Supporting Information

Vancomycin C-Terminus Guanidine Modifications and Further Insights into an Added Mechanism of Action Imparted by a Peripheral Structural Modification

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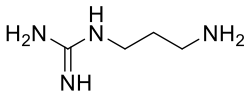
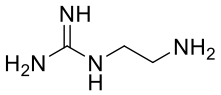
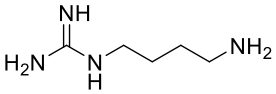
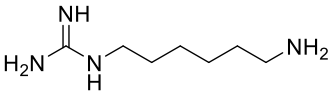
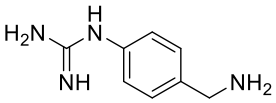
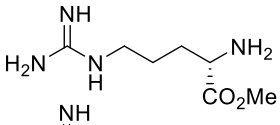
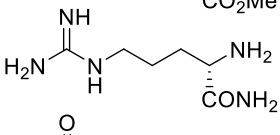
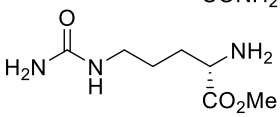
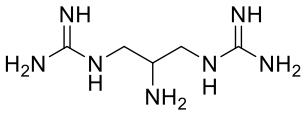
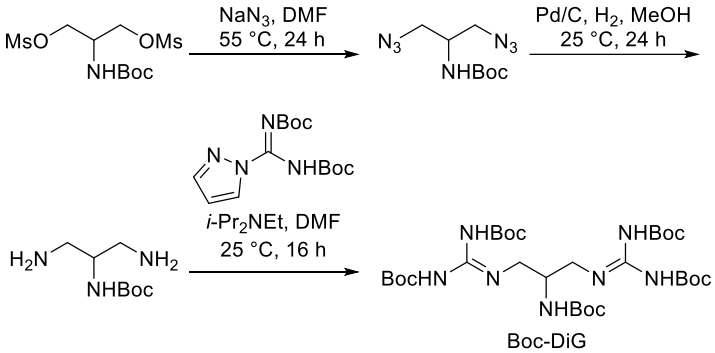
Table S1. Structure and source of guanidine-containing amines used.

Structure of amine	Abbreviation	Used in the synthesis of	Source
	G3	**5**, **15**	Ref. S1
	G2	**6**, **16**	Ref. S1
	G4	**7**, **17**	Ref. S2
	G6	**8**, **18**	Ref. S2
	GBn	**9**, **19**	Ref. S3
	Arg(OMe)	**10**, **20**	Commercial
	Arg(NH_2)	**12**, **22**	Commercial
	Cit(OMe)	**13**, **23**	Commercial
	DiG	**14**, **24**	Synthesis detailed in this SI

Synthesis of DiG

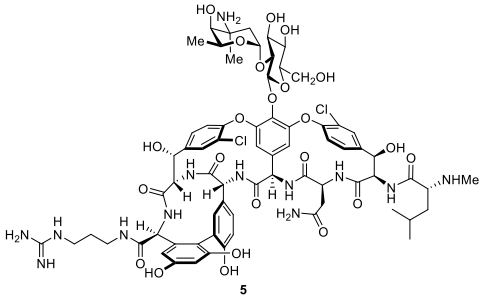


2-((*tert*-Butyloxycarbonyl)amino)propane-1,3-diyl dimethanesulfonate (2.08 g, 6 mmol) was dissolved in DMF (30 mL). NaN_3 (2.34 g, 36 mmol) was added, and the mixture was warmed at 55 °C for 24 h before it was cooled to 25 °C and poured into H_2O (100 mL). The mixture was

extracted by EtOAc (100 mL × 2) and the organic layer dried over Na_2SO_4. The solvent was removed to yield crude *tert*-butyl (1,3-diazidopropan-2-yl)carbamate as a colorless oil. This crude product was dissolved in MeOH (60 mL) and 5% Pd/C (720 mg) was added. The mixture was stirred at 25 °C under 1 atm of H_2 for 24 h before it was filtered over Celite. The solvent was removed to yield crude *tert*-butyl (1,3-diaminopropan-2-yl)carbamate as a colorless oil. This crude product was dissolved in DMF (30 mL) and N,N'-di-Boc-1*H*-pyrazole-1-carboxamidine (3.72 g, 12 mmol) and *i*-Pr_2NEt (1.55 g, 12 mmol) were added. The mixture was stirred at 25 °C for 16 h. H_2O (100 mL) was added and the mixture was extracted with EtOAc (100 mL × 2). The combined organic layer was dried over Na_2SO_4. The solvent was removed, and the residue was purified by column chromatography (SiO_2, EtOAc/hexanes = 1 : 7) to provide Boc-DiG as a white solid (350 mg, 9% over 3 steps): ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.45 (s, 2H), 8.58 (s, 2H), 6.16 (s, 1H), 3.94 – 3.87 (m, 1H), 3.70 – 3.62 (m, 2H), 3.52 – 3.44 (m, 2H), 1.49 (s, 18H), 1.48 (s, 18H), 1.43 (s, 9H); ^{13}C NMR (600 MHz, $CDCl_3$) δ 163.4, 157.1, 156.3, 153.0, 83.4, 79.5, 51.8, 43.0, 30.0, 28.4, 28.2; ESI-TOF HRMS *m/z* 674.4091 ($[M + H]^+$, $[C_{30}H_{55}N_7O_{10} + H]^+$ requires 674.4089). Boc-DiG (350 mg, 0.52 mmol) was dissolved in a mixture of CH_2Cl_2 and CF_3COOH (2 mL, V/V = 1 : 1), and the mixture was stirred at 25 °C for 16 h. The solvent was removed to give DiG (260 mg, 97%) as a colorless oil and the product is used without further purification.

General procedure for the synthesis of 5–10 and 12–14:

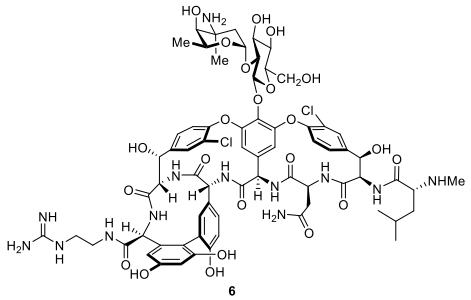
A solution of vancomycin hydrochloride (10.0 mg, 6.7 μmol) in DMF/DMSO (1/1, 670 μL) was treated sequentially with the corresponding amine (1 M in DMF/DMSO = 1/1, 13.4 μL, 13.4 μmol, 2 equiv), N-methylmorpholine (distilled, 1 M in DMF/DMSO = 1/1, 40.2 μL, 40.2 μmol, 6 equiv), and HBTU (0.5 M in DMF/DMSO =1/1, 26.8 μL, 13.4 μmol, 2 equiv). The mixture was stirred at 5 °C for 4 h and quenched with the addition of H_2O (1 mL). The mixture was purified by semi-preparative reverse-phase HPLC (Nacalai Tesque, Inc., ARII-C18, 5 μm, 10 × 150 mm, 1–40% MeCN/H_2O–0.07% TFA gradient over 40 min, 3 mL/min) to afford the desired products as white solids.



5

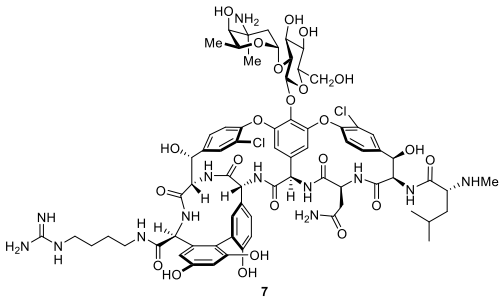
Compound **5** (2.5 mg, 20%, t_R = 20.7 min, >95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.24 (s, 1H), 9.00 (s, 1H), 8.73 – 8.64 (m, 1H), 8.57 – 8.46 (m, 1H), 8.04 (s, 1H), 7.85 (m, 1H), 7.68 (s, 2H), 7.60 (t, *J* = 6.0 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.42 (m, 2H), 7.34 (d, *J* = 8.4 Hz, 1H), 7.25 (d, *J* = 11.3 Hz, 1H), 7.22 – 7.16 (m, 1H), 7.06 (s, br, 1H), 6.83 – 6.73 (m, 2H), 6.70 (d, *J* = 8.5 Hz, 1H), 6.37 (d, *J* = 2.2 Hz, 1H), 6.23 (d, *J* = 2.2 Hz, 1H), 5.76 (d, *J* = 7.6 Hz, 1H), 5.57 (d, *J* = 17.0 Hz, 1H), 5.36 – 5.24 (m, 2H), 5.22 (m, 2H), 4.95 (s, 1H), 4.72 – 4.66 (m, 1H), 4.46 (d, *J* = 5.3 Hz, 2H), 4.35 (d, *J* = 5.3 Hz, 1H), 4.24 (d, *J* = 11.3 Hz, 1H), 3.96 (s, 1H), 3.70 (dd, *J* = 18.0, 8.7 Hz, 1H), 3.66 – 3.58 (m, 1H), 3.54 (q, *J* = 8.7 Hz, 1H), 3.49 – 3.42 (m, 1H), 3.32 – 3.21 (m, 2H), 3.18 – 3.13 (m, 2H), 3.11 (q, *J* = 6.2 Hz, 2H), 2.65 (s, 3H), 1.96 – 1.84 (m, 1H), 1.73 (d, *J* = 13.5 Hz, 1H), 1.69 – 1.65 (m, 3H), 1.61 – 1.53 (m, 1H), 1.29 (d, *J* = 14.0 Hz,

3H), 1.14 – 1.10 (m, 3H), 0.94 – 0.87 (m, 3H), 0.85 (dd, *J* = 6.4, 2.3 Hz, 3H). ESI-TOF HRMS *m/z* 1546.5392 ($[M + H]^+$, $[C_{70}H_{85}Cl_3N_{13}O_{23} + H]^+$ requires 1546.5337).



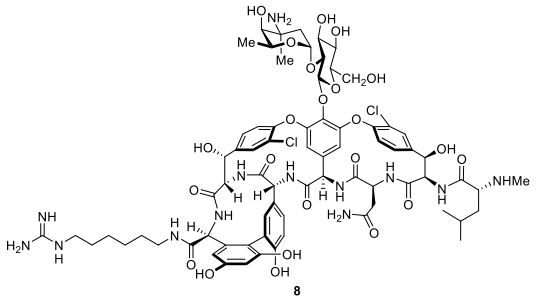
6

Compound **6** (7.3 mg, 57%, t_R = 19.7 min, >95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.37 (s, 1H), 9.07 (s, 1H), 9.03 (s, 1H), 8.69 (s, 1H), 8.60 – 8.41 (m, 1H), 8.13 (s, 1H), 7.93 – 7.77 (m, 1H), 7.67 (s, 2H), 7.59 (t, *J* = 5.7 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.52 – 7.48 (m, 1H), 7.46 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.22 (s, 1H), 7.19 (d, *J* = 8.3 Hz, 1H), 7.11 – 6.99 (m, 1H), 6.76 (dd, *J* = 8.4, 2.0 Hz, 1H), 6.73 (s, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.57 (s, br, 5H), 6.38 (d, *J* = 2.3 Hz, 1H), 6.22 (d, *J* = 2.2 Hz, 1H), 5.99 (s, 1H), 5.88 (d, *J* = 5.9 Hz, 1H), 5.76 (d, *J* = 7.9 Hz, 1H), 5.69 – 5.56 (m, 1H), 5.47 (s, 1H), 5.41 – 5.29 (m, 1H), 5.28 – 5.21 (m, 3H), 5.20 – 5.17 (m, 2H), 5.11 (s, 1H), 4.94 (s, 1H), 4.68 (q, *J* = 7.0, 5.9 Hz, 1H), 4.45 (d, *J* = 5.4 Hz, 1H), 4.38 (d, *J* = 5.4 Hz, 1H), 4.23 (d, *J* = 11.7 Hz, 2H), 4.05 – 3.91 (s, 1H), 3.74 – 3.61 (m, 1H), 3.55 (t, *J* = 8.3 Hz, 1H), 3.28 – 3.25 (m, 2H), 3.25 – 3.20 (m, 2H), 3.18 (s, 1H), 2.64 (s, 3H), 2.23 – 2.07 (m, 1H), 1.90 (d, *J* = 11.2 Hz, 1H), 1.83 – 1.71 (m, 1H), 1.71 – 1.66 (m, 1H), 1.66 – 1.60 (m, 1H), 1.56 (dt, *J* = 12.6, 6.1 Hz, 1H), 1.30 (s, 3H), 1.07 (d, *J* = 6.3 Hz, 3H), 0.91 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.3 Hz, 3H). ESI-TOF HRMS *m/z* 1532.5173 ($[M + H]^+$, $[C_{69}H_{83}Cl_2N_{13}O_{23} + H]^+$ requires 1532.5174).



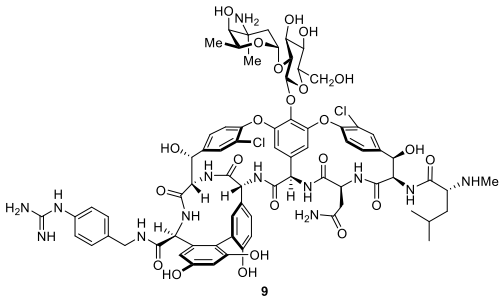
7

Compound **7** (9.8 mg, 76%, t_R = 20.2 min, 95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.29 (s, 1H), 9.02 (s, 2H), 8.45 (s, 1H), 7.96 (s, 1H), 7.85 (s, 1H), 7.69 (s, 3H), 7.61 – 7.54 (m, 2H), 7.53 – 7.39 (m, 2H), 7.33 (d, *J* = 8.4 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.18 (d, *J* = 8.4 Hz, 1H), 7.02 (s, br, 1H), 6.79 – 6.73 (m, 2H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.37 (d, *J* = 2.2 Hz, 1H), 6.23 (d, *J* = 2.2 Hz, 1H), 6.02 (s, 1H), 5.76 (d, *J* = 7.9 Hz, 1H), 5.58 (s, 1H), 5.31 – 5.22 (m, 3H), 5.21 – 5.16 (m, 2H), 4.95 (s, 1H), 4.69 (dd, *J* = 8.7, 4.5 Hz, 1H), 4.45 (d, *J* = 5.5 Hz, 1H), 4.36 (d, *J* = 5.5 Hz, 1H), 4.31 – 4.16 (m, 1H), 3.96 (s, 1H), 3.68 (d, *J* = 10.8 Hz, 1H), 3.64 (s, 2H), 3.27 (d, *J* = 4.9 Hz, 2H), 3.24 – 3.16 (m, 2H), 3.15 – 3.07 (m, 3H), 3.05 (s, 1H), 2.92 (s, 1H), 2.65 (s, 3H), 2.16 (d, *J* = 11.3 Hz, 1H), 1.91 (d, *J* = 10.2 Hz, 1H), 1.79 – 1.70 (m, 1H), 1.68 (q, *J* = 7.0 Hz, 1H), 1.62 (q, *J* = 6.3 Hz, 1H), 1.60 – 1.54 (m, 1H), 1.48 (s, 4H), 1.30 (s, 3H), 1.07 (d, *J* = 6.2 Hz, 3H), 0.90 (d, *J* = 6.2 Hz, 3H), 0.85 (dd, *J* = 6.4, 2.5 Hz, 3H). ESI-TOF HRMS *m/z* 1560.5457 ($[M + H]^+$, $[C_{71}H_{87}Cl_2N_{13}O_{23} + H]^+$ requires 1560.5487).



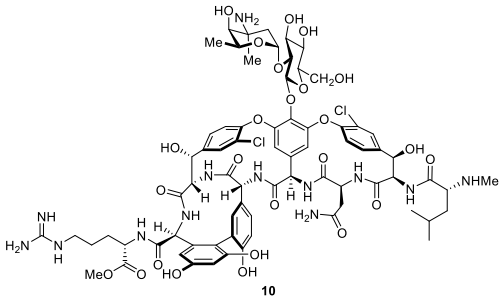
8

Compound **8** (9.0 mg, 69%, t_R = 22.5 min, 95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.33 (s, 1H), 9.00 (s, 2H), 8.64 (s, 1H), 8.43 (s, 1H), 7.92 – 7.79 (m, 2H), 7.69 (t, *J* = 5.5 Hz, 4H), 7.61 – 7.53 (m, 1H), 7.53 – 7.37 (m, 3H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.26 – 7.14 (m, 2H), 7.01 (s, 1H), 6.79 – 6.73 (m, 1H), 6.73 – 6.63 (m, 2H), 6.37 (d, *J* = 2.2 Hz, 1H), 6.24 (d, *J* = 2.2 Hz, 1H), 5.76 (d, *J* = 7.8 Hz, 1H), 5.57 (s, 1H), 5.26 (s, 1H), 5.24 (d, *J* = 8.4 Hz, 2H), 5.22 – 5.17 (m, 2H), 4.95 (s, 1H), 4.68 (d, *J* = 6.0 Hz, 1H), 4.44 (s, 1H), 4.37 (d, *J* = 5.4 Hz, 1H), 4.22 (d, *J* = 11.8 Hz, 1H), 3.96 (s, 1H), 3.57 – 3.52 (m, 3H), 3.47 – 3.41 (m, 1H), 3.27 (d, *J* = 4.7 Hz, 2H), 3.20 (d, *J* = 5.2 Hz, 1H), 3.18 – 3.11 (m, 2H), 3.09 (q, *J* = 6.6 Hz, 3H), 2.65 (s, 3H), 2.21 – 2.08 (m, 1H), 1.91 (d, *J* = 10.8 Hz, 1H), 1.80 – 1.71 (m, 1H), 1.80 – 1.71 (m, 1H), 1.71 – 1.66 (m, 1H), 1.66 – 1.54 (m, 2H), 1.46 (s, 4H), 1.29 (d, *J* = 7.7 Hz, 8H), 1.06 (d, *J* = 6.3 Hz, 3H), 0.91 – 0.84 (m, 6H). ESI-TOF HRMS *m/z* 1588.5770 ([M + H]$^+$, [$C_{73}H_{91}Cl_2N_{13}O_{23}$ + H]$^+$ requires 1588.5800).



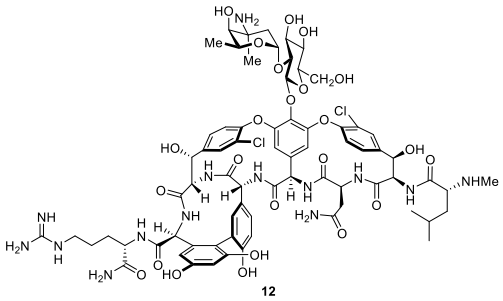
9

Compound **9** (7.0 mg, 54%, t_R = 21.2 min, 95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.95 (s, 1H), 9.27 (s, 1H), 9.05 (s, 1H), 9.01 (s, 1H), 8.67 (s, 1H), 8.50 (s, 2H), 7.86 (s, 1H), 7.68 (s, 3H), 7.57 (d, *J* = 8.1 Hz, 2H), 7.54 (s, 2H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.35 (d, *J* = 8.1 Hz, 3H), 7.24 (s, 1H), 7.20 (d, *J* = 8.4 Hz, 1H), 7.17 (d, *J* = 8.3 Hz, 2H), 7.04 (s, 1H), 6.78 (d, *J* = 7.9 Hz, 2H), 6.72 (d, *J* = 8.7 Hz, 1H), 6.39 (d, *J* = 2.2 Hz, 1H), 6.30 (d, *J* = 2.1 Hz, 1H), 5.77 (d, *J* = 7.8 Hz, 1H), 5.60 (s, 1H), 5.29 – 5.22 (m, 3H), 5.20 (d, *J* = 6.4 Hz, 2H), 4.95 (s, 1H), 4.69 (q, *J* = 6.5 Hz, 1H), 4.52 – 4.42 (m, 3H), 4.37 – 4.30 (m, 1H), 4.26 (d, *J* = 12.3 Hz, 1H), 3.96 (s, 1H), 3.69 (d, *J* = 10.8 Hz, 2H), 3.28 (d, *J* = 4.2 Hz, 2H), 3.19 (s, 1H), 2.65 (s, 3H), 2.21 – 2.12 (m, 1H), 1.97 – 1.87 (m, 1H), 1.79 – 1.71 (m, 1H), 1.71 – 1.67 (m, 1H), 1.67 – 1.61 (m, 1H), 1.61 – 1.54 (m, 1H), 1.31 (s, 3H), 1.08 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.86 (d, *J* = 6.2 Hz, 3H). ESI-TOF HRMS *m/z* 1594.5343 ([M + H]$^+$, [$C_{74}H_{85}Cl_2N_{13}O_{23}$ + H]$^+$ requires 1594.5337).



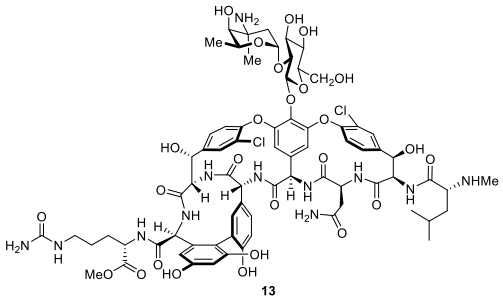
10

Compound **10** (9.9 mg, 75%, t_R = 20.8 min, 95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.01 (s, 2H), 8.57 (s, 1H), 8.49 (d, *J* = 7.5 Hz, 1H), 7.86 (d, *J* = 5.0 Hz, 1H), 7.72 (s, 3H), 7.62 (t, *J* = 5.5 Hz, 1H), 7.58 (s, 1H), 7.47 (t, *J* = 8.7 Hz, 2H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.27 – 7.15 (m, 2H), 7.01 (s, 1H), 6.91 – 6.80 (m, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 8.4, 3.4 Hz, 1H), 6.52 – 6.38 (m, 1H), 6.34 (s, 1H), 5.76 (d, *J* = 7.8 Hz, 1H), 5.59 – 5.53 (m, 1H), 5.30 – 5.22 (m, 2H), 5.22 – 5.14 (m, 3H), 4.96 (s, 1H), 4.77 – 4.60 (m, 1H), 4.51 (d, *J* = 5.6 Hz, 1H), 4.47 (s, 1H), 4.32 (q, *J* = 7.6 Hz, 1H), 4.22 (d, *J* = 11.8 Hz, 1H), 4.01 – 3.89 (m, 2H), 3.69 (s, 3H), 3.66 – 3.60 (m, 3H), 3.27 (s, 1H), 3.20 (s, 1H), 3.13 – 2.99 (m, 2H), 2.69 (s, 3H), 2.66 (s, 3H), 2.16 (s, 1H), 1.95 – 1.85 (m, 1H), 1.85 – 1.73 (m, 2H), 1.72 – 1.65 (m, 2H), 1.63 – 1.54 (m, 2H), 1.52 – 1.45 (m, 2H), 1.30 (s, 2H), 1.28 (s, 1H), 1.07 (d, *J* = 6.2 Hz, 3H), 0.90 (d, *J* = 5.0 Hz, 3H), 0.87 – 0.81 (m, 3H). ESI-TOF HRMS *m/z* 1618.5528 ($[M + H]^+$, $[C_{73}H_{89}Cl_2N_{13}O_{25} + H]^+$ requires 1618.5542).



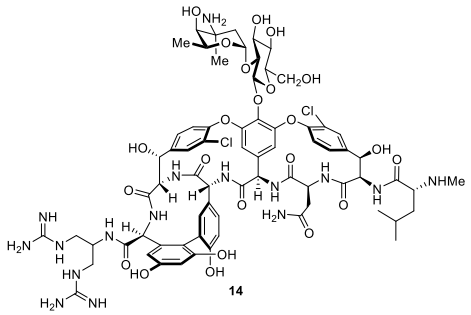
12

Compound **12** (4.0 mg, 31%, t_R = 19.4 min, >95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.37 (s, 1H), 9.21 (s, br, 1H), 9.05 (s, 1H), 8.97 (s, 2H), 8.79 – 8.64 (m, 1H), 8.63 – 8.43 (m, 2H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.65 (s, br, 3H), 7.56 (d, *J* = 7.3 Hz, 1H), 7.52 (t, *J* = 5.8 Hz, 1H), 7.50 – 7.44 (m, 2H), 7.34 (dd, *J* = 8.3, 2.5 Hz, 1H), 7.25 (s, 1H), 7.23 (d, *J* = 5.7 Hz, 1H), 7.18 (s, 1H), 7.13 – 6.98 (m, 1H), 6.84 (d, *J* = 11.3 Hz, 1H), 6.80 – 6.74 (m, 1H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.58 (s, 3H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.25 (d, *J* = 2.2 Hz, 1H), 6.00 (s, 1H), 5.88 (d, *J* = 5.6 Hz, 1H), 5.77 (d, *J* = 7.8 Hz, 1H), 5.67 – 5.54 (m, 2H), 5.48 (s, 1H), 5.41 – 5.30 (m, 1H), 5.24 (dd, *J* = 10.4, 5.8 Hz, 2H), 5.21 – 5.14 (m, 3H), 5.12 (s, 1H), 4.94 (s, 1H), 4.74 – 4.64 (m, 1H), 4.46 (d, *J* = 5.4 Hz, 1H), 4.43 (d, *J* = 5.5 Hz, 1H), 4.32 (q, *J* = 7.6 Hz, 1H), 4.24 (d, *J* = 9.6 Hz, 2H), 4.13 – 3.86 (m, 2H), 3.77 – 3.67 (m, 1H), 3.67 – 3.58 (m, 2H), 3.58 – 3.50 (m, 2H), 3.27 (d, *J* = 5.0 Hz, 2H), 3.18 (s, 2H), 3.14 – 3.05 (m, 2H), 2.70 – 2.59 (m, 3H), 2.15 (s, 1H), 1.94 – 1.87 (m, 1H), 1.81 – 1.70 (m, 2H), 1.70 – 1.65 (m, 1H), 1.65 – 1.54 (m, 3H), 1.53 – 1.47 (m, 2H), 1.30 (s, 2H), 1.27 (s, 1H), 1.09 – 1.01 (m, 3H), 0.91 (dd, *J* = 6.3, 1.8 Hz, 3H), 0.86 (dd, *J* = 6.5, 2.5 Hz, 3H). ESI-TOF HRMS *m/z* 1603.5515 ($[M + H]^+$, $[C_{72}H_{88}Cl_2N_{14}O_{24} + H]^+$ requires 1603.5545).



13

Compound **13** (6.4 mg, 52%, t_R = 22.0 min, >95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.36 (s, 1H), 9.15 (s, 1H), 9.00 (s, 1H), 8.96 (s, 1H), 8.92 (s, 1H), 8.72 (s, 1H), 8.53 (s, 1H), 8.36 (d, *J* = 7.4 Hz, 1H), 7.88 (d, *J* = 3.3 Hz, 1H), 7.65 (s, 4H), 7.59 – 7.54 (m, 2H), 7.51 (s, 1H), 7.47 (t, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.7 Hz, 1H), 7.26 – 7.17 (m, 2H), 6.82 – 6.75 (m, 2H), 6.72 (t, *J* = 8.2 Hz, 2H), 6.56 (s, 3H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 2.2 Hz, 1H), 6.00 (s, 1H), 5.95 (s, 2H), 5.78 (d, *J* = 7.9 Hz, 1H), 5.66 – 5.59 (m, 1H), 5.58 (s, 1H), 5.49 (s, 1H), 5.40 (s, 2H), 5.34 (d, *J* = 7.2 Hz, 1H), 5.25 (t, *J* = 6.3 Hz, 1H), 5.23 – 5.16 (m, 3H), 4.94 (s, 1H), 4.70 (d, *J* = 7.1 Hz, 1H), 4.54 (d, *J* = 5.9 Hz, 1H), 4.46 (d, *J* = 5.4 Hz, 1H), 4.38 – 4.28 (m, 1H), 4.22 (d, *J* = 12.2 Hz, 2H), 4.00 – 3.89 (m, 2H), 3.78 – 3.70 (m, 1H), 3.68 (s, 3H), 3.67 – 3.62 (m, 3H), 3.57 – 3.54 (m, 1H), 3.28 (s, 1H), 3.19 (s, 1H), 2.94 (q, *J* = 9.5, 8.2 Hz, 3H), 2.65 (s, 3H), 2.19 – 2.11 (m, 1H), 1.93 – 1.90 (m, 1H), 1.79 – 1.73 (m, 2H), 1.73 – 1.67 (m, 2H), 1.67 – 1.61 (m, 2H), 1.60 – 1.56 (m, 1H), 1.45 – 1.34 1(m, 2H), 1.30 (s, 1H), 1.28 (s, 2H), 1.11 – 1.05 (m, 3H), 0.92 (dd, *J* = 6.5, 1.8 Hz, 3H), 0.87 (dd, *J* = 6.5, 2.4 Hz, 3H). ESI-TOF HRMS *m/z* 1619.5377 ([M + H]$^+$, [$C_{73}H_{88}Cl_2N_{12}O_{26}$ + H]$^+$ requires 1619.5382).

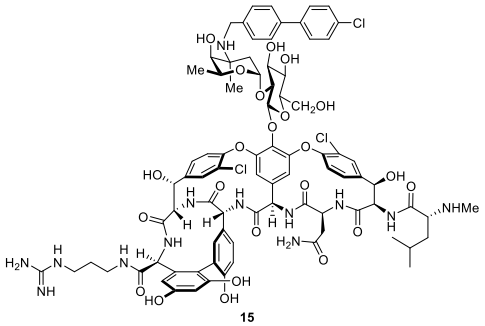


14

Compound **14** (1.7 mg, 12%, t_R = 17.2 min, >95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.37 (s, 1H), 9.14 (s, 1H), 9.06 (s, 1H), 9.00 (s, 1H), 8.73 (s, 1H), 8.66 (s, 1H), 8.23 (d, *J* = 8.0 Hz, 1H), 7.83 (s, 1H), 7.67 (s, 2H), 7.64 (s, 1H), 7.61 – 7.54 (m, 2H), 7.52 (d, *J* = 9.2 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.37 (dd, *J* = 8.2, 3.7 Hz, 1H), 7.29 (s, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 7.15 – 7.06 (m, 1H), 6.96 – 6.91 (m, 1H), 6.79 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.41 (d, *J* = 2.2 Hz, 1H), 6.32 (s, 1H), 6.06 (s, 1H), 5.98 (s, 1H), 5.78 (d, *J* = 8.0 Hz, 1H), 5.68 – 5.56 (m, 1H), 5.49 (dd, *J* = 14.8, 6.7 Hz, 1H), 5.36 (dd, *J* = 11.8, 6.5 Hz, 1H), 5.28 (s, 1H), 5.25 (s, 1H), 5.20 (s, 2H), 5.13 (s, 1H), 4.93 (s, 1H), 4.69 (t, *J* = 6.6 Hz, 1H), 4.49 (s, 1H), 4.37 (d, *J* = 4.9 Hz, 1H), 4.31 (d, *J* = 11.8 Hz, 1H), 4.15 – 4.03 (m, 1H), 4.00 – 3.90 (m, 1H), 3.76 – 3.67 (m, 1H), 3.67 – 3.63 (m, 1H), 3.58 – 3.51 (m, 2H), 3.21 – 3.18 (m, 1H), 3.18 (d, *J* = 3.2 Hz, 1H), 2.64 (s, 3H), 2.21 – 2.09 (m, 1H), 1.98 – 1.88 (m, 1H), 1.80 – 1.72 (m, 1H), 1.72 – 1.60 (m, 2H), 1.60 – 1.53 (m, 1H), 1.31 (s, 2H), 1.29 (s, 1H), 1.08 (d, *J* = 6.3 Hz, 3H), 0.92 (d, *J* = 6.0 Hz, 3H), 0.89 – 0.86 (d, *J* = 6.0 Hz, 3H). ESI-TOF HRMS *m/z* 1603.5669 ([M + H]$^+$, [$C_{71}H_{88}Cl_2N_{16}O_{23}$ + H]$^+$ requires 1603.5658).

General procedure for the synthesis of 15–20 and 22–24:

A solution of CBP-vancomycin·2CF_3COOH (**2**, 12.6 mg, 6.7 μmol) in DMF/DMSO (1/1, 670 μL) was treated sequentially with the corresponding amine (1 M in DMF/DMSO = 1/1, 13.4 μL, 13.4 μmol, 2 equiv), N-methylmorpholine (distilled, 1 M in DMF/DMSO = 1/1, 40.2 μL, 40.2 μmol, 6 equiv), and HBTU (0.5 M in DMF/DMSO =1/1, 26.8 μL, 13.4 μmol, 2 equiv). The mixture was stirred at 5 °C for 4 h and quenched with the addition of H_2O (1 mL). The mixture was purified by semi-preparative reverse-phase HPLC (Nacalai Tesque, Inc., ARII-C18, 5 μm, 10 × 150 mm, 20–80% MeCN/H_2O–0.07% TFA gradient over 40 min, 3 mL/min) to afford the desired products as white solids.

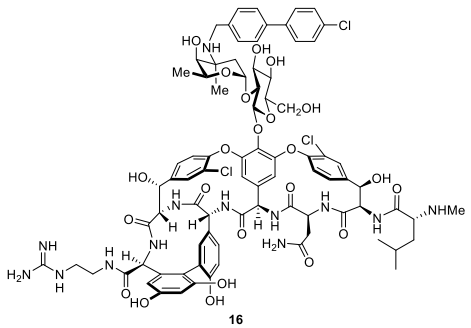


15

Compound **15** (8.5 mg, 61%, t_R = 13.1 min, >95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.33 (m, 1H), 9.07 (s, 1H), 9.03 (s, 1H), 8.72 – 8.65 (m ,1H), 8.52 (s, 1H), 8.23 (s, 1H), 8.05 (s, 1H), 7.89 – 7.83 (m, 1H), 7.73 (m, 4H), 7.64 (t, *J* = 6.0 Hz, 1H), 7.60 – 7.57 (m, 3H), 7.55 – 7.52 (m, 2H), 7.48 (t, *J* = 8.0 Hz, 2H), 7.34 (dd, *J* = 8.3, 3.2 Hz, 1H), 7.29 – 7.17 (m, 2H), 6.78 (m, 2H), 6.71 (d, *J* = 8.4 Hz, 1H), 6.38 (s, 1H), 6.24 (s, 1H), 5.94 – 5.82 (m, 1H), 5.77 (d, *J* = 7.9 Hz, 1H), 5.65 – 5.56 (m, 1H), 5.49 – 5.35 (m, 1H), 5.29 (d, *J* = 10.8 Hz, 2H), 5.25 – 5.16 (m, 2H), 4.96 (s, 1H), 4.77 – 4.63 (m, 1H), 4.56 – 4.42 (m, 1H), 4.35 (d, *J* = 5.1 Hz, 1H), 4.31 – 4.21 (m, 1H), 4.10 – 3.91 (m, 1H), 3.77 – 3.63 (m, 2H), 3.49 (s, 2H), 3.34 – 3.21 (m, 2H), 3.19 – 3.08 (m, 3H), 2.65 (s, 3H), 2.15 (s, 2H), 1.88 – 1.84 (m, 1H), 1.71 – 1.62 (m, 3H), 1.58 (d, *J* = 7.5 Hz, 1H), 1.52 – 1.48 (m, 3H), 1.14 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.86 (dd, *J* = 6.5, 2.6 Hz, 3H). ESI-TOF HRMS *m/z* 1746.5767 ($[M + H]^+$, $[C_{83}H_{94}Cl_3N_{13}O_{23} + H]^+$ requires 1746.5729).

