Supporting Information

Introduction of polar scaffolds in molecular tongs inhibitors of wild-type and mutated HIV-1 protease dimerization

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Pages S56-S57. Figure 2S. Evolution with time of the concentration of molecular tongs **3** and **8** incubated at 37°C in RPMI (Roswell Park Memorial Institute medium) culture medium containing 20% fetal calf serum. Incubations were terminated by adding ethanol. The mixture was poured at 4 □C and centrifuged (10 000 rpm for 10 min). Aliquots of the clear supernatant were injected onto the HPLC column (Chromatograms B1-B2). For comparison, chromatogram of the reaction mixture treated without molecular tong (Blank serum), using the same experimental conditions, is indicated (A1). The chromatograms of the reaction mixture treated without molecular tong (blank) is obtained at t = 0. The 4 chromatograms for each molecular tong are obtained after 0, 16, 24 and 48 h of incubation. HPLC conditions were as follows: HPLC 1260 AGILENT TECHNOLOGIES system; column SUNFIRE, C18, 5 µm, 150 mm x 4.6 mm; mobile phase: a mixture of A, water (0.05% TFA), and B, CH_3CN (0.05% TFA); room temperature; flow rate 1 mL/min; detection at 235 nm. Mixture of A/B from 70/30 to 0/100 in 20 min.

Experimental section

1.1. Chemistry

Usual solvents were purchased from commercial sources and dried and distilled by standard procedures. Naphthalene-2,7-diol, benzyl 4-bromobutanoate, ethyl 4-bromobutanoate, (2,2-dimethyl-[1,3]-dioxolan-4-yl)-methylamine, benzophenone imine, *N*,*N*-dimethylpropargylamine, *N*,*N*-di(benzyloxycarbonyl)propargylamine, 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea were purchased from commercial sources. 3-Bromo-naphthalene-2,7-diol was synthesized from naphtalene-2,7-diol, according to published methods [24,27-28]. *N*-[3-[[[(2S)-2-Amino-3-methyl-butanoyl]amino]carbamoyl]-4-methoxy-phenyl]acetamide **40** and *N*-[(1S)-1-[[(5-acetamido-2-methoxy benzoyl)amino]carbamoyl]-5-amino-pentyl]carbamate **41** were prepared according to published methods [21,22]. Pure products were obtained after liquid chromatography using Merck silica gel 60 (40-63 µm). TLC analyses were performed on silica gel 60 F_{250} (0.26 mm thickness) plates. The plates were visualized with UV light (λ = 254 nm) or revealed with a 4 % solution of phosphomolybdic acid or ninhydrin in EtOH. Elemental analyses (C, H, N) were performed on a Perkin-Elmer CHN Analyser 2400 at the Microanalyses Service of the Faculty of Pharmacy in Châtenay-Malabry (France). Mass spectra were obtained using a Bruker Esquire electrospray ionization apparatus at the SAMM (Faculty of Phamacy at Châtenay-Malabry, France). NMR spectra were recorded on an ultrafield AVANCE 300 (^{1}H, 300 MHz, ^{13}C, 75 MHz) or a Bruker 400 (^{1}H, 400 MHz, ^{13}C, 100 MHz). Chemical shift δ are in parts per million (ppm) and the following abbreviations are used: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), quintuplet (qt), multiplet (m), broad multiplet (bm), and broad singlet (bs). Melting points were determined on Kofler melting point apparatus and are uncorrected. Elemental analysis data are included in the supporting information. Purifications by HPLC were performed using a Waters gradient system (pump + controller E600, UV detector PDA 2996, autosampler 717) with a column SUNFIRE, C18, 5 µm, 150 mm x 4.6 mm.

*1.1.1. Synthesis of molecular tongs **2-4, 6-15** and **43-44***

*1.1.1.1. Molecular tong **2***. To a solution of **21** (150 mg, 0.33 mmol) and **40** (312 mg, 0.72 mmol) in DMF (5 mL) were successively added DIPEA (384 µL, 2.33 mmol), HBTU (308 mg, 0.81 mmol) and HOBt (97 mg, 0.72 mmol). The reaction mixture was stirred under argon atmosphere at room temperature for 48 h. After evaporation of the solvent under reduced pressure, the orange oil obtained was triturated in EtOAc. The solid formed was isolated and successively washed with several portions of EtOAc, CH_2Cl_2, CH_3OH and Et_2O. After recrystallization from CH_3OH/Et_2O, compound **2** was obtained as an orange solid (174 mg, 50%); mp = 188-194ºC; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.33 (s, 1H), 10.32 (s, 1H), 9.93 (s, 4H), 8.00-7.94 (m, 4H), 7.75 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 9.0 Hz, 2H), 7.06 (s, 2H), 6.88 (dd, *J* = 8.8 Hz and 1.7 Hz, 1H), 6.77 (s, 1H), 5.03 (t, *J* = 5.0 Hz, 1H), 4.41-4.31 (m, 3H), 4.08-3.97 (m, 5H), 3.84 (s, 6H), 3.79-3.75 (m, 1H), 3.28 (bs, 2H), 2.44-2.33 (m, 4H), 2.02 (s, 6H). 1.97 (bs, 6H), 1.39 (s, 3H), 1.29 (s, 3H), 0.95 (d, *J* = 6.4 Hz, 6H), 0.90 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.6, 169.5, 168.0, 163.3, 153.9, 152.7, 147.6, 136.6, 132.6, 127.7, 126.5, 124.9, 123.3, 121.3, 121.1, 115.6, 112.4, 106.8, 104.9, 103.1, 73.7, 67.4, 66.9, 66.8, 56.1, 56.0, 45.6, 31.6, 30.7, 26.7, 25.2, 25.0, 23.8, 19.2, 18.3; IR (neat): 3260, 2953, 1604, 1490, 1250 cm^{-1}; $C_{54}H_{71}N_9O_{14}\cdot 1H_2O$**:** C 59.60, H 6.78, N 11.59; found C 59.24, H 6.35, N 11.36; MS (ESI, ion polarity positive) m/z : 1093 $[M+Na]^+$.

*1.1.1.2. Molecular tong **3***. Compound **2** was dissolved in a 1:1:2 mixture of 1M HCl/THF/EtOH (4 mL) and stirred for 1 h at 55 °C. The solvent was evaporated under reduced pressure, and the resulting residue was triturated with Et_2O, filtered and washed again successively with saturated aqueous $NaHCO_3$, distilled H_2O, EtOH, cyclohexane, and Et_2O. Compound **3** was obtained as an orange solid (30 mg, 60%); ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.33 (s, 2H), 9.94 (s, 4H), 8.02-7.93 (m, 4H), 7.77-7.73 (m, 2H), 7.47 (d, *J* = 9.0 Hz,1H), 7.11-7.05 (m, 4H), 6.92-6.88 (m, 1H), 6.73 (s, 1H), 5.03 (bs, 1H), 4.35-4.31 (m, 3H), 4.09-3.99 (m, 5H), 3.84 (s, 6H), 3.83-3.81 (m, 1H), 3.28 (bs, 2H), 2.60-2.55 (m, 2H), 2.06-1.91 (m, 14H), 0.95 (d, *J* = 6.6 Hz, 6H), 0.90 (d, *J* = 6.6 Hz, 6H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.7, 169.5, 168.0, 167.9, 163.3, 152.7, 149.1, 137.0, 135.0, 132.6, 131.6, 128.9, 128.0, 124.8, 123.3, 121.3, 121.2, 114.6, 112.4, 106.8, 103.9, 103.2, 69.5, 67.3, 66.5, 64.3, 56.1, 53.7, 31.5, 30.7, 30.4, 25.0, 23.8, 19.2, 18.3; IR (neat): 3271, 2936, 1641, 1490, 1249 cm^{-1}; $C_{51}H_{67}N_9O_{14}\cdot 2H_2O$: C 57.45, H 6.73, N 11.83; found C 57.66, H 6.57, N 10.97; MS (ESI, ion polarity positive) m/z : 1093 $[M+Na]^+$, 1069 $[M+K]^+$.

*1.1.1.3. Molecular tong **4***. Same procedure as described for **2** from **42** (103 mg, 0.30 mmol) and **40** (285 mg, 0.65 mmol), except that after evaporation of the solvent under reduced pressure, the orange oil obtained was triturated in EtOAc to give a solid. This solid was successively washed with several cycles of EtOAc, CH_2Cl_2, CH_3OH and Et_2O to afford **4** as an orange brown solid (192 mg, 68%); mp = 208-214 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.31 (s, 2H), 9.92 (s, 4H), 8.01-7.92 (m, 4H), 7.75 (d, *J* = 7.2 Hz, 2H), 7.38 (d, *J* = 8.3 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 7.03 (s, 2H), 6.86 (s, 2H), 4.94 (bs , 2H), 4.33 (d, *J* = 6.7 Hz, 2H), 4.08-3.96 (m, 4H), 3.84 (s, 6H), 2.42-2.37 (m, 4H), 2.01 (bs, 12H), 0.95 (s, 6H), 0.90 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.8, 171.7, 169.5, 168.0, 163.3, 157.3, 152.6, 148.0, 136.3, 132.6, 128.0, 126.0, 124.8, 123.3, 121.3, 121.1, 115.6, 112.4, 107.0, 106.7, 105.1, 67.1, 66.9, 56.1, 56.0, 31.7, 31.6, 30.8, 30.7, 25.1, 23.8, 19.2, 18.3; IR (neat): 3258, 1607, 1491, 1250 cm^{-1}; $C_{48}H_{61}N_9O_{12}\cdot 2.5H_2O$: calcd C 57.58, H 6.66, N 12.60; found C 57.94, H 6.32, N 12.26; MS (ESI, ion polarity positive) m/z : 979 $[M+Na]^+$.

*1.1.1.4. Molecular tong **6.*** Same procedure as described for **2** from **21** (71 mg, 0.15 mmol) and **41** (152 mg, 0.34 mmol), except that the residue was taken up with EtOAc (200 mL). The organic layer was successively washed with H_2O (100 mL), 10% aqueous citric acid (50 mL), 10% aqueous K_2CO_3 (50 mL), H_2O (100 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was then purified by flash chromatography on silica gel column (CH_2Cl_2/CH_3OH, 90:10) to afford **6** as a light pink powder (119 mg, 59%); mp = 160-170 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.99 (bs, 2H), 11.34 (s, 2H), 8.93 (s, 2H), 8.43 (s, 2H), 7.97 (s, 1H), 7.95 (s, 1H), 7.42 (d, *J* = 8.3 Hz,1H), 7.00-6.82 (m, 5H), 6.70 (s, 1H), 5.89 (bs, 1H), 5.70-5.63 (m, 3H), 4.92 (bs, 2H), 4.45 (bs, 1H), 4.13-3.81 (m, 12H), 3.48-3.28 (m, 3H), 3.10- 3.03 (m, 4H), 2.28-2.04 (m, 14H), 1.79-1.62 (m, 4H), 1.46-1.19 (m, 32H); ^{13}C NMR (100 MHz, $CDCl_3$): δ =. 172.1, 172.0, 169.2, 169.1, 166.3, 155.6, 154.6, 153.6, 148.0, 136.3, 133.2, 128.4, 126.9, 126.2, 126.1, 125.1, 122.6, 117.8, 116.0, 112.1, 109.5, 107.0, 105.4, 104.4, 79.8, 74.2; 74.1, 67.2, 67.1, 66.7, 56.6, 52.1, 46.5, 39.3, 34.2, 32.8, 32.6, 29.7, 29.3, 28.4, 26.9, 25.2, 25.1, 24.9, 24.6, 22.2; IR (neat): ν = 3309, 2926, 1643, 1492, 1248 cm^{-1}; $C_{66}H_{93}N_{11}O_{18}\cdot 2H_2O$: calcd C 58.09, H 7.18, N 11.29; found C 57.86, H 7.29, N 11.08 MS (ESI, ion polarity positive) m/z : 1351 $[M+Na]^+$.

*1.1.1.5. Molecular tong **7***. To a solution of **6** (23 mg, 17 µmol) in MeOH (1.5 mL), was added Amberlyst^{TM} 15 resin (13 mg). The suspension was stirred for 4 h at room temperature and the reaction mixture was filtered

through a pad of Celite. After washing the pad of Celite several times with MeOH and CH_2Cl_2, the filtrate was concentrated under reduced pressure. The residue obtained was purified by flash chromatography on silica gel column (CH_2Cl_2/CH_3OH, 90:10) to afford **7** as white solid (7 mg, 30%); Rf (CH_2Cl_2/CH_3OH, 80/20) = 0.15; ^{1}H NMR (300 MHz, CD_3OD): δ = 8.06 (m, 2H), 7.78 (m, 2H), 7.45 (m, 1H), 7.10 (m, 2H), 6.95 (m, 2H), 6.85 (m, 1H), 6.80 (m, 1H), 3.98 (m, 4H), 3.85 (m, 9H), 3.31 (m, 2H), 3.55 (m, 2H), 3.11 (m, 4H), 2.32 (m, 4H), 2.01 (m, 10H), 1.79-1.25 (m, 30H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 171.3, 170.5, 167.9, 166.9, 163.0, 152.6, 132.6, 128.0, 125.5, 123.3, 121.2, 112.4, 77.9, 56.1, 52.7, 40.3, 40.0, 39.8, 36.5, 39.2, 38.9, 38.7, 38.3, 31.8, 28.8, 28.2, 24.9, 23.7, 22.8, 20.7;$C_{63}H_{89}N_{11}O_{18}\cdot 5H_2O$: calcd C 54.94, H 7.20, N 11.18; found C 54.37, H 7.01, N 10.57; MS (ESI, ion polarity positive) m/z : 1331 $[M+Na]^+$.

*1.1.1.6. Molecular tong **8***. Same procedure as described for **2** from **42** (100 mg, 0.29 mmol) and **41** (288 mg, 0.64 mmol), except that after evaporation under reduced pressure, the residue was taken up with CH_2Cl_2 (50 mL). After adding water (30 mL) to the organic layer, the precipitate formed was isolated and successively washed with several cycles of H_2O, EtOAc, cyclohexane, and Et_2O. After recrystallization from CH_3OH/Et_2O, compound **8** was obtained as a brown solid (250 mg, 72%); mp = 172-174 °C; Rf (EtOAc/cyclohexane, 80/20) = 0.2; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.28 (s, 2H), 9.99 (s, 2H), 9.94 (s, 2H), 7.93 (s, 2H), 7.83 (t, *J* = 5.0 Hz, 2H), 7.83 (m, 2H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 9.1 Hz, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.03 (s, 2H), 6.88-6.83 (m, 2H), 4.05 (m, 4H), 3.97 (t, *J* = 5.2 Hz, 2H), 3.86 (s, 6H), 3.05 (m, 4H), 2.31 (t, *J* = 6.3 Hz, 2H), 2.26 (t, *J* = 6.5 Hz, 2H), 2.01 (s, 6H), 2.04-1.96 (m, 4H), 1.66 (m, 2H), 1.57 (m, 2H), 1.44-1.35 (m, 26H); ^{13}C NMR (75 MHz, DMSO-d_6): δ =171.6, 171.4, 170.5, 168.0, 163.1, 155.2, 153.9, 152.6, 148.0, 135.9, 132.6, 128.2, 126.1, 124.7, 123.3, 121.2, 121.0, 115.6, 112.9, 112.4, 106.7, 105.2, 78.0, 67.2, 66.9, 56.2, 52.7, 38.3, 32.1, 31.9, 28.8, 28.2, 25.1, 25.0, 23.8, 22.8; IR (neat): ν = 3250, 1642, 1490, 1247, 1161 cm^{-1}; $C_{60}H_{83}N_{11}O_{16}\cdot 4H_2O$: calcd C 56.01, H 7.14, N 11.98; found C 56.01, H 6.57, N 12.11; MS (ESI, ion polarity positive) m/z : 1237 $[M+Na]^+$.

*1.1.1.7. Molecular tong **9***. Same procedure as described for **2** from **27** (60 mg, 0.14 mmol) and **41** (142 mg, 0.31 mmol), except that after evaporation under reduced pressure, the residue was taken up with CH_2Cl_2, (50 mL). The organic layer washed with water (2 x 30 ml) and 10% aqueous citric acid (2 x 30 mL), leading to the formation of a precipitate. The solid was filtered and was successively washed with several portions of H_2O, EtOAc, cyclohexane, and Et_2O. After purification by reverse phase preparative HPLC (H_2O/CH_3OH, 47:53 + 0.05% CF_3COOH), the trifluoroacetic salt of **9** was obtained as a white solid (168 mg, 93%); mp = 158-160 °C; Rf (CH_2Cl_2/CH_3OH, 90/10 + 2% NH_4OH).= 0.3; ^{1}H NMR (400 MHz, DMSO-d_6): δ =10.82 (s, 1H), 10.28 (s, 2H), 9.99 (s, 2H), 9.96 (s, 2H), 8.93 (bs, 2H), 8.40 (s, 1H), 7.96 (m, 2H), 7.92 (bss, 2H), 7.74 (m, 2H), 7.68 (m, 1H), 7.18 (s, 2H), 7.11 (m, 2H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 2H), 4.35 (bs, 2H), 4.13 (m, 2H), 4.04 (m, 4H), 3.85 (s, 6H), 3.06 (m, 4H), 2.66 (bs, 3H), 2.33 (t, *J* = 6.3 Hz, 2H), 2.28 (t, *J* = 6.5 Hz, 2H), 2.08 (m, 2H), 2.01 (s, 6H), 1.99 (m, 2H), 1.64-1.57 (m, 4H), 1.43-1.31 (m, 26H); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 172.0, 171.5, 171.4, 170.6, 168.0, 167.0, 163.1, 152.7, 148.7, 132.7, 132.3, 131.6, 128.7, 123.5, 123.4, 123.0, 121.3, 121.1, 121.0, 118.8, 116.6, 112.5, 112.4, 106.8, 78.0, 68.2, 67.4, 67.0, 56.2, 52.7, 51.1, 50.0, 38.5, 38.4, 38.2, 38.1, 32.8, 32.1, 31.9, 31.8, 29.8, 28.8, 28.2, 25.0, 24.7, 23.8, 23.3, 22.8; IR (neat): 3260, 2978, 1632,

1494, 1250, 1159. cm^{-1} ; $C_{63}H_{88}N_9O_{12}\cdot 2.5H_2O\cdot 2CF_3COOH$: calcd C 51.93, H 6.13, N 10.85; Found C 51.72, H 6.43, N 11.52; ; MS (ESI, ion polarity positive) m/z : 1285 $[M+H]^+$.

*1.1.1.8. Molecular tong **10***. Same procedure as described for **2** from **29** (149 mg, 0.25 mmol) and **41** (245 mg, 0.54 mmol), except that after evaporation under reduced pressure, the residue was taken up in CH_2Cl_2 (50 mL) and successively washed with water (2 x 30 mL), 10% aqueous citric acid (2 x 30 mL) and 10% aqueous K_2CO_3. After drying over $MgSO_4$ and concentration under reduced pressure, the solid obtained was recrystallized from CH_2Cl_2/Et_2O to afford **10** as a light yellow solid (217 mg, 61%); mp = 178-180 °C; Rf (EtOAc/CH_2Cl_2, 80/20) = 0.3; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.70 (bs, 2H), 11.17 (bs, 2H), 9.64 (s, 1H), 8.90 (s, 2H), 8.62 (s, 1H), 8.31 (bs, 2H), 7.94 (s, 2H), 7.55 (d, *J* = 9.2 Hz, 1H), 7.36-7.31 (m, 5H), 6.92-6.88 (m, 5H), 5.97 (bs, 1H), 5.86 (bs, 1H), 5.65 (m, 2H), 5.14 (s, 2H), 4.83 (m, 2H), 4.05 (m, 2H), 3.96 (m, 8H), 3.57 (m, 4H), 3.19 (s, 2H), 3.09 (m, 4H), 2.59 (m, 4H), 2.29-2.33 (m, 4H), 2.17 (s, 6H), 2.12-2.05 (m, 4H), 1.80 (m, 2H), 1.71 (m, 2H), 1.44-1.36 (m, 26H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.2, 156.5, 155.7, 155.1, 153.6, 147.9, 136.5, 133.0, 131.8, 128.9, 128.5, 128.1, 128.0, 126.1, 125.1, 123.9, 122.6, 117.9, 117.0, 116.6, 112.0, 106.2, 105.4, 79.9, 67.5, 67.3, 66.7, 62.3, 56.5, 53.1, 52.2, 44.1, 39.3, 39.2, 33.8, 32.6, 29.1, 29.0, 28.4, 25.0, 24.4, 22.2; IR (neat): 3329, 1653, 1537, 1244, 1153 cm^{-1} ; $C_{74}H_{99}N_{13}O_{19}\cdot 5H_2O$: calcd C 56.80, H 7.04, N 11.64; Found C 56.88, H 6.51, N 11.42; MS (ESI, ion polarity positive) m/z : 1497 $[M+Na]^+$.

*1.1.1.9. Molecular tong **11***. A solution of **10** (50 mg, 0.03 mmol) and Pd/C (7.5 mg, 15% mass) in CH_3OH (4 mL) was stirred at room temperature under hydrogen atmosphere for 18 h. The solution was filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure to afford **11** as a light green solid (164 mg, 99%); mp = 158-160 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.28 (bs, 2H), 10.01 (bs, 2H), 9.95 (s, 2H), 9.84 (bs, 1H), 8.67 (s, 1H), 7.95 (s, 2H), 7.85 (m, 2H), 7.76 (m, 2H), 7.65 (d, *J* = 8.4 Hz, 1H), 7.28 (s, 1H), 7.17 (s, 1H), 7.08 (m, 2H), 6.96, (d, *J* = 8.1 Hz, 1H), 6.83 (m, 2H) 4.16 (m, 2H), 4.03 (m, 4H), 3.85 (s, 6H), 3.17 (s, 2H), 3.05 (m, 4H), 2.57 (m, 8H), 2.37 (m, 2H), 2.27 (m, 2H), 2.14 (m, 2H), 2.01 (s, 6H), 1.98 (m, 2H), 1.66 (m, 2H), 1.57 (m, 2H), 1.37 (m, 26H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.4, 171.1, 170.5, 168.0, 162.9, 156.1, 155.2, 147.5, 132.6, 131.4, 128.5, 125.4, 123.3, 123.2, 121.3, 121.0, 116.4, 115.0, 112.4, 106.3, 105.6, 78.0, 67.9, 67.0, 61.7, 56.2, 53.0, 52.7, 51.2, 38.3, 31.9, 31.7, 28.8, 28.2, 25.0, 23.8, 22.8; IR (neat):. 3383, 1936, 1692, 1641.cm^{-1}; $C_{66}H_{93}N_{13}O_{17}\cdot 5H_2O$: calcd C 55.41, H 7.27, N 12.73; Found C 55.28, H 6.57, N 12.37; MS (ESI, ion polarity positive) m/z : 1341 $[M+H]^+$.

*1.1.1.10.Molecular tong **12***. Same procedure as described for **11** from **43** (46 mg, 0.03 mmol) and Pd/C (6.9 mg, 15% mass) in CH_3OH (5 mL) except that the reaction was stirred for 48 h at room temperature. After purification by reverse phase preparative HPLC (H_2O/CH_3OH, 47:53 + 0.05% CF_3COOH), the trifluoroacetic salt of **12** was obtained (38 mg, 92%); mp = 158-160 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.97 (s, 2H), 7.95 (m, 2H), 7.90 (t, *J* = 5.8 Hz, 1H), 7.85 (t, *J* = 5.5 Hz, 1H), 7.75 (t, *J* = 7.0 Hz, 2H), 7.65 (d, *J* = 8.9 Hz, 1H), 7.55 (s, 1H), 7.17 (s, 2H), 7.10 (d, *J* = 9.0 Hz, 2H), 6.95 (dd, *J* = 8.7, 1.8 Hz, 1H), 6.85 (m, 2H) 4.06-4.01 (m, 6H), 3.86 (s, 6H), 3.06 (m, 4H), 2.80 (m, 2H), 2.74-2.70 (m, 2H), 2.33-2.26 (m, 4H), 2.06-1.96 (m, 10H), 1.87 (m, 2H), 1.67-1.59 (m, 2H), 1.58-1.56 (m, 2H), 1.38 (m, 26H); ^{13}C NMR (400 MHz, DMSO-d_6): δ = 171.5, 171.4, 170.6, 168.0, 163.1, 156.5, 155.6, 155.2, 152.6, 134.6, 132.6, 128.4, 127.9, 127.7, 123.4, 123.3, 121.3, 121.0,

115.9, 112.4, 106.0, 105.2, 78.0, 67.1, 67.0, 66.4, 59.7, 56.2, 52.7, 39.1, 38.3, 32.0, 31.9, 31.8, 28.8, 28.2, 27.6, 26.9, 25.0, 23.8, 22.8; IR (neat): 3343, 2924, 1632, 1495, 1174.cm^{-1}; $C_{63}H_{89}N_{11}O_{16}$·2CF_3COOH·1H_2O: calcd C 51.99, H 6.19, N 10.26; Found C 51.68, H 6.28, N 9.90; MS (ESI, ion polarity positive) m/z : 1257 $[M+H]^+$, 1279 $[M+Na]^+$.

*1.1.1.11.Molecular tong **13***. Same procedure as described for for **2** from **31** (120 mg, 0.29 mmol) and **41** (288 mg, 0.64 mmol), except that after evaporation under reduced pressure, the residue was taken up in CH_2Cl_2 (50 mL). Then, the organic layer was washed with water (100 mL) with precipitation of a solid that was isolated and washed successively with several cycles of H_2O, EtOAc, cyclohexane, and Et_2O. The crude product obtained was purifed by reverse phase preparative HPLC (H_2O/CH_3OH, 42:58 + 0.1% CF_3COOH). The trifluoroacetic salt of **13** was obtained as a white solid (322 mg, 86%); mp = 168-170 °C; Rf = (CH_2Cl_2/CH_3OH, 90/10 + 2% NH_4OH) = 0.3; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.27 (bs, 2H), 9.99 (s, 2H), 9.93 (s, 2H), 7.95 (d, *J* = 5.0 Hz, 2H), 7.83 (m, 2H), 7.74 (m, 2H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.56 (s, 1H), 7.17 (s, 2H), 7.10 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 9.5 Hz, 1H), 6.85 (m, 2H), 4.07-4.02 (m, 6H), 3.85 (s, 6H), 3.05 (m, 4H), 2.97 (m, 2H), 2.69 (m, 8H), 2.33-2.25 (m, 4H), 2.05-1.97 (m, 4H), 2.01 (s, 6H), 1.91 (m, 2H), 1.65 (m, 2H), 1.57 (m, 2H), 1.38 (m, 26H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.6, 170.5, 167.9, 162.9, 156.5, 155.4, 152.7, 134.5, 132.6, 128.4, 128.0, 127.5, 123.3, 121.2, 116.1, 112.4, 105.9, 78.0, 67.3, 66.9, 56.7, 56.1, 52.7, 42.7, 38.2, 31.9, 31.7, 28.8, 28.2, 27.1, 24.5, 24.4, 23.8, 22.8, 22.5; IR (neat):. 2939, 1632, 1494, 1151 cm^{-1}; $C_{65}H_{93}N_{11}O_{16}$·2CF_3COOH·4H_2O: calcd C 52.30, H 6.56, N 9.37; Found C 52.32, H 6.32, N 9.48; MS (ESI, ion polarity positive) m/z : 1284 $[M+H]^+$.

*1.1.1.12.Molecular tong **14***. Same procedure as described for **11** from **44** (49 mg, 0.038 mmol) and Pd/C (7.4 mg,15% mass) in CH_3OH (0.7 mL) except that the reaction was heated at 50 °C and hydrogenated under a pressure of 10 bar over 3 min. Compound **14** was obtained as a white solid (15 mg, 32%); mp = 156-158 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.00 (bs, 2H), 7.95, (s, 2H), 7.86 (m, 2H), 7.81 (s, 1H), 7.75 (m, 2H), 7.71 (s, 1H), 7.27 (s, 1H), 7.22 (s, 1H), 7.10 (m, 2H), 7.01 (d, *J* = 8.8 Hz, 1H), 6.84 (m, 2H), 4.08 (m, 8H), 3.85 (s, 6H), 3.05 (m, 4H), 2.33 (m, 4H), 2.06 (m, 4H), 2.01 (s, 6H), 1.68 (m, 2H), 1.56 (m, 2H), 1.38 (m, 26H); ^{13}C NMR (400 MHz, DMSO-d_6): δ = 171.9, 171.3, 168.0, 167.7, 157.2, 154.7, 152.9, 152.5, 136.2, 132.8, 132.2, 129.9, 128.8, 123.4, 121.3, 120.5, 121.0, 122.5, 116.6, 112.6, 105.9, 78.3, 67.3, 56.3, 53.0, 44.7, 38.4, 32.0, 31.9, 28.2, 24.5, 23.8, 22.7; IR (neat): 3275, 1633, 1493, 1248, 1159 cm^{-1}; $C_{61}H_{85}N_{11}O_{16}$·4H_2O: calcd C 56.33, H 7.22, N 11.85; Found C 56.25, H 6.96, N 11.58; MS (ESI, ion polarity positive) m/z : 1228 $[M+H]^+$.

