Supporting Information

Use of Crystallography and Molecular Modeling for the Inhibition of the Botulinum Neurotoxin A Protease

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Table of Contents

1.0 Supporting Figures

1.1 Figure S1

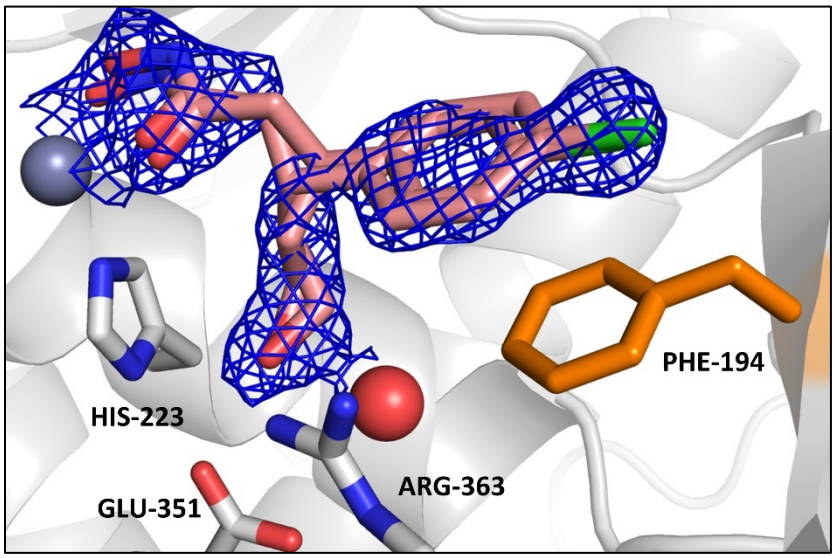


Figure S1: Electron density map (contour level 2.5 σ) of **3** bound within the BoNT/A LC. Crystallization of both enantiomers within the crystal lattice has resulted in poor electron density around the stereogenic center.

1.2 Figure S2

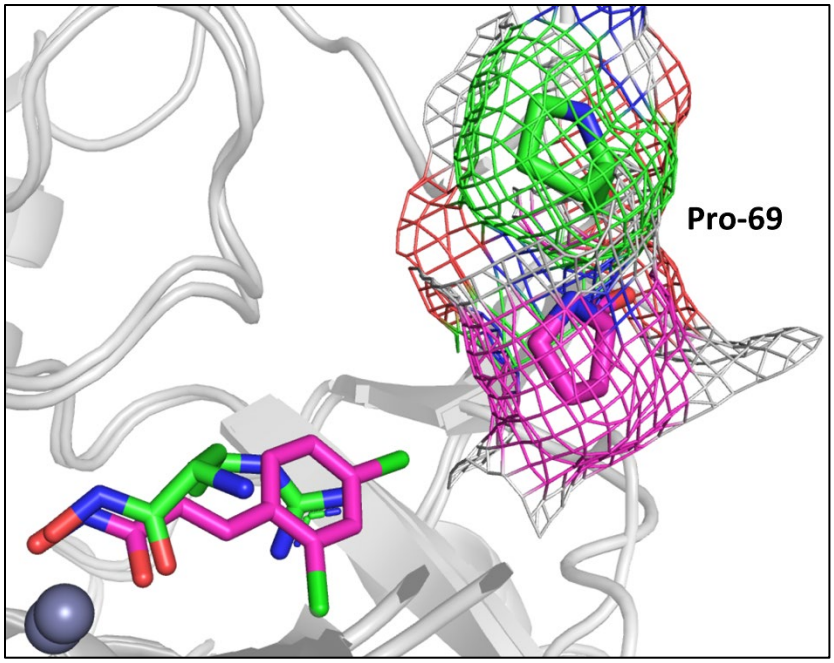


Figure S2: Overlay of 2IMA (DCHA, purple) and 2IMB (**2**, green) with mesh display (contour level 3.0 σ) showing large shift in Pro69 resulting in a larger binding pocket for **2**.

1.3 Figure S3

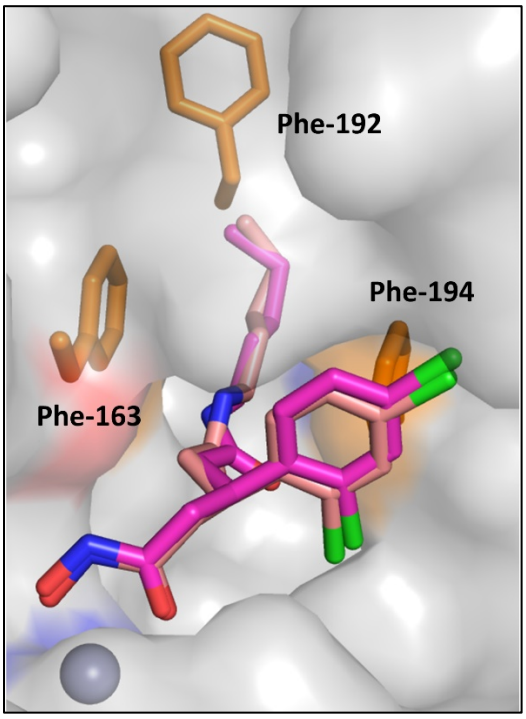


Figure S3: Glide docking model of **6** (purple) bound within the active site of the BoNT/A LC using the PDB 6XCF structure as the template. The Glide docking pose showed excellent overlap with the cocrystal structure of **6** (pink).

1.4 Figure S4

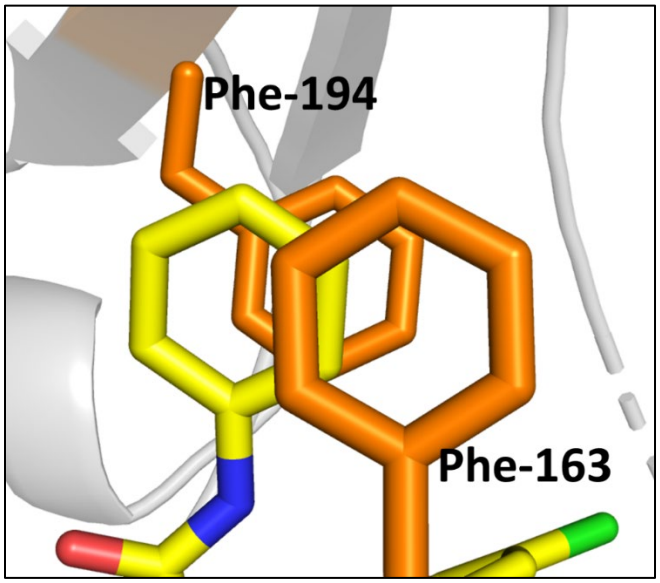
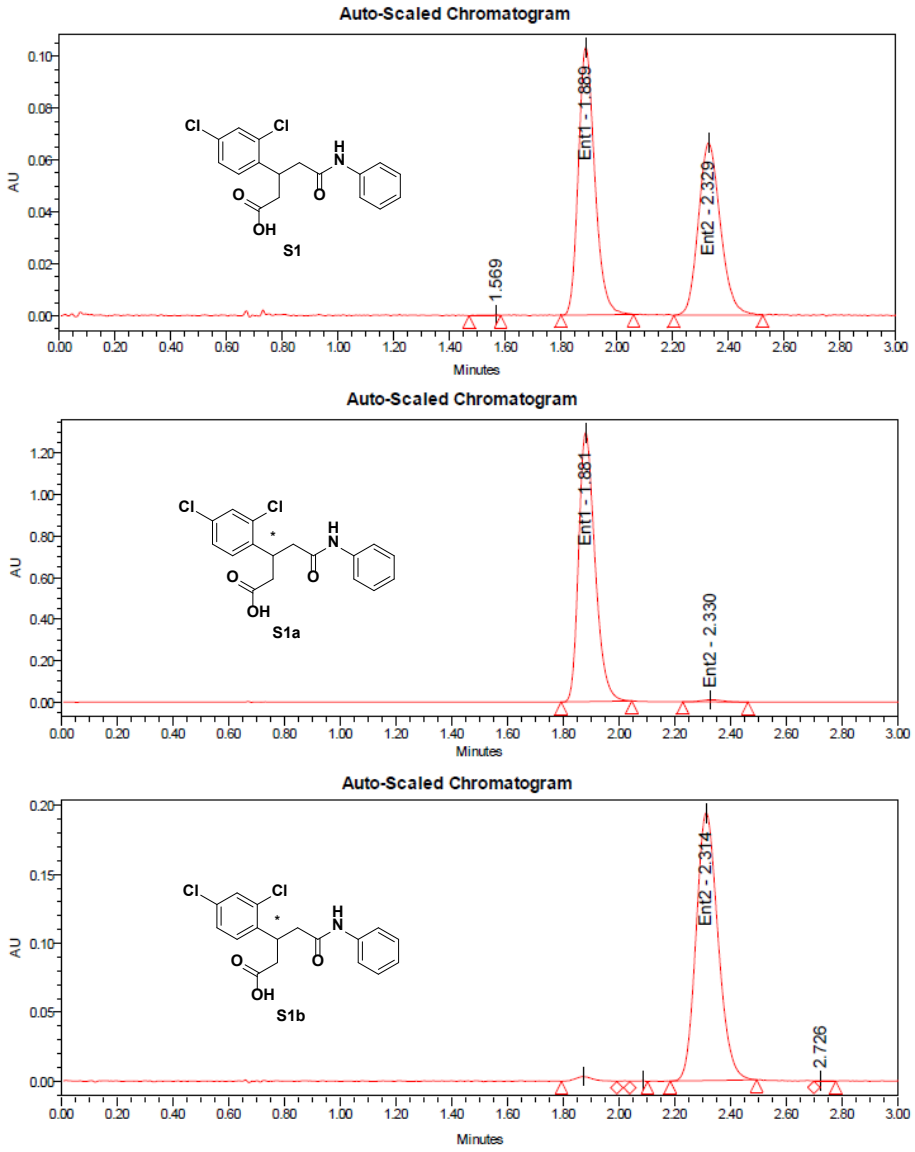


Figure S4: Birdseye view of offset π-sandwich interaction between Phe163 and 194 (orange) and the aniline phenyl ring (yellow) of **18**.

1.5 Figure S5



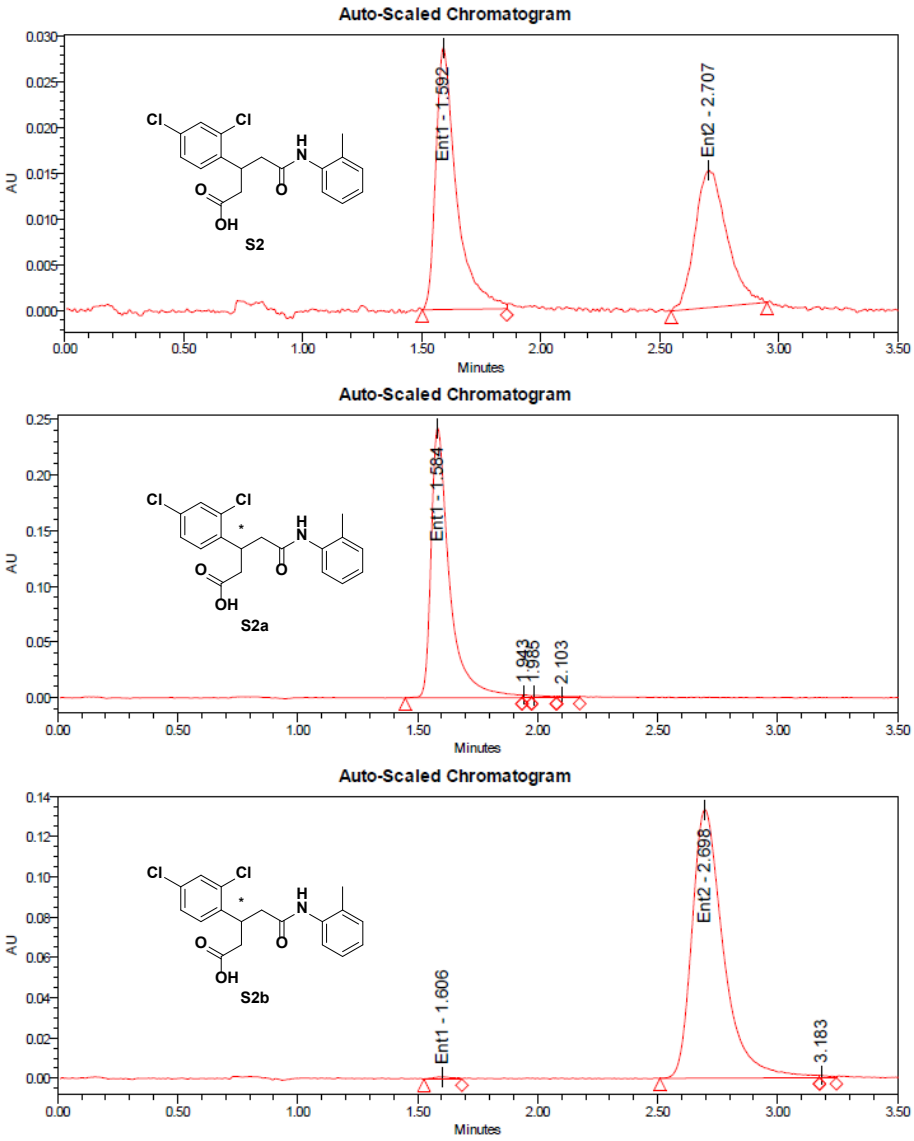
Area Summarized by Name

	SampleName	ent1	ent2	ee	Ent1	Ent2
1	S1	53.75	46.25	7.49	422577	363655
2	S1a	98.96	1.04	97.92	5295499	55666
3	S1b	1.51	98.49	-96.98	16322	1063092

Figure S5: Analytical SFC traces for compound **S1**. First and last eluted enantiomers designated as **S1a** and **S1b**, respectively. Enantiomeric excess determined by AUC of each peak.

Initial attempts at using chiral SFC for separation of final hydroxamate compounds were unsuccessful due to poor resolution. Fortunately, after extensive optimization of stationary and mobile phase conditions, we were able to achieve separation of enantiomers for carboxylic acid intermediates (**S1**–**S3**). Each enantiomer was taken forward separately using the same chemistry as outlined in **Scheme 1**.

1.6 Figure S6

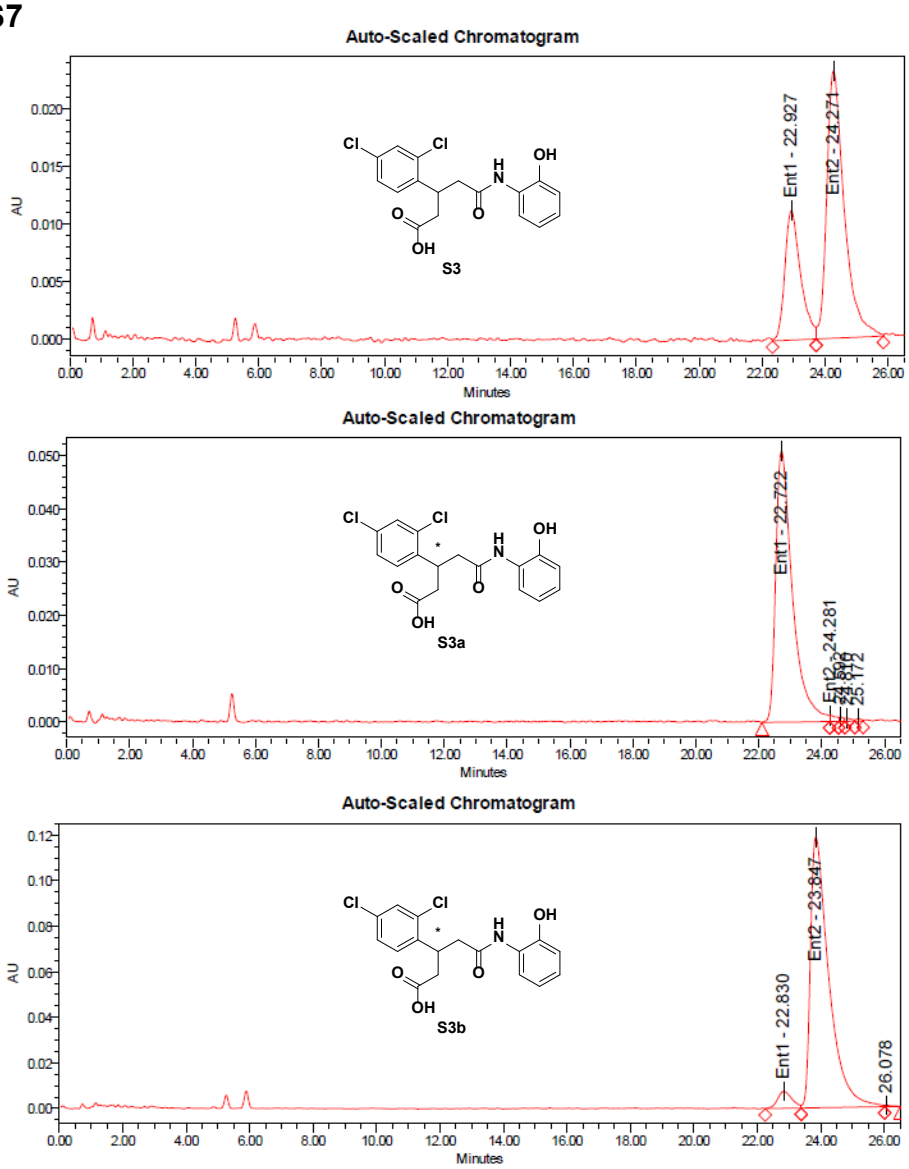


Area Summarized by Name

	SampleName	ent1	ent2	ee	Ent1	Ent2
1	S2	55.36	44.64	10.72	173003	139508
2	S2a	100.00		100.00	1294103	
3	S2b	0.53	99.47	-98.95	6442	1216034

Figure S6: Analytical SFC traces for compound **S2**. First and last eluted enantiomers designated as **S2a** and **S2b**, respectively. Enantiomeric excess determined by AUC of each peak.

1.7 Figure S7



Area Summarized by Name

	SampleName	ent1	ent2	ee	Ent1	Ent2
1	S3	30.33	69.67	-39.34	390946	898110
2	S3a	99.14	0.86	98.28	1879378	16341
3	S3b	4.68	95.32	-90.64	235569	4795726

Figure S7: Analytical SFC traces for compound **S3**. First and last eluted enantiomers designated as **S3a** and **S3b**, respectively. Enantiomeric excess determined by AUC of each peak.

2.0 Supporting Tables

2.1 Table S1

Dpocket data statistics for co-crystallized ligands of the BoNT/A LC.

PDB	Ligand	Ligand Volume	Pocket Volume	No. Alpha Spheres	Mean alpha sphere radius	Mean alp. sph. solvent access	Alpha sphere density	Cent. of mass - Alpha Sphere max dist
2IMA	**DCHA**	166.48	672.82	45	3.77	0.52	6.10	16.55
4HEV	**1**	161.90	455.70	40	3.90	0.57	4.60	13.83
2IMB	**2**	142.59	810.67	34	4.19	0.56	5.55	13.22
7N18	**3**	185.62	578.75	50	3.62	0.53	6.18	15.47
6XCF	**6**	267.59	833.42	56	3.65	0.48	7.17	15.88

2.2 Table S2

Crystallographic data statistics for **3** in complex with the BoNT/A LC (PDB 7N18).

Data Collection	
Resolution Range (Å) (last shell)[a]	31.70–2.03 (2.10–2.03)
Space Group	P 2_1
a, b, c (Å)	73.0, 6.3, 97.5
α, ß, γ (°)	90.0, 105.1, 90.0
R_{merge}[a]	0.109 (0.511)
R_{meas}[a]	0.129 (0.601)
R_{pim}[a]	0.068 (0.315)
$CC_{1/2}$[a]	0.988 (0.663)
No. of unique reflections[a]	59291 (4629)
Completeness (%)[a]	96.7 (78.3)
Multiplicity[a]	3.6 (3.6)
$\langle I/\sigma(I)\rangle$[a]	10.8 (4.4)
Model Refinement	
Reflections used in refinement	57669 (4628)[b]
Reflections used for R_{free}	2000 (160)
R_{cryst} (R_{free})	0.158 (0.196)
Average B factor (Å^2)	31.9
Protein atoms	31.9
Solvent	31.9
Ligand	37.6
Root-mean-square (RMS) deviations	
Bond lengths (Å)	0.011
Bond angles (°)	1.060
Coordinate error (Å)	0.18
Ramachandran statistics	
Favored/allowed/outliers	97.2/2.6/0.2
Rotamer outliers (%)	1.4
Clashscore	2.4

[a]Values in parentheses apply to the high-resolution shell indicated in the resolution row.
[b]The limits of the high-resolution bin for refinement were 2.05–2.02 Å.

3.0 Materials and Methods

3.1 Crystallography

BoNT/A LC was expressed in *E. coli* as a C-terminal truncation mutant (residues 1–425; "LC425") with an N-terminal His_6-tag and thrombin cleavage site and purified and crystallized as described previously.[1] Briefly, purified LC425 was crystallized by mixing equal volumes of protein solution (10–12 mg/mL LC425, 50 mM Na_2HPO_4, 2 mM EDTA, pH 6.5) and crystallization buffer (10–15% polyethylene glycol 2,000 monomethyl ester, 0.2–0.3 M K_2HPO_4, 0.1 M D,L-malic acid, pH 7.0) in the hanging-drop geometry. Clusters of needle and plate-shaped crystals appeared in 2–4 days. Crystal morphology was improved by microseeding. The co-crystal structure of LC425 with racemic **3** bound was obtained by soaking a crystal in a solution containing 25% PEG 2,000 monomethyl ester, 0.3 M K_2HPO_4, 0.1 M D,L-malic acid, 5 mM $Zn(NO_3)_2$, 2.5% DMSO, and 2.0 mM racemic **3**.

Data for the LC425**:3** complex were collected at Beamline X12B of the National Synchrotron Light Source, Brookhaven National Laboratory. The structure was determined by molecular replacement using the high-resolution unliganded structure (PDB 3BON)[2] as the search model, with waters, Zn^{2+} and flexible loops (residues 245–258 and 367–373) removed. The resulting models were refined in the PHENIX suite[3] with riding hydrogen atoms (without contribution to F_{calc}) and translation/libration/screw (TLS) using groups suggested by TLS motion determination analysis[4] (3 groups for chain A and 5 for chain B). After rebuilding parts of the protein model and adding ordered solvent molecules, the inhibitor molecules were modeled into difference electron density (contoured at 2.5–3.0 σ) in the active site of chain B. The quality of the final models was confirmed using the validation tool in the PHENIX suite. Data collection and refinement statistics are presented in **Table S2**.

3.2 Computational modelling

3.2.1 Dpocket calculations

Fpocket is a protein pocket detection algorithm based on alpha spheres which are spheres that contact four atoms on its boundary and contain no internal atom.[5, 6] The size of each sphere correlates to its location within the protein; spheres located on the exterior of proteins will have large radii, spheres located within clefts and cavities will be of intermediate size and spheres located within the protein will have small radii. The default minimal and maximal radii were used to filter the ensemble of alpha spheres. After filtering, the Dpocket algorithm defined a box containing all atoms and vertices located within 4 Å of the ligand. Pocket volume was calculated using a Monte Carlo algorithm that randomly picked a point inside the box and confirmed if it was included in an alpha sphere and then stored the status. This was repeated N=50000 times, and the volume of the pocket was estimated as the number of hits divided by 50000, scaled by the size of the box.

3.2.2 Glide docking

Molecular modeling was performed with modules from the Schrödinger Small Molecule Drug Discovery Suite (Maestro), release 2018–3, using the OPLS3 force field for parameterization.[7] The X-ray co-crystal structure of BoNT/LC and **6** (PDB 6XCF) were imported from the protein data bank and prepared using the Protein Preparation Wizard using default settings.[8] Ligands were imported into and prepared using LigPrep.[2] Compounds were docked using XP Glide redocking[9] and the lowest energy binding mode represented. Figures were generated using PyMol Molecular Graphics System (version 2.3.4., Schrödinger, LLC).

3.3 BoNT/A LC FRET SNAPtide assay

The truncated BoNT/A LC (1–425) was kindly provided by Dr. Joseph Barbieri and the assay was conducted according to a previously reported procedure,[10] with the exception of running the assays at 37 °C.

4.0 Chemistry

4.1 General Experimental

All reagents and solvents were of analytical grade and used without further purification as obtained from commercial suppliers unless otherwise stated. Reactions were conducted under an atmosphere of argon or nitrogen whenever anhydrous solvents were used. Reactions were monitored by thin-layer chromatography (TLC) using silica gel coated glass plates (analytical SiO_2-60, F-254) and/or by high performance liquid chromatography-mass spectrometry (HPLC-MS). TLC plates were visualized under UV light and/or by dipping in either: potassium permanganate stain, ninhydrin stain, or bromocresol green stain, visualizing with heating by heat gun. HPLC-MS analysis was performed on an Agilent 1260 Infinity II instrument coupled to a single quadrupole InfinityLab LC/MSD instrument running a gradient of eluant I (0.1% HCOOH in H_2O) and eluant II (0.1% HCOOH in MeCN) rising linearly from 0% to 95% of II during t = 0.00−6.00 min and then isocratic with eluant II from t = 6.00–10.0 min, at a flow rate of 0.5 mL/min on a Zorbax 300SB-C8 column. Flash liquid automated column chromatography (ACC) was performed by dry-loading crude products on celite and then purified on a CombiFlash Rf+ Lumen using RediSepRf silica-gel cartridges (4–40 g) for NP or RediSepRf Gold C_{18} HP (4–60 g) cartridges for RP at flow rates between 18–35 mL/min.

Nuclear magnetic resonance (NMR) spectra were recorded on either (a) a Bruker AVIII HD 600 equipped with either: a 5 mm CPQCI CryoProbe for ^{1}H at 600 MHz or a 5 mm CPDCH CryoProbe for ^{13}C NMR at 151 MHz, or (b) a Bruker NEO 500 (^{1}H NMR and ^{13}C NMR recorded at 500 and 126 MHz, respectively), or (c) a Bruker NEO 399 (^{1}H NMR and ^{13}C NMR recorded at 400 and 101 MHz, respectively). Chemical shifts are reported in ppm and are reported with reference to the residual solvent peak (δ_H $CDCl_3$ 7.26 ppm; δ_C $CDCl_3$ 77.16 ppm; δ_H DMSO-d_6 2.50 ppm; δ_C DMSO-d_6 39.52 ppm; δ_H MeOD-d_4 3.31 ppm; δ_C MeOD-d_4 49.00 ppm). Multiplicities are reported with coupling constants and are given to the nearest 0.1 Hz. High resolution-mass spectrometry (HR-MS) was carried out using an Agilent 1260 Infinity II instrument coupled to an Agilent 6230 TOF-MS spectrometer using electro spray ionization ($ES^{+/-}$), giving masses correct to four decimal places. Optical rotation was recorded on a PerkinElmer 241 polarimeter equipped with an Hg lamp using a wavelength of 365°. Data were recorded at 24 °C at a concentration of 0.1 mg/mL with a path length of 1 dm.

4.2 General synthetic methods

4.2.3 Method A: EDC acylation reactions*

A mixture of **30** (1.0 equiv.), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC; 1.2–1.5 equiv.) and hydroxybenzotriazole (HOBt; 1.2–1.5 equiv.) was charged with nitrogen and anh. DMF (3–4 mL) added. The chosen amine (1.2–1.5 equiv.) and N,N-diisopropylethylamine (DIPEA; 1.2–1.5 equiv.) were added and the reaction mixture stirred at room temperature until completion (~2 h). Water was added to the reaction mixture until no more precipitation was observed and the mixture extracted with DCM (20–30 mL) and the organic layer separated. The aqueous layer was extracted with DCM (3 × 20 mL) and the combined organic layers washed with brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo* to reveal the crude product as a yellow oil. The crude yellow oil was purified by NP ACC (stepwise: 0→6→100% MeOH–DCM).

4.2.4 Method B: Telescoped final compound formation

A mixture of **30** (1.0 equiv.), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo-[4,5-*b*]pyridinium 3-oxide hexafluorophosphate (HATU; 1.1–1.5 equiv.) and DIPEA (1.5–2.0 equiv.) was charged with nitrogen and anh. DMF (2-3 mL) added. The chosen amine* (1.1–1.5 equiv.) was added and the reaction mixture stirred at room temperature until completion (~30 min). The reaction mixture was worked up as outlined in Method A. The crude yellow oil was either: a) purified by NP and/or RP ACC and isolated or b) dissolved in abs. EtOH (5 mL) and pyridinium *p*-toluenesulfonate (PPTS) (0.5–0.7 equiv.) added and the reaction stirred at 65 °C for 16 h. See individual compounds for details.

*Viscous oils added as a solution in DMF (< 1 mL).

4.2.5 Method C: Telescoped aniline final compound formation

4-(2,4-dichlorophenyl)dihydro-2*H*-pyran-2,6(3*H*)-dione (**29**; 1.0 equiv.) was dissolved in $CHCl_3$ or DCM (2–10 mL) and the appropriate aniline (1.3–1.5 equiv.) was added and the reaction stirred for 30 min. The resulting precipitate was either: a) filtered, washed with DCM and isolated or b) redissolved in DMF (2–5 mL) and O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (OTX; 1.2–1.5 equiv.) and DIPEA (1.5–2.0 equiv.) added and cooled to 0 °C. HATU (1.1–1.2 equiv.) was added and the reaction stirred for 1 h at r.t. The reaction mixture was diluted into EtOAc and water and the organic layer separated. The organic layer was washed with 5% citric acid, dried (Na_2SO_4), and reduced *in vacuo* to give a crude yellow oil. The yellow oil was either: a) purified by NP and/ or RP ACC and isolated or b) dissolved in abs. EtOH (5–15 mL) and PPTS (0.1–0.5 equiv.) was added and the reaction stirred at 65 °C for 16 h. See individual compounds for details.

4.2.6 Method D1: *O*-THP deprotection

The chosen protected hydroxamate (1.0 equiv.) and PPTS (0.2 equiv.) were dissolved in abs. EtOH (3 mL) and the reaction heated to 65 °C overnight. The reaction mixture was reduced *in vacuo* and the crude product purified by NP or RP ACC. See individual compounds for details.

4.2.7 Method D2: *O*-THP deprotection**

The chosen protected hydroxamate (1.0 equiv.) was dissolved in a solution of TFA (0.2 mL) and DCM (1.8 mL) and the reaction closely monitored by HPLC-MS. The reaction was stopped when the HPLC-MS trace began to show significant formation of side products (~3 h). Excess TFA was carefully co-evaporated with abs. EtOH to ensure dilute TFA levels. The crude product was purified by RP ACC (gradient: 0–15% MeCN–H_2O in 0.1% formic acid). Appropriate fractions were pooled and lyophilized and the product further purified by NP ACC (gradient: 5–10% MeOH–DCM).

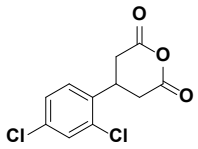
* A common side reaction of uronium-based coupling reagents *i.e.* HATU, is direct nucleophilic attack at the charged aminium center of HATU by the amine reactant;[11] reactions involving methyl- and ethyl-containing amines exhibited significant formation of the guanidinylated by-products which were inseparable from the desired product. Carbodiimide-based coupling reagent EDC does not undergo this side reaction and therefore was employed as a substitute to HATU.

** Using standard PPTS conditions, the THP-protected precursors of **26**–**28** underwent simultaneous removal of the THP group and deamination of the free aniline NH_2. To overcome this, we employed TFA conditions with careful reaction monitoring and work-up procedures to minimize formation of degradation products.

4.3 Compounds

4.3.1 Synthesis of benzylamines

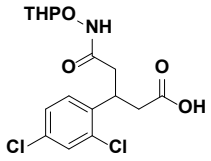
4-(2,4-dichlorophenyl)dihydro-2*H*-pyran-2,6(3*H*)-dione (29)



Synthesized as previously reported[10] using 3-(2,4-dichlorophenyl)pentanedioic acid (3.00 g, 10.83 mmol, 1.0 equiv.) and acetic anhydride (10 mL). The titled compound (2.66 g, 10.29 mmol, 95%) was collected as colorless microcrystals. Characterization data agrees with literature.[10]

TLC (5% MeOH–DCM): R_f = 0.14. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 7.65 (d, *J* = 2.3 Hz, 1H), 7.49 (dd, *J* = 8.5, 2.2 Hz, 1H), 7.42 (d, *J* = 8.5 Hz, 1H), 4.01–3.93 (m, 1H), 3.06 (ddt, *J* = 17.1, 12.0, 1.1 Hz, 2H), 2.97–2.90 (m, 2H).**^{13}C NMR** (151 MHz, DMSO-d_6) δ 166.9, 137.0, 133.8, 132.7, 129.2, 128.8, 128.0, 34.8, 29.6. **HRMS** (ES^+) *m/z* calcd for $[C_{11}H_9Cl_2O_3]^+$: 258.9923; found 258.9920 ($M+H^+$).

3-(2,4-dichlorophenyl)-5-oxo-5-(((tetrahydro-2*H*-pyran-2-yl)oxy)amino)pentanoic acid (30).



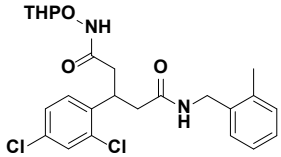
Synthesized as previously reported[10] using **29** (920 mg, 3.55 mmol, 1.0 equiv.), OTX (832 mg, 7.10 mmol, 2.0 equiv.) and $CHCl_3$ (20 mL). The titled compound (820 mg, 2.18 mmol, 61%) was collected as an off-white fluffy semi-solid. Characterization data agrees with literature.[10]

TLC (5% MeOH–DCM–0.1% AcOH): R_f = 0.11. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.22 (br.s, 2H), 10.97 (br.s, 2H), 7.54 (d, *J* = 1.4 Hz, 2H), 7.42–7.35 (m, 4H), 4.74* (br.s, 1H), 4.60* (br.s, 1H), 3.96–3.79 (m, 4H), 3.50–3.37 (m, 2H), 2.61 (d, *J* = 7.4 Hz, 4H), 2.41–2.28 (m, 4H), 1.64–1.43 (m, 12H).**^{13}C NMR** (151 MHz, DMSO-d_6) δ 172.4, 166.6, 139.6, 134.0**, 131.5**, 129.6**, 128.7, 127.3**, 101.0**, 61.4**, 38.3, 36.7**, 33.9, 22.7**, 24.6, 18.4**. **HRMS** (ES^-) *m/z* calcd for $[C_{16}H_{18}Cl_2NO_5]^-$: 374.0568; found 374.0580 ($M-H^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

3-(2,4-dichlorophenyl)-*N*^{1}-(2-methylbenzyl)-*N*^{5}-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanediamide



(S4). Synthesized by method A using **30** (200 mg, 0.53 mmol, 1.0 equiv.), EDC (99 mg, 0.64 mmol, 1.2 equiv.), HOBt (86 mg, 0.64 mmol, 1.2 equiv.), 2-methylbenzylamine (79 µL, 0.64 mmol, 1.2 equiv.), DIPEA (109 µL, 0.64 mmol, 1.2 equiv.) and DMF (3 mL). The titled compound (69 mg, 0.14 mmol, 27%) was collected as a colorless solid.

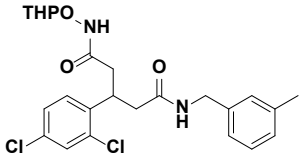
TLC (5% MeOH–DCM): R_f = 0.14. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.96 (d, *J* = 14.1 Hz, 2H), 8.18 (t, *J* = 5.7 Hz, 2H), 7.53 (s, 2H), 7.41–7.31 (m, 4H), 7.16–7.08 (m, 4H), 7.07–6.98 (m, 2H), 6.91–6.77 (m, 2H), 4.74* (br.s, 1H), 4.60* (br.s, 1H), 4.18 (dd, *J* = 15.3, 5.9 Hz, 2H), 4.12–4.04 (m, 2H), 3.99 (quint, *J* 7.6 =

Hz, 2H), 3.91–3.81 (m, 2H), 3.49–3.39 (m, 2H), 2.62–2.55 (m, 2H), 2.54–2.48 (m, 2H, overlap with solvent peak), 2.44–2.29 (m, 4H), 2.14 (s, 6H), 1.71–1.41 (m, 12H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 169.6, 166.7**, 139.6, 136.8, 135.5, 134.1**, 131.4**, 129.8, 128.7, 127.4, 127.2, 127.1**, 127.0, 126.7**, 125.5, 101.0**, 61.5**, 48.6, 36.9, 37.5, 34.4, 27.7**, 24.6, 18.4**. **HRMS** (ES$^+$) *m/z* calcd for $[C_{24}H_{29}Cl_2N_2O_4]^+$: 479.1499; found 479.1506 (M+H$^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

3-(2,4-dichlorophenyl)-*N*^{1}-(3-methylbenzyl)-*N*^{5}-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanediamide



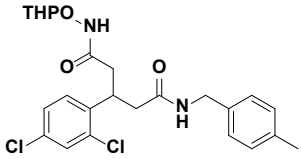
(S5). Synthesized by method A using **30** (200 mg, 0.53 mmol, 1.0 equiv.), EDC (99 mg, 0.64 mmol, 1.2 equiv.), HOBt (86 mg, 0.64 mmol, 1.2 equiv.), 3-methylbenzylamine (80 µL, 0.64 mmol, 1.2 equiv.), DIPEA (109 µL, 0.64 mmol, 1.2 equiv.) and DMF (3 mL). The titled compound 130 mg, 0.27 mmol, 51%) was collected as a colorless solid.

TLC (5% MeOH–DCM): R_f = 0.17. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.96 (d, *J* = 11.8 Hz, 2H), 8.29 (t, *J* = 6.0 Hz, 2H), 7.53 (d, *J* = 1.6 Hz, 2H), 7.39–7.30 (m, 4H), 7.11 (t, *J* = 7.5 Hz, 2H), 7.00 (d, *J* = 7.6 Hz, 2H), 6.85 (s, 2H), 6.77 (d, *J* = 7.2 Hz, 2H), 4.76–4.73* (m, 1H), 4.61–4.58* (m, 1H), 4.20 (dd, *J* = 15.2, 6.2 Hz, 2H), 4.13–3.94 (m, 4H), 3.93–3.76 (m, 2H), 3.53–3.37 (m, 2H), 2.62–2.54 (m, 2H), 2.53–2.46 (m, 2H, overlap with solvent peak), 2.44–2.26 (m, 4H), 2.24 (s, 6H), 1.69–1.38 (m, 12H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 169.7, 166.7, 139.6, 139.3, 137.2, 134.0, 131.4, 129.7, 128.7, 128.0, 127.6, 127.2, 127.1, 124.1, 101.0**, 100.9, 61.4, 41.8, 36.9, 34.4, 27.7**, 24.6, 21.0, 18.4. **HRMS** (ES$^+$) *m/z* calcd for $[C_{24}H_{29}Cl_2N_2O_4]^+$: 479.1499; found 479.1503 (M+H$^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

3-(2,4-dichlorophenyl)-*N*^{1}-(4-methylbenzyl)-*N*^{5}-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanediamide



(S6). Synthesized by method A using **30** (200 mg, 0.53 mmol, 1.0 equiv.), EDC (99 mg, 0.64 mmol, 1.2 equiv.), HOBt (86 mg, 0.64 mmol, 1.2 equiv.), 4-methylbenzylamine (81 µL, 0.64 mmol, 1.2 equiv.), DIPEA (109 µL, 0.64 mmol, 1.2 equiv.) and DMF (3 mL). The titled compound (122 mg, 0.26 mmol, 48%) was collected as a colorless solid.

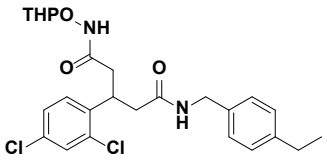
TLC (5% MeOH–DCM): R_f = 0.17. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.95 (d, *J* = 14.6 Hz, 2H), 8.26 (t, *J* = 6.0 Hz, 2H), 7.53 (s, 2H), 7.38–7.30 (m, 4H), 7.03 (d, *J* = 7.6 Hz, 4H), 6.86 (dd, *J* = 8.1, 2.9 Hz, 4H), 4.74* (br.s, 1H), 4.60* (br.s, 1H), 4.17 (dd, *J* = 15.1, 6.2 Hz, 2H), 4.09–3.93 (m, 4H), 3.92–3.79 (m, 2H), 3.53–3.37 (m, 2H), 2.59–2.44 (m, 4H, overlap with solvent peak), 2.42–2.29 (m, 4H), 2.26 (s, 6H), 1.69–

1.43 (m, 12H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 169.7, 166.7, 139.6, 136.3, 135.6, 134.1, 131.4, 129.8, 128.7, 128.6, 127.1, 126.9, 101.0**, 61.5, 41.6, 36.9, 34.4, 27.74, 27.69, 24.6, 20.6, 18.4. **HRMS** (ES^+) *m/z* calcd for $[C_{24}H_{29}Cl_2N_2O_4]^+$: 479.1499; found 479.1503 ($M+H^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

3-(2,4-dichlorophenyl)-*N*^{1}-(4-ethylbenzyl)-*N*^{5}-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanediamide (S7).



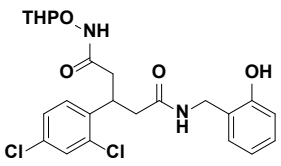
Synthesized by method A using **30** (200 mg, 0.53 mmol, 1.0 equiv.), EDC (99 mg, 0.64 mmol, 1.2 equiv.), HOBt (86 mg, 0.64 mmol, 1.2 equiv.), 4-ethylbenzylamine (88 µL, 0.64 mmol, 1.2 equiv.), DIPEA (109 µL, 0.64 mmol, 1.2 equiv.) and DMF (3 mL). The titled compound (42 mg, 0.09 mmol, 16%) was collected as a colorless solid.

TLC (5% MeOH–DCM): R_f = 0.14. **^{1}H NMR** (500 MHz, DMSO-d_6) δ 10.96 (d, *J* = 14.8 Hz, 2H), 8.26 (t, *J* = 5.9 Hz, 2H), 7.54–7.51 (m, 2H), 7.38–7.30 (m, 4H), 7.06 (d, *J* = 7.7 Hz, 4H), 6.88 (dd, *J* = 8.2, 2.9 Hz, 4H), 4.74* (br.s 1H), 4.60* (br.s, 1H), 4.19 (dd, *J* = 15.1, 6.3 Hz, 2H), 4.08–3.95 (m, 4H), 3.92–3.80 (m, 2H), 3.49–3.38 (m, 2H), 2.55–2.45 (m, 6H, overlap with solvent peak), 2.43–2.29 (m, 4H), 1.69–1.42 (m, 12H), 1.15 (t, *J* = 7.6 Hz, 6H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 169.7, 166.7, 142.1, 139.6, 136.6, 134.1, 131.4, 129.8**, 128.7, 127.5, 127.1, 127.1**, 101.0, 61.5, 41.7, 41.6, 36.9, 34.4, 27.8, 24.6, 18.4, 15.7, 15.6. **HRMS** (ES^+) *m/z* calcd for $[C_{25}H_{31}Cl_2N_2O_4]^+$: 493.1655; found 493.1665 ($M+H^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

3-(2,4-dichlorophenyl)-*N*^{1}-(3-hydroxybenzyl)-*N*^{5}-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanediamide (S8)



Synthesized by Method B using **30** (100 mg, 0.27 mmol, 1.0 equiv.), HATU (111 mg, 0.29 mmol, 1.1 equiv.), DIPEA (93 µL, 0.53 mmol, 2.0 equiv.), 2-hydroxybenzylamine (49 mg, 0.40 mmol, 1.5 equiv.), and DMF (2 mL). The crude product was purified by RP ACC (gradient: 10–30% MeCN–H_2O in 0.1% formic acid). Appropriate fractions were pooled, 10% $NaHCO_3$ solution added and the aqueous phase extracted with DCM (×2). The combined organic layers were dried (Na_2SO_4) and reduced *in vacuo* to give the titled compound (100 mg, 0.21 mmol, 78%) was collected as a fluffy colorless solid.

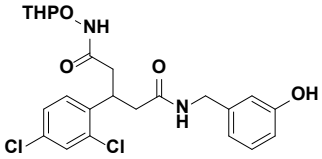
TLC (5% MeOH–DCM): R_f = 0.14. **^{1}H NMR** (500 MHz, MeOD-d_4) δ 7.34 (d, *J* = 2.2 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.16 (dd, *J* = 8.5, 2.2 Hz, 2H), 7.06 (td, *J* = 7.8, 1.8 Hz, 2H), 6.87–6.81 (m, 2H), 6.74 (d, *J* = 8.0 Hz, 2H), 6.70 (t, *J* = 7.4 Hz, 2H), 4.81–4.76* (m, 1H), 4.62–4.57* (m, 1H), 4.27–4.11 (m, 6H), 3.95–3.86 (m, 2H), 3.55–3.45 (m, 2H), 2.70–2.59 (m, 4H), 2.59–2.46 (m, 4H), 1.78–1.63 (m, 6H), 1.62–1.47

(m, 6H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 173.4**, 169.8**, 156.4, 139.6**, 135.9, 134.0, 130.8, 130.4**, 130.3, 129.6**, 128.4**, 125.6, 120.5, 116.4, 103.4**, 63.3**, 41.4**, 39.7, 38.4**, 36.6, 28.9**, 26.1, 19.6**. **HRMS** (ES^+) *m/z* calcd for $[C_{23}H_{27}Cl_2N_2O_5]^+$: 481.1292; found 481.1316 ($M+H^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

3-(2,4-dichlorophenyl)-*N*^{1}-(3-hydroxybenzyl)-*N*^{5}-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanediamide (S9)



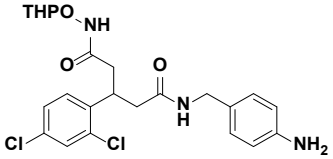
Synthesized by Method B using **30** (100 mg, 0.27 mmol, 1.0 equiv.), HATU (111 mg, 0.29 mmol, 1.1 equiv.), DIPEA (93 µL, 0.53 mmol, 2.0 equiv.), 3-hydroxybenzylamine (49 mg, 0.40 mmol, 1.5 equiv.) and DMF (2 mL). The crude product was purified using the same protocol outlined in the synthesis of **S8**. The titled compound (100 mg, 0.21 mmol, 78%) was collected as a fluffy colorless solid.

TLC (5% MeOH–DCM): R_f = 0.08. **^{1}H NMR** (500 MHz, MeOD-d_4) δ 7.39 (d, *J* = 2.2 Hz, 2H), 7.30 (d, *J* = 8.5 Hz, 2H), 7.23 (dd, *J* = 8.4, 2.2 Hz, 2H), 7.04 (t, *J* = 7.8 Hz, 2H), 6.64 (dd, *J* = 8.0, 2.4 Hz, 2H), 6.60 (d, *J* = 2.7 Hz, 2H), 6.48 (d, *J* = 7.5 Hz, 2H), 4.81–4.77* (m, 1H), 4.61* (t, *J* = 3.3 Hz, 1H), 4.25–4.09 (m, 6H), 3.99–3.86 (m, 2H), 3.55–3.46 (m, 2H), 2.72–2.59 (m, 4H), 2.58–2.46 (m, 4H), 1.80–1.63 (m, 6H), 1.60–1.47 (m, 6H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.9**, 169.8**, 158.6, 141.2, 139.7**, 135.9, 134.0, 130.8, 130.4**, 128.4**, 119.5, 115.4, 115.0, 103.4**, 63.2**, 44.0, 41.5**, 38.5**, 36.6**, 33.4, 28.9**, 26.1, 19.5**. **HRMS** (ES^+) *m/z* calcd for $[C_{23}H_{27}Cl_2N_2O_5]^+$: 481.1292; found 481.1309 ($M+H^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

***N*^{1}-(4-aminobenzyl)-3-(2,4-dichlorophenyl)-*N*^{5}-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanediamide**



(S10) Synthesized by Method B using **30** (100 mg, 0.27 mmol, 1.0 equiv.), HATU (111 mg, 0.29 mmol, 1.1 equiv.), DIPEA (93 µL, 0.53 mmol, 2.0 equiv.), freshly distilled 4-aminobenzylamine (45 µL, 0.40 mmol, 1.5 equiv.), and DMF (2 mL). The crude product was purified by RP ACC (gradient: 10–20% MeCN–H_2O in 0.1% formic acid). Appropriate fractions were pooled, 10% $NaHCO_3$ solution added, and the aqueous phase extracted with DCM (×2). The combined organic layers were dried (Na_2SO_4) and reduced *in vacuo* to give the titled compound (93 mg, 0.19 mmol, 73%) as a fluffy colorless semi-solid.

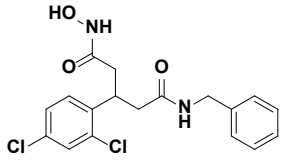
TLC (5% 7.0 M NH_3 in MeOH–DCM): R_f = 0.17. **^{1}H NMR** (500 MHz, MeOD-d_4) δ 7.40 (dd, *J* = 2.2, 1.2 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.23 (dd, *J* = 8.4, 2.2 Hz, 2H), 6.80 (d, *J* = 8.1 Hz, 4H), 6.65–6.60 (m, 4H), 4.78* (t, *J* = 3.2 Hz, 1H), 4.61* (t, *J* = 3.3 Hz, 1H), 4.21–4.13 (m, 4H), 4.05 (dd, *J* = 14.5, 2.5 Hz, 2H),

3.95–3.86 (m, 2H), 3.57–3.46 (m, 2H), 2.68–2.56 (m, 4H), 2.56–2.41 (m, 4H), 1.80–1.65 (m, 6H), 1.65–1.47 (m, 6H). **^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.7**, 169.7, 147.8, 139.8**, 136.0, 134.0, 130.9, 130.4**, 129.6, 129.1, 128.4**, 116.5, 103.4**, 63.2**, 43.8, 41.6**, 38.9, 38.5**, 36.7**, 28.9**, 26.1, 19.6**. **HRMS** (ES^+) *m/z* calcd for $[C_{23}H_{28}Cl_2N_3O_4]^+$: 480.1451; found 480.1460 ($M+H^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

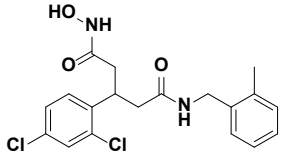
***N*^{1}-benzyl-3-(2,4-dichlorophenyl)-*N*^{5}-hydroxypentanediamide (7).** Synthesized by Method B using **30**



(43 mg, 0.11 mmol, 1.0 equiv.), HATU (48 mg, 0.13 mmol, 1.1 equiv.), DIPEA (40 µL, 0.23 mmol, 2.0 equiv.), benzylamine (14 µL, 0.13 mmol, 1.1 equiv.), and DMF (2 mL) and the reaction stirred for 2 h. Deprotection was carried out using PPTS (16 mg, 0.06 mmol, 0.5 equiv.) and abs. EtOH (5 mL). The crude product was purified using RP ACC (gradient: 10–90% MeCN–H_2O in 0.1% formic acid). The titled compound (111 mg, 0.23 mmol, 44%–over two steps) was collected as a colorless fluffy material after lyophilization.

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.38 (s, 1H), 8.70 (br.s, 1H), 8.31 (t, *J* = 6.0 Hz, 1H), 7.55–7.52 (m, 1H), 7.35 (d, *J* = 1.3 Hz, 2H), 7.25–7.17 (m, 3H), 7.02–6.93 (m, 2H), 4.22 (dd, *J* = 15.3, 6.3 Hz, 1H), 4.10 (dd, *J* = 15.3, 5.6 Hz, 1H), 4.03–3.96 (m, 1H), 2.54 (dd, *J* = 14.4, 8.6 Hz, 1H), 2.51–2.46 (m, 1H, overlap with solvent peak), 2.36 (dd, *J* = 14.5, 7.9 Hz, 1H), 2.29 (dd, *J* = 14.5, 7.2 Hz, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 169.8, 166.8, 139.8, 139.4, 134.1, 131.4, 129.8, 128.8, 128.1, 127.2, 126.9, 126.6, 41.8, 39.7 (overlap with solvent peak), 36.9, 34.4. **HPLC**, t_R 5.52 min (>98%, UV_{214}). **HRMS** (ES^+) *m/z* calcd for $[C_{18}H_{19}Cl_2N_2O_3]^+$: 381.0767; found 381.0785 ($M+H^+$).

3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(2-methylbenzyl)pentanediamide (8). Synthesized by method

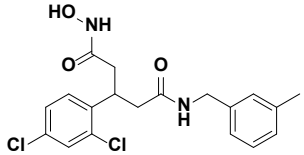


D1 using **S4** (62 mg, 0.13 mmol, 1.0 equiv.), PPTS (7 mg, 0.03 mmol, 0.2 equiv.) and abs. EtOH (3 mL). The crude product was purified by NP ACC (stepwise: 1→5→10% MeOH–DCM). The titled compound (42 mg, 0.11 mmol, 82%) was collected as a colorless solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (br.s, 1H), 8.70 (br.s, 1H), 8.17 (br.t, *J* = 5.7 Hz, 1H), 7.52 (br.t, *J* = 1.3 Hz, 1H), 7.35 (d, *J* = 1.3 Hz, 2H), 7.15–7.08 (m, 2H), 7.08–6.99 (m, 1H), 6.83 (br.d, *J* 7.6, 1H), 4.17 (dd, *J* = 15.3, 5.8 Hz, 1H), 4.07 (dd, *J* = 15.3, 5.4 Hz, 1H), 3.99 (q, *J* = 7.5 Hz, 1H) 2.60–2.45 (m, 2H, overlap with solvent peak), 2.36 (dd, *J* = 14.5, 7.8 Hz, 1H), 2.28 (dd, *J* = 14.5, 7.2 Hz, 1H) 2.14 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 169.7, 166.8, 139.8, 136.8, 135.5, 134.1, 131.4, 129.8, 128.7, 127.17, 127.16, 126.7, 125.5, 40.1, 39.5 (overlap with solvent peak), 36.9, 34.4, 18.4, one Ar-q missing. **HPLC**,

t_R 5.70 min (>98%, UV_{214}). **HRMS** (ES^+) *m/z* calcd for $[C_{19}H_{21}Cl_2N_2O_3]^+$: 395.0924; found 395.0918 ($M+H^+$).

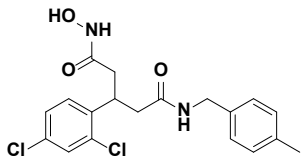
3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(3-methylbenzyl)pentanediamide (9). Synthesized by method



D1 using **S5** (106 mg, 0.22 mmol, 1.0 equiv.), PPTS (12.5 mg, 0.05 mmol, 0.2 equiv.) and abs. EtOH (3 mL). The product was purified in the same manner as outlined in the synthesis of **8**. The titled compound (49 mg, 0.12 mmol, 56%) was collected as a colorless solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (br.s, 1H), 8.70 (br.s, 1H), 8.28 (br.t, *J* = 5.9 Hz, 1H), 7.53 (t, *J* = 1.2 Hz, 1H), 7.45–7.26 (m, 2H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.00 (br.d, *J* = 7.5 Hz, 1H), 6.85 (br.s, 1H), 6.77 (br.d, *J* = 7.6 Hz, 1H), 4.19 (dd, *J* = 15.2, 6.2 Hz, 1H), 4.11–3.95 (m, 2H), 2.59–2.44 (m, 2H, overlap with solvent peak), 2.36 (dd, *J* = 14.6, 7.8 Hz, 1H), 2.28 (dd, *J* = 14.5, 7.3 Hz, 1H), 2.23 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 169.8, 166.8, 139.8, 139.3, 137.2, 134.1, 131.4, 129.7, 128.8, 128.0, 127.6, 127.3, 127.2, 124.1, 41.8, 39.5 (overlap with solvent peak), 36.9, 34.4, 21.0. **HPLC**, t_R 5.76 min (>98%, UV_{280}). **HRMS** (ES^+) *m/z* calcd for $[C_{19}H_{21}Cl_2N_2O_3]^+$: 395.0924; found 395.0936 ($M+H^+$).

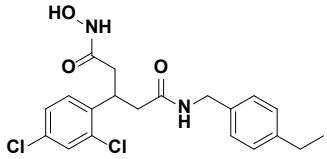
3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(4-methylbenzyl)pentanediamide (10). Synthesized by



method D1 using **S6** (80 mg, 0.17 mmol, 1.0 equiv.), PPTS (9 mg, 0.03 mmol, 0.2 equiv.) and abs. EtOH (3 mL). The product was purified in the same manner as outlined in the synthesis of **8**. The titled compound (53 mg, 0.13 mmol, 79%) was collected as a colorless solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (s, 1H), 8.69 (s, 1H), 8.25 (t, *J* = 5.9 Hz, 1H), 7.53 (t, *J* = 1.2 Hz, 1H), 7.34 (d, *J* = 1.3 Hz, 2H), 7.03 (d, *J* = 7.9 Hz, 2H), 6.87 (d, *J* = 8.0 Hz, 2H), 4.17 (dd, *J* = 15.1, 6.2 Hz, 1H), 4.09–3.94 (m, 2H), 2.56–2.43 (m, 2H, overlap with solvent peak), 2.40–2.27 (m, 2H), 2.25 (s, 3H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 169.7, 166.8, 139.8, 136.3, 135.6, 134.1, 131.4, 129.7, 128.7, 128.6, 127.1, 126.9, 41.5, 39.5 (overlap with solvent peak), 36.9, 34.4, 20.7. **HPLC**, t_R 5.74 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{19}H_{21}Cl_2N_2O_3]^+$: 395.0924; found 274.2738 – debenzylated fragment.

