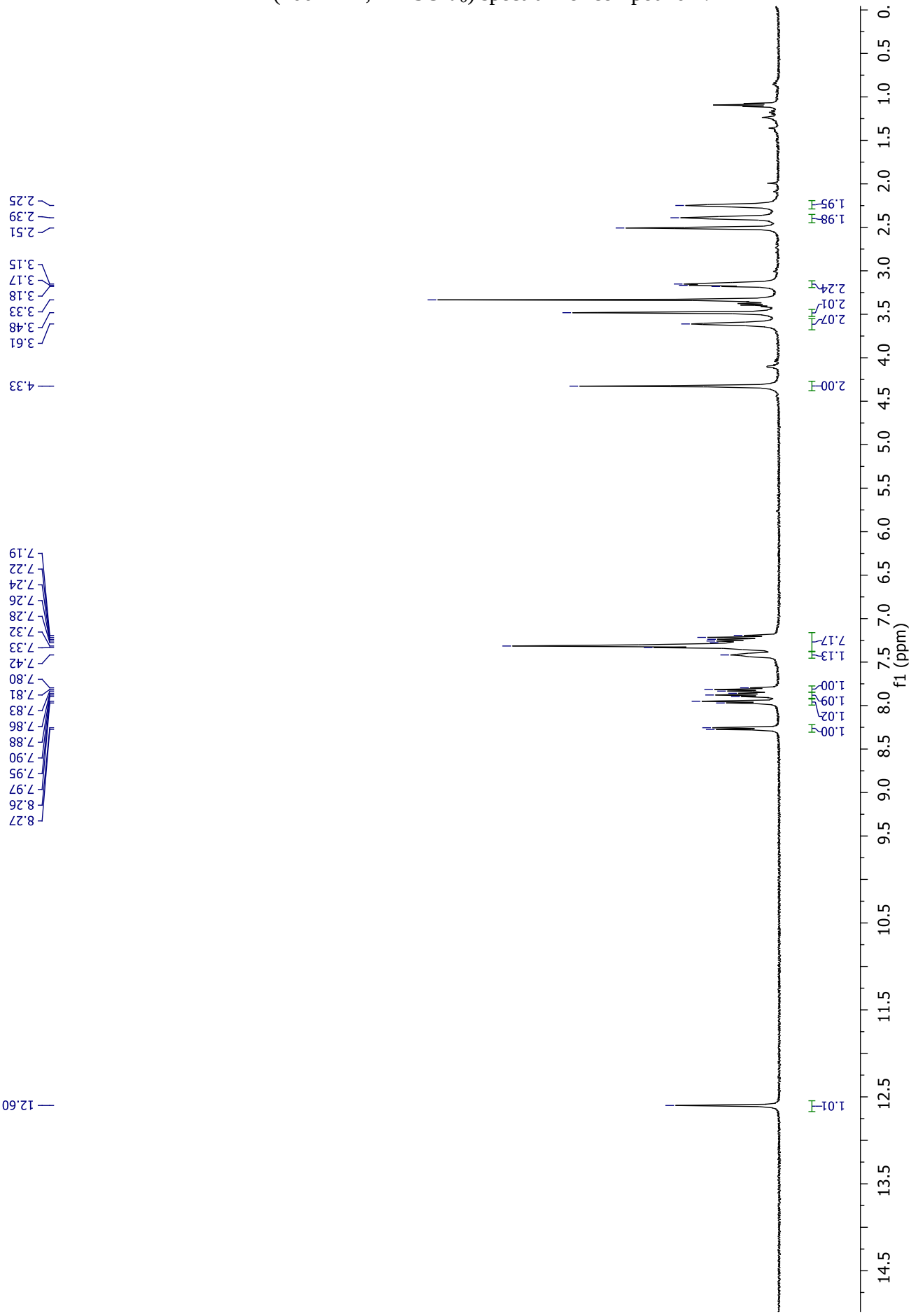
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **4**.



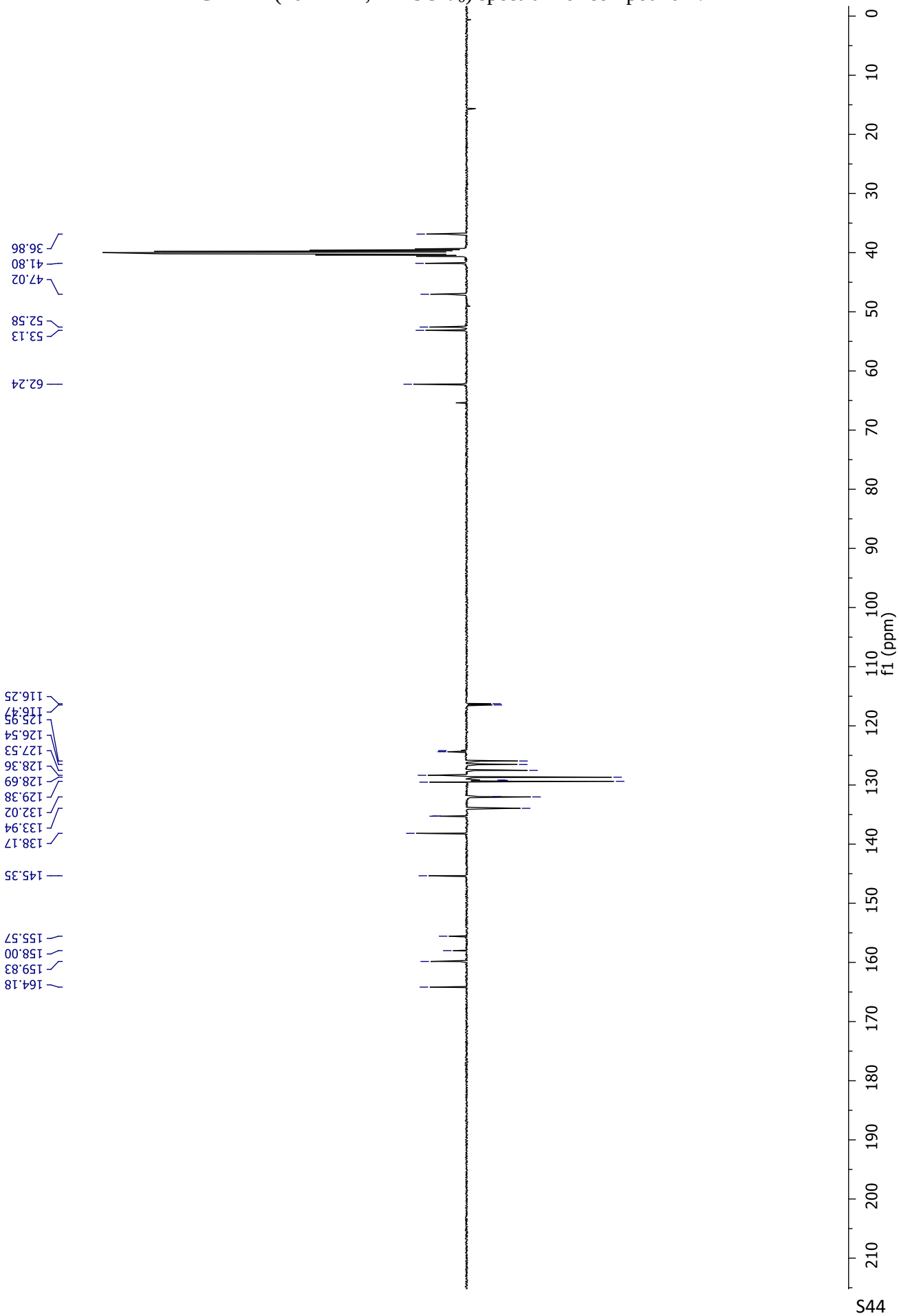
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **5**.



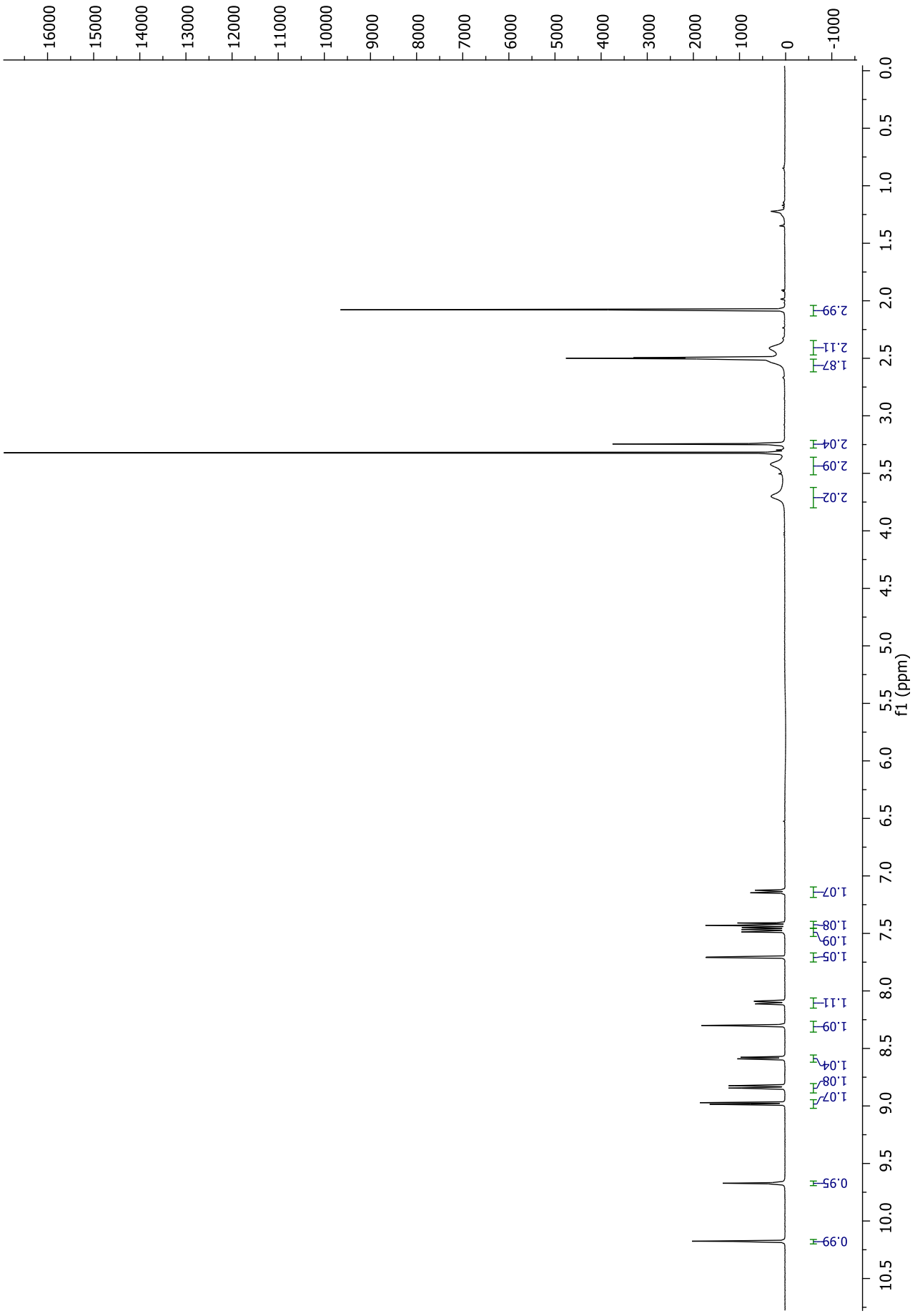
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound **7**.



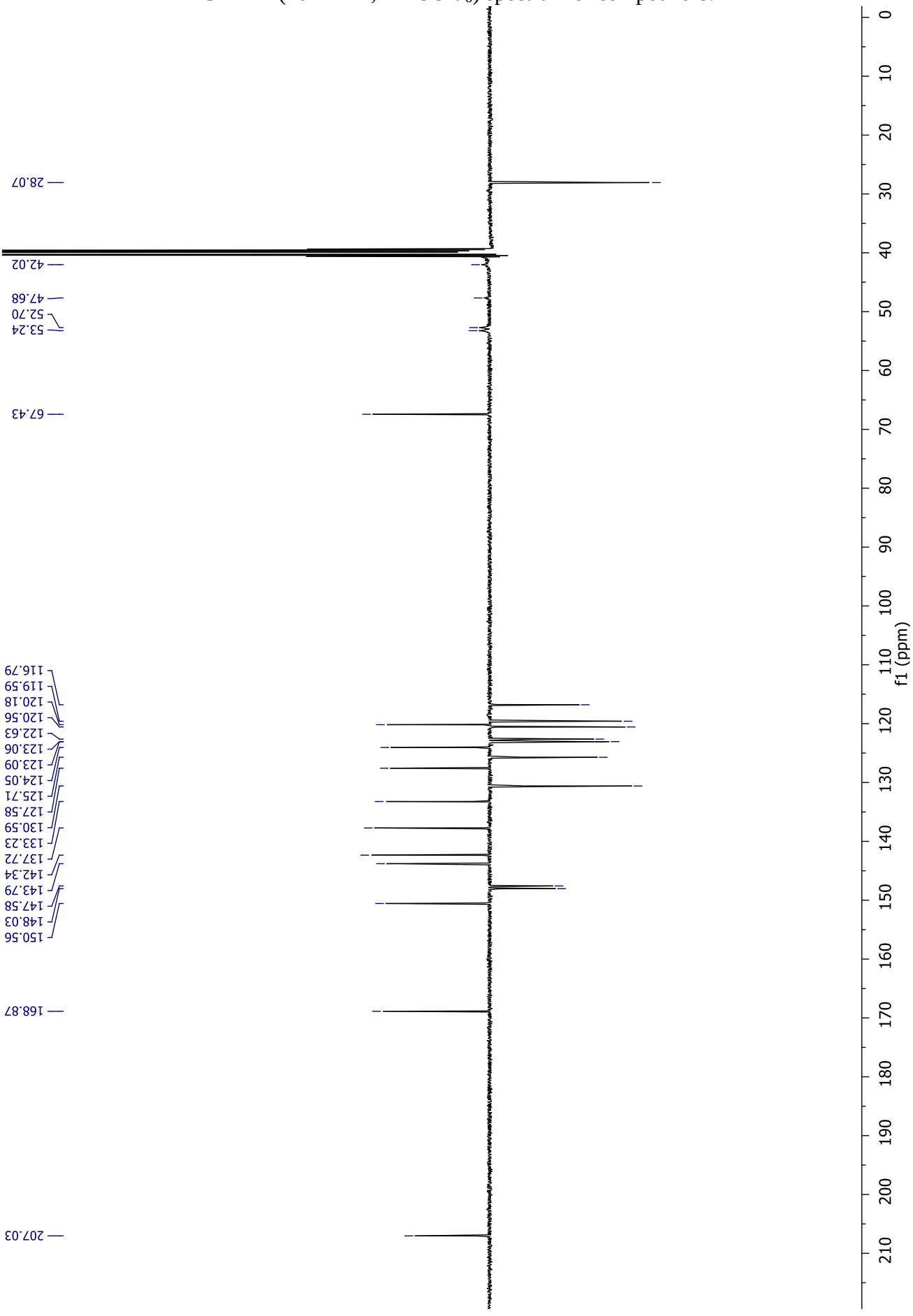
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of compound **7**.



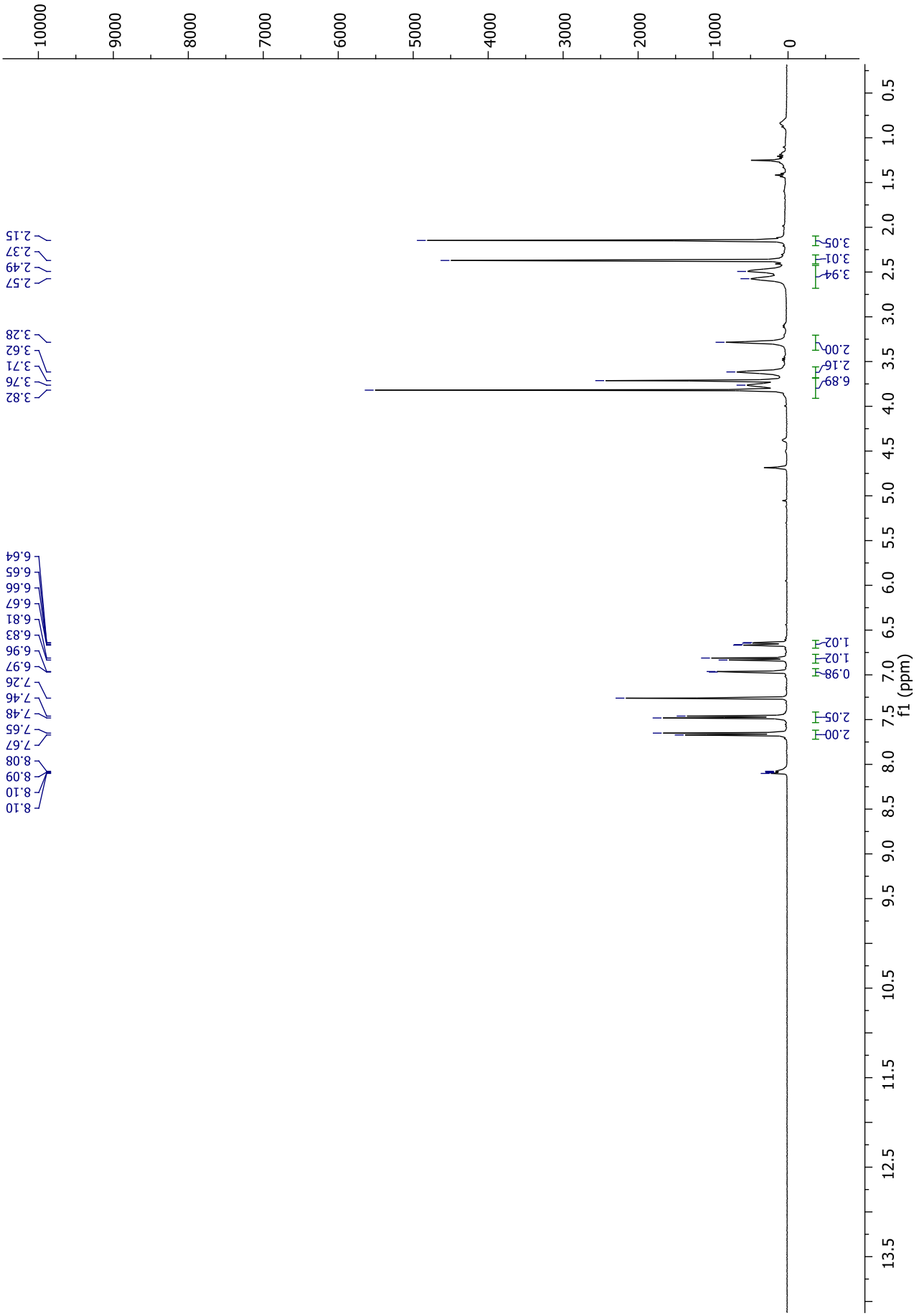
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of compound **8**.



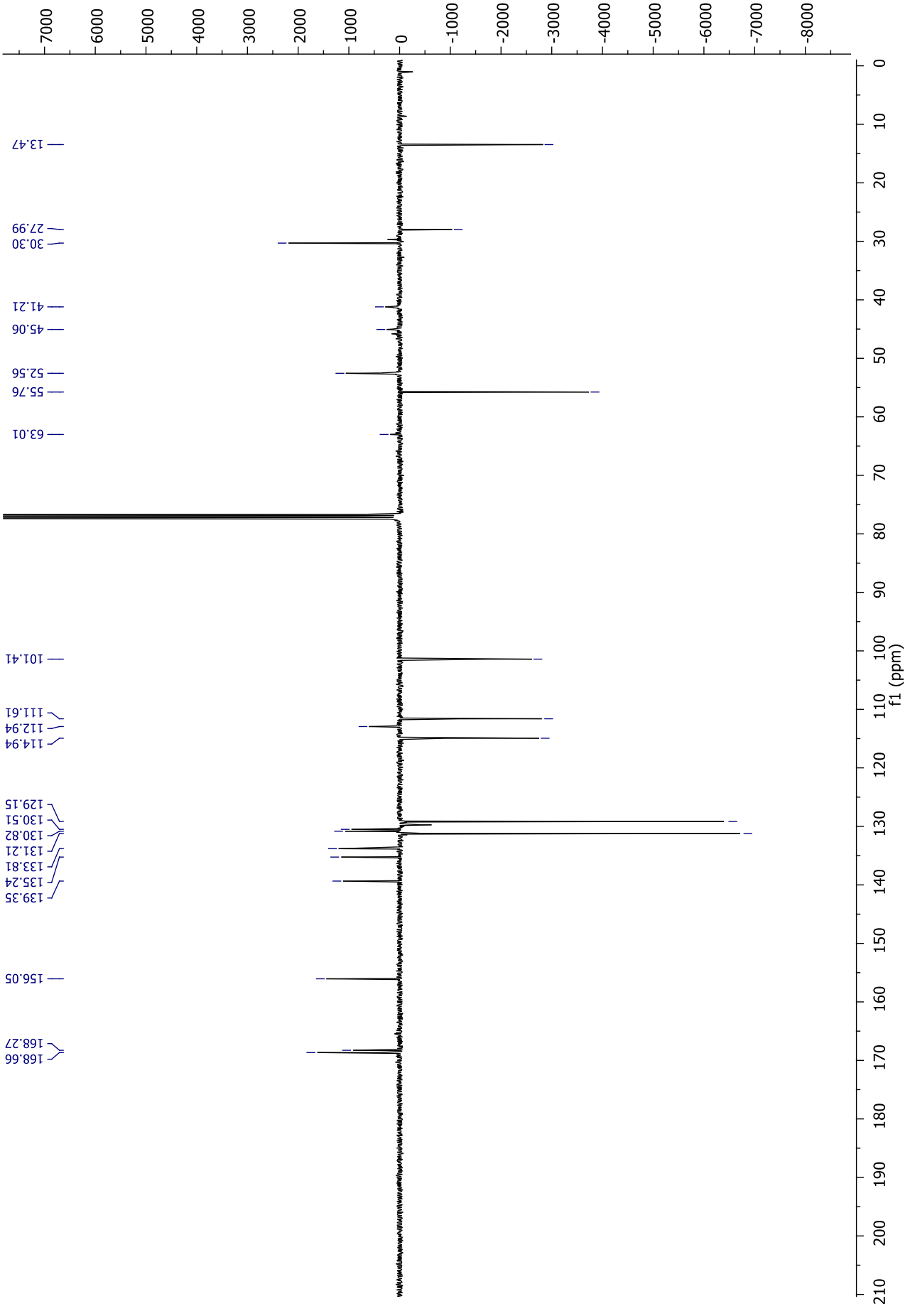
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of compound **8**.



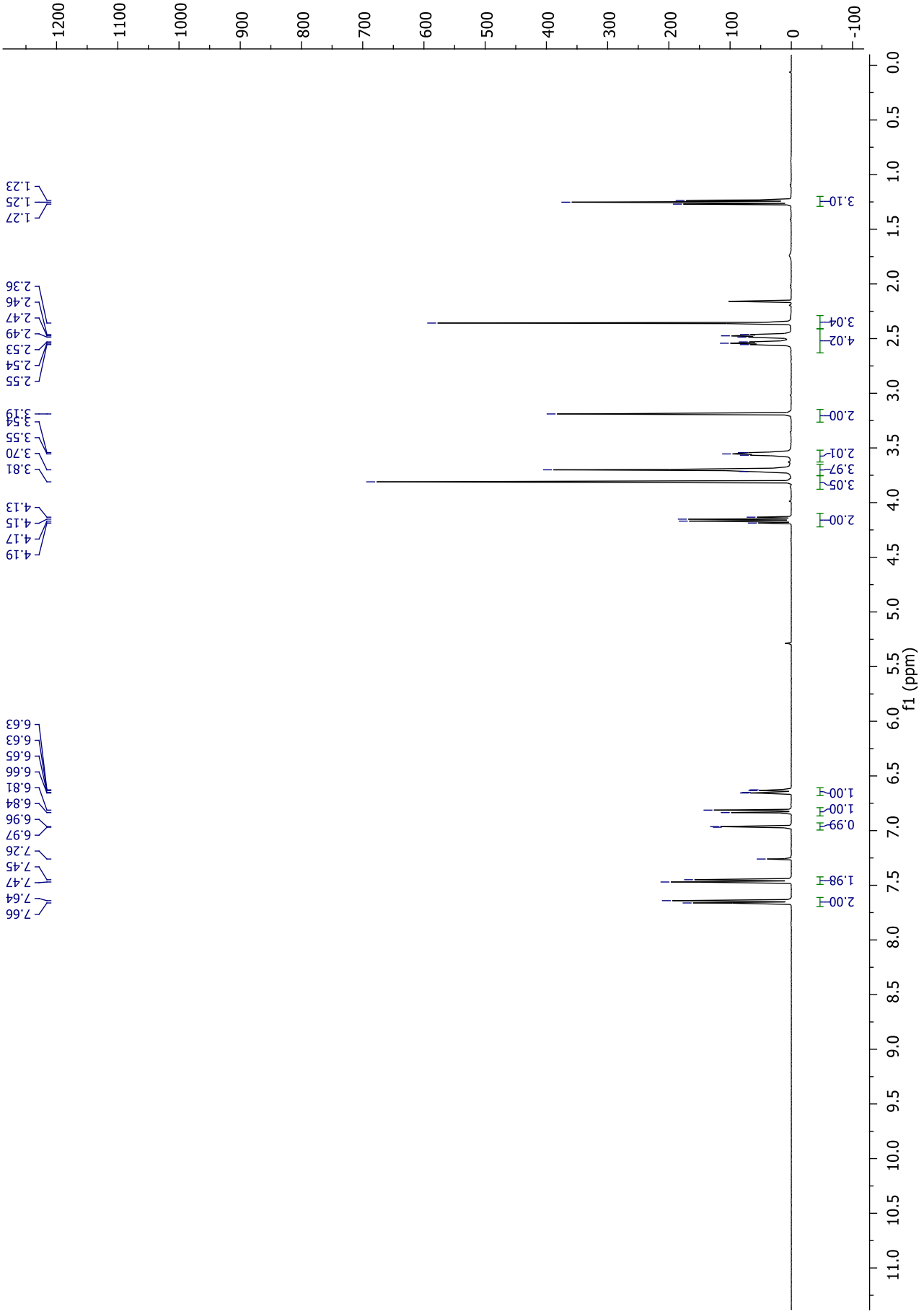
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **9**.