*1.1.1.13.Molecular tong **15***. Same procedure as described for **2** from **39 (**60 mg, 0.14 mmol) and **41** (142 mg, 0.31 mmol), except that after evaporation under reduced pressure, the residue was taken up with a 1:1 mixture of EtOAc/THF (50 mL). The organic layer was washed with water (2 x 30 mL) and 10% aqueous K_2CO_3 (2 x 30 mL) with precipitation of a solid that was isolated and washed successively with several cycles of H_2O, EtOAc, Et_2O, and dried over P_2O_5 under vacuum. Compound **15** was obtained as a light yellow solid (120 mg, 52%); mp = 222-224 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.96 (bs, 2H), 8.06 (s, 1H), 8.00 (s, 1H), 7.85 (m, 2H), 7.75 (m, 2H), 7.69 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.20 (s, 1H), 7.17 (s, 1H), 7.04 (m, 2H), 6.93 (d, *J* = 8.0 Hz, 1H),

6.50 (bs, 1H), 6.31 (bs, 1H), 4.45 (bs, 2H), 4.09 (m, 2H), 4.03 (m, 2H), 3.91 (m, 2H), 3.85 (s, 6H), 3.03 (m, 4H), 2.34-2.25 (m, 4H), 2.02 (m, 10H), 1.59 (m, 2H), 1.48 (m, 2H), 1.37-1.26 (m, 26H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.4, 168.0, 157.3, 157.0, 155.0, 152.5, 134.9, 132.6, 128.8, 127.4, 123.0, 122.7, 121.8, 121.6, 116.2, 112.2, 105.6, 77.7, 67.0, 56.1, 53.2, 40.6, 38.5, 32.7, 31.9, 28.2, 25.0, 23.8, 22.9; IR (neat): 3454, 3306, 1633, 1494, 1248, 1162 cm^{-1}; $C_{62}H_{87}N_{13}O_{16}$·3.5H_2O: calcd C 55.84, H 7.12, N 13.66; Found C 55.70, H 6.85, N 13.37; MS (ESI, ion polarity negative) m/z : 1269 $[M-H]^-$.

*1.1.1.14.Molecular tong **43***. Same procedure as described for **2** from **33** (70 mg, 0.13 mmol) and **41** (135 mg, 0.29 mmol), except that after evaporation under reduced pressure, the residue was taken up with CH_2Cl_2 (50 mL) and successively washed with water (2 x 30 mL), 10% aqueous citric acid (2 x 30 mL) and brine (2 x 30 mL). After drying over Na_2SO_4, and concentrated under reduced pressure, the crude product was purified by reverse phase preparative HPLC (H_2O/CH_3OH, 30:70 + 0.1% CF_3COOH). Compound **43** was obtained as a yellow solid (322 mg, 86%); mp = 170-172 °C; Rf (CH_2Cl_2/CH_3OH, 90/10 + 2% NH_4OH) = 0.3; ^{1}H NMR (400 MHz, 323K, CD_3OD): δ = 8.02 (s, 2H), 7.75-7.72 (m, 3H) 7.55 (d, *J* = 8.4 Hz, 1H), 7.37-7.26 (m, 5H), 7.06-7.03 (m, 4H), 6.92 (d, *J* = 6.5 Hz, 1H), 5.13 (s, 2H) 4.18 (s, 2H), 4.16 (m, 2H), 4.07 (m, 4H), 3.93 (s, 6H), 3.22-3.17 (m, 4H), 2.44-2.39 (m, 4H), 2.10 (m, 4H), 2.07 (s, 6H), 1.84-1.80 (m, 2H), 1.79-1.66 (m, 2H), 1.56-1.44 (m, 26H); ^{13}C NMR (100 MHz, 323K, CD_3OD): δ = 175.5, 172.9, 172.8, 171.5, 165.5, 165.4, 159.5, 158.2, 155.7, 138.2, 137.3, 134.2, 133.5, 129.9, 129.4, 128.9, 128.7, 126.9, 125.1, 124.4, 121.2, 117.9, 113.5, 112.7, 107.3, 90.1, 80.8, 80.2, 68.9, 68.4, 67.8, 57.0, 54.7, 53.4, 40.0, 39.7, 33.8, 33.7, 33.1, 32.3, 29.9, 28.7, 26.6, 26.5, 23.9, 23.6; IR (neat): 2934, 1629, 1495, 1250, 1164 cm^{-1}; $C_{71}H_{91}N_{11}O_{18}$·5H_2O: calcd C 57.75, H 6.91, N 10.44; Found C 57.60, H 6.48, N 10.95; MS (ESI, ion polarity positive) m/z : 1409.1 $[M+Na]^+$.

*1.1.1.15.Molecular tong **44***. Same procedure as described for **2** from **37** (114 mg, 0.23 mol) and **41** (225 mg, 0.51 mmol), except that after evaporation under reduced pressure, the residue was taken up with CH_2Cl_2 (50 mL) and successively washed with water (2 x 30 mL), 10% aqueous citric acid (2 x 30 mL) and 10% aqueous $NaHCO_3$. After drying over Na_2SO_4 , and concentrated under reduced pressure, the crude product was purified by chromatography on silica gel column (EtOAc/CH_3OH, 90:10). to yield **44** as a light yellow solid (198 mg, 65%); mp = 151-153 °C; Rf (EtOAc/CH_3OH, 80/20) = 0.5; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.28 (bs, 2H), 10.02 (bs, 2H), 9.96 (s, 2H), 7.94, (s, 2H), 7.85 (m, 2H), 7.76 (dd, *J* = 2.1, 8.8 Hz, 2H), 7.67 (t, *J* = 5.5 Hz, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.51 (s, 1H), 7.39-7.33 (m, 5H), 7.17 (s, 2H), 7.09 (d, *J* = 8.9 Hz, 2H), 6.94 (dd, *J* = 1.9, 8.5 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 2H), 5.08 (s, 2H), 4.30 (d, *J* = 5.6 Hz, 2H), 4.04 (m, 6H), 3.85 (s, 6H), 3.05 (m, 4H), 2.32-2.26 (m, 4H), 2.01 (s, 6H), 1.98 (m, 4H), 1.65 (m, 2H), 1.55 (m, 2H), 1.38 (m, 26H); ^{13}C NMR (100 MHz, DMSO- d_6): δ = 171.6, 171.4, 170.6, 168.0, 163.1, 156.7, 156.4, 155.3, 155.0, 152.7, 137.3, 134.8, 132.7, 128.7, 128.4, 127.8, 127.7, 126.3, 125.6, 123.4, 123.1, 121.3, 121.0, 116.0, 112.4, 106.0, 105.1, 78.0, 67.1, 67.0, 65.4, 56.2, 52.7, 39.5, 38.4, 32.0, 31.9, 28.8, 28.2, 25.0, 24.9, 23.8, 22.9; IR (neat): 3268, 2932, 1634, 1493, 1247, 1159 cm^{-1}; $C_{69}H_{91}N_{11}O_{18}$·1.5H_2O: calcd C 59.64, H 6.83, N 11.09; Found C 59.40, H 6.51, N 11.11; MS (ESI, ion polarity negative) m/z : 1360.9 $[M-H]^-$.

*1.1.2. Synthesis of naphthalene scaffolds **17-39** and **42***

*1.1.2.1. 3-Bromo-naphthalene-2,7-diol **17*** [27-28]. Bromine (1.28 mL, 25 mmol) in acetic acid (10 mL) was added dropwise to a solution of naphtalene-2,7-diol (2 g, 12.5 mmol) in acetic acid (30 mL) over 1.5 h. The mixture was heated in an oil bath for 15 min and H_2O (8 mL) and Sn powder (3.08 g, 25.96 mmol) were successively added to the reaction mixture. After stirring at 80 °C for 24 h, the mixture was cooled to room temperature, Sn was removed by filtration over a Buchner funnel. The filtrate was diluted with ice-cold water (150 mL) and was extracted with EtOAc (3 x 100 mL). The combined organic layers were dried over Na_2SO_4, filtered and after evaporation of the solvent under reduced pressure, the crude product was purified by chromatography on a silica gel column (EtOAc/cyclohexane, 20:80) to furnish **17** as a light pink solid (2.56 g, 86%). Rf (EtOAc/cyclohexane: 40/60) = 0.5; mp = 184-186 (litt. 190-191 °C [28]). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.36 (bs, 1H, OH), 9.72 (bs, 1H, OH), 7.98 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.02 (bs, 1H), 6.88 (m, 2H); ^{13}C NMR (75 MHz, CD_3OD)**:** δ = 157.2, 153.3, 137.1, 132.8, 129.4, 125.7, 117.3, 110.1, 109.7, 108.3; IR (neat): ν = 3218, 1200 cm^{-1}; MS (APCI$^-$) m/z: 238 [M-H]$^-$

*1.1.2.2. Benzyl 4-[[7-(4-benzyloxy-4-oxo-butoxy)-6-bromo-2-naphthyl]oxy]butanoate **18***. A solution of **17** (827 mg, 3.46 mmol), K_2CO_3 (1.19 g, 8.65 mmol) and benzyl 4-bromobutanoate (2.67 g, 10.38 mmol) in anhydrous DMF (50 mL) was stirred for 24 h at 50 °C. DMF was evaporated under reduced pressure and the residue was redissolved in EtOAc (200 mL). The organic phase was successively washed with 10 % aqueous citric acid (50 mL), 10 % aqueous K_2CO_3 (50 mL), water (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on a silica gel column (cyclohexane/EtOAc, 90:10) to afford **18** as a white solid (1.76 g, 86%). Rf (EtOAc/cyclohexane, 25/75) = 0.3; mp = 61-62 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (s, 1H), 7.56 (d, *J* = 9.5 Hz, 1H), 7.31-7.34 (m, 10H), 6.97-7.01 (m, 3H), 5.15 (s, 4H), 4.16 (t, *J* = 6.2 Hz, 2H), 4.10 (t, *J* = 6.0 Hz, 2H), 2.71 (t, *J* = 7.3 Hz, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 2.29-2.18 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$)**:** δ = 173.0, 157.5, 153.2, 135.9, 134.8, 131.9, 128.5, 128.2, 124.9, 124.9, 117.2, 110.8, 106.9, 105.9, 67.6, 66.7, 66.3, 30.8, 30.7, 24.6, 24.4; IR (neat): ν = 3218, 2947, 1718, 1621, 1382, 1209, 1157, 1037, 965, 739, 696. cm^{-1}; $C_{32}H_{31}BrO_6$: calcd C 64.98, H 5.28; Found C 64.86, H 5.38; MS (ESI, ion polarity positive) m/z: 614 [M+Na]$^+$.

*1.1.2.3. Ethyl 4-[[6-bromo-7-(4-ethoxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoate **19***. Same procedure as described for **18** from the reaction of **17** (1.5 g, 6.27 mmol) and ethyl 4-bromobutanoate (3.7 g, 18.81 mmol) except that the crude product obtained was recrystallized from EtOAc/petroleum ether to give a white solid (2.4 g, 82%); Rf (EtOAc/cyclohexane, 30/70) = 0.4; mp = 64-66 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.86 (s, 1H), 7.49 (d, *J* = 9.1 Hz, 1H), 6.96-6.90 (m, 3H), 4.12–4.01 (m, 8H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.48 (t, *J* = 7.2 Hz, 2H), 2.17-2.07 (m, 4H), 1.19 (t, *J* =7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 157.5, 153.2, 134.8, 131.8, 128.2, 124.8, 117.9, 110.7, 106.8, 105.8, 67.7, 66.7, 60.4, 30.8, 30.7, 24.6, 24.4, 14.2; IR (neat): ν = 1729, 1205, 1172. cm^{-1}; $C_{22}H_{27}BrO_6$: calcd C 56.54, , H 5.82; Found C 56.56, H 5.72; MS (APCI$^+$) m/z: 468.2 [M+H]$^+$.

*1.1.2.4. Benzyl 4-[[7-(4-benzyloxy-4-oxo-butoxy)-6-[(2,2-dimethyl-1,3-dioxolan-4-yl)methylamino]-2-naphthyl]oxy]butanoate **20***. A Schlenk tube was charged with **18** (100 mg, 0.17 mmol), palladium acetate (4 mg, 17 µmol, 10 mol%), Xantphos (20 mg, 34 µmol, 20 mol%) and potassium carbonate (467 mg, 3.4 mmol). Then,

under argon atmosphere, dry dioxane (2.3 mL) and (2,2-dimethyl-[1,3]-dioxolan-4-yl)-methylamine (34 µL, 0.25 mmol) were added. The reaction mixture was stirred under argon atmosphere for 15 h at 110 °C. The mixture was allowed to cool down to room temperature andfiltered through a small pad of silica gel which was washed with EtOAc (3 x 20 mL). The filtrate was evaporated under reduced pressure and the residue was directly purified by flash chromatography on silica gel column (CH_2Cl_2,100%) to afford **20** as a yellow oil (76 mg, 70%);^{1}H NMR (400 MHz, $CDCl_3$)**:** δ = 7.49 (d, *J* = 8.6 Hz, 1H), 7.35-7.32 (m, 10H), 6.96-6.90 (m, 3H), 6.76 (s, 1H), 5.15 (s, 4H), 4.70 (bs, 1H), 4.47 (m, 1H), 4.17-4.06 (m, 5H), 3.88-3.84 (m, 1H), 3.39 (dd, *J* = 12.7 and 4.8 Hz, 1H), 3.33 (dd, *J* =12.7 and 5.3 Hz, 1H), 2.63 (t, *J* = 6.8 Hz, 4H), 2.25 (qt, *J* = 6.5 Hz, 2H), 2.18 (qt, *J* = 6.5 Hz, 2H), 1.47 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 172.9, 154.6, 147.9, 136.6, 136.0, 135.8, 128.5, 128.2, 126.8, 125.3, 116.1, 109.4, 106.8, 104.9, 104.2, 74.3, 67.3, 67.1, 66.7, 66.4, 66.3, 46.2, 31.0, 30.9, 26.8, 25.3, 24.8, 24.6; IR (neat): ν = 3423, 1731, 1153.cm^{-1}; $C_{38}H_{43}NO_8$: calcd C 71.12, H 6.75, N 2.18;. Found C 71.05, H 6.79, N 2.14; MS (ESI, ion polarity positive) m/z: 643 $[M+H]^+$.

*1.1.2.5. 4-[[6-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methylamino]-7-(4-hydroxy-4-oxo-butoxy)-2-naphtyl] oxy]butanoic acid **21*** . A solution of **20** (282 mg, 0.44 mmol) in CH_3OH/EtOAc (1:1, 40 mL) and Pd/C (56 mg, 20% mass) was stirred at room temperature under hydrogen atmosphere for 24 h. The solution was filtered through a pad of Celite, and the filtrate was evaporated under reduced pressure to afford **21** as a beige solid (201 mg, 99%); mp = 90-92 °C; ^{1}H NMR (300 MHz, CD_3OD): δ = 7.46 (d , *J* = 9.0 Hz,1H), 7.03 (d, *J* = 2.1 Hz, 1H), 7.02 (s, 1H), 6.89 (dd *J* = 8.7 and 2.4 Hz, 1H), 6.79 (s, 1H), 4.45 (m, 1H), 4.03-4.17 (m, 5H), 3.84 (dd, *J* = 12.7 and 6.2 Hz, 1H), 3.23-3.36 (m, 2H), 2.48-2.53 (m, 4H), 2.16 (qt, *J* = 6.6 Hz, 2H), 2.08 (qt, *J* = 6.6 Hz, 2H), 1.46 (s, 3H), 1.36 (s, 3H); ^{13}C NMR (75 MHz, CD3OD): δ = 175.8, 154.4, 147.8, 136.5, 128.3, 126.3, 125.2, 115.4, 109.0, 106.4, 104.5, 103.8, 74.2, 66.9, 66.7, 66.5, 45.5, 30.3, 25.7, 24.5, 24.3, 24.0; IR (neat): ν = 2918, 1703, 1248.cm^{-1}; $C_{24}H_{31}NO_8$: calcd C 62.46, H 6.77, N 3.04; Found C 62.13, H 6.63, N 2.90; MS (APCI$^+$) m/z: 462 $[M+H]^+$.

*1.1.2.6. Benzyl 4-[[6-amino-7-(4-benzyloxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoate **22**. A* Schlenk tube was charged with **18** (500 mg, 0.85 mmol), palladium acetate (19 mg, 8.5 µmol, 10 mol%), Xantphos (98 mg, 17 µmol, 20 mol%), and potassium carbonate (2.34 g, 17 mmol). Then, under argon atmosphere, dry dioxane (11.5 mL) and benzophenone imine (213 µL, 1.27 mmol) were added. The reaction mixture was stirred, under argon atmosphere, for 15 h at 110 °C. The mixture was allowed to cool down to room temperature, then filtered through a small pad of silica gel which was washed with EtOAc (3 x 50 mL). The filtrate was evaporated under reduced pressure. To the resulting crude imine dissolved in dioxane (7.5 mL) was successively added methanol (27.5 mL), $NaOAc{\cdot}3H_2O$ (428 mg, 3.54 mmol), and $NH_2OH{\cdot}HCl$ (171 mg, 2.56 mmol). The mixture was stirred for 6 h at room temperature and after evaporation under reduced pressure, the crude product was purified by flash chromatography on a silica gel column (cyclohexane/EtOAc, 80:20) to afford compound **22** as a light pink solid (273 mg, 62%); Rf = (cyclohexane/EtOAc, 70/30) = 0.3; mp = 87-89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.7 Hz, 1H), 7.26 (m, 10H), 6.91 (s, 1H), 6.83-6.87 (m, 3H), 5.07 (s, 4H), 4.08 (t, *J* = 6.0 Hz, 2H), 3.99 (t, *J* = 6.0 Hz, 2H), 2.58-2.52 (m, 4H), 2.19-2.07 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 173.1, 154.9, 148.3, 136.0, 135.9, 134.9, 129.2, 128.6, 128.3, 128.2, 126.8, 125.1, 116.3, 109.3, 106.7, 105.4, 67.1,

66.7, 66.5, 66.3, 31.2, 31.0, 24.8, 24.6; IR (neat): ν = 3367, 1725, 1160. cm^{-1}; $C_{32}H_{33}NO_6 \cdot 0.15H_2O$: calcd C 72.47, H 6.34, N 2.60; Found C 72.15, H 6.14, N 2.60; MS ($APCI^+$) m/z: 528 $[M+H]^+$.

*1.1.2.7. Ethyl 4-[[6-amino-7-(4-benzyloxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoate **23***. Same procedure as described for **22** from **19** (600 mg, 1.28 mmol) and benzophenone imine (322 µL, 1.92 mmol) in dry dioxane (13 mL) to afford **23** as a pink solid (264 mg, 51%); Rf (cyclohexane/EtOAc: 70/30) = 0.2; mp = 72-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36 (d, *J* = 8.7 Hz, 1H), 6.88-6.83 (m, 4H), 4.11-4.03 (m, 6H), 3.98 (t, *J* = 6.0 Hz, 2H), 3.70 (bs, 2H), 2.50-2.44 (m, 4H), 2.18-2.02 (m, 4H), 1.18 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.3, 173.2, 154.9, 148.2, 134.7, 134.0, 129.2, 128.2, 126.7, 124.9, 116.2, 109.4, 106.6, 105.4, 67.1, 66.7, 60.5, 60.3, 31.1, 30.9, 29.6, 24.7, 24.6, 14.2; IR (neat): ν = 3454, 3361, 1722, 1616, 1515, 1162. cm^{-1}; $C_{22}H_{29}NO_6 \cdot 0.15H_2O$: calcd C 65.49, H 7.24, N 3.47; Found C 65.46, H 7.24, N 3.31; MS ($APCI^+$) m/z: 404 $[M+H]^+$.

*1.1.2.8. Benzyl 4-[[7-(4-benzyloxy-4-oxo-butoxy)-6-[(2-chloroacetyl)amino]-2-naphthyl] oxy]butanoate **24***. To a solution of compound **22** (100 mg, 0.19 mmol) in dry CH_2Cl_2 (2 mL) was added Et_3N (31.5 µL, 0.22 mmol). The solution was stirred at 0 °C for 10 min, and chloroacetyl chloride (18 µL, 0.22 mmol), dissolved in dry CH_2Cl_2 (1 mL) was then added dropwise. After stirring the reaction for 2 h at room temperature, the organic layer was successively washed with 10% aqueous $KHSO_4$ (3 x 5 mL), and brine (3 x 5 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel column (CH_2Cl_2, 100%) to yield **24** as a pink solid (91 mg, 80%); Rf (CH_2Cl_2) = 0.3; mp = 96-98 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.07 (s, 1H), 8.65 (s, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.24 (m, 10H), 6.93 (s, 1H), 6.91 (m, 2H), 5.06 (s, 4H), 4.16 (s, 2H), 4.12 (t, *J* = 6.0 Hz, 2H), 4.02 (t, *J* = 6.0 Hz, 2H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.55 (t, *J* = 7.1 Hz, 2H), 2.23-2.07 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.1, 172.9, 163.6, 156.9, 147.5, 131.9, 129.3, 128.6, 128.3, 128.2, 128.1, 124.8, 123.9, 117.0, 116.9, 106.1, 105.3, 67.4, 66.7, 66.5, 66.3, 43.3, 30.9, 30.8, 24.7, 24.5 ; IR (neat): ν = 3379, 1724, 1672, 1548, 1243, 1156. cm^{-1}; $C_{34}H_{34}ClNO_7 \cdot 0.25H_2O$: calcd C 67.10, H 5.73, N 2.30; Found C 67.13, H 5.59, N 2.18; MS (ESI, ion polarity positive) m/z: 626 $[M+Na]^+$.

*1.1.2.9. Ethyl 4-[[7-(4-benzyloxy-4-oxo-butoxy)-6-[(2-chloroacetyl)amino]-2-naphthyl] oxy]butanoate **25***. Same procedure as described for **24** from **23** (260 mg, 0.64 mmol) and chloroacetyl chloride (102 µl, 1.28 mmol) in dry CH_2Cl_2 (2 mL). The crude product was purified by flash chromatography on silica gel column (cyclohexane/EtOAc, 80:20) to yield compound **25** as a light green solid (230 mg, 75%); Rf (cyclohexane/EtOAc: 80/20) = 0.32; mp = 78-80 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.16 (s, 1H), 8.73 (s, 1H), 7.67 (d, *J* = 9.1 Hz, 1H), 7.01 (d, *J* = 10.0 Hz, 3H), 4.25 (s, 2H), 4.22-4.07 (m, 8H), 2.62-2.52 (m, 4H), 2.29-2.14 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) : δ = 173.2, 173.0, 163.5, 156.9, 147.5, 131.9, 129.3, 124.8, 123.9, 116.8, 106.1, 105.2, 67.5, 66.7, 60.6, 60.4, 43.3, 30.8, 30.7, 24.6, 24.4, 14.2; IR (neat): ν = 3378, 1725, 1666, 1543. cm^{-1}; $C_{24}H_{30}ClNO_7$: calcd C 60.06, H 6.30, N 2.92; Found C 60.26, H 6.32, N 2.95; MS ($APCI^+$) m/z: 480 $[M+H]^+$.

*4.1.2.10. Benzyl 4-[[7-(4-benzyloxy-4-oxo-butoxy)-6-[[2-(methylamino)acetyl]amino]-2-naphthyl]oxy]butanoate **26***. To a solution of compound **24** (180 mg, 0.3 mmol) in dry DMF (8 mL) were added NH_2CH_3 HCl (304 mg,

4.5 mmol) and Et_3N (668 µL, 4.8 mmol). The mixture was stirred for 48 h at room temperature. After removal of the solvent under reduced pressure, the residue was dissolved in EtOAc (15 mL) and washed successively with 10 % aqueous citric acid (2 x 5 mL), saturated $NaHCO_3$ (2 x 5 mL), and brine (10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel column (CH_2Cl_2, 100% to CH_2Cl_2/CH_3OH, 100:1) to afford**26** as a yellow solid (105 mg, 60%); Rf (CH_2Cl_2/CH_3OH, 20/1) = 0.23; mp = 80-82 °C; ^1H NMR (300 MHz, $CDCl_3$) : δ = 9.89 (s, 1H), 8.71 (s, 1H), 7.59 (d, *J* = 9.7 Hz, 1H), 7.27 (m,10H), 6.92 (s, 1H), 6.89 (m, 3H), 5.07 (s, 4 H), 4.10 (t, *J* = 5.9 Hz, 2H), 4.02 (t, *J* = 6.0 Hz, 2H),3.29 (s, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 2.55 (t, *J* = 7.3 Hz, 2H), 2.40 (s, 3H), 2.23-2.07 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) : δ = 173.1, 172.9, 169.4, 156.6, 147.8, 135.7, 131.5, 129.2, 128.6,128.4, 125.6, 124.3, 116.6, 106.1, 105.1, 66.9, 66.6, 66.4, 66.3, 55.3, 36.7, 30.9, 30.7, 24.7; IR (neat): 2928, 1992, 1730, 1149 cm^{-1}; $C_{35}H_{38}N_2O_7 \cdot 0.3H_2O$:calcd C 69.59, H 6.45, N 4.64; Found C 69.51, H 6.10, N 4.40; MS ($APCI^+$) m/z: 599 $[M+H]^+$.

4.1.2.11.*4-[[7-(4-Hydroxy-4-oxo-butoxy)-6-[[2-(methylamino)acetyl]amino]-2-naphthyl]oxy]butanoic acid **27***. Same procedure as described for **21** from **26** (105 mg, 0.18 mmol) and Pd/C (16 mg, 15% mass) in CH_3OH (10 mL) to afford **27** as a white solid (61 mg, 84%); Rf (CH_2Cl_2/CH_3OH, 20/1)= 0.23; mp = 72-74 °C; ^1H NMR (300 MHz, DMSO-d_6): δ = 9.95 (s, 1H), 8.57 (s, 1H), 7.67 (d, *J* = 8.9 Hz, 1H), 7.30 (s,1H), 7.19 (d, *J* = 2.3 Hz, 1H), 6.98 (dd, *J* = 2.3, and 8.9 Hz, 1H), 4.17 (t, *J* = 6.0 Hz, 2H), 4.06 (t, *J* = 6.3 Hz, 2H), 3.42 (s, 2H), 2.44-2.36 (m, 4H), 2.43 (s, 3H), 2.12-1.95 (m, 4H); IR (neat): ν = 2947, 1731 cm^{-1}; MS (ESI, ion polarity positive) m/z: 419 $[M+H]^+$.

*4.1.2.12.Ethyl 4-[2-[[3,6-bis(4-ethoxy-4-oxo-butoxy)-2-naphthyl]amino]-2-oxo-ethyl]piperazine-1-carboxylate **28***. Same procedure as described for **26** from **25** (350 mg, 0.73 mmol) and benzyl 1-piperazine carboxylate (282 µL, 1.46 mmol). The crude product was purified by flash chromatography on silica gel column (cyclohexane/EtOAc, 70:30) to yield compound **28** as a light yellow solid (423 mg, 88 %); mp = 76-78 °C; Rf (cyclohexane/EtOAc, 70/30) = 0.2; ^1H NMR (300 MHz, $CDCl_3$): δ = 9.69 (s, 1H), 9.80 (s, 1H), 7.65 (d, *J* = 9.6 Hz, 1H), 7.36-7.31 (m, 5H), 7.01-6.98 (m, 3H), 5.15 (s, 2H), 4.19-4.06 (m, 8H), 3.60 (m, 4H), 3.21 (s, 2H), 2.60-2.52 (m, 8H), 2.24-2.13 (m, 4H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =.173.0, 172.4, 167.5, 156.5, 154.9, 147.5, 136.4, 131.4, 129.0, 128.3, 127.9, 127.8, 125.2, 124.0, 116.6, 105.9, 105.0, 67.2, 67.1, 66.6, 62.4, 60.5, 60.2, 53.1, 43.8, 30.8, 30.7, 24.6, 24.5, 14.1, 14.0; IR (neat): ν = 2945, 1731, 1686, 1531 cm^{-1}; $C_{36}H_{45}N_3O_9$: calcd C 65.14, H 6.83, N 6.33; found C 65.36, H 6.82, N 6.32; MS ($APCI^+$) m/z: 664.7 $[M+H]^+$.

*4.1.2.13.4-[[6-[[2-(4-Benzyloxycarbonylpiperazin-1-yl)acetyl]amino]-7-(4-hydroxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoic acid **29***. To a solution of compound **28** (190 mg, 0.28 mmol) in CH_3OH (6 mL), was added aqueous NaOH 2N (1 mL) and the solution was stirred at room temperature for 3.5 h. After evaporation under reduced pressure, the residue was taken up with water (15 mL) and washed with Et_2O (2 x 10 mL). The organic layer was washed with NaOH 2N (10 mL) and the combined aqueous layers were acidified with aqueous HCl 1N. After extraction with EtOAc (3 x 20 mL) the combined organic layers were washed with aqueous HCl 1N (25 mL), dried over Na_2SO_4 and evaporated under reduced pressure to afford compound **29** as a yellow solid (149 mg, 86%); mp = 92-94 °C; ^1H NMR (300 MHz, CD_3OD): δ = 8.61 (s, 1H), 7.61 (d, *J* = 8.9

Hz, 1H), 7.38-7.34 (m, 5H), 7.22 (s, 1H), 7.14 (m, 1H), 7.02-6.98 (dd, *J* = 8.9 and 2.4 Hz, 1H), 5.16 (s, 2H), 4.24 (t, *J* = 6.1 Hz, 2H), 4.12 (t, *J* = 6.1 Hz, 2H), 3.68 (m, 4H), 3.45 (s, 2H), 2.79 (m, 4H), 2.62-2.51 (m, 4H), 2.26-2.08 (m, 4H); ^{13}C NMR (75 MHz, CD_3OD): δ = 177.0, 158.4, 149.6, 133.9, 129.8, 129.6, 129.2, 129.0,126.1, 125.2, 118.9, 117.9, 107.3, 106.9, 69.1, 68.6, 68.0, 53.9, 43.9, 31.9, 31.4, 25.8; IR (neat): ν = 2888, 1729, 1692, 1609, 1434, 1235. cm^{-1}; $C_{32}H_{37}N_3O_6 \cdot 1H_2O$: calcd C 61.43, H 6.30, N 6.72; found C 61.15, H 6.26, N 6.56; MS (APCI$^-$) m/z: 606 $[M-H]^-$.