3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(4-ethylbenzyl)pentanediamide (11). Synthesized by method

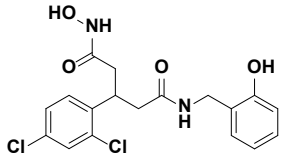


D1 using **S7** (40 mg, 0.08 mmol, 1.0 equiv.), PPTS (4 mg, 0.02 mmol, 0.2 equiv.) and abs. EtOH (3 mL). The product was purified in the same manner as outlined in the synthesis of **8**. The titled compound (20 mg, 0.05 mmol, 61%) was collected as a colorless solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.3 (br.s, 1H), 8.71 (br.s, 1H), 8.26 (br.t, *J* = 6.0 Hz, 1H), 7.54 (t, *J* = 1.2 Hz, 1H), 7.35 (d, *J* = 1.3 Hz, 2H), 7.07 (d, *J* = 7.9 Hz, 2H), 6.89 (d, *J* = 7.9 Hz, 2H), 4.19 (dd, *J* = 15.1, 6.2 Hz, 1H), 4.12–3.94 (m, 2H), 2.57 (q, *J* 7.5 Hz, 2H), 2.56–2.45 (m, 2H, overlap with solvent peak),

2.38 (dd, *J* = 14.5, 7.9 Hz, 1H), 2.31 (dd, *J* = 14.5, 7.3 Hz, 1H), 1.15 (t, *J* = 7.6 Hz, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 169.7, 166.8, 142.1, 139.8, 136.6, 134.1, 131.4, 129.8, 128.7, 127.5, 127.2, 127.0, 41.6, 40.1, 36.9, 34.4, 27.8, 15.7. **HPLC**, t_R 5.98 min (>95%, UV_{280}). **HRMS** (ES^+) *m/z* calcd for $[C_{20}H_{23}Cl_2N_2O_3]^+$: 409.1080; found 409.1072 ($M+H^+$).

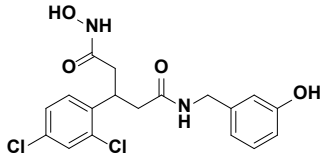
3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(2-hydroxybenzyl)pentanediamide (12)



Synthesized by Method D1 using **S8** (46 mg, 0.096 mmol, 1.0 equiv.), PPTS (5 mg, 0.019 mmol, 0.2 equiv.) and abs. EtOH (3 mL). The crude product was purified by RP ACC (gradient: 10–50% MeCN–H_2O in 0.1% formic acid). The titled compound (25 mg, 0.063 mmol, 66%) was collected as a fluffy colorless solid after lyophilization.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.34 (d, *J* = 2.2 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.16 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.06 (td, *J* = 7.7, 1.7 Hz, 1H), 6.83 (dd, *J* = 7.5, 1.7 Hz, 1H), 6.73 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.70 (td, *J* = 7.4, 1.2 Hz, 1H), 4.27–4.16 (m, 2H), 4.16–4.10 (m, 1H), 2.69–2.58 (m, 2H), 2.54–2.44 (m, 2H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 173.5, 170.2, 156.4, 139.6, 135.9, 134.0, 130.8, 130.4, 130.3, 129.6, 128.4, 125.7, 120.5, 116.4, 41.3, 39.7, 38.3, 36.7. **HPLC**, t_R 5.29 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{18}H_{19}Cl_2N_2O_4]^+$: 397.0716; found 397.0720 ($M+H^+$).

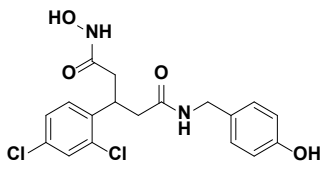
3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(3-hydroxybenzyl)pentanediamide (13)



Synthesized by Method D1 using **S9** (44 mg, 0.091 mmol, 1.0 equiv.), PPTS (5 mg, 0.018 mmol, 0.2 equiv.) and abs. EtOH (3 mL). The crude product was purified by RP ACC (gradient: 10–35% MeCN–H_2O in 0.1% formic acid). The titled compound (20 mg, 0.05 mmol, 55%) was collected as a fluffy colorless solid after lyophilization.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.40 (d, *J* = 2.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.23 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.04 (t, *J* = 7.8 Hz, 1H), 6.63 (ddd, *J* = 8.1, 2.6, 1.0 Hz, 1H), 6.60 (t, *J* = 2.0 Hz, 1H), 6.48 (ddd, *J* = 7.6, 1.7, 0.9 Hz, 1H), 4.25–4.07 (m, 3H), 2.71–2.57 (m, 2H), 2.52–2.44 (m, 2H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.9, 170.2, 158.6, 141.2, 139.8, 135.9, 134.0, 130.8, 130.5, 130.4, 128.4, 119.5, 115.5, 115.0, 44.0, 41.4, 38.4, 36.7. **HPLC**, t_R 4.99 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{18}H_{19}Cl_2N_2O_4]^+$: 397.0716; found 397.0721 ($M+H^+$).

3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(4-hydroxybenzyl)pentanediamide (14). Synthesized by

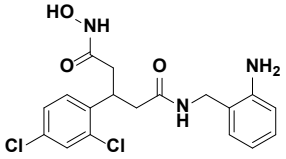


Method B using **30** (49 mg, 0.13 mmol, 1.0 equiv.), HATU (54 mg, 0.14 mmol, 1.1 equiv.), DIPEA (45 µL, 0.26 mmol, 2.0 equiv.), 4-(aminomethyl)phenol (17 mg, 0.14 mmol, 1.1 equiv.), and DMF (2 mL) and the reaction stirred for 2 h. Deprotection was carried out using PPTS (23 mg, 0.09 mmol, 0.7 equiv.)

and abs. EtOH (5 mL).The crude product was purified by RP ACC (gradient: 10–40% MeCN–H_2O in 0.1% formic acid). The titled compound (24 mg, 0.06 mmol, 47%–over two steps) was collected as a colorless fluffy material after lyophilization.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.40 (d, J = 2.2 Hz, 1H), 7.30 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 8.4, 2.2 Hz, 1H), 6.87–6.83 (m, 2H), 6.68–6.63 (m, 2H), 4.22–4.13 (m, 2H), 4.06 (d, J = 14.6 Hz, 1H), 2.69–2.57 (m, 2H), 2.47 (d, J = 7.4 Hz, 2H). **^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.8, 170.1, 157.6, 139.8, 136.0, 134.0, 130.9, 130.5, 130.4, 129.8, 128.4, 116.1, 43.6, 41.4, 38.5, 36.7. **HPLC**, t_R 4.83 min (>98%, UV_{280}). **HRMS** (ES^+) *m/z* calcd for $[C_{18}H_{19}Cl_2N_2O_4]^+$: 397.0716; found 397.0735 ($M+H^+$).

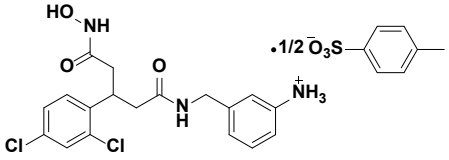
***N*^{1}-(2-aminobenzyl)-3-(2,4-dichlorophenyl)-*N*^{5}-hydroxypentanediamide (15).** Synthesized by Method



B using **30** (200 mg, 0.53 mmol, 1.0 equiv.), HATU (243 mg, 0.64 mmol, 1.2 equiv.), DIPEA (137 µL, 1.06 mmol, 2.0 equiv.), freshly purified 2-(aminomethyl)aniline (78 mg, 0.64 mmol, 1.2 equiv.), and DMF (2 mL) and the reaction stirred for 1 h. Deprotection was carried out using PPTS (35 mg, 0.14 mmol, 0.5 equiv.) and abs. EtOH (5 mL). The crude product was purified using RP ACC (gradient: 5–30% MeCN–H_2O in 0.1% formic acid). Appropriate fractions were pooled and reduced *in vacuo* to a volume of ~3 mL and the resulting precipitate filtered. The titled compound (5 mg, 0.01 mmol, 3%–over two steps) was collected as colorless microcrystals.

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.38 (br.s, 1H), 8.69 (br.s, 1H), 8.22 (t, J = 6.1 Hz, 1H), 7.52 (s, 1H), 7.34 (s, 2H), 6.92 (td, J = 7.6, 1.6 Hz, 1H), 6.69 (d, J = 7.4 Hz, 1H), 6.57 (d, J = 7.9 Hz, 1H), 6.42 (t, J = 7.3 Hz, 1H), 4.93 (s, 2H), 4.06–3.96 (m, 3H), 2.55–2.49 (m, 1H, overlap with solvent peak), 2.46 (dd, J = 14.6, 6.8 Hz, 1H), 2.36 (dd, J = 14.6, 8.1 Hz, 1H), 2.30 (dd, J = 14.6, 7.0 Hz, 1H).**^{13}C NMR** (151 MHz, DMSO-d_6) δ 170.1, 166.8, 146.0, 139.8, 134.0, 131.4, 129.6, 128.8, 128.5, 127.6, 127.2, 121.9, 115.6, 114.4, 39.8, 38.9, 36.7, 34.3. **HPLC**, t_R 4.55 min (>98%, UV_{280}). **HRMS** (ES^+) *m/z* calcd for $[C_{18}H_{20}Cl_2N_3O_3]^+$: 396.0876; found 396.0893 ($M+H^+$).

***N*^{1}-(3-aminobenzyl)-3-(2,4-dichlorophenyl)-*N*^{5}-hydroxypentanediamide, 4-methylbenzenesulfonate salt (16)**



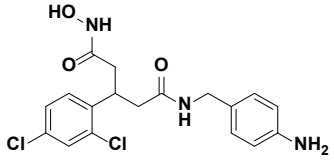
Synthesized by Method B using **30** (200 mg, 0.53 mmol, 1.0 equiv.), HATU (243 mg, 0.64 mmol, 1.2 equiv.), DIPEA (137 µL, 1.06 mmol, 2.0 equiv.), freshly purified 3-(aminomethyl)aniline (78 mg, 0.64 mmol, 1.2 equiv.), and DMF (2 mL) and the reaction stirred for 1 h. Deprotection was carried out using PPTS (35 mg, 0.14 mmol, 0.5 equiv.) and abs. EtOH (5 mL). Reaction monitoring outlined formation of other side products and therefore the reaction was halted prior to completion. The crude product was purified by RP ACC (gradient: 5–15% MeCN–H_2O in 0.1% formic

acid). The titled compound (8 mg, 0.020 mmol, 24%) was collected as a fluffy off-white solid after lyophilization. Tosylate salt formation occurred during deprotection and was carried through purification. **^{1}H NMR** (600 MHz, MeOD-d_4) δ 8.36 (br.t, J = 6.0 Hz, 1H), 7.73–7.68* (m, 1H), 7.41 (d, J = 2.2 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.25 (dd, J = 8.5, 2.1 Hz, 1H), 7.24–7.21* (m, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.89–6.84 (m, 1H), 6.83 (t, J = 2.0 Hz, 1H), 6.68 (d, J = 7.6 Hz, 1H), 4.28–4.22 (m, 1H), 4.22–4.12 (m, 2H), 2.69 (dd, J = 14.2, 6.6 Hz, 1H), 2.63 (dd, J = 14.3, 8.6 Hz, 1H), 2.52–2.43 (m, 2H), 2.37* (s, 2H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 173.2, 173.1, 170.1, 143.6, 141.7, 141.6, 139.9, 135.9, 134.0, 130.9, 130.7, 130.5, 129.8, 128.4, 127.0, 122.8, 118.8, 118.5, 43.9**, 41.5**, 38.4, 36.7, 21.3. **HPLC**, t_R 4.34 min (>95%, UV_{214}). **HRMS** (ES^+) *m/z* calcd for parent compound $[C_{18}H_{20}Cl_2N_3O_3]^+$: 396.0876; found 396.0882 ($M+H^+$).

*Peaks account for tosylate protons – integrates to ½ of parent compound.

**Peaks appear as doublets from differences in salt and free-base forms.

***N*^{1}-(4-aminobenzyl)-3-(2,4-dichlorophenyl)-*N*^{5}-hydroxypentanediamide (17)**

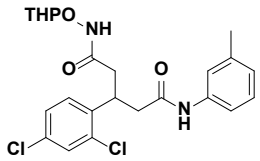


Synthesized by Method D1 using **S10** (26 mg, 0.05 mmol, 1.0 equiv.), PPTS (3 mg, 0.01 mmol, 0.2 equiv.) and abs. EtOH (3 mL). Reaction monitoring outlined formation of other side products and therefore the reaction was halted prior to completion. The crude product was purified by RP ACC (gradient: 5–8% MeCN–H_2O in 0.1% formic acid). The titled compound (3 mg, 0.008 mmol, 14%) was collected as a fluffy off-white solid after lyophilization.

^{1}H NMR (600 MHz, MeOD-d_4) δ 8.35 (br.s, 1H), 8.15 (t, J = 5.8 Hz, 1H), 7.41 (d, J = 2.2 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 8.4, 2.2 Hz, 1H), 6.83–6.78 (m, 2H), 6.64–6.60 (m, 2H), 4.21–4.12 (m, 2H), 4.05 (dd, J = 14.5, 4.8 Hz, 1H), 2.68–2.55 (m, 2H), 2.50–2.44 (m, 2H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.8, 170.1, 147.7, 139.8, 136.0, 134.0, 130.9, 130.4, 129.6, 129.2, 128.4, 116.6, 43.8, 41.5, 38.5, 36.7. **HPLC**, t_R 4.05 min (>98%, UV_{214}). **HRMS** (ES^+) *m/z* calcd for $[C_{18}H_{20}Cl_2N_3O_3]^+$: 396.0876; found 396.0877 ($M+H^+$).

4.3.2 Synthesis of anilines

3-(2,4-dichlorophenyl)-*N*^{1}-((tetrahydro-2*H*-pyran-2-yl)oxy)-*N*^{5}-(*m*-tolyl)pentanediamide. (S11)



Synthesized by method A using **30** (300 mg, 0.8 mmol, 1.0 equiv.), EDC (186 mg, 1.2 mmol, 1.5 equiv.), HOBt (162 mg, 1.2 mmol, 1.5 equiv.), *m*-toluidine (130 µL, 1.2 mmol, 1.5 equiv.), DIPEA (205 µL, 1.2 mmol, 1.5 equiv.) and DMF (4 mL). HPLC-MS analysis showed the reaction to be incomplete therefore *m*-toluidine (43 µL, 0.4 mmol, 0.5 equiv.), EDC (62 mg, 0.4 mmol, 0.5 equiv.), HOBt (54 mg, 0.4 mmol, 0.5 equiv.),

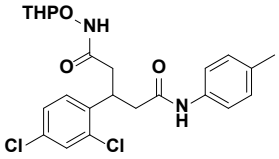
and DIPEA (68 µL, 0.4 mmol, 0.5 equiv.) were added and the reaction stirred 4 h. The titled compound (19 mg, 0.04 mmol, 8%) was collected as a colorless solid.

TLC (5% MeOH–DCM): R_f = 0.2. **^{1}H NMR** (600 MHz, DMSO-d_6) δ 10.97 (d, *J* = 14.2 Hz, 2H), 9.83 (d, *J* = 2.2 Hz, 2H), 7.53 (d, *J* = 1.9 Hz, 2H), 7.38 (dd, *J* = 5.2, 1.9 Hz, 4H), 7.35 (br.s, 2H), 7.25 (br.d, *J* = 7.8 Hz, 2H), 7.12 (t, *J* = 7.8 Hz, 2H), 6.86–6.78 (m, 2H), 4.74–4.70* (m, 1H), 4.60–4.57* (m, 1H), 4.12–3.96 (m, 2H), 3.91–3.80 (m, 2H), 3.48–3.40 (m, 2H, overlap with residual water), 2.76–2.64 (m, 4H), 2.47–2.32 (m, 4H), 2.24 (s, 6H), 1.67–1.56 (m, 4H), 1.56 –1.42 (m, 8H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 168.8, 166.7, 139.6, 138.9, 137.8, 134.0, 131.4, 129.6, 128.7, 128.5, 127.2, 123.8, 119.6, 116.3, 101.1**, 61.5, 40.6, 39.5, 34.1, 27.7**, 24.6, 21.2, 18.4. **HRMS** (ES$^+$) *m/z* calcd for $[C_{23}H_{27}Cl_2N_2O_4]^+$: 465.1342; found 465.1345 (M+H$^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

3-(2,4-dichlorophenyl)-*N*^{1}-((tetrahydro-2*H*-pyran-2-yl)oxy)-*N*^{5}-(*p*-tolyl)pentanediamide (S12).



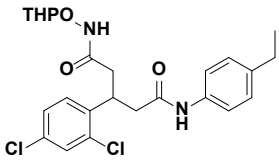
Synthesized by Method B using **30** (190 mg, 0.51 mmol, 1.0 equiv.), HATU (285 mg, 0.75 mmol, 1.5 equiv.), DIPEA (128 µL, 0.75 mmol, 1.5 equiv.), *p*-toluidine (80 mg, 0.75 mmol, 1.5 equiv.), and DMF (3 mL). The crude yellow oil was purified by NP ACC (stepwise: 0→6→100% MeOH–DCM). The product was further purified by RP ACC (gradient: 10–100% MeCN–H_2O in 0.1% formic acid). Appropriate fractions were pooled, extracted with DCM, dried (Na_2SO_4) and reduced *in vacuo* to give the titled compound (53 mg, 0.11 mmol, 23%) was collected as a colorless solid.

TLC (5% MeOH–DCM): R_f = 0.2. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.97 (d, *J* = 10.0 Hz, 2H), 9.81 (s, 2H), 7.55–7.51 (m, 2H), 7.42–7.33 (m, 8H), 7.08–7.02 (m, 4H), 4.72* (br.s, 1H), 4.58* (br.s, 1H), 4.02 (quint, *J* = 7.1 Hz, 2H), 3.93–3.77 (m, 2H), 3.49–3.36 (m, 2H), 2.75–2.63 (m, 4H), 2.47–2.30 (m, 4H), 2.22 (s, 6H), 1.69–1.55 (m, 4H), 1.55–1.39 (m, 8H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 168.6, 166.7, 139.7, 136.5, 134.0, 132.0, 131.4, 129.6, 129.0, 128.7, 127.2, 119.2, 101.1**, 61.5, 40.6, 36.7, 34.2, 27.7, 24.6, 20.4, 18.4 **HRMS** (ES$^+$) *m/z* calcd for $[C_{23}H_{27}Cl_2N_2O_4]^+$: 465.1342; found 465.1348 (M+H$^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

3-(2,4-dichlorophenyl)-*N*^{1}-(4-ethylphenyl)-*N*^{5}-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanediamide



(S13). Synthesized by Method B using **30** (200 mg, 0.53 mmol, 1.0 equiv.), HATU (302 mg, 0.79 mmol, 1.5 equiv.), DIPEA (136 µL, 0.79 mmol, 1.5 equiv.), 4-ethylaniline (99 µL, 0.79 mmol, 1.5 equiv.), and DMF (3 mL). The product was

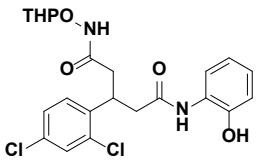
purified further in the same manner as outlined in the synthesis of **S12**. The titled compound (111 mg, 0.23 mmol, 44%) was collected as a colorless solid.

TLC (5% MeOH–DCM): R_f = 0.3. **^{1}H NMR** (400 MHz, DMSO-d_6) δ 10.97 (d, *J* = 9.9 Hz, 2H), 9.82 (s, 2H), 7.53 (d, *J* = 1.9 Hz, 2H), 7.43–7.32 (m, 8H), 7.08 (d, *J* = 8.5 Hz, 4H), 4.72* (br.s, 1H), 4.58* (br.s, 1H), 4.03 (p, *J* = 7.1 Hz, 2H), 3.93–3.76 (m, 2H), 3.51–3.37 (m, 4H), 2.79–2.61 (m, 4H), 2.54 (q, *J* = 7.6 Hz, 4H, overlap with solvent peak), 2.46–2.30 (m, 4H), 1.70–1.55 (m, 4H), 1.55–1.38 (m, 8H), 1.13 (t, *J* = 7.6 Hz, 6H). **^{13}C NMR** (126 MHz, DMSO-d_6) δ 168.6, 166.7, 139.7, 138.5, 136.7, 134.0, 131.4, 129.6, 128.7, 127.8, 127.2, 119.2, 101.1**, 61.5, 40.6, 36.6, 34.2, 27.7, 27.6, 24.6, 18.4, 15.7. **HRMS** (ES^+) *m/z* calcd for $[C_{24}H_{29}Cl_2N_2O_4]^+$: 479.1499; found 479.1502 ($M+H^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

3-(2,4-dichlorophenyl)-*N*^{1}-(2-hydroxyphenyl)-*N*^{5}-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanediamide



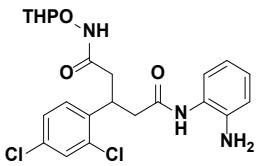
(S14) Synthesized by Method C using **29** (200 mg, 0.77 mmol, 1.0 equiv.), 2-aminophenol (109 mg, 1.00 mmol, 1.3 equiv.), DCM (4 mL), OTX (135 mg, 1.16 mmol, 1.5 equiv.), DIPEA (268 µL, 1.54 mmol, 2.0 equiv.), HATU (322 mg, 0.85 mmol, 1.1 equiv.) and DMF (5 mL). The crude yellow oil was purified by RP ACC (gradient: 10–40% hold MeCN–H_2O in 0.1% formic acid). Appropriate fractions were pooled, extracted with DCM, dried (Na_2SO_4) and reduced *in vacuo* to give the titled compound (316 mg, 0.68 mmol, 88%-over two steps) was collected as an orange semi-solid.

TLC (5% MeOH–DCM): R_f = 0.2. **^{1}H NMR** (500 MHz, MeOD-d_4) δ 7.49 (dt, *J* = 8.0, 1.4 Hz, 2H), 7.41 (d, *J* = 2.2 Hz, 2H), 7.41–7.35 (m, 2H), 7.27 (dd, *J* = 8.5, 2.2 Hz, 2H), 7.00–6.93 (m, 2H), 6.82 (dd, *J* = 8.1, 1.4 Hz, 2H), 6.76 (td, *J* = 7.7, 1.4 Hz, 2H), 4.79* (t, *J* = 3.2 Hz, 1H), 4.62* (t, *J* = 3.3 Hz, 1H), 4.25 (quint, *J* = 7.4 Hz, 2H), 3.90 (m, 2H), 3.54–3.45 (m, 2H), 2.89 (ddd, *J* = 14.6, 7.1, 2.5 Hz, 2H), 2.81 (ddd, *J* = 14.6, 7.8, 3.9 Hz, 2H), 2.65–2.52 (m, 4H), 1.77–1.62 (m, 6H), 1.63–1.45 (m, 6H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.0**, 169.7, 149.6, 139.9**, 135.8, 134.0, 130.7, 130.4**, 128.4**, 126.8, 123.9, 120.6, 117.2, 103.3**, 63.2**, 49.8, 42.0**, 38.2**, 36.5**, 28.8**, 26.1, 19.5**. **HRMS** (ES^+) *m/z* calcd for $[C_{22}H_{25}Cl_2N_2O_5]^+$: 467.1135; found 465.1143 ($M+H^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

***N*^{1}-(2-aminophenyl)-3-(2,4-dichlorophenyl)-*N*^{5}-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanediamide**



(**S15)** Synthesized by Method C using **29** (200 mg, 0.77 mmol, 1.0 equiv.), 1,2-phenylenediamine (108 mg, 1.00 mmol, 1.3 equiv.), DCM (4 mL), OTX (135 mg, 1.16 mmol, 1.5 equiv.), DIPEA (268 µL, 1.54 mmol, 2.0 equiv.), HATU (322 mg,

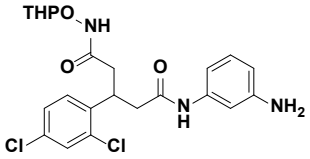
0.85 mmol, 1.1 equiv.) and DMF (5 mL). The crude yellow oil was purified using the same procedure as outlined for **S14**. The titled compound (292 mg, 0.63 mmol, 81%-over two steps) as an off-white foamy semi-solid.

TLC (5% 7.0 M NH_3 in MeOH–DCM): R_f = 0.1. **^{1}H NMR** (500 MHz, MeOD-d_4) δ 7.45 (dd, *J* = 2.2, 1.3 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.32 (dd, *J* = 8.4, 2.2 Hz, 2H), 7.00 (ddd, *J* = 7.9, 7.3, 1.5 Hz, 2H), 6.93 (dd, *J* = 7.9, 1.5 Hz, 2H), 6.80 (dd, *J* = 8.0, 1.4 Hz, 2H), 6.71–6.64 (m, 2H), 4.80* (t, *J* = 3.2 Hz, 1H), 4.64* (t, *J* = 3.3 Hz, 1H), 4.26 (quint, *J* = 7.4 Hz, 2H), 3.97–3.88 (m, 2H), 3.57–3.48 (m, 2H), 2.94–2.77 (m, 4H), 2.66–2.53 (m, 4H), 1.78–1.68 (m, 6H), 1.67–1.48 (m, 6H). **^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.1**, 169.8, 143.1, 140.0**, 135.9, 134.2, 130.9, 130.5**, 128.5**, 128.4, 127.3, 124.8, 119.6, 118.4, 103.3**, 63.2**, 41.5**, 38.4**, 36.5**, 28.9**, 26.2, 19.6**. **HRMS** (ES^+) *m/z* calcd for $[C_{22}H_{26}Cl_2N_3O_4]^+$: 466.1295; found 466.1305 ($M+H^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

N^1-(3-aminophenyl)-3-(2,4-dichlorophenyl)-*N*^{5}-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanediamide



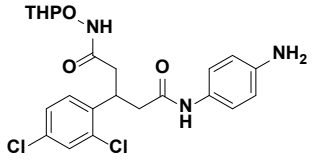
(S16) Synthesized by Method C using **29** (200 mg, 0.77 mmol, 1.0 equiv.), 1,3-phenylenediamine (108 mg, 1.00 mmol, 1.3 equiv.), DCM (4 mL), OTX (135 mg, 1.16 mmol, 1.5 equiv.), DIPEA (268 µL, 1.54 mmol, 2.0 equiv.), HATU (322 mg, 0.85 mmol, 1.1 equiv.) and DMF (5 mL). The crude yellow oil was purified using the same procedure as outlined for **S14**. The titled compound (199 mg, 0.43 mmol, 55%-over two steps) was collected as an off-white foamy semi-solid.

TLC (5% 7.0 M NH_3 in MeOH–DCM): R_f = 0.2. **^{1}H NMR** (500 MHz, MeOD-d_4) δ 7.42 (t, *J* = 1.8 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.29 (dd, *J* = 8.3, 2.2 Hz, 2H), 7.05–6.99 (m, 4H), 6.77–6.71 (m, 2H), 6.50 (ddd, *J* = 7.9, 2.2, 1.0 Hz, 2H), 4.78* (t, *J* = 3.3 Hz, 1H), 4.61* (t, *J* = 3.3 Hz, 1H), 4.23 (quint, *J* = 7.4 Hz, 2H), 3.94–3.87 (m, 2H), 3.53–3.50 (m, 2H), 2.80 (ddd, *J* = 14.6, 7.0, 3.8 Hz, 2H), 2.76–2.68 (m, 2H), 2.64–2.51 (m, 4H), 1.77–1.65 (m, 6H), 1.65–1.49 (m, 6H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 171.4**, 169.8, 147.9, 140.4, 140.0**, 135.9, 134.0, 130.8, 130.41**, 130.35, 128.4**, 113.2, 112.1, 109.1, 103.4**, 63.2**, 42.4**, 38.3**, 36.5**, 28.9**, 26.2, 19.6**. **HRMS** (ES^+) *m/z* calcd for $[C_{22}H_{26}Cl_2N_3O_4]^+$: 466.1295; found 466.1296 ($M+H^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

***N*^{1}-(4-aminophenyl)-3-(2,4-dichlorophenyl)-*N*^{5}-((tetrahydro-2*H*-pyran-2-yl)oxy)pentanediamide**



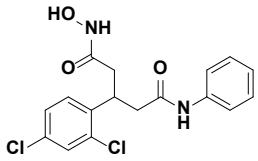
(S17) Synthesized by Method C using **29** (200 mg, 0.77 mmol, 1.0 equiv.), 1,4-phenylenediamine (108 mg, 1.00 mmol, 1.3 equiv.), DCM (4 mL), OTX (135 mg, 1.16 mmol, 1.5 equiv.), DIPEA (268 µL, 1.54 mmol, 2.0 equiv.), HATU (322 mg, 0.85 mmol, 1.1 equiv.) and DMF (5 mL). The crude yellow oil was purified using the same procedure as outlined for **S14**. The titled compound (91 mg, 0.20 mmol, 25%-over two steps) was collected as a pale-red semi-solid.

TLC (5% 7.0 M NH_3 in MeOH–DCM): R_f = 0.3. **^{1}H NMR** (500 MHz, MeOD-d_4) δ 7.41 (dd, *J* = 2.2, 1.0 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.29 (dd, *J* = 8.4, 2.2 Hz, 2H), 7.27–7.21 (m, 4H), 6.83–6.77 (m, 4H), 4.78* (t, *J* = 3.2 Hz, 1H), 4.61* (t, *J* = 3.4 Hz, 1H), 4.23 (quint, *J* = 7.4 Hz, 2H), 3.96–3.86 (m, 2H), 3.56–3.46 (m, 2H), 2.79 (ddd, *J* = 14.4, 7.0, 3.3 Hz, 2H), 2.75–2.66 (m, 2H), 2.64–2.51 (m, 4H), 1.79–1.65 (m, 6H), 1.64–1.48 (m, 6H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 171.3**, 169.8, 141.2, 140.0**, 135.9, 134.0, 132.8, 130.8, 130.4**, 128.4**, 123.1, 118.5, 103.4**, 63.2**, 42.3**, 38.3**, 36.5**, 28.9**, 26.1, 19.6**. **HRMS** (ES$^+$) *m/z* calcd for $[C_{22}H_{26}Cl_2N_3O_4]^+$: 466.1295; found 466.1299 (M+H$^+$).

* Anomeric protons distinct in diastereomeric mixture – all other peaks overlap.

** Diastereomeric carbons visible as doublets.

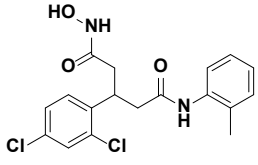
3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-phenylpentanediamide (18). Synthesized by Method C using



29 (116 mg, 0.48 mmol, 1.0 equiv.), aniline (61 µL, 0.67 mmol, 1.5 equiv.), DCM (5 mL), OTX (79 mg, 0.67 mmol, 1.5 equiv.), DIPEA (156 µL, 0.96 mmol, 2.0 equiv.), HATU (187 mg, 0.53 mmol, 1.1 equiv.) and DMF (2 mL), PPTS (13 mg, 0.05 mmol, 0.1 equiv.) and abs. EtOH (8 mL). The crude yellow oil was purified by RP ACC (gradient: 10–50% MeCN–H_2O in 0.1% formic acid). The titled compound (96 mg, 0.26 mmol, 54%-over three steps) was collected as a fluffy pale-pink material after lyophilization.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.44–7.40 (m, 3H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.31–7.23 (m, 3H), 7.06 (tt, *J* = 8.1, 6.7 Hz, 1H), 4.25 (quint, *J* = 8.1, 7.3 Hz, 1H), 2.84 (dd, *J* = 14.5, 6.7 Hz, 1H), 2.74 (dd, *J* = 14.5, 8.1 Hz, 1H), 2.60–2.50 (m, 2H). **^{13}C NMR** (151 MHz, MeOD-d_4) δ 171.5, 170.1, 140.0, 139.5, 135.9, 134.0, 130.7, 130.4, 129.7, 128.4, 125.3, 121.4, 42.3, 38.2, 36.5. **HPLC**, t_R 5.59 min (>98%, UV_{254}). **HRMS** (ES$^+$) *m/z* calcd for $[C_{17}H_{17}Cl_2N_2O_3]^+$: 367.0611; found 367.0628 (M+H$^+$).

3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(*o*-tolyl)pentanediamide (19). Synthesized by Method C using

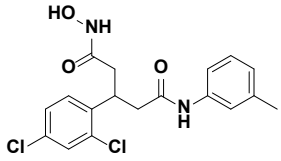


29 (67 mg, 0.26 mmol, 1.0 equiv.), 2-methylaniline (92 µL, 0.39 mmol, 1.5 equiv.), DCM (2 mL), OTX (46 mg, 0.39 mmol, 1.5 equiv.), DIPEA (90 µL, 0.52 mmol, 2.0 equiv.), HATU (108 mg, 0.29 mmol, 1.1 equiv.) and DMF (2 mL), PPTS (25 mg, 0.10 mmol, 0.4 equiv.) and abs. EtOH (10 mL). The crude yellow oil was purified

by RP ACC (gradient: 15–50% MeCN–H_2O in 0.1% formic acid). The titled compound (16 mg, 0.04 mmol, 16%-over three steps) was collected as a fluffy colorless material after lyophilization.

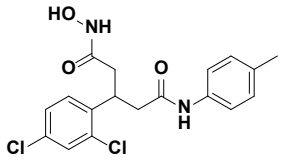
^{1}H NMR (600 MHz, DMSO-d_6) δ 10.43 (br.s, 1H), 9.28 (s, 1H), 8.75 (br.s, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 7.47–7.38 (m, 2H), 7.23 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.19–7.13 (m, 1H), 7.11 (td, *J* = 7.7, 1.6 Hz, 1H), 7.04 (td, *J* = 7.4, 1.4 Hz, 1H), 4.06 (quint, *J* = 7.4 Hz, 1H), 2.78–2.66 (m, 2H), 2.43 (dd, *J* = 14.5, 7.8 Hz, 1H), 2.36 (dd, *J* = 14.5, 7.1 Hz, 1H), 2.02 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ. 168.8, 166.8, 139.8, 136.1, 134.1, 131.8, 131.5, 130.2, 129.7, 129.1, 128.8, 127.2, 125.8, 125.1, 40.1, 36.9, 34.4, 17.6. **HPLC**, t_R 5.59 min (>95%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{18}H_{19}Cl_2N_2O_3]^+$: 381.0767; found 381.0789 ($M+H^+$).

3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(*m*-tolyl)pentanediamide (20). Synthesized by method D1 using **S11** (17 mg, 0.04 mmol, 1.0 equiv.), PPTS (2 mg, 0.01 mmol, 0.2 equiv.) and abs. EtOH (3 mL). The crude product was purified by NP ACC (stepwise: 1→5→15% MeOH–DCM). The titled compound (5 mg, 0.01 mmol, 30%) was collected as a colorless solid.



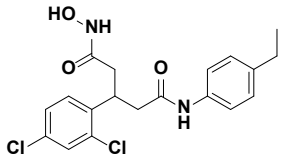
^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (br.s, 1H), 9.83 (br.s, 1H), 8.70 (br.s, 1H), 7.53 (t, *J* = 1.2 Hz, 1H), 7.44–7.33 (m, 3H), 7.25 (d, *J* = 8.1 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H), 4.04 (quint, *J* = 7.4 Hz, 1H), 2.74–2.64 (m, 2H), 2.41 (dd, *J* = 14.6, 7.9 Hz, 1H), 2.33 (dd, *J* = 14.6, 6.9 Hz, 1H), 2.24 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 168.8, 166.8, 139.9, 138.9, 137.8, 134.0, 131.4, 129.6, 128.8, 128.5, 127.2, 123.8, 119.6, 116.3, 36.6, 34.1, 21.2. **HPLC**, t_R 5.74 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{18}H_{19}Cl_2N_2O_3]^+$: 381.0767; found 381.0772 ($M+H^+$).

3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(*p*-tolyl)pentanediamide (21). Synthesized by method D1 using **S12** (34 mg, 0.07 mmol, 1.0 equiv.), PPTS (4 mg, 0.02 mmol, 0.2 equiv.) and abs. EtOH (3 mL). The product was purified in the same manner as outlined in the synthesis of **20**. The titled compound (9 mg, 0.02 mmol, 34%) was collected as a colorless solid.



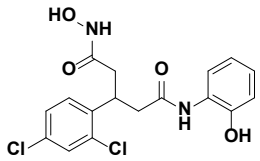
^{1}H NMR (500 MHz, DMSO-d_6) δ 10.38 (br.s, 1H), 9.80 (br.s, 1H), 8.70 (br.s, 1H), 7.53 (s, 1H), 7.42–7.34 (m, 4H), 7.05 (d, *J* = 8.1 Hz, 2H), 4.04 (quint, *J* 7.5 Hz, 2H), 2.67 (d, *J* 8.0 Hz, 2H), 2.41 (dd, *J* = 14.6, 8.0 Hz, 1H), 2.33 (dd, *J* = 14.6, 6.9 Hz, 1H), 2.22 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 168.6, 166.8, 139.9, 136.5, 134.0, 132.0, 131.4, 129.6, 129.0, 128.8, 127.2, 119.1, 40.7, 36.6, 34.1, 20.4. **HPLC**, t_R 5.68 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{18}H_{19}Cl_2N_2O_3]^+$: 381.0767; found 381.0776 ($M+H^+$).

3-(2,4-dichlorophenyl)-*N*^{1}-(4-ethylphenyl)-*N*^{5}-hydroxypentanediamide (22). Synthesized by method D1 using **S13** (25 mg, 0.05 mmol, 1.0 equiv.), PPTS (3 mg, 0.01 mmol, 0.2 equiv.) and abs. EtOH (3 mL). The product was purified in the same manner as outlined in the synthesis of **20**. The titled compound (10 mg, 0.03 mmol, 50%) was collected as a colorless solid.



^{1}H NMR (500 MHz, DMSO-d_6) δ 10.38 (d, *J* = 1.8 Hz, 1H), 9.81 (s, 1H), 8.70 (d, *J* = 1.8 Hz, 1H), 7.53 (s, 1H), 7.42–7.35 (m, 4H), 7.08 (d, *J* = 8.2 Hz, 2H), 4.04 (quint, *J* = 7.4 Hz, 1H), 2.67 (d, *J* = 7.5 Hz, 2H), 2.53 (q, *J* = 7.6 Hz, 2H, overlap with solvent peak), 2.41 (dd, *J* = 14.7, 8.0 Hz, 1H), 2.33 (dd, *J* = 14.6, 6.9 Hz, 1H), 1.13 (t, *J* = 7.6 Hz, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 168.6, 166.8, 139.9, 138.5, 136.7, 134.0, 131.4, 129.6, 128.8, 127.8, 127.2, 119.2, 40.7, 36.6, 34.2, 27.6, 15.7. **HPLC**, t_R 6.01 min (>98%, UV_{254}). HRMS (ES^+) *m/z* calcd for $[C_{19}H_{21}Cl_2N_2O_3]^+$: 395.0924; found 395.0921 ($M+H^+$).

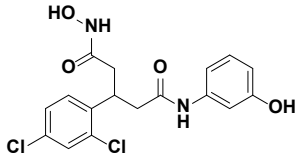
3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(2-hydroxyphenyl)pentanediamide (23)



Synthesized by Method D1 using **S14** (47 mg, 0.10 mmol, 1.0 equiv.), PPTS (5 mg, 0.02 mmol, 0.2 equiv.) and abs. EtOH (3 mL). The crude product was purified by RP ACC (gradient: 10–30% hold MeCN–H_2O in 0.1% formic acid). Appropriate fractions were pooled and lyophilized, and the product further purified by NP ACC (gradient: 5–10% MeOH–DCM). The titled compound (18 mg, 0.05 mmol, 47%) was collected as a colorless semi-solid.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.47 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.39 (d, *J* = 8.5 Hz, 1H), 7.29 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.96 (ddd, *J* = 8.1, 7.4, 1.6 Hz, 1H), 6.82 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.77–6.73 (m, 1H), 4.24 (quint, *J* = 7.4 Hz, 1H), 2.90 (dd, *J* = 14.5, 6.9 Hz, 1H), 2.81 (dd, *J* = 14.5, 8.0 Hz, 1H), 2.61–2.50 (m, 2H). **^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.0, 170.1, 149.9, 140.0, 135.9, 134.1, 130.7, 130.4, 128.4, 126.9, 126.8, 123.9, 120.4, 117.2, 42.0, 38.1, 36.6. **HPLC**, t_R 5.41 min (>98%, UV_{214}). **HRMS** (ES^+) *m/z* calcd for $[C_{17}H_{17}Cl_2N_2O_4]^+$: 383.0560; found 383.0571 ($M+H^+$).

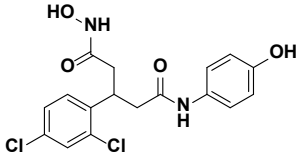
3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(3-hydroxyphenyl)pentanediamide (24)



Synthesized by Method C using **29** (87 mg, 0.34 mmol, 1.0 equiv.), 3-aminophenol (60 mg, 0.56 mmol, 1.7 equiv.), DCM (5 mL), OTX (56 mg, 0.48 mmol, 1.5 equiv.), DIPEA (111 µL, 0.69 mmol, 2.0 equiv.), HATU (133 mg, 0.35 mmol, 1.1 equiv.), DMF (2 mL), PPTS (18 mg, 0.07 mmol, 0.2 equiv.) and abs. EtOH (10 mL). The crude yellow oil was purified by RP ACC (gradient: 5–30% MeCN–H_2O in 0.1% formic acid). The titled compound (60 mg, 0.16 mmol, 47%-over three steps) was collected as a fluffy colorless material after lyophilization.

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.39 (d, J = 1.7 Hz, 1H), 9.77 (s, 1H), 9.30 (s, 1H), 8.70 (d, J = 1.7 Hz, 1H), 7.53 (t, J = 1.2 Hz, 1H), 7.38 (d, J = 1.3 Hz, 2H), 7.09 (t, J = 2.2 Hz, 1H), 7.01 (t, J = 8.1 Hz, 1H), 6.88–6.79 (m, 1H), 6.46–6.36 (m, 1H), 4.03 (quint, J = 7.4 Hz, 1H), 2.72–2.64 (m, 2H), 2.40 (dd, J = 14.6, 8.0 Hz, 1H), 2.32 (dd, J = 14.7, 6.9 Hz, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 168.7, 166.8, 157.5, 140.0, 139.9, 134.0, 131.4, 129.6 129.2, 128.8, 127.2, 110.2, 109.8, 106.3, 40.7, 36.7, 34.1. **HPLC**, t_R 5.14 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{17}H_{17}Cl_2N_2O_4]^+$: 383.0560; found 383.0576 ($M+H^+$).

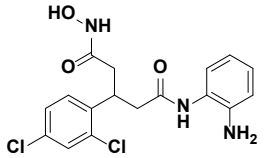
3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(4-hydroxyphenyl)pentanediamide (25)



Synthesized by Method C using **29** (106 mg, 0.41 mmol, 1.0 equiv.), 4-aminophenol (60 mg, 0.56 mmol, 1.7 equiv.), DCM (5 mL), OTX (56 mg, 0.48 mmol, 1.5 equiv.), DIPEA (111 µL, 0.69 mmol, 2.0 equiv.), HATU (133 mg, 0.35 mmol, 1.1 equiv.) and DMF (2 mL), PPTS (56 mg, 0.21 mmol, 0.5 equiv.) and abs. EtOH (15 mL). The crude yellow oil was purified by RP ACC (gradient: 5–35% MeCN–H_2O in 0.1% formic acid). The titled compound (16 mg, 0.09 mmol, 22%-over three steps) was collected as a fluffy colorless material after lyophilization.

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.39 (br.s, 1H), 9.64 (s, 1H), 9.15 (br.s, 1H), 8.71 (br.s, 1H), 7.52 (t, J = 1.2 Hz, 1H), 7.42–7.34 (m, 2H), 7.28–7.21 (m, 2H), 6.66–6.61 (m, 2H), 4.03 (quint, J = 7.4 Hz, 1H), 2.68–2.58 (m, 2H), 2.40 (dd, J = 14.6, 8.1 Hz, 1H), 2.33 (dd, J = 14.6, 6.8 Hz, 1H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 168.1, 166.8, 153.3, 139.9, 134.0, 131.4, 130.7, 129.6, 128.8, 127.2, 121.0, 115.0, 40.6, 36.6, 34.2. **HPLC**, t_R 4.94 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{17}H_{17}Cl_2N_2O_4]^+$: 383.0560; found 383.0572 ($M+H^+$).

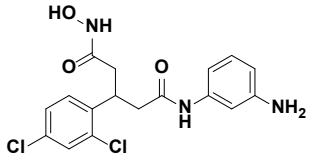
***N*^{1}-(2-aminophenyl)-3-(2,4-dichlorophenyl)-*N*^{5}-hydroxypentanediamide (26)**



Synthesized by Method D2 using **S15** (50 mg, 0.11 mmol, 1.0 equiv.), TFA (0.2 mL) and DCM (1.8 mL). The titled compound (13 mg, 0.034 mmol, 32%) was collected as a colorless semi-solid.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.45 (d, J = 2.3 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.32 (dd, J = 8.4, 2.2 Hz, 1H), 7.02–6.97 (m, 1H), 6.91 (dd, J = 7.9, 1.5 Hz, 1H), 6.79 (dd, J = 8.1, 1.4 Hz, 1H), 6.66 (td, J = 7.6, 1.4 Hz, 1H), 4.25 (quint, J = 7.4 Hz, 1H), 2.89 (dd, J = 14.4, 6.8 Hz, 1H), 2.80 (dd, J = 14.4, 8.1 Hz, 1H), 2.60–2.52 (m, 2H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.1, 170.1, 143.4, 140.1, 135.9, 134.1, 130.9, 130.5, 128.5, 128.4, 127.3, 124.7, 119.3, 118.3, 41.5, 38.3, 36.6. **HPLC**, t_R 4.96 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{17}H_{18}Cl_2N_3O_3]^+$: 382.0720; found 382.0738 ($M+H^+$).

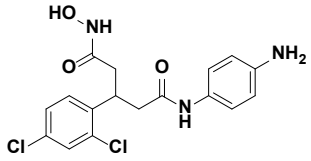
***N*^{1}-(3-aminophenyl)-3-(2,4-dichlorophenyl)-*N*^{5}-hydroxypentanediamide (27)**



Synthesized by Method D2 using **S16** (50 mg, 0.14 mmol, 1.0 equiv.), TFA (0.2 mL) and DCM (1.8 mL). The titled compound (4 mg, 0.010 mmol, 8%) was collected as a colorless semi-solid.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.42 (d, J = 2.2 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.4, 2.2 Hz, 1H), 6.98 (t, J = 8.0 Hz, 1H), 6.93 (t, J = 2.1 Hz, 1H), 6.68 (ddd, J = 8.0, 2.0, 1.0 Hz, 1H), 6.45 (ddd, J = 8.0, 2.2, 0.9 Hz, 1H), 4.22 (quint, J = 7.4 Hz, 1H), 2.80 (dd, J = 14.5, 6.8 Hz, 1H), 2.71 (dd, J = 14.5, 8.1 Hz, 1H), 2.58–2.50 (m, 2H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 171.4, 170.1, 149.3, 140.2, 140.1, 135.9, 134.0, 130.7, 130.4, 130.2, 128.4, 112.7, 111.3, 108.6, 42.3, 38.2, 36.5. **HPLC**, t_R 4.56 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{17}H_{18}Cl_2N_3O_3]^+$: 382.0720; found 382.0739 ($M+H^+$).

***N*^{1}-(4-aminophenyl)-3-(2,4-dichlorophenyl)-*N*^{5}-hydroxypentanediamide (28)**



Synthesized by Method D2 using **S17** (63 mg, 0.11 mol, 1.0 equiv.), TFA (0.2 mL) and DCM (1.8 mL). The titled compound (6 mg, 0.016 mmol, 15%) was collected as a colorless semi-solid.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.42 (d, J = 2.2 Hz, 1H), 7.37 (d, J = 8.5 Hz, 1H), 7.29 (dd, J = 8.4, 2.2 Hz, 1H), 7.13–7.08 (m, 2H), 6.66–6.63 (m, 2H), 4.21 (quint, J = 7.4 Hz, 1H), 2.77 (dd, J = 14.3, 6.8 Hz, 1H), 2.68 (dd, J = 14.3, 8.1 Hz, 1H), 2.59–2.49 (m, 2H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 171.2, 170.2, 145.7, 140.0, 135.9, 134.0, 130.8, 130.4, 130.3, 128.4, 123.4, 116.6, 42.1, 38.2, 36.6. **HPLC**, t_R 4.38 min (>95%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{17}H_{18}Cl_2N_3O_3]^+$: 382.0720; found 382.0731 ($M+H^+$).

4.4 SFC

4.4.3 Analytical Methods

Analytical SFC was carried out on a Waters ACQUITY UPC2 system under isocratic conditions at a flow rate of 4.0 mL/min, 1600 psi backpressure at 30 °C. Specifically, **S1** was separated using 35% MeOH/CO_2 on a Phenomenex AMY-1 column (3 μm, 4.6 × 250 mm) with enantiomers detected at UV_{240}. **S2** was separated using 40% *i*PrOH/CO_2 on a Daicel IC column (3 μm, 4.6 × 250 mm) with enantiomers detected at UV_{240}. **S3** was separated using 15% *i*PrOH/CO_2 on a Phenomenex CEL-1 column (3 μm, 4.6 × 250 mm) with enantiomers detected at UV_{212}.

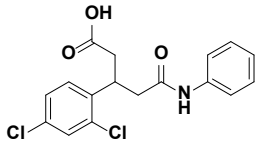
4.4.4 Preparative Methods

Preparative SFC was carried out on a Waters Prep SFC 150 AP system under isocratic conditions at a flow rate of 4.0 mL/min, 1600 psi backpressure. Specifically, **S1** was separated using 40% MeOH/CO_2 on a Phenomenex AMY-1 column (5 μm, 21.2 × 250 mm) at 35 °C with enantiomers detected and collected using UV_{240}. **S2** was separated using 40% *i*PrOH/CO_2 on a Phenomenex i-CEL-5 column (5

μm, 21.2 × 250 mm) at 40 °C with enantiomers detected and collected using UV_{240}. **S3** was separated using 10% MeOH + 0.5% formic acid/CO_2 on a Phenomenex CEL-1 column (5 μm, 21.2 × 250 mm) at 35 °C with enantiomers detected and collected using mass spec detection ($M+H^+$).

4.4.5 Compounds

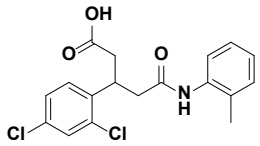
3-(2,4-dichlorophenyl)-5-oxo-5-(phenylamino)pentanoic acid (S1).



Synthesized by Method C using **29** (272 mg, 1.05 mmol, 1.0 equiv.), aniline (144 μL, 1.57 mmol, 1.5 equiv.) and DCM (10 mL). The filtered precipitate was purified by RP ACC (10–65% MeCN–H_2O in 0.1% formic acid). The titled compound (337 mg, 0.96 mmol, 91%) was collected as a fluffy colorless solid after lyophilization. Enantiomers were separated as outlined above and designated as **S1a** and **S1b**.

^{1}H NMR (600 MHz, DMSO-d_6) δ 12.18 (s, 1H), 9.91 (s, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 7.52–7.48 (m, 2H), 7.47 (d, *J* = 8.5 Hz, 1H), 7.39 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.28–7.22 (m, 2H), 7.01 (tt, *J* = 7.3, 1.2 Hz, 1H), 4.02 (quint, *J* = 7.4 Hz, 1H), 2.74–2.64 (m, 4H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 172.5, 168.8, 140.0, 139.0, 134.0, 131.5, 129.6, 128.8, 128.6, 127.3, 123.1, 119.1, 40.7, 38.5, 33.9. **HRMS** (ES^-) *m/z* calcd for $[C_{17}H_{14}Cl_2NO_3]^-$: 350.0356; found 350.0363 ($M-H^+$). **Analytical SFC**, **S1a**: t_R 1.88 min, ee 97.9%; **S1b**: t_R 2.31 min, ee 97.0%.

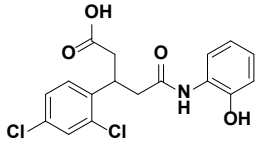
3-(2,4-dichlorophenyl)-5-oxo-5-(*o*-tolylamino)pentanoic acid (S2).



Synthesized by Method C using **29** (120 mg, 0.46 mmol, 1.0 equiv.), 2-methylaniline (74 μL, 0.70 mmol, 1.5 equiv.) and DCM (3 mL). No precipitate formation and therefore solvent was removed *in vacuo* and the crude product purified by RP ACC (10–70% MeCN–H_2O in 0.1% formic acid). The titled compound (157 mg, 0.43 mmol, 93%) was collected as a fluffy colorless solid after lyophilization. Enantiomers were separated as outlined above and designated as **S2a** and **S2b**.

^{1}H NMR (600 MHz, DMSO-d_6) δ 12.19 (br.s, 1H), 9.28 (s, 1H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.41 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.25 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.15 (d, *J* = 7.4 Hz, 1H), 7.11 (td, *J* = 7.6, 1.7 Hz, 1H), 7.04 (td, *J* = 7.4, 1.4 Hz, 1H), 4.03 (quint, *J* = 7.4 Hz, 1H), 2.79–2.65 (m, 4H), 2.03 (s, 3H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 172.5, 168.8, 139.9, 136.1, 134.1, 131.7, 131.5, 130.2, 129.7, 128.8, 127.3, 125.8, 125.2, 125.2, 40.2, 38.7, 34.2, 17.6. **HRMS** (ES^-) *m/z* calcd for $[C_{18}H_{16}Cl_2NO_3]^-$: 364.0513; found 364.0523 ($M-H^+$). **Analytical SFC**, **S2a**: t_R 1.58 min, ee 100%; **S2b**: t_R 2.70 min, ee 99.0%.

3-(2,4-dichlorophenyl)-5-((2-hydroxyphenyl)amino)-5-oxopentanoic acid (S3).

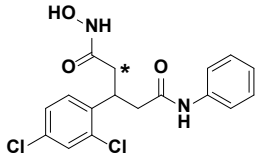


Synthesized by Method C using **29** (137 mg, 0.53 mmol, 1.0 equiv.), 2-aminophenol (87 mg, 0.79 mmol, 1.5 equiv.) and DCM (3 mL). No precipitate formation and therefore solvent was removed *in vacuo* and the crude product purified by RP ACC (10–55% MeCN–H_2O in 0.1% formic acid). The titled compound (178 mg, 0.48 mmol, 91%) was collected as an off-white solid after lyophilization. Enantiomers were separated as outlined above and designated as **S3a** and **S3b**.

^{1}H NMR (600 MHz, DMSO-d_6) δ 12.17 (br.s, 1H), 9.67 (br.s, 1H), 9.22 (s, 1H), 7.63 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.55 (d, *J* = 2.2 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.39 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.91 (td, *J* = 7.7, 1.6 Hz, 1H), 6.83 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.72 (td, *J* = 7.7, 1.5 Hz, 1H), 4.01 (quint, *J* = 7.5 Hz, 1H), 2.81–2.73 (m, 2H), 2.71–2.63 (m, 2H). **^{13}C NMR** (151 MHz, DMSO-d_6) δ 172.5, 169.3, 147.8, 140.0, 134.0, 131.5, 129.6, 128.7, 127.3, 126.1, 124.6, 122.3, 118.9, 115.6, 40.6, 38.5, 34.1. **HRMS** (ES^-) *m/z* calcd for $[C_{17}H_{14}Cl_2NO_4]^-$: 366.0305; found 366.0291 ($M-H^+$). **Analytical SFC***, **S3a**: t_R 22.72 min, ee 98.3%; **S3b**: t_R 23.85 min, ee 90.6%.

*Compound required longer residence times to achieve appreciable separation of enantiomers.