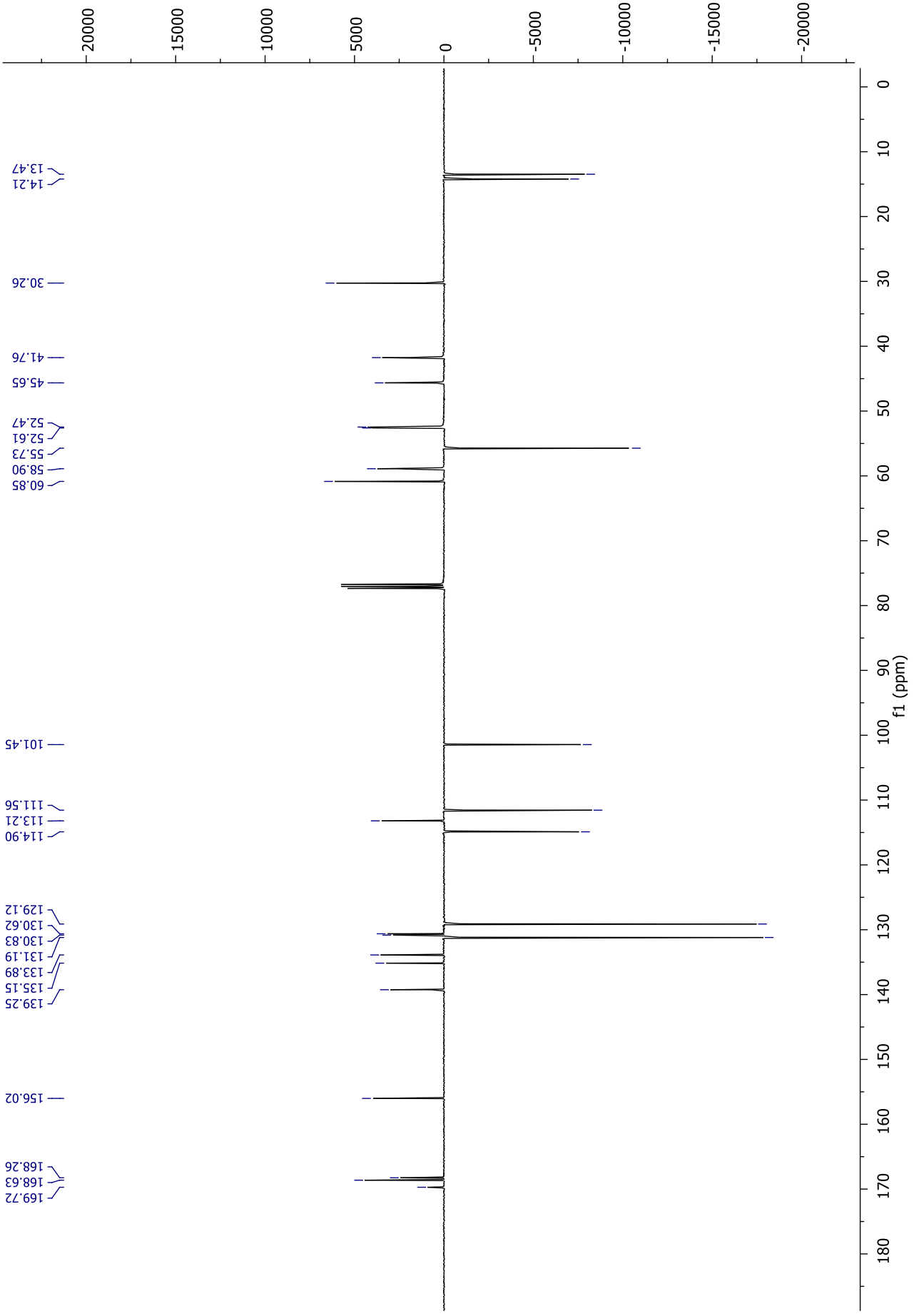
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **9**.



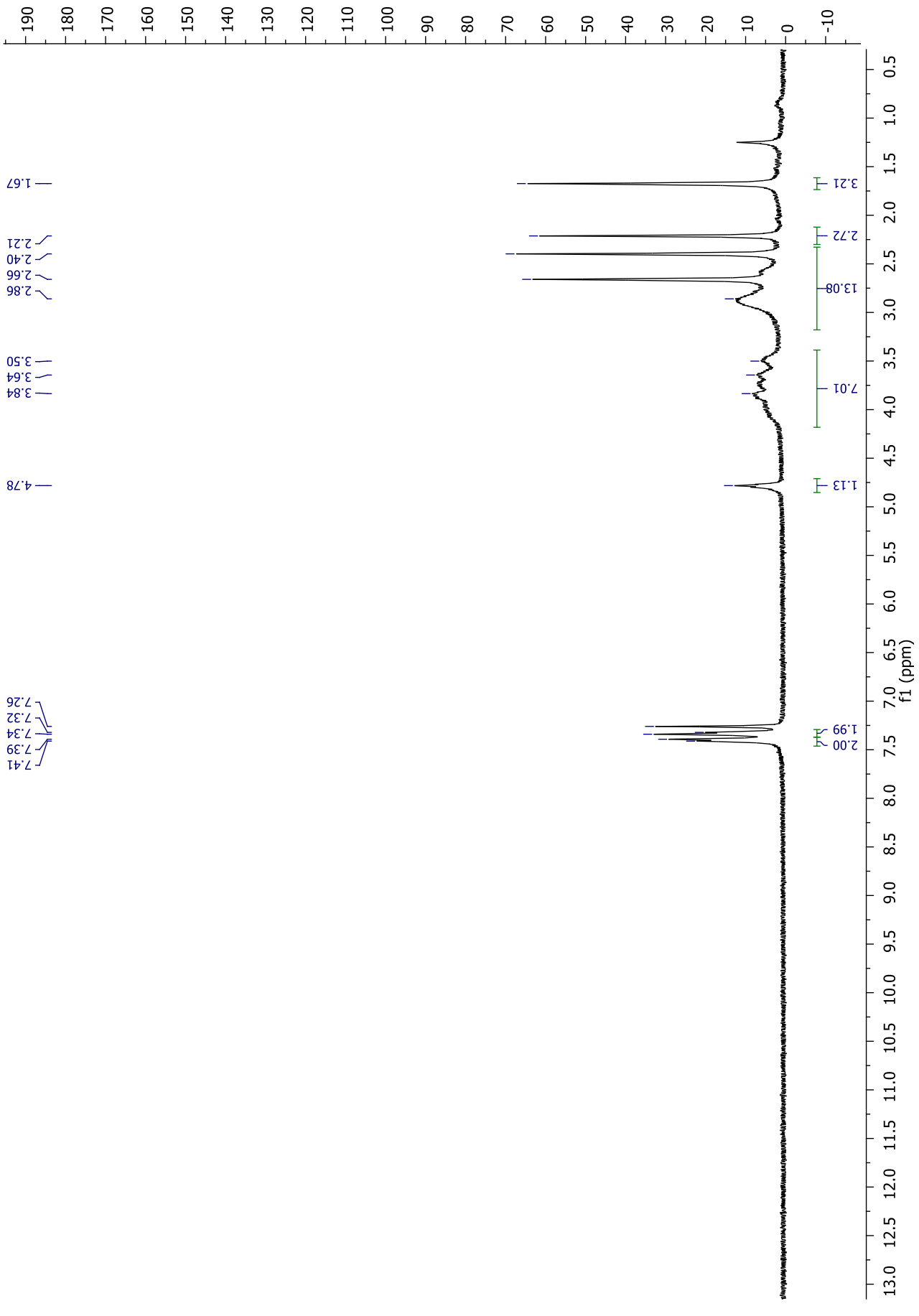
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **10**.



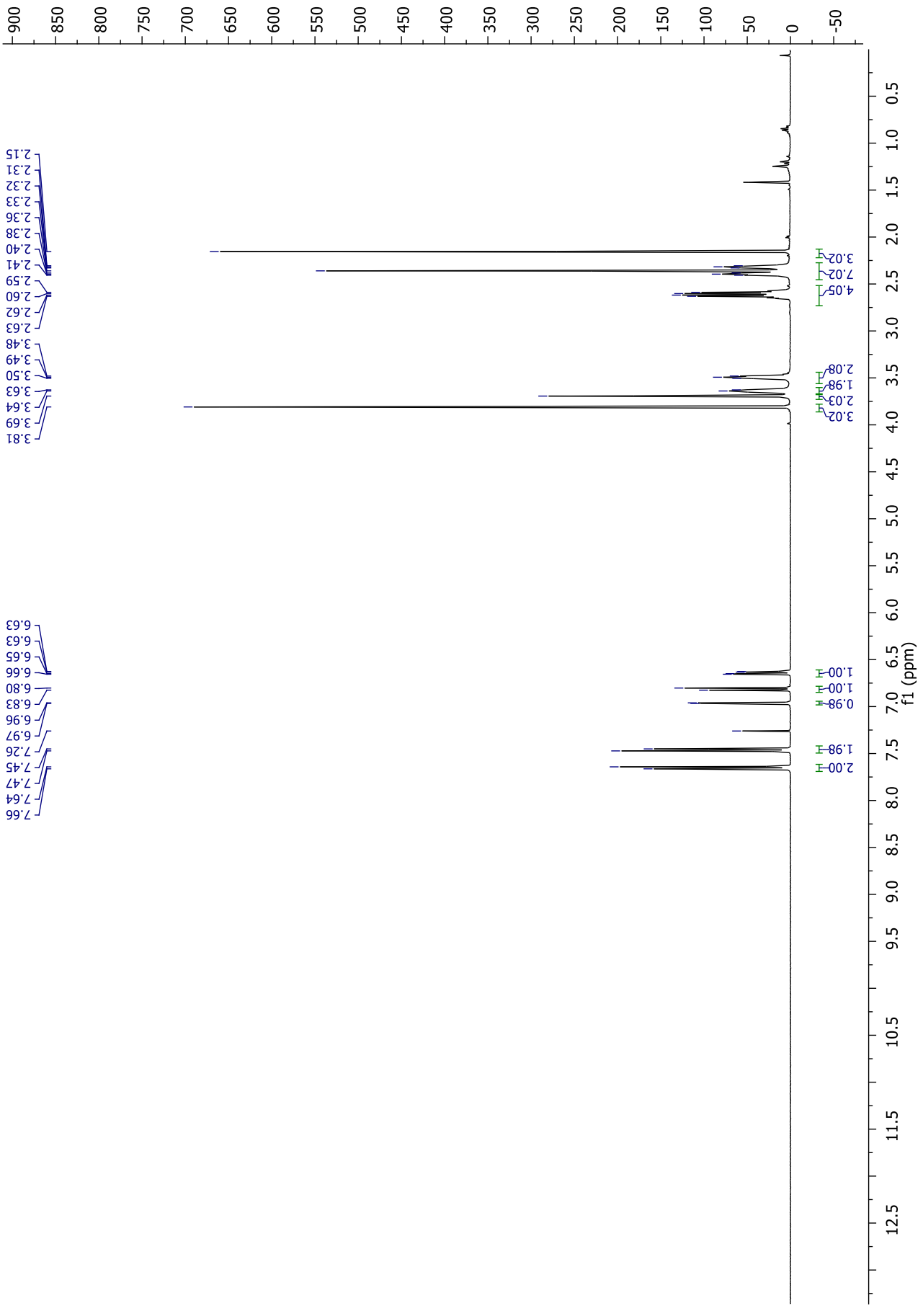
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **10**.



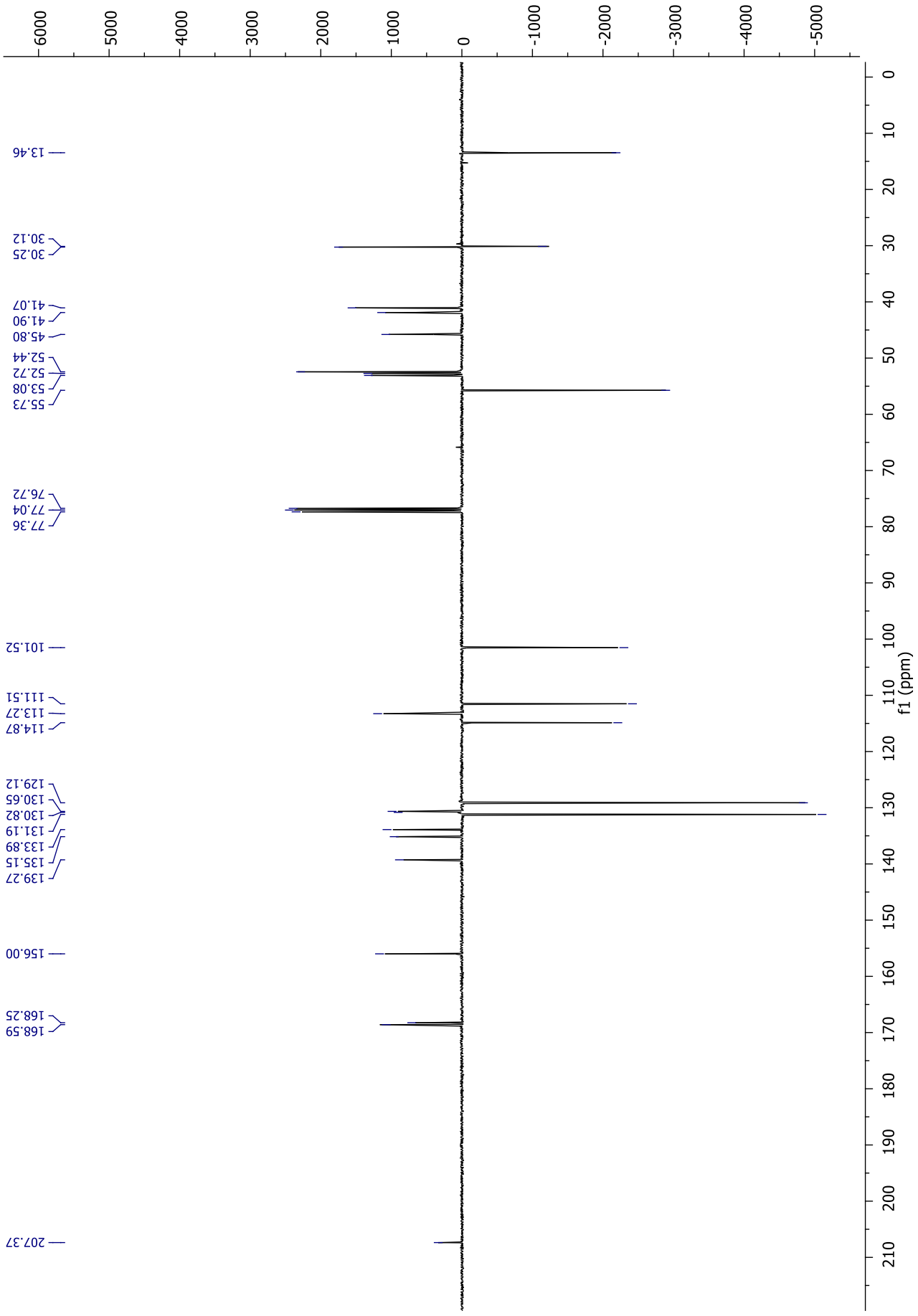
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **11**.



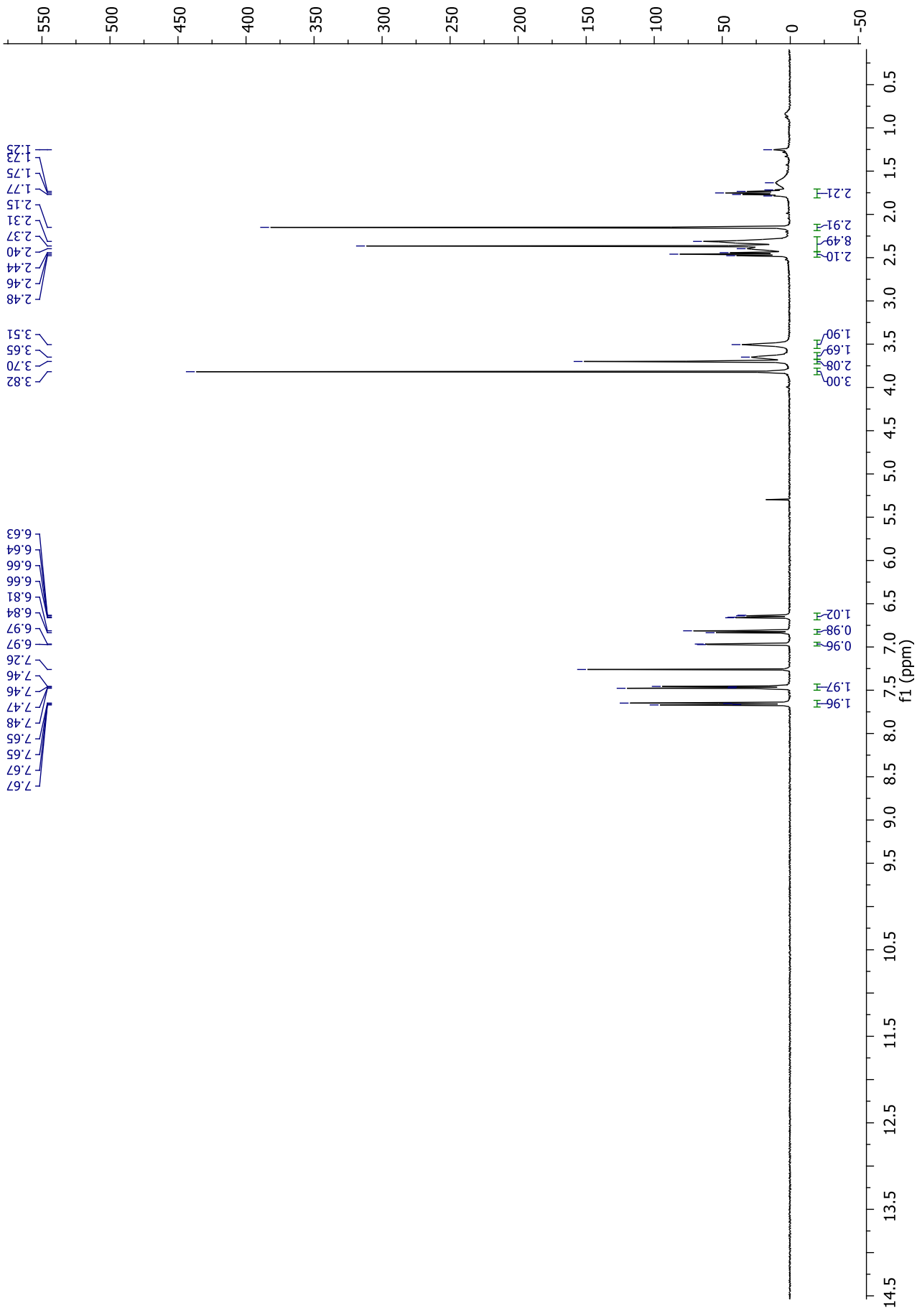
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **12**.



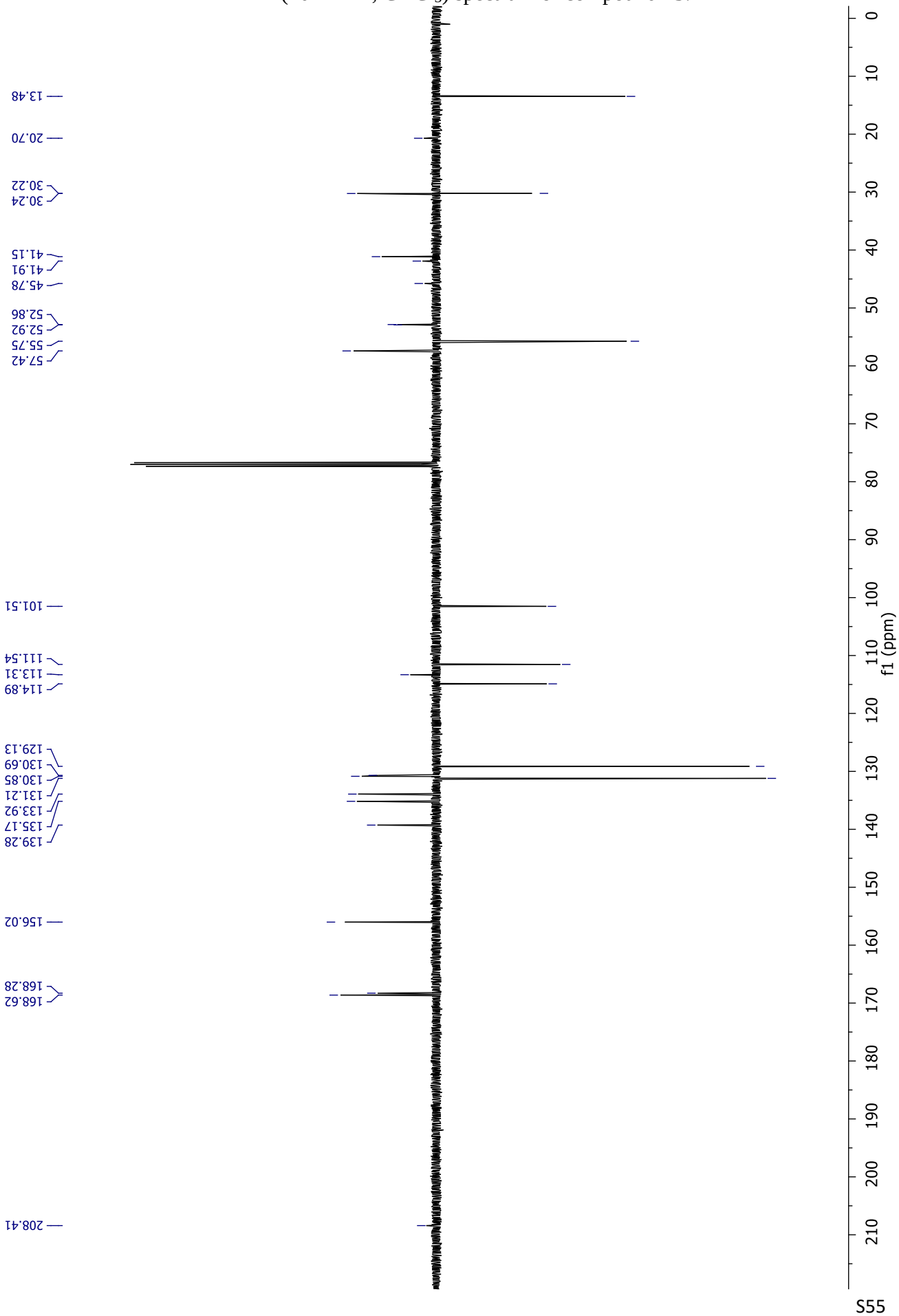
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **12**.



