Phenyldihydropyrazolones as novel lead compounds against *Trypanosoma cruzi*

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Supporting information

Table of Contents

Supporting information table 1

Table S1 Overview of the calculated physicochemical properties of all compounds. Numbers were calculated using CDD vault.[1]

Cmpnd	Mw	clog P	clog S	cTPSA (Å²)	Cmpnd	Mw	clog P	clog S	cTPSA (Å²)
4	366.46	4.57	-5.08	51.13	**48**	343.47	3.97	-4.17	45.14
22	336.44	4.66	-5.69	41.9	**49**	358.49	2.96	-2.74	48.38
23	354.43	4.8	-5.94	41.9	**50**	345.44	2.9	-3.66	54.37
24	354.43	4.8	-5.94	41.9	**51**	295.34	2.44	-3.68	63.58
25	354.43	4.8	-5.94	41.9	**52**	309.37	2.66	-4.04	54.79
26	370.88	5.26	-6.37	41.9	**53**	323.40	3.02	-4.36	54.79
27	370.88	5.26	-6.37	41.9	**54**	349.43	3.44	-5.03	54.79
28	366.46	4.5	-5.65	51.13	**55**	363.46	3.89	-5.52	54.79
29	366.46	4.5	-5.65	51.13	**56**	365.48	4.48	-5.24	54.79
30	361.45	4.51	-5.92	65.69	**57**	363.46	4.02	-5.1	54.79
31	361.45	4.51	-5.92	65.69	**58**	391.52	4.91	-6.07	54.79
32	396.49	4.34	-5.6	60.36	**59**	339.40	1.97	-3.83	75.02
33	337.42	3.82	-4.4	54.79	**60**	362.43	2.73	-4.61	78.58
34	337.42	3.44	-4.51	54.79	**61**	376.46	3.17	-4.86	78.58
35	337.42	3.44	-4.51	54.79	**62**	386.46	3.25	-4.68	67.68
36	355.41	3.97	-5.47	54.79	**63**	386.46	3.17	-4.55	67.68
37	351.45	3.57	-4.65	54.79	**64**	386.46	3.17	-4.54	67.68
38	367.45	3.87	-5.03	64.02	**75**	351.45	3.79	-4.83	54.79
39	362.43	3.68	-4.97	78.58	**76**	365.48	4.21	-4.97	54.79
40	351.45	3.95	-5	54.79	**77**	377.49	4.22	-5.49	54.79
41	355.41	3.97	-5.47	54.79	**78**	391.52	4.66	-5.97	54.79
42	351.45	3.57	-4.65	54.79	**79**	391.52	4.79	-5.56	54.79
43	338.41	2.73	-4.61	67.68	**80**	413.52	5.16	-6.16	54.79
44	375.47	4.75	-6.52	57.69	**81**	362.43	2.97	-4.92	78.58
45	387.48	4.81	-6.17	54.79	**82**	393.49	3.34	-5.08	64.02
46	326.40	3.72	-4.79	55.04	**83**	407.51	3.4	-5.17	64.02
47	342.46	4.44	-5.36	41.9					

Supporting information table 2

Table S2 Overview of all pharmacological data on TcrCYP51, TcrPDEC and TcrPDEB1 combined with the phenotypic inhibition on *T. cruzi*.

Compound	TcrCYP51 (pIC_{50})	% TcrPDEC inhibition (10 µM)	% TcrPDEB1 inhibition (10 µM)	*T. cruzi* (pEC_{50})
24	4.2	35	0	5.9
25	4.4	27	0	6.0
28	4.4	18	0	5.6
30	4.3	12	0	6.4
31	4.4	10	0	5.6
34	6	21	0	6.4
36	4	8	0	6.3
37	4	32	0	5.5
38	4.1	9	0	5.6
41	4	39	0	6.3
42	4.1	49	11	6.4
55	6.2	26	0	6.4
56	6	28	0	6.0
57	6	36	0	6.5
61	6	21	0	5.9
64	6	19	0	5.8
77	7.2	28	0	6.2
78	7.2	12	0	6.1
79	6.2	42	3	5.6

Supporting information table 3

Table S3 *In vitro* activity of NPD-0227 (34) against intracellular and bloodstream stages of different *T. cruzi* strains and on cardiac cells (pLC_{50} and pLC_{90}).

	Benznidazole (**1**)				NPD-0227 (**34**)			
Strain (DTU) (form)	pIC_{50}[a]	pIC_{90} [a]	pLC_{50} [a, b]	SI	pIC_{50}[a]	pIC_{90} [a]	pLC_{50} [a,b]	SI[b]
Colombiana (DTU I) (intracellular)	ND	ND	<3.0	ND	6.3	<5.3	<4.3	>95
Y strain (DTU II) (intracellular)	5.4	5.0	<3.0	>277	7.0	6.3	<4.3	>476
Y strain (DTU II) (bloodstream)	4.9	5.4	<3.0	>77	<4.3	<4.3	<4.3	ND

[a]: all reported values are within a standard deviation of ± 0.2, [b]: measured on primary cultures of mice cardiac cells.

Supporting information figure 1

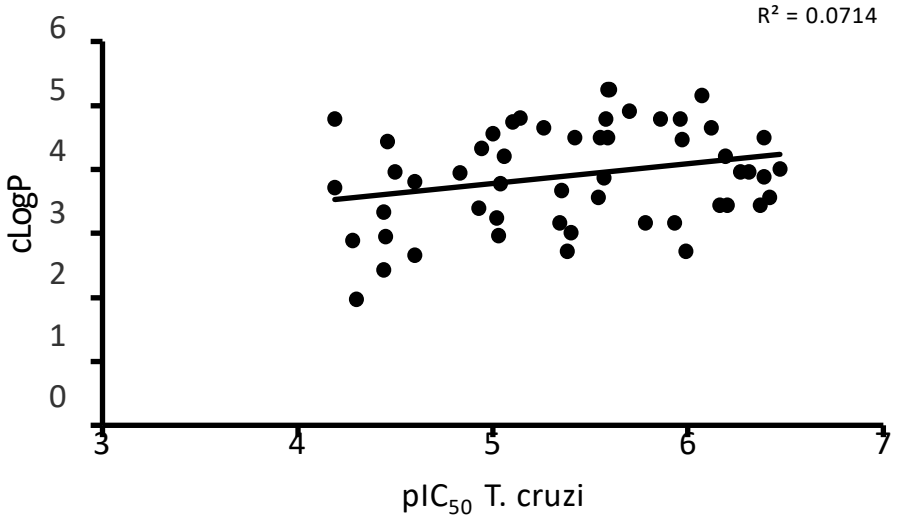

Figure S1 Correlation between *T. cruzi* inhibition and cLogP.

Supporting information figure 2

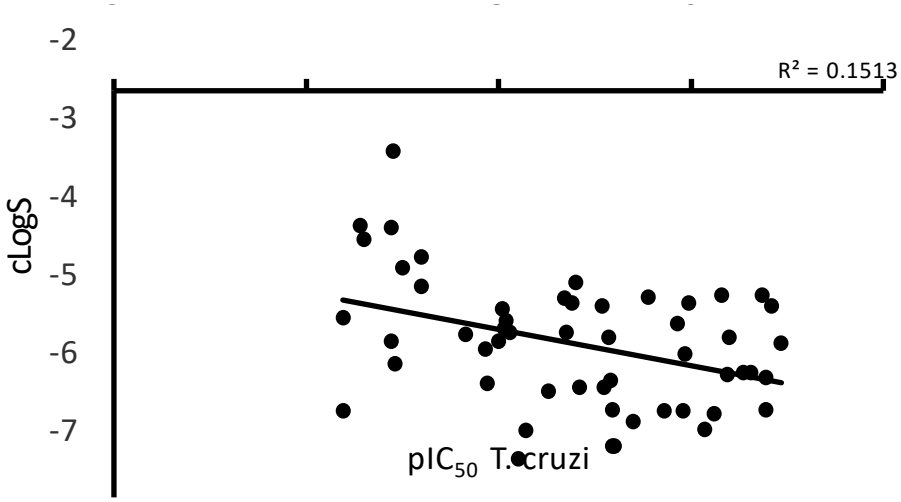

Figure S2 Correlation between *T. cruzi* inhibition and cLogS.

Supporting information figure 3

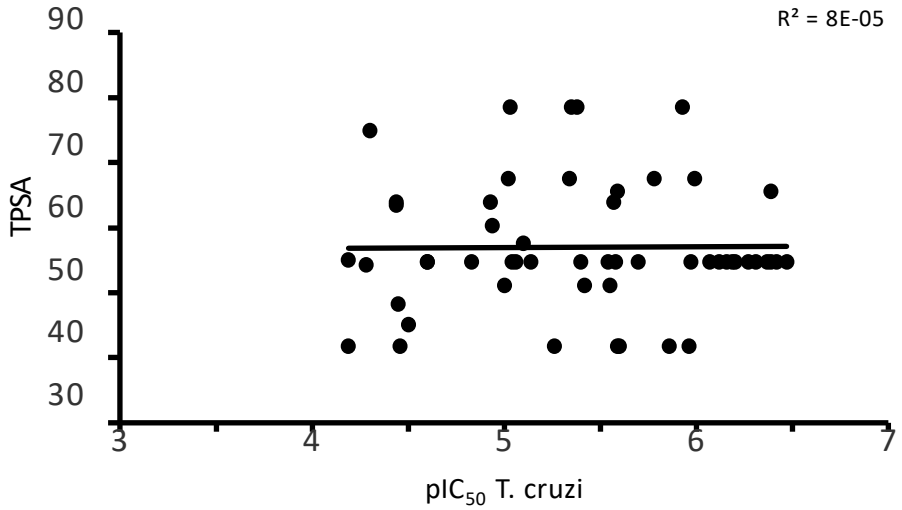

Figure S3 Correlation between *T. cruzi* inhibition and TPSA.

Supporting information figure 4

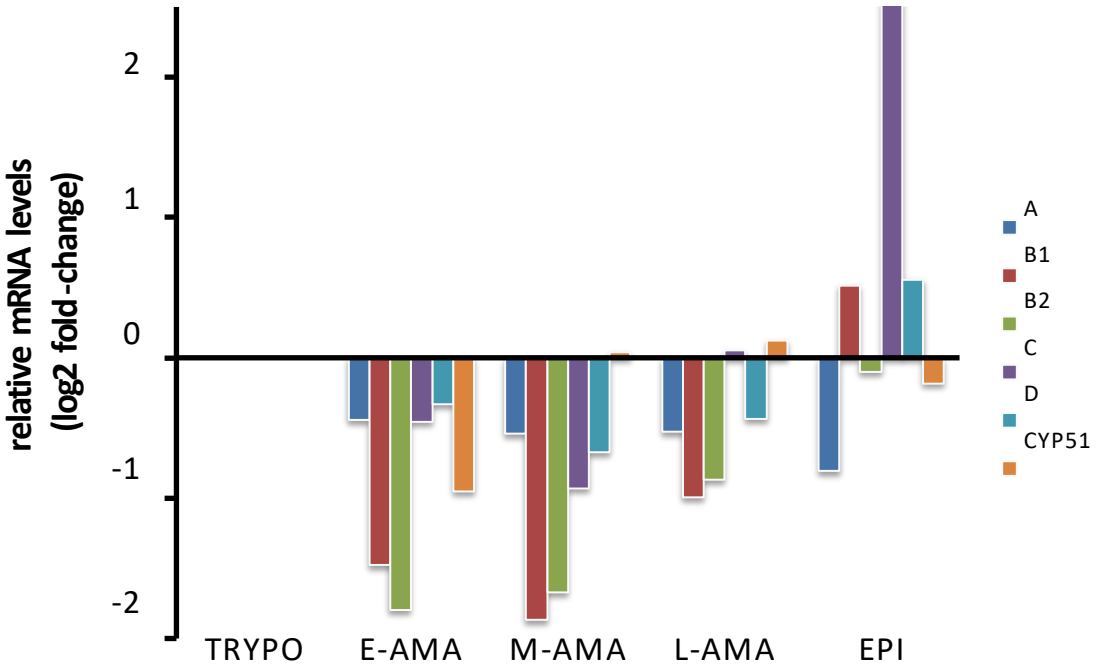

Figure S4 Relative mRNA expression levels of TcrPDEs (A, B1, B2, C, D) and CYP51 in different *Trypanosoma cruzi* (Y strain) life stages: extracellular trypomastigotes (TRYPO), intracellular amastigotes at 4 hours (E-AMA, early stage, nascent amastigotes), 24 hours (M-AMA, mid-stage, mature replicative amastigotes) and 72 hours (L-AMA, late stage, mature replicative amastigotes) post-infection of human fibroblasts, and axenically-cultured epimastigotes (EPI). All shown values were extracted from the RNA-sequence data set of Li *et al.*.[2]

General experimental information

Chemicals and reagents were obtained from commercial suppliers and were used without further purification. ^{1}H NMR spectra were recorded on a Bruker 250(250 MHz), a Bruker 400(400 MHz) or a Bruker 500 (500 MHz) spectrometer. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, dd = double doublet), t = triplet, bs = broad singlet, m = multiplet), and coupling constants (Hz). Chemical shifts are reported in ppm with the natural abundance of deuterium in the solvent as the internal reference ($CHCl_3$in $CDCl_3$: δ 7.26, $(CH_3)_2SO$ in $(CD_3)_2SO$: δ 2.50). ^{13}C NMR spectra were recorded on a Bruker 500 (126 MHz) or Bruker 600 (150 MHz). Chemical shifts are reported in ppm with the solvent resonance resulting from incomplete deuteration as the internal reference ($CDCl_3$: δ 77.16). Systematic names for molecules according to IUPAC rules were generated using the Chemdraw AutoName program. LC-MS data was gathered using a Shimadzu HPLC/MS workstation with a LC-20AD pump system, SPD-M20A diode array detection, and a LCMS-2010 EV mass spectrometer. The column used is an Xbridge C18 5 μm column (100 mm ×4.6 mm). Solvents used were the following: solvent B = ACN, 0.1% formic Acid; solvent A = water, 0.1% formic acid. The analysis was conducted using a flow rate of 1.0 mL/min, start 5% B, linear gradient to 90% B in 4.5 min, then 1.5 min at 90% B, linear gradient to 5% B in 0.5 min and then 1.5 min at 5% B, total run time of 8 min. All reported compounds have purities >95% measured at 254 nm, unless otherwise mentioned. Column purifications were either carried out automatically using Biotage equipment or manually, using 60-200 mesh silica.TLC analyses were performed with Merck F254 alumina silica plates using UV visualization. All reactions were done under N_2 atmosphere, unless specifically mentioned.

General synthetic methodology

General method A: synthesis of β-keto-esters

Benzoic acid **6** (25 g, 108 mmol) was suspended in DCM (50 mL) while cooling to 0°C. Subsequently oxalyl dichloride (13.7 mL, 162 mmol) and DMF (0.08 mL, 1.08 mmol) were added and the mixture was allowed to warm up to room temperature. The mixture was stirred for 2 h after which volatiles were evaporated. The remaining solids were re-dissolved in 50 ml of THF. In a separate flask methyl isobutyrate (18.6 mL, 162 mmol) was stirred in THF (50 mL) at -78°C and a 2M LDA (65 mL, 130 mmol) was added dropwise while maintaining -78°C. Upon full addition, the mixture was stirred for 45m after which the acid chloride of **6** in THF was added dropwise, again maintaining the temperate at -78°C. The reaction was allowed to warm up to room temperature after which crude was quenched with water and extracted with diethyl ether. The organic phase was washed twice with water and once with brine. The organic layer was then dried with $MgSO_4$, filtered and evaporated to dryness. The crude was used in the next step without further purification.

General method B: ring closure of β-keto-esters

Crude keto-ester **7** (25 g, 79 mmol) was dissolved in ethanol (75 mL) and hydrazine hydrate (38.6 mL, 793 mmol) was added. The reaction was stirred at room temperature for 48h after which white precipitation was visible. To the stirred solution 20 mL of water was added to allow further precipitation, after which solids were filtered off. Collected solids were dried *in vacuo* yielding the desired product.

General method C: *N*-alkylation of pyrazolones

Pyrazolone **8** (10 g, 34 mmol) was dissolved in dry DMF (25 mL) and cooled to 0°C. Sodium hydride (60% in mineral oil)(1.48 g, 37 mmol) was added and the reaction was stirred for 30 m at room temperature after which 2-bromopropane (3.54 mL, 38 mmol) was added. The reaction was stirred for 2h at 50°C after which the reaction mixture was quenched with 50 mL water. White solids precipitated after quenching, which were filtered off and washed with water (2x 25 mL). The white solids were dried *in vacuo*, yielding the target compound as a white solid. On a small scale (<0.5g) not all analogues precipitated after quenching; instead a purification over SiO_2 was done.

General method D: Suzuki coupling

Pyrazolone **11** (1.0 g, 3.0 mmol) and pyridin-3-ylboronic acid (0.54 g, 4.4 mmol) were charged to a microwave vial after which DME (12 mL) and 1M Na_2CO_3 (8.84 mL, 8.84 mmol) were added. The mixture was degassed with N_2 for 5m after which $Pd(dppf)Cl_2$ (120 mg, 0.15 mmol) was added. The reaction was then heated in the microwave for 1h at 120°C. The reaction mixture was diluted with MTBE and filtered over Celite. The residue was extracted with saturated $NaHCO_3$ (2x) and brine (1x). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to be further purified over SiO_2 using a gradient of 40% EtOAc in heptane towards 60% heptane. Target compound was obtained as a white solid.

General method E: Buchwald coupling

Pyrazolone **11** (50 mg, 0.15 mmol), piperidine (0.017 mL, 0.18 mmol), $Pd_2(dba)_3$ (13 mg, 0.015 mmol), Xantphos (17 mg, 0.029 mmol) and Na*t*BuO (28 mg, 0.29 mmol) were added to a microwave tube. The mixture was diluted with dry toluene (2 mL) and degassed with N_2 for

5m. The mixture was heated in the microwave at 130 °C for 30m. The reaction mixture was diluted with MTBE and filtered over Celite. The residue was extracted with 1M Na_2CO_3 (2x) and brine (1x) after which the organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The remaining crude was purified over SiO_2 using a gradient from 50% EtOAc in n-heptane towards 100% EtOAc yielding the desired product as a white solid.

General method F: demethylation

Pyrazolone **11** (10 g, 29.5 mmol) was dissolved in dry DCM (50 mL) and mixture was cooled towards -78°C. Subsequently 1M BBr_3 in DCM (59 mL, 59 mmol) was added dropwise over approximately 30m. The dry-ice acetone bath was removed and the mixture allowed to warm towards room temperature and was stirred overnight. The reaction mixture was then quenched and diluted with water and extracted with MTBE. The organic layer was washed with brine (1x) and dried over $MgSO_4$. The crude was filtered after which remaining volatiles were evaporated *in vacuo*. The resulting crude was recrystallized from a DCM/MTBE mixture yielding the product as a white solid.

General method G: *O*-alkylation of demethylated pyrazolones

Pyrazolone **65** (500 mg, 1.5 mmol) was dissolved in dry DMF (5 mL) and Cs_2CO_3 (1.0g, 3.1 mmol) was added followed by (bromomethyl)cyclobutane (0.19 mL, 1.7 mmol). The reaction mixture was stirred for 3h at room temperature after which the mixture was poured in 30 mL of water. The aqueous phase was extracted with EtOAc after which the organic layer was washed twice with water followed by brine (1x). The organic layer was dried over $MgSO_4$, filtered and evaporated to dryness. The resulting crude was purified over SiO_2 using a gradient

of 20% EtOAc in heptane towards 50% EtOAc in heptane. Evaporation of pure fractions yielded the desired product as a white solid.

Experimental data of compounds 9-10, 12-33, 35-64, 66, 68-74, 75 and 77-83

The experimental data of compound **7**, **8**, **11**, **34**, **65**, **67**, **76** can be found in the main text.

5-(3-bromo-4-methoxyphenyl)-2,4,4-trimethyl-2,4-dihydro-3H-pyrazol-3-one (9).

Prepared according general method C using methyliodide (0.12 mL, 1.85 mmol) to afford 420 mg (1.68 mmol, 80%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 2.2 Hz, 1H), 7.68 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 3.94 (s, 3H), 3.40 (s, 3H), 1.47 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.4, 160.6, 157.1, 131.2, 126.5, 124.8, 112.3, 111.6, 56.4, 48.1, 31.5, 22.7. LC-MS (ESI) *m*/*z* found: 311 $[M+H]^+$; retention time: 4.41 minutes.

5-(3-bromo-4-methoxyphenyl)-2-ethyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (10).

Prepared according general method C using iodoethane (0.15 mL, 1.85 mmol) to afford 510 mg (1.7 mmol, 93%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.2 Hz, 1H), 7.67 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.91 (d, *J* = 8.6 Hz, 1H), 3.93 (s, 3H), 3.79 (q, *J* = 7.2 Hz, 2H), 1.45 (s, 6H), 1.32 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 160.4, 157.0, 131.2, 126.5, 125.0, 112.3, 111.6, 56.4, 48.4, 39.2, 22.6, 13.7. LC-MS (ESI) *m*/*z* found: 325 $[M+H]^+$; retention time: 4.74 minutes.

5-(3-bromo-4-methoxyphenyl)-2-(cyclopropylmethyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (12).

Prepared according general method C using (bromomethyl)cyclopropane (0.78 mL, 8.1 mmol) to afford 2.0 g (5.7 mmol, 85%) of the title compound as a white solid. ^{1}H NMR (500

MHz, $CDCl_3$) δ 8.05 (d, *J* = 2.0 Hz, 1H), 7.69 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 3.94 (s, 3H), 3.62 (d, *J* = 7.0 Hz, 2H), 1.48 (s, 6H), 1.31-1.16 (m, 1H), 0.63-0.47 (m, 2H), 0.44-0.31 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.8, 160.6, 157.4, 131.6, 126.9, 125.5, 112.7, 112.0, 56.8, 49.1, 48.6, 23.1, 10.6, 3.9, 1.4. LC-MS (ESI) *m*/*z* found: 351 $[M+H]^+$; retention time: 5.09 minutes.

5-(3-bromo-4-methoxyphenyl)-2-(cyclobutylmethyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (13).

Prepared according general method C using (bromomethyl)cyclobutane (0.45 mL, 4.0 mmol) to afford 0.48 g (3.4 mmol, 39%) of the title compound as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.2 Hz, 1H), 7.68 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 3.95 (s, 3H), 3.77 (d, *J* = 7.3 Hz, 2H), 2.85 – 2.72 (m, 1H), 2.11 – 2.00 (m, 2H), 1.95 – 1.75 (m, 4H), 1.46 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6, 160.1, 156.9, 131.1, 126.4, 125.0, 112.3, 111.5, 56.3, 49.2, 48.2, 34.5, 25.8, 22.7, 18.3. LC-MS (ESI) *m*/*z* found: 365 $[M+H]^+$; retention time: 5.46 minutes.

5-(3-bromo-4-methoxyphenyl)-4,4-dimethyl-2-(pentan-3-yl)-2,4-dihydro-3H-pyrazol-3-one (14).

Prepared according general method C using 3-bromopentane (0.84 mL, 6.7 mmol) to afford 1.8 g (4.8 mmol, 71%) of the title compound as a white solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 2.1 Hz, 1H), 7.68 (dd, *J* = 8.5, 2.2 Hz), 6.91 (d, *J* = 8.6 Hz, 1H), 3.99 (tt, *J* = 9.7, 4.8 Hz, 1H), 3.94 (s, 3H), 1.88 – 1.63 (m, 4H), 1.47 (d, *J* = 0.8 Hz, 6H), 0.84 (t, *J* = 7.4, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.1, 160.1, 156.9, 131.2, 126.4, 125.3, 112.3, 111.5, 57.1, 56.4, 48.8, 26.4, 22.9, 10.8. LC-MS (ESI) *m*/*z* found: 367 $[M+H]^+$; retention time: 5.52 minutes.

5-(3-bromo-4-methoxyphenyl)-2-cyclopentyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (15).

Prepared according general method C using bromocyclopentane (0.87 mL, 8.1 mmol) to afford 1.4 g (6.7 mmol, 55%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 2.2 Hz, 1 H), 7.67 (dd, *J* = 8.5, 1.9 Hz, 1 H), 6.91 (d, *J* = 8.8 Hz, 1 H), 4.65 (quin, *J* = 1.0 Hz, 1 H), 3.93 (s, 3 H), 1.99 - 1.84 (m, 6 H), 1.68 - 1.56 (m, 2 H), 1.44 (s, 6 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 160.1, 156.9, 131.2, 126.5, 125.3, 112.3, 111.6, 56.4, 54.3, 48.7, 30.7, 24.7, 22.6. LC-MS (ESI) *m*/*z* found: 365 $[M+H]^+$; retention time: 5.92 minutes.

5-(3-bromo-4-methoxyphenyl)-2-cycloheptyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (16).

Prepared according general method C using bromocycloheptane to afford 5.8 g (14.8 mmol, 88%) of the title compound as a white solid. ^{1}H NMR (250 MHz, $CDCl_3$) δ (ppm) 8.03 (d, *J* = 2.1 Hz, 1H), 7.65 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.96 – 6.80 (m, 1H), 4.36 – 4.18 (m, 1H), 3.91 (s, 3H), 2.07 – 1.70 (m, 6H), 1.69 – 1.47 (m, 6H), 1.42 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 160.2, 157.0, 131.3, 126.5, 125.5, 112.5, 111.7, 56.5, 54.8, 48.5, 33.54, 28.24, 24.85, 22.64. LC-MS (ESI) *m*/*z* found: 392 $[M+H]^+$; retention time: 6.22 minutes.

4-(3-(3-bromo-4-methoxyphenyl)-4,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)butanenitrile (17).

Prepared according general method C using 4-bromobutanenitrile (1.51 mL, 8.1 mmol) to afford 2.2 g (6.0 mmol, 90%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 1.9 Hz, 1H), 7.69 (dd, *J* = 8.5, 1.9 Hz, 1H), 6.94 (d, *J* = 8.5 Hz, 1H), 3.95 (s, 3H), 3.89 (t, *J* = 6.5 Hz, 2H), 2.46 (t, *J* = 7.3, 2H), 2.15 (p, *J* = 6.8 Hz, 2H), 1.49 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.0, 161.4, 157.7, 131.7, 127.0, 125.0, 119.4, 112.8, 112.0, 56.8, 48.7, 43.3, 25.0, 23.0, 15.4. LC-MS (ESI) *m*/*z* found: 364 $[M+H]^+$; retention time: 4.41 minutes.

5-(3-(3-bromo-4-methoxyphenyl)-4,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)pentanenitrile (18).

Prepared according general method C using 5-bromopentanenitrile (0.94 mL, 8.1 mmol) to afford 1.9 g (5.0 mmol, 74%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.2 Hz, 1H), 7.68 (dd, *J* = 8.7, 2.2 Hz, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 3.88 (s, 3H), 3.73 (t, *J* = 6.6 Hz, 2H), 2.38 (t, *J* = 7.0 Hz, 2H), 1.98 - 1.76 (m, 2H), 1.74 - 1.47 (m, 2H), 1.40 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.6, 160.9, 157.3, 131.3, 126.7, 124.8, 119.5, 112.5, 111.7, 56.5, 48.5, 43.0, 27.4, 22.8, 22.6, 16.8. LC-MS (ESI) *m*/*z* found: 378 $[M+H]^+$; retention time: 4.57 minutes.

5-(3-bromo-4-methoxyphenyl)-4,4-dimethyl-2-(pyridin-2-ylmethyl)-2,4-dihydro-3H-pyrazol-3-one (19).

Prepared according general method C using 2-(bromomethyl)pyridine.HBr (1.02 g, 4.0 mmol), using an extra equivalent of base, to afford 510 mg (3.4 mmol, 39%) of the title compound as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 – 8.52 (m, 1H), 8.03 (d, *J* = 2.1 Hz, 1H), 7.72 – 7.60 (m, 2H), 7.21 – 7.16 (m, 2H), 6.90 (d, *J* = 8.7 Hz, 1H), 5.10 (s, 2H), 3.92 (s, 3H), 1.53 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.8, 160.9, 157.1, 156.3, 149.6, 136.8, 131.4, 126.7, 124.8, 122.5, 121.4, 112.3, 111.5, 56.4, 49.8, 48.1, 22.7. LC-MS (ESI) *m*/*z* found: 388 $[M+H]^+$; retention time: 4.30 minutes.

5-(3-bromo-4-methoxyphenyl)-4,4-dimethyl-2-(pyridin-3-ylmethyl)-2,4-dihydro-3H-pyrazol-3-one (20).

Prepared according general method C using 3-(bromomethyl)pyridine.HBr (511 mg, 2.0 mmol), using an extra equivalent of base, to afford 640 mg (1.7 mmol, 98%) of the title compound as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 2.0 Hz, 1H), 8.56 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.00 (d, *J* = 2.1 Hz, 1H), 7.69 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.66 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.29 (dd, *J* = 7.8, 4.9 Hz, 1H), 6.90 (d, *J* =8.7 Hz, 1H), 4.94 (s, 2H), 3.93 (s, 3H), 1.48 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.3, 161.1, 157.2, 149.4, 149.1, 135.9, 132.3, 131.3, 126.7, 124.6, 123.7, 112.3, 111.6, 56.4, 48.2, 45.6, 22.6. LC-MS (ESI) *m*/*z* found: 388 $[M+H]^+$; retention time: 3.67 minutes.

5-(3-bromo-4-methoxyphenyl)-4,4-dimethyl-2-(pyridin-4-ylmethyl)-2,4-dihydro-3H-pyrazol-3-one (21).

Prepared according general method C using 4-(bromomethyl)pyridine.HBr (511 mg, 2.0 mmol), using an extra equivalent of base, to afford 636 mg (1.6 mmol, 97%) of the title compound as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 4.5, 1.7 Hz, 2H), 8.03 (d, *J* = 2.1 Hz, 1H), 7.69 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.25 (d, *J* = 5.9 Hz, 2H), 6.93 (d, *J* = 8.7 Hz, 1H), 4.96 (s, 2H), 3.95 (s, 3H), 1.54 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 161.2, 157.3, 150.1, 145.5, 131.3, 126.7, 124.5, 122.6, 112.4, 111.6, 56.4, 48.2, 46.9, 22.7. LC-MS (ESI) *m*/*z* found: 388 $[M+H]^+$; retention time: 3.46 minutes.

2-isopropyl-5-(6-methoxy-[1,1'-biphenyl]-3-yl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (22).

This compound was prepared according to general method E using phenylboronic acid (54 mg, 0.44 mmol) to afford 85 mg (86 %, 0.25 mmol) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 2.3 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.45 (m, 2H), 7.38 (tt, *J* = 7.4, 1.3 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 4.51 (hept, *J* =

6.7 Hz, 1H), 3.86 (s, 3H), 1.48 (s, 6H), 1.36 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 161.4, 157.7, 137.9, 131.1, 129.5, 128.9, 128.2, 127.4, 126.7, 124.0, 111.0, 55.7, 48.9, 45.2, 22.7, 20.8. LC-MS (ESI) *m/z* found: 337 $[M+H]^+$; retention time: 5.35 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{25}N_2O2$: 337.1911 , found: 337.1897.

3-(2'-fluoro-6-methoxy-[1,1'-biphenyl]-3-yl)-1-isopropyl-4,4-dimethyl-1H-pyrazol-5(4H)-one (23).

Prepared according general method D using (2-fluorophenyl)boronic acid (54 mg, 0.38 mmol) to afford 52 mg (0.15 mmol, 50%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.22 (td, *J* = 7.5, 1.2 Hz, 1H), 7.20 – 7.15 (m, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 4.51 (hept, *J* = 6.7 Hz, 1H), 3.85 (s, 3H), 1.48 (s, 6H), 1.35 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 161.2, 160.0 (d, *J* = 250 Hz), 158.1, 131.8 (d, *J* = 4Hz), 129.4 (d, *J* = 8 Hz), 129.3 (d, *J* = 2 Hz), 127.5, 125.7, 125.5, 123.9 (d, *J* = 4Hz), 123.8, 115.6 (d, *J* = 22 Hz), 110.9, 55.9, 48.9, 45.2, 22.7, 20.8. LC-MS (ESI) *m/z* found: 355 $[M+H]^+$; retention time: 5.23 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{24}FN_2O_2$: 355.1816, found: 355.1801.

5-(3'-fluoro-6-methoxy-[1,1'-biphenyl]-3-yl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (24).

Prepared according general method D using (3-fluorophenyl)boronic acid (25 mg, 0.18 mmol) to afford 45 mg (0.13 mmol, 86%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 2.3 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.43-7.36 (m, 1H), 7.32 – 7.24 (m, 2H), 7.09-7.05 (m, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 4.51 (hept, *J* = 6.7 Hz, 1H), 3.86 (s, 3H), 1.48 (s, 6H), 1.36 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR

(126 MHz, $CDCl_3$) δ 177.8, 163.5 (d, *J* = 234 Hz), 161.2, 157.5, 140.0 (d, *J* = 7 Hz), 129.9 (d, *J* = 3 Hz), 129.6 (d, *J* = 8.6 Hz), 128.7, 127.2, 125.2 (d, *J* = 2 Hz), 124.2, 116.6 (d, *J* = 23 Hz), 114.2 (d, *J* = 23 Hz), 111.1, 55.8, 48.9, 45.3, 22.7, 20.8. LC-MS (ESI) *m/z* found: 355 $[M+H]^+$; retention time: 5.775 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{24}FN_2O_2^+$: 355.1816, found: 355.1800.

5-(4'-fluoro-6-methoxy-[1,1'-biphenyl]-3-yl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (25).

Prepared according general method D using (4-fluorophenyl)boronic acid (25 mg, 0.18 mmol) to afford 38 mg (0.11 mmol, 73%) of the title compound as a transparent oil which solidified over time. ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, *J* = 2.4 Hz, 1H), 7.74 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.50 (m, 7.54 – 7.47, 2H), 7.17 – 7.10 (m, 2H), 7.00 (d, *J* = 8.6 Hz, 1H), 4.51 (hept, *J* = 6.7 Hz, 1H), 3.86 (s, 3H), 1.48 (s, 6H), 1.36 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 162.2 (d, *J* = 241 Hz), 161.3, 157.6, 133.8 (d, *J* = 3.8 Hz), 131.1 (d, *J* =7.6 Hz), 130.2, 128.7, 126.8, 124.1, 115.1 (d, *J* = 23 Hz), 111.0, 55.7, 48.9, 45.2, 22.7, 20.8. LC-MS (ESI) *m/z* found: 355 $[M+H]^+$; retention time: 5.778 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{24}FN_2O_2^+$: 355.1816, found: 355.1802.

3-(3'-chloro-6-methoxy-[1,1'-biphenyl]-3-yl)-1-isopropyl-4,4-dimethyl-1H-pyrazol-5(4H)-one (26).

Prepared according general method D using (3-chlorophenyl)boronic acid (90 mg, 0.58 mmol) to afford 120 mg (0.3 mmol, 73%) of the title compound as a transparent oil which solidified over time. ^1H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, *J* = 2.3 Hz, 1H), 7.78 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.55 (t, *J* = 1.8 Hz, 1H), 7.43 (dt, *J* = 7.4, 1.6 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 1H), 7.35 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 4.53 (hept, *J* = 6.7 Hz, 1H), 3.88 (s,

3H), 1.51 (s, 6H), 1.39 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 161.2, 157.5, 139.7, 133.9, 129.8, 129.6, 129.4, 128.7, 127.7, 127.4, 127.2, 124.2, 111.1, 55.8, 48.9, 45.3, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 371 $[M+H]^+$; retention time: 5.65 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{24}ClN_2O_2$: 371.1521, found: 371.1503

3-(4'-chloro-6-methoxy-[1,1'-biphenyl]-3-yl)-1-isopropyl-4,4-dimethyl-1H-pyrazol-5(4H)-one (27).

Prepared according general method D using (4-chlorophenyl)boronic acid (90 mg, 0.58 mmol) to afford 110 mg (0.3 mmol, 67%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, *J* = 2.3 Hz, 1H), 7.75 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.49 – 7.45 (m, 2H), 7.43 – 7.38 (m, 2H), 7.00 (d, *J* = 8.6 Hz, 1H), 4.51 (hept, *J* = 6.7 Hz, 1H), 3.86 (s, 3H), 1.48 (s, 6H), 1.36 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 161.2, 157.5, 136.3, 133.3, 130.8, 130.0, 128.6, 128.3, 127.0, 124.2, 111.1, 55.8, 48.9, 45.2, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 371 $[M+H]^+$; retention time: 5.70 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{24}ClN_2O_2$: 371.1521, found: 371.1504

5-(3',6-dimethoxy-[1,1'-biphenyl]-3-yl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (28).

Prepared according general method D using (3-methoxyphenyl)boronic acid (27 mg, 0.18 mmol) to afford 48 mg (0.13 mmol, 89%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ δ 7.82 (d, *J* = 2.3 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.17 – 7.07 (m, 2H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.92 (ddd, *J* = 8.2, 2.7, 1.0 Hz, 1H), 4.51 (hept, *J* = 6.7 Hz, 1H), 3.86 (s, 6H), 1.48 (s, 6H), 1.36 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 161.4, 159.3, 157.7, 139.3, 131.0, 129.1, 128.8, 126.8, 124.0, 122.0, 115.5, 112.6, 111.1, 55.8, 55.3, 48.9, 45.2, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 367 $[M+H]^+$; retention

time: 5.655 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{22}H_{27}N_2O_3^+$: 367.2016, found: 367.2011.

5-(4',6-dimethoxy-[1,1'-biphenyl]-3-yl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (29).

Prepared according general method D using (4-methoxyphenyl)boronic acid (27 mg, 0.18 mmol) to afford 48 mg (0.13 mmol, 89%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 (d, *J* = 2.4 Hz, 1H), 7.73 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.59 – 7.39 (m, 2H), 6.99 (m, 3H), 4.51 (hept, *J* = 6.7 Hz, 1H), 3.86 (d, *J* = 1.2 Hz, 6H), 1.49 (s, 6H), 1.36 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 161.5, 158.9, 157.7, 130.8, 130.6, 130.2, 128.7, 126.3, 124.0, 113.6, 111.0, 55.7, 55.3, 48.9, 45.2, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 367 $[M+H]^+$; retention time: 5.639 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{22}H_{27}N_2O_3^+$: 367.2016, found: 367.2000.

5'-(1-isopropyl-4,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-3-yl)-2'-methoxy-[1,1'-biphenyl]-3-carbonitrile (30).

Prepared according general method D using (3-cyanophenyl)boronic acid (26 mg, 0.18 mmol) to afford 41 mg (0.12 mmol, 79%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (t, *J* = 1.7 Hz, 1H), 7.81 – 7.73 (m, 3H), 7.67 – 7.63 (m, 1H), 7.54 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 8.6 Hz, 1H), 4.51 (hept, *J* = 6.7 Hz, 1H), 3.87 (s, 3H), 1.48 (s, 6H), 1.36 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 160.9, 157.4, 139.1, 133.9, 133.2, 130.8, 129.0, 128.8, 128.6, 127.7, 124.4, 119.0, 112.3, 111.2, 55.8, 48.8, 45.3, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 362 $[M+H]^+$; retention time: 5.55 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{22}H_{24}N_3O_2^+$: 362.1863, found: 362.1852.

5'-(1-isopropyl-4,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-3-yl)-2'-methoxy-[1,1'-biphenyl]-4-carbonitrile (31).

Prepared according general method D using (4-cyanophenyl)boronic acid (26 mg, 0.18 mmol) to afford 46 mg (0.13 mmol, 86%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 – 7.76 (m, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.65 (d, *J* = 8.3, 2H), 7.03 (d, *J* = 8.6 Hz, 1H), 4.51 (hept, *J* = 6.7 Hz, 1H), 3.87 (s, 3H), 1.48 (s, 6H), 1.36 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 160.9, 157.4, 142.7, 131.9, 130.3, 129.3, 128.6, 127.8, 124.4, 119.0, 111.2, 110.9, 55.8, 48.8, 45.3, 22.7, 20.8. LC-MS (ESI) *m/z* found: 362 $[M+H]^+$; retention time: 5.53 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{22}H_{24}N_3O_2^+$: 362.1863, found: 362.1858.

2-isopropyl-4,4-dimethyl-5-(3',4',6-trimethoxy-[1,1'-biphenyl]-3-yl)-2,4-dihydro-3H-pyrazol-3-one (32).

Prepared according general method D using (3,4-dimethoxyphenyl)boronic acid (32 mg, 0.18 mmol) to afford 48 mg (0.12 mmol, 82%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 – 7.76 (m, 2H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.78 – 6.74 (m, 1H), 6.27 – 6.23 (m, 1H), 6.19 (dd, *J* = 3.5, 1.7 Hz, 1H), 4.50 (hept, *J* = 6.6 Hz, 1H), 3.86 (s, 3H), 3.60 (s, 3H), 3.51 (s, 3H), 1.47 (s, 6H), 1.35 (d, *J* = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 161.2, 158.5, 130.4, 130.3, 127.3, 123.9, 123.0, 122.9, 110.6, 109.3, 107.7, 55.6, 48.8, 45.2, 34.6, 22.7, 20.8. LC-MS (ESI) *m/z* found: 397 $[M+H]^+$; retention time: 5.39 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{23}H_{29}N_2O_4^+$: 397.2122, found: 397.2129.

2-isopropyl-5-(4-methoxy-3-(pyridin-2-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (33).

Prepared according general method using 6-phenyl-2-(pyridin-2-yl)-1,3,6,2-dioxazaborocane-4,8-dione (112 mg, 0.42 mmol) to afford 10 mg (14%, 0.03 mmol) of the title compound as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (d, *J* = 5.1, 1H), 8.23 (d, *J* = 2.4, 1H), 7.85 – 7.76 (m, 2H), 7.72 (td, *J* = 7.7, 1.9, 1H), 7.03 (d, *J* = 8.7, 1H), 4.50 (hept, *J* = 6.7, 1H), 3.90 (s, 3H), 1.49 (s, 6H), 1.36 (d, *J* = 6.7, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.6, 158.2, 155.6, 149.8, 135.9, 129.8, 129.6, 128.0, 125.2, 124.5, 122.2, 111.5, 100.1, 77.5, 77.2, 76.8, 55.9, 49.1, 45.4, 22.8, 20.9. LC-MS (ESI) *m*/*z* found: 367 $[M+H]^+$; retention time: 4.50 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{20}H_{24}N_3O_2$: 338.1863, found: 338.1849.

2-isopropyl-5-(4-methoxy-3-(pyridin-4-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (35).

Prepared according general method D using pyridine-4-ylboronic acid (0.47 g, 3.8 mmol) to afford 74 mg (0.22 mmol, 74%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 5.7 Hz, 2H), 7.83 (d, *J* = 2.2 Hz, 1H), 7.79 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.48 (dd, *J* = 4.6, 1.4 Hz, 2H), 7.03 (d, *J* = 8.7 Hz, 1H), 4.51 (hept, *J* = 6.7 Hz, 1H), 3.88 (s, 3H), 1.48 (s, 6H), 1.36 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 160.9, 157.6, 149.5, 145.8, 128.5, 128.2, 128. 0, 124.4, 124.3, 111.3, 55.8, 48.8, 45.3, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 338 $[M+H]^+$; retention time: 3.25 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{20}H_{24}N_3O_2^+$: 338.1863, found: 338.1854.

3-(3-(6-fluoropyridin-3-yl)-4-methoxyphenyl)-1-isopropyl-4,4-dimethyl-1H-pyrazol-5(4H)-one (36).

Prepared according general method D using (6-fluoropyridin-3-yl)boronic acid (108 mg, 0.77 mmol) to afford 172 mg (0.48 mmol, 82%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.35 (d, *J* = 2.3 Hz, 1H), 7.97 (td, *J* = 8.1,

2.5 Hz, 1H), 7.81 (d, *J* = 2.2 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 6.99 (dd, *J* = 8.5, 2.9 Hz, 1H), 4.49 (hept, *J* = 6.7 Hz, 1H), 3.86 (s, 3H), 1.47 (s, 6H), 1.35 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 162.8 (d, *J* = 240 Hz), 160.9, 157.6, 147.7 (d, *J* = 14 Hz), 142.2 (d, *J* = 8 Hz), 131.5 (d, *J* = 5 Hz), 128.5, 127.6, 126.5, 124.4, 111.1, 108.8 (d, *J* = 40 Hz), 55.8, 48.8, 45.3, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 356 $[M+H]^+$; retention time: 4.83 minutes HRMS-ESI $[M+H]^+$ calculated for $C_{20}H_{23}FN_3O_2$: 356.1769, found: 356.1765.

2-isopropyl-5-(4-methoxy-3-(6-methylpyridin-3-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (37).

Prepared according general method D using (6-methylpyridin-3-yl)boronic acid (24 mg, 0.18 mmol) to afford 40 mg (0.12 mmol, 77%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 2.4 Hz, 1H), 7.81 (d, *J* = 2.4 Hz, 1H), 7.79 – 7.73 (m, 2H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 4.50 (h, *J* = 6.7 Hz, 1H), 3.85 (s, 3H), 2.60 (s, 3H), 1.47 (s, 6H), 1.34 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, CDCl3) δ 177.9, 161.2, 157.8, 157.2, 149.4, 137.3, 130.8, 1287, 127.8, 127.3, 124.4, 122.7, 111.2, 55.8, 48.9, 45.3, 24.3, 22.8, 20.9. LC-MS (ESI) *m*/*z* found: 352 $[M+H]^+$; retention time: 3.84 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{26}N_3O_2^+$: 352.2020, found: 352.20044.

2-isopropyl-5-(4-methoxy-3-(6-methoxypyridin-3-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (38).

Prepared according general method D using (6-methoxypyridin-3-yl)boronic acid (27 mg, 0.18 mmol) to afford 45 mg (0.12 mmol, 83%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (d, *J* = 2.4 Hz, 1H), 7.83 – 7.78 (m,

2H), 7.74 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 1H), 4.50 (hept, *J* = 6.7 Hz, 1H), 3.99 (s, 3H), 3.86 (s, 3H), 1.48 (s, 6H), 1.35 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 163.3, 161.1, 157.7, 146.8, 140.0, 128.3, 127.6, 126.9, 126.8, 124.3, 111.0, 110.2, 55.7, 53.6, 48.8, 45.2, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 369 $[M+H]^+$; retention time: 5.59 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{26}N_3O_3^+$: 368.1969, found: 368.1977.

5-(5-(1-isopropyl-4,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-3-yl)-2-methoxyphenyl)picolinonitrile (39).

Prepared according general method D using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile (68 mg, 0.30 mmol) to afford 35 mg (0.10 mmol, 33%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, *J* = 1.9 Hz, 1H), 8.02 (dd, *J* = 8.1, 2.2 Hz, 1H), 7.84 (d, *J* = 2.2 Hz, 1H), 7.80 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 1H), 4.50 (hept, *J* = 6.8 Hz, 1H), 3.88 (s, 3H), 1.47 (s, 6H), 1.35 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 160.6, 157.5, 151.6, 137.5, 137.2, 132.0, 128.5, 128.5, 128.0, 125.8, 124.6, 117.4, 111.3, 55.9, 48.8, 45.3, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 363 $[M+H]^+$; retention time: 4.65 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{23}N_4O_2$: 363.1816, found: 363.1816.

2-isopropyl-5-(4-methoxy-3-(4-methylpyridin-3-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (40).

Prepared according general method D using (4-methylpyridin-3-yl)boronic acid (24 mg, 0.18 mmol) to afford 35 mg (0.10 mmol, 68%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.42 (s, 1H), 7.81 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.68 (d, *J* = 2.3 Hz, 1H), 7.01 (d, *J* = 8.6 Hz, 1H), 4.50 (hept, *J* = 6.7 Hz, 1H),

3.82 (s, 3H), 2.22 (s, 3H), 1.47 (s, 6H), 1.35 (d, J = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 161.0, 158.0, 149.2, 147.6, 134.6, 128.9, 127.7, 127.0, 125.1, 124.1, 110.7, 55.7, 48.8, 45.3, 22.7, 20.8, 19.7. LC-MS (ESI) *m/z* found: 406 $[M+H]^+$; retention time: 3.93 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{26}N_3O_2^+$: 352.2020, found: 352.2022.

3-(3-(2-fluoropyridin-4-yl)-4-methoxyphenyl)-1-isopropyl-4,4-dimethyl-1H-pyrazol-5(4H)-one (41).

Prepared according general method D using (2-fluoropyridin-4-yl)boronic acid (108 mg, 0.77 mmol) to afford 154 mg (0.43 mmol, 74%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.27 (d, J = 5.1 Hz, 1H), 7.86 (d, J = 2.2 Hz, 1H), 7.82 (dd, J = 8.7, 2.2 Hz, 1H), 7.38 (d, J = 5.1 Hz, 1H), 7.15 (s, 1H), 7.06 (d, J = 8.7 Hz, 1H), 4.52 (hept, J = 6.7 Hz, 1H), 3.91 (s, 3H), 1.49 (s, 6H), 1.38 (d, J = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 163.9 (d, J = 250 Hz) 160.7, 157.5, 151.2 (d, J = 8.3 Hz), 147.2 (d, J = 15 Hz) 128.4 (d, J = 17 Hz), 127.2 (d, J = 3 Hz), 124.4, 122.1 (d, J = 4 Hz), 111.4, 110.1, 109.8, 55.8, 48.8, 45.3, 22.7, 20.8. LC-MS (ESI) *m/z* found: 356 $[M+H]^+$; retention time: 4.82 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{20}H_{23}FN_3O_2$: 356.1769, found: 356.1769.

2-isopropyl-5-(4-methoxy-3-(2-methylpyridin-4-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (42).

Prepared according general method D using (2-methylpyridin-4-yl)boronic acid (24 mg, 0.18 mmol) to afford 46 mg (0.13 mmol, 89%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, J = 5.2 Hz, 1H), 7.83 – 7.73 (m, 2H), 7.31 (d, J = 1.6 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.02 (d, J = 8.4 Hz, 1H), 4.51 (hept, J = 6.7 Hz, 1H), 3.87 (s, 3H), 2.63 (s, 3H), 1.48 (s, 6H), 1.36 (d, J = 6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 161.1, 158.3, 157.7, 148.9, 146.3, 128.7, 128.5, 128.0, 124.4, 123.9, 121.6,

111.3, 55.9, 48.9, 45.4, 24.7, 22.8, 20.9. LC-MS (ESI) *m/z* found: 352 $[M+H]^+$; retention time: 3.821 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{26}N_3O_2^+$: 352.2020, found: 352.2011.

1-isopropyl-3-(4-methoxy-3-(pyrimidin-5-yl)phenyl)-4,4-dimethyl-1H-pyrazol-5(4H)-one (43).

Prepared according general method D using pyrimidin-5-ylboronic acid (48 mg, 0.38 mmol) to afford 70 mg (0.2 mmol, 70%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.92 (s, 2H), 7.85 (d, *J* = 2.2 Hz, 1H), 7.79 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.04 (d, *J* = 8.7 Hz, 1H), 4.50 (hept, *J* = 6.7 Hz, 1H), 3.88 (s, 3H), 1.47 (s, 6H), 1.35 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 160.7, 157.6, 157.2, 156.9, 131.7, 128.3, 128.3, 124.6, 124.1, 111.2, 55.8, 48.8, 45.3, 22.7, 20.8. LC-MS (ESI) *m/z* found: 339 $[M+H]^+$; retention time: 4.13 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{19}H_{23}N_4O_2$: 339.1816, found: 339.1802.

5-(3-(1H-indol-6-yl)-4-methoxyphenyl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (44).

Prepared according general method D using (1H-indol-6-yl)boronic acid (29 mg, 0.18 mmol) to afford 35 mg (0.09 mmol, 63%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (broad s, 1H), 7.88 (d, *J* = 2.4 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.70 (d, *J* = 8.1 Hz, 1H), 7.57 (s, 1H), 7.30 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.27-7.25 (m, 2H), 7.02 (d, *J* = 8.7 Hz, 1H), 6.59 (t, *J* = 2.6 Hz, 1H), 4.51 (hept, *J* = 6.7 Hz, 1H), 3.86 (s, 3H), 1.49 (s, 6H), 1.36 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 161.6, 157.9, 135.8, 132.2, 131.7, 129.3, 127.2, 126.2, 124.8, 124.0, 121.8, 120.2, 112.0, 111.1, 102.6, 55.8, 49.0, 45.2, 22.7, 20.8. LC-MS (ESI) *m/z* found: 376 $[M+H]^+$; retention time: 5.47 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{23}H_{26}N_3O_2^+$: 376.2020, found: 376.2013.

2-isopropyl-5-(4-methoxy-3-(quinolin-3-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (45).

Prepared according general method D using quinolin-3-ylboronic acid (153 mg, 0.88 mmol) to afford 37 mg (0.10 mmol, 16%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.10 (d, *J* = 2.2 Hz, 1H), 8.29 (d, *J* = 2.0 Hz, 1H), 8.15 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 2.3 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.81 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.77 – 7.70 (m, 1H), 7.58 (t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 4.51 (hept, *J* = 6.7 Hz, 1H), 3.89 (s, 3H), 1.50 (s, 6H), 1.36 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 161.0, 157.9, 151.7, 147.0, 135.7, 131.1, 129.5, 129.2, 129.0, 128.0, 127.8, 127.6, 126.8, 124.5, 111.2, 55.8, 48.8, 45.3, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 388 $[M+H]^+$; retention time: 4.63 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{24}H_{26}N_3O_2$: 388.2020, found: 388.2017.

5-(3-(furan-2-yl)-4-methoxyphenyl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (46).

Prepared according general method D using furan-2-ylboronic acid (20 mg, 0.18 mmol) to afford 38 mg (0.12 mmol, 79%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 2.2 Hz, 1H), 7.73 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.51 (d, *J* = 2.0 Hz, 1H), 7.03 – 6.96 (m, 2H), 6.51 (dd, *J* = 3.4, 1.8 Hz, 1H), 4.52 (hept, *J* = 6.7 Hz, 1H), 3.99 (s, 3H), 1.50 (s, 6H), 1.39 (d, *J* = 6.7 Hz, 6H).^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 161.4, 156.1, 149.3, 141.4, 126.0, 123.9, 123.7, 119.9, 111.7, 111.0, 110.4, 55.5, 48.8, 45.1, 22.6, 20.7. LC-MS (ESI) *m*/*z* found: 327 $[M+H]^+$; retention time: 5.72 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{19}H_{23}N_2O_3^+$: 327.1703, found: 327.1693.

2-isopropyl-5-(4-methoxy-3-(thiophen-3-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (47).

Prepared according general method D using thiophen-3-ylboronic acid (23 mg, 0.18 mmol) to afford 34 mg (0.10 mmol, 67%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, *J* = 2.3 Hz, 1H), 7.71 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.63 (d, *J* = 3.4 Hz, 1H), 7.45 (d, *J* = 5.2 Hz, 1H), 7.38 (dd, *J* = 5.0, 3.0 Hz, 1H), 7.00 (d, *J* = 8.6 Hz, 1H), 4.52 (hept, *J* = 6.7 Hz, 1H), 3.92 (s, 3H), 1.49 (s, 6H), 1.37 (d, *J* = 6.6 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 161.5, 157.7, 137.8, 128.6, 127.9, 126.5, 125.7, 124.9, 124.1, 123.8, 111.3, 55.8, 49.0, 45.3, 22.9, 20.9. LC-MS (ESI) *m/z* found: 343 $[M+H]^+$; retention time: 5.81 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{19}H_{23}N_2O_2S^+$: 343.1475, found: 343.1456.

2-isopropyl-5-(4-methoxy-3-(piperidin-1-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (48).

Prepared according general method E using piperidine (15 mg, 0.18 mmol). To afford 46 mg (0.13 mmol, 91%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 2.1 Hz, 1H), 7.36 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.84 (d, *J* = 8.4 Hz, 1H), 4.50 (hept, *J* = 6.7 Hz, 1H), 3.90 (s, 3H), 3.02 (app. s, 4H), 1.78 (p, *J* = 5.5 Hz, 4H), 1.59 (p, *J* = 6.0 Hz, 2H), 1.46 (s, 6H), 1.37 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 161.8, 153.8, 143.0, 124.0, 121.0, 116.2, 110.6, 55.6, 52.2, 48.9, 45.2, 26.3, 24.4, 22.9, 20.8. LC-MS (ESI) *m/z* found: 344 $[M+H]^+$; retention time: 4.03 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{20}H_{30}N_3O_2^+$: 344.2333, found: 344.2316.

2-isopropyl-5-(4-methoxy-3-(4-methylpiperazin-1-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (49).

Prepared according general method E using 1-methylpiperazine (18 mg, 0.18 mmol) to afford 40 mg (0.11 mmol, 76%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.49 (d, *J* = 2.2 Hz, 1H), 7.38 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 4.49 (hept, *J* = 6.8 Hz, 1H), 3.90 (s, 3H), 3.15 (app. s, 4H), 2.67 (app. s, 4H), 2.39 (s, 3H), 1.45 (s, 6H), 1.36 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 161.8, 153.9, 141.8, 124.4, 121.6, 116.3, 110.9, 55.8, 55.4, 50.7, 49.1, 46.3, 45.5, 23.0, 21.0. LC-MS (ESI) *m*/*z* found: 359 $[M+H]^+$; retention time: 3.59 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{20}H_{31}N_4O_2^+$: 359.2442, found: 359.2425.

2-isopropyl-5-(4-methoxy-3-morpholinophenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (50).

Prepared according general method E using morpholine (15 mg, 0.18 mmol) to afford 40 mg (0.12 mmol, 79%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (app. s, 1H), 7.39 (app. s, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 4.50 (hept, *J* = 6.7 Hz, 1H), 3.91 (s, 7H), 3.12 (s, 4H), 1.46 (s, 6H), 1.37 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 161.5, 153.6, 141.5, 124.3, 121.5, 115.8, 110.8, 67.1, 55.6, 51.1, 48.9, 45.3, 22.8, 20.8. LC-MS (ESI) *m*/*z* found: 346 $[M+H]^+$; retention time: 3.840 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{19}H_{28}N_3O_3^+$: 346.2125, found: 346.2116.

5-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (51).

Prepared according general method D using pyridin-3-ylboronic acid (620 mg, 5.1 mmol) to afford 700 mg (2.4 mmol, 70%) of the title compound as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.90 (s, 1H), 8.70 (s, 1H), 7.90 (d, *J* = 7.3 Hz, 1H), 7.86 – 7.74 (m, 2H), 7.43 (s, 1H), 7.05 (d, *J* = 8.9 Hz, 1H), 3.88 (s, 3H), 1.53 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 181.8, 162.8, 158.1, 149.9, 148.1, 137.2, 134.2, 128.8, 127.8, 124.3, 123.9. 123.1, 121.5, 111.4, 55.9, 47.3, 22.7. LC-MS (ESI) *m*/*z* found: 338 $[M+H]^+$; retention time: 4.01 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{17}H_{18}N_3O_2^+$: 296.1394, found: 296.1387.

5-(4-methoxy-3-(pyridin-3-yl)phenyl)-2,4,4-trimethyl-2,4-dihydro-3H-pyrazol-3-one (52).

Prepared according general method D using pyridin-3-ylboronic acid (60 mg, 0.48 mmol) to afford 30 mg (30%, 0.10 mmol) of the title compound as a light brown oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ δ 8.78 (d, *J* = 92.8 Hz, 2H), 7.89 (d, *J* = 6.7 Hz, 1H), 7.82 (s, 1H), 7.77 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 25.0 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 3.88 (s, 3H), 3.41 (s, 3H), 1.50 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 161.5, 157.9, 150.1, 148.2, 145.8, 136.9, 128.7, 127.7, 127.6, 123.9, 111.2, 55.8, 48.2, 31.5, 22.8. LC-MS (ESI) *m*/*z* found: 310 $[M+H]^+$; retention time: 2.88 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{18}H_{20}N_3O_2$:310.1550, found: 310.1542.

2-ethyl-5-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (53).

Prepared according general method D using pyridin-3-ylboronic acid (57 mg, 0.46 mmol) to afford 92 mg (93%, 0.28 mmol) of the title compound as a colourless oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H), 8.58 (d, *J* = 4.4 Hz, 1H), 7.87 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.82 (d, *J* = 2.3 Hz, 1H), 7.76 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.36 (dd, *J* = 7.9, 4.7 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 3.86 (s, 3H), 3.79 (q, *J* = 7.2 Hz, 2H), 1.48 (s, 6H), 1.31 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 161.3, 157.8, 150.0, 148.2, 137.0, 133.6, 128.7, 127.6, 127.5, 124.1, 123.1, 111.2, 55.8, 48.5, 39.2, 22.7, 13.7. LC-MS (ESI) *m*/*z* found: 324 $[M+H]^+$; retention time: 3.10 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{19}H_{22}N_3O_2$: 324.1707, found: 324.1704 .

2-(cyclopropylmethyl)-5-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (54).