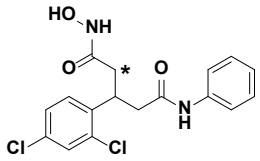
(-)-3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-phenylpentanediamide ((-)18)



Synthesized by continuation of Method C using **S1a** (50 mg, 0.14 mmol, 1.0 equiv.), OTX (20 mg, 0.17 mmol, 1.2 equiv.), DIPEA (37 µL, 0.21 mmol, 1.5 equiv.), HATU (65 mg, 0.17 mmol, 1.2 equiv.) and DMF (2 mL), PPTS (4 mg, 0.01 mmol, 0.1 equiv.) and abs. EtOH (5 mL). The crude yellow oil was purified by RP ACC (gradient: 5–50% MeCN–H_2O in 0.1% formic acid). Appropriate fractions were pooled, extracted with DCM, dried (Na_2SO_4) and reduced *in vacuo* to give a purple oil. The product was further purified by NP ACC (50–100% EtOAC–hexane). Fractions were reduced *in vacuo* and the resulting gummy solid dissolved in MeCN (1 mL) and water (9 mL) added and the titled compound (11 mg, 0.03 mmol, 21%- over two steps) was collected as a colorless fluffy solid after lyophilization.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.44–7.40 (m, 3H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.31–7.23 (m, 3H), 7.06 (dd, *J* = 8.1, 6.7 Hz, 1H), 4.24 (quint, *J* = 7.4 Hz, 1H), 2.84 (dd, *J* = 14.5, 6.7 Hz, 1H), 2.74 (dd, *J* = 14.5, 8.1 Hz, 1H), 2.60–2.50 (m, 2H). **^{13}C NMR** (151 MHz, MeOD-d_4) δ 171.5, 170.1, 140.0, 139.5, 135.9, 134.0, 130.7, 130.4, 129.7, 128.4, 125.3, 121.4, 42.3, 38.2, 36.5. **HPLC**, t_R 5.59 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{17}H_{17}Cl_2N_2O_3]^+$: 367.0611; found 367.0625 ($M+H^+$). $[\alpha]_{365}^{24}$, -1.8 (c 0.10, MeOH).

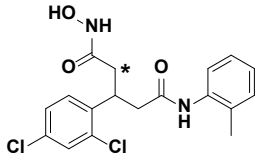
(+)-3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-phenylpentanediamide ((+)18)



Synthesized in the same manner as outlined by **(-)18** using **S1b** (55 mg, 0.16 mmol, 1.0 equiv.), OTX (22 mg, 0.19 mmol, 1.2 equiv.), DIPEA (41 µL, 0.23 mmol, 1.5 equiv.), HATU (71 mg, 0.19 mmol, 1.2 equiv.) and DMF (2 mL), PPTS (4 mg, 0.02 mmol, 0.1 equiv.) and abs. EtOH (5 mL). The titled compound (7 mg, 0.02 mmol, 12%-over two steps) was collected as a colorless fluffy solid after lyophilization.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.44–7.40 (m, 3H), 7.38 (d, J = 8.4 Hz, 1H), 7.30–7.23 (m, 3H), 7.08–7.03 (m, 1H), 4.24 (quint, J = 7.4 Hz, 1H), 2.84 (dd, J = 14.5, 6.7 Hz, 1H), 2.74 (dd, J = 14.5, 8.1 Hz, 1H), 2.61–2.51 (m, 2H). **^{13}C NMR** (151 MHz, MeOD-d_4) δ 171.5, 170.1, 140.0, 139.6, 135.9, 134.1, 130.7, 130.4, 129.7, 128.4, 125.3, 121.4, 42.3, 38.2, 36.5. **HPLC**, t_R 5.59 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{17}H_{17}Cl_2N_2O_3]^+$: 367.0611; found 367.0624 ($M+H^+$). $[\alpha]_{365}^{24}$, +1.7 (c 0.10, MeOH).

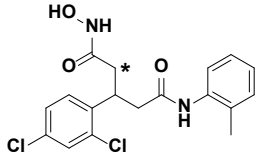
(-)-3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(*o*-tolyl)pentanediamide ((-)19)



Synthesized in the same manner as outlined by **(-)18** using **S2a** (52 mg, 0.14 mmol, 1.0 equiv.), OTX (20 mg, 0.17 mmol, 1.2 equiv.), DIPEA (37 µL, 0.21 mmol, 1.5 equiv.), HATU (65 mg, 0.17 mmol, 1.2 equiv.) and DMF (2 mL), PPTS (4 mg, 0.01 mmol, 0.1 equiv.) and abs. EtOH (5 mL). The titled compound (15 mg, 0.04 mmol, 28%-over two steps) was collected as a colorless fluffy solid after lyophilization.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.47–7.40 (m, 2H), 7.31 (dd, J = 8.4, 2.2 Hz, 1H), 7.18–7.12 (m, 1H), 7.10 (ddd, J = 15.5, 7.0, 2.2 Hz, 3H), 4.29–4.22 (m, 1H), 2.88 (dd, J = 14.4, 6.4 Hz, 1H), 2.82 (dd, J = 14.3, 8.7 Hz, 1H), 2.56 (d, J = 7.3 Hz, 2H), 2.01 (s, 3H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.1, 170.0, 140.0, 136.6, 136.0, 134.5, 134.1, 131.5, 131.0, 130.5, 128.5, 127.5, 127.2, 127.1, 41.5, 38.4, 36.7, 17.9. **HPLC**, t_R 5.62 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{18}H_{19}Cl_2N_2O_3]^+$: 381.0767; found 381.0782 ($M+H^+$). $[\alpha]_{365}^{24}$, -5.9 (c 0.10, MeOH).

(+)-3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(*o*-tolyl)pentanediamide ((+)19)

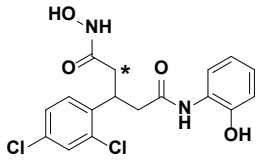


Synthesized in the same manner as outlined by **(-)18** using **S2b** (59 mg, 0.16 mmol, 1.0 equiv.), OTX (23 mg, 0.19 mmol, 1.2 equiv.), DIPEA (42 µL, 0.24 mmol, 1.5 equiv.), HATU (74 mg, 0.19 mmol, 1.2 equiv.) and DMF (2 mL), PPTS (5 mg, 0.02 mmol, 0.1 equiv.) and abs. EtOH (5 mL). The titled compound (12 mg, 0.03 mmol, 20%-over two steps) was collected as a colorless fluffy solid after lyophilization.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.46–7.40 (m, 2H), 7.31 (dd, J = 8.4, 2.2 Hz, 1H), 7.18–7.06 (m, 4H), 4.25 (quint, J = 7.5 Hz, 1H), 2.88 (dd, J = 14.4, 6.3 Hz, 1H), 2.82 (dd, J = 14.3, 8.7 Hz, 1H), 2.56 (d, J = 7.3 Hz, 2H), 2.01 (s, 3H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.1, 170.0, 140.0, 136.6, 136.0, 134.5, 134.1, 131.5, 131.0, 130.5, 128.5, 127.5, 127.2, 127.1, 41.5, 38.4, 36.7, 17.9. **HPLC**, t_R 5.62 min (>98%,

UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{18}H_{19}Cl_2N_2O_3]^+$: 381.0767; found 381.0781 ($M+H^+$). $[\alpha]_{365}^{24}$, +5.9 (c 0.10, MeOH).

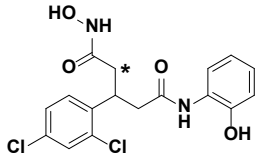
(-)-3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(2-hydroxyphenyl)-pentanediamide ((-)23)



Synthesized in the same manner as outlined by **(-)18** using **S3a** (34 mg, 0.09 mmol, 1.0 equiv.), OTX (12 mg, 0.11 mmol, 1.2 equiv.), DIPEA (23 µL, 0.13 mmol, 1.4 equiv.), HATU (41 mg, 0.11 mmol, 1.2 equiv.) and DMF (2 mL), PPTS (3 mg, 0.01 mmol, 0.1 equiv.) and abs. EtOH (4 mL). The titled compound (5 mg, 0.01 mmol, 14%-over two steps) was collected as a colorless fluffy solid after lyophilization.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.46 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 7.29 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.97 (td, *J* = 7.7, 1.5 Hz, 1H), 6.82 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.76 (td, *J* = 7.7, 1.3 Hz, 1H), 4.24 (quint, *J* = 7.3 Hz, 1H), 2.91 (dd, *J* = 14.6, 6.8 Hz, 1H), 2.82 (dd, *J* = 14.4, 8.0 Hz, 1H), 2.62–2.52 (m, 2H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.1, 149.8, 140.0, 135.9, 134.1, 130.8, 130.4, 128.5, 126.8, 124.0, 120.6, 117.2, 41.9, 38.0, 36.6. **HPLC**, t_R 5.45 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{17}H_{17}Cl_2N_2O_4]^+$: 383.0560; found 383.0565 ($M+H^+$). $[\alpha]_{365}^{24}$, -0.2 (c 0.10, MeOH).

(+)-3-(2,4-dichlorophenyl)-*N*^{1}-hydroxy-*N*^{5}-(2-hydroxyphenyl)-pentanediamide ((+)23)



Synthesized in the same manner as outlined by **(-)18** using **S3b** (44 mg, 0.12 mmol, 1.0 equiv.), OTX (16 mg, 0.14 mmol, 1.2 equiv.), DIPEA (30 µL, 0.17 mmol, 1.5 equiv.), HATU (52 mg, 0.14 mmol, 1.2 equiv.) and DMF (2 mL), PPTS (4 mg, 0.01 mmol, 0.1 equiv.) and abs. EtOH (4 mL). The titled compound (7 mg, 0.02 mmol, 15%-over two steps) was collected as a colorless fluffy solid after lyophilization.

^{1}H NMR (600 MHz, MeOD-d_4) δ 7.46 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.42 (d, *J* = 2.1 Hz, 1H), 7.39 (d, *J* = 8.4 Hz, 1H), 7.29 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.97 (td, *J* = 7.7, 1.5 Hz, 1H), 6.82 (dd, *J* = 8.1, 1.4 Hz, 1H), 6.76 (td, *J* = 7.7, 1.3 Hz, 1H), 4.24 (p, *J* = 7.4 Hz, 1H), 2.91 (dd, *J* = 14.6, 6.7 Hz, 1H), 2.82 (dd, *J* = 14.5, 7.9 Hz, 1H), 2.62–2.51 (m, 2H).**^{13}C NMR** (151 MHz, MeOD-d_4) δ 172.1, 149.8, 139.9, 135.9, 134.1, 130.8, 130.4, 128.5, 126.8, 124.0, 120.6, 117.2, 41.9, 38.0, 36.6, 30.8. **HPLC**, t_R 5.45 min (>98%, UV_{254}). **HRMS** (ES^+) *m/z* calcd for $[C_{17}H_{17}Cl_2N_2O_4]^+$: 383.0560; found 383.0568 ($M+H^+$). $[\alpha]_{365}^{24}$, +0.2 (c 0.10, MeOH).

5.0 Supporting References

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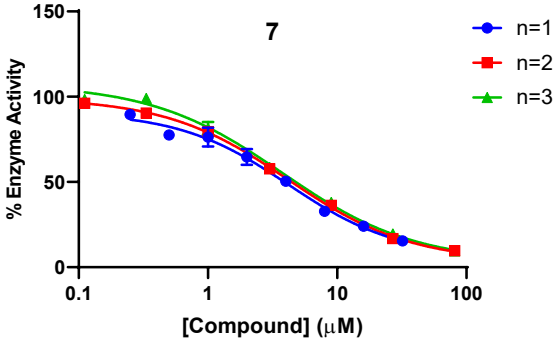
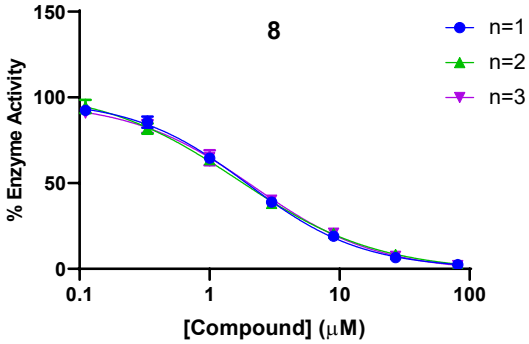
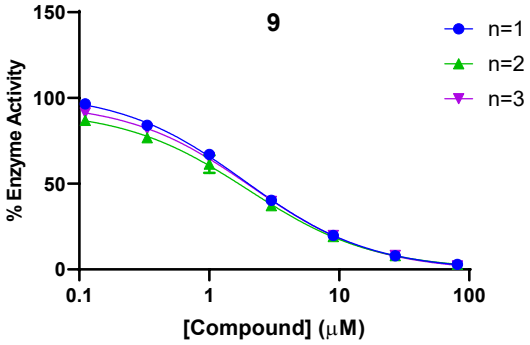
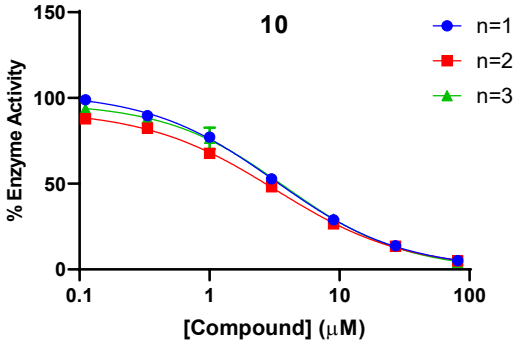
6.0 Appendix

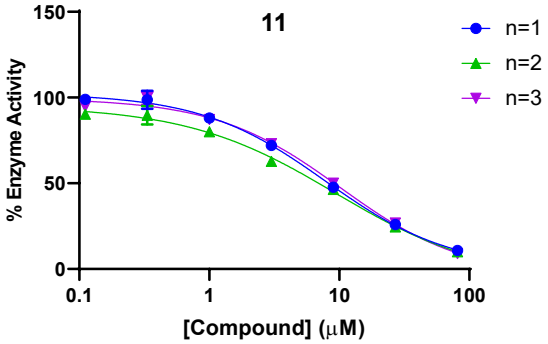
6.1 Dose response curves

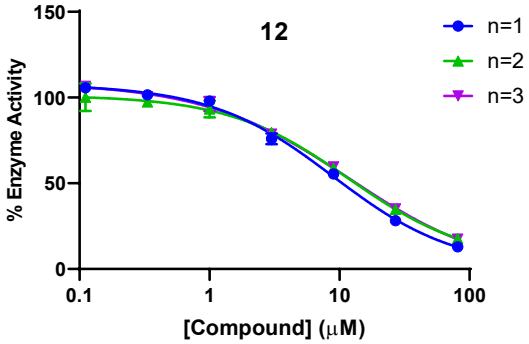


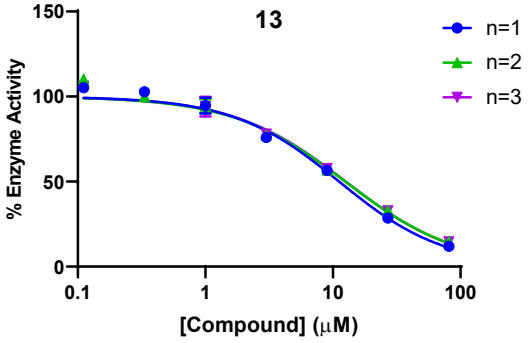








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10
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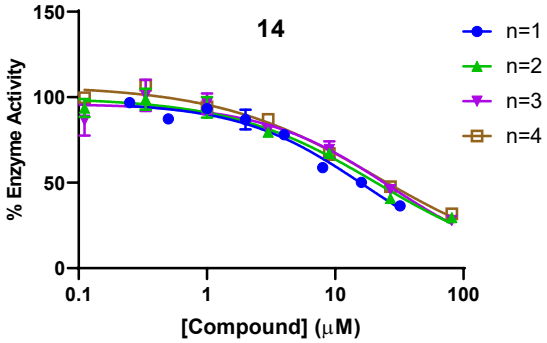
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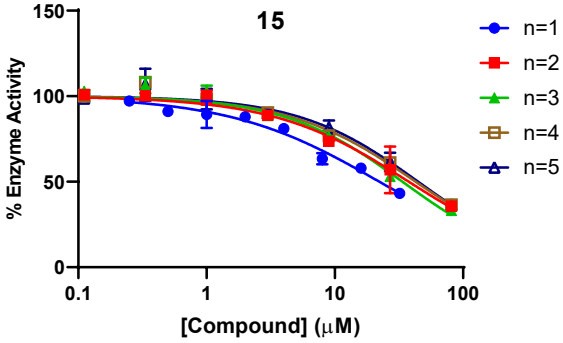
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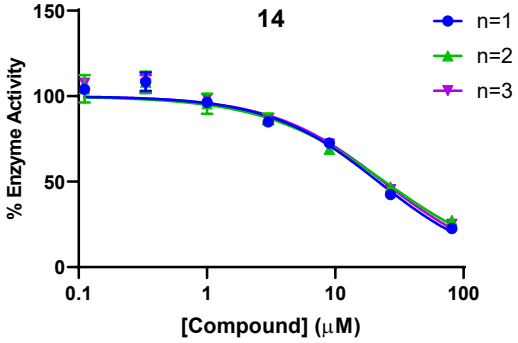
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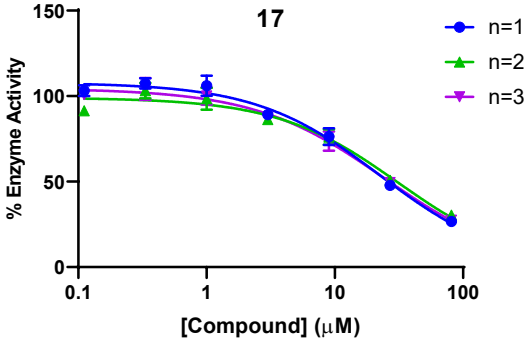
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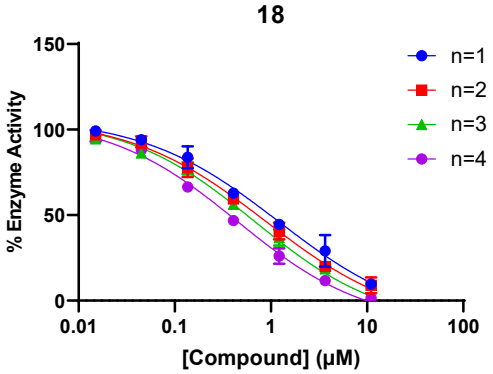
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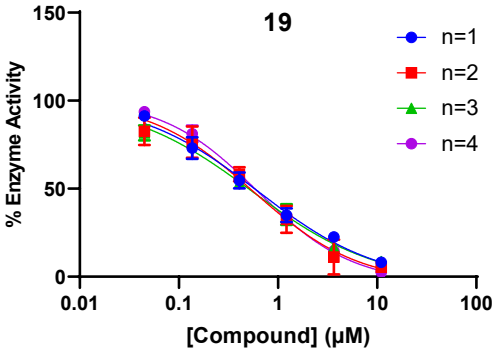
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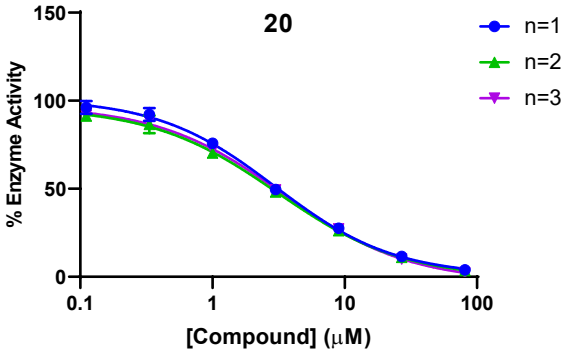
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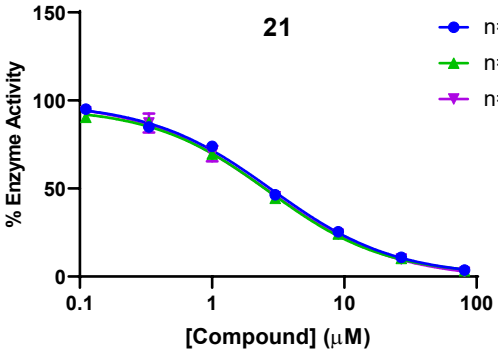
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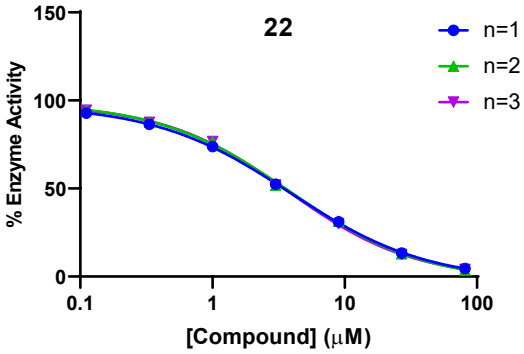
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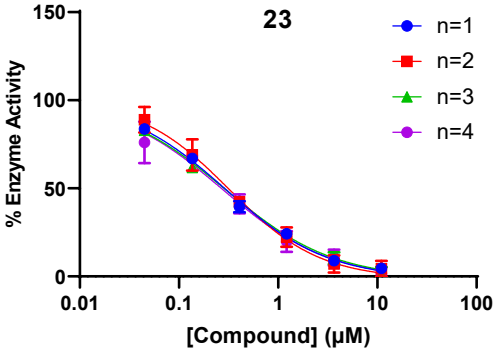
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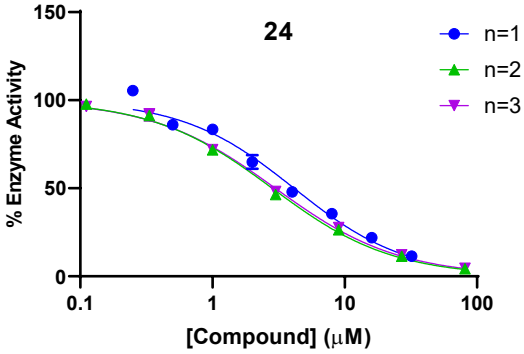
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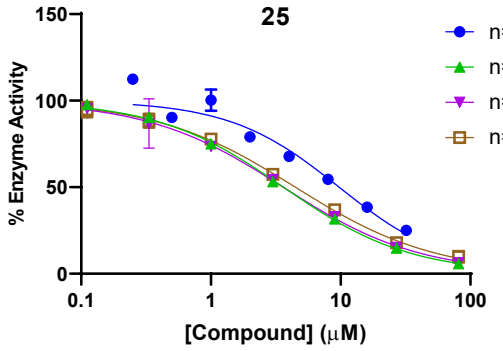
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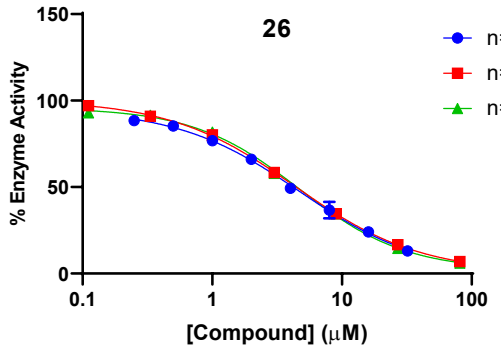
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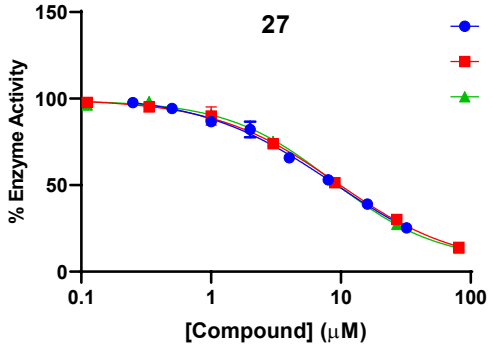
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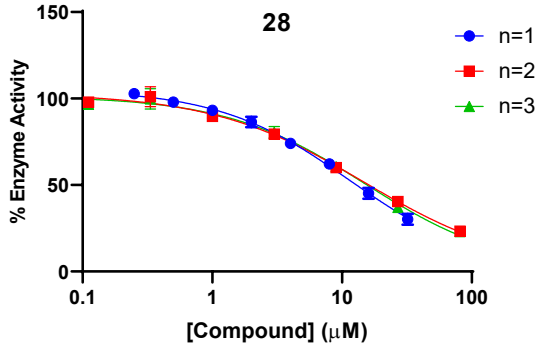
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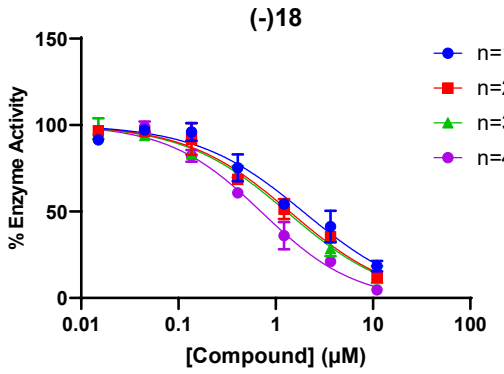
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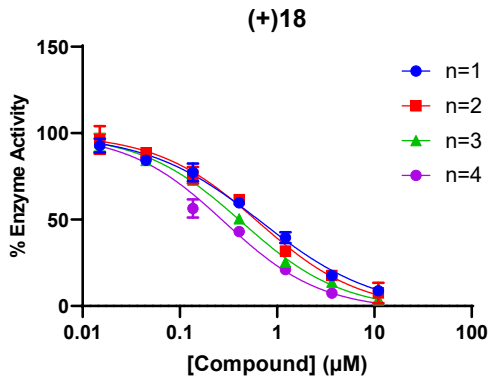
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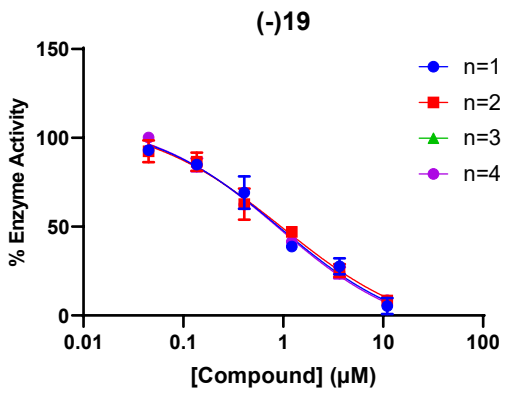
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10
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[Compound] (μM)
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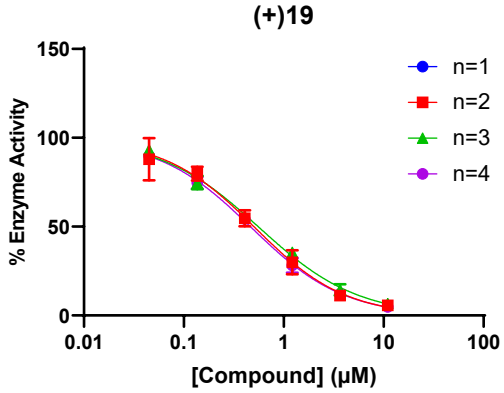
n=4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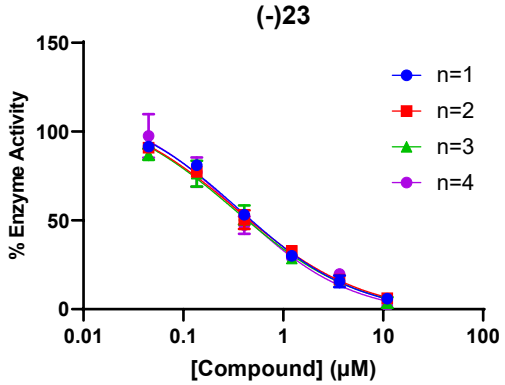
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[Compound] (μM)
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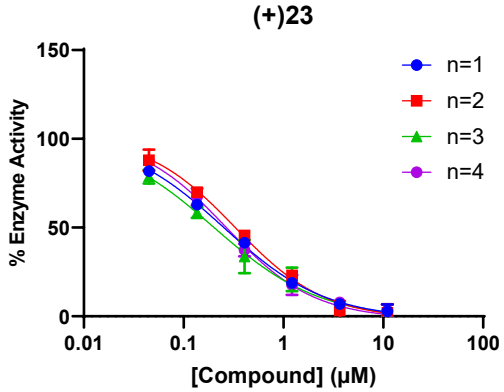
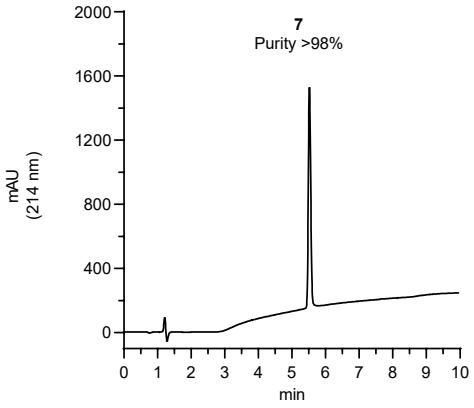
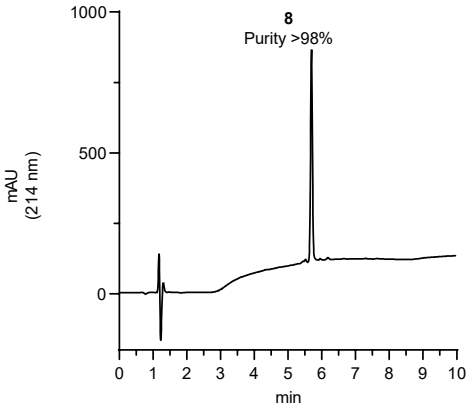
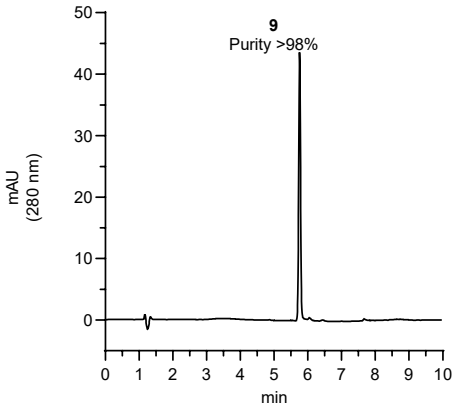
n=3
n=4

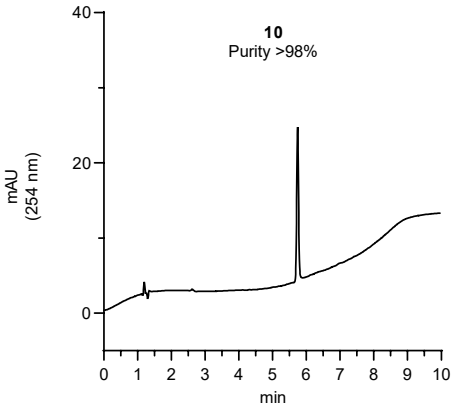

(+)23
% Enzyme Activity
150
100
50
0
0.01
0.1
1
10
100
[Compound] (μM)
n=1
n=2
n=3
n=4

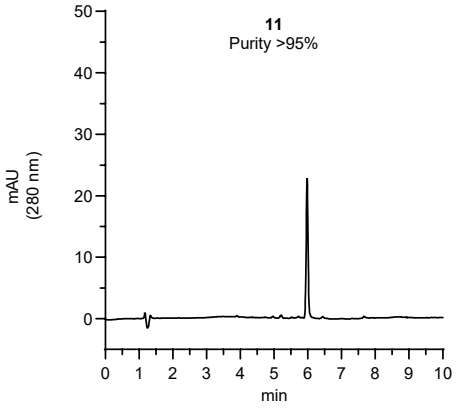
6.2 HPLC chromatograms

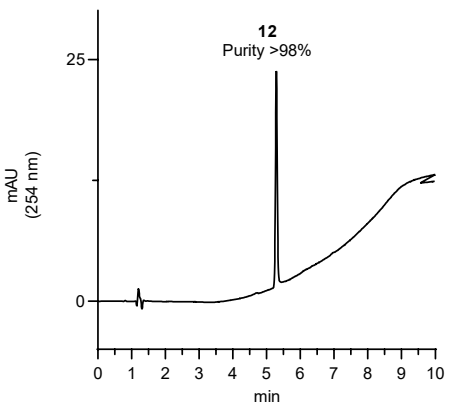


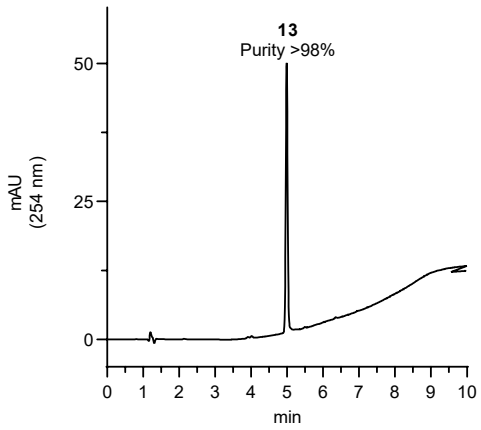


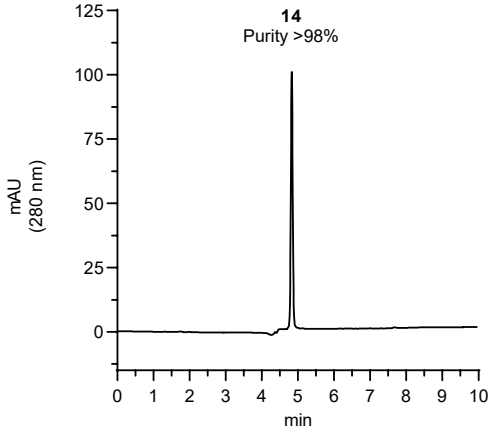


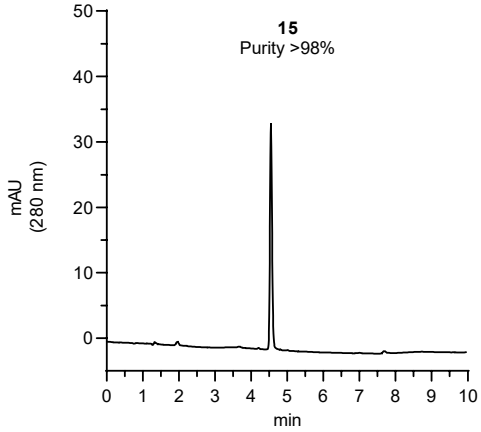







13
Purity >98%
mAU
(254 nm)
min


14
Purity >98%
mAU
(280 nm)
min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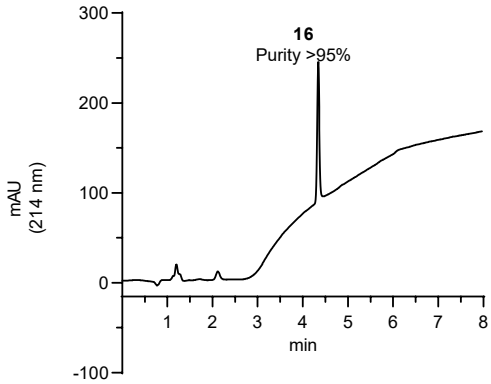
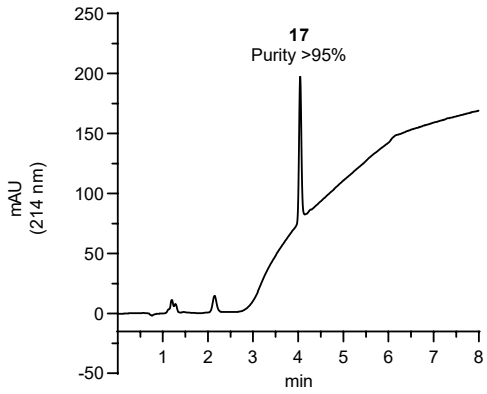
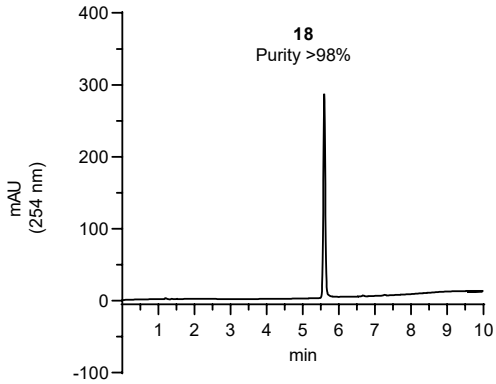
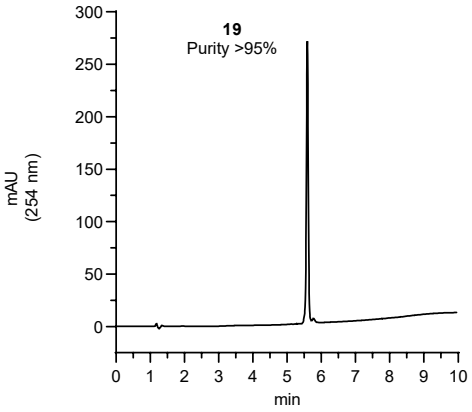
Purity >98%
mAU
(280 nm)
min


16
Purity >95%
mAU
(214 nm)
min


17
Purity >95%
mAU
(214 nm)
min


18
Purity >98%
mAU
(254 nm)
min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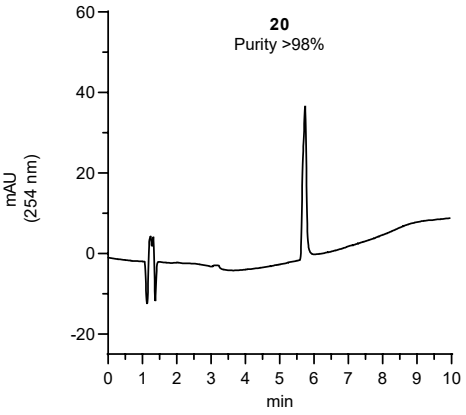
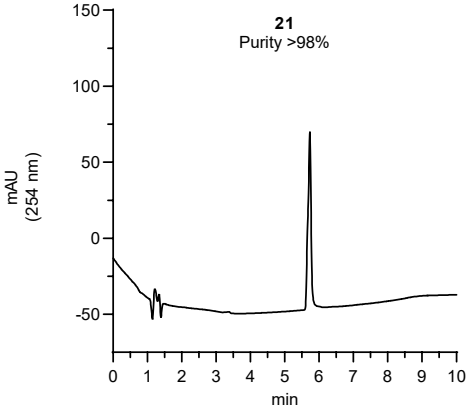
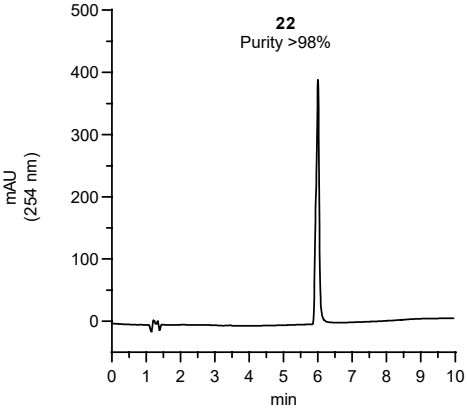
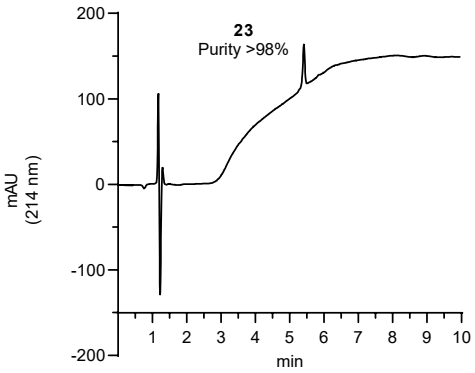
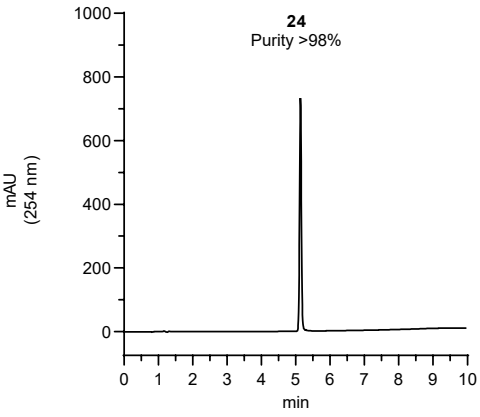
mAU
(254 nm)
min


20
Purity >98%
mAU
(254 nm)
min


21
Purity >98%
mAU
(254 nm)
min


22
Purity >98%
mAU
(254 nm)
min


23
Purity >98%
mAU
(214 nm)
min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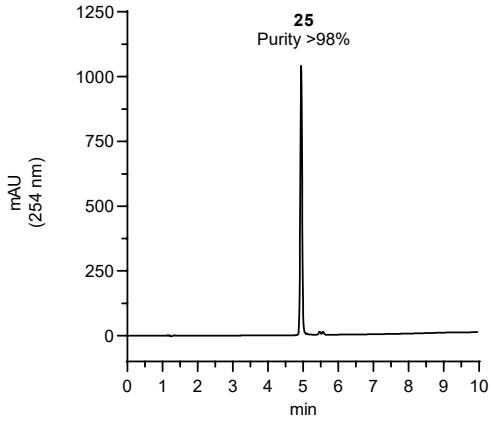
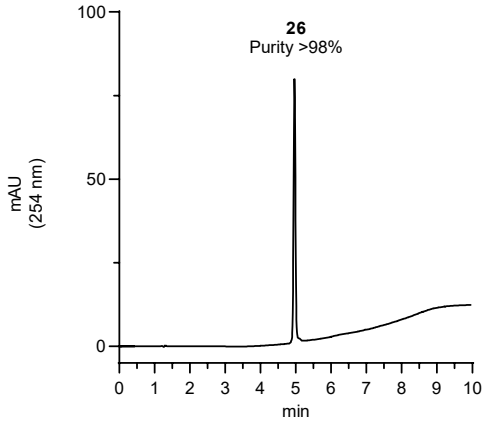
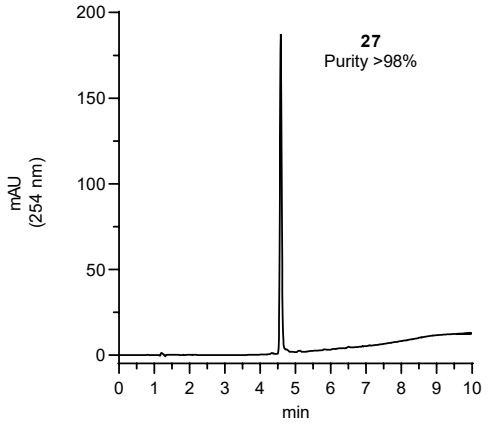
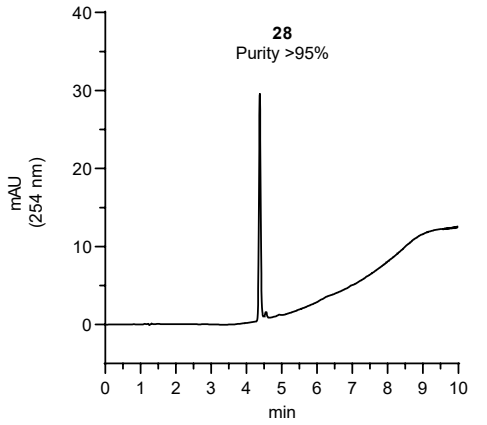
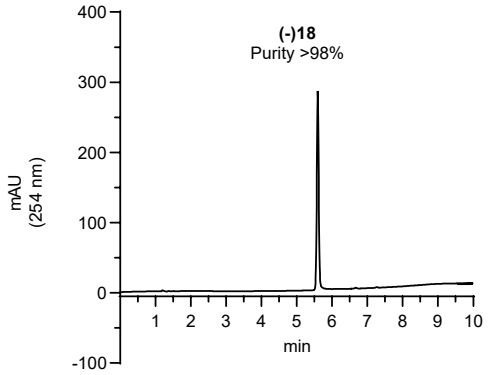
mAU
(254 nm)
min

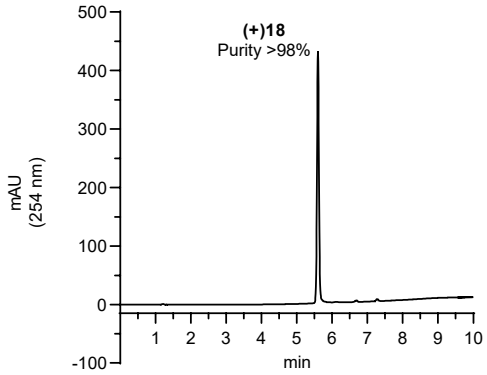

25
Purity >98%
mAU
(254 nm)
1250
1000
750
500
250
0
0 1 2 3 4 5 6 7 8 9 10
min

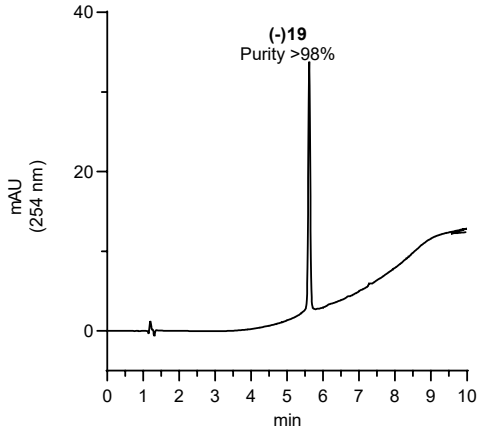

26
Purity >98%
mAU
(254 nm)
100
50
0
0 1 2 3 4 5 6 7 8 9 10
min

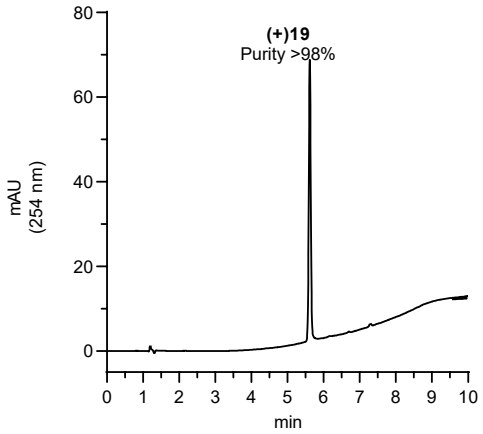

27
Purity >98%
mAU
(254 nm)
200
150
100
50
0
0 1 2 3 4 5 6 7 8 9 10
min

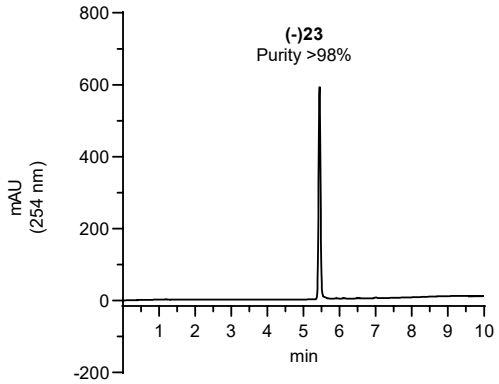

28
Purity >95%
mAU
(254 nm)
40
30
20
10
0
0 1 2 3 4 5 6 7 8 9 10
min


(-)18
Purity >98%
mAU
(254 nm)
400
300
200
100
0
-100
1 2 3 4 5 6 7 8 9 10
min


(+)18
Purity >98%
mAU
(254 nm)
500
400
300
200
100
0
-100
1 2 3 4 5 6 7 8 9 10
min


(-)19
Purity >98%
mAU
(254 nm)
40
20
0
0 1 2 3 4 5 6 7 8 9 10
min


(+)19
Purity >98%
mAU
(254 nm)
80
60
40
20
0
0 1 2 3 4 5 6 7 8 9 10
min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Purity >98%
mAU
(254 nm)
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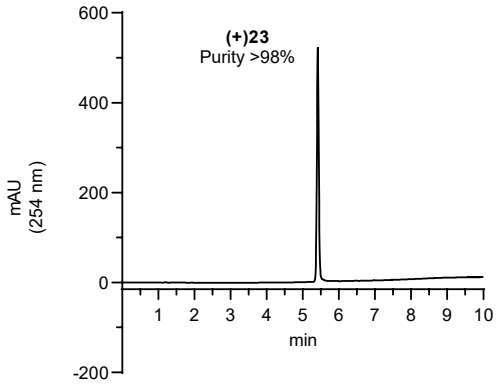
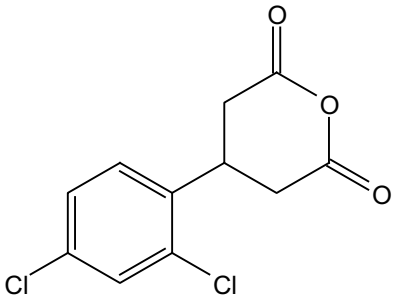
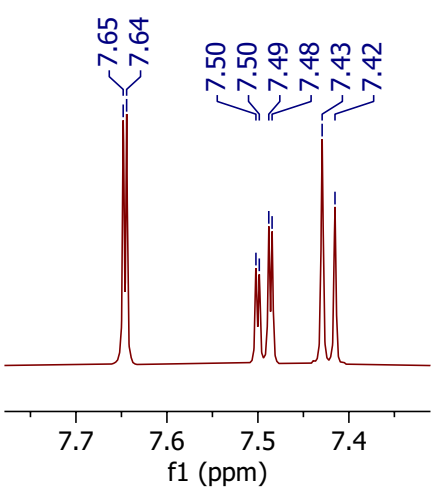
600
400
200
0
-200
1 2 3 4 5 6 7 8 9 10
min

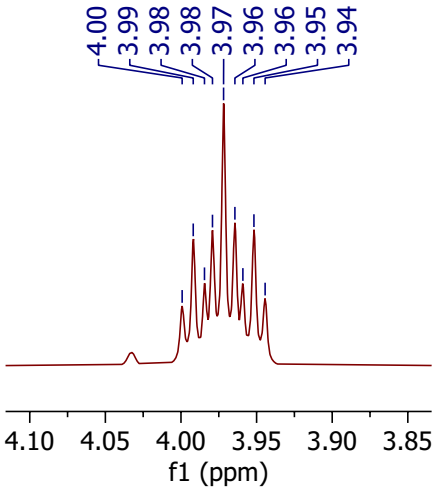

(+)23
Purity >98%
mAU
(254 nm)
600
400
200
0
-200
1 2 3 4 5 6 7 8 9 10
min

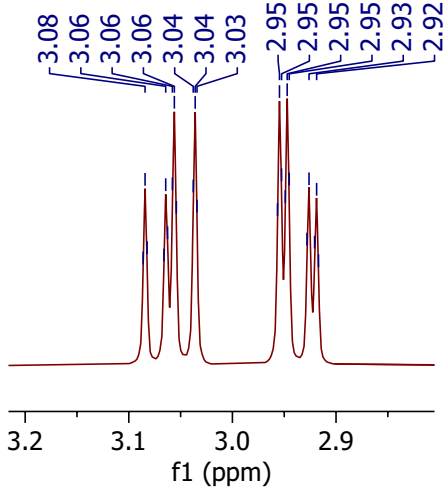
Compound 29
^{1}H NMR (600 MHz, DMSO-d6)

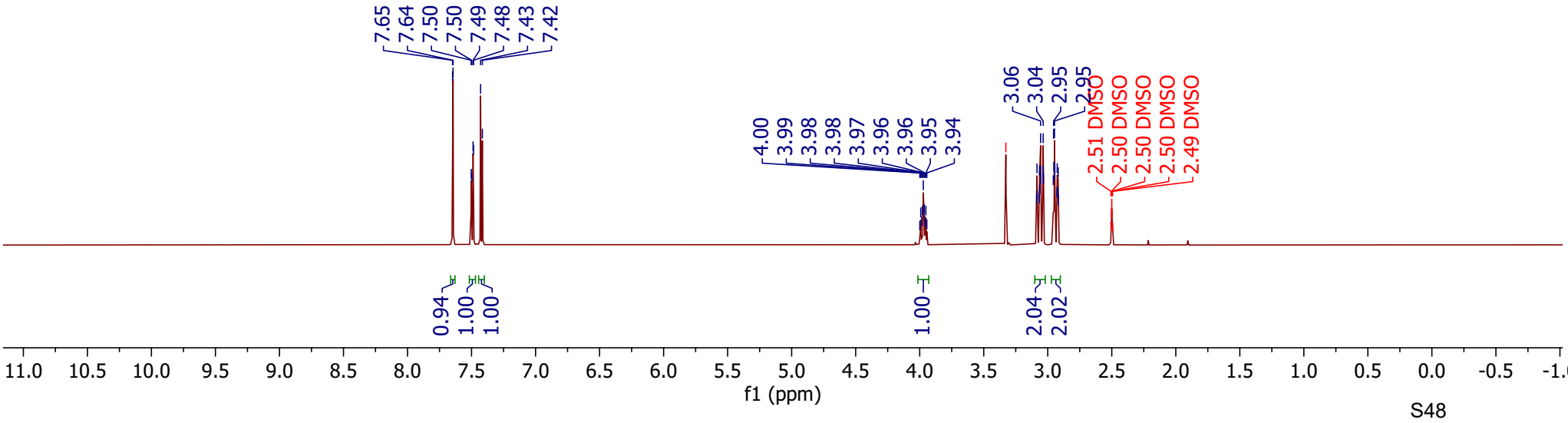
6.3 NMR spectra





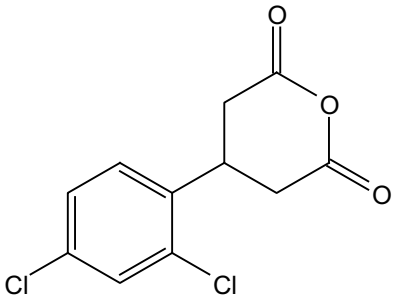




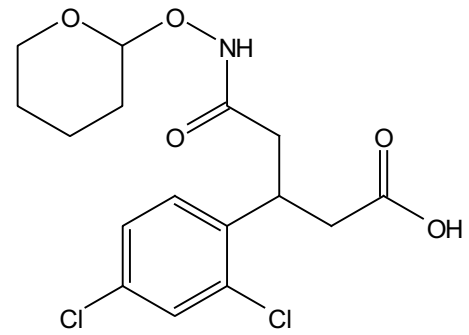


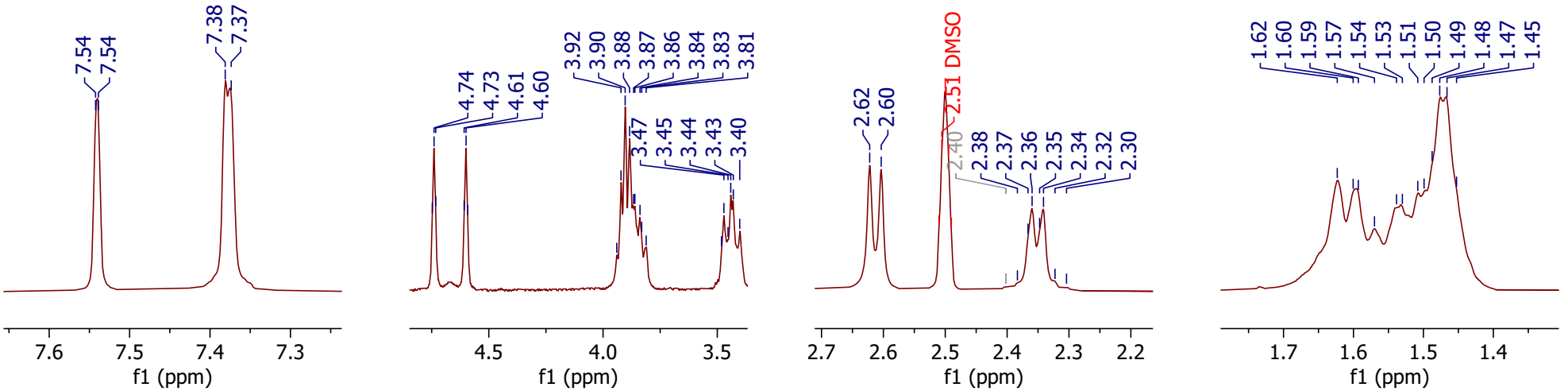
Compound 29

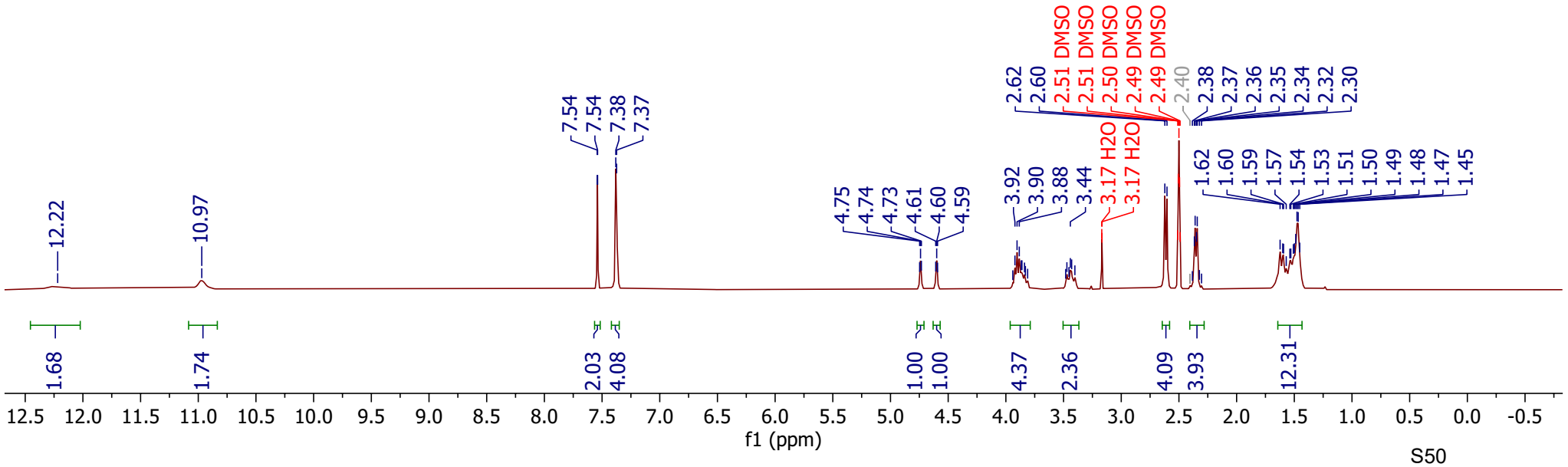
^{13}C NMR (151 MHz, DMSO-d6)