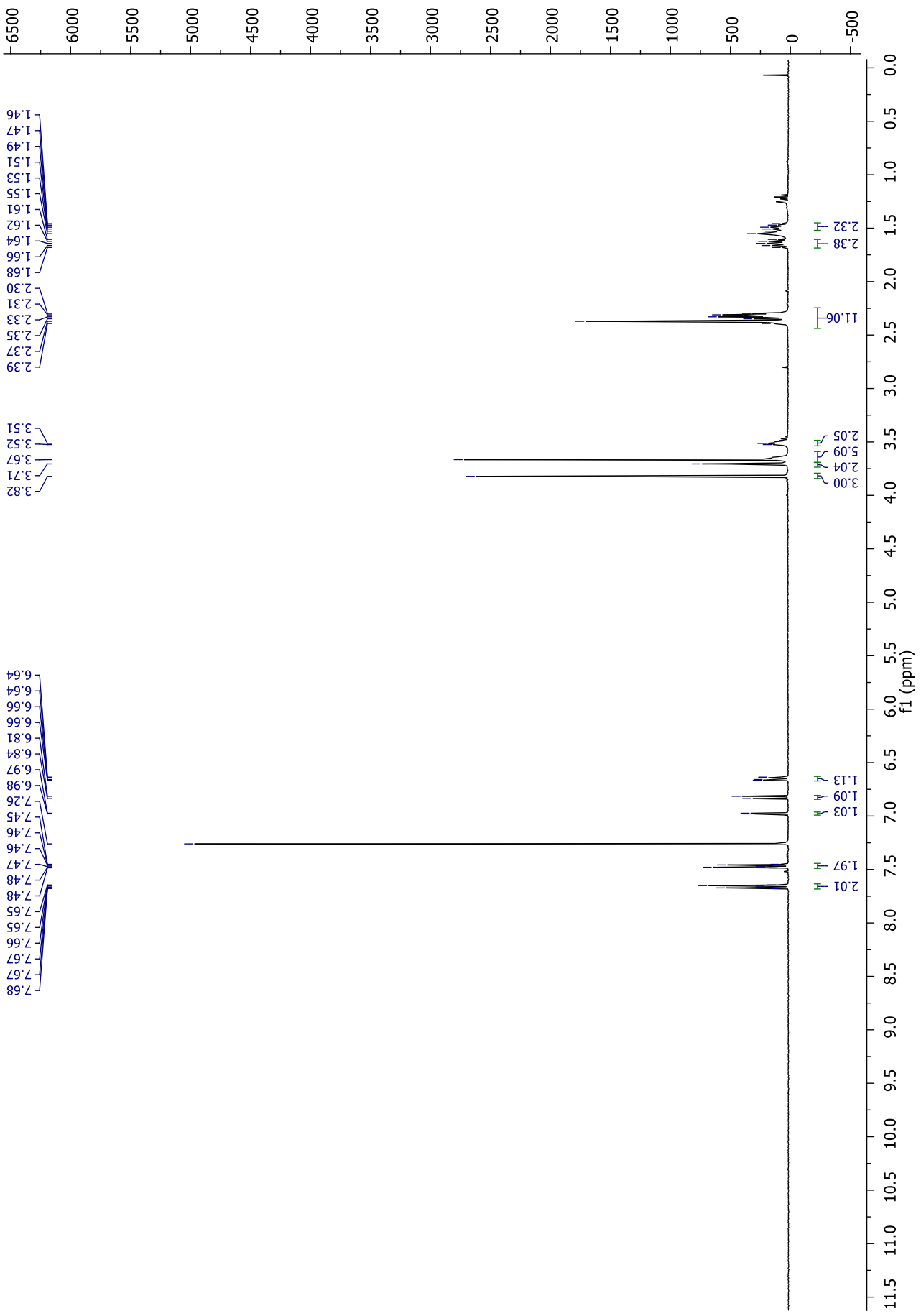
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **13**.



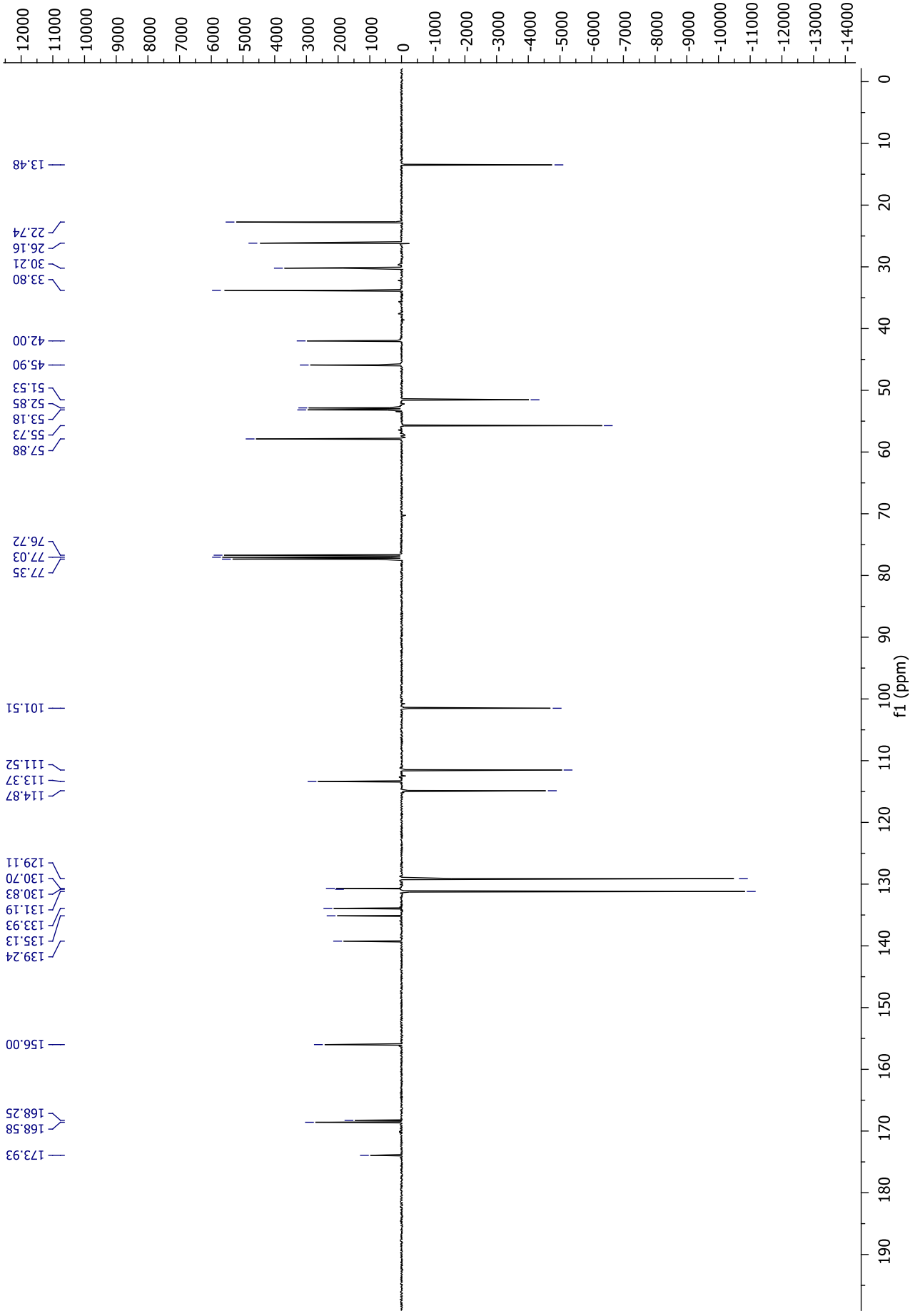
^{1}H NMR (101 MHz, $CDCl_3$) spectrum of compound **13**.



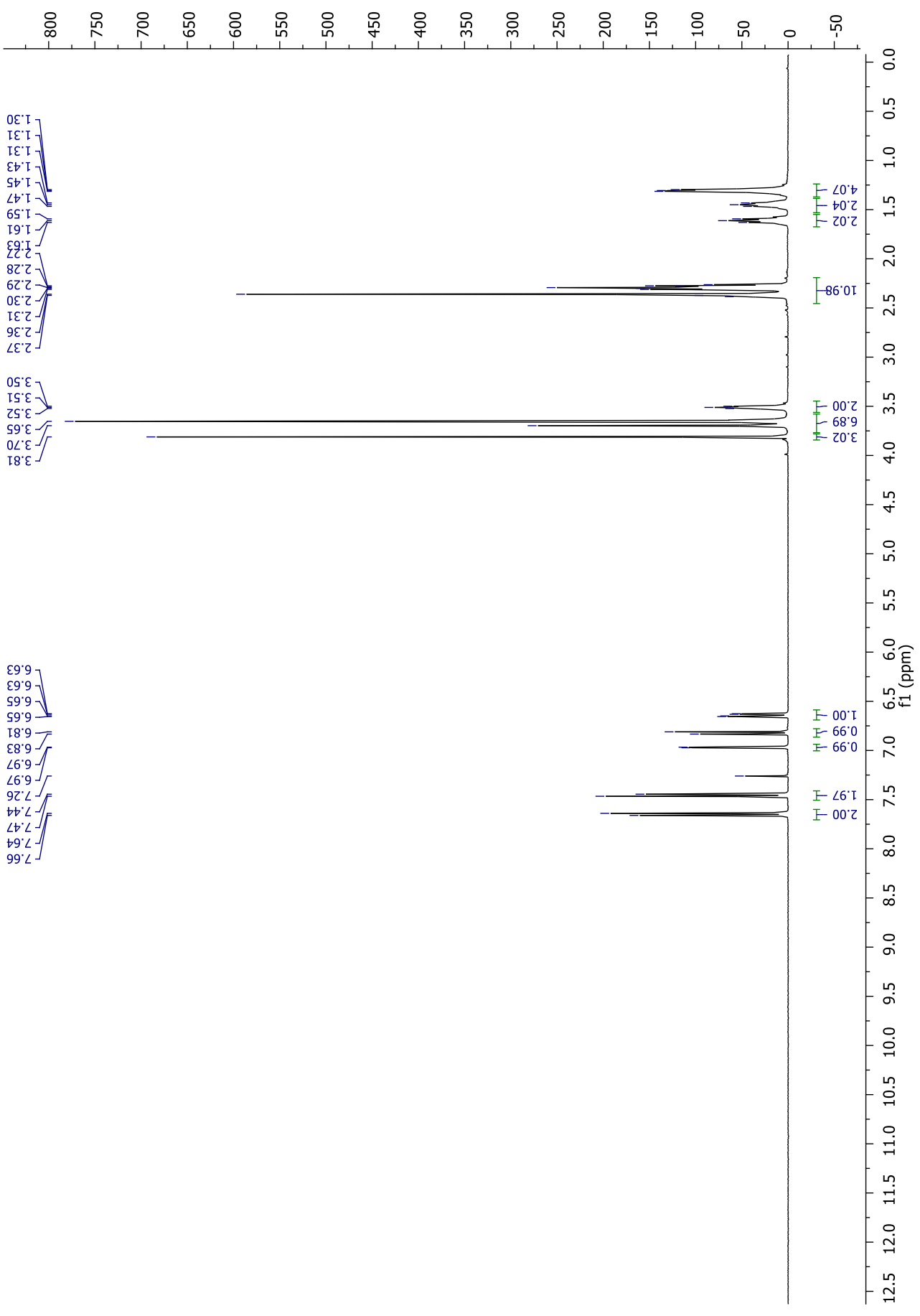
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **14**.



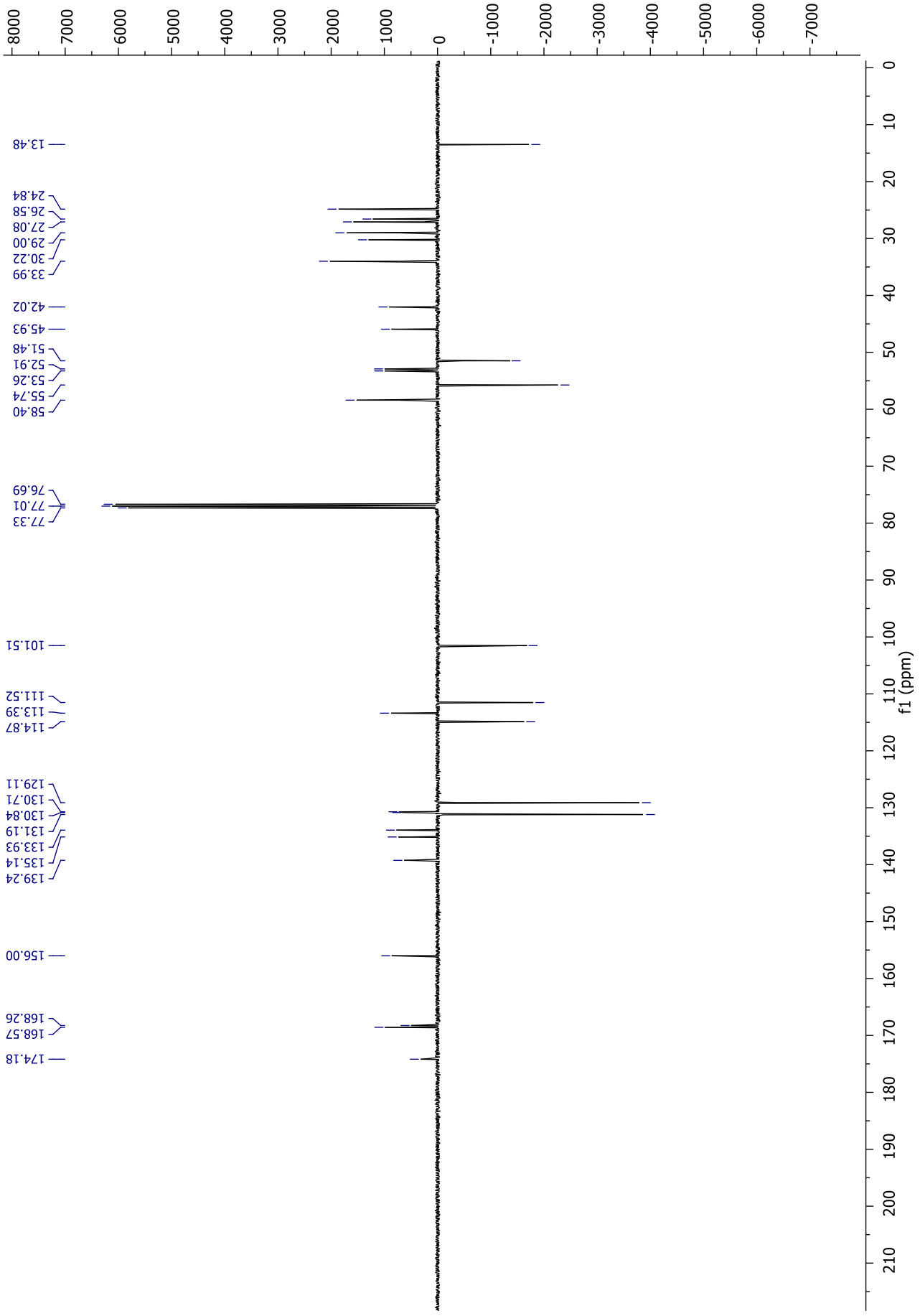
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **14**.



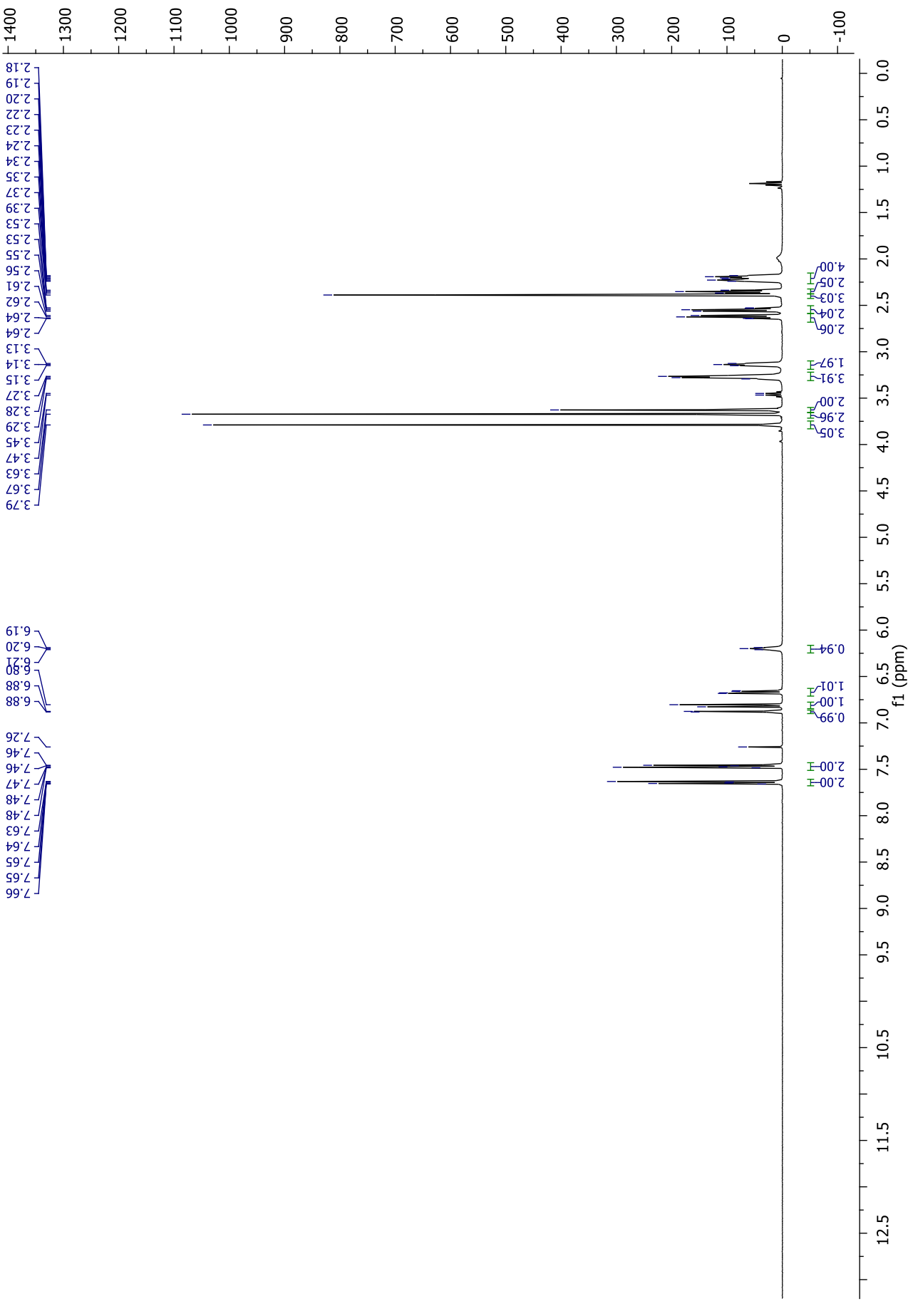
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **15**.



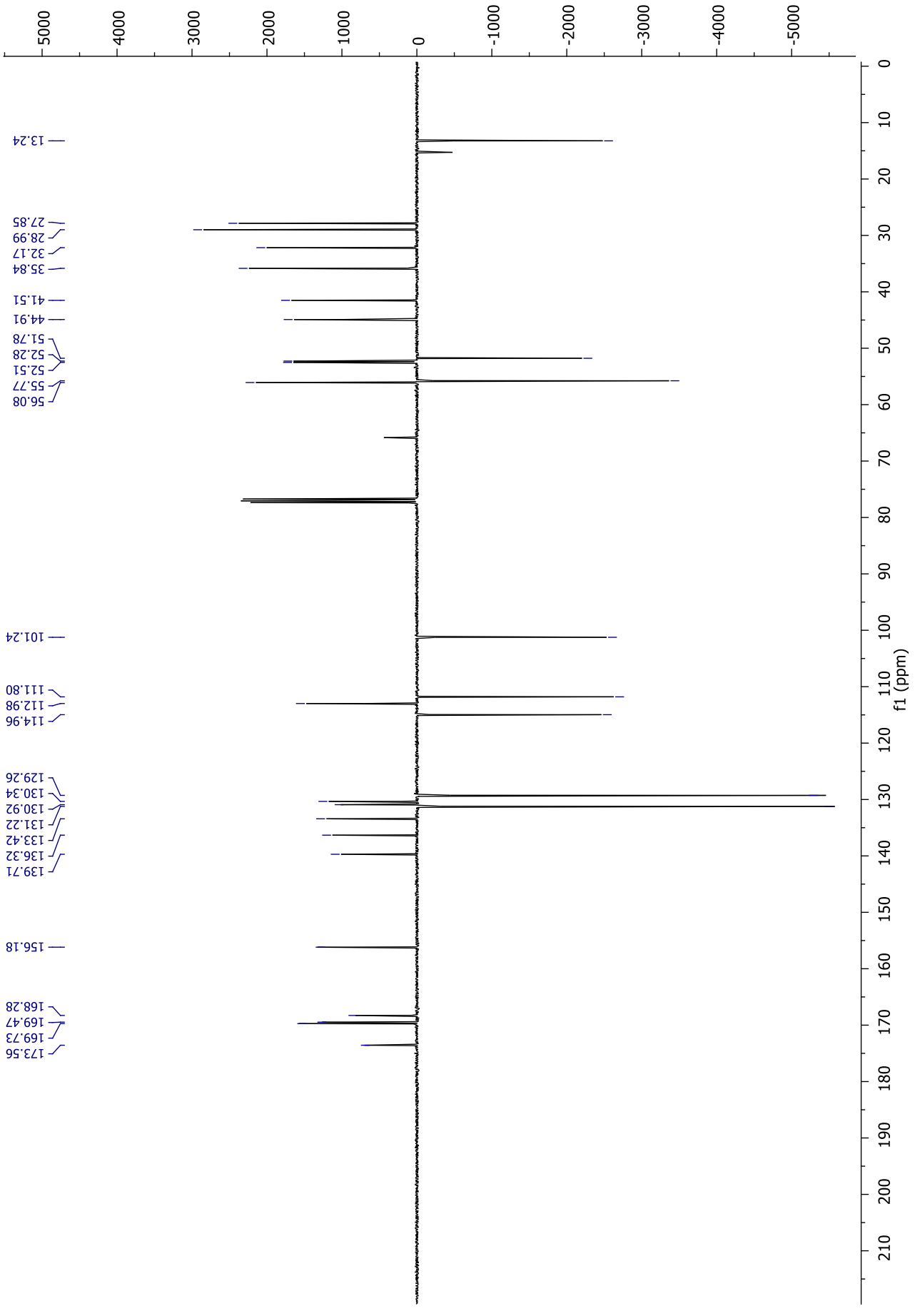
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **15**.



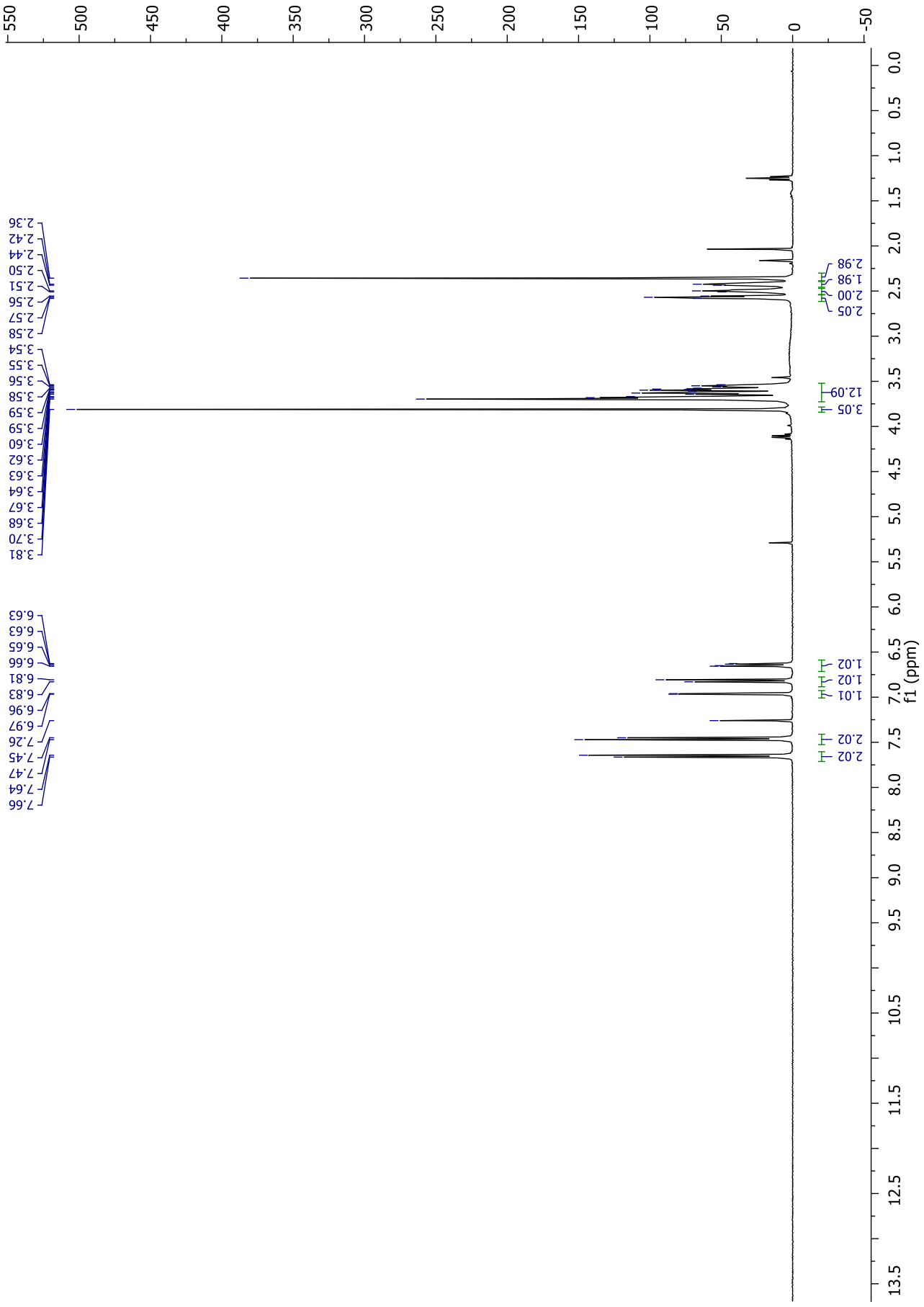
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **16**.