*4.1.2.14.Benzyl 4-[[7-(4-benzyloxy-4-oxo-butoxy)-6-[3-(dimethylamino)prop-1-ynyl]-2- naphthyl]oxy]butanoate **30***. A Schlenk tube was charged with **18** (150 mg, 0.25 mmol), $Pd(PPh_3)_4$ (15 mg, 12.5 µmol, 5 mol%), CuI (5 mg, 24.4 µmol, 10 mol%), and Et_3N (1.27 mL), then *N*,*N*-dimethylpropargylamine in solution in dry DMF (1.1 mL) was added under an argon atmosphere. The mixture was stirred at 80 °C for 6.5 h and the solvent was removed under reduced pressure. The residue was taken up in EtOAc (20 mL) and the organic layer was successively washed with 10% aqueous $KHSO_4$ (3 x 10 mL), saturated $NaHCO_3$ (2 x 10 mL), and brine (3 x 10 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel column (CH_2Cl_2, 100% to CH_2Cl_2/CH_3OH, 20:1) to yield compound **30** as a yellow solid (87 mg, 60%); Rf (CH_2Cl_2/CH_3OH, 20/1) = 0.37; mp = 65-67 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (s, 1H), 7.49 (d, *J* = 9.6 Hz, 1H), 7.27 (m, 10H), 6.87 (m, 3H), 5.06 (s, 4H), 4.06 (t, *J* = 6.0 Hz, 2H), 4.02 (t, *J* = 6.0 Hz, 2H), 3.47 (s, 2H), 2.60 (t, *J* = 7.3 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 2.29 (s, 6H), 2.19-2.07 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 157.8, 156.8, 135.9, 135.4, 133.2, 132.1, 132.0, 131.9, 128.9, 128.5, 128.4, 128.2, 123.6, 116.8, 111.7, 105.9, 105.5, 87.9, 81.8, 67.0, 66.7, 66.33, 66.31; 48.7, 44.0, 30.8, 30.7, 29.7, 24.6; $C_{37}H_{39}NO_6$ $0.5H_2O$: calcd C 73.73, H 6.70, N 2.32; found C 73.78, H 6.34, N 2.32; MS (ESI, ion polarity positive) m/z: 594 $[M+H]^+$.

*4.1.2.15.4-[[6-[3-(Dimethylamino)propyl]-7-(4-hydroxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoic acid **31***. Same procedure as described for **21** from **30** (429 mg, 0.72 mmol) and Pd/C (64 mg, 15% mass) to afford **31** as a light yellow solid (295 mg, 98%); mp = 66-68 °C; ^{1}H NMR (400 MHz, CD_3OD): δ = 7.54 (d, *J* = 8.9 Hz, 1H), 7.44 (s, 1H), 7.07 (m, 2H), 6.91 (dd, *J* = 8.9 and 1.9 Hz, 1H), 4.11 (t, *J* = 4.1 Hz, 2H), 4.06 (t, *J* = 6.3 Hz, 2H), 3.09 (m, 2H), 2.78 (m,6H), 2.75 (t, *J* = 8.0 Hz, 2H), 2.48-2.41 (m, 4H), 2.20-2.04 (m, 4H), 2.00-1.94 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ = 181.1, 179.6, 158.6, 157.4, 136.6, 129.5, 129.3, 128.9, 125.4, 117.2, 107.1, 106.4, 69.2, 68.4, 58.8, 43.2, 35.6, 33.5, 29.5, 26.8, 26.7, 26.6; IR (neat): ν = 1714, 1632, 1388, 1211, 1147 cm^{-1}; $C_{23}H_{31}$ $NO_6 \cdot 1H_2O$: calcd C 63.43, H 7.65, N 3.22; found C 63.65, H 7.74, N 3.00; MS (APCI$^+$) m/z: 418 $[M+H]^+$.

*4.1.2.16.Ethyl4-[[6-[2-[bis(benzyloxycarbonyl)amino]ethynyl]-7-(4-ethoxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoate **32***. Same procedure as described for **30** from **19** (300 mg, 0.64 mmol) and *N*,*N*-di(benzyloxycarbonyl)propargylamine except that the reaction was stirred for 15 h. The crude product was purified by chromatography on silica gel column (cyclohexane/EtOAc, 90:10) to yield **32** as a yellow solid (186 mg, 41%); Rf (cyclohexane/EtOAc, 70/30) = 0.3; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73 (s, 1H), 7.56 (d, *J* = 9.7 Hz, 1H), 7.43-7.42 (m, 3H), 7.32-7.30 (m, 7H), 6.99-6.97 (m, 3H), 5.33 (s, 4 H), 4.82 (s, 2H), 4.19-4.10 (m, 8H), 2.58-2.54 (t, *J* = 6.9 Hz, 4H), 2.21-2.11 (m, 4H), 1.27 (t, *J* = 7.0 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) δ = 173.1, 173.0, 157.9, 156.8, 152.6, 135.6, 135.2, 133.6, 128.9, 128.4, 128.2, 127.9, 123.5, 116.8, 111.0, 105.8, 105.6, 87.6, 79.7, 68.7, 67.1, 66.6, 60.3, 60.2, 37.3, 30.7, 30.4, 24.5, 24.3, 14.1; IR (neat): ν = 2949, 1758, 1716, 1203, 1164. cm^{-1}; $C_{41}H_{43}NO_{10}$: calcd C 69.38, H 6.11, N 1.97; found C 69.13, H 5.95, N 2.04; MS (ESI, ion polarity positive) m/z : 732.6 $[M+Na]^+$.

*4.1.2.17.4-[[6-[2-(Benzyloxycarbonylamino)ethynyl]-7-(4-hydroxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoic acid **33***. To a solution of compound **32** (155 mg, 0.22 mmol) in CH_3OH/THF (1:1, 5 mL), aqueous NaOH 2N (580 µL) was added and the solution was stirred at room temperature for 5 h. After concentration under reduced pressure, the residue was taken up with water (20 mL) and extracted with Et_2O (2 x 10 mL). The organic layer was washed with aqueous NaOH 2N (10 mL). The combined aqueous layers were acidified using aqueous HCl 1N and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with HCl 1N (25 mL), dried over Na_2SO_4 and evaporated under reduced pressure to afford compound **33** as a light brown solid (70 mg, 61%); mp = 92-94 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.18 (bs, 2H), 7.87 (s, 1H), 7.83 (t, *J* = 7.1 Hz, 1H), 7.80 (d, *J* = 9.1 Hz, 1H), 7.38 (m, 7H), 6.99 (dd, *J* = 8.7 and 2.3 Hz, 1H), 5.07 (s, 2H), 4.12-4.08 (m, 6H), 2.46-2.39 (m, 4H), 2.06-1.95 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 174.2, 157.5, 156.1, 135.4, 132.9, 128.8, 128.3, 127.7, 123.0, 116.7, 110.5, 105.9, 78.4, 67.0, 66.6, 65.5, 48.5, 30.2, 30.0, 24.1; IR (neat): ν = 2918, 1694, 1627, 1215.cm^{-1}; MS ($APCI^-$) m/z: 518 $[M-H]^-$; HRMS calcd for $C_{29}H_{29}NO_8Na$: 542.1791; found: 542.1789.

4.1.2.18.*Ethyl 4-[[6-cyano-7-(4-ethoxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoate **34***. A sealed tube was charged with **19** (2.6 g, 5.56 mmol), $K_4[Fe(CN)_6]$ (587 mg, 1.39 mmol), CuI (106 mg, 0.56 mmol), 1-butyl-1*H*-imidazole (1.46 mL, 11.12 mmol) and dry toluene (8.5 mL), under argon atmosphere. After stirring at 160 °C for 46 h, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc (100 mL) .The organic layer was successively washed with water (3 x 50 mL), brine (3 x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel column (cyclohexane/EtOAc, 85:15) to afford compound **34** as a white solid (1.61 g, 70%); mp = 98-100 °C; Rf (cyclohexane/EtOAc, 70/30) = 0.23; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (s, 1H), 7.65 (d, *J* = 8.9 Hz, 1H), 7.04-7.00 (m, 3H), 4.21-4.11 (m, 8H,), 2.61 (t, *J* = 7.1 Hz, 2H), 2.55 (t, *J* = 7.3 Hz, 2H), 2.25-2.14 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, CD_3OD): δ = 173.2, 173.0, 150.6, 156.1, 138.1, 135.5, 129.8, 122.9, 118.1, 116.6, 106.1, 105.8, 100.8, 67.9, 66.9, 60.4, 30.7, 30.4, 24.4, 24.2, 14.2; IR (neat): ν = 2219, 1720, 1624.cm^{-1}; $C_{23}H_{27}NO_6 \cdot 0.15H_2O$: calcd C 66.38, H 6.63, N 3.37; found C 66.22, H 6.27, N 3.35; MS (ESI, ion polarity positive) m/z: 436 $[M+Na]^+$.

*4.1.2.19.Ethyl 4-[[6-(aminomethyl)-7-(4-ethoxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoate **35***. To a solution of **34** (1.0 g, 2.4 mmol) in DMF (8 mL), were added NH_3 1N in EtOH (15 mL) and Raney nickel (200 mg, prewashed with EtOH). After stirring the reaction under hydrogen atmosphere for 2 days at room temperature, the solution was filtered through a pad of Celite, and concentrated under reduced pressure. The residue obtained was recrystallized from petroleum ether to afford compound **35** as a white solid (985 mg, 98%); mp = 88-90 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.62 (d, *J* = 8.9 Hz, 1H), 7.56 (s, 1H), 7.02-6.95 (m, 3H), 4.19-4.08 (m, 8H,), 3.92 (s, 2H), 2.59-2.52 (m, 4H), 2.26-2.11 (m, 4H), 1.64 (bs, 2H), 1.26 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ = 173.1, 173.0, 157.1, 155.7, 134.9, 130.8, 129.0, 128.8, 126.7, 123.9, 116.0, 105.9, 105.0, 66.6, 66.5, 60.5, 60.4, 42.8, 30.9, 30.8, 24.6, 24.5, 14.2; IR (neat): ν = 2938, 1730, 1633, 1506, 1169 cm^{-1}; $C_{23}H_{31}NO_6 \cdot 0.15H_2O$: calcd C 65.74, H 7.52, N 3.33; found C 65.58, H 7.11, N 3.29; MS (ESI, ion polarity positive) m/z: 418 $[M+H]^+$.

*4.1.2.20.Ethyl 4-[[6-(benzyloxycarbonylaminomethyl)-7-(4-ethoxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoate **36**.* To a solution of **35** (300 mg, 0.72 mmol) and Et_3N (300 µL, 2.16 mmol) in CH_2Cl_2 (10 mL), was slowly added CbzCl (205 µL, 1.44 mmol) in CH_2Cl_2 (2 mL). The reaction was stirred at 0°C for 30 min at room temperature overnight. The organic layer was successively washed with aqueous HCl 1N (2 x 10 mL), water (2 x 10 mL), brine (2 x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel column (cyclohexane/EtOAc, 85:15) to yield compound **36** as a colorless solid (330 mg, 83 %); Rf (cyclohexane/EtOAc, 70/30) = 0.23; ^{1}H NMR (300 MHz, $CDCl_3$): δ =*:* 7.54-7.51 (m, 2H), 7.25-7.20 (m, 5H), 6.91-6.86 (m, 3H), 5.32 (t, *J* = 5.4 Hz, 1H), 5.02 (s, 2H), 4.38 (d, *J* = 6.0 Hz, 2H), 4.10-3.98 (m, 8H,), 2.48-2.43 (m, 4H), 2.14-2.02 (m, 4H), 1.96-1.19 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ =. 173.2, 173.1, 157.4, 156.4, 155.5, 136.7, 135.4, 129.1, 128.5, 128.3, 128.1, 128.0, 125.5, 123.8, 116.4, 105.9, 105.2, 66.8, 66.7, 60.5, 60.4, 41.3, 30.9, 30.8, 24.6, 24.5, 14.2; IR (neat): ν = 2967, 1723, 1634, 1507.cm^{-1}; $C_{31}H_{37}NO_8$: calcd C 67.50, H 6.76, N 2.54; found C 67.33, H 6.64, N 2.52 ; MS (ESI, ion polarity positive) m/z: 474 $[M+Na]^+$.

*4.1.2.21.4-[[6-(Benzyloxycarbonylaminomethyl)-7-(4-hydroxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoic acid **37**.* Same procedure as described for **29**, from **36** (330 mg, 0.59 mmol) to afford compound **37** as a white solid (284 mg, 96%); mp = 138-140 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.19 (bs, 2H), 7.67-7.62 (m, 2H), 7.53 (s, 1H), 7.39-7.38 (m, 4H), 7.31-7.20 (m, 3H), 6.98-6.95 (m, 1H), 5.08 (s, 2H), 4.30 (d, *J* = 2.1 Hz, 2H), 4.12-4.05 (m, 4H), 2.46-2.40 (m, 4H), 2.08-1.92 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 174.2, 174.0, 156.6, 156.3, 154.9, 137.2, 134.8, 128.6, 128.3, 127.7, 126.2, 125.8, 123.2, 115.9, 105.9, 105.0, 66.7, 66.5, 65.3, 30.3, 30.1, 24.2, 24.1; IR (neat): ν = 2936,1681, 1524, 1253, 1216 cm^{-1}; $C_{27}H_{29}NO_8 \cdot 0.3H_2O$: calcd C 64.73, H 5.97, N 2.80; found C 64.74, H 5.77, N 2.65; (APCI$^-$) m/z: 494 $[M-H]^-$.

*4.1.2.22.Ethyl 4-[[6-[[[(E)-N,N'-bis(tert-butoxycarbonyl)carbamimidoyl]amino]methyl]-7-(4-ethoxy-4 oxo-butoxy)-2-naphthyl]oxy]butanoate **38**.* To an ice-cooled solution of compound **35** (120 mg, 0.29 mmol) in dry CH_2Cl_2 (5 mL), were successively added Et_3N (202 µL, 1.45 mmol), 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (110 mg, 0.38 mmol) and mercury (II) chloride (103 mg, 0.38 mmol). The solution was then stirred at room temperaturefor 17 h. After filtration of the suspension through a pad of Celite, the fitrate was successively washed with 10% aqueous citric acid (3 x 10 mL), water (2 x 10 mL), and brine (3 x 10 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel column (cyclohexane/EtOAc, 85:15) to yield compound **38** as a colorless oil (120 mg, 62%); Rf (cyclohexane/EtOAc, 60/40) = 0.5; ^{1}H NMR (300 MHz, $CDCl_3$): δ =. 11.46 (s, 1H), 8.76 (t, *J* = 5.2 Hz, 1H), 7.58 (s, 1H), 7.55 (d, *J* = 8.2 Hz, 1H), 6.94-6.88 (m, 3H), 4.65 (d, *J* = 5.4 Hz, 2H), 4.11-4.00 (m, 8H,), 2.53-2.45 (m, 4H), 2.19-2.04 (m, 4H), 1.45 (s, 9H), 1.39 (s, 9H), 1.18 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.2, 163.7, 157.4, 155.9, 155.8, 153.0, 135.4, 129.1, 128.7, 124.3, 123.7, 116.4,

116.2, 106.0, 105.8, 105.2, 82.8, 79.1, 66.8, 66.7, 60.4, 41.2, 30.8, 28.3, 28.0, 24.6, 24.4, 14.2; IR (neat): ν = 2976, 1722, 1633, 1147 cm^{-1}; MS (ESI, ion polarity positive) m/z : 660 $[M+H]^+$, 682 $[M+Na]^+$; HRMS calcd for $C_{34}H_{49}N_3O_{10}Na$: 682.3316; found: 682.3299.

*4.1.2.23.4-[[6-(Guanidinomethyl)-7-(4-hydroxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoic acid, hydrochloride salt **39***. To a solution of compound **38** (118 mg, 0.18 mmol) in CH_3OH/THF (1:1, 4 mL), aqueous NaOH 2N (260 μL) was added and the solution was stirred at room temperature for 4h. After concentration under reduced pressure, the residue was taken up with water (20 mL) and extracted with Et_2O (2 x 10 mL). The organic layer was washed with aqueous NaOH 2N (10 mL). The combined aqueous layers were acidified using aqueous HCl 1N and then extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with HCl 1N (25 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was directly dissolved in a 4N HCl dioxane solution (5 mL) and stirred at room temperature overnight. After evaporation of the solvent under reduced pressure, the hydrochloride salt of compound **39** was obtained as a light yellow solid (80 mg, 100%); mp = 101-103 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.15 (bs, 2H), 7.79 (t, *J* = 5.3 Hz, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.64 (s, 1H), 7.27-7.24 (m, 6H), 7.00 (dd, *J* = 8.8 and 2.4 Hz, 1H), 4.42 (d, *J* = 5.6 Hz, 2H), 4.15-4.06 (m, 4H), 2.47-2.40 (m, 4H), 2.08-1.98 (m, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 174.2, 174.0, 157.0, 154.8, 135.3, 128.8, 126.8, 123.8, 123.0, 106.0, 105.5, 66.9, 66.5, 30.2, 30.1, 24.2; IR (neat): ν = 2960, 1713, 1631, 1402. cm^{-1}; MS (ESI, ion polarity positive) m/z : 404 $[M+H]^+$; HRMS calcd for $C_{20}H_{25}N_3O_6$ $[M+H]^+$: 404.1822; found: 404.1837.

*4.1.2.24.4,4'-(3-aminonaphthalene-2,7-diyl)bis(oxy)dibutanoic acid **42***. Same procedure as described for **21** from **22** (156 mg, 0.30 mmol) and Pd/C (31 mg, 20% mass) to afford **42** as a light-pink solid (102 mg, 99%); mp = 144-146 ºC; ^{1}H NMR (300 MHz, CD_3OD): δ = 7.40 (d, *J* = 9.0 Hz, 1H), 7.04 (s, 2H), 7.00 (s, 1H), 6.88 (dd, J_1 = 9.0 Hz, J_2 = 2.1 Hz, 1H), 4.17 (t, J = 6.6 Hz, 2H), 4.03 (t, J = 6.6 Hz, 2H), 2.57-2.48 (m, 4H), 2.17 (quint, *J* = 6.6 Hz, 2H), 2.08 (quint, *J* = 6.6 Hz, 2H); ^{13}C NMR (75 MHz, CD_3OD): δ = 177.3, 177.2, 156.4, 150.1, 136.1, 131.2, 127.8, 126.6, 117.2, 111.3, 107.8, 106.6, 68.5, 68.1, 31.9, 31.6, 26.0, 25.9; IR (neat): ν = 2923, 1714, 1253 cm^{-1}; MS ($APCI^+$) m/z : 348 $[M+H]^+$

4.1.2.25.

4.2. Enzymatic studies

The fluorogenic substrate for PR and mutated proteases was DABCYL-γ-abu-Ser-Gln-Asn-Tyr-Pro-Ile-Val-Gln-EDANS [DABCYL, 4-(4'-dimethylaminophenylazo)benzoyl; γ-abu, γ-aminobutyric acid. EDANS, 5-[(2-aminoethyl)amino]naphthalene-1-sulfonic acid)], was purchased from Bachem (Germany). 1-Anilino-8-naphthalenesulfonate (ANS) was purchased from Sigma-Aldrich, saquinavir and amprenavir were purchased from the NIH (USA). The fluorogenic pepsin substrate Arg-Glu(EDANS)-Ile-His-Pro-Phe-His-Leu-Val-Ile-His-Thr-Lys(DABCYL)-Arg, the renin substrate Abz-Thr-Ile-Nle-(*p*-NO_2-Phe)-Gln-Arg-NH_2, and recombinant renin and pepsin were purchased from Sigma–Aldrich. Other reagents and solvents were purchased from commercial sources. Absorbance measurements were made with a Perkin Elmer LS 50B spectrophotometer. Fluorescence intensities were measured in a BMG Fluostar microplate reader.

4.2.1. *Wild-type and mutated proteases*. The HIV-1 proteases (PR, MDR-HM and ANAM-11[22]) used in this study were expressed and purified as described before[14]. They were produced in *E. coli* using the expression vector pET-9 and the host bacterium strain Rosetta (DE3)pLysS. The protease domain (PR) has 5 protective mutations, Q7K, L33I, L63I to minimize the autoproteolysis of the protease and C67A and C95A to prevent cysteine-thiol oxidation. The multi-mutated HIV-1 protease ANAM-11 contains 11 mutations (L10I/M36I/S37D/M46I/R57K/ L63P/A71V/G73S/I84V/L90M/I93L) [51].

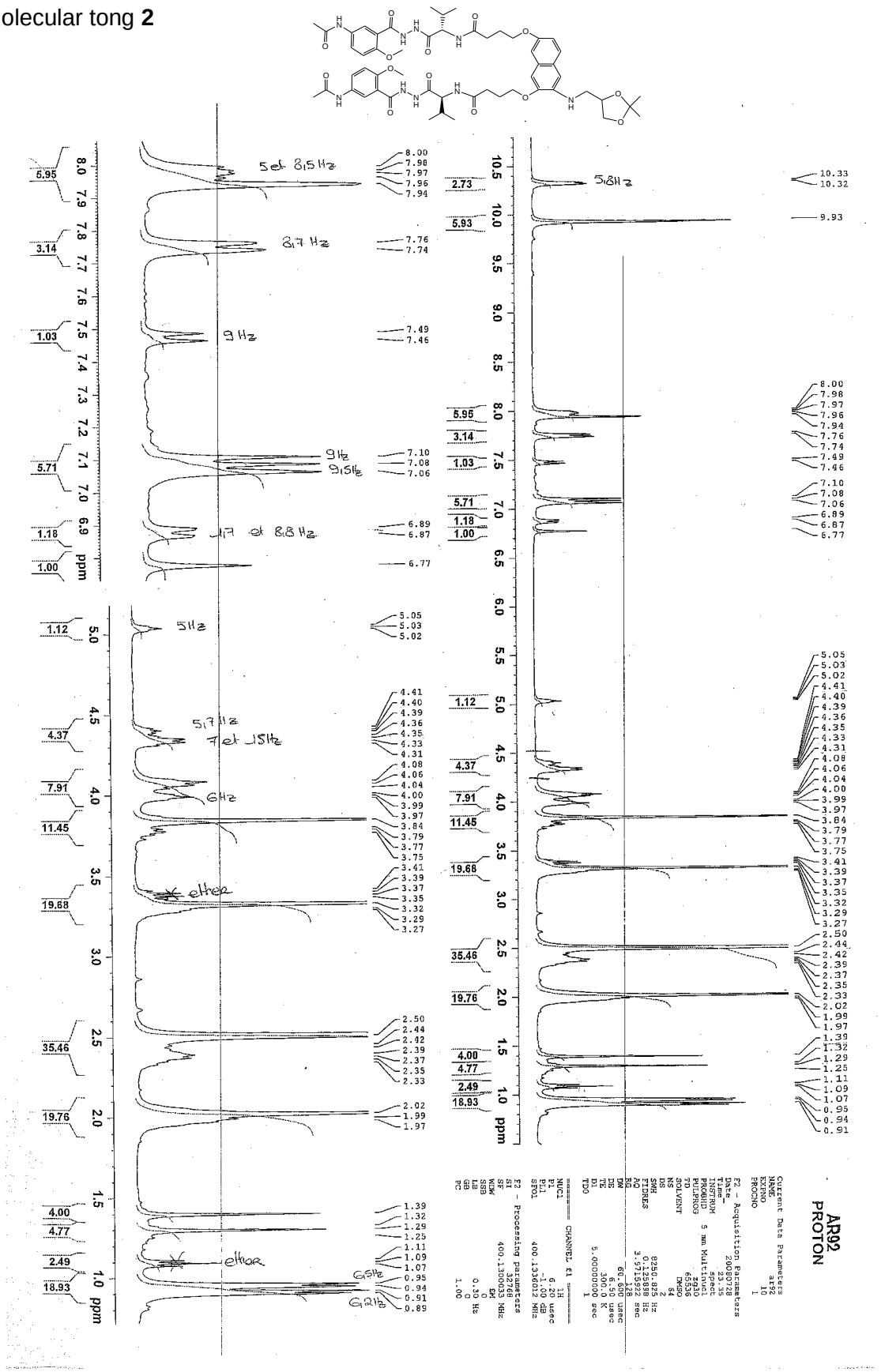
4.2.2. *Enzyme and inhibition assays*. The proteolytic activities of PR and mutated proteases were determined fluorometrically using the fluorogenic substrate DABCYL-□-abu-SQNYPIVQ-EDANS (λ_{ex} = 340 nm; λ_{em} = 490 nm) in 100 mM sodium acetate, 1 mM EDTA, and 1 M NaCl at pH 4.7 and 30 °C (final volume, 150 µL). The substrate and the compound(s) were first dissolved in DMSO. The final DMSO concentration was kept at 3 % (v/v). The mechanism of inhibition and the corresponding kinetic constants K_{id} (dimerization inhibition) or K_{ic} (competitive inhibition) were determined using Zhang-Poorman kinetic analysis.[11] Kinetic experiments were carried out at a constant substrate concentration (5.2 µM) with at least six enzyme concentrations (5.33-18.6 nM), and inhibitor concentrations varying from 0.5 to 28 µM. The experimental data were fitted according to ref. 14. All experiments were performed at least in triplicate.

4.2.3. *Evaluation of Metabolic Stability*. The stability of inhibitors in RPMI (Roswell Park Memorial Institute medium) culture medium containing 20% fetal calf serum was assessed by studying their kinetics of breakdown at 37 °C for up to 2 days. Incubations were terminated by adding ethanol. The mixture was poured at 4 °C and centrifuged (10 000 rpm for 10 min). Aliquots of the clear supernatant were injected onto the HPLC column (Waters E600). The half-life of breakdown was obtained by least-squares linear regression analysis of a plot of the log[I] *versus* time using a minimum of five points [23].

4.3. Molecular modelling.

3D coordinates for the likely ionic form at pH 4.7 (i.e. with protonated amines) of compounds **1**-**15** were generated with CORINA v3.44 software [52] and energy was minimized using OPLS_2005 force field [53] as implemented in MacroModel v9.9 [54] using default parameters from the LigPrep v2.5 interface [55] in the Schrödinger 2012 software suite. Solvent-accessible surface areas and estimated logP were calculated for these models using QikProp 3.5 [56]. Hydrophobic surface area values reported include π surface area.