Prepared according general method C using (bromomethyl)cyclopropane to afford 300 mg (0.86 mmol, 85%) of the title compound as a light yellow oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 2.4 Hz, 1H), 8.54 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.83 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.80 (d, *J* = 2.4 Hz, 1H), 7.75 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.32 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 3.83 (s, 3H), 3.58 (d, *J* = 7.1 Hz, 2H), 1.46 (s, 6H), 1.25 – 1.13 (m, 1H), 0.54 – 0.42 (m, 2H), 0.38 – 0.26 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.4, 161.0, 157.8, 150.1, 148.3, 136.8, 133.6, 128.6, 127.6, 127.5, 124.1, 123.0, 111.2, 55.7, 48.6, 48.3, 22.8, 10.3, 3.5. LC-MS (ESI) *m*/*z* found: 350 $[M+H]^+$; retention time: 4.05 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{24}N_3O_2^+$: 350.1863, found: 350.1847.

2-(cyclobutylmethyl)-5-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (55).

Prepared according general method C using (bromomethyl)cyclobutane (28 mg, 0.19 mmol) to afford 30 mg (0.08 mmol, 49%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.2 Hz, 1H), 8.57 (dd, *J* = 4.8, 1.8 Hz, 1H), 7.85 (dt, *J* = 7.8, 2.0 Hz, 1H), 7.80 (d, *J* = 2.5 Hz, 1H), 7.75 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.35 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 3.85 (s, 3H), 3.76 (d, *J* = 7.4 Hz, 2H), 2.78 (hept, *J* = 7.7 Hz, 1H), 2.07-1.98 (m, 2H), 1.92 – 1.75 (m, 4H), 1.47 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7, 161.1, 157.8, 150.2, 148.4, 136.9, 133.7, 128.7, 127.7, 127.6, 124.2, 123.1, 111.2, 55.8, 49.2, 48.3, 34.6, 25.8, 22.9, 18.4. LC-MS (ESI) *m*/*z* found: 364 $[M+H]^+$; retention time: 4.43 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{22}H_{26}N_3O_2^+$: 364.2020, found: 364.2012.

5-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-2-(pentan-3-yl)-2,4-dihydro-3H-pyrazol-3-one (56).

Prepared according general method D using pyridin-3-ylboronic acid (100 mg, 0.82 mmol) to afford 144 mg (0.39 mmol, 72%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 2.2 Hz, 1H), 8.60 – 8.51 (m, 1H), 7.84 (dd, *J* = 6.1, 1.8 Hz, 1H), 7.81 (d, *J* = 2.2 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.33 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 3.97 (p, *J* = 4.8 Hz, 1H), 3.84 (s, 3H), 1.86 – 1.59 (m, 4H), 1.48 (d, J = 1.8 Hz, 6H), 0.82 (t, J = 7.4 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 161.0, 157.7, 150.2, 148.3, 136.8, 133.6, 128.6, 127.6, 127.5, 124.4, 123.0, 111.2, 57.0, 55.7, 48.8, 26.3, 23.0, 10.8. LC-MS (ESI) *m*/*z* found: 366 $[M+H]^+$; retention time: 3.99 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{22}H_{26}N_3O_2^+$: 366.2176, found: 366.2159.

2-cyclopentyl-5-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (57).

Prepared according general method C using iodocyclopentane (33 mg, 0.17 mmol) to afford 41 mg (0.11 mmol, 67%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66 (d, *J* = 2.0 Hz, 1H), 8.58 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.86 (dt, *J* = 7.9, 2.0 Hz, 1H), 7.80 (d, *J* = 2.3 Hz, 1H), 7.76 (dd, *J* = 8.7, 2.4 Hz, 1H), 7.36 (ddd, *J* = 7.9, 4.9, 0.9 Hz, 1H), 7.01 (d, *J* = 8.7 Hz, 1H), 4.74 – 4.55 (m, 1H), 3.85 (s, 3H), 2.02 – 1.81 (m, 6H), 1.62 (m, 2H), 1.47 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 161.1, 157.8, 150.2, 148.3, 137.0, 133.7, 128.7, 127.7, 127.6, 124.4, 123.1, 111.2, 55.8, 54.3, 48.8, 30.8, 24.8, 22.8. LC-MS (ESI) *m*/*z* found: 364 $[M+H]^+$; retention time: 4.42 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{22}H_{26}N_3O_2^+$: 364.2020, found: 364.2014.

2-cycloheptyl-5-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (58).

Prepared according general method D using pyridin-3-ylboronic acid (39 mg, 0.32 mmol) to afford 49 mg (0.13 mmol, 42%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, *J* = 1.9, 1H), 8.57 (dd, *J* = 4.8, 1.5, 1H), 7.85 (dt, *J* = 7.8, 1.9, 1H), 7.80 (d, *J* = 2.2, 1H), 7.75 (dd, *J* = 8.6, 2.2, 1H), 7.34 (dd, *J* = 7.8, 4.9, 1H), 7.01 (d, *J* = 8.7, 1H), 4.27 (m, 1H), 3.85 (s, 3H), 2.03 – 1.91 (m, 2H), 1.90 – 1.82 (m, 2H), 1.82 – 1.71 (m, 2H), 1.68 – 1.47 (m, 7H), 1.45 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 161.0, 157.8, 150.3, 148.4, 136.9, 133.7, 128.7, 127.7, 127.5, 124.4, 123.1, 111.2, 55.8, 54.7, 48.6, 33.5, 28.1, 24.8, 22.7. LC-MS (ESI) *m*/*z* found: 380 $[M+H]^+$; retention time: 4.80 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{24}H_{30}N_3O_2$: 392.2333, found: 392.2286.

2-(2-hydroxyethyl)-5-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (59).

Prepared according general method C using 2-iodoetanol (53 mg, 0.31 mmol) to afford 23 mg (38%, 0.07 mmol) of the title compound as an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.74 (d, *J* = 1.6, 1H), 8.57 (dd, *J* = 4.7, 1.3, 1H), 7.89 - 7.70 (m, 3H), 7.35 (dd, J = 7.6, 4.9, 1H), 7.02 (d, *J* = 8.5, 1H), 3.95 (m, 4H), 3.85 (s, 3H), 3.22 (broad s, 1H), 1.51 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 179.3, 162.1, 158.2, 150.2, 148.5, 136.9, 133.6, 127.8, 123.7, 123.2, 111.4, 61.3, 55.9, 48.6, 47.6, 22.9. LC-MS (ESI) *m*/*z* found: 340 $[M+H]^+$; retention time: 2.64 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{19}H_{22}N_3O_3$: 340.1656, found: 340.1652.

4-(3-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)butanenitrile (60).

Prepared according general method D using pyridin-3-ylboronic acid (101 mg, 0.82 mmol) to afford 48 mg (0.13 mmol, 24%) of the title compound as a white solid. ^{1}H NMR (500 MHz, DMSO-*d*6) δ 8.69 (d, *J* = 1.8 Hz, 1H), 8.56 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.91 (dt, *J* = 7.9, 1.9 Hz,

1H), 7.87 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.77 (d, *J* = 2.3 Hz, 1H), 7.47 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 3.85 (s, 3H), 3.76 (t, *J* = 6.6 Hz, 2H), 2.54 (t, *J* = 7.0 Hz, 2H), 1.97 (p, *J* = 6.8 Hz, 2H), 1.42 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 178.4, 161.3, 158.0, 150.0, 148.7, 137.1, 133.6, 128.4, 127.6, 123.8, 123.7, 120.7, 112.5, 56.4, 48.2, 42.9, 24.3, 22.6, 14.5. LC-MS (ESI) *m*/*z* found: 363 $[M+H]^+$; retention time: 3.05 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{23}N_4O_2$: 363.1816, found: 363.1832.

5-(3-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)pentanenitrile (61).

Prepared according general method D using pyridin-3-ylboronic acid (97 mg, 0.80 mmol) to afford 57 mg (0.15 mmol, 29%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76 (d, 1H), 8.57 (dd, 1H), 7.85 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.80 (d, *J* = 2.2 Hz, 1H), 7.76 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.35 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 3.86 (s, 3H), 3.79 (t, *J* = 6.7 Hz, 2H), 2.42 (t, *J* = 7.1 Hz, 2H), 1.92 (p, *J* = 6.7 Hz, 2H), 1.70 (p, *J* = 7.2 Hz, 2H), 1.49 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.5, 161.7, 158.0, 150.2, 148.4, 136.8, 133.5, 128.7, 127.8, 127.6, 123.8, 123.0, 119.3, 111.2, 55.8, 48.4, 42.8, 27.3, 22.8, 22.5, 16.7. LC-MS (ESI) *m*/*z* found: 377 $[M+H]^+$; retention time: 3.19 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{22}H_{25}N_4O_2$: 377.1972, found: 377.1971.

5-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-2-(pyridin-2-ylmethyl)-2,4-dihydro-3H-pyrazol-3-one (62).

Prepared according general method D using pyridin-3-ylboronic acid (62 mg, 0.50 mmol) to afford 106 mg (0.27 mmol, 71%) of the title compound as a white solid. ^{1}H NMR (500 MHz, DMSO-*d*6) δ 8.80 (d, *J* = 1.7 Hz, 1H), 8.66 (dd, *J* = 5.1, 1.3 Hz, 1H), 8.52 (d, *J* = 4.2 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.90 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.80 (td, *J* = 7.7, 1.7 Hz, 1H), 7.76 (d, *J* = 2.2 Hz, 1H), 7.66 (dd, *J* = 7.8, 5.1 Hz, 1H), 7.32 (dd, *J* = 7.0, 5.2 Hz, 1H), 7.25 (dd, *J* = 8.3,

5.3 Hz, 2H), 5.02 (s, 2H), 3.85 (s, 3H), 1.49 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 178.8, 161.4, 158.0, 156.4, 149.5, 147.5, 146.1, 140.3, 137.9, 134.5, 128.9, 128.5, 126.5, 124.9, 123.7, 123.2, 121.8, 112.6, 56.5, 49.2, 47.9, 22.6. LC-MS (ESI) *m*/*z* found: 387 $[M+H]^+$; retention time: 2.63 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{22}H_{25}N_4O_2$: 387.1816, found: 387.1797.

5-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-2-(pyridin-3-ylmethyl)-2,4-dihydro-3H-pyrazol-3-one (63).

Prepared according general method D using pyridin-3-ylboronic acid (62 mg, 0.50 mmol) to afford 141 mg (0.37 mmol, 94%) of the title compound as a white solid. ^{1}H NMR (500 MHz, DMSO-*d*6) δ 8.73 (d, *J* = 1.8 Hz, 1H), 8.61 (dd, *J* = 4.9, 1.4 Hz, 1H), 8.59 – 8.56 (m, 1H), 8.56 – 8.51 (m, 1H), 8.02 (dt, *J* = 7.9, 1.7 Hz, 1H), 7.88 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.78 (d, *J* = 7.9 Hz, 1H), 7.75 (d, *J* = 2.3 Hz, 1H), 7.56 (dd, *J* = 7.9, 5.0 Hz, 1H), 7.47 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.23 (d, *J* = 8.8 Hz, 1H), 4.98 (s, 2H), 3.84 (s, 3H), 1.45 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 178.4, 161.8, 158.1, 148.8, 148.3, 148.2, 147.4, 138.7, 136.9, 134.0, 133.6, 128.7, 128.4, 127.1, 124.7, 124.3, 123.5, 112.6, 56.4, 48.0, 45.2, 22.6. LC-MS (ESI) *m*/*z* found: 387 $[M+H]^+$; retention time: 2.63 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{22}H_{25}N_4O_2$: 387.1816, found: 387.1800.

5-(4-methoxy-3-(pyridin-3-yl)phenyl)-4,4-dimethyl-2-(pyridin-4-ylmethyl)-2,4-dihydro-3H-pyrazol-3-one (64).

Prepared according general method D using pyridin-3-ylboronic acid (62 mg, 0.50 mmol) to afford 129 mg (0.33 mmol, 86%) of the title compound as a white solid. ^{1}H NMR (500 MHz, DMSO-*d*6) δ 8.66 (d, *J* = 1.7 Hz, 1H), 8.54 (ddd, *J* = 6.1, 4.7, 1.5 Hz, 3H), 7.88 (ddd, *J* = 8.6, 4.8, 2.2 Hz, 2H), 7.73 (d, *J* = 2.3 Hz, 1H), 7.48 – 7.42 (m, 1H), 7.28 – 7.18 (m, 3H), 4.96 (s,

2H), 3.84 (s, 3H), 1.49 (s, 6H). ^{13}C NMR (126 MHz, DMSO) δ 178.6, 161.9, 158.2, 150.3, 150.0, 148.7, 146.4, 137.1, 133.5, 128.5, 128.4, 127.6, 123.8, 123.5, 122.5, 112.5, 56.4, 48.0, 46.5, 22.7.LC-MS (ESI) *m/z* found: 387 $[M+H]^+$; retention time: 2.51 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{22}H_{25}N_4O_2$: 387.1816, found: 387.1810.

5-(3-bromo-4-ethoxyphenyl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (66).

Prepared according general method G using bromoethane (0.13 mL, 1.7 mmol) to afford 450 mg (1.3 mmol, 83%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 2.2 Hz, 1H), 7.64 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 4.47 (hept, *J* = 6.7 Hz, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 1.47 (t, *J* = 7.0 Hz, 3H), 1.42 (s, 6H), 1.34 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 160.1, 156.3, 131.2, 126.4, 125.0, 112.6, 112.5, 64.9, 48.7, 45.2, 22.6, 20.8, 14.6. LC-MS (ESI) *m/z* found: 353 $[M+H]^+$; retention time: 5.33 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{16}H_{22}BrN_2O_2$: 353.0859, found: 353.0853.

5-(3-bromo-4-(cyclopropylmethoxy)phenyl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (68).

Prepared according general method G using (bromomethyl)cyclopropane (0.16 mL, 1.7 mmol) to afford 500 mg (1.3 mmol, 86%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, *J* = 2.2 Hz, 1H), 7.62 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 4.47 (hept, *J* = 6.7 Hz, 1H), 3.91 (d, *J* = 6.7 Hz, 2H), 1.42 (s, 6H), 1.33 (d, *J* = 6.7 Hz, 6H), 1.31 – 1.24 (m, 1H), 0.70 – 0.59 (m, 2H), 0.39 (q, *J* = 4.8 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 160.1, 156.4, 131.2, 126.3, 125.1, 113.0, 112.9, 73.7, 48.7, 45.2, 22.5, 20.8, 10.1, 3.3. LC-MS (ESI) *m/z* found: 379 $[M+H]^+$; retention time: 5.15 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{23}H_{28}N_3O_2^+$: 379.1016, found: 379.1017.

5-(3-bromo-4-(cyclobutylmethoxy)phenyl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (69).

Prepared according general method G using (bromomethyl)cyclobutane (0.19 mL, 1.7 mmol) to afford 480 mg (1.2 mmol, 79%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 2.2 Hz, 1H), 7.64 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 4.48 (hept, *J* = 6.7 Hz, 1H), 4.00 (d, *J* = 6.1 Hz, 2H), 2.87 – 2.74 (m, 1H), 2.19 – 2.06 (m, 2H), 2.01 – 1.89 (m, 4H), 1.42 (s, 6H), 1.34 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 160.2, 156.6, 131.1, 126.3, 124.9, 112.9, 112.7, 72.9, 48.7, 45.2, 34.5, 24.7, 22.6, 20.8, 18.6. LC-MS (ESI) *m*/*z* found: 393 $[M+H]^+$; retention time: 6.04 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{19}H_{26}BrN_2O_2$: 393.1172, found: 393.117

5-(3-bromo-4-(cyclopentyloxy)phenyl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (70).

Prepared according general method G using bromocyclopentane (0.019 mL, 0.19 mmol) to afford 32 mg (0.08 mmol, 66%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, *J* = 2.1 Hz, 1H), 7.67 (dd, *J* = 8.6, 2.1 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 1H), 4.87 (p, *J* = 4.1 Hz, 1H), 4.51 (p, *J* = 6.7 Hz, 1H), 2.00 – 1.81 (m, 6H), 1.75-1.61 (m, 2H), 1.46 (d, *J* = 1.7 Hz, 6H), 1.37 (d, *J* = 7.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 160.3, 155.7, 131.2, 126.2, 124.7, 114.0, 113.5, 81.0, 48.7, 45.2, 32.8, 24.0, 22.6, 20.8. LC-MS (ESI) *m*/*z* found: 393 $[M+H]^+$; retention time: 6.10 minutes.

3-(4-(benzyloxy)-3-bromophenyl)-1-isopropyl-4,4-dimethyl-1H-pyrazol-5(4H)-one (71).

Prepared according general method G using (bromomethyl)benzene (0.31 mL, 2.6 mmol) to afford 650 mg (1.6 mmol, 73%) of the title compound as a white solid. ^{1}H NMR (500 MHz,

$CDCl_3$) δ 8.07 (d, *J* = 2.1 Hz, 1H), 7.64 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.43 – 7.37 (m, 2H), 7.37 – 7.31 (m, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 5.22 (s, 2H), 4.50 (hept, *J* = 6.7 Hz, 1H), 1.44 (s, 6H), 1.35 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 160.1, 156.0, 136.0, 131.3, 128.7, 128.1, 126.9, 126.3, 125.5, 113.3, 113.0, 70.8, 48.7, 45.3, 22.6, 20.8. LC-MS (ESI) *m/z* found: 415 $[M+H]^+$; retention time: 5.73 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{22}H_{28}N_3O_2$: 415.1016, found: 415.1010.

2-(2-bromo-4-(1-isopropyl-4,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-3-yl)phenoxy)acetonitrile (72).

Prepared according general method G using bromoacetonitrile (0.12 mL, 1.7 mmol) to afford 540 mg (1.5 mmol, 96%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ8.10 (d, *J* = 2.1 Hz, 1H), 7.73 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.07 (d, *J* = 8.6 Hz, 1H), 4.90 (s, 2H), 4.49 (hept, *J* = 6.7 Hz, 1H), 1.44 (s, 6H), 1.35 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 159.4, 153.8, 131.8, 127.9, 126.5, 114.5, 114.2, 113.4, 54.6, 48.6, 45.4, 22.5, 20.8. LC-MS (ESI) *m/z* found: 364 $[M+H]^+$; retention time: 4.70 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{16}H_{19}BrN_3O_2$: 364.0655, found: 364.0642.

3-(3-bromo-4-((tetrahydrofuran-3-yl)oxy)phenyl)-1-isopropyl-4,4-dimethyl-1H-pyrazol-5(4H)-one (73).

Prepared according general method G using 3-bromotetrahydrofuran (93 mg, 0.62 mmol) to afford 128 mg (0.32 mmol, 53%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (d, *J* = 2.2 Hz, 1H), 7.65 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.83 (d, *J* = 8.6 Hz, 1H), 5.01 – 4.97 (m, 1H), 4.48 (hept, *J* = 6.7 Hz, 1H), 4.09 – 3.97 (m, 3H), 3.97 – 3.89 (m, 1H), 2.28 – 2.13 (m, 2H), 1.43 (s, 6H), 1.34 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, CDCl3) δ 177.6, 160.0, 155.0, 131.5, 126.2, 125.5, 113.7, 113.6, 79.0, 72.9, 67.2, 48.7, 45.3, 33.1, 22.5, 20.8.

LC-MS (ESI) *m/z* found: 395 $[M+H]^+$; retention time: 4.93 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{18}H_{24}BrN_2O_3$: 395.0965, found: 395.0961.

5-(3-bromo-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (74).

Prepared according general method G using 4-bromotetrahydro-2H-pyran (0.43 mL, 3.8 mmol) to afford 110 mg (0.27 mmol, 17%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 2.2 Hz, 1H), 7.62 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.90 (d, *J* = 8.7 Hz, 1H), 4.64 – 4.58 (m, 1H), 4.45 (hept, *J* = 6.7 Hz, 1H), 4.00 – 3.93 (m, 2H), 3.62 – 3.53 (m, 2H), 2.03 – 1.95 (m, 2H), 1.87 – 1.78 (m, 2H), 1.40 (s, 6H), 1.31 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 160.0, 154.7, 131.4, 126.2, 125.5, 114.8, 114.2, 72.7, 64.4, 48.6, 45.2, 31.2, 22.5, 20.8. LC-MS (ESI) *m/z* found: 409 $[M+H]^+$; retention time: 5.01 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{19}H_{26}BrN_2O_3$: 409.1121, found: 409.1125.

5-(4-ethoxy-3-(pyridin-3-yl)phenyl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (75).

Prepared according general method D using pyridin-3-ylboronic acid (90 mg, 0.74 mmol) to afford 120 mg (0.34 mmol, 60%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.81 (d, *J* = 1.8 Hz, 1H), 8.58 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.89 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.83 (d, *J* = 2.3 Hz, 1H), 7.75 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.36 (dd, *J* = 7.6, 4.8 Hz, 1H), 7.00 (d, *J* = 8.7 Hz, 1H), 4.50 (hept, *J* = 6.7 Hz, 1H), 4.10 (q, *J* = 7.0 Hz, 2H), 1.48 (s, 6H), 1.40 – 1.31 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 161.1, 157.1, 150.2, 148.1, 136.8, 133.8, 128.6, 127.6, 127.5, 124.1, 123.0, 112.0, 64.2, 48.8, 45.2, 22.7, 20.8, 14.6. LC-MS (ESI) *m/z* found: 352 $[M+H]^+$; retention time: 3.68 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{26}N_3O_2$: 352.2020, found: 352.2031.

3-(4-(cyclopropylmethoxy)-3-(pyridin-3-yl)phenyl)-1-isopropyl-4,4-dimethyl-1H-pyrazol-5(4H)-one (77).

Prepared according general method D using pyridin-3-ylboronic acid (84 mg, 0.69 mmol) to afford 112 mg (0.30 mmol, 56%) of the title compound as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.82 (d, *J* = 1.7 Hz, 1H), 8.61 – 8.54 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.91 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.83 (d, *J* = 2.3 Hz, 1H), 7.73 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.36 (dd, *J* = 7.8, 4.9 Hz, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 4.49 (hept, *J* = 6.7 Hz, 1H), 3.88 (d, *J* = 6.8 Hz, 2H), 1.47 (s, 6H), 1.35 (d, *J* = 6.7 Hz, 6H), 1.23 – 1.14 (m, 1H), 0.61 – 0.54 (m, 2H), 0.29 (m, 0.31 – 0.27, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 161.1, 157.2, 150.2, 148.2, 136.9, 133.8, 128.6, 127.8, 127.4, 124.3, 123.0, 112.5, 73.2, 48.8, 45.2, 22.7, 20.8, 10.0, 3.2. LC-MS (ESI) *m*/*z* found: 378 $[M+H]^+$; retention time: 4.42 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{23}N_4O_2$: 378.2176, found: 378.2192.

5-(4-(cyclobutylmethoxy)-3-(pyridin-3-yl)phenyl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (78).

Prepared according general method D using pyridin-3-ylboronic acid (81 mg, 0.66 mmol) to afford 151 mg (0.39 mmol, 76%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, *J* = 1.8 Hz, 1H), 8.57 (dd, *J* = 4.8, 1.4 Hz, 1H), 7.89 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.83 (d, *J* = 2.3 Hz, 1H), 7.75 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.34 (dd, *J* = 7.8, 4.8 Hz, 1H), 6.99 (d, *J* = 8.7 Hz, 1H), 4.50 (hept, *J* = 6.7 Hz, 1H), 3.98 (d, *J* = 6.3 Hz, 2H), 2.72 (hept, *J* = 8.0, 7.3 Hz, 1H), 2.10 – 1.99 (m, 2H), 1.95 – 1.86 (m, 1H), 1.86 – 1.74 (m, 3H), 1.47 (s, 6H), 1.35 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 161.1, 157.4, 150.1, 148.2, 136.9, 133.7, 128.6, 127.7, 127.5, 124.2, 122.8, 112.2, 72.5, 48.8, 45.2, 34.4, 24.8, 22.7, 20.8, 18.4. LC-MS (ESI) *m*/*z* found: 392 $[M+H]^+$; retention time: 4.50 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{24}H_{30}N_3O_2$: 392.2333, found: 392.2349.

5-(4-(cyclopentyloxy)-3-(pyridin-3-yl)phenyl)-2-isopropyl-4,4-dimethyl-2,4-dihydro-3H-pyrazol-3-one (79).

Prepared according general method D using pyridine-3-ylboronic acid (15 mg, 0.12 mmol) to afford 10 mg (0.03 mmol, 31%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (app. s, 1H), 8.60 (app. s, 1H), 7.90 (d, *J* = 7.7 Hz, 1H), 7.84 (s, 1H), 7.77 (app. d, *J* = 8.6 Hz, 1H), 7.39 (t, *J* = 6.7 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 4.94 – 4.82 (m, 1H), 4.61 – 4.46 (hept, *J* = 6.8 Hz, 1H), 1.96 – 1.77 (m, 4H), 1.78 – 1.57 (m, 4H), 1.50 (d, *J* = 1.8 Hz, 6H), 1.38 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 161.2, 156.2, 150.0, 147.9, 137.0, 134.1, 128.7, 128.1, 127.4, 123.9, 123.0, 113.4, 80.1, 48.8, 45.2, 32.8, 23.9, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 392 $[M+H]^+$; retention time: 4.42 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{24}H_{30}N_3O_2$: 392.2333, found: 392.2314.

3-(4-(benzyloxy)-3-(pyridin-3-yl)phenyl)-1-isopropyl-4,4-dimethyl-1H-pyrazol-5(4H)-one (80).

Prepared according general method D. Yield: 565 mg (1.4 mmol, 91%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (d, *J* = 2.3 Hz, 1H), 8.60 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.94 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.85 (d, *J* = 2.3 Hz, 1H), 7.75 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.40 – 7.27 (m, 6H), 7.07 (d, *J* = 8.7 Hz, 1H), 5.16 (s, 2H), 4.51 (hept, *J* = 6.7 Hz, 1H), 1.47 (s, 6H), 1.36 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ177.7, 160.9, 156.7, 149.9, 148.1, 137.2, 136.2, 133.8, 128.8, 128.7, 128.0, 128.0, 127.5, 126.9, 124.7, 123.1, 112.9, 70.5, 48.8, 45.3, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 414 $[M+H]^+$; retention time: 4.34 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{26}H_{28}N_3O_2$: 414.2176, found: 414.2170.

2-(4-(1-isopropyl-4,4-dimethyl-5-oxo-4,5-dihydro-1H-pyrazol-3-yl)-2-(pyridin-3-yl)phenoxy)acetonitrile (81).

Prepared according general method D using pyridin-3-ylboronic acid (88 mg, 0.71 mmol) to afford 128 mg (0.37 mmol, 64%) of the tile compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (app. s, 1H), 8.63 (app. s, 1H), 7.86 (d, *J* = 2.2 Hz, 1H), 7.85 – 7.79 (m, 2H), 7.39 (dd, *J* = 7.7, 4.9 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 4.80 (s, 2H), 4.49 (hept, *J* = 6.5 Hz, 1H), 1.46 (s, 6H), 1.34 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 160.3, 154.2, 149.9, 148.8, 136.9, 132.7, 129.3, 128.9, 127.5, 126.9, 123.3, 114.6, 112.9, 53.8, 48.7, 45.4, 22.6, 20.8. LC-MS (ESI) *m*/*z* found: 363 $[M+H]^+$; retention time: 3.39 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{21}H_{23}N_4O_2$: 363.1816, found: 363.1827.

1-isopropyl-4,4-dimethyl-3-(3-(pyridin-3-yl)-4-((tetrahydrofuran-3-yl)oxy)phenyl)-1H-pyrazol-5(4H)-one (82).

Prepared according general method D using pyridin-3-ylboronic acid (40 mg, 0.33 mmol) to afford 40 mg (0.10 mmol, 40%) of the title compound which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.75 (app. s, 1H), 8.57 (d, *J* = 3.9 Hz, 1H), 7.84 (d, *J* = 7.7 Hz, 1H), 7.83 (d, *J* = 2.4 Hz, 1H) 7.75 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.35 (dd, *J* = 7.7, 4.8 Hz, 1H), 6.93 (d, *J* = 8.7 Hz, 1H), 5.00 (app. t, *J* = 5.3 Hz, 1H), 4.49 (hept, *J* = 6.7 Hz, 1H), 4.02 – 3.81 (m, 4H), 2.24 – 2.03 (m, 2H), 1.47 (s, 6H), 1.34 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 160.9, 155.4, 150.0, 148.3, 136.9, 133.6, 129.0, 128.4, 127.3, 124.7, 123.0, 113.1, 78.1, 72.8, 67.2, 48.8, 45.3, 33.0, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 394 $[M+H]^+$; retention time: 4.70 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{23}H_{28}N_3O_3$: 394.2125, found: 394.2135.

2-isopropyl-4,4-dimethyl-5-(3-(pyridin-3-yl)-4-((tetrahydro-2H-pyran-4-yl)oxy)phenyl)-2,4-dihydro-3H-pyrazol-3-one (83).

Prepared according general method D using pyridin-3-ylboronic acid (39 mg, 0.32 mmol) to afford 72 mg (0.18 mmol, 73%) of the title compound as a transparent oil which solidified over time. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (app. s, 1H), 8.59 (d, *J* = 4.2 Hz, 1H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 2.2 Hz, 1H), 7.74 (dd, *J* = 8.7, 2.2 Hz, 1H), 7.36 (dd, *J* = 7.5, 4.8 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 1H), 4.61 – 4.54 (m, 1H), 4.48 (hept, *J* = 6.7 Hz, 1H), 3.78 – 3.69 (m, 2H), 3.57 – 3.48 (m, 2H), 2.01 – 1.90 (m, 2H), 1.77 – 1.67 (m, 2H), 1.46 (s, 6H), 1.34 (d, *J* = 6.7 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.7, 160.9, 155.3, 150.1, 148.3, 136.9, 133.8, 128.9, 128.8, 127.3, 124.6, 123.0, 114.0, 72.1, 64.6, 48.8, 45.3, 31.3, 22.7, 20.8. LC-MS (ESI) *m*/*z* found: 408 $[M+H]^+$; retention time: 3.64 minutes. HRMS-ESI $[M+H]^+$ calculated for $C_{24}H_{30}N_3O_3$: 408.2282, found: 408.2299.