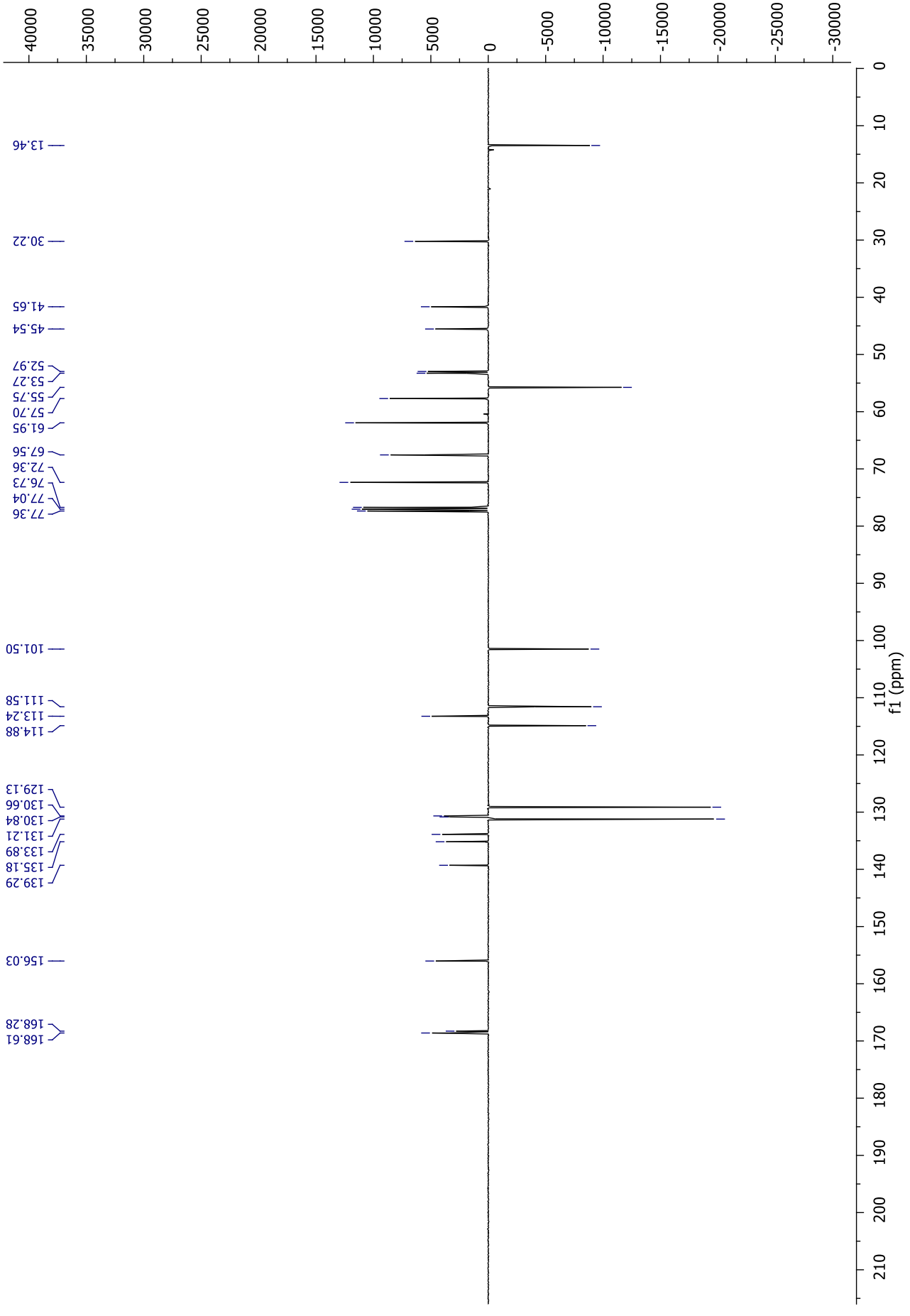
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of compound **16**.



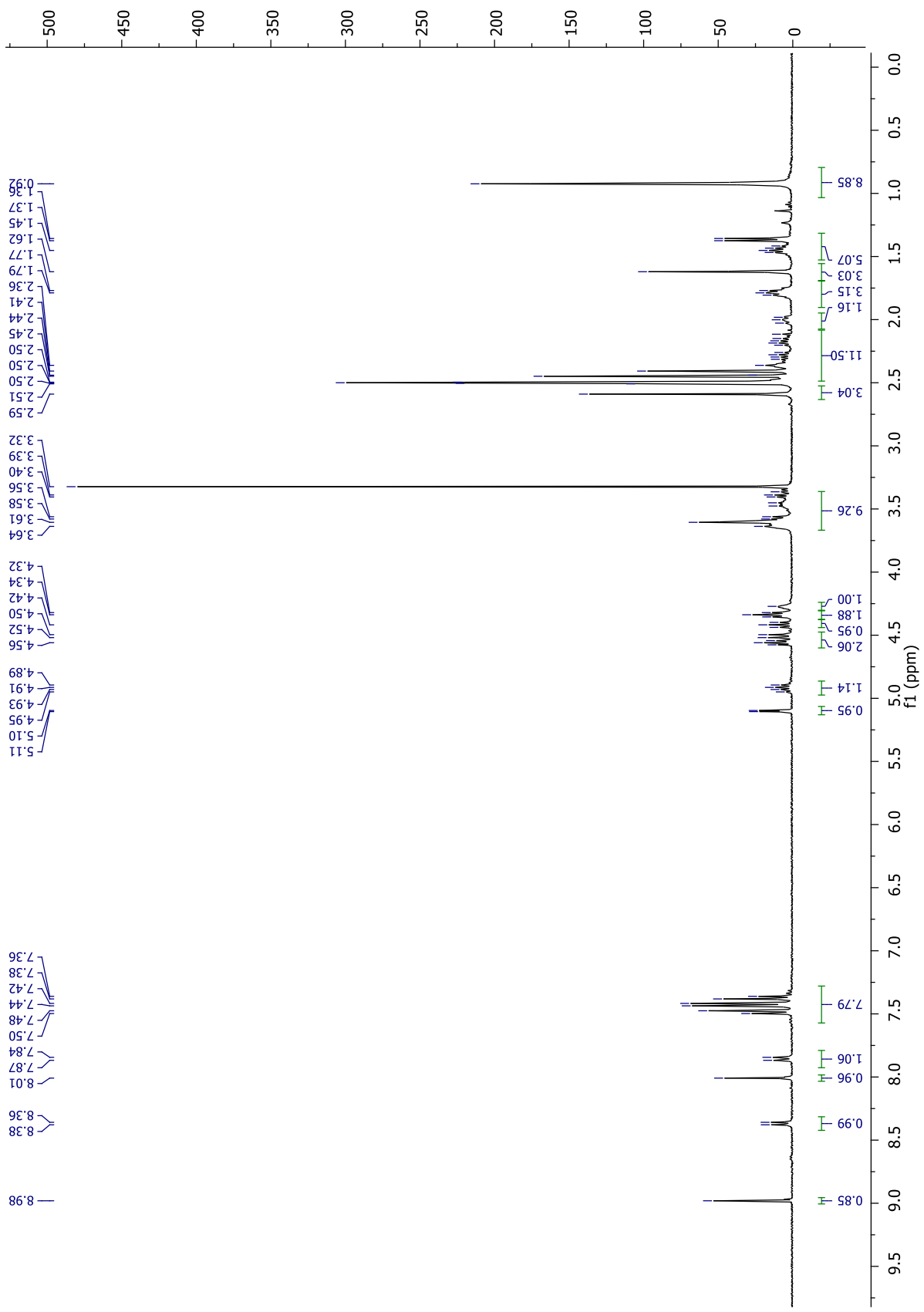
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **17**.



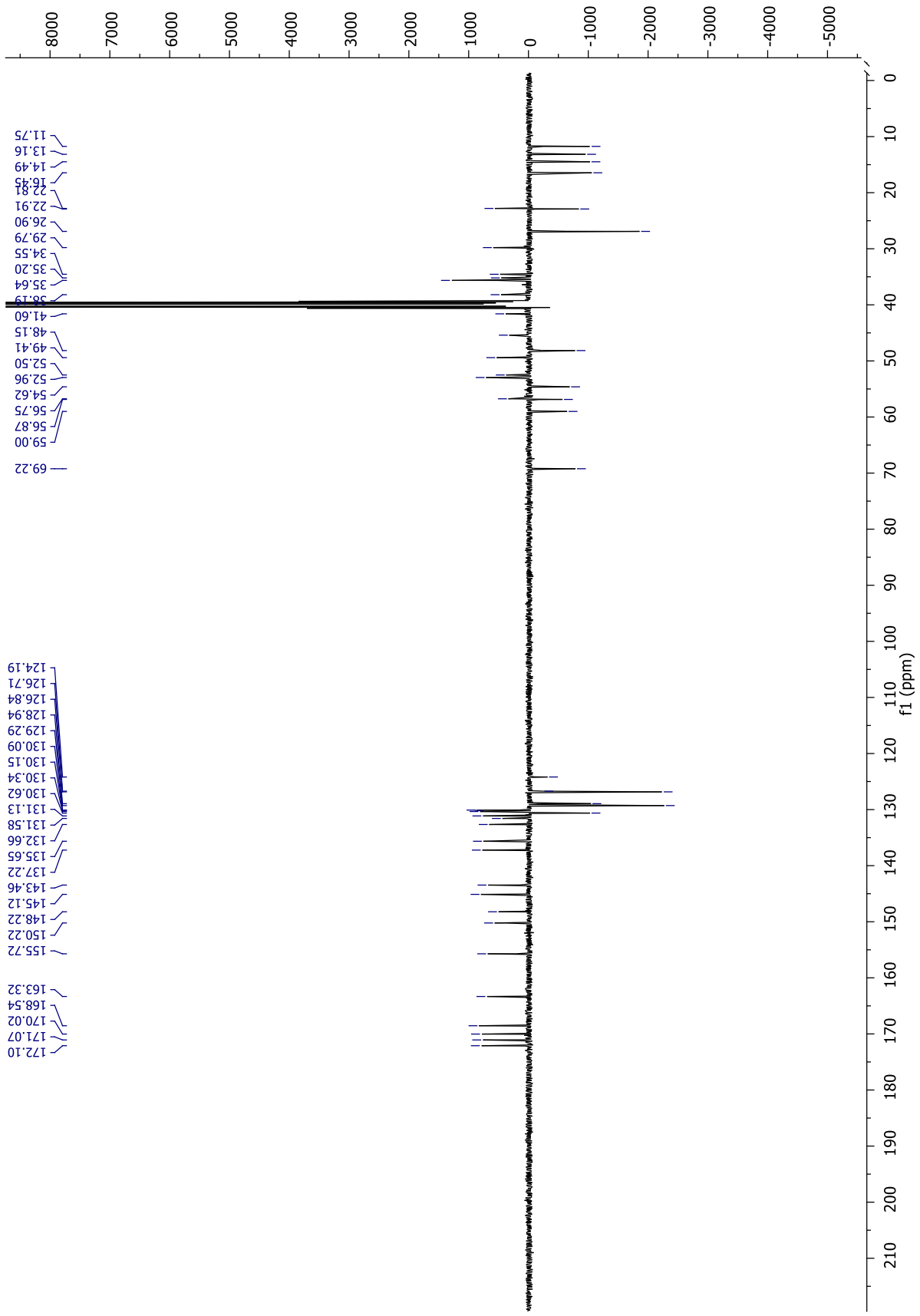
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of compound **17**.



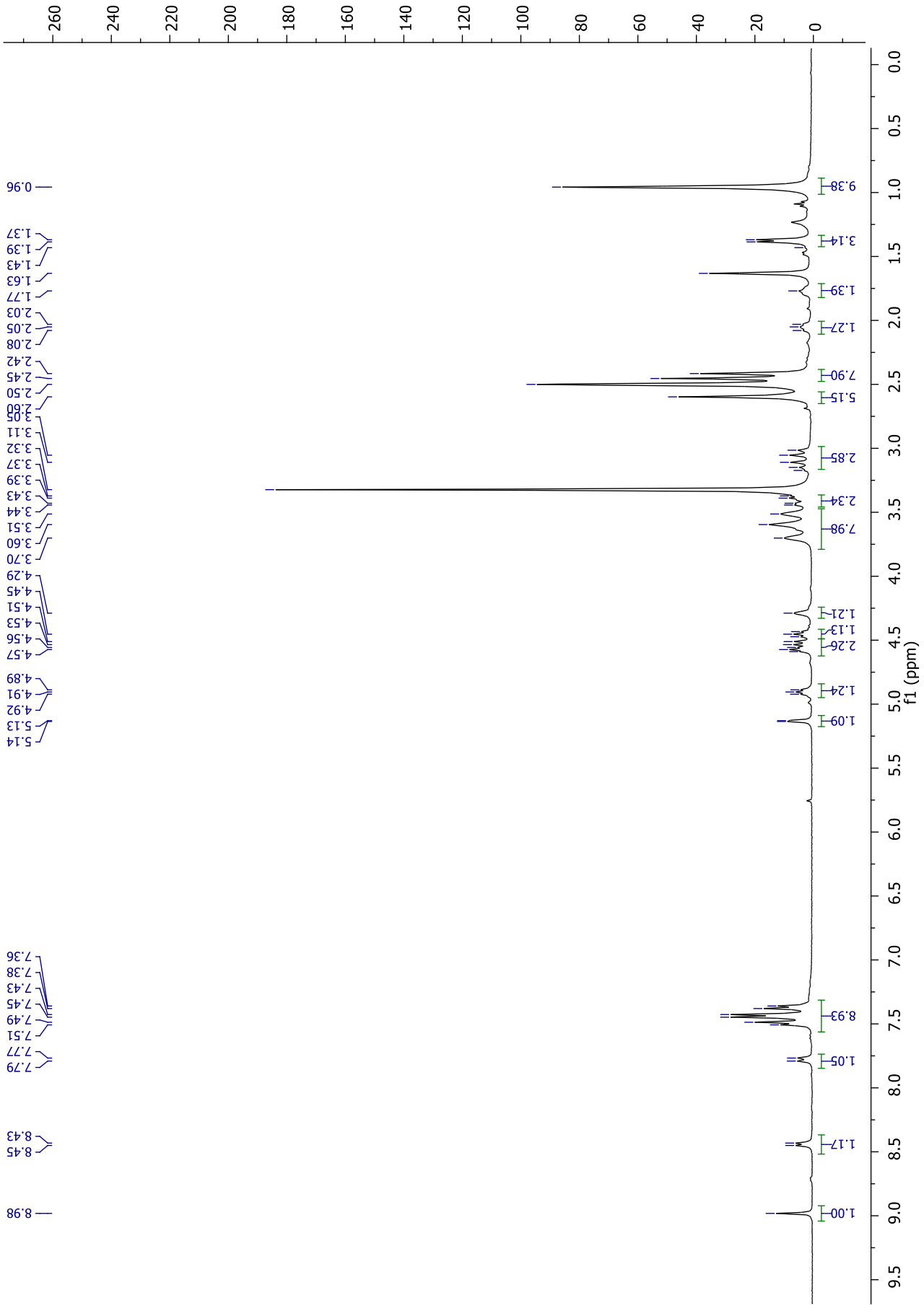
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **PROTAC-1**.



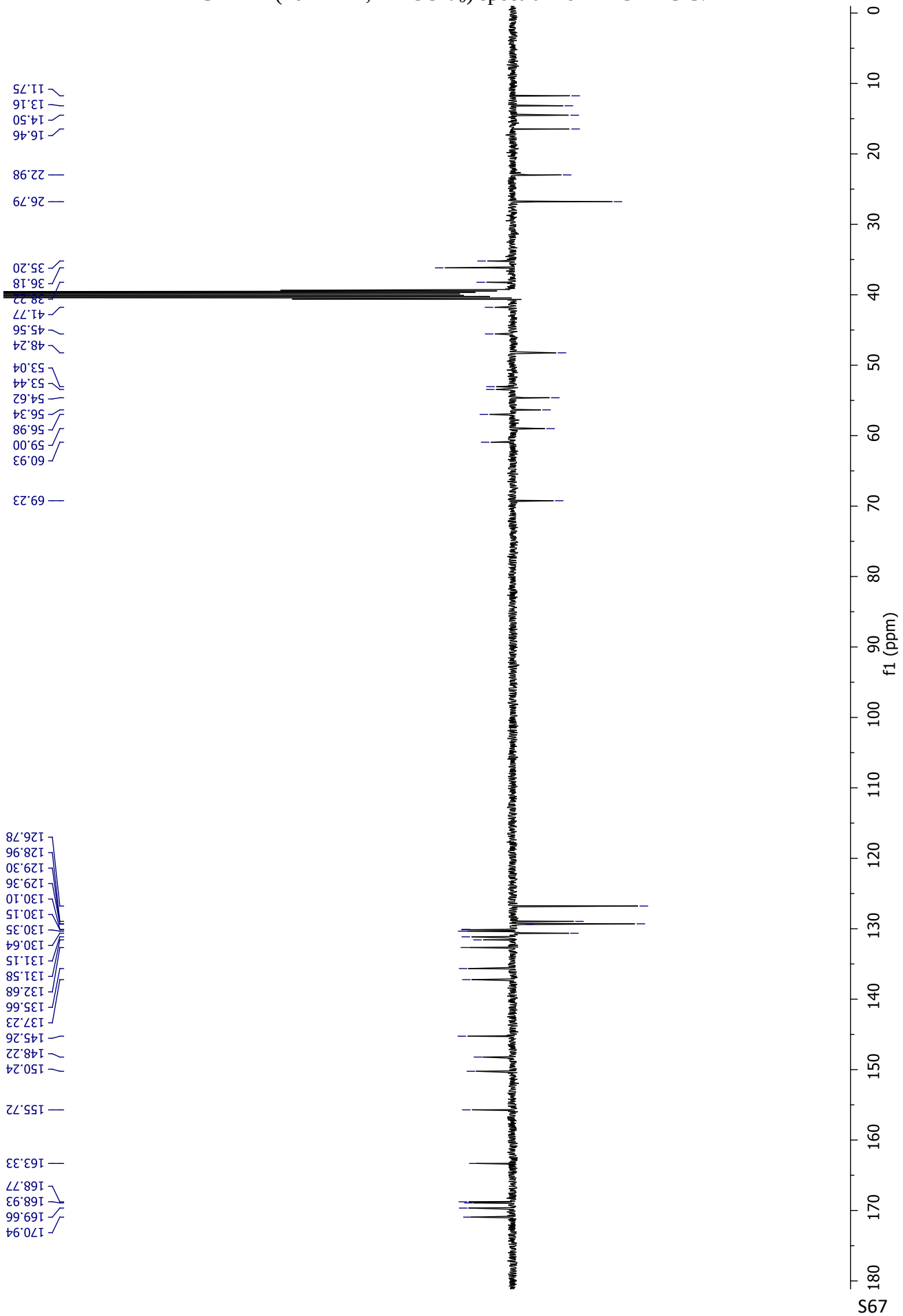
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **PROTAC-1**.



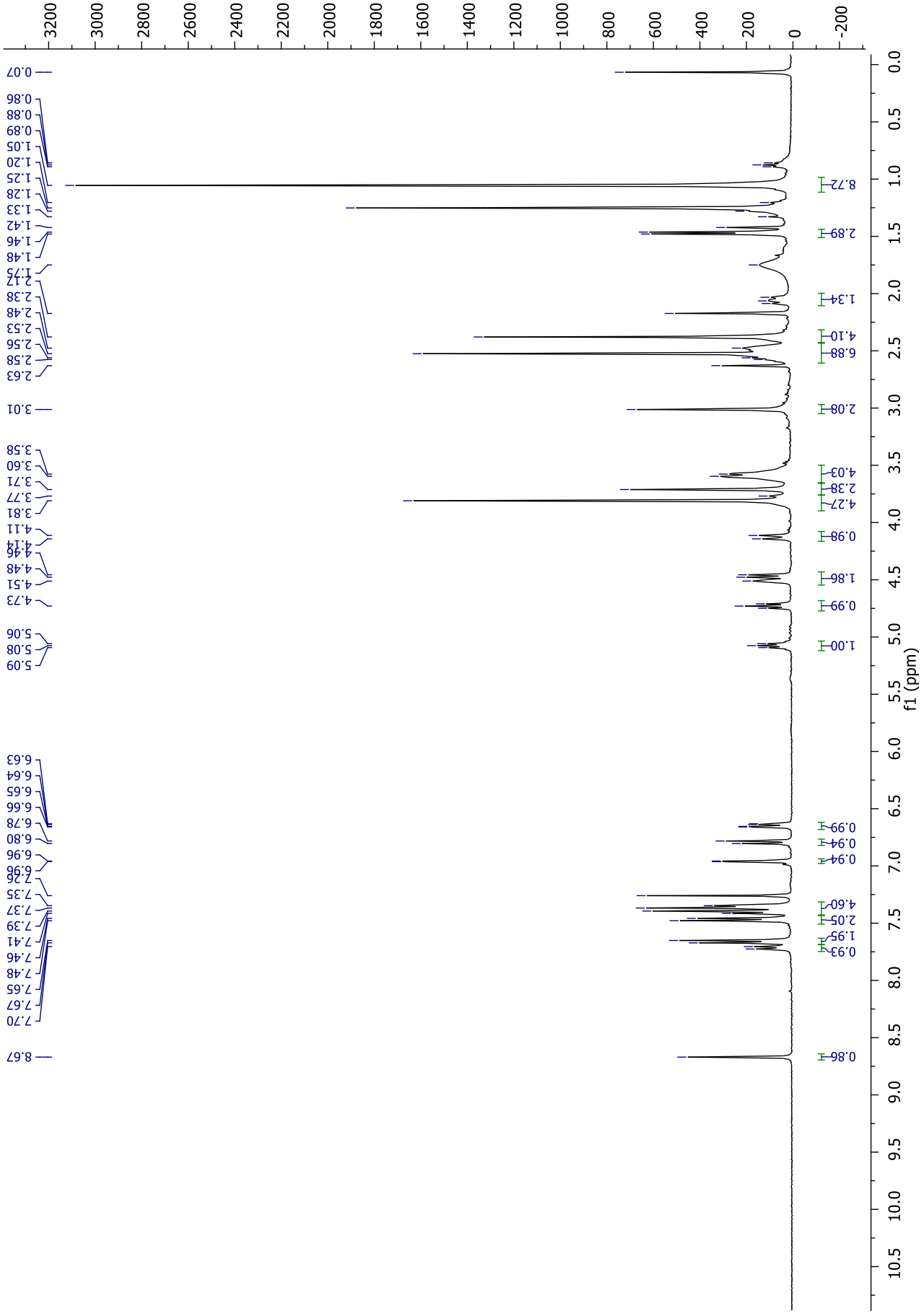
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **PROTAC-3**.