Molecular tong **2**



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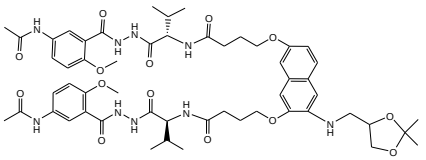

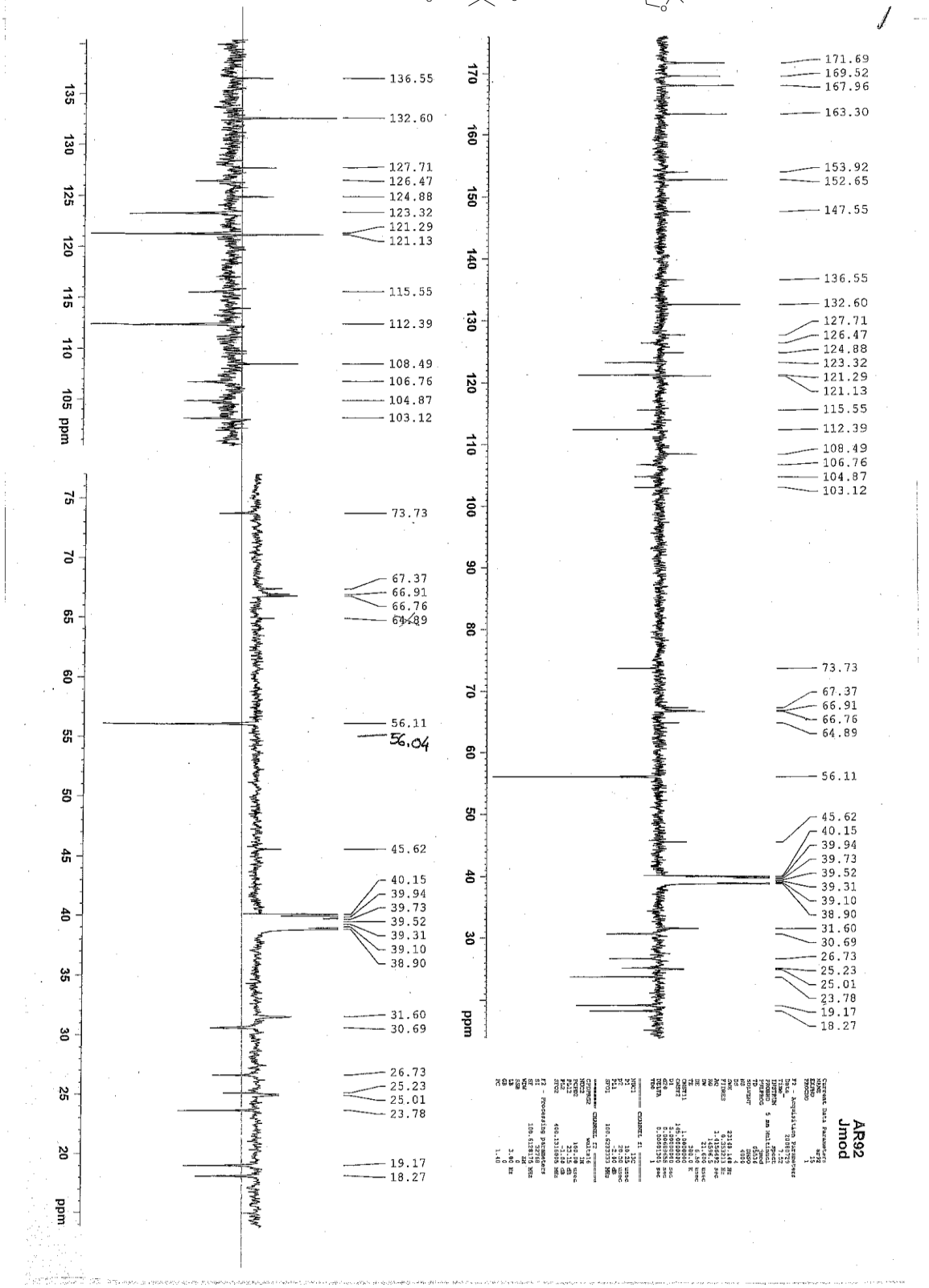

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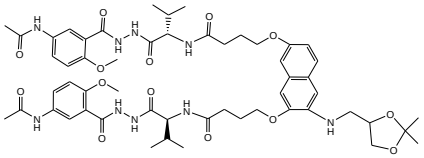

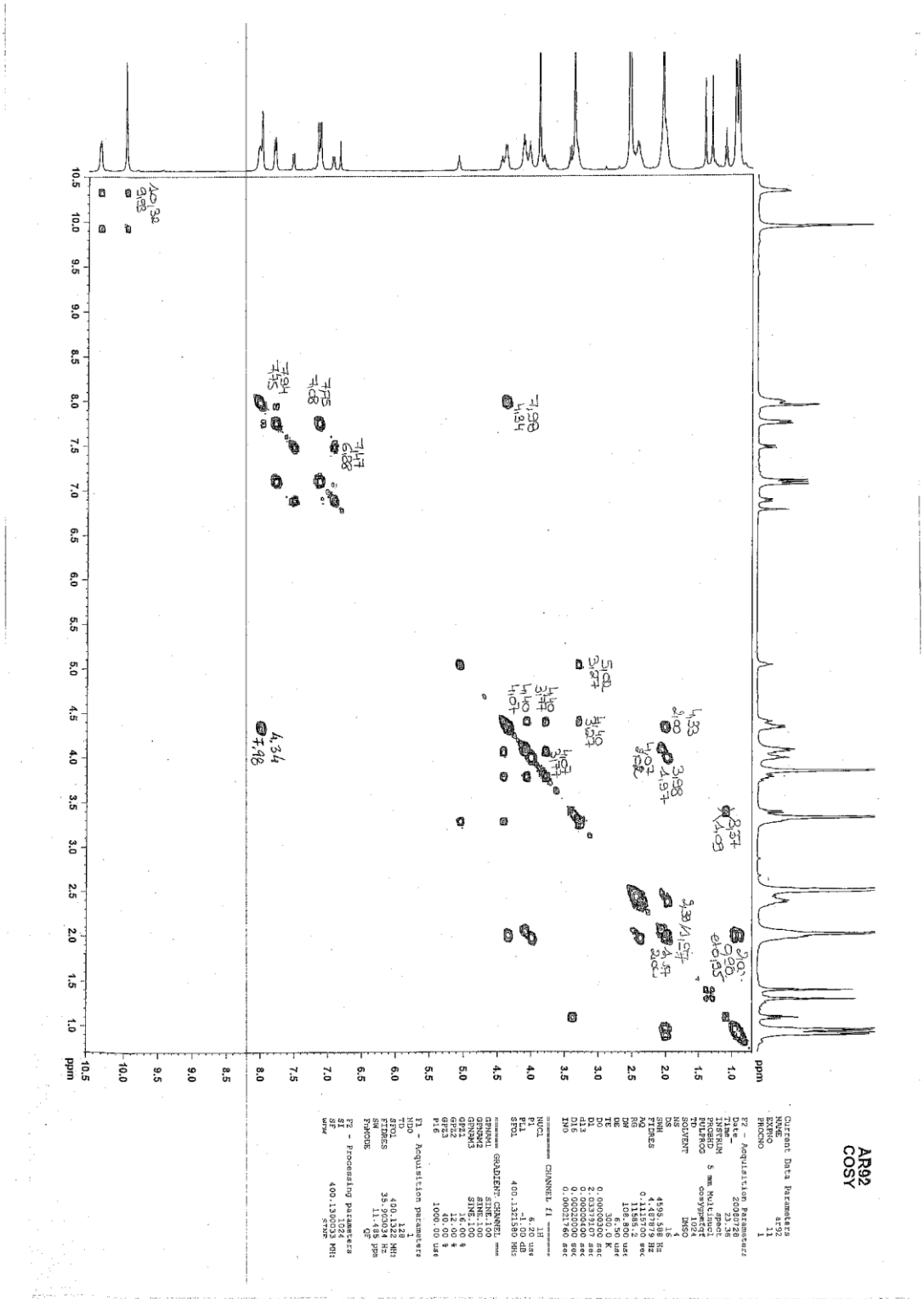

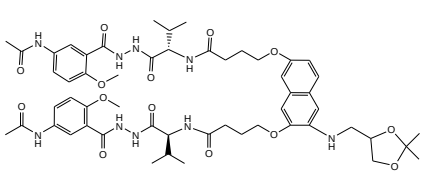

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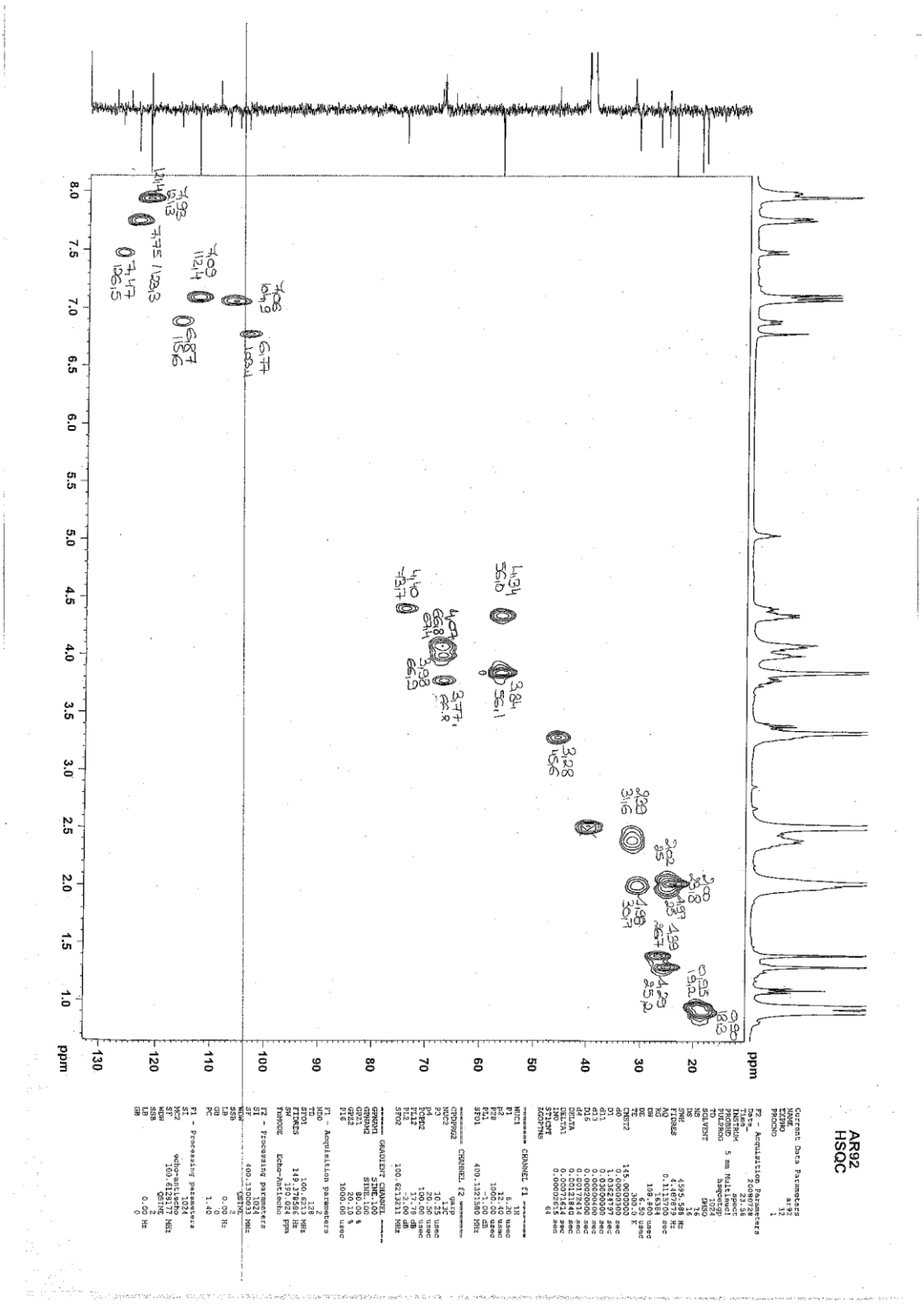

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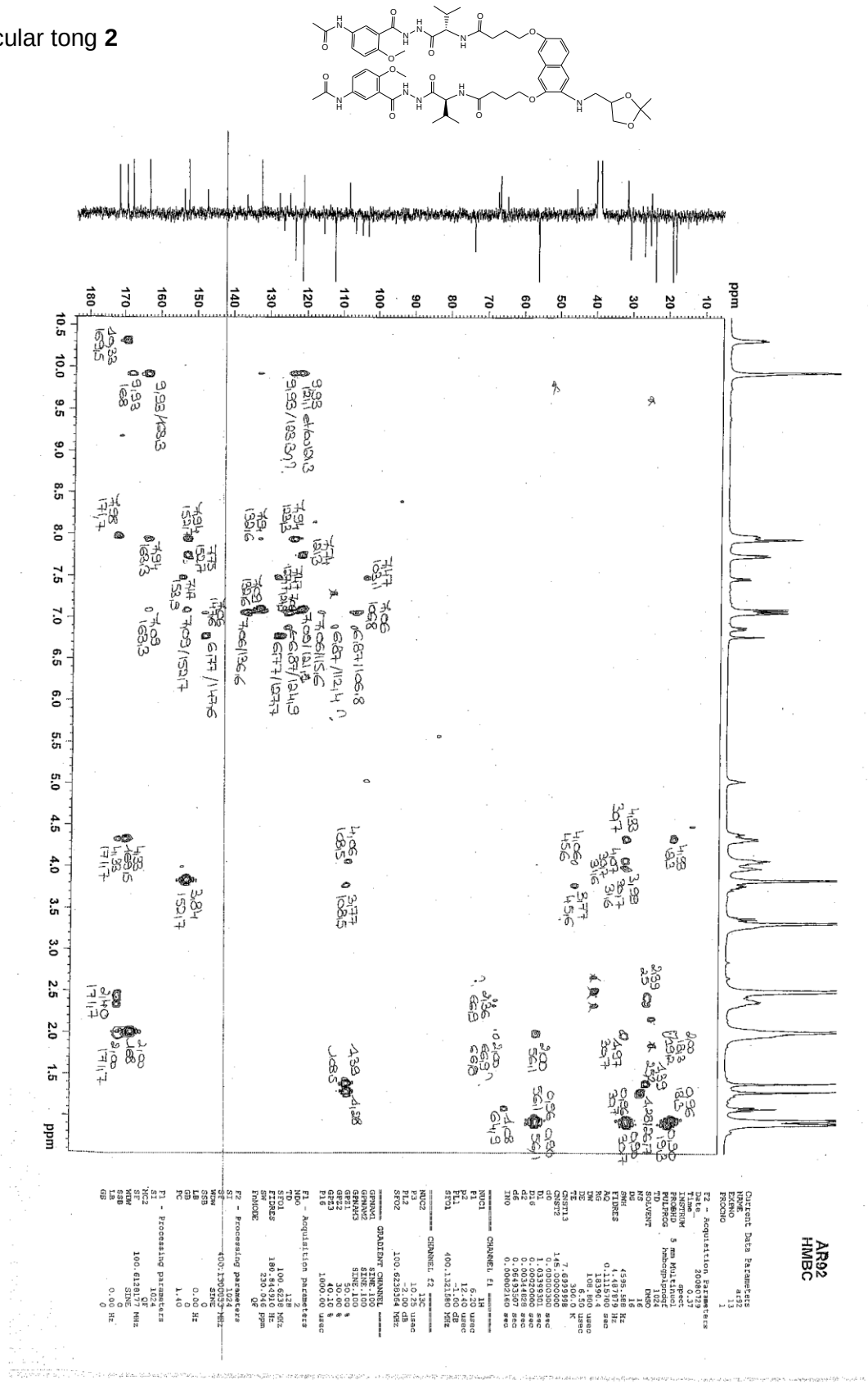

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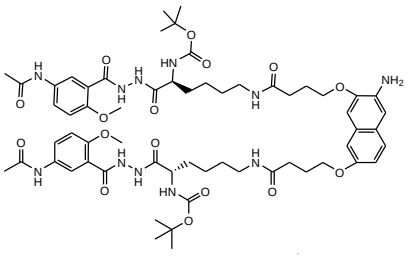

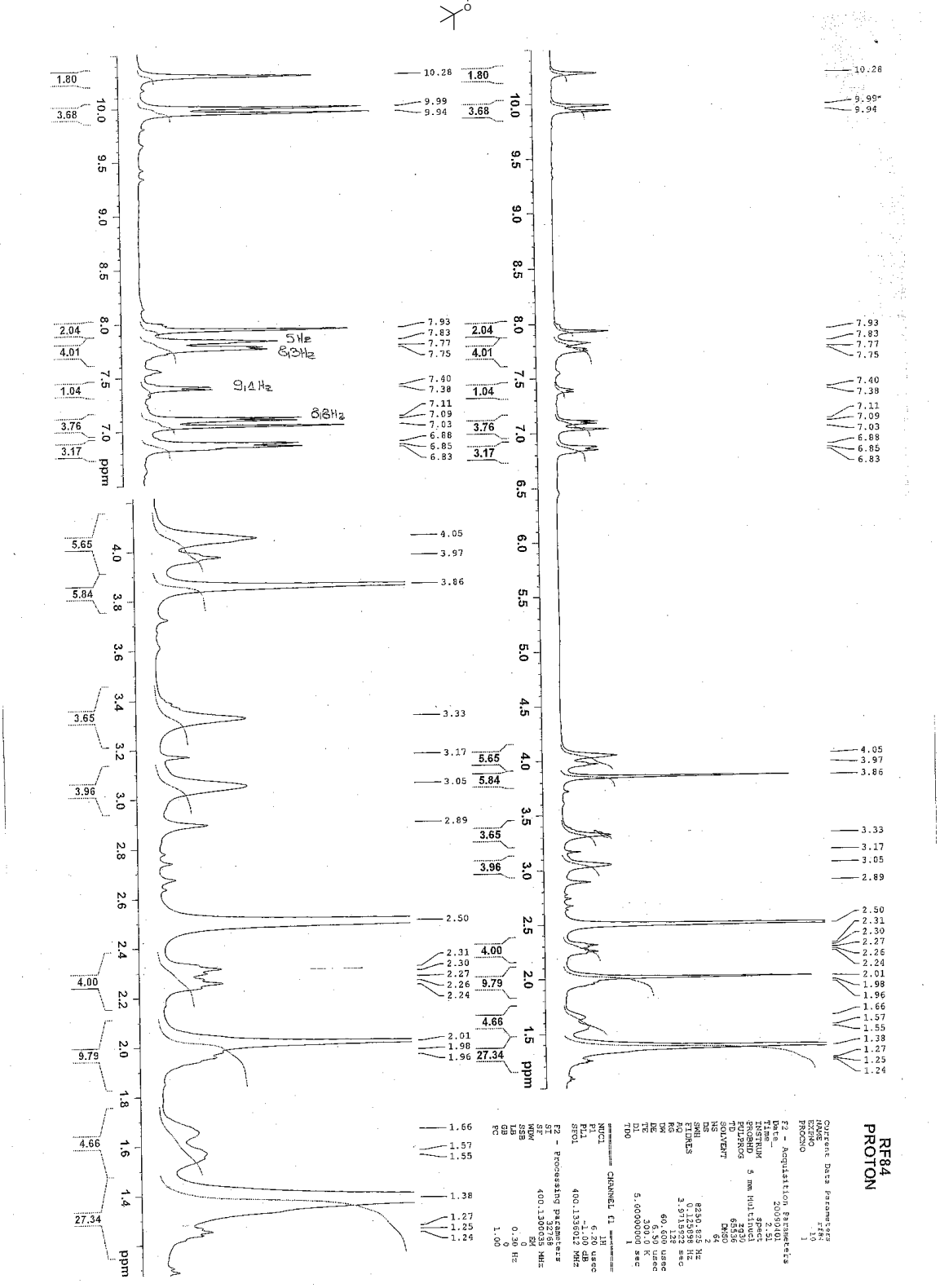

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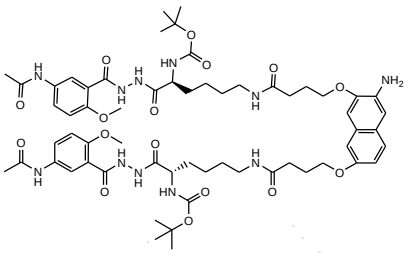

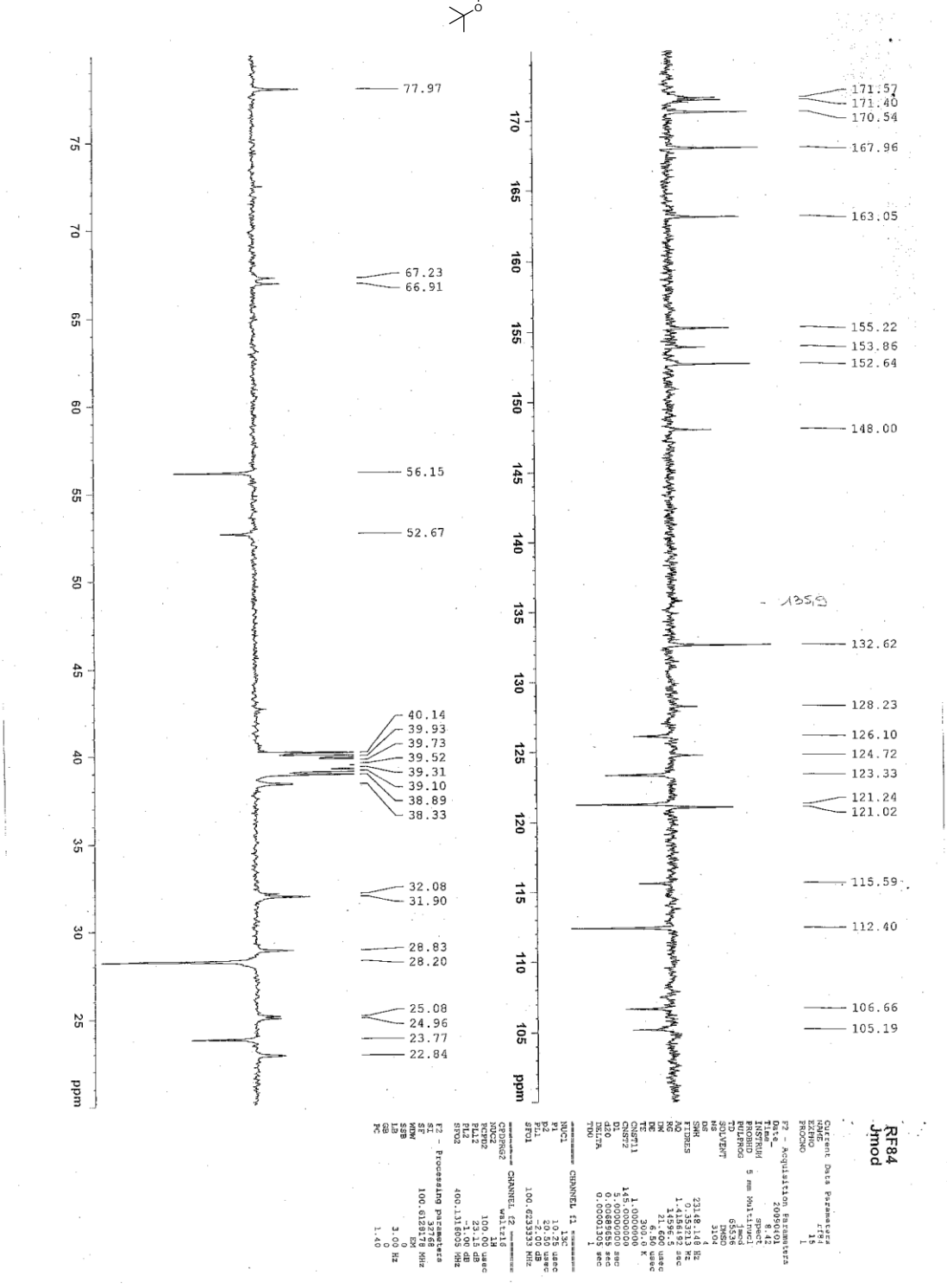

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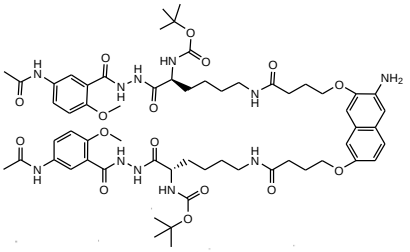

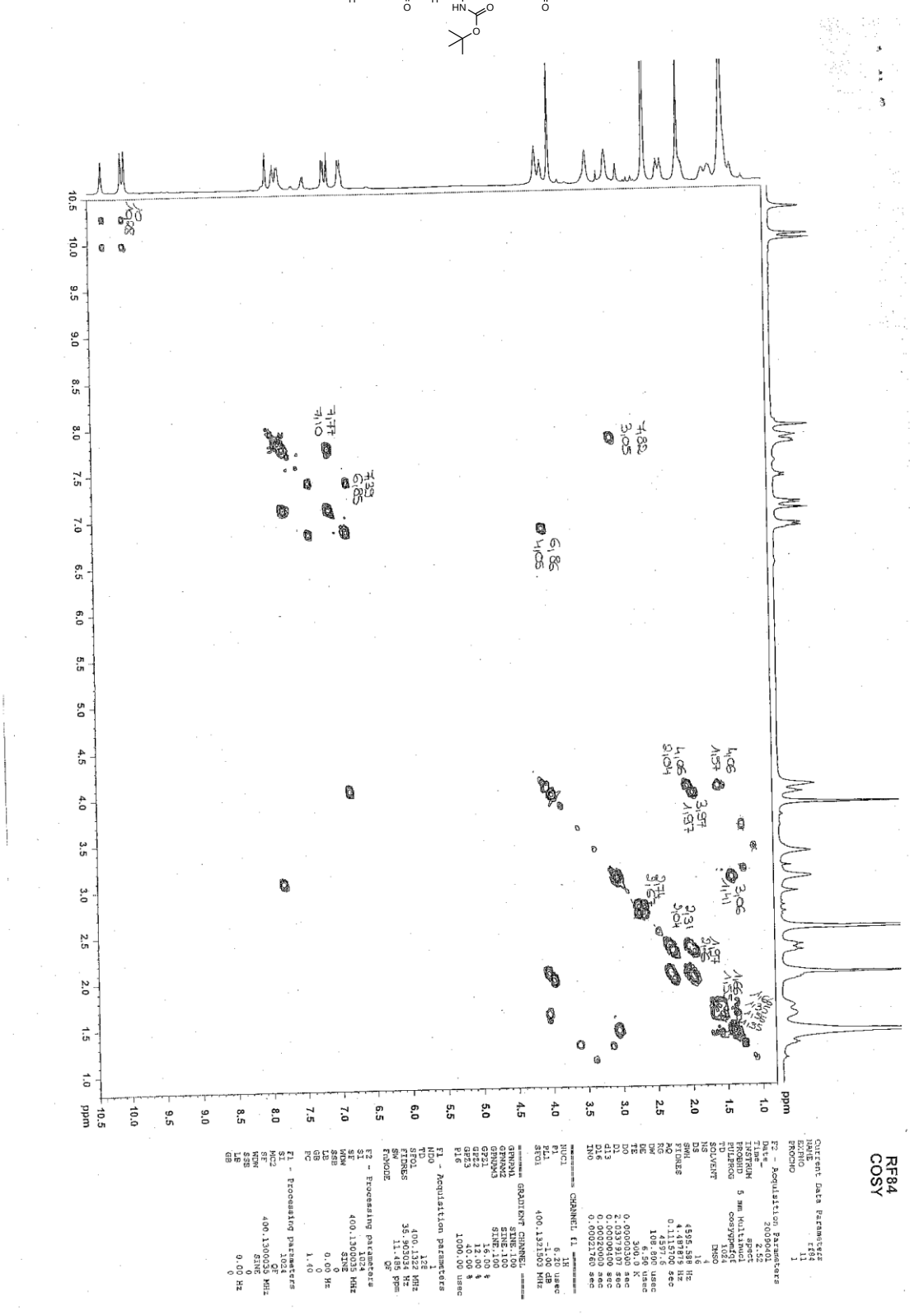

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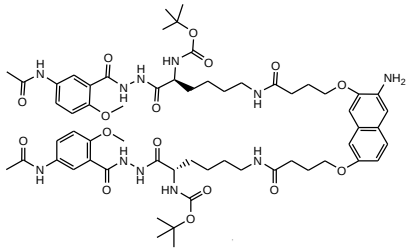

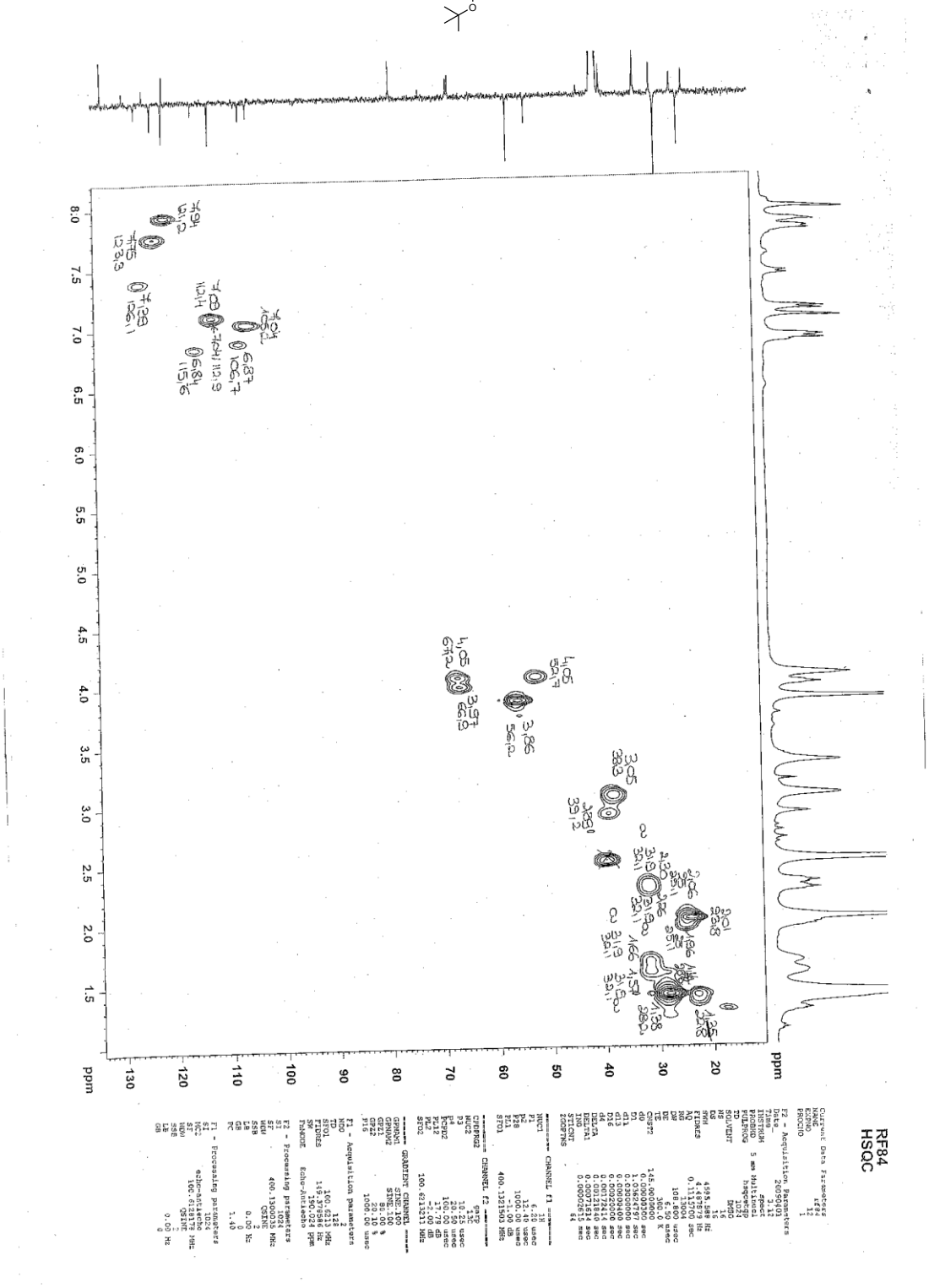

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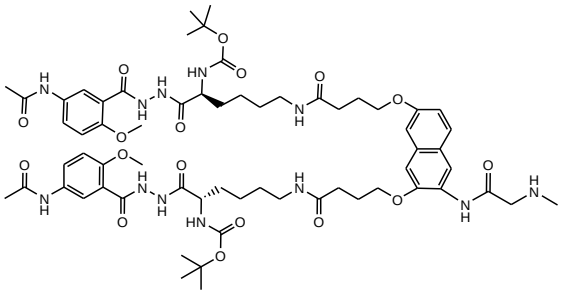