^{1}H-NMR and ^{13}C-NMR spectra

^{1}H NMR compound 22

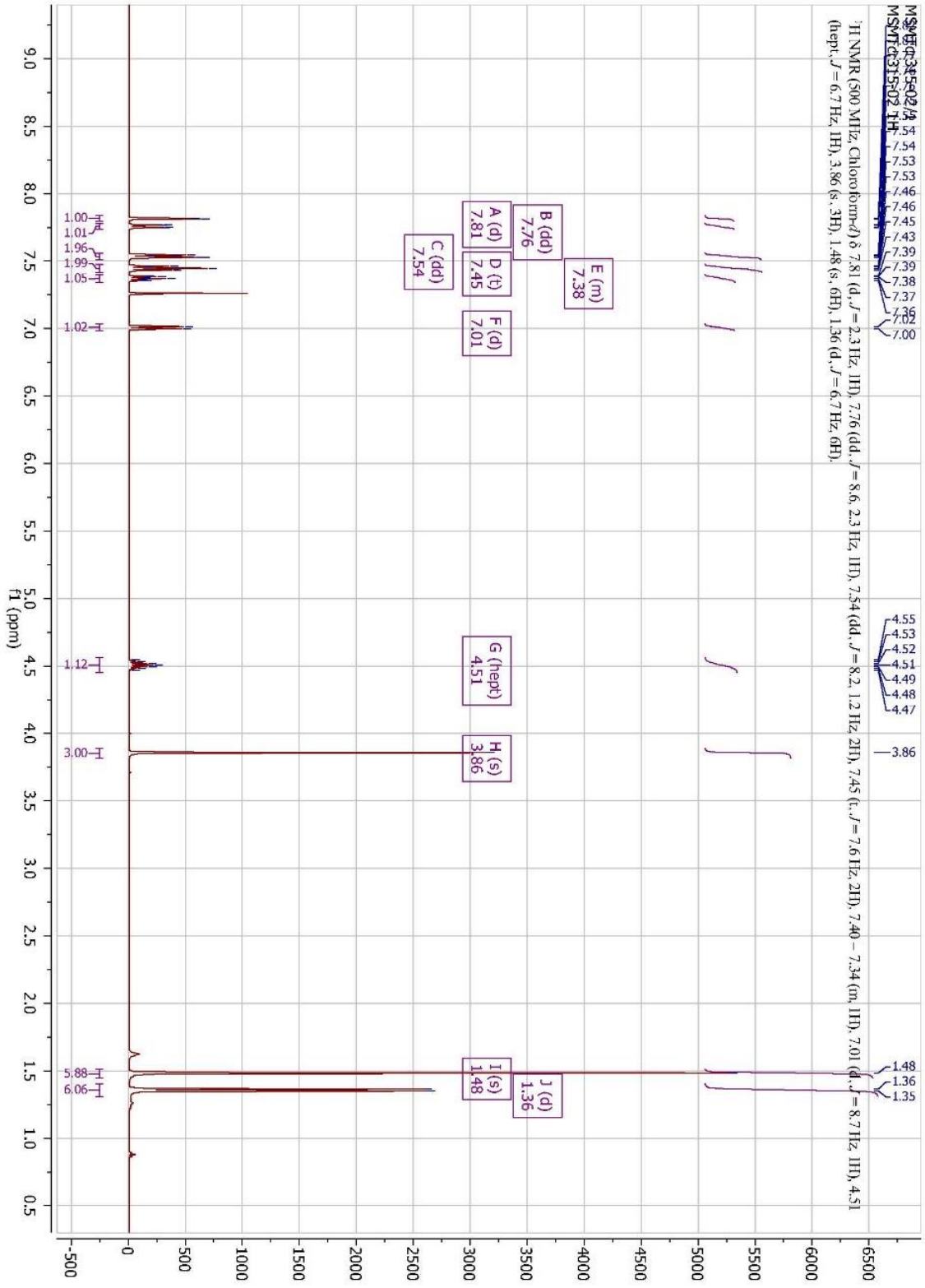

Figure S5 ^{1}H-NMR of compound **22**

^{13}C NMR compound 22

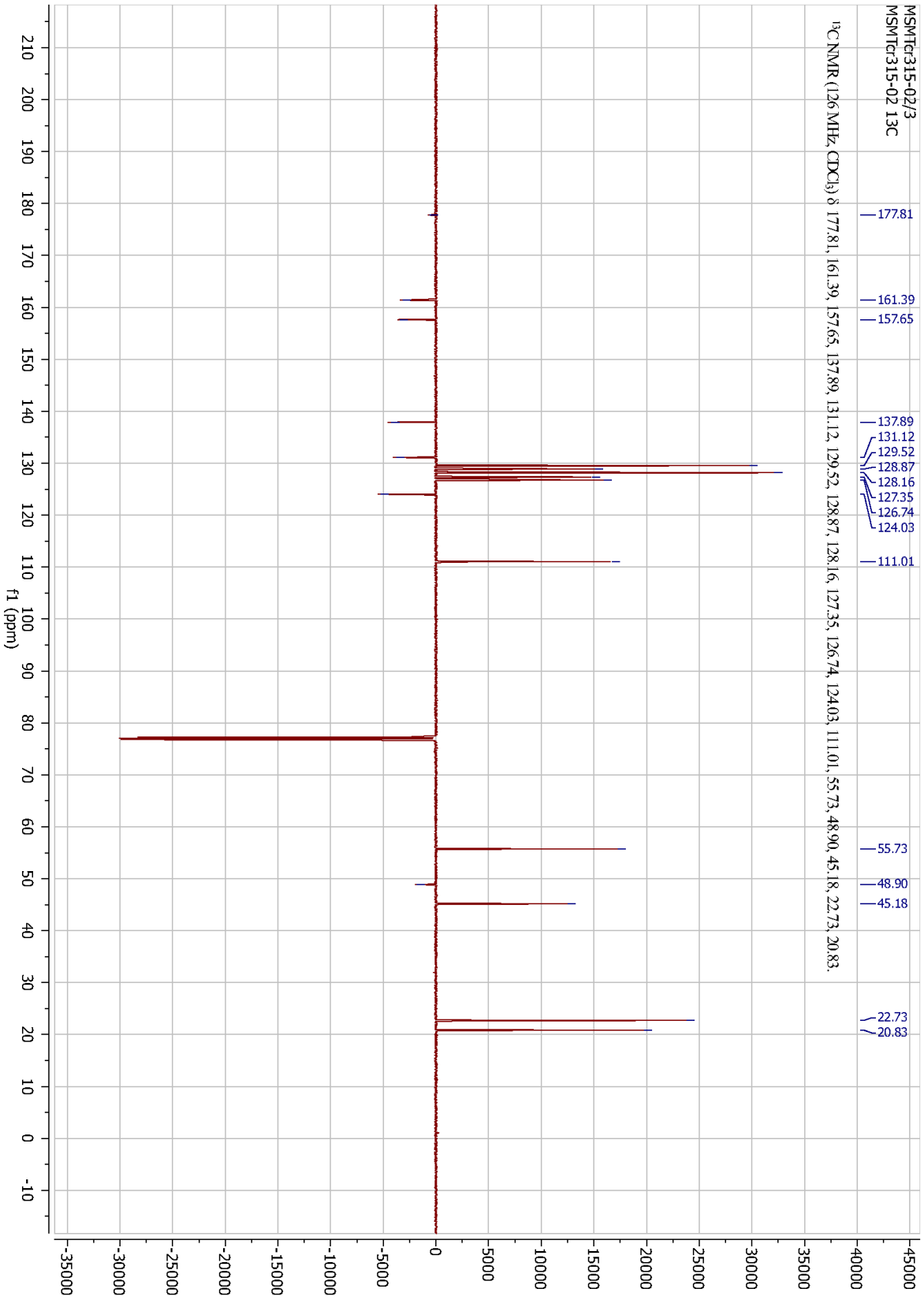

Figure S6 ^{13}C-NMR of compound **22**

^{1}H NMR compound 23

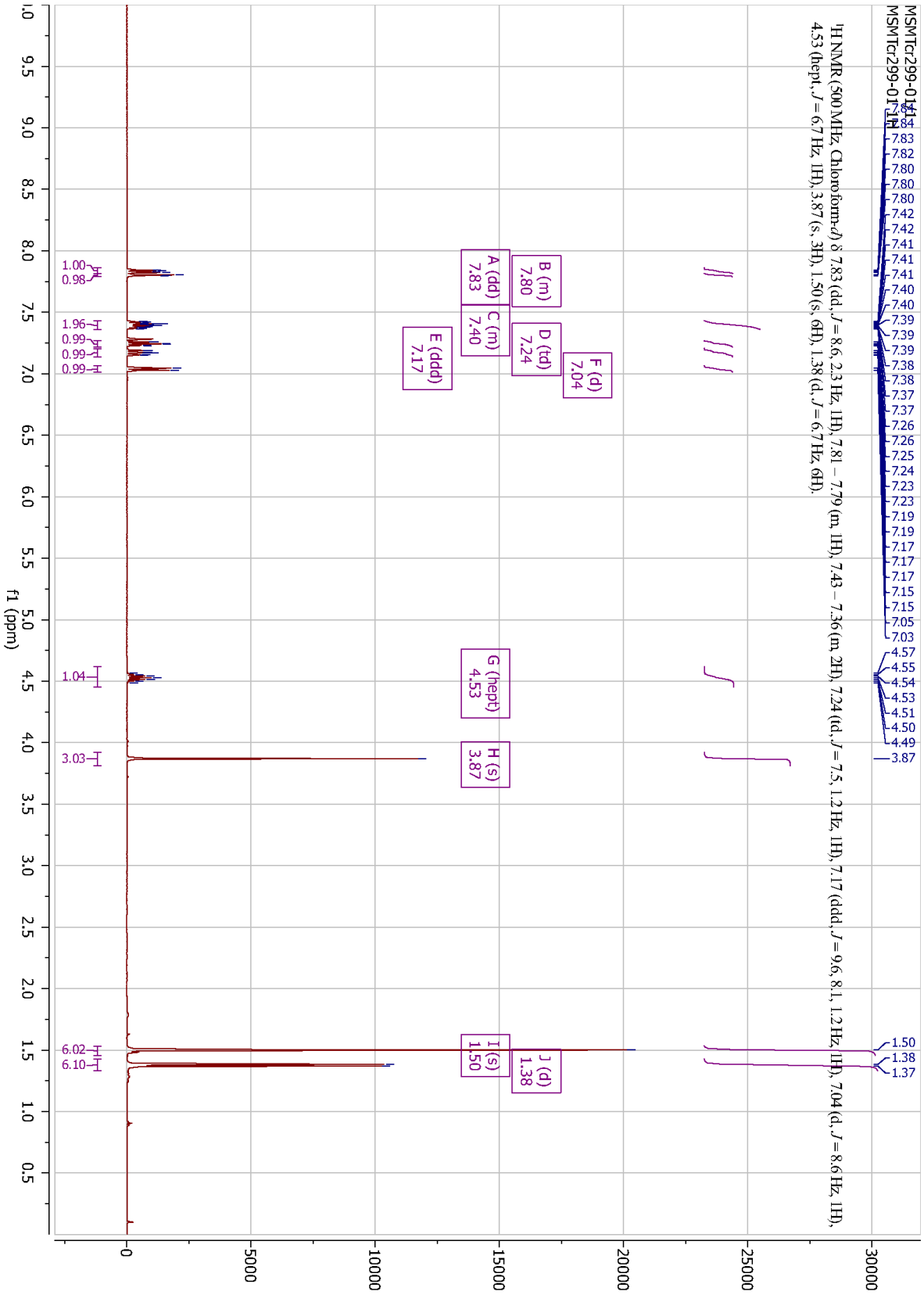

Figure S7 ^{1}H-NMR of compound **23**

^{13}C NMR compound 23

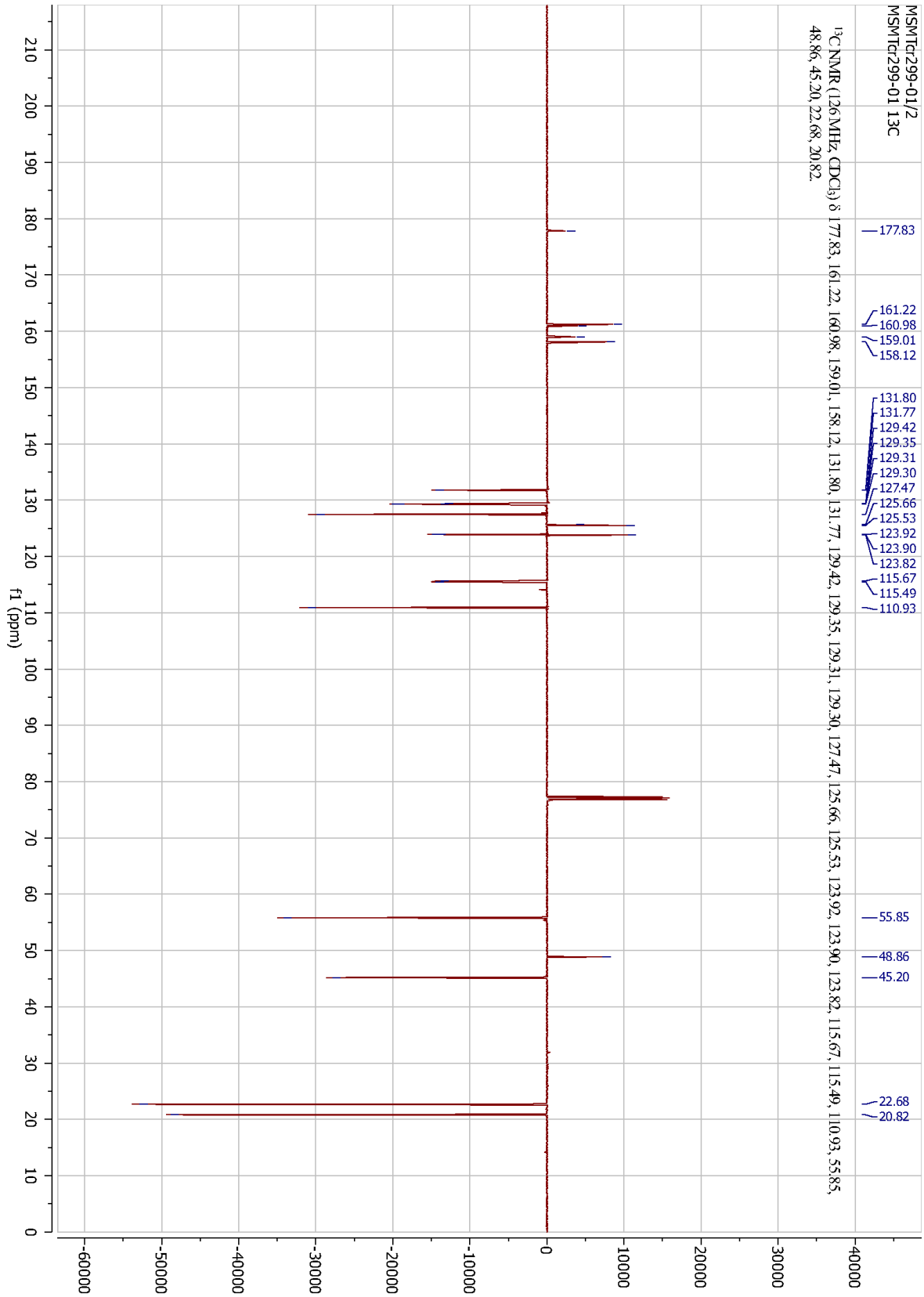

Figure S8 ^{13}C-NMR of compound **23**

^{1}H NMR compound 24

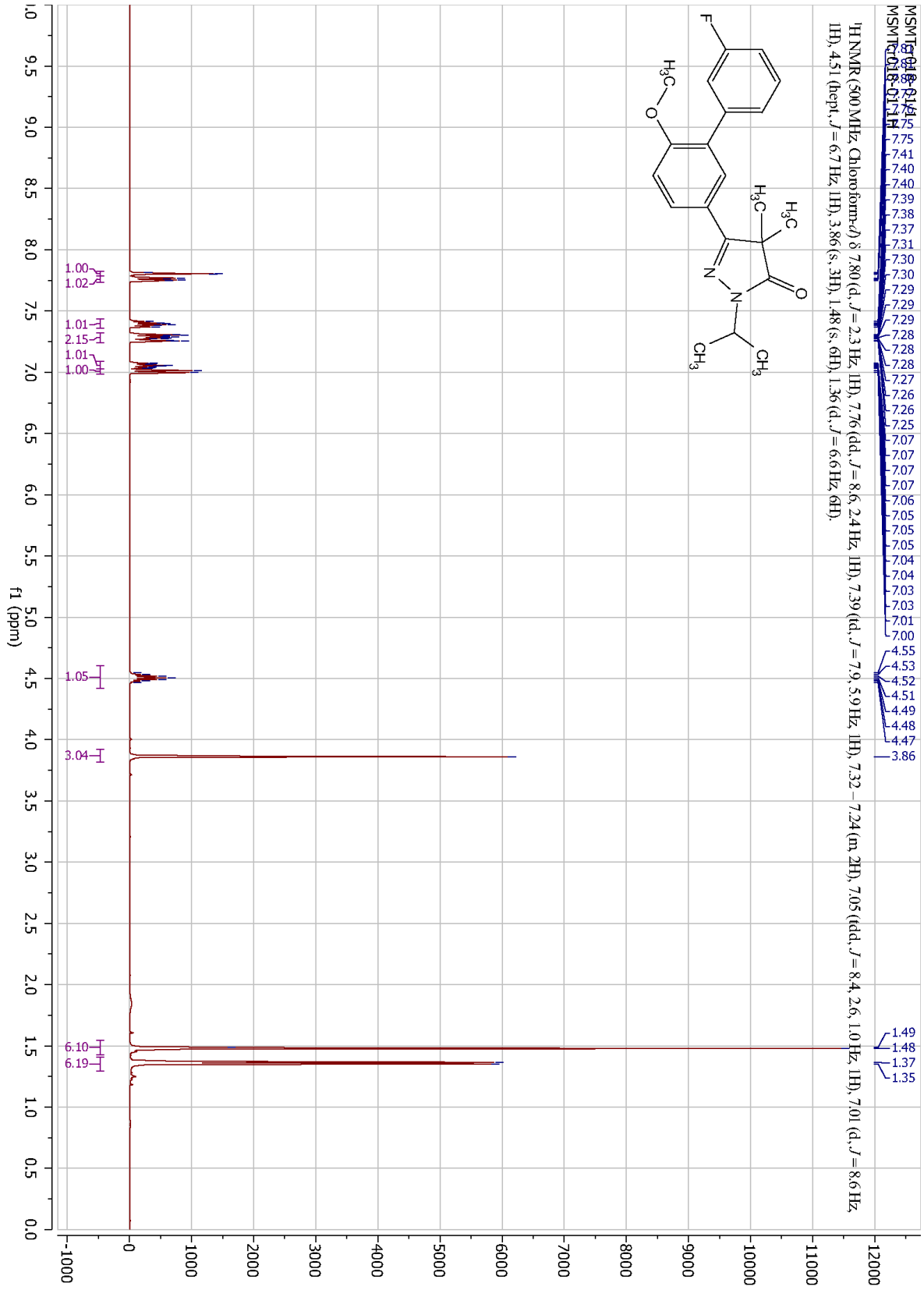

Figure S9 ^{1}H-NMR of compound **24**

^{13}C NMR compound 24

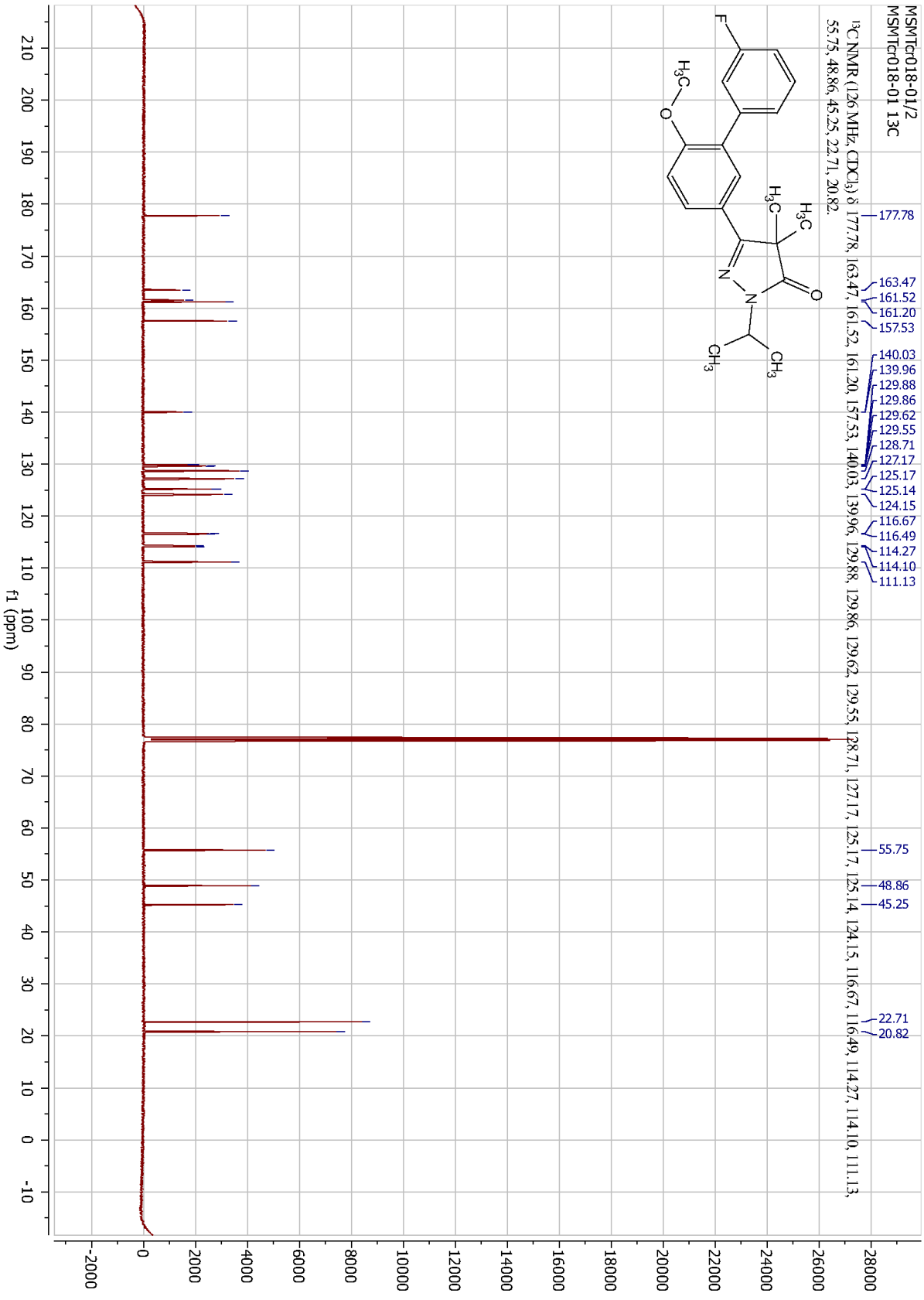

Figure S10 ^{13}C-NMR of compound **24**

^{1}H NMR compound 25

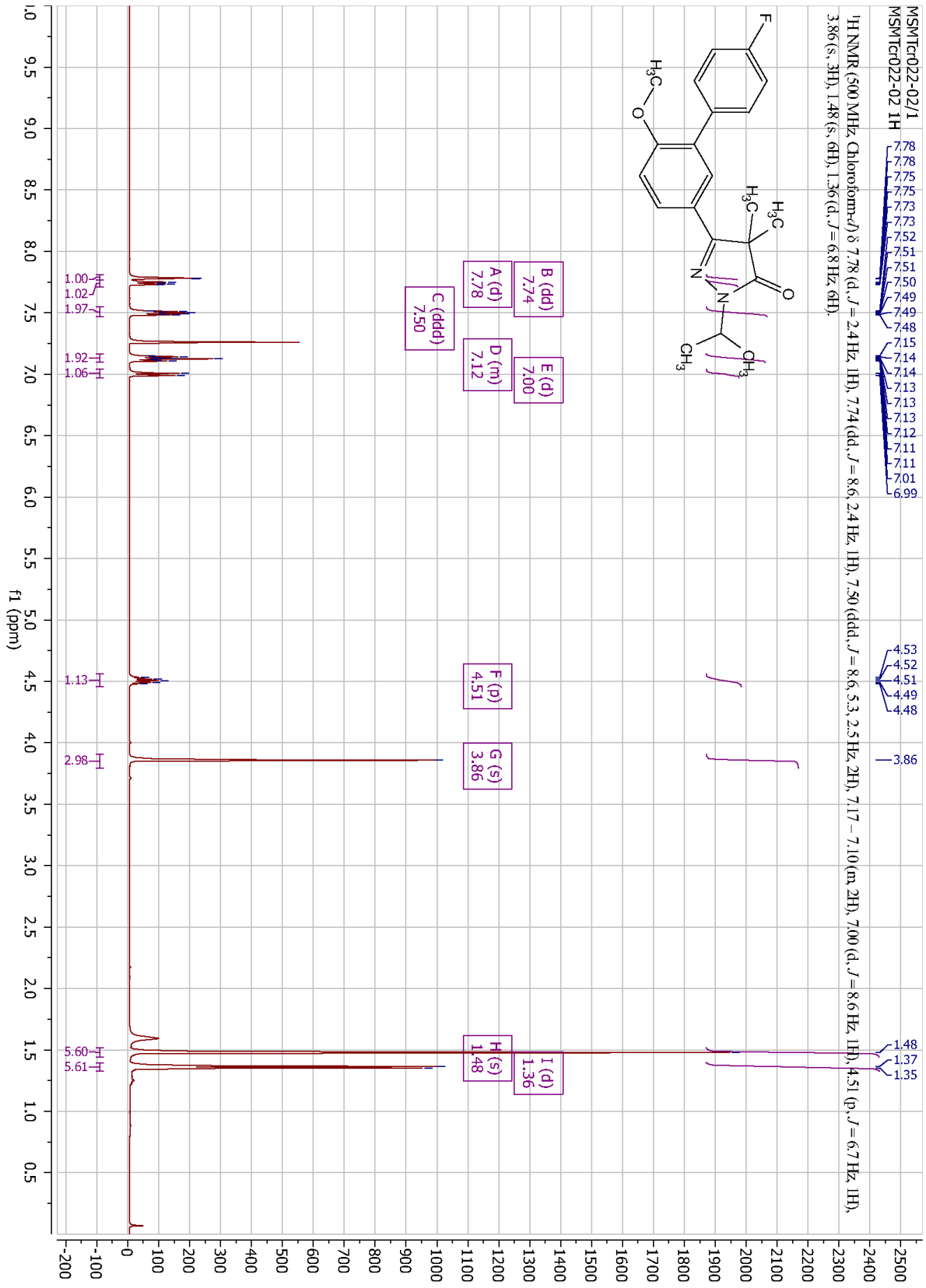

Figure S11 ^{1}H-NMR of compound **25**

^{13}C NMR compound 25

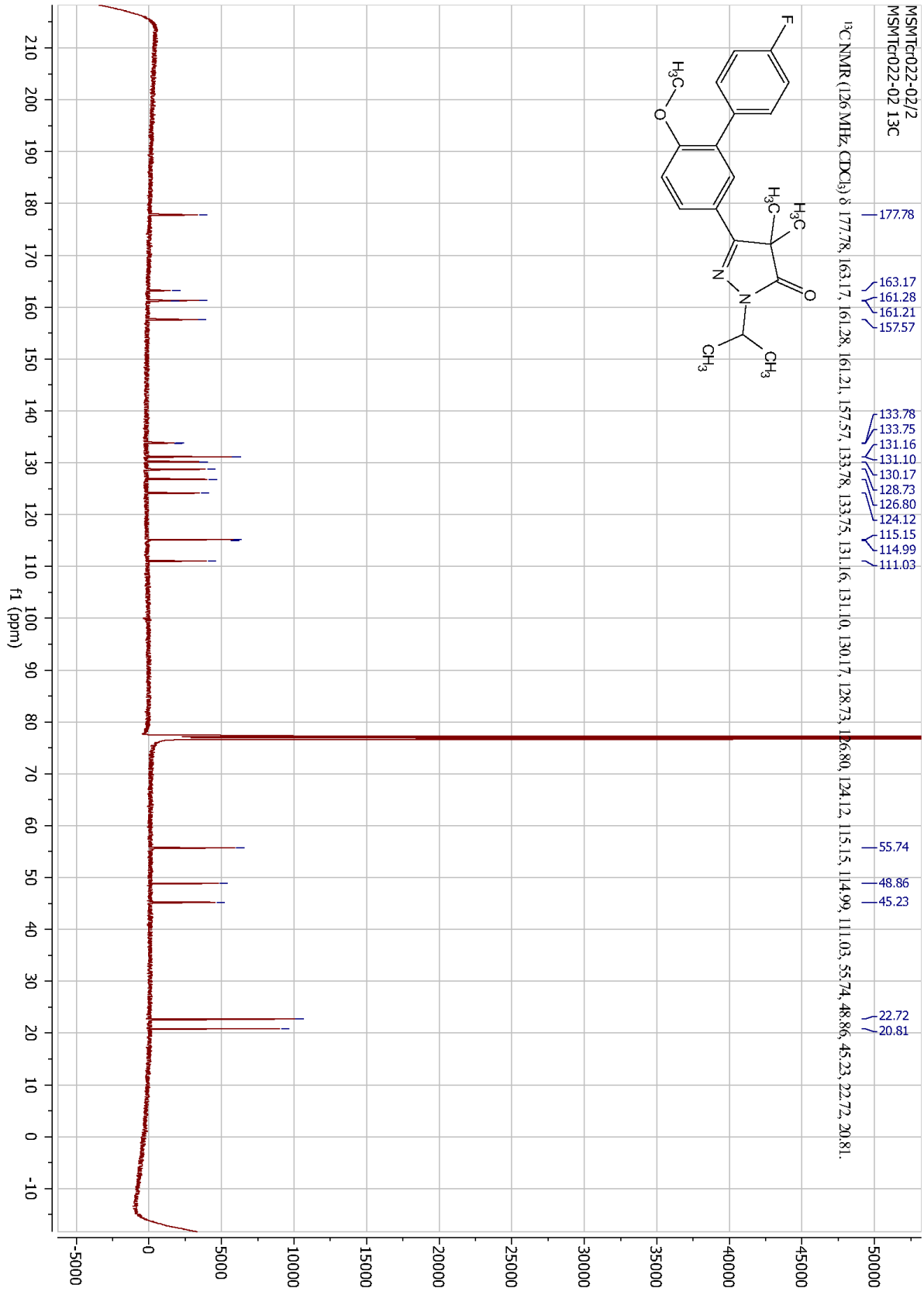

Figure S12 ^{13}C-NMR of compound **25**

^{1}H NMR compound 26

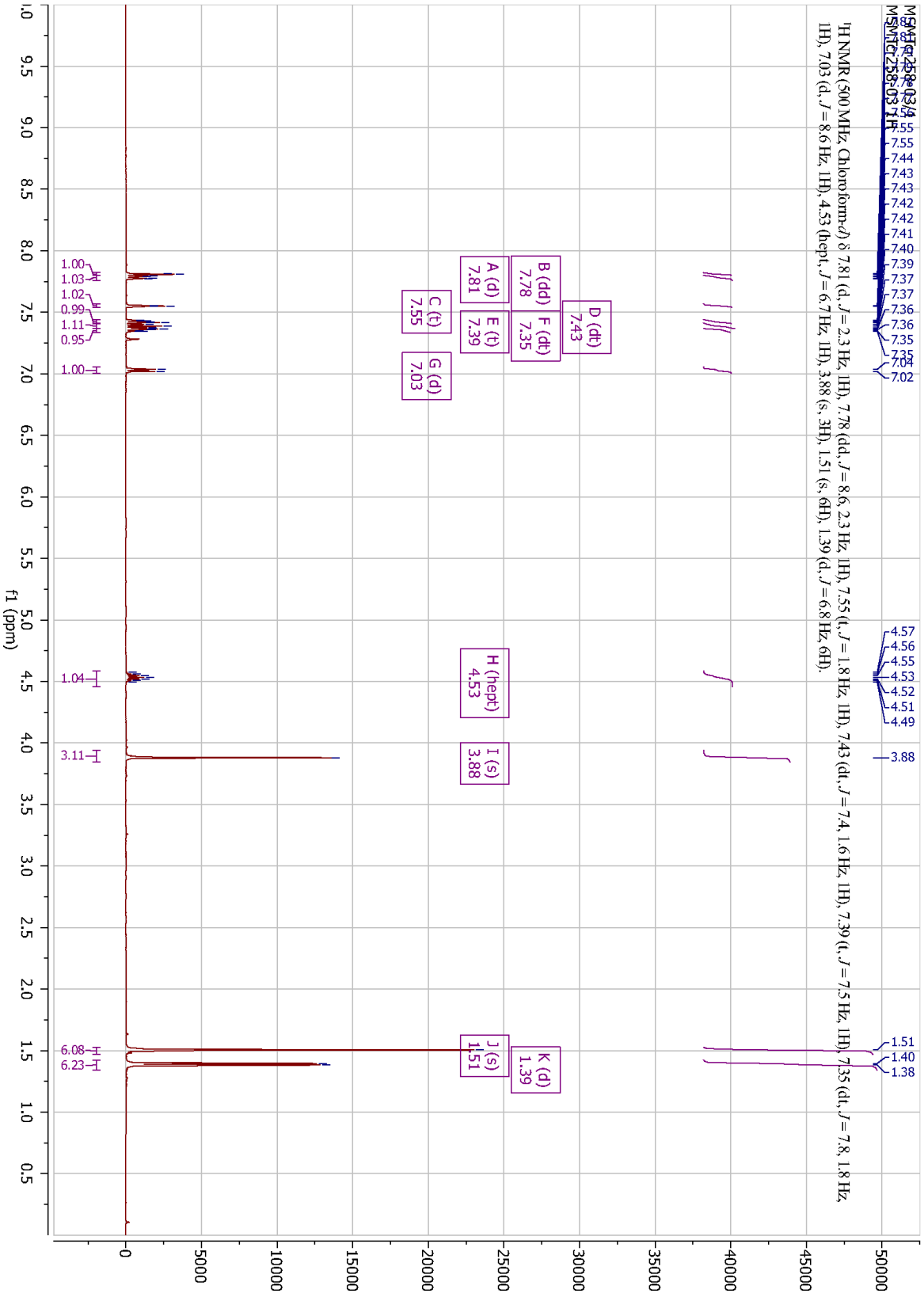

Figure S13 ^{1}H-NMR of compound **26**

^{13}C NMR compound 26

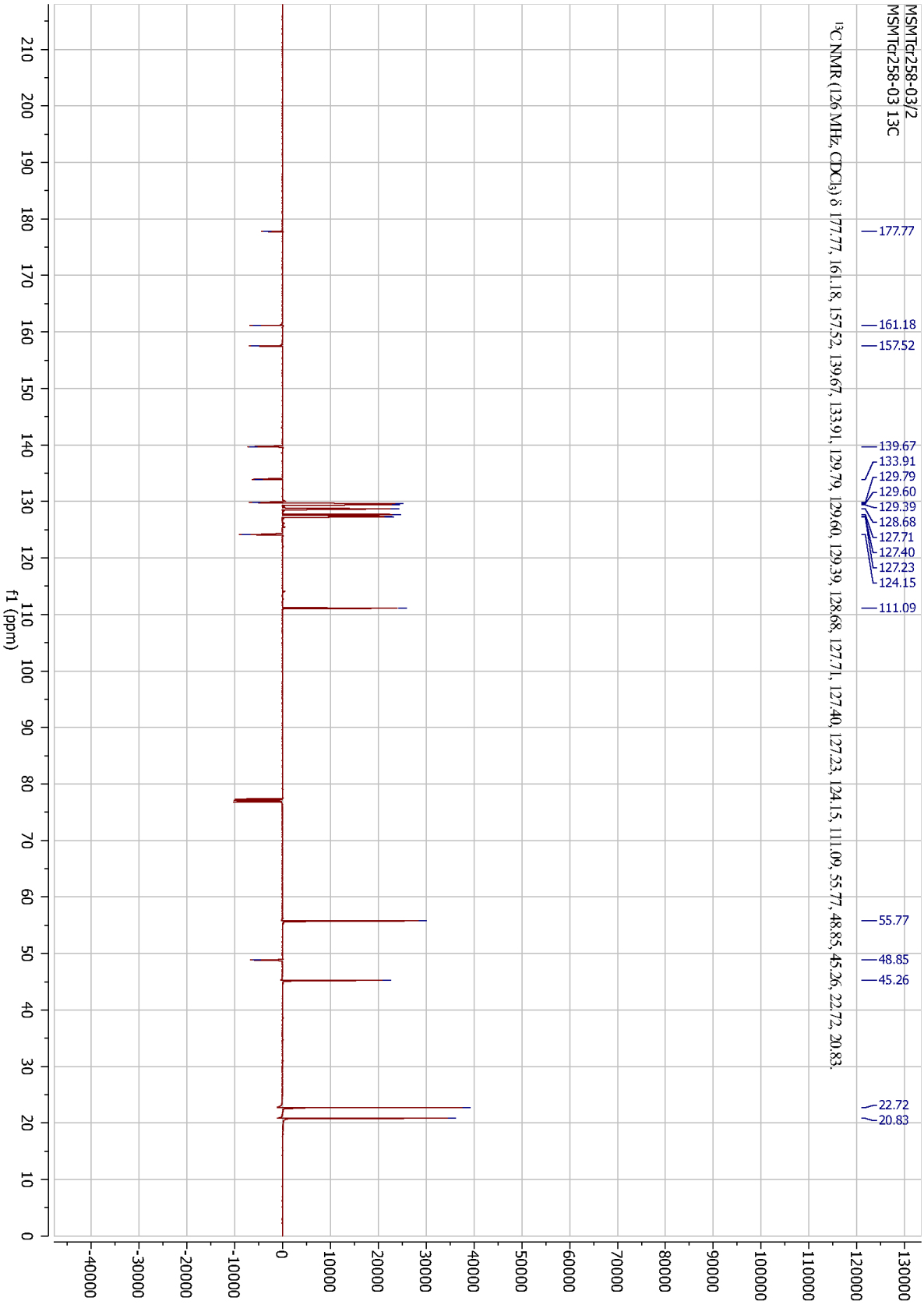

Figure S14 ^{13}C-NMR of compound **26**

^{1}H NMR compound 27

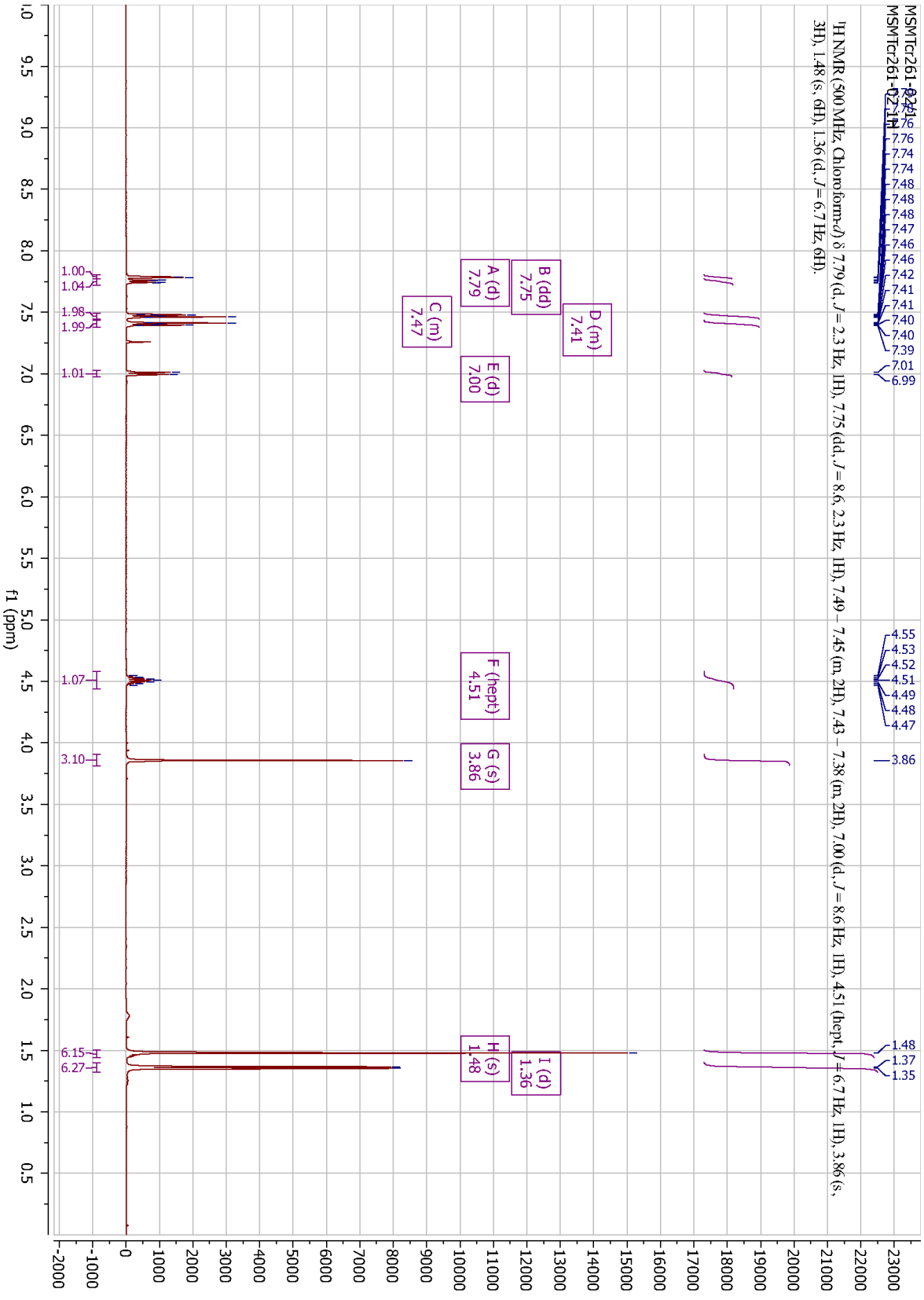

Figure S15 ^{1}H-NMR of compound **27**

^{13}C NMR compound 27

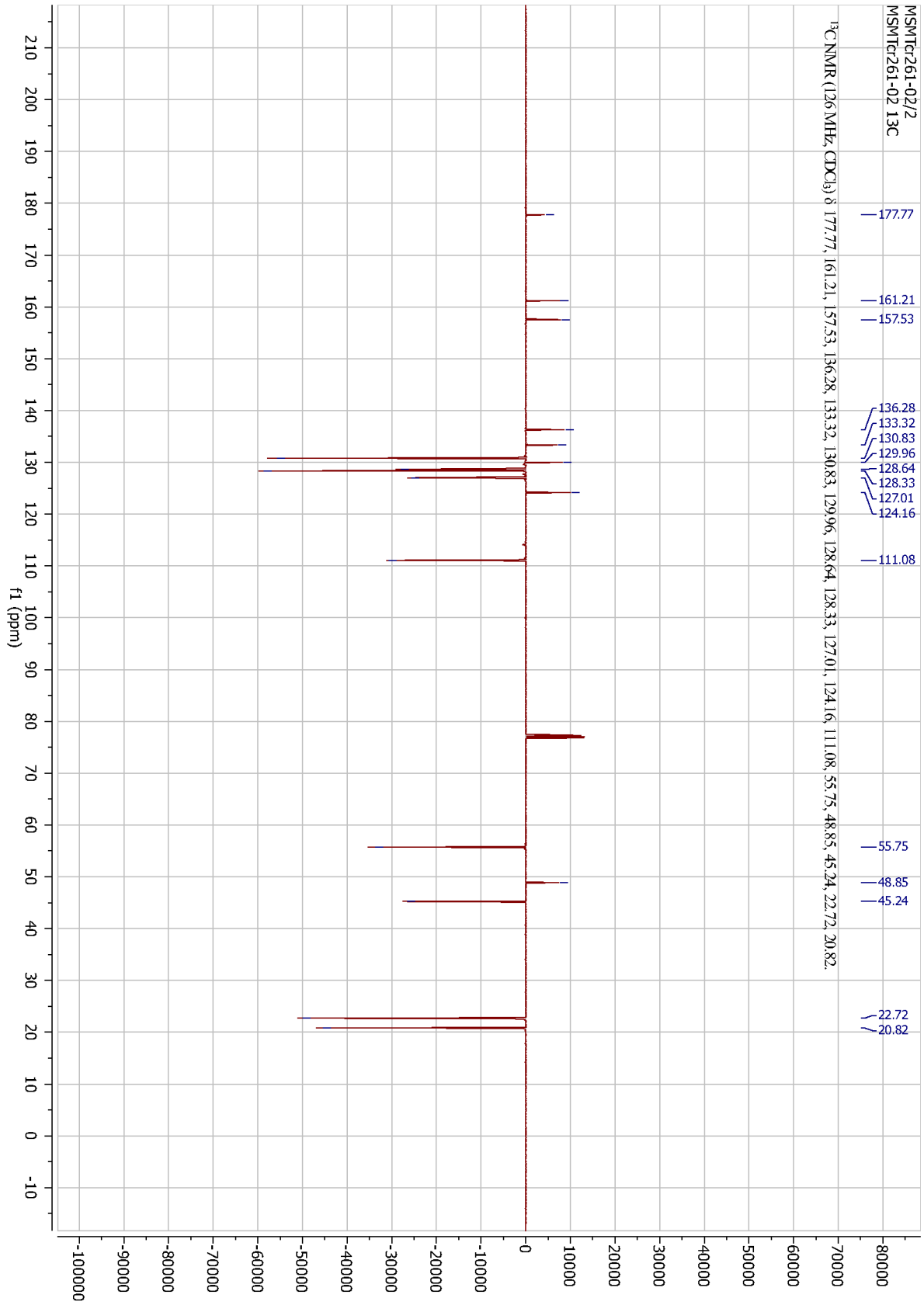

Figure S16 ^{13}C-NMR of compound **27**

^{1}H NMR compound 28

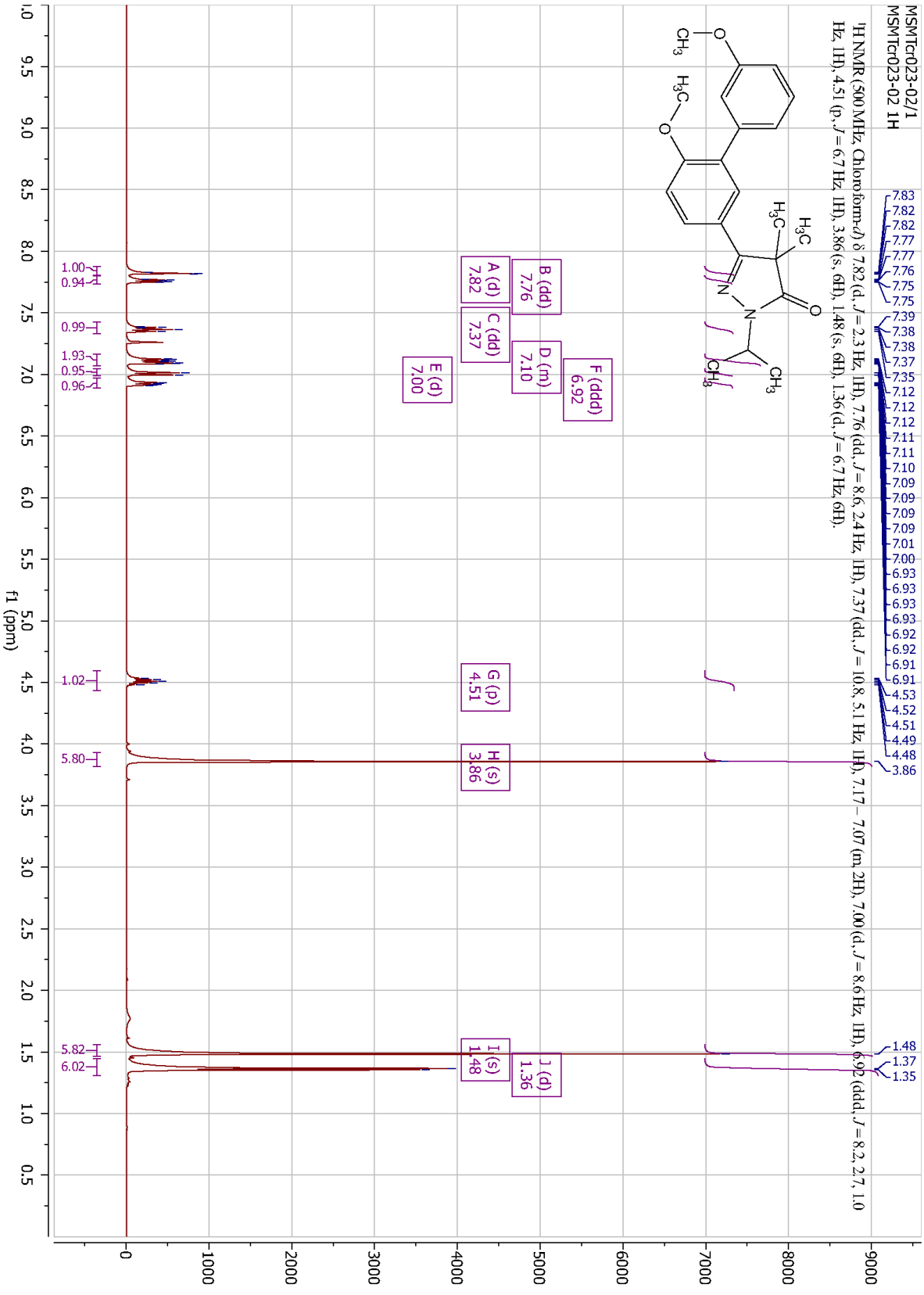

Figure S17 ^{1}H-NMR of compound **28**

^{13}C NMR compound 28

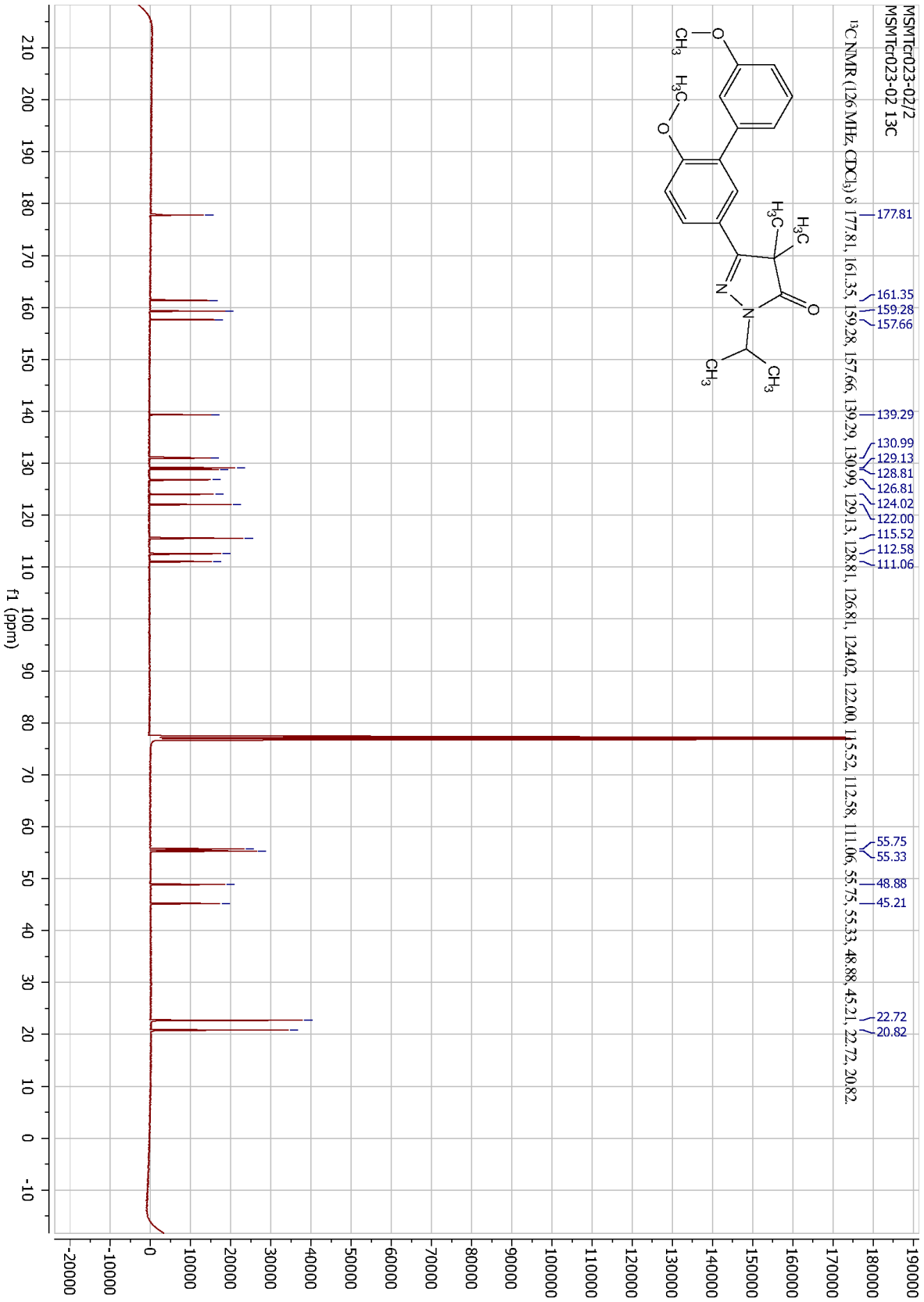

Figure S18 ^{13}C-NMR of compound **28**

[1]H NMR compound 29

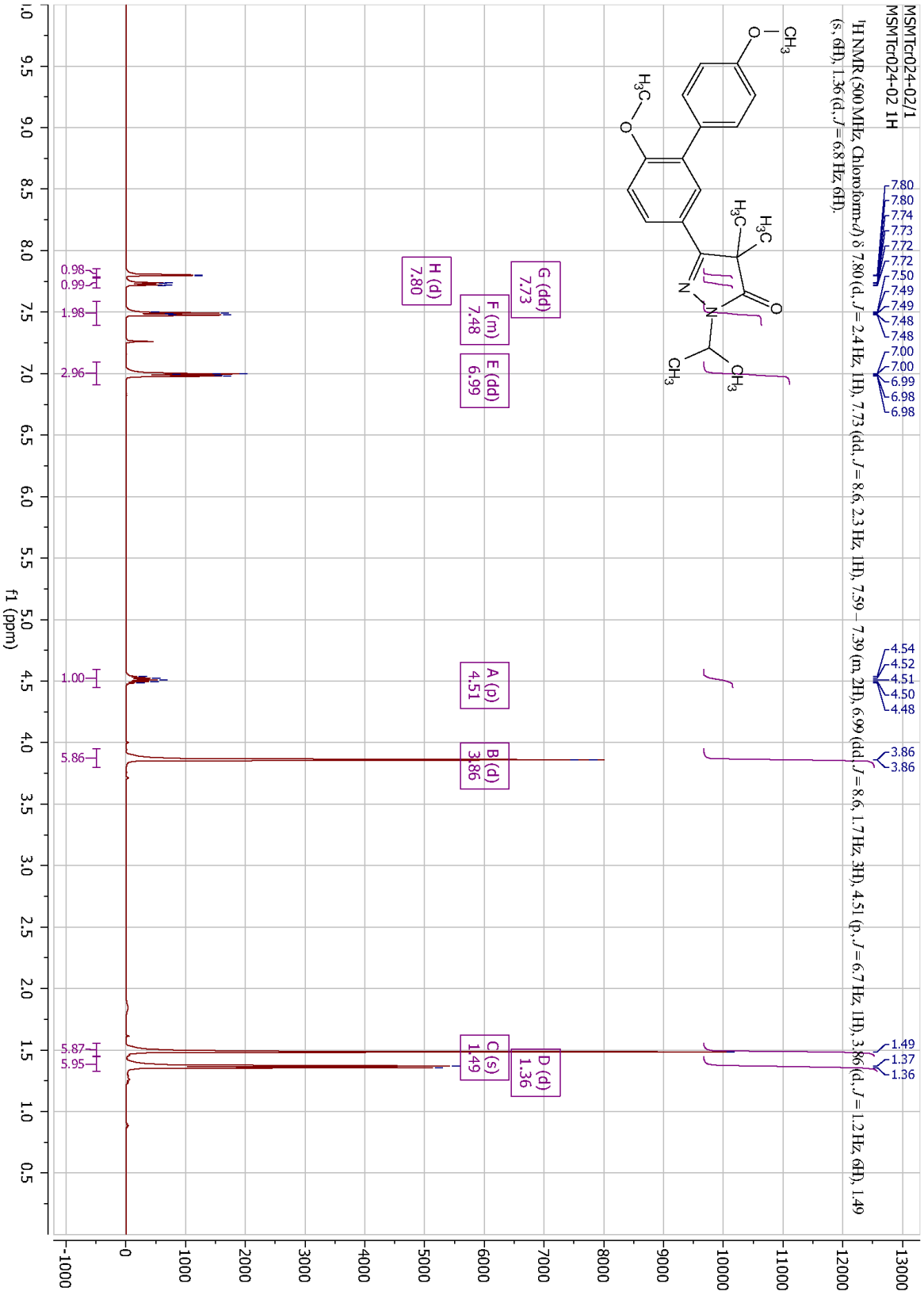

Figure S19 [1]H-NMR of compound **29**

^{13}C NMR compound 29

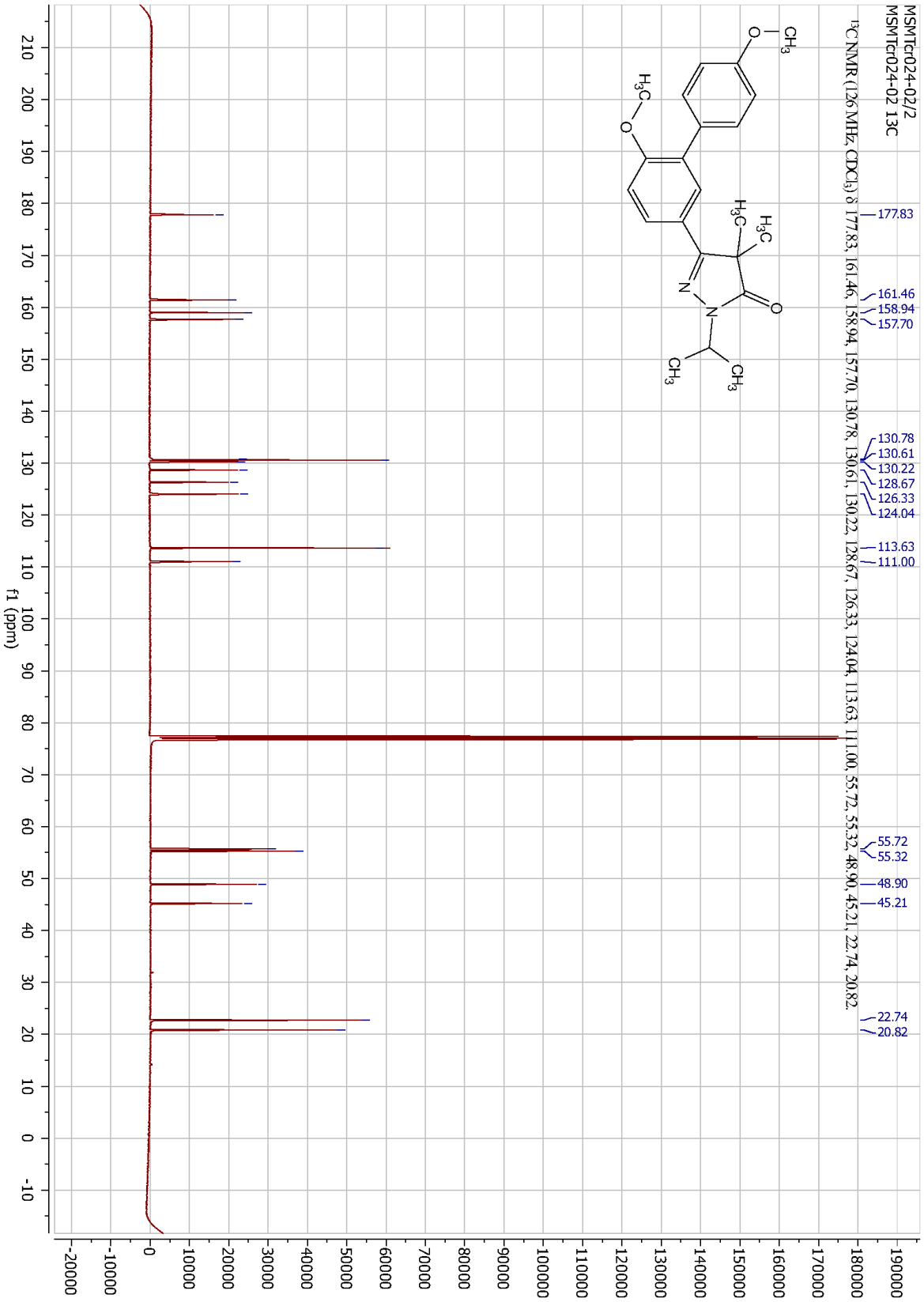

Figure S20 ^{13}C-NMR of compound **29**

^{1}H NMR compound 30

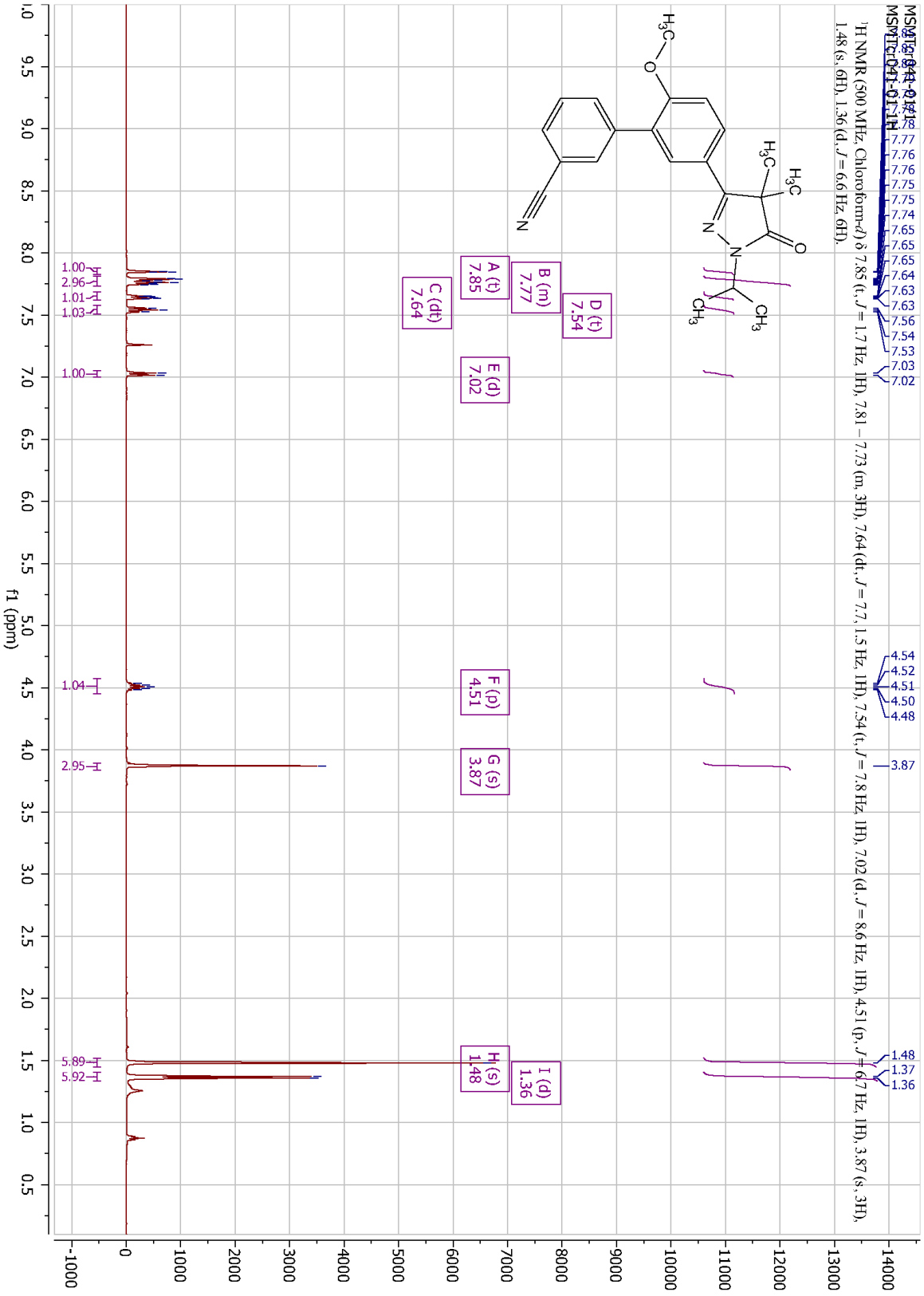

Figure S21 ^{1}H-NMR of compound **30**

^{13}C NMR compound 30

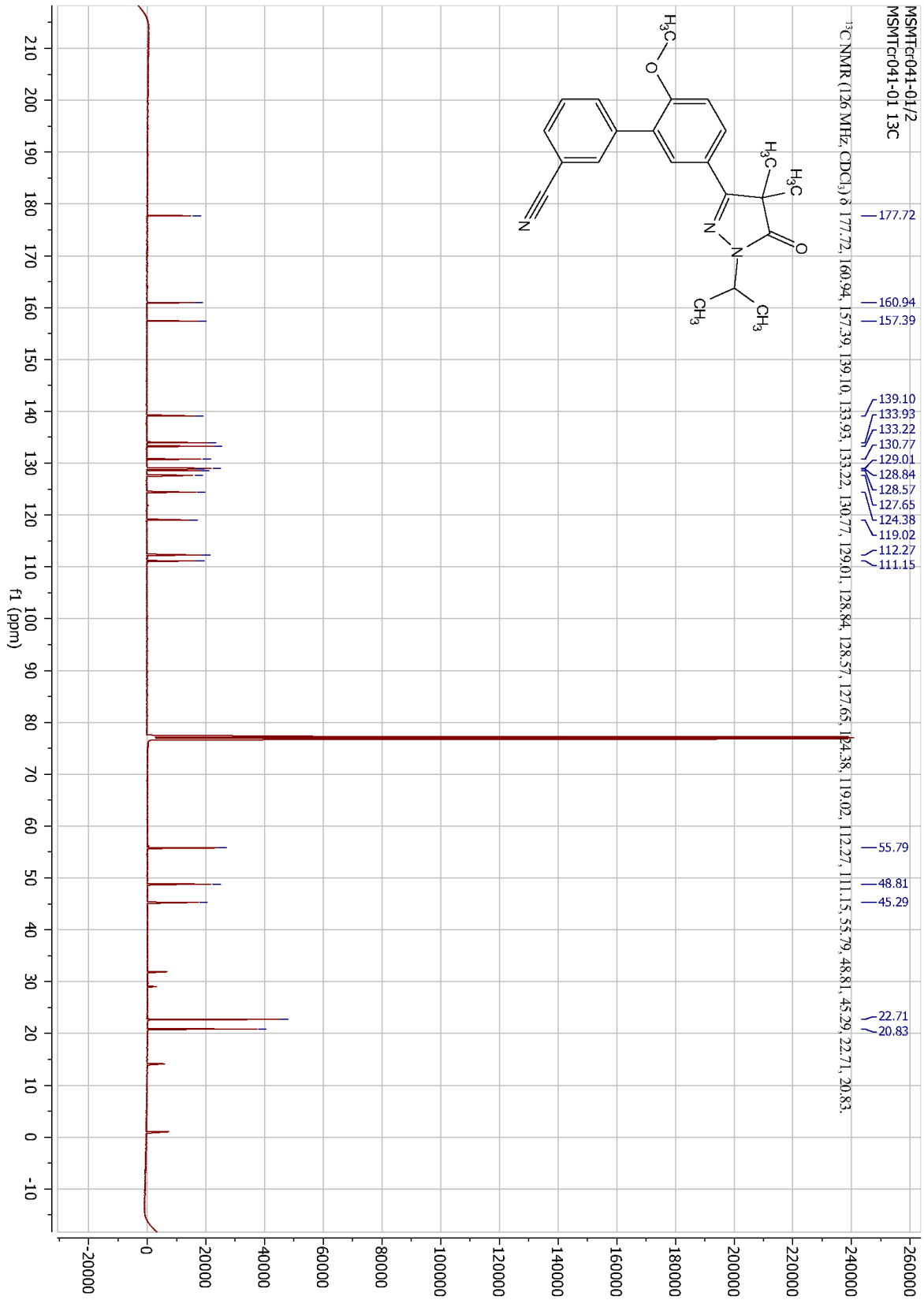

Figure S22 ^{13}C-NMR of compound **30**