Compound 30
^{1}H NMR (400 MHz, DMSO-d6)

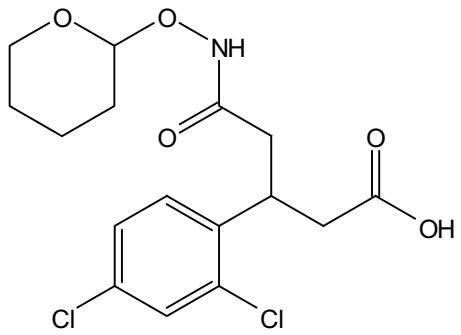






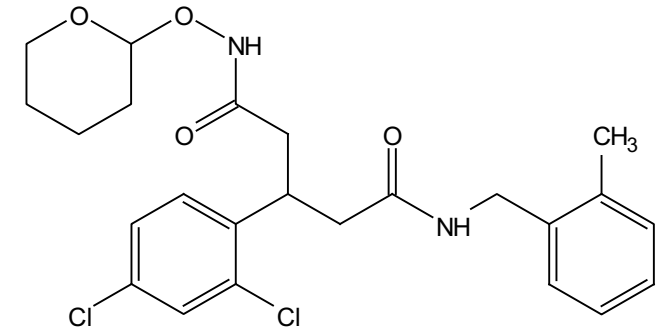
Compound 30

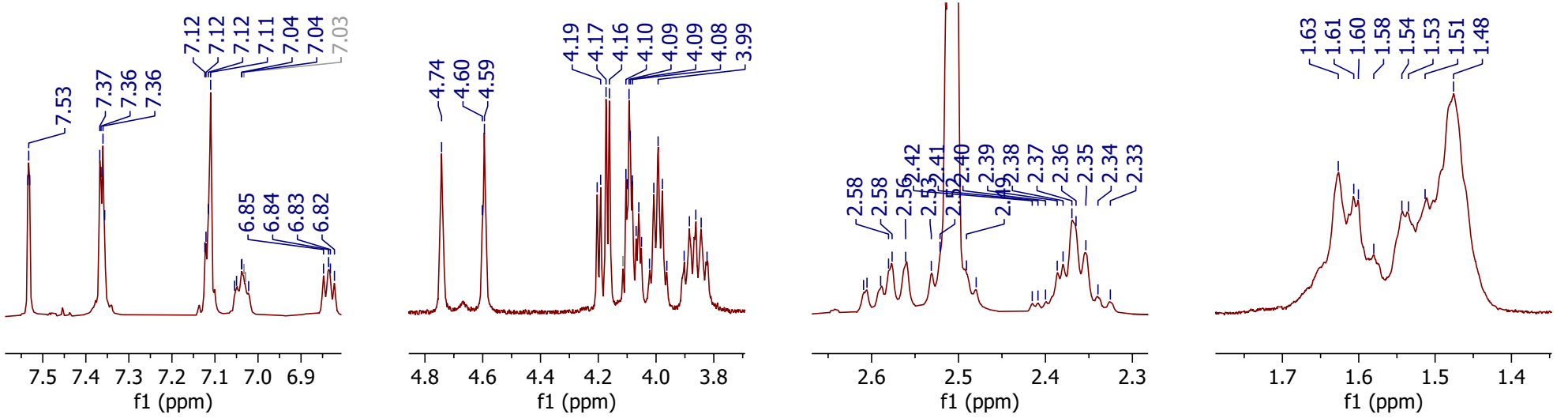
^{13}C NMR (151 MHz, DMSO-d6)

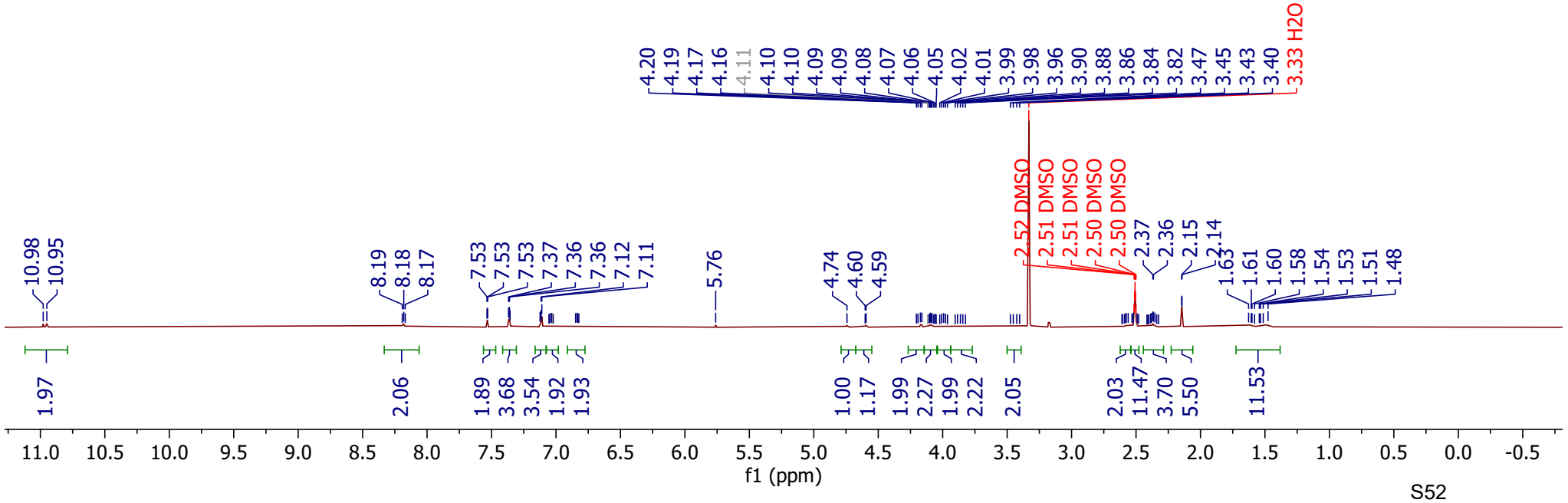


Compound S4

^{1}H NMR (500 MHz, DMSO-d6)

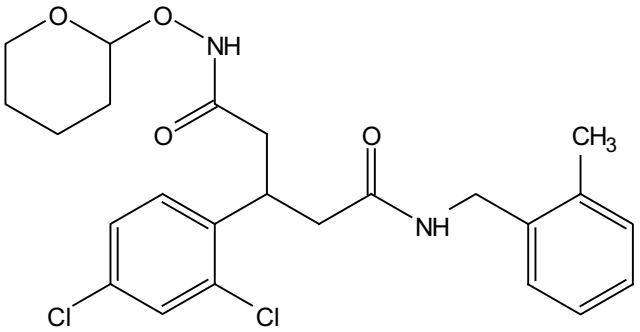




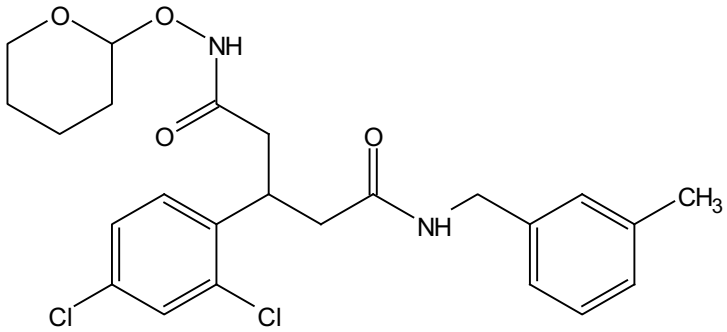


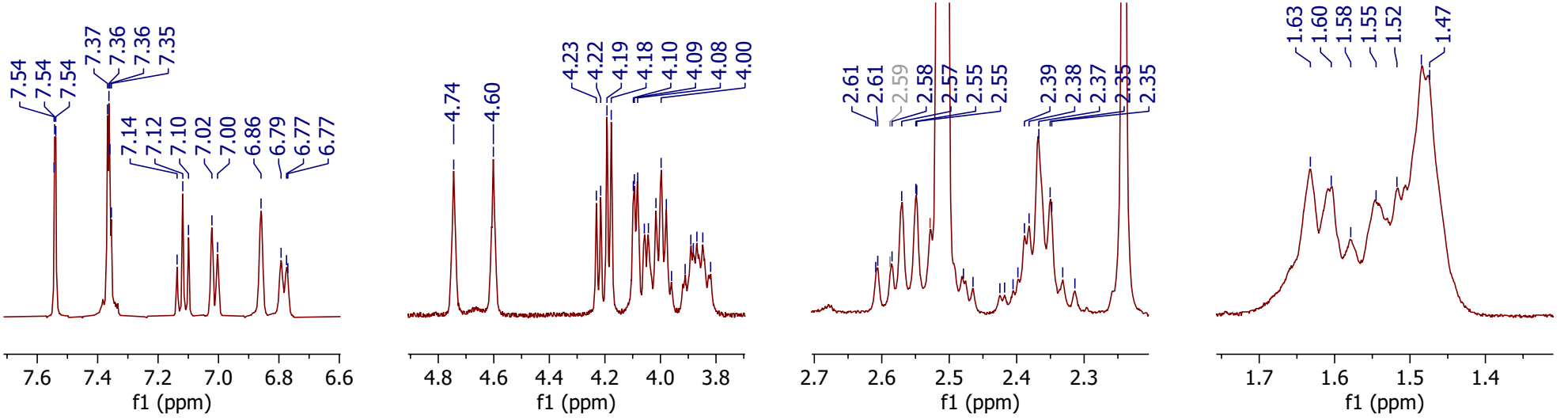
Compound S4

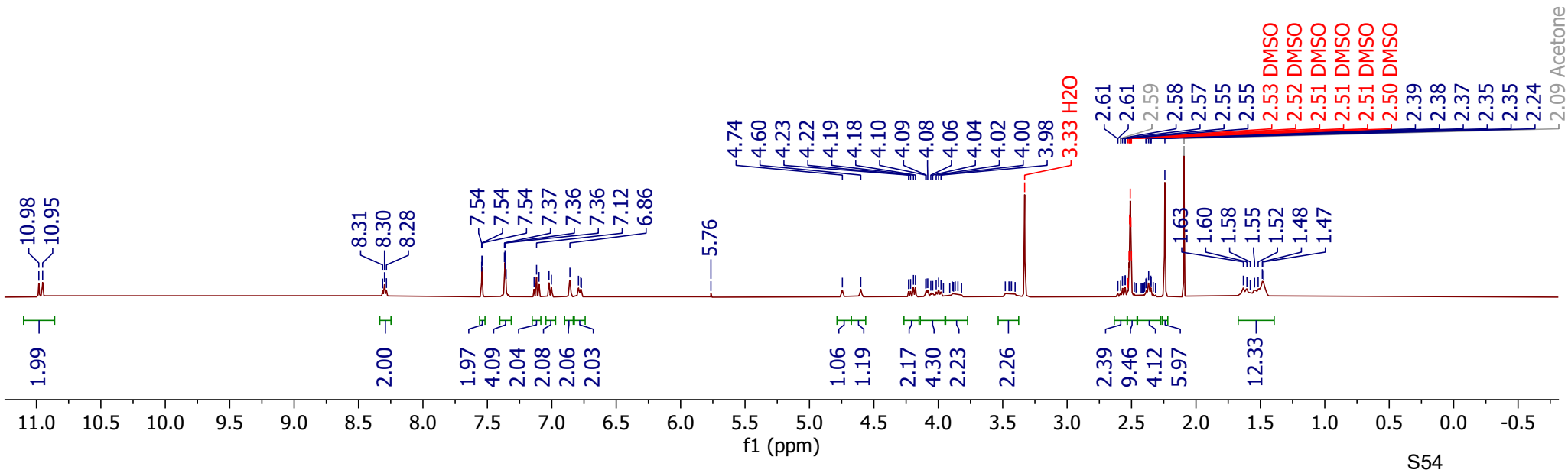
^{13}C NMR (126 MHz, DMSO-d6)



Compound S5
^{1}H NMR (400 MHz, DMSO-d6)

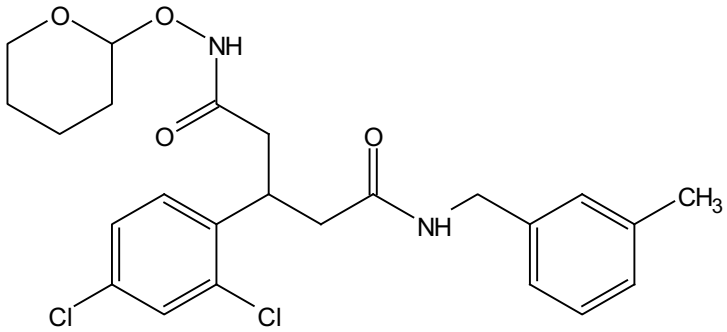


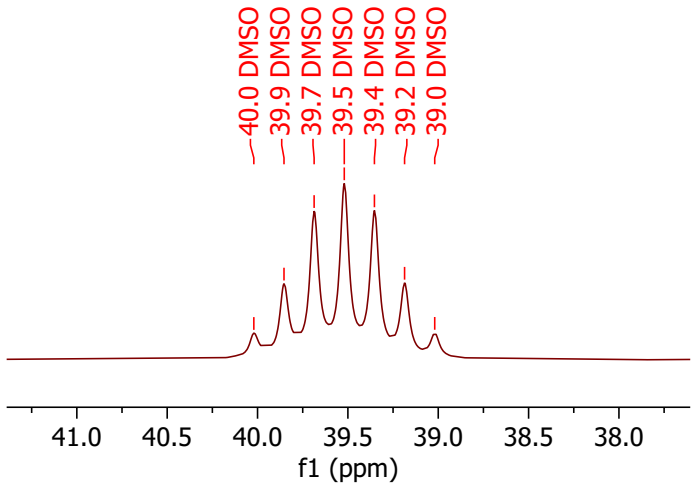


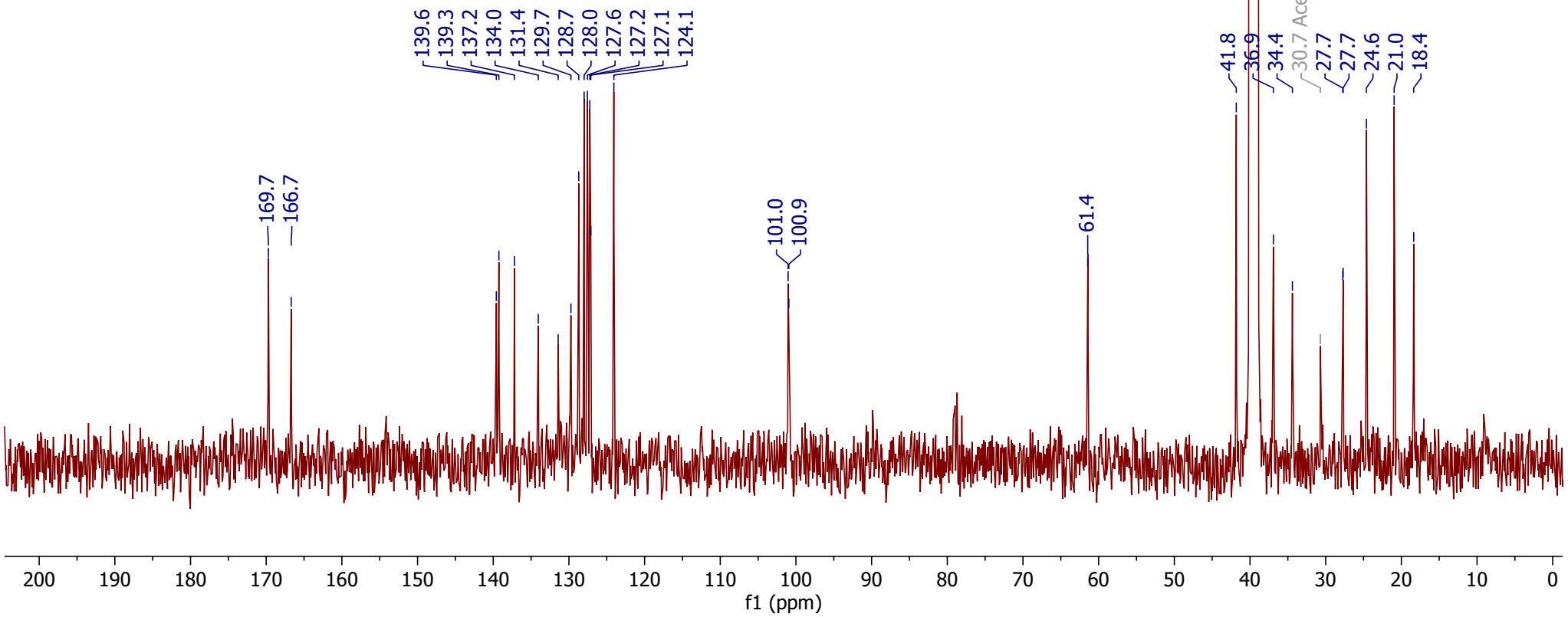


Compound S5

^{13}C NMR (126 MHz, DMSO-d6)

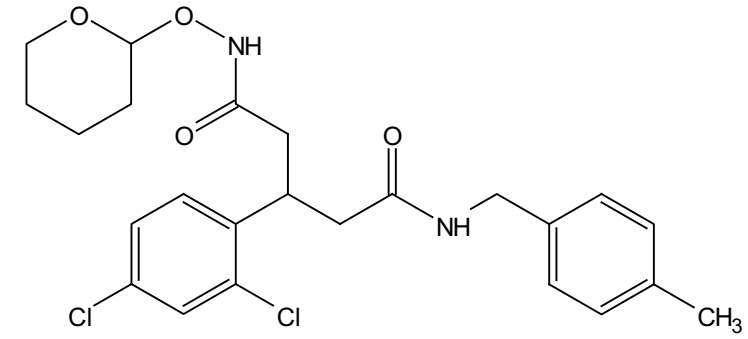


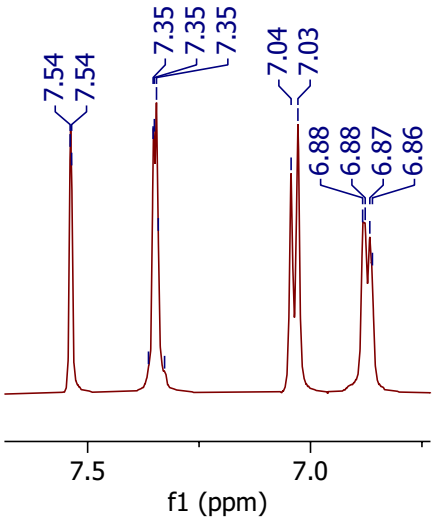


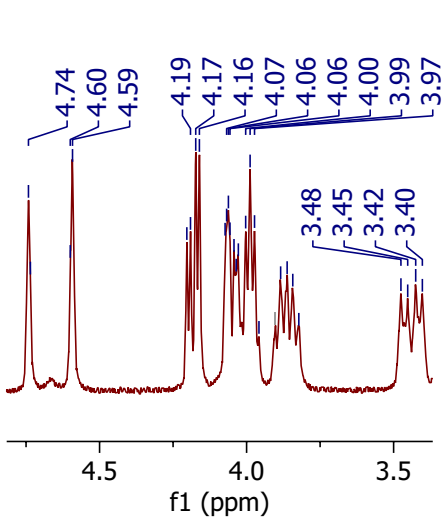


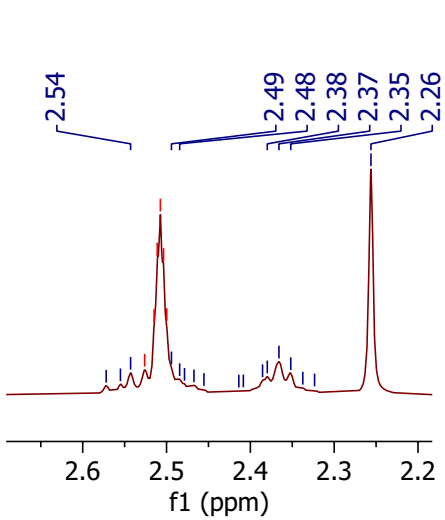
Compound S6

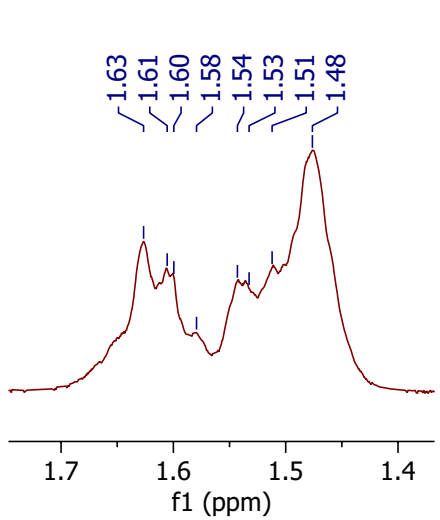
^{1}H NMR (500 MHz, DMSO-d6)

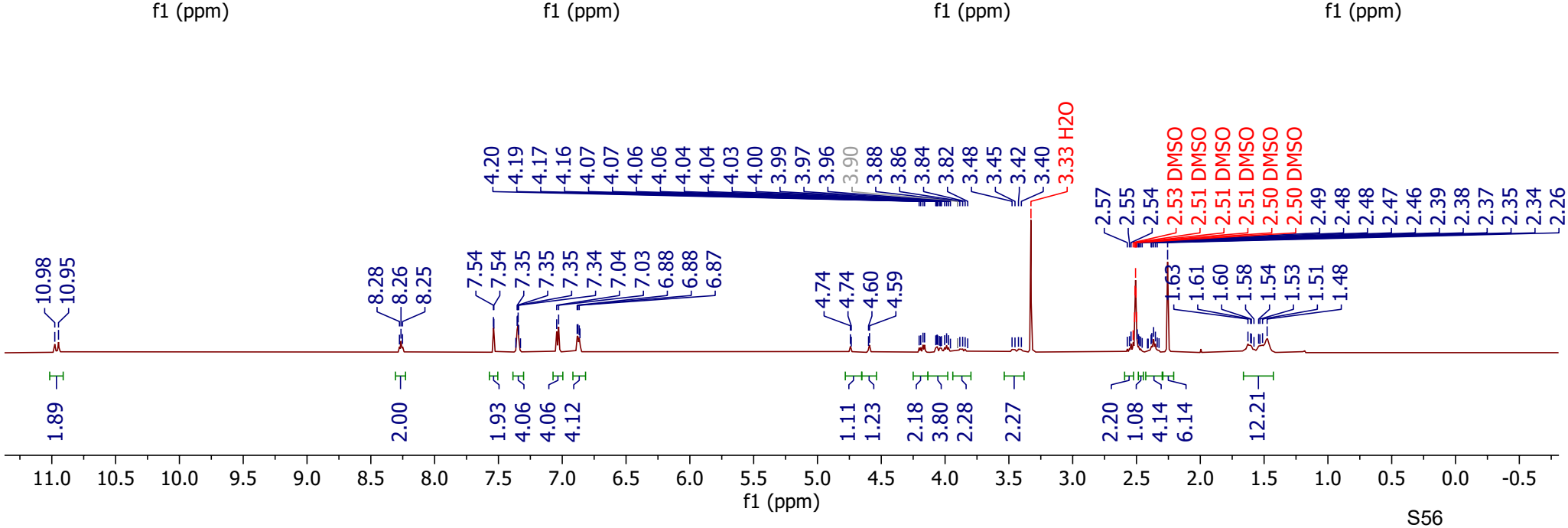






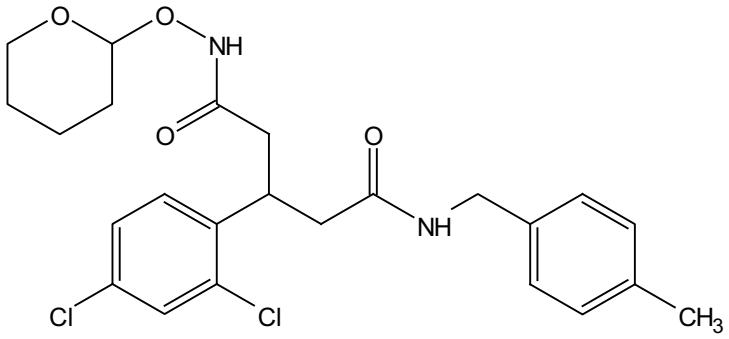






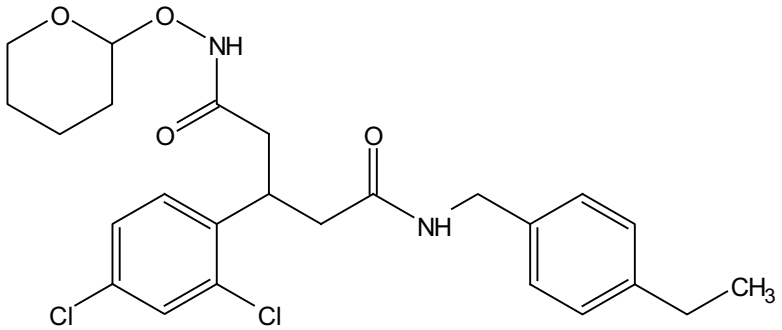
Compound S6

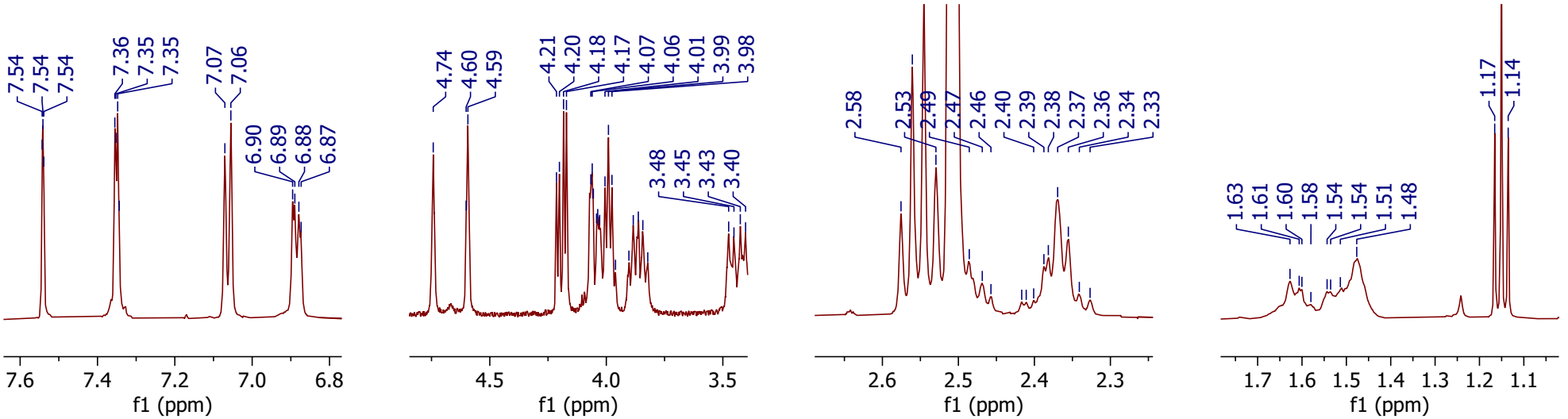
^{13}C NMR (126 MHz, DMSO-d6)

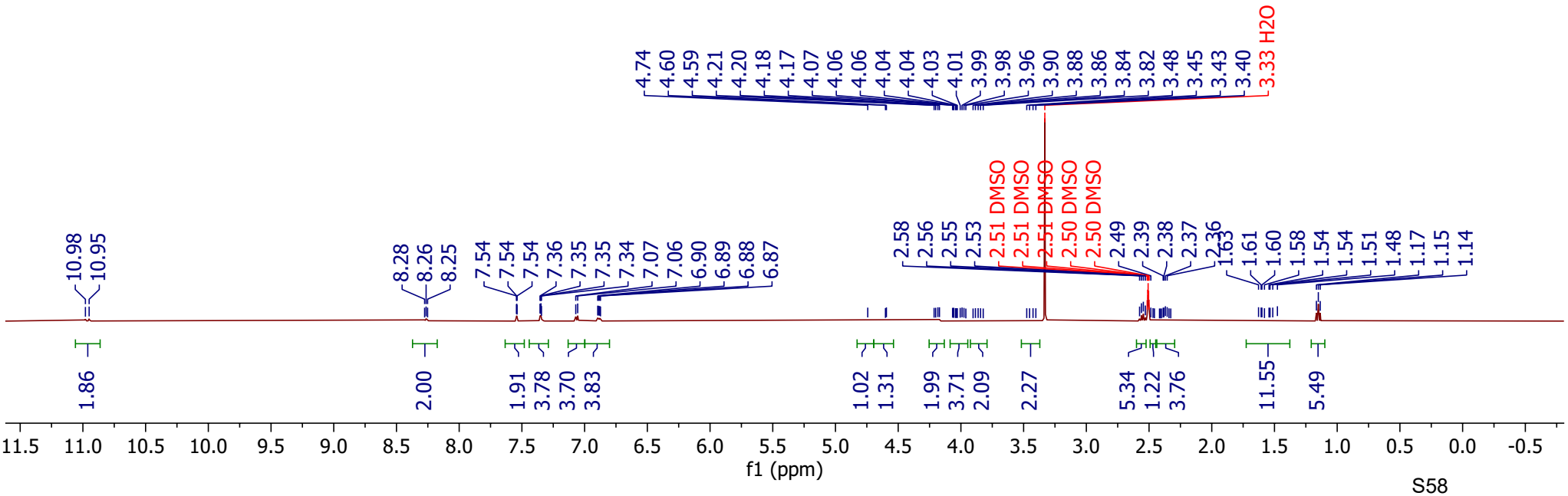


Compound S7

^{1}H NMR (500 MHz, DMSO-d6)

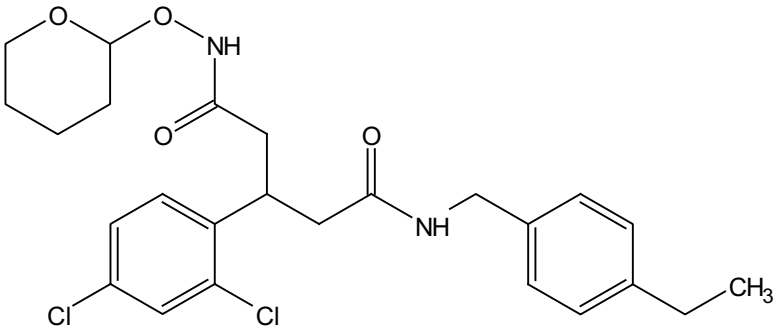






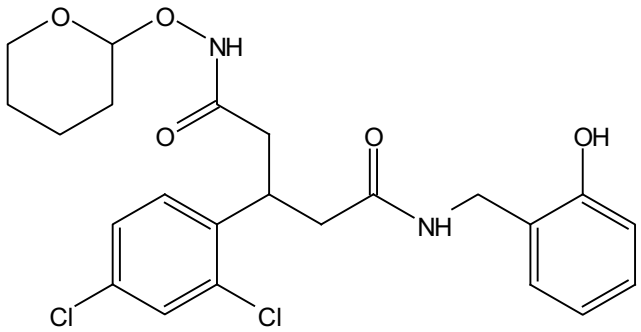
Compound S7

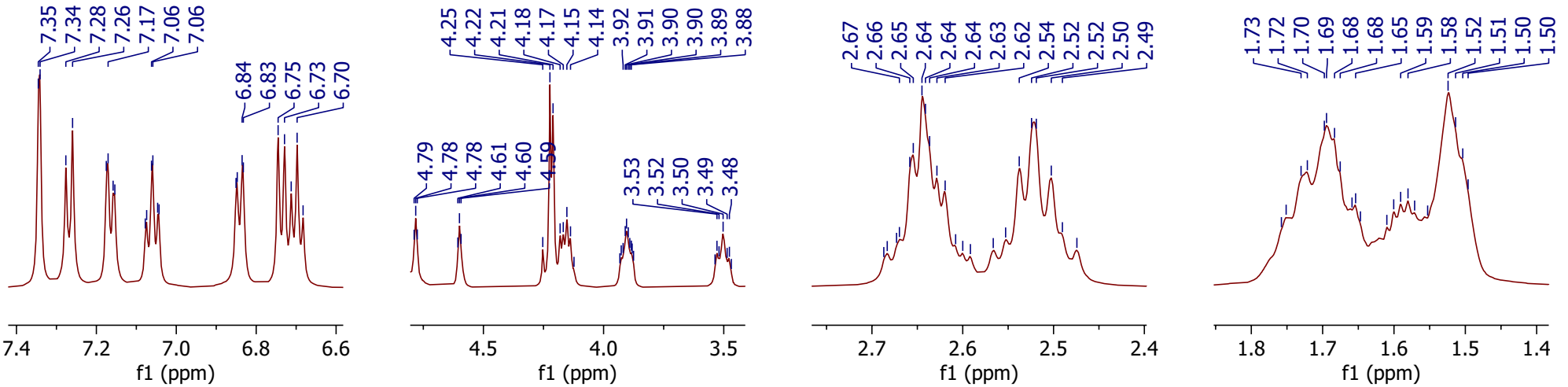
^{13}C NMR (126 MHz, DMSO-d6)

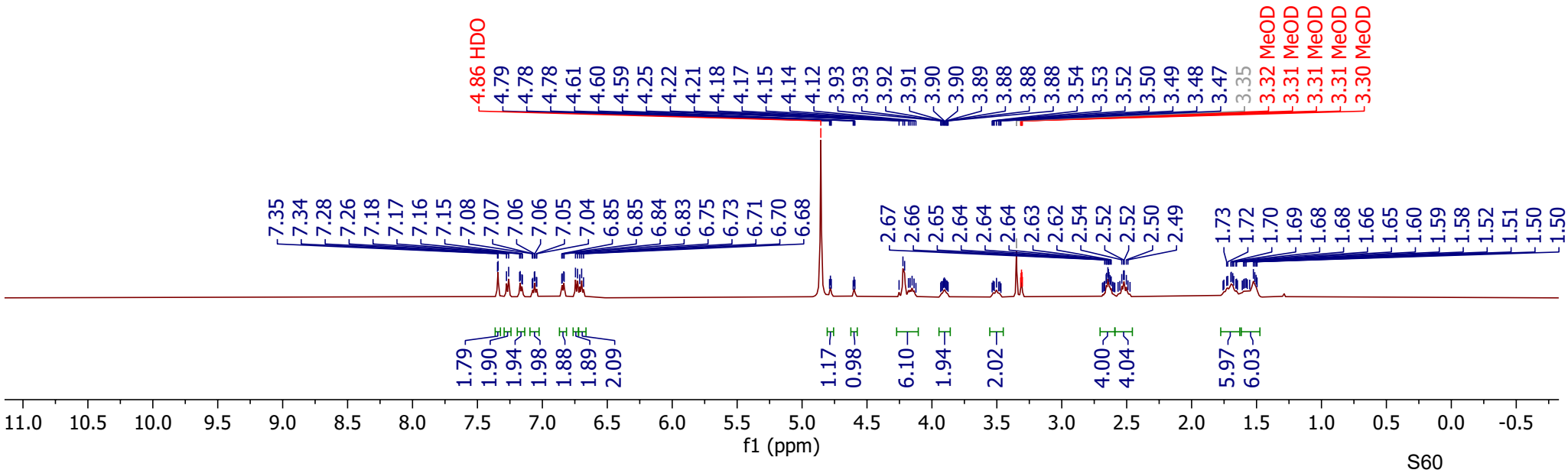


Compound S8

^{1}H NMR (500 MHz, MeOD-d4)

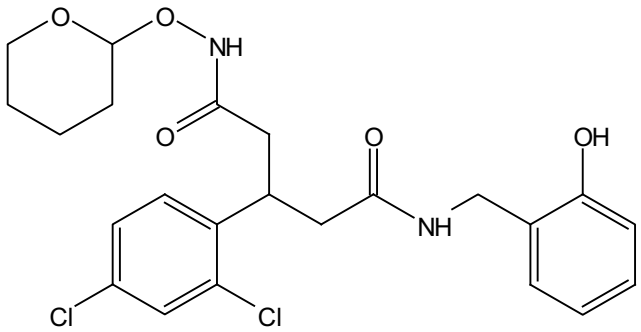




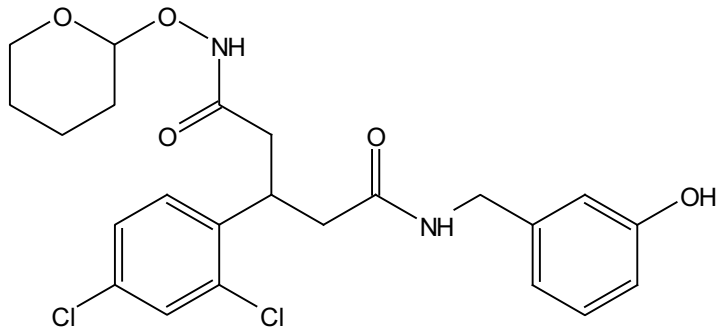


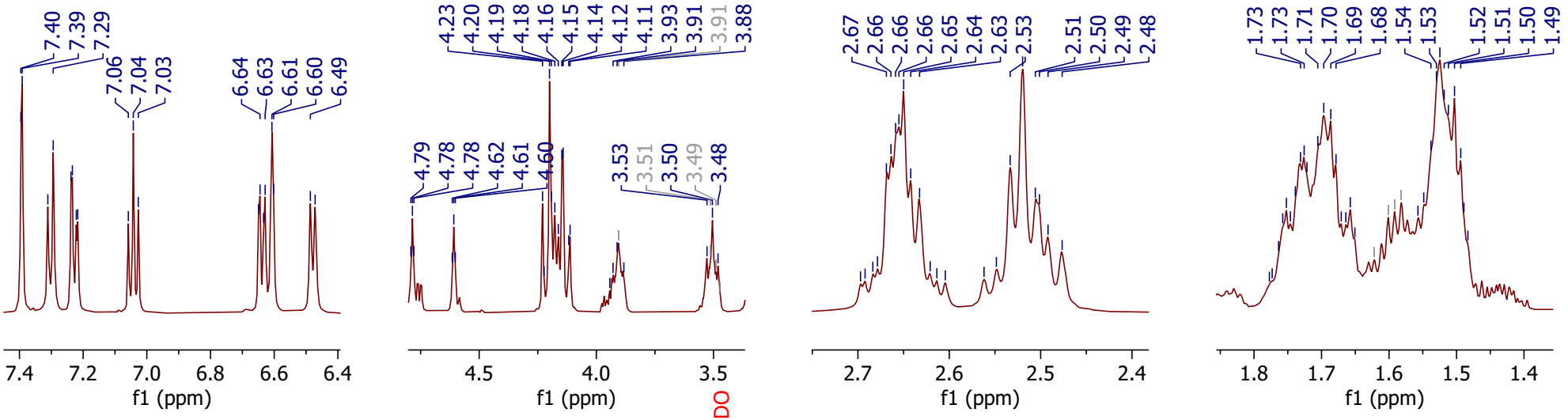
Compound S8

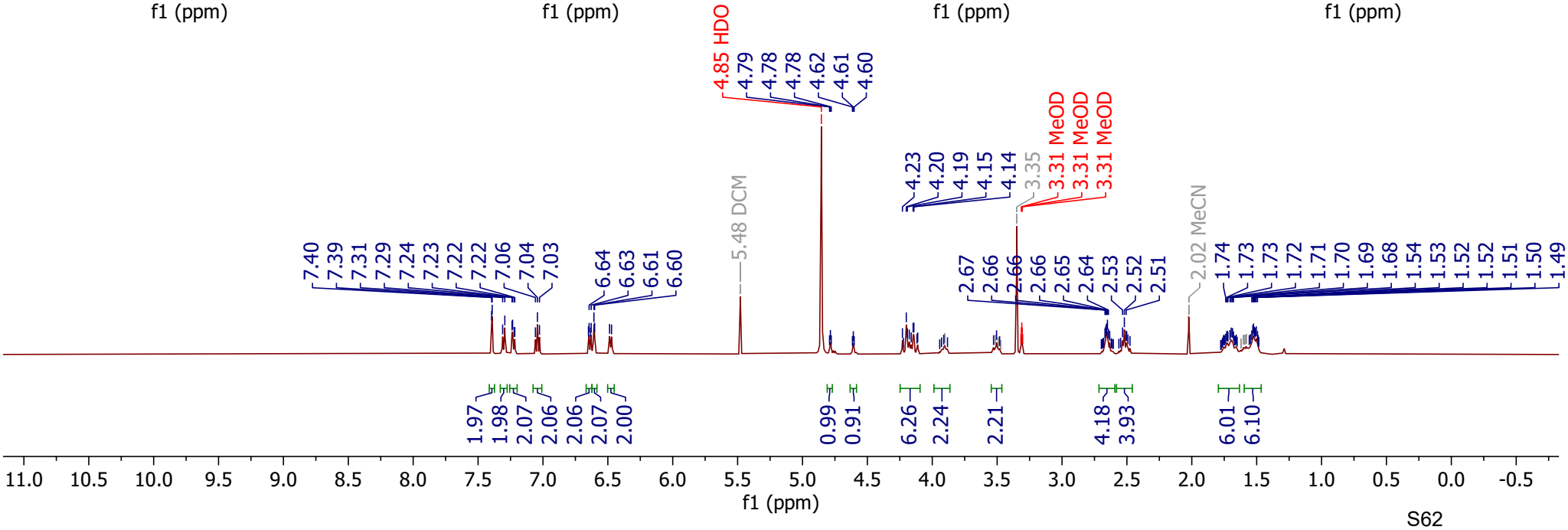
^{13}C NMR (151 MHz, MeOD-d4)



Compound S9
^{1}H NMR (500 MHz, MeOD-d4)

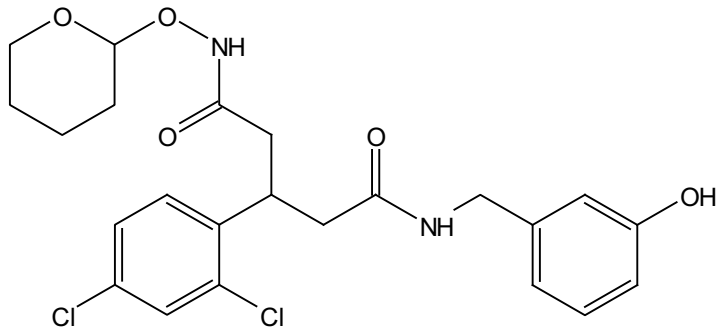




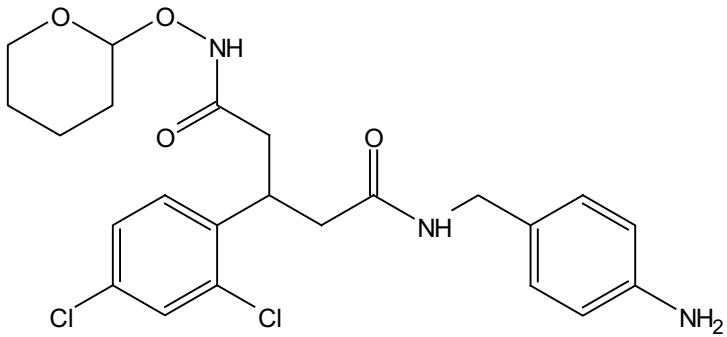


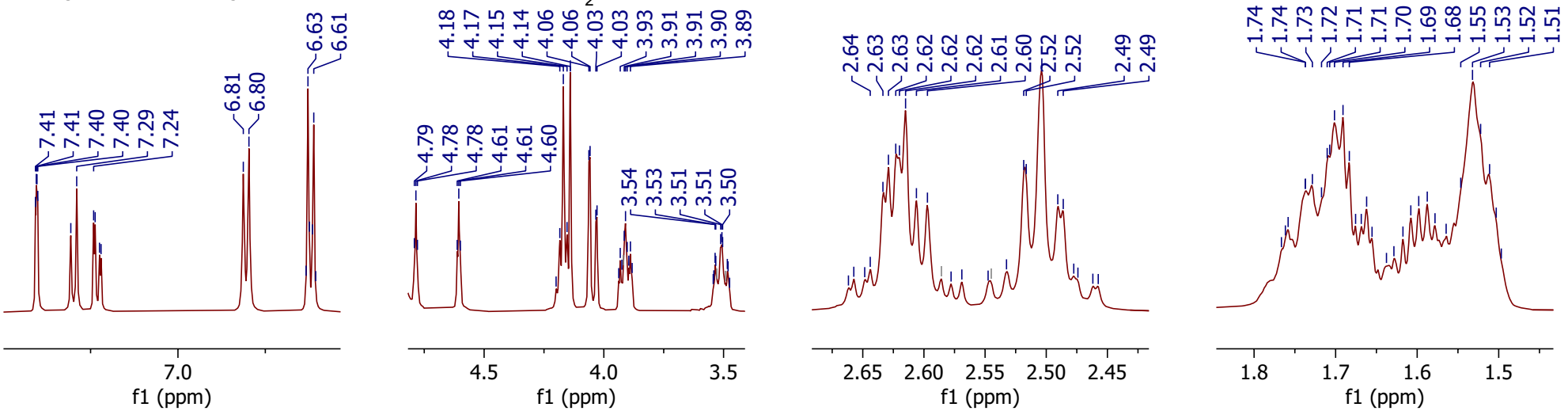
Compound S9

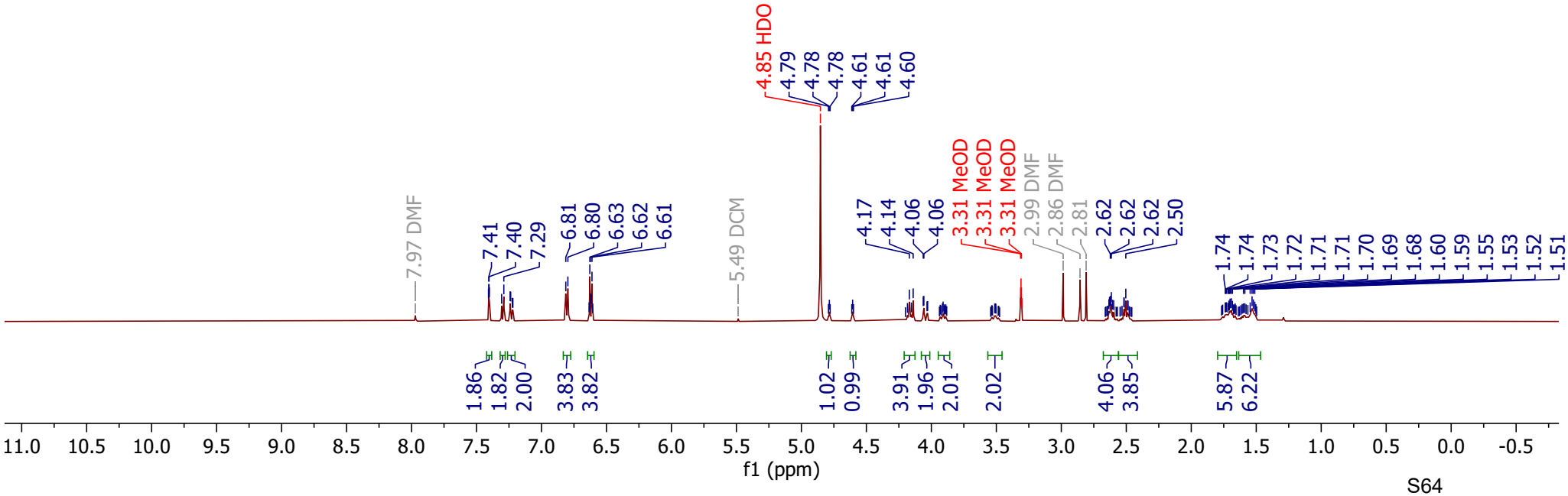
^{13}C NMR (151 MHz, MeOD-d4)



Compound S10
^{1}H NMR (500 MHz, MeOD-d4)

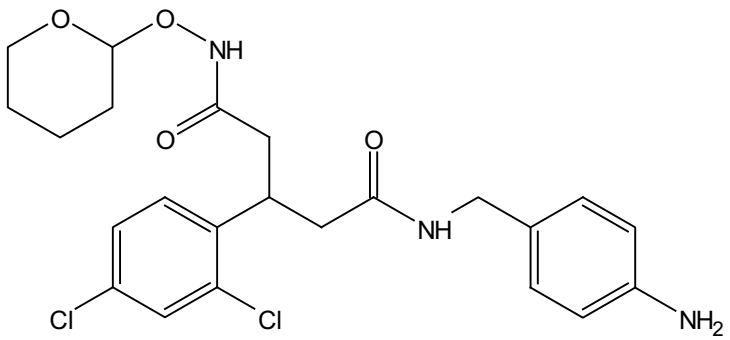




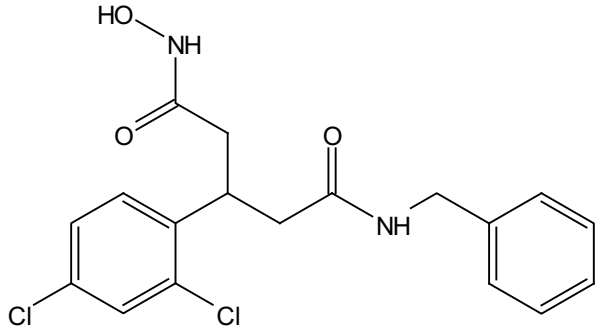


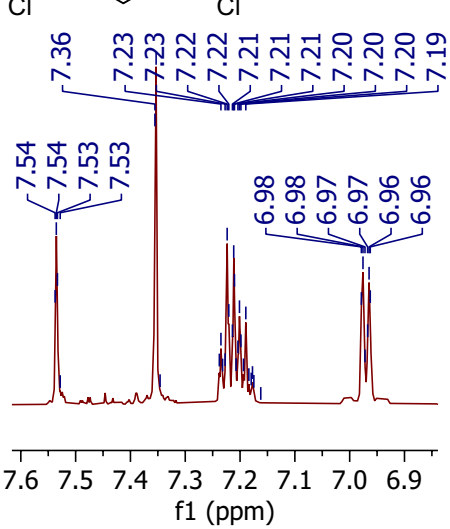
Compound S10

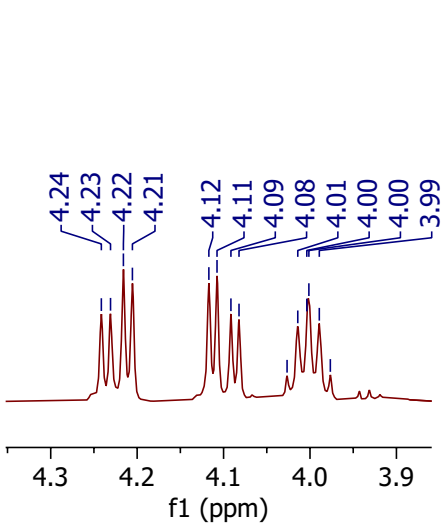
^{13}C NMR (151 MHz, MeOD-d4)

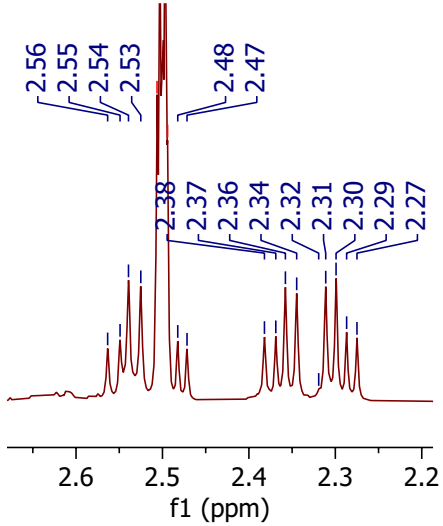


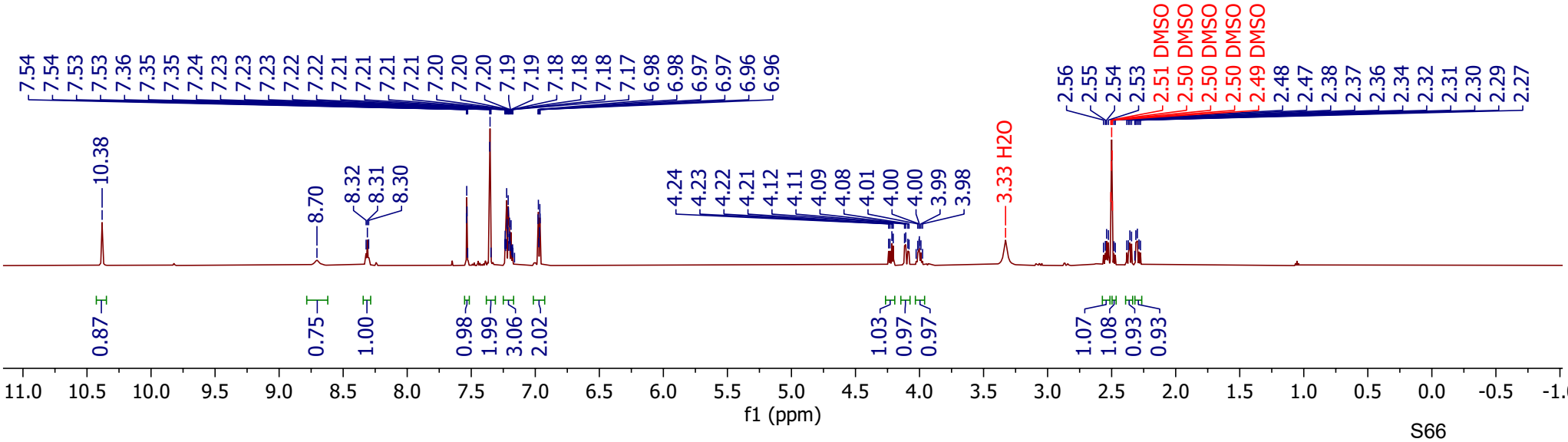
Compound 7
^{1}H NMR (600 MHz, DMSO-d6)