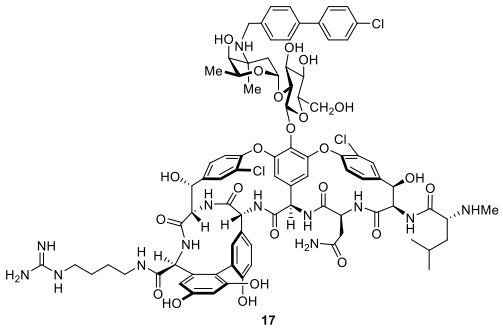
Scaled synthesis of compound **15**

A solution of CBP-vancomycin·2CF_3COOH (315 mg, 0.166 mmol) in DMF/DMSO (1/1, 17 mL) was treated sequentially with $H_2NCH_2CH_2CH_2NHC(NH_2)=NH_2^+$ ($G3^+$, 1 M in DMF/DMSO = 1/1, 0.33 mL, 0.33 mmol, 2 equiv), N-methylmorpholine (distilled, 1 M in DMF/DMSO = 1/1, 1.0 mL, 1.0 mmol, 6 equiv), and HBTU (0.5 M in DMF/DMSO =1/1, 0.67 mL, 0.33 mmol, 2 equiv). The mixture was stirred at 25 °C for 16 h and quenched with the addition of H_2O (2 mL). The mixture was purified by semi-preparative reverse-phase HPLC (Vydac 218TP1022-C18, 10 μm, 22 × 250 mm, 20–80% MeCN/H_2O–0.07% TFA gradient over 40 min, 10 mL/min, t_R = 14.6 min) to afford **15** (195 mg) as a white solid.



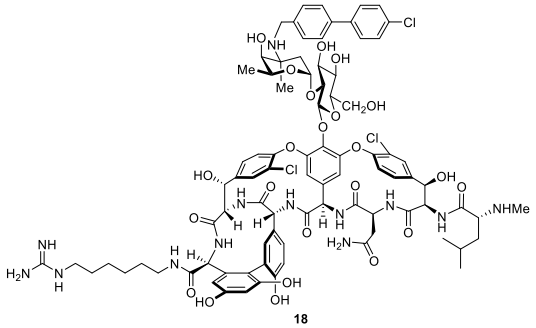
16

Compound **16** (8.4 mg, 60%, t_R = 12.8 min, 95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.37 (s, 1H), 9.17 (s, 1H), 9.08 (s, 1H), 9.04 (s, 1H), 9.00 (s, 1H), 8.76 (s, 1H), 8.70 (s, 1H), 8.52 (s, 1H), 8.22 (s, 1H), 8.13 (t, *J* = 5.9 Hz, 1H), 7.87 (d, *J* = 2.0 Hz, 1H), 7.78 – 7.70 (m, 4H), 7.58 (d, *J* = 8.0 Hz, 4H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 1H), 7.34 (dd, *J* = 8.3, 3.9 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.07 (s, 1H), 6.80 – 6.73 (m, 2H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.58 (s, 2H), 6.38 (d, *J* = 2.2 Hz, 1H), 6.23 (d, *J* = 2.1 Hz, 1H), 6.01 (d, *J* = 12.2 Hz, 1H), 5.91 (d, *J* = 6.0 Hz, 1H), 5.83 (s, 1H), 5.77 (d, *J* = 7.9 Hz, 1H), 5.63 (s, 1H), 5.37 (d, *J* = 7.7 Hz, 1H), 5.30 (s, 1H), 5.25 (s, 1H), 5.22 – 5.16 (m, 2H), 4.95 (s, 1H), 4.69 (q, *J* = 6.5 Hz, 1H), 4.47 (s, 1H), 4.38 (d, *J* = 5.3 Hz, 1H), 4.25 (d, *J* = 12.1 Hz, 2H), 4.13 (s, 1H), 4.09 – 4.01 (m, 2H), 3.96 (s, 1H), 3.79 – 3.62 (m, 2H), 3.59 (t, *J* = 8.5 Hz, 1H), 3.54 (s, 1H), 3.48 (s, 2H), 3.31 – 3.27 (m, 4H), 2.64 (s, 3H), 2.54 (s, 1H), 2.21 – 2.09 (m, 2H), 1.91 – 1.79 (m, 1H), 1.73 – 1.66 (m, 1H), 1.66 – 1.60 (m, 1H), 1.60 – 1.54 (m, 1H), 1.52 (s, 2H), 1.48 (s, 1H), 1.14 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.86 (t, *J* = 4.4 Hz, 3H). ESI-TOF HRMS *m/z* 1732.5573 ($[M + H]^+$, $[C_{82}H_{92}Cl_3N_{13}O_{23} + H]^+$ requires 1732.5567).



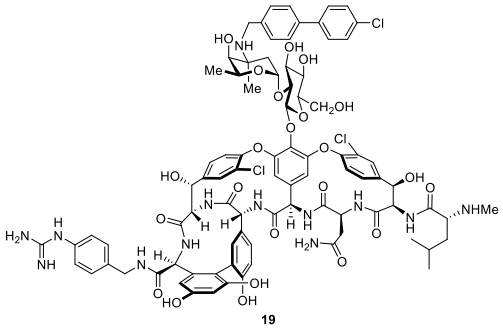
17

Compound **17** (8.8 mg, 62%, t_R = 13.1 min, 95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.35 (s, 1H), 9.20 (s, 1H), 9.03 (s, 1H), 9.00 (s, 1H), 8.77 (s, 1H), 8.73 – 8.65 (m, 1H), 8.47 (s, 1H), 8.22 (s, 1H), 7.97 – 7.93 (m, 1H), 7.87 (s, 1H), 7.73 (dd, *J* = 11.4, 8.4 Hz, 4H), 7.63 – 7.56 (m, 3H), 7.54 (d, *J* = 8.5 Hz, 3H), 7.49 (d, *J* = 8.3 Hz, 2H), 7.33 (dd, *J* = 8.3, 3.8 Hz, 1H), 7.22 (d, *J* = 8.7 Hz, 2H), 7.05 (s, br, 1H), 6.81 – 6.73 (m, 2H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.24 (d, *J* = 2.1 Hz, 1H), 6.09 – 5.89 (m, 1H), 5.77 (d, *J* = 7.9 Hz, 1H), 5.61 (s, 1H), 5.37 (d, *J* = 7.3 Hz, 1H), 5.33 – 5.28 (m, 1H), 5.26 (s, 1H), 5.19 (dt, *J* = 7.8, 4.7 Hz, 2H), 5.02 – 4.85 (m, 1H), 4.69 (q, *J* = 6.5 Hz, 1H), 4.47 (s, 1H), 4.37 (d, *J* = 5.4 Hz, 1H), 4.24 (d, *J* = 11.9 Hz, 2H), 4.10 – 4.00 (m, 2H), 3.96 (s, 1H), 3.74 – 3.64 (m, 2H), 3.59 (t, *J* = 8.5 Hz, 2H), 3.31 – 3.26 (m, 2H), 3.20 (dd, *J* = 13.3, 6.6 Hz, 1H), 3.15 – 3.07 (m, 3H), 2.93 (s, 1H), 2.65 (s, 3H), 2.20 – 2.08 (m, 2H), 1.93 – 1.79 (m, 1H), 1.74 – 1.66 (m, 1H), 1.66 – 1.60 (m, 1H), 1.60 – 1.54 (m, 1H), 1.52 (s, 3H), 1.50 – 1.43 (m, 4H), 1.14 (d, *J* = 6.2 Hz, 3H), 0.91 (d, *J* = 6.2 Hz, 3H), 0.89 – 0.82 (m, 3H). ESI-TOF HRMS *m/z* 1760.5835 ($[M + H]^+$, $[C_{84}H_{96}Cl_3N_{13}O_{23} + H]^+$ requires 1760.5880).



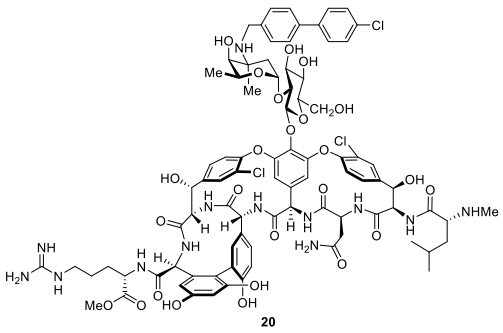
18

Compound **18** (10.0 mg, 70%, t_R = 13.5 min, >95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.34 (s, 1H), 9.27 (s, 1H), 9.01 (s, 3H), 8.79 (s, 1H), 8.72 – 8.60 (m, 1H), 8.45 (s, 1H), 8.22 (s, 1H), 7.93 – 7.83 (m, 2H), 7.76 – 7.69 (m, 4H), 7.63 (t, *J* = 5.7 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 3H), 7.54 (d, *J* = 8.4 Hz, 3H), 7.48 (t, *J* = 7.7 Hz, 2H), 7.33 (dd, *J* = 8.4, 3.6 Hz, 1H), 7.29 – 7.22 (m, 1H), 7.21 (s, 1H), 7.05 (s, br, 1H), 6.80 – 6.73 (m, 1H), 6.70 (d, *J* = 8.9 Hz, 2H), 6.58 (s, br, 3H), 6.37 (d, *J* = 2.3 Hz, 1H), 6.24 (d, *J* = 2.2 Hz, 1H), 6.02 (s, 1H), 5.92 (s, 1H), 5.84 (s, 1H), 5.77 (d, *J* = 7.8 Hz, 1H), 5.67 – 5.56 (m, 1H), 5.46 – 5.35 (m, 1H), 5.30 (t, *J* = 6.3 Hz, 1H), 5.26 (s, 1H), 5.23 – 5.08 (m, 2H), 4.95 (s, 1H), 4.76 – 4.64 (m, 1H), 4.46 (d, *J* = 5.1 Hz, 1H), 4.37 (d, *J* = 5.5 Hz, 1H), 4.23 (d, *J* = 12.0 Hz, 2H), 4.06 (s, 2H), 4.00 – 3.87 (m, 1H), 3.78 – 3.63 (m, 3H), 3.59 (t, *J* = 8.5 Hz, 2H), 3.54 (s, 2H), 3.31 – 3.26 (m, 2H), 3.17 (s, 2H), 3.13 – 3.06 (m, 3H), 2.65 (s, 3H), 2.14 (s, 2H), 1.91 – 1.79 (m, 1H), 1.73 – 1.66 (m, 1H), 1.63 (t, *J* = 6.5 Hz, 1H), 1.57 (dd, *J* = 10.3, 4.5 Hz, 1H), 1.52 (s, 2H), 1.48 (s, 2H), 1.46 (d, *J* = 7.5 Hz, 3H), 1.32 – 1.25 (m, 4H), 1.16 – 1.09 (m, 3H), 0.91 (d, *J* = 6.1 Hz, 3H), 0.86 (dd, *J* = 6.4, 2.6 Hz, 3H). ESI-TOF HRMS *m/z* 1788.6130 ($[M + H]^+$, $[C_{86}H_{100}Cl_3N_{13}O_{23} + H]^+$ requires 1788.6193).



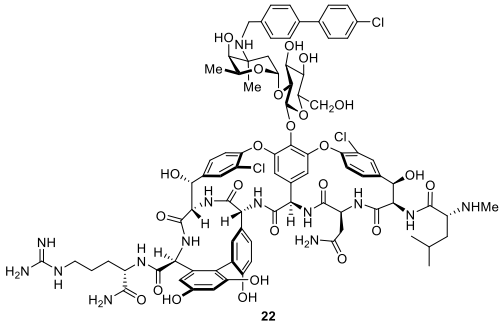
19

Compound **19** (9.0 mg, 63%, t_R = 13.4 min, 95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.93 (s, 1H), 9.23 (s, 1H), 9.03 (s, 2H), 8.78 (s, 1H), 8.70 (s, 1H), 8.53 – 8.47 (m, 2H), 8.23 (s, 1H), 7.92 – 7.84 (m, 1H), 7.78 – 7.71 (m, 4H), 7.59 (d, *J* = 7.8 Hz, 3H), 7.56 – 7.54 (m, 3H), 7.52 (s, 3H), 7.49 (d, *J* = 9.0 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 3H), 7.30 – 7.22 (m, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.05 (s, 1H), 6.87 – 6.76 (m, 2H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.39 (d, *J* = 2.2 Hz, 1H), 6.31 (d, *J* = 2.2 Hz, 1H), 5.79 (d, *J* = 7.8 Hz, 1H), 5.64 (s, 1H), 5.38 (d, *J* = 7.5 Hz, 1H), 5.33 – 5.28 (m, 1H), 5.27 (s, 1H), 5.25 – 5.16 (m, 2H), 4.96 (s, 1H), 4.74 – 4.66 (m, 1H), 4.53 – 4.44 (m, 3H), 4.39 – 4.30 (m, 1H), 4.28 (d, *J* = 12.2 Hz, 1H), 4.10 – 4.01 (m, 2H), 3.97 (s, 1H), 3.50 (s, 2H), 3.34 – 3.25 (m, 2H), 2.65 (s, 3H), 2.20 – 2.11 (m, 2H), 1.91 – 1.81 (m, 1H), 1.74 – 1.67 (m, 1H), 1.67 – 1.61 (m, 1H), 1.61 – 1.55 (m, 1H), 1.52 (s, 2H), 1.49 (s, 1H), 1.20 – 1.10 (m, 3H), 0.92 (d, *J* = 6.2 Hz, 3H), 0.87 (dd, *J* = 6.4, 2.4 Hz, 3H). ESI-TOF HRMS *m/z* 1794.5762 ($[M + H]^+$, $[C_{87}H_{94}Cl_3N_{13}O_{23} + H]^+$ requires 1794.5729).



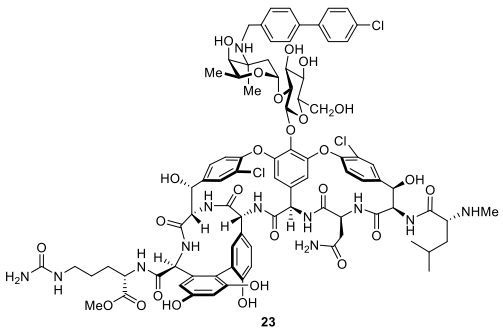
20

Compound **20** (8.9 mg, 61%, t_R = 12.7 min, >95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.33 (s, 2H), 9.02 (s, 2H), 8.98 (s, 1H), 8.83 (s, 1H), 8.68 (s, 1H), 8.59 (s, 1H), 8.48 (d, *J* = 7.4 Hz, 1H), 8.23 (s, 1H), 7.88 (s, 1H), 7.73 (d, *J* = 6.1 Hz, 2H), 7.72 (d, *J* = 5.8 Hz, 2H), 7.61 – 7.56 (m, 4H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.49 (t, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 2.6 Hz, 1H), 7.30 – 7.20 (m, 2H), 6.84 (d, *J* = 10.8 Hz, 1H), 6.81 – 6.75 (m, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.63 (s, 2H), 6.41 (d, *J* = 2.2 Hz, 1H), 6.34 (d, *J* = 2.1 Hz, 1H), 6.06 (s, 1H), 5.96 (s, 1H), 5.88 (s, 1H), 5.78 (d, *J* = 7.9 Hz, 1H), 5.72 – 5.55 (m, 1H), 5.41 (d, *J* = 7.1 Hz, 1H), 5.29 (s, 1H), 5.22 – 5.15 (m, 3H), 4.96 (s, 1H), 4.70 (q, *J* = 6.2 Hz, 1H), 4.52 (d, *J* = 5.6 Hz, 1H), 4.49 (s, 1H), 4.32 (q, *J* = 7.6 Hz, 1H), 4.24 (d, *J* = 12.2 Hz, 1H), 4.10 – 4.00 (m, 2H), 4.00 – 3.92 (m, 2H), 3.69 (s, 3H), 3.67 (s, 2H), 3.49 (s, 2H), 3.29 (s, 1H), 3.12 – 3.01 (m, 2H), 2.65 (s, 3H), 2.18 – 2.11 (m, 2H), 1.91 – 1.82 (m, 1H), 1.82 – 1.74 (m, 1H), 1.72 – 1.65 (m, 2H), 1.65 – 1.61 (m, 1H), 1.61 – 1.55 (m, 1H), 1.51 (s, 2H), 1.49 (s, 3H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.91 (d, *J* = 6.0 Hz, 3H), 0.86 (d, *J* = 6.1 Hz, 3H). ESI-TOF HRMS *m/z* 1818.5902 ($[M + H]^+$, $[C_{86}H_{98}Cl_3N_{13}O_{25} + H]^+$ requires 1818.5935).



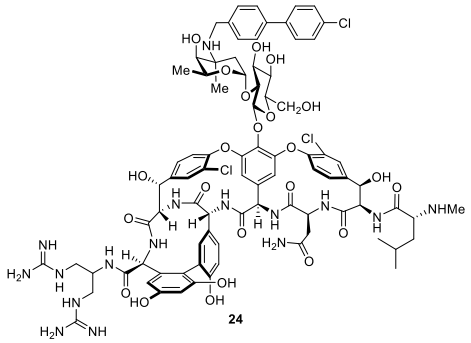
22

Compound **22** (8.8 mg, 61%, t_R = 12.5 min, >95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.37 (s, 1H), 9.20 (s, 1H), 9.05 (s, 1H), 8.98 (s, 1H), 8.87 – 8.67 (m, 2H), 8.59 (s, 1H), 8.21 (s, 1H), 7.99 – 7.83 (m, 2H), 7.77 – 7.69 (m, 4H), 7.62 – 7.56 (m, 3H), 7.53 (d, *J* = 7.9, 3H), 7.49 (t, *J* = 8.1 Hz, 2H), 7.40 – 7.31 (m, 2H), 7.31 – 7.20 (m, 4H), 7.18 (s, 1H), 7.05 (s, 2H), 6.85 (d, *J* = 11.0 Hz, 1H), 6.82 – 6.76 (m, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.59 (s, 4H), 6.40 (d, *J* = 2.2 Hz, 1H), 6.26 (d, *J* = 2.2 Hz, 1H), 6.01 (d, *J* = 11.8 Hz, 1H), 5.91 (s, 1H), 5.84 (s, 1H), 5.78 (d, *J* = 7.8 Hz, 1H), 5.66 – 5.59 (m, 1H), 5.41 (d, *J* = 7.1 Hz, 1H), 5.37 (d, *J* = 7.8 Hz, 1H), 5.30 (dd, *J* = 9.3, 3.8 Hz, 1H), 5.25 – 5.09 (m, 3H), 4.95 (s, 1H), 4.70 (q, *J* = 6.2 Hz, 1H), 4.54 – 4.46 (m, 1H), 4.43 (d, *J* = 5.3 Hz, 1H), 4.32 (q, *J* = 7.5 Hz, 1H), 4.29 – 4.22 (m, 1H), 4.14 – 4.02 (m, 2H), 3.99 – 3.91 (m, 1H), 3.78 – 3.69 (m, 1H), 3.67 (s, 2H), 3.59 (t, *J* = 8.5 Hz, 1H), 3.54 (d, *J* = 8.7 Hz, 1H), 3.51 – 3.46 (m, 2H), 3.29 (s, 1H), 3.15 – 3.05 (m, 2H), 2.64 (s, 3H), 2.15 (s, 2H), 1.88 – 1.84 (m, 1H), 1.81 – 1.73 (m, 1H), 1.73 – 1.69 (m, 1H), 1.66 – 1.54 (m, 3H), 1.51 (s, 3H), 1.49 – 1.45 (m, 2H), 1.18 – 1.09 (m, 3H), 0.96 – 0.89 (m, 3H), 0.86 (dd, *J* = 6.4, 2.5 Hz, 3H). ESI-TOF HRMS *m/z* 1803.5951 ($[M + H]^+$, $[C_{85}H_{97}Cl_3N_{14}O_{24} + H]^+$ requires 1803.5938).



23

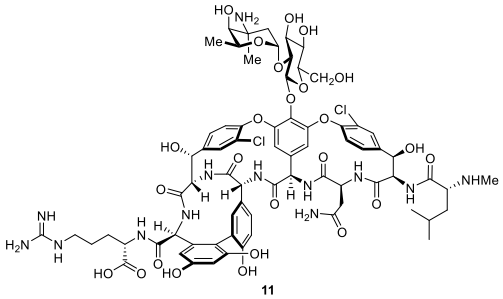
Compound **23** (7.5 mg, 55%, t_R = 14.8 min, 95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.36 (s, 1H), 9.18 (s, 1H), 9.00 (s, 1H), 8.96 (s, 1H), 8.93 (s, 1H), 8.73 (s, 2H), 8.55 (s, 2H), 8.36 (d, *J* = 7.4 Hz, 1H), 8.21 (s, 1H), 7.89 (s, 1H), 7.76 – 7.74 (m, 2H), 7.74 – 7.72 (m, 2H), 7.64 (s, 1H), 7.58 (dd, *J* = 8.1, 2.2 Hz, 3H), 7.56 – 7.53 (m, 3H), 7.48 (t, *J* = 8.1 Hz, 2H), 7.34 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 7.23 (d, *J* = 3.4 Hz, 1H), 7.09 (s, 1H), 6.83 – 6.76 (m, 2H), 6.75 (s, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.57 (s, 3H), 6.40 (d, *J* = 2.3 Hz, 1H), 6.34 (d, *J* = 2.2 Hz, 1H), 6.02 (s, 1H), 5.96 (s, 2H), 5.83 (s, 1H), 5.78 (d, *J* = 7.8 Hz, 1H), 5.65 (s, 1H), 5.61 (s, 1H), 5.44 – 5.36 (m, 3H), 5.30 (s, 1H), 5.23 – 5.16 (m, 3H), 4.95 (s, 1H), 4.71 (q, *J* = 6.0 Hz, 1H), 4.54 (d, *J* = 5.9 Hz, 1H), 4.48 (s, 1H), 4.32 (q, *J* = 7.5 Hz, 1H), 4.23 (d, *J* = 11.7 Hz, 2H), 4.13 – 4.02 (m, 3H), 4.02 – 3.95 (m, 2H), 3.76 – 3.71 (m, 1H), 3.68 (s, 3H), 3.62 – 3.57 (m, 1H), 3.29 (d, *J* = 8.9 Hz, 2H), 2.97 – 2.91 (m, 2H), 2.65 (s, 3H), 2.20 – 2.15 (m, 2H), 1.90 – 1.82 (m, 1H), 1.78 – 1.68 (m, 2H), 1.68 – 1.62 (m, 2H), 1.62 – 1.55 (m, 2H), 1.52 (s, 1H), 1.48 (s, 2H), 1.43 – 1.35 (m, 2H), 1.15 (dd, *J* = 6.4, 2.8 Hz, 3H), 0.92 (d, *J* = 6.2 Hz, 3H), 0.87 (dd, *J* = 6.5, 2.5 Hz, 3H). ESI-TOF HRMS *m/z* 1819.5785 ($[M + H]^+$, $[C_{86}H_{97}Cl_3N_{12}O_{26} + H]^+$ requires 1819.5775).



24

Compound **24** (4.4 mg, 29%, t_R = 12.1 min, >95% HPLC purity): ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.39 (s, 1H), 9.15 (s, 1H), 9.08 (s, 1H), 8.76 (s, 1H), 8.68 (s, 1H), 8.23 (d, *J* = 7.6 Hz, 2H), 7.85 (s, 1H), 7.76 – 7.71 (m, 4H), 7.65 (s, 1H), 7.60 – 7.57 (m, 3H), 7.56 – 7.53 (m, 3H), 7.53 – 7.49 (m, 3H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.31 (s, 1H), 7.28 (d, *J* = 8.2 Hz, 1H), 6.95 (d, *J* = 10.9 Hz, 1H), 6.80 (d, *J* = 8.5 Hz, 1H), 6.72 (d, *J* = 8.5 Hz, 1H), 6.41 (d, *J* = 2.3 Hz, 1H), 6.32 (d, *J* = 2.2 Hz, 1H), 6.10 (s, 1H), 6.04 (s, 1H), 5.86 (s, 1H), 5.79 (d, *J* = 7.8 Hz, 1H), 5.65 (s, 1H), 5.61 (s, 1H), 5.45 – 5.37 (m, 1H), 5.32 – 5.25 (m, 2H), 5.25 – 5.17 (m, 2H), 4.95 (s, 1H), 4.70 (t, *J* = 6.4 Hz, 1H), 4.51 (s, 1H), 4.37 (d, *J* = 4.9 Hz, 1H), 4.32 (d, *J* = 11.6 Hz, 1H), 4.11 (d, *J* = 7.2 Hz, 1H), 4.04 – 3.93 (m, 1H), 3.67 (s, 2H), 3.50 (s, 2H), 2.65 (s, 3H), 2.19 – 2.12 (m, 2H), 1.92 – 1.83 (m, 1H), 1.72 – 1.62 (m, 1H), 1.62 – 1.55 (m, 1H), 1.53 (s, 1H), 1.50 (s, 2H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.92 (d, *J* = 6.2 Hz, 3H), 0.87 (dd, *J* = 6.5, 2.7 Hz, 3H). ESI-TOF HRMS *m/z* 1803.5835 ($[M + H]^+$, $[C_{84}H_{97}Cl_3N_{16}O_{23} + H]^+$ requires 1803.6051).

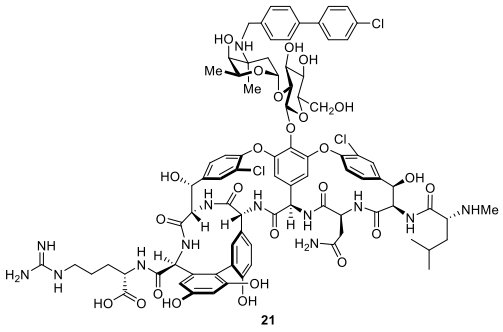
Synthesis of **11**



11

Compound **10** (5.0 mg, 2.5 μmol) in H_2O/THF (1/1, 250 μL) was treated with LiOH (0.6 mg, 25 μmol, 10 equiv) and the mixture was stirred at 25 °C for 30 min and quenched with the addition of H_2O (1 mL). THF was removed under a gentle stream of N_2 and the mixture was purified by semi-preparative reverse-phase HPLC (Nacalai Tesque, Inc., ARII-C18, 5 μm, 10 × 150 mm, 1–40% MeCN/H_2O–0.07% TFA gradient over 40 min, 3 mL/min, t_R = 19.9 min) to afford **11** (3.5 mg, 70%, >95% HPLC purity) as a white solid: ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.27 (s, 1H), 8.97 (s, 2H), 8.94 (s, 1H), 8.69 (s, 1H), 8.57 (s, 1H), 8.32 (dd, *J* = 8.3, 5.4 Hz, 1H), 7.89 – 7.82 (m, 1H), 7.64 (s, 3H), 7.56 (t, *J* = 6.9 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.39 (t, *J* = 5.9 Hz, 1H), 7.34 (dd, *J* = 8.3, 2.9 Hz, 1H), 7.27 – 7.17 (m, 2H), 7.06 (s, 1H), 6.85 (d, *J* = 11.5 Hz, 1H), 6.80 – 6.74 (m, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.56 (s, 4H), 6.42 – 6.36 (m, 2H), 5.98 (dd, *J* = 9.3, 4.1 Hz, 1H), 5.91 (t, *J* = 5.2 Hz, 1H), 5.77 (d, *J* = 7.9 Hz, 1H), 5.66 – 5.54 (m, 1H), 5.47 (t, *J* = 8.8 Hz, 1H), 5.40 – 5.30 (m, 1H), 5.25 (d, *J* = 8.5 Hz, 1H), 5.23 – 5.18 (m, 2H), 5.18 – 5.15 (m, 1H), 5.13 (s, 1H), 4.93 (s, 1H), 4.75 – 4.63 (m, 1H), 4.57 – 4.50 (m, 1H), 4.46 (d, *J* = 5.5 Hz, 1H), 4.28 (td, *J* = 8.4, 5.5 Hz, 1H), 4.26 – 4.15 (m, 2H), 4.07 – 3.95 (m, 1H), 3.94 (s, 1H), 3.80 – 3.66 (m, 1H), 3.64 (q, *J* = 8.0 Hz, 1H), 3.57 – 3.50 (m, 1H), 3.27 (s, 2H), 3.18 (s, 1H), 3.12 – 3.01 (m, 2H), 3.01 – 2.96 (m, 1H), 2.64 (d, *J* = 6.2 Hz, 3H), 2.20 – 2.09 (m, 1H), 1.95 – 1.86 (m, 1H), 1.83 – 1.76 (m, 1H), 1.76 – 1.70 (m, 1H), 1.70 – 1.60 (m, 3H), 1.60 – 1.53 (m, 1H), 1.53 – 1.46 (m, 2H), 1.29 (s, 2H), 1.27 (s, 1H), 1.07 (d, *J* = 6.0 Hz, 3H), 0.91 (dd, *J* = 6.3, 1.8 Hz, 3H), 0.86 (dd, *J* = 6.5, 2.6 Hz, 3H). ESI-TOF HRMS *m/z* 1604.5327 ($[M + H]^+$, $[C_{72}H_{87}Cl_2N_{13}O_{25} + H]^+$ requires 1604.5386).

Synthesis of **21**

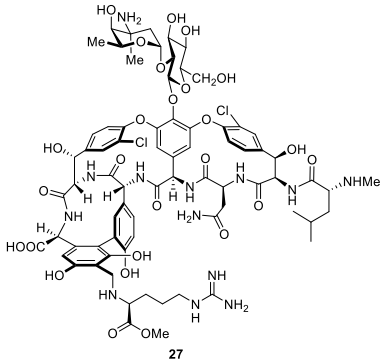


21

Compound **20** (2.5 mg, 1.25 μmol) in H_2O/THF (1/1, 125 μL) was treated with LiOH (0.3 mg, 12.5 μmol, 10 equiv) and the mixture was stirred at 25 °C for 30 min and quenched with the addition of H_2O (1 mL). THF was removed under a gentle stream of N_2 and the mixture was purified by semi-preparative reverse-phase HPLC (Nacalai Tesque, Inc., ARII-C18, 5 μm, 10 × 150 mm, 20–80% MeCN/H_2O–0.07% TFA gradient over 40 min, 3 mL/min, t_R = 13.3 min) to

afford **21** (2.3 mg, 92%, >95% HPLC purity) as a white solid: ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.28 (s, 1H), 8.99 (s, 1H), 8.96 (s, 1H), 8.67 (s, 1H), 8.58 (s, 1H), 8.27 (s, 1H), 7.87 (s, 1H), 7.77 – 7.69 (m, 3H), 7.69 – 7.61 (m, 1H), 7.61 – 7.56 (m, 2H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.52 – 7.43 (m, 3H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.23 (s, 1H), 6.85 (d, *J* = 10.7 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 6.39 (s, 1H), 6.36 (s, 1H), 5.95 (s, 1H), 5.82 (s, 1H), 5.77 (s, 1H), 5.67 – 5.55 (m, 1H), 5.37 (d, *J* = 5.3 Hz, 1H), 5.29 (d, *J* = 9.3 Hz, 1H), 5.22 – 5.12 (m, 3H), 4.93 (s, 1H), 4.74 – 4.64 (m, 1H), 4.49 (d, *J* = 12.0 Hz, 2H), 4.24 (s, 2H), 4.12 (t, *J* = 5.4 Hz, 1H), 4.04 (s, 1H), 3.75 – 3.64 (m, 2H), 3.64 – 3.56 (m, 2H), 3.11 – 3.04 (m, 2H), 2.61 (s, 3H), 2.18 – 2.10 (m, 1H), 1.91 – 1.81 (m, 1H), 1.81 – 1.74 (m, 1H), 1.71 – 1.61 (m, 2H), 1.51 (s, 3H), 1.47 (s, 1H), 1.13 (d, *J* = 6.1 Hz, 3H), 0.91 (d, *J* = 6.1 Hz, 3H), 0.86 (d, *J* = 6.1 Hz, 3H). ESI-TOF HRMS *m/z* 1804.5828 ($[M + H]^+$, $[C_{85}H_{96}Cl_3N_{13}O_{25} + H]^+$ requires 1804.5784).

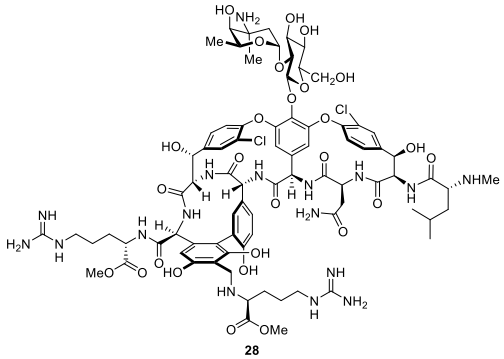
Synthesis of **27**



27

A solution of vancomycin hydrochloride (10.0 mg, 6.7 μmol) and L-arginine methyl ester dihydrochloride (13.6 mg, 50 μmol, 7.5 equiv) in H_2O (50 μL) was treated sequentially with Na_2CO_3 solution (3 M in H_2O, 25 μL) and formaldehyde (37% in H_2O, 0.5 μL, 6.7 μmol, 1 equiv). The mixture was stirred at 5 °C for 16 h and quenched with the addition of H_2O (1 mL). The mixture was purified by semi-preparative reverse-phase HPLC (Nacalai Tesque, Inc., ARII-C18, 5 μm, 10 × 150 mm, 1–40% MeCN/H_2O–0.07% TFA gradient over 40 min, 3 mL/min, t_R = 20.4 min) to afford **27** (4.4 mg, 31%, >95% HPLC purity) as a white solid: ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.24 (s, 1H), 9.08 (s, 1H), 8.98 (s, 1H), 8.79 (s, 1H), 8.64 (s, 1H), 7.84 (s, 1H), 7.65 (s, 3H), 7.53 (s, 2H), 7.47 (d, *J* = 8.4 Hz, 1H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.22 (d, *J* = 8.1 Hz, 1H), 7.13 (s, 1H), 6.86 (s, 1H), 6.81 – 6.71 (m, 2H), 6.61 – 6.31 (m, 1H), 5.98 (d, *J* = 4.3 Hz, 2H), 5.75 (d, *J* = 7.4 Hz, 1H), 5.71 (s, 1H), 5.47 (d, *J* = 6.5 Hz, 1H), 5.37 (s, 1H), 5.26 (s, 2H), 5.14 (s, 3H), 4.69 (q, *J* = 6.7 Hz, 1H), 4.45 (t, *J* = 8.5 Hz, 2H), 4.14 (s, 2H), 4.08 – 3.97 (m, 2H), 3.75 (s, 2H), 3.18 (d, *J* = 5.6 Hz, 2H), 3.10 (s, 3H), 2.61 (s, 3H), 2.21 – 2.11 (m, 1H), 2.02 (d, *J* = 4.9 Hz, 1H), 1.95 – 1.86 (m, 1H), 1.73 (d, *J* = 12.9 Hz, 1H), 1.70 – 1.61 (m, 2H), 1.61 – 1.50 (m, 2H), 1.50 – 1.43 (m, 1H), 1.31 (m, 3H), 1.07 (d, *J* = 6.1 Hz, 3H), 0.93 (d, *J* = 5.9 Hz, 3H), 0.88 (d, *J* = 6.0 Hz, 3H). ESI-TOF HRMS *m/z* 1648.5629 ($[M + H]^+$, $[C_{74}H_{91}Cl_2N_{13}O_{26} + H]^+$ requires 1648.5648).