^{1}H NMR compound 31

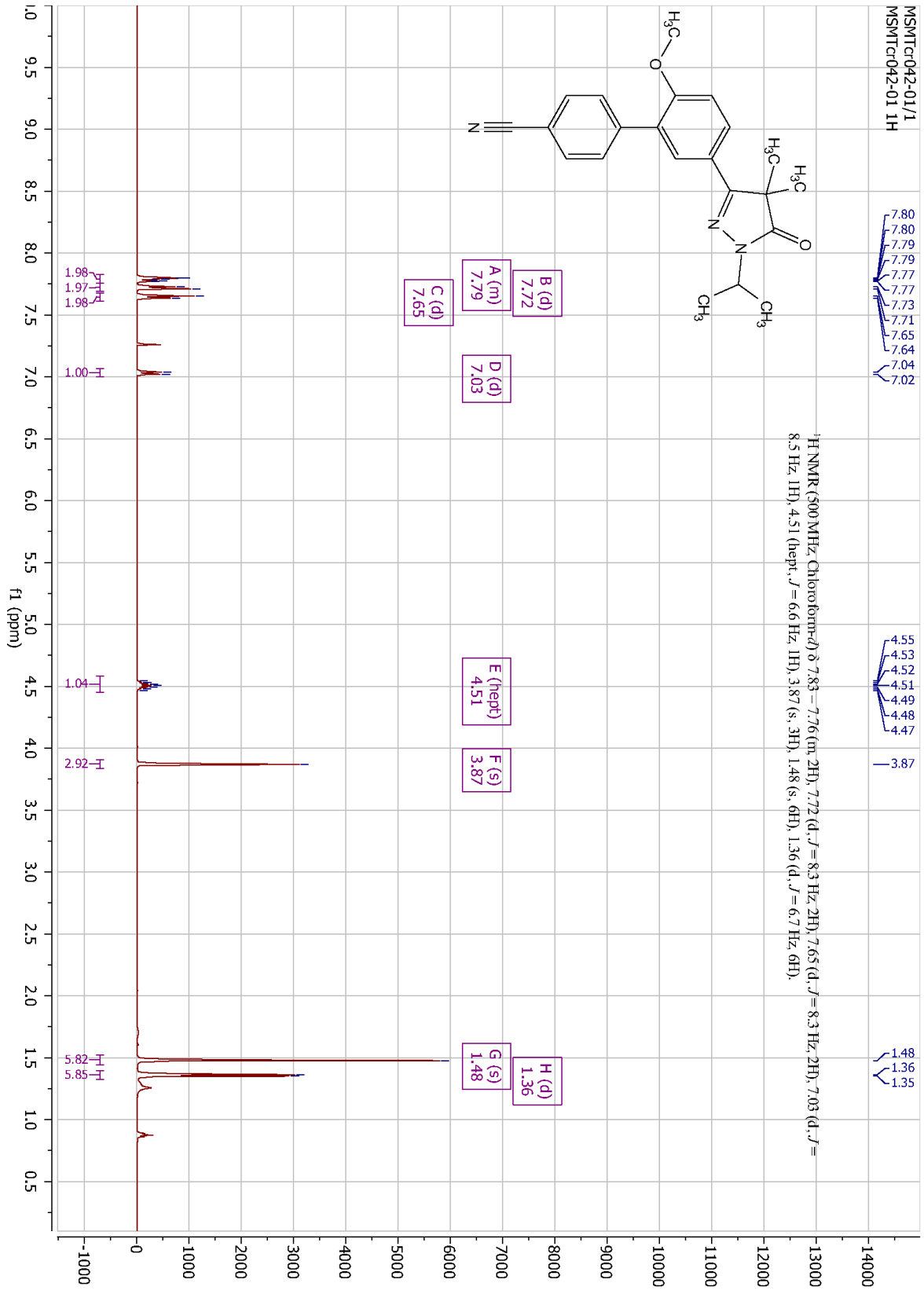

Figure S23 ^{1}H-NMR of compound **31**

^{13}C NMR compound 31

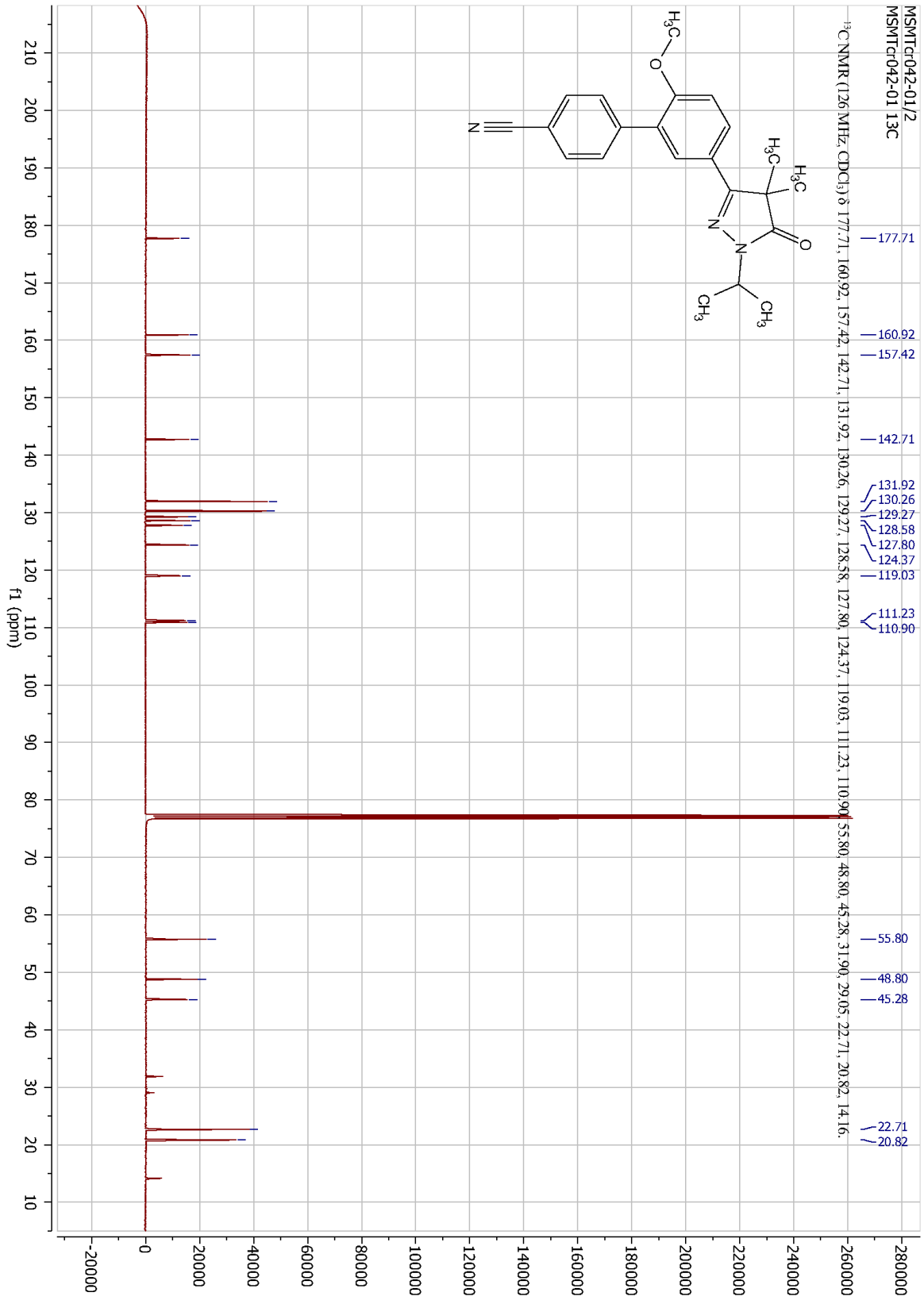

Figure S24 ^{13}C-NMR of compound **31**

^{1}H NMR compound 32

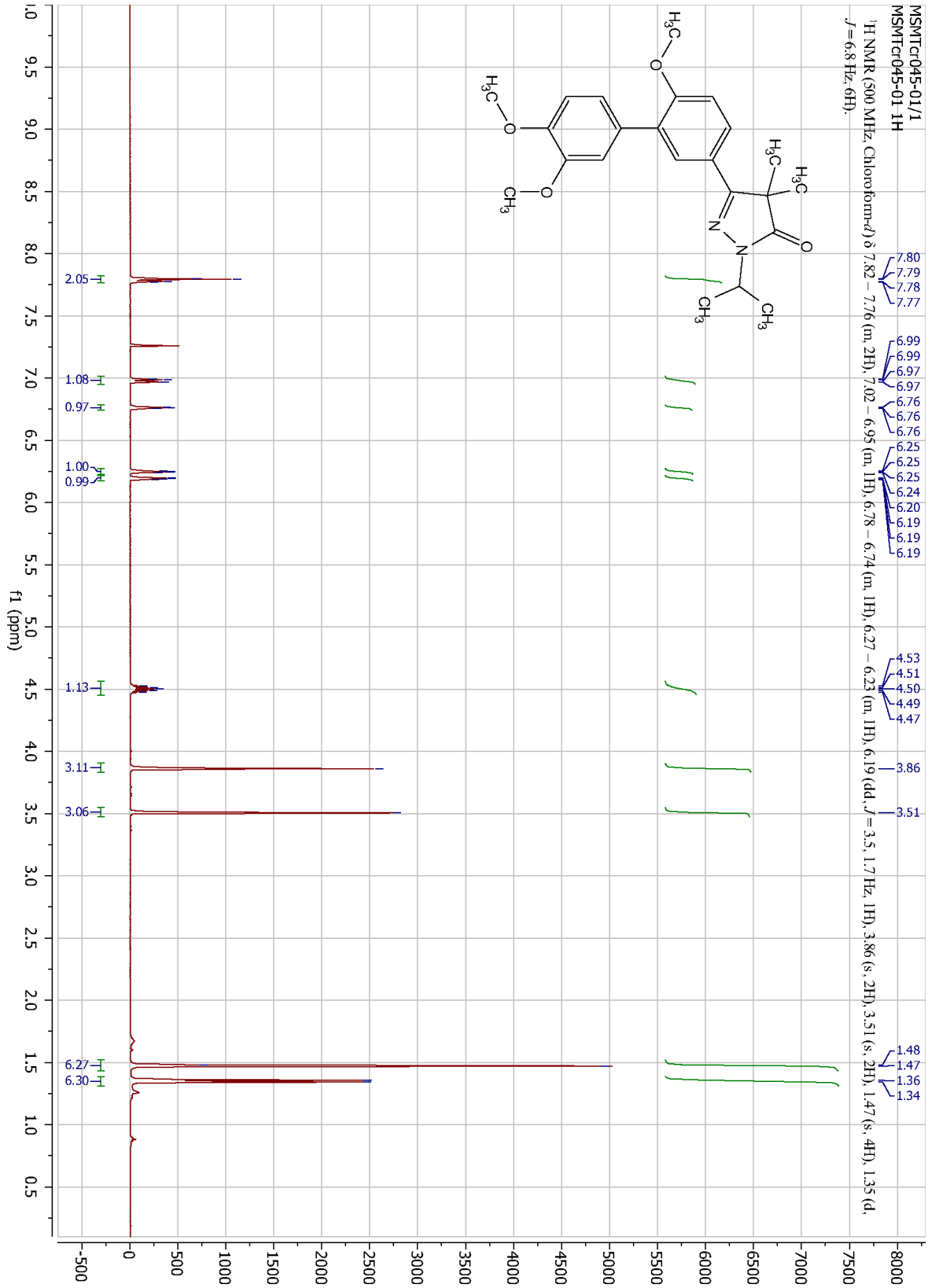

Figure S25 ^{1}H-NMR of compound **32**

^{13}C NMR compound 32

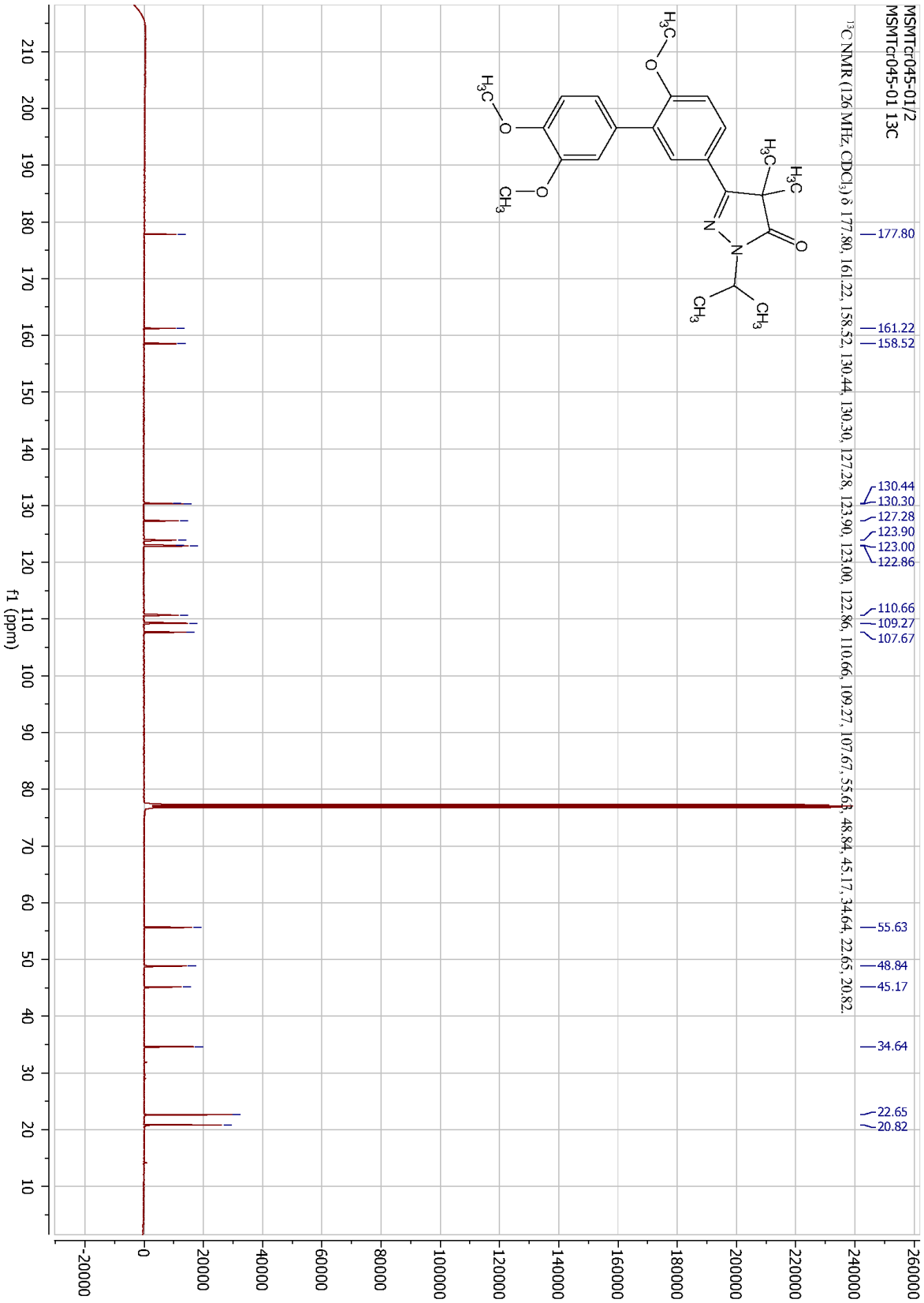

Figure S26 ^{13}C-NMR of compound **32**

^{1}H NMR compound 33

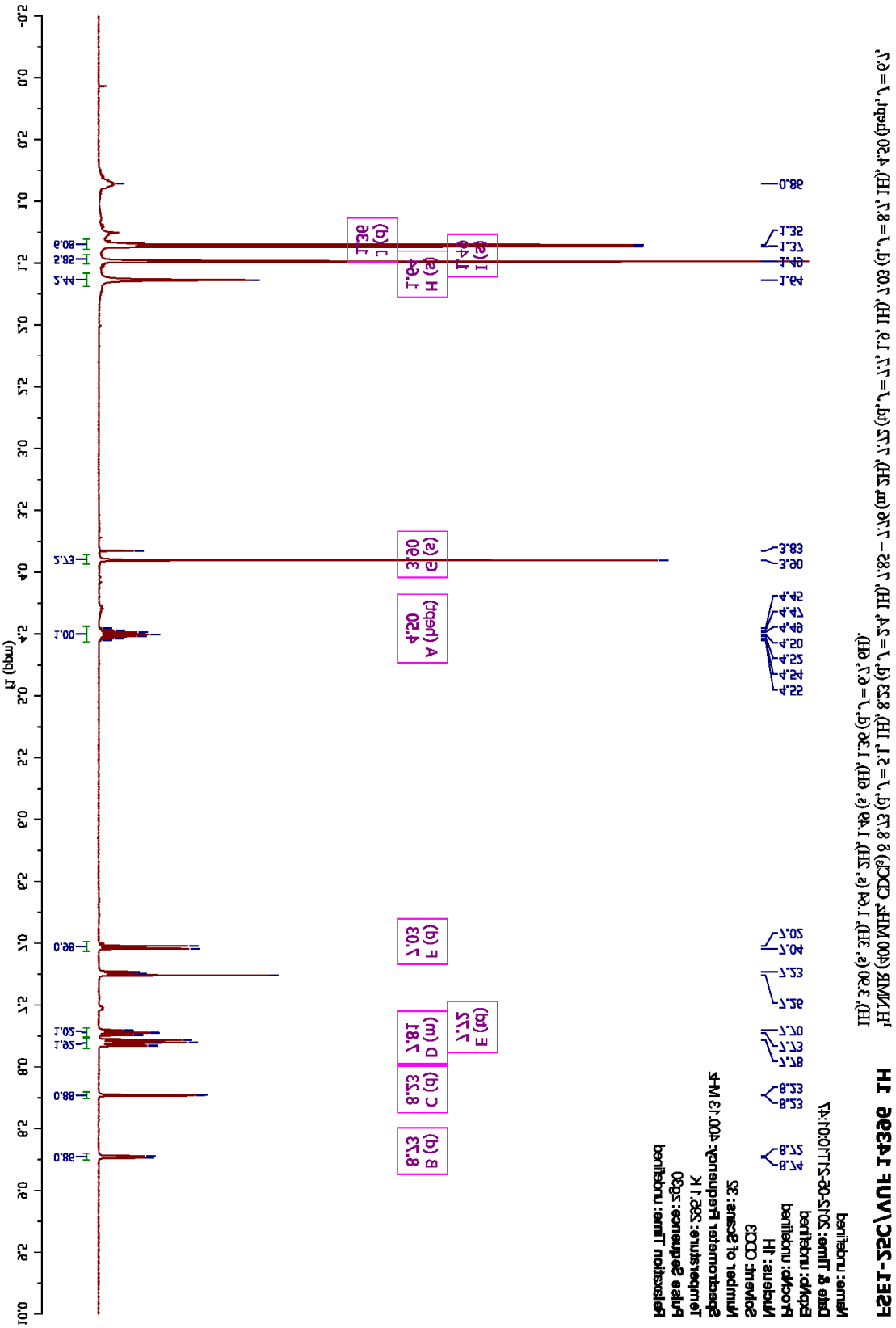

Figure S27 ^{1}H-NMR of compound **33**

^{13}C NMR compound 33

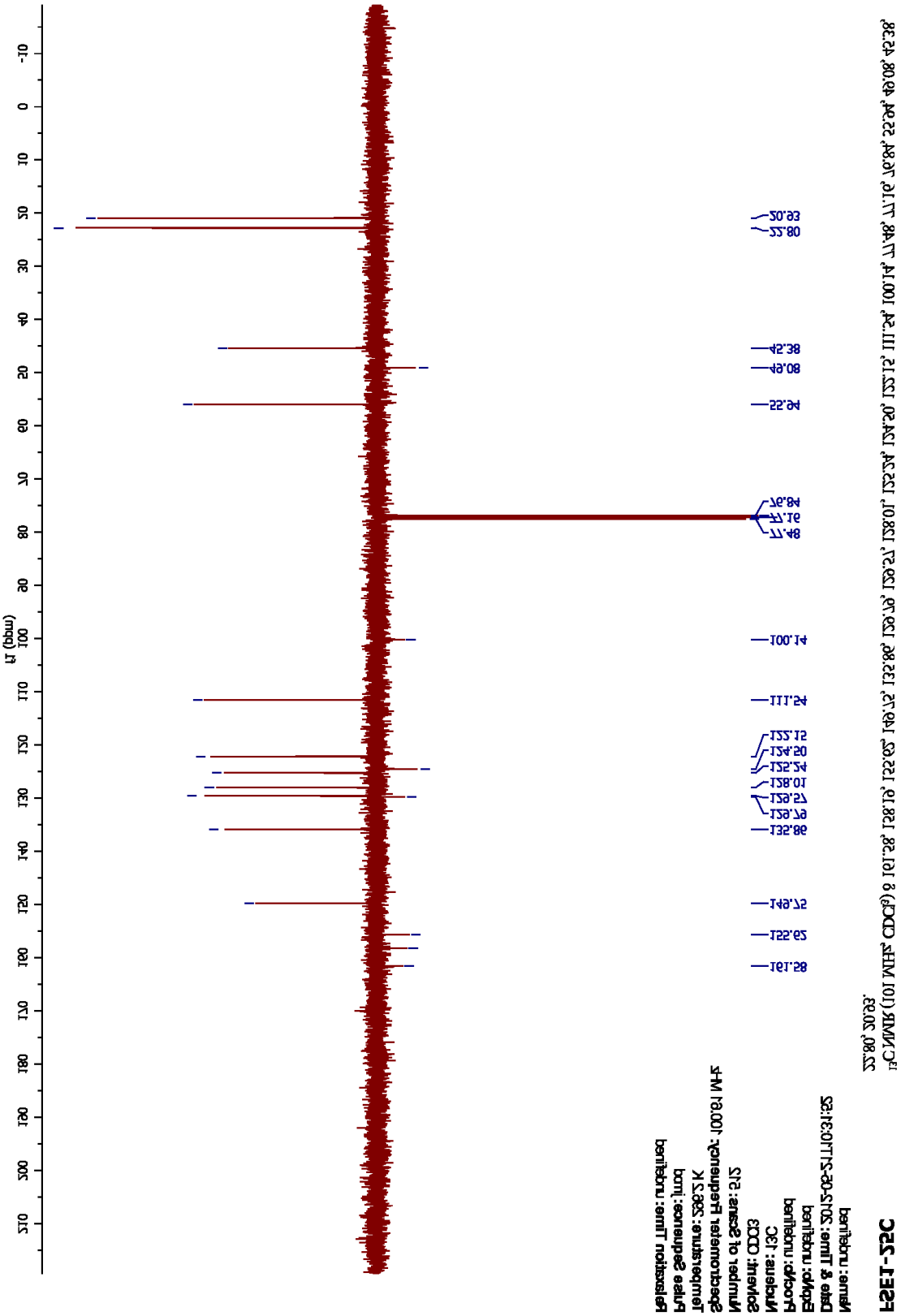

Figure S28 ^{13}C-NMR of compound **33**

[1]H NMR compound 34

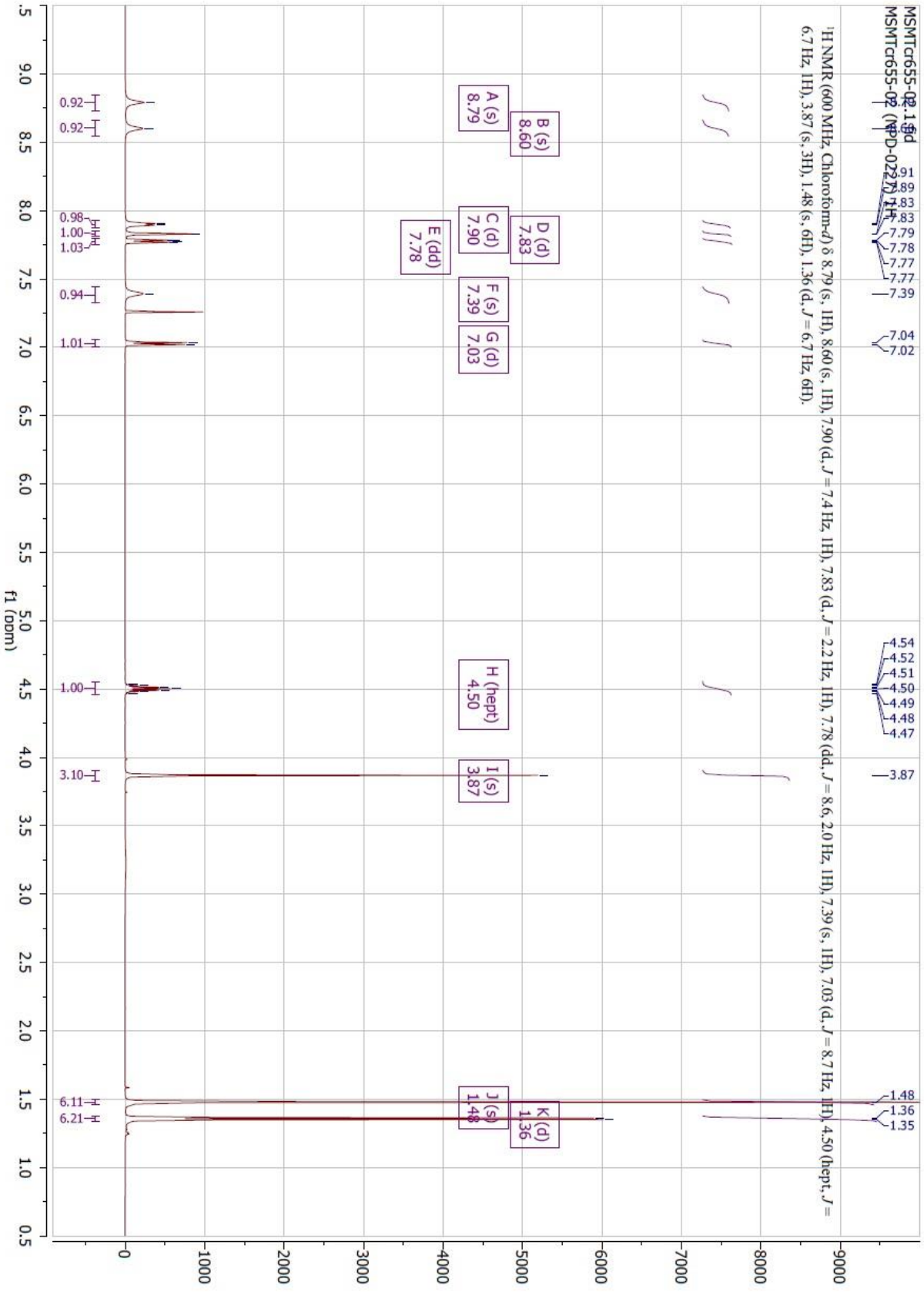

Figure S29 [1]H-NMR of compound **34**

^{13}C NMR compound 34

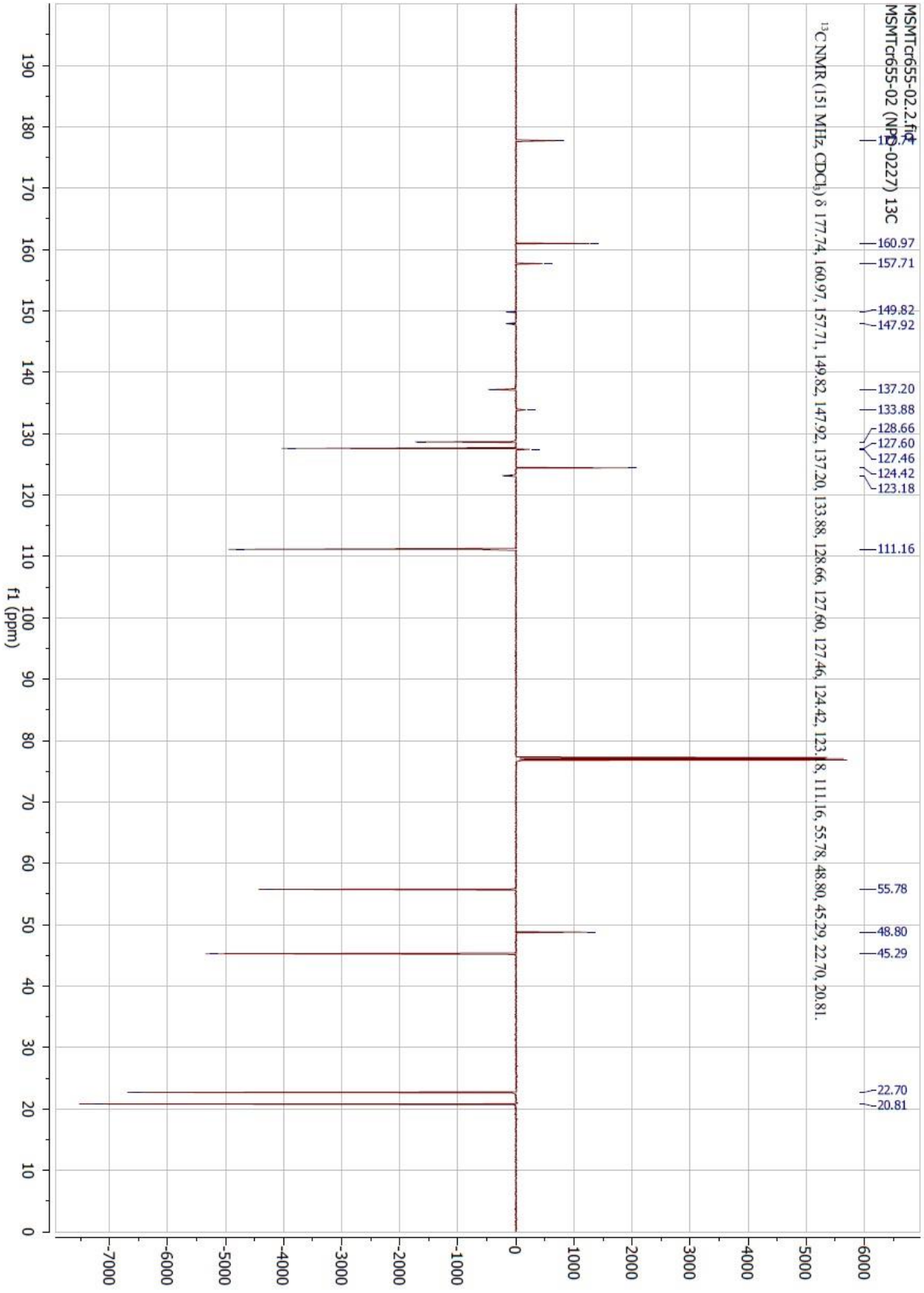

Figure S30 ^{13}C-NMR of compound **34**

^{1}H NMR compound 35

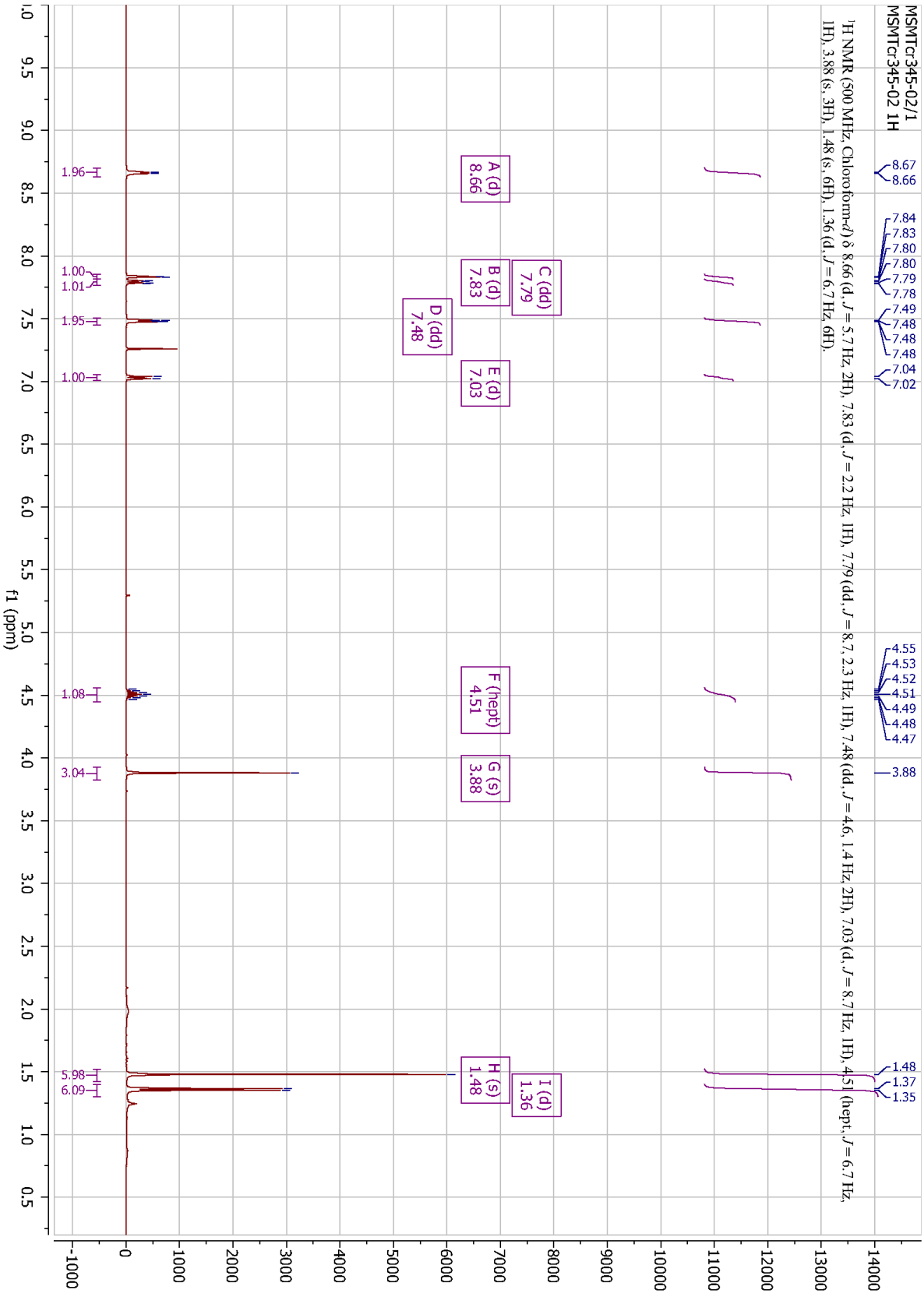

Figure S31 ^{1}H-NMR of compound **35**

^{13}C NMR compound 35

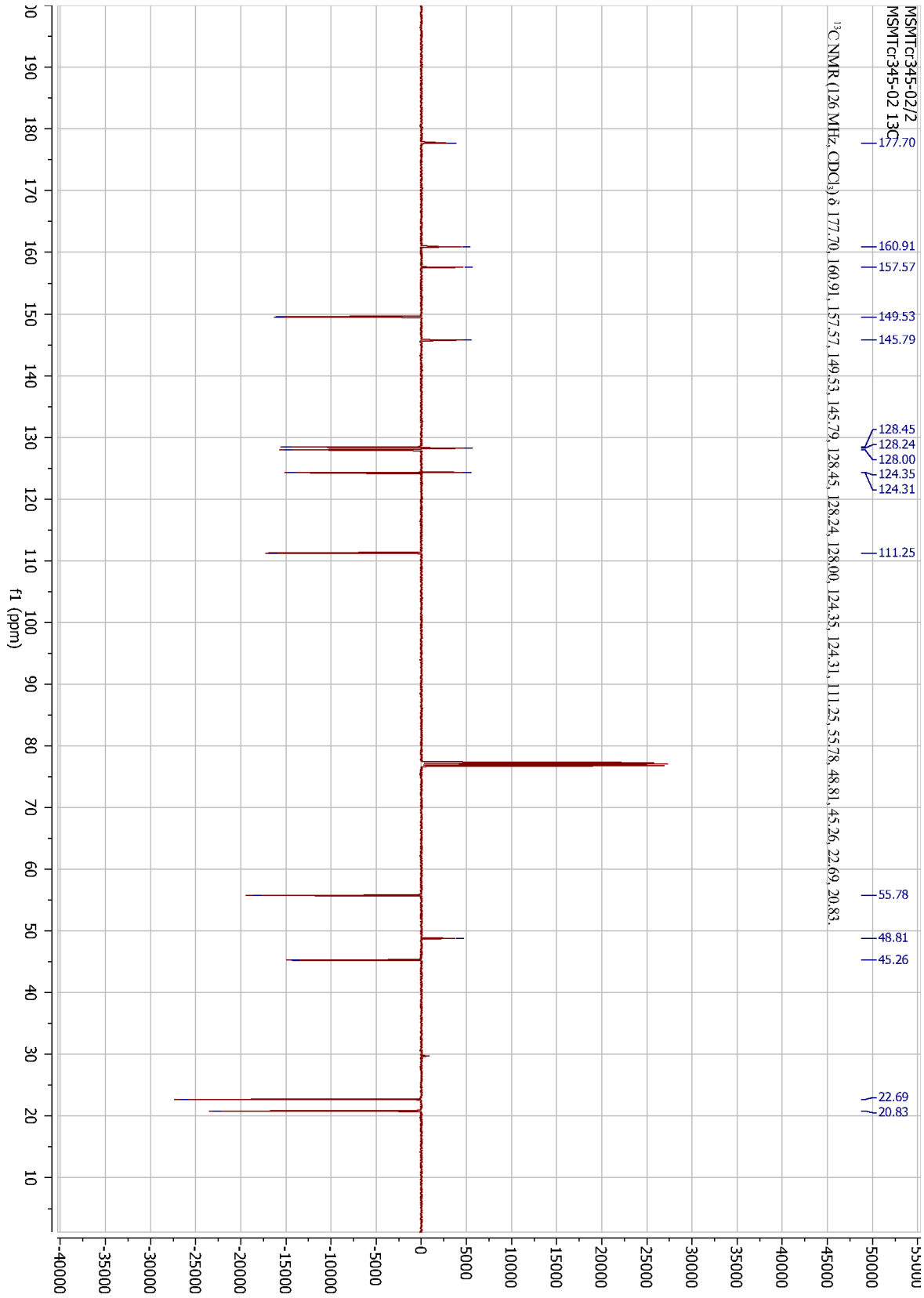

Figure S32 ^{13}C-NMR of compound **35**

^{1}H NMR compound 36

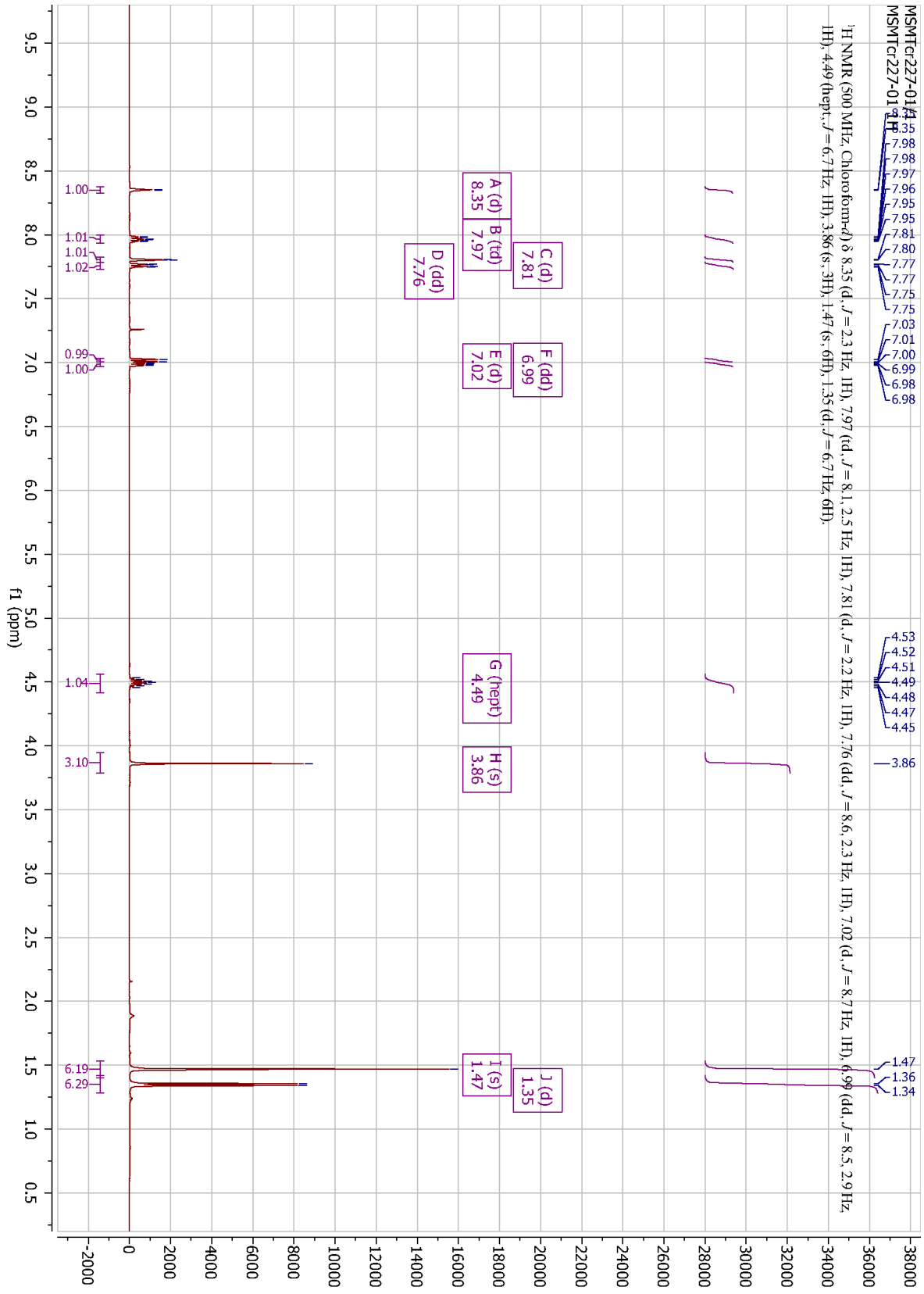

Figure S33 ^{1}H-NMR of compound **36**

^{13}C NMR compound 36

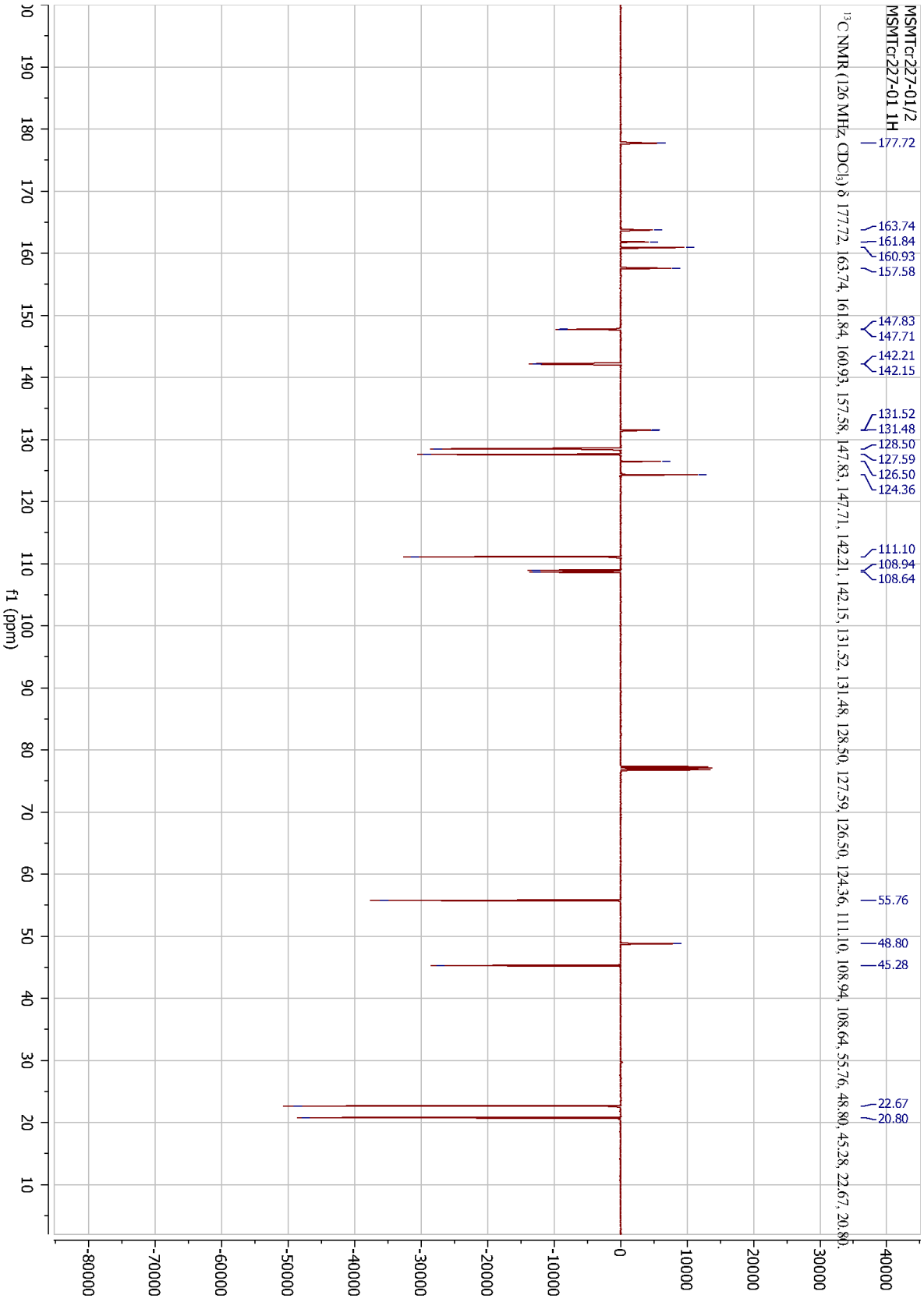

Figure S34 ^{13}C-NMR of compound **36**

^{1}H NMR compound 37

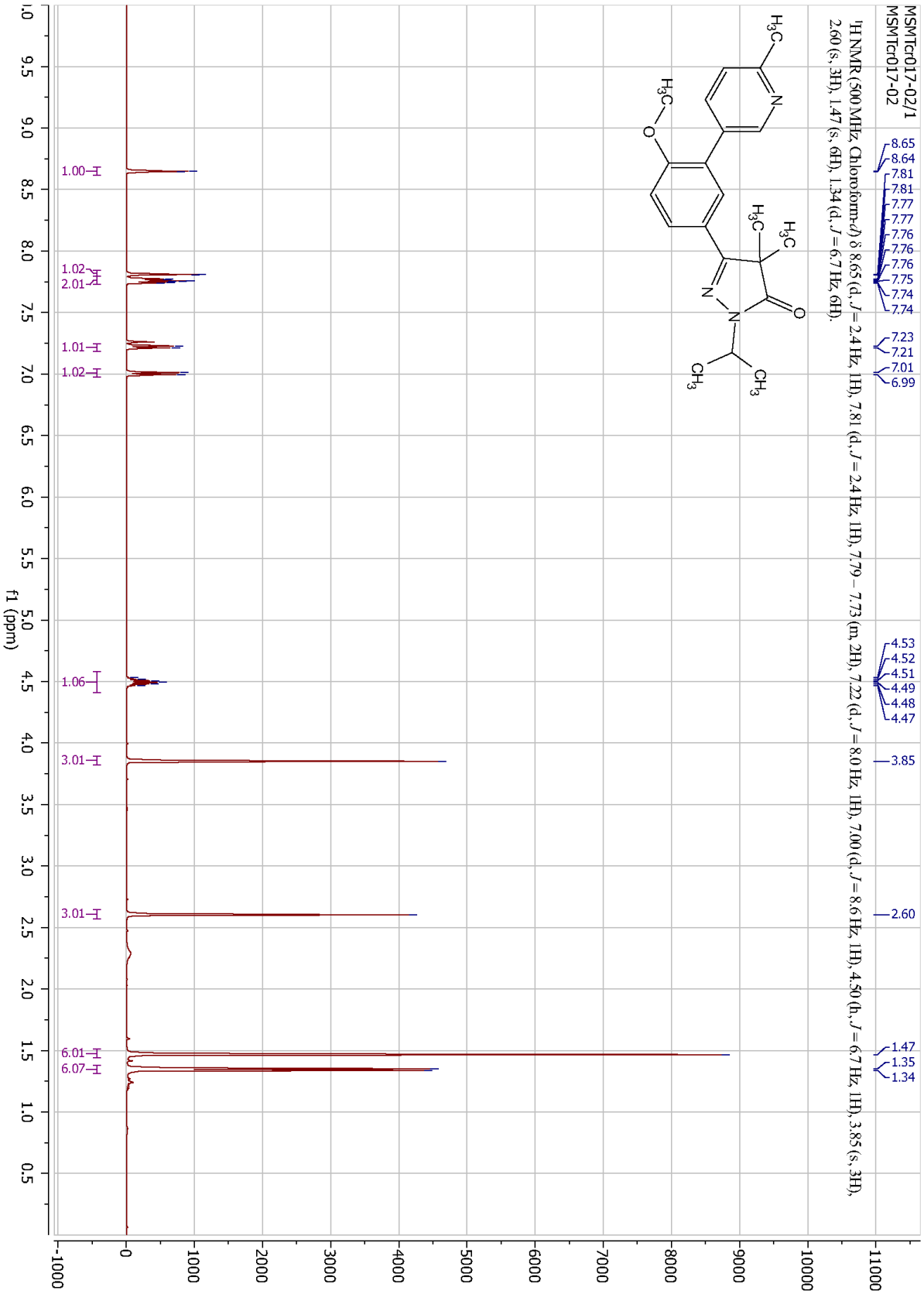

Figure S35 ^{1}H-NMR of compound **37**

^{13}C NMR compound 37

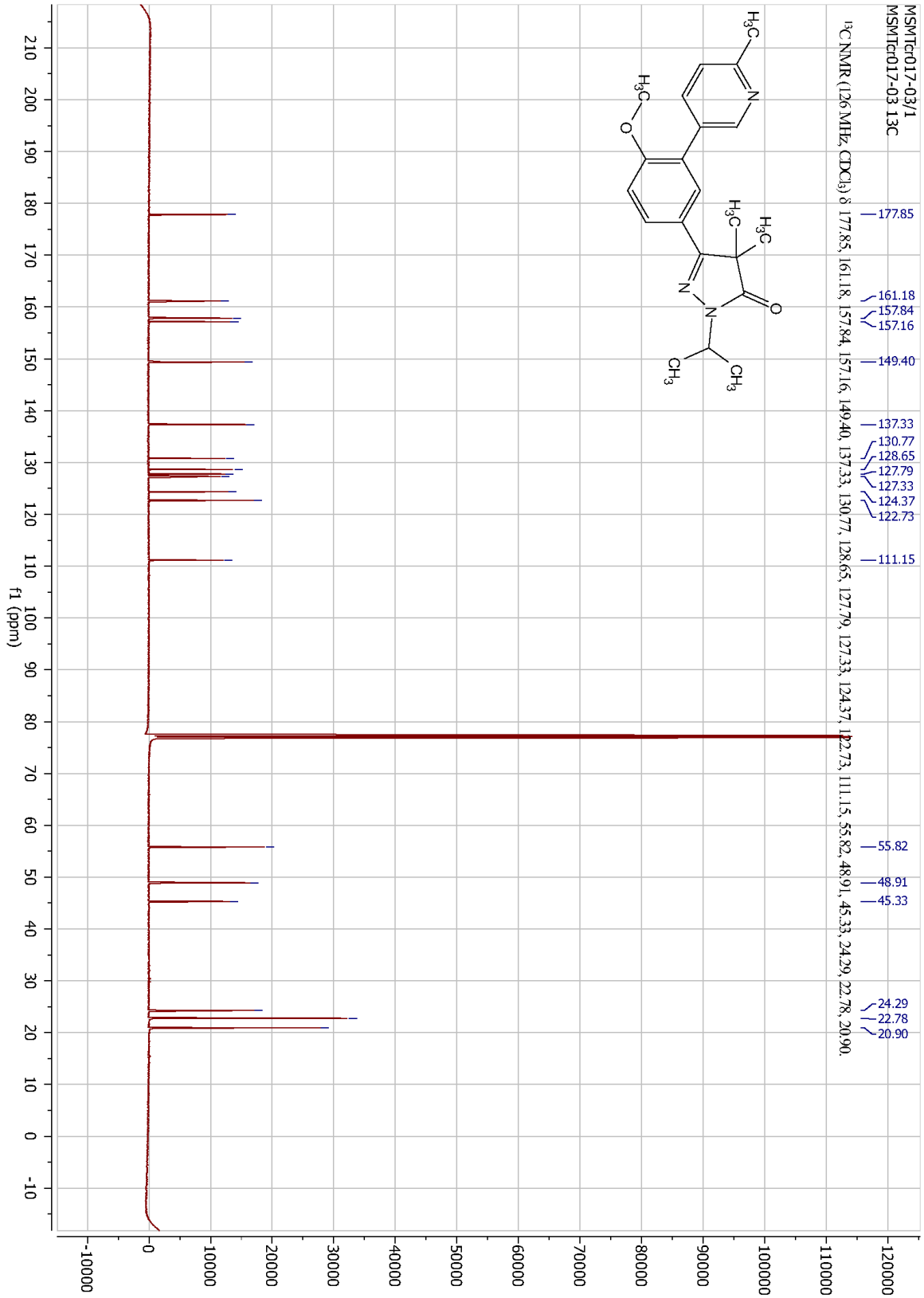

Figure S36 ^{13}C-NMR of compound **37**

^{1}H NMR compound 38

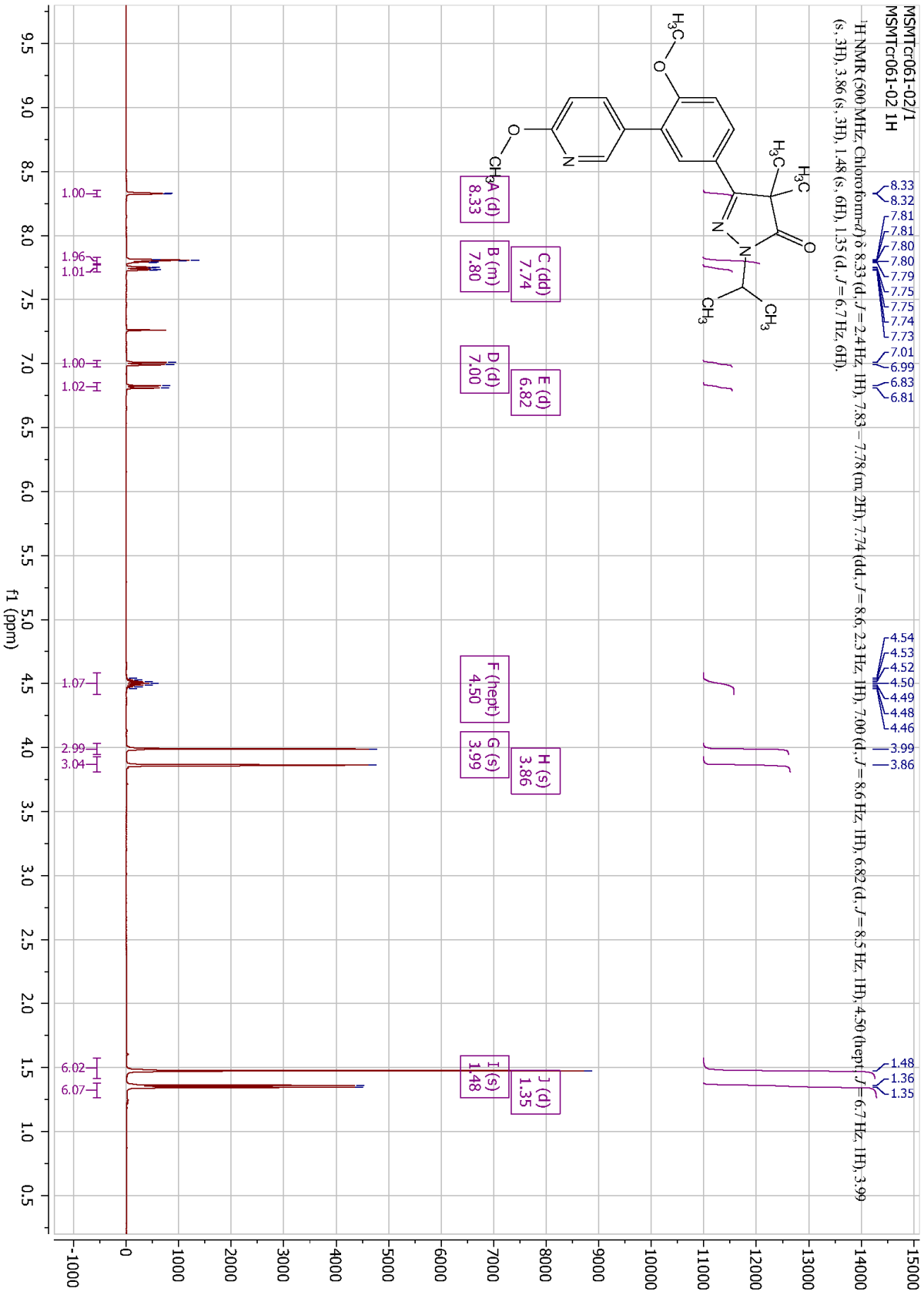

Figure S37 ^{1}H-NMR of compound **38**

^{13}C NMR compound 38

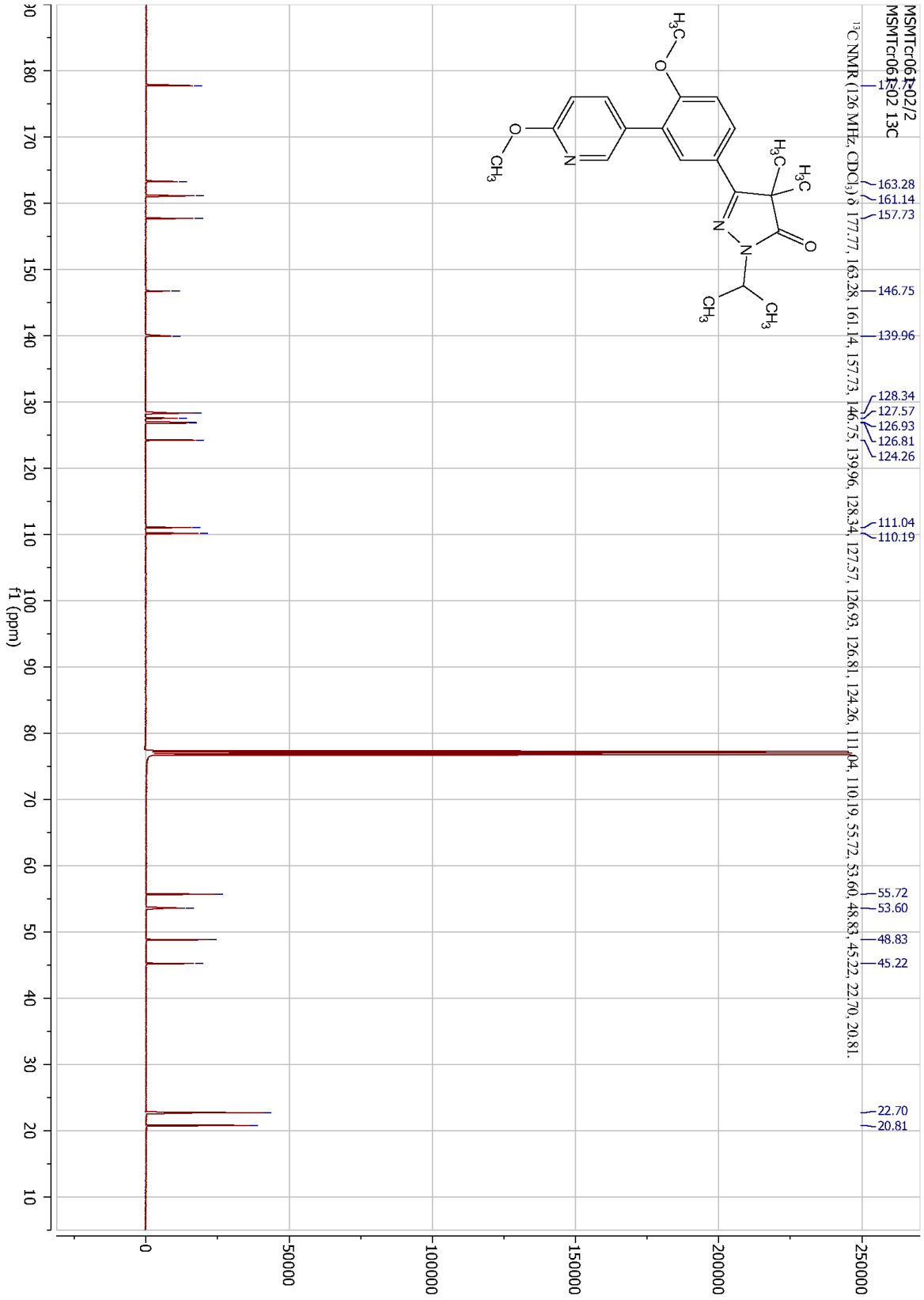

Figure S38 ^{13}C-NMR of compound **38**

^{1}H NMR compound 39

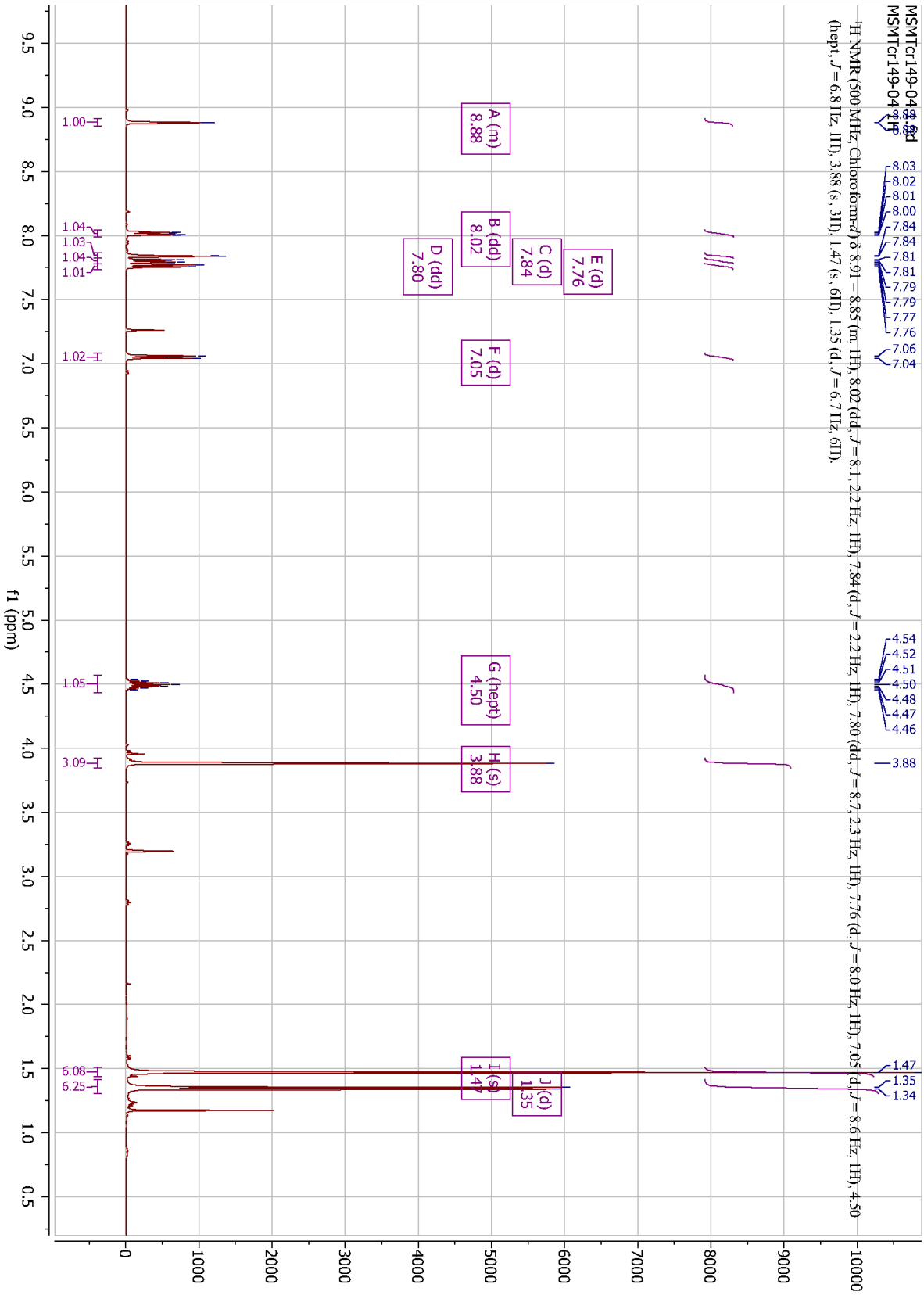

Figure S39 ^{1}H-NMR of compound **39**

^{13}C NMR compound 39

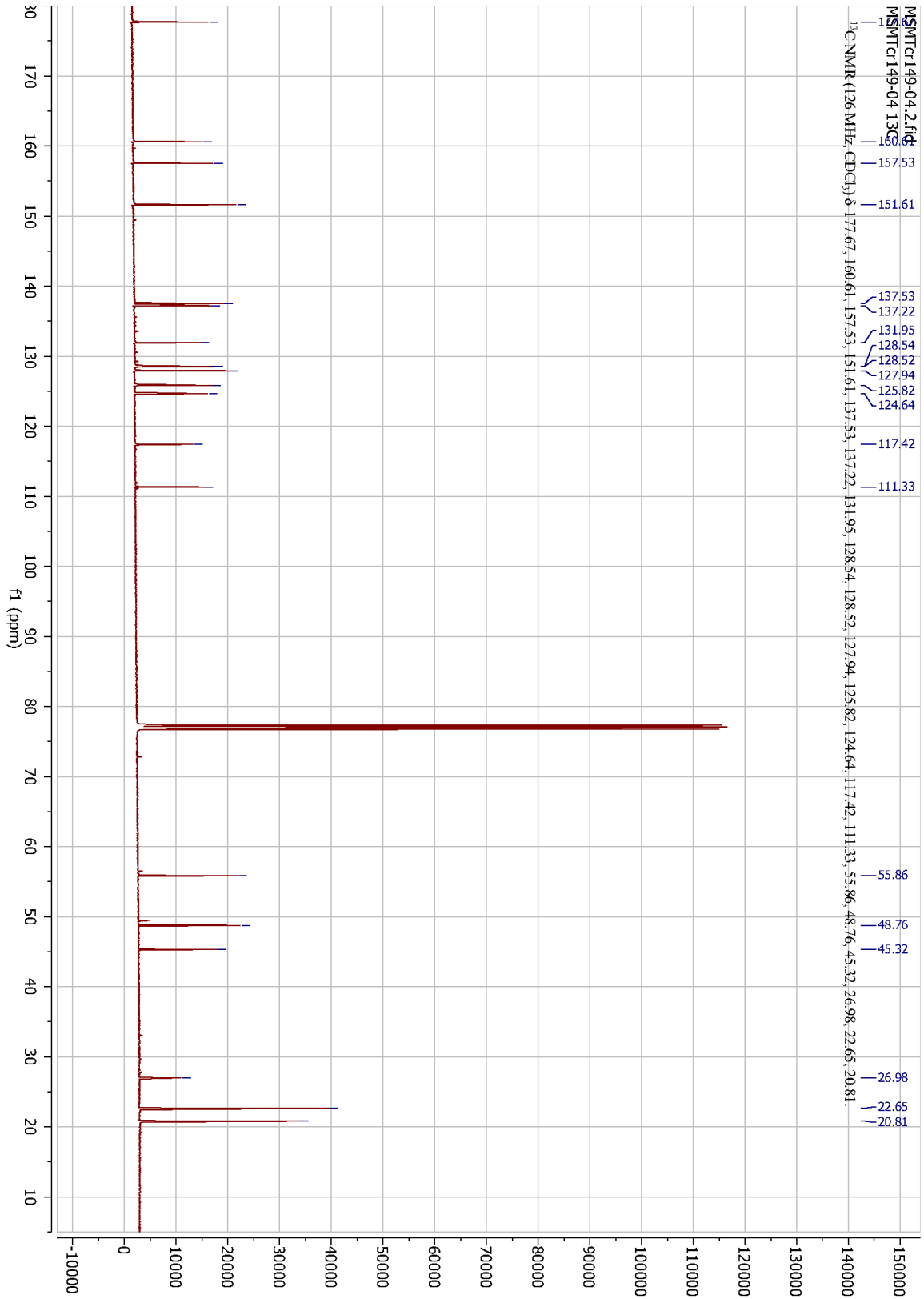

Figure S40 ^{13}C-NMR of compound **39**