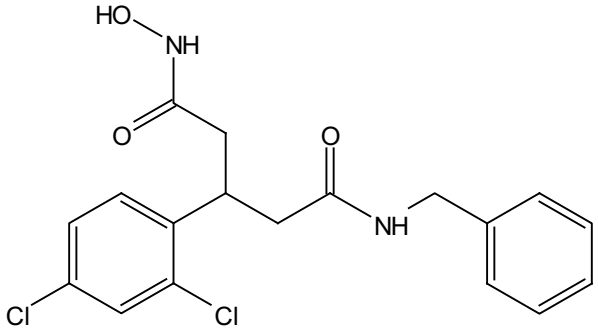




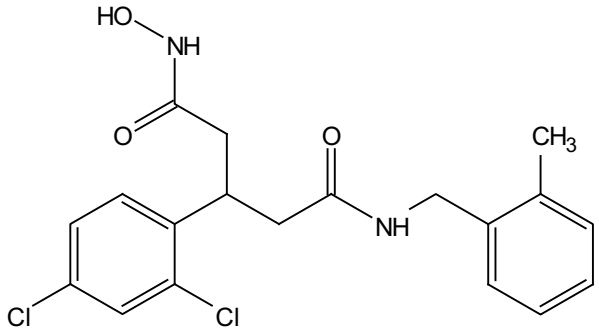


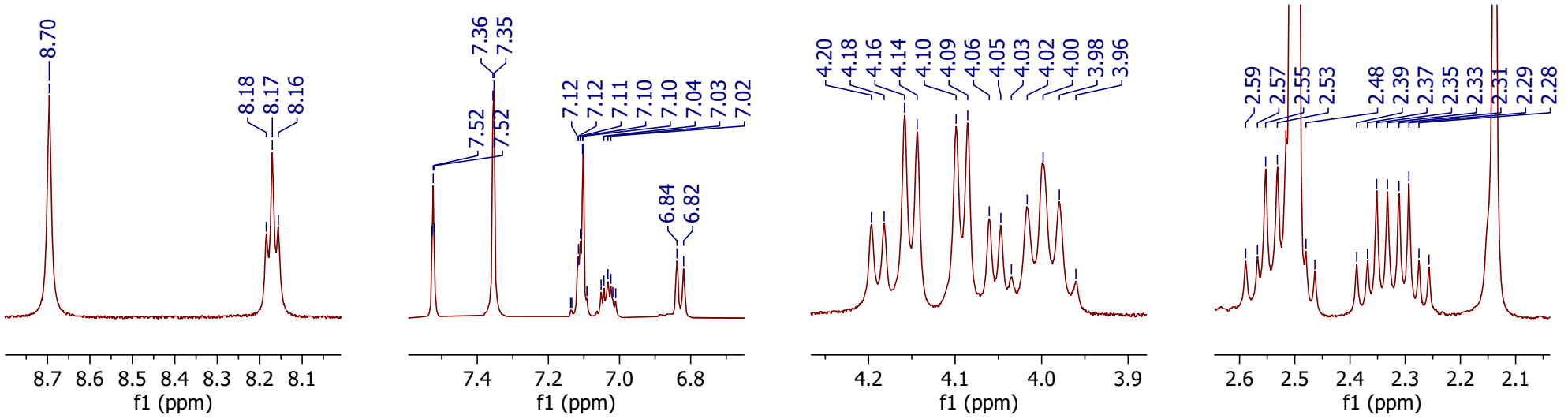


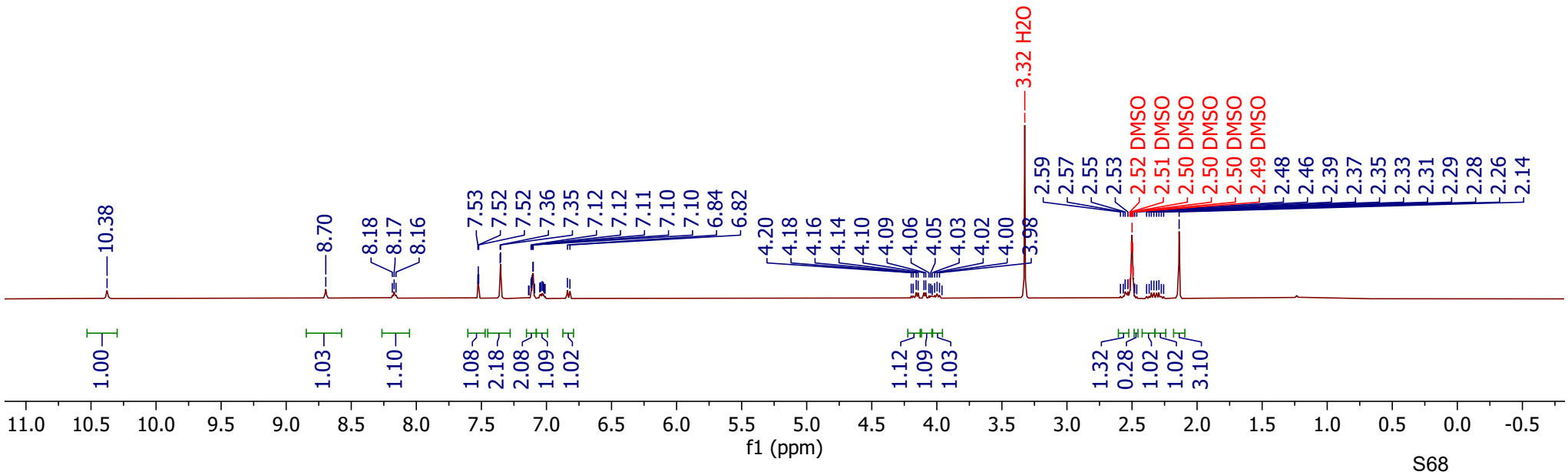
Compound 7
^{13}C NMR (151 MHz, DMSO-d6)



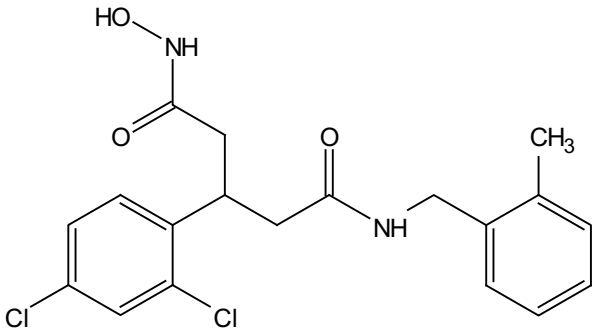
Compound 8
^{1}H NMR (400 MHz, DMSO-d6)



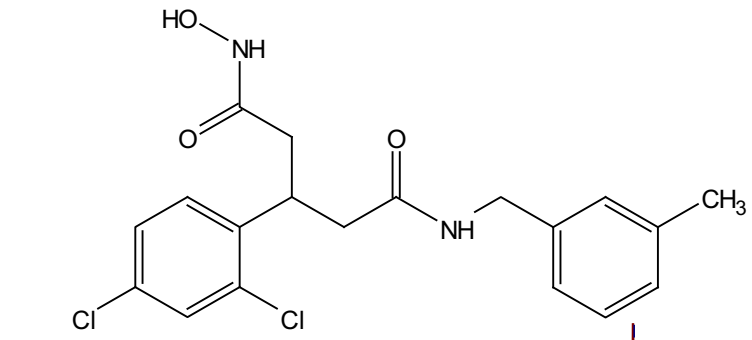


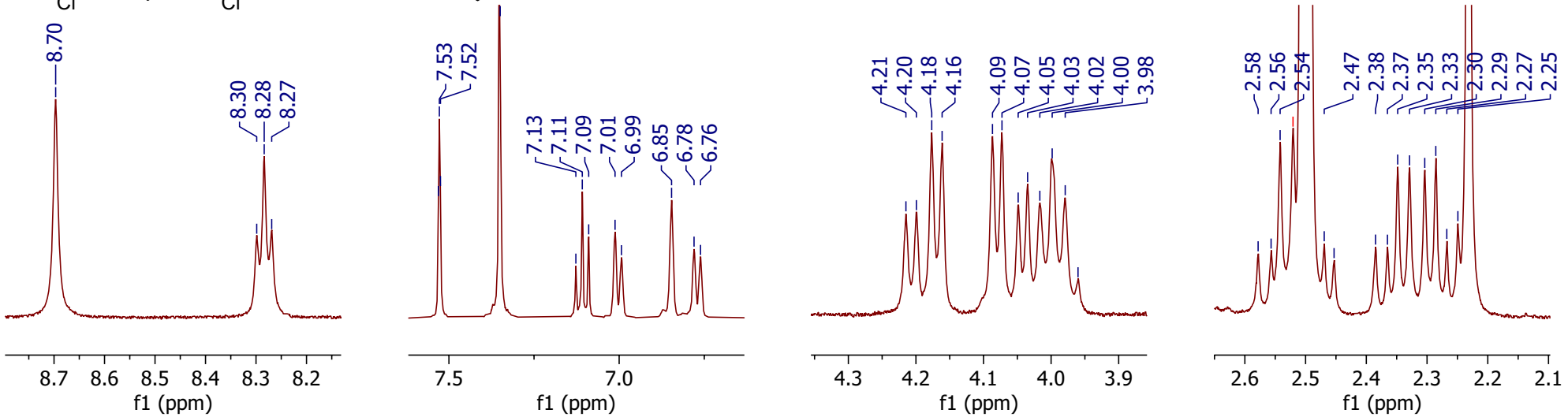


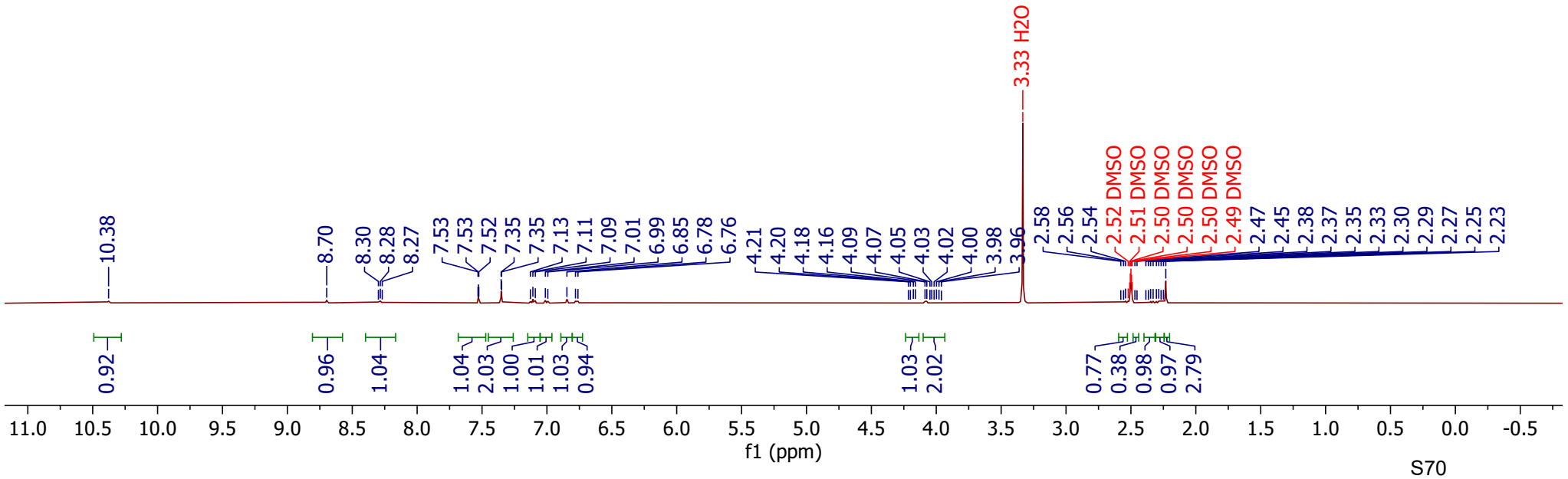
Compound 8
^{13}C NMR (151 MHz, DMSO-d6)



Compound 9
^{1}H NMR (400 MHz, DMSO-d6)

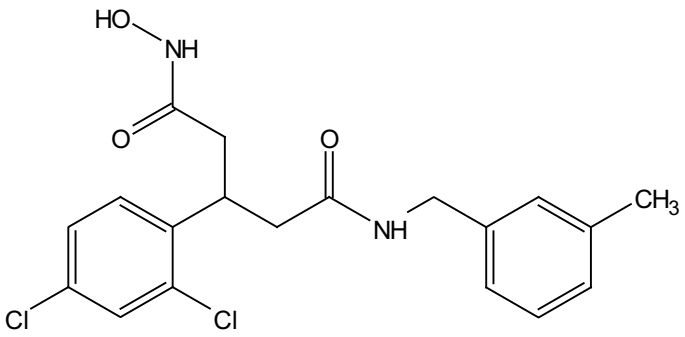




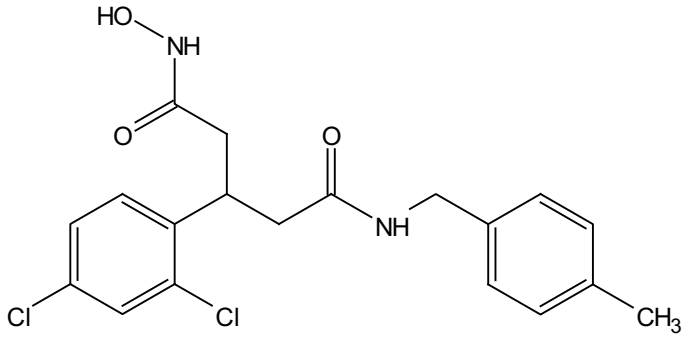


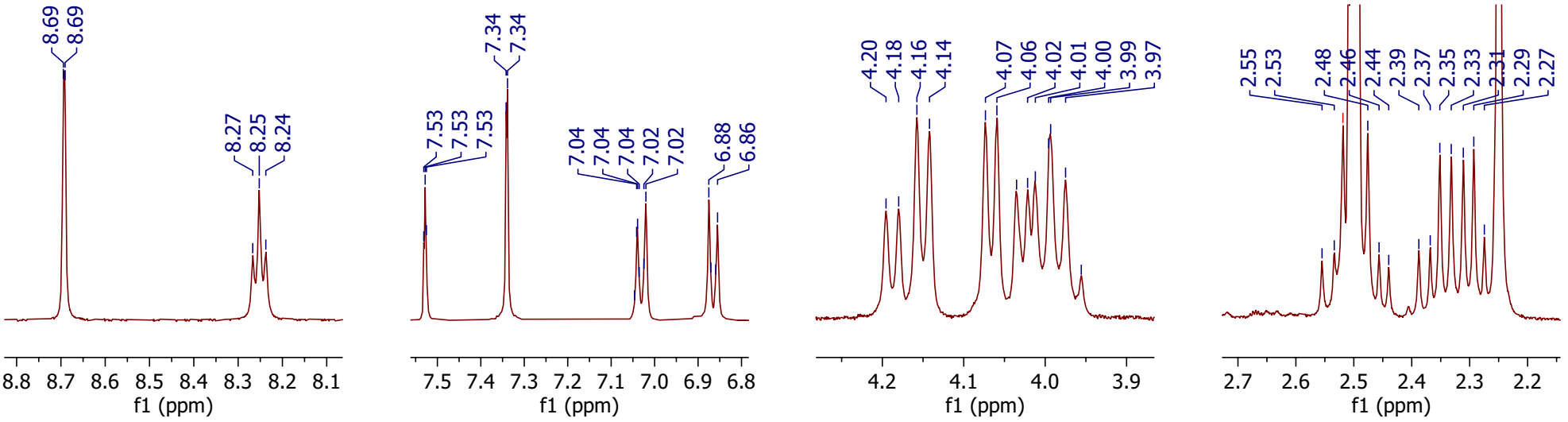
Compound 9

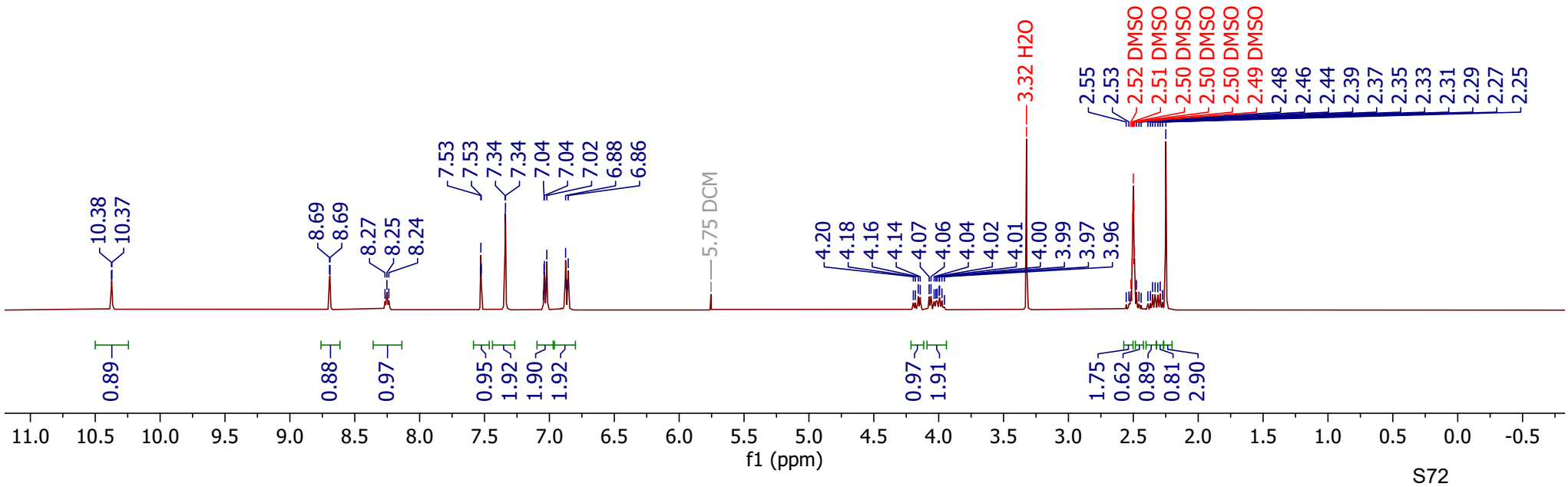
^{13}C NMR (126 MHz, DMSO-d6)



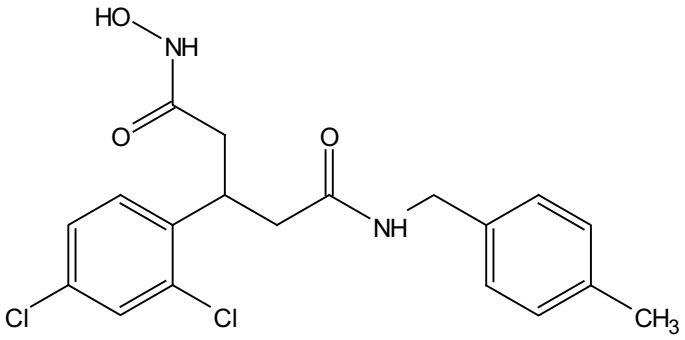
Compound 10
^{1}H NMR (400 MHz, DMSO-d6)



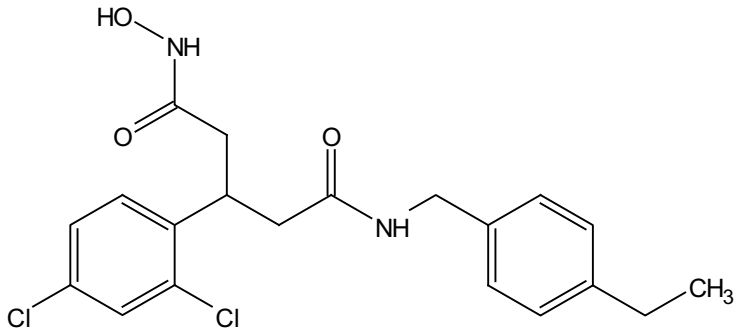


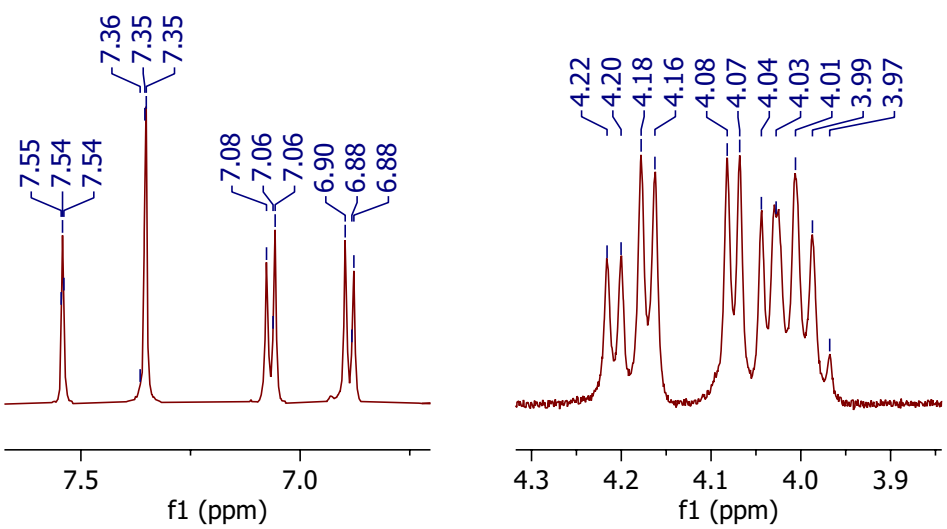


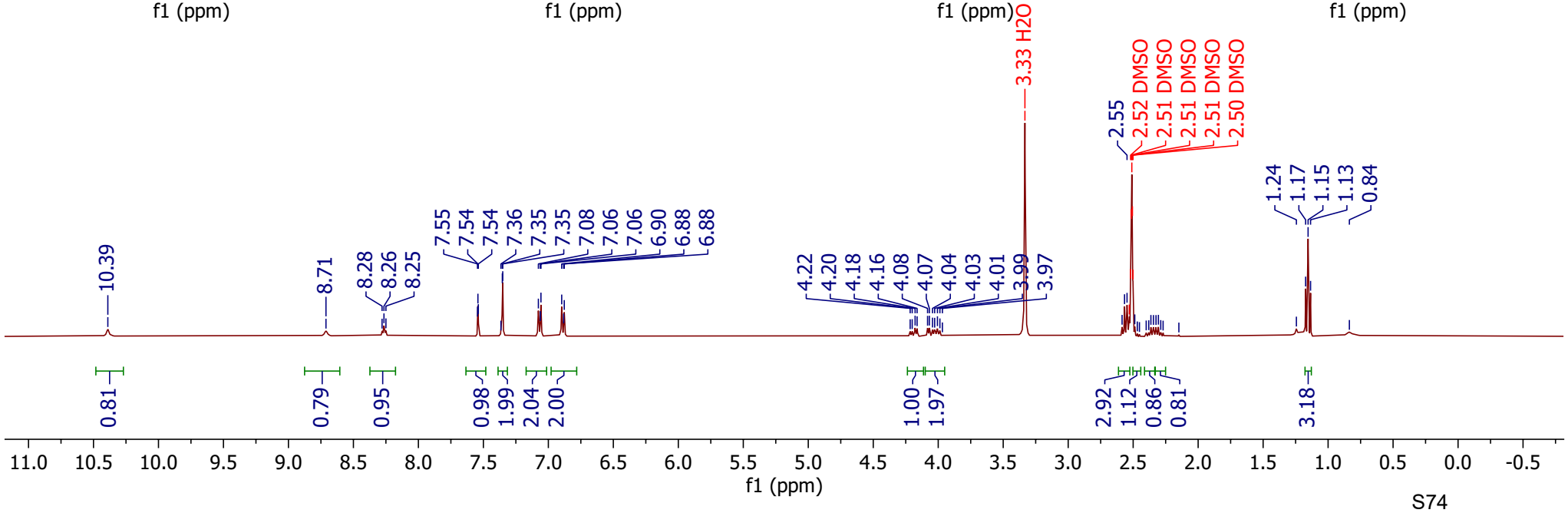
Compound 10
^{13}C NMR (126 MHz, DMSO-d6)



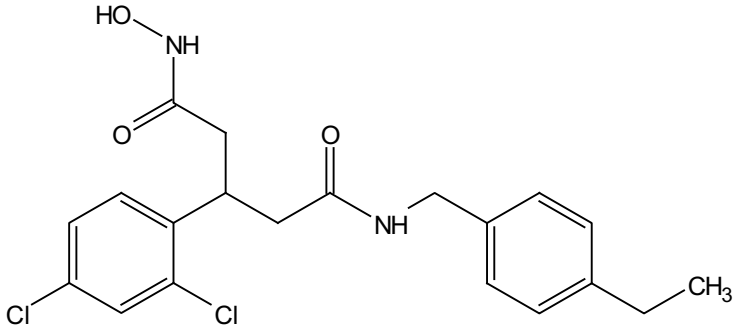
Compound 11
^{1}H NMR (400 MHz, DMSO-d6)



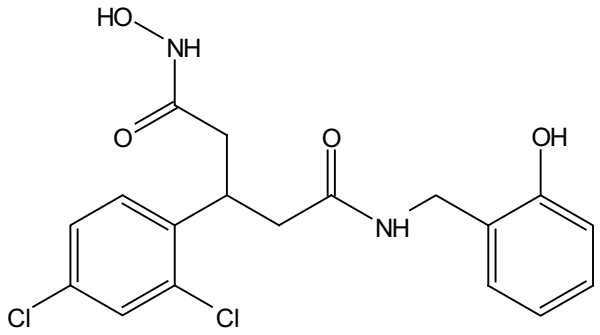


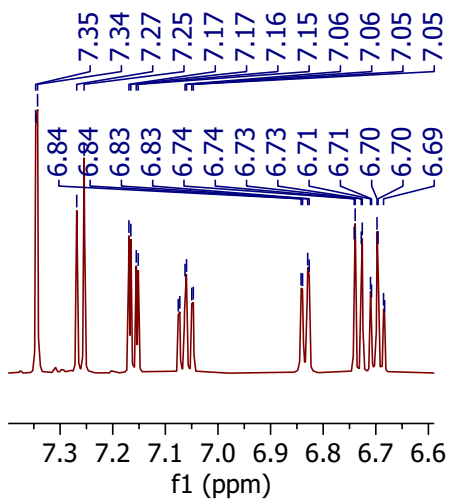


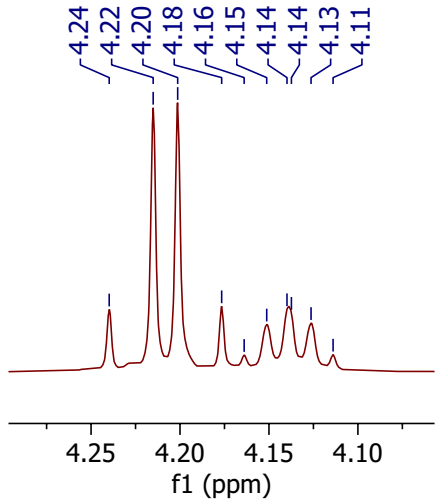
Compound 11
^{13}C NMR (151 MHz, DMSO-d6)

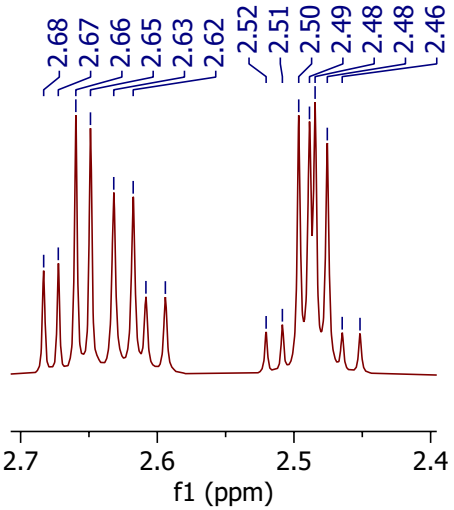


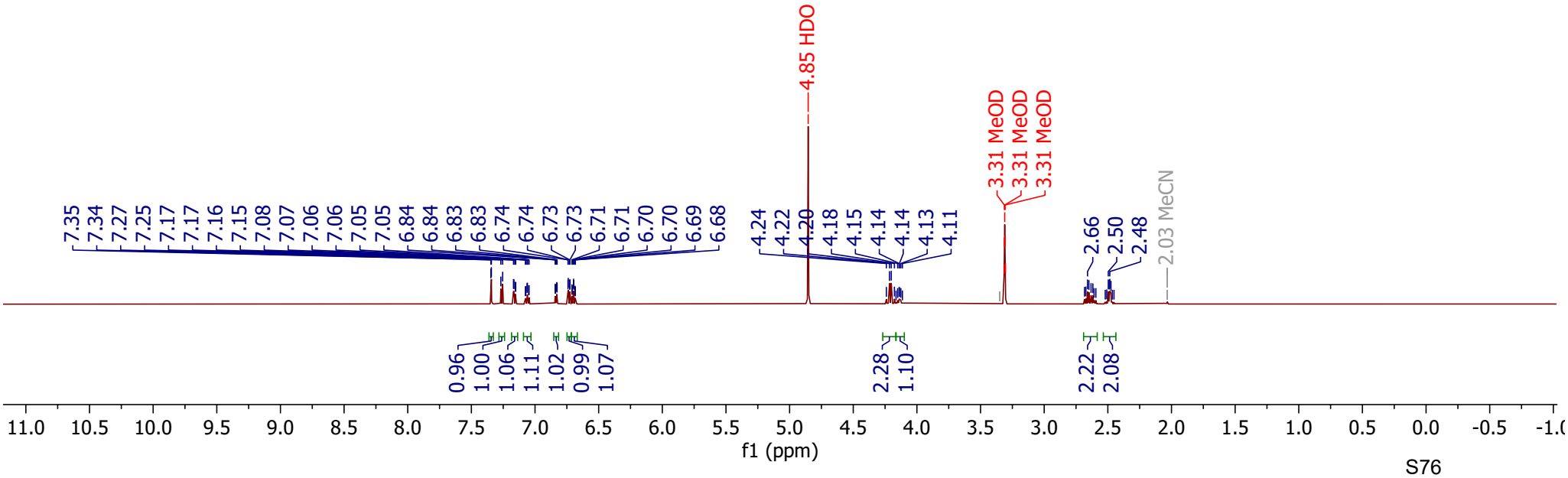
Compound 12
^{1}H NMR (600 MHz, MeOD-d4)



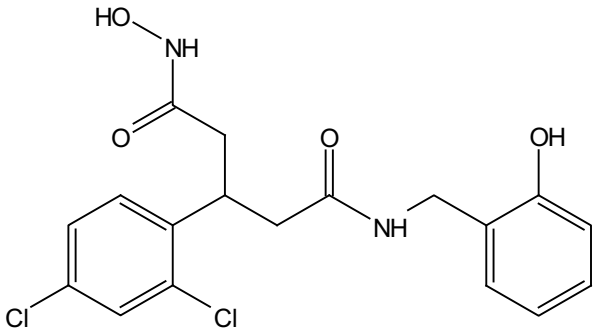




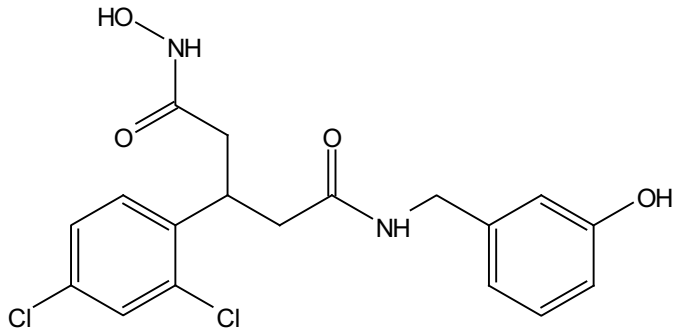


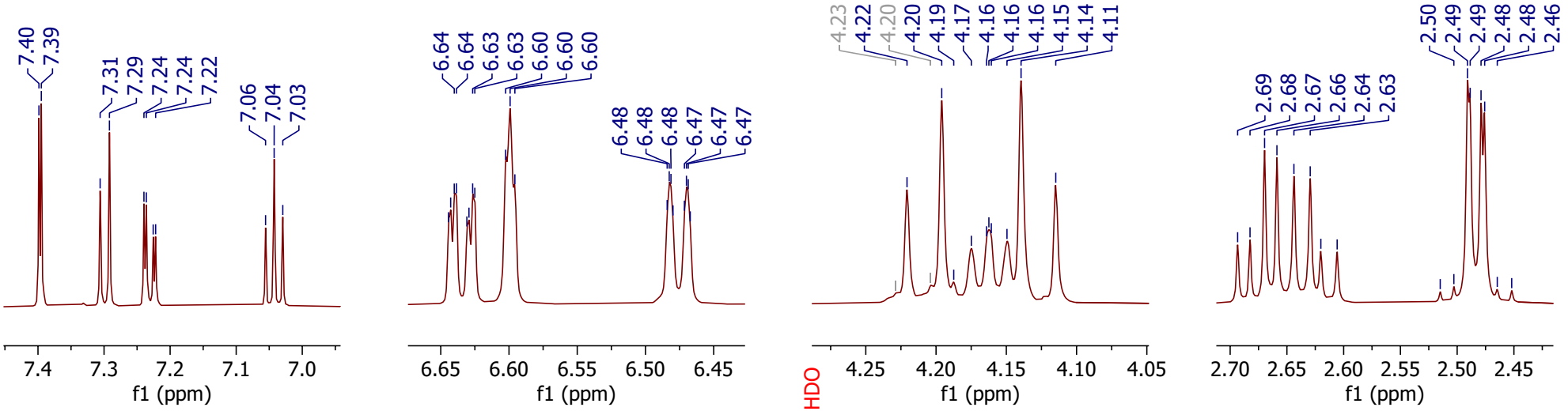


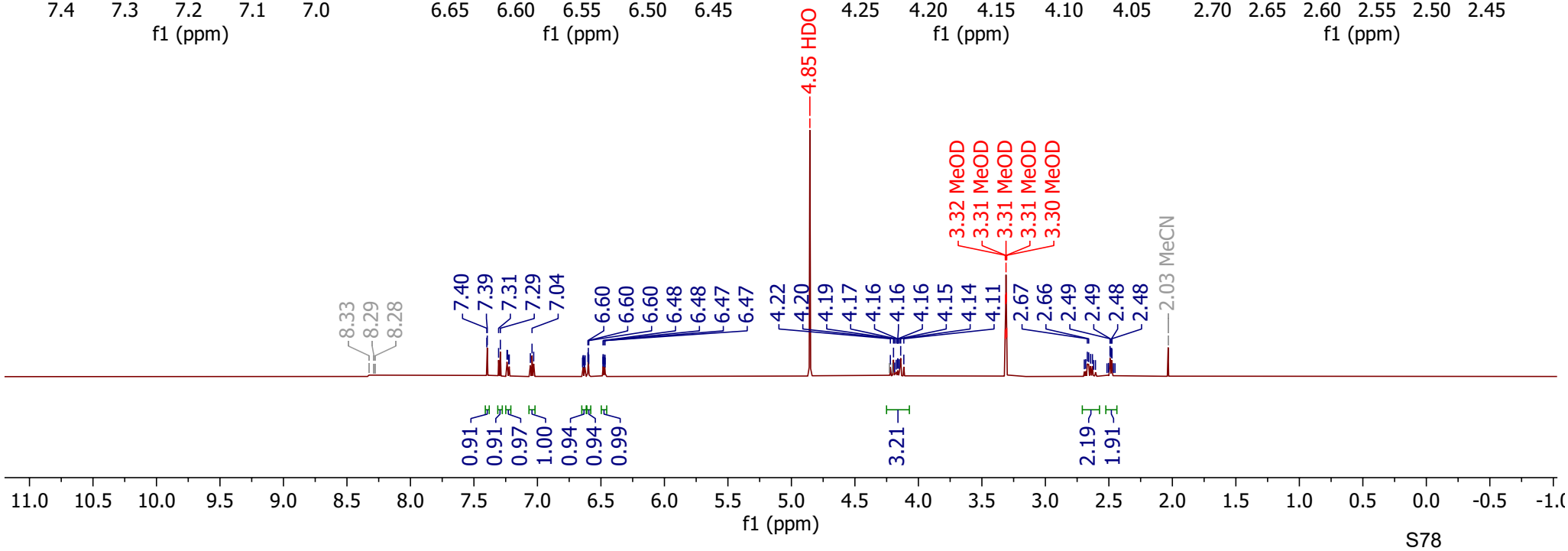
Compound 12
^{13}C NMR (151 MHz, MeOD-d6)



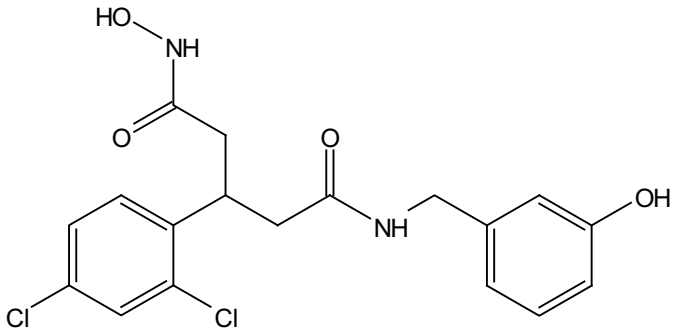
Compound 13
^{1}H NMR (600 MHz, MeOD-d4)



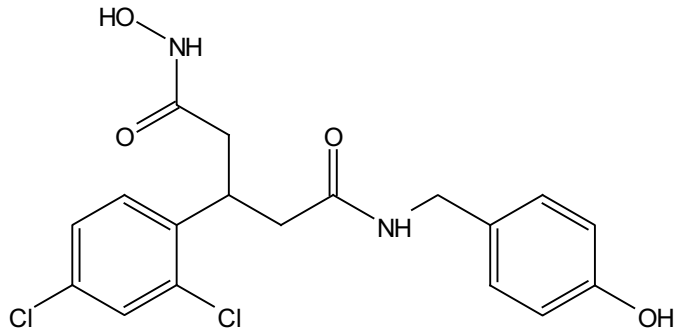


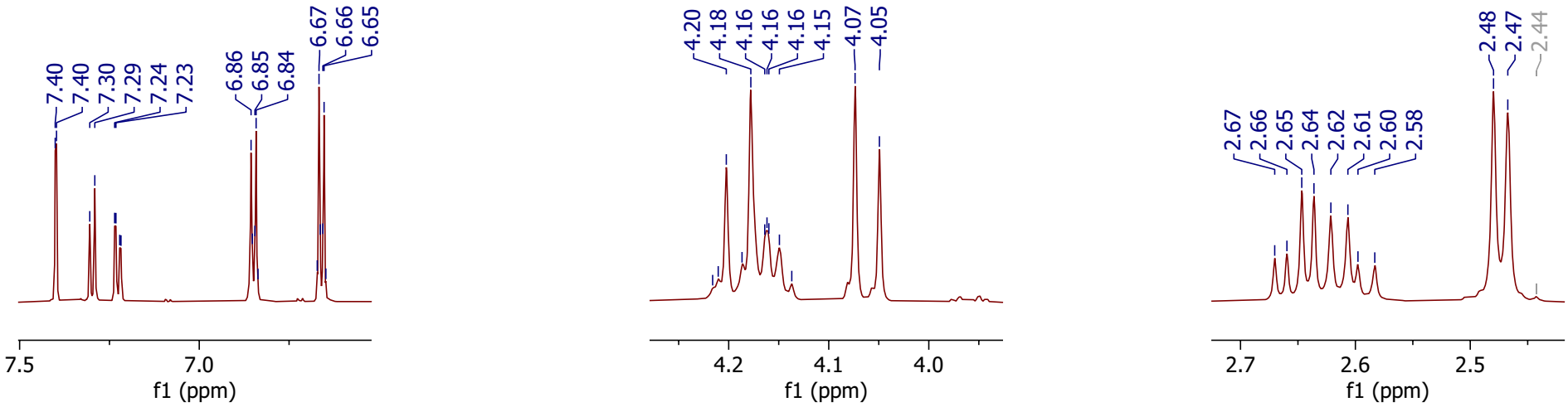


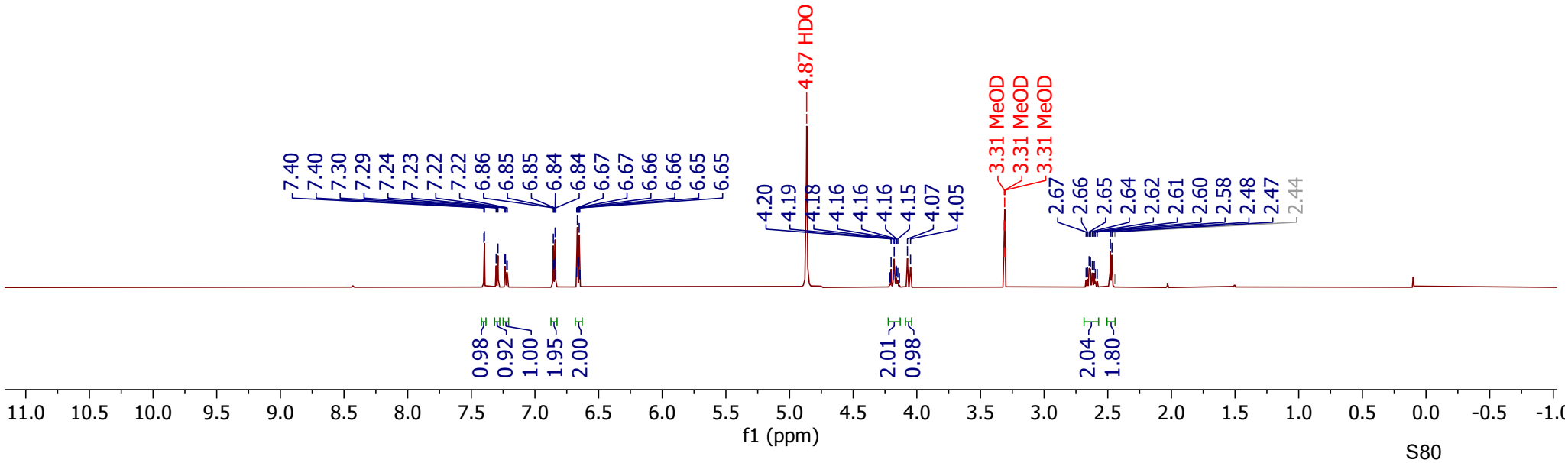
Compound 13
^{13}C NMR (151 MHz, MeOD-d4)



Compound 14
^{1}H NMR (600 MHz, MeOD-d4)

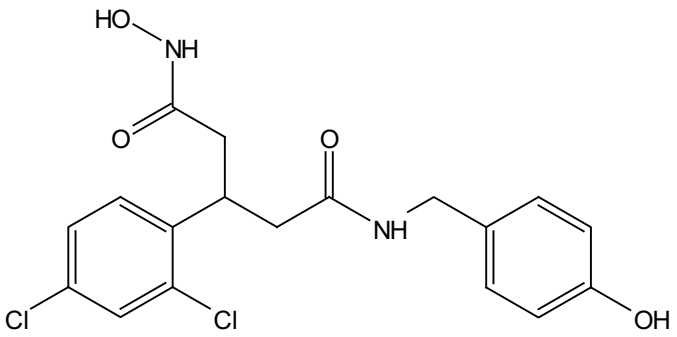




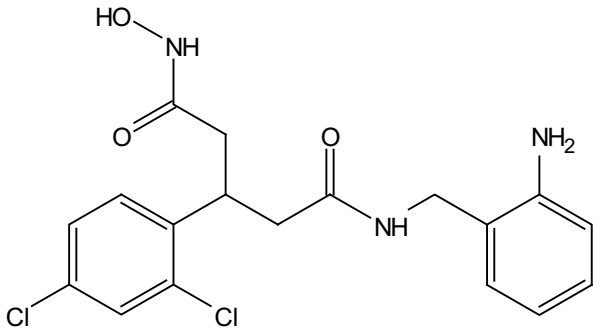


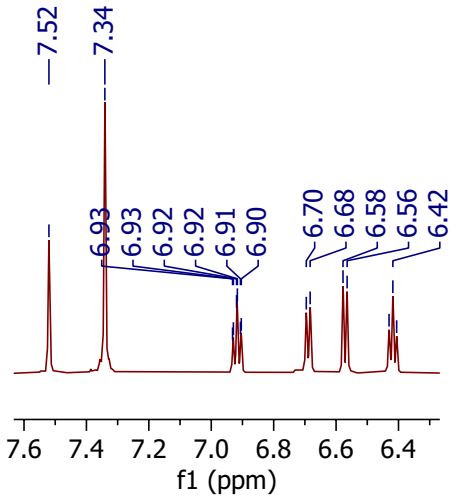
Compound 14

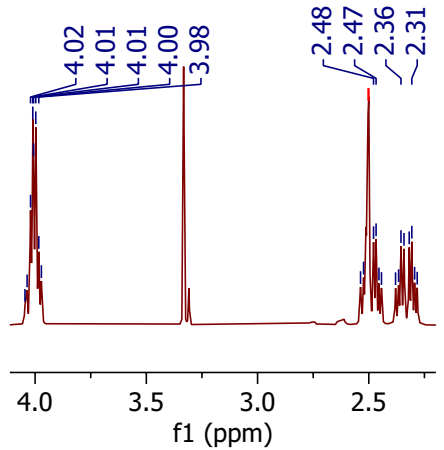
^{13}C NMR (151 MHz, MeOD-d4)

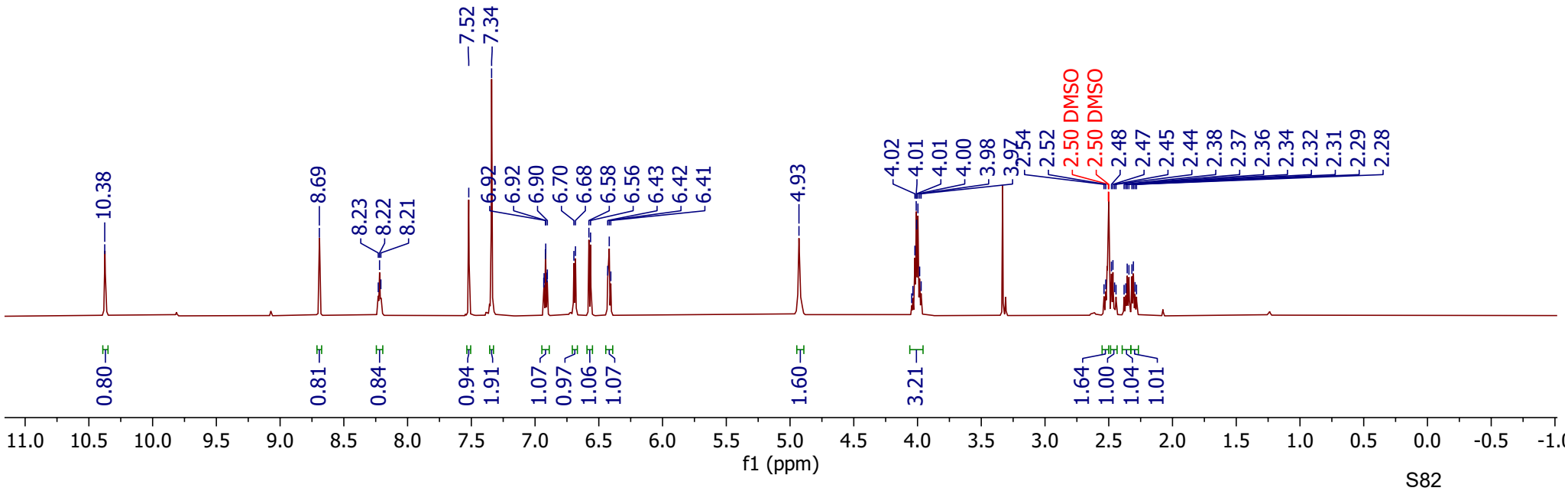


Compound 15
^{1}H NMR (600 MHz, DMSO-d6)



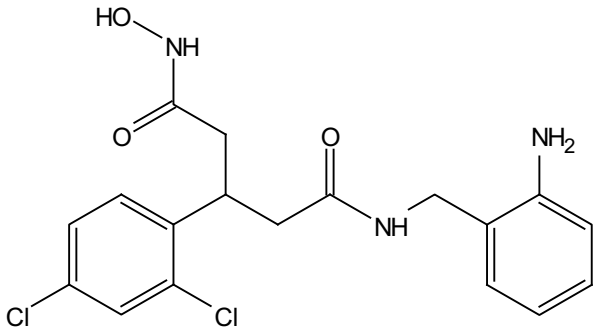




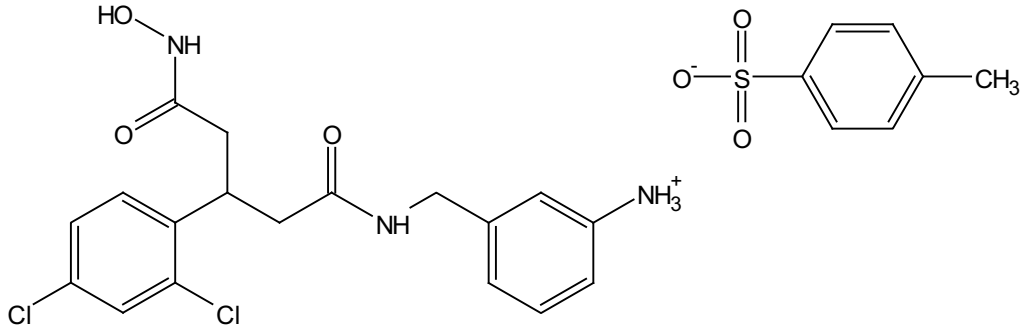


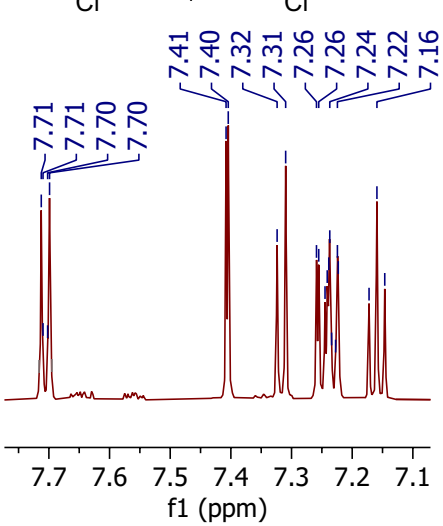
Compound 15

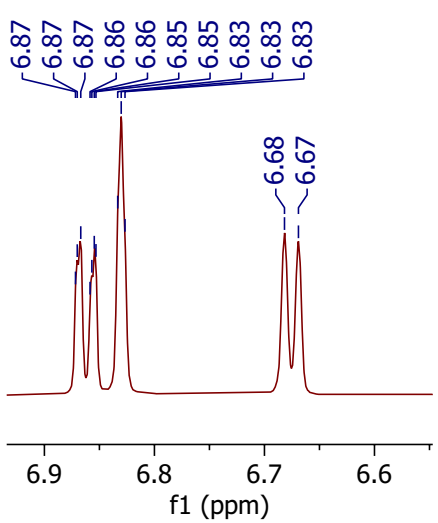
^{13}C NMR (151 MHz, DMSO-d6)

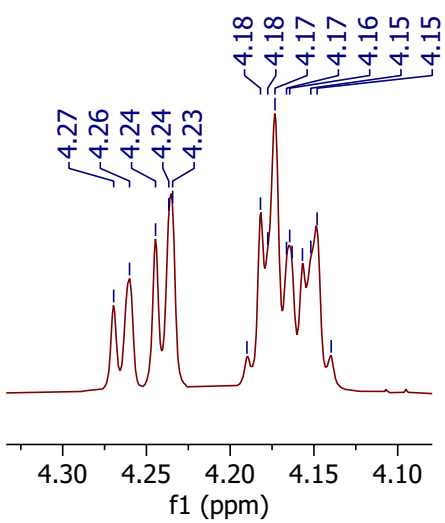


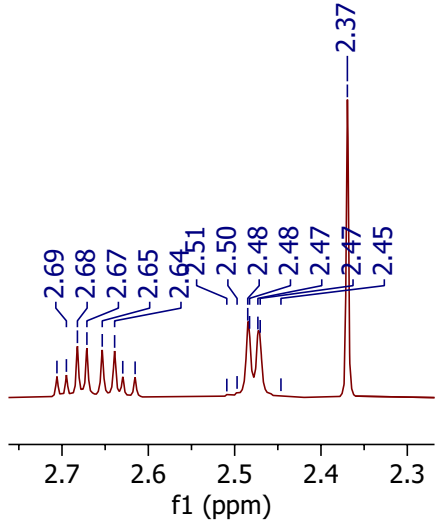
Compound 16
^{1}H NMR (600 MHz, MeOD-d4)

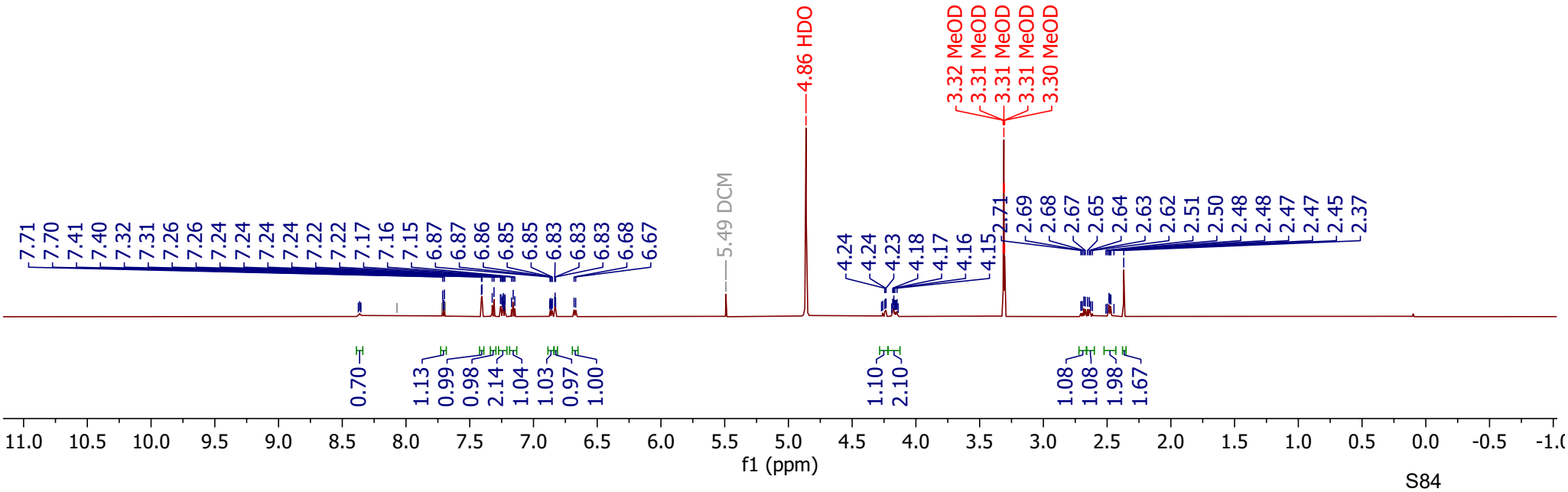




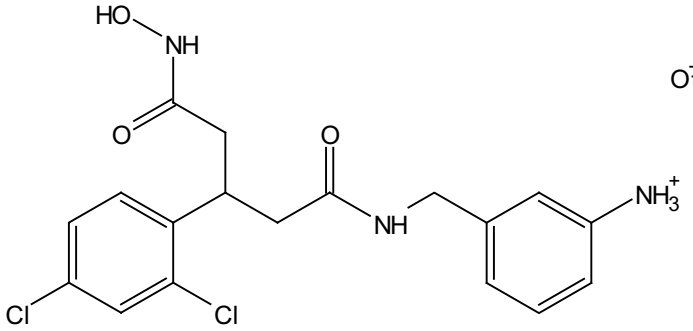


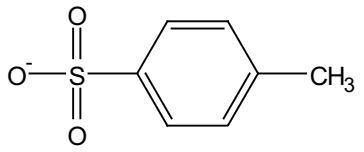


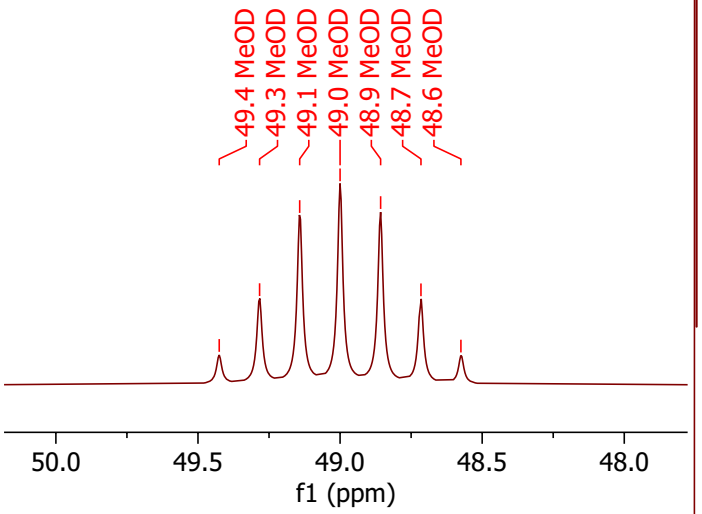




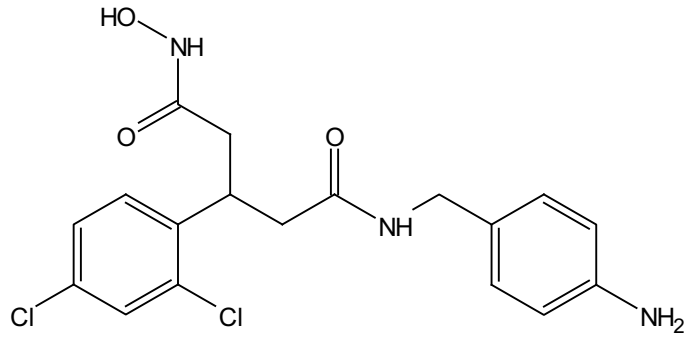
Compound 16
^{13}C NMR (151 MHz, MeOD-d4)