Synthesis of **28**



28

Compound **27** (3.9 mg, 2.0 μmol) in DMF/DMSO (1/1, 200 μL) was treated sequentially with L-arginine methyl ester dihydrochloride (1.0 mg, 4.0 μmol, 2 equiv), N-methylmorpholine (distilled, 1 M in DMF/DMSO = 1/1, 12 μL, 12 μmol, 6 equiv), and HBTU (0.5 M in DMF/DMSO =1/1, 8 μL, 4.0 μmol, 2 equiv). The mixture was stirred at 5 °C for 16 h and quenched with the addition of H_2O (1 mL). The mixture was purified by semi-preparative reverse-phase HPLC (Nacalai Tesque, Inc., ARII-C18, 5 μm, 10 × 150 mm, 1–40% MeCN/H_2O–0.07% TFA gradient over 40 min, 3 mL/min, t_R = 19.7 min) to afford **28** (2.6 mg, 54%, >95% HPLC purity) as white solid: ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.27 (s, 1H), 9.34 (s, 1H), 9.25 (s, 1H), 9.03 (s, 1H), 8.95 (s, 1H), 8.79 (s, 2H), 8.60 (s, 1H), 8.43 (s, 1H), 7.84 (d, *J* = 6.4 Hz, 1H), 7.66 (s, 4H), 7.52 (t, *J* = 9.8 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.32 (d, *J* = 8.3 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 1H), 7.23 (d, *J* = 8.3 Hz, 1H), 7.18 (s, 1H), 6.98 (s, 1H), 6.93 (s, 1H), 6.85 (s, 1H), 6.79 (s, 1H), 6.62 (s, 1H), 5.98 (s, 1H), 5.94 (s, 1H), 5.75 (d, *J* = 7.1 Hz, 1H), 5.72 – 5.62 (m, 1H), 5.47 (s, 1H), 5.33 (d, *J* = 7.3 Hz, 1H), 5.29 – 5.19 (m, 2H), 5.16 (d, *J* = 11.9 Hz, 2H), 5.13 (s, 1H), 4.83 (s, 1H), 4.68 (q, *J* = 7.9 Hz, 1H), 4.54 (d, *J* = 5.9 Hz, 1H), 4.48 (s, 1H), 4.41 (q, *J* = 7.9 Hz, 1H), 4.16 (s, 3H), 4.09 – 3.99 (m, 3H), 3.97 – 3.78 (m, 3H), 3.74 (s, 4H), 3.67 (s, 3H), 3.66 – 3.61 (m, 2H), 3.54 (d, *J* = 8.4 Hz, 2H), 3.27 (s, 2H), 3.18 (s, 2H), 3.11 – 3.06 (m, 3H), 3.06 – 3.00 (m, 2H), 2.59 (s, 3H), 2.17 – 1.99 (m, 1H), 1.90 (d, *J* = 9.3 Hz, 1H), 1.84 – 1.73 (m, 1H), 1.73 – 1.69 (m, 1H), 1.68 – 1.62 (m, 2H), 1.54 – 1.47 (m, 3H), 1.30 (s, 2H), 1.27 (s, 1H), 1.10 – 1.03 (m, 3H), 0.93 (d, *J* = 5.8 Hz, 3H), 0.87 (d, *J* = 6.0 Hz, 3H). ESI-TOF HRMS *m/z* 1818.6778 ($[M + H]^+$, $[C_{81}H_{105}Cl_2N_{17}O_{27} + H]^+$ requires 1818.6815).

II. *In vitro* antimicrobial assays[S4]

One day before experiments were run, fresh cultures of vancomycin-sensitive *Staphlococcus aureus* (VSSA strain ATCC 25923), methicillin and oxacillin-resistant *Staphlococcus aureus* (MRSA strain ATCC 43300), vancomycin-resistant *Enterococcus faecalis* (VanA VRE, BM4166 and ATCC BAA-2573), *Enterococcus faecium* (VanA VRE, ATCC BAA-2317 and TX-2465), vancomycin-resistant *Enterococcus faecalis* (VanB VRE, strain ATCC 51299), *Escherichia coli* (ATCC 25922), *Acinetobacter baumannii* (ATCC BAA-1710), *Pseudomonas aeruginosa* (ATCC 15442), *Klebsiella pneumoniae* (ATCC 700603) were inoculated and grown in an orbital shaker at 37 °C in 100% Mueller-Hinton broth (VSSA, MRSA and VanB VRE), 100% brain-heart infusion broth (VanA VRE, *A. baumannii* and *K. pneumoniae*) or 100% Luria broth (*E. coli* and *P. aeruginosa*). After 24 h, the bacterial stock solutions were serial diluted with the culture medium (10% Mueller-Hinton broth for VSSA, MRSA and VanB VRE or 10% brain-heart infusion broth for VanA VRE *A. baumannii* and *K. pneumoniae* or 10% Luria Broth for *E. coli* and *P. aeruginosa*, containing 0.002% Tween-80) to achieve a turbidity equivalent to a 1:100 dilution of a 0.5 M McFarland solution. This diluted bacterial stock solution was then inoculated in a 96-well flat-bottom non-treated microtiter plate (Corning 3370), supplemented with serial diluted aliquots of the antibiotic solution in DMSO (4 μL), to achieve a total assay volume of 0.1 mL. The plate was then incubated at 37 °C for 18 h, after which minimal inhibitory concentrations (MICs) were determined by monitoring the cell growth (observed as a pellet) in the wells. The lowest concentration of antibiotic (in μg/mL) capable of eliminating cell growth in the wells is the reported MIC value. The reported MIC values for the vancomycin analogues were determined against vancomycin as a standard in the first well.

Table S2. Antimicrobial activity of equimolar mixtures of CBP-vancomycin (**2**) and C-terminus vancomycin analogues (**5** and **9**) against VanA *E. faecalis* and VanA *E. faecium*, present alongside individual activity of compounds **2**, **5**, **9**, **15**, **19**, MIC (μg/mL).

Compound	VanA *E. faecalis*	VanA *E. faecium*
	BM 4166	ATCC BAA-2317
CBP-vancomycin (**2**)	5	2.5
G3-vancomycin (**5**)	16	4
G3-CBP-vancomycin (**15**)	0.6	0.3
CBP-vancomycin (**2**) + G3-vancomycin (**5**)	5 + 5	2.5 + 2.5
GBn-vancomycin (**9**)	16	4
GBn-CBP-vancomycin (**19**)	0.6	0.3
CBP-vancomycin (**2**) + GBn-vancomycin (**9**)	5 + 5	2.5 + 2.5

Although all of the analogues tested exhibited slightly less potency against VanA *E. faecalis* (BM 4166) compared with VanA *E. faecium* (ATCC BAA-2317), the same results were observed where the equimolar mixtures of the singly modified vancomycins did not display the enhanced potency

found in G3-CBP-vancomycin (**15**) and GBn-CBP-vancomycin (**19**), exhibiting antimicrobial activity only at the level of the most potent compound in the mixture (CBP-vancomycin, **2**).

Table S3. Antimicrobial activity of vancomycin (**1**), C-terminus vancomycin analogues (**5** and **9**) and their CBP derivatives (**2**, **15** and **19**) against Gram-negative pathogens in full strength broth and 10-fold reduced strength broth, MIC (μg/mL).

Full strength broth

Compound	*A. baumannii*	*K. pneumoniae*	*E. coli*	*P. aeruginosa*
	ATCC BAA-1710	ATCC 700603	ATCC 25922	ATCC 15442
vancomycin (**1**)	>125	>125	>125	>125
G3-vancomycin (**5**)	>125	>125	>125	>125
GBn-vancomycin (**9**)	>125	>125	>125	>125
CBP-vancomycin (**2**)	>125	>125	>125	>125
G3-CBP-vancomycin (**15**)	>125	>125	>125	>125
GBn-CBP-vancomycin (**19**)	>125	>125	>125	>125

10-fold reduced strength broth

Compound	*A. baumannii*	*K. pneumoniae*	*E. coli*	*P. aeruginosa*
	ATCC BAA-1710	ATCC 700603	ATCC 25922	ATCC 15442
vancomycin (**1**)	63	125	16	125
G3-vancomycin (**5**)	2	31	1	4
GBn-vancomycin (**9**)	2	16	1	2
CBP-vancomycin (**2**)	32	>125	>125	>125
G3-CBP-vancomycin (**15**)	8	64	32	16
GBn-CBP-vancomycin (**19**)	16	125	32	32

III. Site specificity of guanidinium-modified analogues

In order to investigate if the guanidinium modification on vancomycin is site-specific like the trimethylammonium cation modification, analogue **27** bearing a guanidinium modification on vancomycin A-ring and analogue **28** bearing guanidinium modifications on both the A-ring and at the C-terminus were synthesized and the antimicrobial activity of these analogues were established against vancomycin-resistant organisms (VRE, VanA, 4 strains). The results are summarized in Table S2 alongside vancomycin and our earlier trimethylammonium salt modified analogues[S4]. Compared with Arg(OMe)-vancomycin (**10**), Arg(OMe)^{Ar}-vancomycin (**25**) bearing the same modification on A-ring is as much as 8-fold less potent against the resistant organisms. This observation is consistent with our previous results on the site-specific nature of the permanent positive charge modification on vancomycin. Arg(OMe)-Arg(OMe)^{Ar}-vancomycin (**26**) bearing both a C-terminus and an A-ring guanidinium modification exhibited a potency essentially equal to that of Arg(OMe)-vancomycin (**10**) but not significantly further enhanced against vancomycin-resistant organisms. Similarly, guanidinium vancomycin analogues **27** and **28** was also found to be more potent than corresponding trimethylammonium modified vancomycin analogues **29** and **30** against the VanA VRE strains (2 to 4-fold).

Table S4. Antimicrobial activity of **1**, **3**, **10** and **27**–**30**, MIC(μg/mL).[S5]

Compound	VanA *E. faecalis* BM 4166	VanA *E. faecium* ATCC BAA-2317	VanA *E. faecalis* ATCC BAA-2573	VanA *E. faecium* TX 2465
vancomycin (**1**)	250	250	125	250
Arg(OMe)-vancomycin (**10**)	8	8	4	8
Arg(OMe)^{Ar}-vancomycin (**27**)	31	8	16	63
Arg(OMe)-Arg(OMe)^{Ar}-vancomycin (**28**)	8	2	1	8
C1-vancomycin (**3**)	63	31	N. D.	N. D.
C1^{Ar}-vancomycin (**29**)	125	31	N. D.	N. D.
C1-C1^{Ar}-vancomycin (**30**)	16	4	N. D.	N. D.

IV. Resistance Development Assay, Durability[S6]

G3-vancomycin (**5**), G3-CBP-vancomycin (**15**) and other front-line antibiotics (daptomycin, linezolid and tigecycline) were examined against vancomycin-resistant *Enterococcus faecalis* (VanA VRE, BM4166) and *Enterococcus faecium* (VanA VRE, ATCC BAA-2317). One day before experiments were run, fresh cultures of vancomycin-resistant *Enterococcus faecalis* (VanA VRE, BM 4166) and *Enterococcus faecium* (VanA VRE, ATCC BAA-2317) were inoculated and grown in an orbital shaker at 37 °C in 100% brain-heart infusion broth. After 24 h, the bacterial stock solutions were serial diluted with the culture medium (10% brain-heart infusion broth, containing 0.002% Tween-80) to achieve a turbidity equivalent to a 1:100 dilution of a 0.5 M McFarland solution (1.5×10^6 CFU/mL). This diluted bacterial stock solution was then inoculated in a 96-well flat-bottom non-treated microtiter plate (Corning 3370), supplemented with antibiotic solution in DMSO (4 μL), to achieve a total assay volume of 100 μL. The plate was then incubated at 37 °C for 18 h, after which minimum inhibitory concentrations (MICs) were determined by monitoring the cell growth (observed as a pellet) in the wells. The lowest concentration of antibiotic (in μg/mL) capable of eliminating cell growth in the wells is the reported MIC value. The bacterial suspension (40 μL) in the 96-well plate at sub-MIC concentrations of **5** and **15** (0.5 × MIC) was inoculated with 100% brain-heart infusion broth and the bacteria were grown in an orbital shaker at 37 °C for 6 h until the value of OD_{600} became 0.6. A new MIC assay was performed with the same protocol above. This process was repeated for 50 passages, and the fold increase in MIC was determined at each passage.

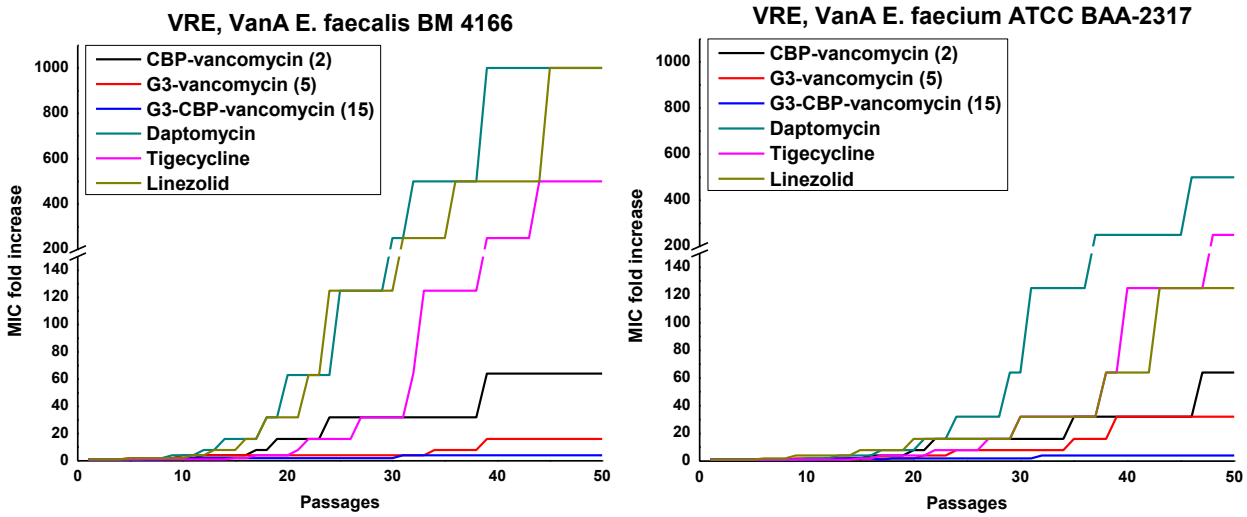


Figure S1. Resistance acquisition on serial passaging of two strains of VanA VRE in the presence of 0.5 × MIC levels of compound: CBP-vancomycin (**2**), G3-vancomycin (**5**), G3-CBP-vancomycin (**15**), daptomycin, linezolid and tigecycline.

V. Permeability Assay[S7-S8]

One day before experiments were run, cultures of vancomycin-resistant *Enterococcus faecalis* (VanA VRE, BM 4166) and *Enterococcus faecium* (VanA VRE, ATCC BAA-2317) were inoculated and grown in an orbital shaker at 37 °C in 100% brain-heart infusion broth for 12 h. The above bacterial solution was subjected to a subculture to obtain fresh mid log phase bacterial cells (incubation time = 6 h). The bacterial suspension was diluted to a total volume of 7 mL with OD_{600} = 0.6. After the cultured bacteria was harvested (3000 rpm, 4 °C, 20 min), the white bacterial precipitate was washed and resuspended in 5 mM glucose and 5 mM HEPES buffer (1:1, 5.00 mL, pH = 7.2). This bacterial suspension (130 µL) was charged in a 96-well black plate with a clear bottom (Corning 3651). The propidium iodide dye (10 µL, 150 µM DMSO solution) was added to the above suspension and the fluorescence was monitored at 25 °C for 5 min at 20 or 30 second intervals using a microplate reader (Molecular Devices®, Max Gemini EX) at an excitation wavelength of 535 nm and an emission wavelength of 617 nm. The antibiotic solution (10 µL, 150 µM buffer solution) was added to the cell suspension and the fluorescence was monitored at 25 °C for an additional 15 min.

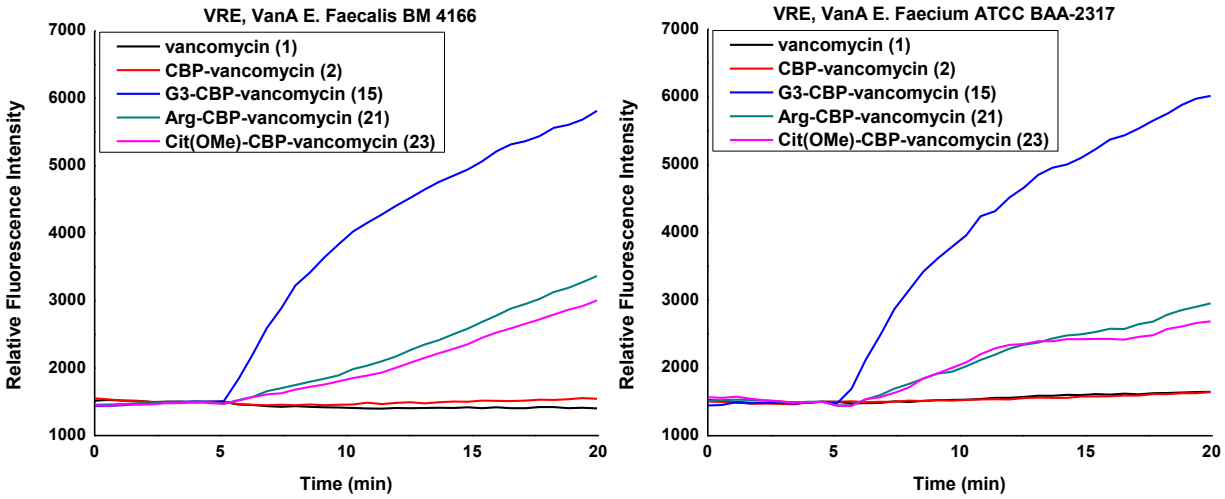


Figure S2. Examination of cell membrane permeability induced by compounds **1**, **2**, **15**, **21** and **23** (10µM added at 5 min) in VanA VRE *E. faecalis* BM 4166 and *E. faecium* ATCC BAA-2317.

VI. Impact of Lipoteichoic Acid (LTA) on *in vitro* Antimicrobial Activity of Vancomycin Analogues[S9]

One day before experiments were run, fresh cultures of vancomycin-resistant *Enterococcus faecalis* (VanA VRE, BM 4166) and *Enterococcus faecium* (VanA VRE, ATCC BAA-2317) were inoculated and grown in an orbital shaker at 37 °C in 100% brain-heart infusion broth. After 24 h, the bacterial stock solutions were serial diluted with the culture medium (10% brain-heart infusion broth containing 0.002% Tween-80 with 100 µg/mL lipoteichoic acid (Sigma-Aldrich, from *S. aureus*) as experiment group and 10% brain-heart infusion broth containing 0.002% Tween-80 as control group) to achieve a turbidity equivalent to a 1:100 dilution of a 0.5 M McFarland solution (1.5×10^6 CFU/mL). This diluted bacterial stock solution was then inoculated in a 96-well flat-bottom non-treated microtiter plate (Corning 3370), supplemented with serial diluted aliquots of

the antibiotic solution in DMSO (4 μL), to achieve a total assay volume of 100 μL. The plate was then incubated at 37 °C for 18 h, after which minimum inhibitory concentrations (MICs) were determined by monitoring the cell growth (observed as a pellet) in the wells. The lowest concentration of antibiotic (in μg/mL) capable of eliminating cell growth in the wells is the reported MIC value. The reported MIC values for the vancomycin analogues were determined against vancomycin as a standard in the first well. When NaH_2PO_4 or POPE was used instead of LTA, 10% brain-heart infusion broth containing 0.002% Tween-80 with 100 μg/mL NaH_2PO_4 or 100 μg/mL POPE was used as the culture medium used for serial dilution. When additional **G3** ($H_3N^+(CH_2)_3NHC(NH_2)=NH_2^+ \cdot$ 2TFA) or Mg^{2+} was used, 10% brain-heart infusion broth containing 0.002% Tween-80 with 100 μg/mL **G3** or 100 μg/mL $MgCl_2$ and 100 μg/mL lipoteichoic acid was used as the culture medium used for serial dilution of experimental group, 10% brain-heart infusion broth containing 0.002% Tween-80 with 100 μg/mL **G3** was used as the culture medium used for serial dilution of control group.

Table S5. Antimicrobial activity of **5** and **15** in the presence of exogeneous LTA (10, 100 or 1000 μg/mL).

Strain	VanA VRE *E. faecium* ATCC BAA-2317	
Compound	G3-vancomycin (**5**)	G3-CBP-vancomycin (**15**)
LTA concentration (μg/mL)	MIC (μg/mL)	
0	4	0.3
10	4	0.6
100	8	2.5
1000	63	10

VII. Impact of Lipoteichoic Acid (LTA) on Bacterial Cell Membrane Permeability Induced by G3-CBP-Vancomycin (15)

One day before experiments were run, cultures of vancomycin-resistant *Enterococcus faecalis* (VanA VRE, BM 4166) and *Enterococcus faecium* (VanA VRE, ATCC BAA-2317) were inoculated and grown in an orbital shaker at 37 °C in 100% brain-heart infusion broth for 12 h. The above bacterial solution was subjected to a subculture to obtain fresh mid log phase bacterial cells (incubation time = 6 h). The bacterial suspension was diluted to a total volume of 7 mL with OD_{600} = 0.6. After the cultured bacteria was harvested (3000 rpm, 4 °C, 20 min), the white bacterial precipitate was washed and resuspended in 5 mM glucose and 5 mM HEPES buffer (1:1, 5.00 mL, pH = 7.2) with lipoteichoic acid (100 μg/mL), or in 5 mM glucose and 5 mM HEPES buffer (1:1, 5.00 mL, pH = 7.2) as control. This bacterial suspension (130 μL) was charged in a 96-well black plate with a clear bottom (Corning 3651). The propidium iodide dye (10 μL, 150 μM DMSO solution) was added to the above suspension and the fluorescence was monitored at 25 °C for 5 min at 20 or 30 second intervals using a microplate reader (Molecular Devices®, Max Gemini EX) at an excitation wavelength of 535 nm and an emission wavelength of 617 nm. The antibiotic solution (10 μL, 150 μM buffer solution) was added to the cell suspension and the fluorescence was monitored at 25 °C for an additional 15 min.

VIII. Hemolysis Assay[S10]

Following an established procedure and as previously reported, the blood cells in pig whole blood (2 mL, Pel-Freez Biologicals, non-sterile, sodium citrate) were harvested (3000 rpm, 4 °C, 20 min), and the red blood precipitate was washed and resuspended in phosphate buffer saline (pH 7.4). This diluted red blood cell stock solution (384 µL) was incubated with the compound solution in DMSO (16 µL) in a 1 mL microtube to achieve the final concentration of the test compounds. The mixture was then incubated at 37 °C for 1 h. The solution was diluted with phosphate buffer saline (pH 7.4, 200 µL) at 25 °C and centrifuged (3000 rpm, 4 °C, 20 min). The supernatant (200 µL) was transferred to a microtiter plate. A positive control (0.2 % vol% Triton X-100, 100% total hemolysis) and the negative control (no antibiotic, 0% hemolysis) were prepared. A_{350} was measured using a microplate reader (Molecular Devices®, Max Gemini EX). The % hemolysis was determined by equation 1 and the results are presented in Figure S3.

$$\text{Hemolysis (\%)} = \frac{(A_{test} - A_{zero})}{(A_{total} - A_{zero})} \times 100 \quad \text{(eq. 1)}$$

A_{test} : Absorbance with test compound
A_{total} : Absorbance of 100% hemolysis
A_{zero} : Absorbance of 0% hemolysis

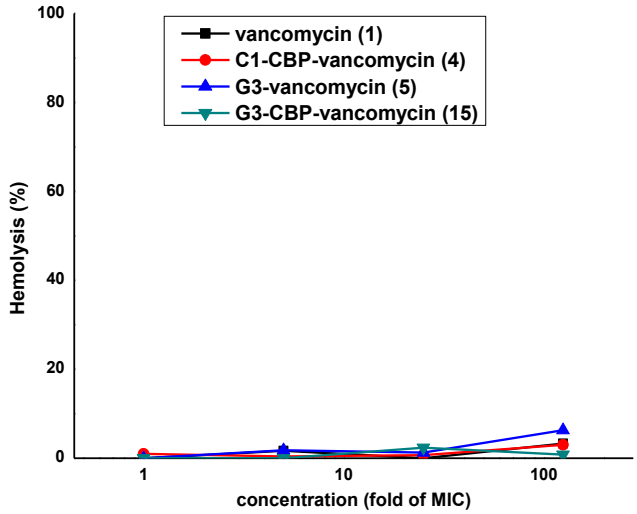


Figure S3. Hemolytic assay of red blood cells. % Hemolysis observed versus concentration expressed as fold concentration over measured MIC of G3-vancomycin (**5**) and G3-CBP-vancomycin (**15**) alongside vancomycin (**1**) and C1-CBP-vancomycin (**4**).

Although the differences in mammalian and bacterial cell wall composition are extensive, including the more highly anionic composition of the bacterial cell wall responsible for a preferential and differential cation binding, lysis of mammalian cell membranes (red blood cells) are potential off-target consequences of cationic compounds that impact bacterial cell membrane integrity. The standard red blood cell hemolysis assay was conducted and measures the extent of red blood cell lysis after 1 h exposure to the compound (pH 7.4, PBS, 37 ºC, 1 h). No compound in the series exhibited any hemolytic activity even at concentrations >100-fold above their MICs.

IX. PK studies, mouse pharmacokinetics

Pharmacokinetic behavior of G3-CBP-vancomycin and C1-CBP-vancomycin were examined in 7–8 week-old female CD-1 mice by intravenous dosing utilizing the tail vein. Test compounds were formulated v:v:v in 10% DMSO : 15% PEG-400 : 75% (30% w:v hydroxypropyl β-cyclodextrin in water) by first dissolving in DMSO then adding PEG-400 and the 30% w:v solution of hydroxypropyl β-cyclodextrin. Formulation solutions of 2 or 10 mg/mL were used for 10 and 50 mg/kg PK studies, respectively. Triplicate mice were dosed and 20 µL blood was collected into Li-heparin coated hematocrit tubes 5, 15, 30, 60, 120, 240, 360, 480, and 1440 min after dosing. Plasma was generated by centrifugation using a microcentrifuge fit with a hematocrit rotor and plasma was immediately frozen. The use of micro-sampling blood collection reduces the total blood taken from the mouse and allows a single mouse to be used for the entire time course, reducing inter-individual variability and maintaining the health of the mouse. Drug levels were determined by mass spectrometry using an ABSciex 5500 mass spectrometer using multiple reaction monitoring. G3-CBP-vancomycin and C1-CBP-vancomycin were detected as their 3+ charged molecular ion. HPLC and MS/MS parameters are provided below. Pharmacokinetic parameters were calculated using a non-compartmental model (Phoenix WinNonlin, Pharsight Inc.). All PK work was conducted in the Scripps Florida vivarium which is fully AAALAC accredited. Procedures were approved by the Scripps Florida IACUC, protocol number 15-022.

Table S6. Comparison PK properties of **15** with those of **2**, **4**, and vancomycin established in our earlier study (ref 38).[a]

Parameter	vancomycin		CBP-vancomycin (**2**)		C1-CBP-vancomycin (**4**)		G3-CBP-vancomycin (**15**)	
	300 mg/kg	10 mg/kg	75 mg/kg	10 mg/kg	50 mg/kg	10 mg/kg	50 mg/kg	10 mg/kg
C_{max} (µg/mL)	1665	62.8	125	65.0	58.9	14.1 (14.5)[b]	152	35.9
t_{max} (h)	0.083	0.083	0.25	0.083	0.25	0.50 (0.08)	0.28	0.14
AUC (µg-h/mL)	935	21.8	575	135	430	81.1 (48.4)	312	66.0
V_d (L/kg)	0.62	0.34	1.24	1.28	1.04	1.25 (0.64)	0.35	0.41
CL (L/h/kg)	0.32	0.46	0.13	0.074	0.12	0.12 (0.12)	0.09	0.09
$t_{1/2}$ (h)	1.35	0.52	6.6	12.0	6.2	7.0 (5.1)	4.4	4.3

[a]Compounds administered iv @ MTD and 10 mg/kg in mice (n = 3/time point, measured at 0.083, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h). [b]Values in parentheses were determined in this study.

G3-CBP-Vancomycin Instrument Settings

LC (Shimadzu UFLC XR) conditions

Compound	G3-CBP-Vancomycin	I.S. (Carbamazepine)
Column	Thermo Betasil C18 5μ, 50x2.1mm	
Mobile phase	A: Water with 0.1% Formic Acid B: Acetonitrile with 0.1% Formic Acid	
Flow rate (ml/min)	0.35	
Temperature (°C)	35	
Injection volume(μl)	10	
RT(min)	0.43	2.5

Gradient elution conditions:

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0.2	90	10
0.5	90	10
2.0	5	95
3.0	5	95
4.0	90	10
5.9	90	10

MS (API5500) conditions

Compound	G3-CBP-Vancomycin (3+)	I.S. (Carbamazepine)
MRM(+)	583.2/201	237.2/194.1
Collision Gas	7	
Curtain GAS	36	
Ion Source Gas1	55	
Ion Source Gas2	50	
Ion Spray Voltage	5500	
Temperature (°C)	550	
Collision Energy	25	26
Declustering Potential	65	136
Entrance Potential	10	
Collision Cell Exit Potential	14	

C1-CBP-Vancomycin Instrument Settings

LC (Shimadzu UFLC XR) conditions

Compound	C1-CBP-Vancomycin	I.S. (Carbamazepine)
Column	Thermo Betasil C18 5µ, 50x2.1mm	
Mobile phase	A: Water with 0.1% Formic Acid B: Acetonitrile with 0.1% Formic Acid	
Flow rate (ml/min)	0.35	
Temperature (°C)	35	
Injection volume(µl)	10	
RT(min)	0.42	2.5

Gradient elution conditions:

Time (min)	Mobile phase A (%)	Mobile phase B (%)
0.2	90	10
0.5	90	10
2.0	5	95
3.0	5	95
4.0	90	10
5.9	90	10

MS (API5500) conditions

Compound	C1-CBP-Vancomycin (3+)	I.S. (Carbamazepine)
MRM(+)	583.1/702.1	237.2/194.1
Collision Gas	7	
Curtain GAS	36	
Ion Source Gas1	55	
Ion Source Gas2	50	
Ion Spray Voltage	5500	
Temperature (°C)	550	
Collision Energy	20	26
Declustering Potential	21	136
Entrance Potential	10	
Collision Cell Exit Potential	14	

X. In vivo Antimicrobial Efficacy Study

Neutropenic ICR (CD-1) mice, age 5–6 weeks weighing 22 ± 2 g, were used for this study. Cyclophosphamide (CP) was administered by two intraperitoneal (ip) injections to induce neutropenia following a standard method for mouse thigh infection models. The first CP dose (150 mg/kg) was administered 4 days before infection (day –4) and the second (100 mg/kg) was given 24 h (day –1) prior to infection on day 0. This cyclophosphamide treatment schedule results in neutropenia (<100 neutrophils/mL) until day 2 after infection. On day 0, animals were infected with the pathogen suspension (0.1 mL, 1.01×10^5 CFU/mL) by intramuscular injection into the right thigh. The challenging multidrug resistant and vancomycin-resistant *S. aureus* strain (VanA VRSA, VRS2)[50] was used. Compound **15** alongside linezolid were administered to animals (n = 5 for each dose) by subcutaneous (sc, **15**) or oral (po, linezolid) administration using doses defined by the MTD/PK studies and given as single dose 2 h following injection of the pathogen. This was a single dose given at 12.5, 25, 50 and 100 mg/kg (for **15**), at 50 mg/kg (for reference standard linezolid, po administration twice at 2 and 12 h) and at 0 (vehicle control) (Figure 6). Vehicle was 10% DMSO, 15% PEG-400, 22.5% hpbCD in water and the dose volume was 10 mL/kg for all test groups. Linezolid was dissolved in water for injection with 1% Tween 80 for oral (po) administration. Animals were monitored for 30 min after dosing to detect acute toxicity and were checked periodically after infection for humane endpoints. Animals were sacrificed with CO_2 asphyxiation at the scheduled time points for tissue harvest, at 2 h (for baseline) or 26 h after infection. Thigh muscle tissue is aseptically harvested from each of the sacrificed animals, weighed, and homogenized in 3 mL sterile PBS (pH 7.4) with a polytron homogenizer. Bacterial burden in the tissue homogenates was determined by performing 10-fold serial dilutions and plating 0.1 mL of each to nutrient agar (NA) plates. Colonies were counted after 18–24 h incubation. The colony forming units per gram tissue (CFU/g) were calculated. For each animal, the following raw data is recorded and tabulated: tissue weight and bacterial counts in each tissue homogenate dilution. For each tissue, the homogenate dilution that yielded the largest number of colonies, between 10 to 300 colonies per plate, was selected to calculate the bacterial counts per gram of tissue (CFU/g). Bacterial counts per gram of tissue (CFU/g) were calculated and tabulated and plotted in GraphPad Prism. The raw colony count data of the homogenate dilutions was inspected for proportionality within the dilution series. The 10-fold serial dilutions are expected to show 10-fold reductions in counts. Disproportionate data, such as fewer counts in the undiluted homogenate samples compared to the diluted sample, would indicate inhibition of colony growth due to drug carry over from the thigh tissue to the test plate. Aberrant titration data was not observed. Data was plotted as the bacterial counts per gram tissue of control and treatment groups to assess the dose responsive effects. The difference in bacterial density between the baseline group (2 h initial counts) and the treatment group was also calculated and plotted: Δ = CFU/g of treatment – CFU/g of baseline. The doses that result in a net static effect relative to baseline, and those that result in 1-$\log_{10}$, 2-$\log_{10}$ or more bactericidal effects were determined. The results obtained herein are recorded in Figure 6 and a comparison with the results obtained earlier[38] for **4** and CBP-vancomycin (**2**) are summarized in Figure S4.

Inoculum preparation. A 0.2 mL aliquot of a single-use glycerol stock of the pathogen (at –80 °C) was used to seed 20 mL of brain-heart infusion (BHI) broth and then incubated at 35–37 °C with shaking (250 rpm) for 8 h. Cells in the 20 mL culture were pelleted by centrifugation (3,500 × g) for 15 min, and then re-suspended in 10 mL cold phosphate buffer saline (PBS). The

optical density, OD_{620nm}, was measured and used to guide dilution. The PBS suspensions were stored on ice for no more than one hour prior to animal inoculation. Bacterial count in the challenge organism suspension was enumerated by dilution plating to NA plates followed by 20–24 h incubation. The target inoculum was 1×10^6 CFU/mL and actual CFU count was 1.24×10^5 CFU/mL. These studies were performed by Pharmacology Discovery Services Taiwan, Ltd., a partner lab of Eurofins Pharma Discovery Services.

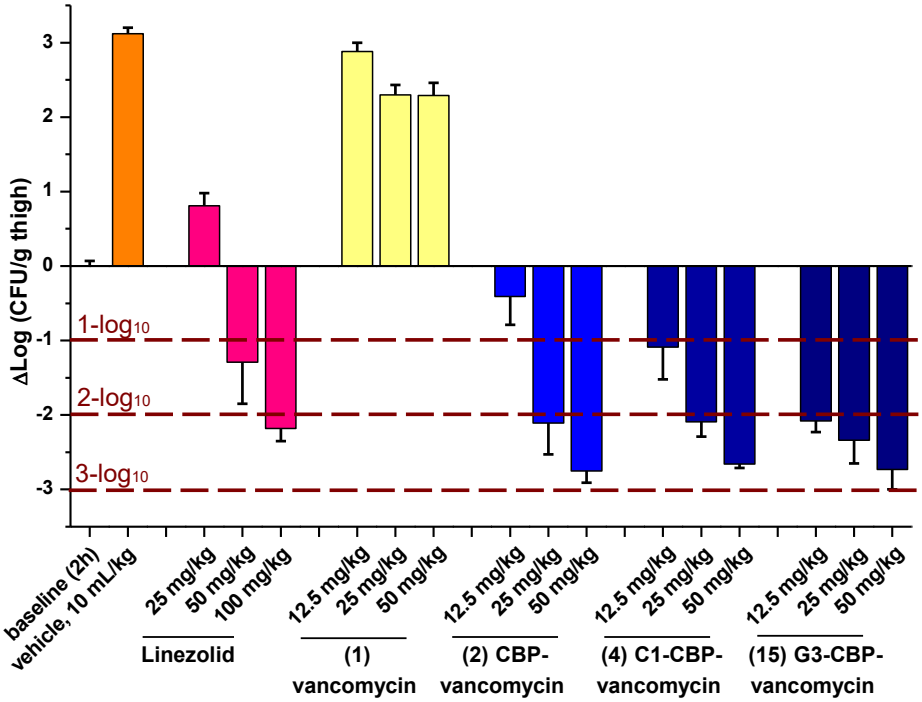


Figure S4. A summary of efficacy study of vancomycin (**1**), CBP-vancomycin (**2**), C1-CBP-vancomycin (**4**) and G3-CBP-vancomycin (**15**) against the multidrug resistant and VanA vancomycin-resistant *S. aureus* (VRSA) strain VRS-2 in the mouse thigh infection model (n = 5/dose). The test compounds and control vehicle were administered sc once at 2 h at the doses indicated. The reference standard linezolid was administered orally (po) twice at 2 and 12 h at 50 mg/kg. Left: dose-dependent reduction in bacterial load. Right: dose-dependent bactericidal effect (relative to 2 h baseline).