^{1}H NMR compound 40

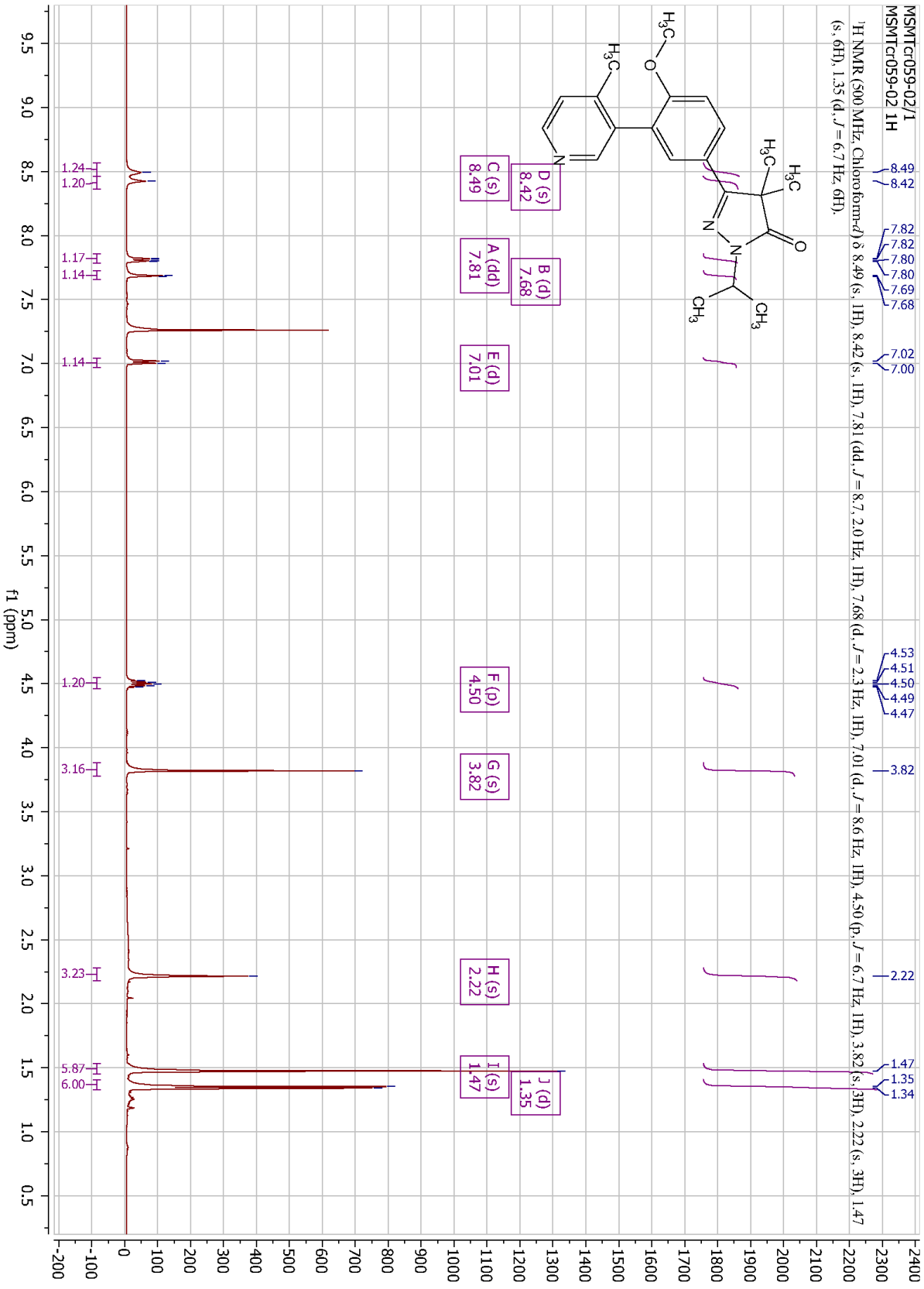

Figure S41 ^{1}H-NMR of compound **40**

^{13}C NMR compound 40

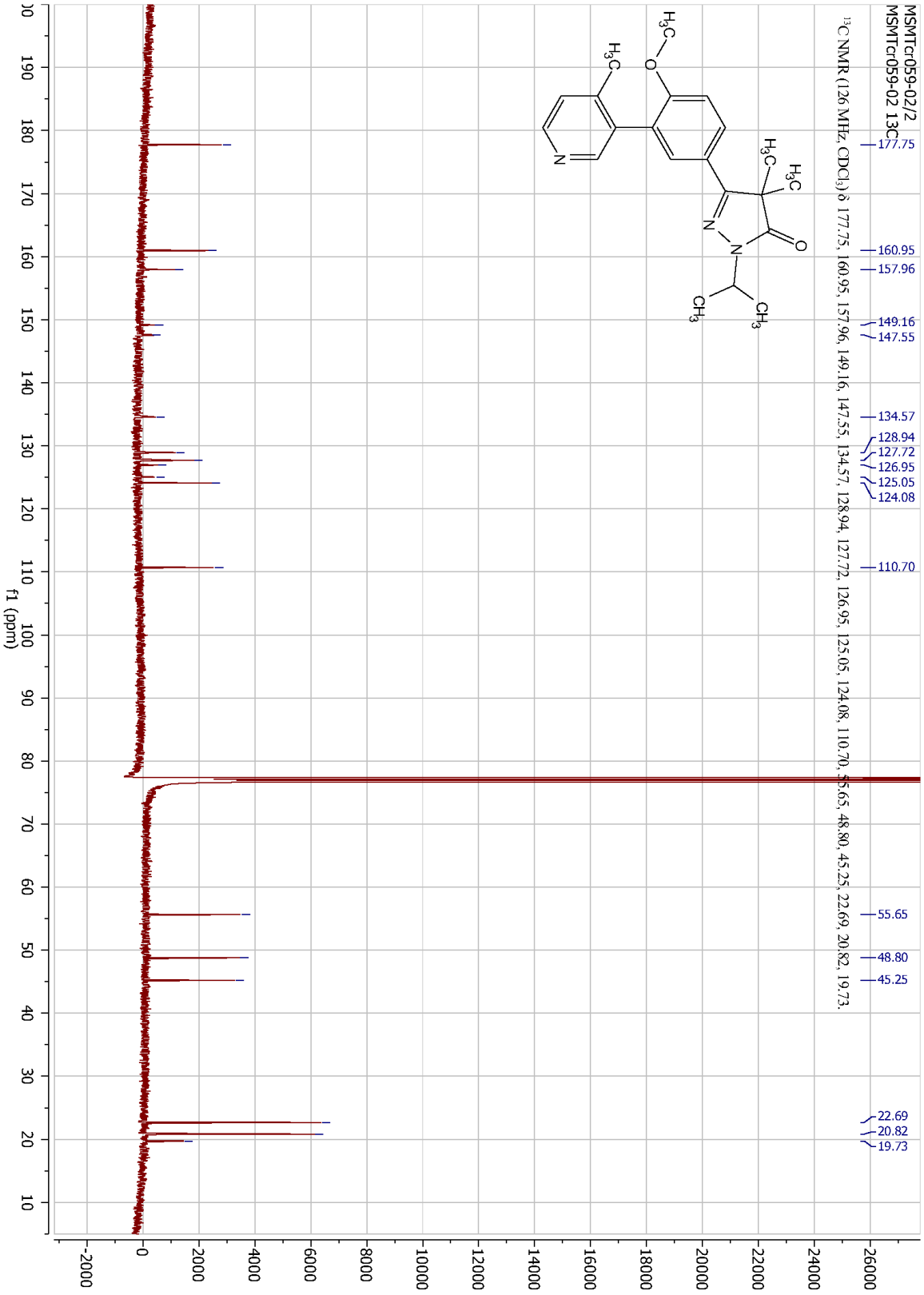

Figure S42 ^{13}C-NMR of compound **40**

^{1}H NMR compound 41

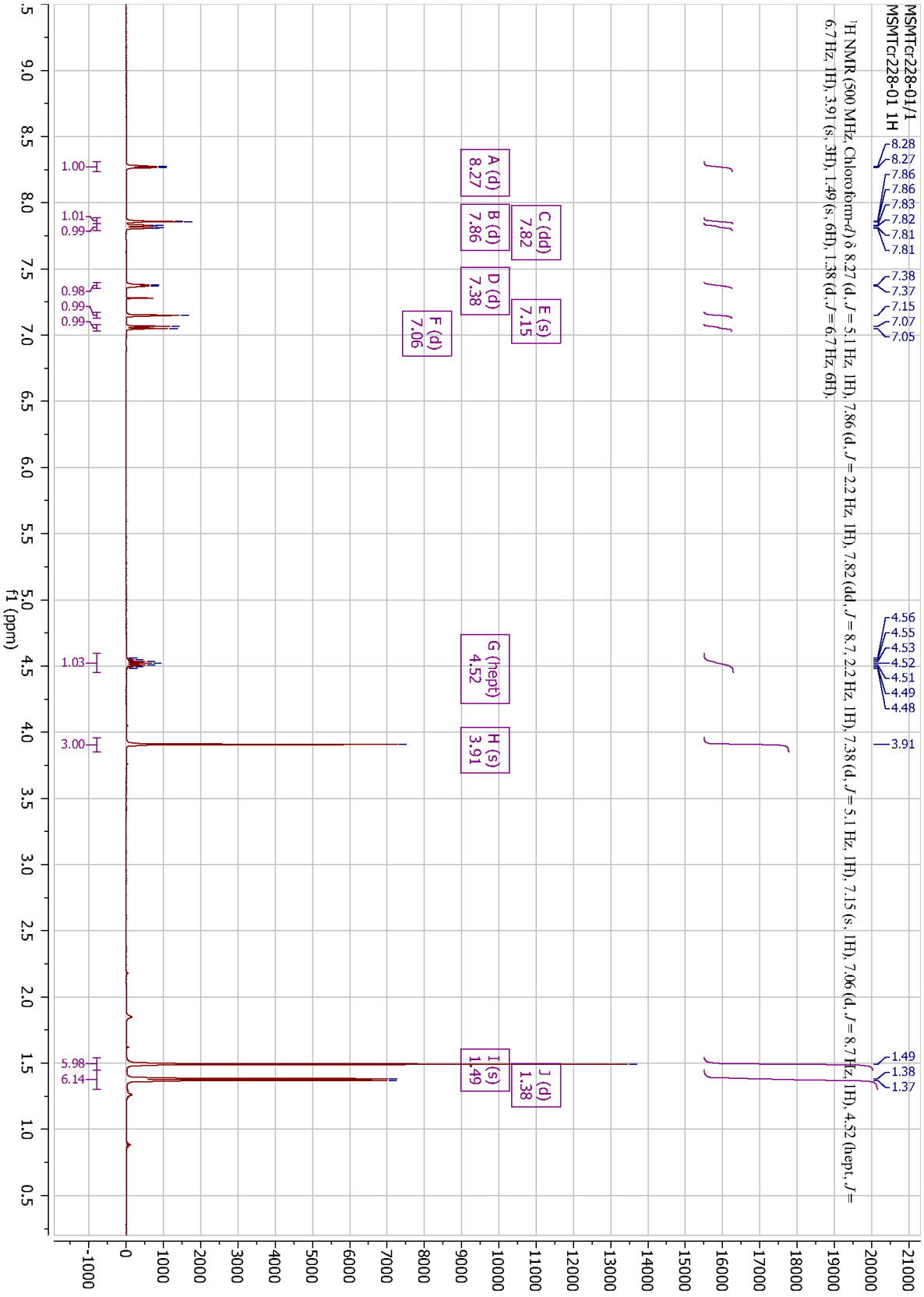

Figure S43 ^{1}H-NMR of compound **41**

^{13}C NMR compound 41

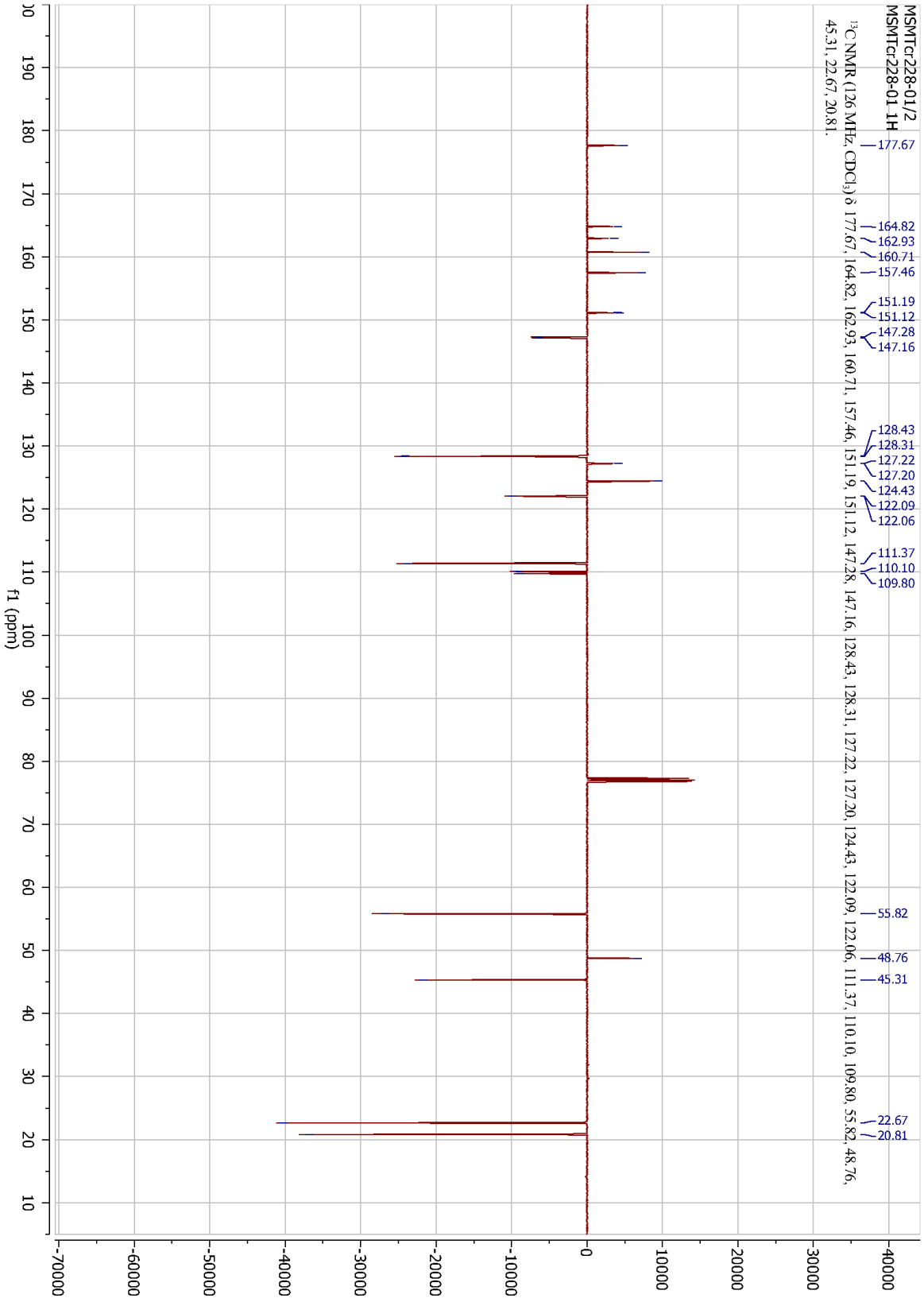

Figure S44 ^{13}C-NMR of compound **41**

^{1}H NMR compound 42

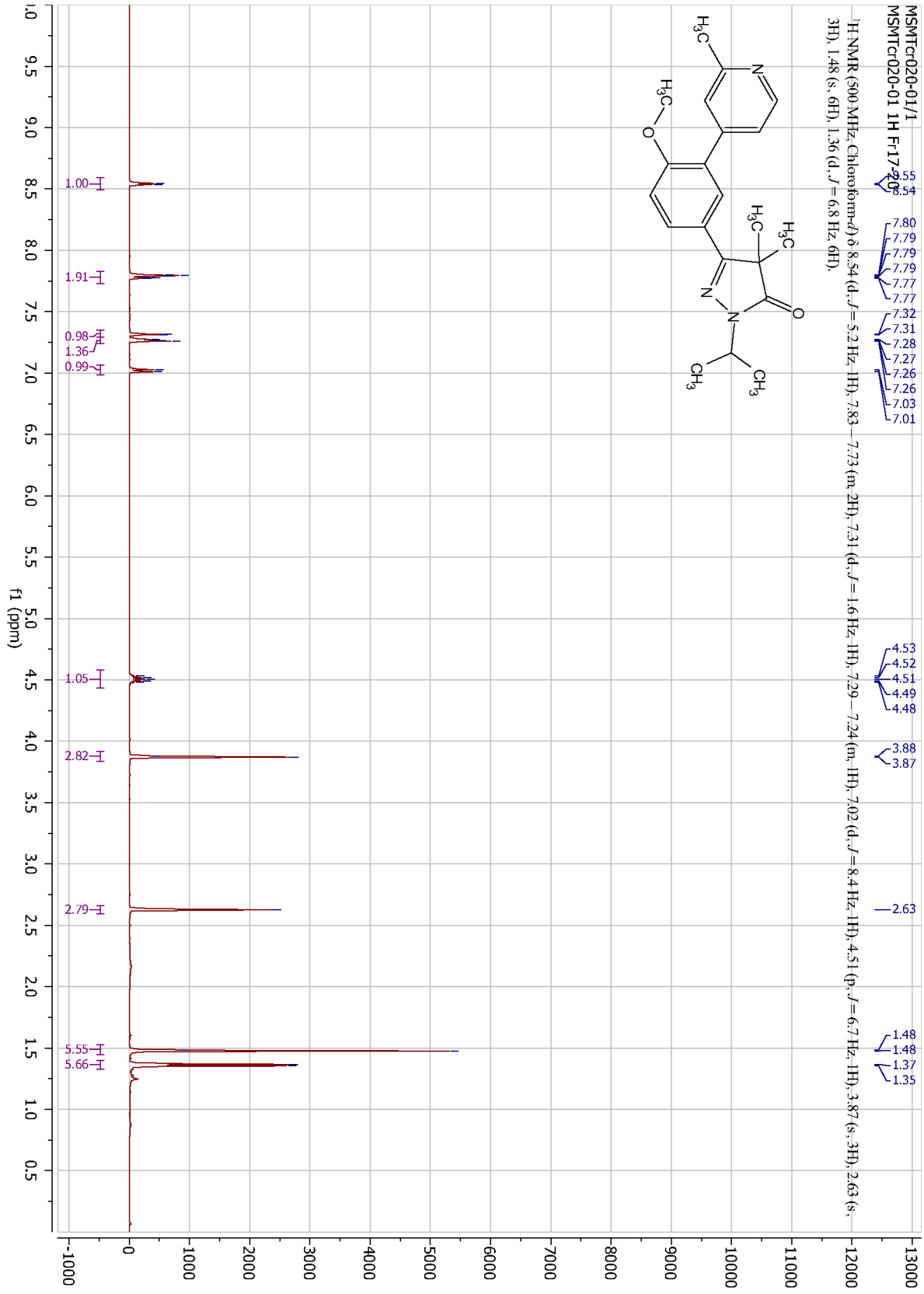

Figure S45 ^{1}H-NMR of compound **42**

^{13}C NMR compound 42

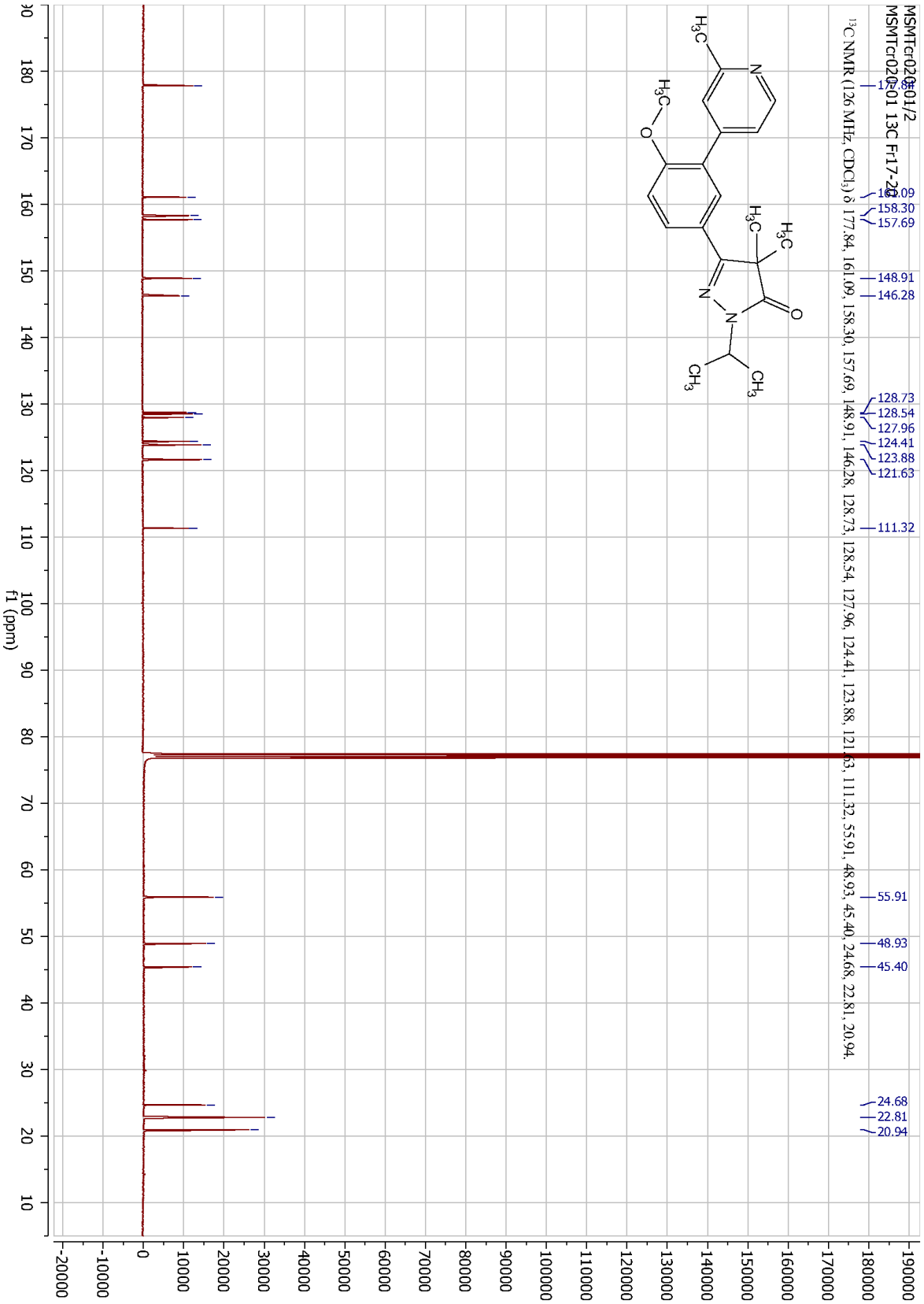

Figure S46 ^{13}C-NMR of compound **42**

^{1}H NMR compound 43

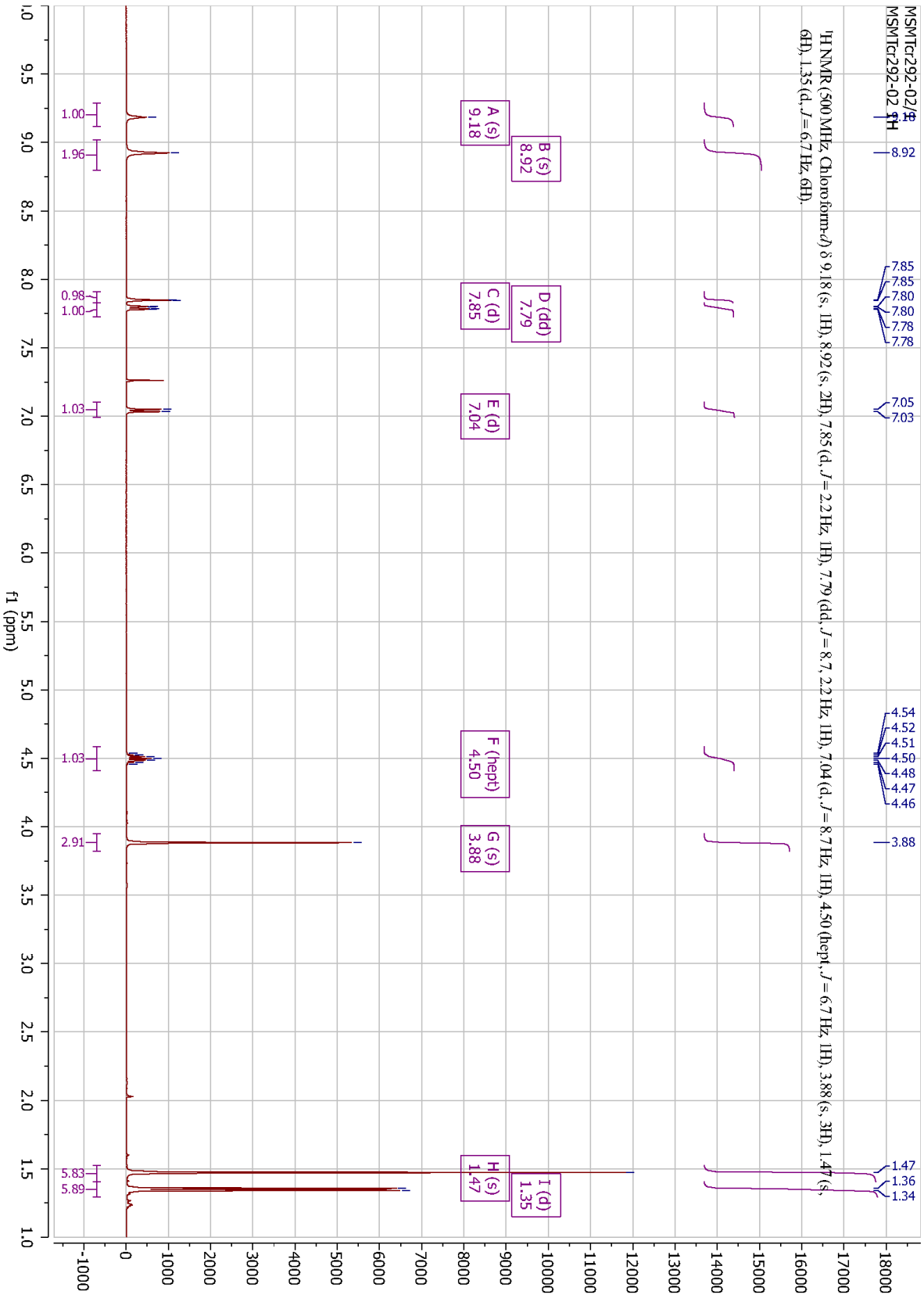

Figure S47 ^{1}H-NMR of compound **43**

^{13}C NMR compound 43

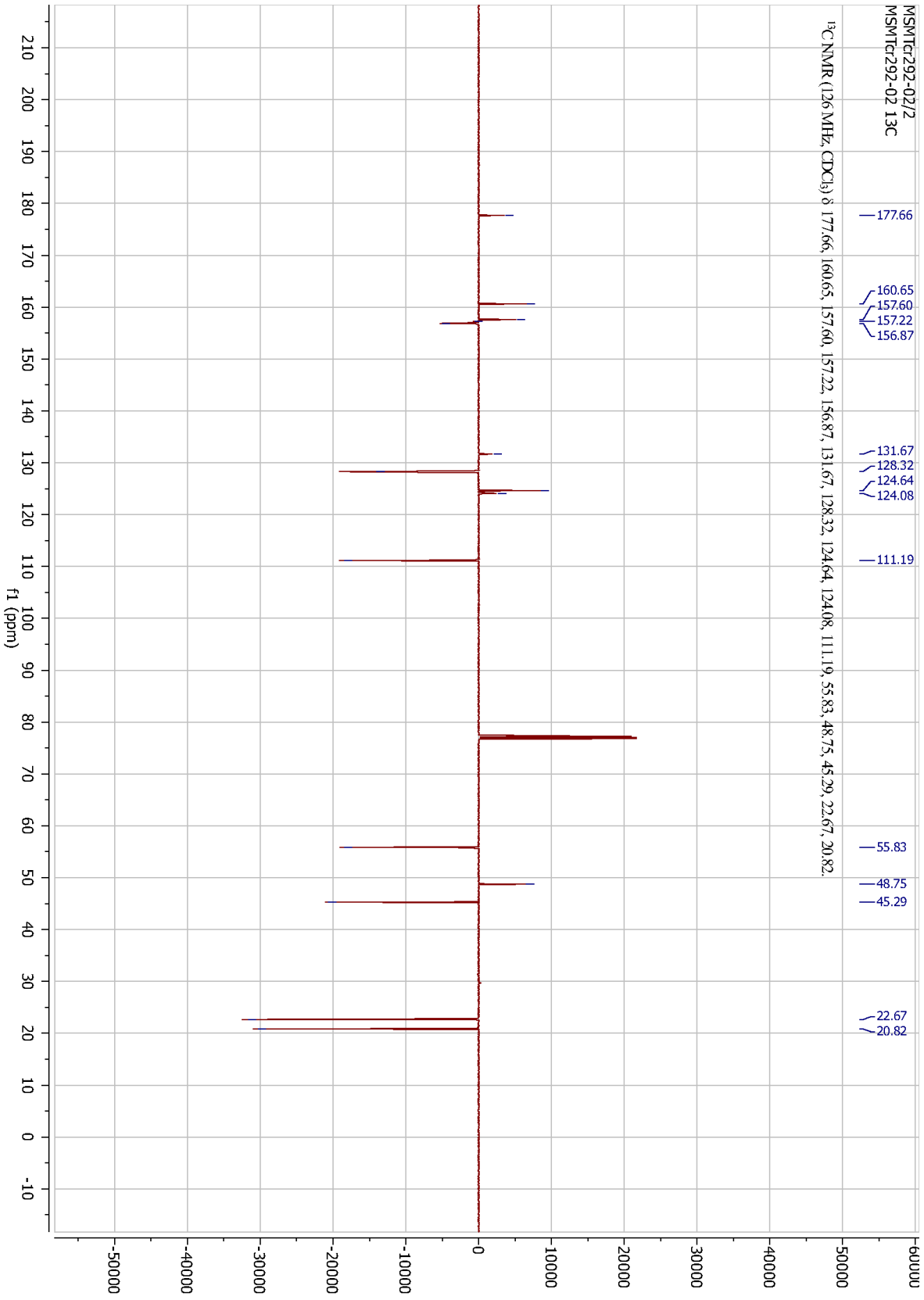

Figure S48 ^{13}C-NMR of compound **43**

^{1}H NMR compound 44

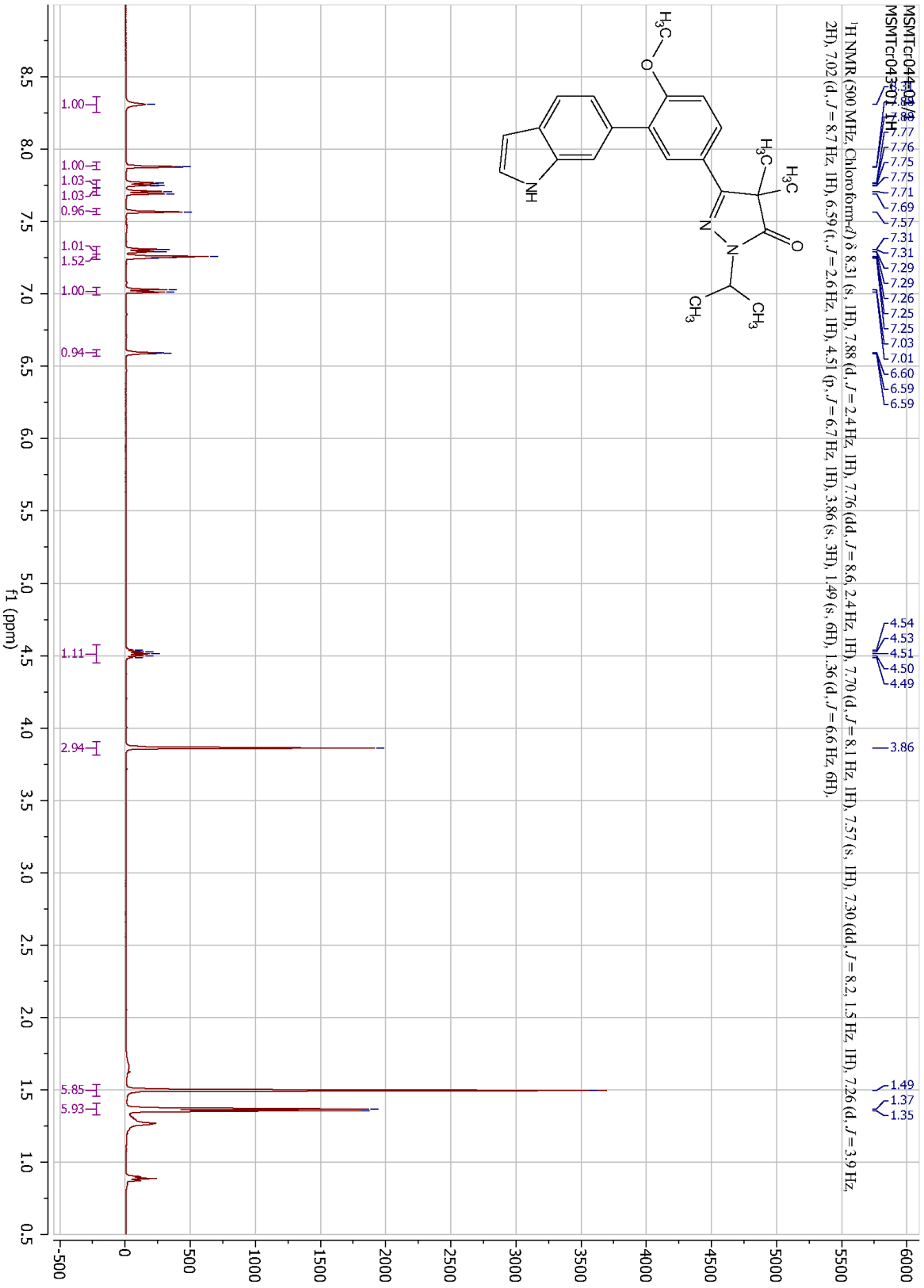

Figure S49 ^{1}H-NMR of compound **44**

^{13}C NMR compound 44

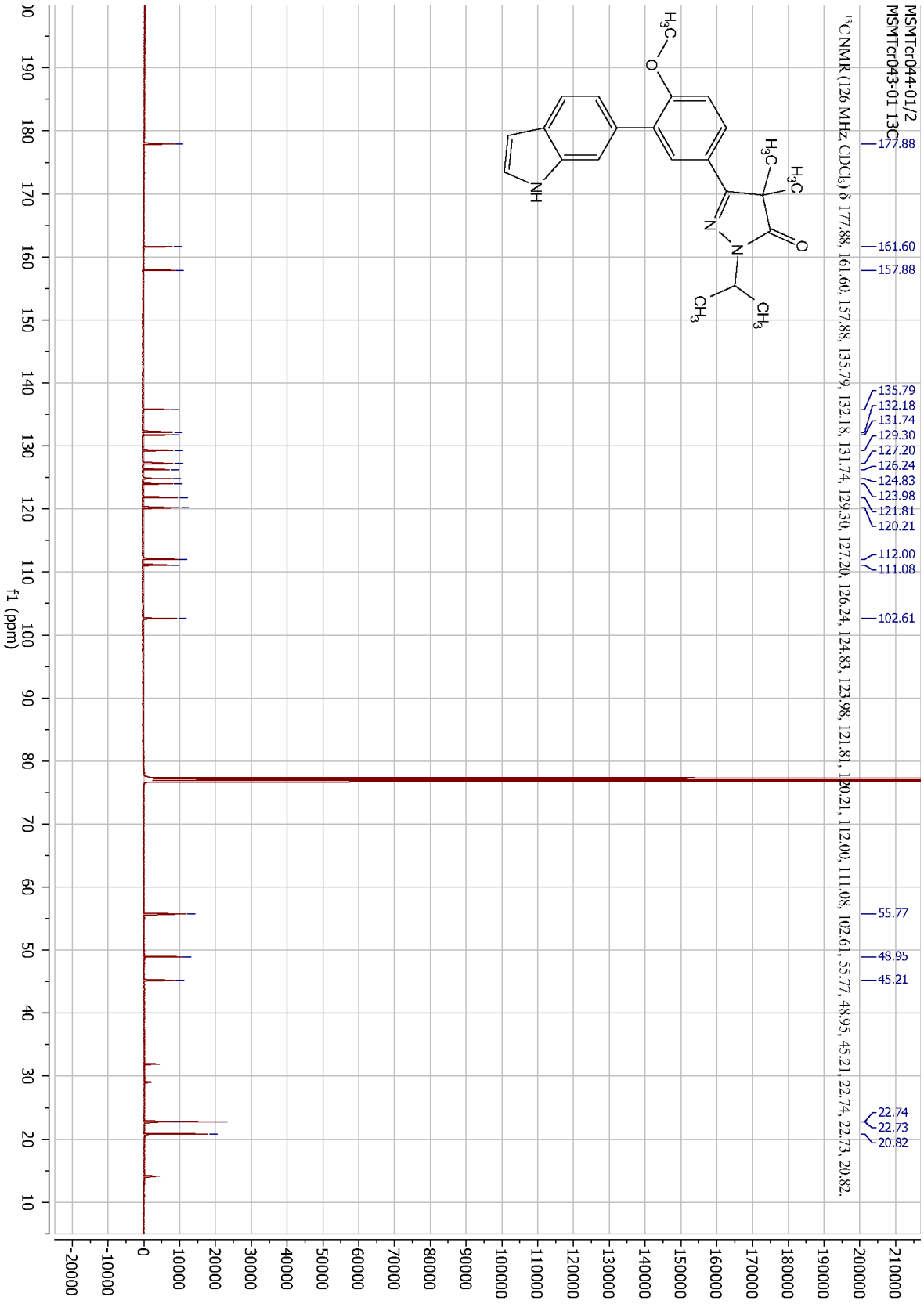

Figure S50 ^{13}C-NMR of compound **44**

[1]H NMR compound 45

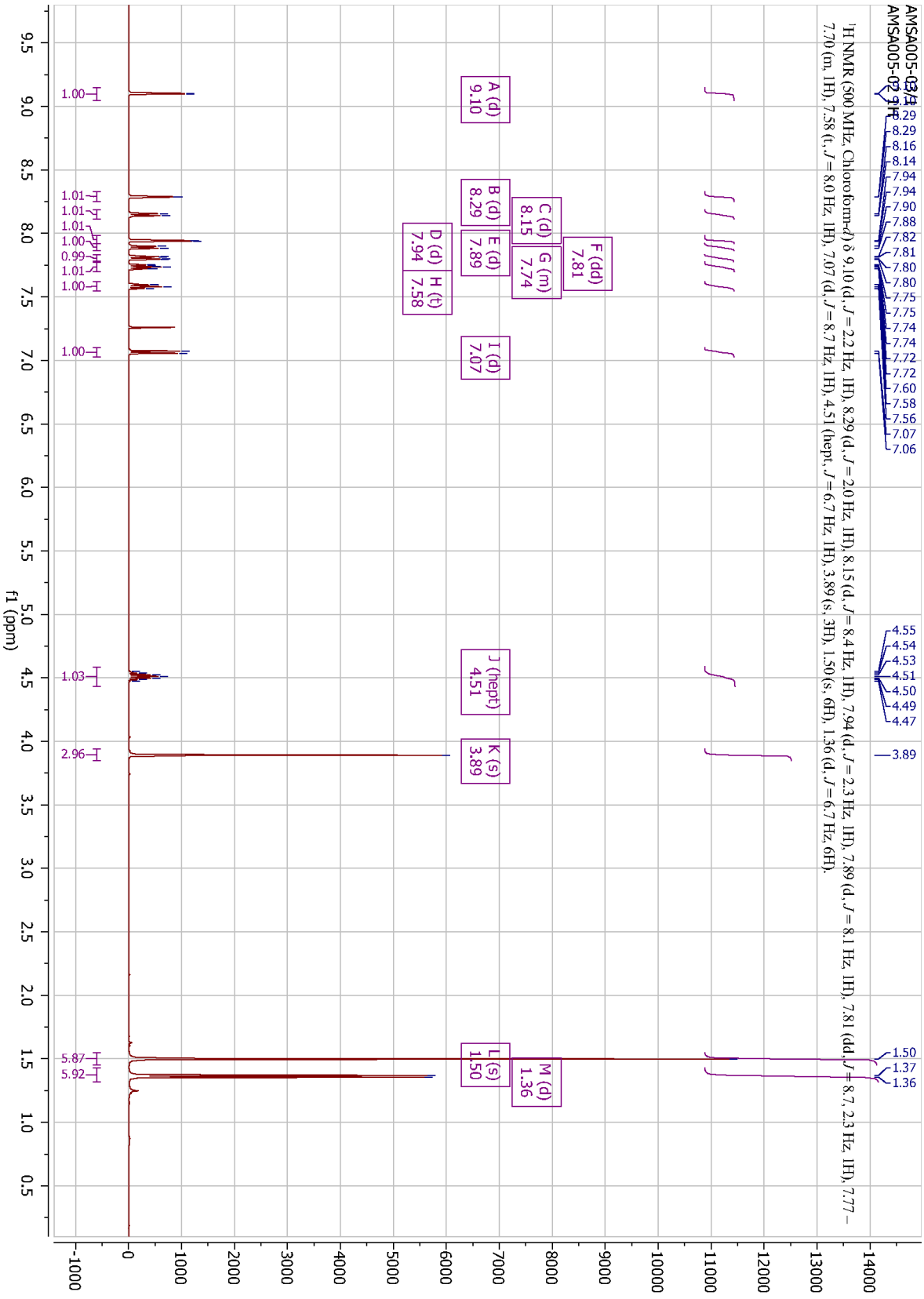

Figure S51 [1]H-NMR of compound **45**

^{13}C NMR compound 45

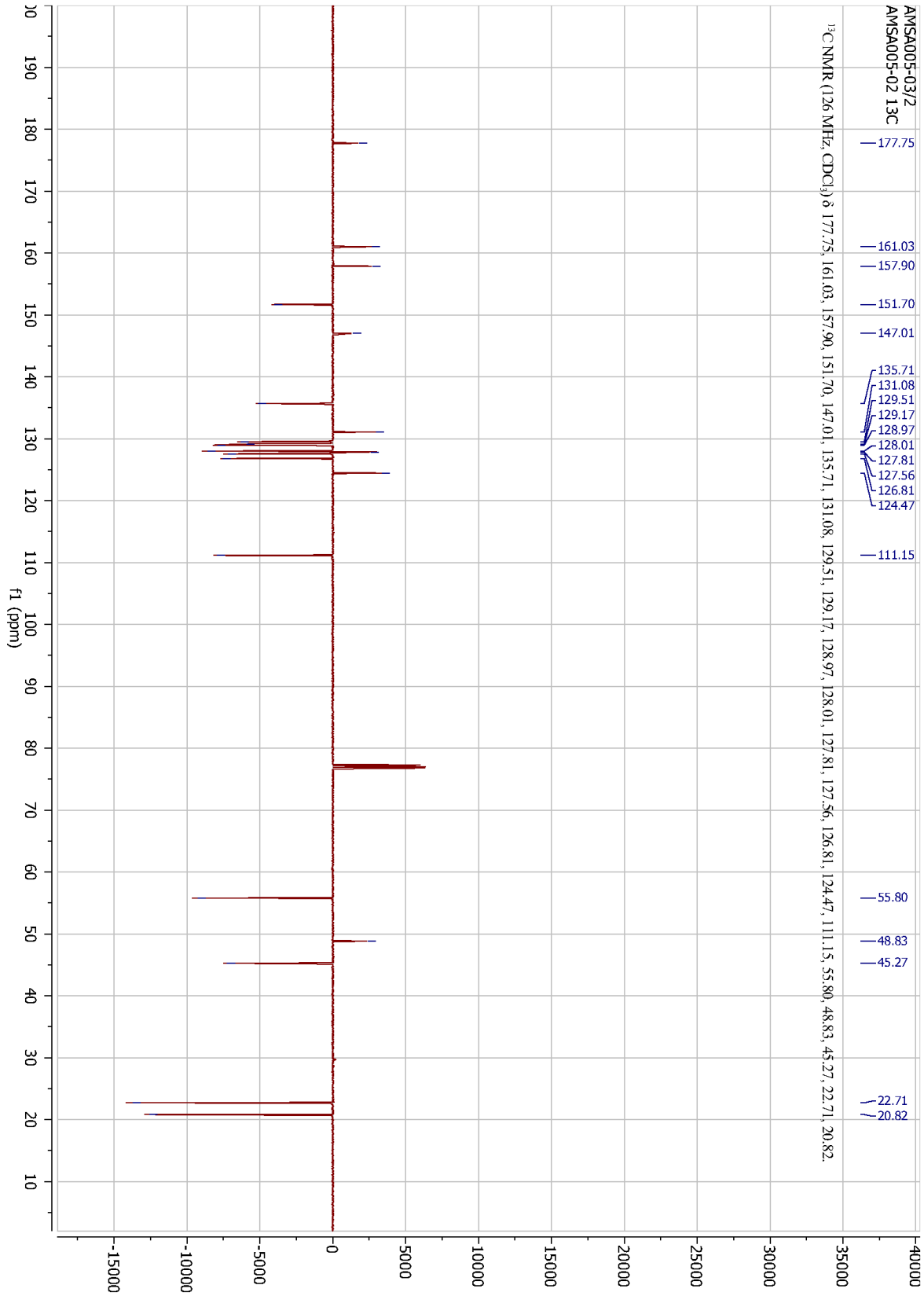

Figure S52 ^{13}C-NMR of compound **45**

^{1}H NMR compound 46

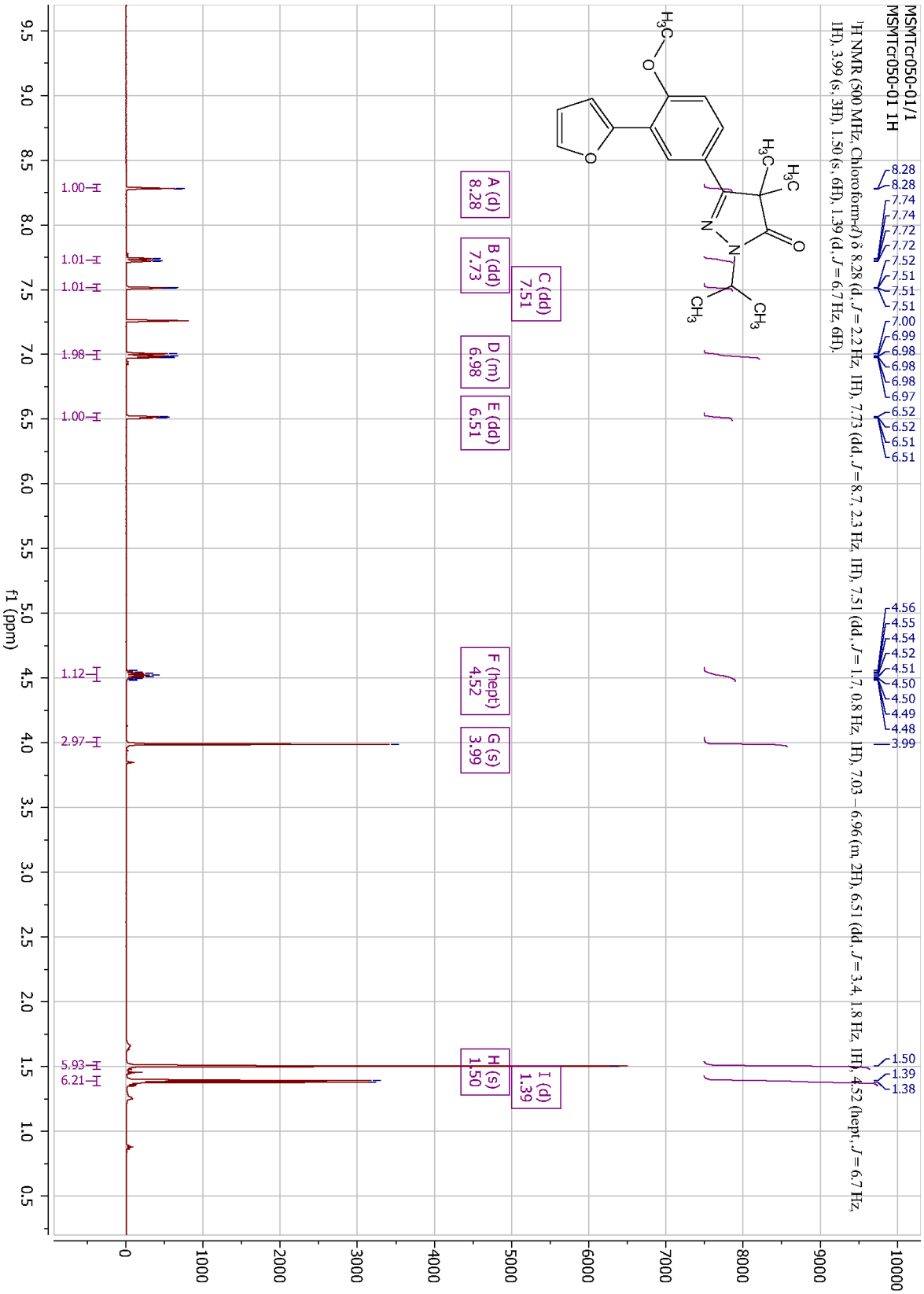

Figure S53 ^{1}H-NMR of compound **46**

^{13}C NMR compound 46

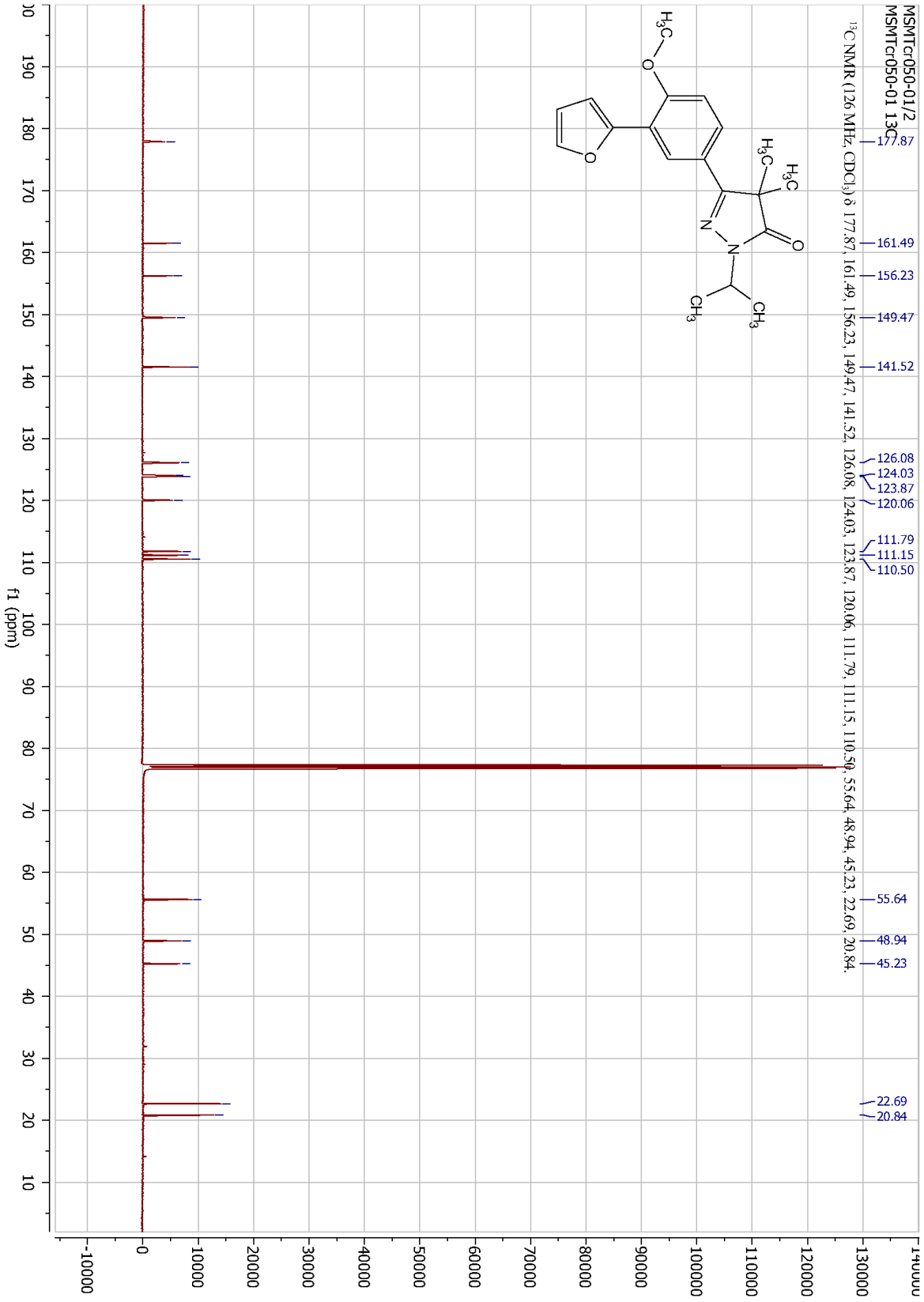

Figure S54 ^{13}C-NMR of compound **46**

[1]H NMR compound 47

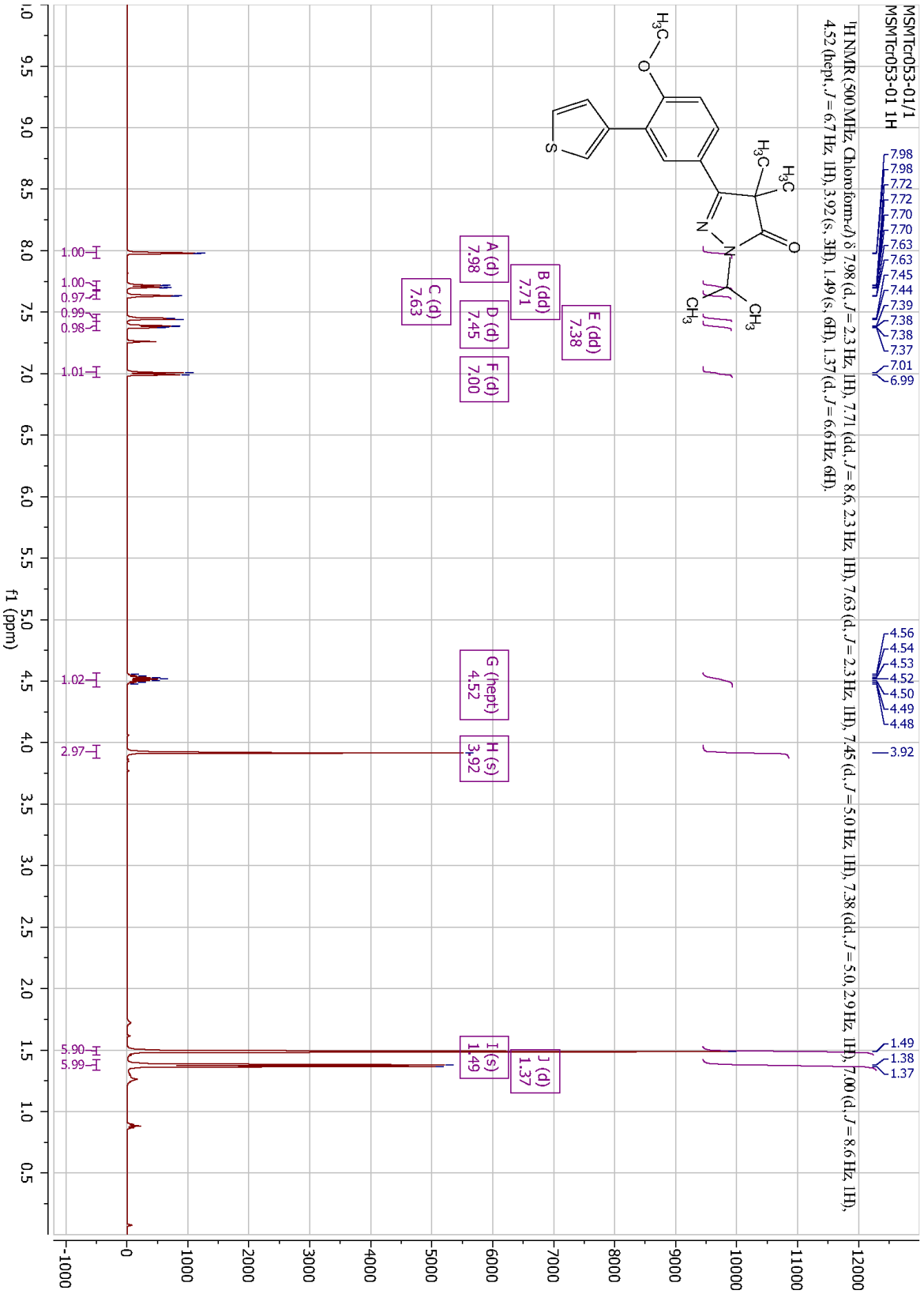

Figure S55 [1]H-NMR of compound **47**

^{13}C NMR compound 47

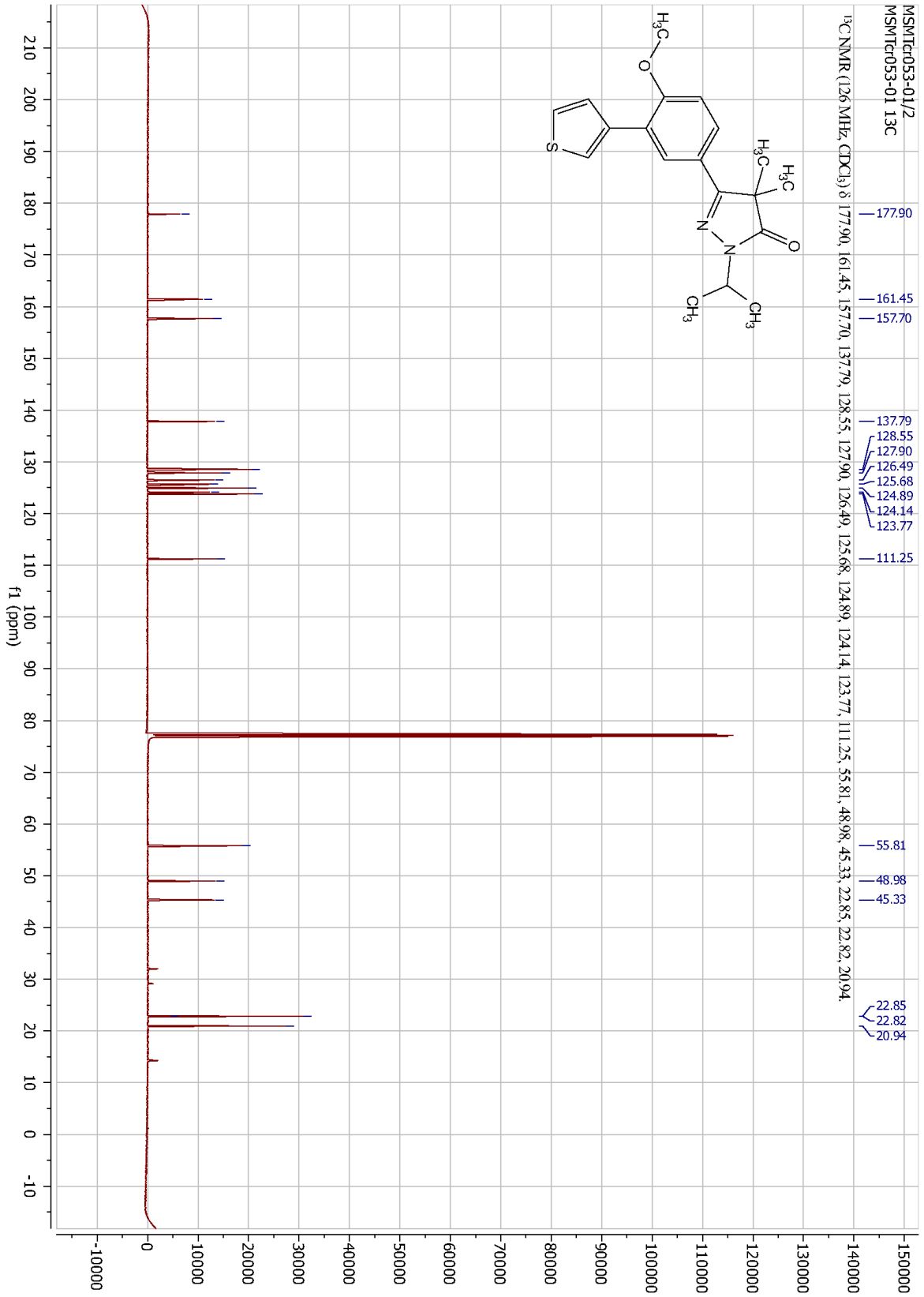

Figure S56 ^{13}C-NMR of compound **47**

^{1}H NMR compound 48

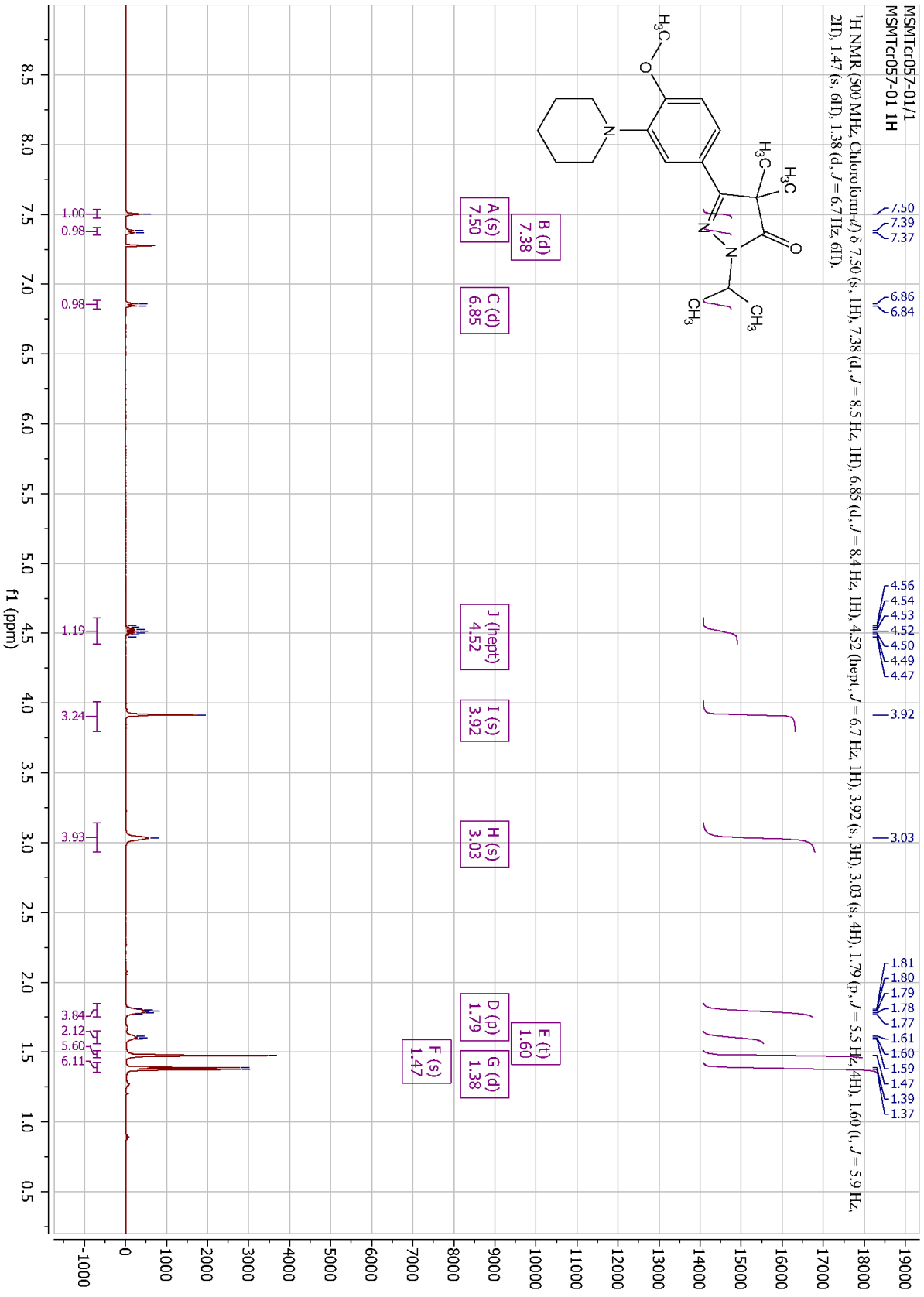

Figure S57 ^{1}H-NMR of compound **48**

^{13}C NMR compound 48

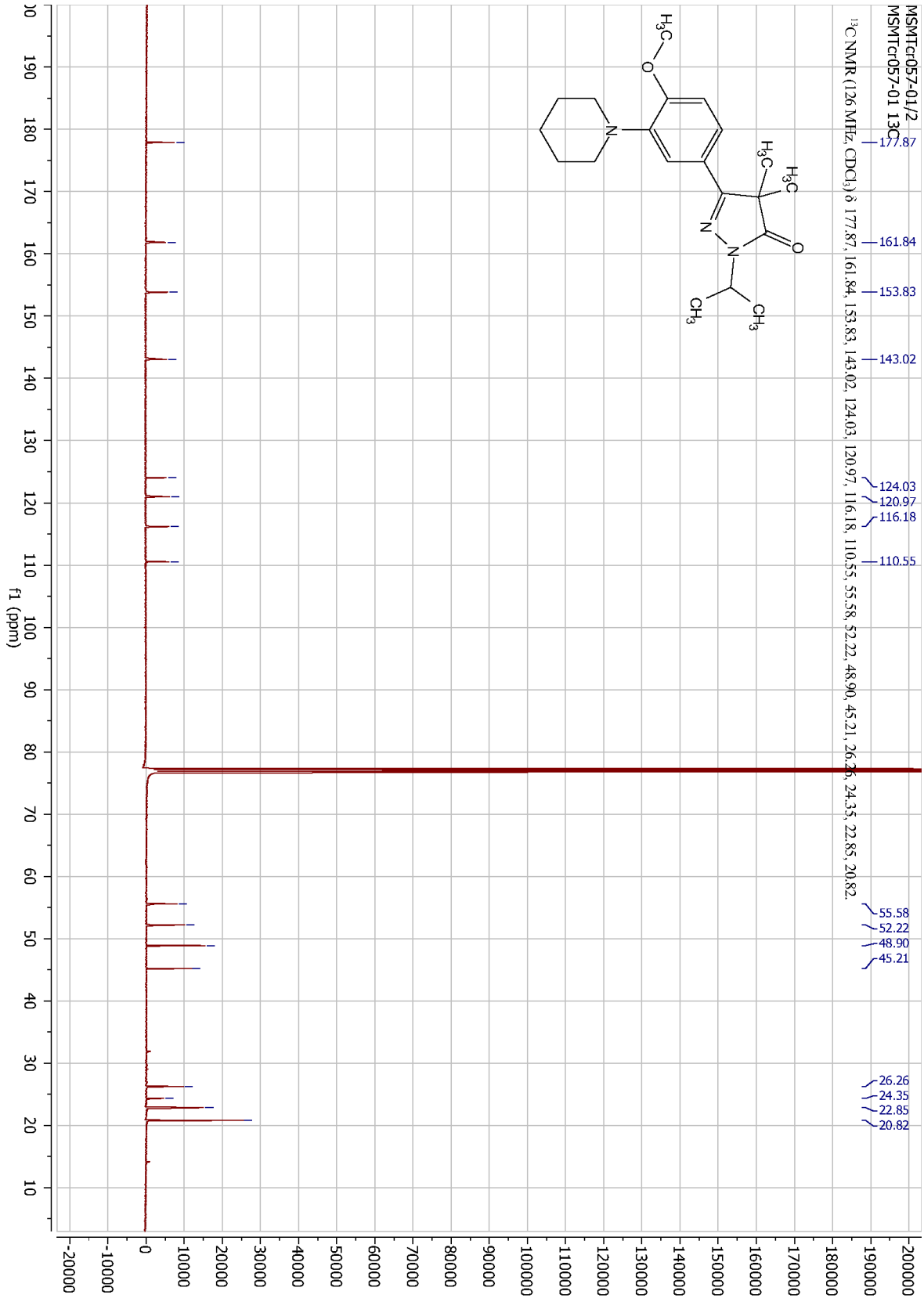

Figure S58 ^{13}C-NMR of compound **48**