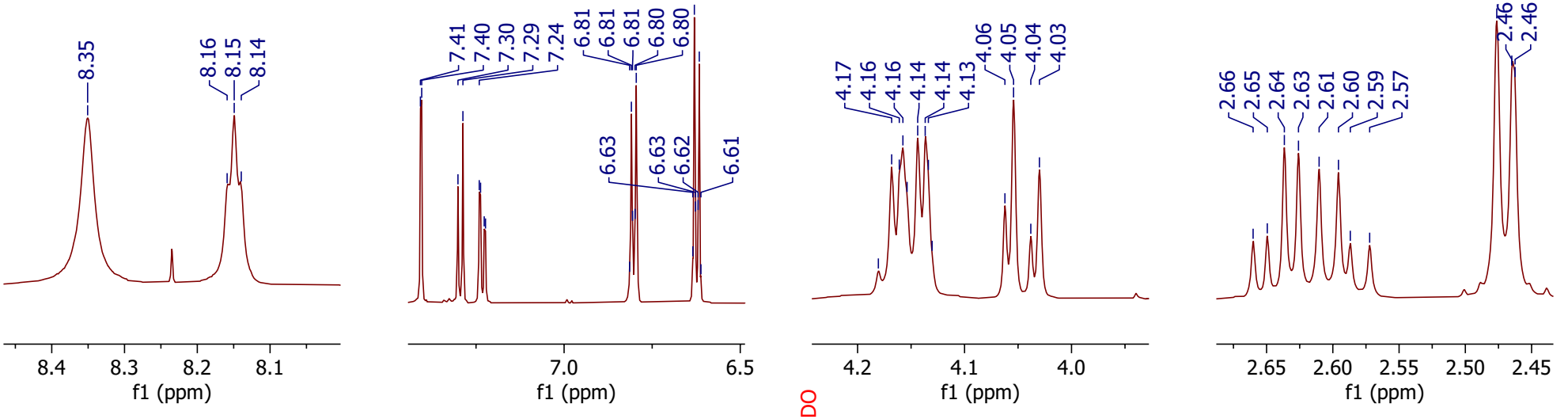


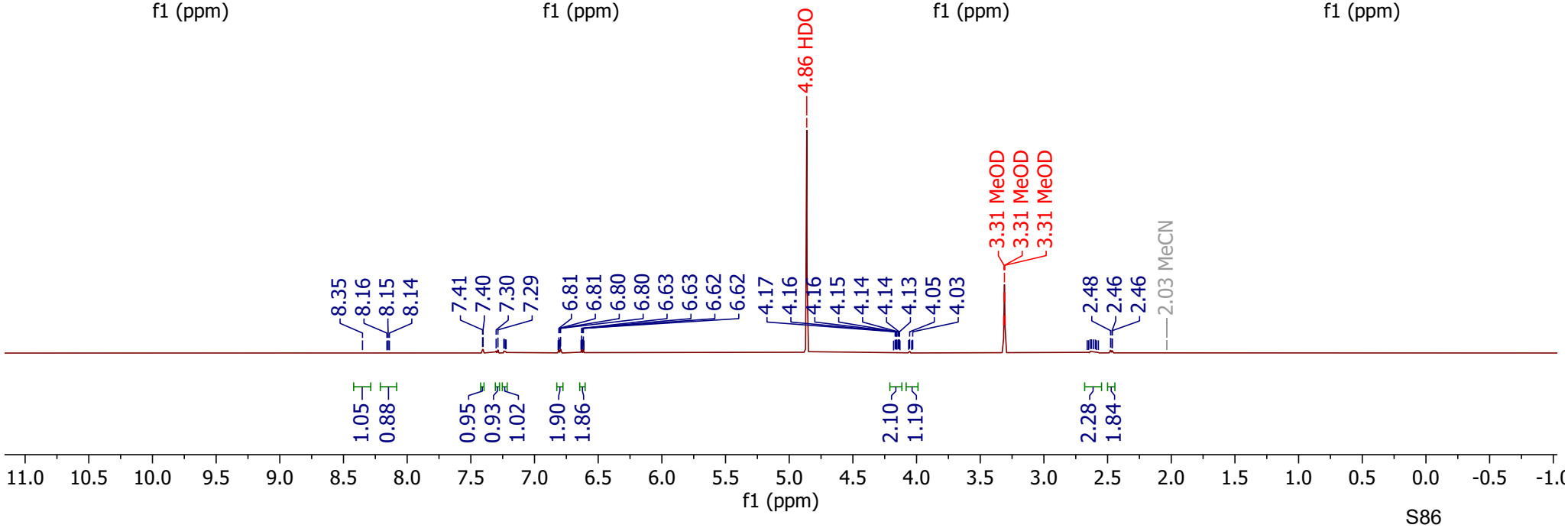




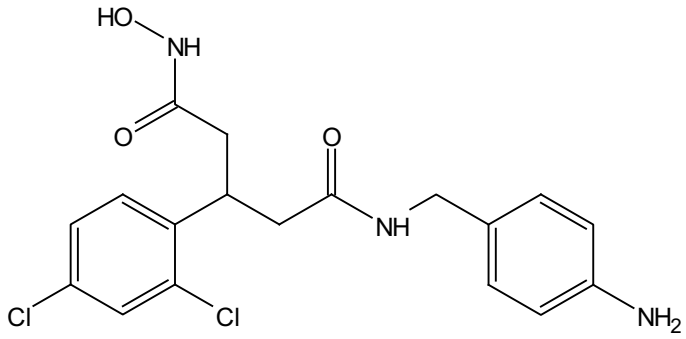
Compound 17
^{1}H NMR (600 MHz, MeOD-d4)





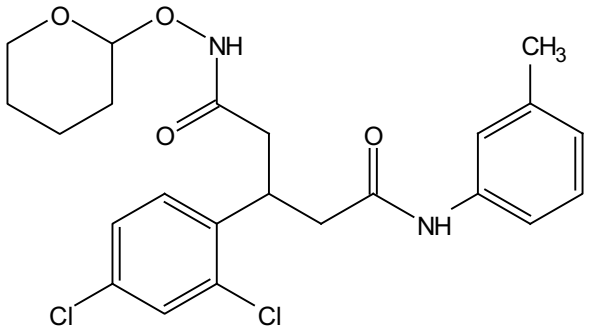


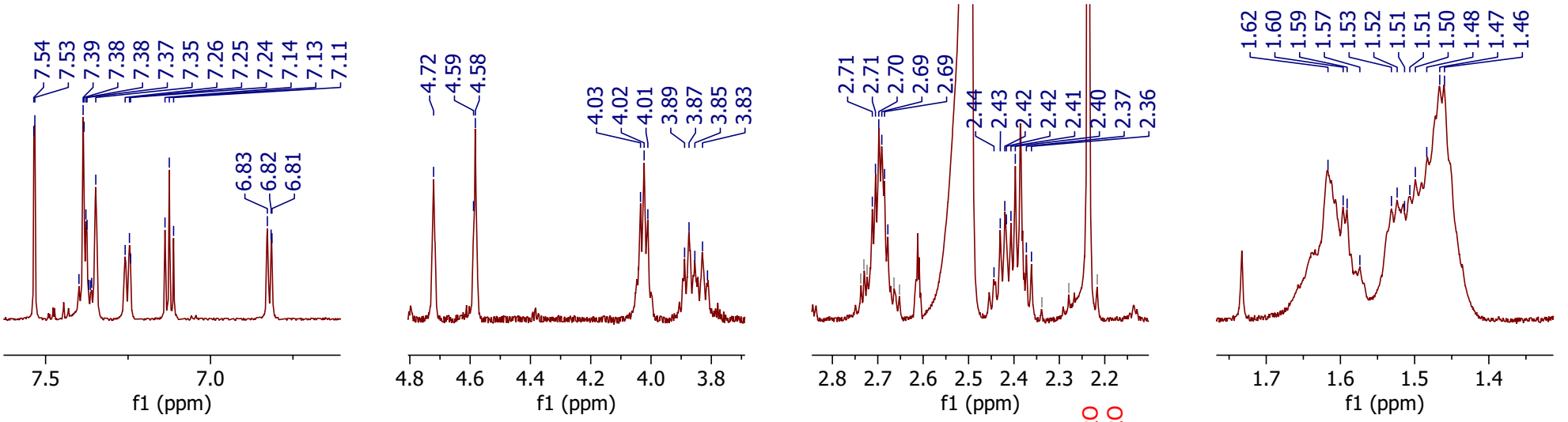
Compound 17
^{13}C NMR (151 MHz, MeOD-d4)

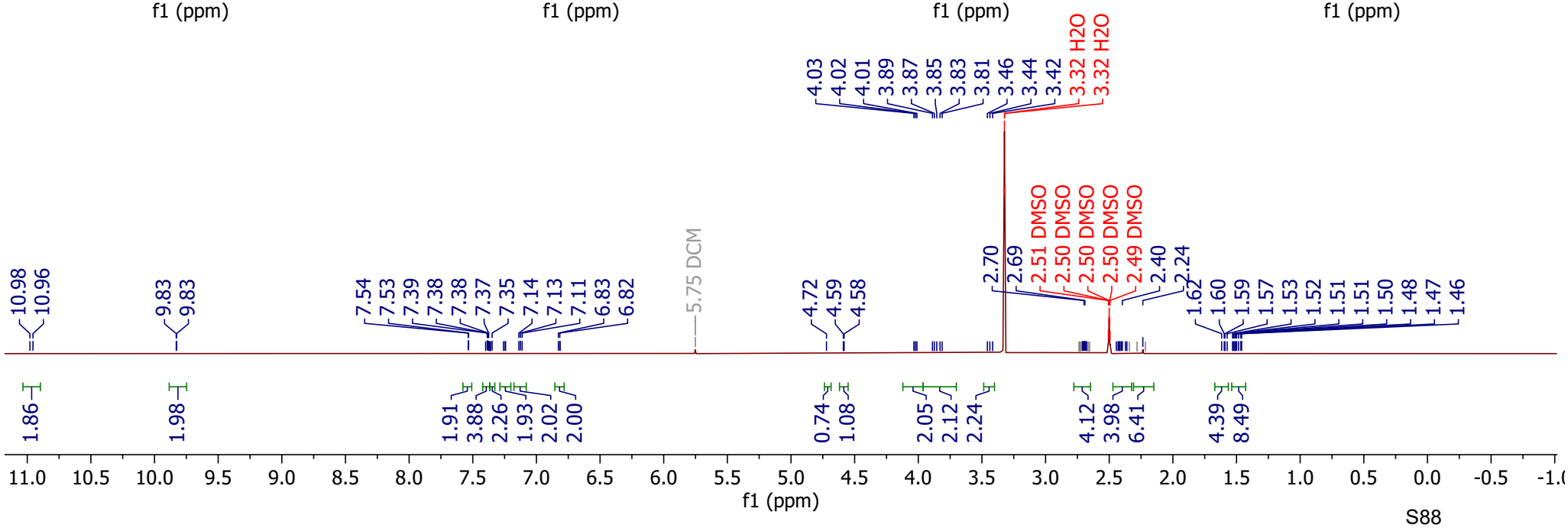


Compound S11

^{1}H NMR (600 MHz, DMSO-d6)

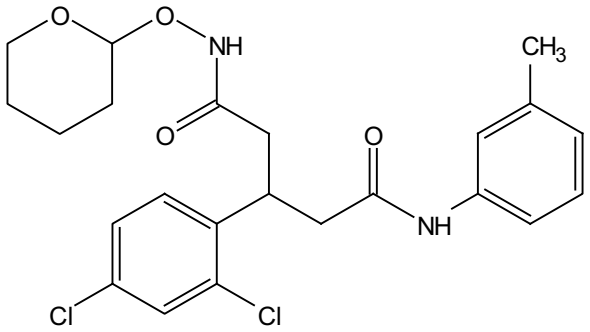






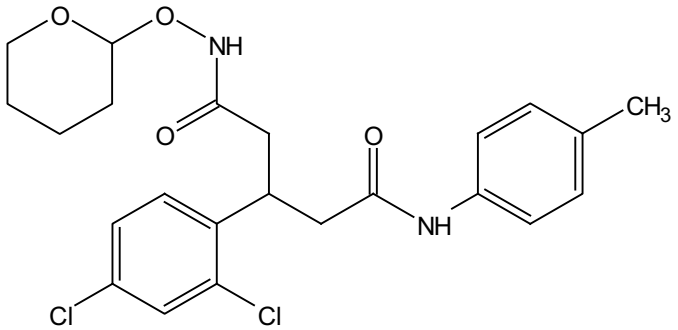
Compound S11

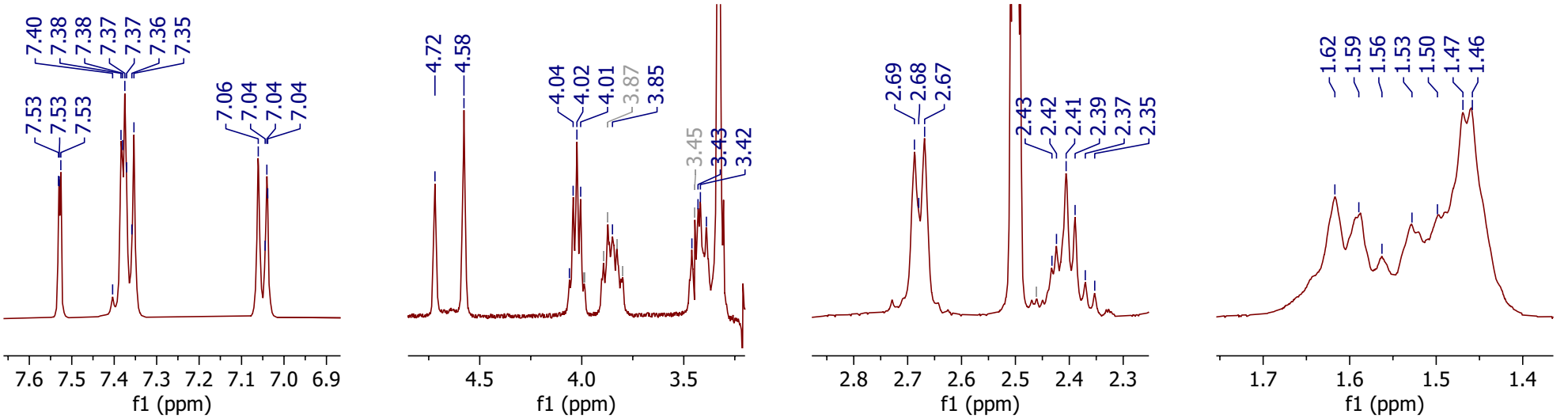
^{13}C NMR (151 MHz, DMSO-d6)

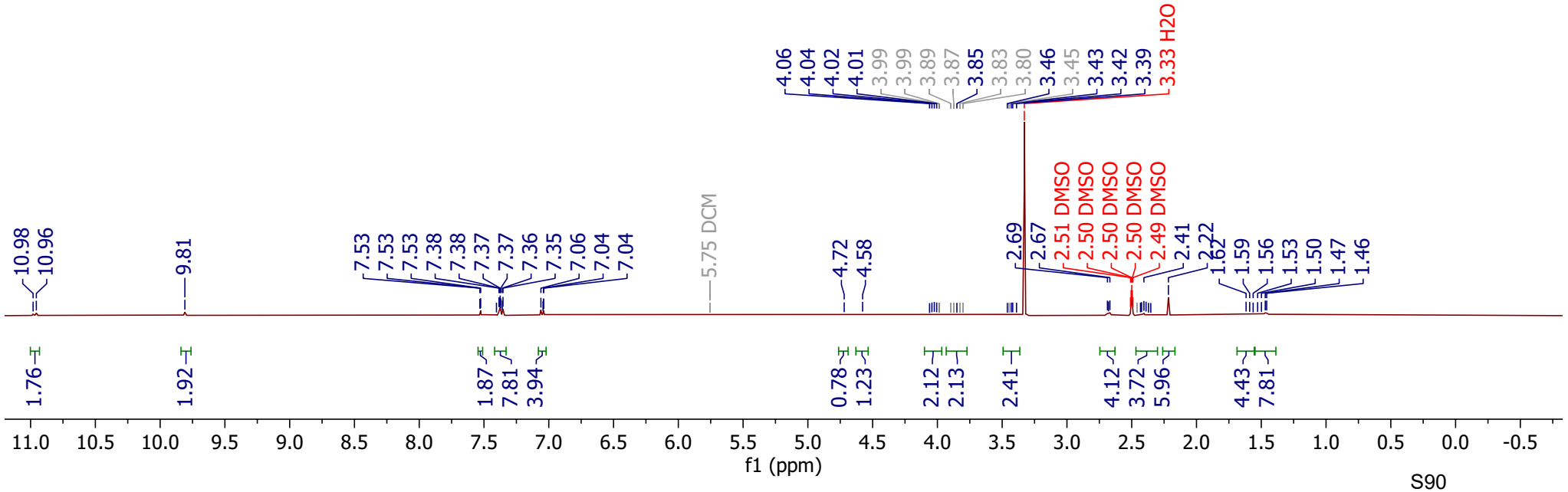


Compound S12

^{1}H NMR (400 MHz, DMSO-d6)

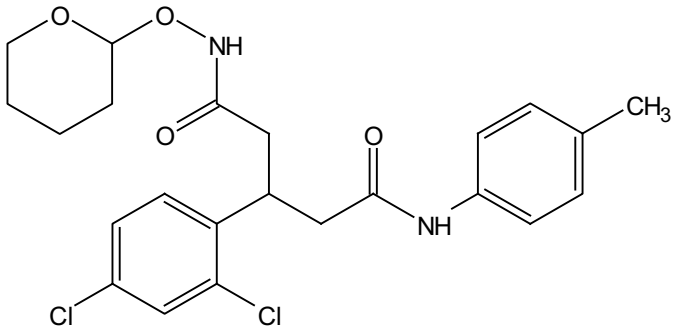


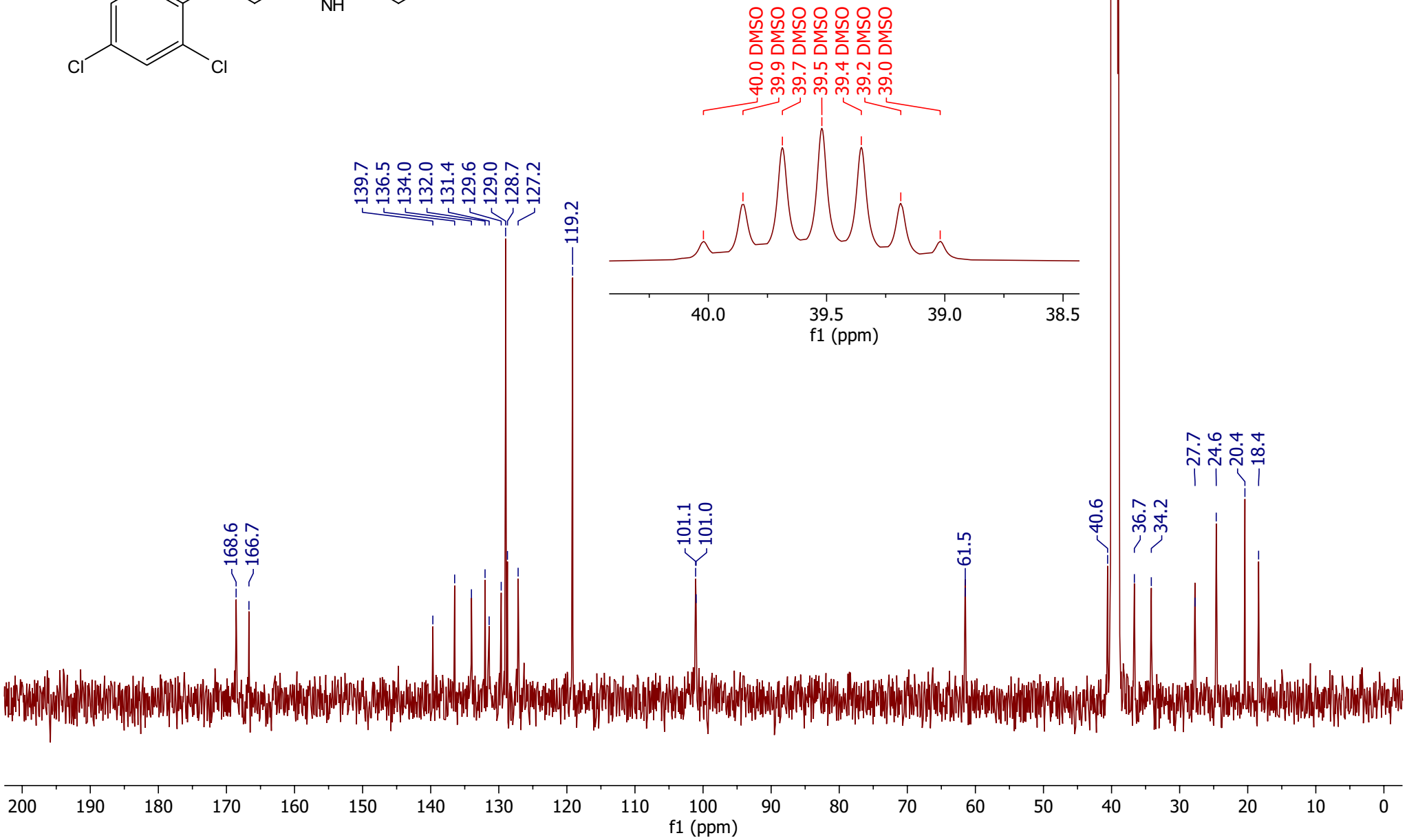




Compound S12

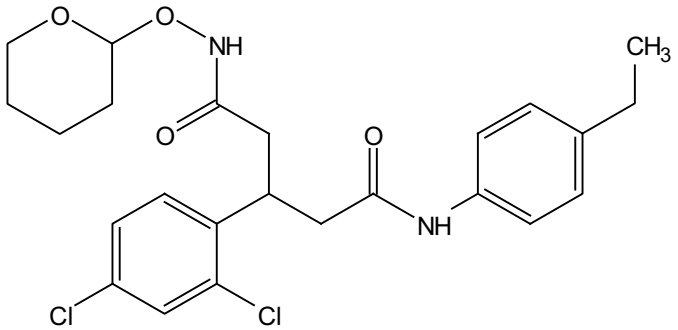
^{13}C NMR (126 MHz, DMSO-d6)

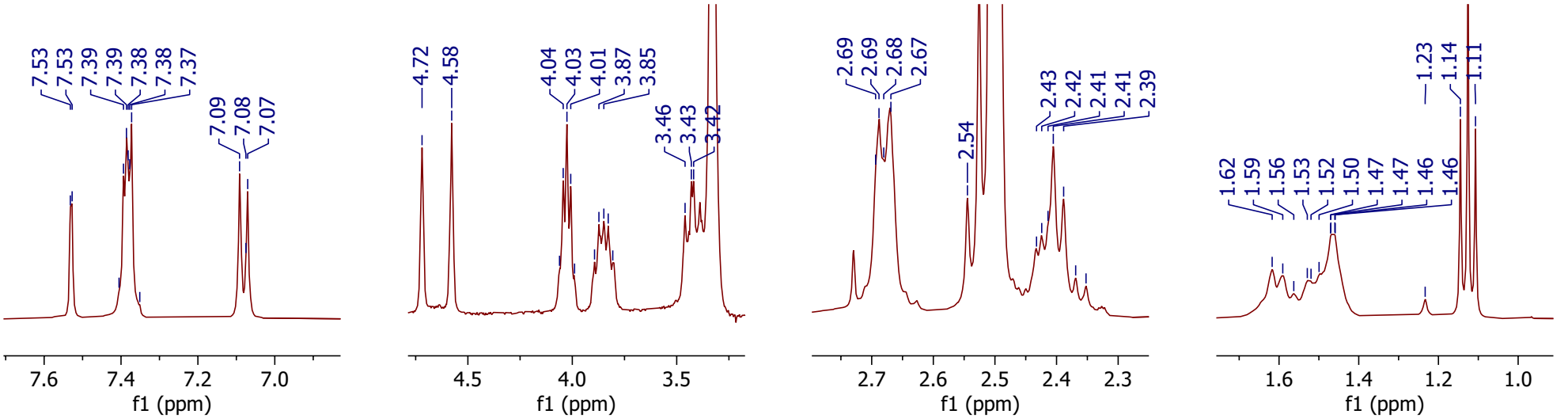


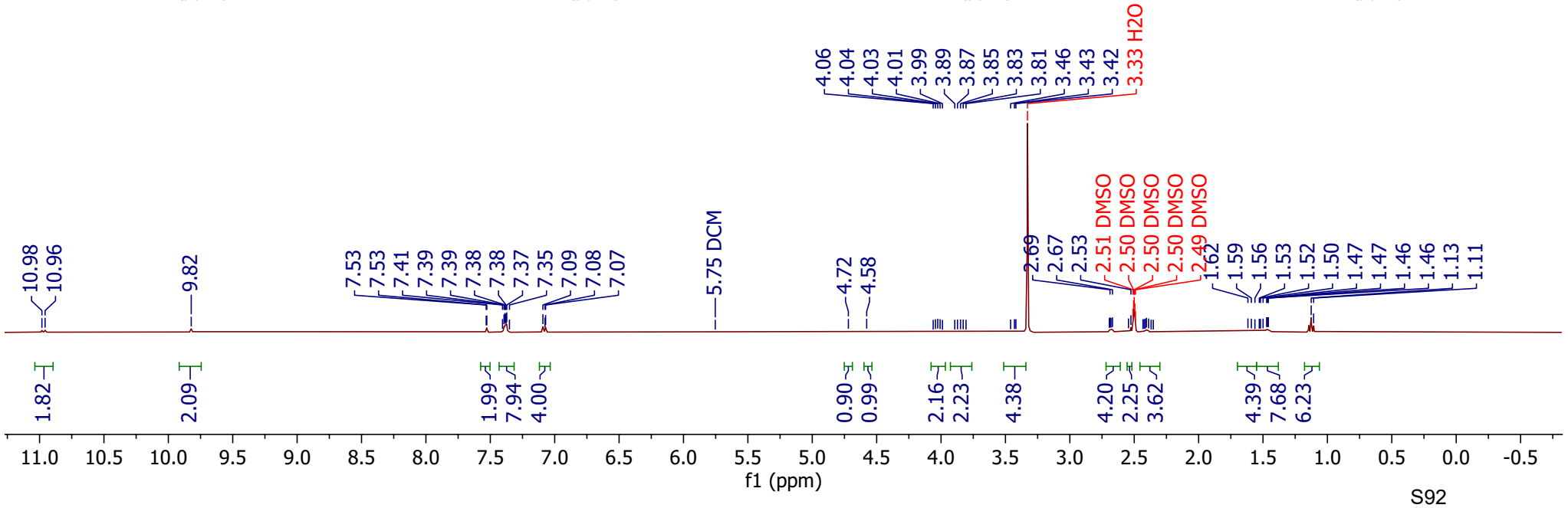


Compound S13

^{1}H NMR (400 MHz, DMSO-d6)

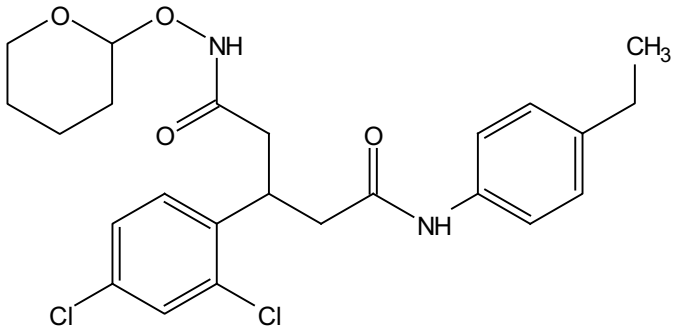




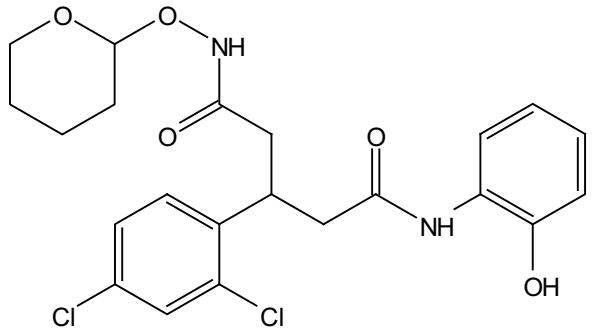


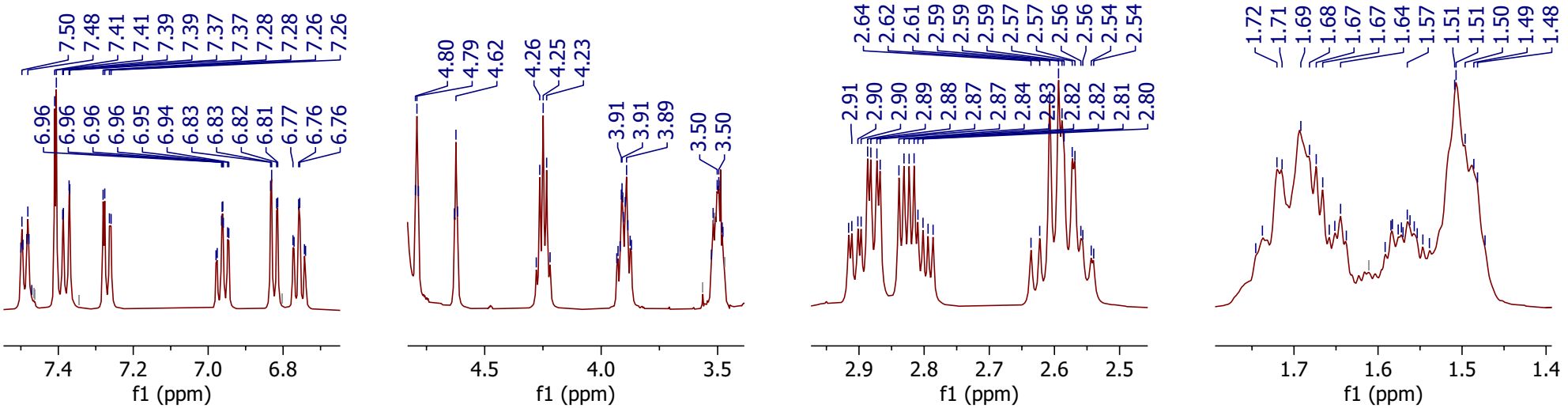
Compound S13

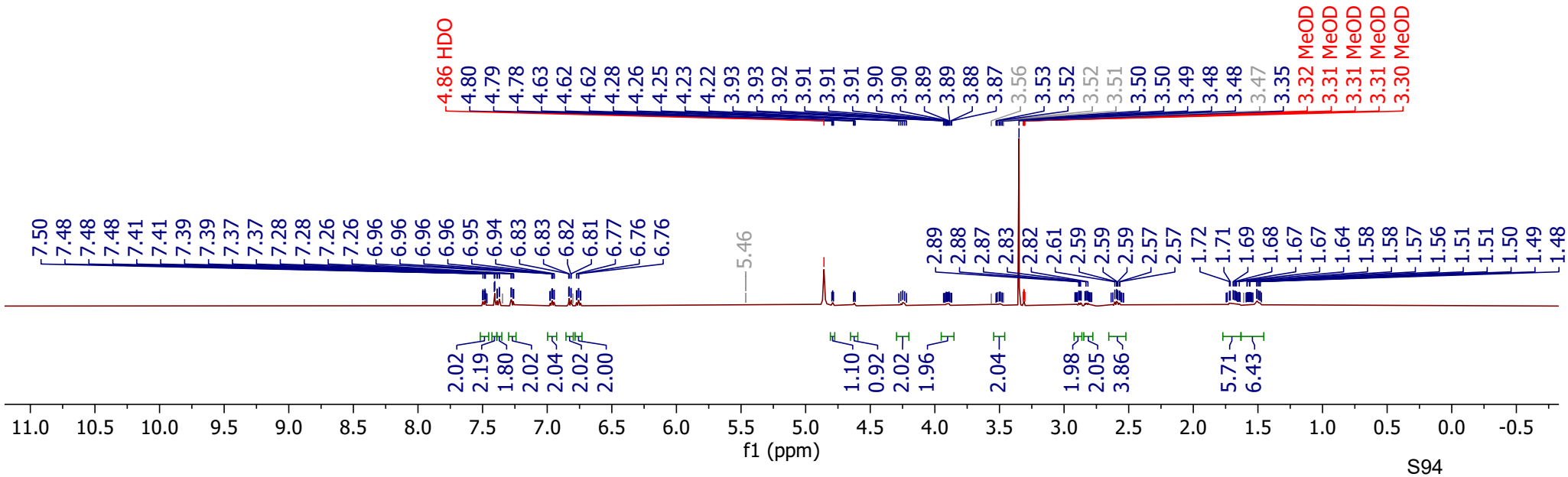
^{13}C NMR (126 MHz, DMSO-d6)



Compound S14
^{1}H NMR (500 MHz, MeOD-d4)

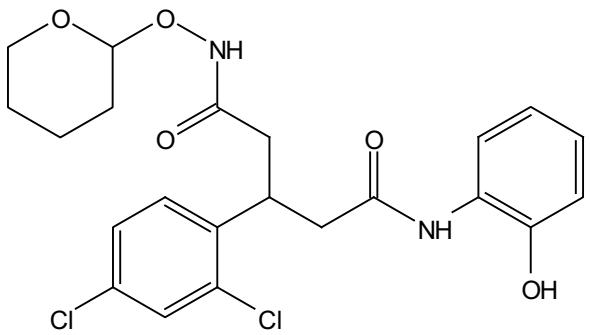






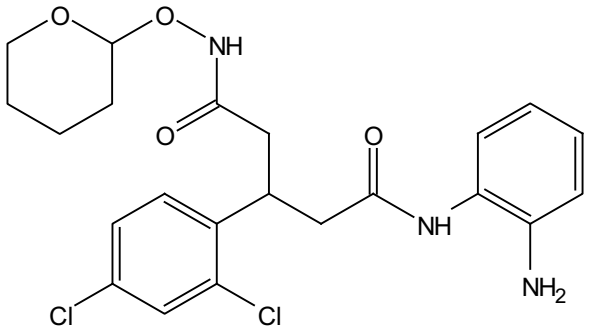
Compound S14

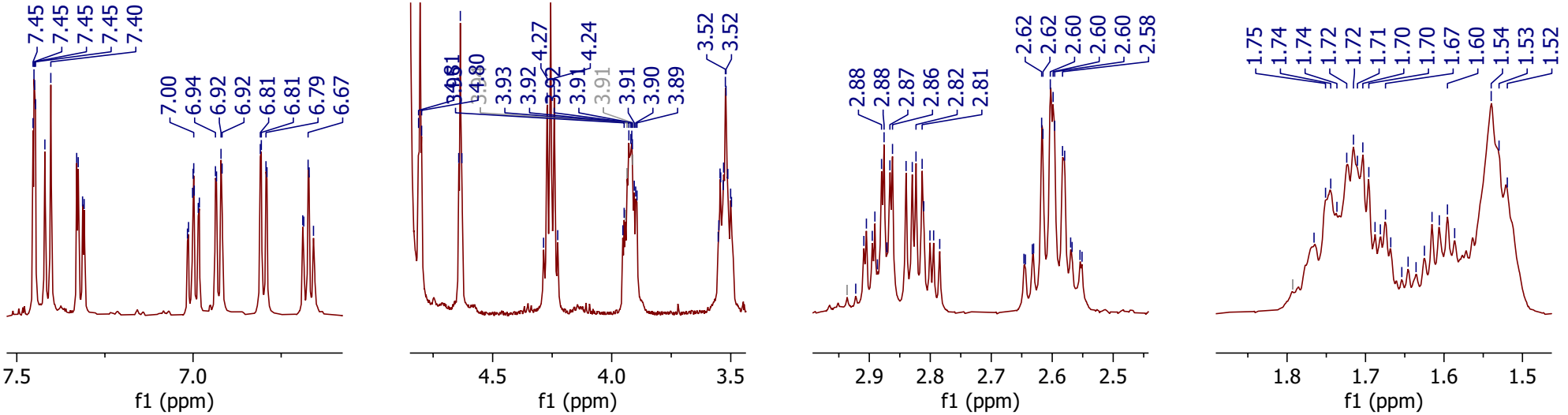
^{13}C NMR (151 MHz, MeOD-d4)

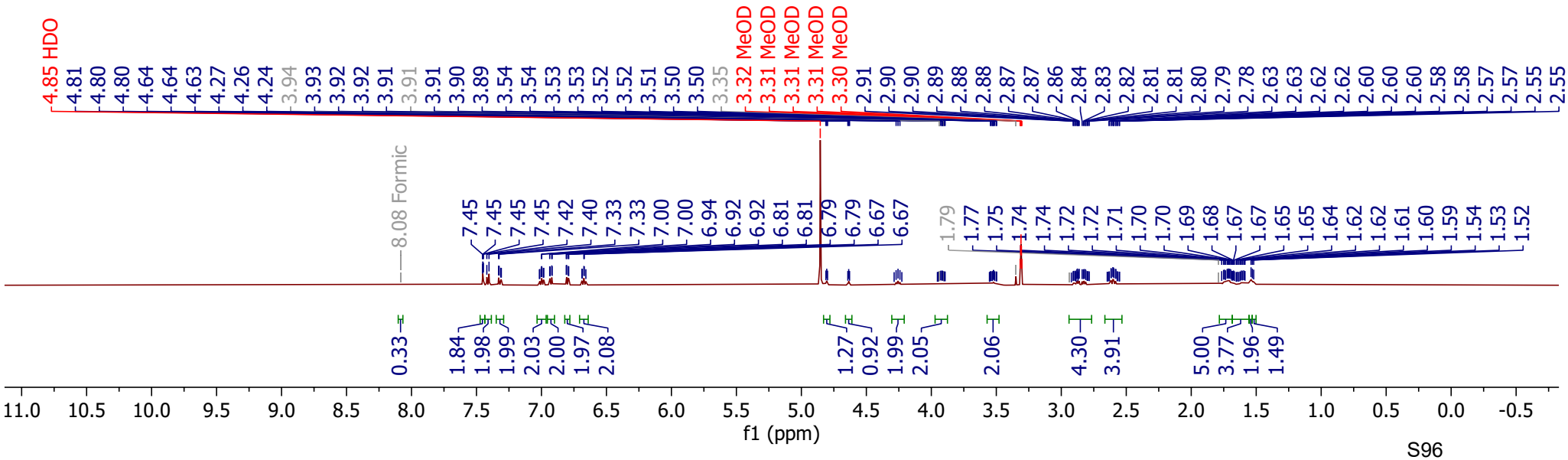


Compound S15

^{1}H NMR (500 MHz, MeOD-d4)

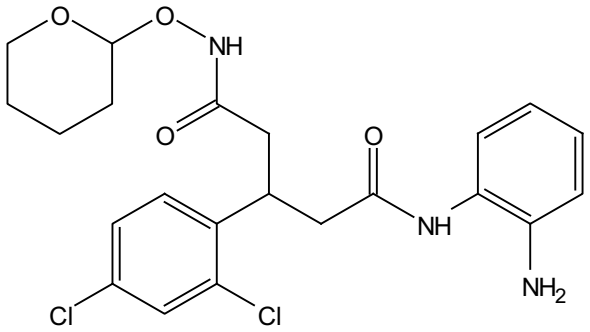


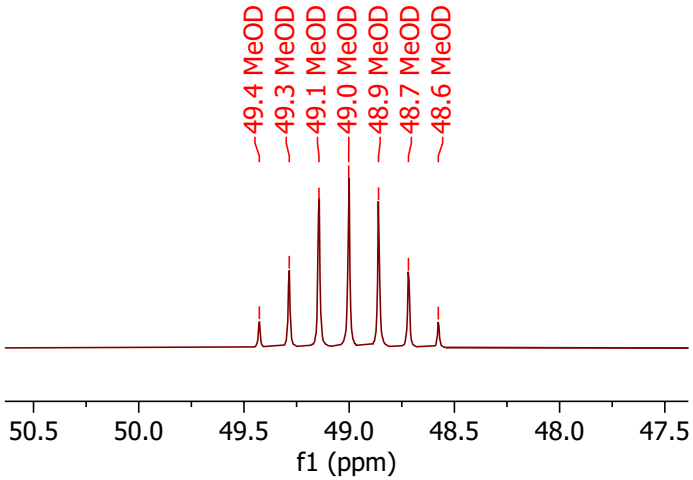




Compound S15

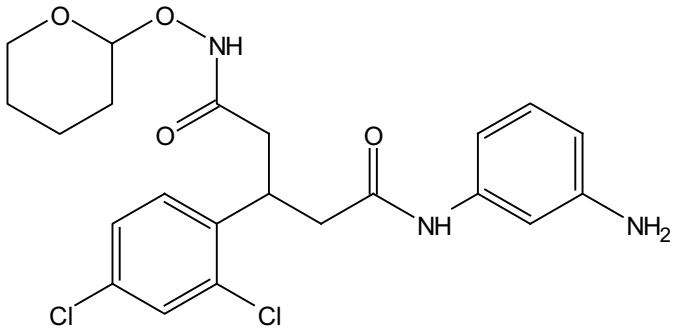
^{13}C NMR (151 MHz, MeOD-d4)

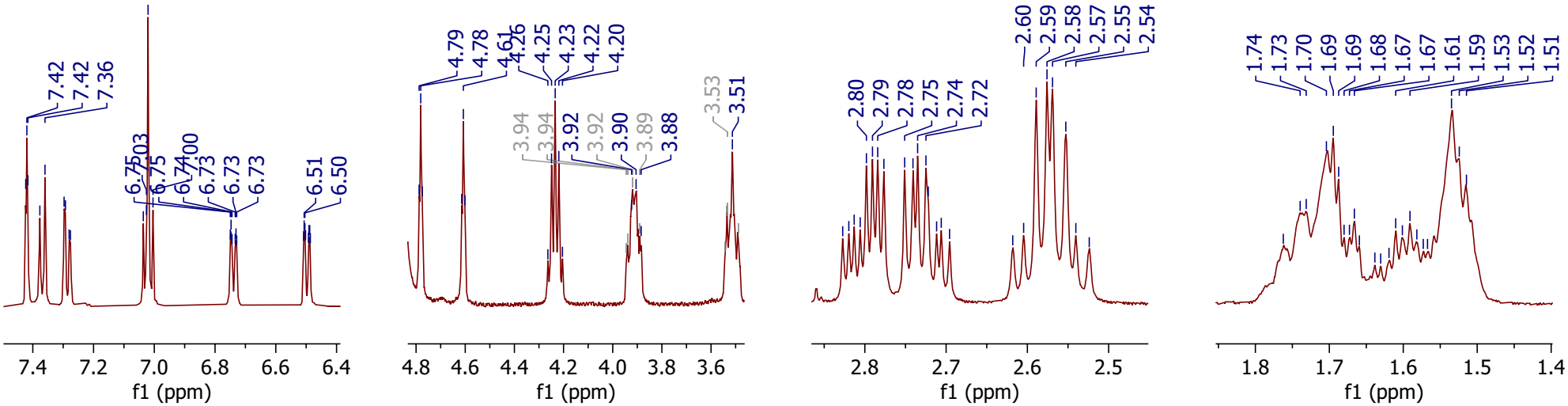


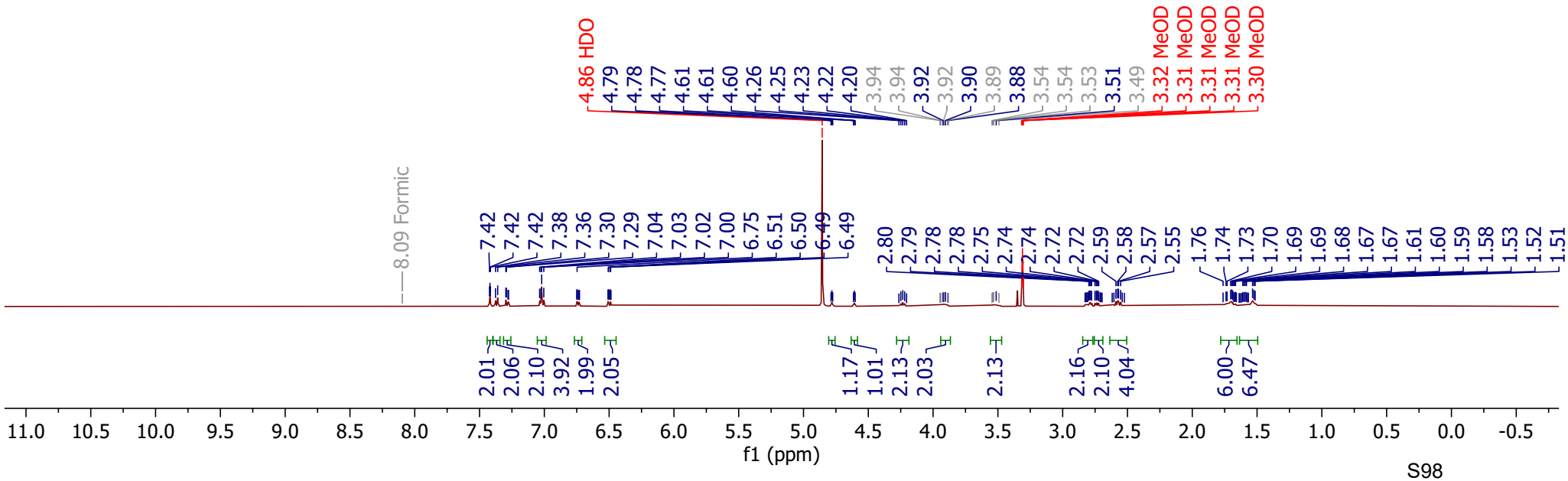


Compound S16

^{1}H NMR (500 MHz, MeOD-d4)

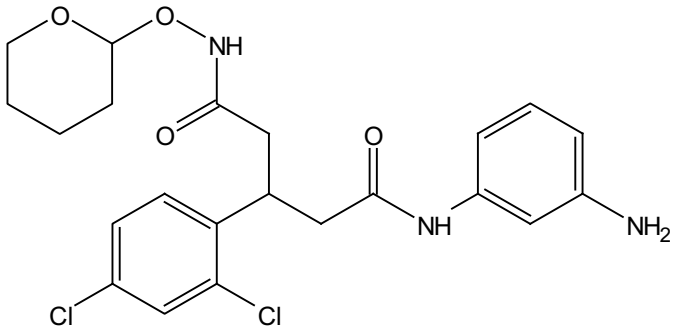




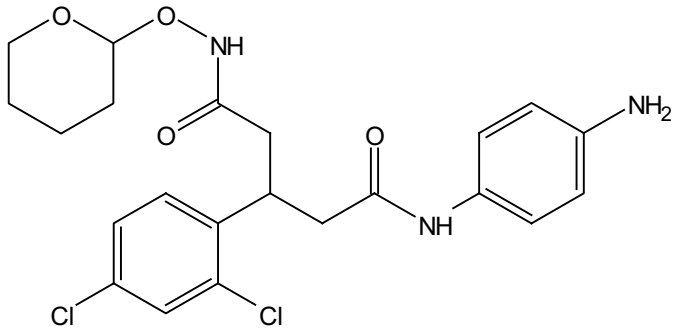


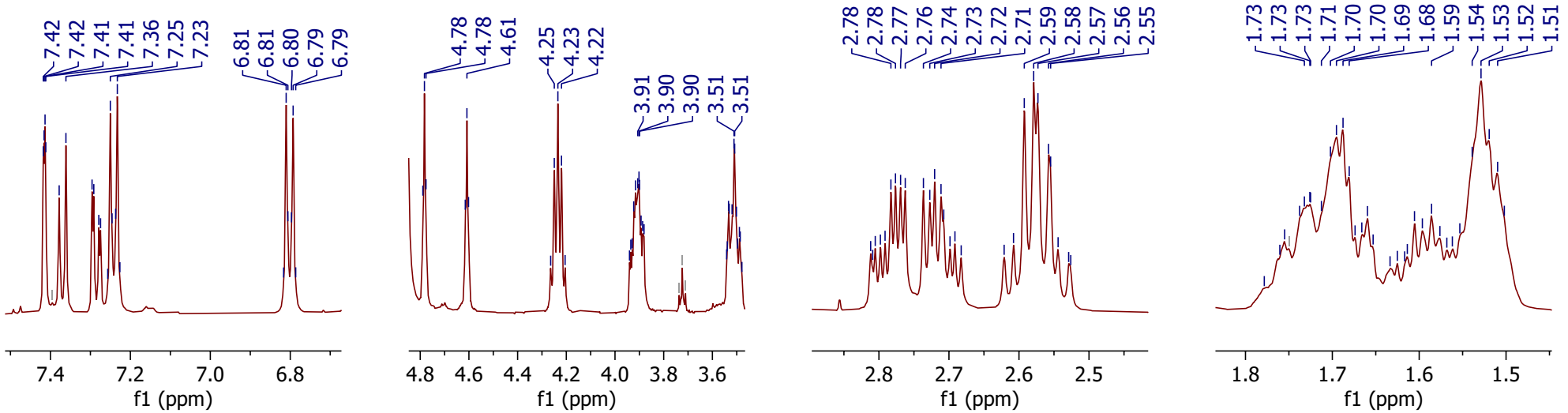
Compound S16

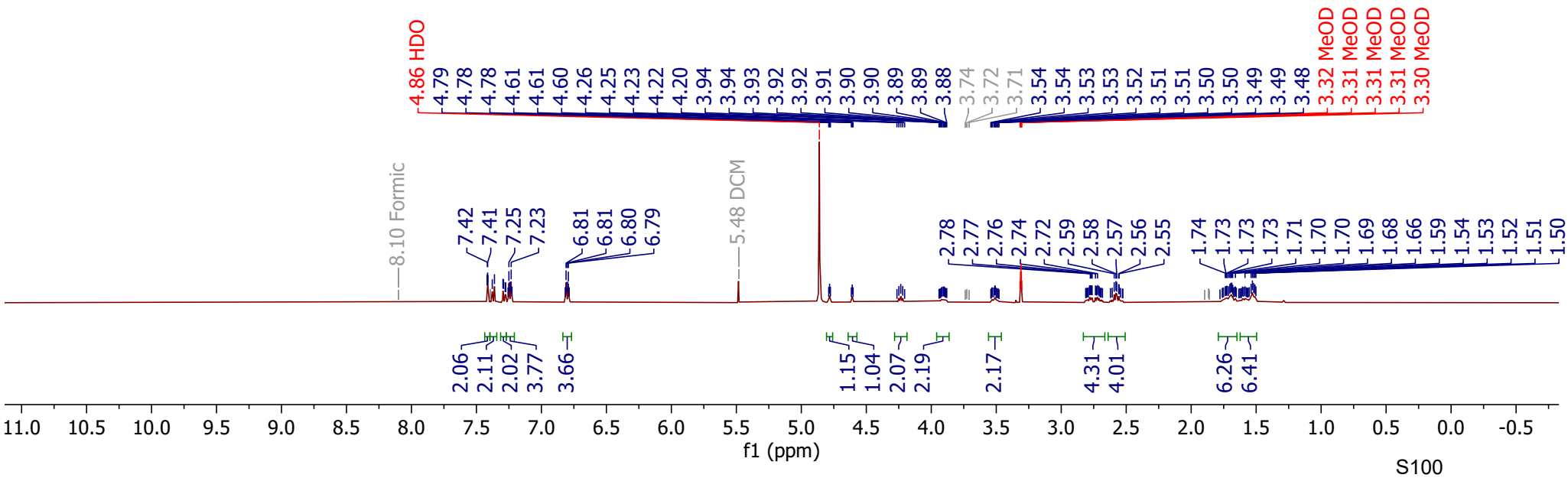
^{13}C NMR (151 MHz, MeOD-d6)



Compound S17
^{1}H NMR (500 MHz, MeOD-d4)

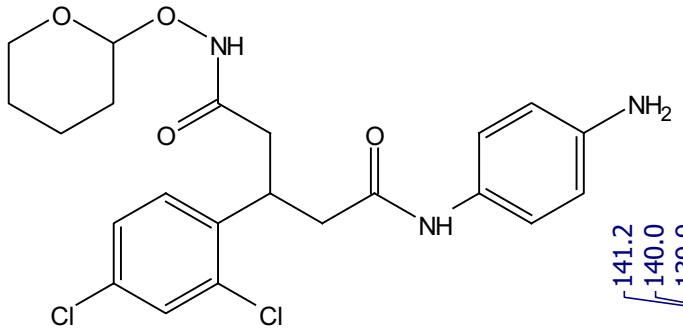




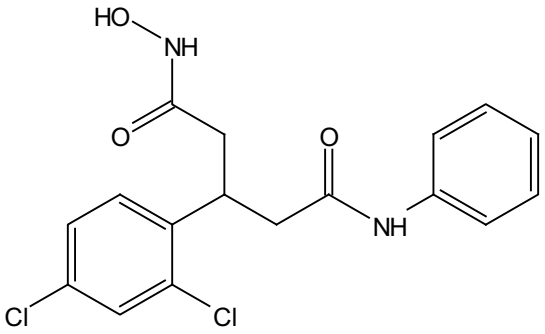


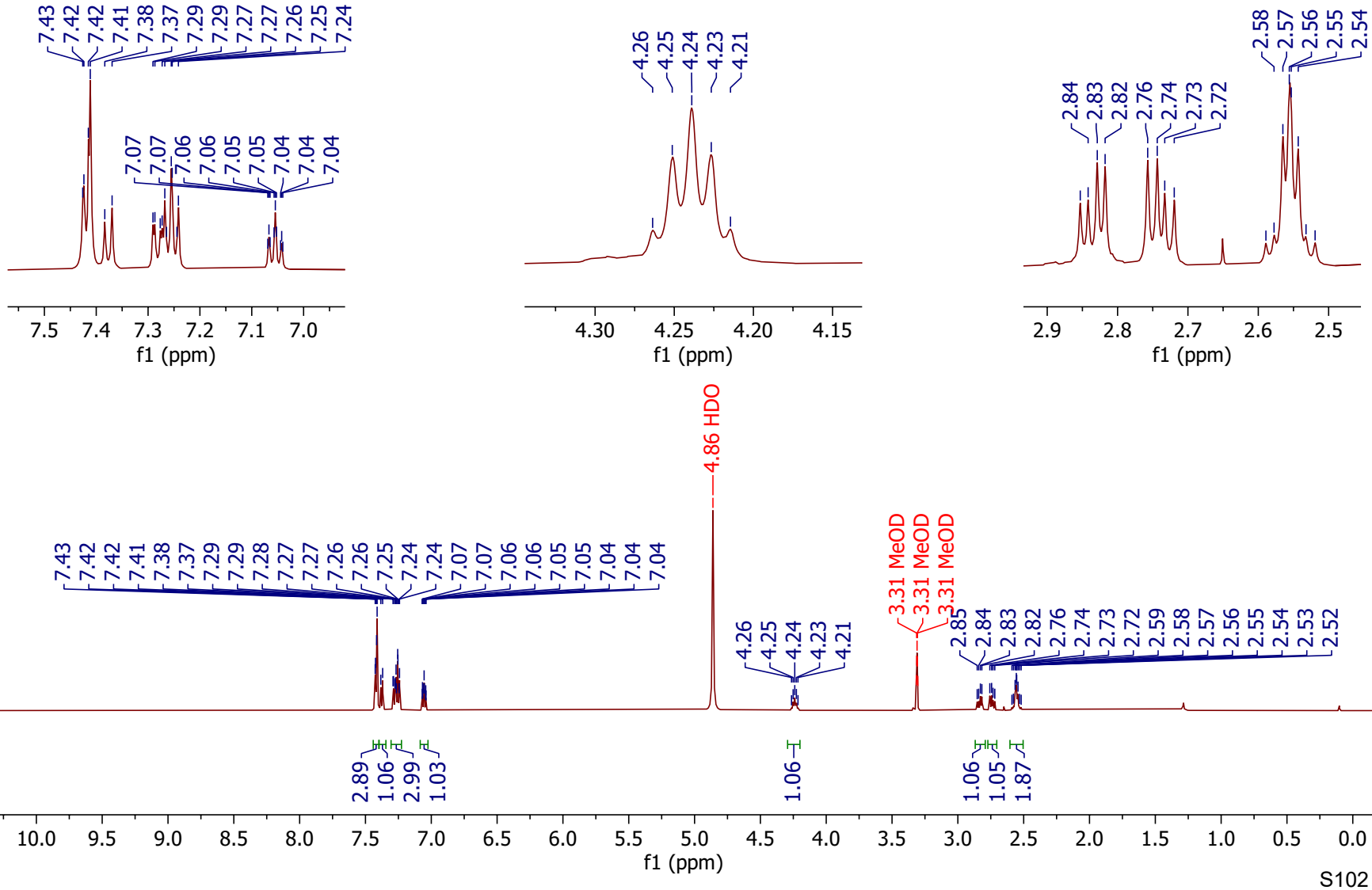
Compound S17

^{13}C NMR (151 MHz, MeOD-d4)



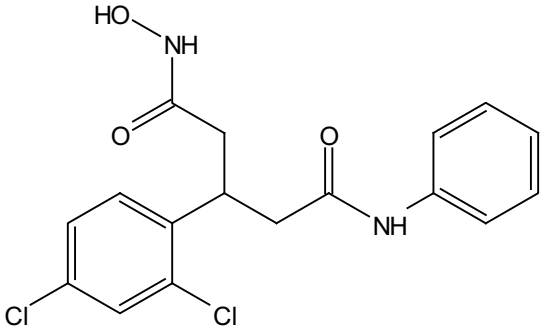
Compound 18
^{1}H NMR (600 MHz, MeODd4)