XI. References

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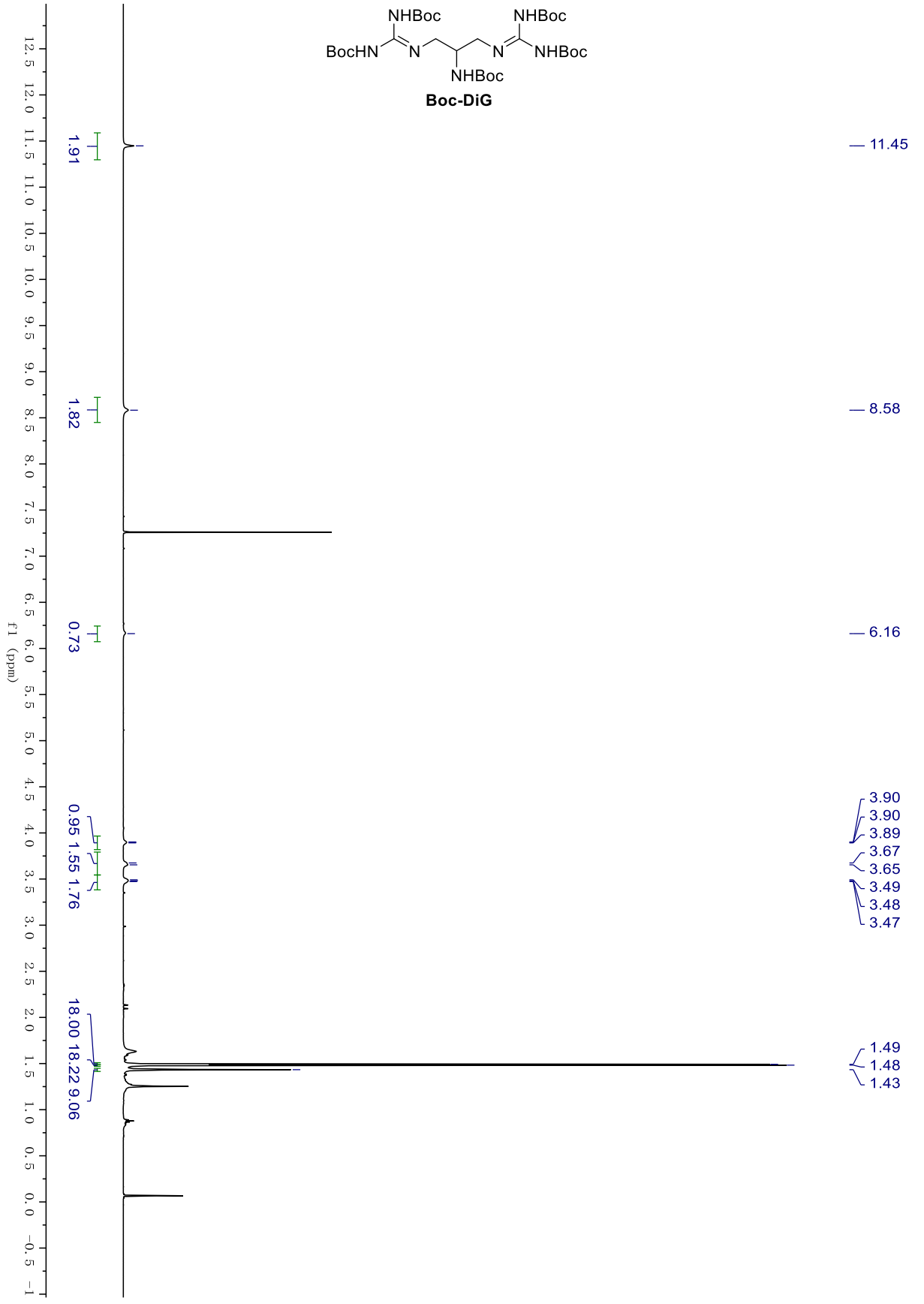
XII. Spectra and HPLC traces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NHBoc
NHBoc
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3.89
3.67
3.65
3.49
3.48
3.47
1.49
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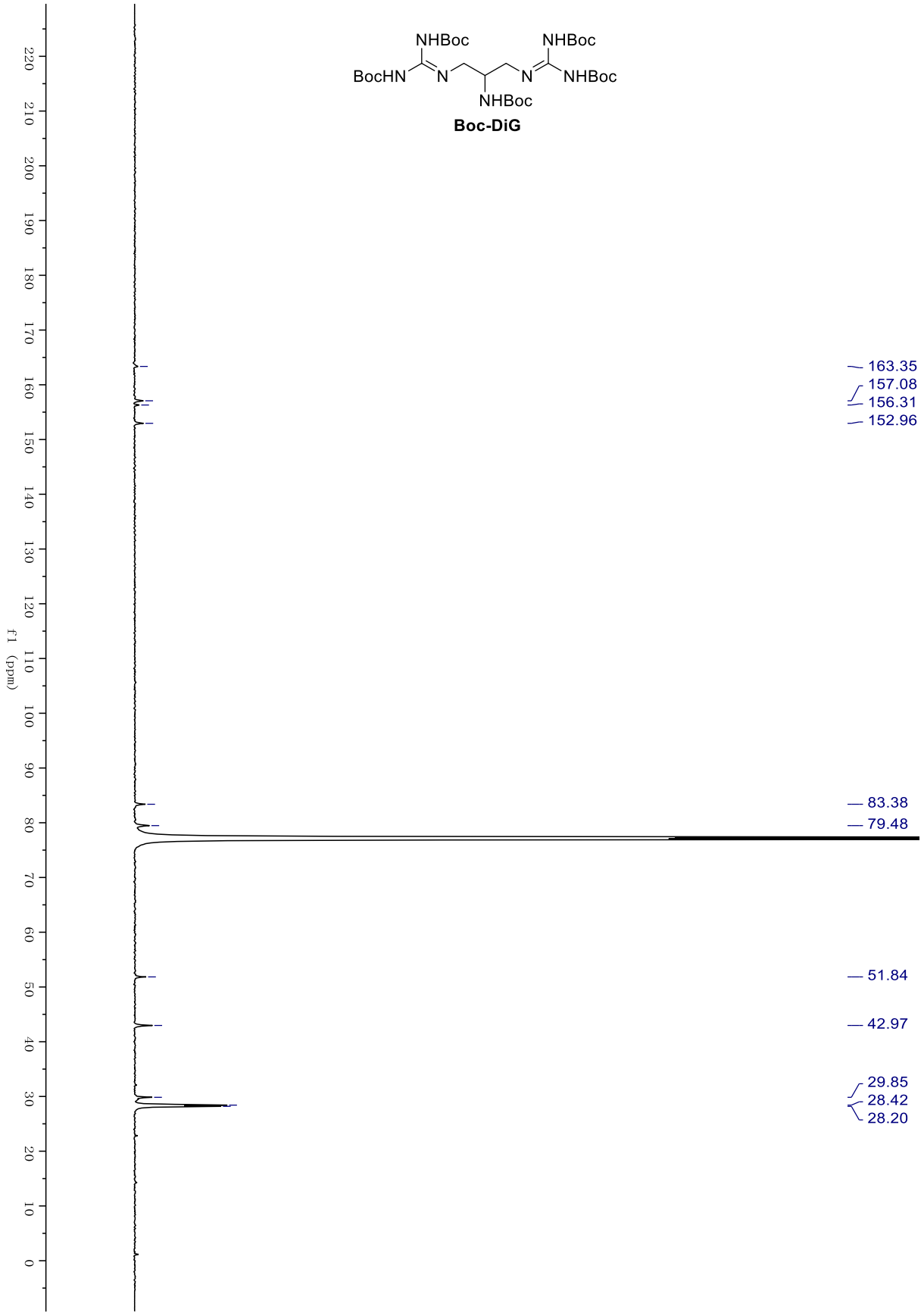
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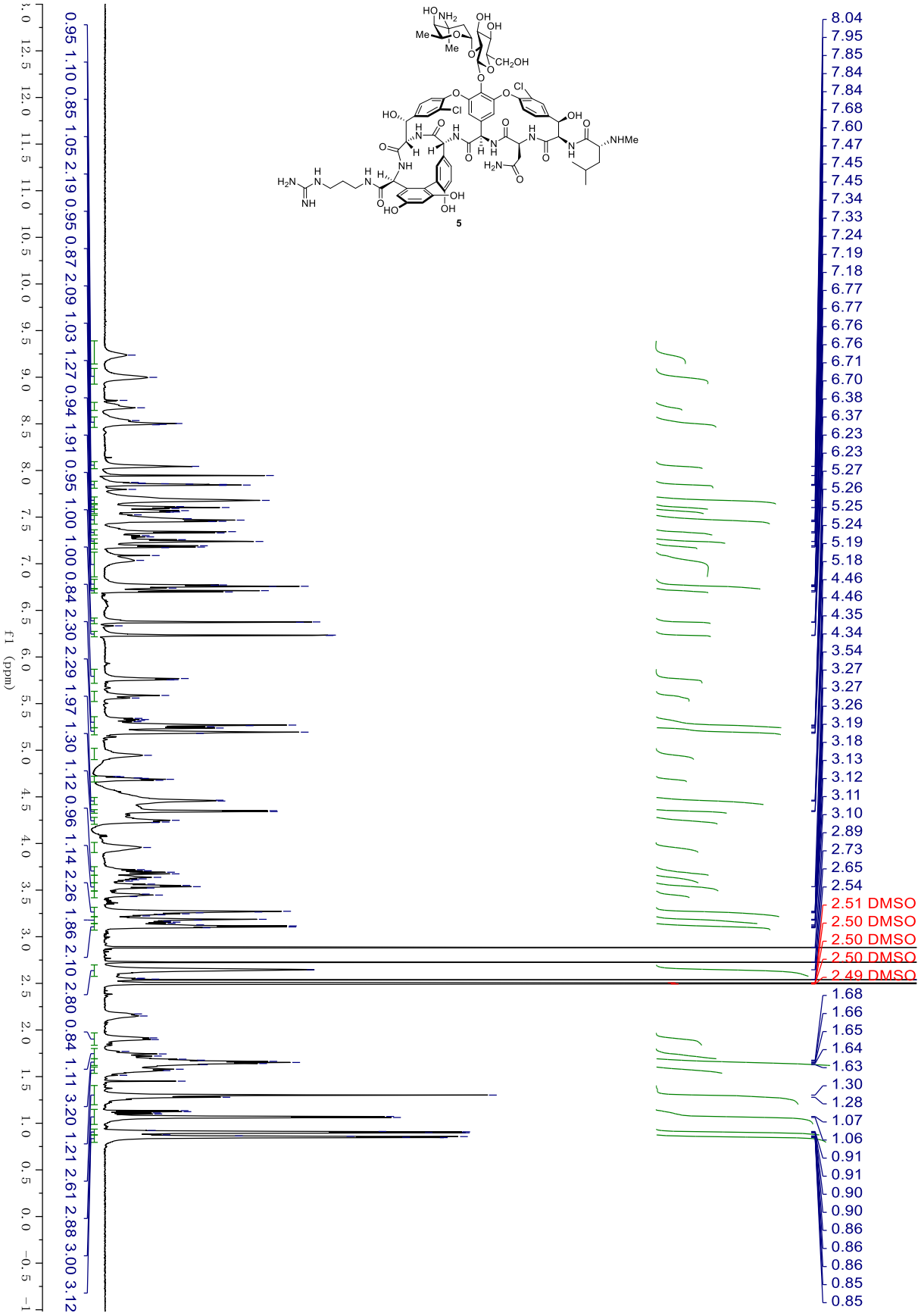
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1.06
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0.90
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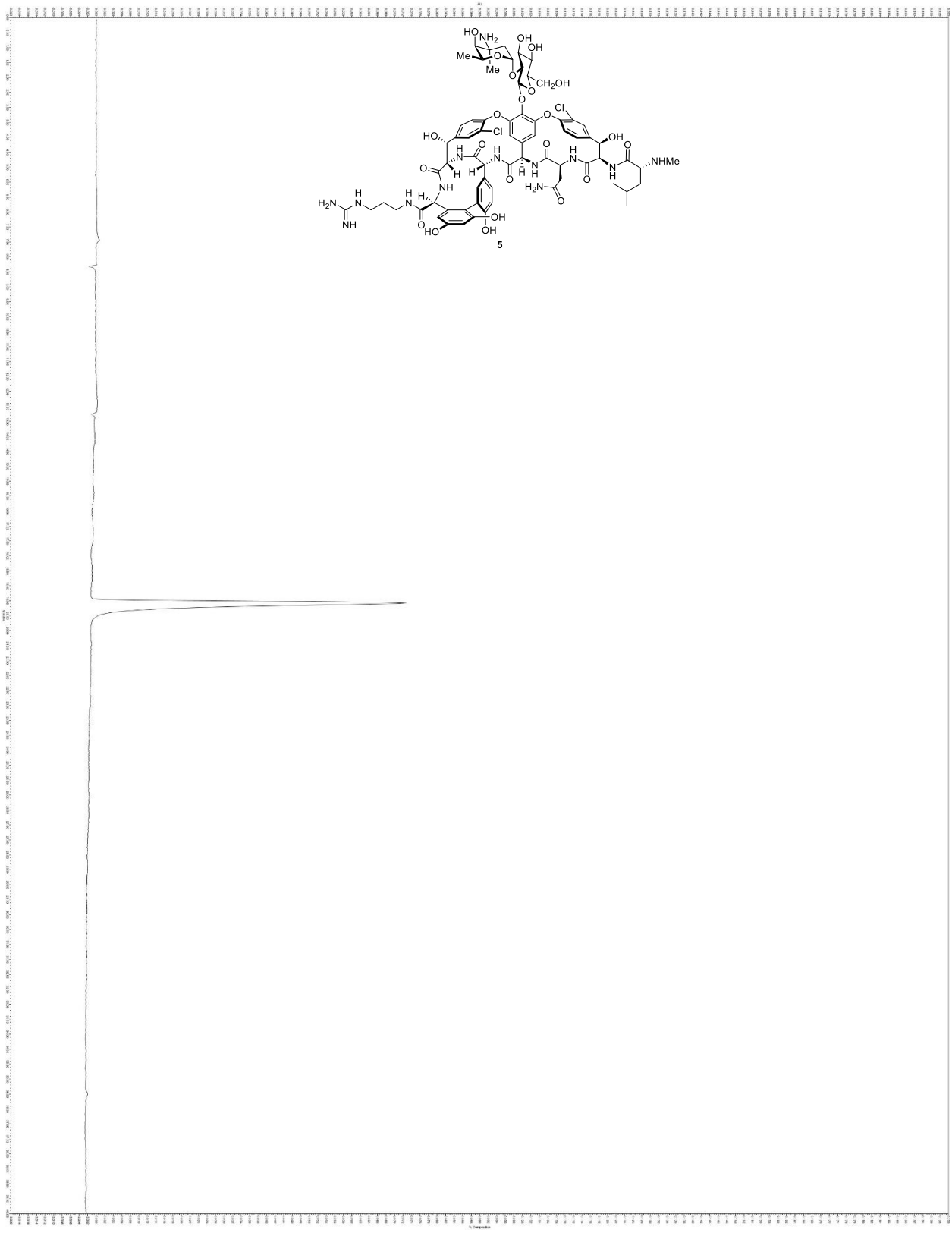
0.86
0.86
0.86
0.86
0.85
0.85
0.95 1.10 0.85 1.05 2.19 0.95 0.87 2.09 1.03 1.27 0.94 1.91 0.95 1.00 1.00 0.84 2.30 2.29 1.97 1.30 1.12 0.96 1.14 2.26 1.86 2.10 2.80 0.84 1.11 3.20 1.21 2.61 2.88 3.00 3.12



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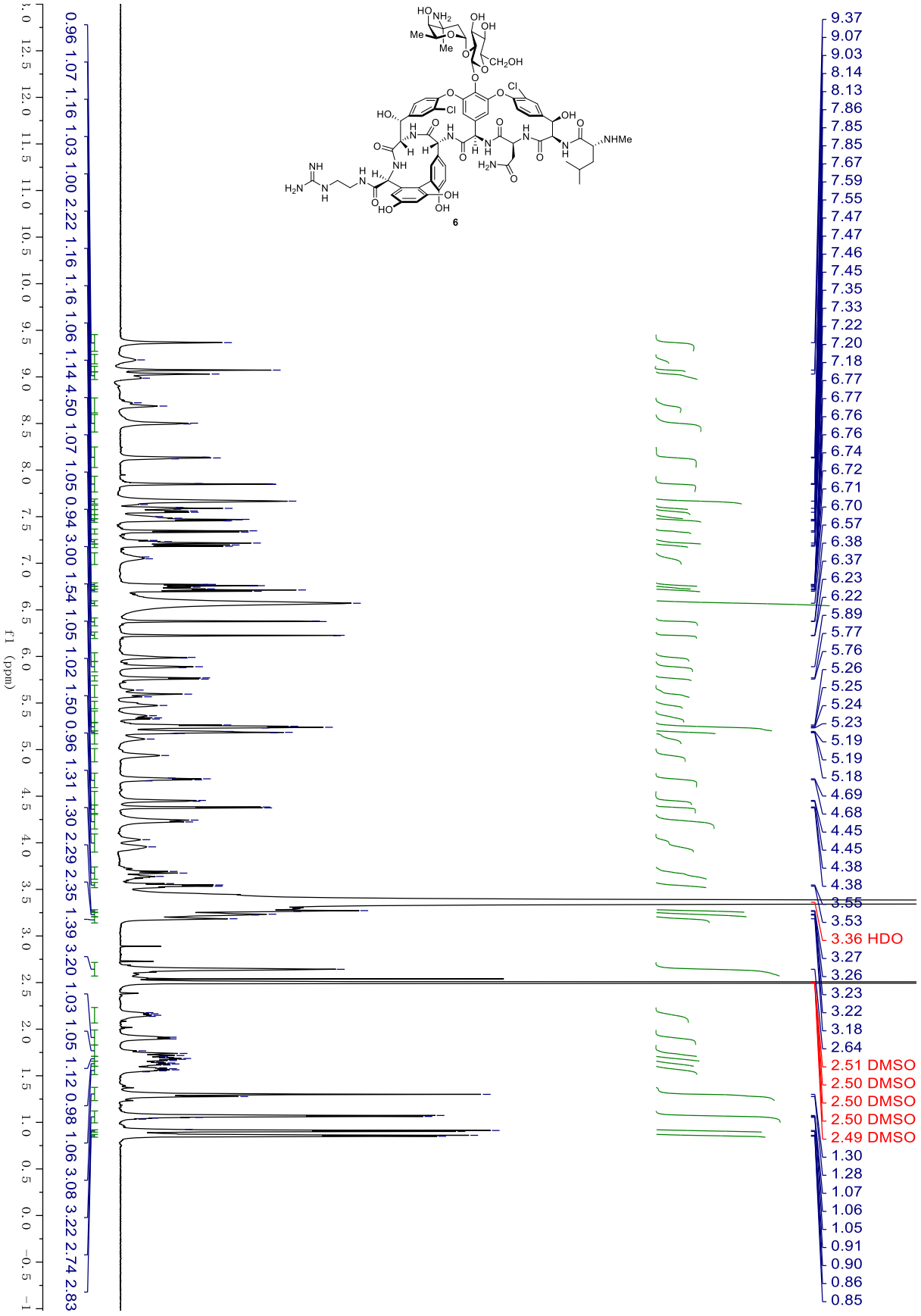
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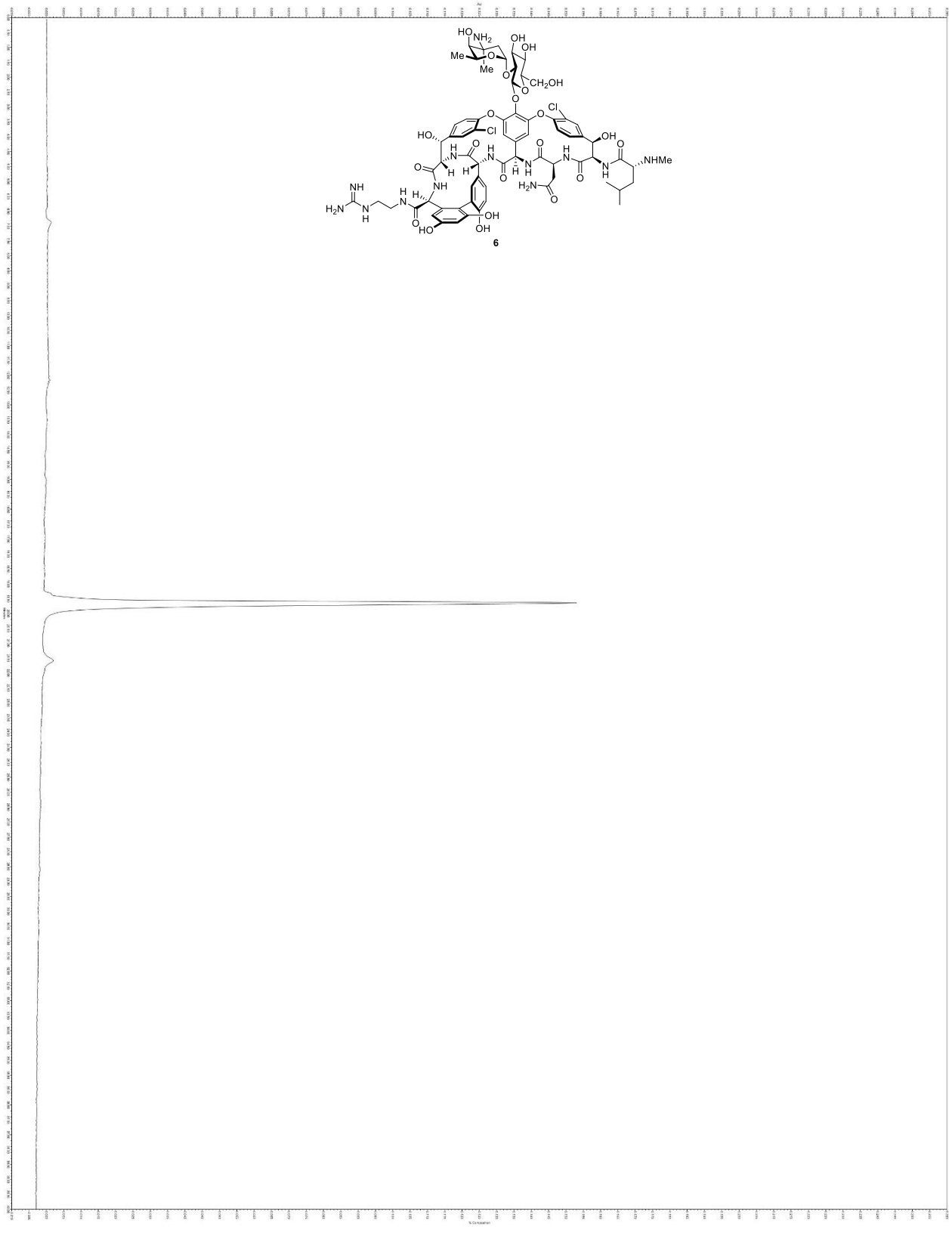
0.96 1.07 1.16 1.03 1.00 2.22 1.16 1.16 1.06 1.14 4.50 1.07 1.05 0.94 3.00 1.54 1.05 1.02 1.50 0.96 1.31 1.30 2.29 2.35 1.39 3.20 1.03 1.05 1.12 0.98 1.06 3.08 3.22 2.74 2.83
f1 (ppm)



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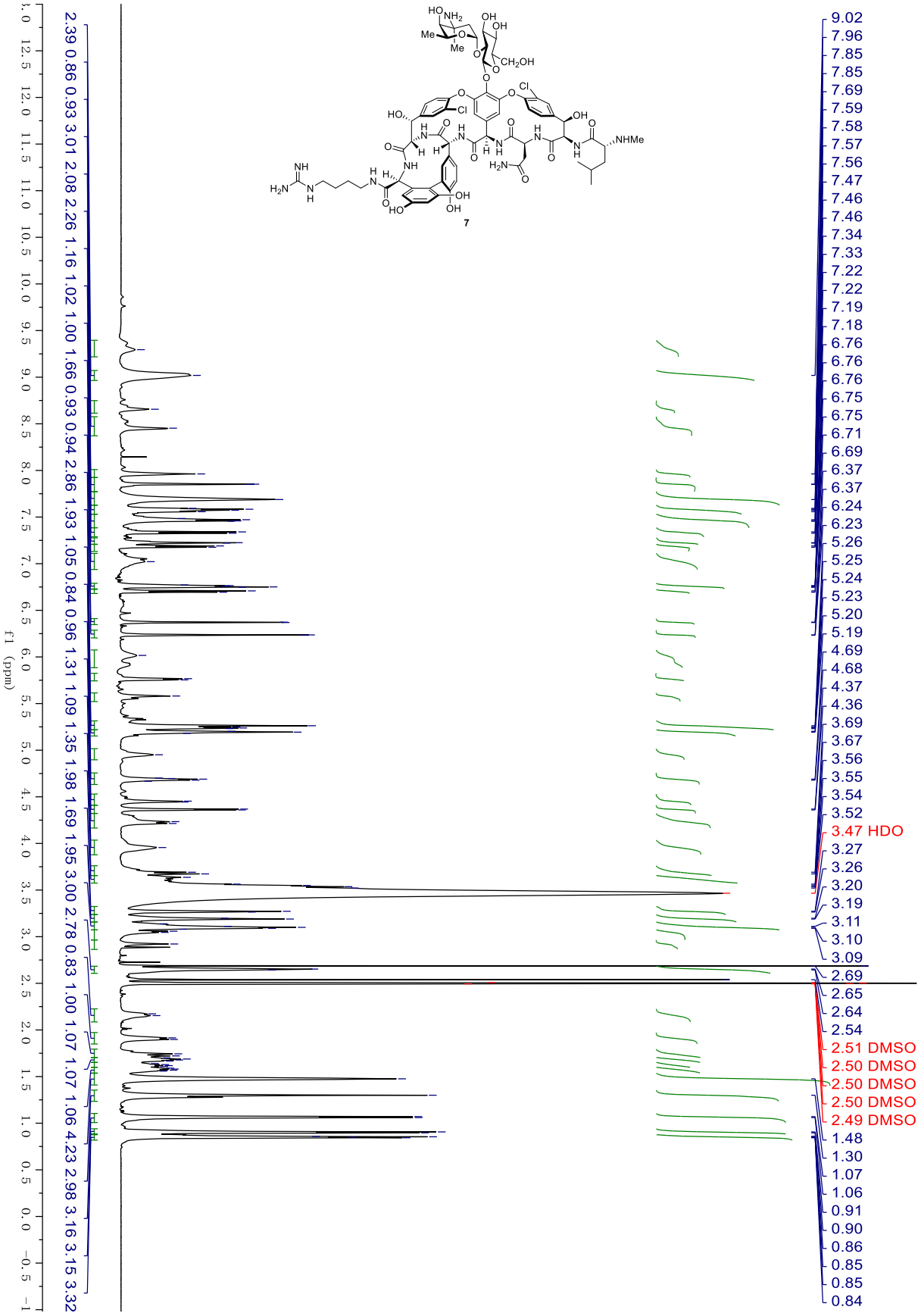
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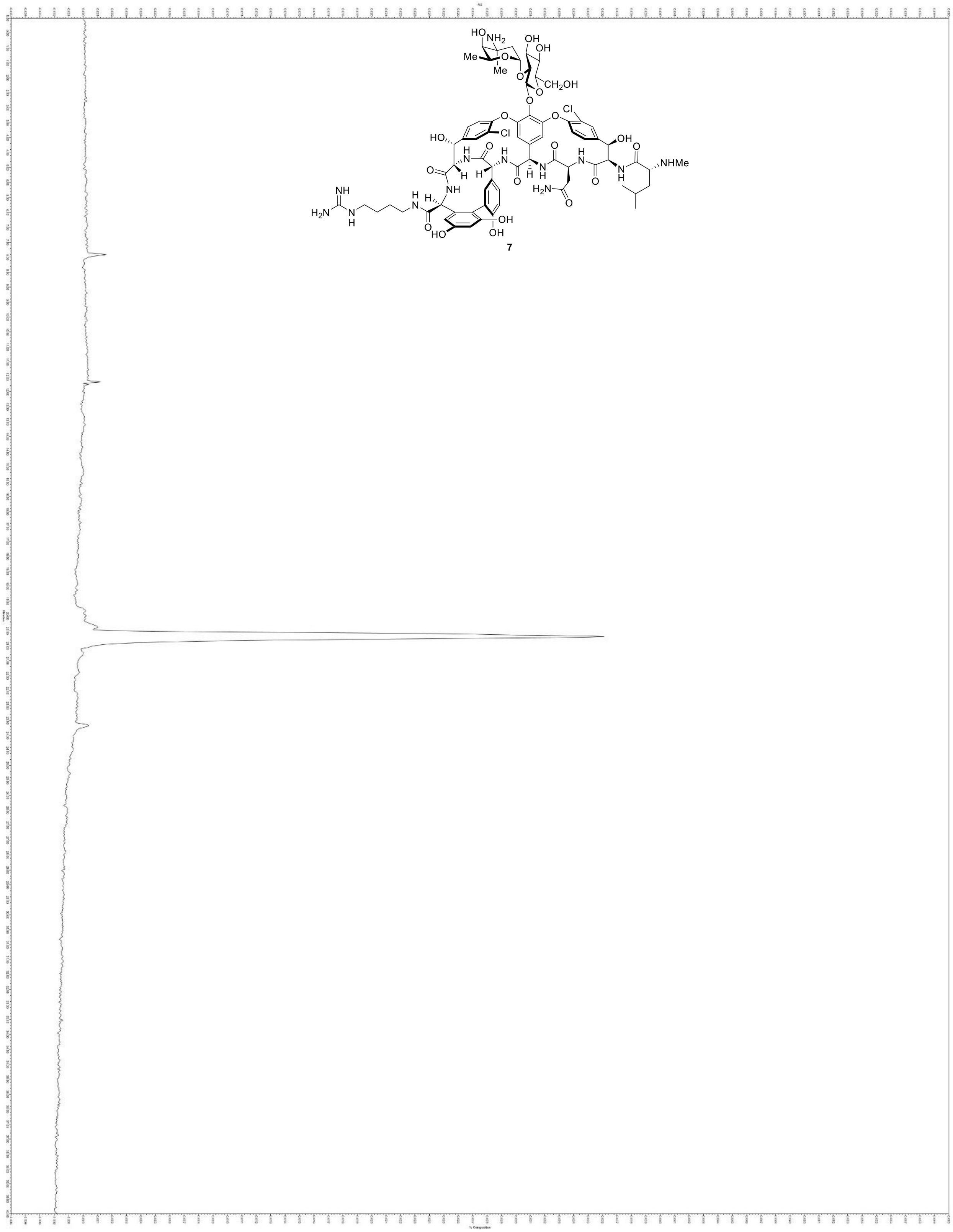
f1 (ppm)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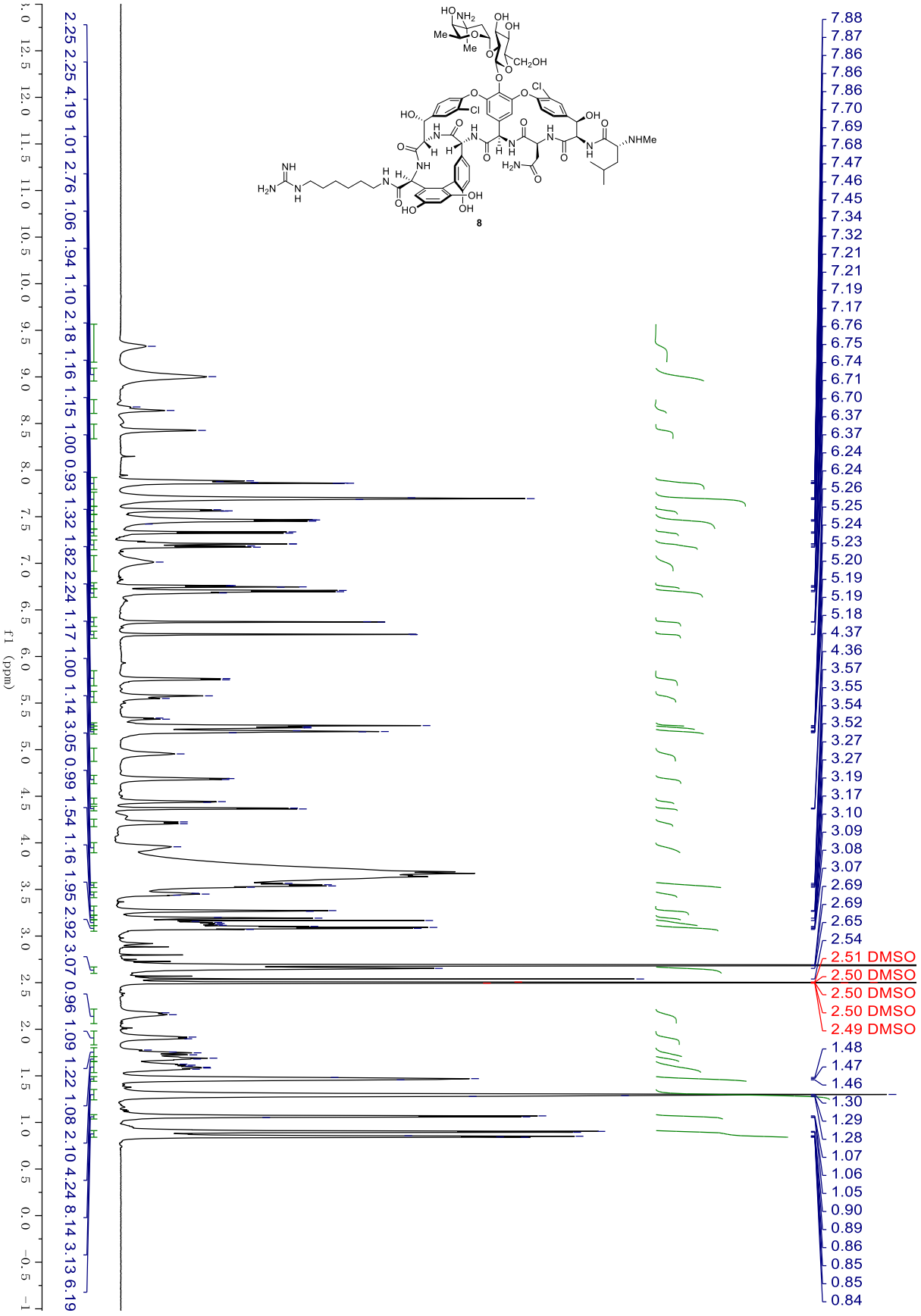
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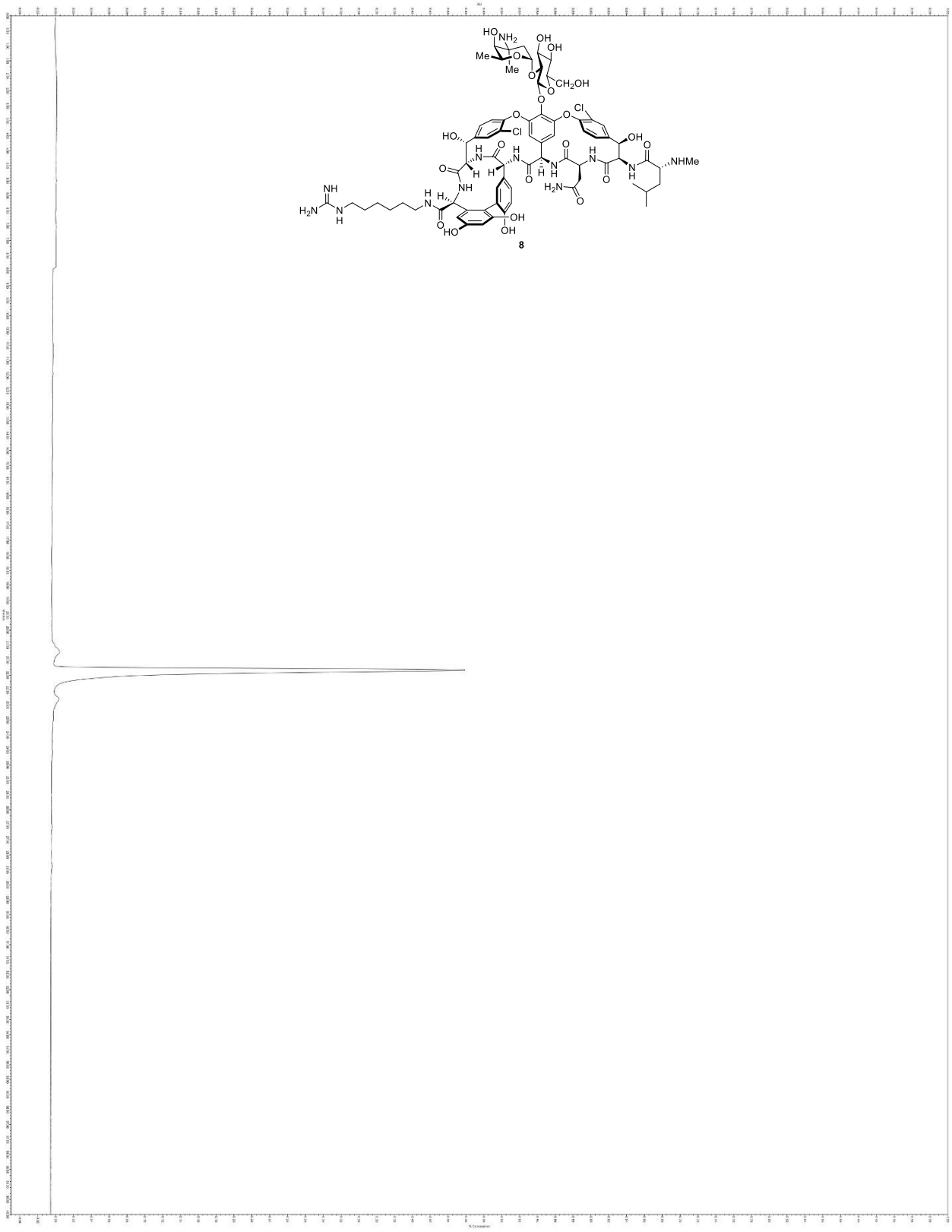