^{1}H NMR compound 49

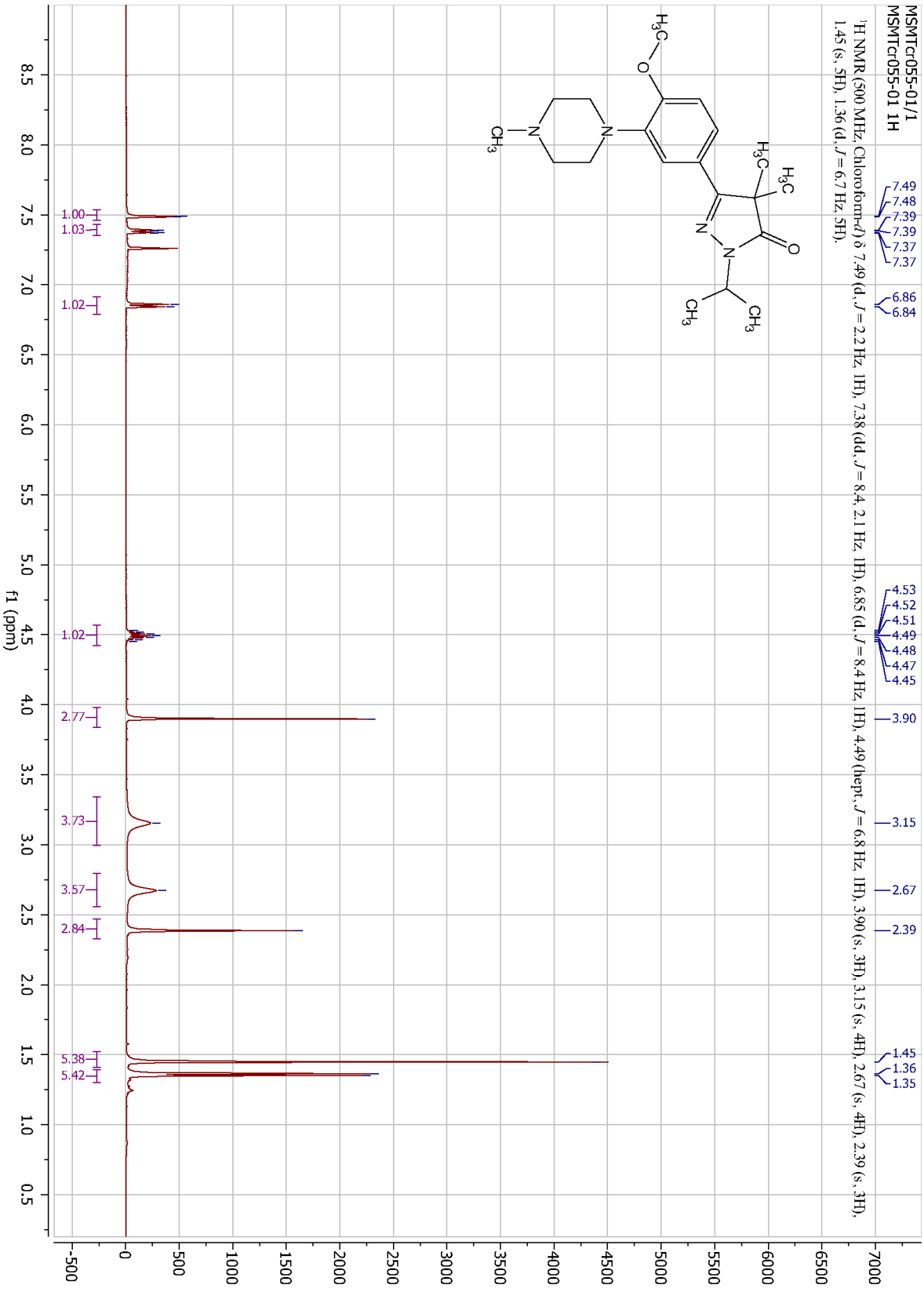

Figure S59 ^{1}H-NMR of compound **49**

^{13}C NMR compound 49

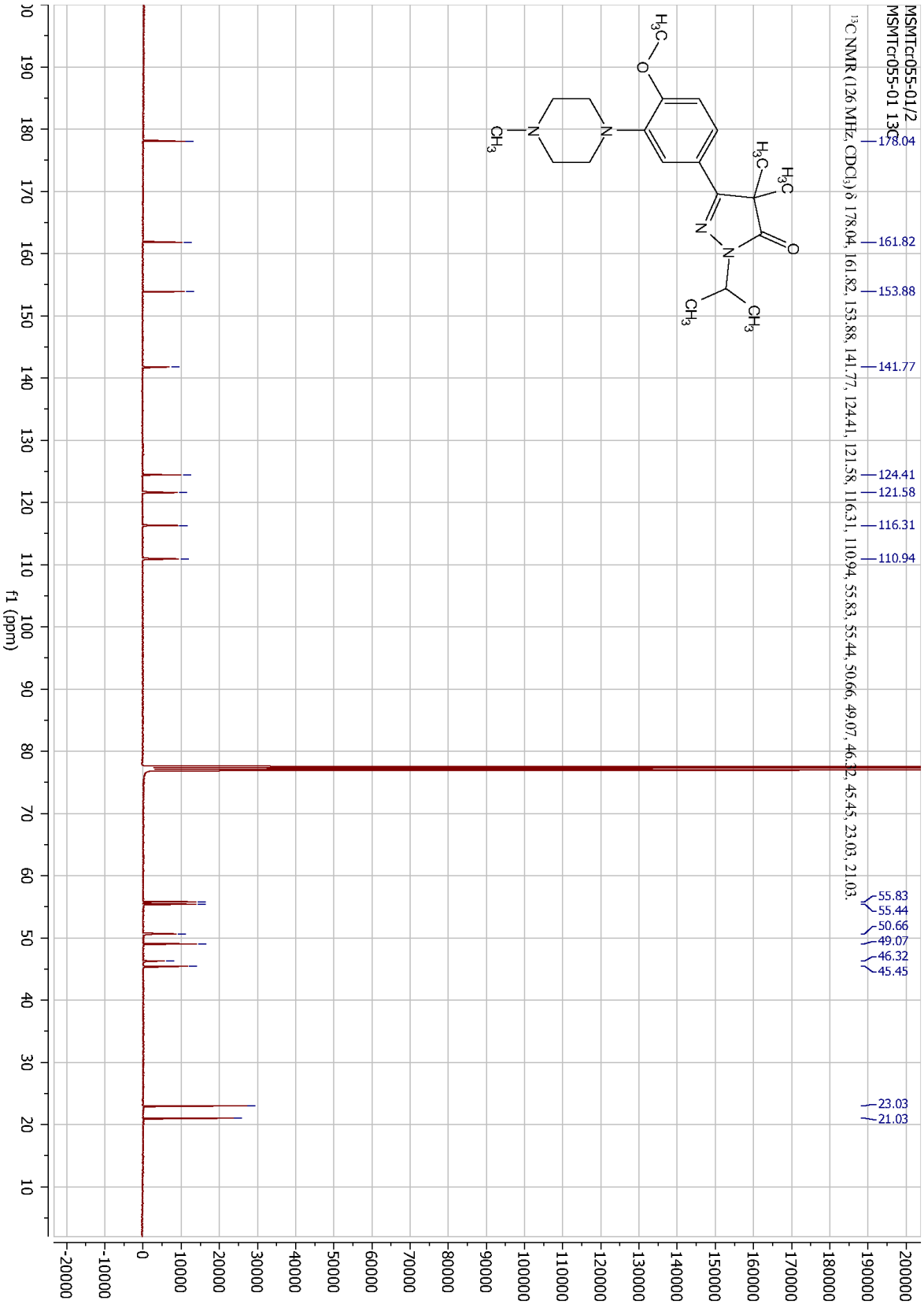

Figure S60 ^{13}C-NMR of compound **49**

^{1}H NMR compound 50

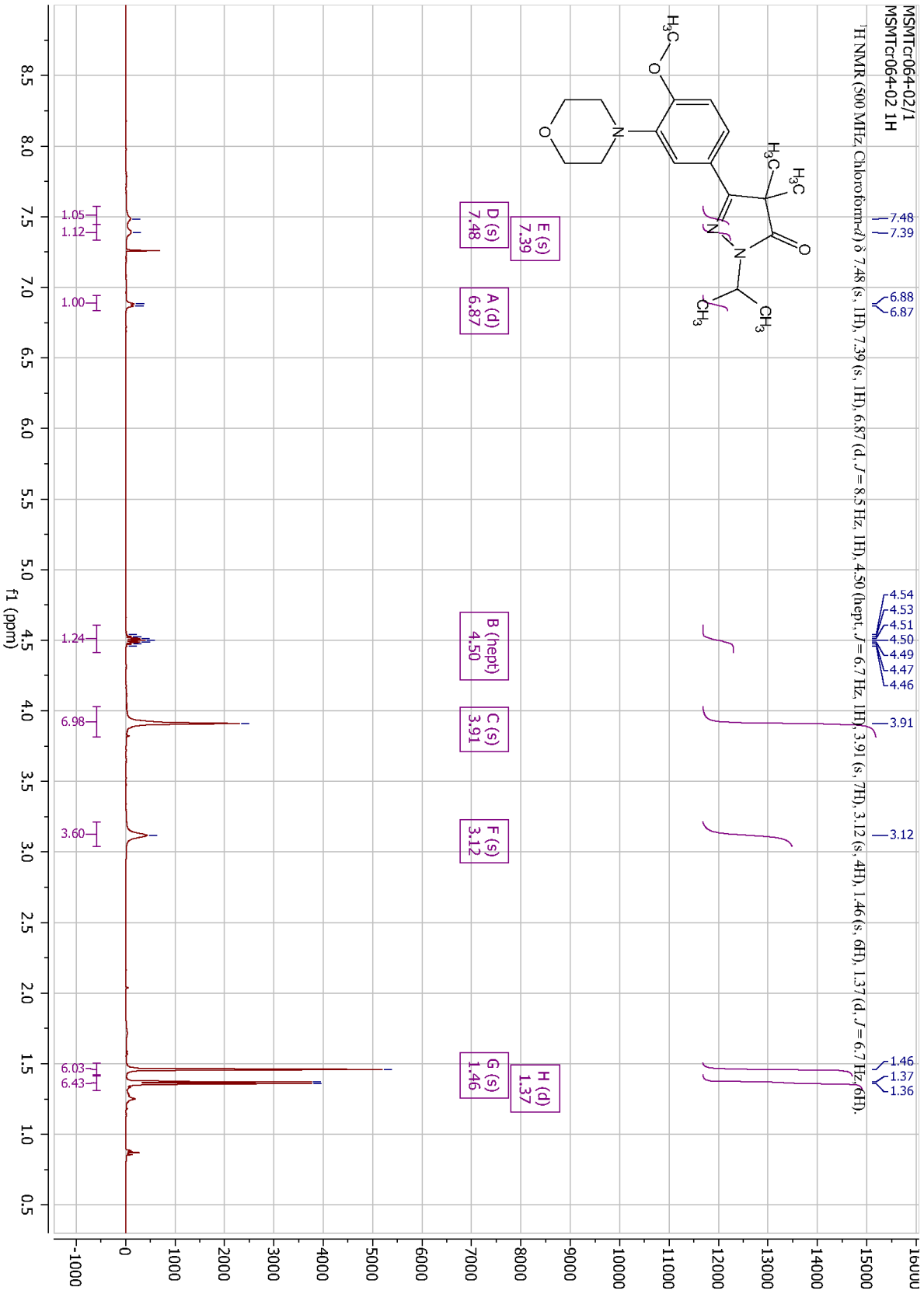

Figure S61 ^{1}H-NMR of compound **50**

^{13}C NMR compound 50

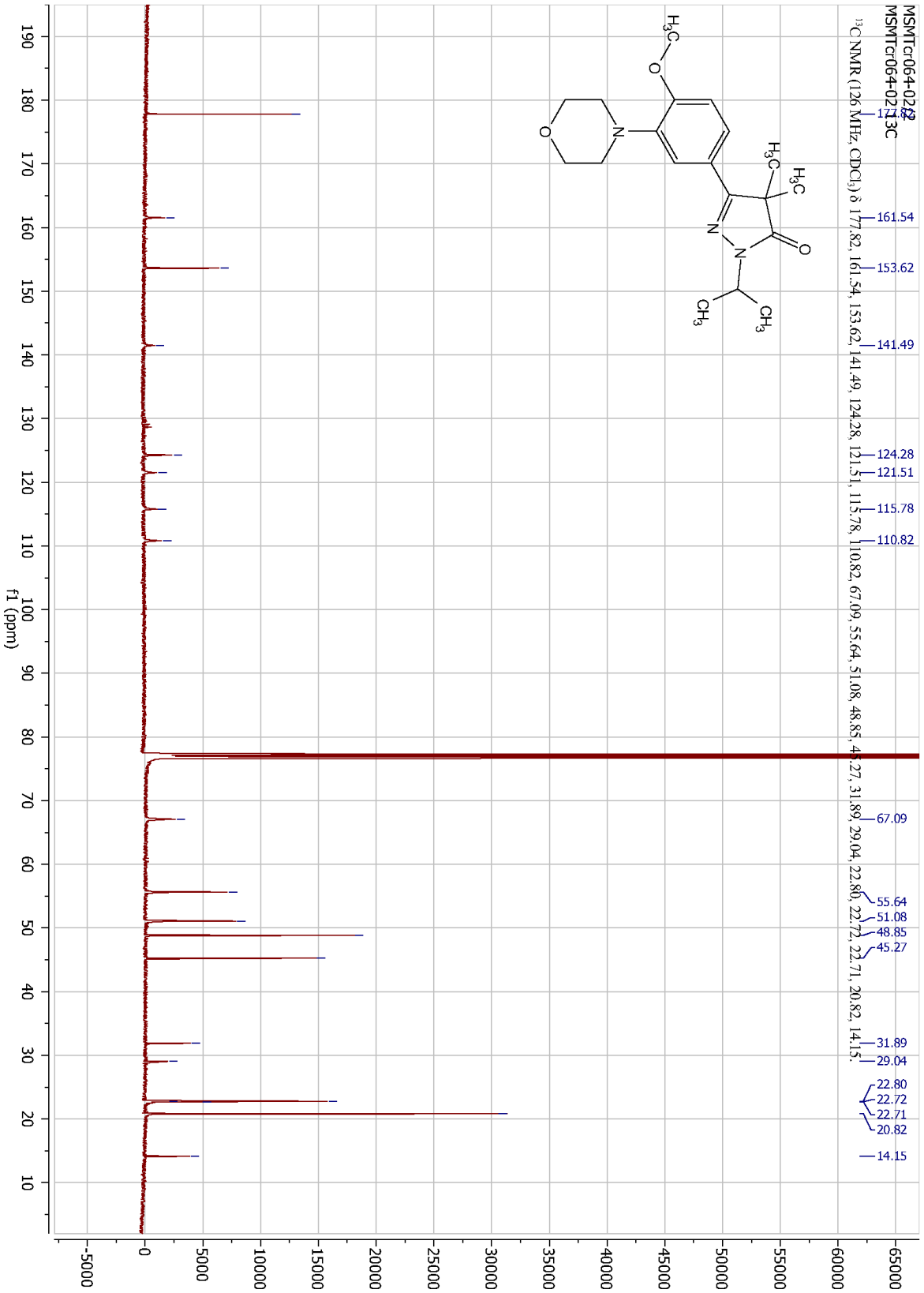

Figure S62 ^{13}C-NMR of compound **50**

^{1}H NMR compound 51

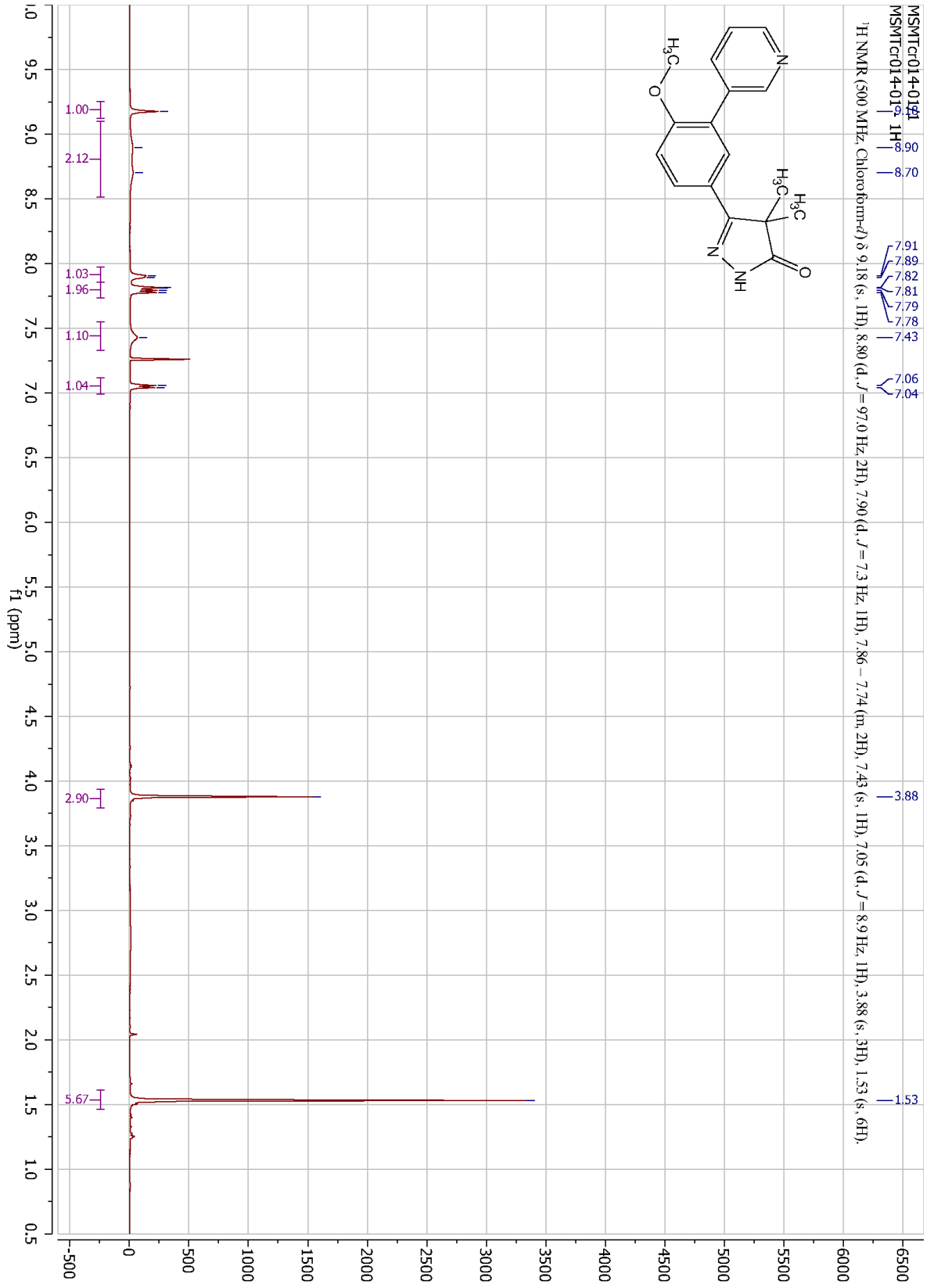

Figure S63 ^{1}H-NMR of compound **51**

^{13}C NMR compound 51

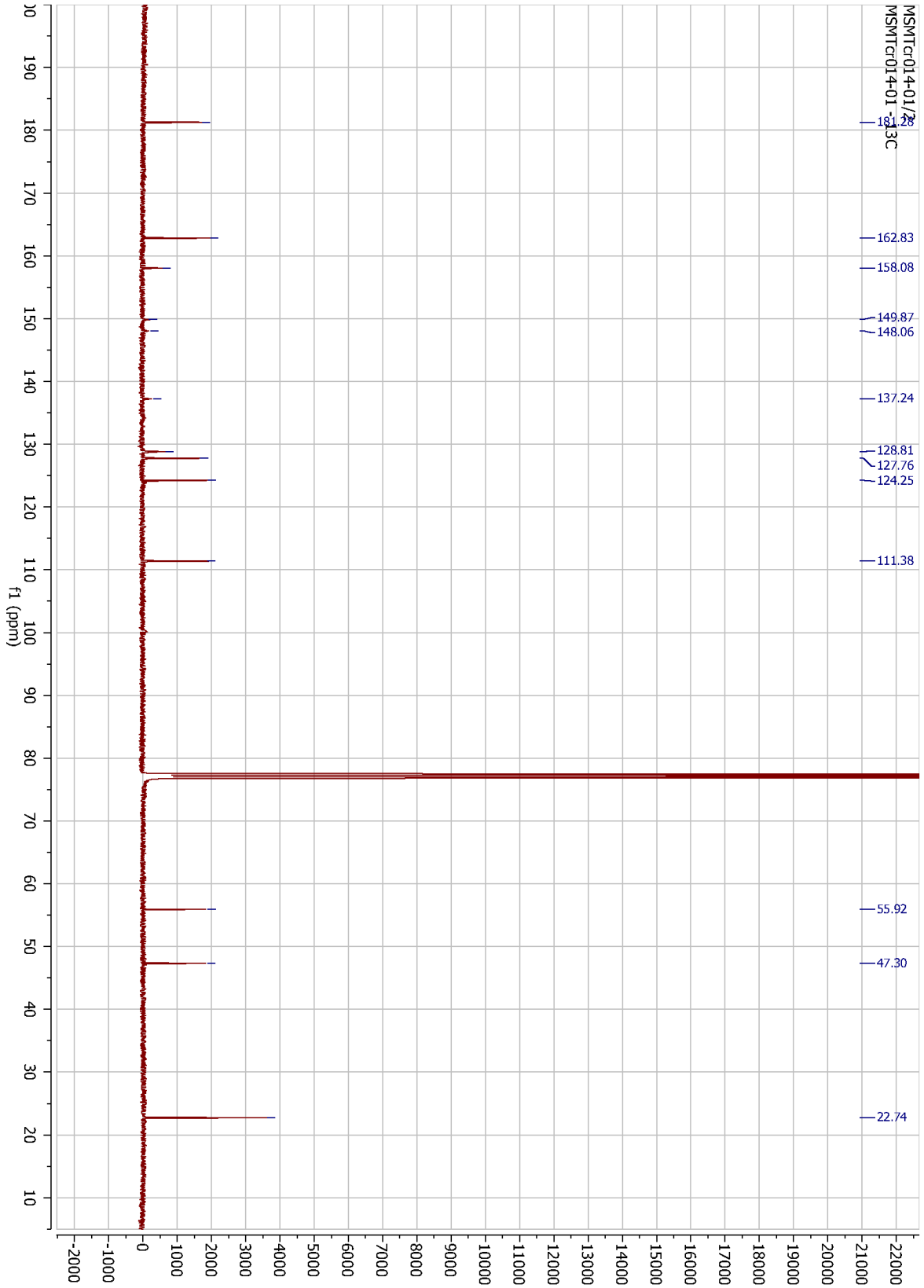

Figure S64 ^{13}C-NMR of compound **51**

^{1}H NMR compound 52

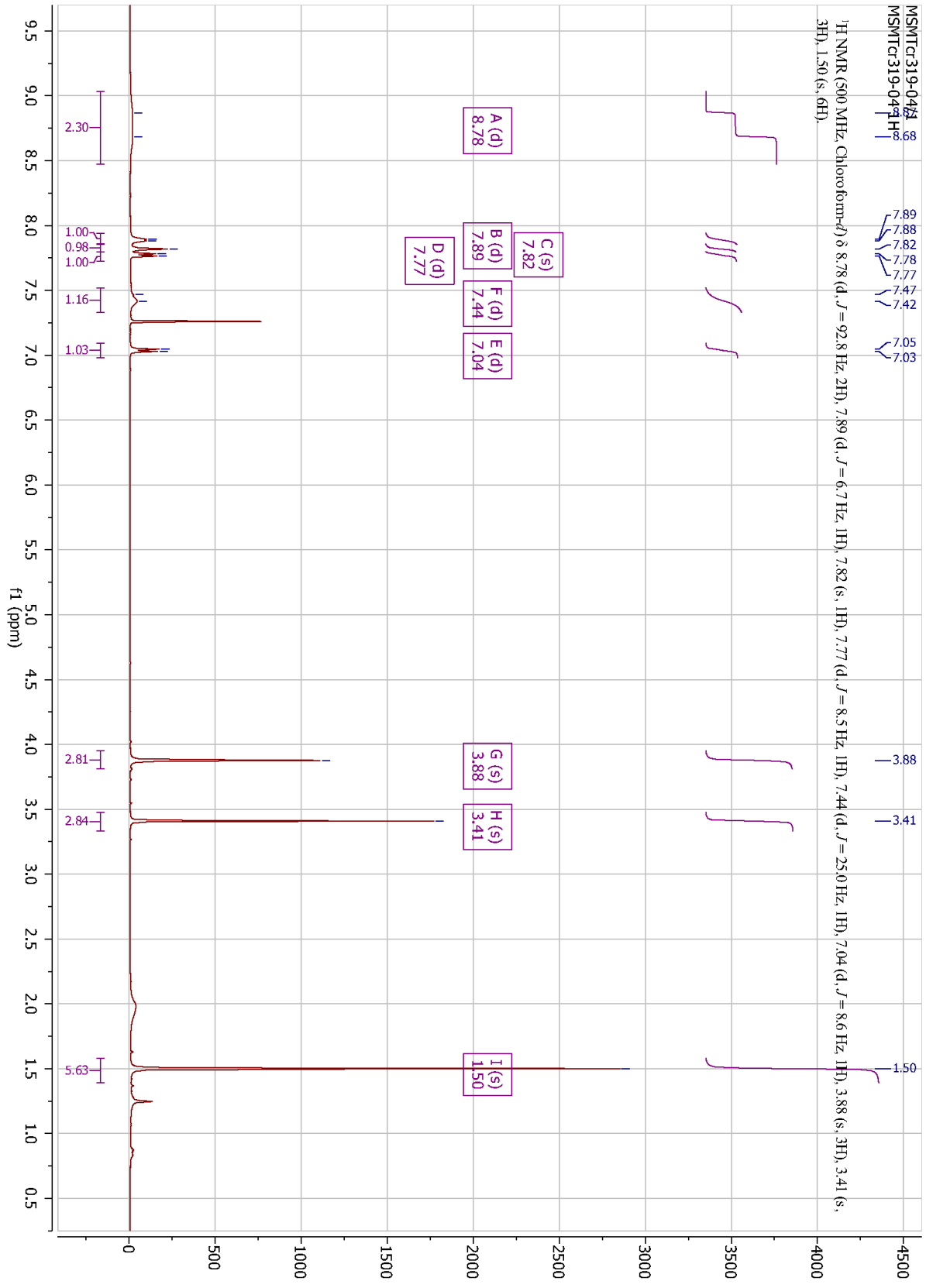

Figure S65 ^{1}H-NMR of compound **52**

^{13}C NMR compound 52

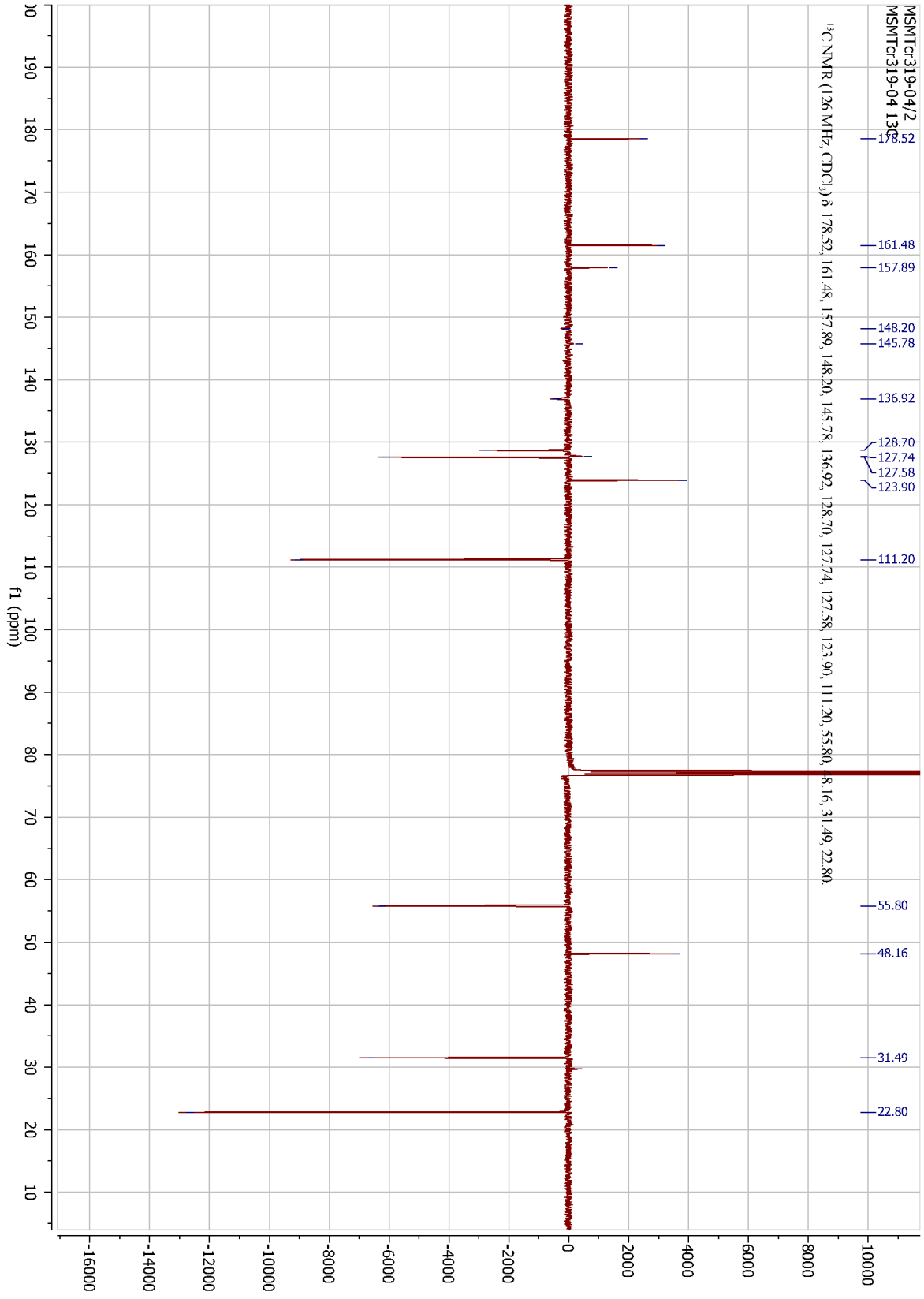

Figure S66 ^{13}C-NMR of compound **52**

^{1}H NMR compound 53

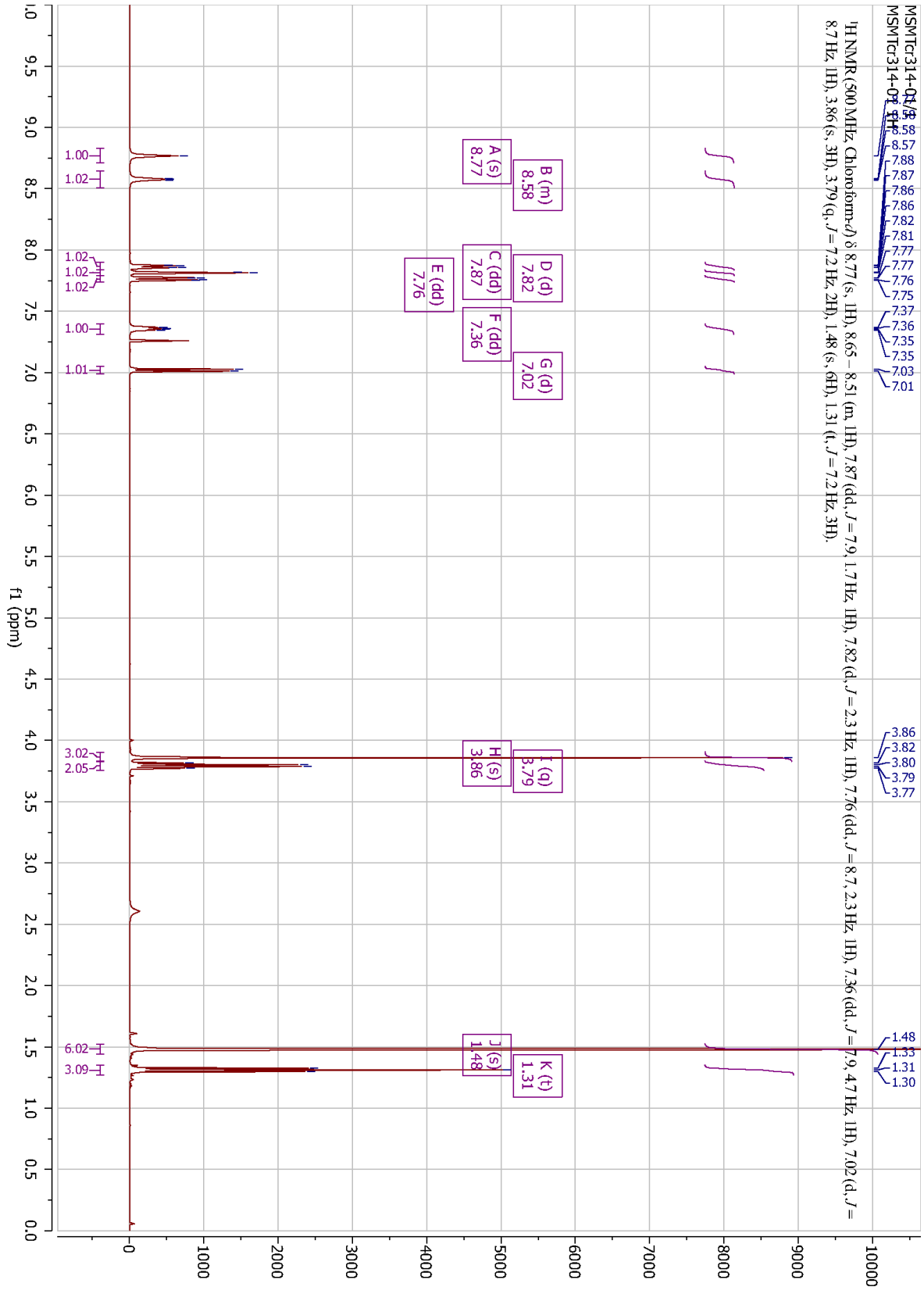

Figure S67 ^{1}H-NMR of compound **53**

^{13}C NMR compound 53

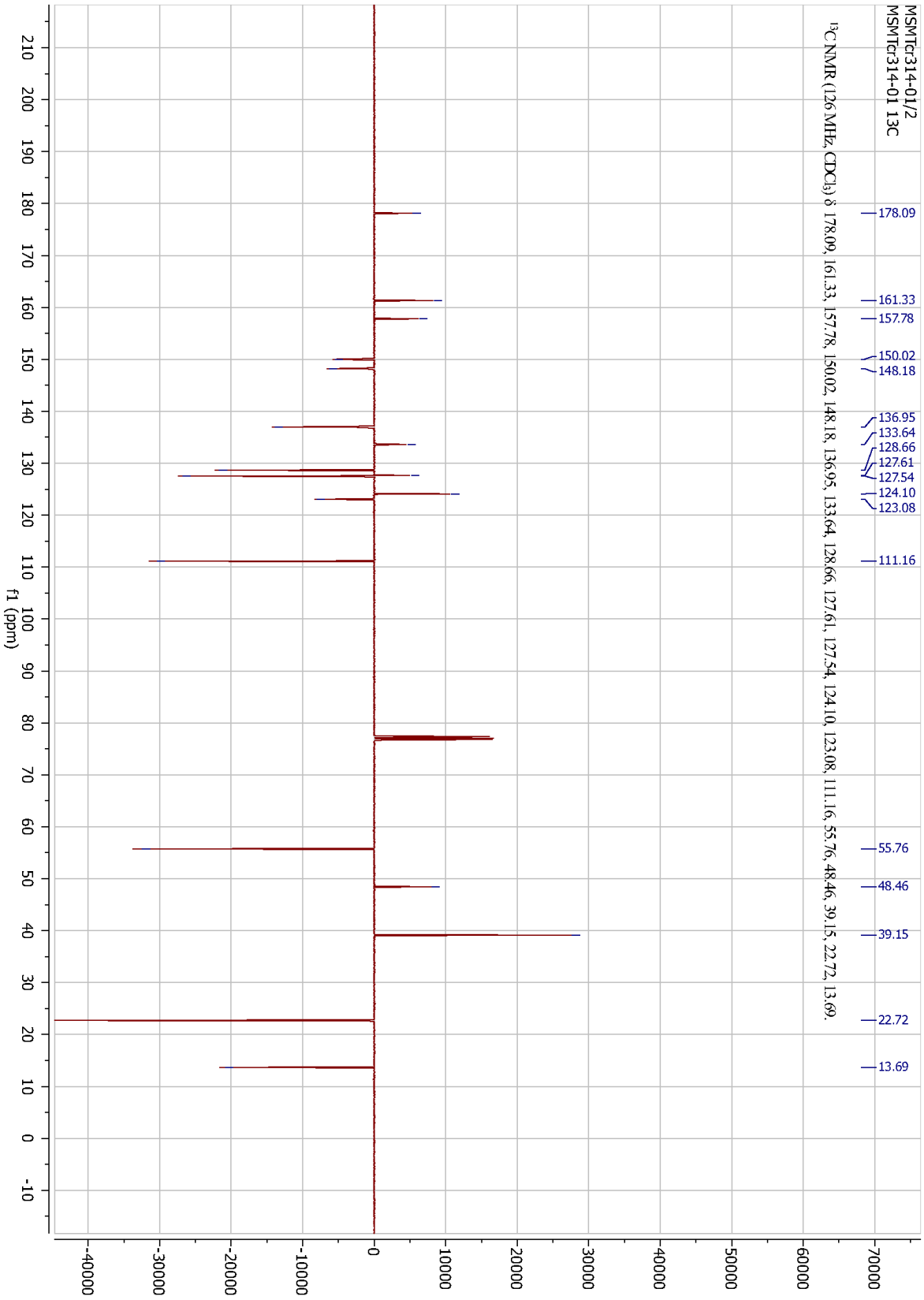

Figure S68 ^{13}C-NMR of compound **53**

^{1}H NMR compound 54

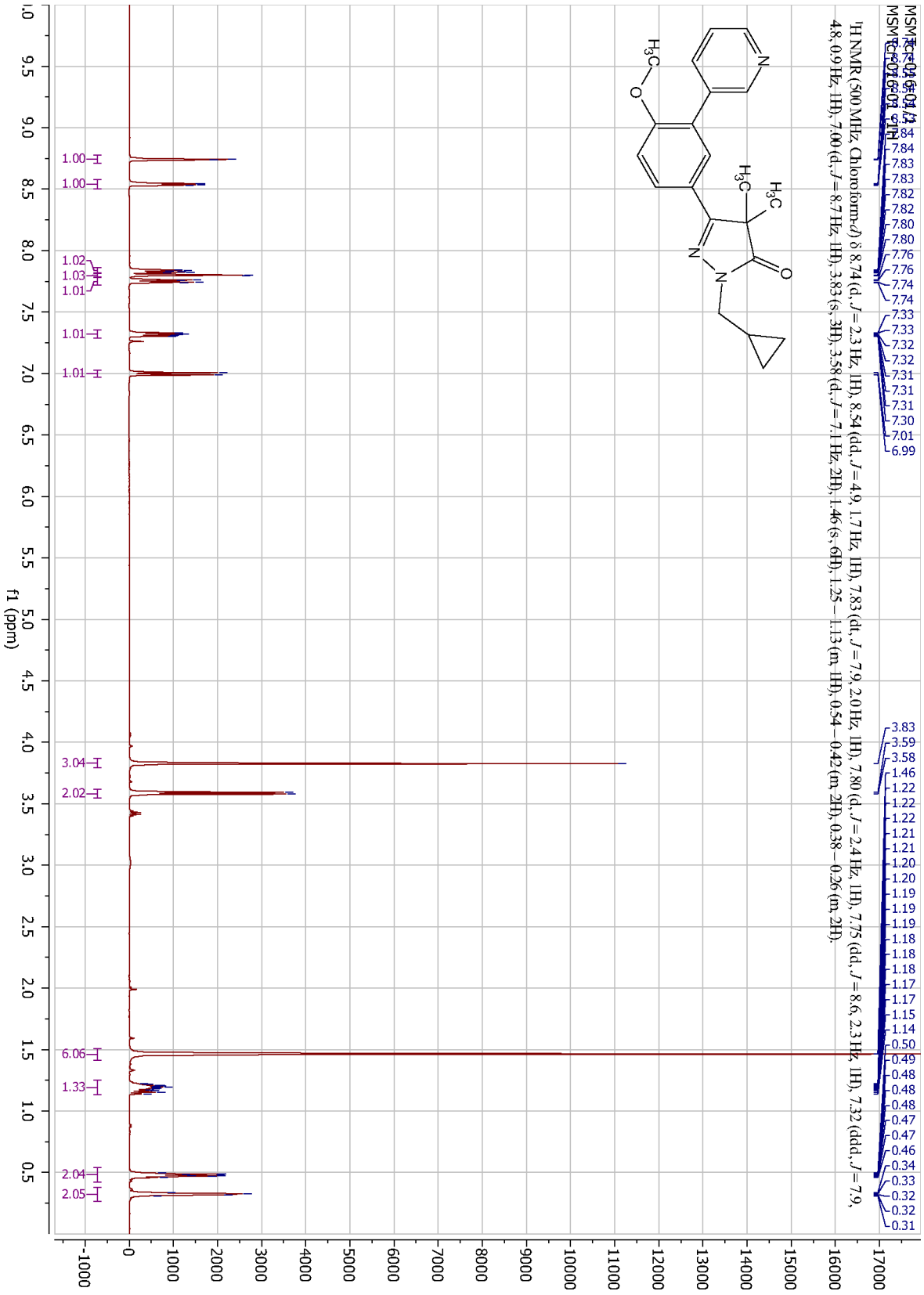

Figure S69 ^{1}H-NMR of compound **54**

^{13}C NMR compound 54

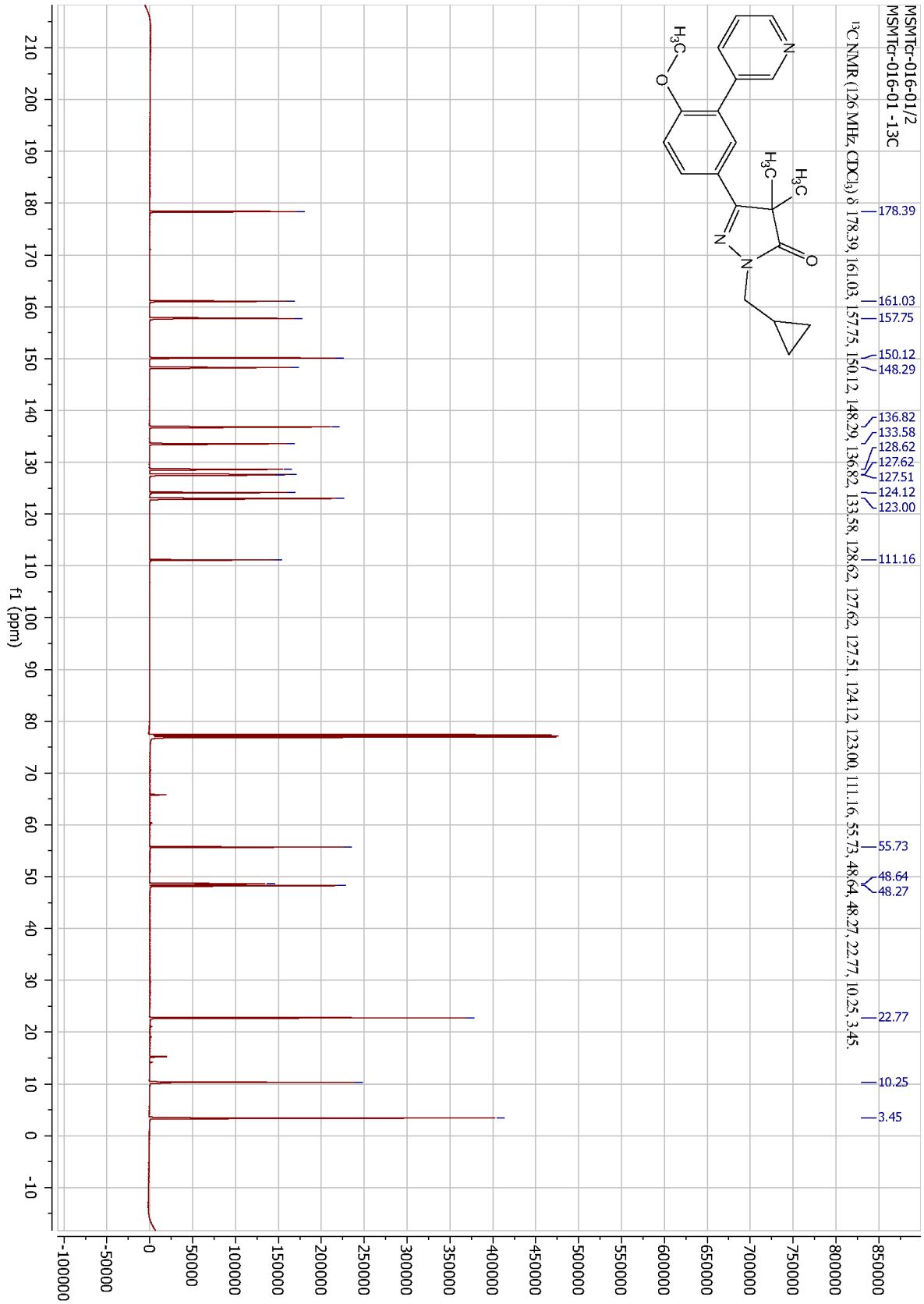

Figure S70 ^{13}C-NMR of compound **54**

^{1}H NMR compound 55

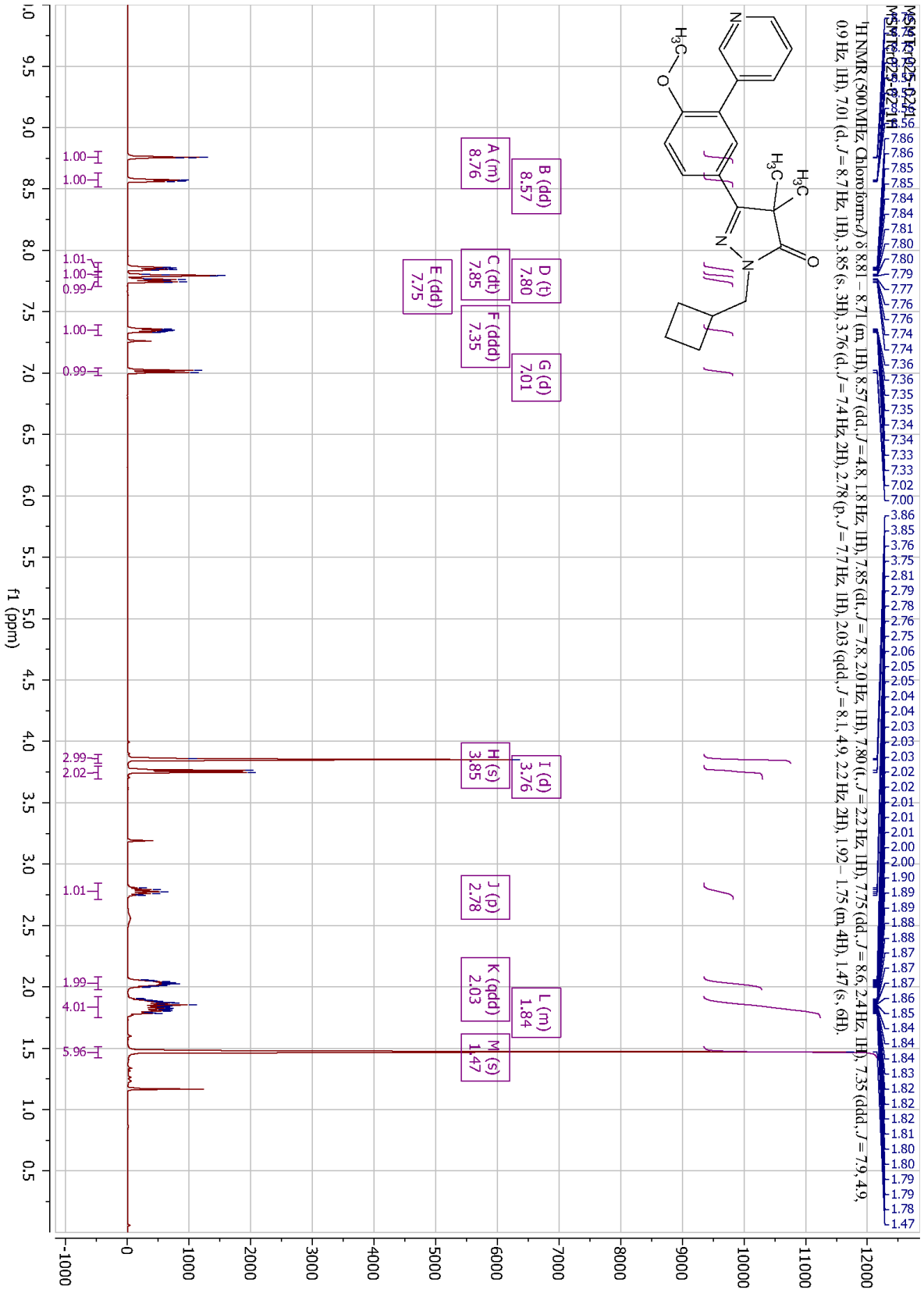

Figure S71 ^{1}H-NMR of compound **55**

^{13}C NMR compound 55

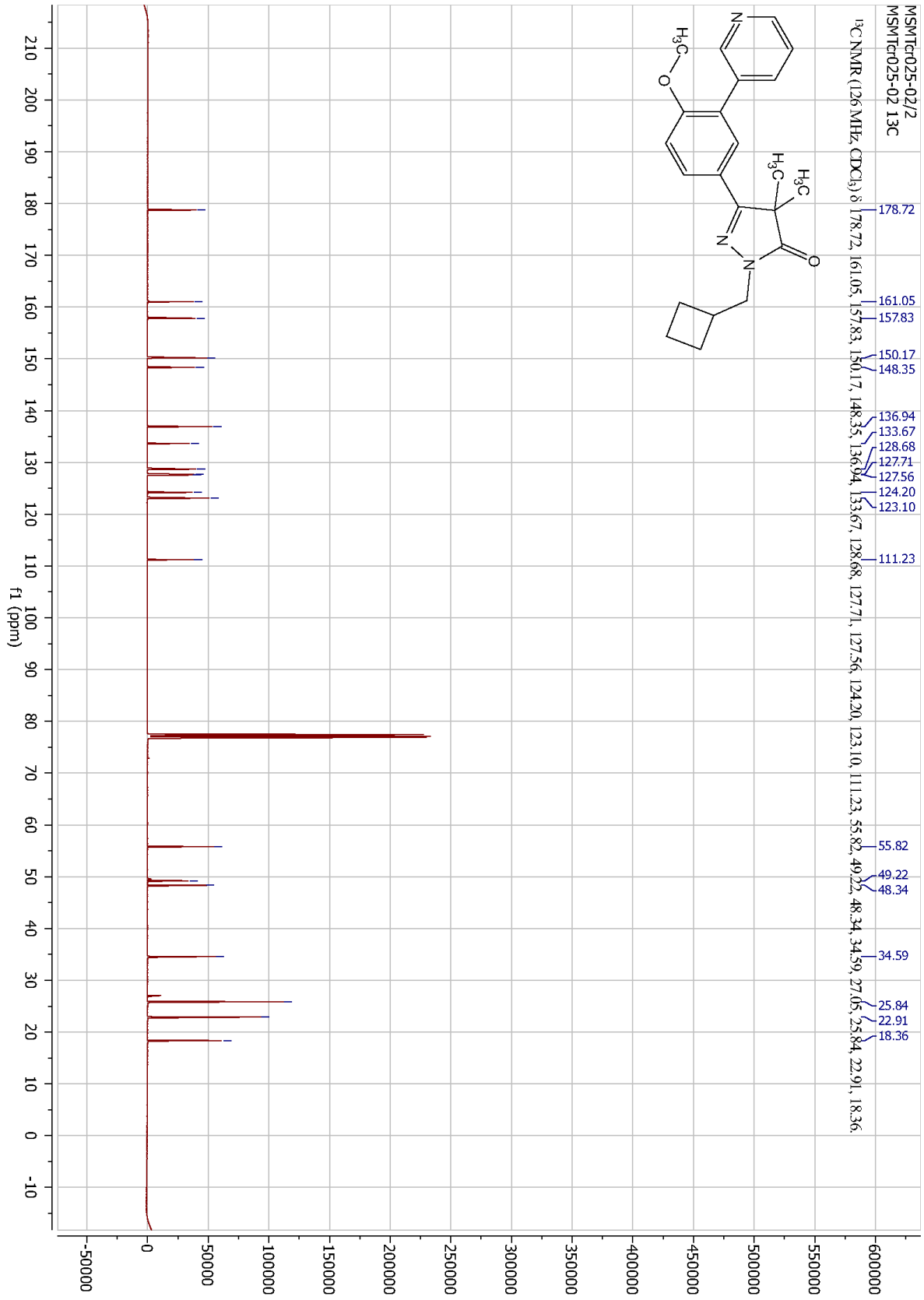

Figure S72 ^{13}C-NMR of compound **55**

[1]H NMR compound 56

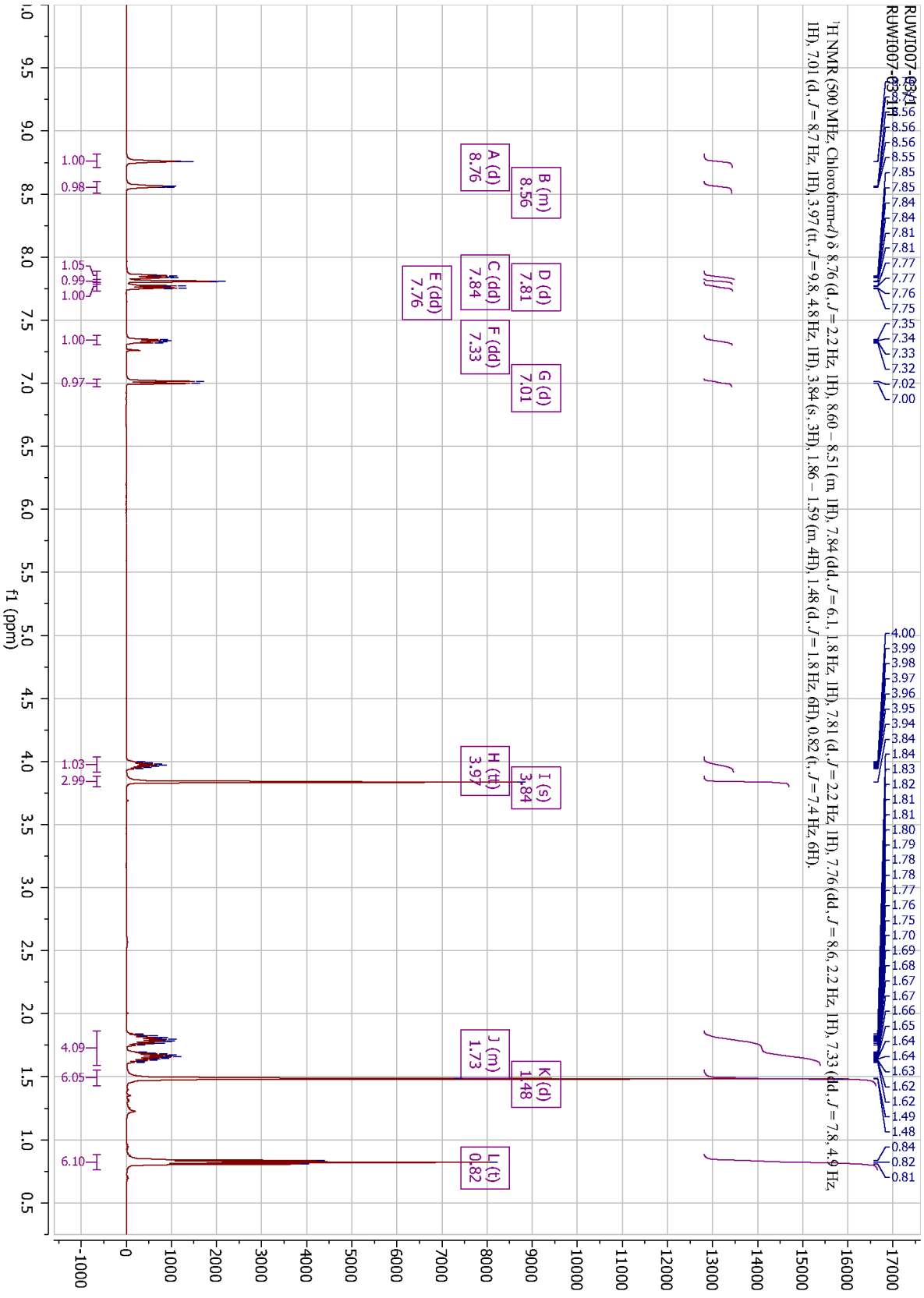

Figure S73 [1]H-NMR of compound **56**

^{13}C NMR compound 56

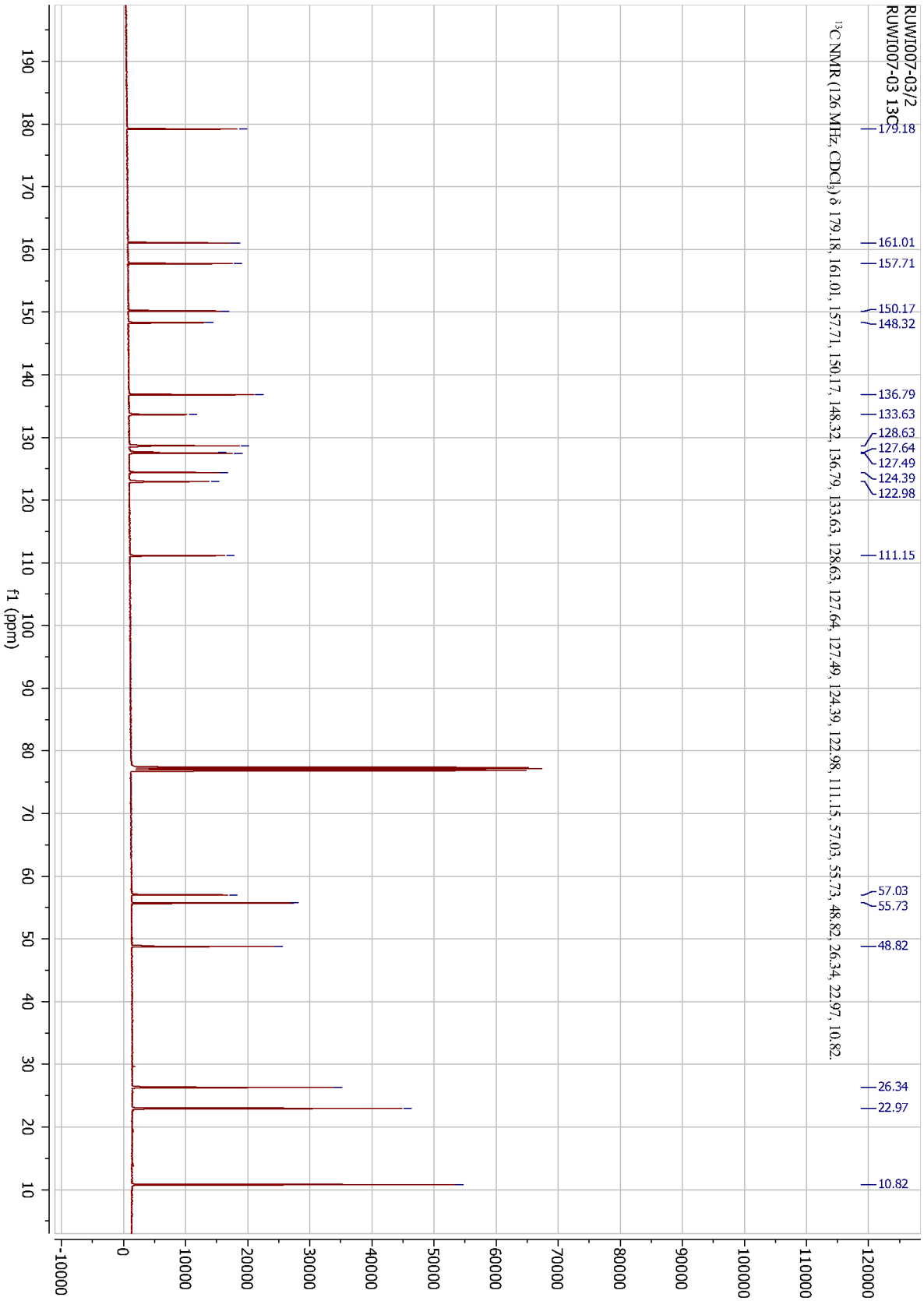

Figure S74 ^{13}C-NMR of compound **56**

^{1}H NMR compound 57

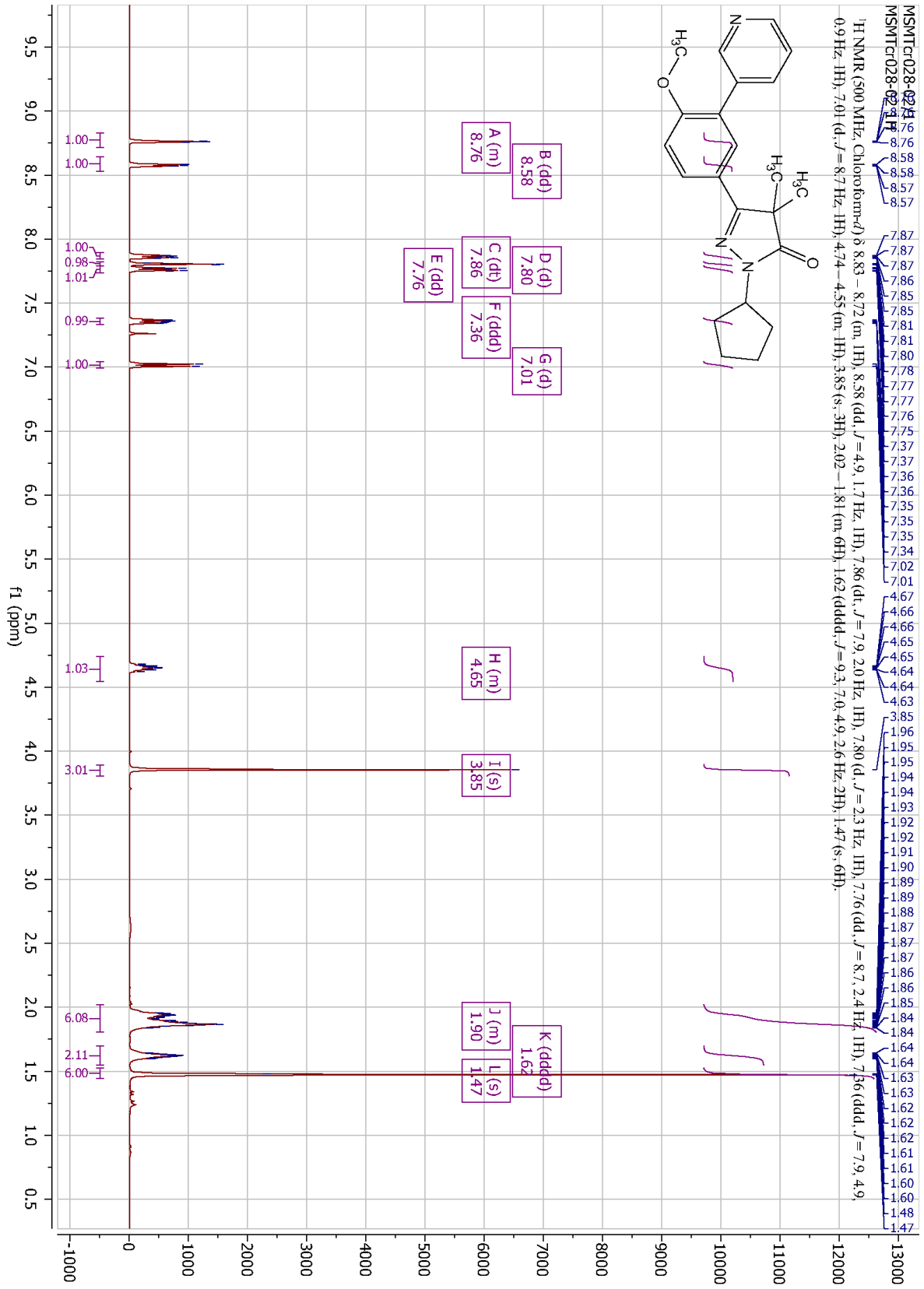

Figure S75 ^{1}H-NMR of compound **57**

^{13}C NMR compound 57

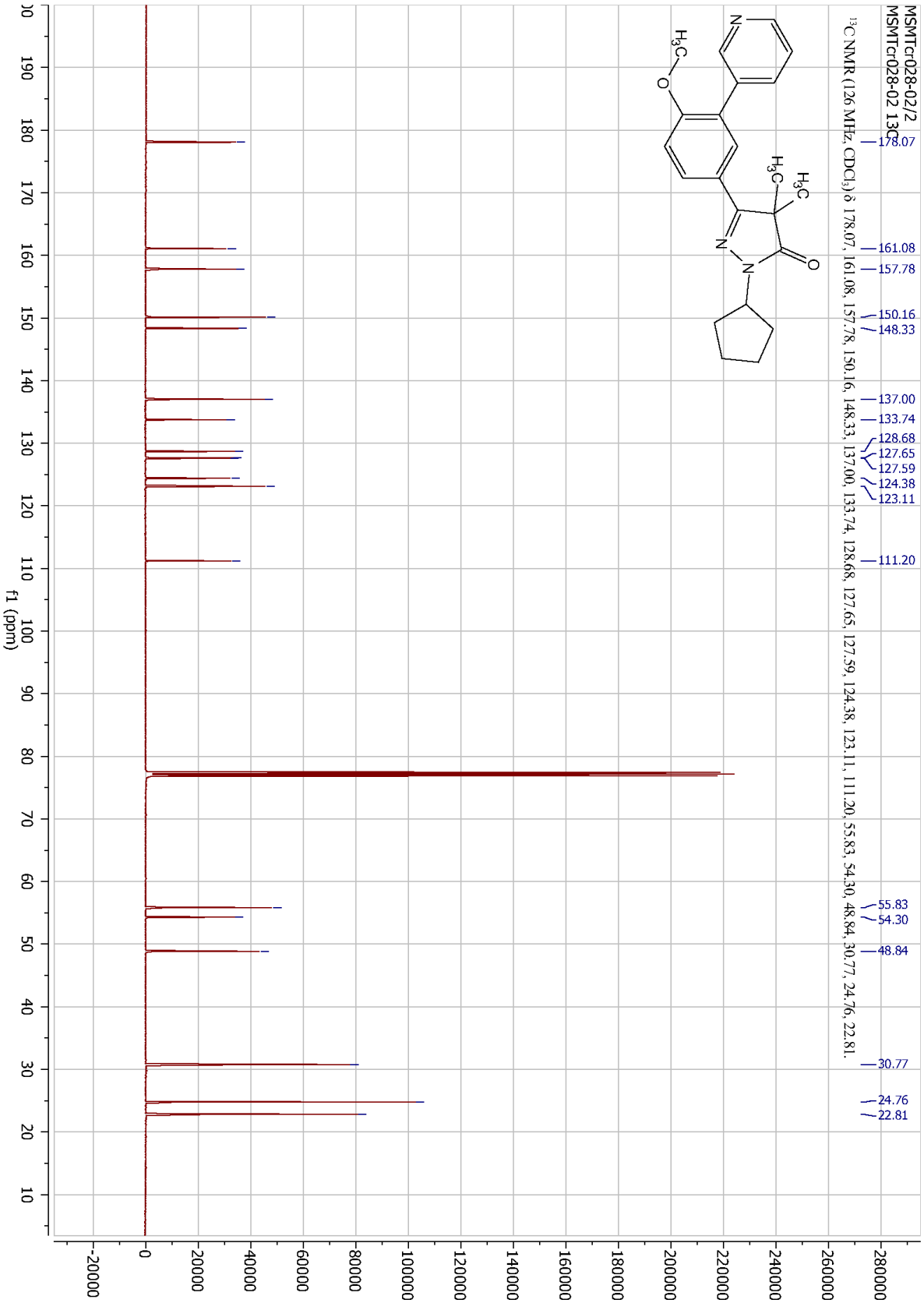

Figure S76 ^{13}C-NMR of compound **57**

^{1}H NMR compound 58