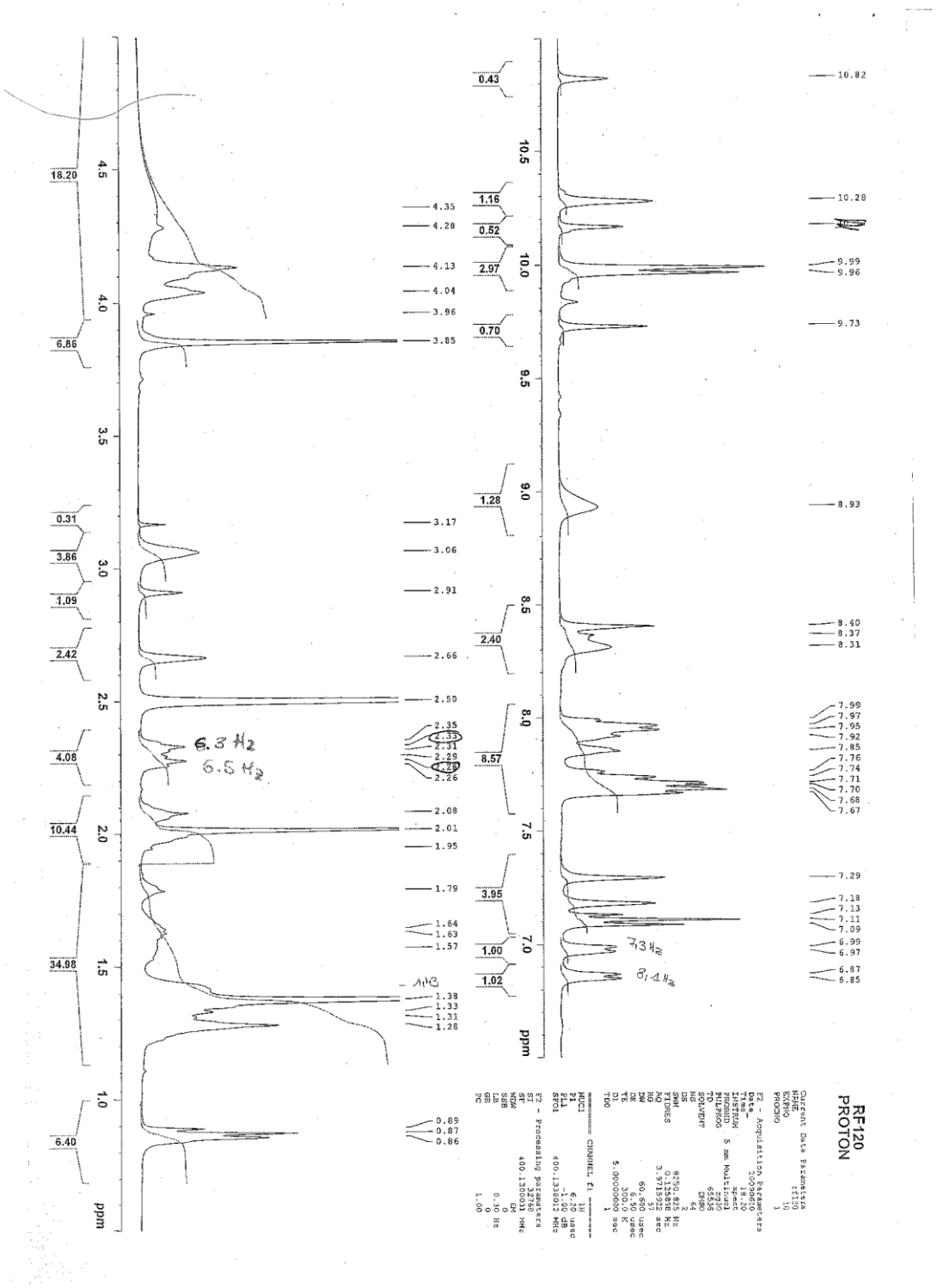

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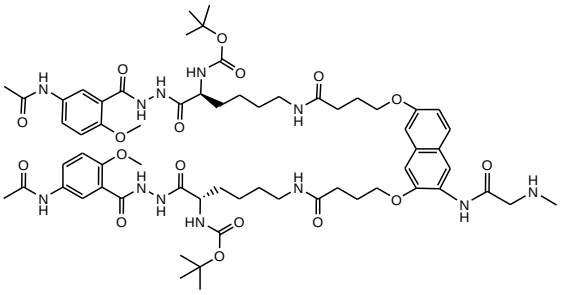

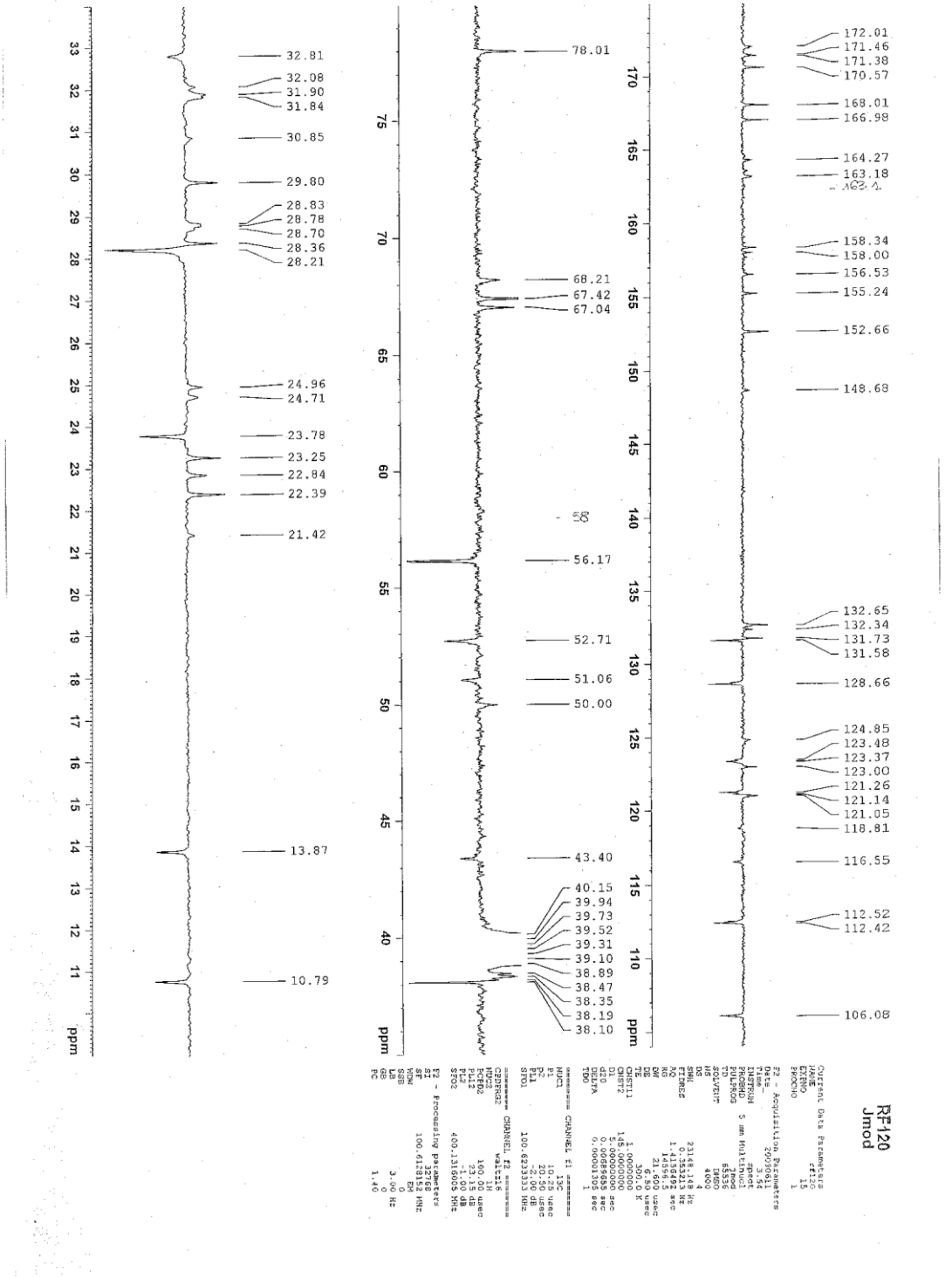

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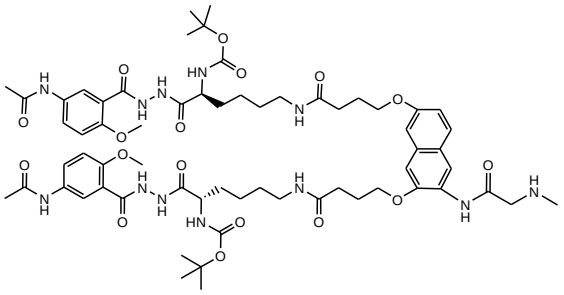

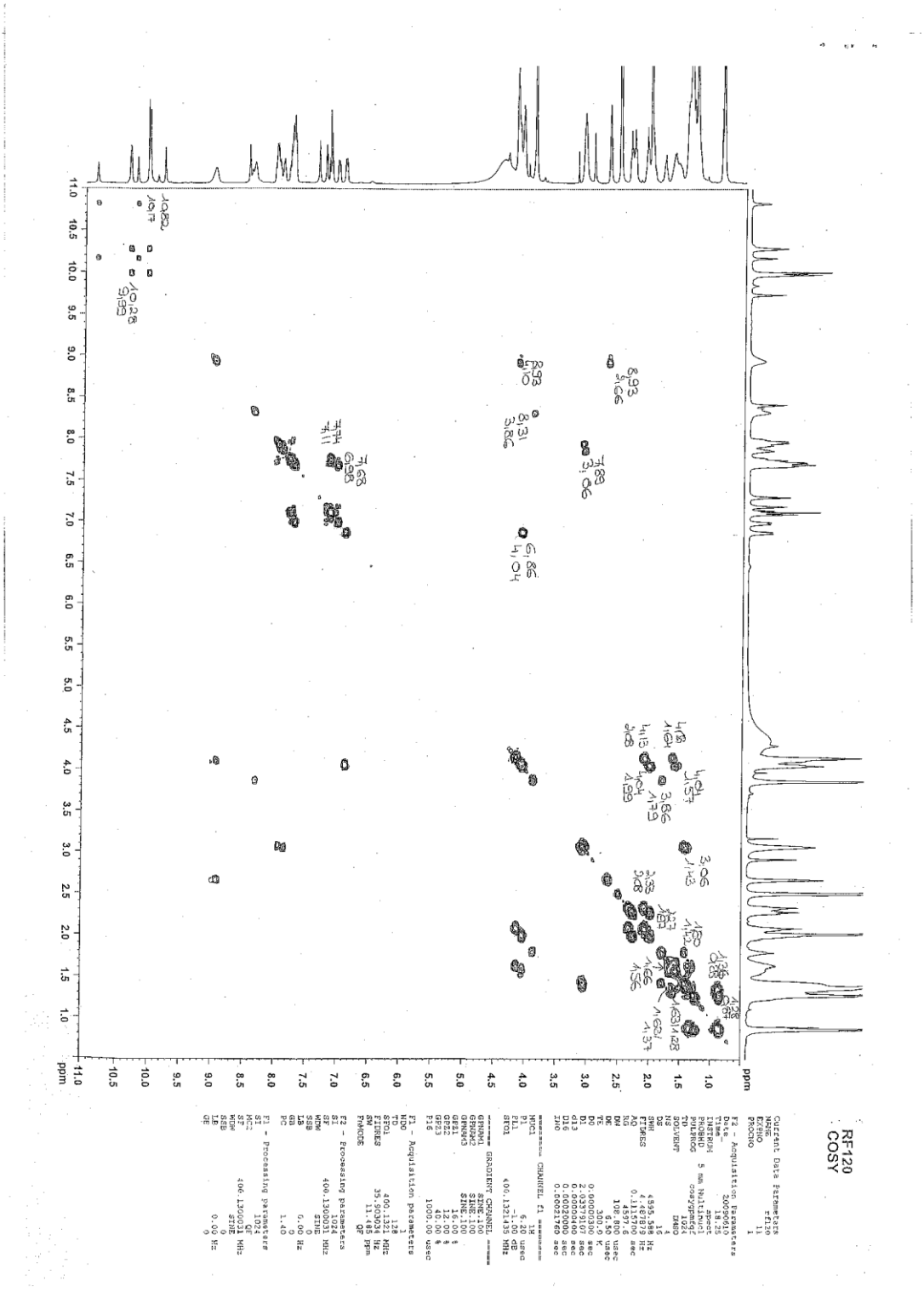

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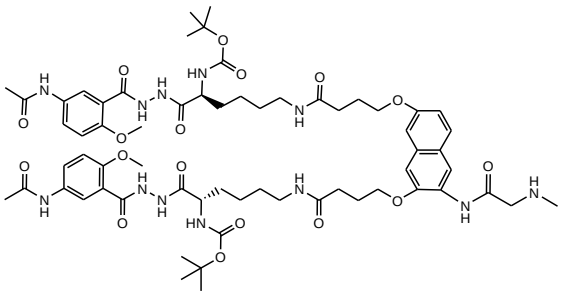

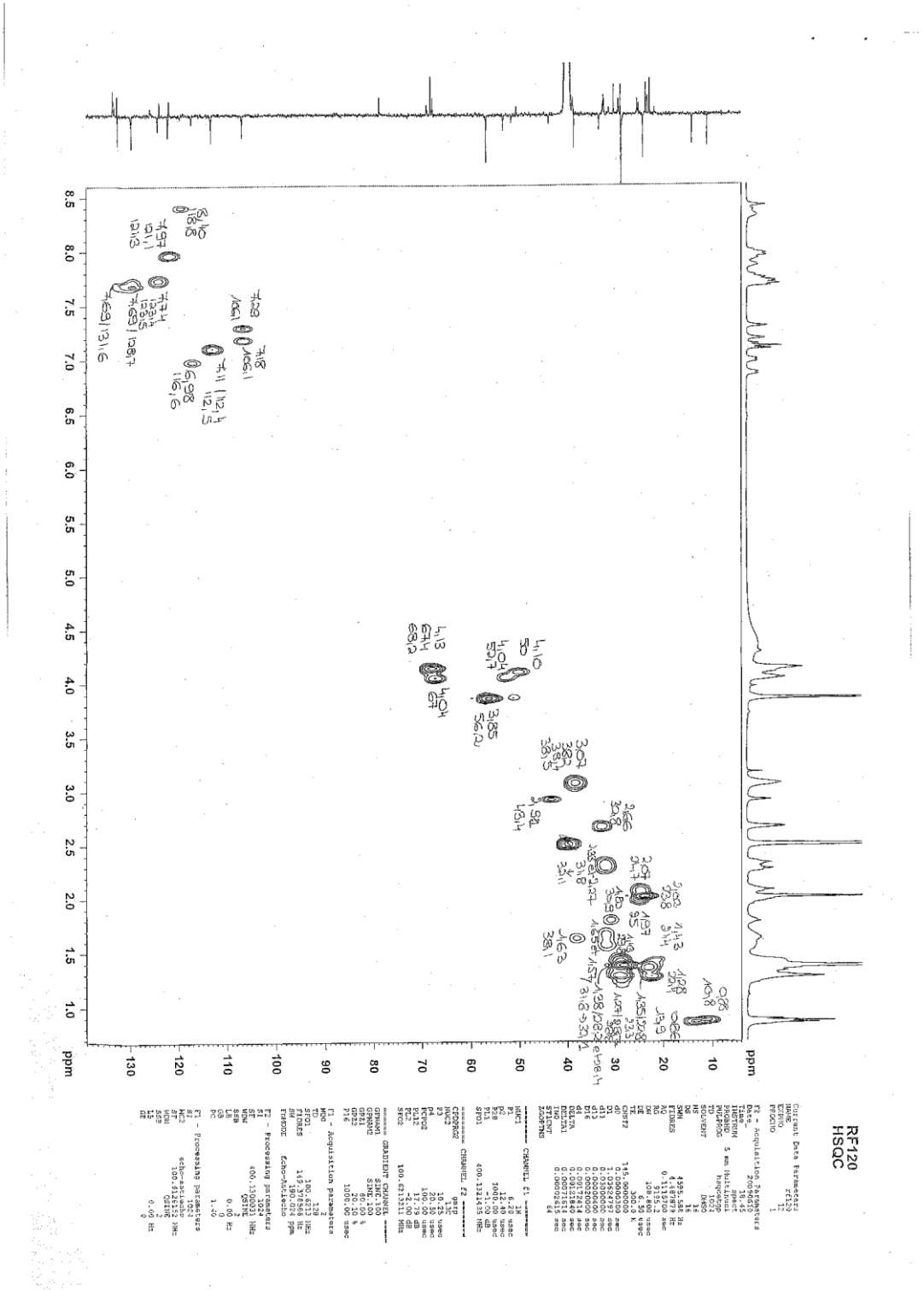

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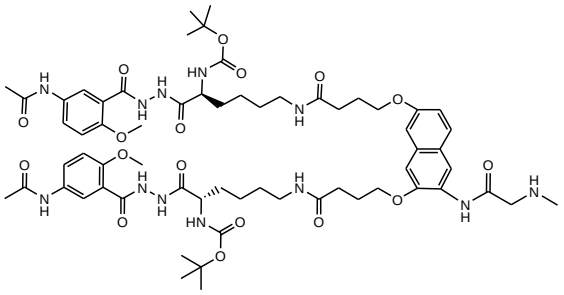

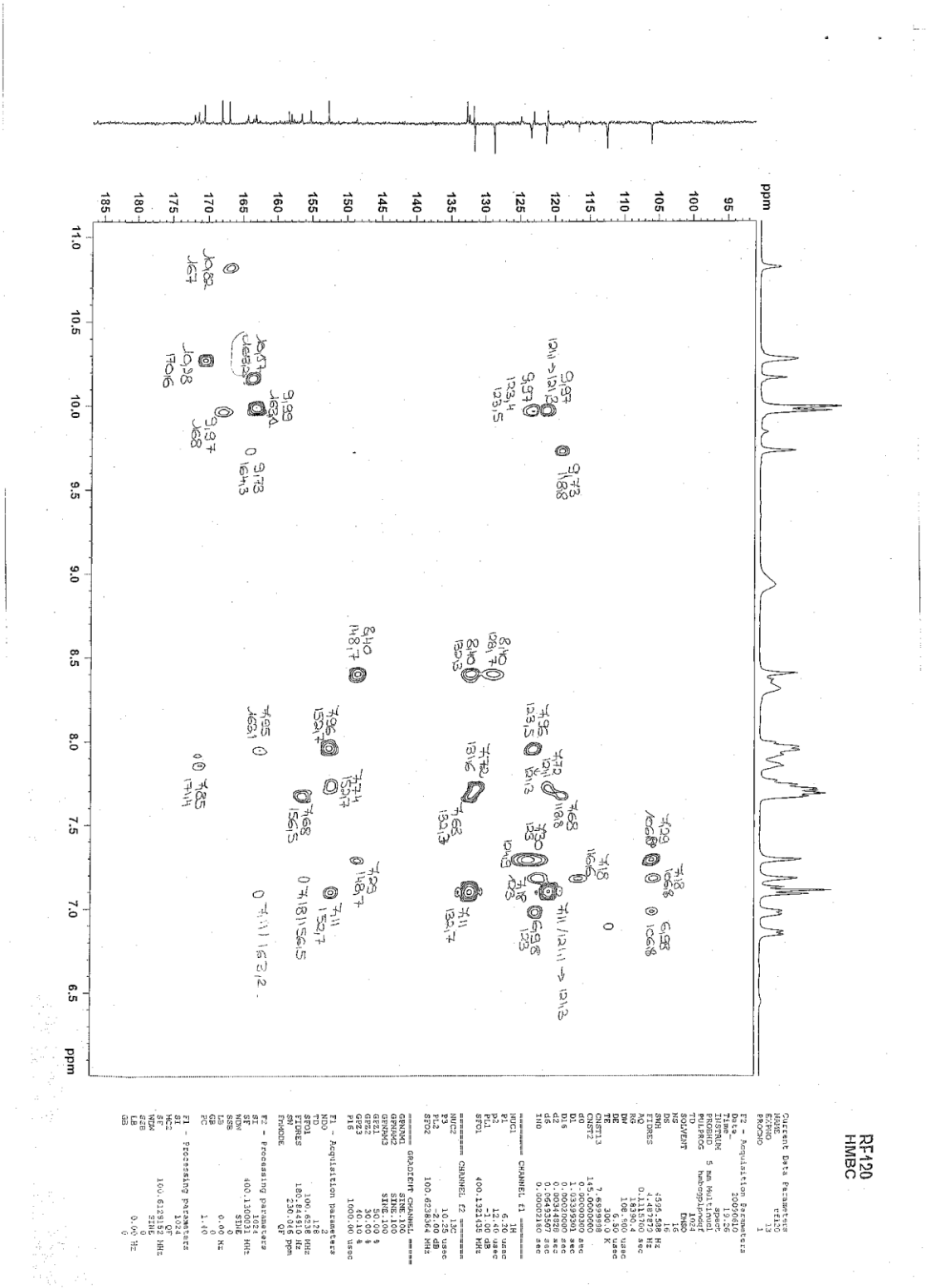

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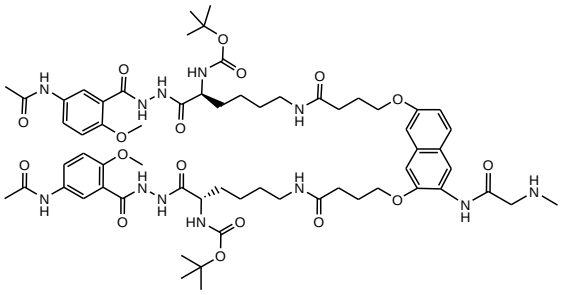

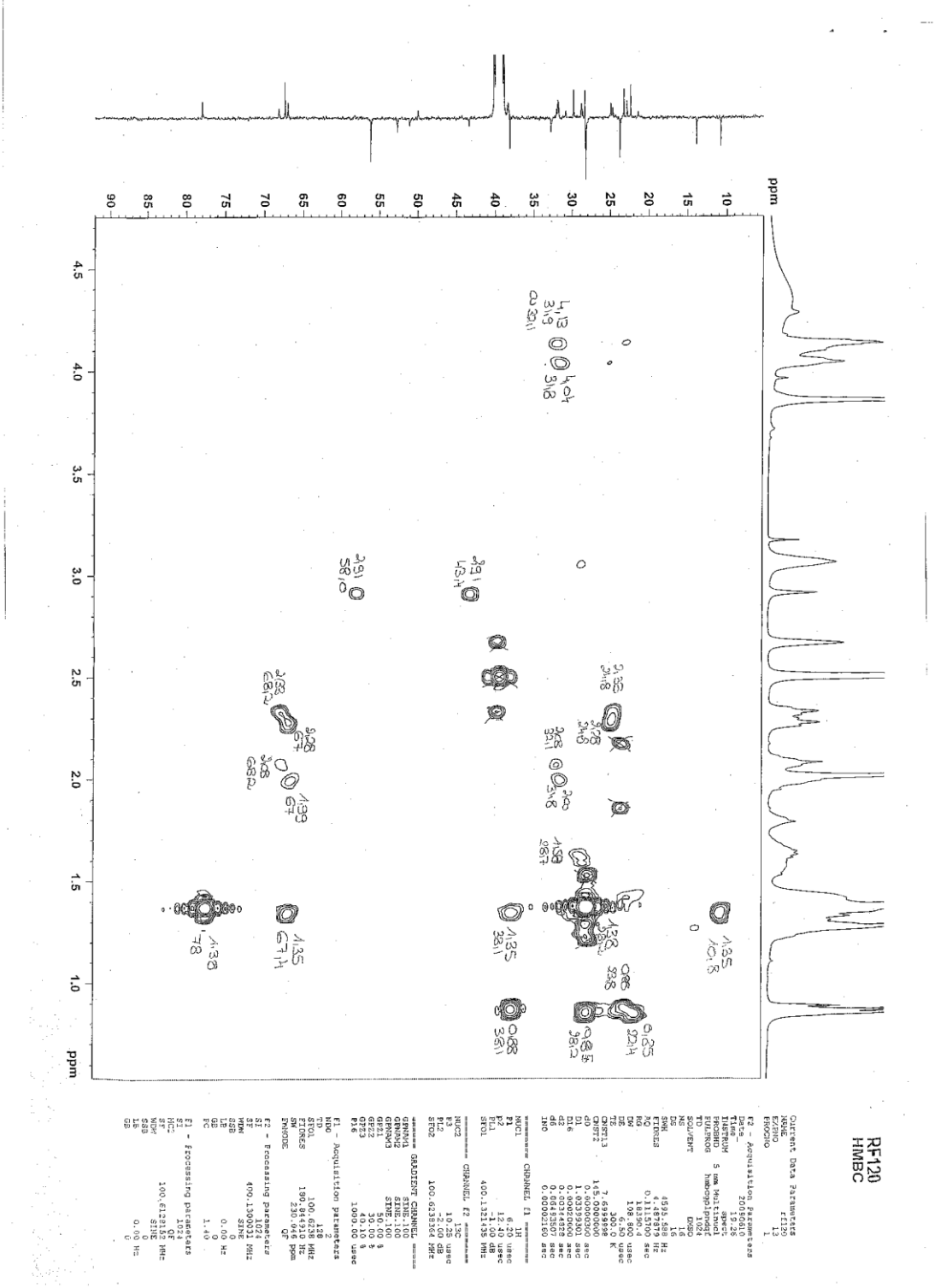

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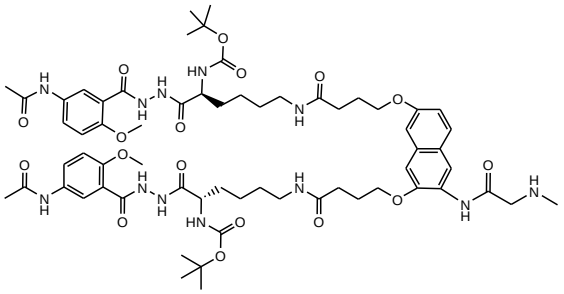

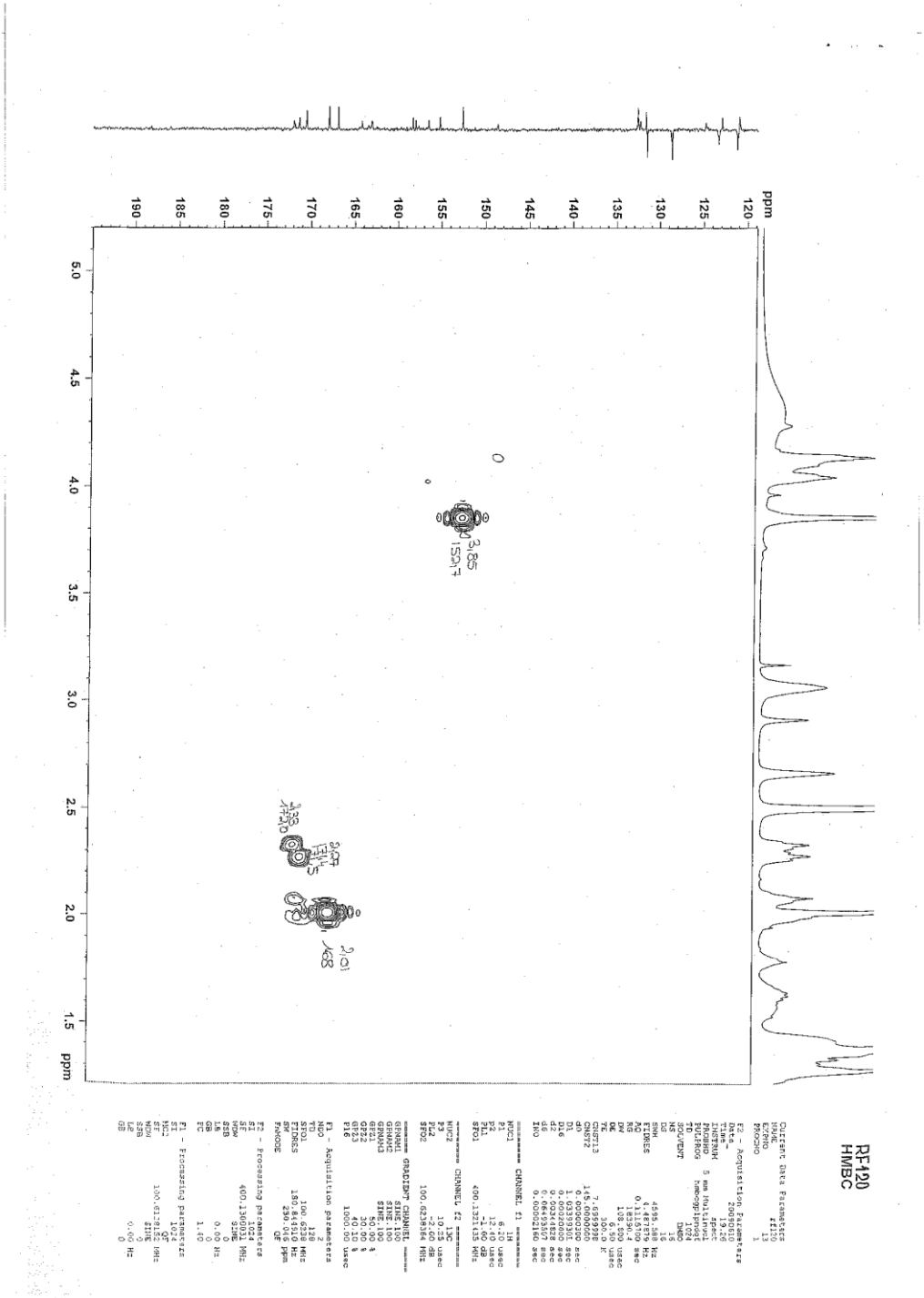

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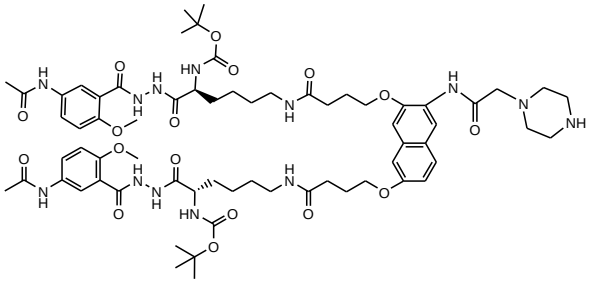