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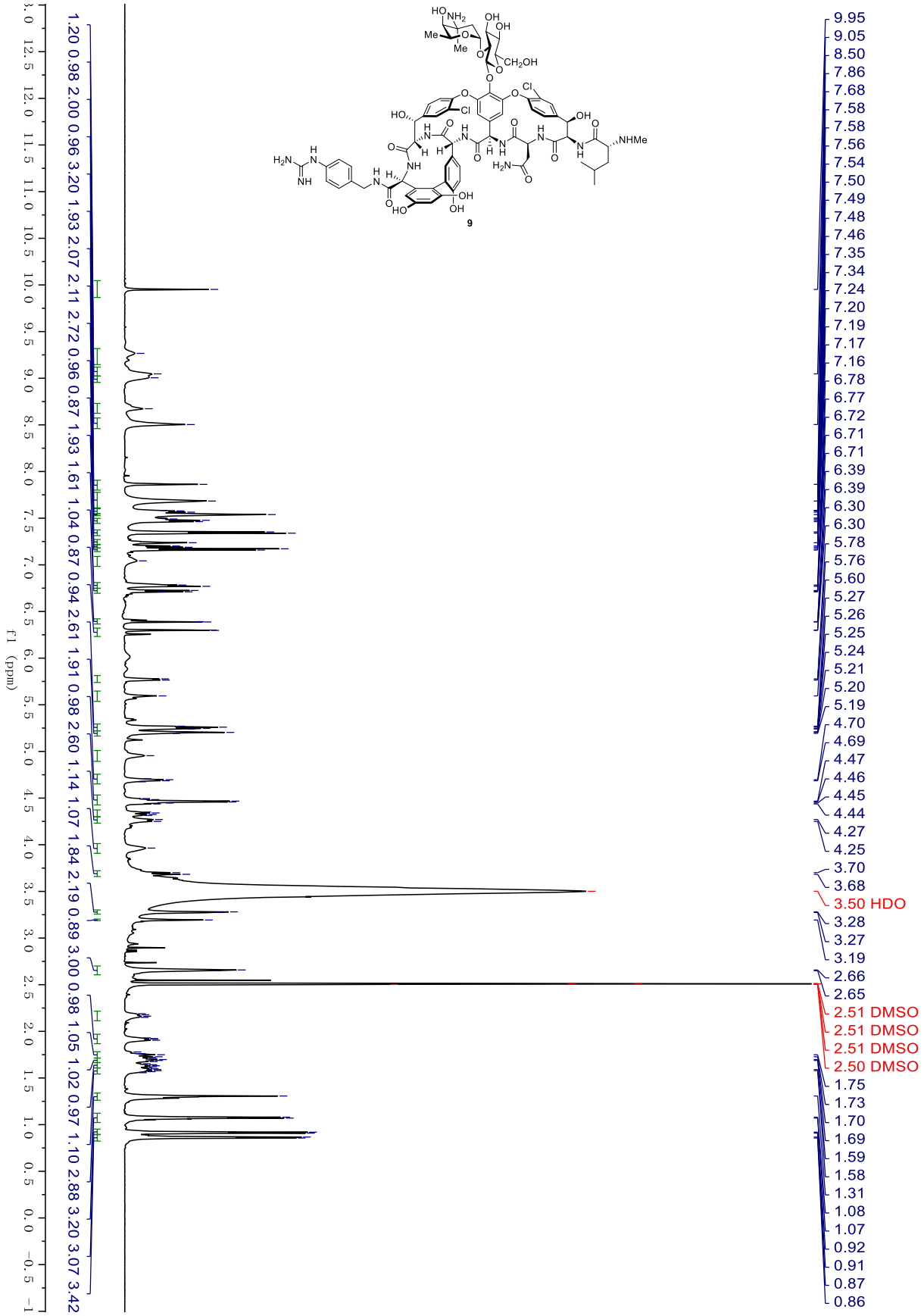
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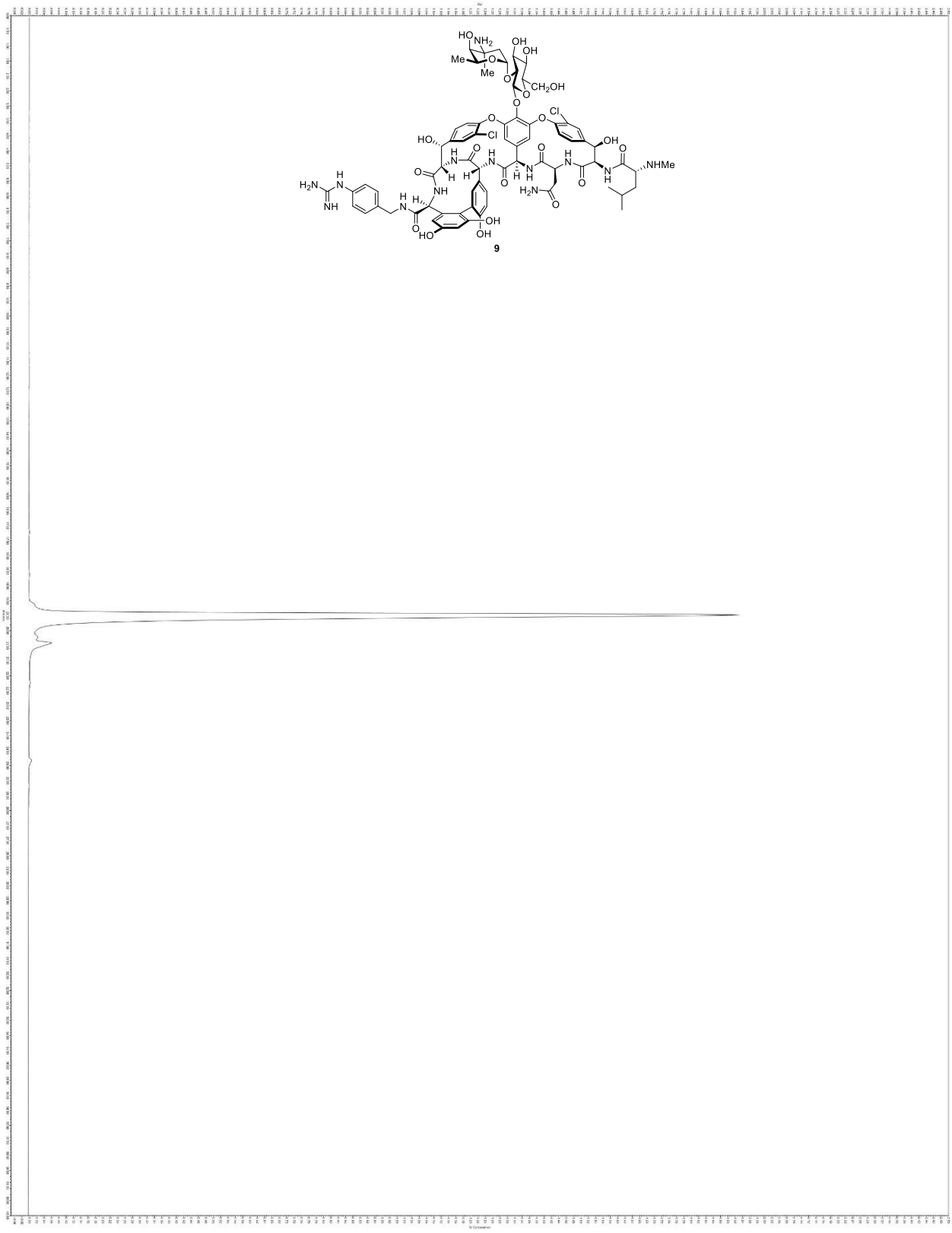

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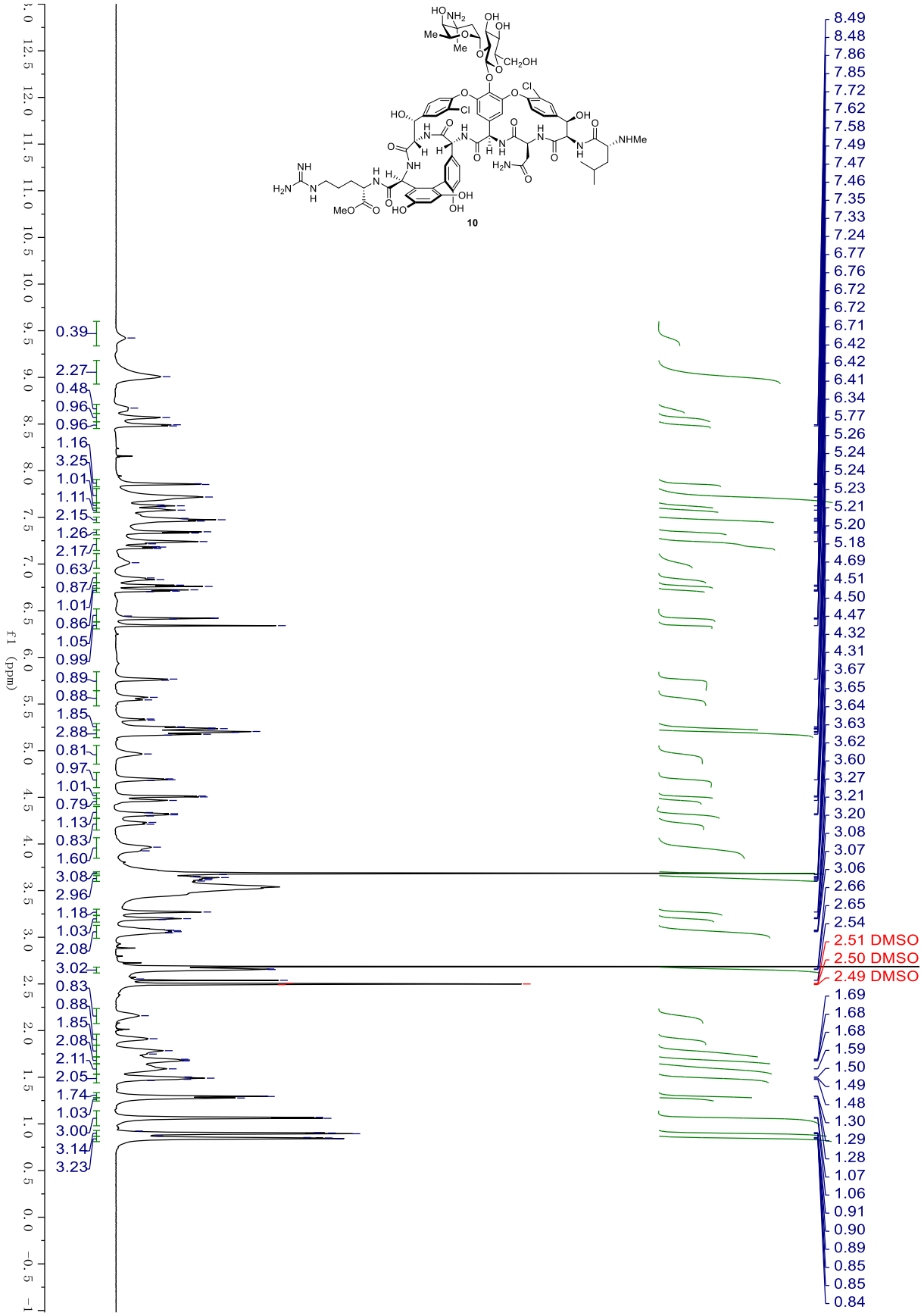
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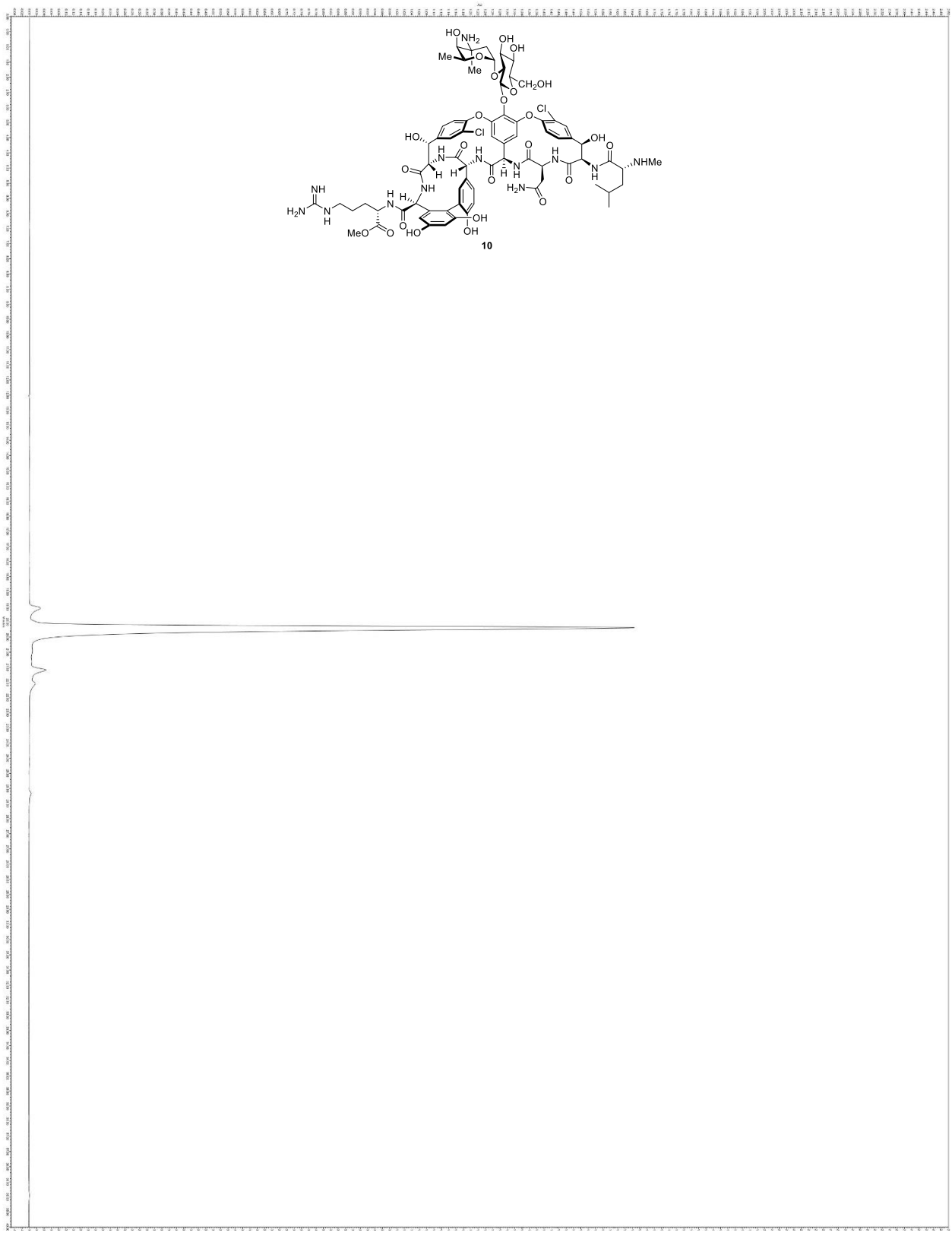
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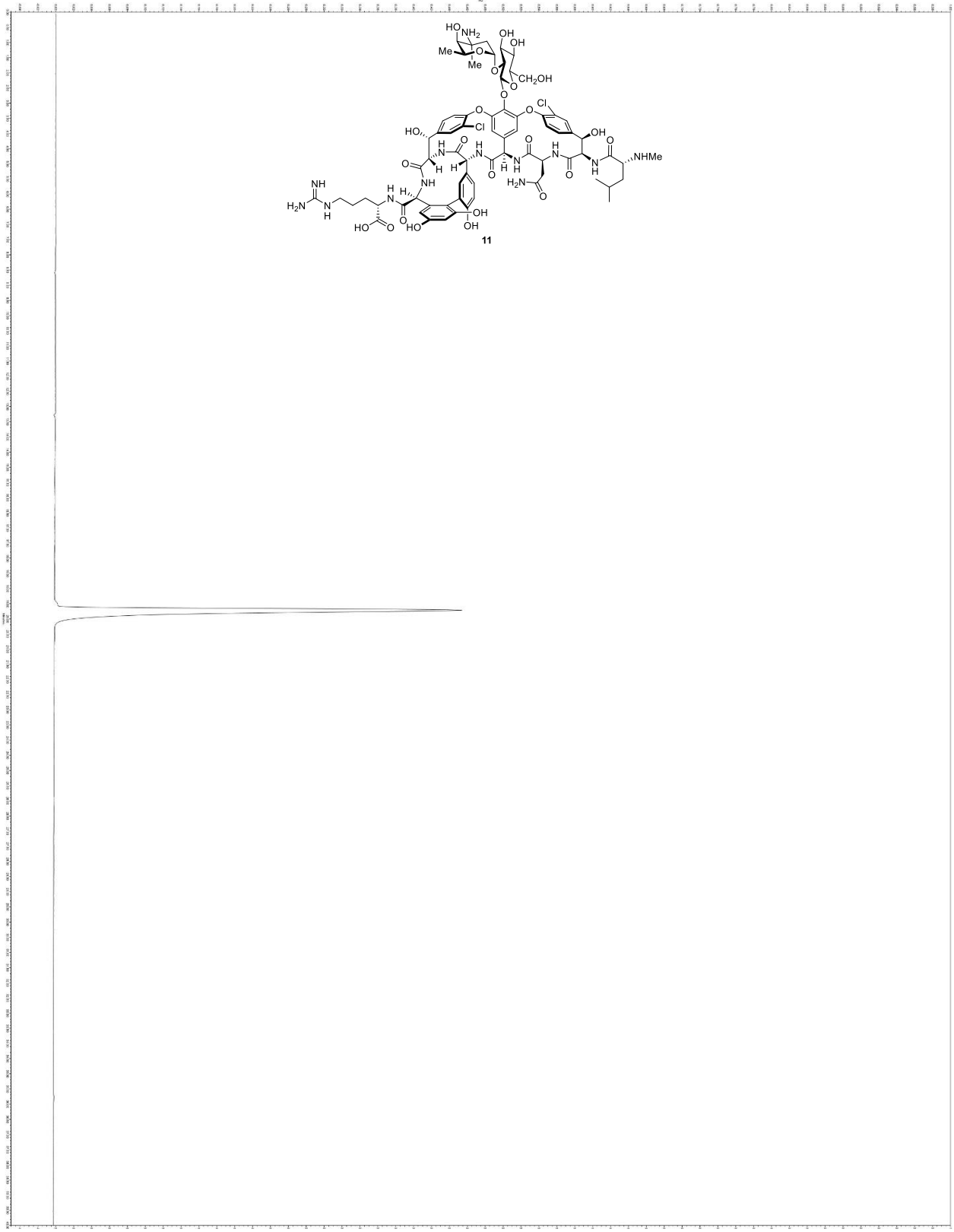

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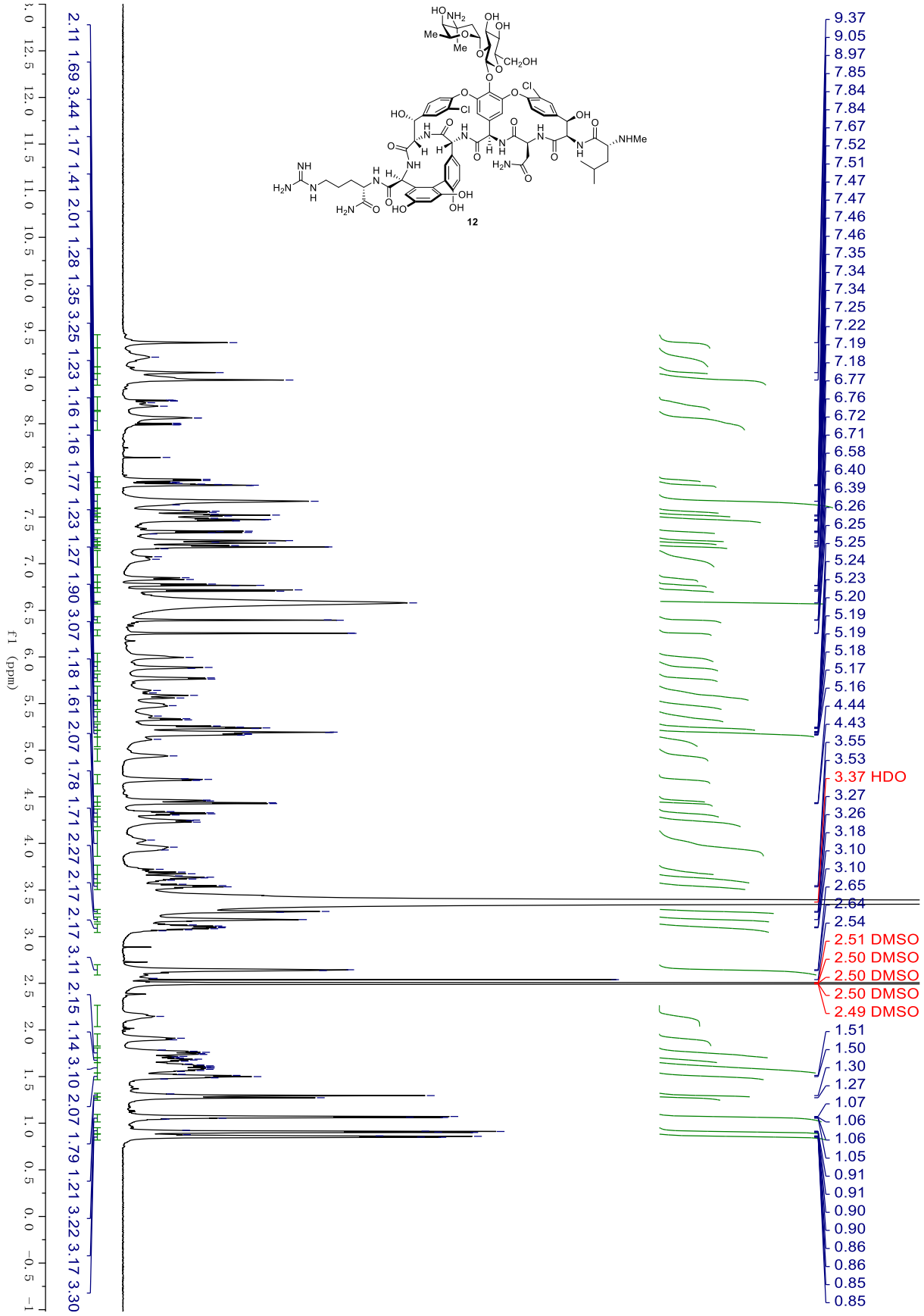
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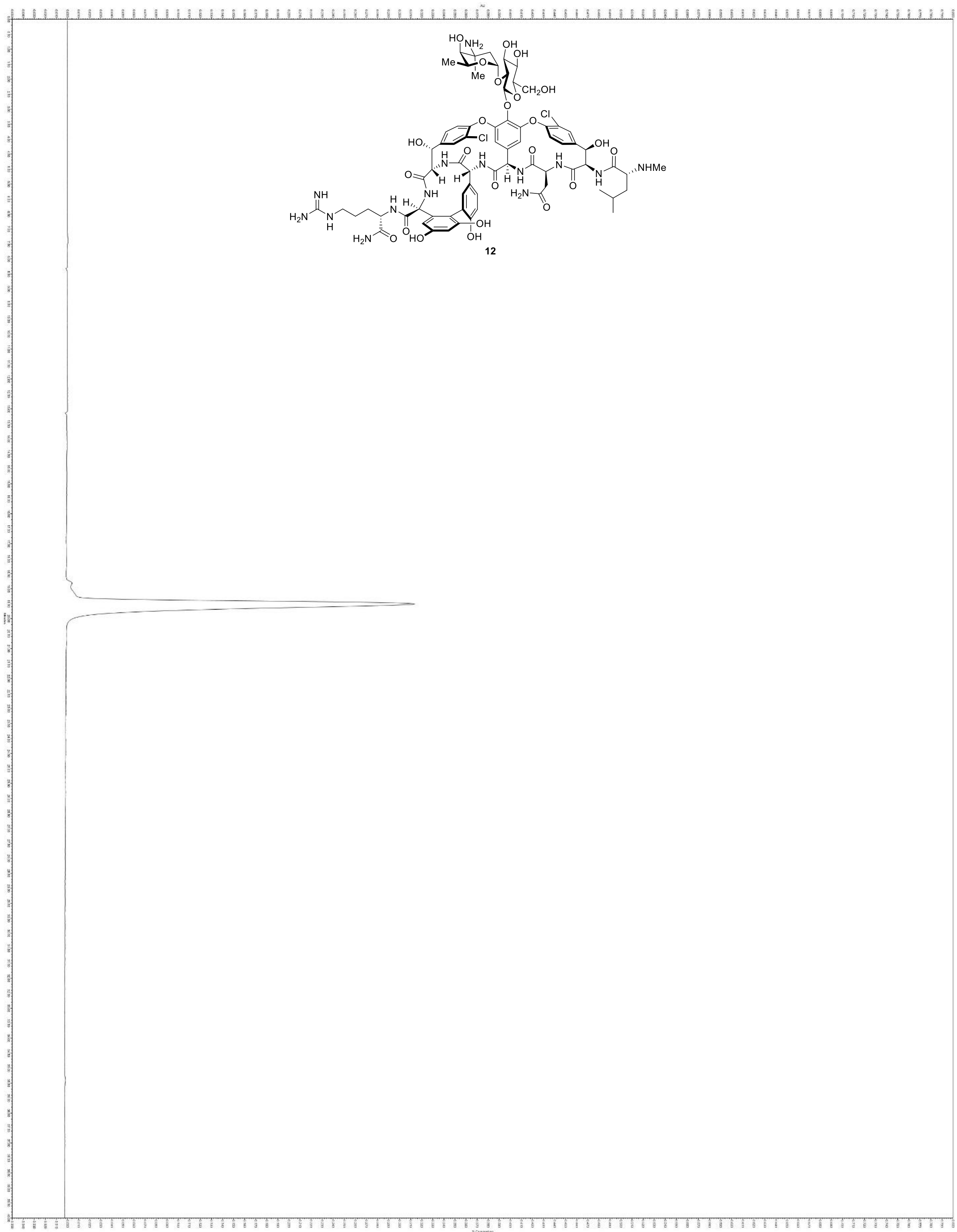
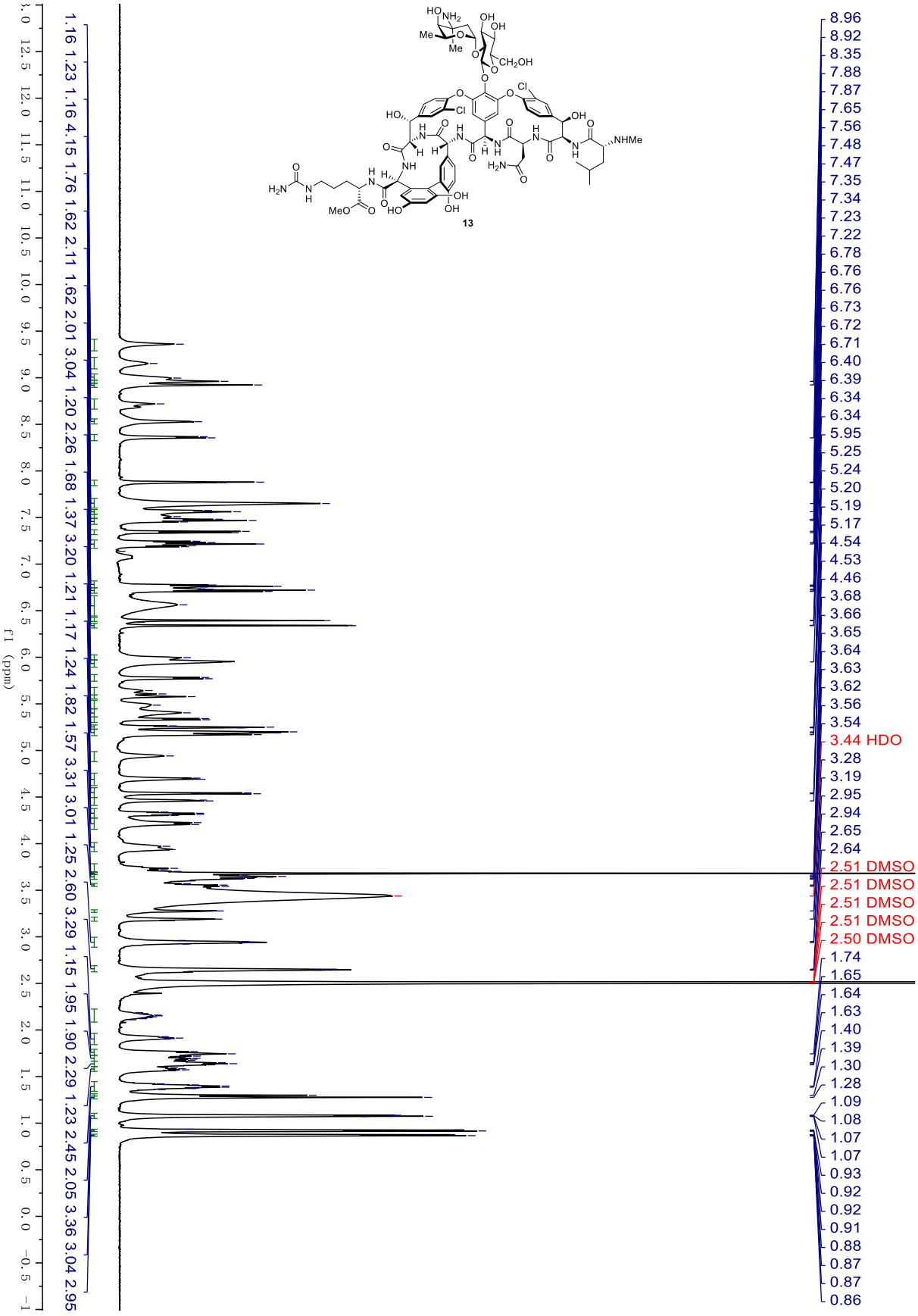
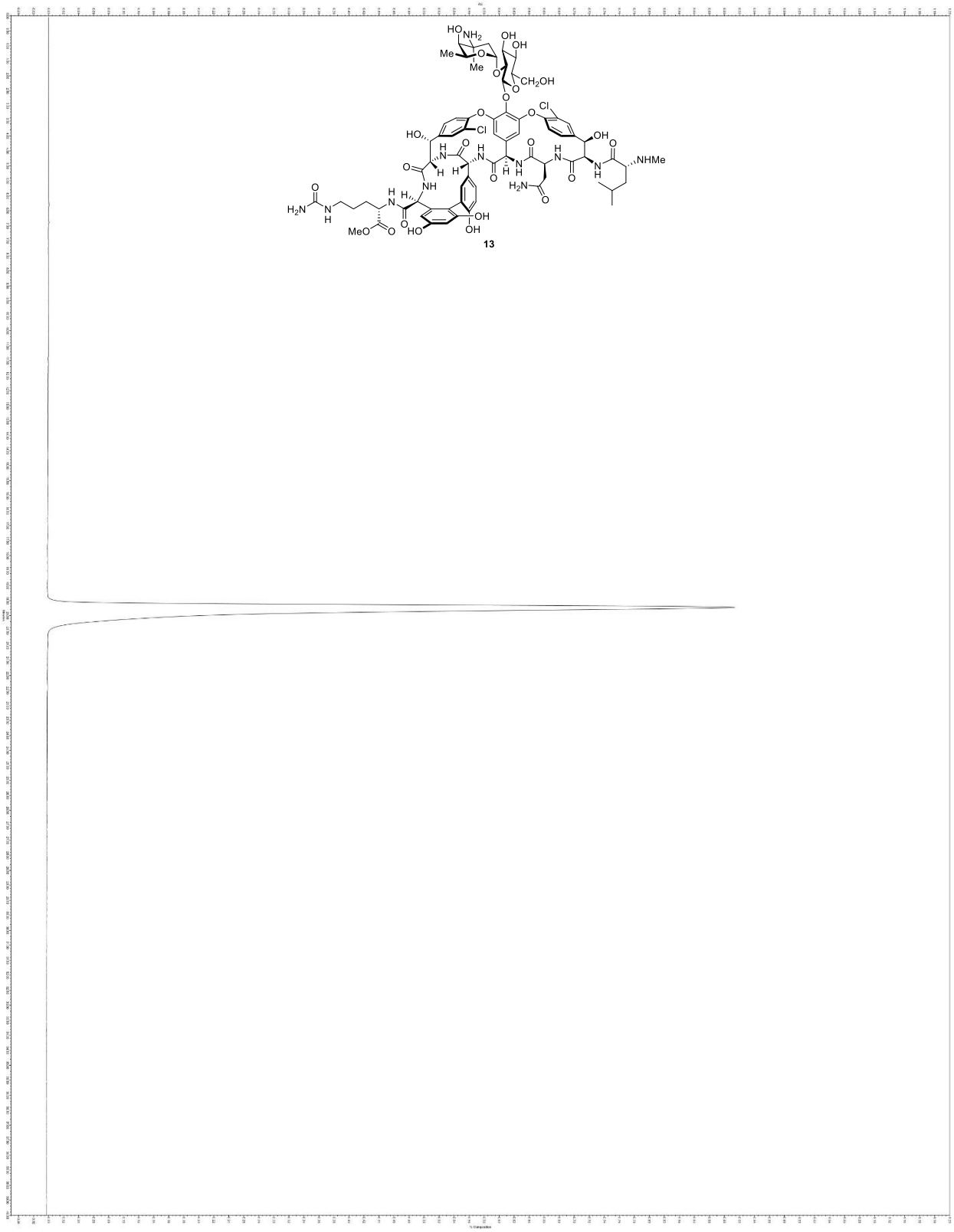
0.85
0.85
2.11 1.69 3.44 1.17 1.41 2.01 1.28 1.35 3.25 1.23 1.16 1.16 1.77 1.23 1.27 1.90 3.07 1.18 1.61 2.07 1.78 1.71 2.27 2.17 2.17 3.11 2.15 1.14 3.10 2.07 1.79 1.21 3.22 3.17 3.30