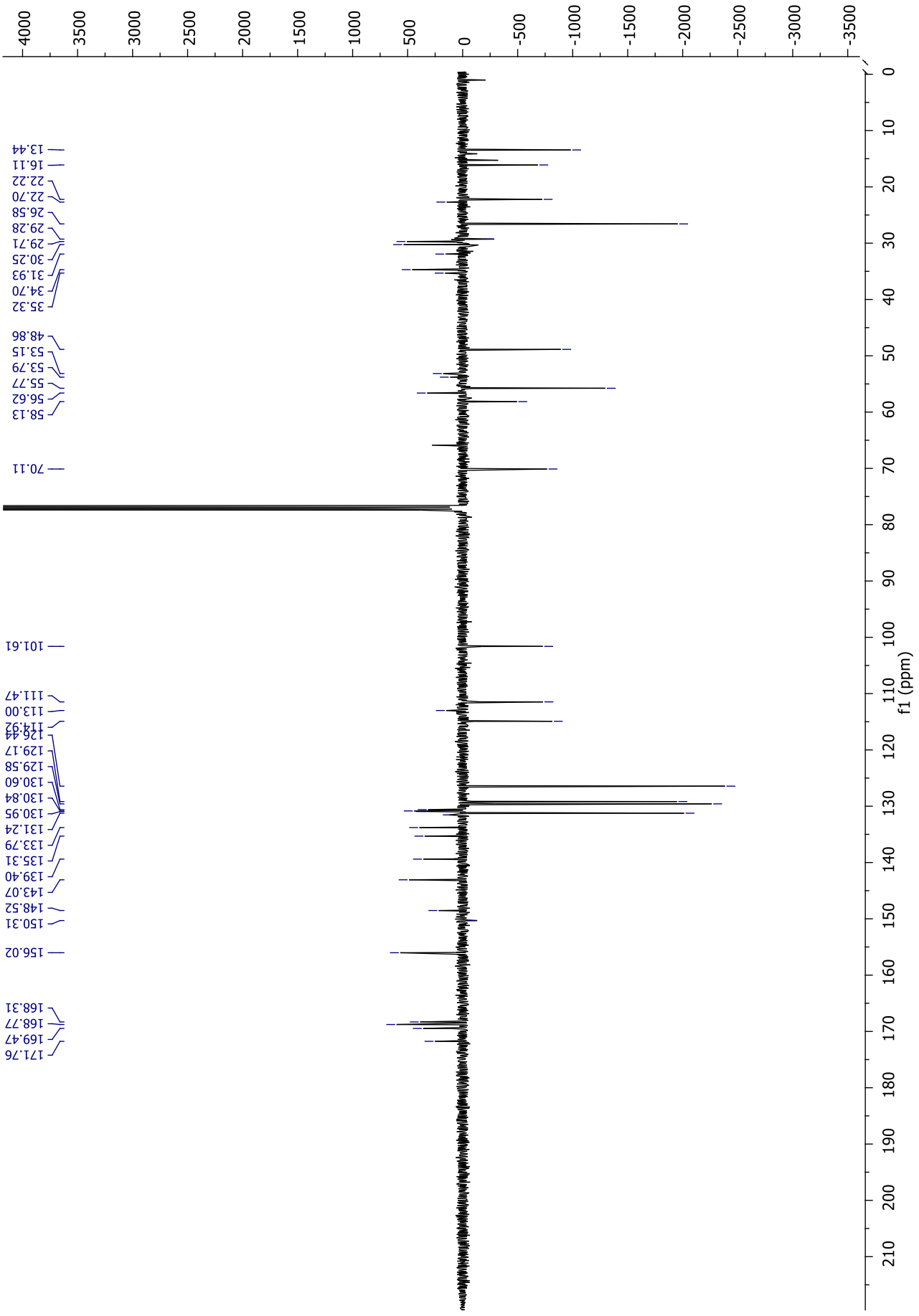
^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **PROTAC-3**.



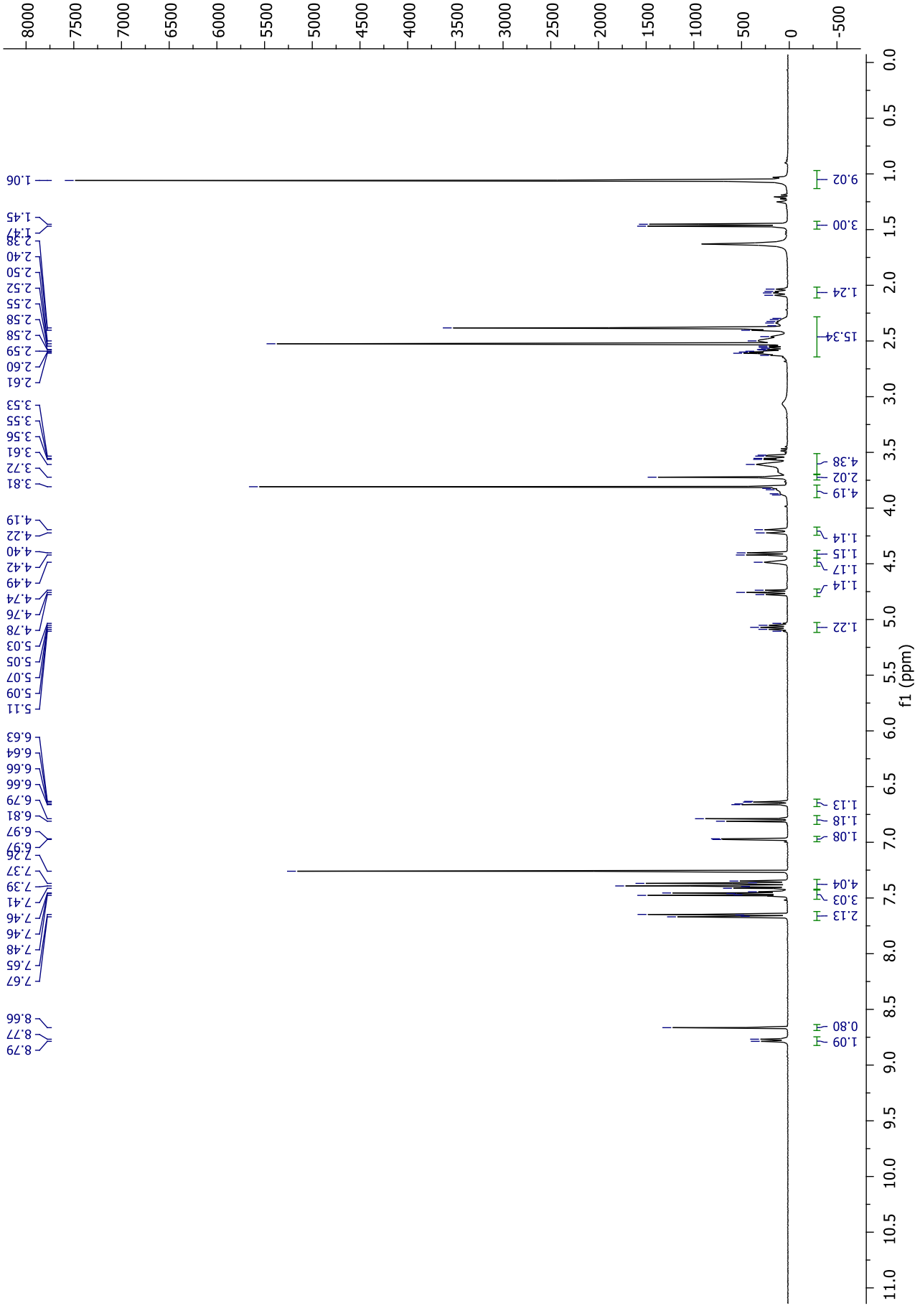
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **PROTAC-4**.



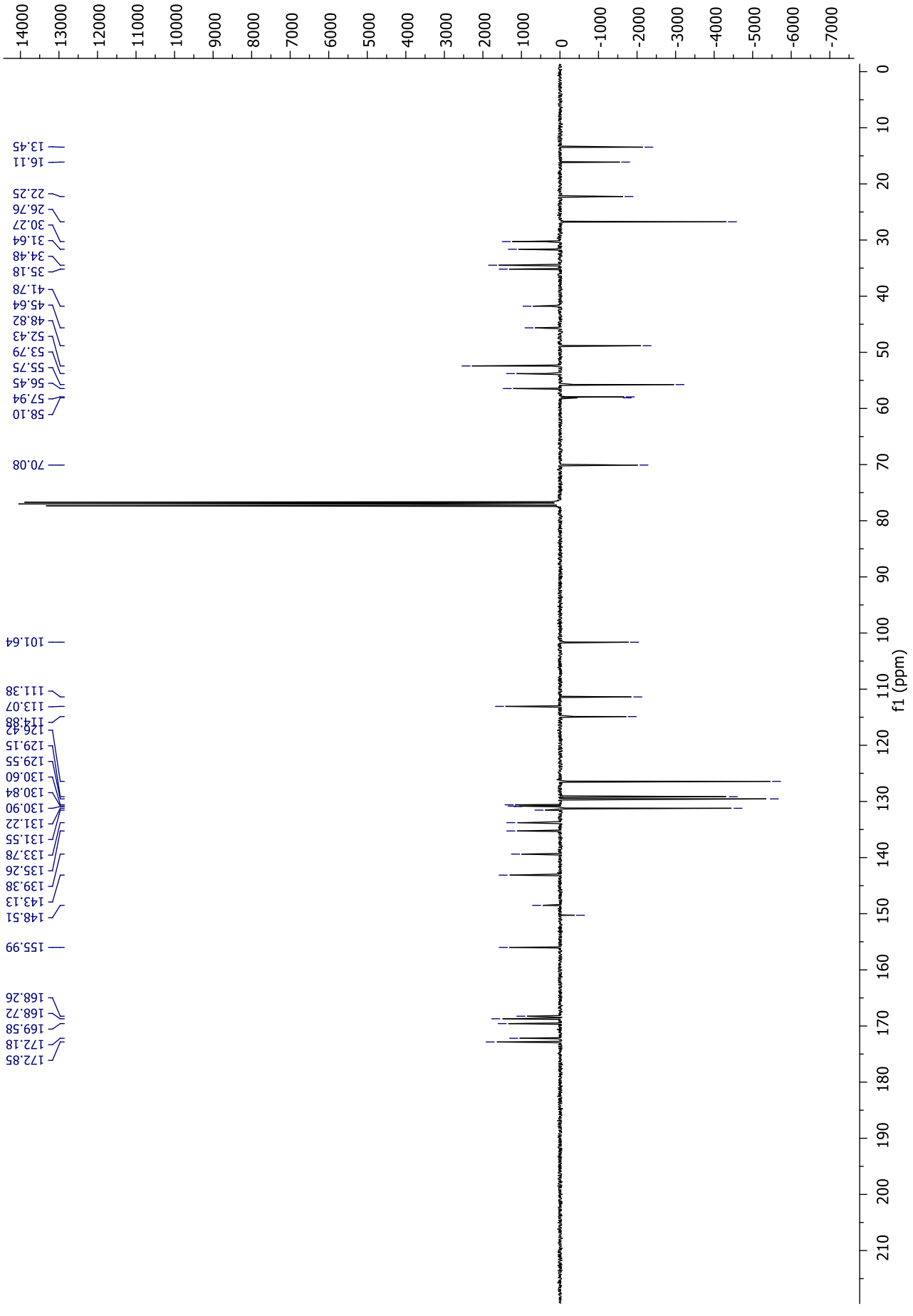
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **PROTAC-4**.



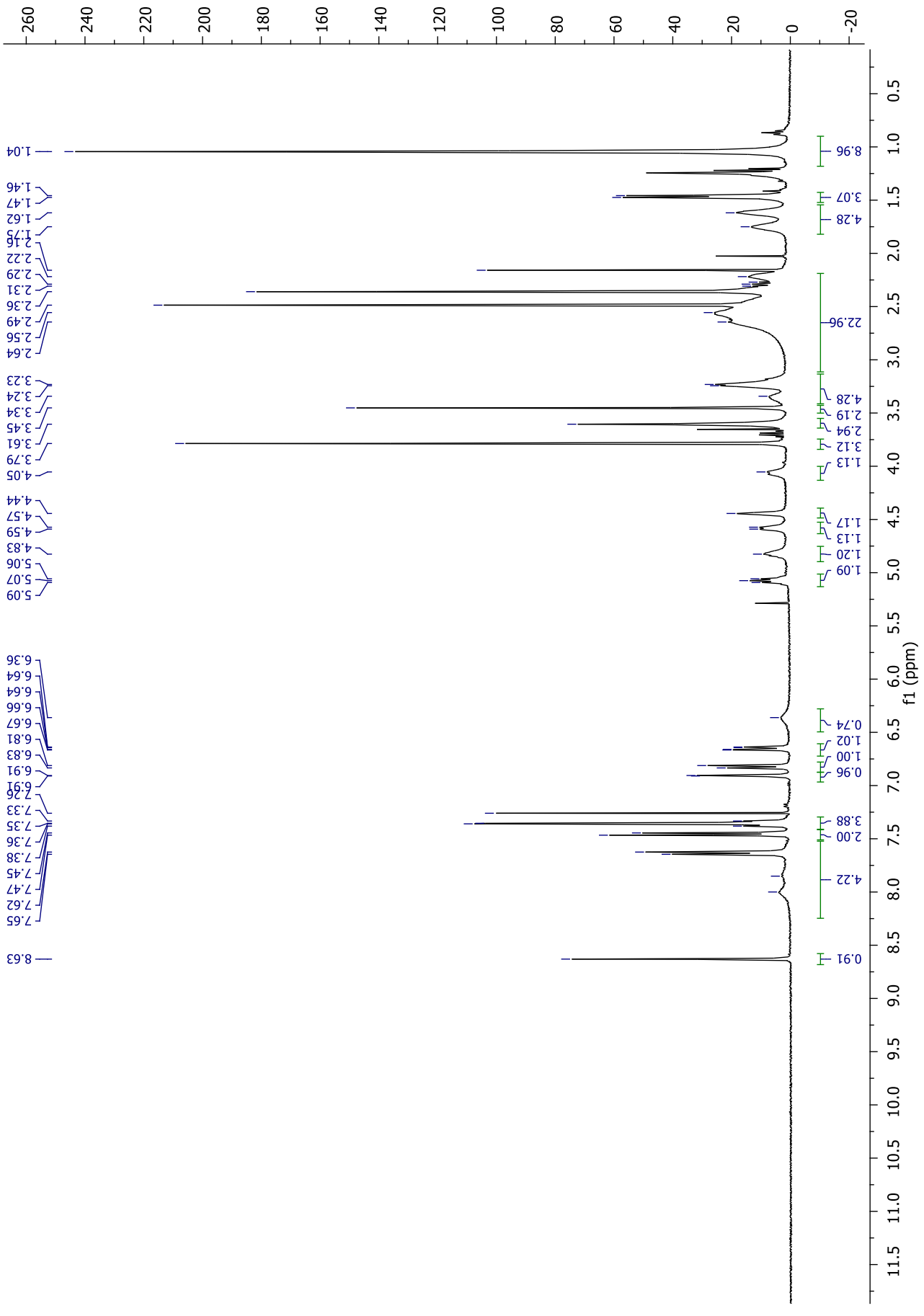
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **PROTAC-6**.



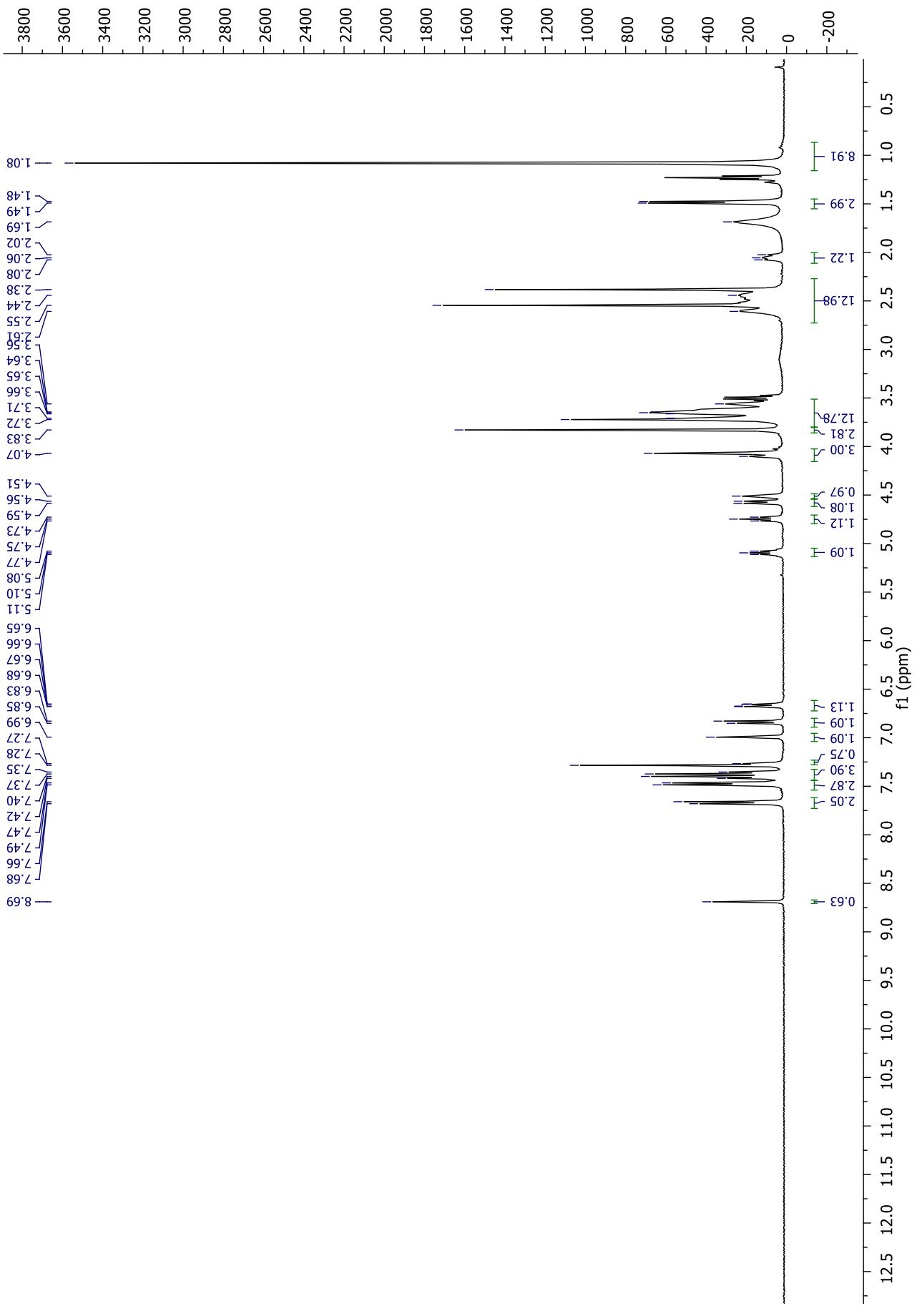
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **PROTAC-6**.



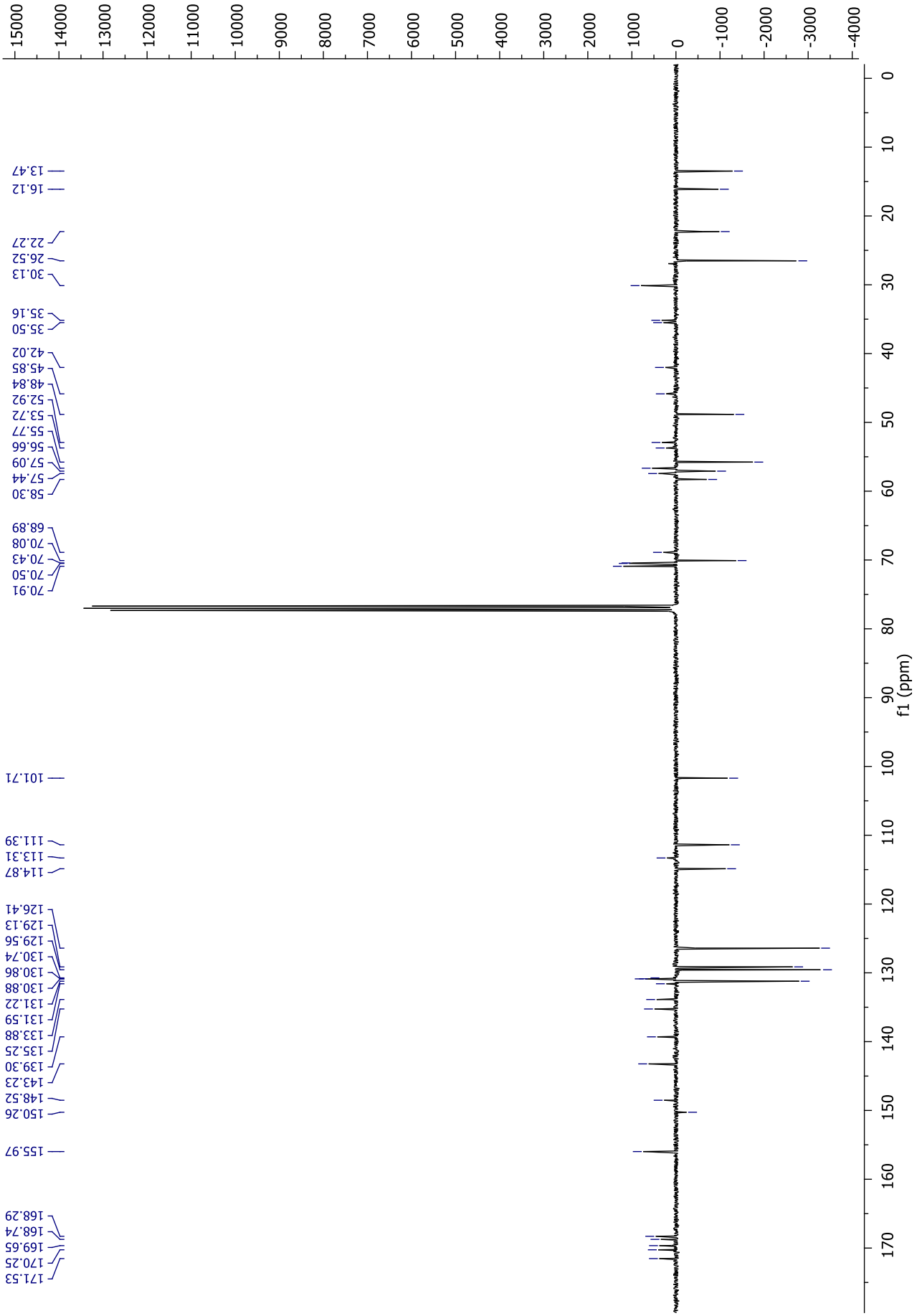
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **PROTAC-8**.



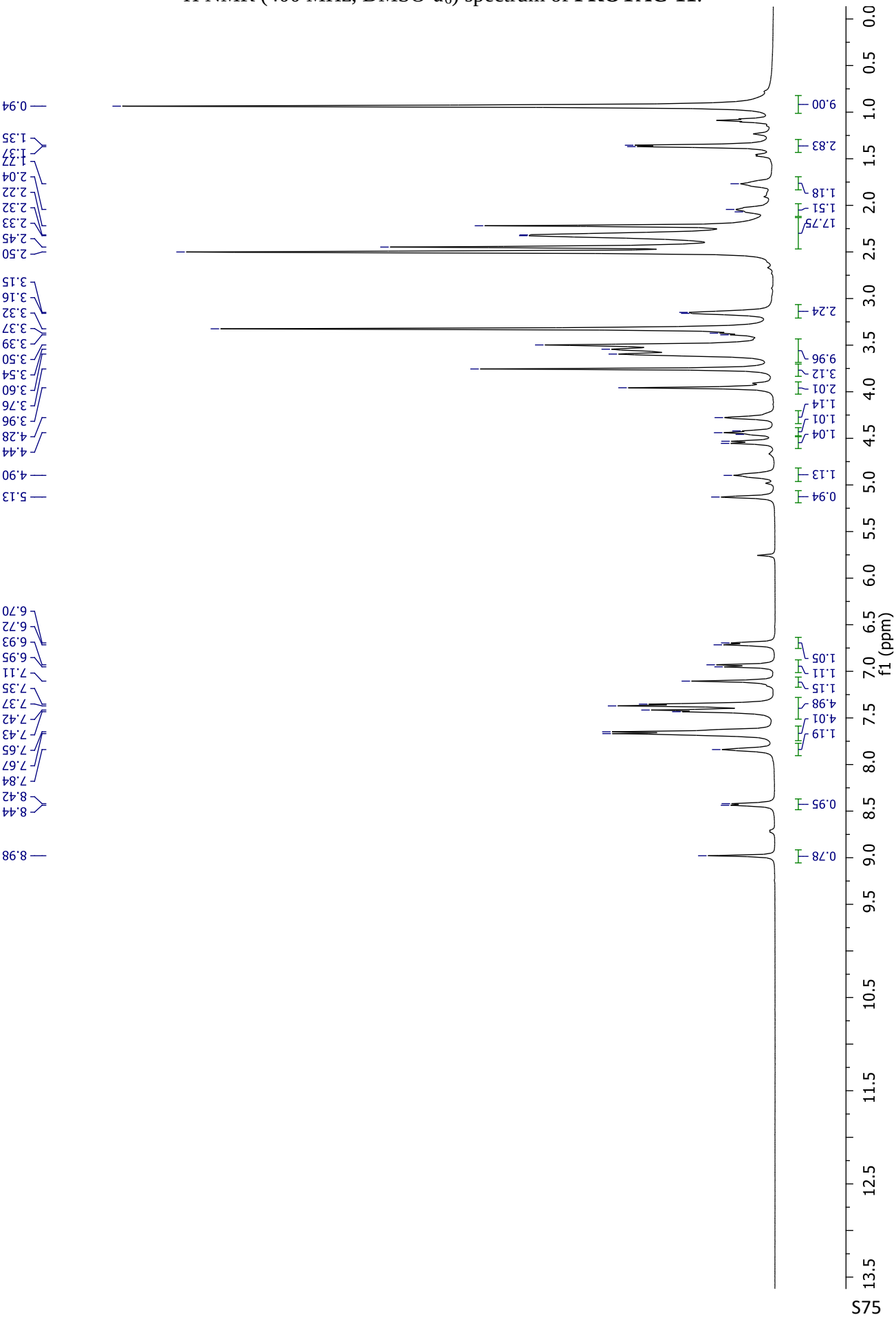
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **PROTAC-10**.