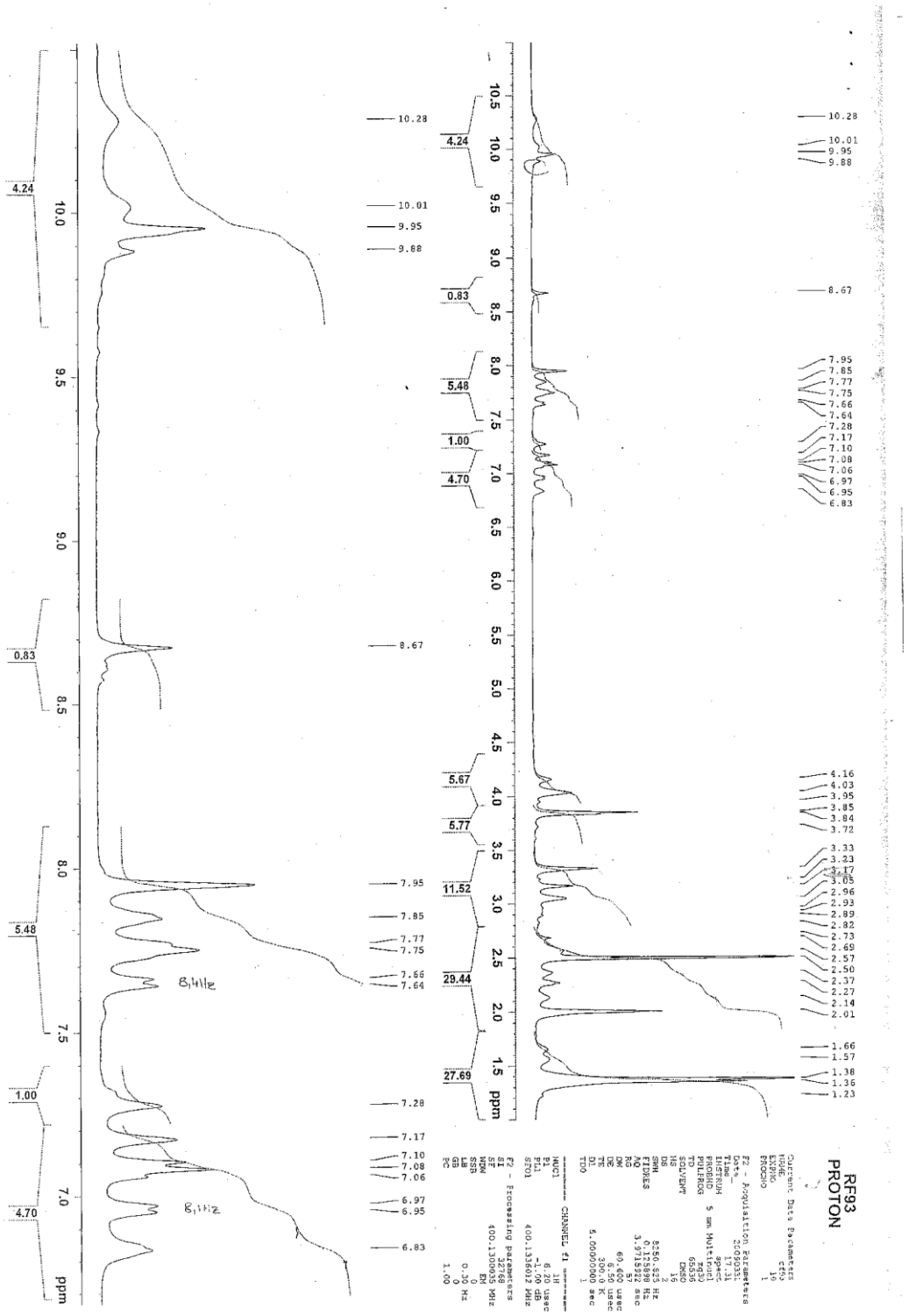

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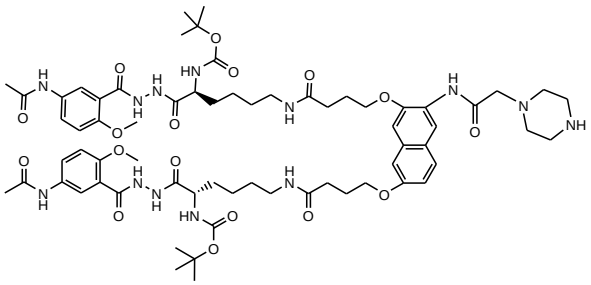

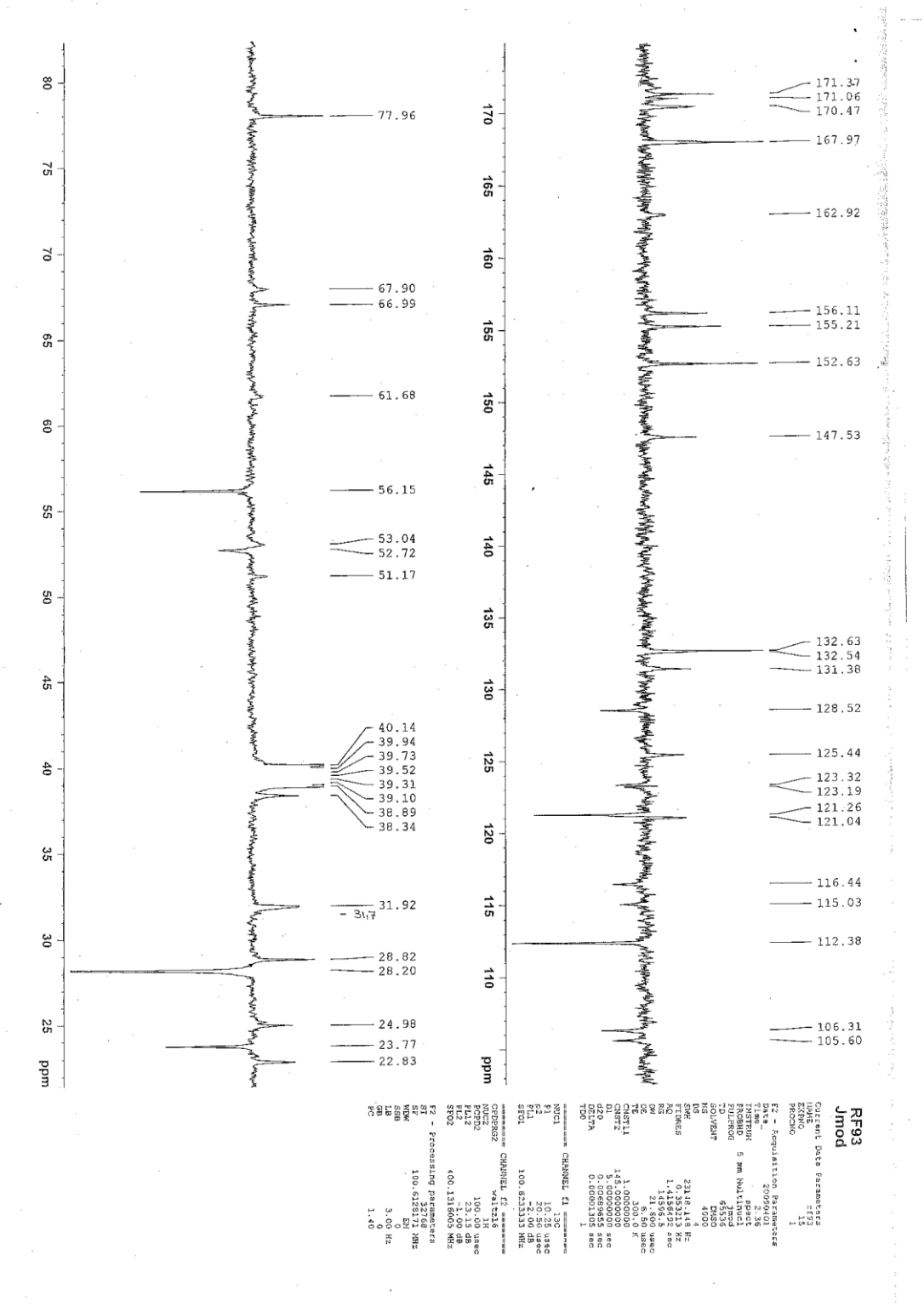

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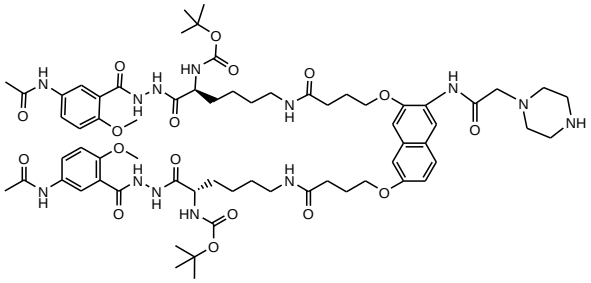

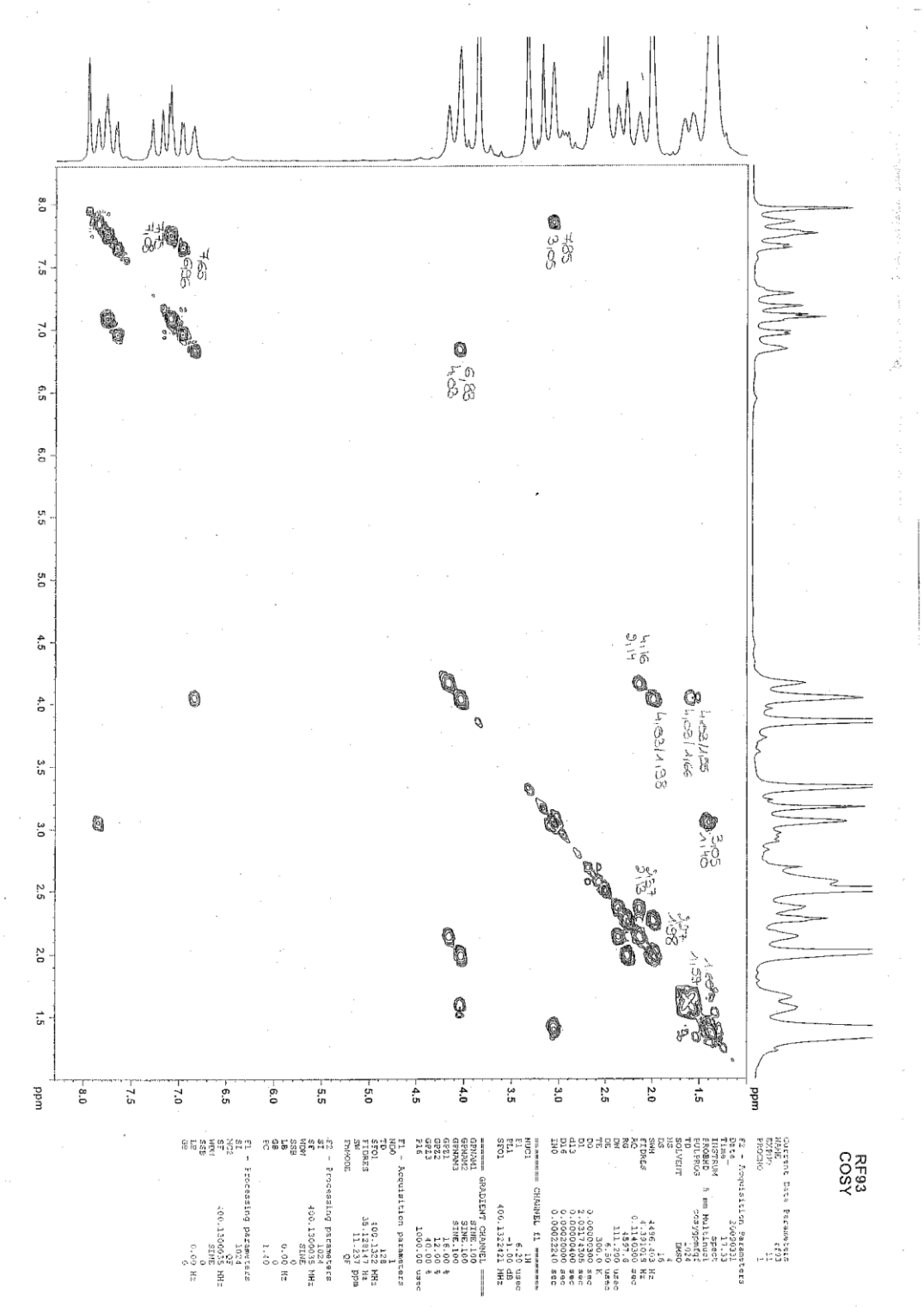

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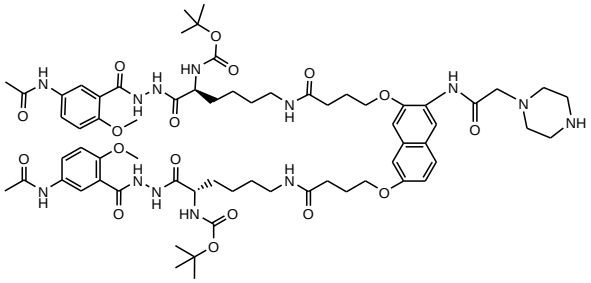

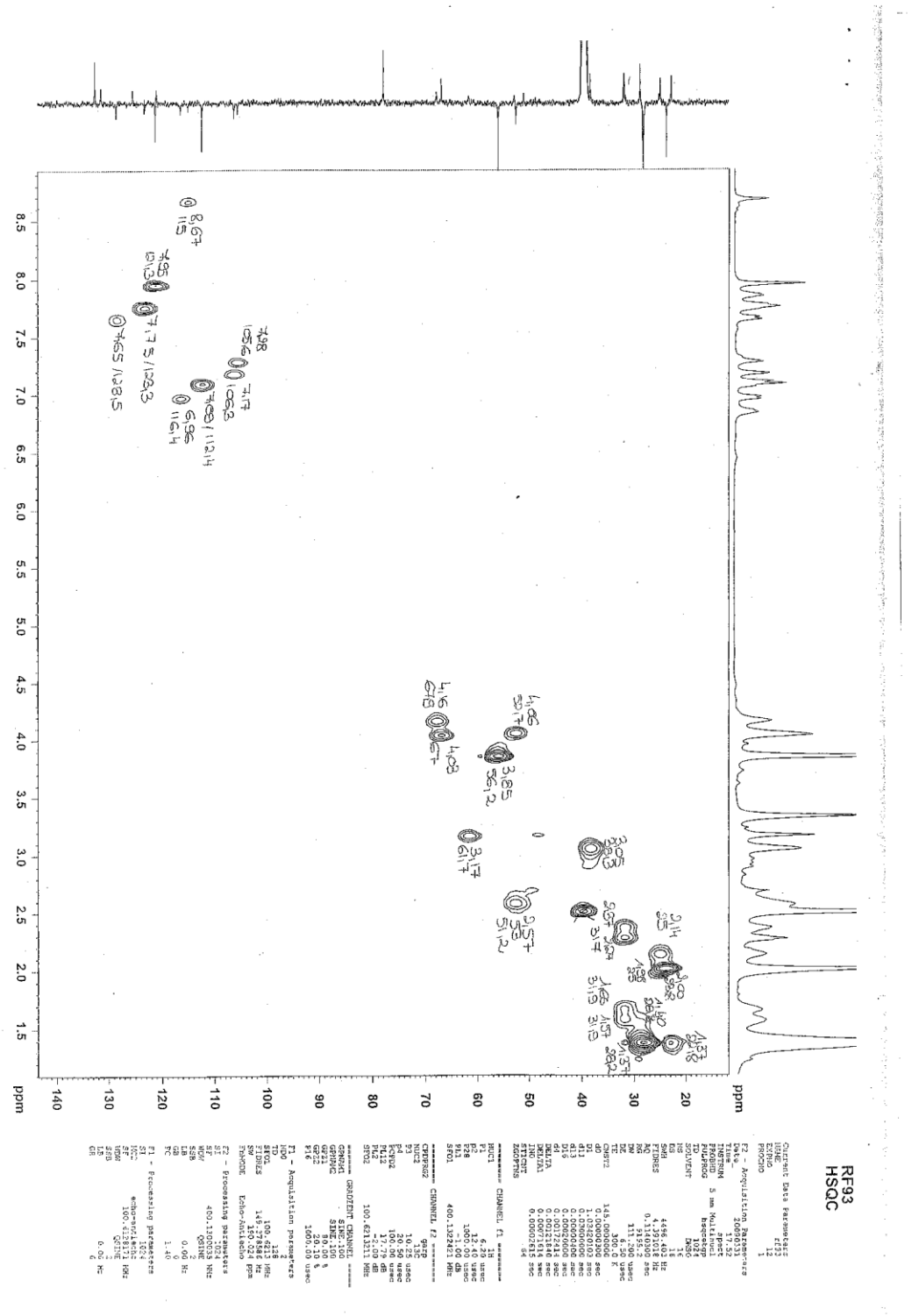

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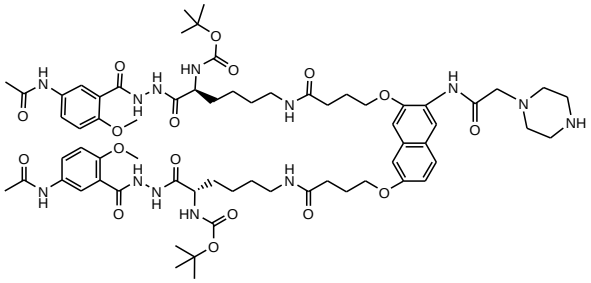

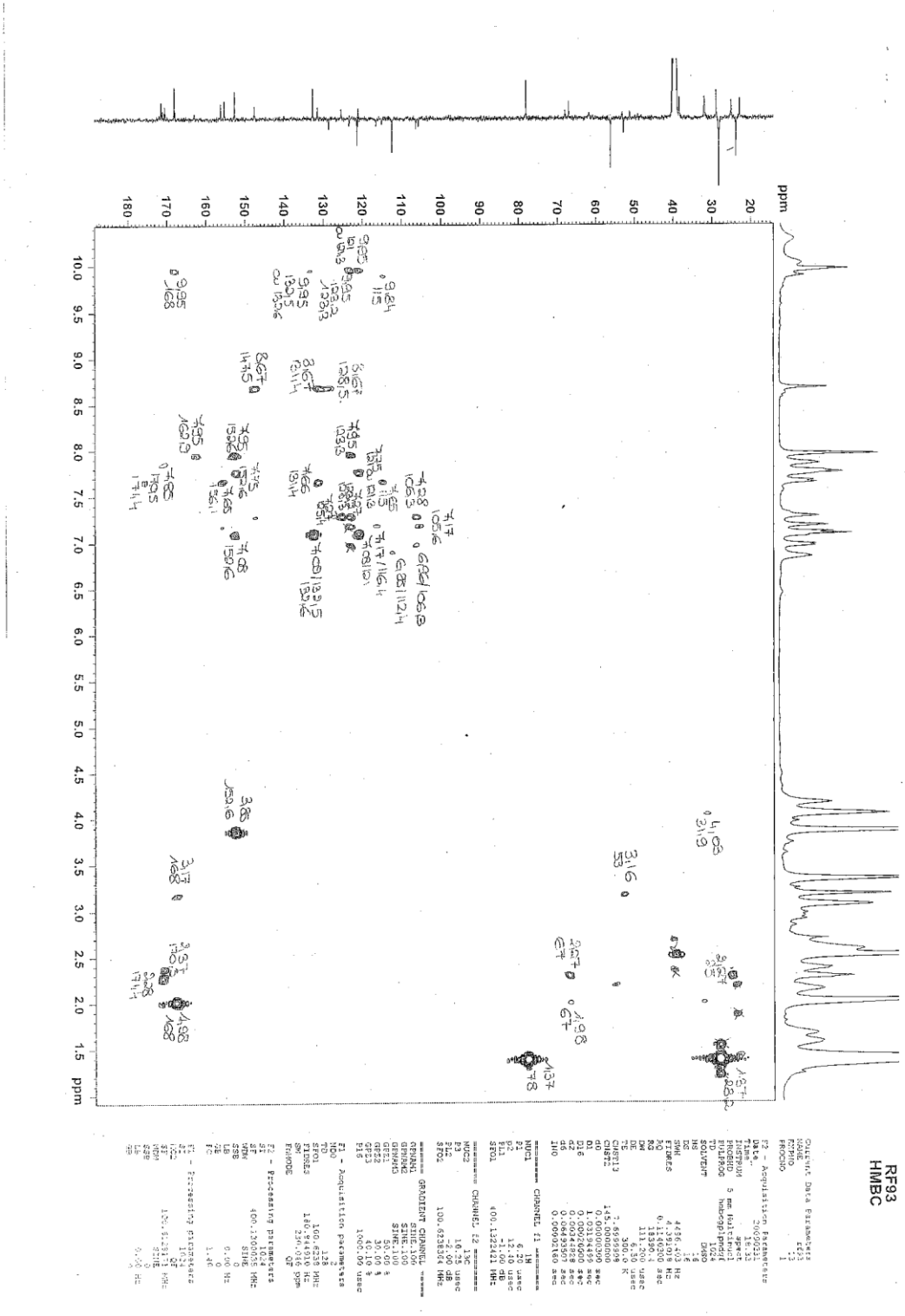

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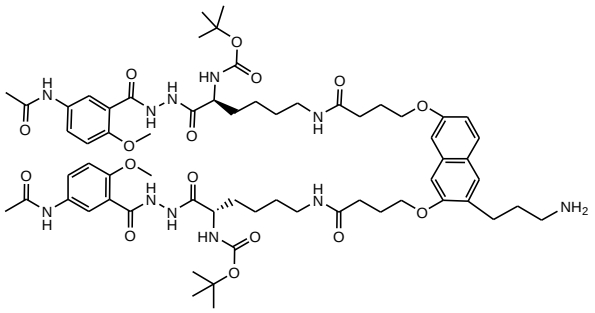

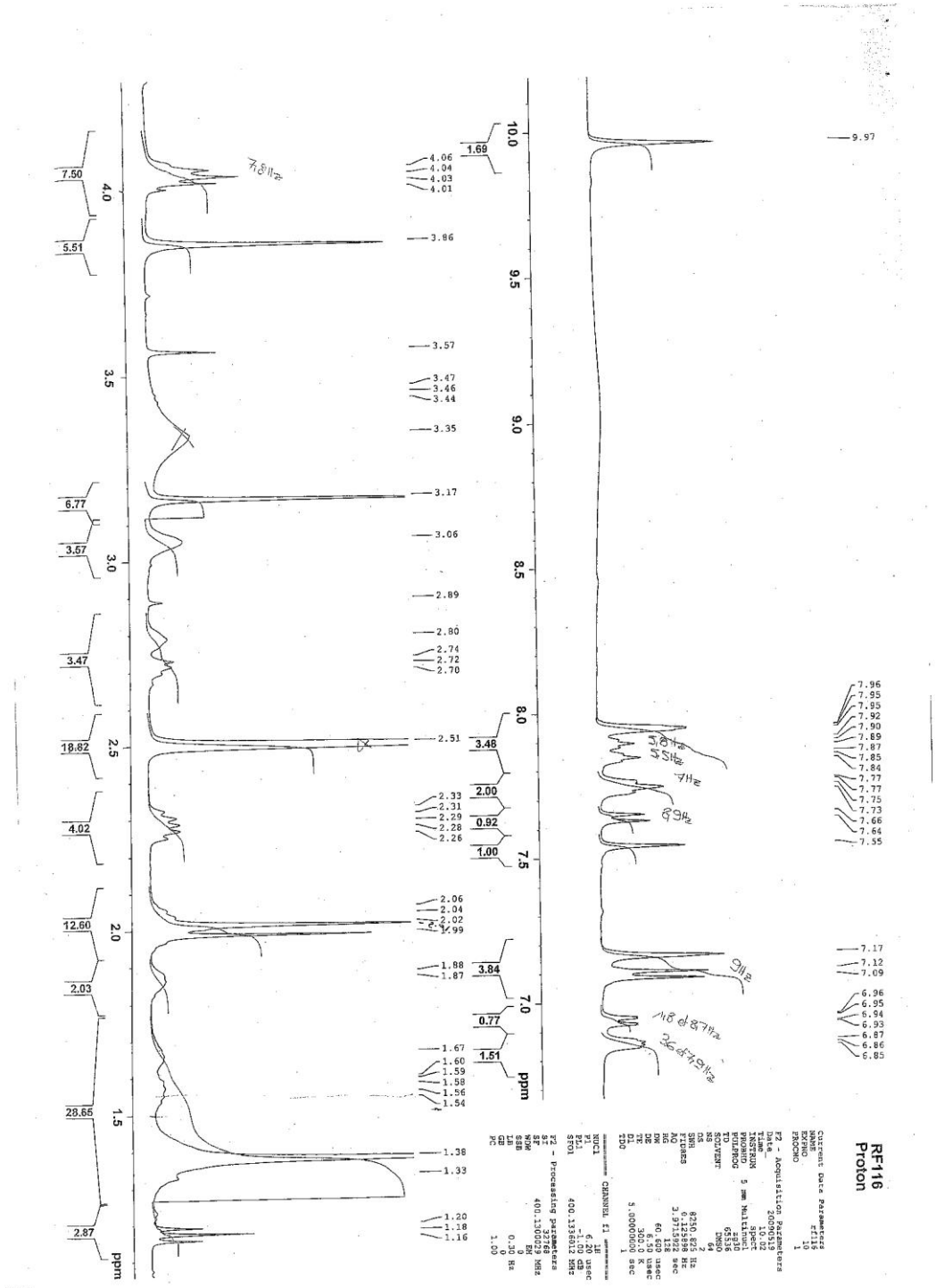

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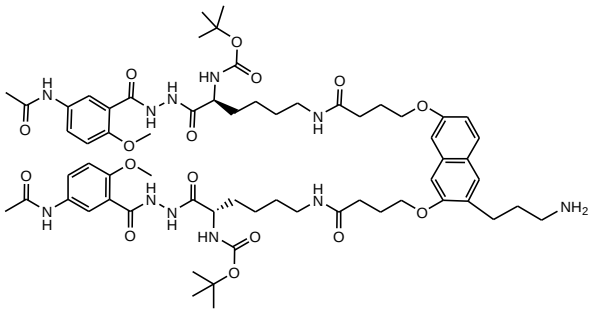