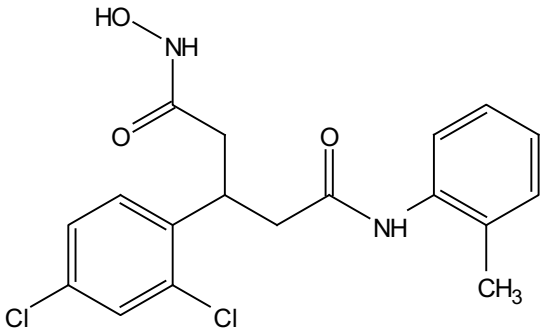


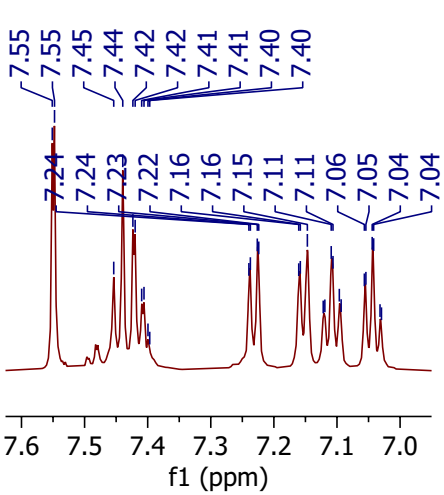
Compound 18

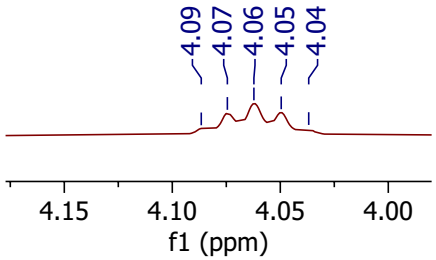
^{13}C NMR (151 MHz, MeOD-d4)

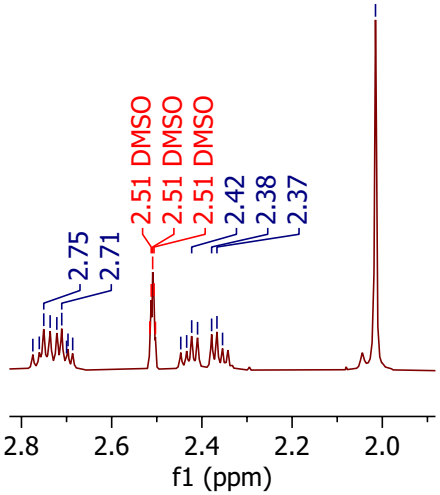


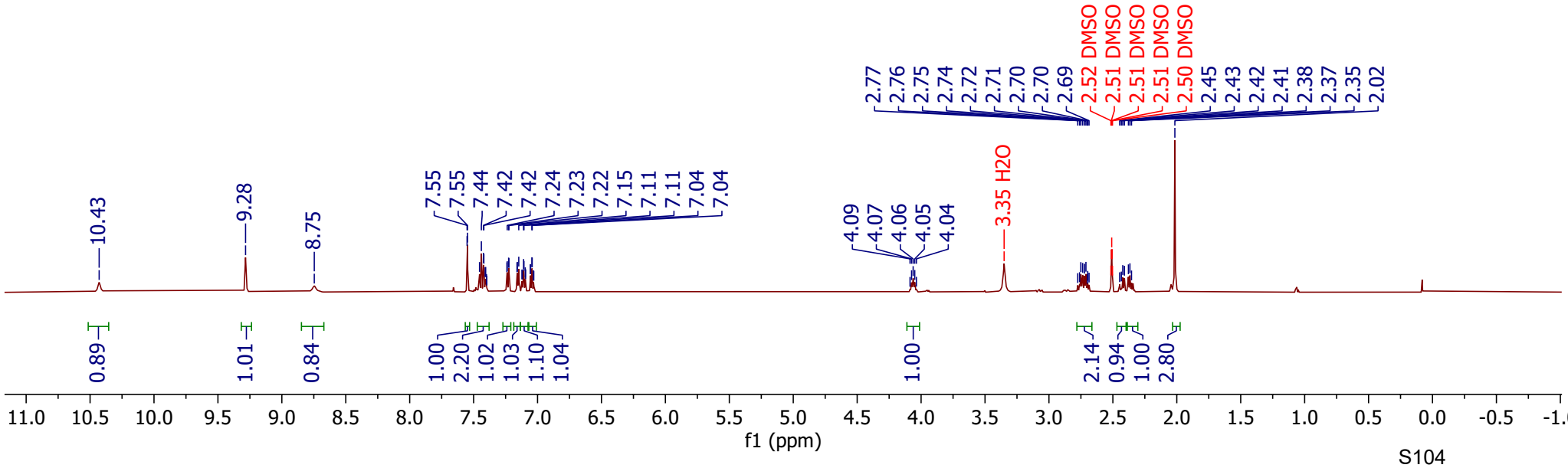
Compound 19
^{1}H NMR (600 MHz, DMSO-d6)



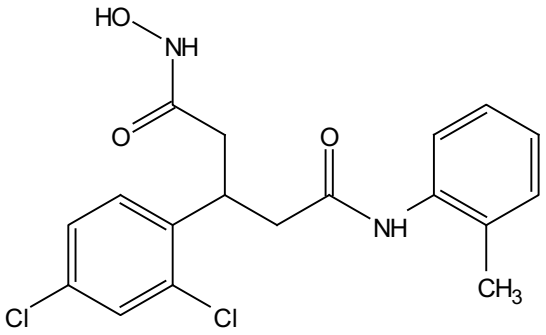




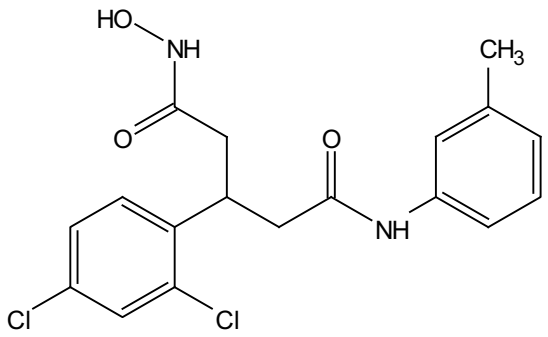


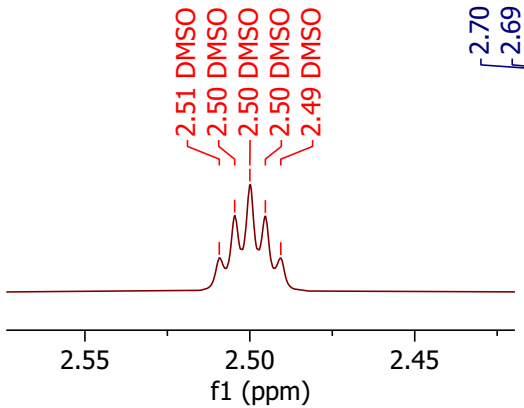


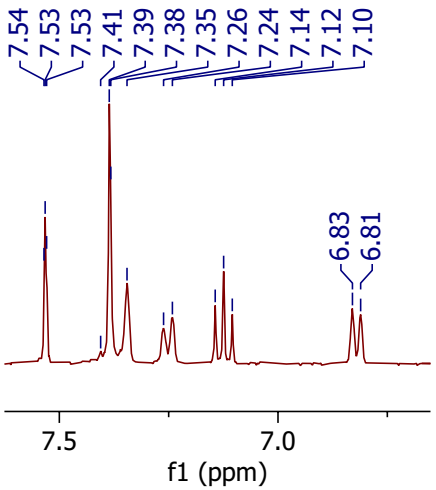
Compound 19
^{13}C NMR (151 MHz, DMSO-d6)

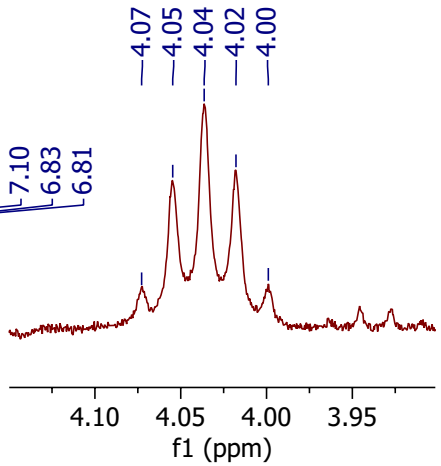


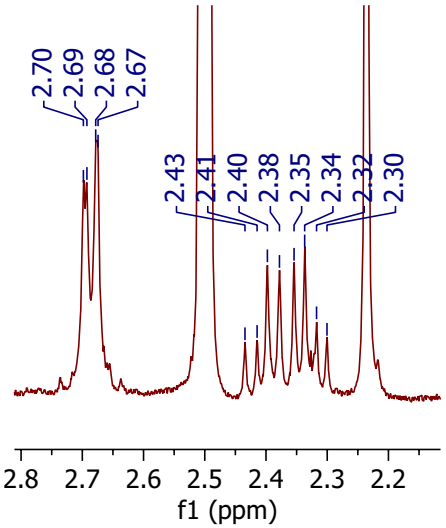
Compound 20
^{1}H NMR (400 MHz, DMSO-d6)



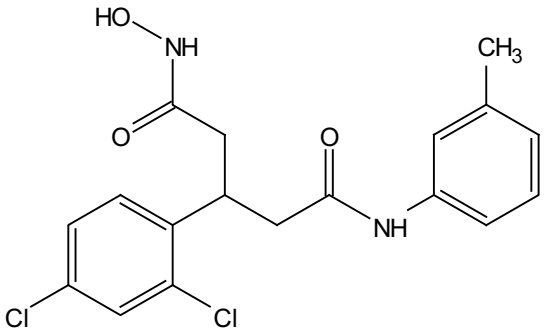


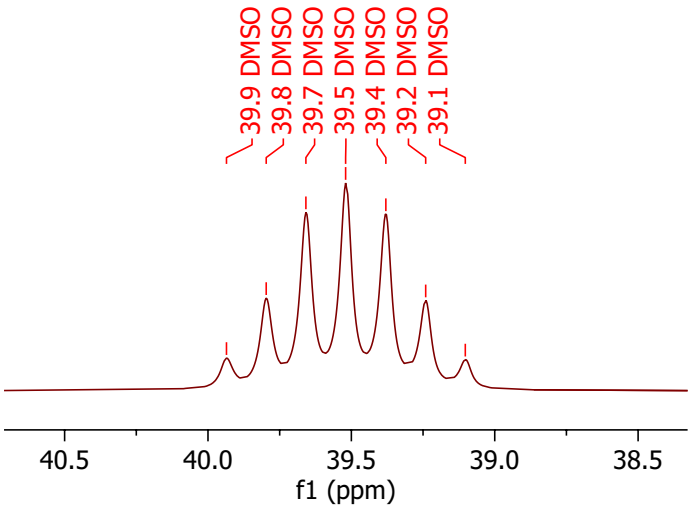




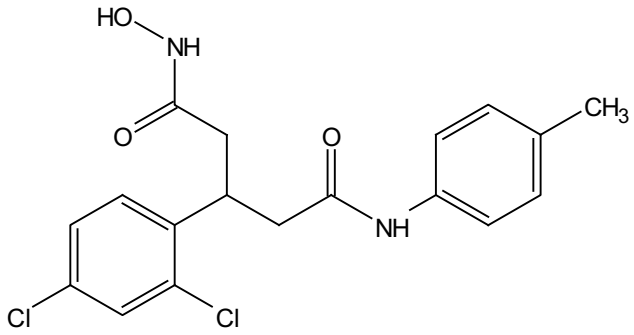


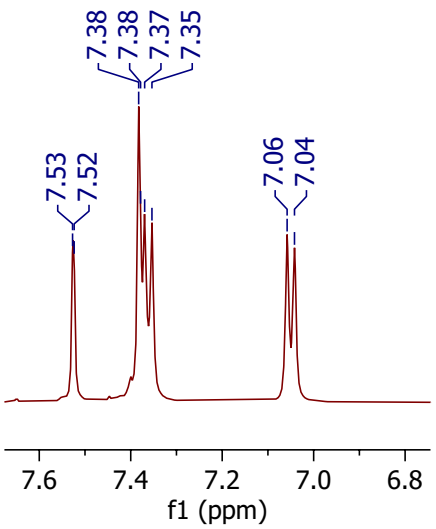
Compound 20
^{13}C NMR (151 MHz, DMSO-d6)

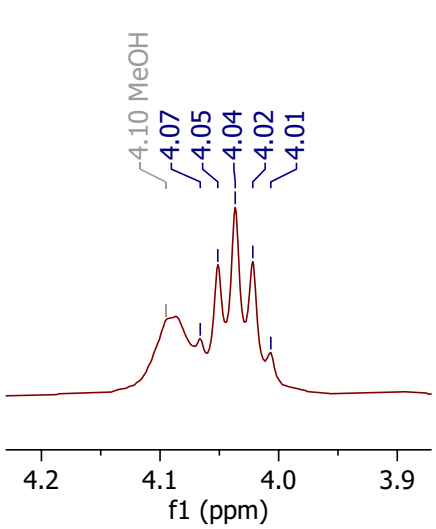


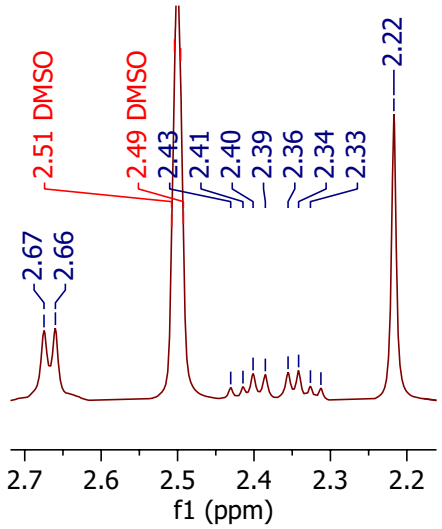


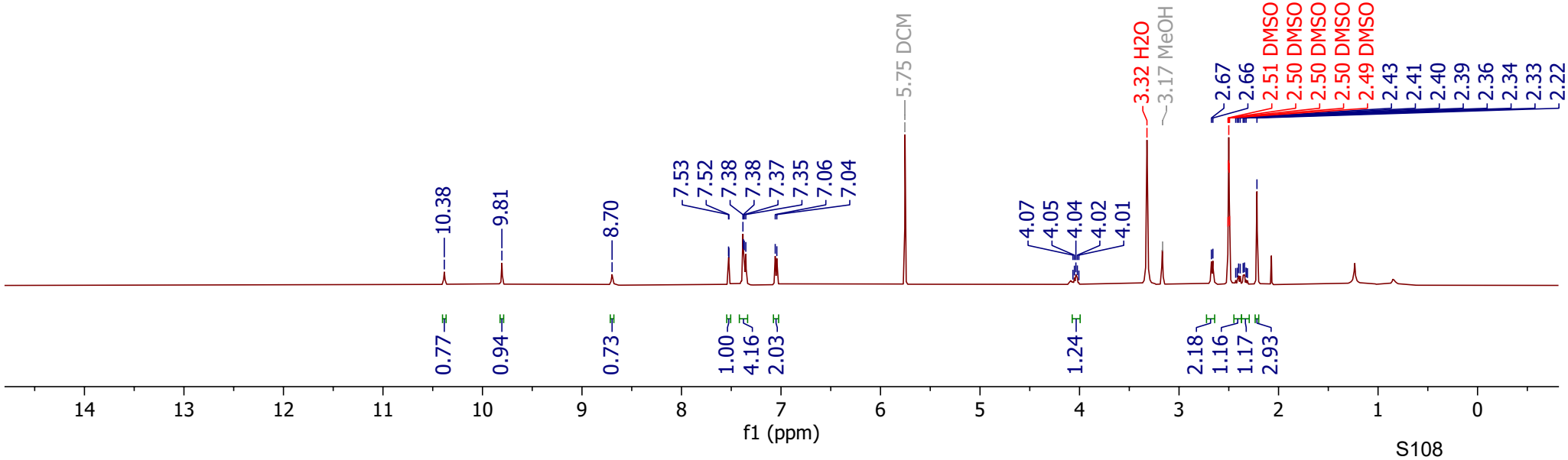
Compound 21
^{1}H NMR (500 MHz, DMSO-d6)



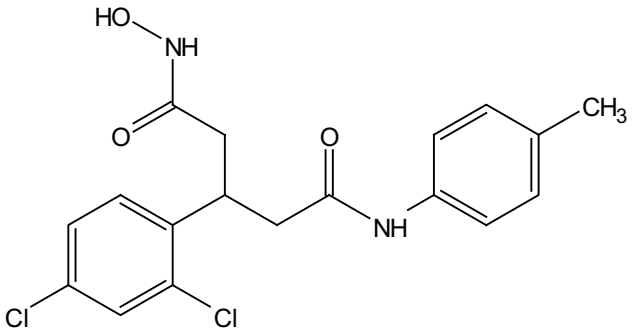




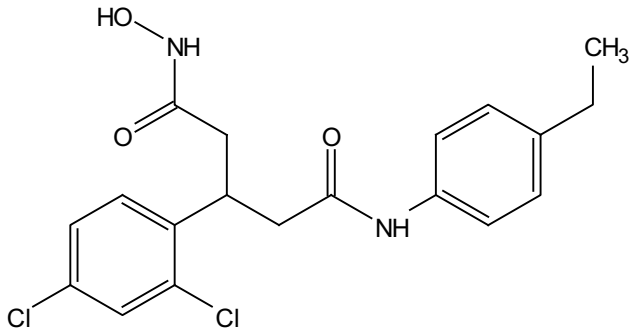


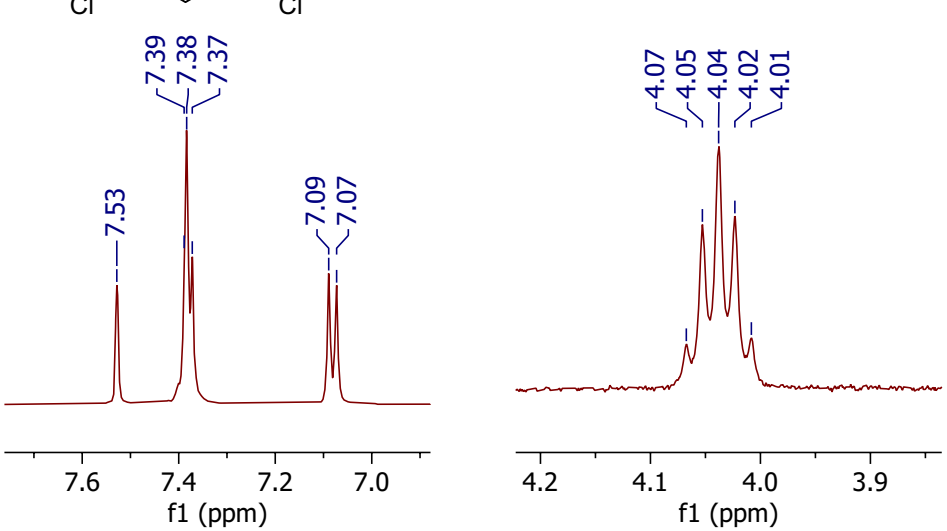


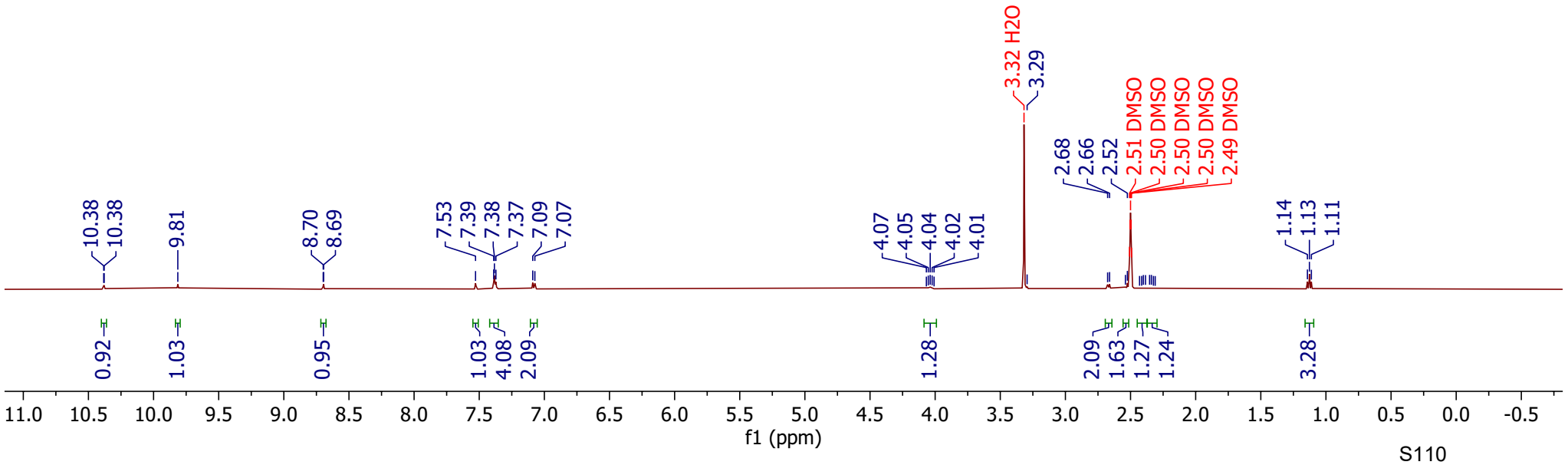
Compound 21
^{13}C NMR (151 MHz, DMSO-d6)



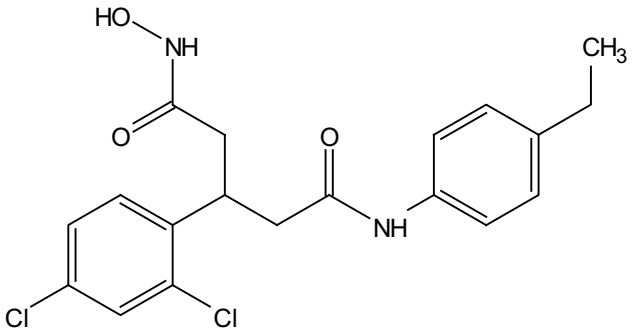
Compound 22
^{1}H NMR (500 MHz, DMSO-d6)



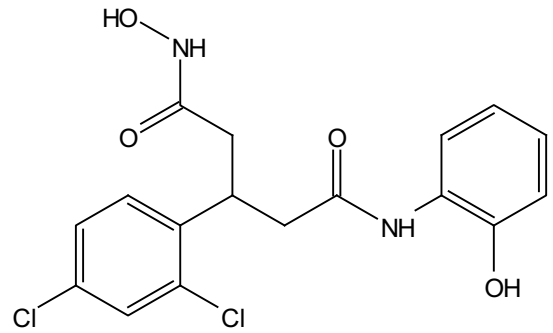


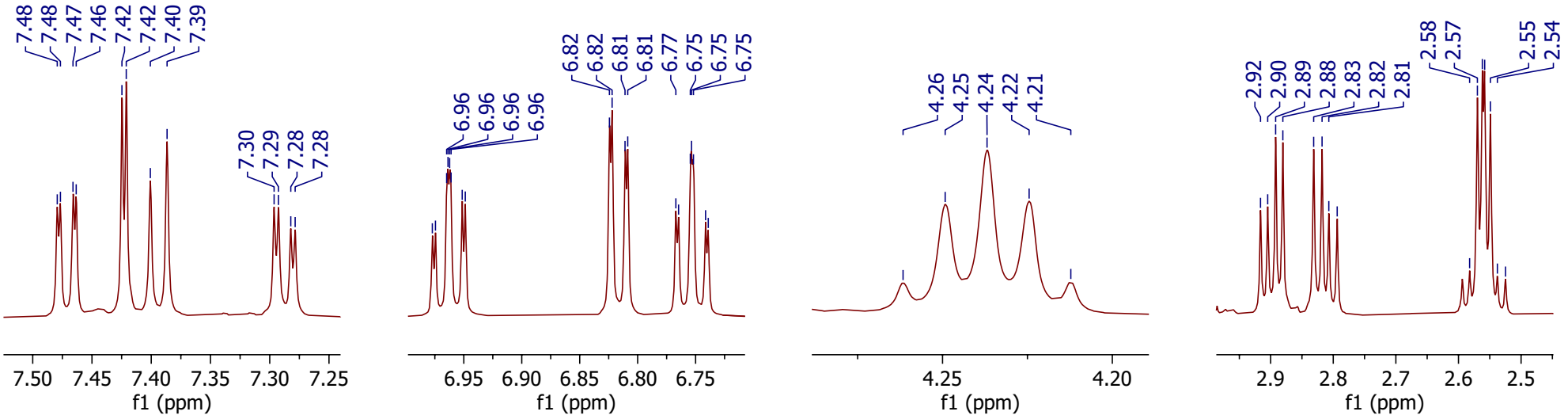


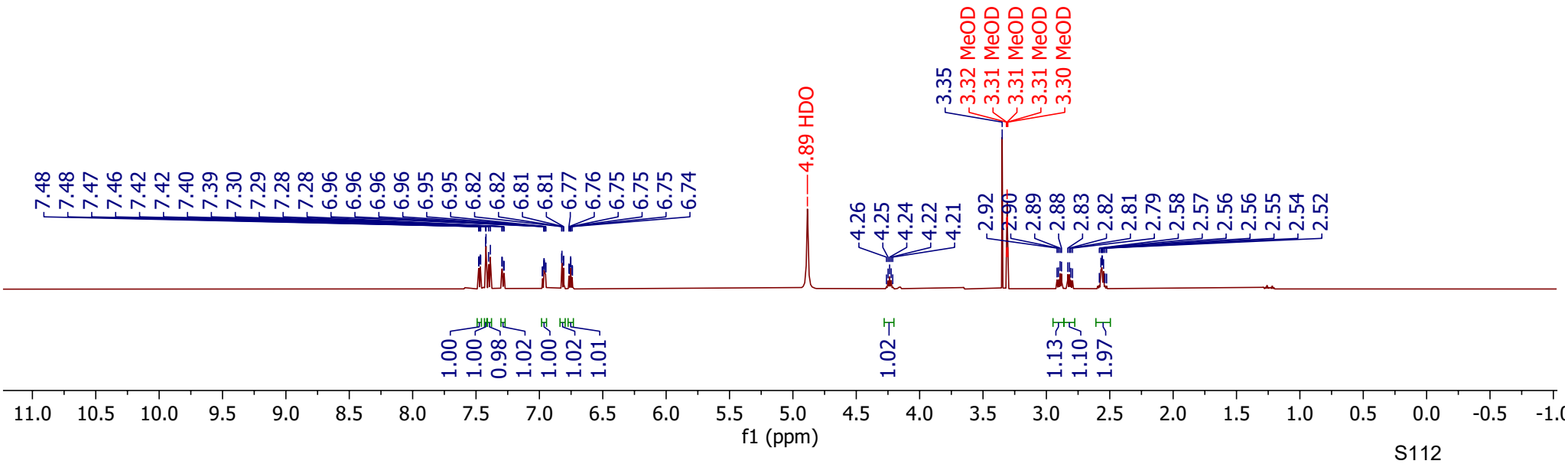
Compound 22
^{13}C NMR (151 MHz, DMSO-d6)



Compound 23
^{1}H NMR (600 MHz, MeOD-d4)

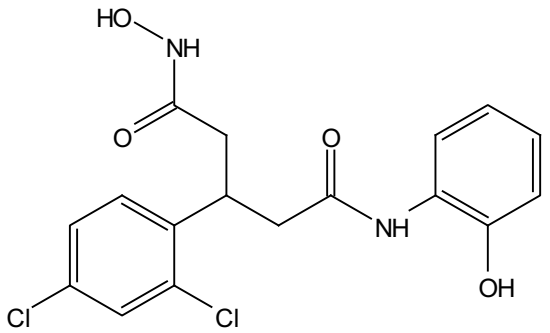




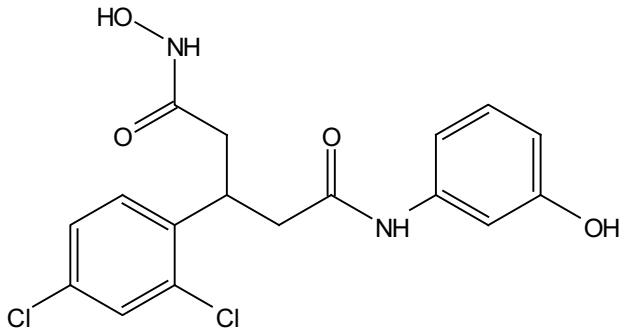


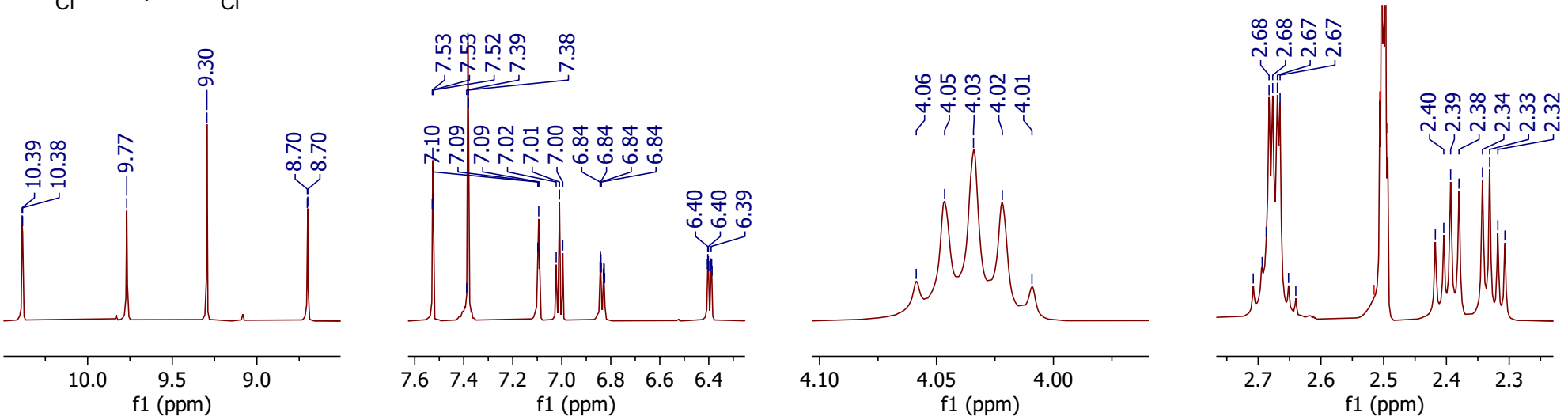
Compound 23

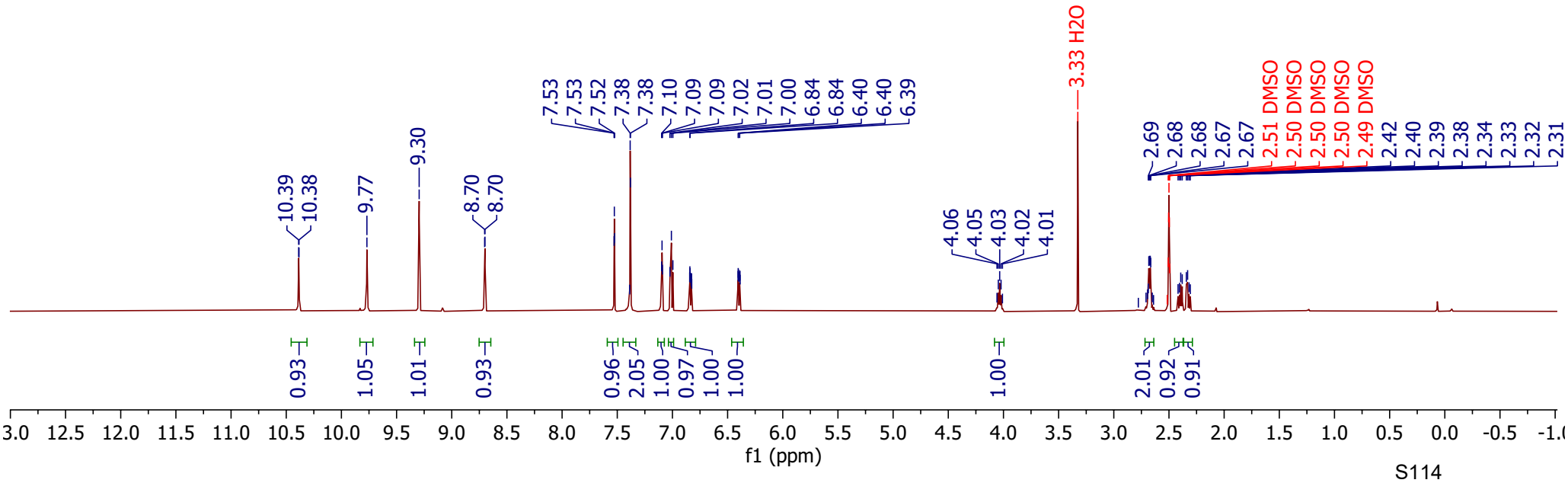
^{13}C NMR (151 MHz, MeOD-d4)



Compound 24
^{1}H NMR (600 MHz, DMSO-d6)

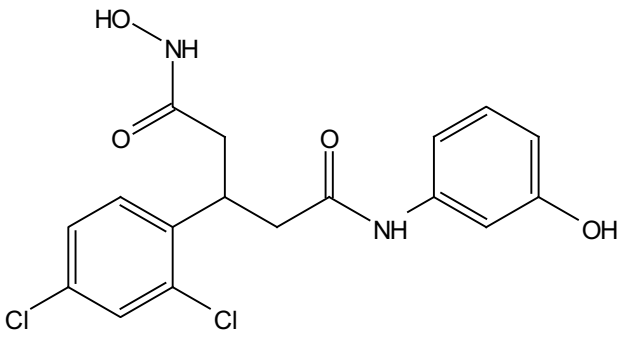




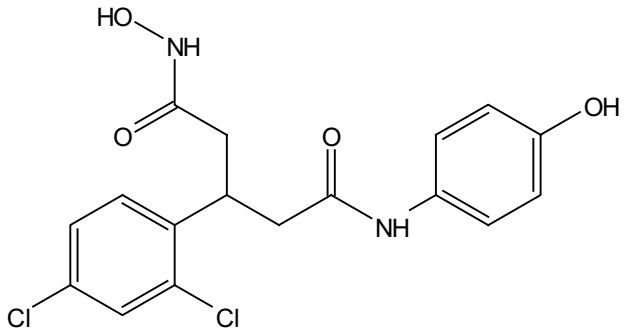


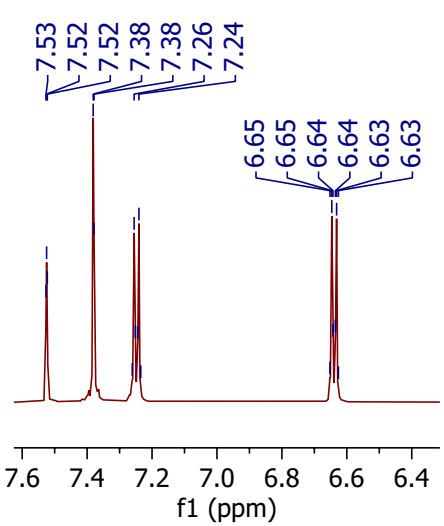
Compound 24

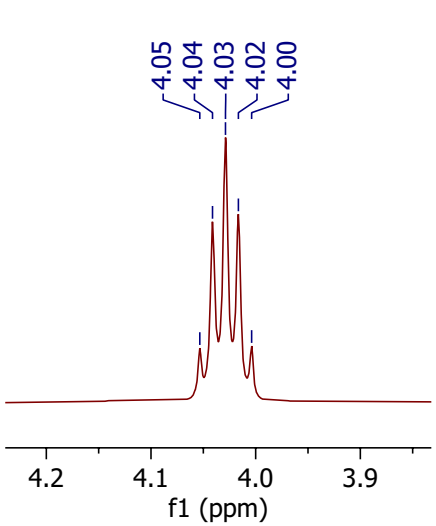
^{13}C NMR (151 MHz, DMSO-d6)

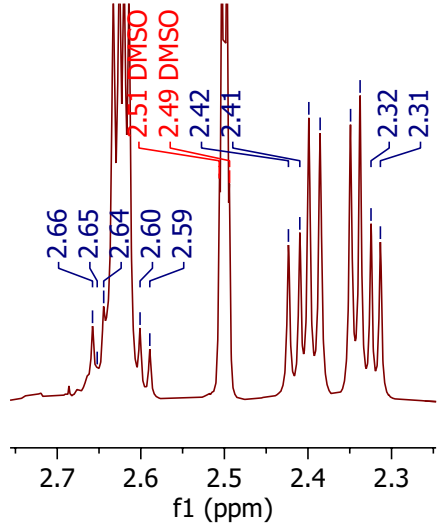


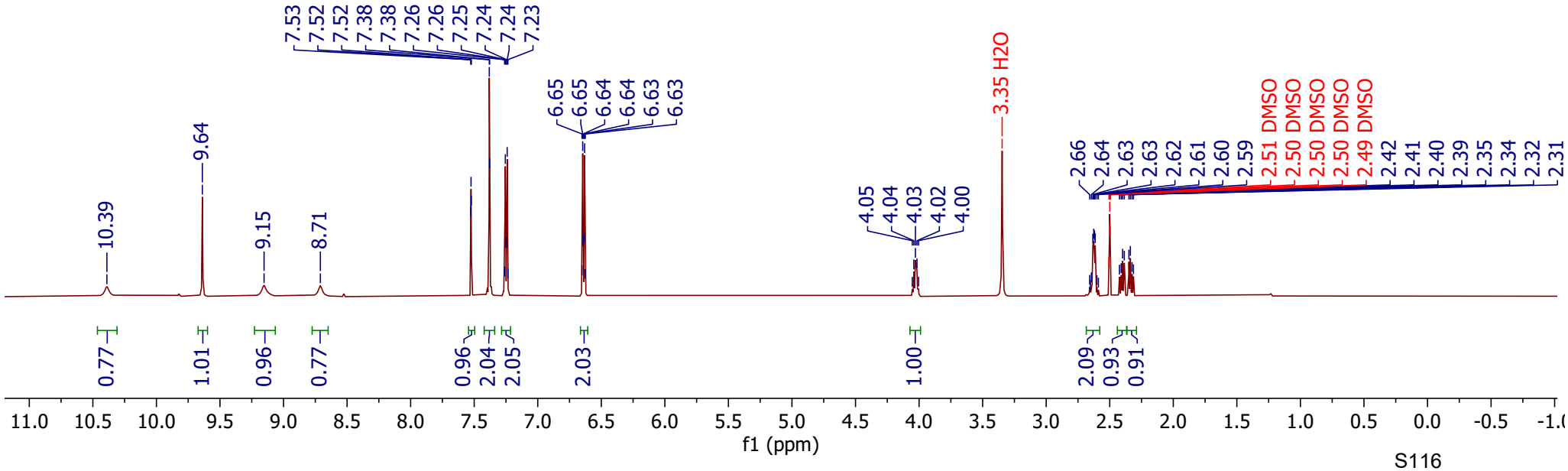
Compound 25
^{1}H NMR (600 MHz, DMSO-d6)



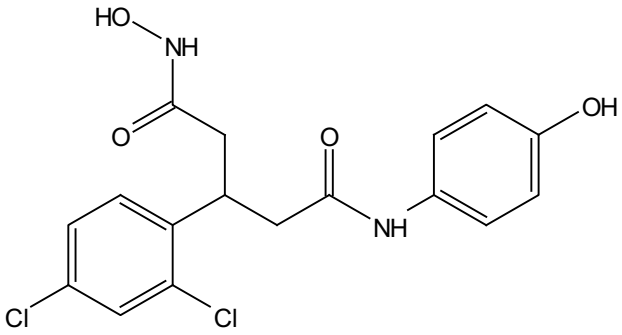






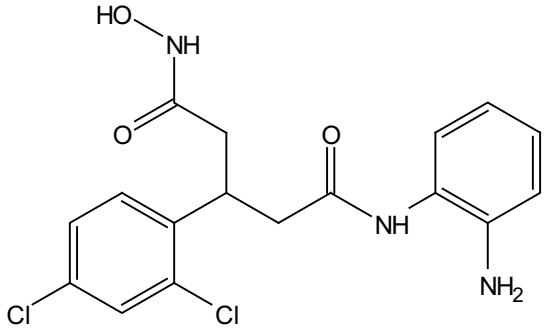


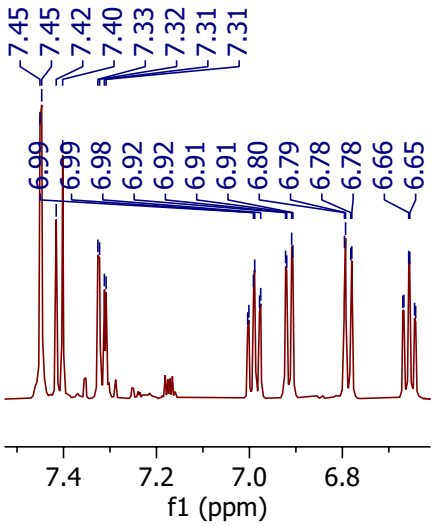
Compound 25
^{13}C NMR (151 MHz, DMSO-d6)

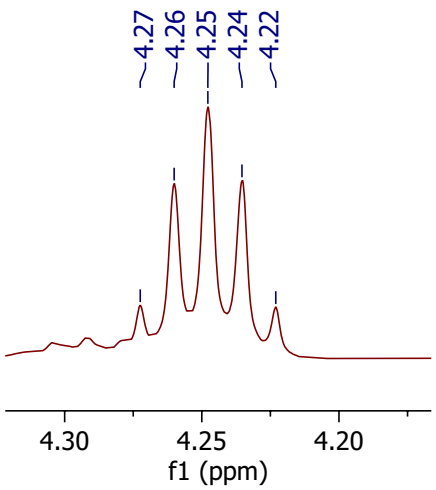


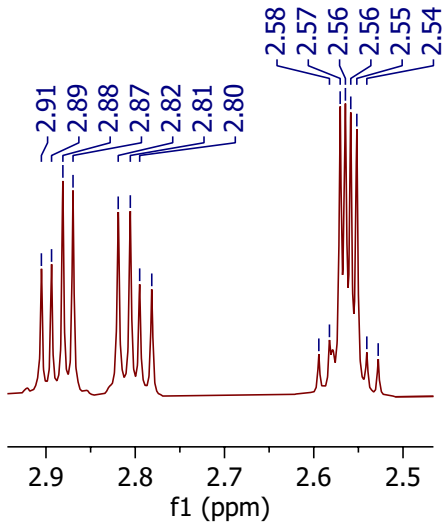
Compound 26

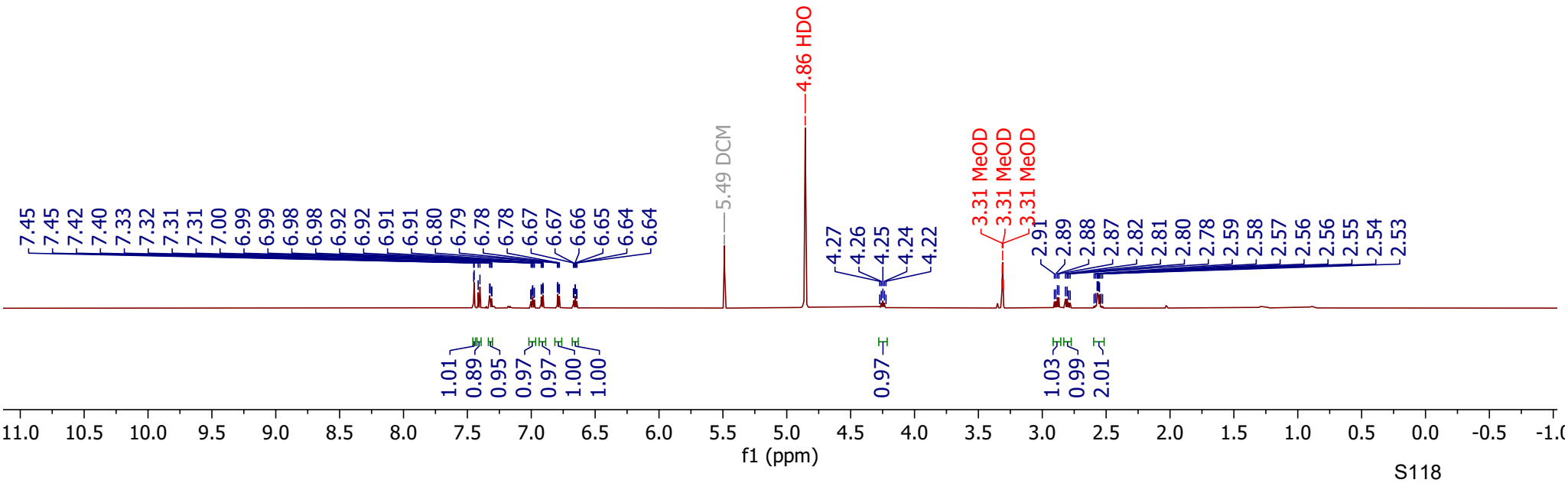
^{1}H NMR (600 MHz, MeOD-d4)





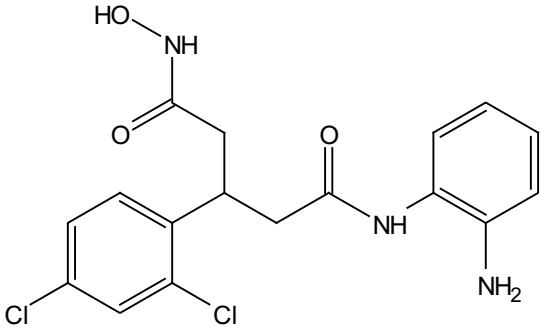




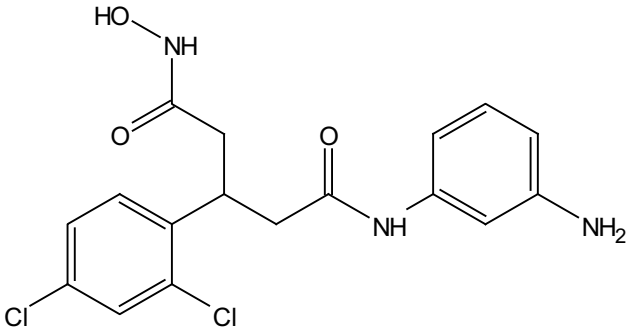


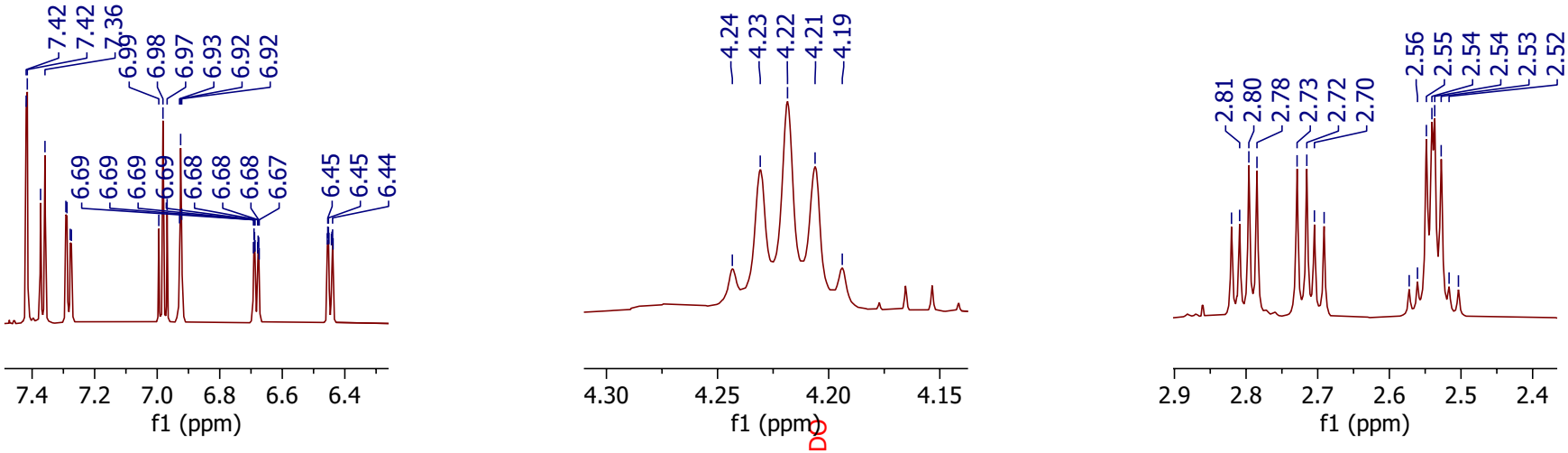
Compound 26

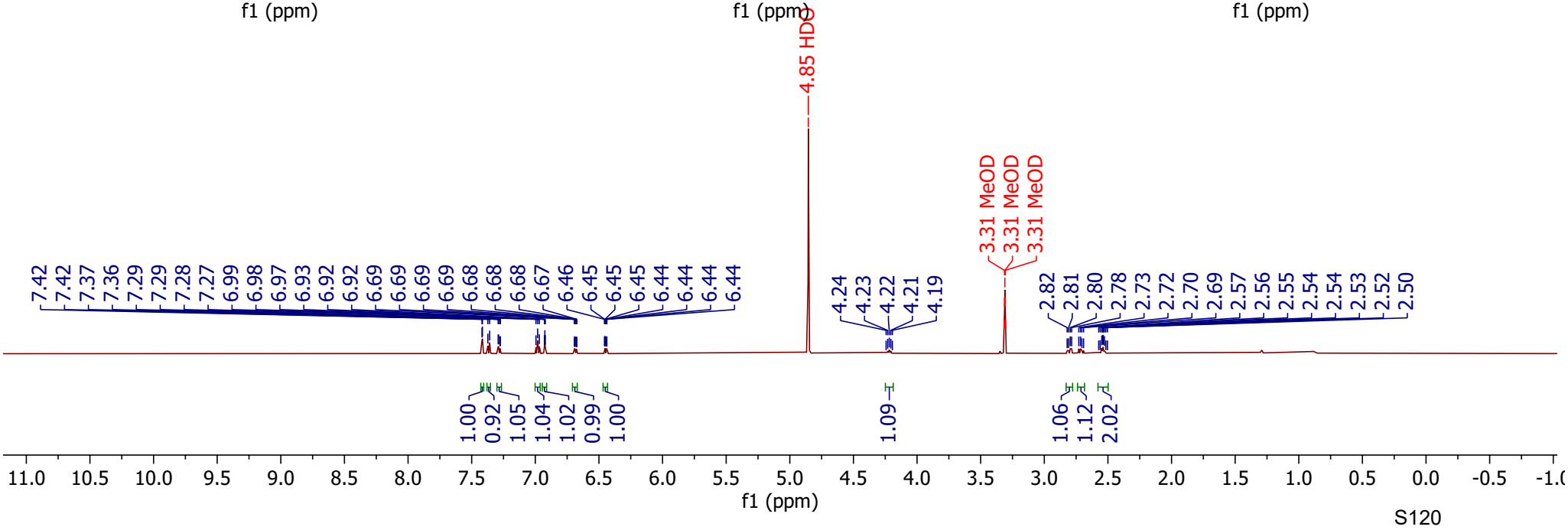
^{13}C NMR (151 MHz, MeOD-d4)



Compound 27
^{1}H NMR (600 MHz, MeOD-d4)

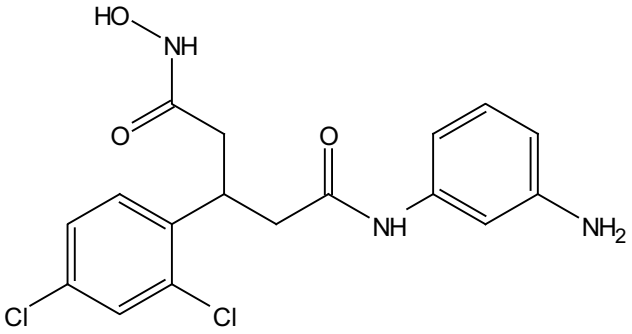




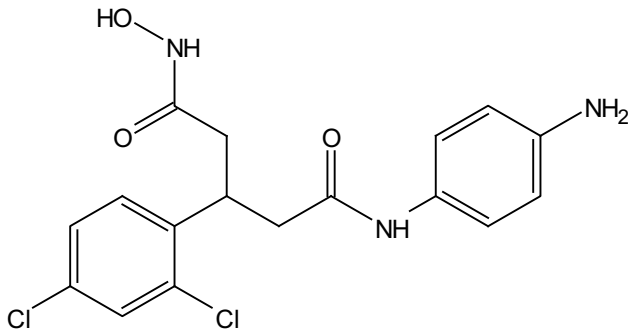


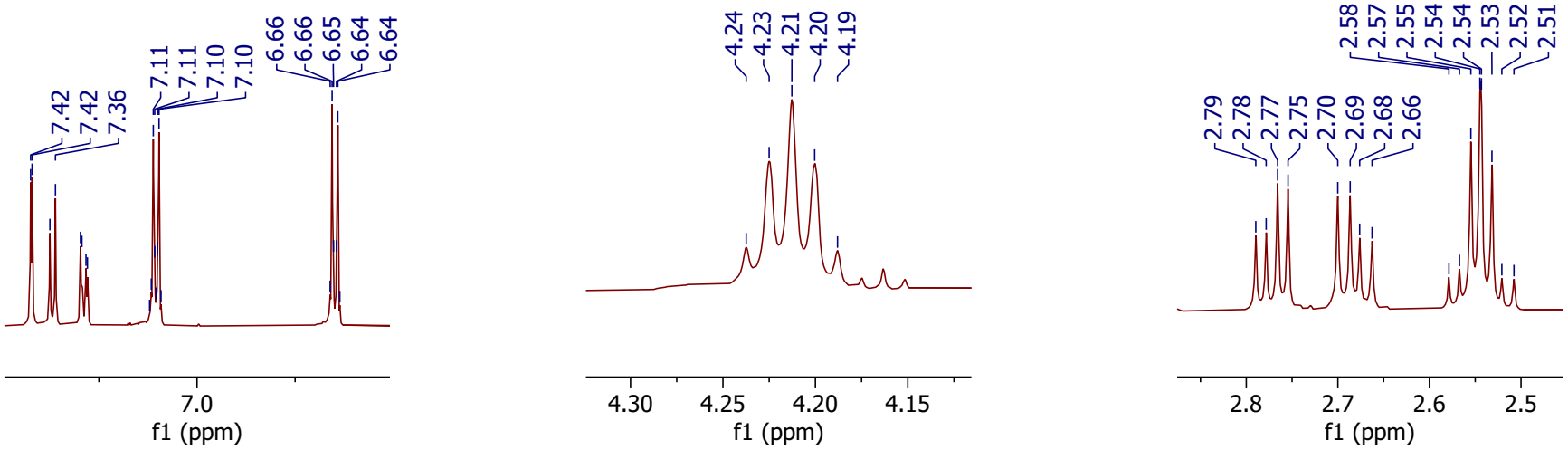
Compound 27

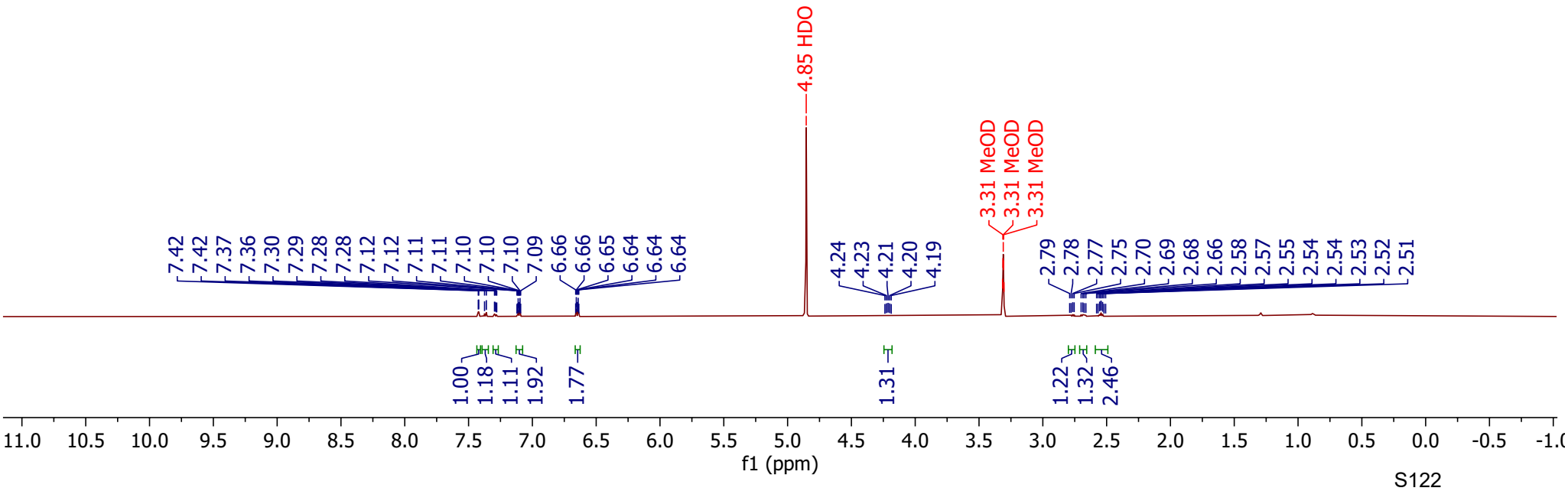
^{13}C NMR (151 MHz, MeOD-d4)