12


13
f1 (ppm)
8.96
8.92
8.35
7.88
7.87
7.65
7.56
7.48
7.47
7.35
7.34
7.23
7.22
6.78
6.76
6.76
6.73
6.72
6.71
6.40
6.39
6.34
6.34
5.95
5.25
5.24
5.20
5.19
5.17
4.54
4.53
4.46
3.68
3.66
3.65
3.64
3.63
3.62
3.56
3.54
3.44 HDO
3.28
3.19
2.95
2.94
2.65
2.64
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
1.74
1.65
1.64
1.63
1.40
1.39
1.30
1.28
1.09
1.08
1.07
1.07
0.93
0.92
0.92
0.91
0.88
0.87
0.87
0.86
1.16 1.23 1.16 4.15 1.76 1.62 2.11 1.62 2.01 3.04 1.20 2.26 1.68 1.37 3.20 1.21 1.17 1.24 1.82 1.57 3.31 3.01 1.25 2.60 3.29 1.15 1.95 1.90 2.29 1.23 2.45 2.05 3.36 3.04 2.95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OH
OH
Me
O
Me
O
O
CH2OH
O
Cl
O
O
Cl
HO
OH
H
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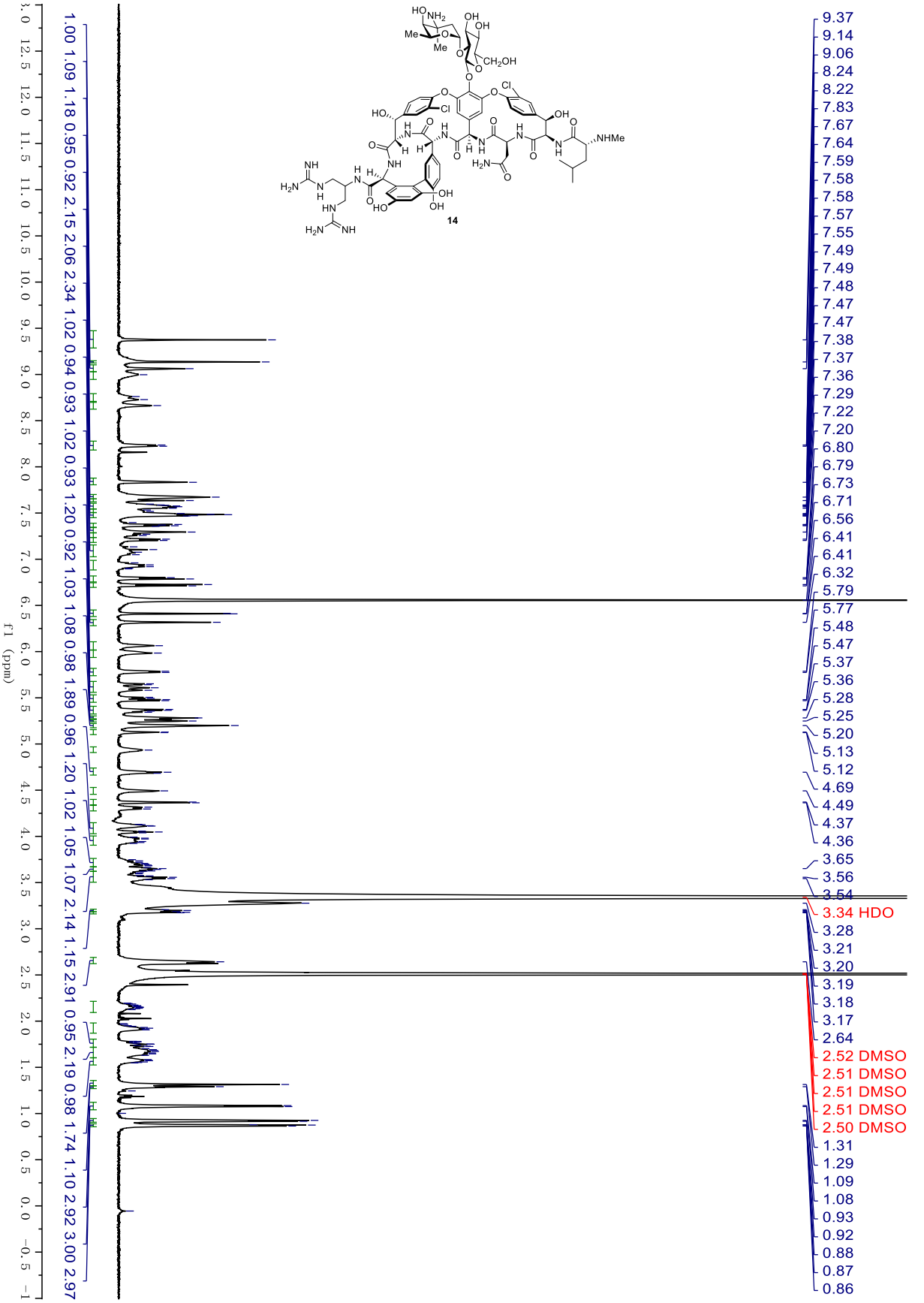
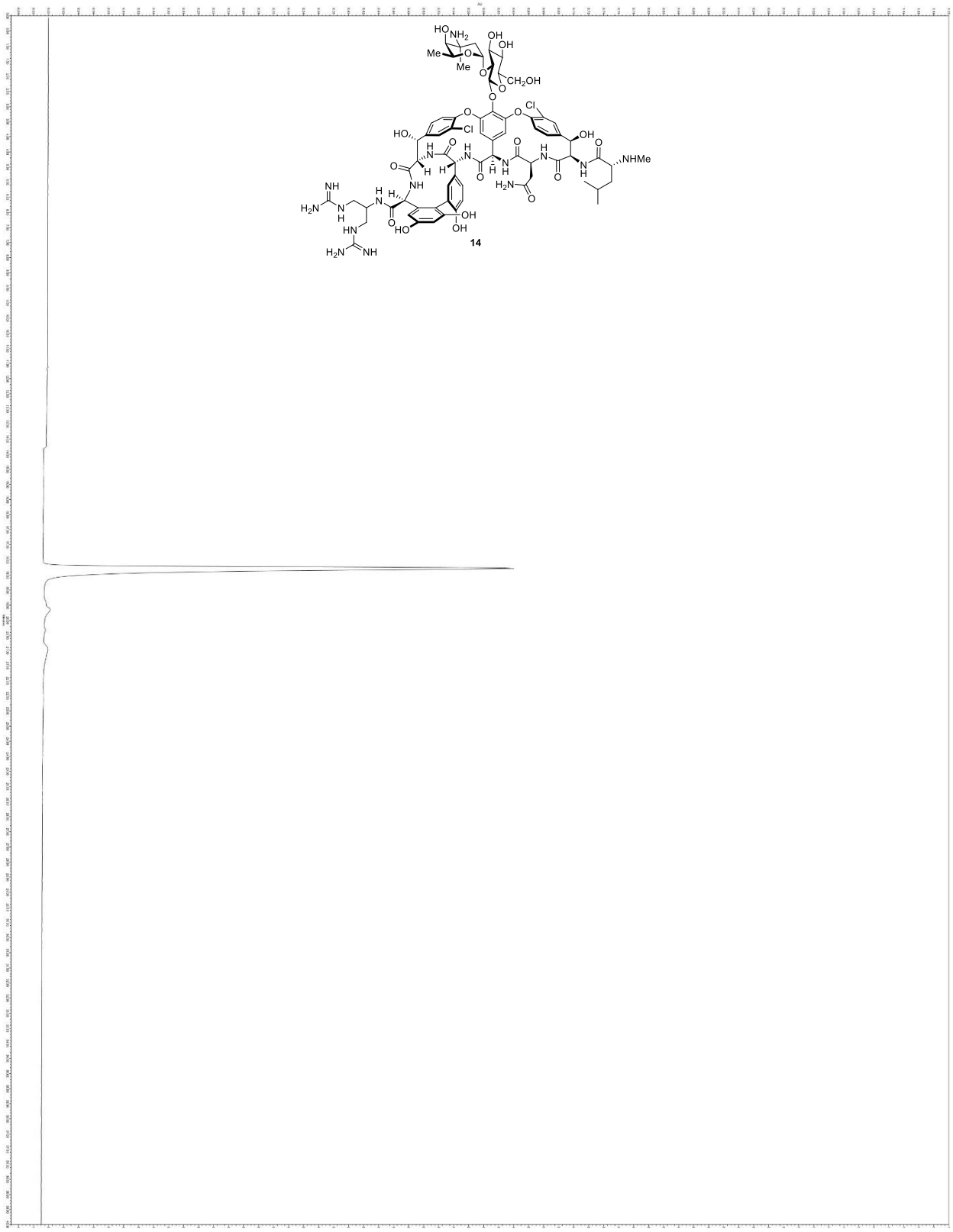
O
H
N
O
H
N
O
H
N
O
NHMe
O
H
N
O
NH
H
N
H
N
O
H2N
O
O
H2N
N
H
O
MeO
O
HO
OH
OH

13


14
f1 (ppm)
1.00 1.09 1.18 0.95 0.92 2.15 2.06 2.34 1.02 0.94 0.93 1.02 0.93 1.20 0.92 1.03 1.08 0.98 1.89 0.96 1.20 1.02 1.05 1.07 2.14 1.15 2.91 0.95 2.19 0.98 1.74 1.10 2.92 3.00 2.97
9.37
9.14
9.06
8.24
8.22
7.83
7.67
7.64
7.59
7.58
7.58
7.57
7.55
7.49
7.49
7.48
7.47
7.47
7.38
7.37
7.36
7.29
7.22
7.20
6.80
6.79
6.73
6.71
6.56
6.41
6.41
6.32
5.79
5.77
5.48
5.47
5.37
5.36
5.28
5.25
5.20
5.13
5.12
4.69
4.49
4.37
4.36
3.65
3.56
3.54
3.34 HDO
3.28
3.21
3.20
3.19
3.18
3.17
2.64
2.52 DMSO
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
1.31
1.29
1.09
1.08
0.93
0.92
0.88
0.87
0.86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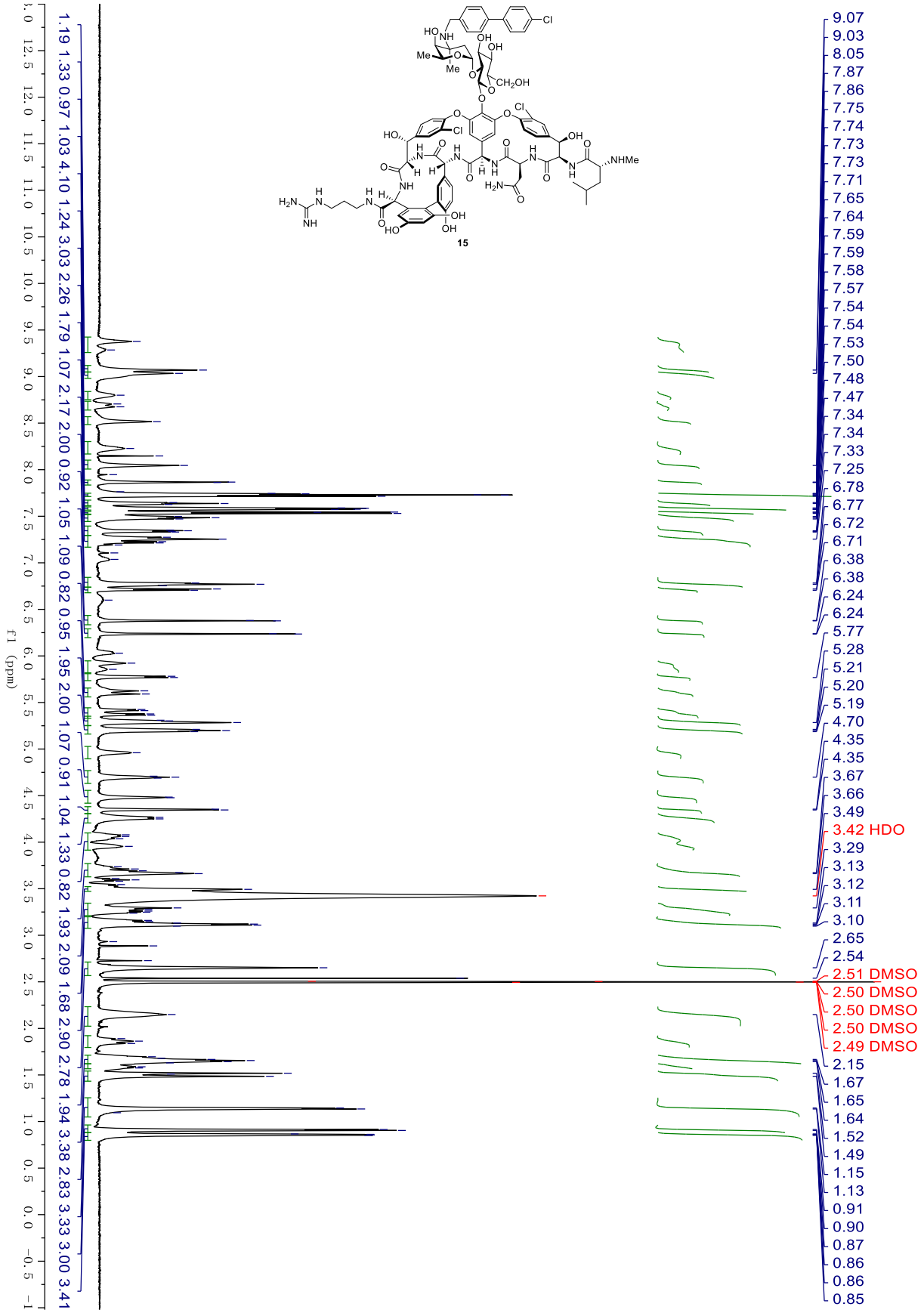
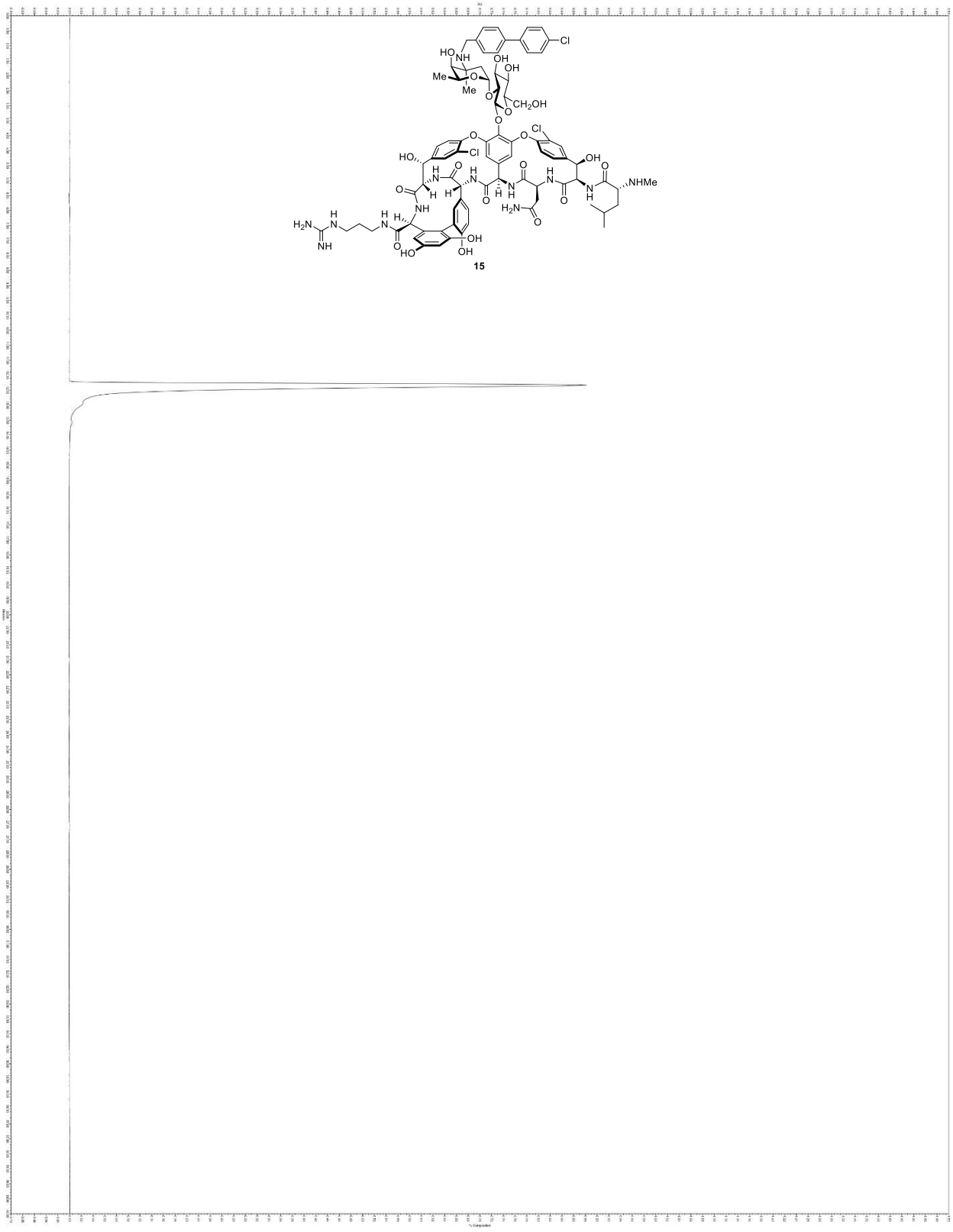
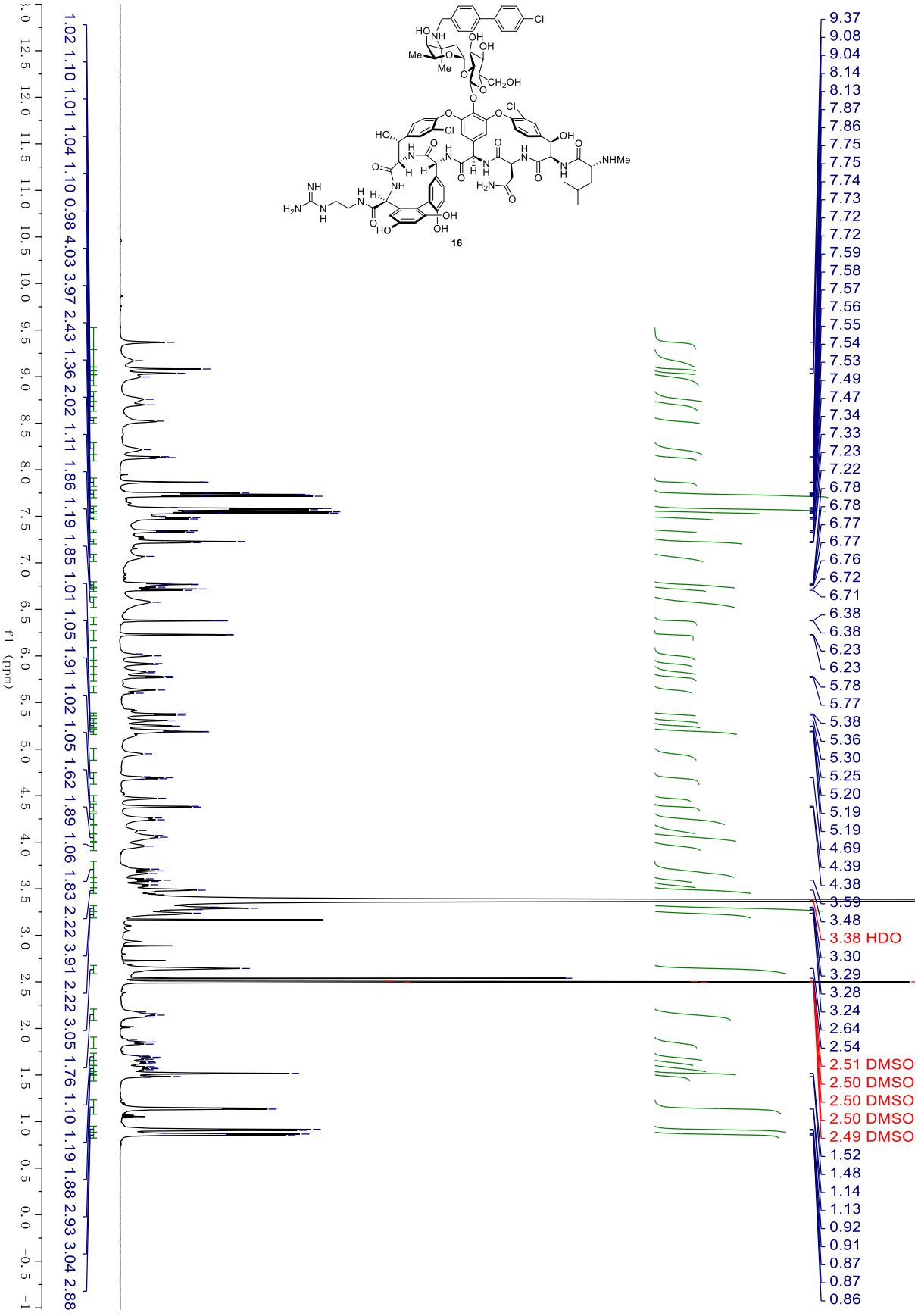

15
f1 (ppm)
1.19 1.33 0.97 1.03 4.10 1.24 3.03 2.26 1.79 1.07 2.17 2.00 0.92 1.05 1.09 0.82 0.95 1.95 2.00 1.07 0.91 1.04 1.33 0.82 1.93 2.09 1.68 2.90 2.78 1.94 3.38 2.83 3.33 3.00 3.41
9.07 9.03 8.05 7.87 7.86 7.75 7.74 7.73 7.73 7.71 7.65 7.64 7.59 7.59 7.58 7.57 7.54 7.54 7.53 7.50 7.48 7.47 7.34 7.34 7.33 7.25 6.78 6.77 6.72 6.71 6.38 6.38 6.24 6.24 5.77 5.28 5.21 5.20 5.19 4.70 4.35 4.35 3.67 3.66 3.49 3.42 HDO 3.29 3.13 3.12 3.11 3.10 2.65 2.54 2.51 DMSO 2.50 DMSO 2.50 DMSO 2.50 DMSO 2.49 DMSO 2.15 1.67 1.65 1.64 1.52 1.49 1.15 1.13 0.91 0.90 0.87 0.86 0.86 0.85


15


16
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9.08
9.04
8.14
8.13
7.87
7.86
7.75
7.75
7.74
7.73
7.72
7.72
7.59
7.58
7.57
7.56
7.55
7.54
7.53
7.49
7.47
7.34
7.33
7.23
7.22
6.78
6.78
6.77
6.77
6.76
6.72
6.71
6.38
6.38
6.23
6.23
5.78
5.77
5.38
5.36
5.30
5.25
5.20
5.19
5.19
4.69
4.39
4.38
3.59
3.48
3.38 HDO
3.30
3.29
3.28
3.24
2.64
2.54
2.51 DMSO
2.50 DMSO
2.50 DMSO
2.50 DMSO
2.49 DMSO
1.52
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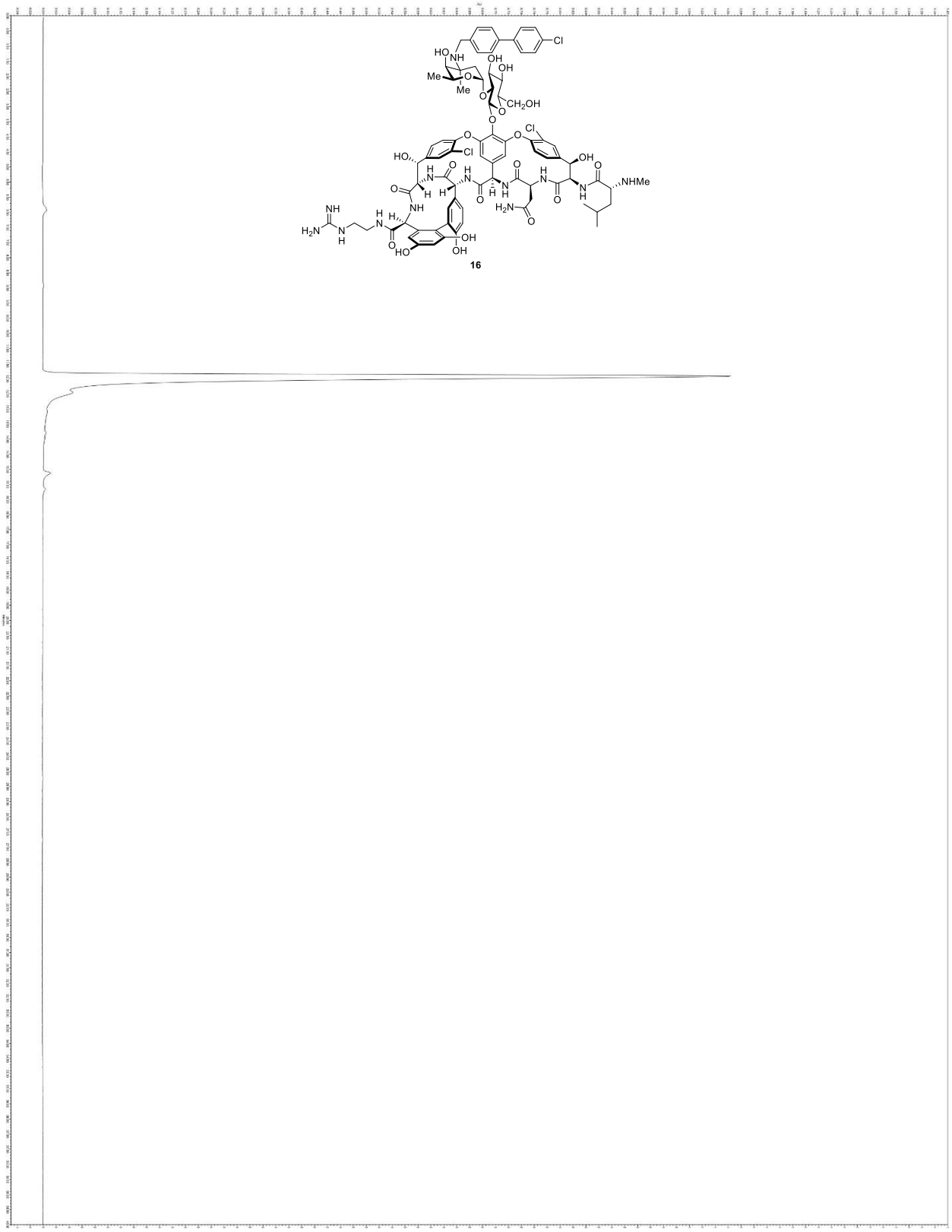
1.14
1.13
0.92
0.91
0.87
0.87
0.86
1.02 1.10 1.01 1.04 1.10 0.98 4.03 3.97 2.43 1.36 2.02 1.11 1.86 1.19 1.85 1.01 1.05 1.91 1.02 1.05 1.62 1.89 1.06 1.83 2.22 3.91 2.22 3.05 1.76 1.10 1.19 1.88 2.93 3.04 2.88
f1 (ppm)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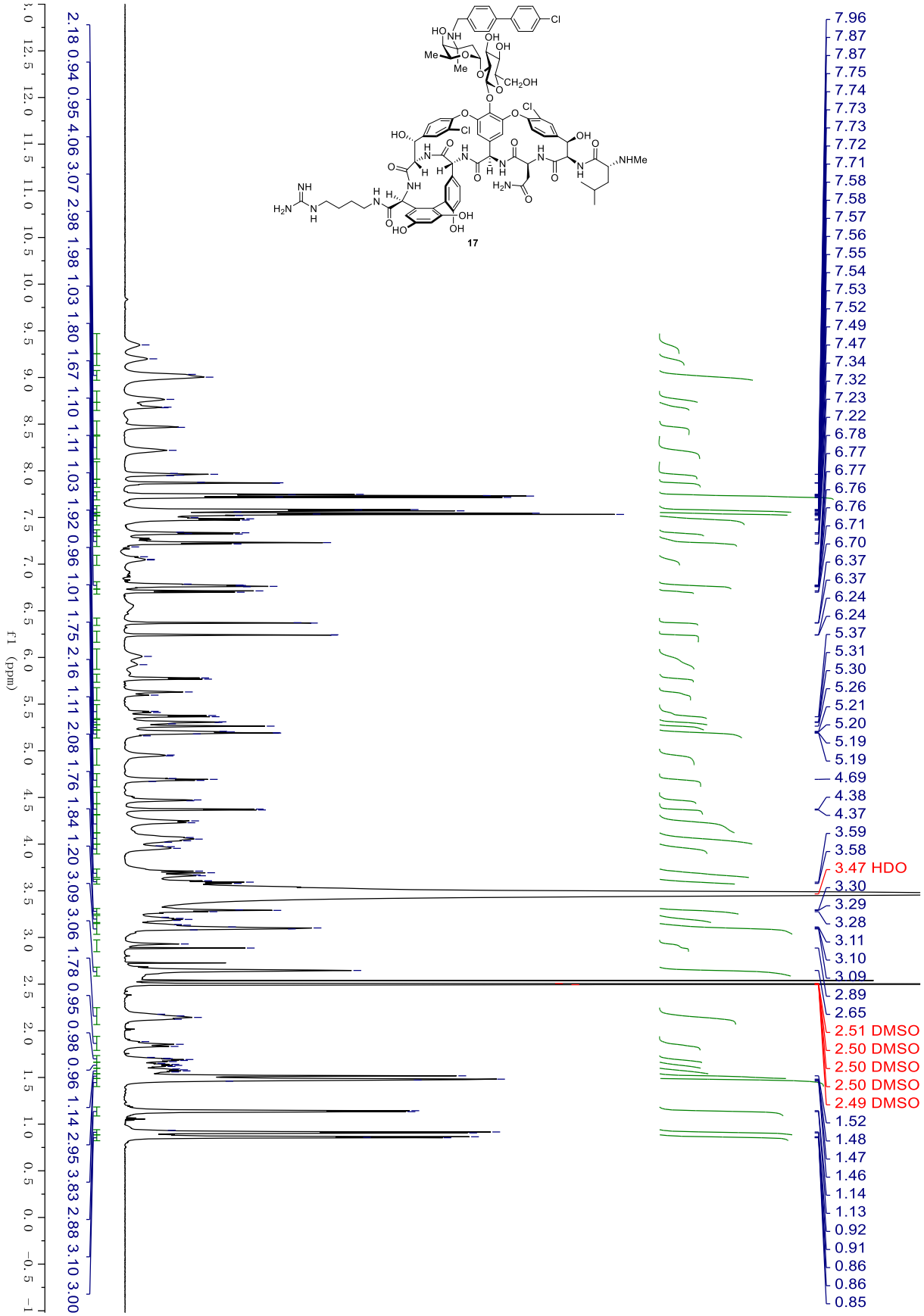
17
7.96
7.87
7.87
7.75
7.74
7.73
7.73
7.72
7.71
7.58
7.58
7.57
7.56
7.55
7.54
7.53
7.52
7.49
7.47
7.34
7.32
7.23
7.22
6.78
6.77
6.77
6.76
6.76
6.71
6.70
6.37
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6.24
6.24
5.37
5.31
5.30
5.26
5.21
5.20
5.19
5.19
4.69
4.38
4.37
3.59
3.58
3.47 HDO
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3.28
3.11
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3.09
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2.51 DMSO
2.50 DMSO
2.50 DMSO
2.50 DMSO
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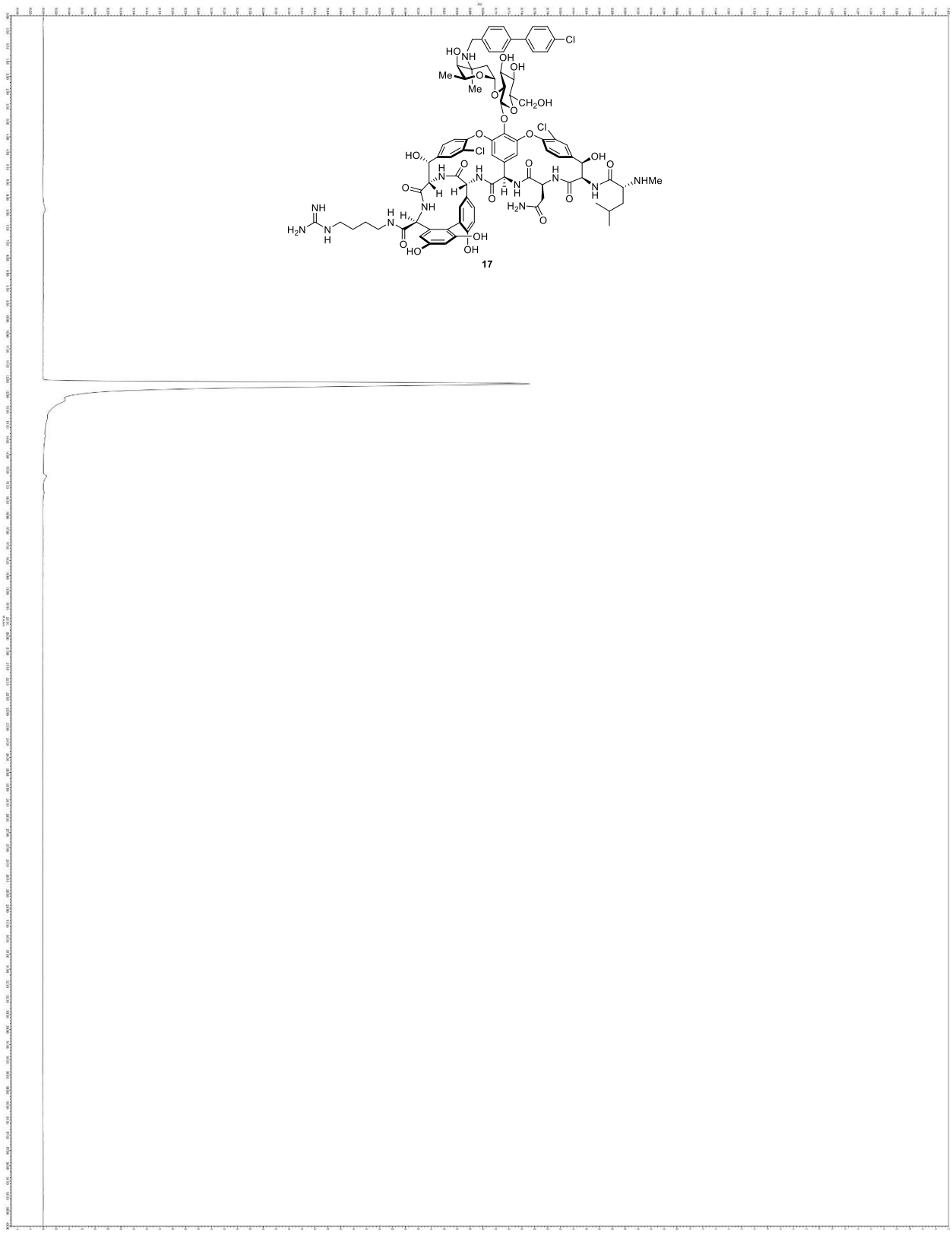
0.85
2.18 0.94 0.95 4.06 3.07 2.98 1.98 1.03 1.80 1.67 1.10 1.11 1.03 1.92 0.96 1.01 1.75 2.16 1.11 2.08 1.76 1.84 1.20 3.09 3.06 1.78 0.95 0.98 0.96 1.14 2.95 3.83 2.88 3.10 3.00
f1 (ppm)