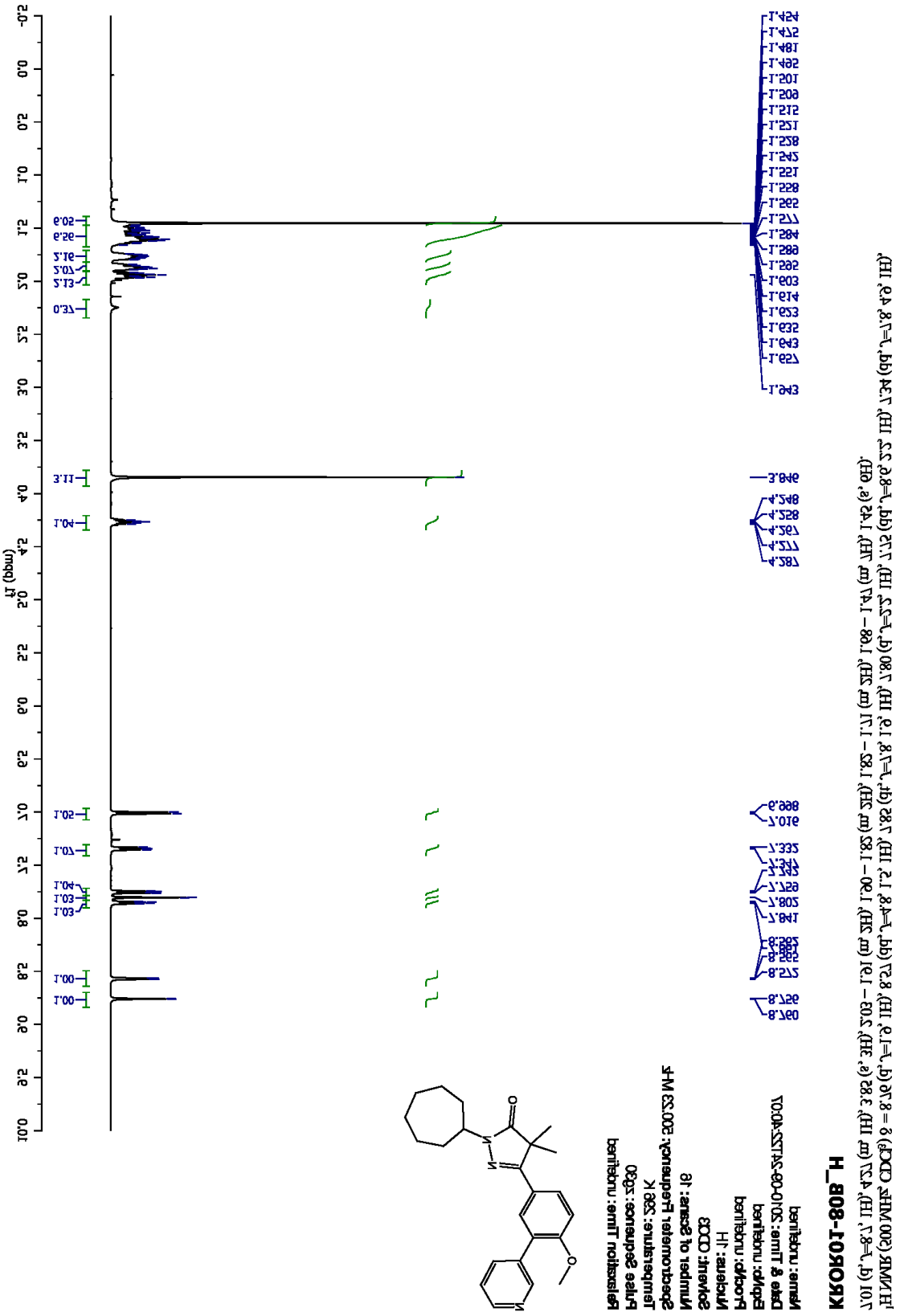

Figure S77 ^{1}H-NMR of compound **58**

^{13}C NMR compound 58

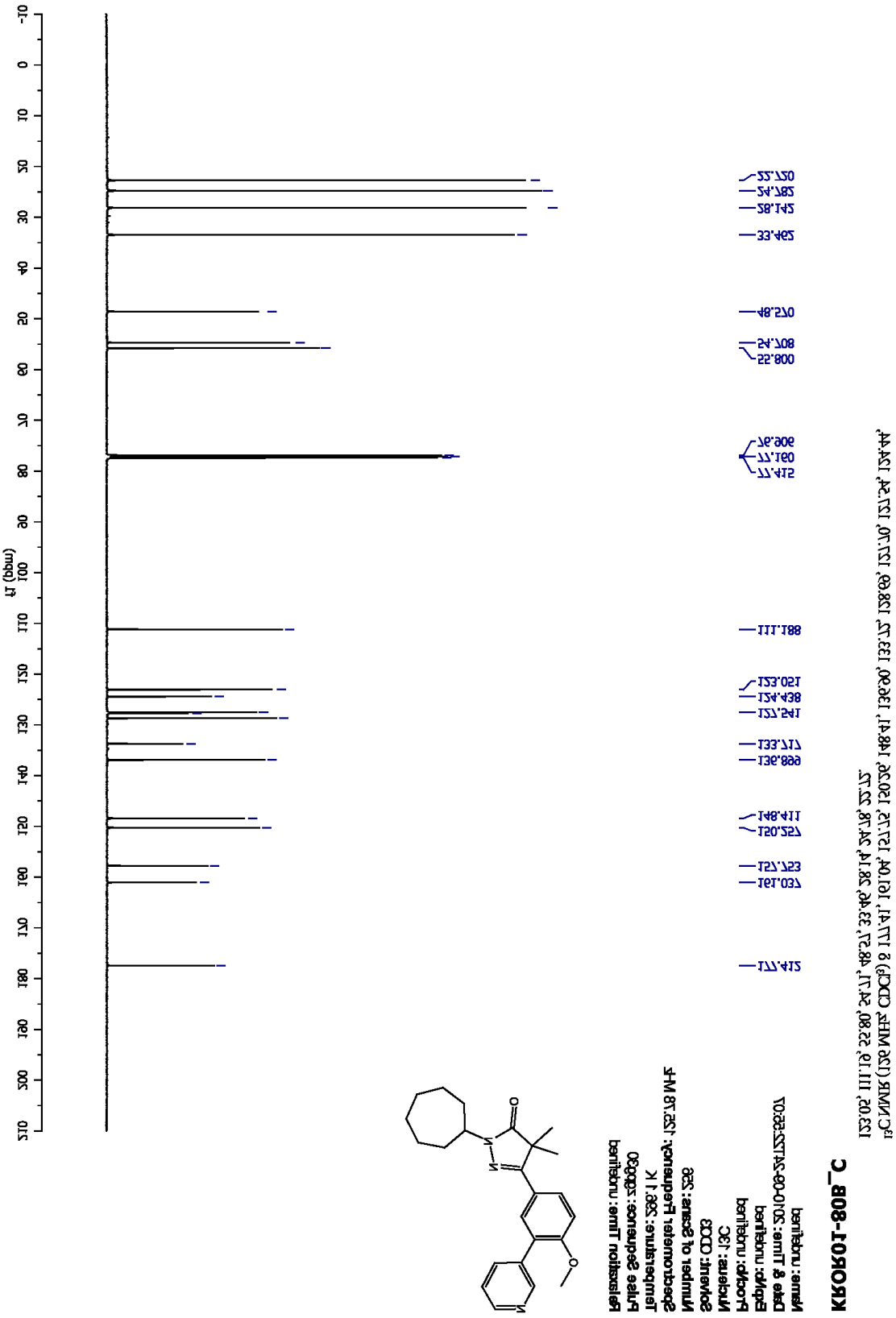

Figure S78 ^{13}C-NMR of compound **58**

^{1}H NMR compound 59

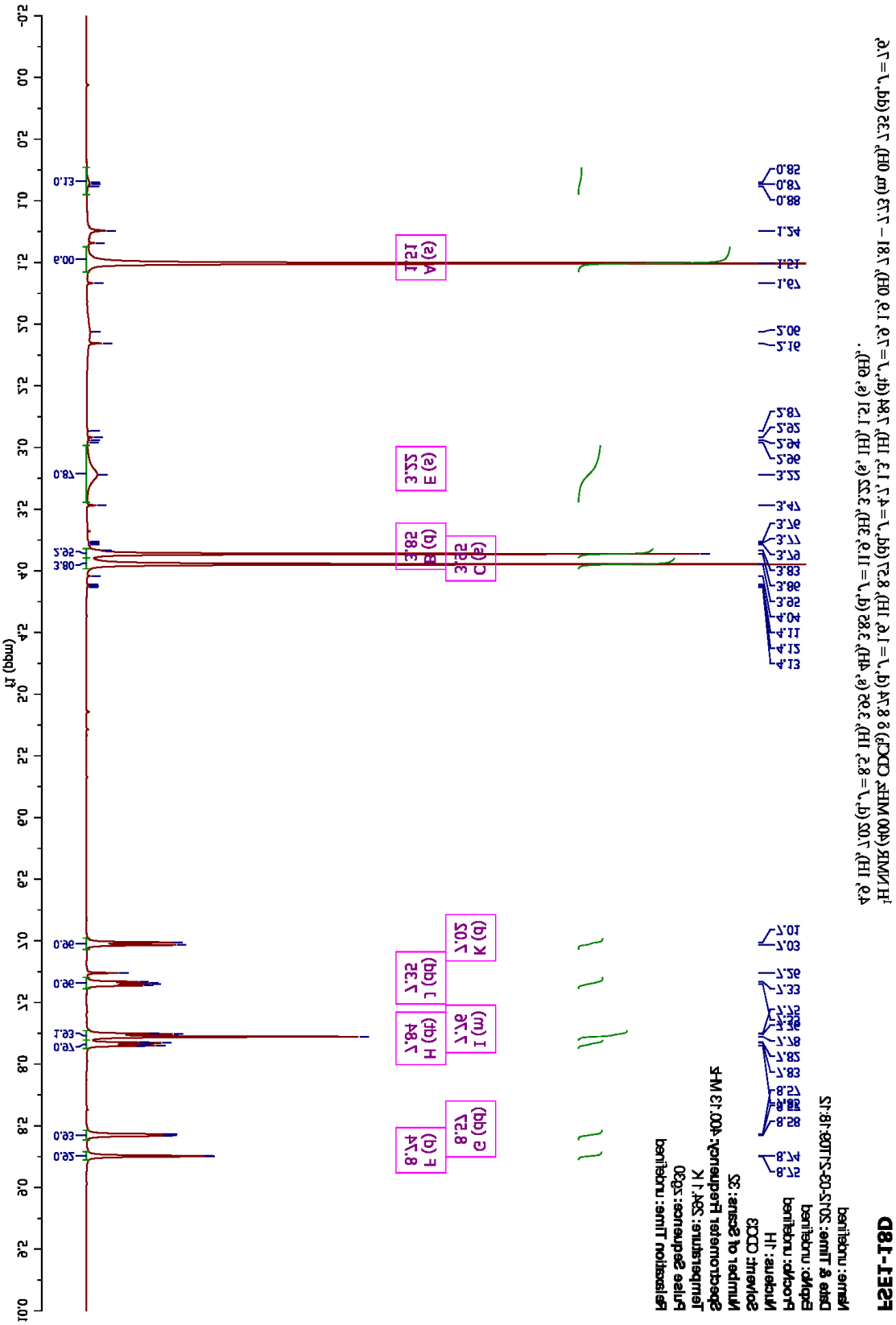

Figure S79 ^{1}H-NMR of compound **59**

^{13}C NMR compound 59

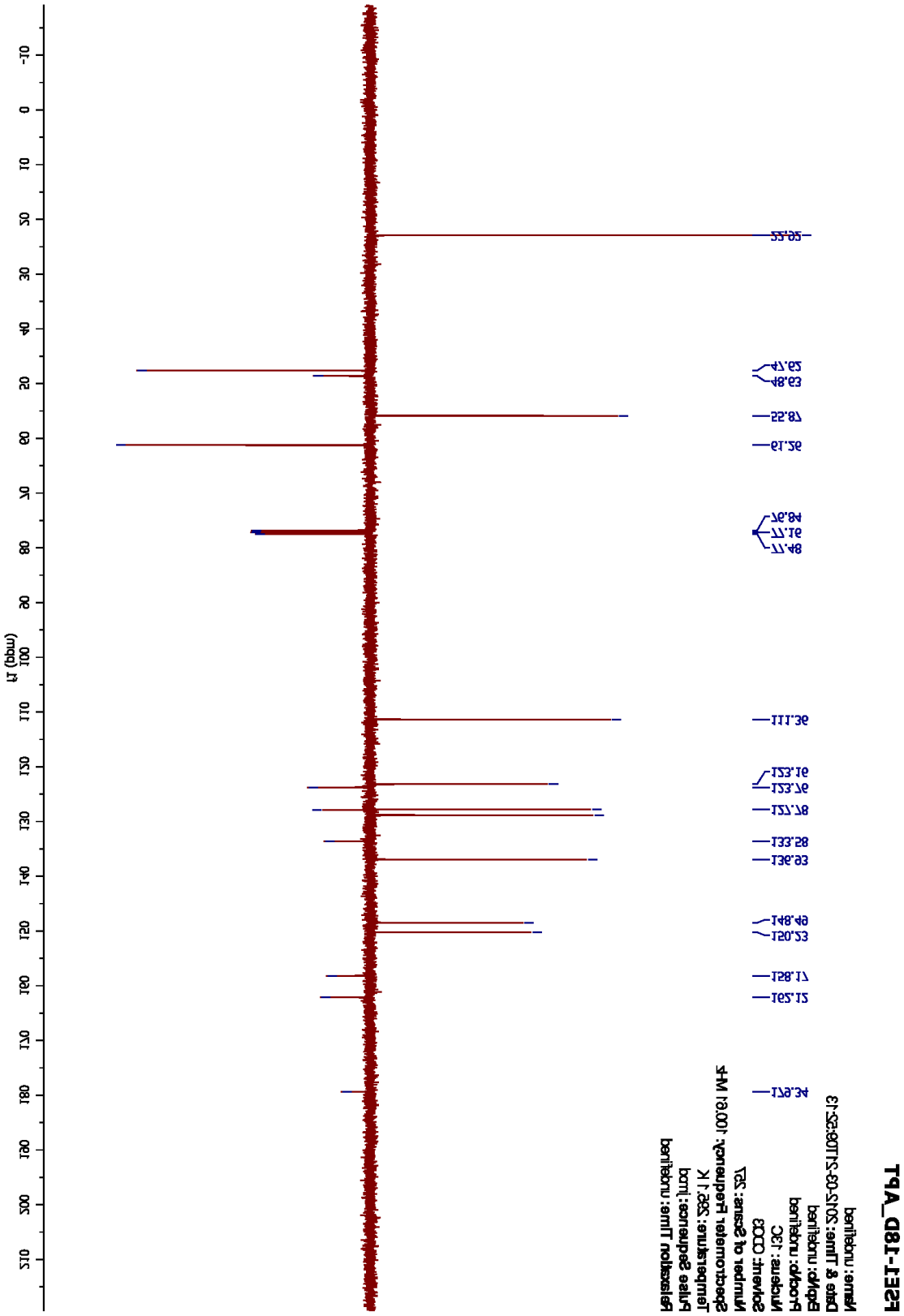

Figure S80 ^{13}C-NMR of compound **59**

^{1}H NMR compound 60

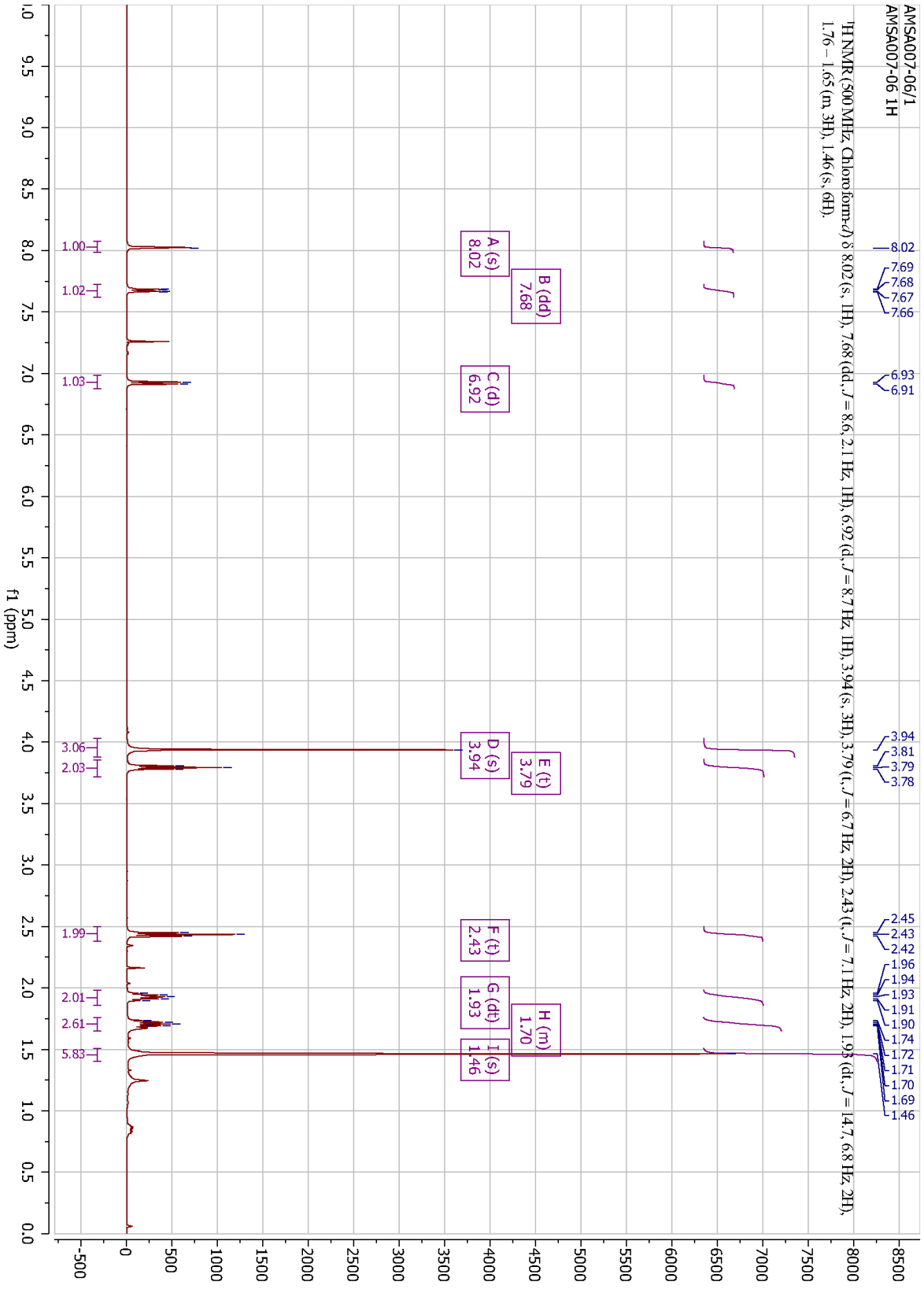

Figure S81 ^{1}H-NMR of compound **60**

^{13}C NMR compound 60

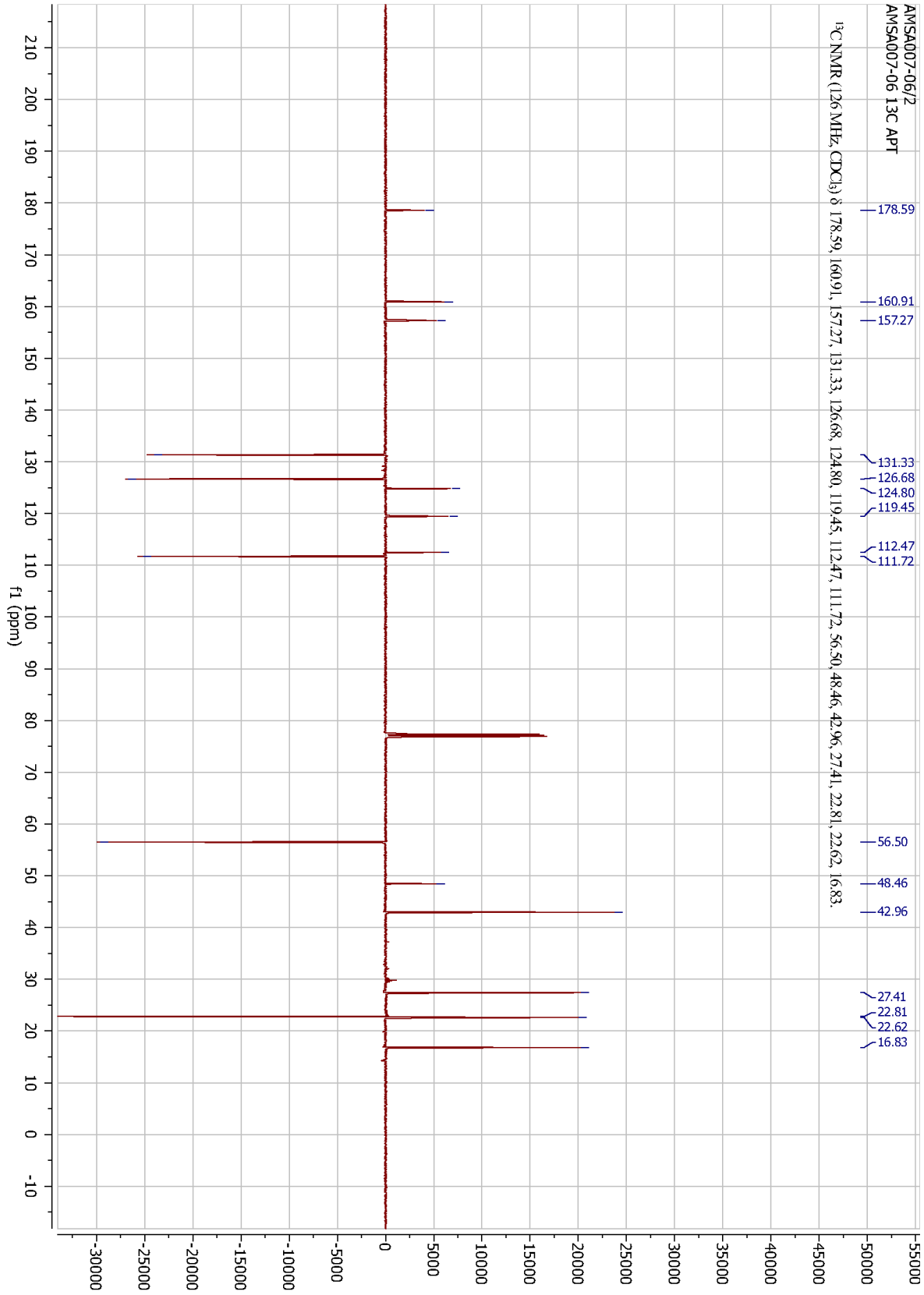

Figure S82 ^{13}C-NMR of compound **60**

^{1}H NMR compound 61

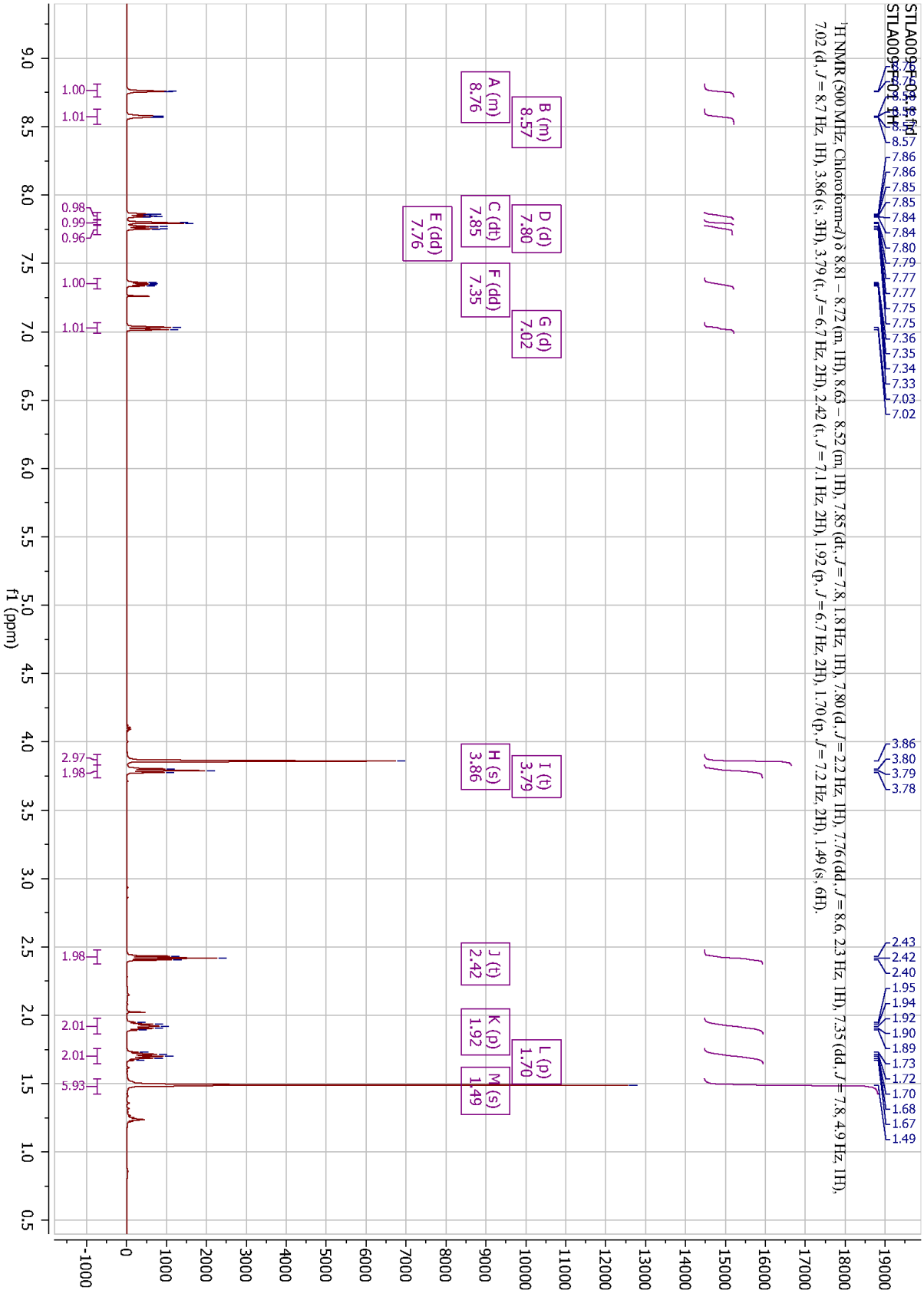

Figure S83 ^{1}H-NMR of compound **61**

^{13}C NMR compound 61

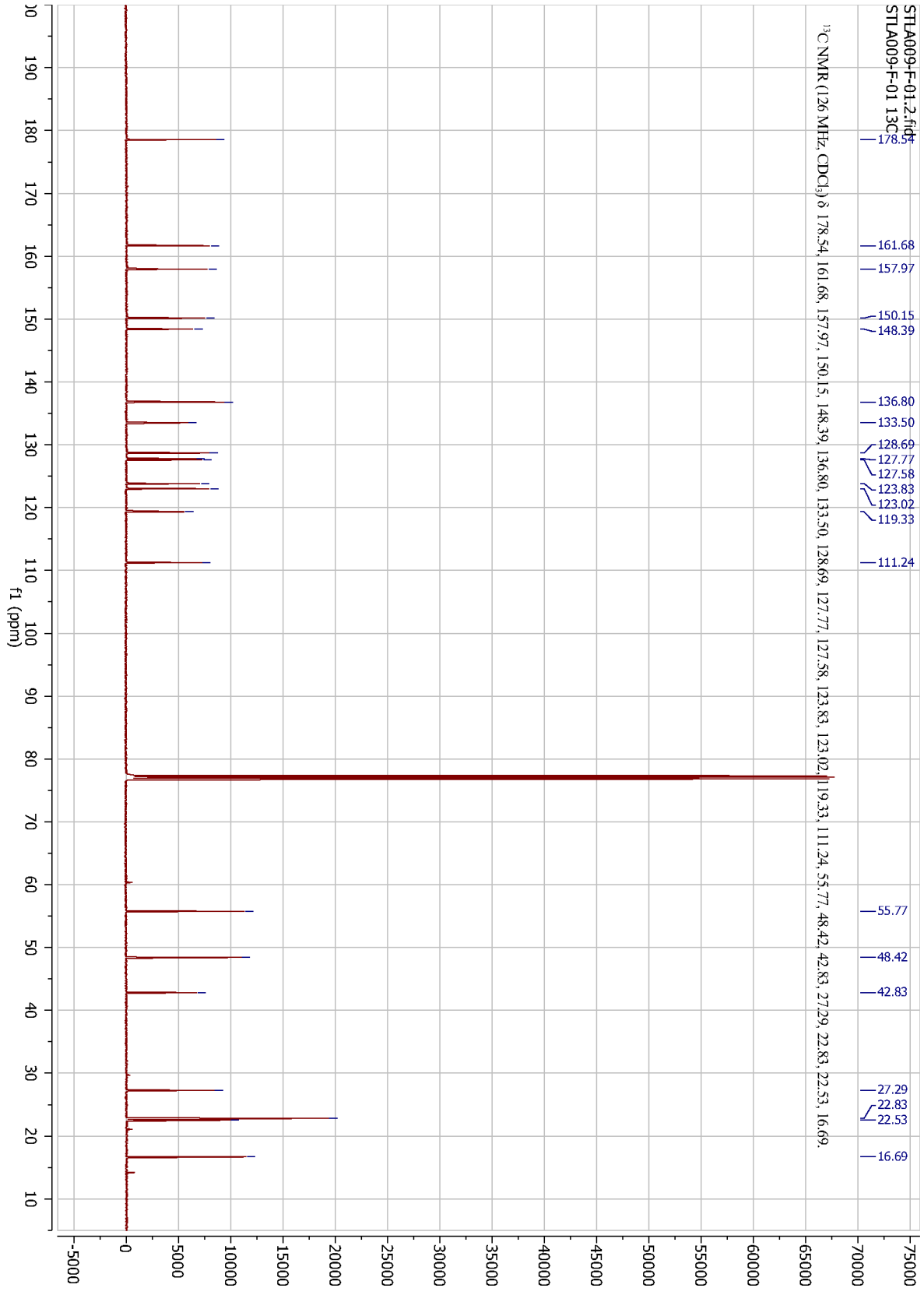

Figure S84 ^{13}C-NMR of compound **61**

^{1}H NMR compound 62

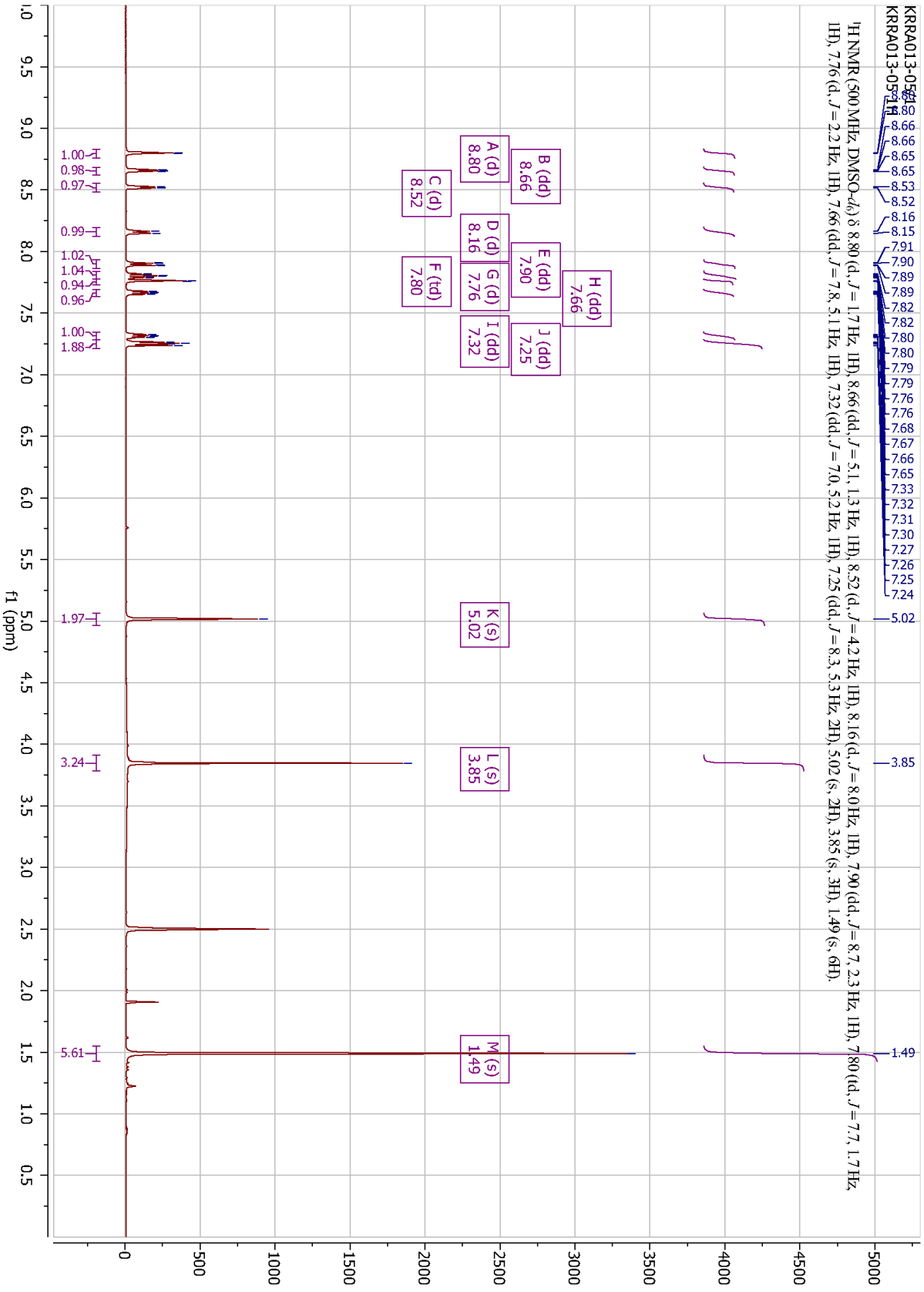

Figure S85 ^{1}H-NMR of compound **62**

^{13}C NMR compound 62

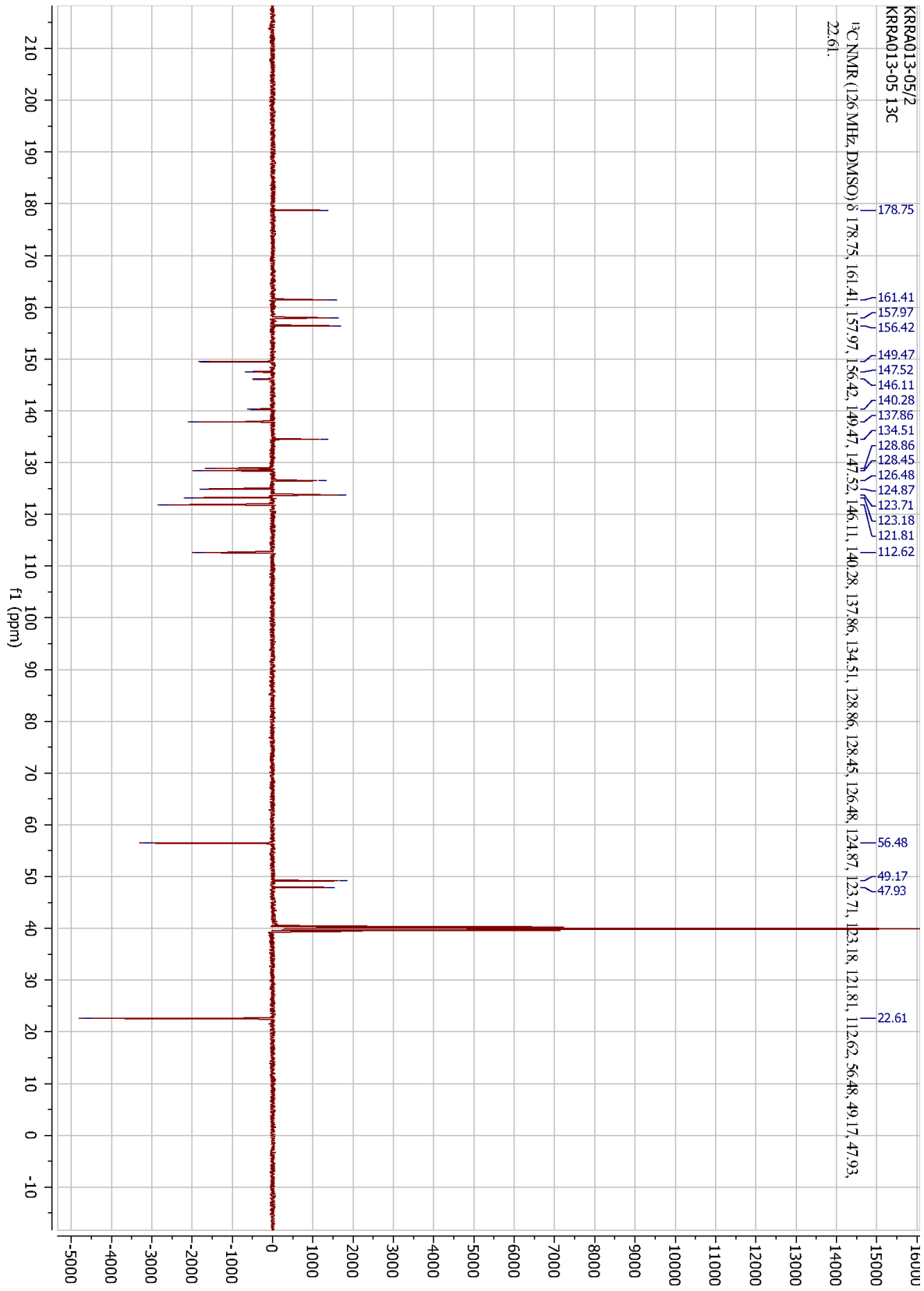

Figure S86 ^{13}C-NMR of compound **62**

^{1}H NMR compound 63

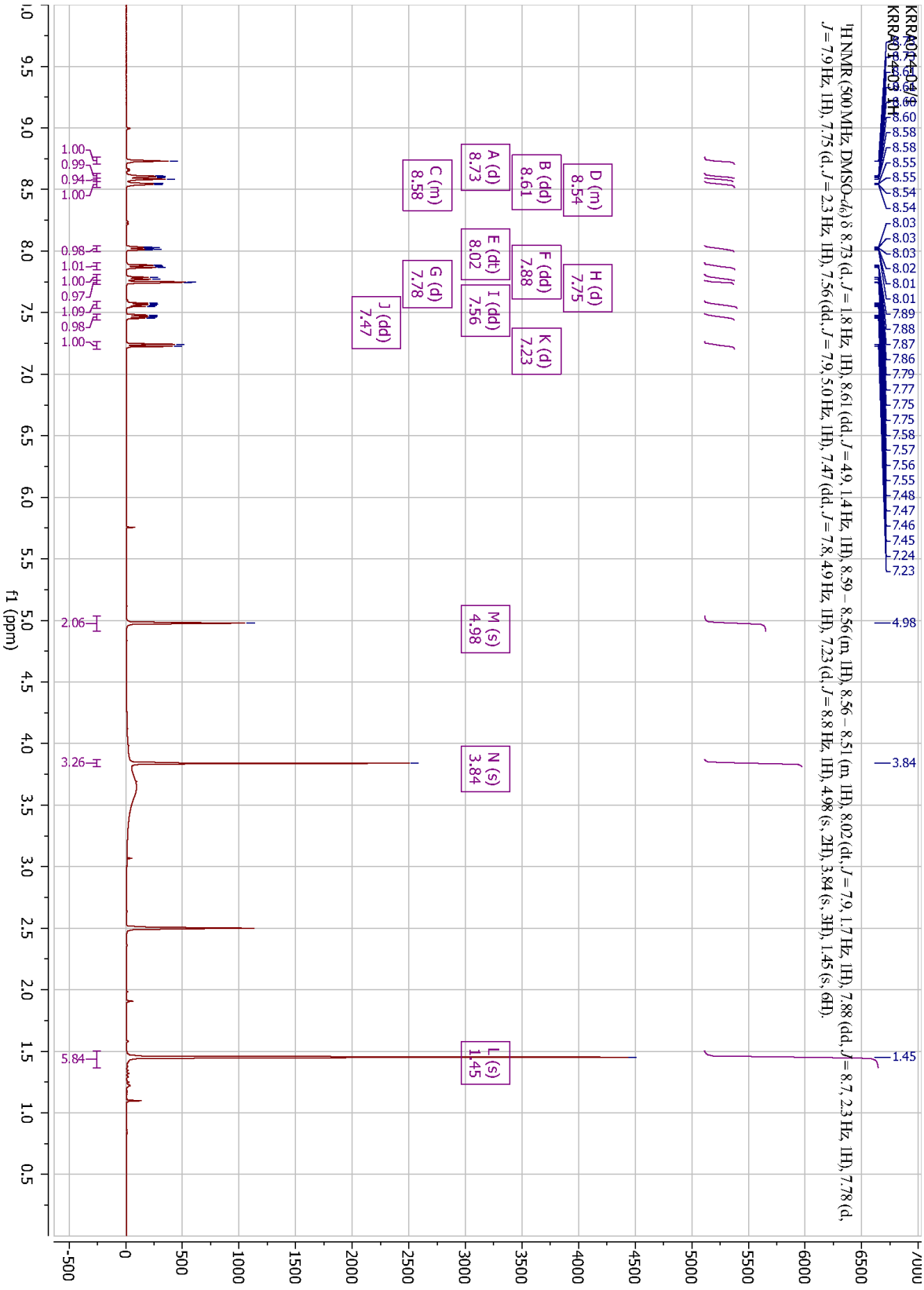

Figure S87 ^{1}H-NMR of compound **63**

^{13}C NMR compound 63

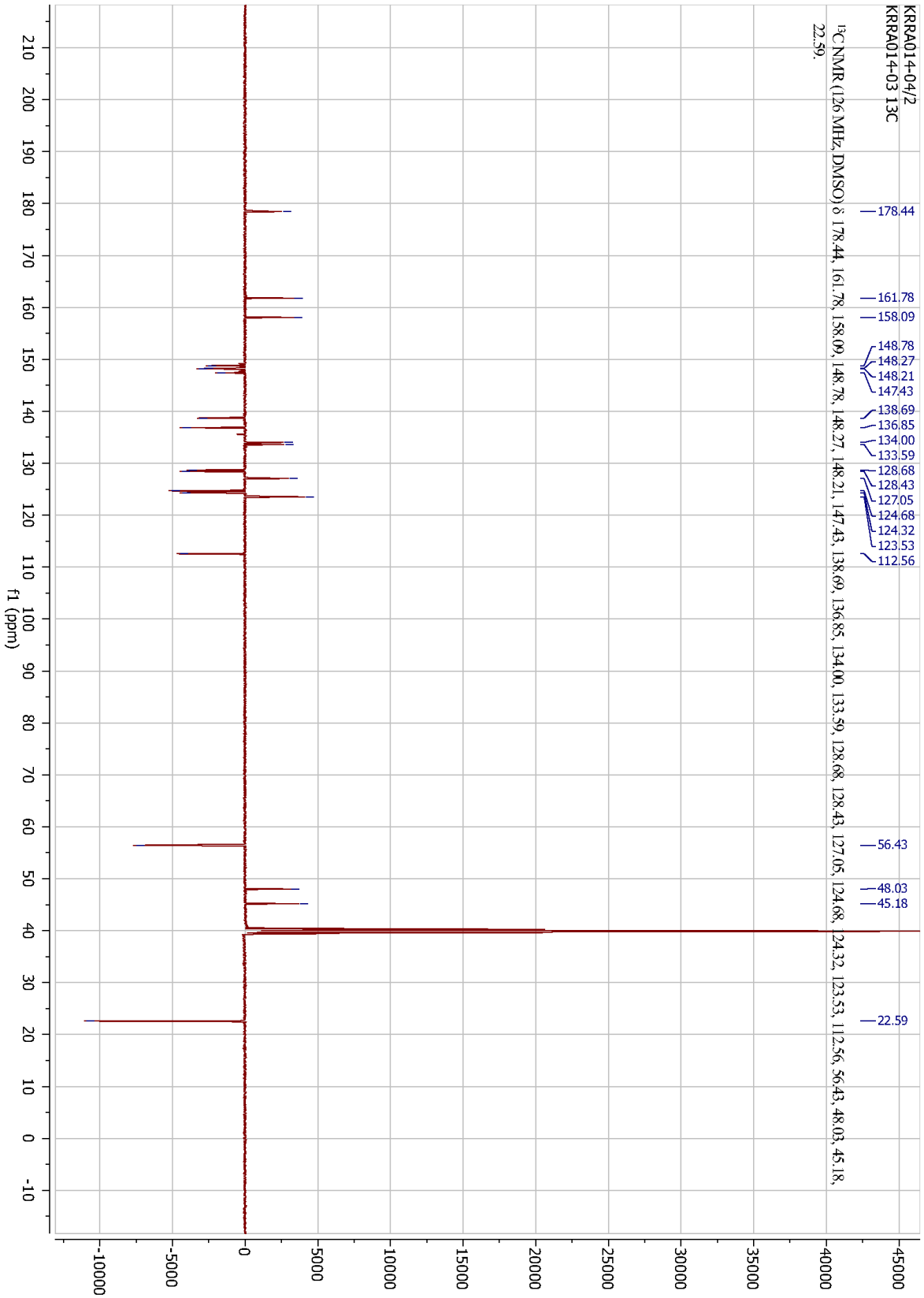

Figure S88 ^{13}C-NMR of compound **63**

^{1}H NMR compound 64

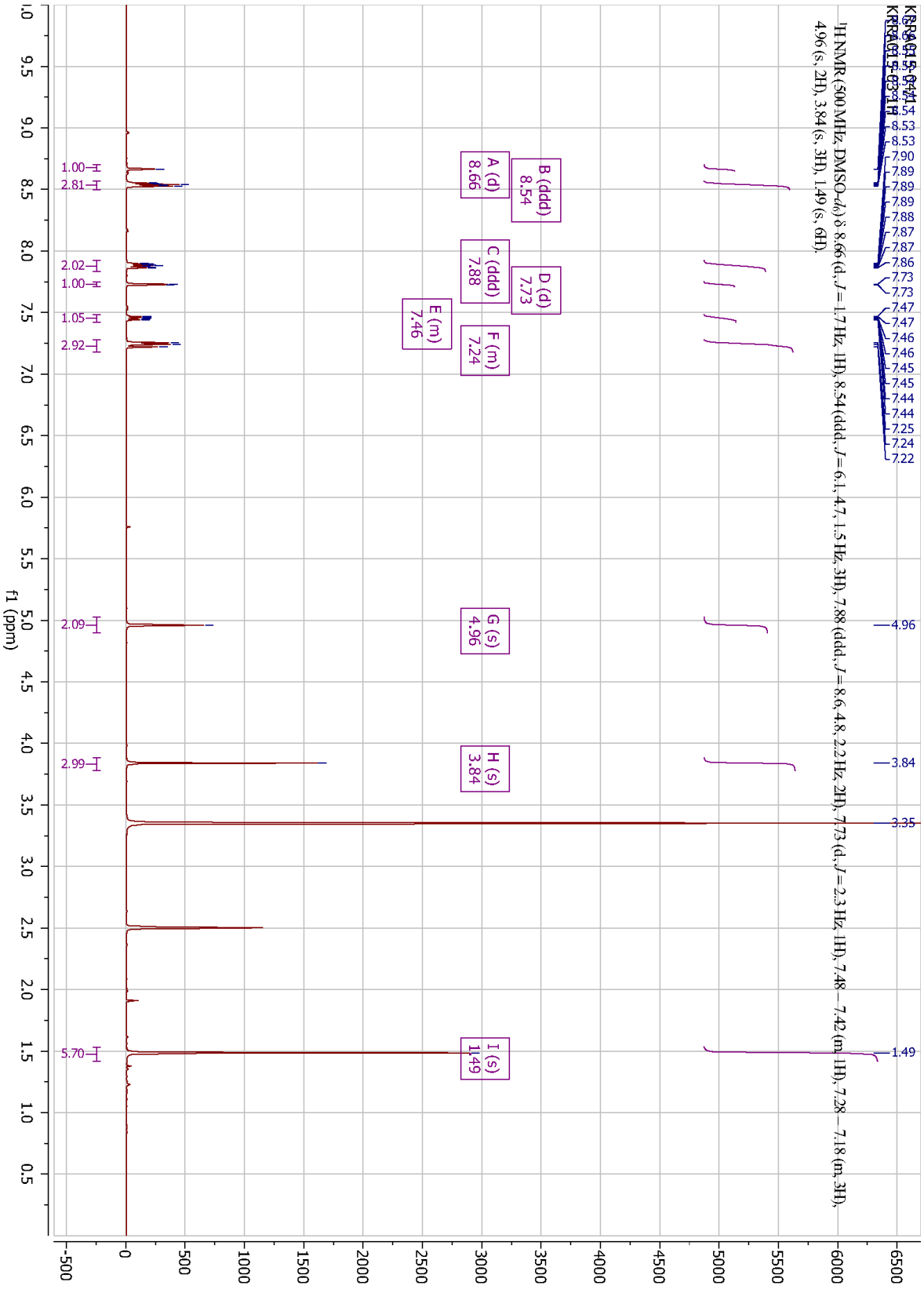

Figure S89 ^{1}H-NMR of compound **64**

^{13}C NMR compound 64

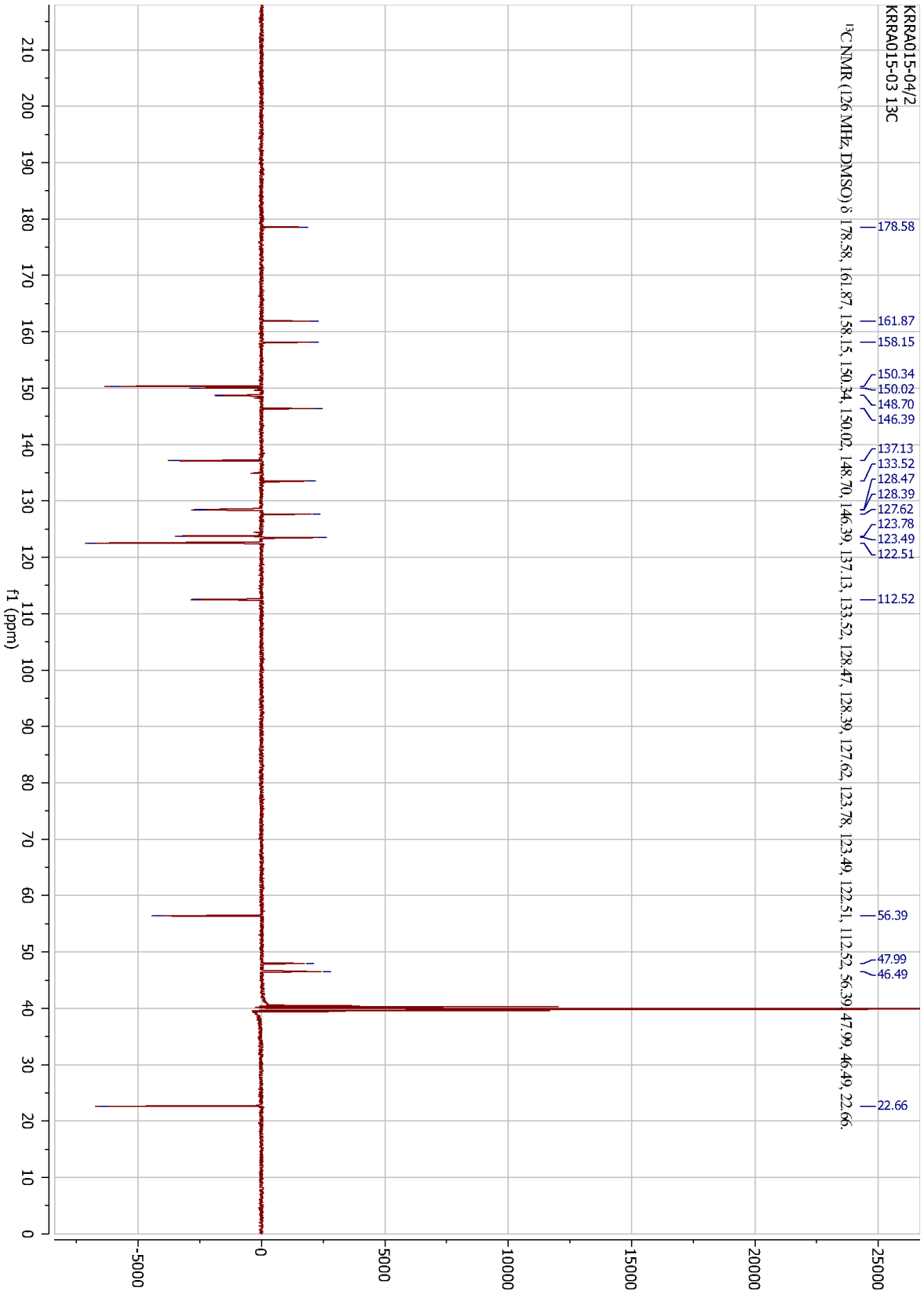

Figure S90 ^{13}C-NMR of compound **64**

^{1}H NMR compound 75

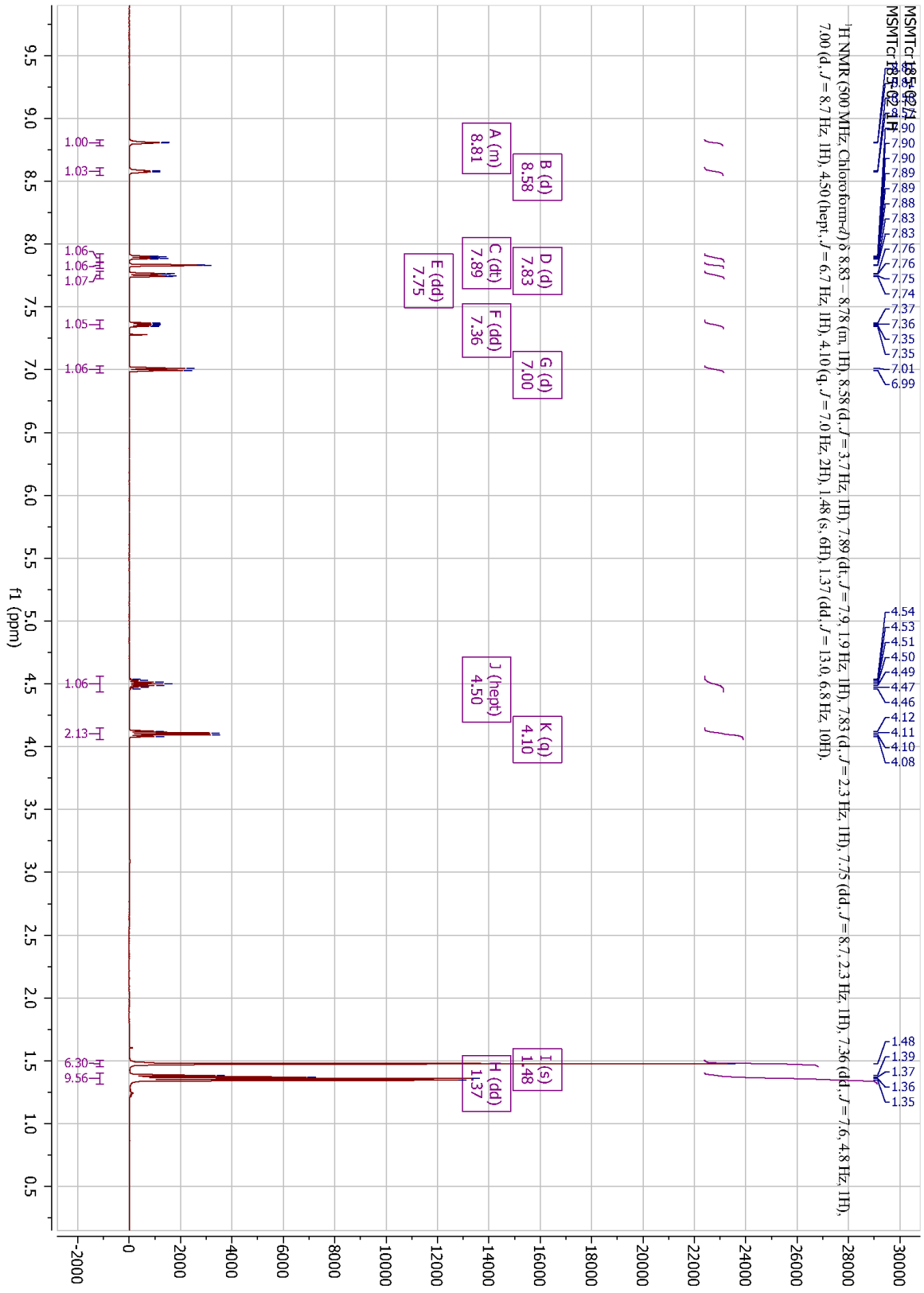

Figure S91 ^{1}H-NMR of compound **75**

^{13}C NMR compound 75

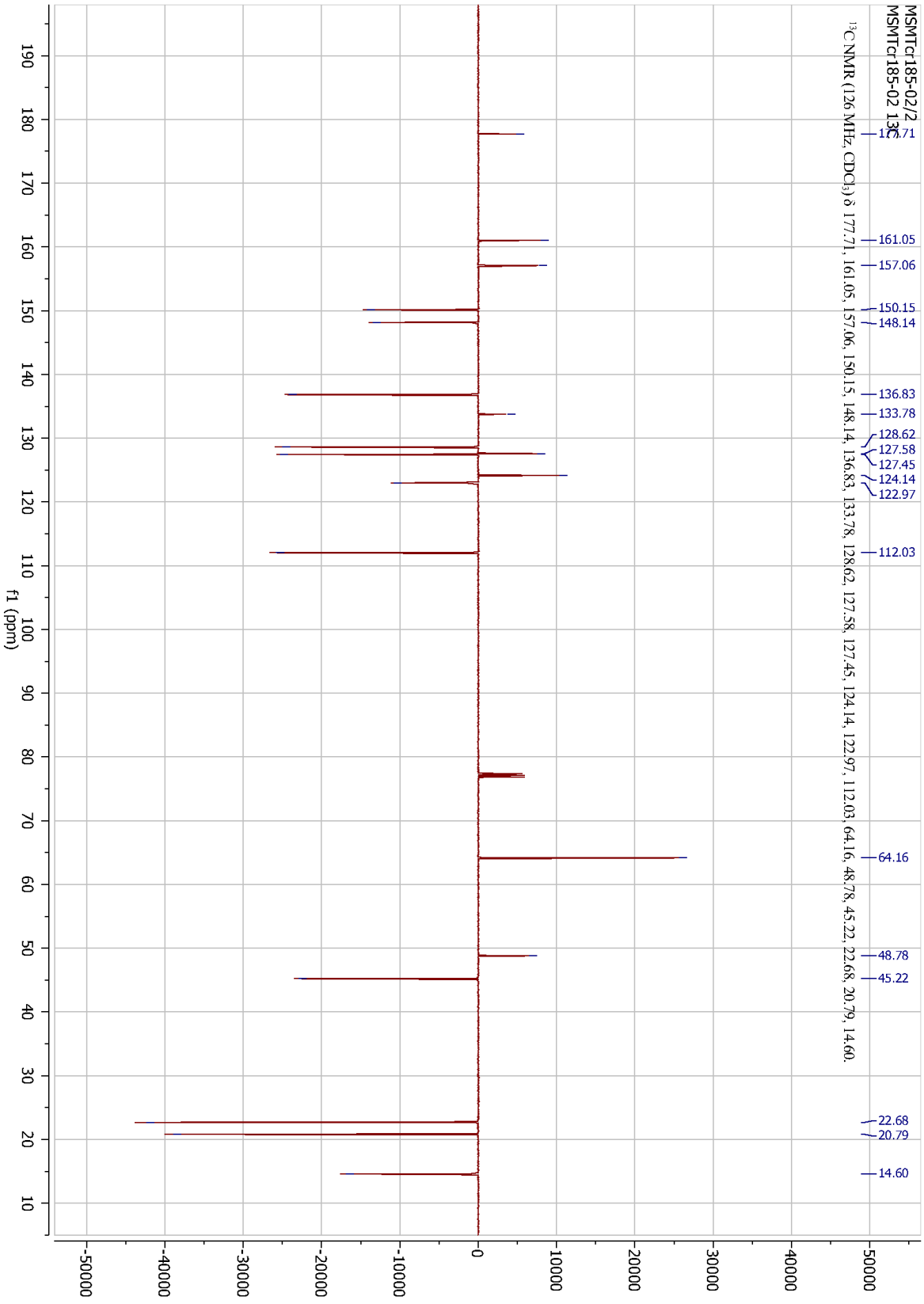

Figure S92 ^{13}C-NMR of compound **75**

^{1}H NMR compound 76

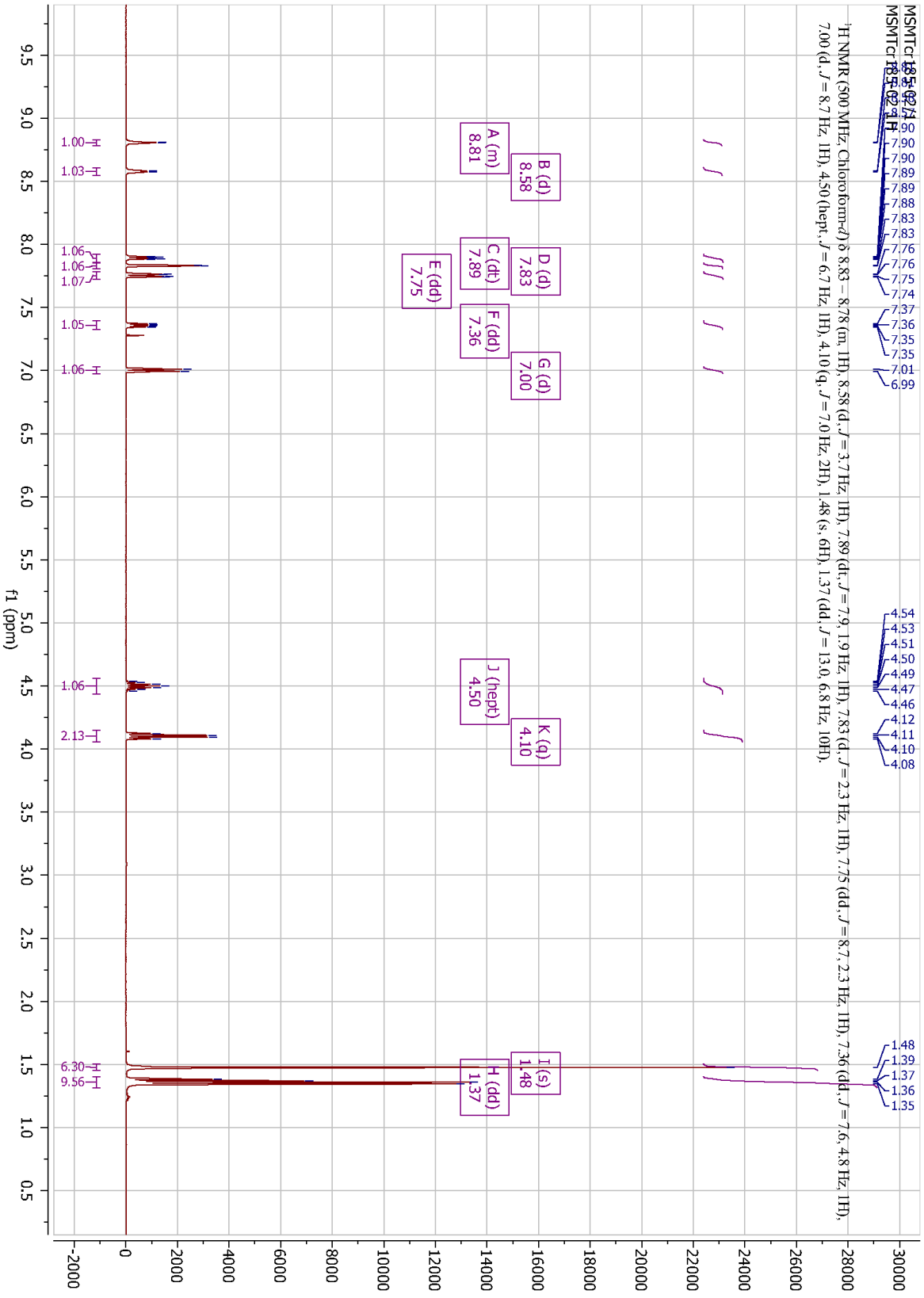

Figure S93 ^{1}H-NMR of compound **76**

^{13}C NMR compound 76

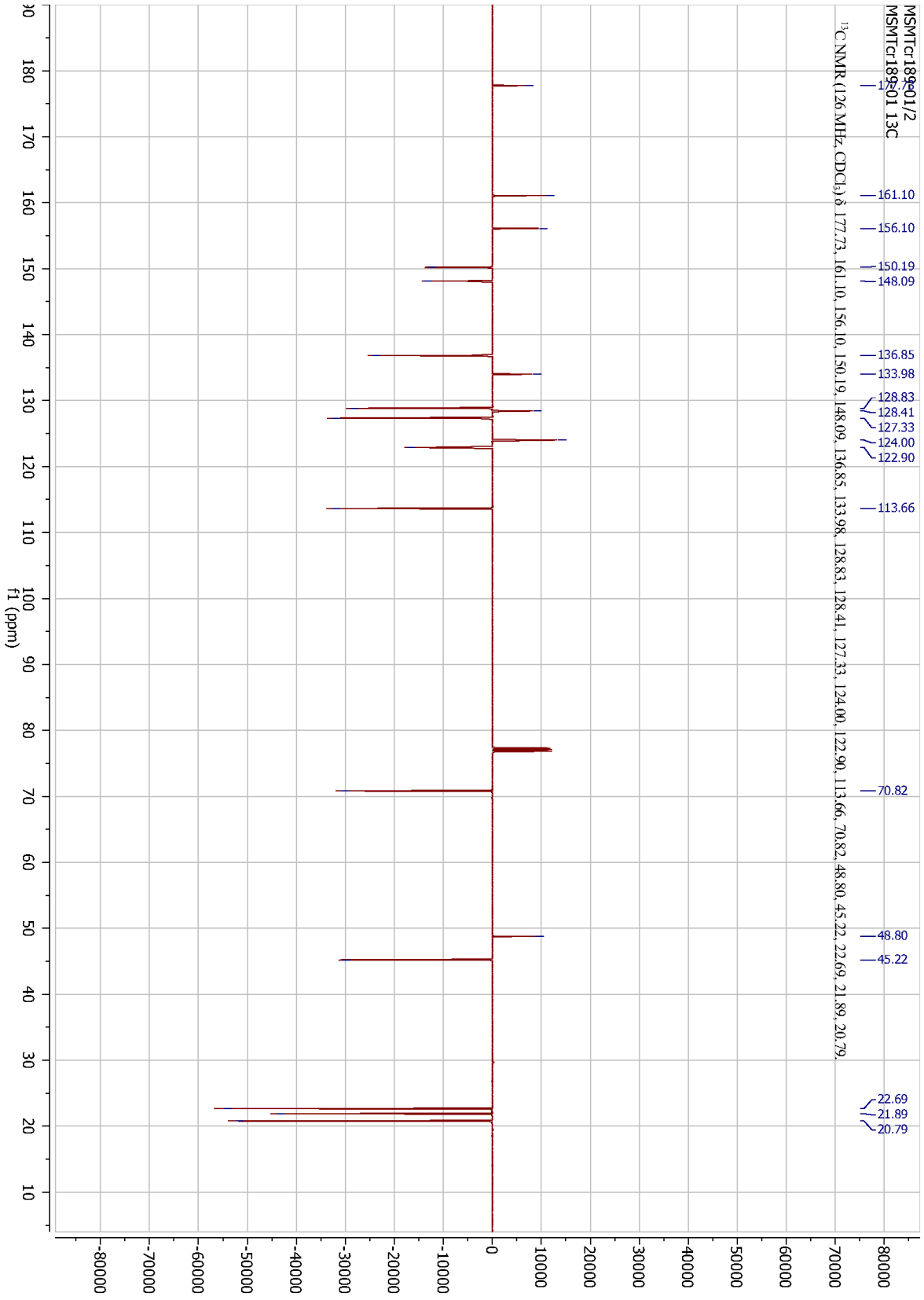

Figure S94 ^{13}C-NMR of compound **76**

^{1}H NMR compound 77