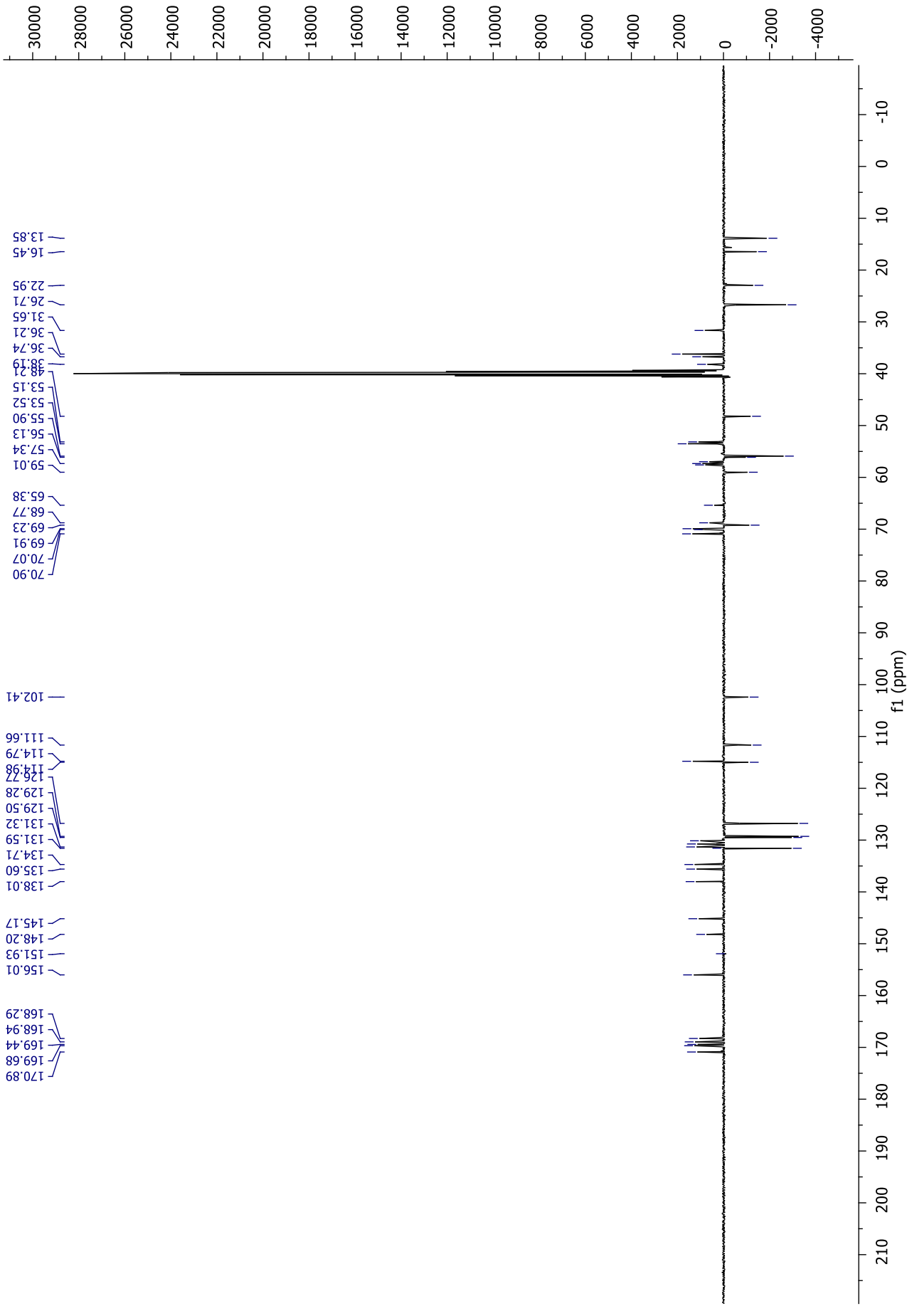
^{13}C NMR (101 MHz, $CDCl_3$) spectrum of **PROTAC-10**.



^{1}H NMR (400 MHz, DMSO-d_6) spectrum of **PROTAC-11**.



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of **PROTAC-11**.

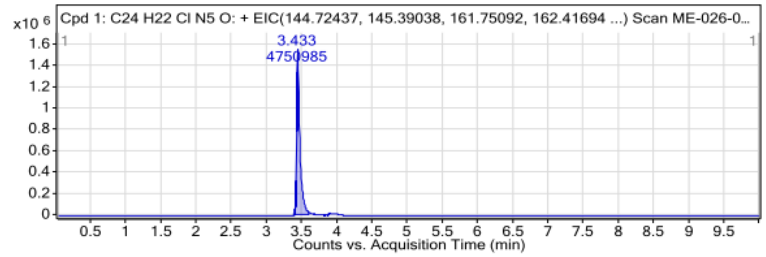


HRMS spectrum of compound **1**.

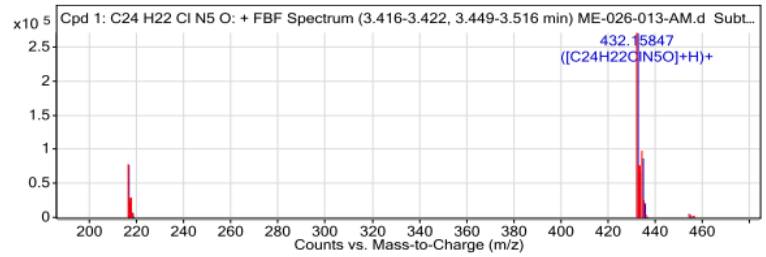
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C24 H22 Cl N5 O	3.433	431.1515	77890	C24 H22 Cl N5 O	431.15129	0.5	C24 H22 Cl N5 O	C24 H22 Cl N5 O

Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C24 H22 Cl N5 O	216.5833	3.433	Find By Formula	431.1515



MS Zoomed Spectrum



MS Spectrum Peak List

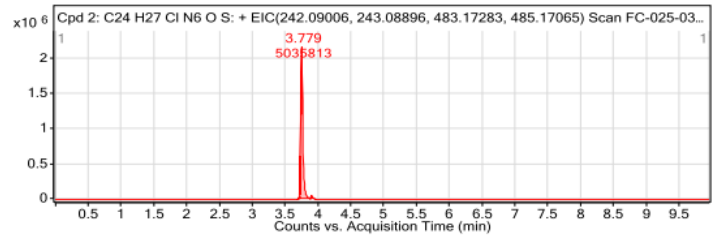
m/z	z	Abund	Formula	Ion
216.5833	2	77889.99	C24H22ClN5O	(M+2H)+2
217.08471	2	23385.09	C24H22ClN5O	(M+2H)+2
217.58224	2	27406.07	C24H22ClN5O	(M+2H)+2
218.08336	2	7813.81	C24H22ClN5O	(M+2H)+2
432.15847	1	270760.97	C24H22ClN5O	(M+H)+
433.16198	1	68625.46	C24H22ClN5O	(M+H)+
434.15691	1	87947.71	C24H22ClN5O	(M+H)+
435.15908	1	22893.99	C24H22ClN5O	(M+H)+
436.16114	1	3042.03	C24H22ClN5O	(M+H)+
454.14063	1	5555.31	C24H22ClN5O	(M+Na)+

HRMS spectrum of compound **2**.

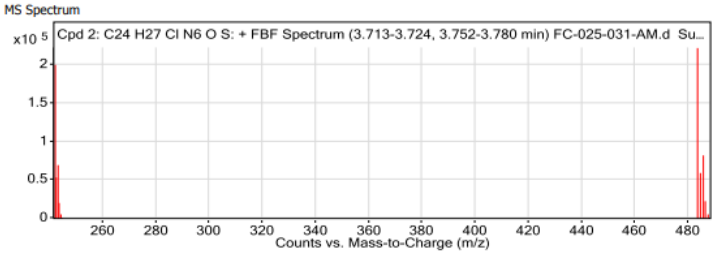
Compound Table

Compound Label	Data File	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 2: C24 H27 Cl N6 O S	FC-025-031-AM.d	3.735	482.16607	221941	C24 H27 Cl N6 O S	482.16556	1.07	C24 H27 Cl N6 O S	C24 H27 Cl N6 O S

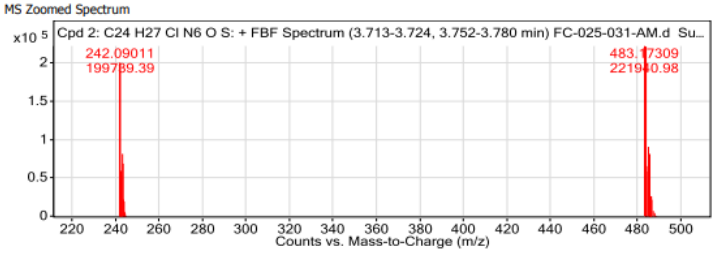
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 2: C24 H27 Cl N6 O S	483.17309	3.735	Find By Formula	482.16607



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

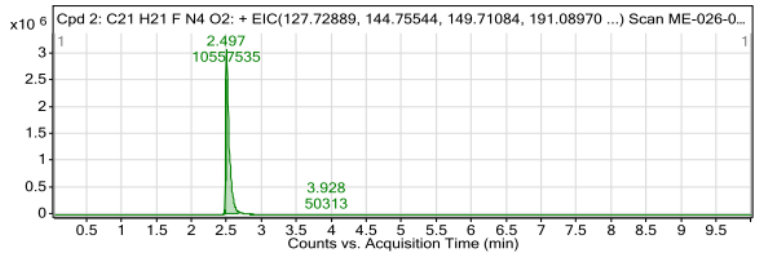
m/z	z	Abund	Formula	Ion
242.09011	2	199739.39	C24H27ClN6OS	(M+2H)+2
242.59181	2	53855.64	C24H27ClN6OS	(M+2H)+2
243.0897	2	70304.95	C24H27ClN6OS	(M+2H)+2
243.59068	2	20498.16	C24H27ClN6OS	(M+2H)+2
244.08987	2	5999.6	C24H27ClN6OS	(M+2H)+2
483.17309	1	221940.98	C24H27ClN6OS	(M+H)+
484.17648	1	59753.84	C24H27ClN6OS	(M+H)+
485.17134	1	83745.75	C24H27ClN6OS	(M+H)+
486.17308	1	23604.06	C24H27ClN6OS	(M+H)+
487.17244	1	5521.31	C24H27ClN6OS	(M+H)+

HRMS spectrum of compound **3**.

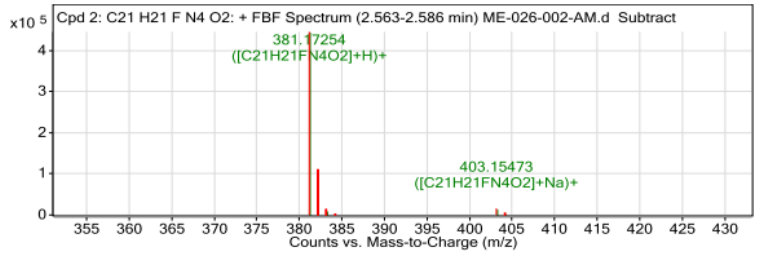
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 2: C21 H21 F N4 O2	2.497	380.16542	17094	C21 H21 F N4 O2	380.16485	1.48	C21 H21 F N4 O2	C21 H21 F N4 O2

Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 2: C21 H21 F N4 O2	403.15473	2.497	Find By Formula	380.16542



MS Zoomed Spectrum



MS Spectrum Peak List

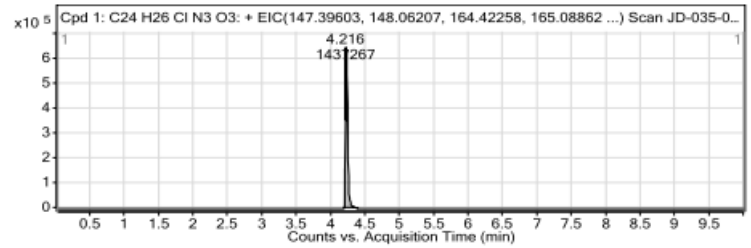
m/z	z	Abund	Formula	Ion
381.17254	1	445260.34	C21H21FN4O2	(M+H)+
382.17625	1	103009.89	C21H21FN4O2	(M+H)+
383.17887	1	12315.31	C21H21FN4O2	(M+H)+
384.18241	1	1354.61	C21H21FN4O2	(M+H)+
403.15473	1	17094.26	C21H21FN4O2	(M+Na)+
404.15767	1	4194.51	C21H21FN4O2	(M+Na)+
405.16263	1	533.82	C21H21FN4O2	(M+Na)+

HRMS spectrum of compound **4**.

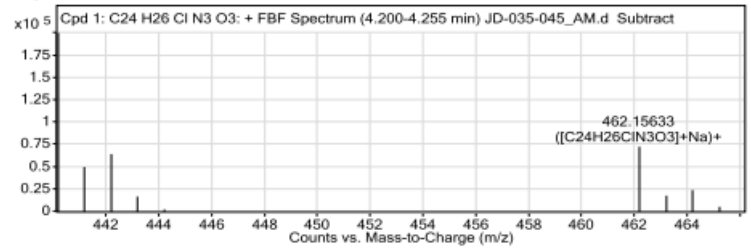
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C24 H26 Cl N3 O3	4.216	439.167	72866	C24 H26 Cl N3 O3	439.16627	1.66	C24 H26 Cl N3 O3	C24 H26 Cl N3 O3

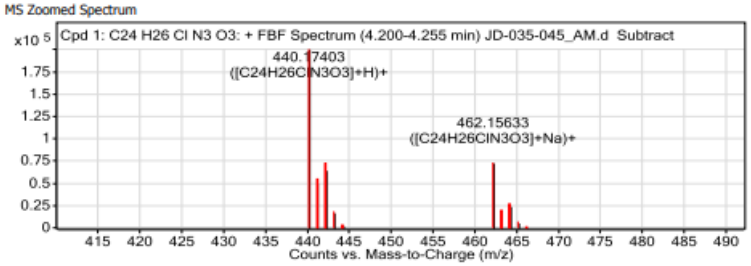
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C24 H26 Cl N3 O3	462.15633	4.216	Find By Formula	439.167



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

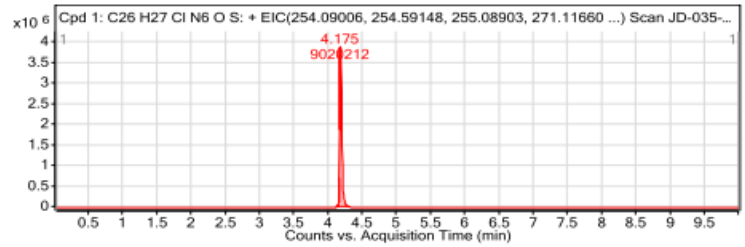
m/z	z	Abund	Formula	Ion
440.17403	1	200508.66	C24H26ClN3O3	(M+H)+
441.17762	1	50471.35	C24H26ClN3O3	(M+H)+
442.17274	1	65504.16	C24H26ClN3O3	(M+H)+
443.17494	1	17502.03	C24H26ClN3O3	(M+H)+
444.17678	1	2706.38	C24H26ClN3O3	(M+H)+
462.15633	1	72865.53	C24H26ClN3O3	(M+Na)+
463.15968	1	18891.42	C24H26ClN3O3	(M+Na)+
464.15441	1	25094.98	C24H26ClN3O3	(M+Na)+
465.15664	1	6470.82	C24H26ClN3O3	(M+Na)+
466.16047	1	1088.37	C24H26ClN3O3	(M+Na)+

HRMS spectrum of compound **5**.

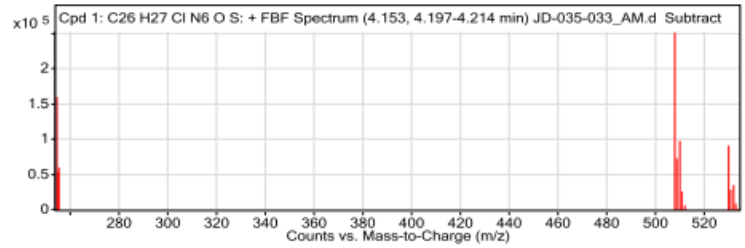
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C26 H27 Cl N6 O S	4.175	506.16704	252444	C26 H27 Cl N6 O S	506.16556	2.93	C26 H27 Cl N6 O S	C26 H27 Cl N6 O S

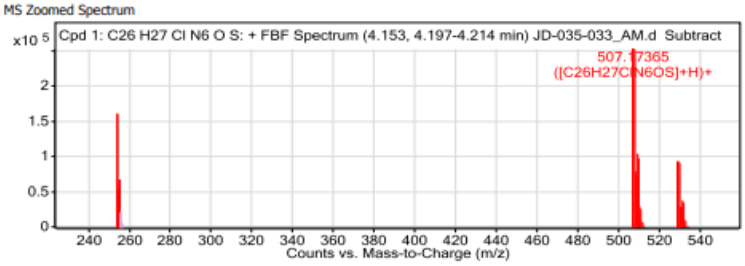
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C26 H27 Cl N6 O S	507.17365	4.175	Find By Formula	506.16704



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

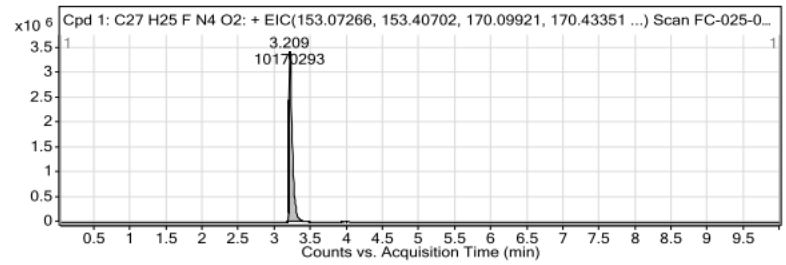
m/z	z	Abund	Formula	Ion
254.09114	2	161391.13	C26H27ClN6OS	(M+2H)+2
254.59275	2	55129.11	C26H27ClN6OS	(M+2H)+2
255.09029	2	61427.01	C26H27ClN6OS	(M+2H)+2
507.17365	1	252444.22	C26H27ClN6OS	(M+H)+
508.17713	1	74720.04	C26H27ClN6OS	(M+H)+
509.17235	1	98611.59	C26H27ClN6OS	(M+H)+
510.17383	1	26748.6	C26H27ClN6OS	(M+H)+
529.1561	1	91951.59	C26H27ClN6OS	(M+Na)+
530.15825	1	29348.04	C26H27ClN6OS	(M+Na)+
531.15398	1	36182.77	C26H27ClN6OS	(M+Na)+

HRMS spectrum of compound **7**.

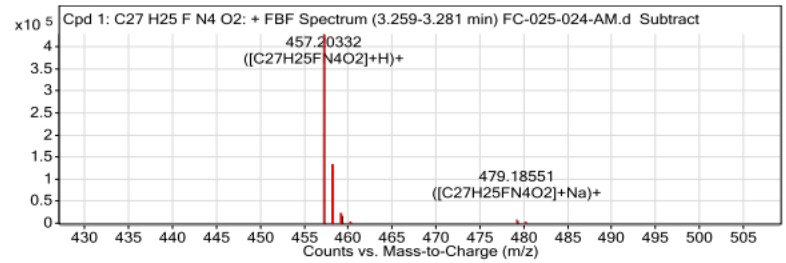
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C27 H25 F N4 O2	3.209	456.19619	9569	C27 H25 F N4 O2	456.19615	0.09	C27 H25 F N4 O2	C27 H25 F N4 O2

Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C27 H25 F N4 O2	479.18551	3.209	Find By Formula	456.19619



MS Zoomed Spectrum



MS Spectrum Peak List

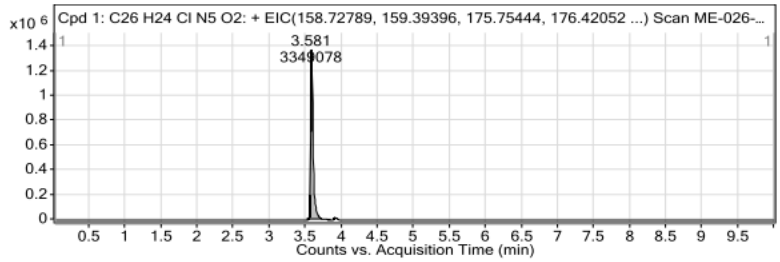
m/z	z	Abund	Formula	Ion
457.20332	1	429313.41	C27H25FN4O2	(M+H)+
458.20707	1	124024.29	C27H25FN4O2	(M+H)+
459.20943	1	19469.61	C27H25FN4O2	(M+H)+
460.2128	1	2220.07	C27H25FN4O2	(M+H)+
479.18551	1	9568.84	C27H25FN4O2	(M+Na)+
480.1888	1	2850.79	C27H25FN4O2	(M+Na)+
481.19254	1	422.58	C27H25FN4O2	(M+Na)+

HRMS spectrum of compound **8**.

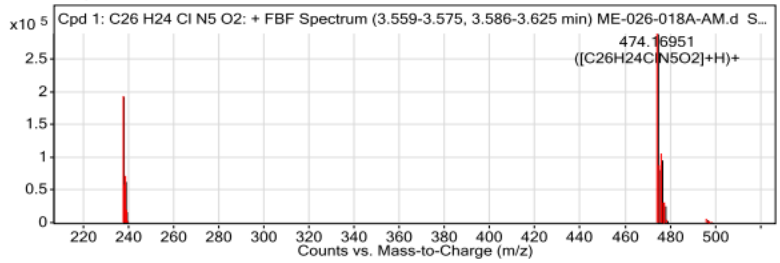
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C26 H24 Cl N5 O2	3.581	473.16269	289435	C26 H24 Cl N5 O2	473.16185	1.76	C26 H24 Cl N5 O2	C26 H24 Cl N5 O2

Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C26 H24 Cl N5 O2	474.16951	3.581	Find By Formula	473.16269



MS Zoomed Spectrum



MS Spectrum Peak List

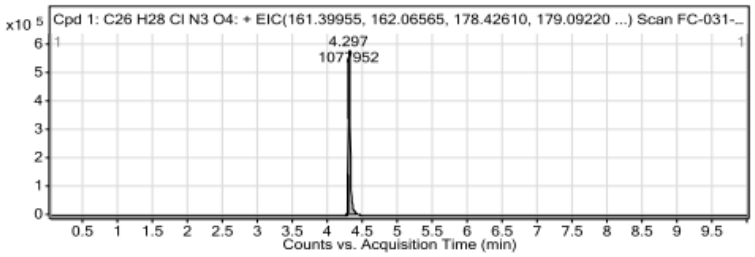
m/z	z	Abund	Formula	Ion
237.58853	2	193613.3	C26H24ClN5O2	(M+2H)+2
238.09059	2	53172.35	C26H24ClN5O2	(M+2H)+2
238.58835	2	63947.56	C26H24ClN5O2	(M+2H)+2
239.08921	2	18574.45	C26H24ClN5O2	(M+2H)+2
474.16951	1	289434.91	C26H24ClN5O2	(M+H)+
475.17305	1	82300.32	C26H24ClN5O2	(M+H)+
476.16842	1	97417.02	C26H24ClN5O2	(M+H)+
477.1703	1	27186.92	C26H24ClN5O2	(M+H)+
478.17241	1	3926.4	C26H24ClN5O2	(M+H)+
496.15186	1	5851.76	C26H24ClN5O2	(M+Na)+

HRMS spectrum of compound **9**.