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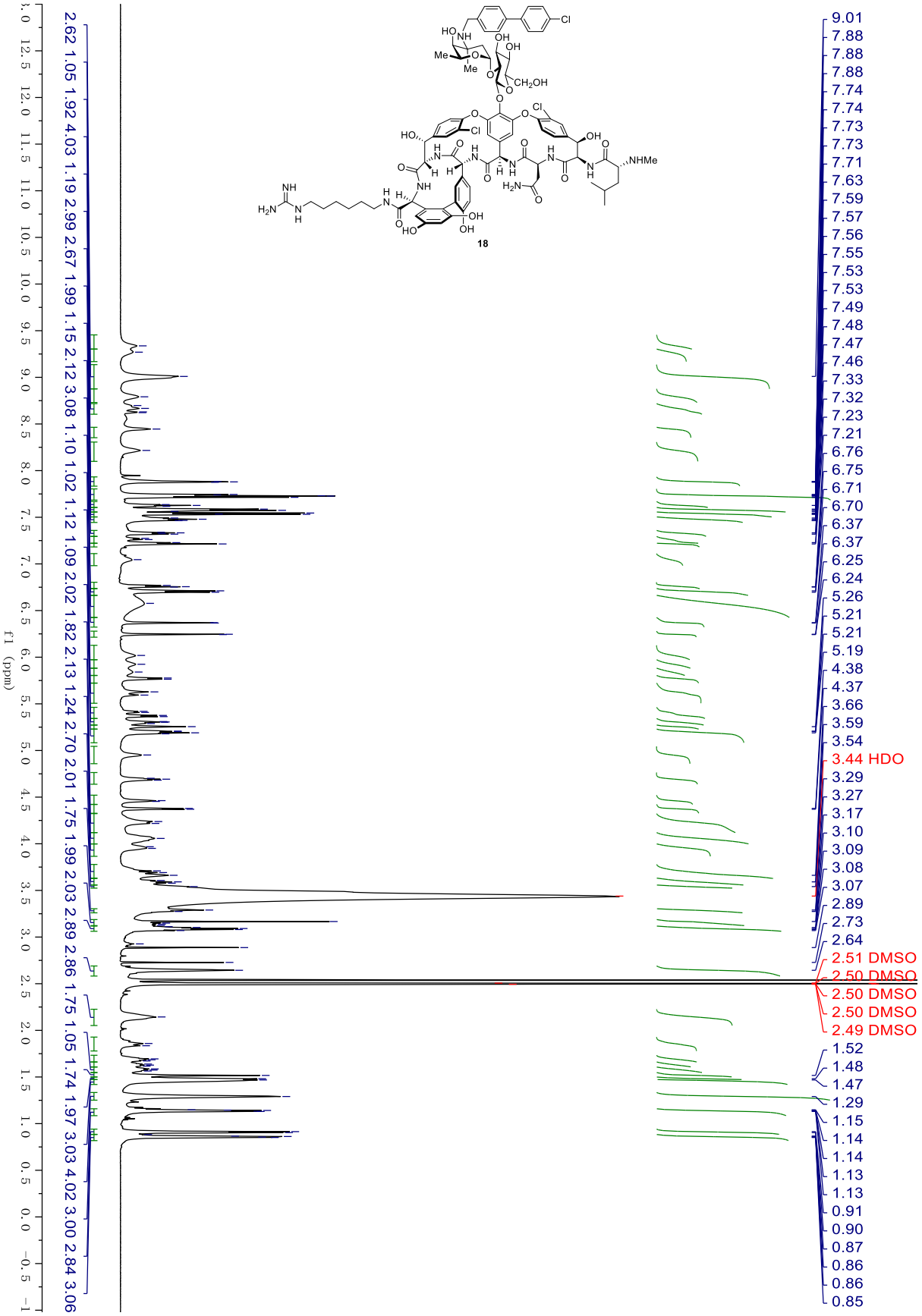
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7.49
7.48
7.47
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7.32
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7.21
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6.71
6.70
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5.19
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3.54
3.44 HDO
3.29
3.27
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0.91
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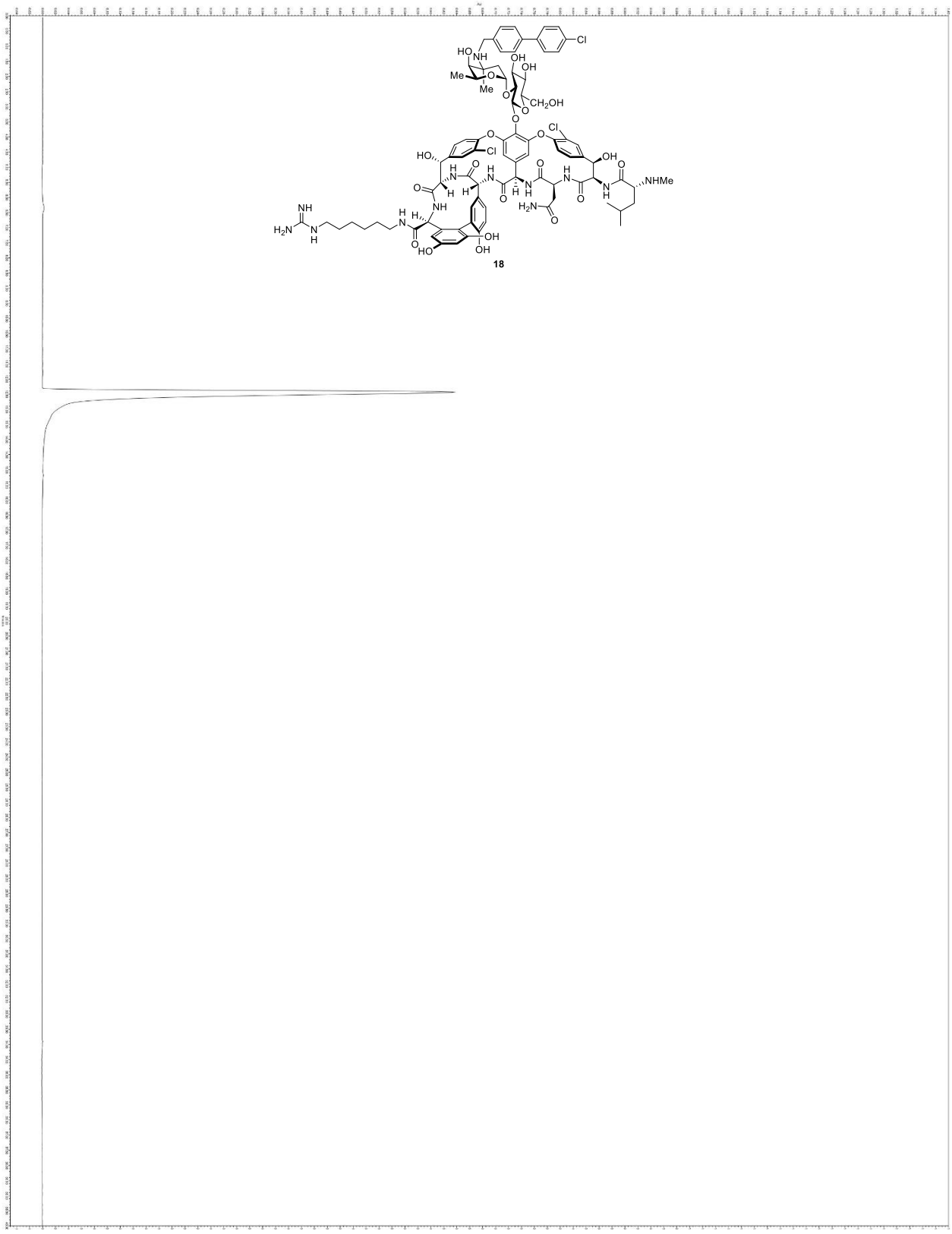
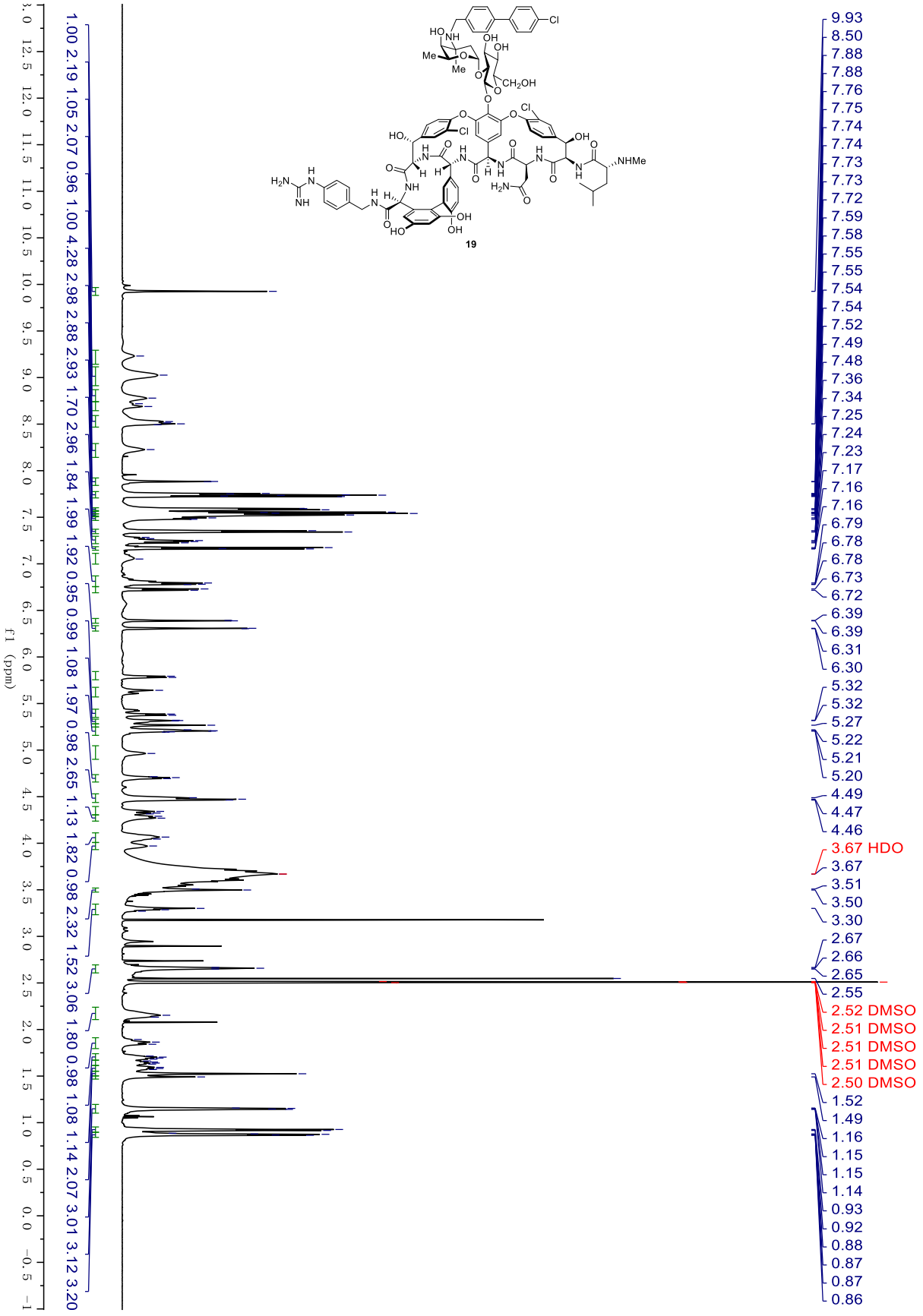
0.85
2.62 1.05 1.92 4.03 1.19 2.99 2.67 1.99 1.15 2.12 3.08 1.10 1.02 1.12 1.09 2.02 1.82 2.13 1.24 2.70 2.01 1.75 1.99 2.03 2.89 2.86 1.75 1.05 1.74 1.97 3.03 4.02 3.00 2.84 3.06
f1 (ppm)


18


19
f1 (ppm)
1.00 2.19 1.05 2.07 0.96 1.00 4.28 2.98 2.88 2.93 1.70 2.96 1.84 1.99 1.92 0.95 0.99 1.08 1.97 0.98 2.65 1.13 1.82 0.98 2.32 1.52 3.06 1.80 0.98 1.08 1.14 2.07 3.01 3.12 3.20
9.93
8.50
7.88
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7.76
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7.74
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7.52
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7.25
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7.16
7.16
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6.78
6.78
6.73
6.72
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5.21
5.20
4.49
4.47
4.46
3.67 HDO
3.67
3.51
3.50
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2.52 DMSO
2.51 DMSO
2.51 DMSO
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2.50 DMSO
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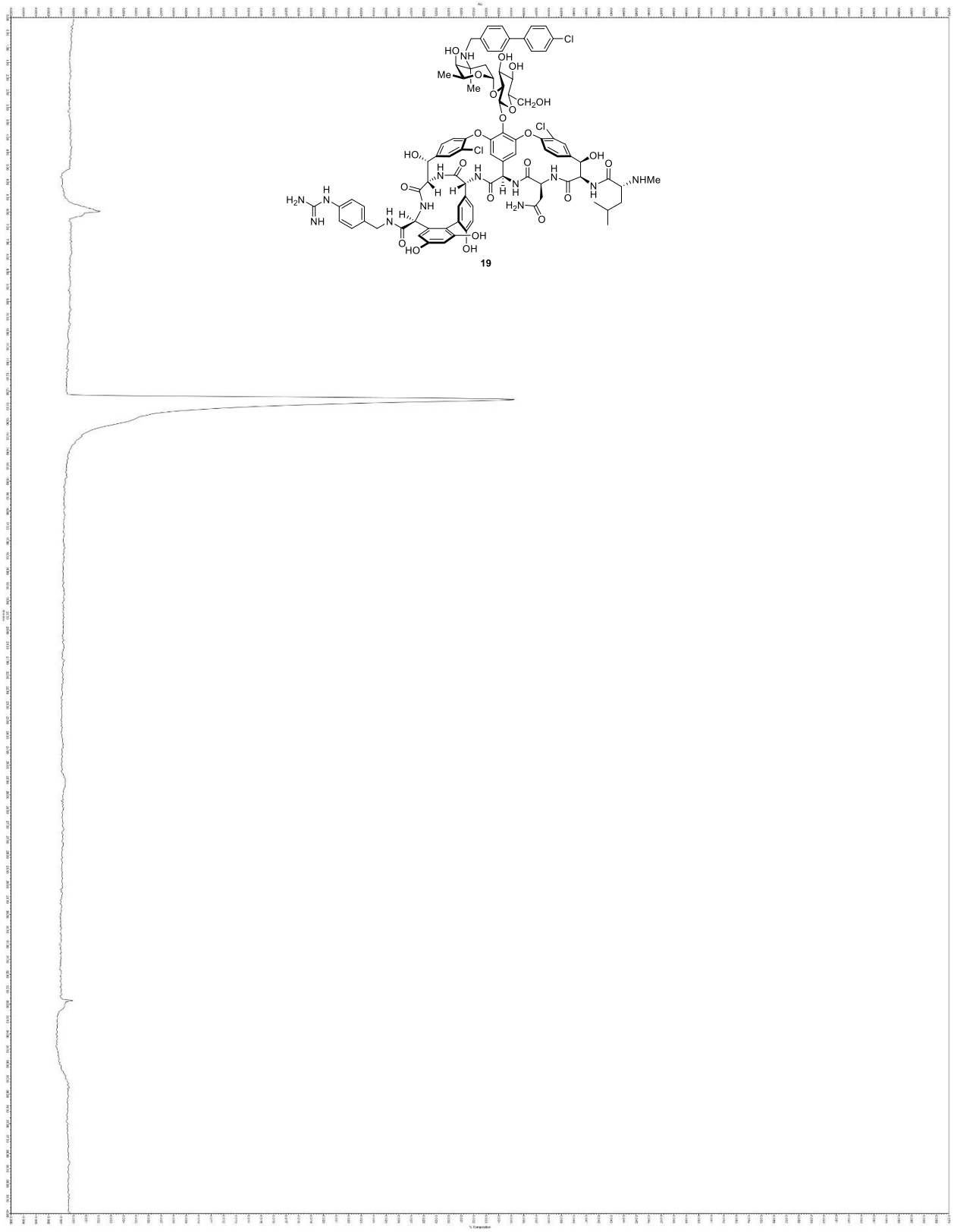
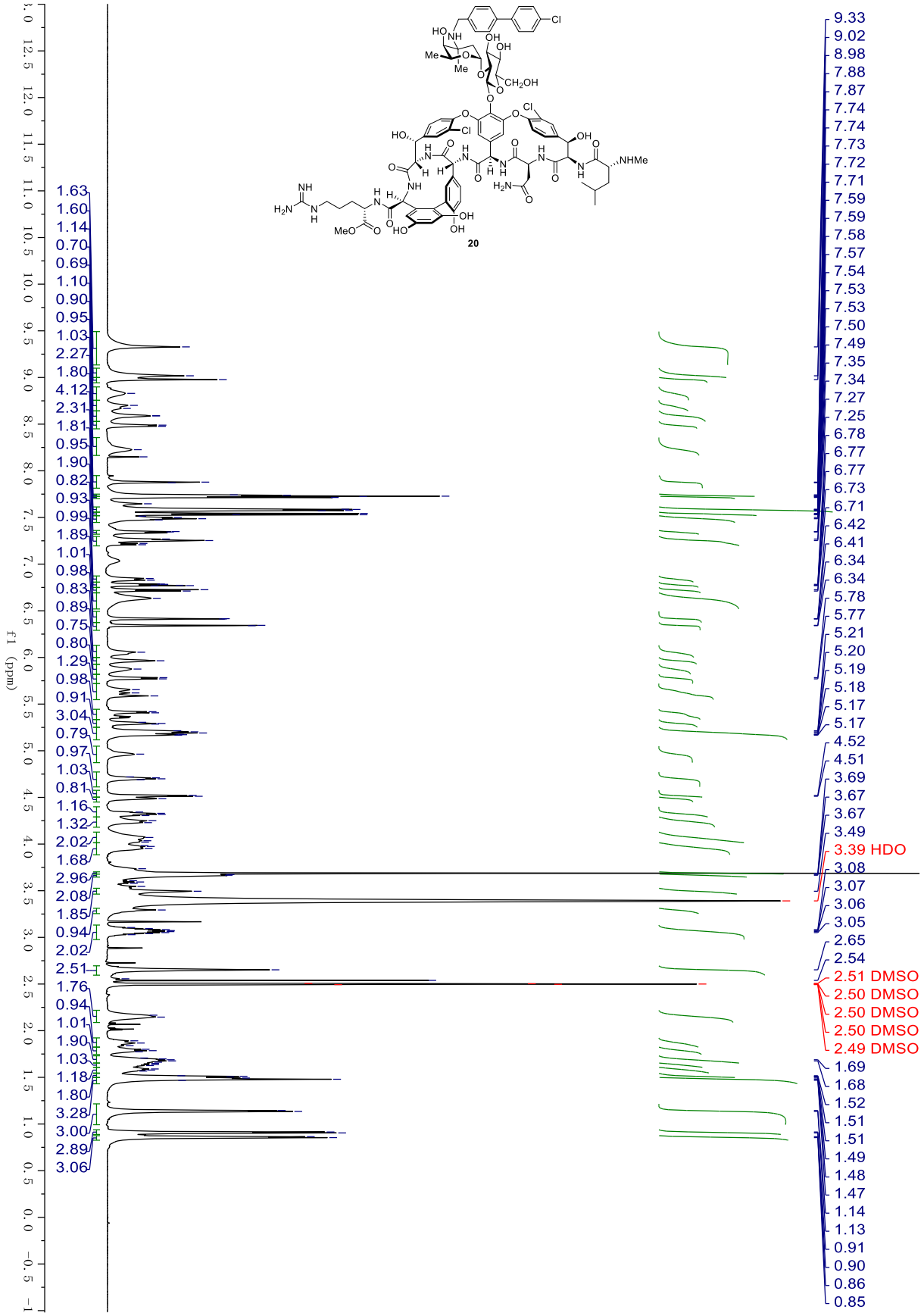
0.86


19


20
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0.70
0.69
1.10
0.90
0.95
1.03
2.27
1.80
4.12
2.31
1.81
0.95
1.90
0.82
0.93
0.99
1.89
1.01
0.98
0.83
0.89
0.75
0.80
1.29
0.98
0.91
3.04
0.79
0.97
1.03
0.81
1.16
1.32
2.02
1.68
2.96
2.08
1.85
0.94
2.02
2.51
1.76
0.94
1.01
1.90
1.03
1.18
1.80
3.28
3.00
2.89
3.06
9.33
9.02
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7.74
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5.17
4.52
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3.49
3.39 HDO
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2.50 DMSO
2.50 DMSO
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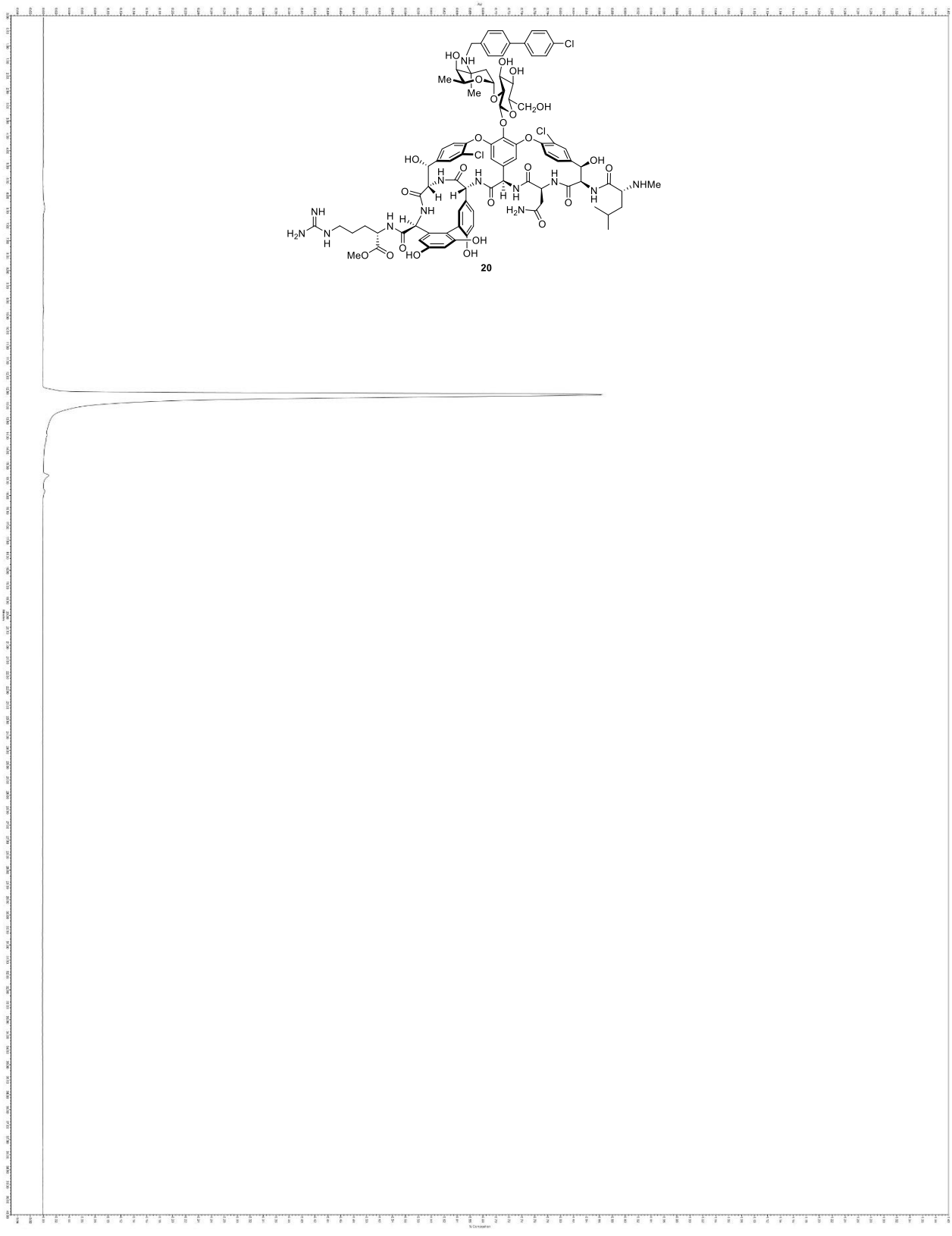
0.90
0.86
0.85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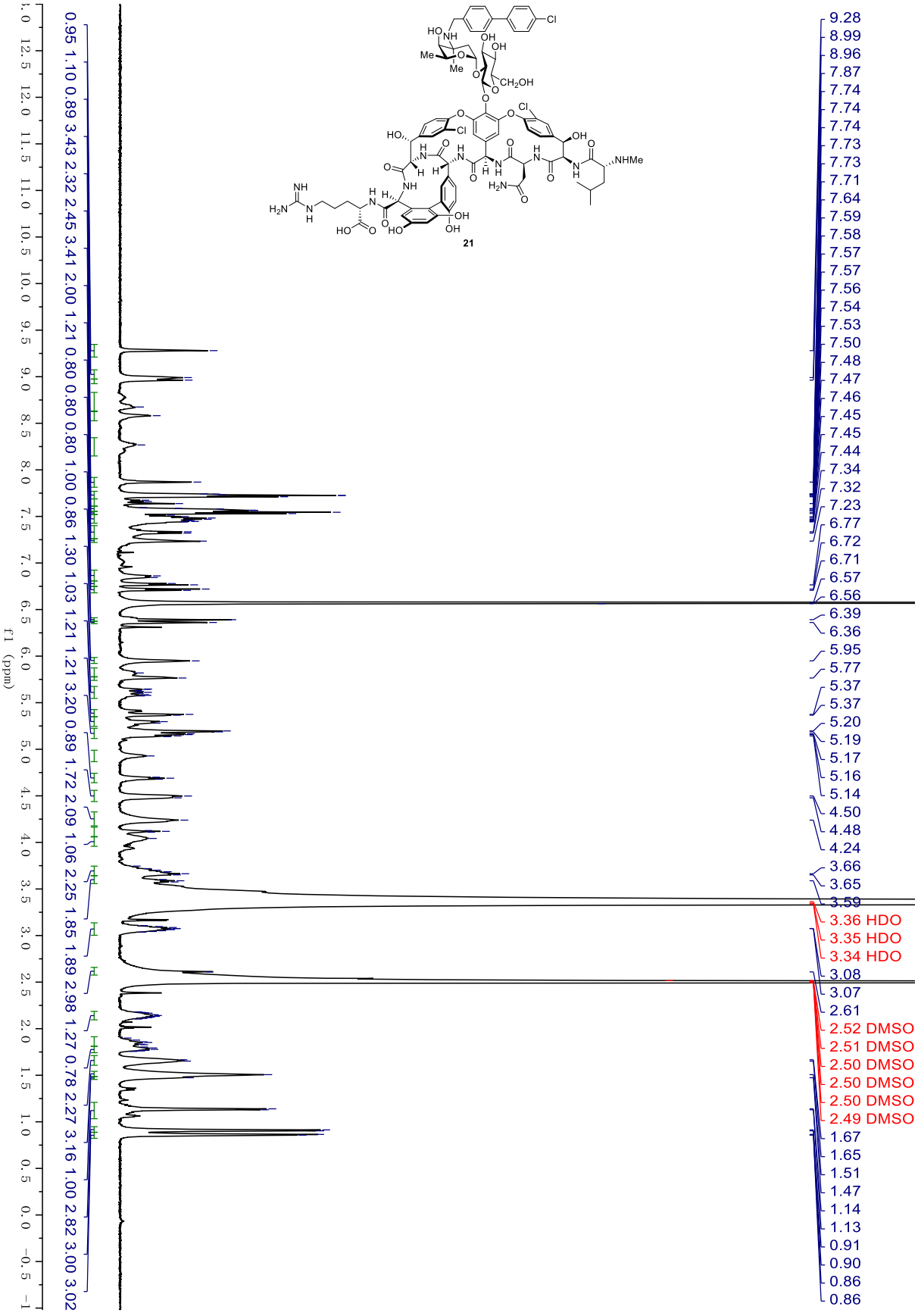
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8.96
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3.59
3.36 HDO
3.35 HDO
3.34 HDO
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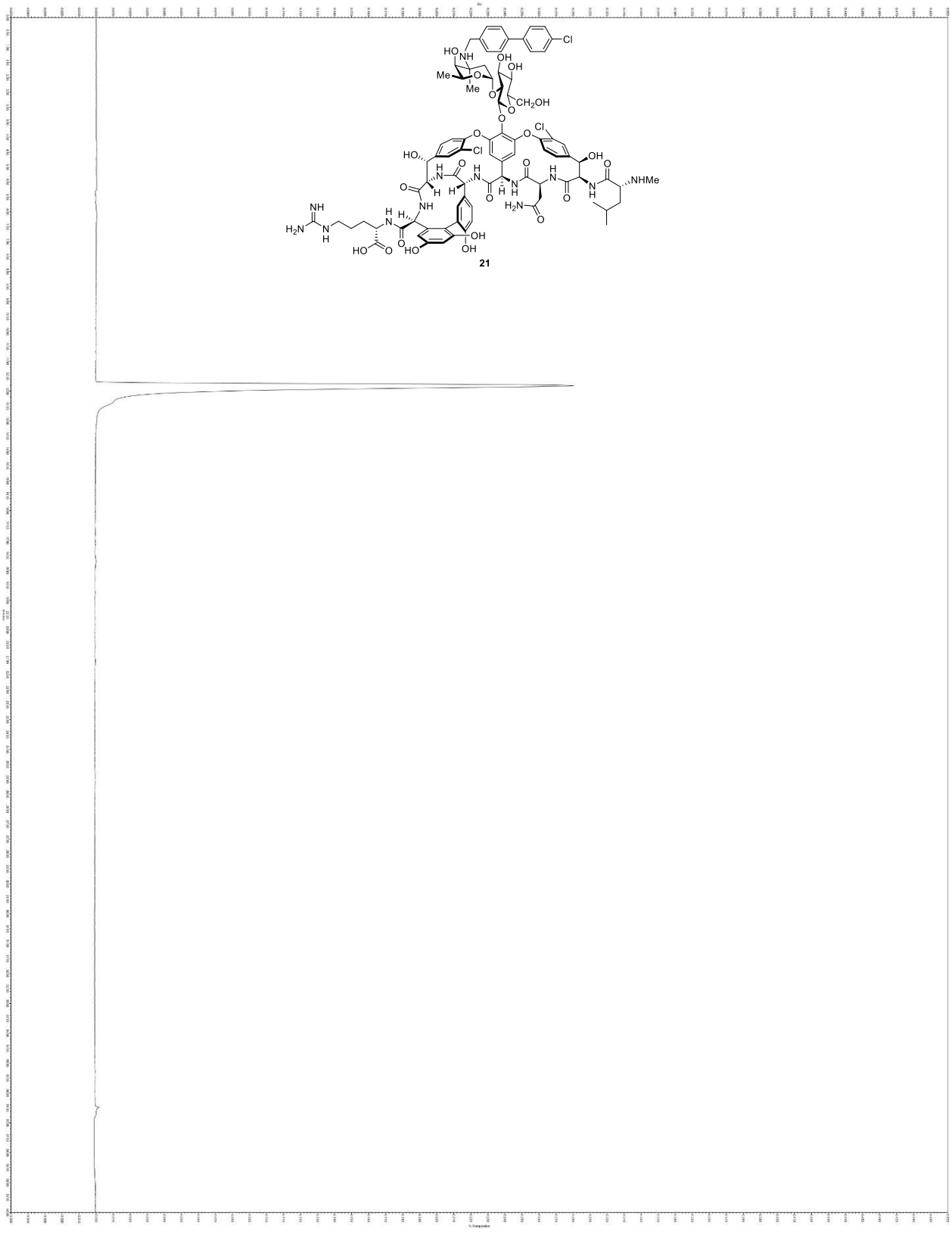
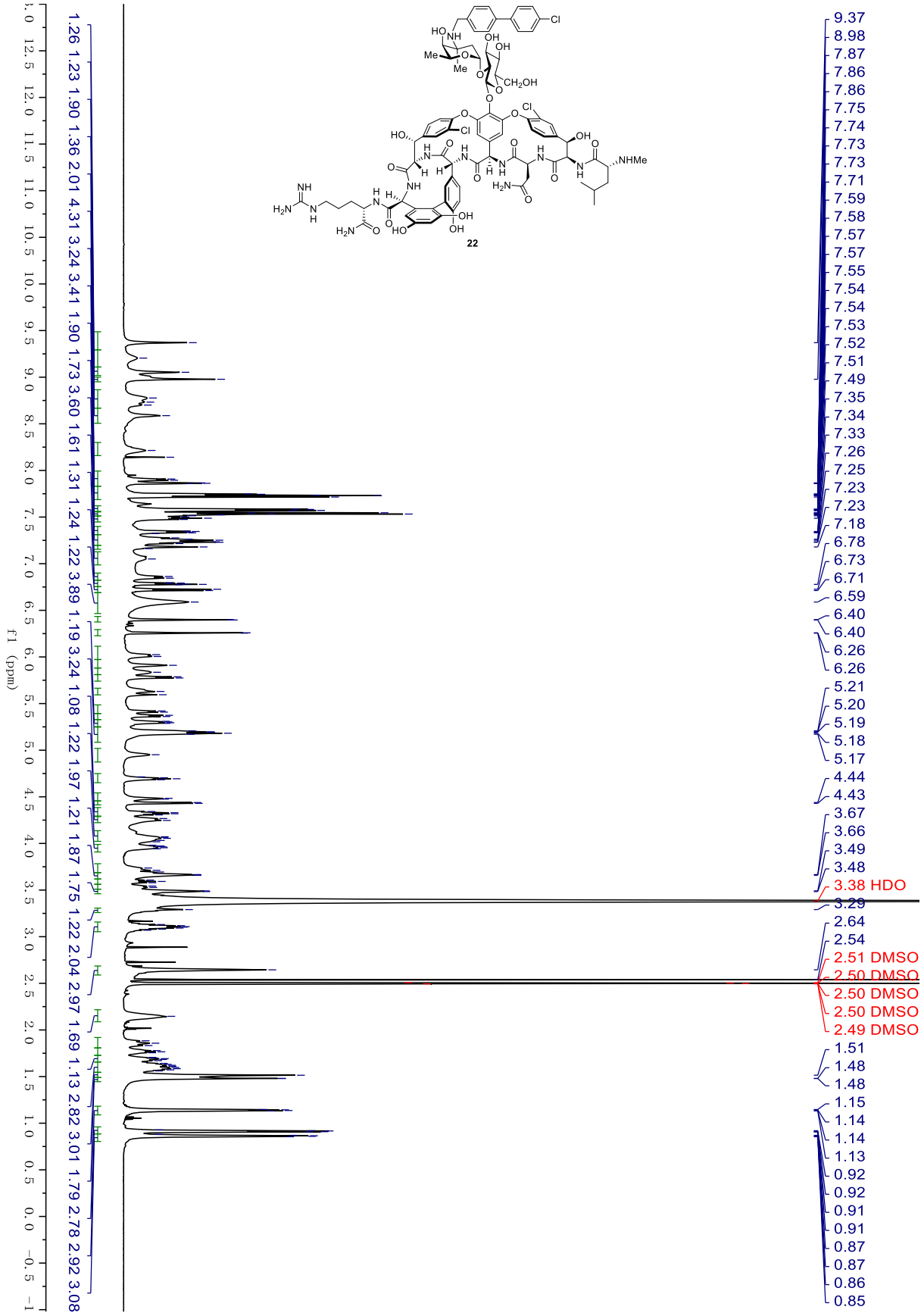
0.95 1.10 0.89 3.43 2.32 2.45 3.41 2.00 1.21 0.80 0.80 0.80 1.00 0.86 1.30 1.03 1.21 1.21 3.20 0.89 1.72 2.09 1.06 2.25 1.85 1.89 2.98 1.27 0.78 2.27 3.16 1.00 2.82 3.00 3.02
f1 (ppm)