Compound 28
^{1}H NMR (600 MHz, MeOD-d4)

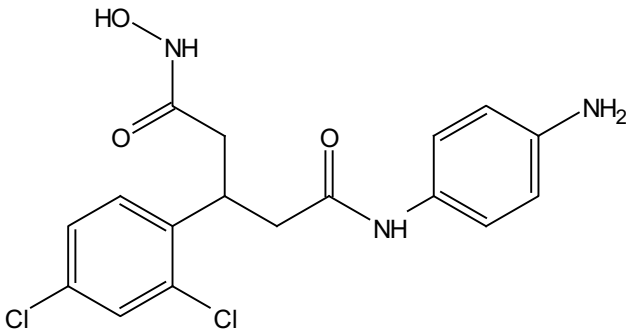




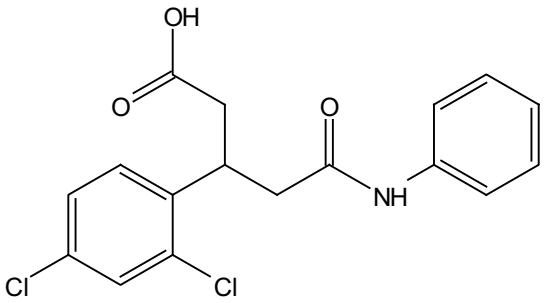


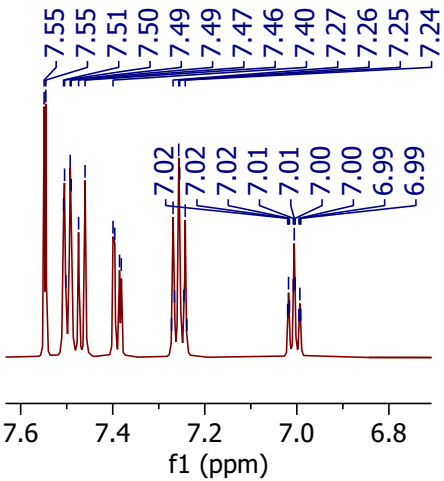
Compound 28

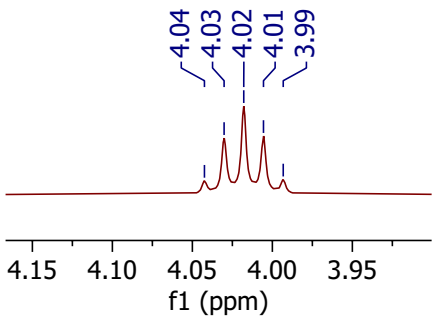
^{13}C NMR (151 MHz, MeOD-d4)

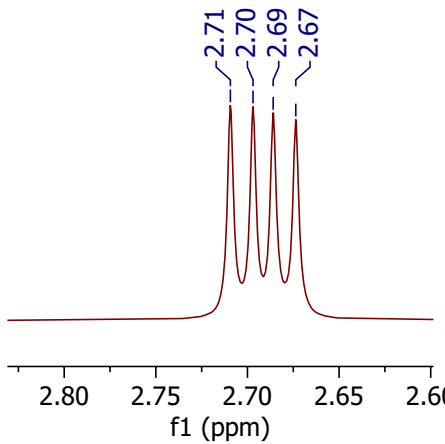


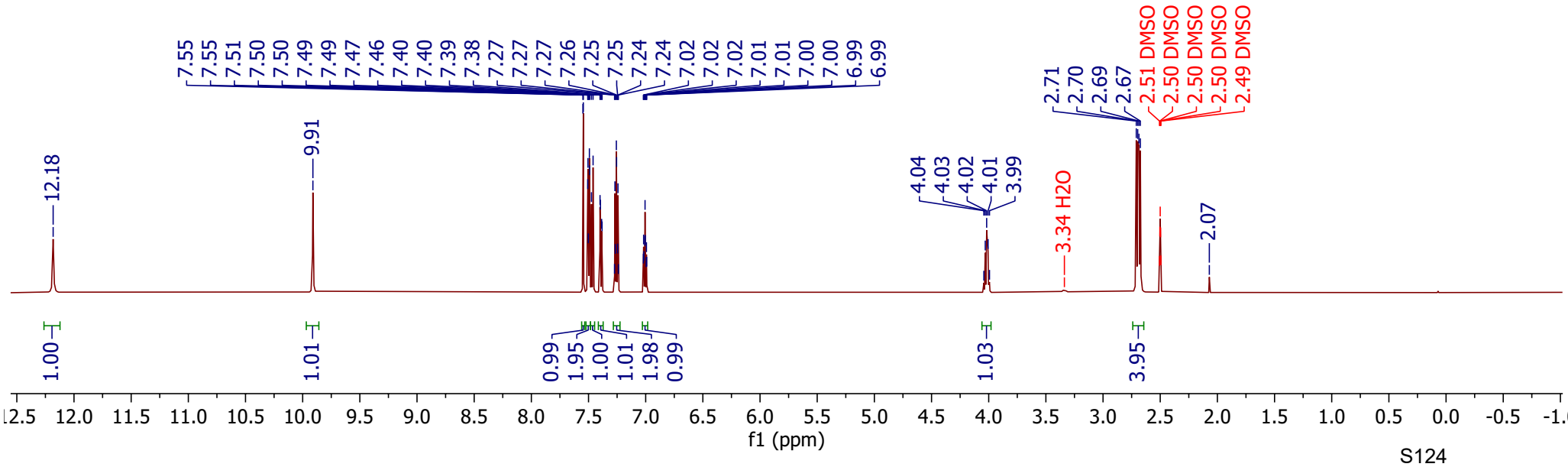
Compound S1
^{1}H NMR (600 MHz, DMSO-d6)



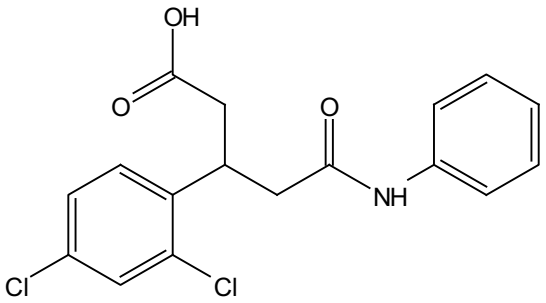


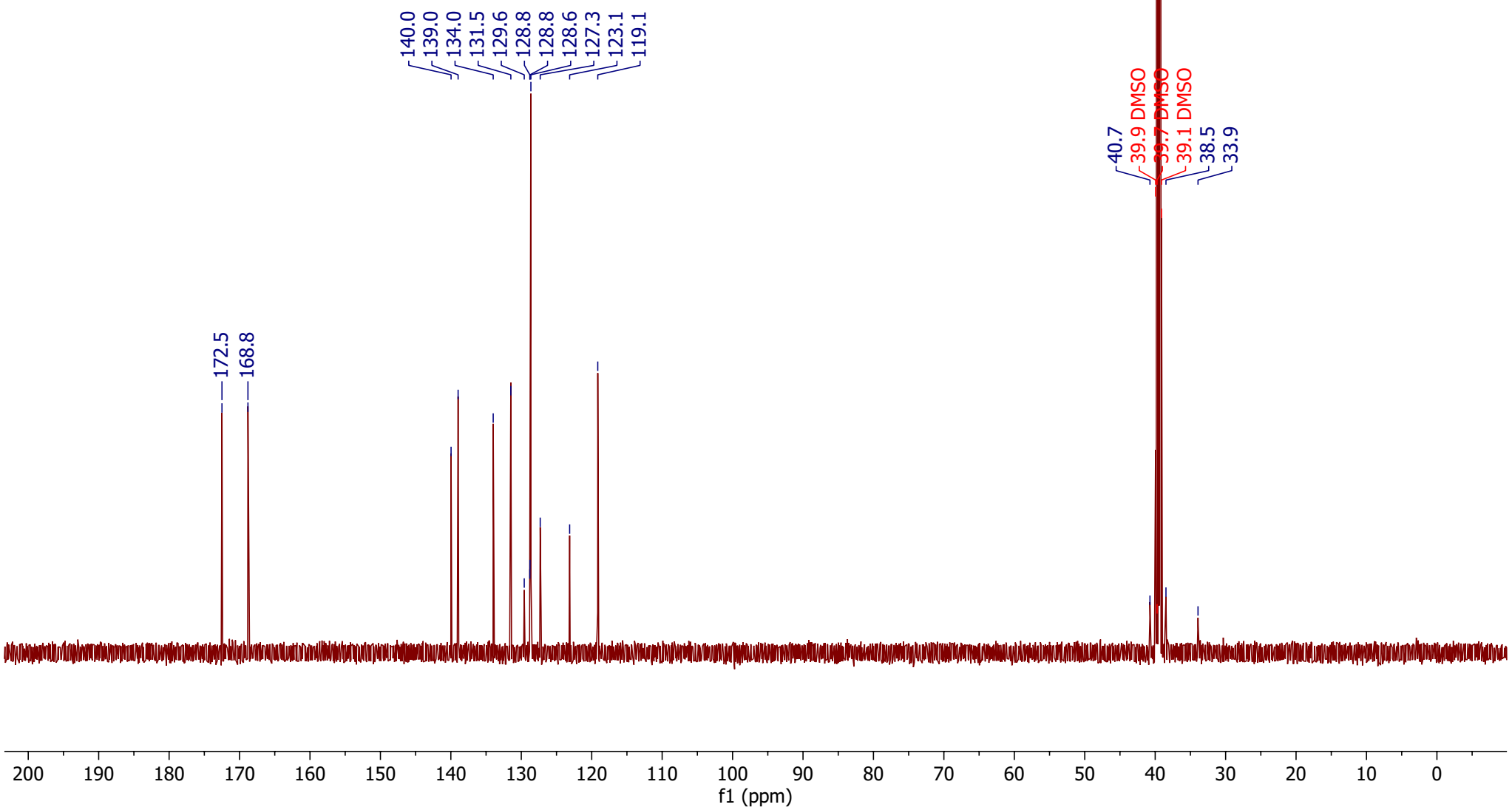




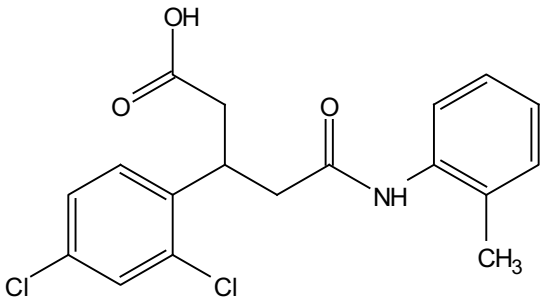


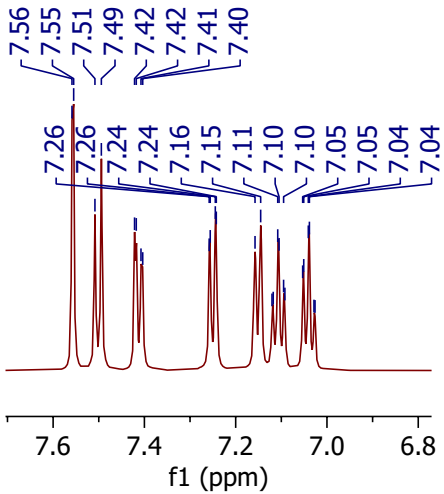
Compound S1
^{13}C NMR (151 MHz, DMSO-d6)

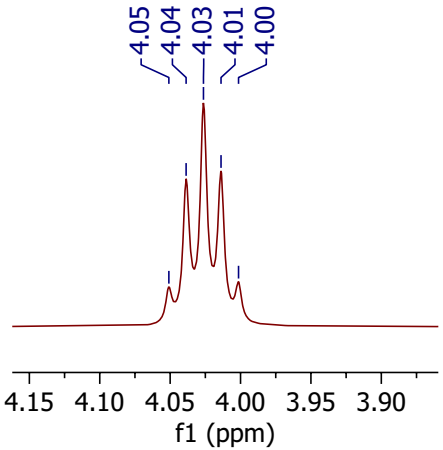


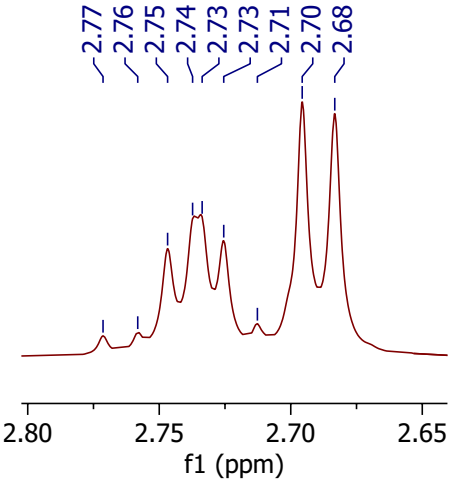


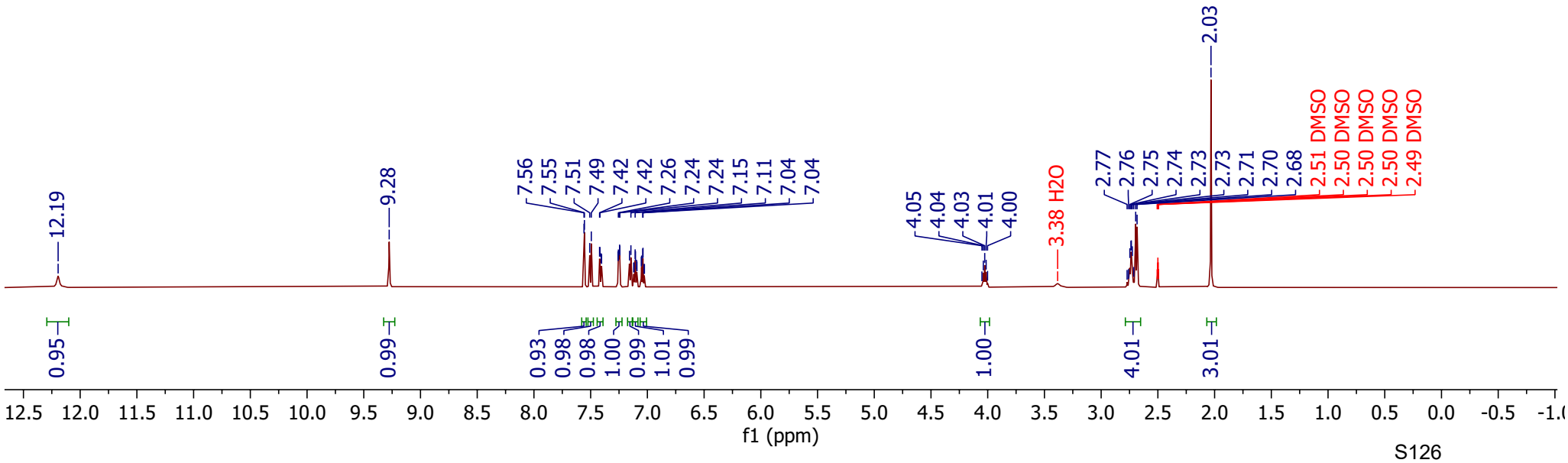
Compound S2
^{1}H NMR (600 MHz, DMSO-d6)





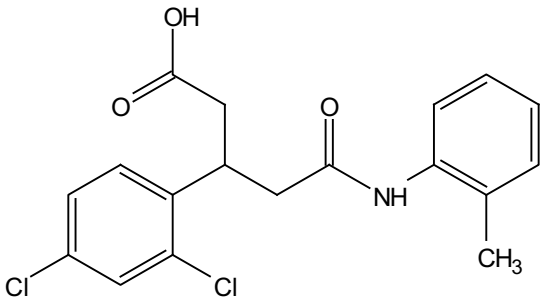




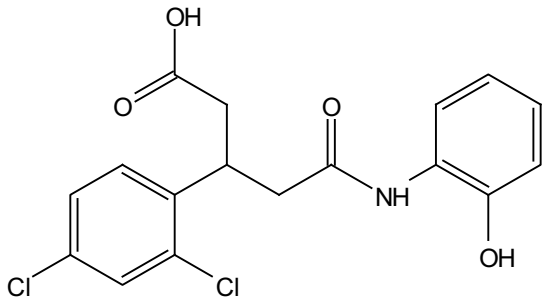


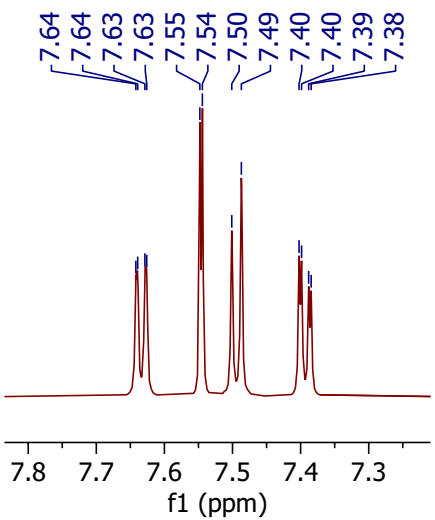
Compound S2

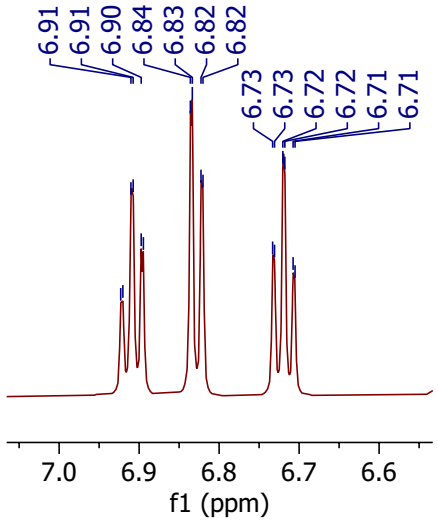
^{13}C NMR (151 MHz, DMSO-d6)

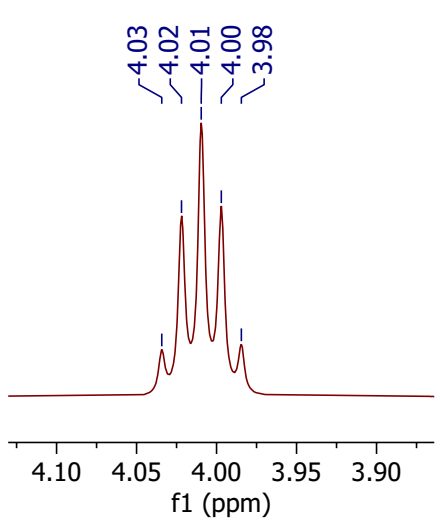


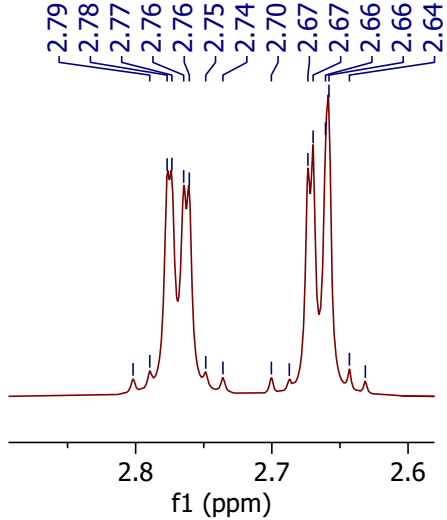
Compound S3
^{1}H NMR (600 MHz, DMSO-d6)

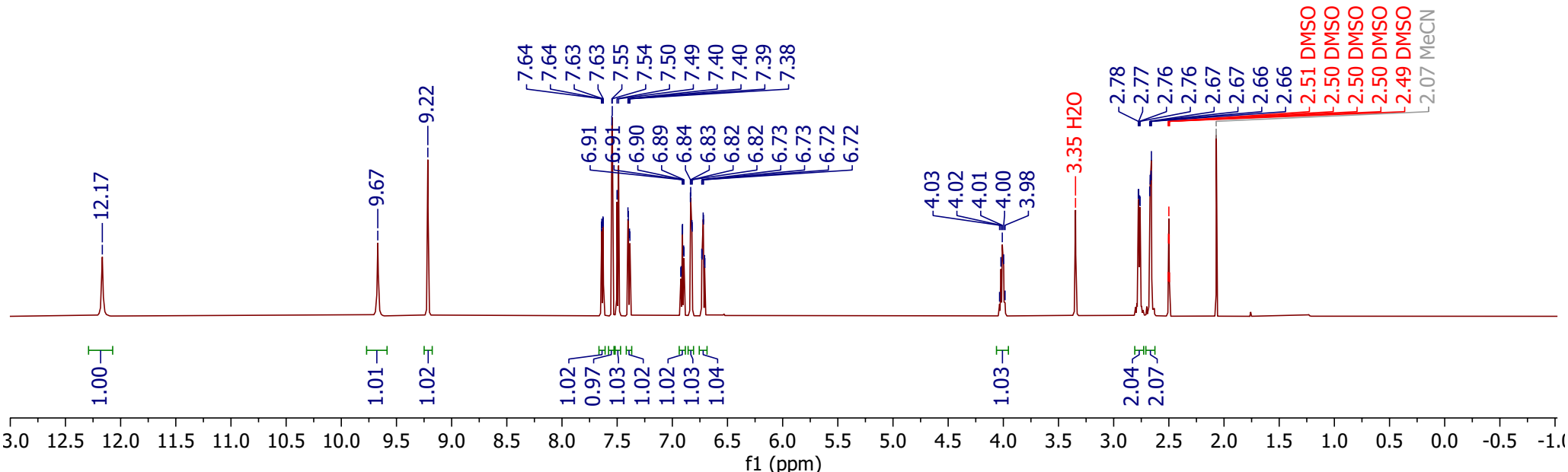




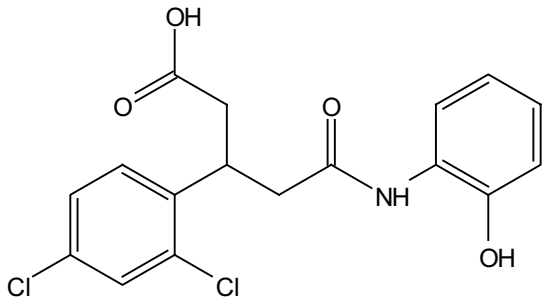


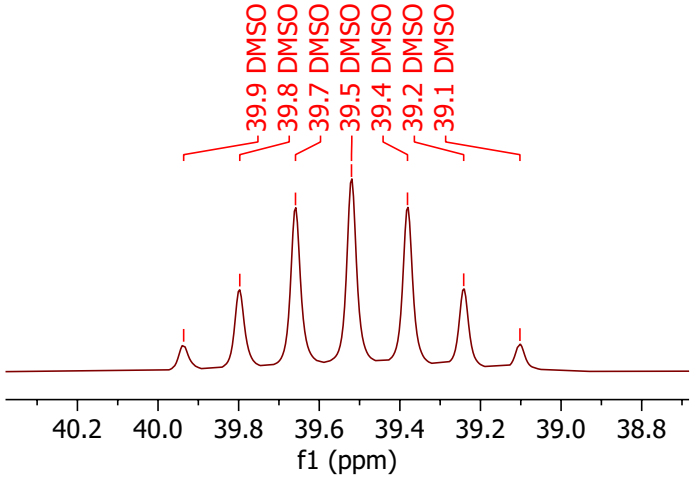




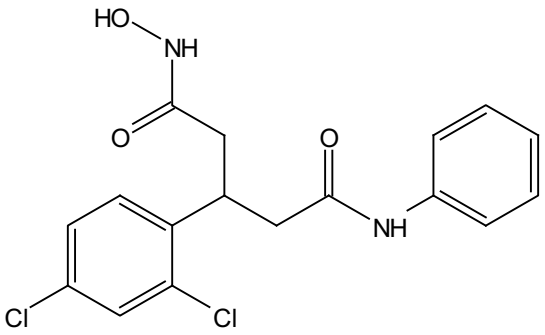


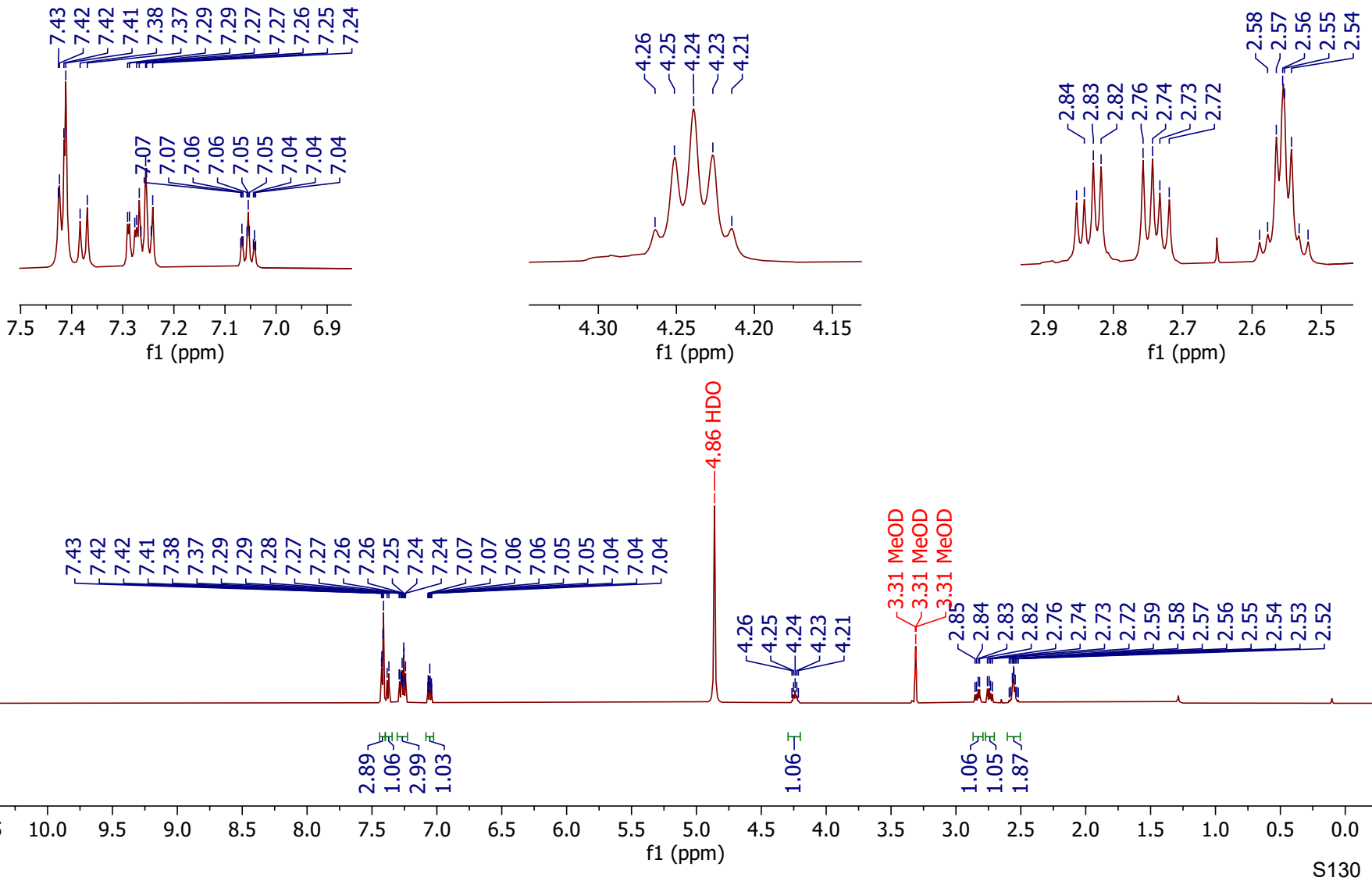
Compound S3
^{13}C NMR (151 MHz, DMSO-d6)



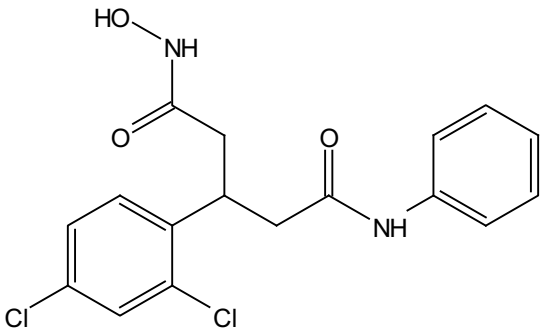


Compound (-)18
^{1}H NMR (600 MHz, MeOD-d4)

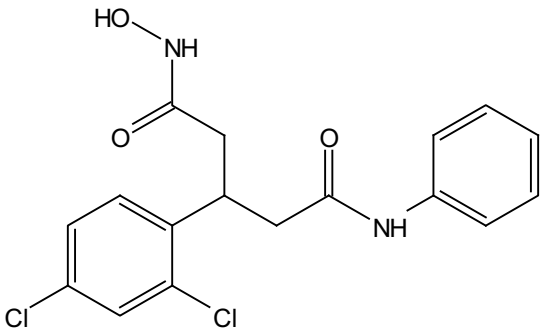


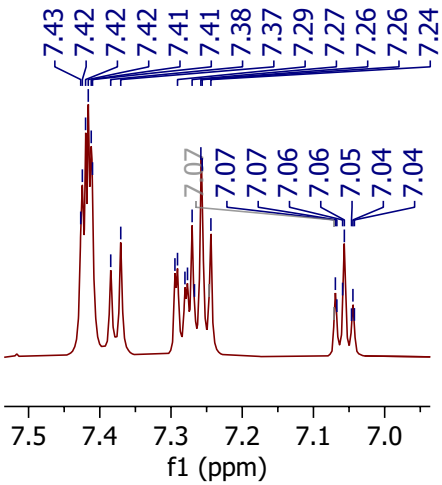


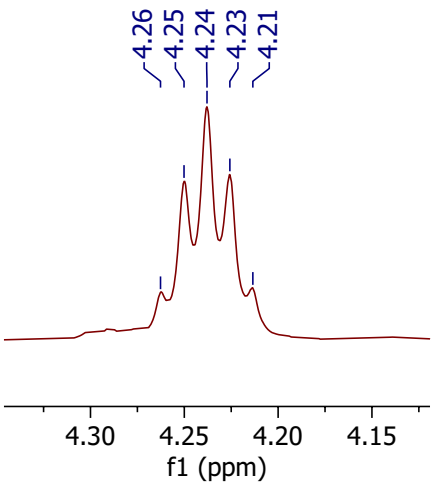
Compound (-)18
^{13}C NMR (151 MHz, MeOD-d4)

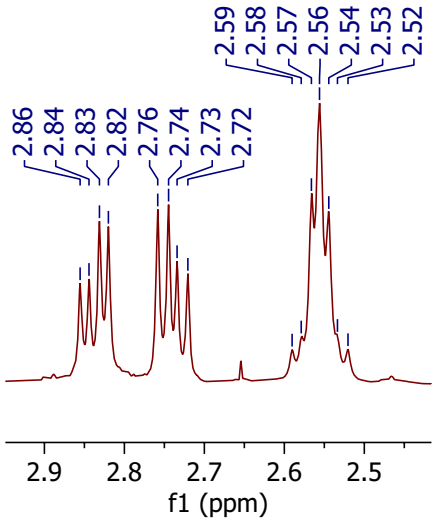


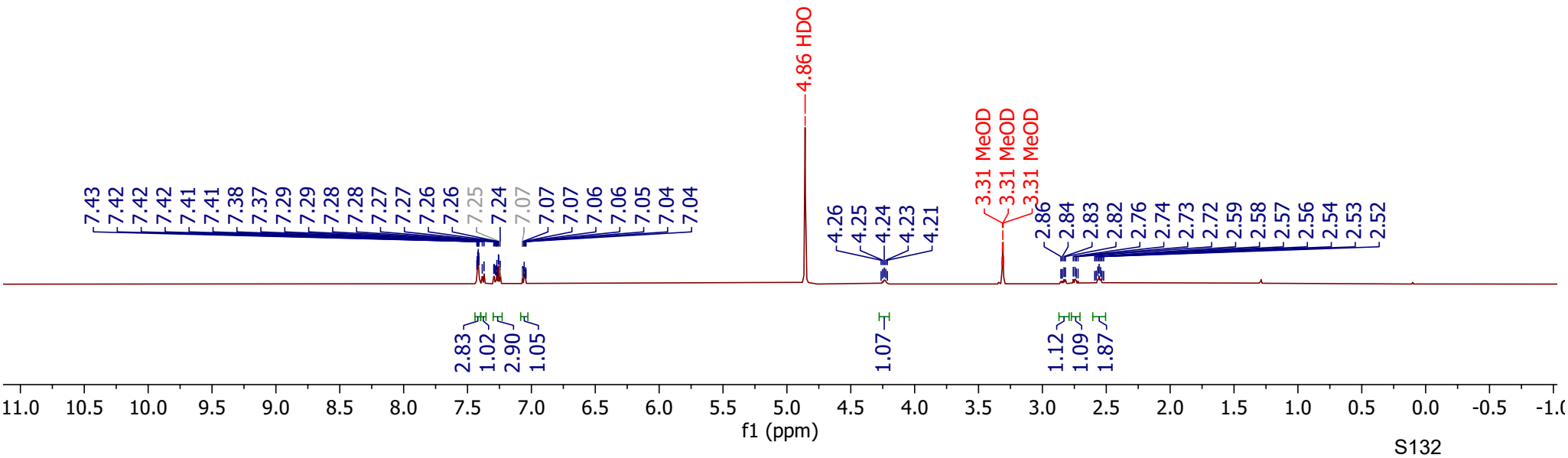
Compound (+)18
^{1}H NMR (600 MHz, MeOD-d4)



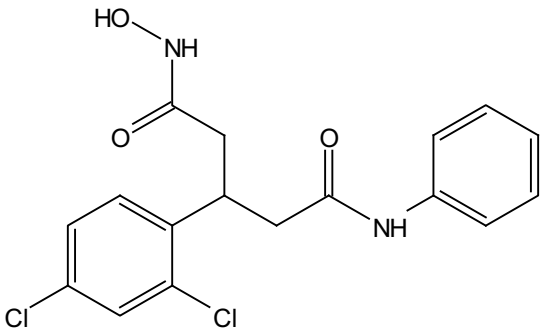




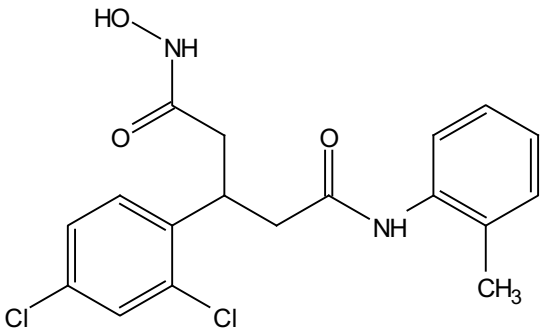


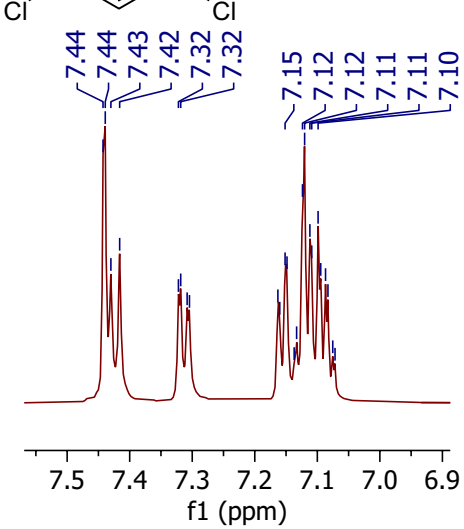


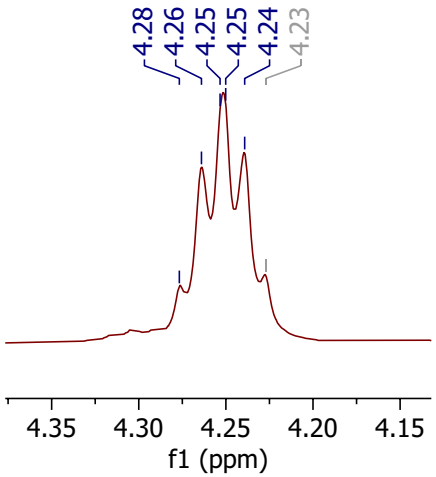
Compound (+)18
^{13}C NMR (151 MHz, MeOD-d4)

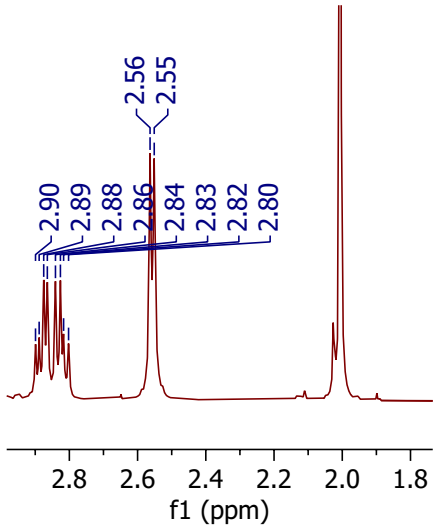


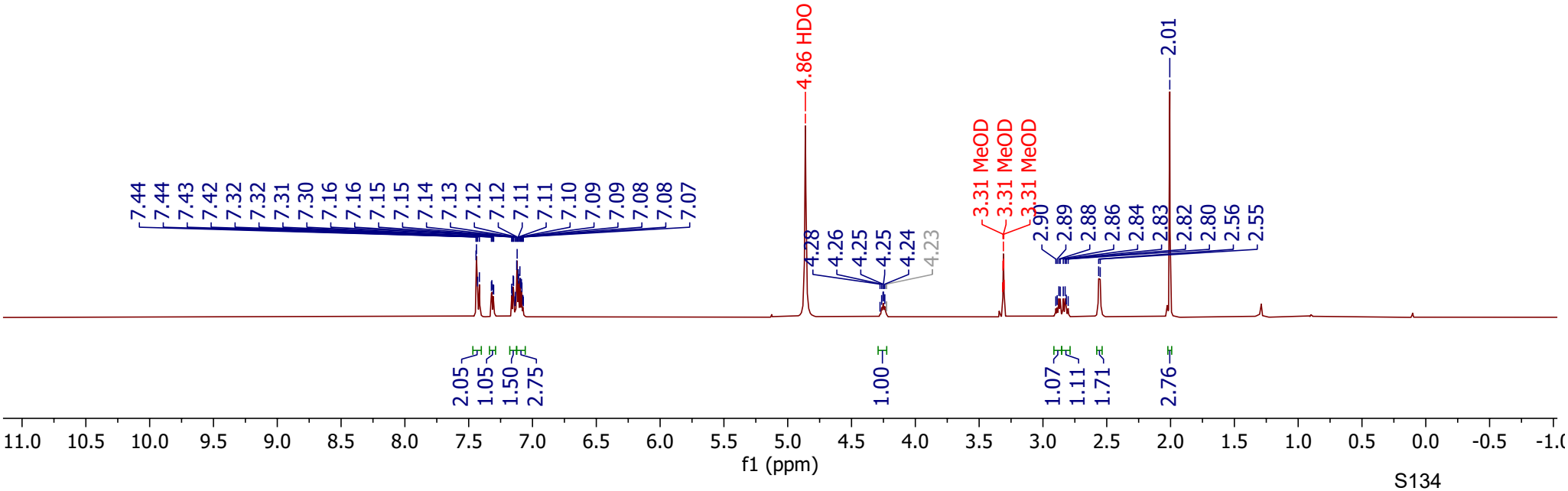
Compound (-)19
^{1}H NMR (600 MHz, MeOD-d4)



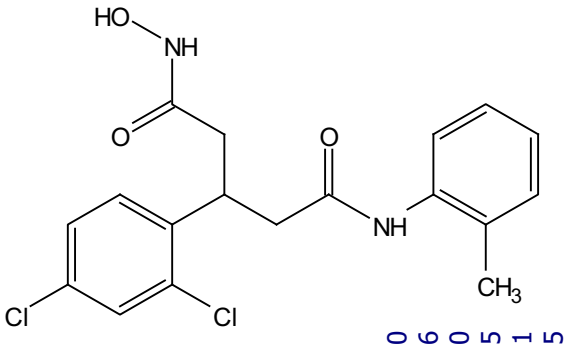




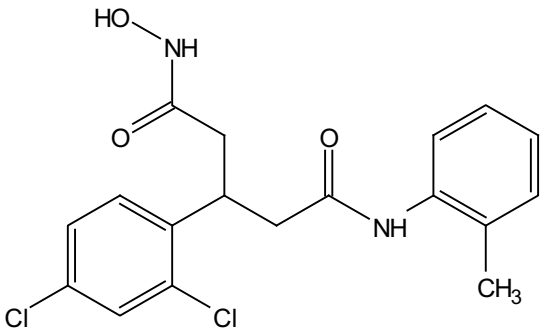


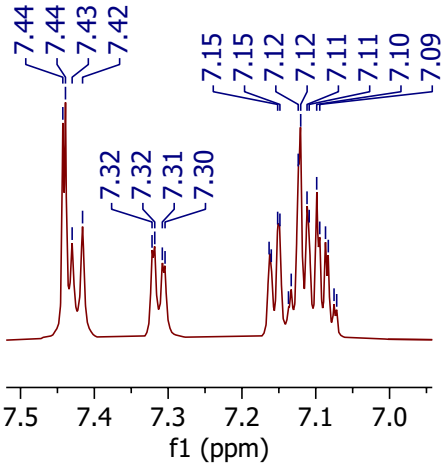


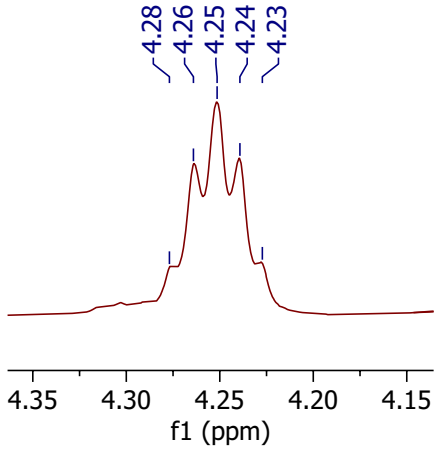
Compound (-)19
^{13}C NMR (151 MHz, MeOD-d4)

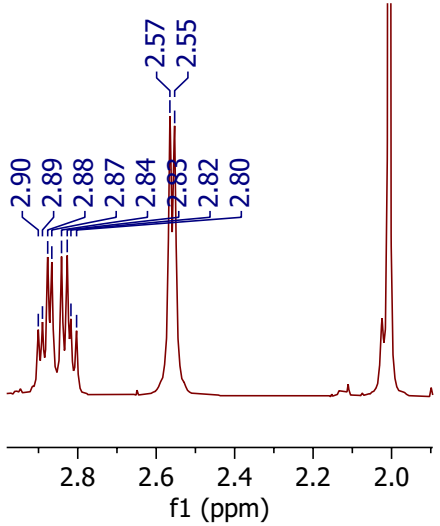


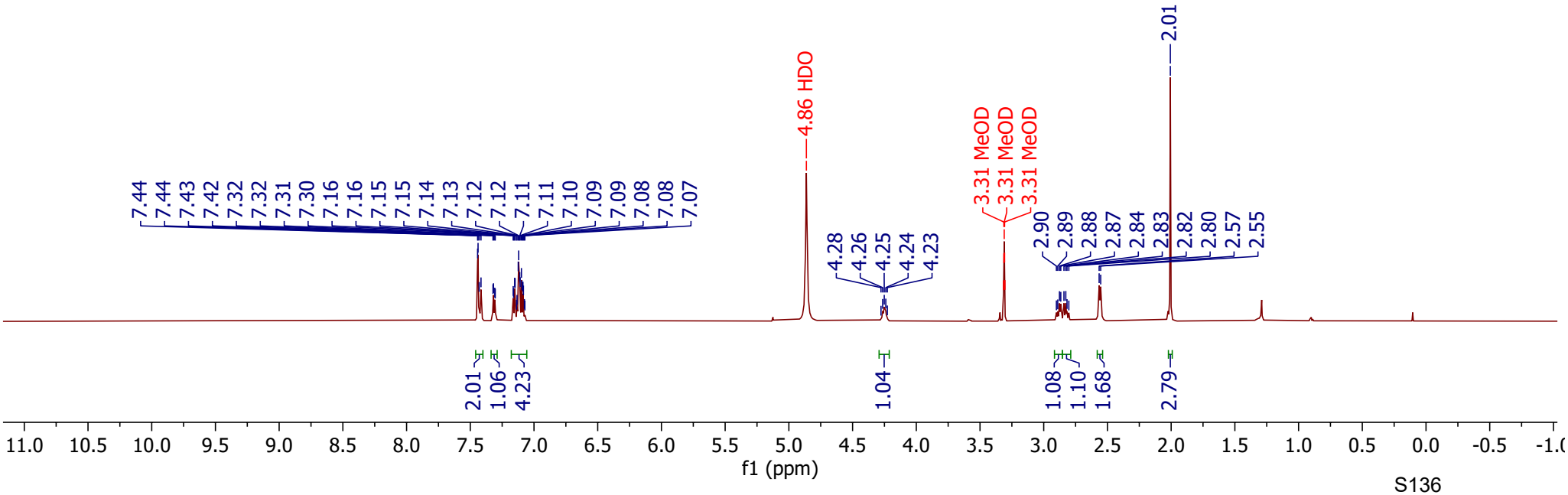
Compound (+)19
^{1}H NMR (600 MHz, MeOD-d4)





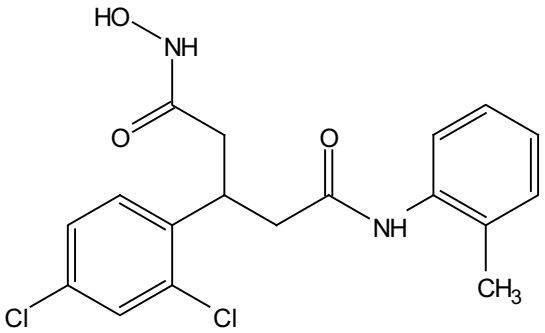




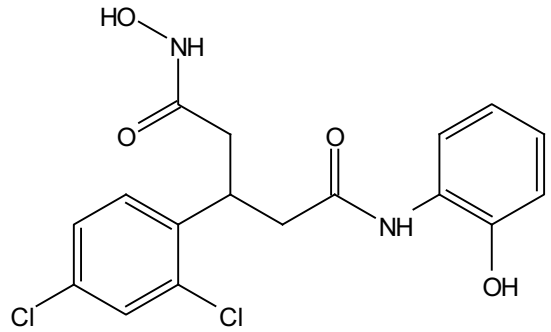


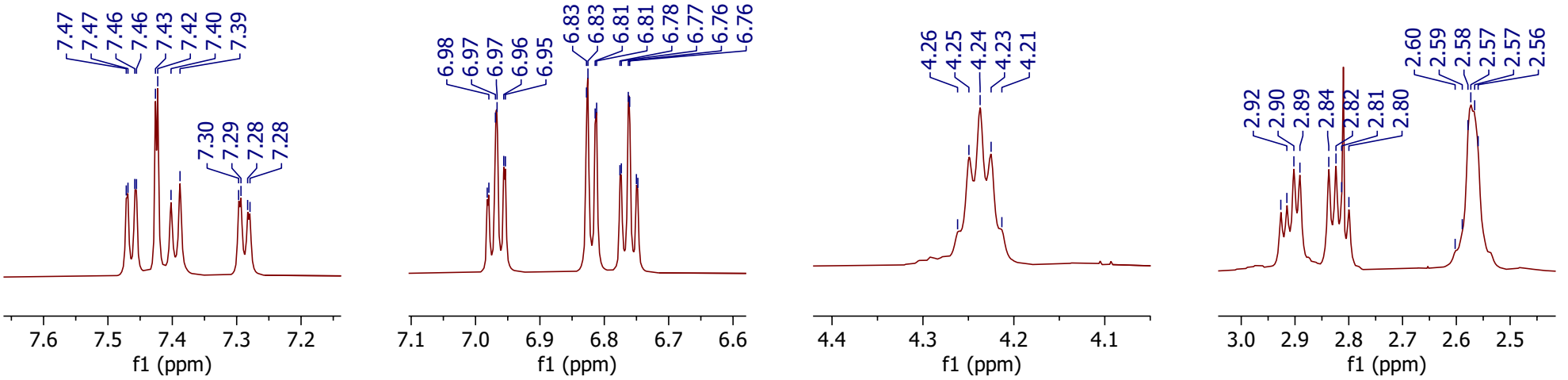
Compound (+)19

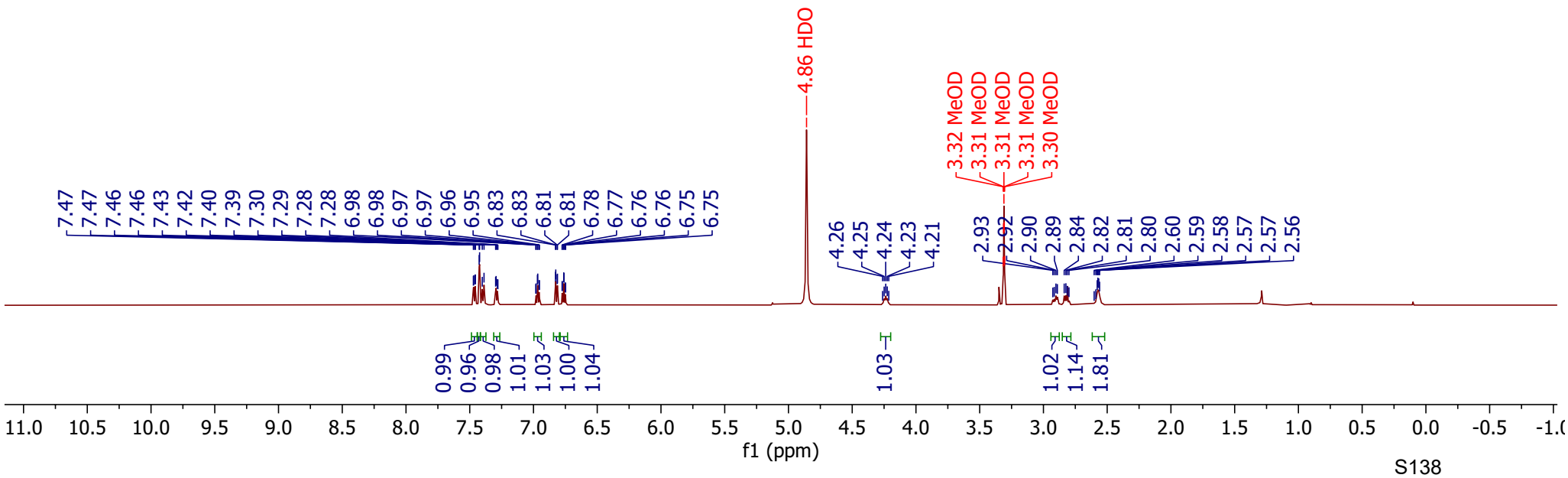
^{13}C NMR (151 MHz, MeOD-d4)



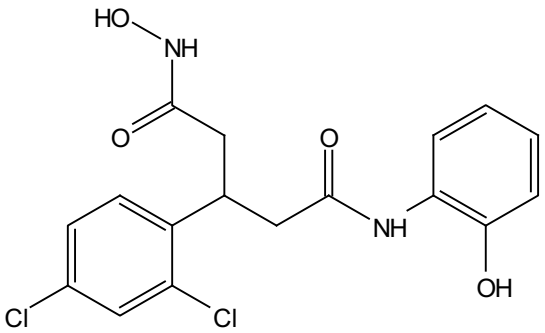
Compound (-)23
^{1}H NMR (600 MHz, MeOD-d4)



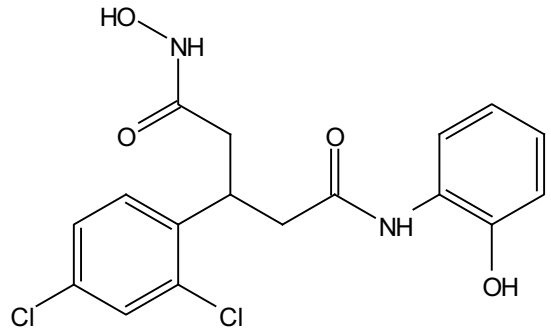


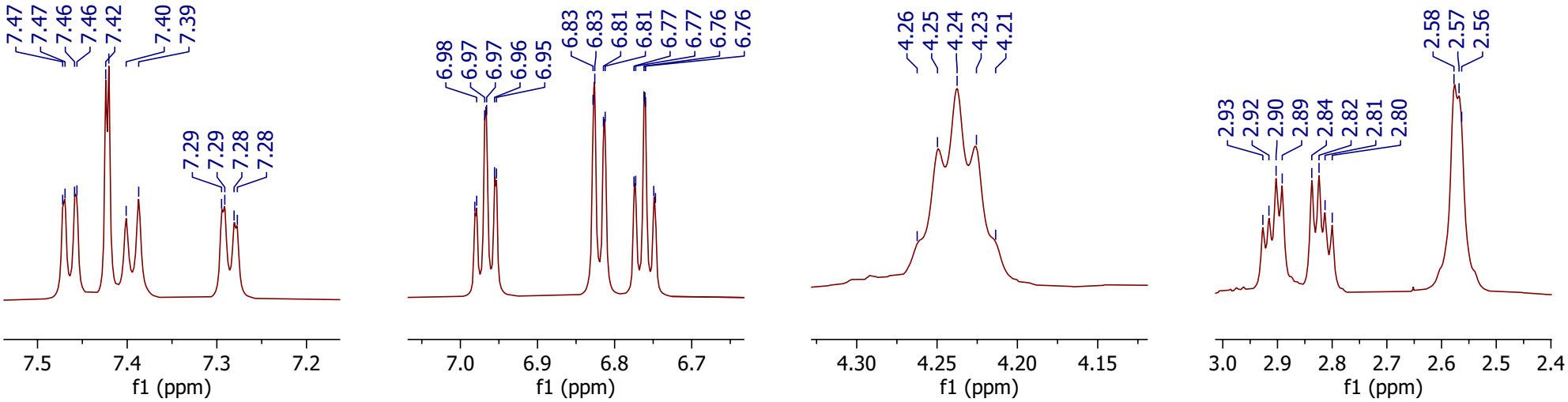


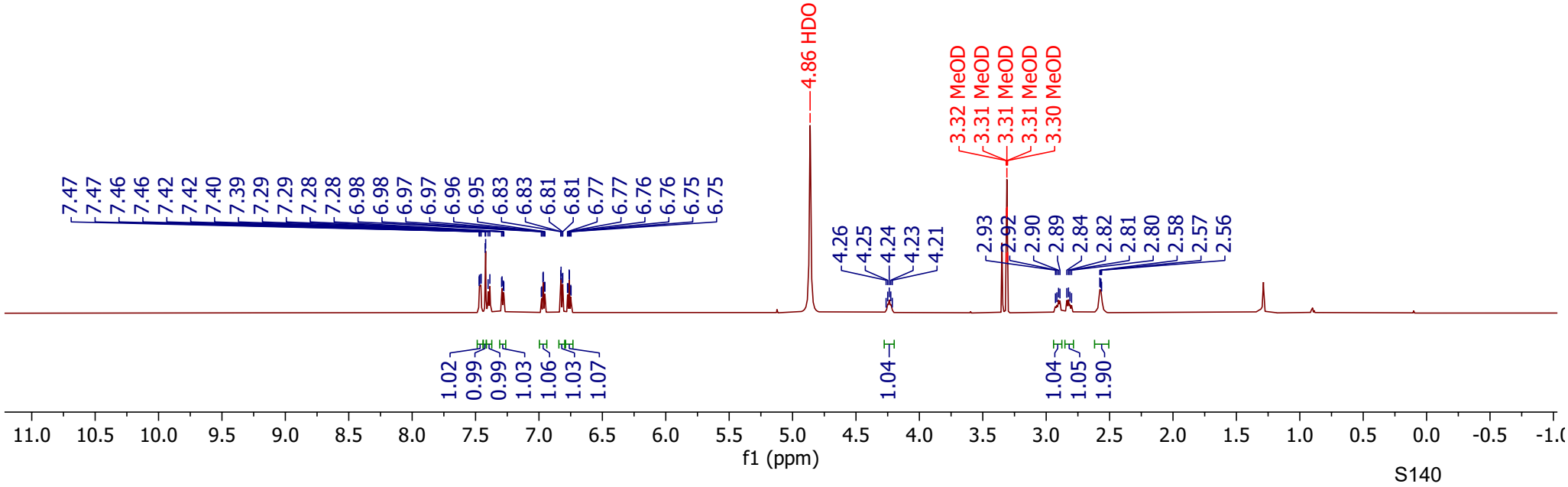
Compound (-)23
^{13}C NMR (151 MHz, MeOD-d4)



Compound (+)23
^{1}H NMR (600 MHz, MeOD-d4)







Compound (+)23
^{13}C NMR (151 MHz, MeOD-d4)