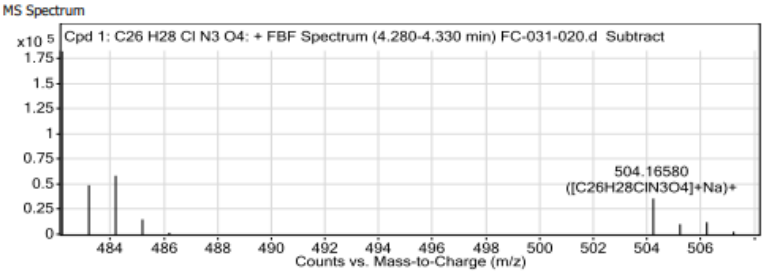
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C26 H28 Cl N3 O4	4.297	481.17663	37232	C26 H28 Cl N3 O4	481.17683	-0.42	C26 H28 Cl N3 O4	C26 H28 Cl N3 O4

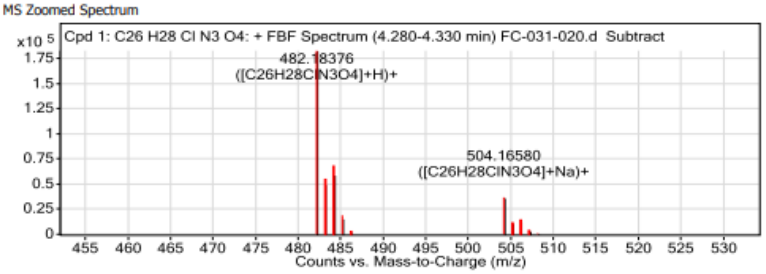
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C26 H28 Cl N3 O4	504.1658	4.297	Find By Formula	481.17663



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

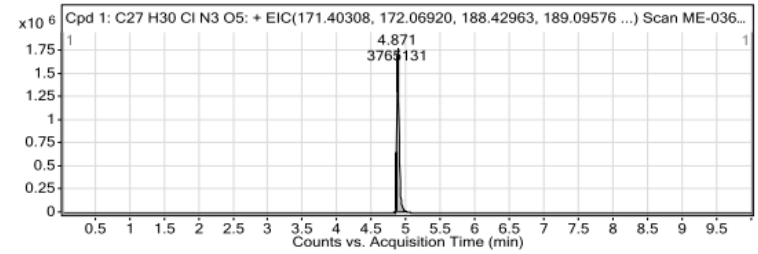
m/z	z	Abund	Formula	Ion
482.18376	1	182996.75	C26H28ClN3O4	(M+H)+
483.18716	1	49737.66	C26H28ClN3O4	(M+H)+
484.18257	1	59264.19	C26H28ClN3O4	(M+H)+
485.18465	1	16443.3	C26H28ClN3O4	(M+H)+
486.18721	1	2825.65	C26H28ClN3O4	(M+H)+
504.1658	1	37232.25	C26H28ClN3O4	(M+Na)+
505.16878	1	11131.56	C26H28ClN3O4	(M+Na)+
506.16439	1	12921.83	C26H28ClN3O4	(M+Na)+
507.1668	1	3852.73	C26H28ClN3O4	(M+Na)+
508.16935	1	614.85	C26H28ClN3O4	(M+Na)+

HRMS spectrum of compound **10**.

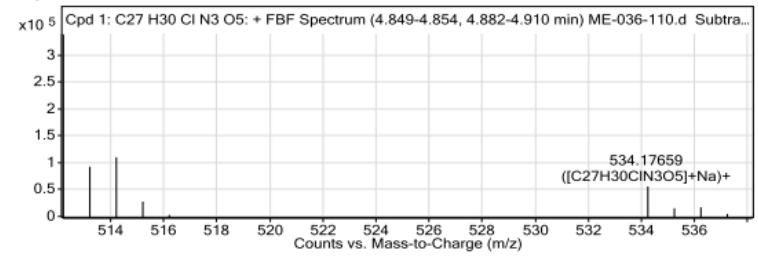
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C27 H30 Cl N3 O5	4.871	511.18739	57351	C27 H30 Cl N3 O5	511.1874	-0.02	C27 H30 Cl N3 O5	C27 H30 Cl N3 O5

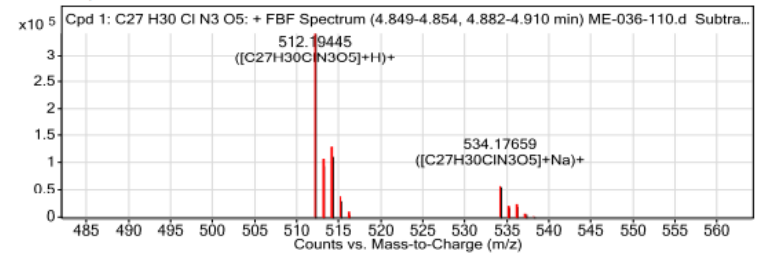
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C27 H30 Cl N3 O5	534.17659	4.871	Find By Formula	511.18739



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

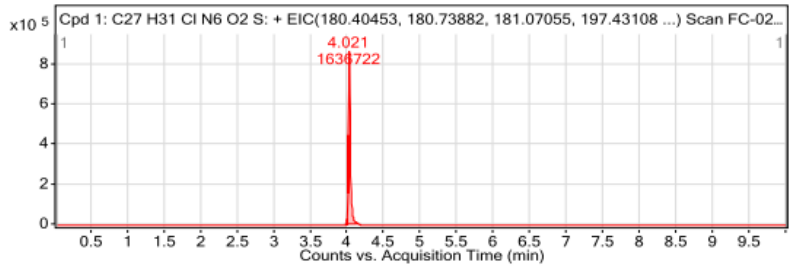
m/z	z	Abund	Formula	Ion
512.19445	1	339386.69	C27H30ClN3O5	(M+H)+
513.19826	1	94116.85	C27H30ClN3O5	(M+H)+
514.19328	1	111604.04	C27H30ClN3O5	(M+H)+
515.19565	1	29840.23	C27H30ClN3O5	(M+H)+
516.19829	1	5702.67	C27H30ClN3O5	(M+H)+
534.17659	1	57350.79	C27H30ClN3O5	(M+Na)+
535.17963	1	17943.2	C27H30ClN3O5	(M+Na)+
536.17515	1	19294.82	C27H30ClN3O5	(M+Na)+
537.17738	1	6173.54	C27H30ClN3O5	(M+Na)+
538.18016	1	1050.19	C27H30ClN3O5	(M+Na)+

HRMS spectrum of compound **11**.

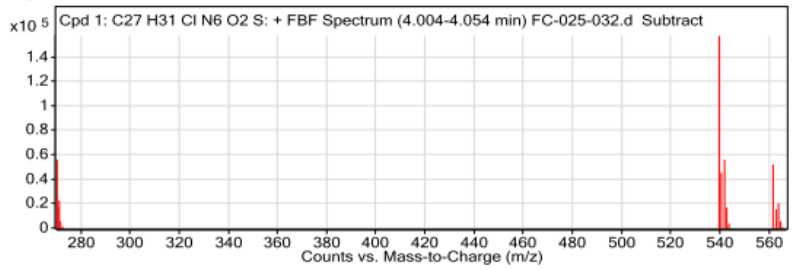
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C27 H31 Cl N6 O2 S	4.021	538.19225	52774	C27 H31 Cl N6 O2 S	538.19177	0.88	C27 H31 Cl N6 O2 S	C27 H31 Cl N6 O2 S

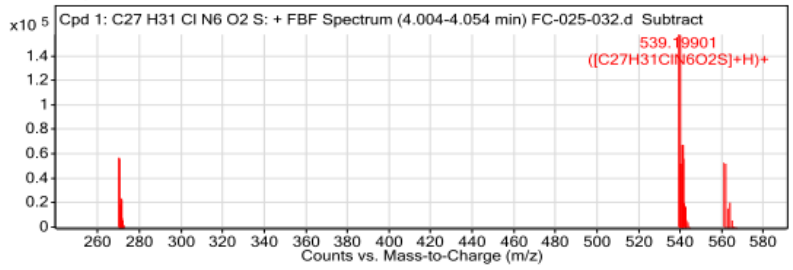
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C27 H31 Cl N6 O2 S	561.18112	4.021	Find By Formula	538.19225



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

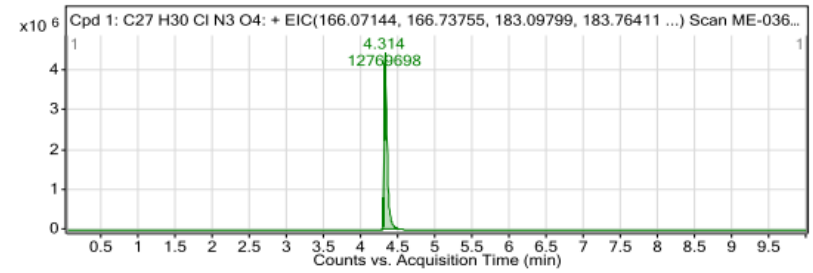
m/z	z	Abund	Formula	Ion
270.10405	2	56714.16	C27H31ClN6O2S	(M+2H)+2
270.60526	2	17889.2	C27H31ClN6O2S	(M+2H)+2
271.10304	2	23503.15	C27H31ClN6O2S	(M+2H)+2
539.19901	1	157504.05	C27H31ClN6O2S	(M+H)+
540.20206	1	46342.99	C27H31ClN6O2S	(M+H)+
541.19763	1	56692.84	C27H31ClN6O2S	(M+H)+
542.19947	1	17576.69	C27H31ClN6O2S	(M+H)+
561.18112	1	52773.51	C27H31ClN6O2S	(M+Na)+
562.18393	1	16455.31	C27H31ClN6O2S	(M+Na)+
563.1792	1	21010.46	C27H31ClN6O2S	(M+Na)+

HRMS spectrum of compound **12**.

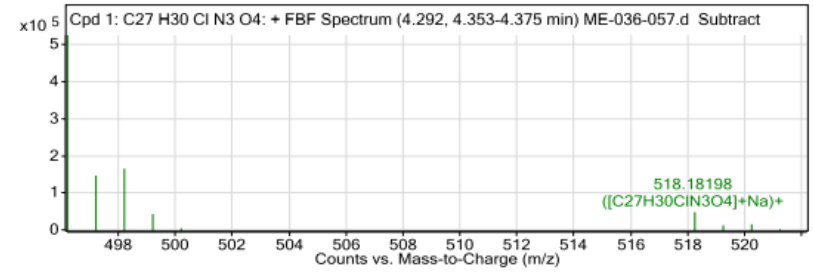
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C27 H30 Cl N3 O4	4.314	495.19277	50546	C27 H30 Cl N3 O4	495.19248	0.58	C27 H30 Cl N3 O4	C27 H30 Cl N3 O4

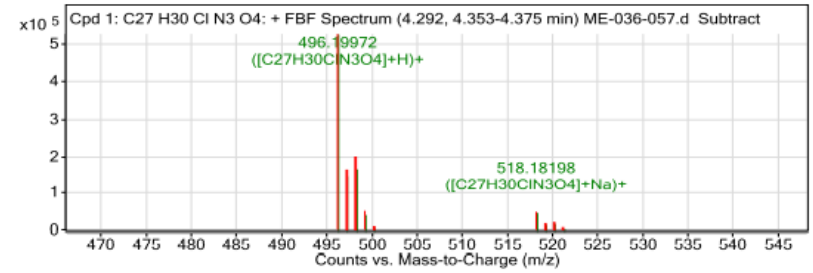
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C27 H30 Cl N3 O4	518.18198	4.314	Find By Formula	495.19277



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

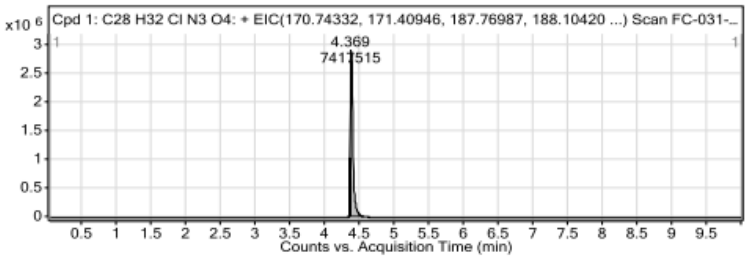
m/z	z	Abund	Formula	Ion
496.19972	1	527992.94	C27H30ClN3O4	(M+H)+
497.20368	1	148344.42	C27H30ClN3O4	(M+H)+
498.19902	1	169254.53	C27H30ClN3O4	(M+H)+
499.20092	1	47283.12	C27H30ClN3O4	(M+H)+
500.20347	1	8687.98	C27H30ClN3O4	(M+H)+
501.20541	1	996.71	C27H30ClN3O4	(M+H)+
518.18198	1	50545.79	C27H30ClN3O4	(M+Na)+
519.18513	1	16134.46	C27H30ClN3O4	(M+Na)+
520.1801	1	18399.74	C27H30ClN3O4	(M+Na)+
521.1822	1	5792.38	C27H30ClN3O4	(M+Na)+

HRMS spectrum of compound **13**.

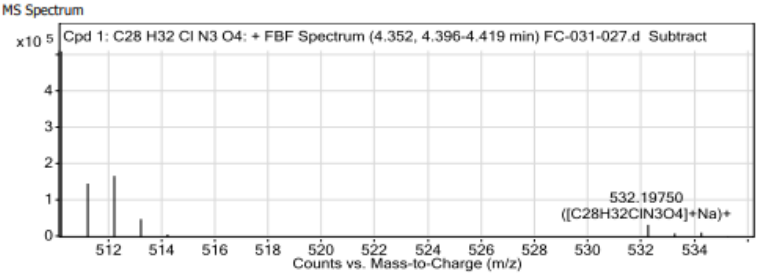
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C28 H32 Cl N3 O4	4.369	509.20848	35024	C28 H32 Cl N3 O4	509.20813	0.67	C28 H32 Cl N3 O4	C28 H32 Cl N3 O4

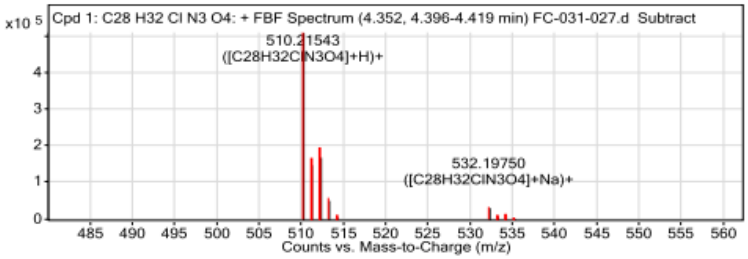
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C28 H32 Cl N3 O4	532.1975	4.369	Find By Formula	509.20848



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

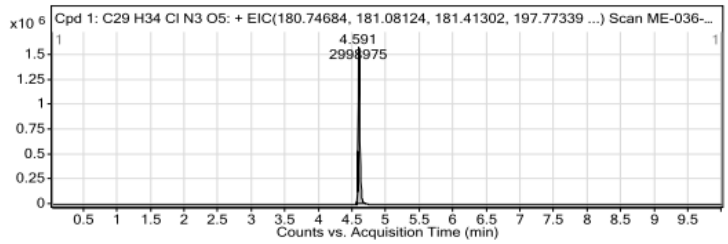
m/z	z	Abund	Formula	Ion
510.21543	1	511181.84	C28H32ClN3O4	(M+H)+
511.21948	1	147762.09	C28H32ClN3O4	(M+H)+
512.21465	1	168180.02	C28H32ClN3O4	(M+H)+
513.21672	1	49121.18	C28H32ClN3O4	(M+H)+
514.2194	1	8512.21	C28H32ClN3O4	(M+H)+
515.22187	1	1247.41	C28H32ClN3O4	(M+H)+
532.1975	1	35024.35	C28H32ClN3O4	(M+Na)+
533.20099	1	10584.68	C28H32ClN3O4	(M+Na)+
534.19626	1	12706.97	C28H32ClN3O4	(M+Na)+
535.19772	1	3672.92	C28H32ClN3O4	(M+Na)+

HRMS spectrum of compound **14**.

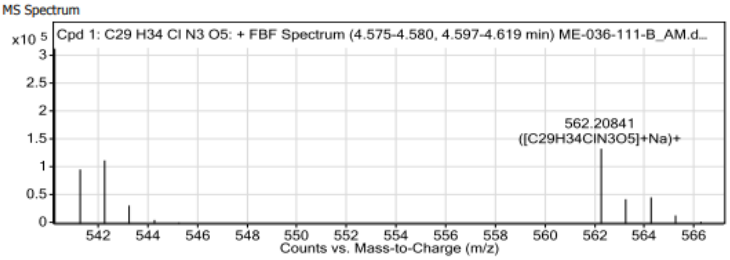
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C29 H34 Cl N3 O5	4.591	539.21911	134312	C29 H34 Cl N3 O5	539.2187	0.76	C29 H34 Cl N3 O5	C29 H34 Cl N3 O5

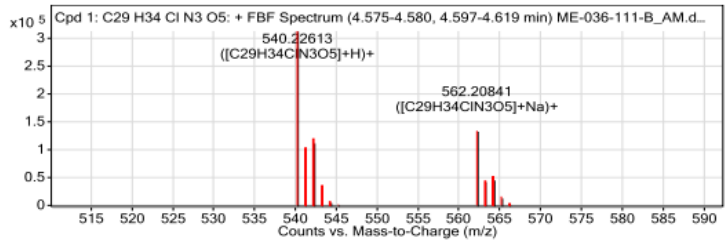
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C29 H34 Cl N3 O5	562.20841	4.591	Find By Formula	539.21911



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

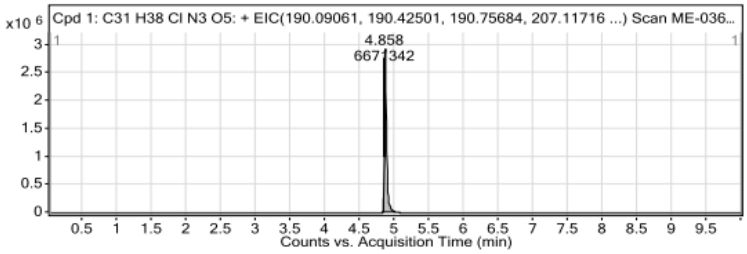
m/z	z	Abund	Formula	Ion
540.22613	1	313373.69	C29H34ClN3O5	(M+H)+
541.23003	1	96632.58	C29H34ClN3O5	(M+H)+
542.22528	1	112542.21	C29H34ClN3O5	(M+H)+
543.22737	1	31792.41	C29H34ClN3O5	(M+H)+
544.22946	1	6094.23	C29H34ClN3O5	(M+H)+
562.20841	1	134312.09	C29H34ClN3O5	(M+Na)+
563.21115	1	43242.53	C29H34ClN3O5	(M+Na)+
564.2069	1	46677.24	C29H34ClN3O5	(M+Na)+
565.20909	1	14458.06	C29H34ClN3O5	(M+Na)+
566.21185	1	2893.19	C29H34ClN3O5	(M+Na)+

HRMS spectrum of compound **15**.

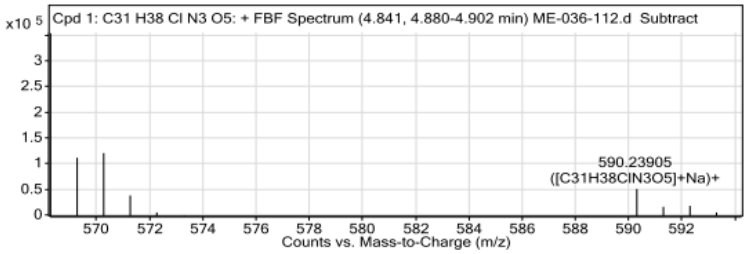
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C31 H38 Cl N3 O5	4.858	567.2501	53373	C31 H38 Cl N3 O5	567.25	0.19	C31 H38 Cl N3 O5	C31 H38 Cl N3 O5

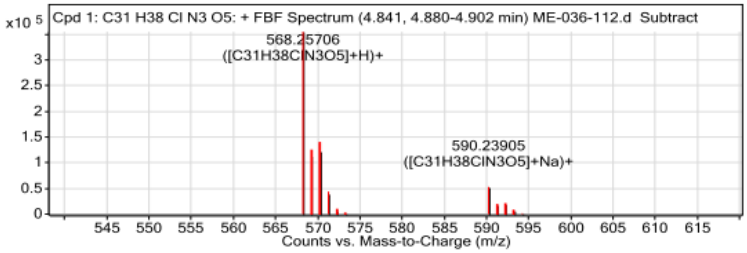
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C31 H38 Cl N3 O5	590.23905	4.858	Find By Formula	567.2501



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

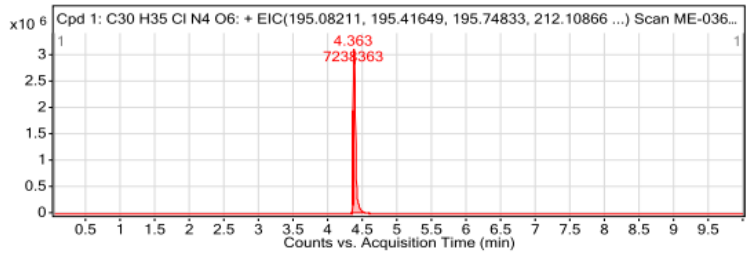
m/z	z	Abund	Formula	Ion
568.25706	1	354780.25	C31H38ClN3O5	(M+H)+
569.26094	1	113831.38	C31H38ClN3O5	(M+H)+
570.25682	1	122164.05	C31H38ClN3O5	(M+H)+
571.25829	1	39661.86	C31H38ClN3O5	(M+H)+
572.26115	1	7175.91	C31H38ClN3O5	(M+H)+
590.23905	1	53373.13	C31H38ClN3O5	(M+Na)+
591.24211	1	19025.9	C31H38ClN3O5	(M+Na)+
592.23807	1	19559.61	C31H38ClN3O5	(M+Na)+
593.24063	1	6599.79	C31H38ClN3O5	(M+Na)+
594.24234	1	1380.94	C31H38ClN3O5	(M+Na)+

HRMS spectrum of compound **16**.

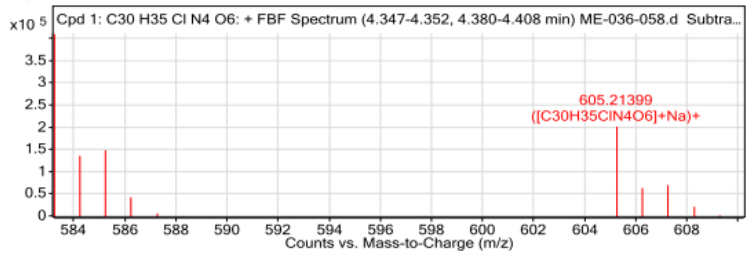
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C30 H35 Cl N4 O6	4.363	582.22474	410649	C30 H35 Cl N4 O6	582.22451	0.4	C30 H35 Cl N4 O6	C30 H35 Cl N4 O6

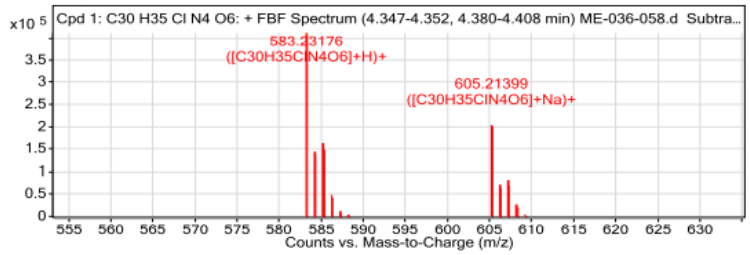
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C30 H35 Cl N4 O6	583.23176	4.363	Find By Formula	582.22474



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

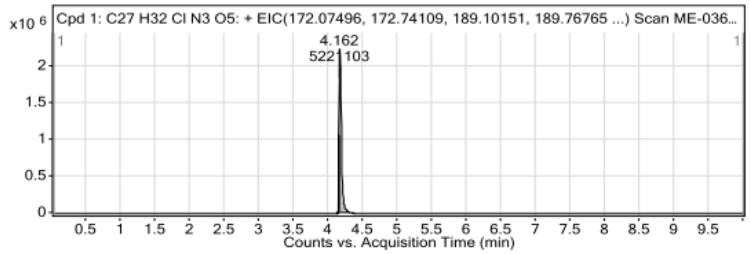
m/z	z	Abund	Formula	Ion
583.23176	1	410649.41	C30H35ClN4O6	(M+H)+
584.23541	1	138070.45	C30H35ClN4O6	(M+H)+
585.23108	1	151338.73	C30H35ClN4O6	(M+H)+
586.233	1	45319.11	C30H35ClN4O6	(M+H)+
587.23544	1	8956.27	C30H35ClN4O6	(M+H)+
605.21399	1	203937.5	C30H35ClN4O6	(M+Na)+
606.21691	1	66147.31	C30H35ClN4O6	(M+Na)+
607.21292	1	72221.36	C30H35ClN4O6	(M+Na)+
608.21428	1	22598.62	C30H35ClN4O6	(M+Na)+
609.21733	1	4529.93	C30H35ClN4O6	(M+Na)+

HRMS spectrum of compound **17**.