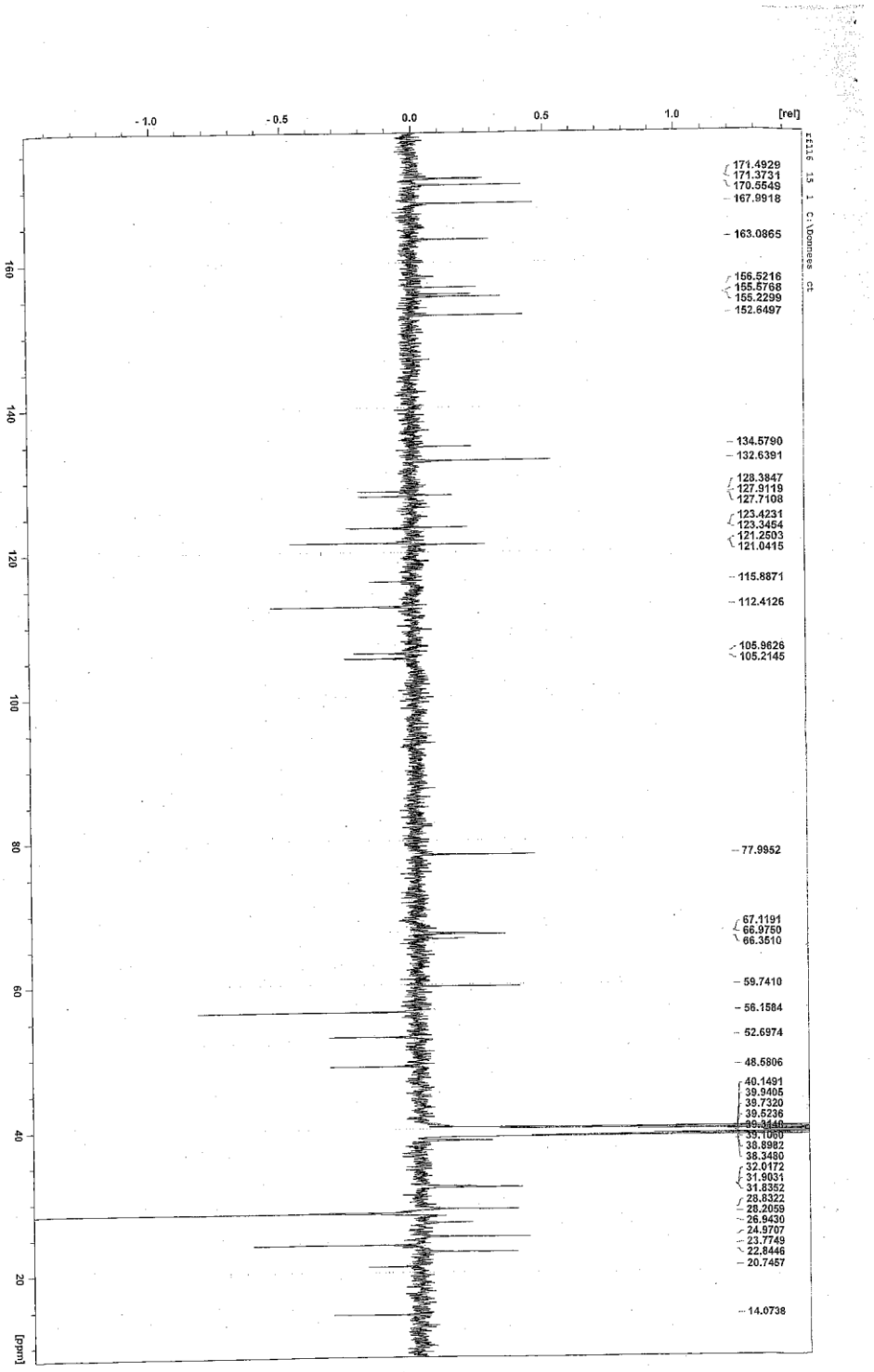

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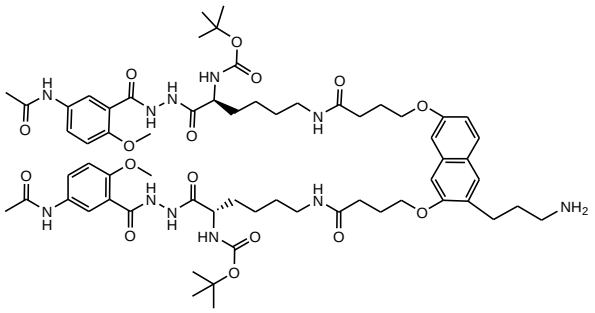

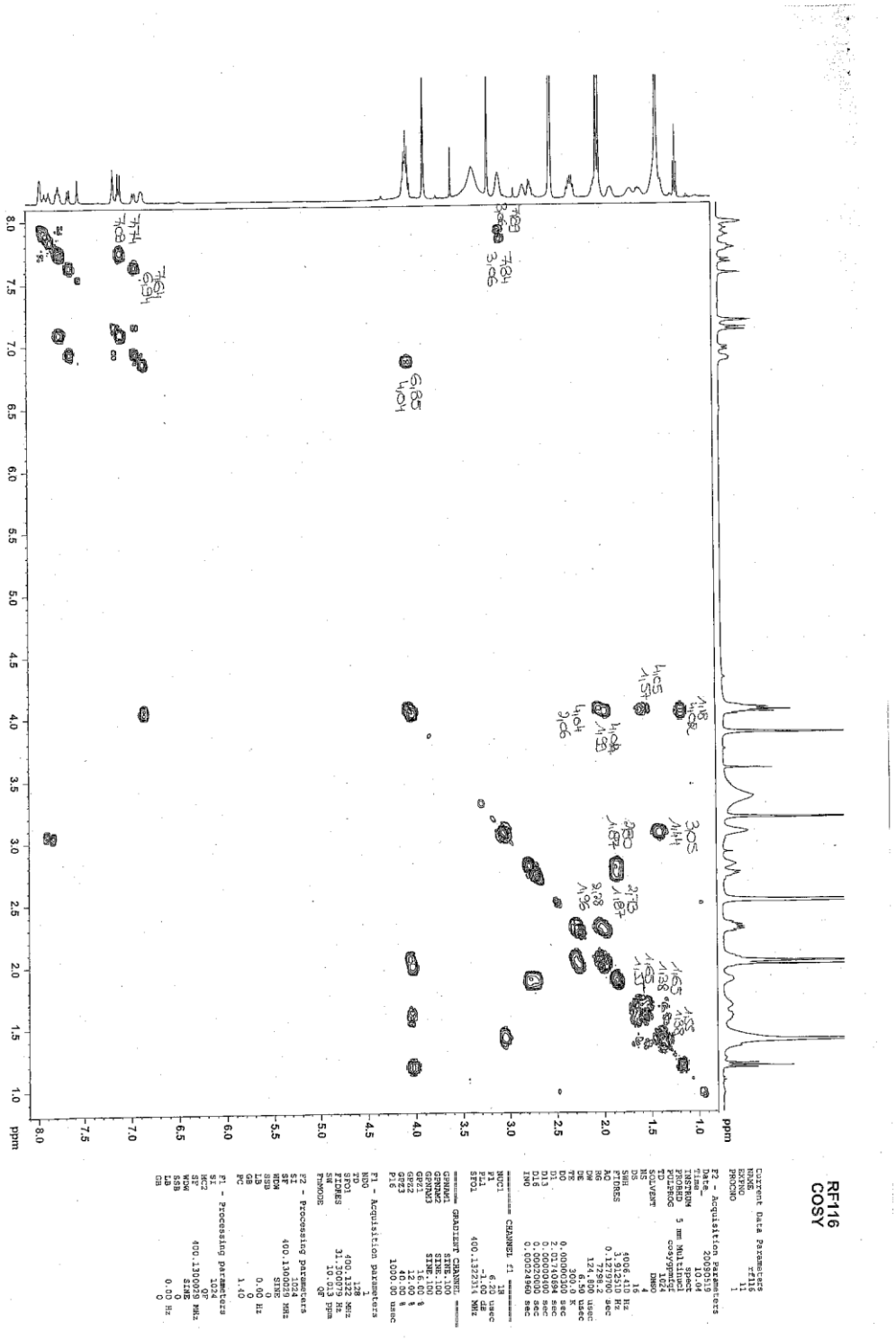

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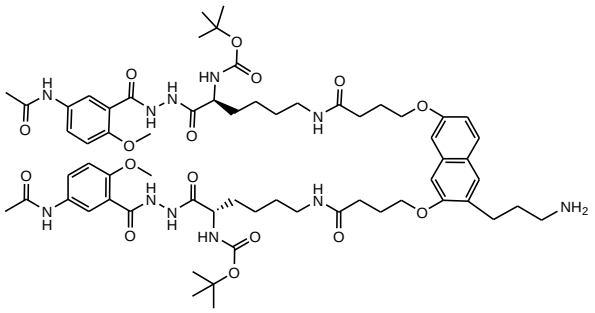

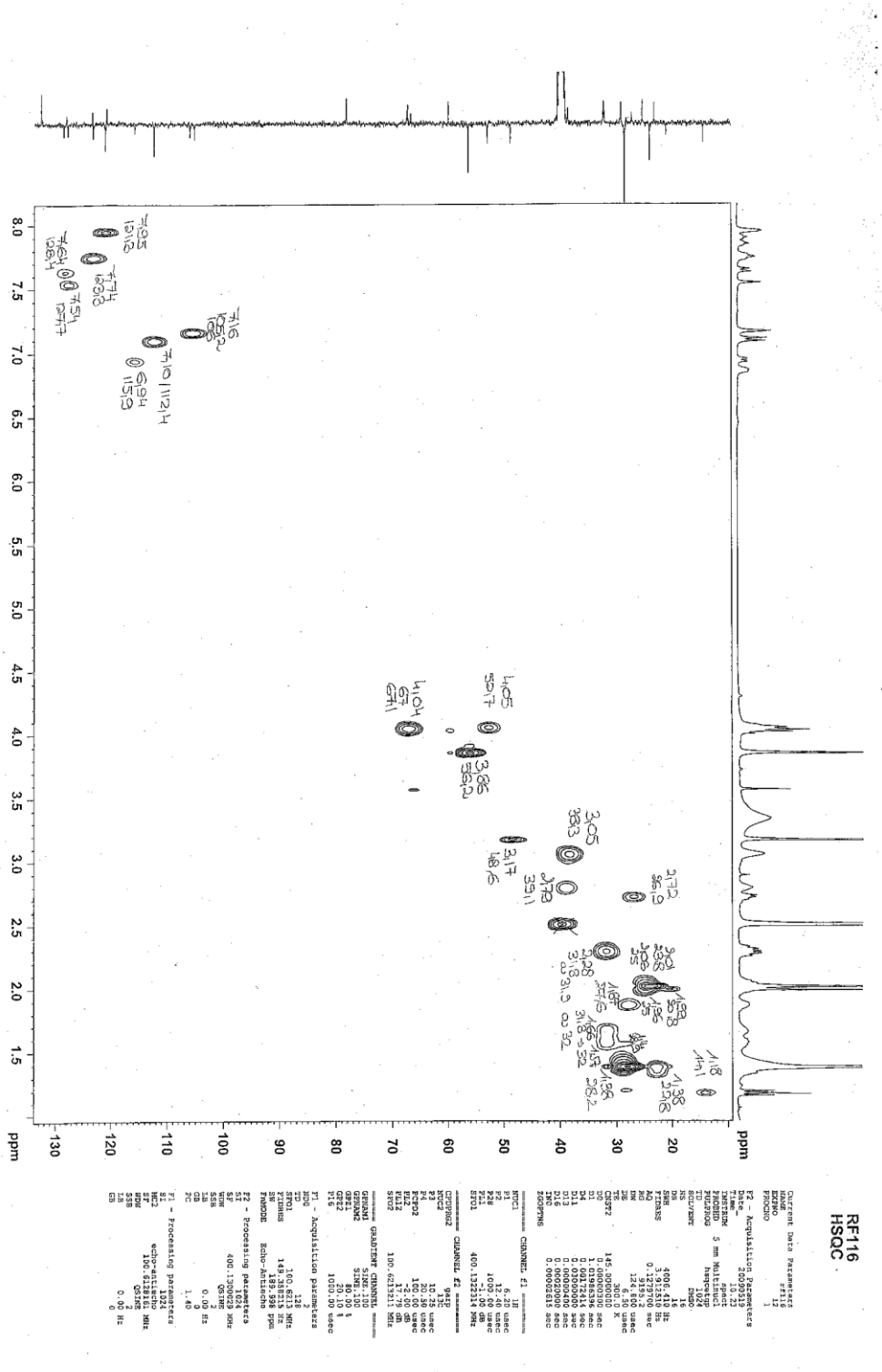

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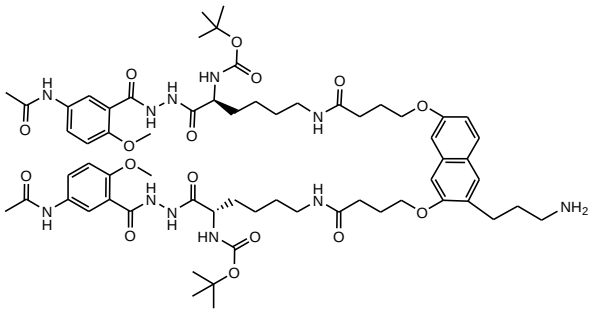

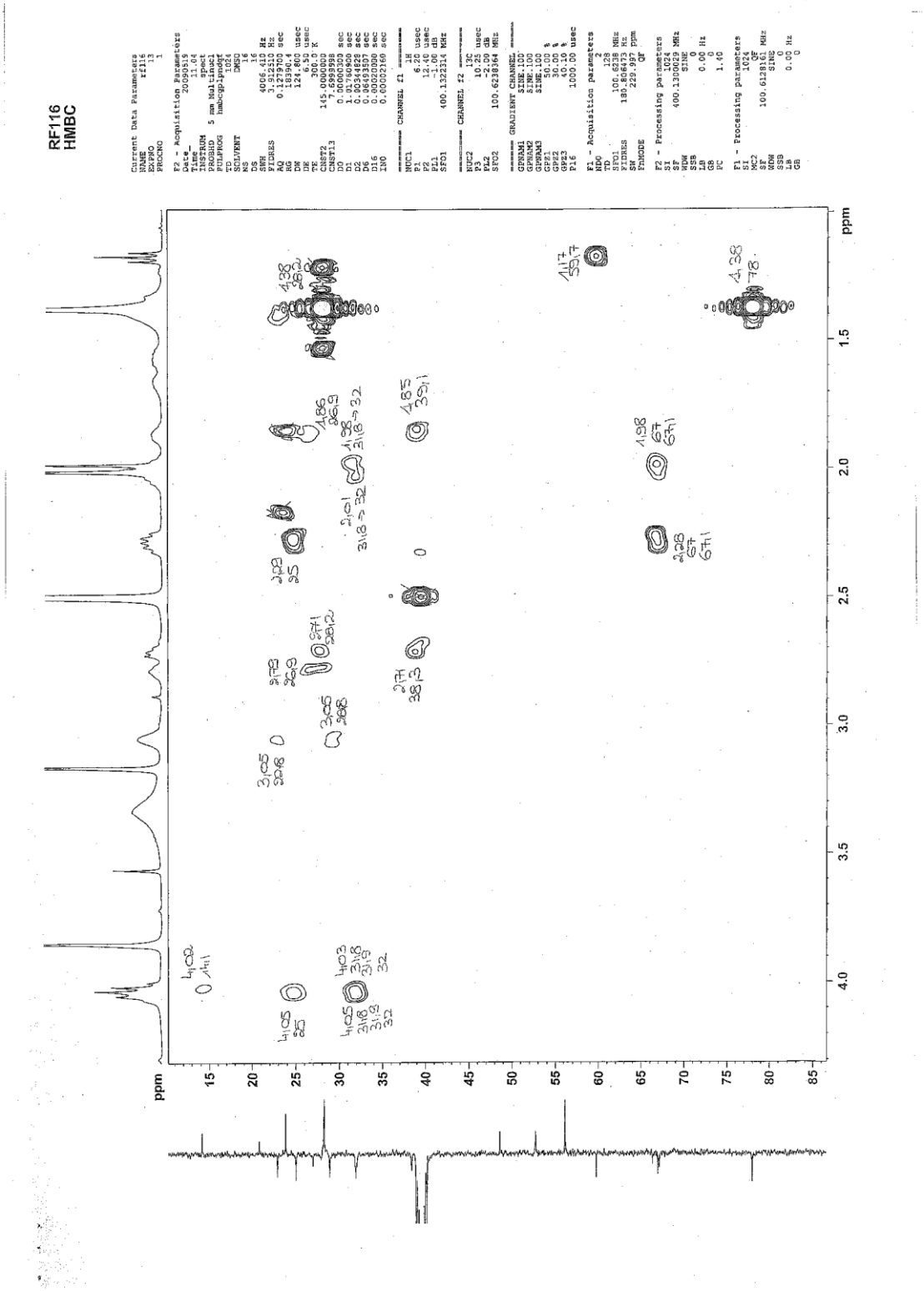

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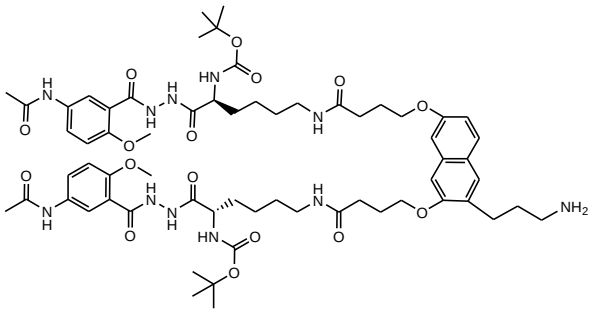

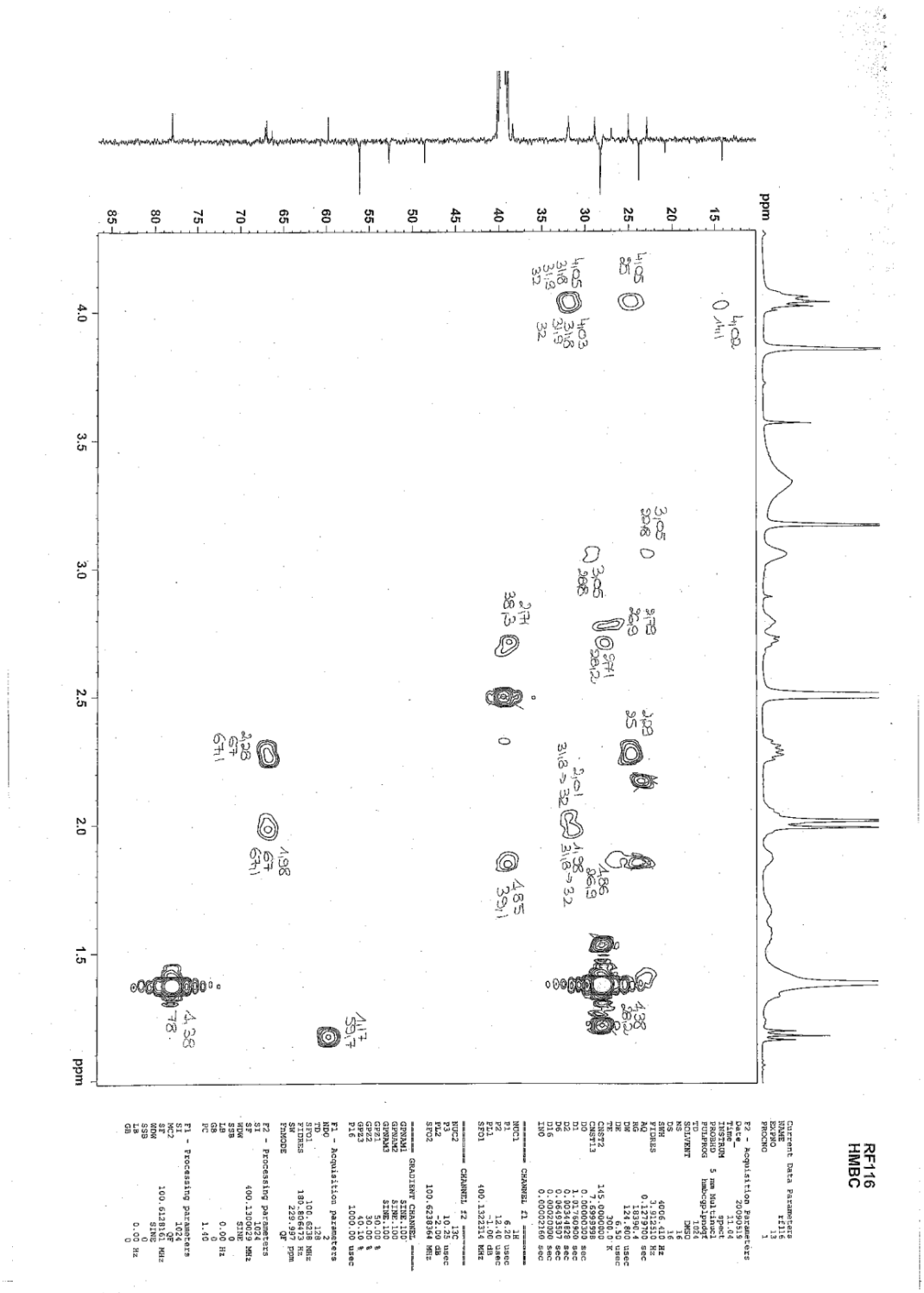

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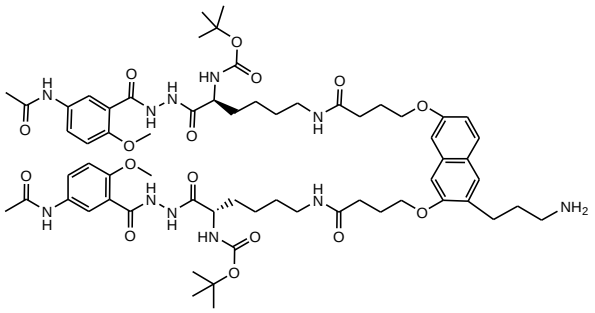

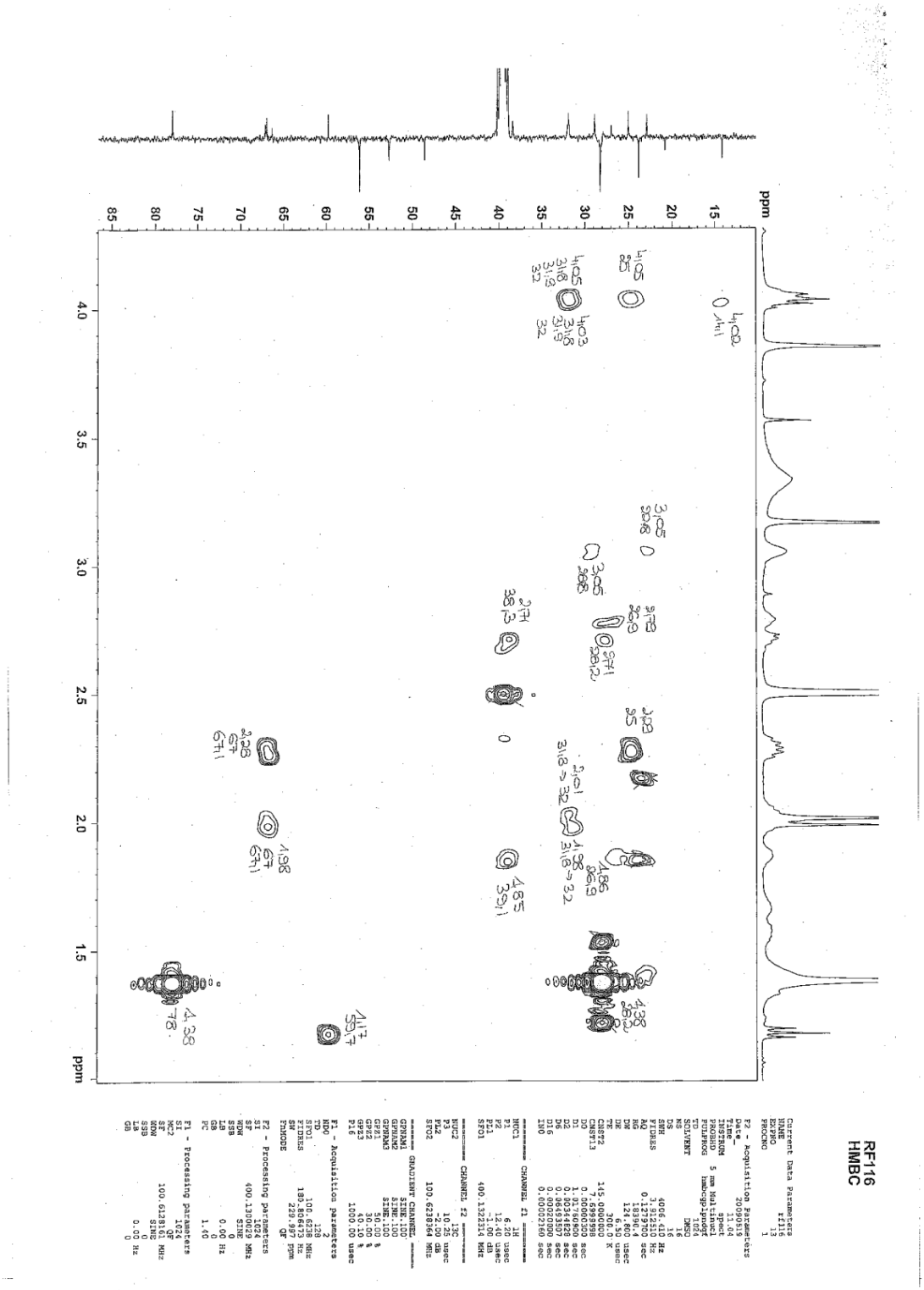

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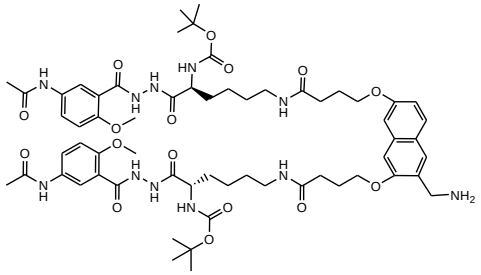

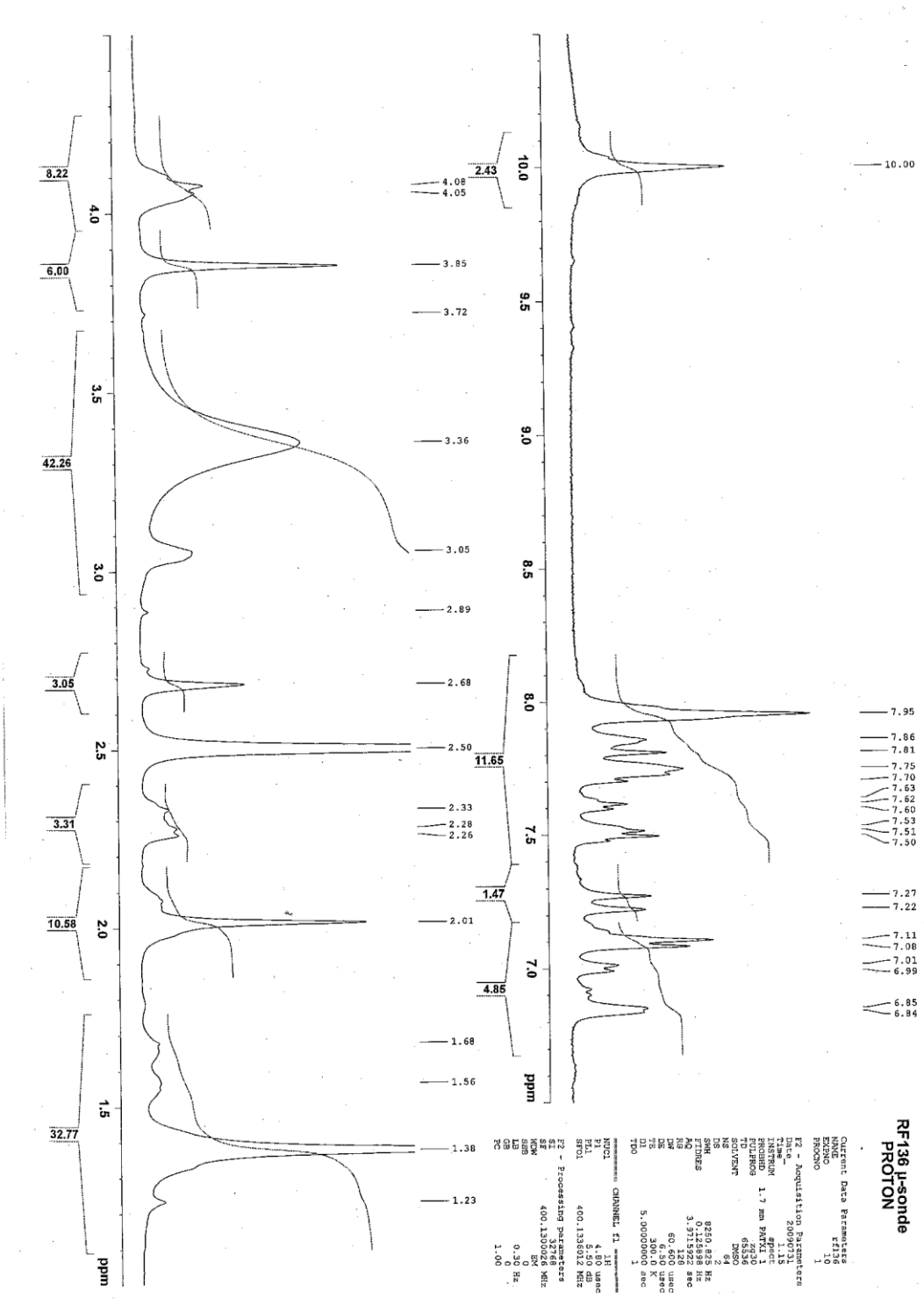

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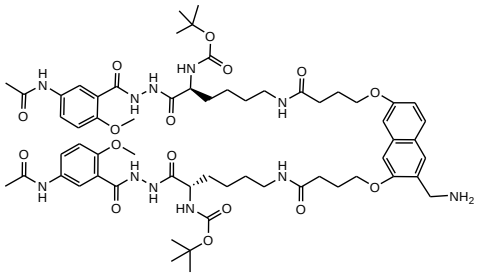