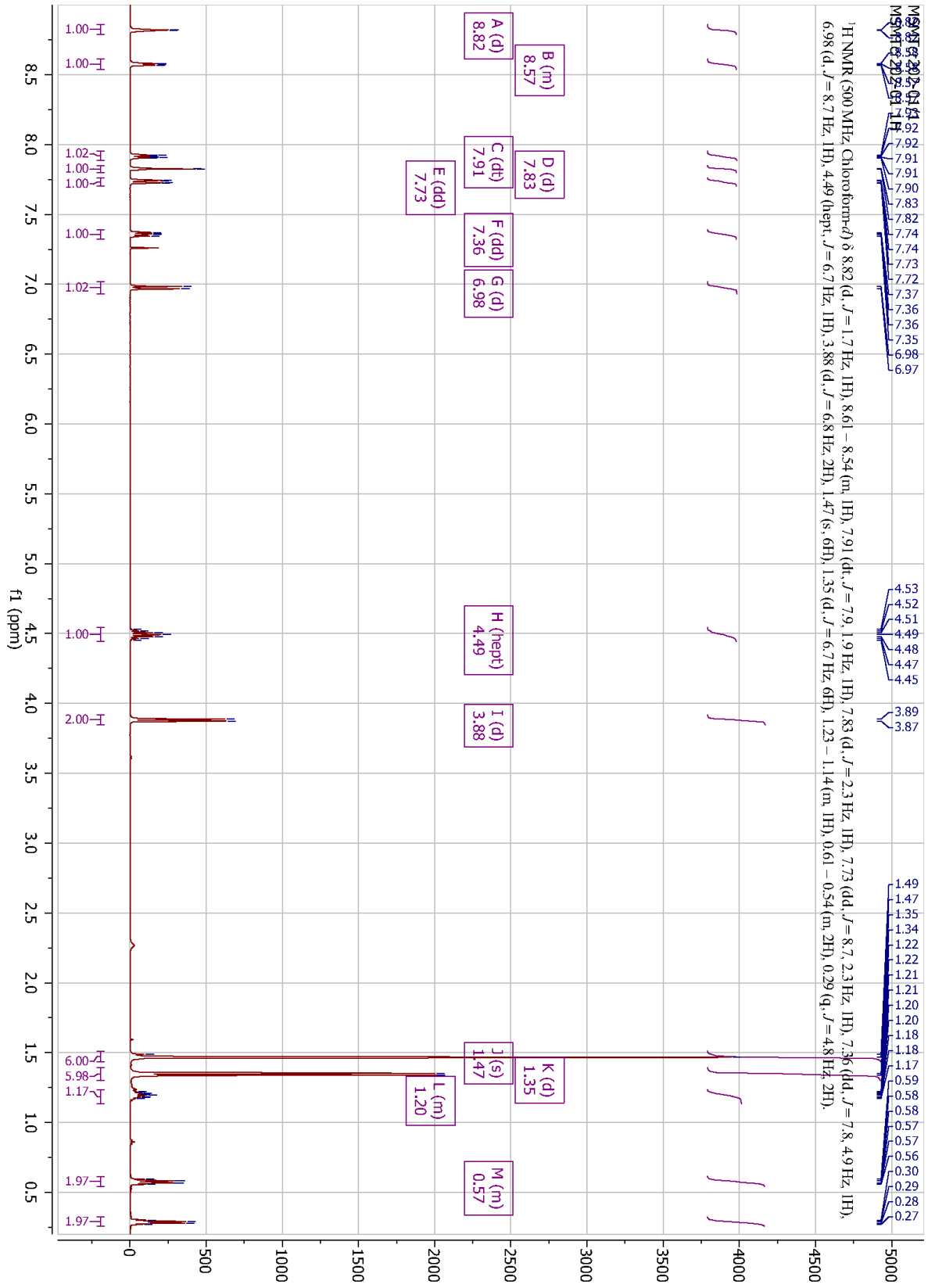

Figure S95 ^{1}H-NMR of compound **77**

^{13}C NMR compound 77

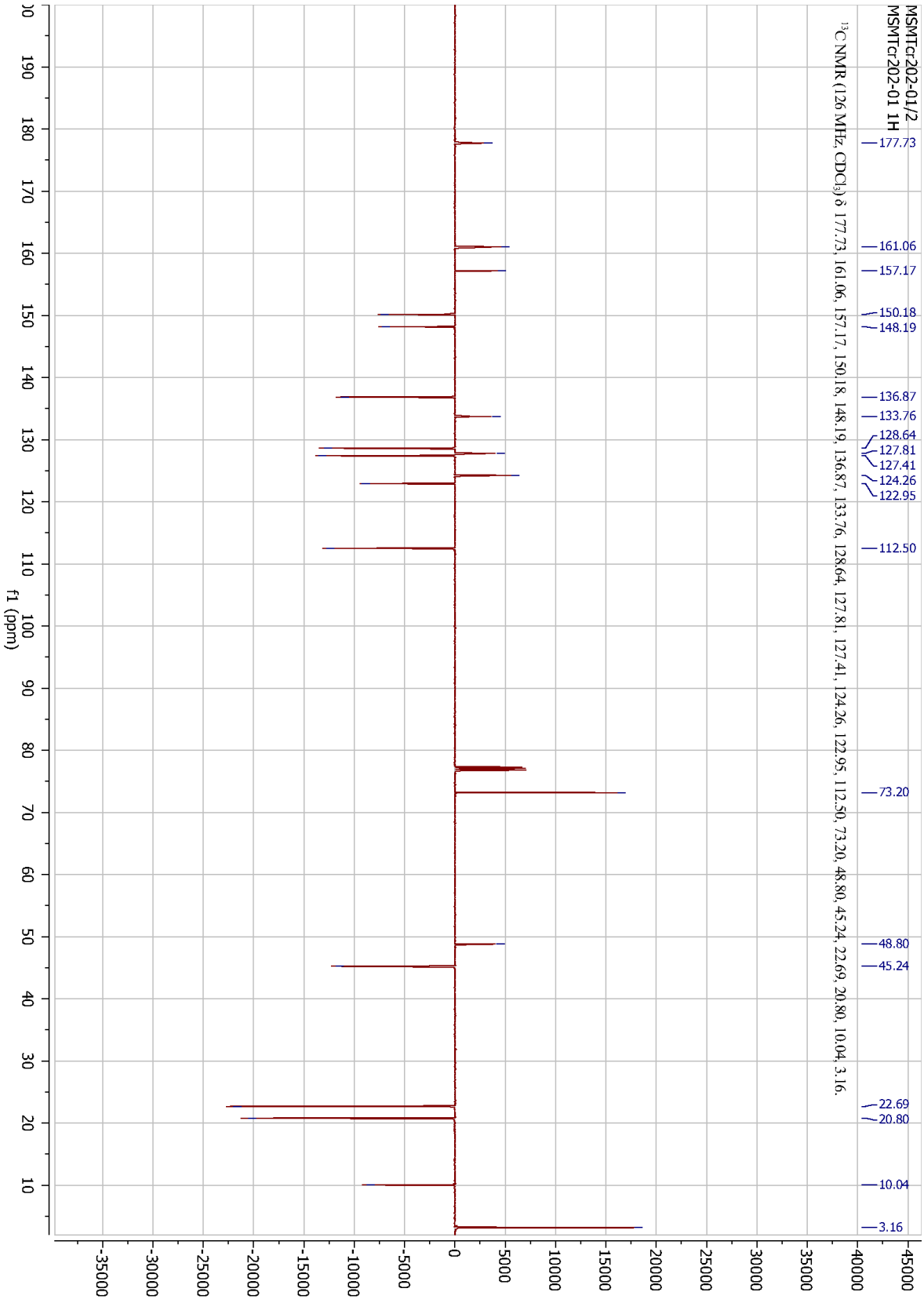

Figure S96 ^{13}C-NMR of compound **77**

^{1}H NMR compound 78

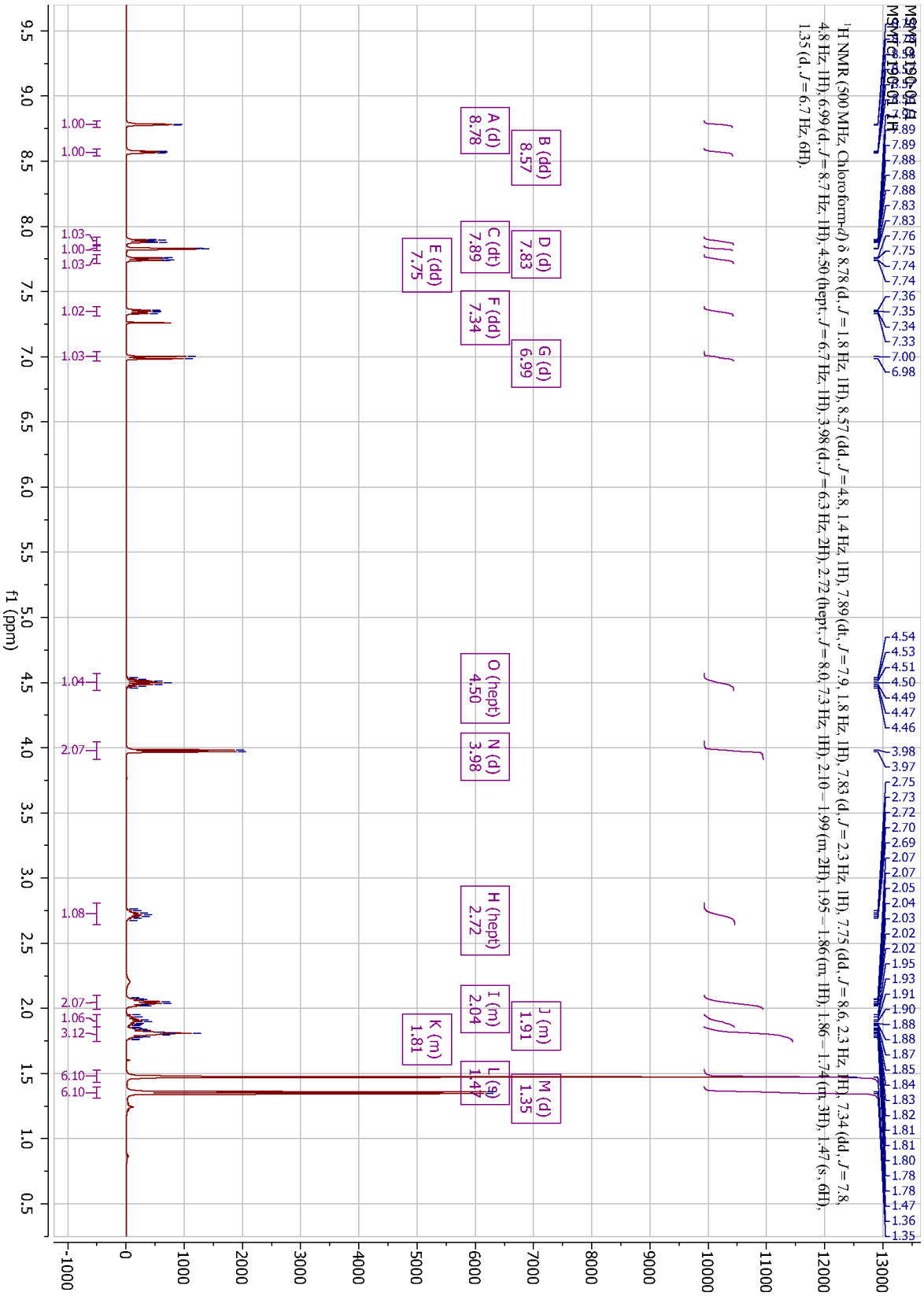

Figure S97 ^{1}H-NMR of compound **78**

^{13}C NMR compound 78

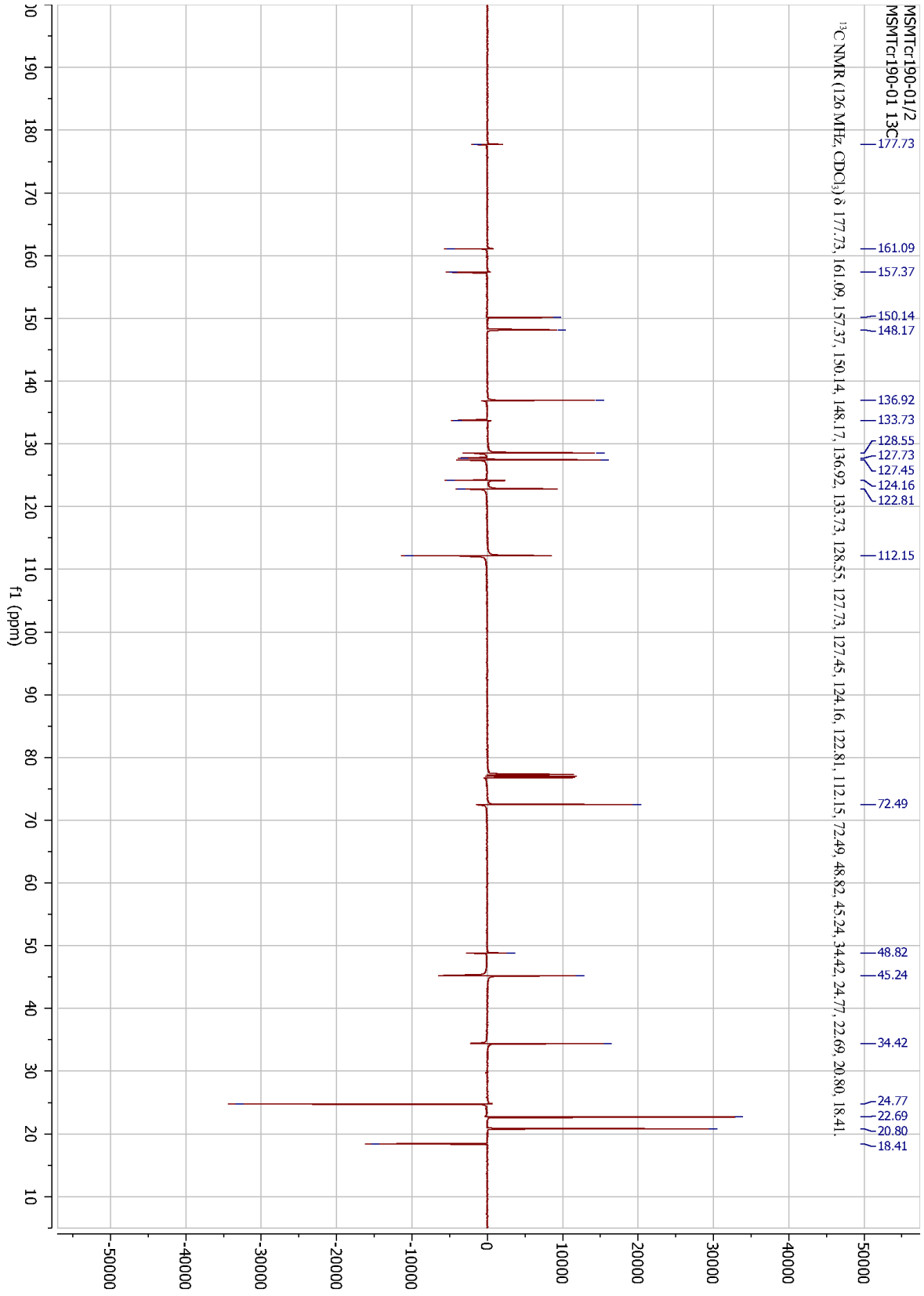

Figure S98 ^{13}C-NMR of compound **78**

^{1}H NMR compound 79

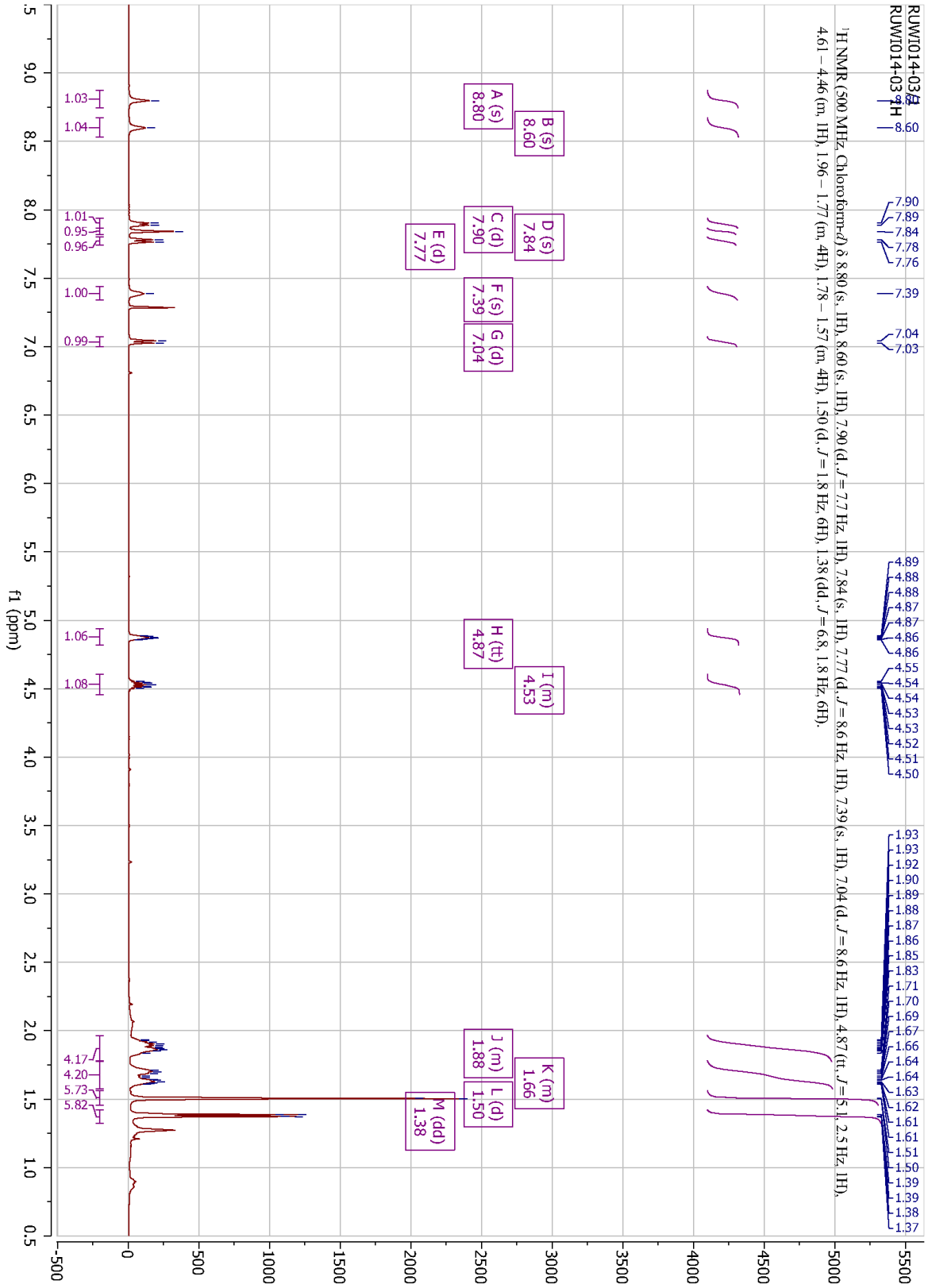

Figure S99 ^{1}H-NMR of compound **79**

^{13}C NMR compound 79

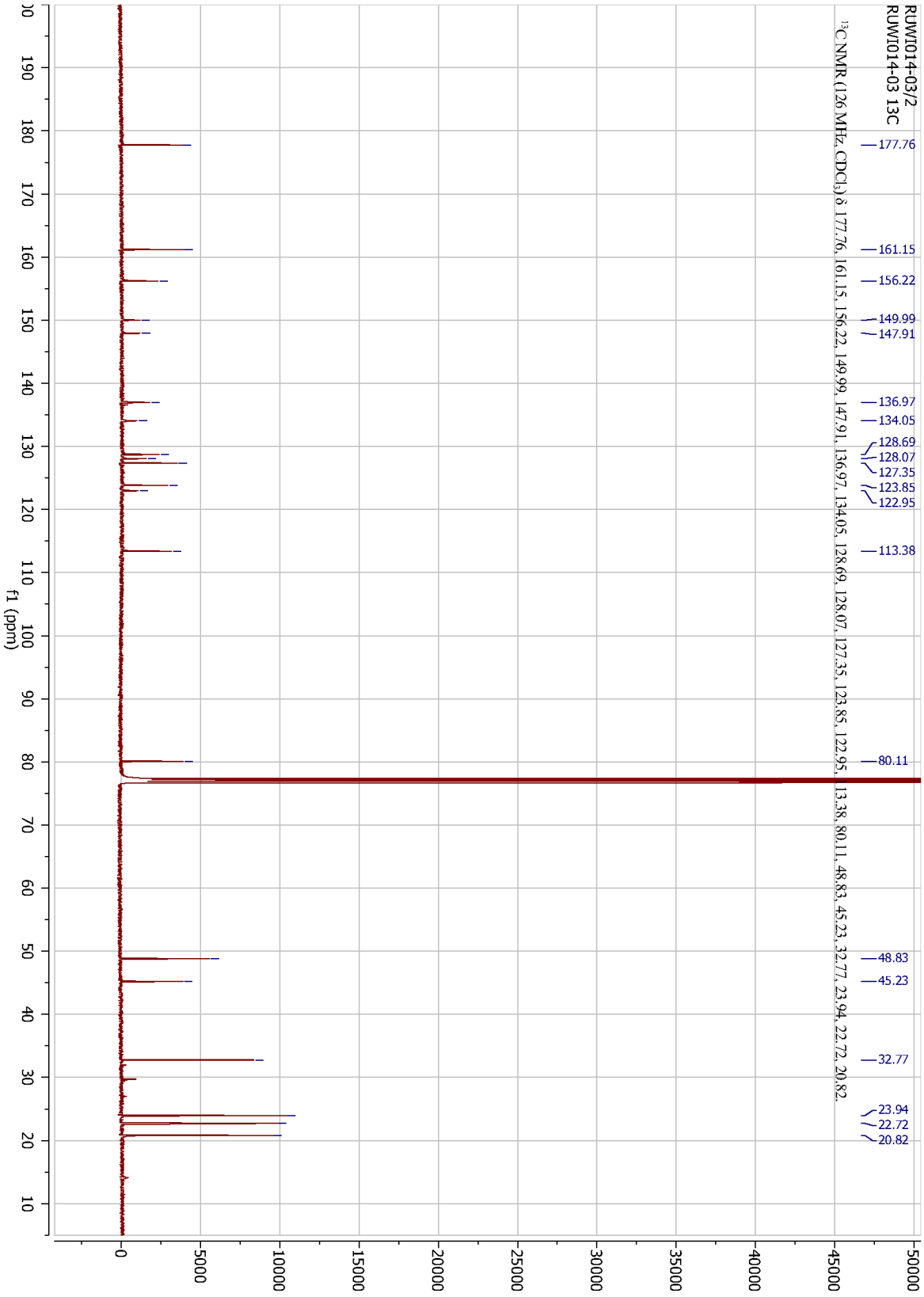

Figure S100 ^{13}C-NMR of compound **79**

^{1}H NMR compound 80

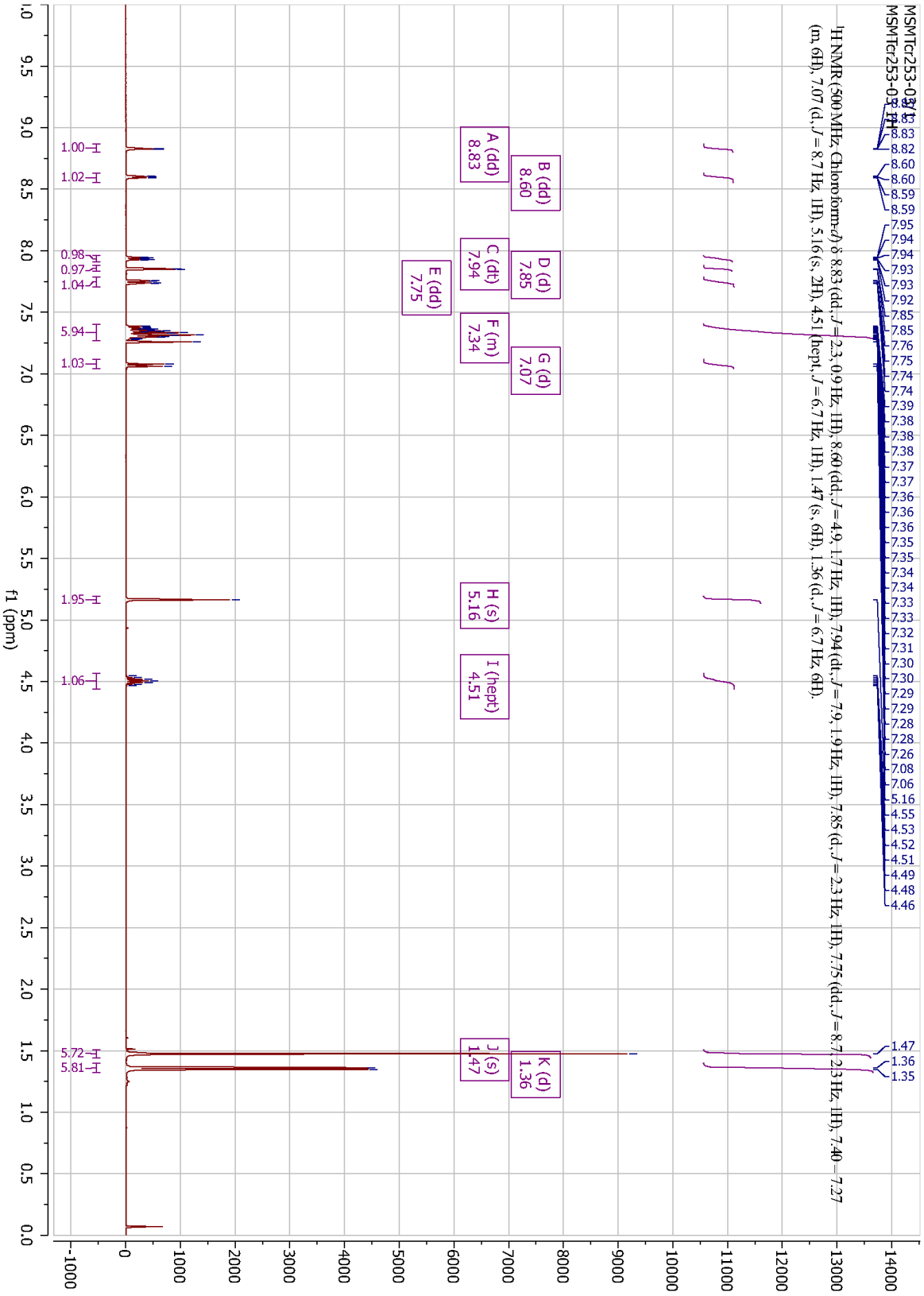

Figure S101 ^{1}H-NMR of compound **80**

^{13}C NMR compound 80

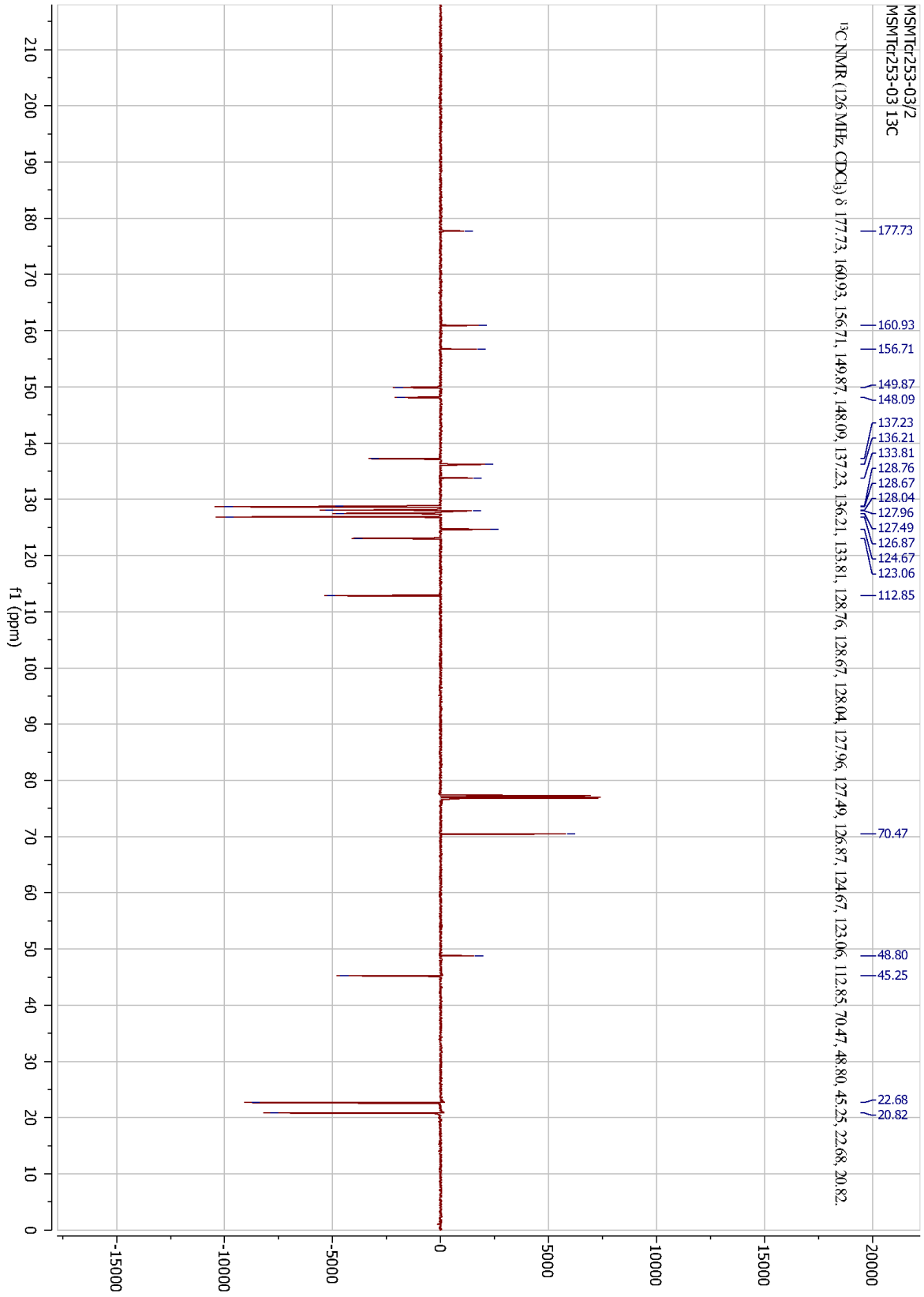

Figure S102 ^{13}C-NMR of compound **80**

^{1}H NMR compound 81

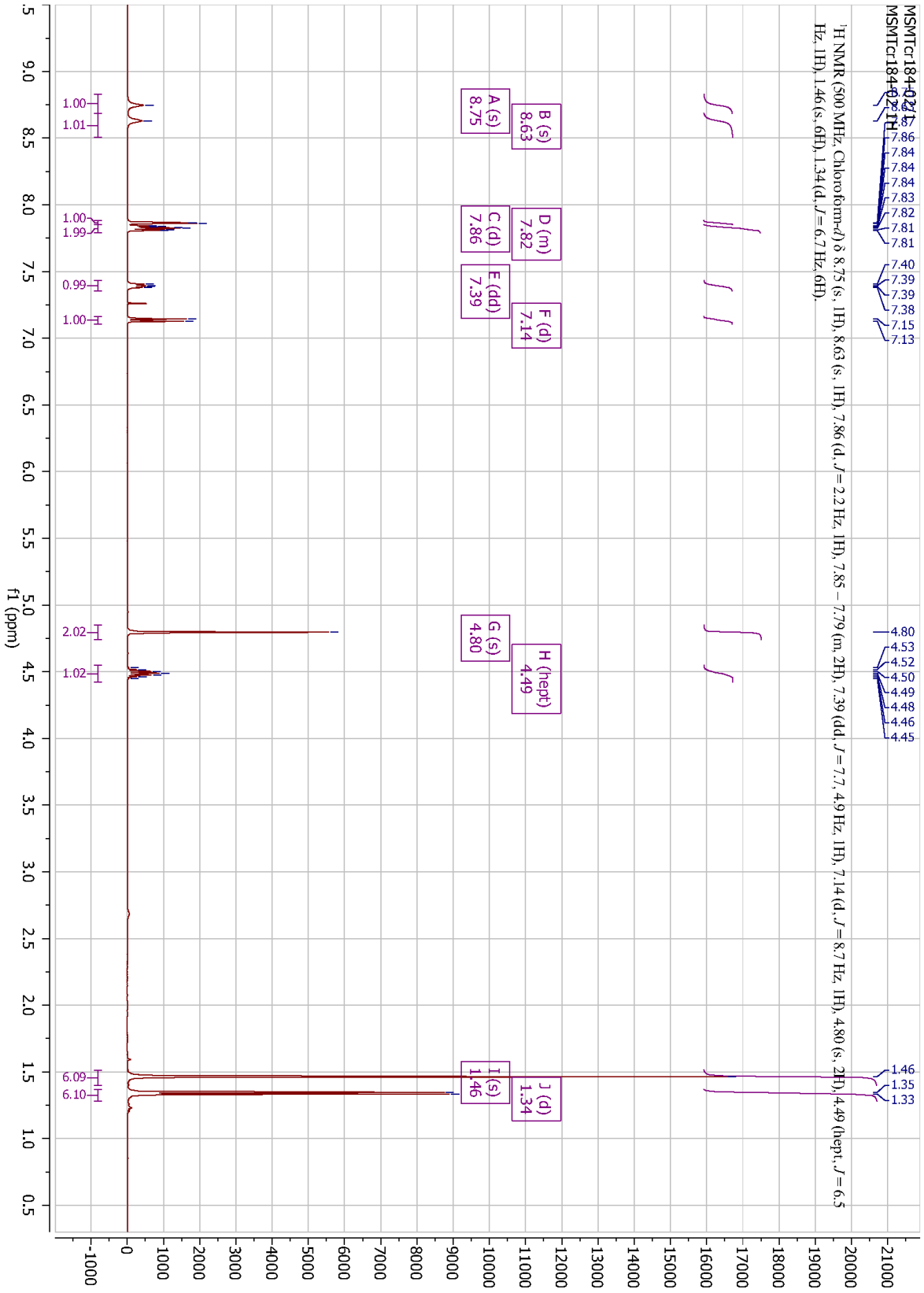

Figure S103 ^{1}H-NMR of compound **81**

^{13}C NMR compound 81

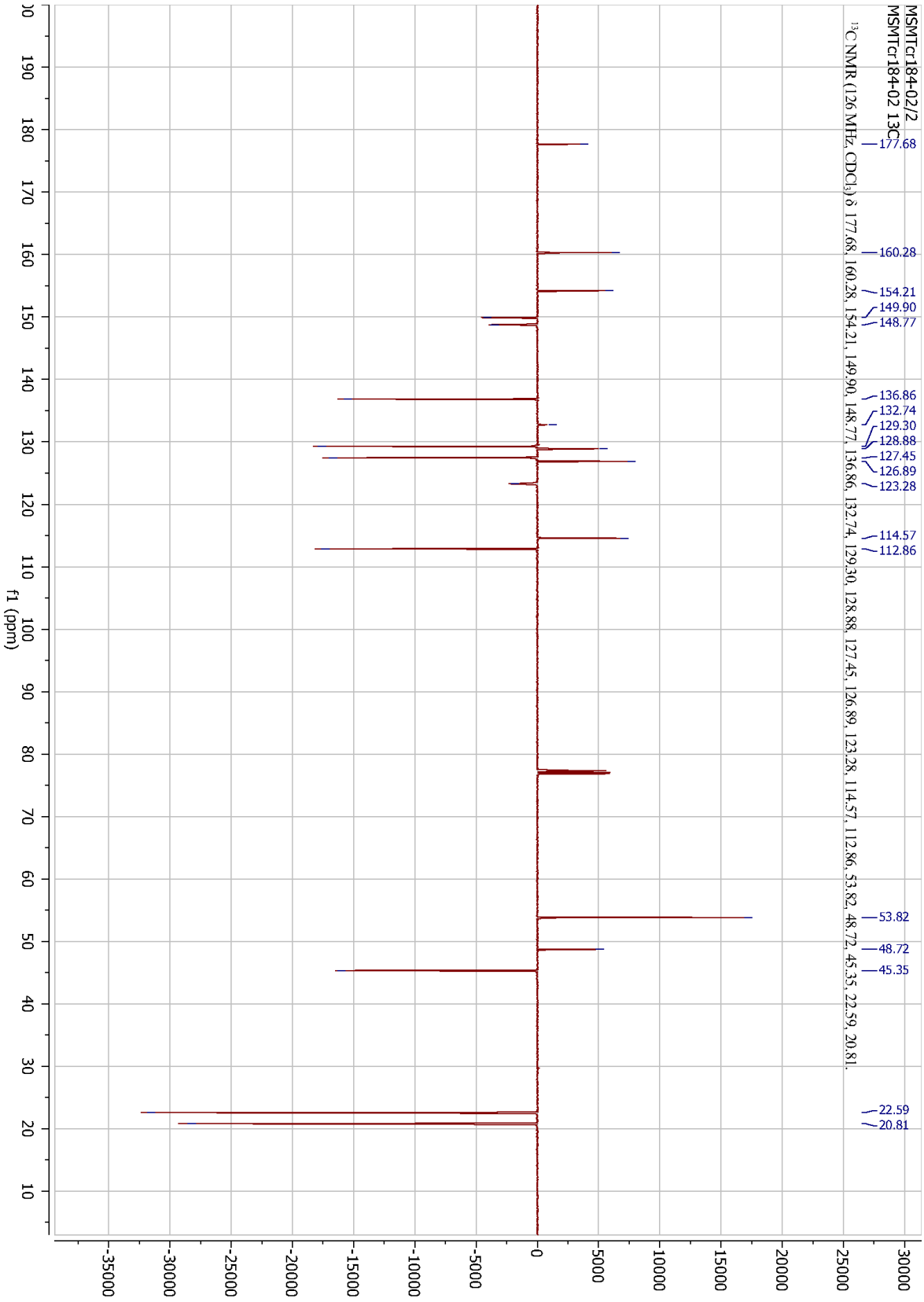

Figure S104 ^{13}C-NMR of compound **81**

^{1}H NMR compound 82

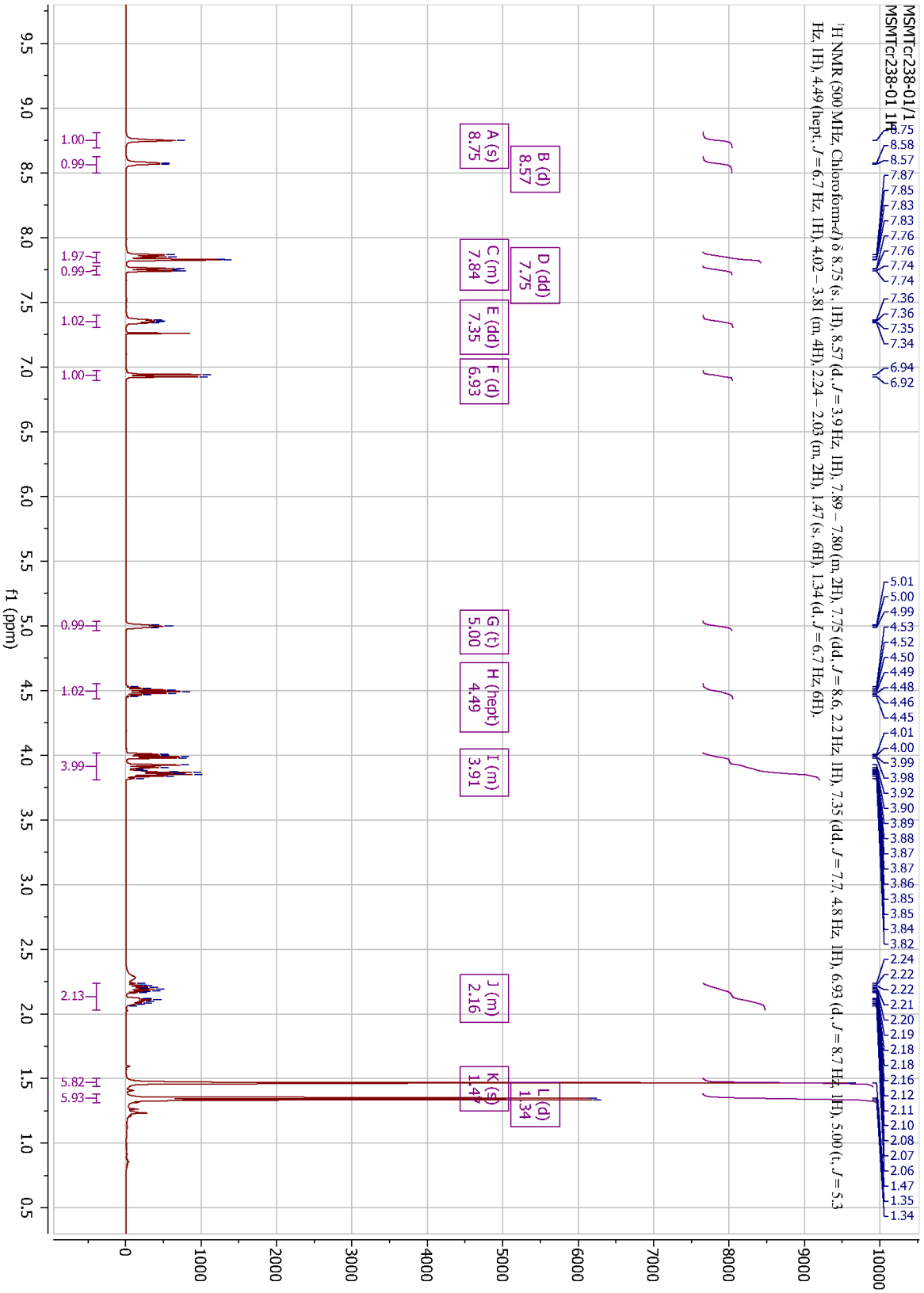

Figure S105 ^{1}H-NMR of compound **82**

^{13}C NMR compound 82

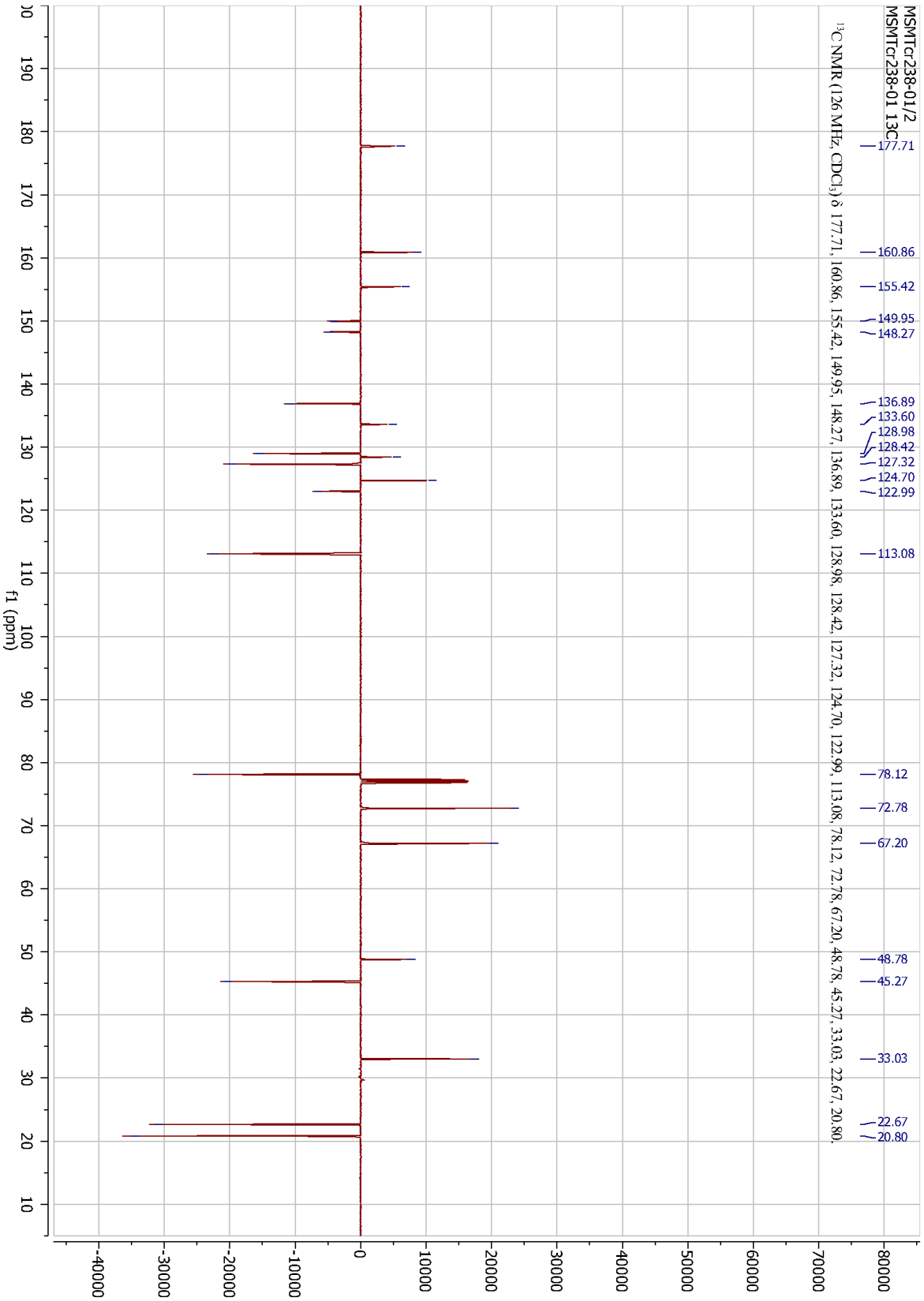

Figure S106 ^{13}C-NMR of compound **82**

^{1}H NMR compound 83

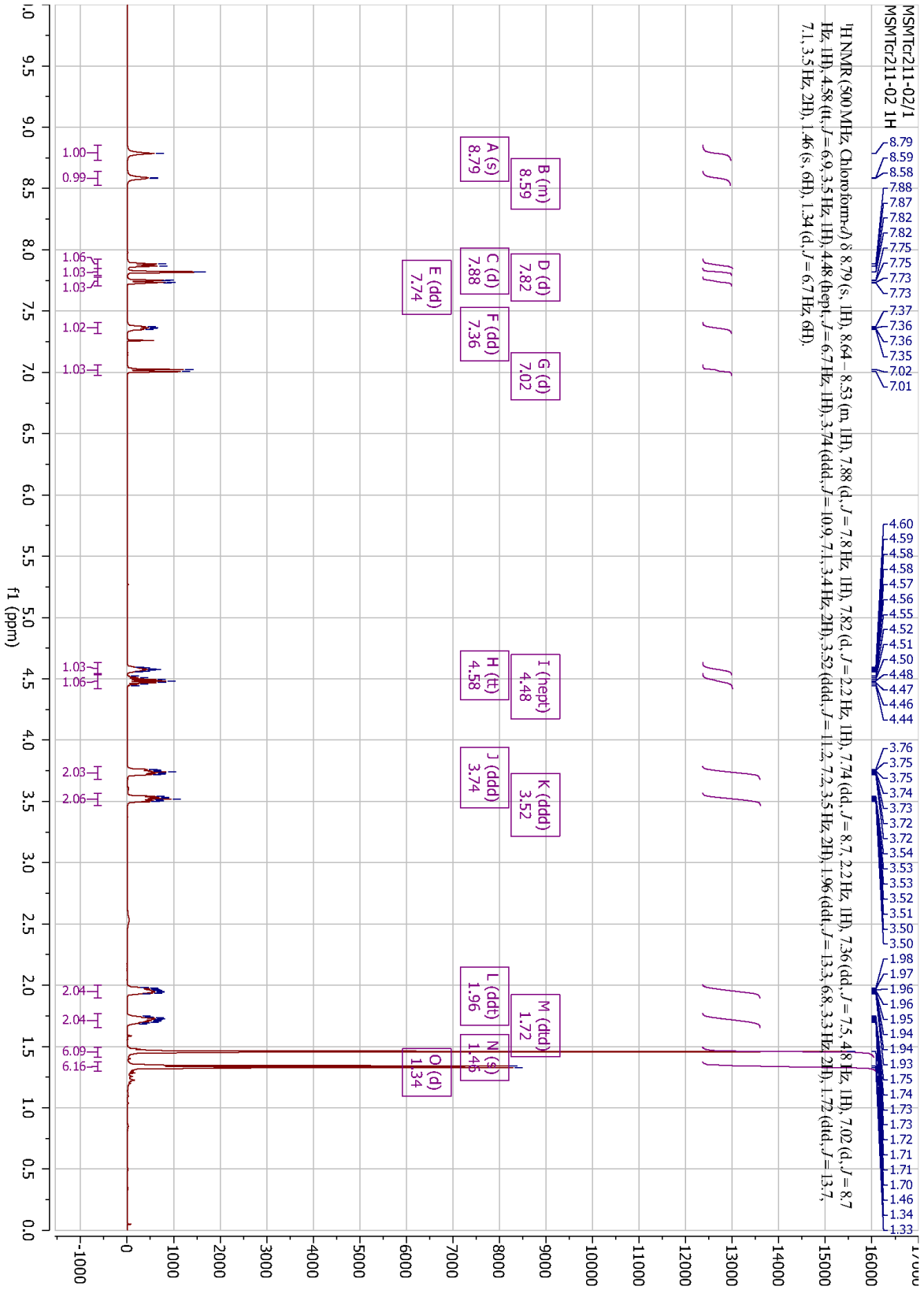

Figure S107 ^{1}H-NMR of compound **83**

^{13}C NMR compound 83

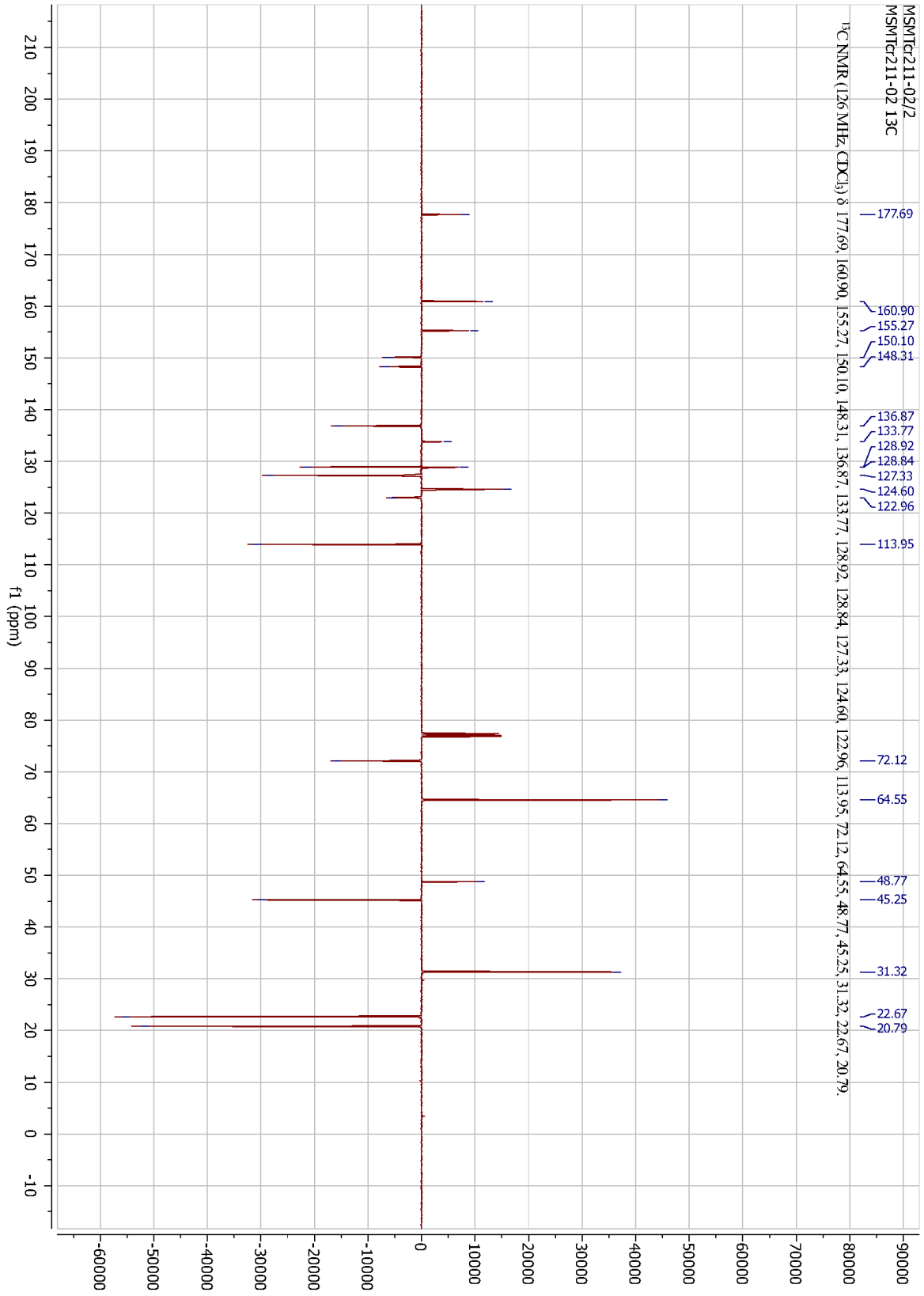

Figure S108 ^{13}C-NMR of compound **83**

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1. Collaborative Drug Discovery, https://www.collaborativedrug.com/ (20-12-2018)
2. Li, Y.; Shah-Simpson, S.; Okrah, K.; Belew, A. T.; Choi, J.; Caradonna, K. L.; Padmanabhan, P.; Ndegwa, D. M.; Temanni, M. R.; Corrada Bravo, H.; El-Sayed, N. M.; Burleigh, B. A. Transcriptome Remodeling in Trypanosoma cruzi and Human Cells during Intracellular Infection. *PLOS Pathogens* **2016,** 12, e1005511.