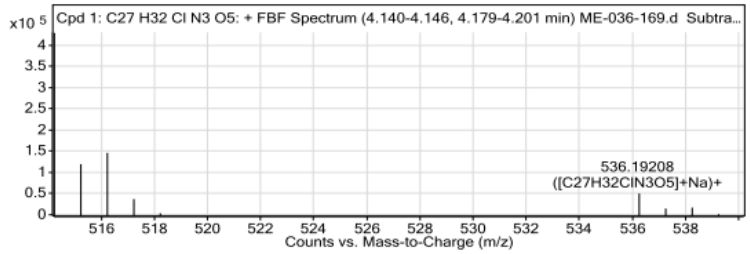
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C27 H32 Cl N3 O5	4.162	513.20287	53862	C27 H32 Cl N3 O5	513.20305	-0.35	C27 H32 Cl N3 O5	C27 H32 Cl N3 O5

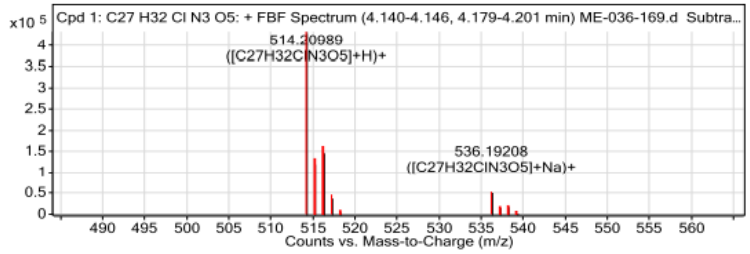
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C27 H32 Cl N3 O5	536.19208	4.162	Find By Formula	513.20287



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

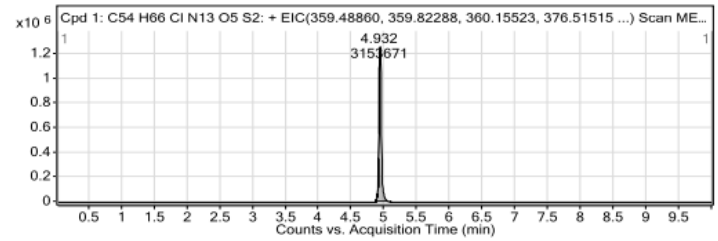
m/z	z	Abund	Formula	Ion
514.20989	1	430828.34	C27H32ClN3O5	(M+H)+
515.21368	1	122883.82	C27H32ClN3O5	(M+H)+
516.20897	1	148415.59	C27H32ClN3O5	(M+H)+
517.21108	1	40932.54	C27H32ClN3O5	(M+H)+
518.21359	1	7345.8	C27H32ClN3O5	(M+H)+
519.21576	1	929.75	C27H32ClN3O5	(M+H)+
536.19208	1	53861.61	C27H32ClN3O5	(M+Na)+
537.1952	1	17825.01	C27H32ClN3O5	(M+Na)+
538.19038	1	20086.78	C27H32ClN3O5	(M+Na)+
539.19301	1	5546.55	C27H32ClN3O5	(M+Na)+

HRMS spectrum of **PROTAC-1**.

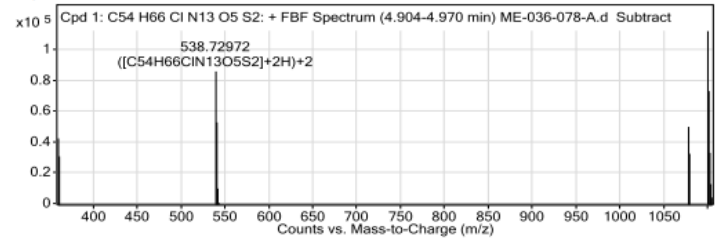
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C54 H66 Cl N13 O5 S2	4.932	1075.44564	86228	C54 H66 Cl N13 O5 S2	1075.44398	1.54	C54 H66 Cl N13 O5 S2	C54 H66 Cl N13 O5 S2

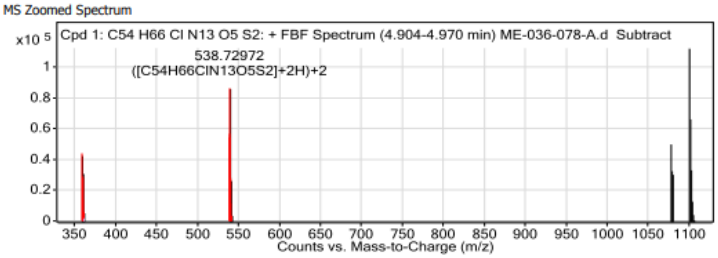
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C54 H66 Cl N13 O5 S2	538.72972	4.932	Find By Formula	1075.44564



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

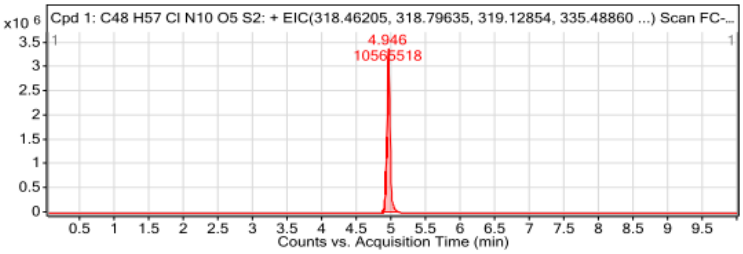
m/z	z	Abund	Formula	Ion
359.48937	3	42551.19	C54H66ClN13O5S2	(M+3H)+3
538.72972	2	86228.26	C54H66ClN13O5S2	(M+2H)+2
539.23101	2	56998.94	C54H66ClN13O5S2	(M+2H)+2
539.72985	2	52932.13	C54H66ClN13O5S2	(M+2H)+2
1076.45214	1	50325.52	C54H66ClN13O5S2	(M+H)+
1077.4548	1	32705.15	C54H66ClN13O5S2	(M+H)+
1098.4348	1	112150.84	C54H66ClN13O5S2	(M+Na)+
1099.43727	1	73579.83	C54H66ClN13O5S2	(M+Na)+
1100.43482	1	66654.02	C54H66ClN13O5S2	(M+Na)+

HRMS spectrum of **PROTAC-3**.

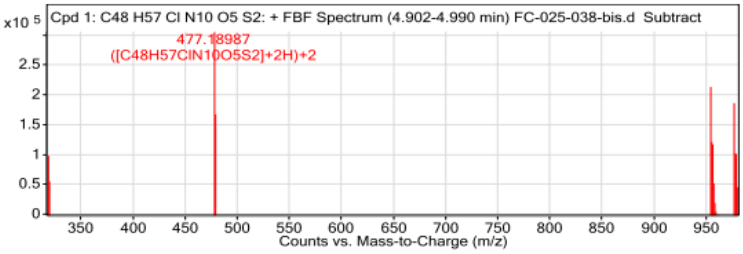
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C48 H57 Cl N10 O5 S2	4.946	952.36612	187628	C48 H57 Cl N10 O5 S2	952.36433	1.88	C48 H57 Cl N10 O5 S2	C48 H57 Cl N10 O5 S2

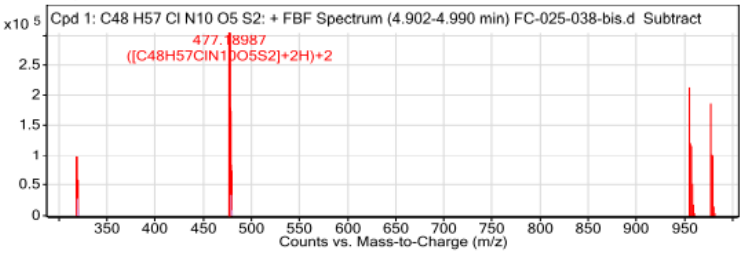
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C48 H57 Cl N10 O5 S2	975.35491	4.946	Find By Formula	952.36612



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

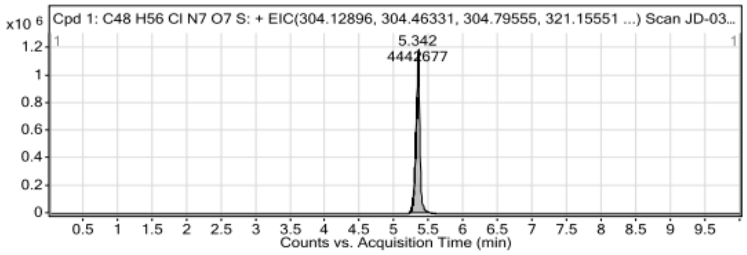
m/z	z	Abund	Formula	Ion
318.46373	3	98772.32	C48H57ClN10O5S2	(M+3H)+3
477.18987	2	305792.28	C48H57ClN10O5S2	(M+2H)+2
477.69164	2	175349.25	C48H57ClN10O5S2	(M+2H)+2
478.19023	2	168724.97	C48H57ClN10O5S2	(M+2H)+2
953.37249	1	214087.47	C48H57ClN10O5S2	(M+H)+
954.37579	1	122565.81	C48H57ClN10O5S2	(M+H)+
955.37308	1	117945.91	C48H57ClN10O5S2	(M+H)+
975.35491	1	187627.59	C48H57ClN10O5S2	(M+Na)+
976.35799	1	104013.87	C48H57ClN10O5S2	(M+Na)+
977.35484	1	102033.73	C48H57ClN10O5S2	(M+Na)+

HRMS spectrum of **PROTAC-4**.

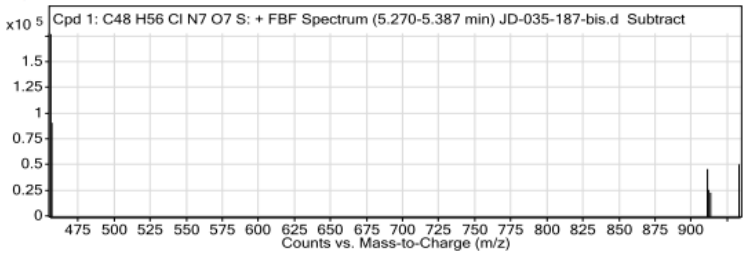
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C48 H56 Cl N7 O7 S	5.342	909.36635	46708	C48 H56 Cl N7 O7 S	909.36505	1.44	C48 H56 Cl N7 O7 S	C48 H56 Cl N7 O7 S

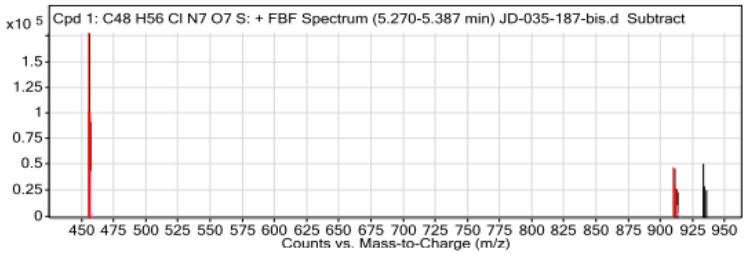
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C48 H56 Cl N7 O7 S	910.373	5.342	Find By Formula	909.36635



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

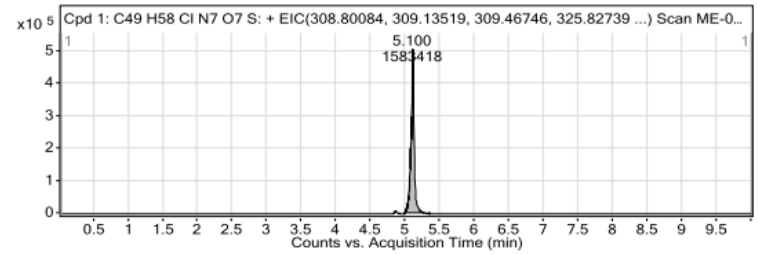
m/z	z	Abund	Formula	Ion
455.69041	2	177490.5	C48H56ClN7O7S	(M+2H)+2
456.19229	2	91558.75	C48H56ClN7O7S	(M+2H)+2
456.69079	2	86404.15	C48H56ClN7O7S	(M+2H)+2
910.373	1	46707.92	C48H56ClN7O7S	(M+H)+
911.3759	1	26835.89	C48H56ClN7O7S	(M+H)+
912.37282	1	24063.18	C48H56ClN7O7S	(M+H)+
932.35509	1	51225.63	C48H56ClN7O7S	(M+Na)+
933.35797	1	29151.69	C48H56ClN7O7S	(M+Na)+
934.35489	1	25987.66	C48H56ClN7O7S	(M+Na)+

HRMS spectrum of **PROTAC-6**.

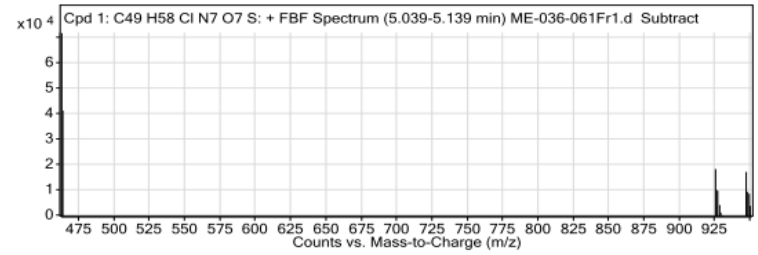
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C49 H58 Cl N7 O7 S	5.1	923.3814	18496	C49 H58 Cl N7 O7 S	923.3807	0.77	C49 H58 Cl N7 O7 S	C49 H58 Cl N7 O7 S

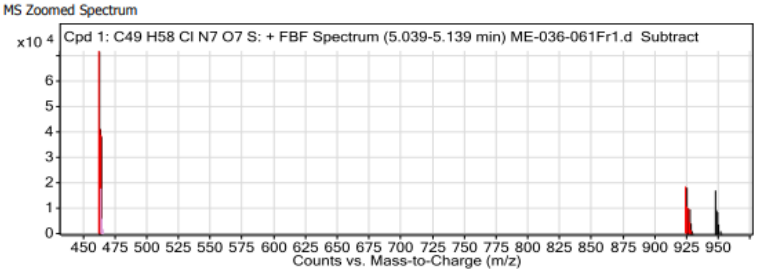
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C49 H58 Cl N7 O7 S	924.38821	5.1	Find By Formula	923.3814



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

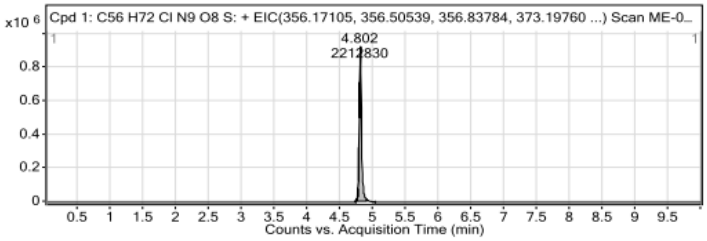
m/z	z	Abund	Formula	Ion
462.69813	2	71804.44	C49H58ClN7O7S	(M+2H)+2
463.19944	2	41459.43	C49H58ClN7O7S	(M+2H)+2
463.69822	2	38654.32	C49H58ClN7O7S	(M+2H)+2
924.38821	1	18495.57	C49H58ClN7O7S	(M+H)+
925.39104	1	10433.06	C49H58ClN7O7S	(M+H)+
926.38806	1	9895.21	C49H58ClN7O7S	(M+H)+
927.38958	1	4310.14	C49H58ClN7O7S	(M+H)+
946.37011	1	17570.33	C49H58ClN7O7S	(M+Na)+
947.37328	1	9555.73	C49H58ClN7O7S	(M+Na)+
948.37043	1	8915.02	C49H58ClN7O7S	(M+Na)+

HRMS spectrum of **PROTAC-8**.

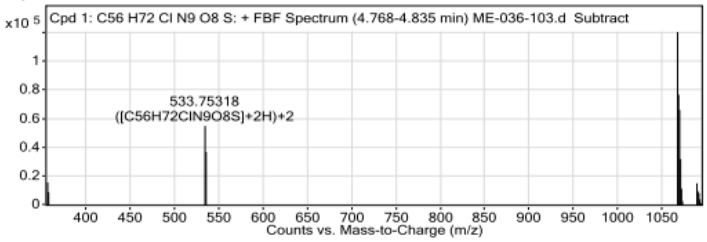
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C56 H72 Cl N9 O8 S	4.802	1065.49232	15606	C56 H72 Cl N9 O8 S	1065.49131	0.95	C56 H72 Cl N9 O8 S	C56 H72 Cl N9 O8 S

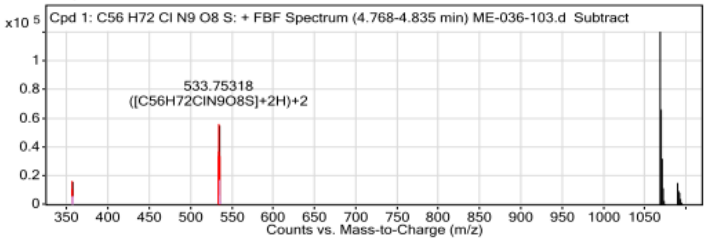
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C56 H72 Cl N9 O8 S	1088.48075	4.802	Find By Formula	1065.49232



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

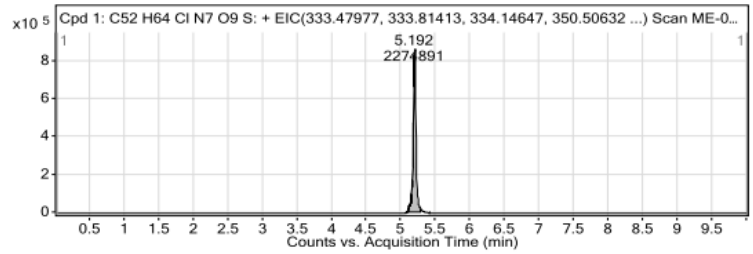
m/z	z	Abund	Formula	Ion
356.17161	3	16011.19	C56H72ClN9O8S	(M+3H)+3
533.75318	2	55289.61	C56H72ClN9O8S	(M+2H)+2
534.25473	2	37199.16	C56H72ClN9O8S	(M+2H)+2
534.75367	2	33498.54	C56H72ClN9O8S	(M+2H)+2
1066.49941	1	120649.41	C56H72ClN9O8S	(M+H)+
1067.50277	1	76876.41	C56H72ClN9O8S	(M+H)+
1068.50057	1	66258.23	C56H72ClN9O8S	(M+H)+
1069.50122	1	32397.3	C56H72ClN9O8S	(M+H)+
1070.50172	1	11563.65	C56H72ClN9O8S	(M+H)+
1088.48075	1	15606.01	C56H72ClN9O8S	(M+Na)+

HRMS spectrum of **PROTAC-10**.

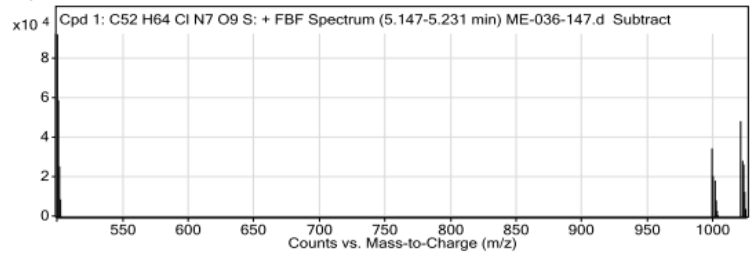
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C52 H64 Cl N7 O9 S	5.192	997.41841	48673	C52 H64 Cl N7 O9 S	997.41748	0.93	C52 H64 Cl N7 O9 S	C52 H64 Cl N7 O9 S

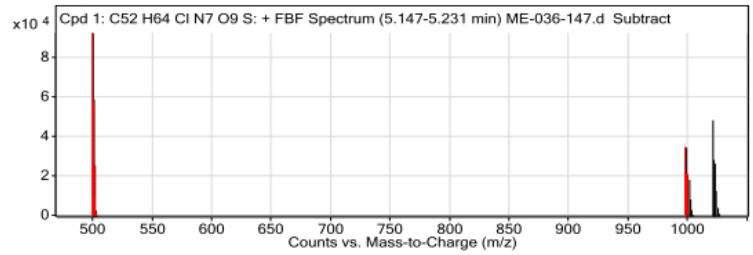
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C52 H64 Cl N7 O9 S	1020.40766	5.192	Find By Formula	997.41841



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

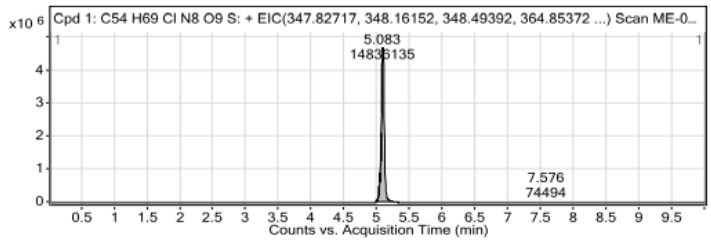
m/z	z	Abund	Formula	Ion
499.7166	2	92544.39	C52H64ClN7O9S	(M+2H)+2
500.218	2	59315.34	C52H64ClN7O9S	(M+2H)+2
500.71671	2	55807.32	C52H64ClN7O9S	(M+2H)+2
501.2172	2	25997.51	C52H64ClN7O9S	(M+2H)+2
998.42541	1	34756.67	C52H64ClN7O9S	(M+H)+
999.42826	1	20916.03	C52H64ClN7O9S	(M+H)+
1000.42579	1	18528.41	C52H64ClN7O9S	(M+H)+
1020.40766	1	48673.25	C52H64ClN7O9S	(M+Na)+
1021.41037	1	28632.3	C52H64ClN7O9S	(M+Na)+
1022.40775	1	26817.67	C52H64ClN7O9S	(M+Na)+

HRMS spectrum of **PROTAC-11**.

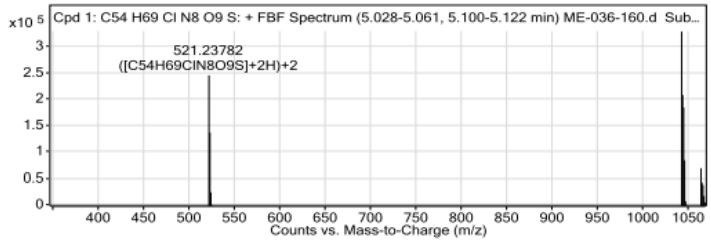
Compound Table

Compound Label	RT	Mass	Abund	Formula	Tgt Mass	Diff (ppm)	MFG Formula	DB Formula
Cpd 1: C54 H69 Cl N8 O9 S	5.083	1040.46143	69860	C54 H69 Cl N8 O9 S	1040.45967	1.69	C54 H69 Cl N8 O9 S	C54 H69 Cl N8 O9 S

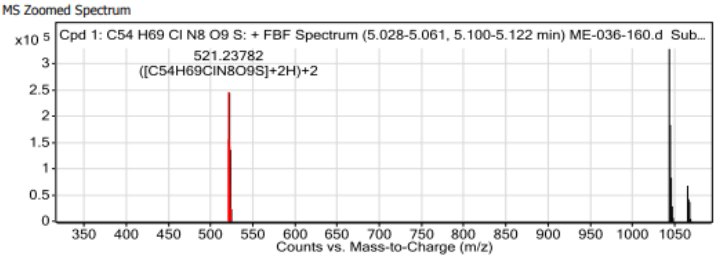
Compound Label	*m/z*	RT	Algorithm	Mass
Cpd 1: C54 H69 Cl N8 O9 S	1063.45014	5.083	Find By Formula	1040.46143



MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

m/z	z	Abund	Formula	Ion
347.82731	3	567.09	C54H69ClN8O9S	(M+3H)+3
521.23782	2	246895.86	C54H69ClN8O9S	(M+2H)+2
521.73985	2	152410.08	C54H69ClN8O9S	(M+2H)+2
522.2387	2	137520.28	C54H69ClN8O9S	(M+2H)+2
522.73901	2	65446.45	C54H69ClN8O9S	(M+2H)+2
1041.46818	1	329456.59	C54H69ClN8O9S	(M+H)+
1042.47176	1	209486.42	C54H69ClN8O9S	(M+H)+
1043.46929	1	185773.55	C54H69ClN8O9S	(M+H)+
1044.47053	1	85317.9	C54H69ClN8O9S	(M+H)+
1063.45014	1	69859.77	C54H69ClN8O9S	(M+Na)+

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