21


22
f1 (ppm)
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7.86
7.86
7.75
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7.73
7.73
7.71
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5.18
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4.44
4.43
3.67
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3.48
3.38 HDO
3.29
2.64
2.54
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2.50 DMSO
2.50 DMSO
2.50 DMSO
2.49 DMSO
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0.92
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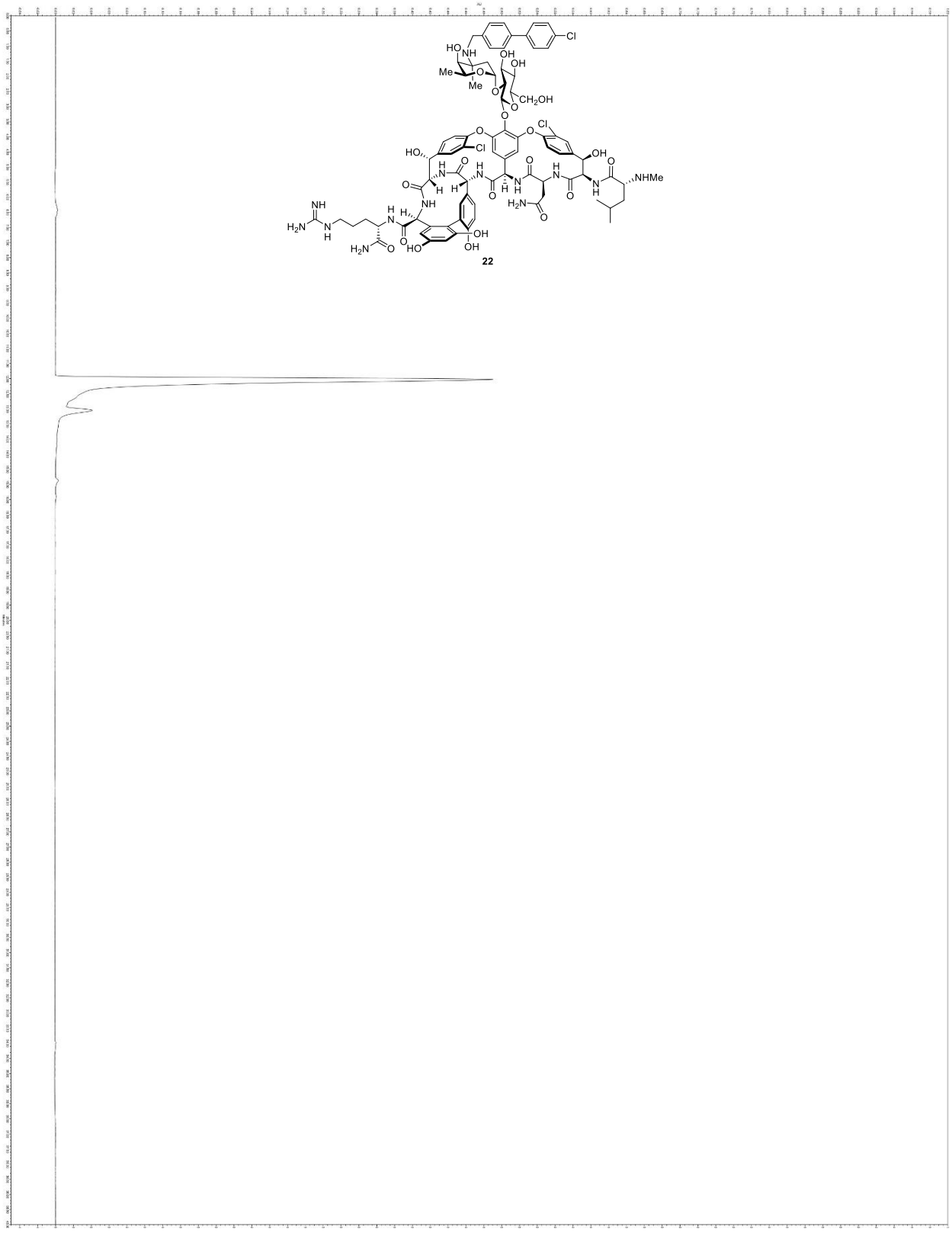
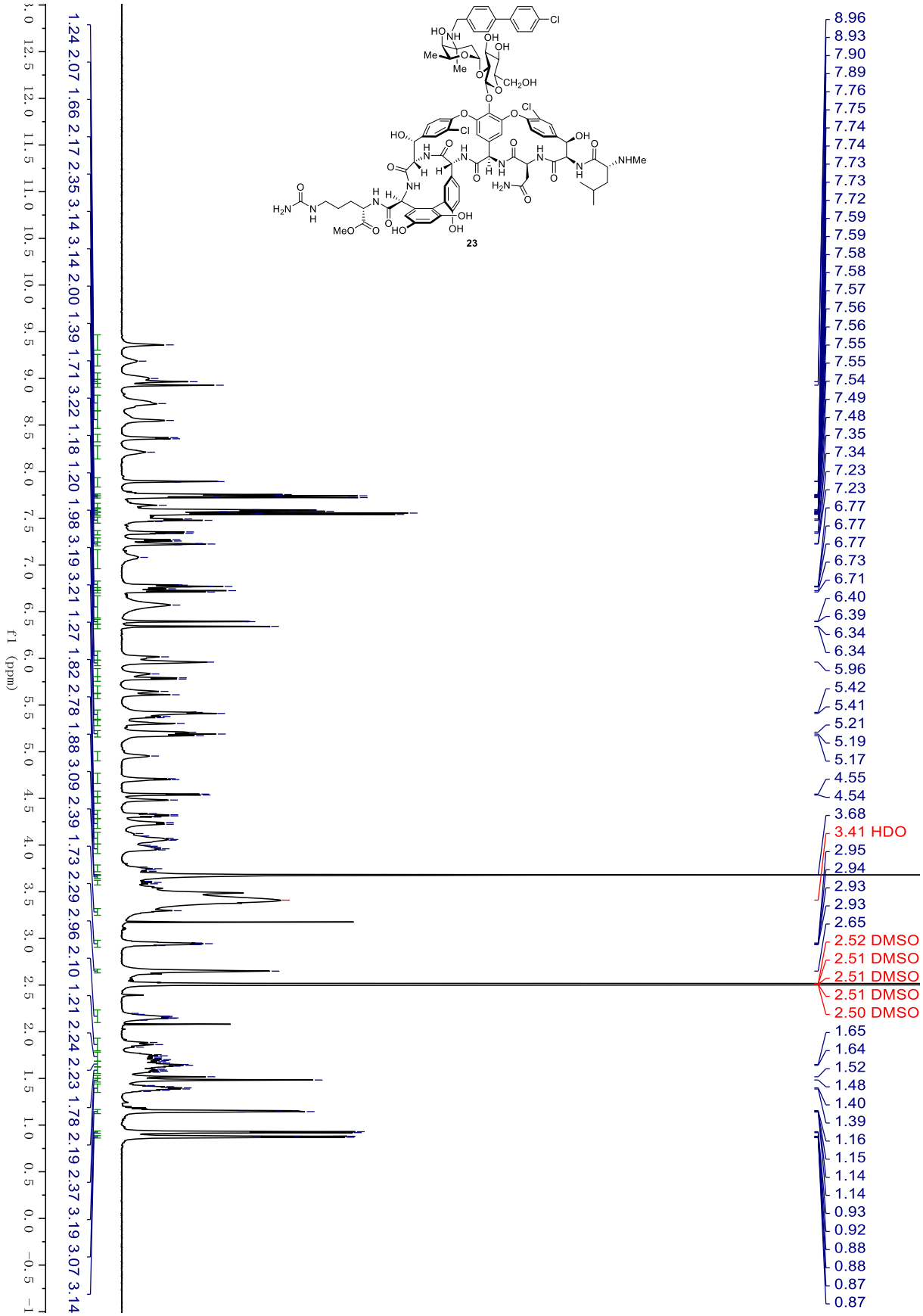
0.86
0.85
1.26 1.23 1.90 1.36 2.01 4.31 3.24 3.41 1.90 1.73 3.60 1.61 1.31 1.24 1.22 3.89 1.19 3.24 1.08 1.22 1.97 1.21 1.87 1.75 1.22 2.04 2.97 1.69 1.13 2.82 3.01 1.79 2.78 2.92 3.08


22


23
f1 (ppm)
1.24 2.07 1.66 2.17 2.35 3.14 3.14 2.00 1.39 1.71 3.22 1.18 1.20 1.98 3.19 3.21 1.27 1.82 2.78 1.88 3.09 2.39 1.73 2.29 2.96 2.10 1.21 2.24 2.23 1.78 2.19 2.37 3.19 3.07 3.14
8.96
8.93
7.90
7.89
7.76
7.75
7.74
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6.77
6.77
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6.39
6.34
6.34
5.96
5.42
5.41
5.21
5.19
5.17
4.55
4.54
3.68
3.41 HDO
2.95
2.94
2.93
2.93
2.65
2.52 DMSO
2.51 DMSO
2.51 DMSO
2.51 DMSO
2.50 DMSO
1.65
1.64
1.52
1.48
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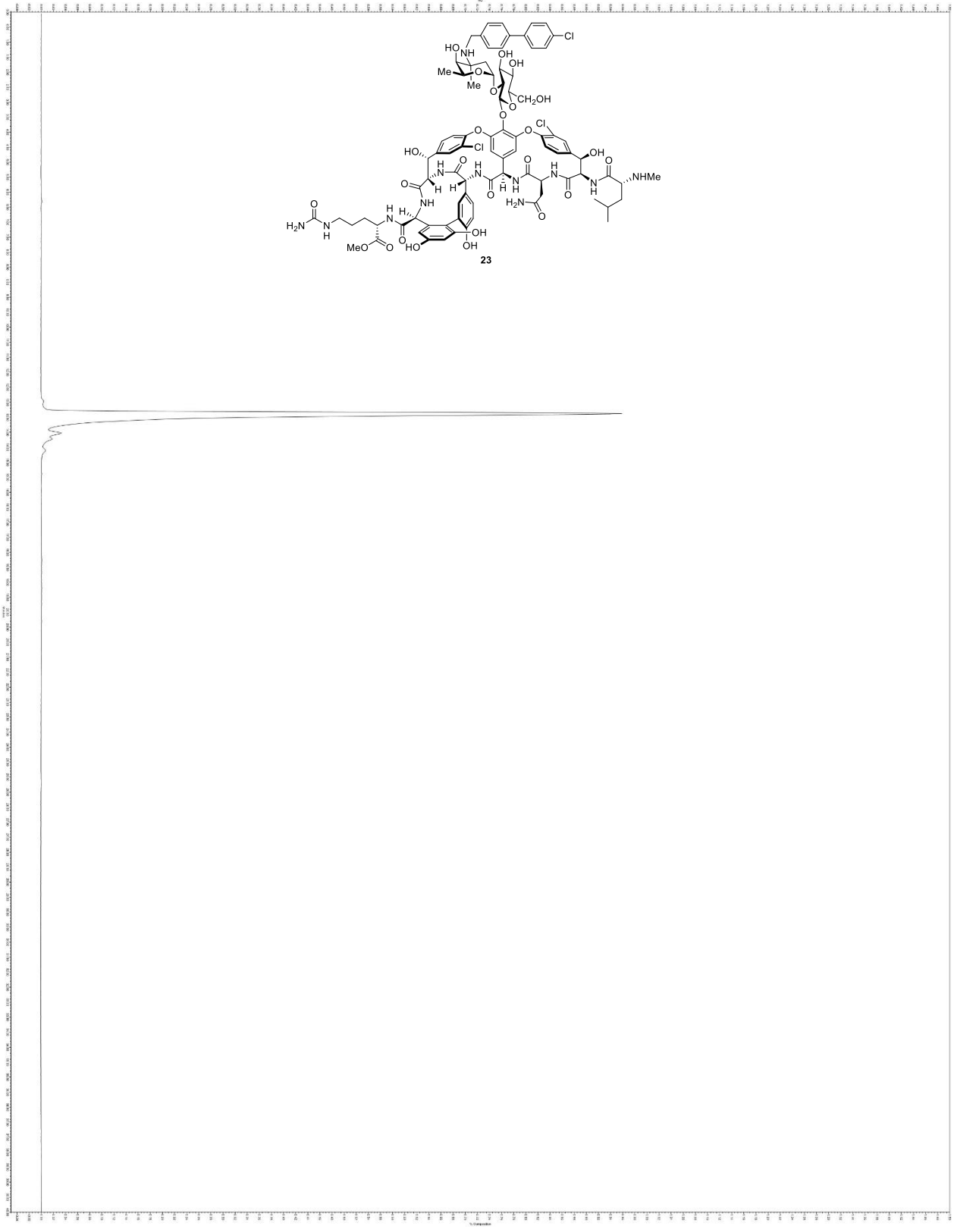
0.87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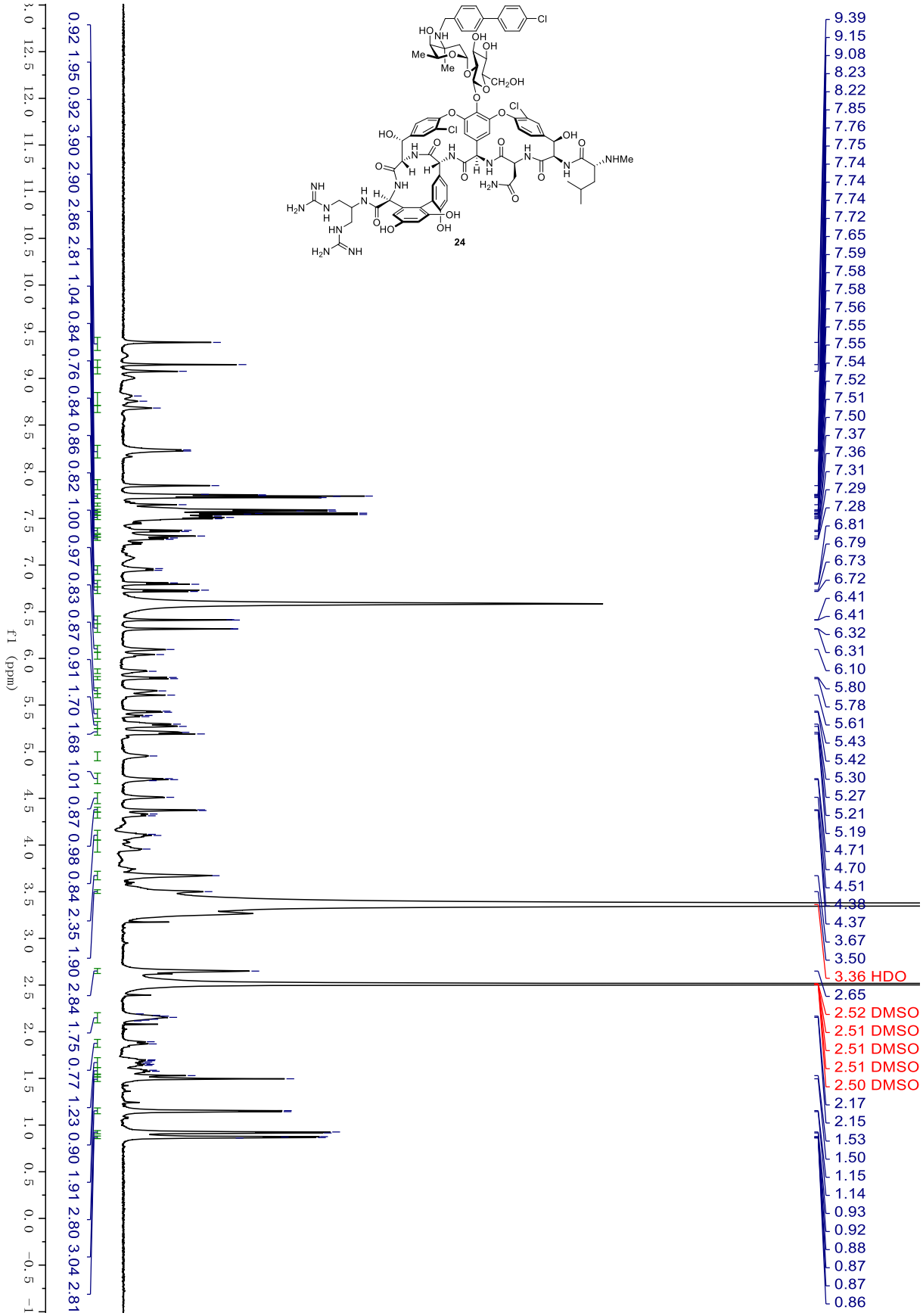
24
9.39
9.15
9.08
8.23
8.22
7.85
7.76
7.75
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7.72
7.65
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6.72
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6.32
6.31
6.10
5.80
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5.61
5.43
5.42
5.30
5.27
5.21
5.19
4.71
4.70
4.51
4.38
4.37
3.67
3.50
3.36 HDO
2.65
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2.51 DMSO
2.51 DMSO
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2.17
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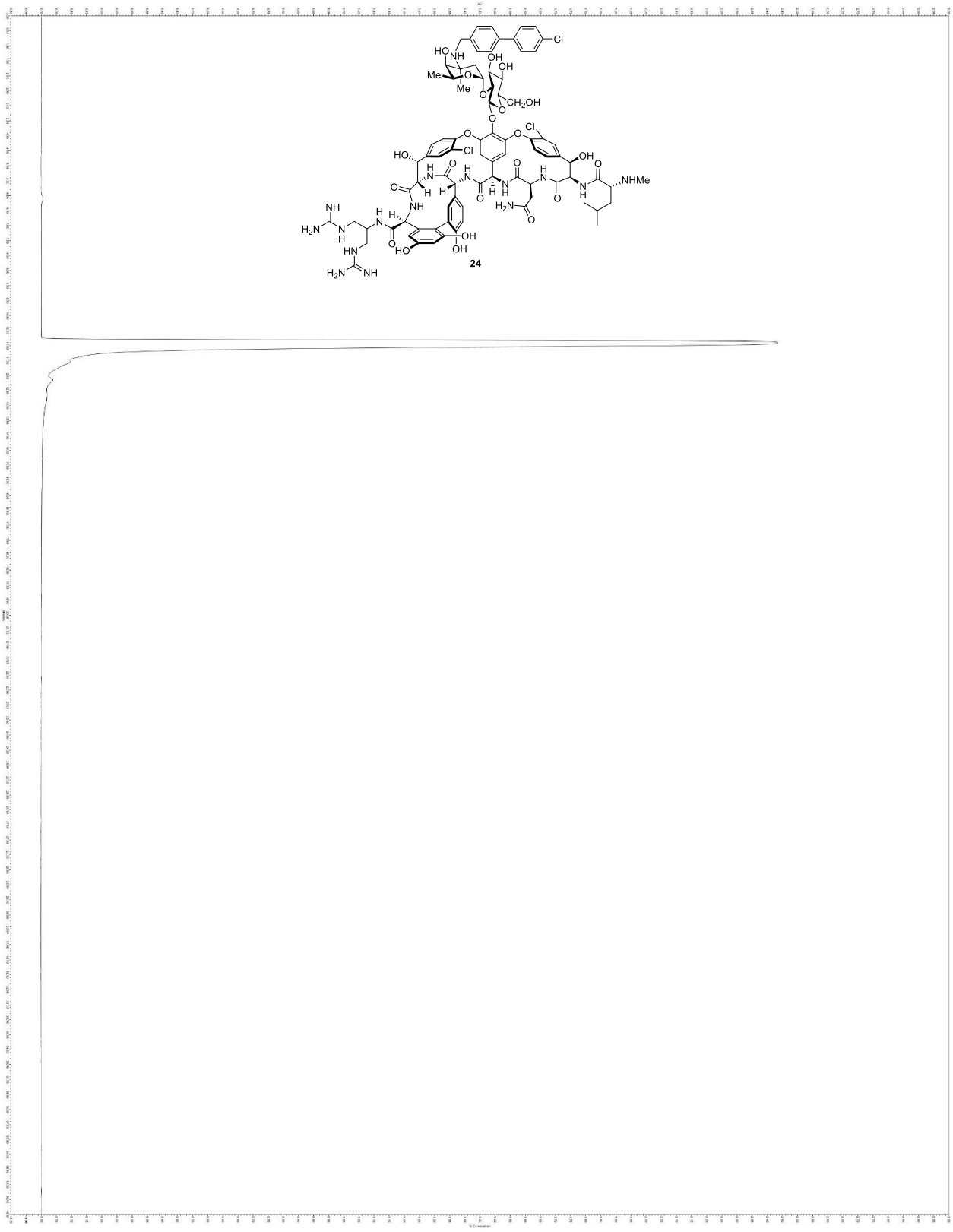
1.15
1.14
0.93
0.92
0.88
0.87
0.87
0.86
0.92 1.95 0.92 3.90 2.90 2.86 2.81 1.04 0.84 0.76 0.84 0.86 0.82 1.00 0.97 0.83 0.87 0.91 1.70 1.68 1.01 0.87 0.98 0.84 2.35 1.90 2.84 1.75 0.77 1.23 0.90 1.91 2.80 3.04 2.81
f1 (ppm)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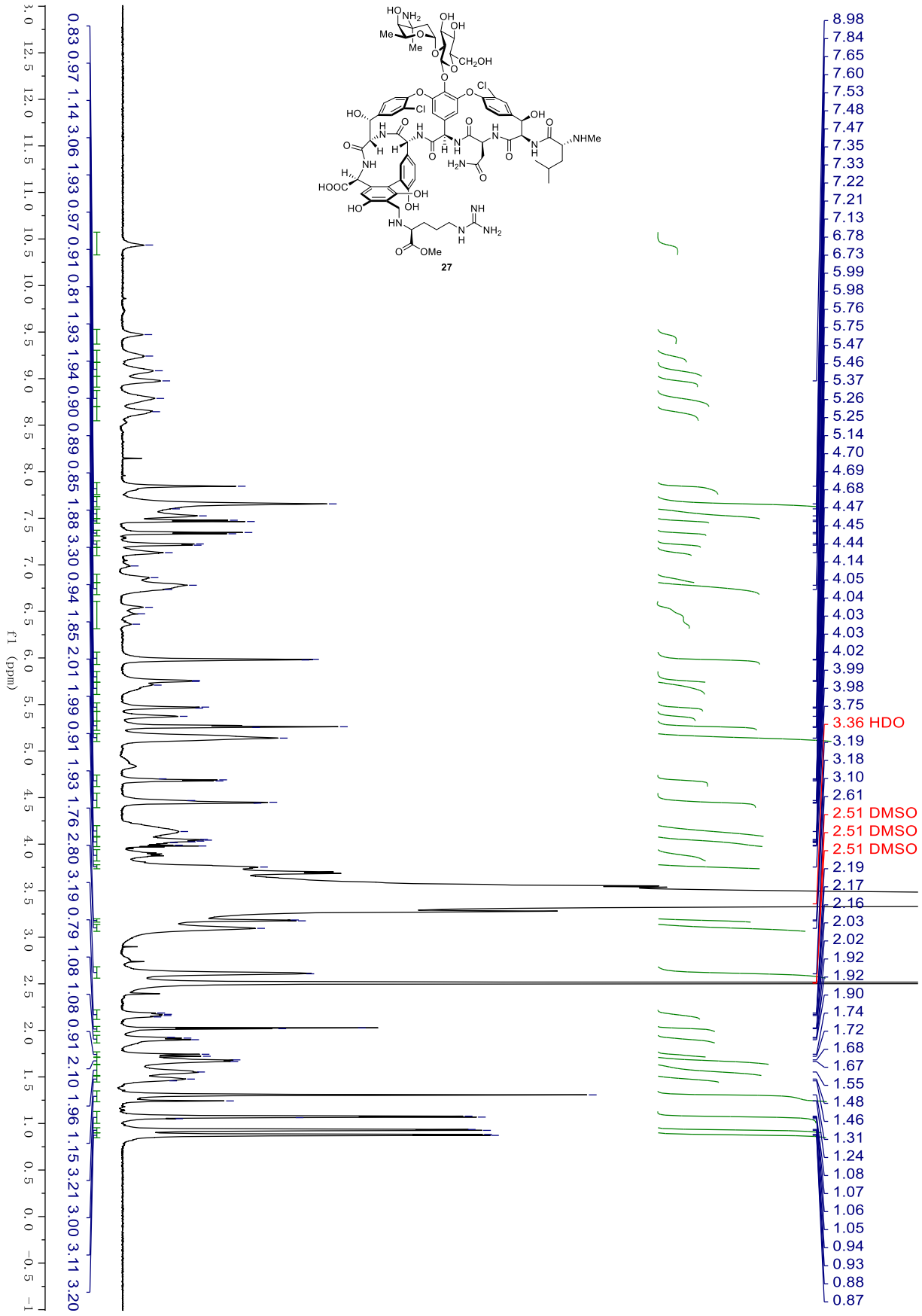
27
8.98
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7.60
7.53
7.48
7.47
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7.33
7.22
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7.13
6.78
6.73
5.99
5.98
5.76
5.75
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5.37
5.26
5.25
5.14
4.70
4.69
4.68
4.47
4.45
4.44
4.14
4.05
4.04
4.03
4.03
4.02
3.99
3.98
3.75
3.36 HDO
3.19
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3.10
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2.51 DMSO
2.51 DMSO
2.19
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2.03
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1.46
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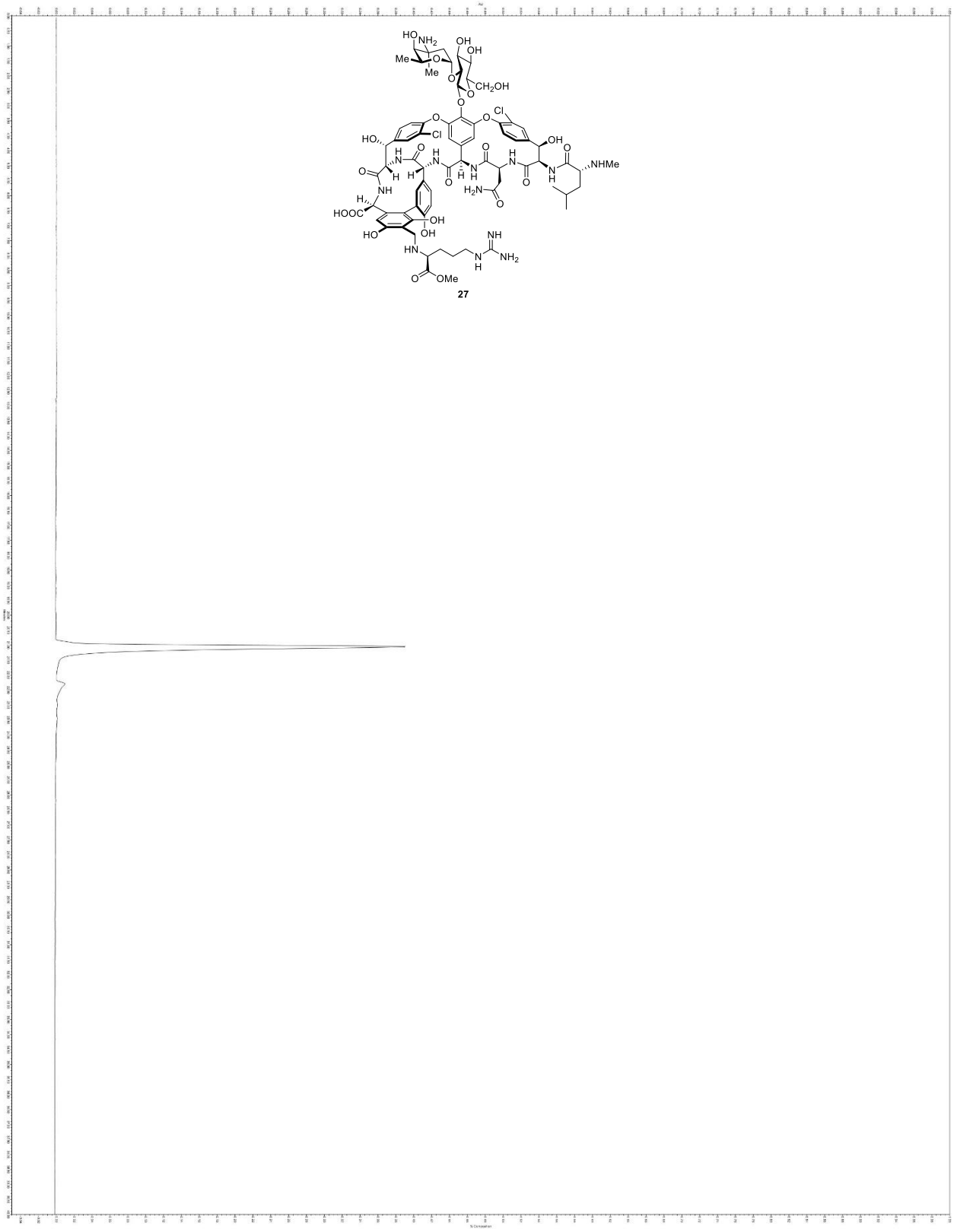
1.06
1.05
0.94
0.93
0.88
0.87
f1 (ppm)



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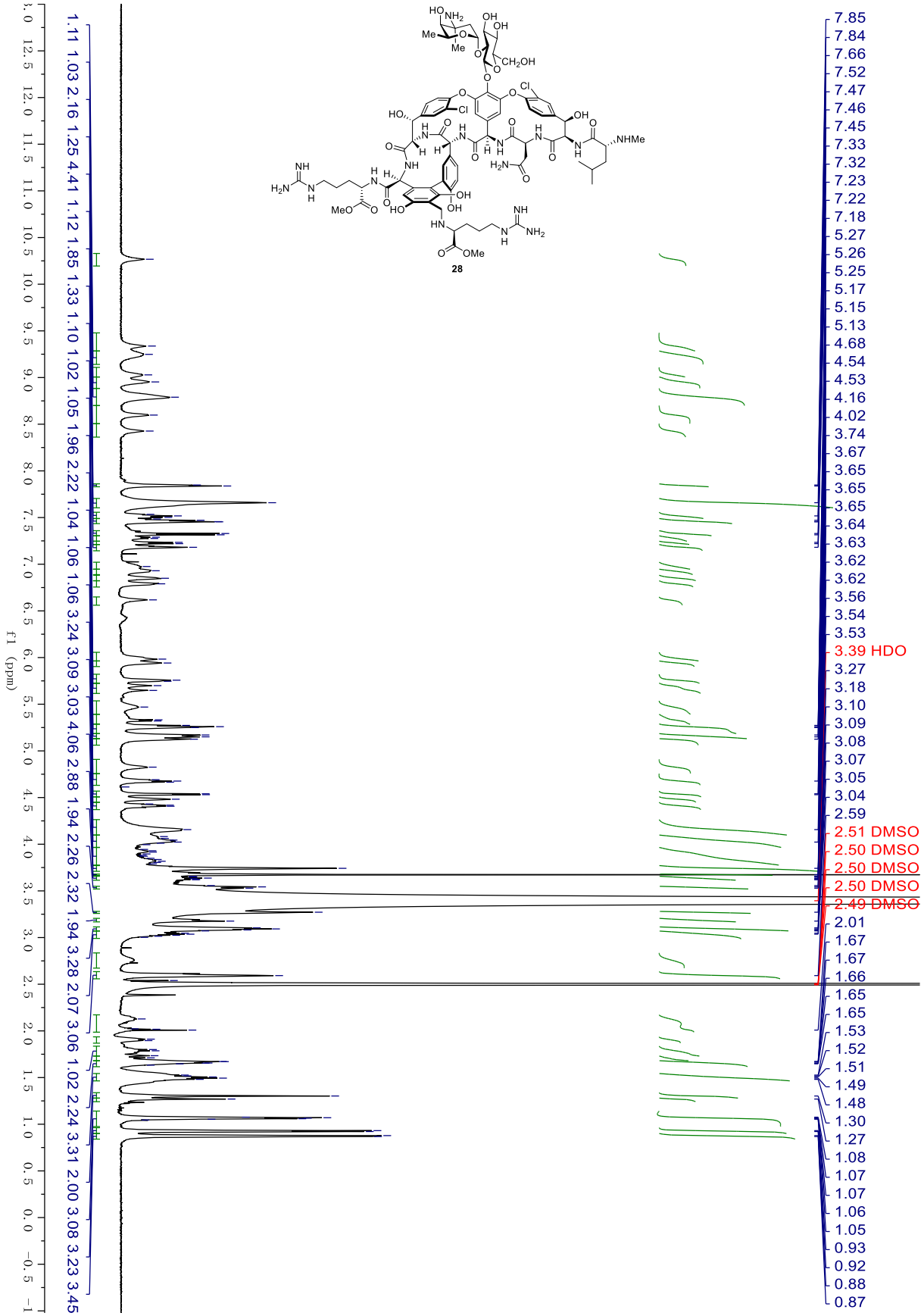
28
f1 (ppm)
7.85
7.84
7.66
7.52
7.47
7.46
7.45
7.33
7.32
7.23
7.22
7.18
5.27
5.26
5.25
5.17
5.15
5.13
4.68
4.54
4.53
4.16
4.02
3.74
3.67
3.65
3.65
3.65
3.64
3.63
3.62
3.62
3.56
3.54
3.53
3.39 HDO
3.27
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2.51 DMSO
2.50 DMSO
2.50 DMSO
2.50 DMSO
2.49 DMSO
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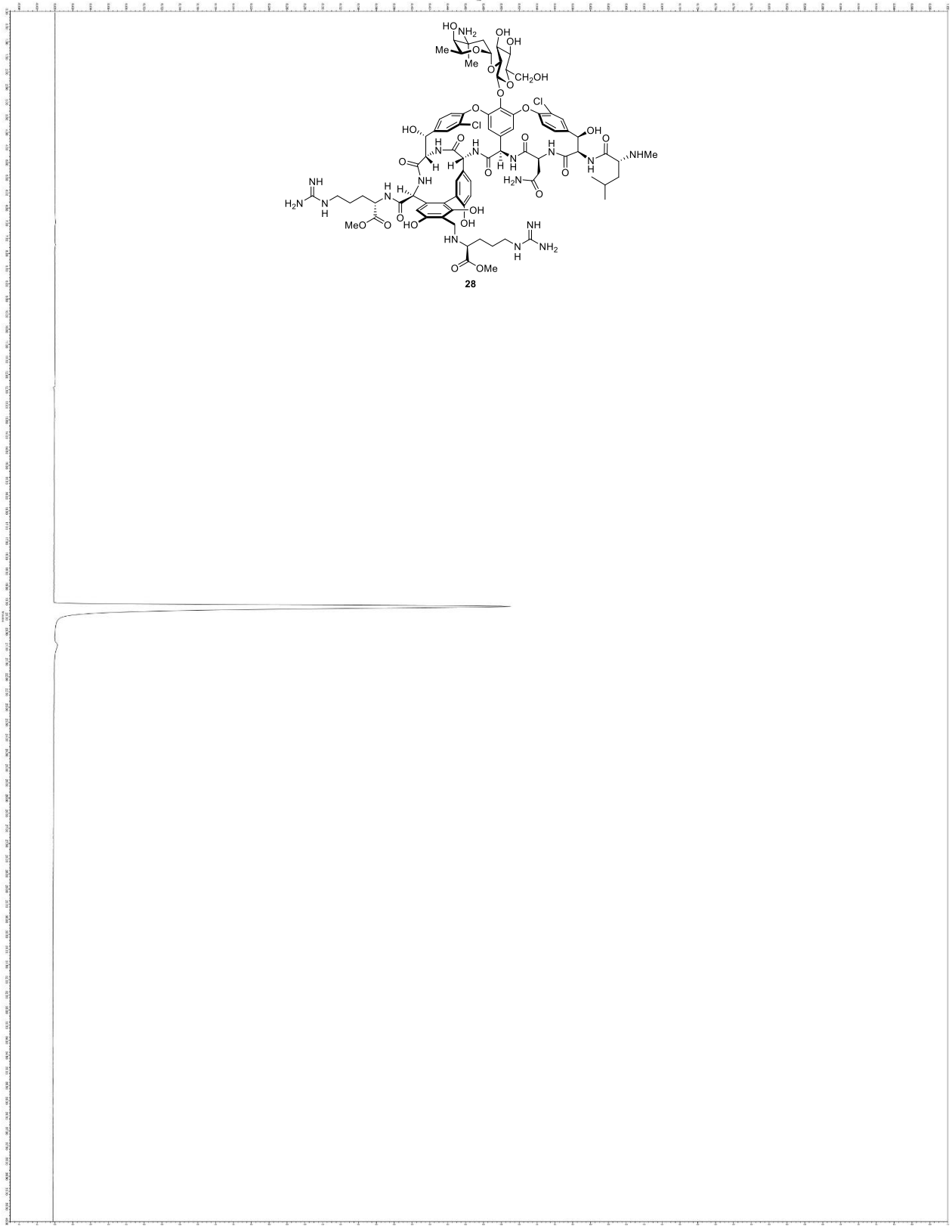

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