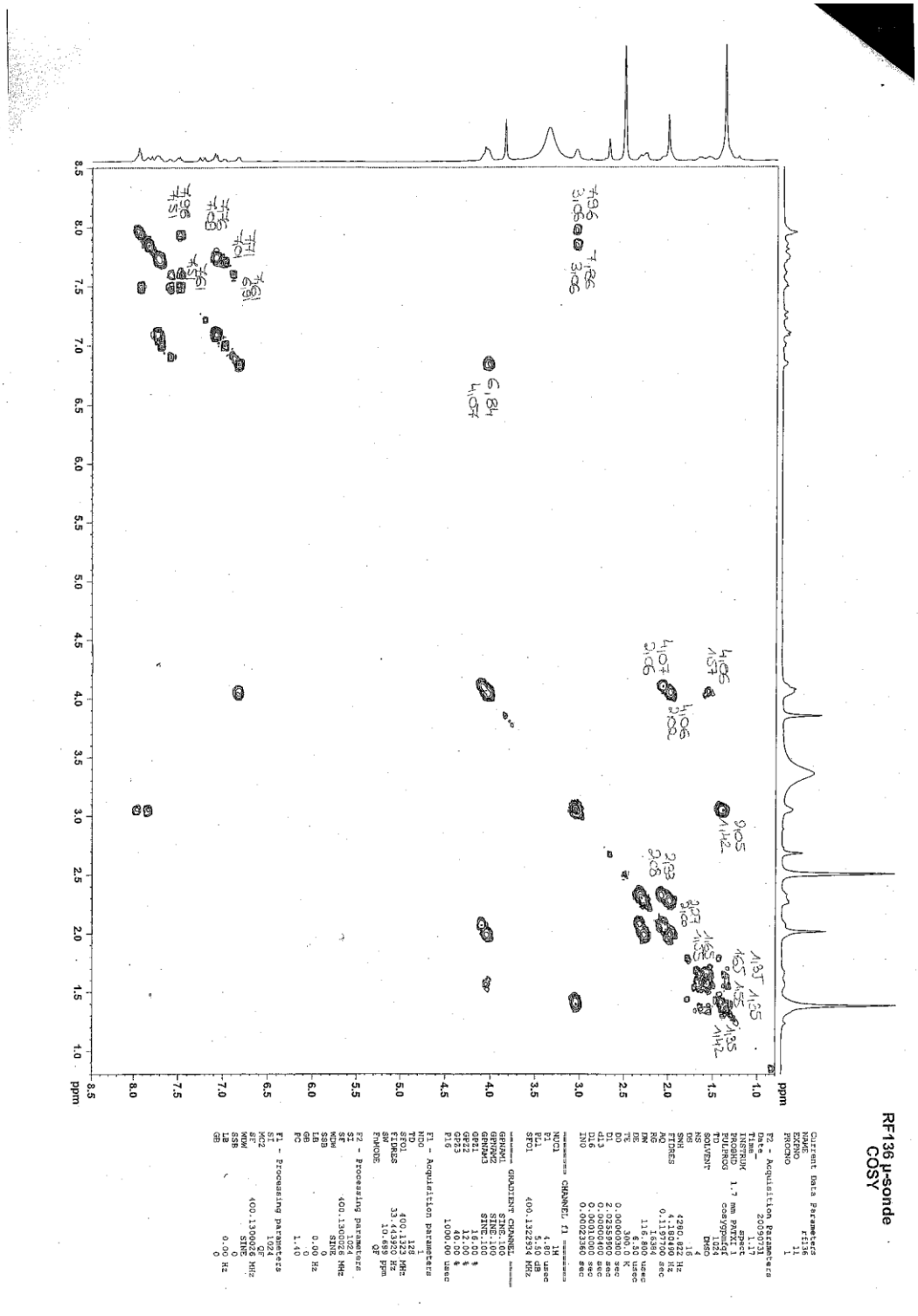

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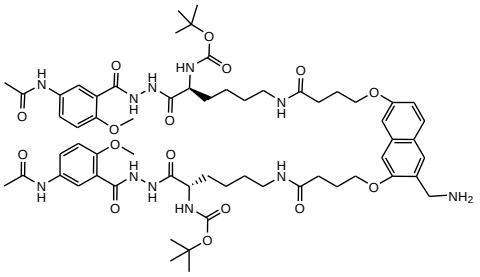

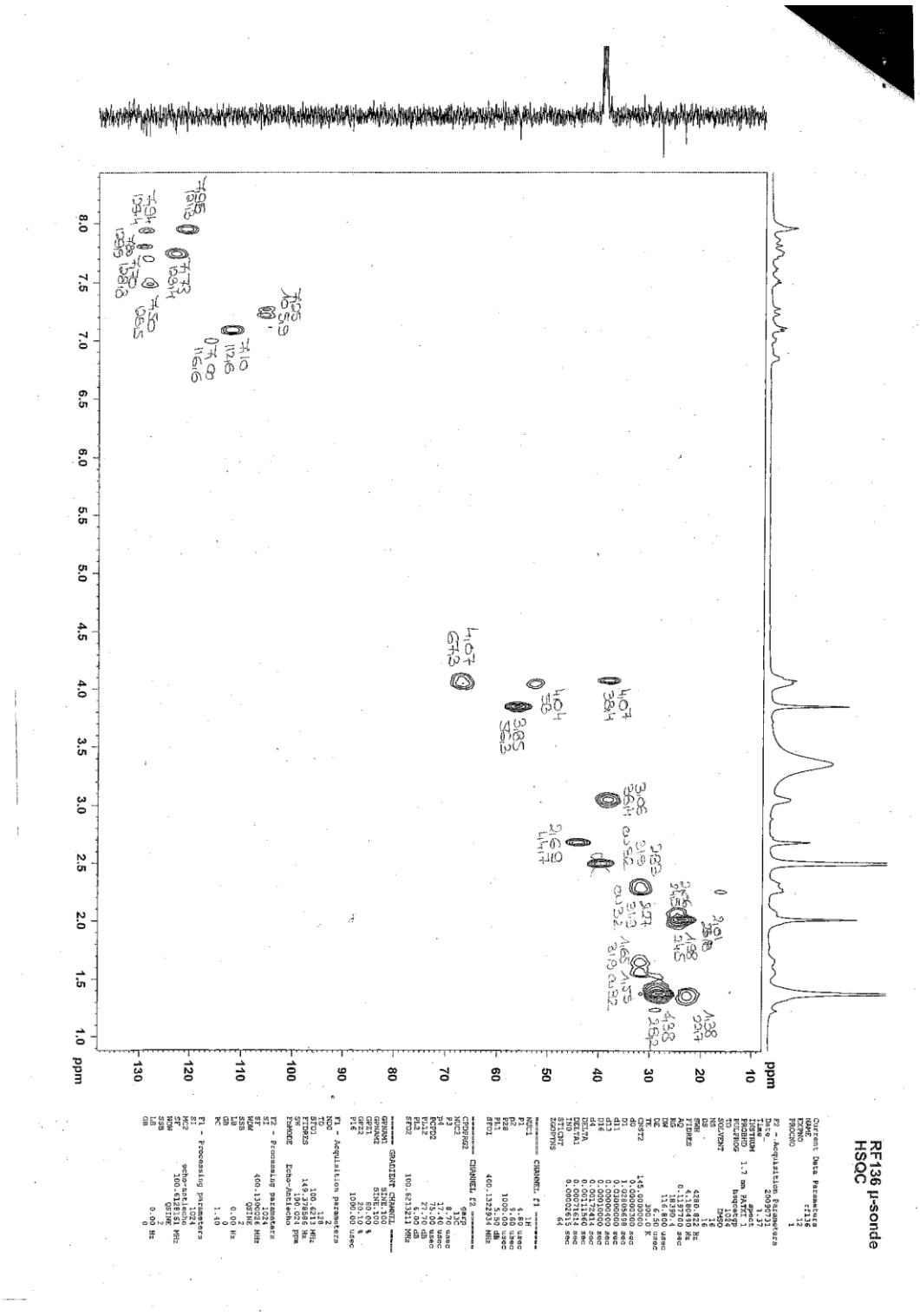

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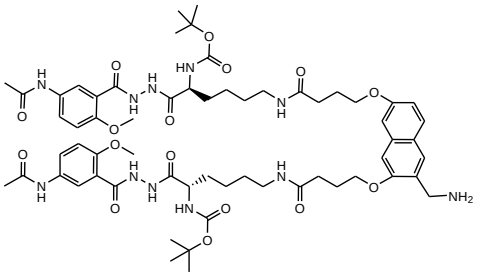

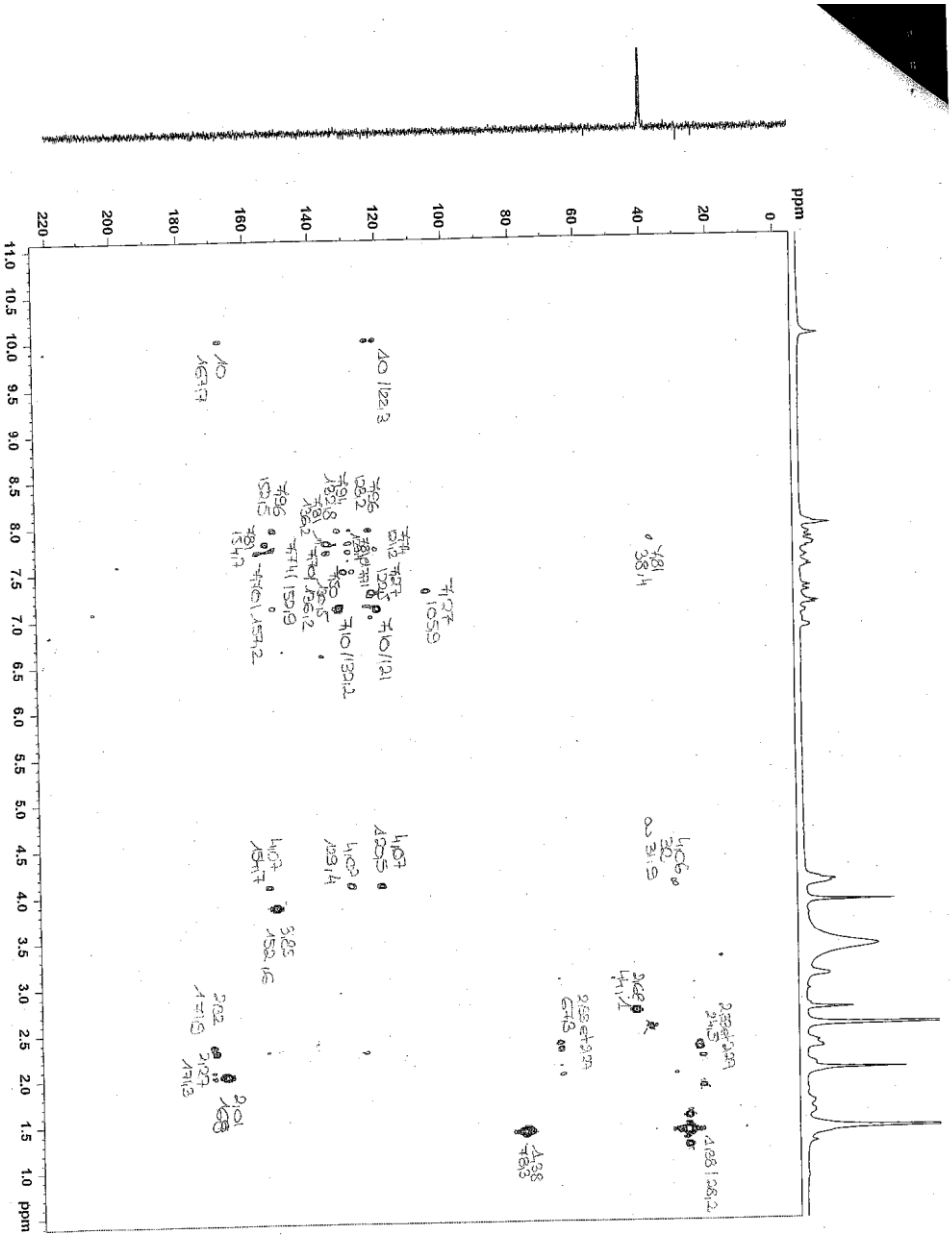

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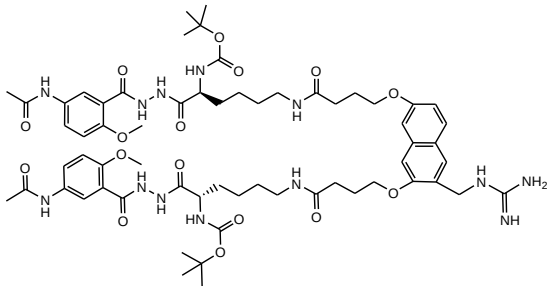

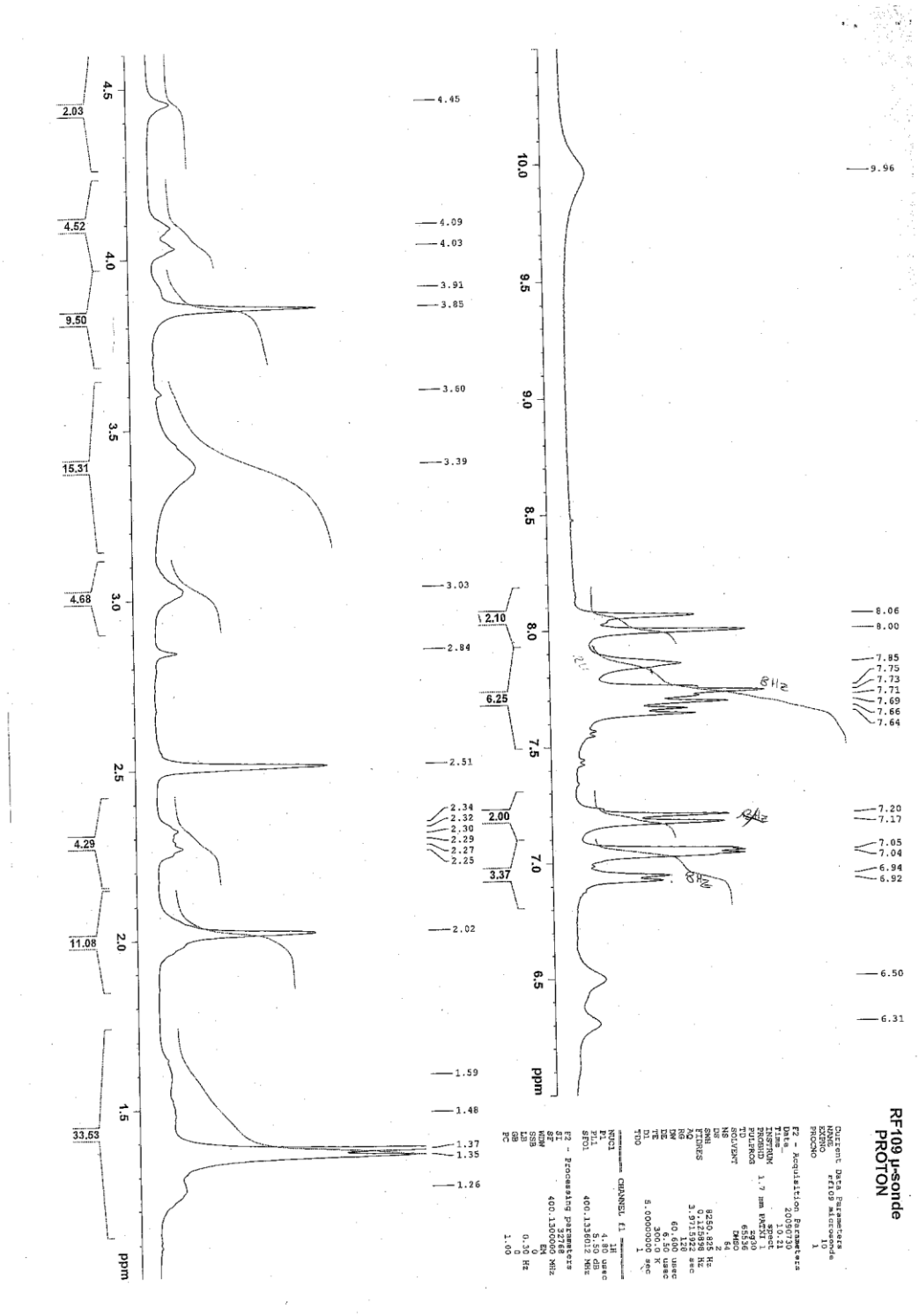

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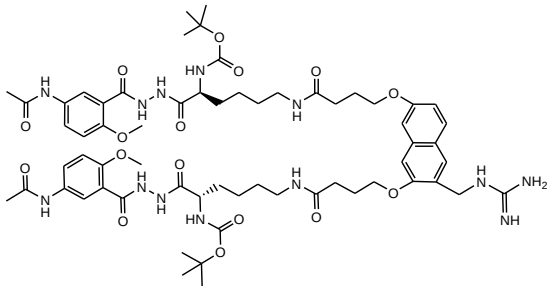

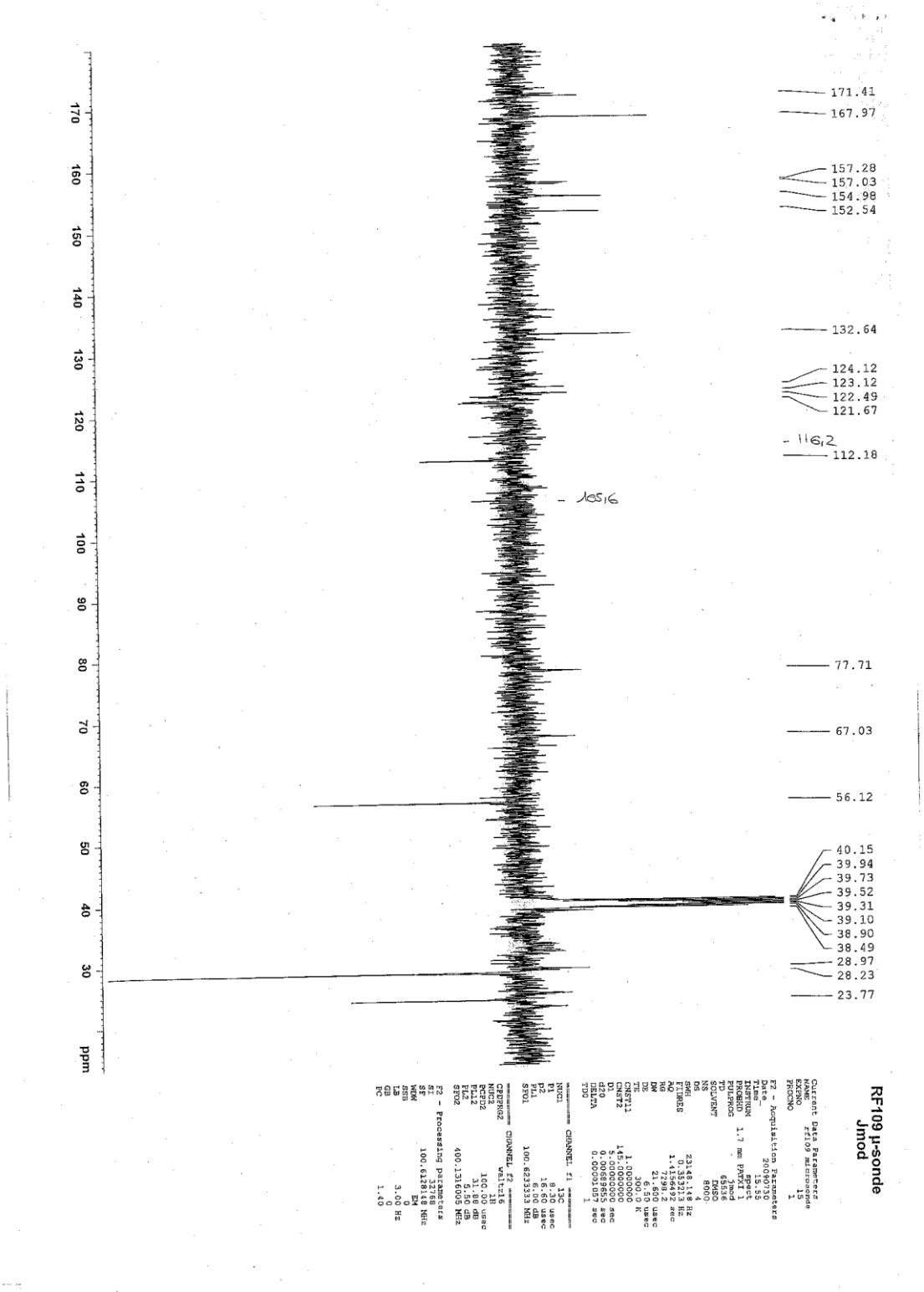

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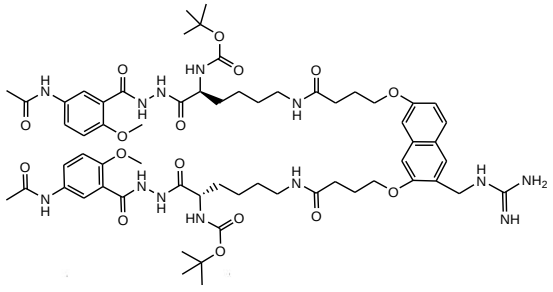

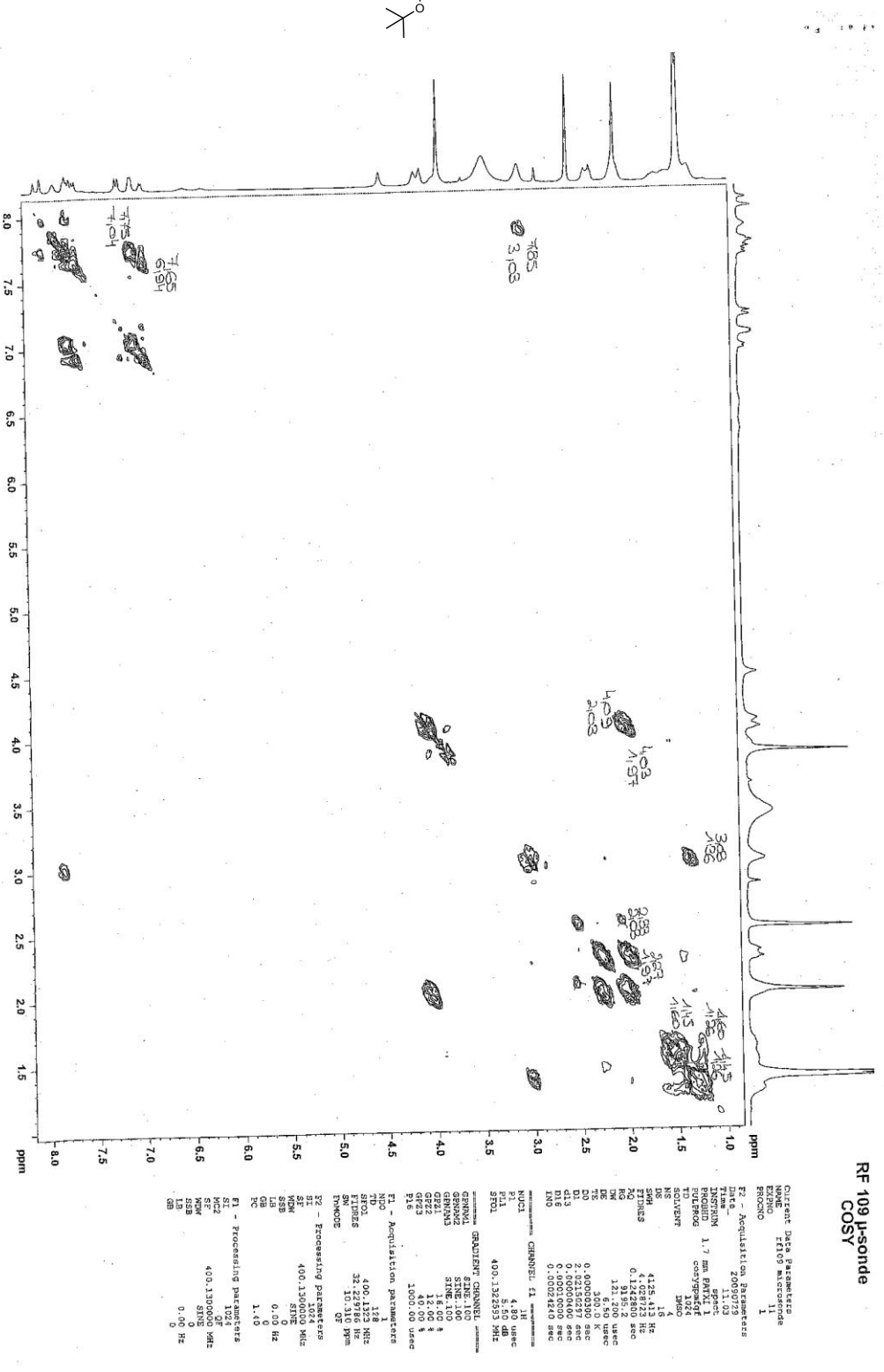

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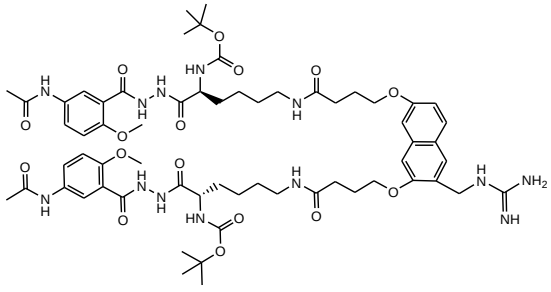

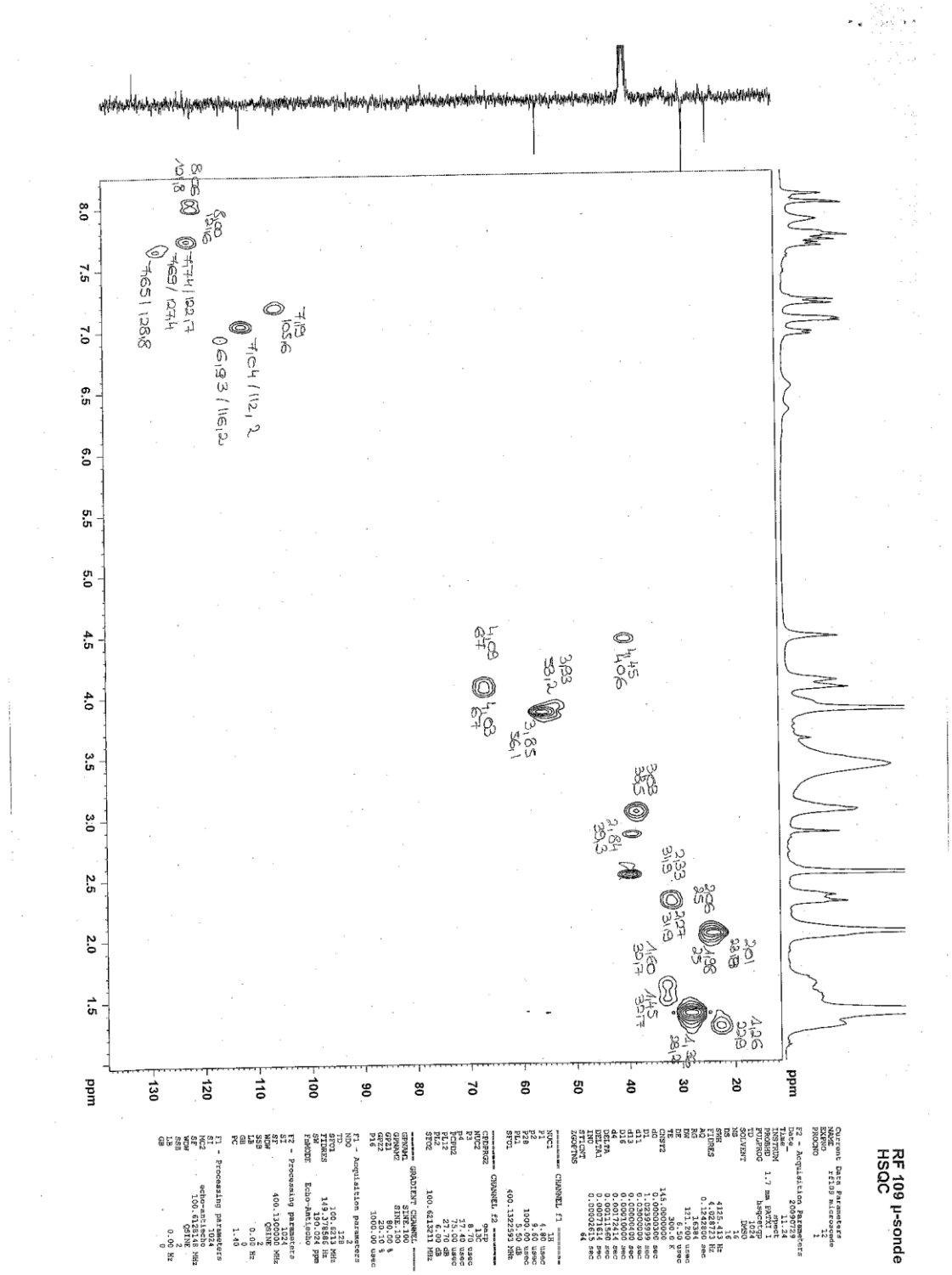

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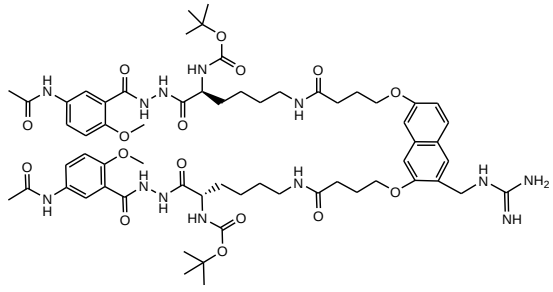

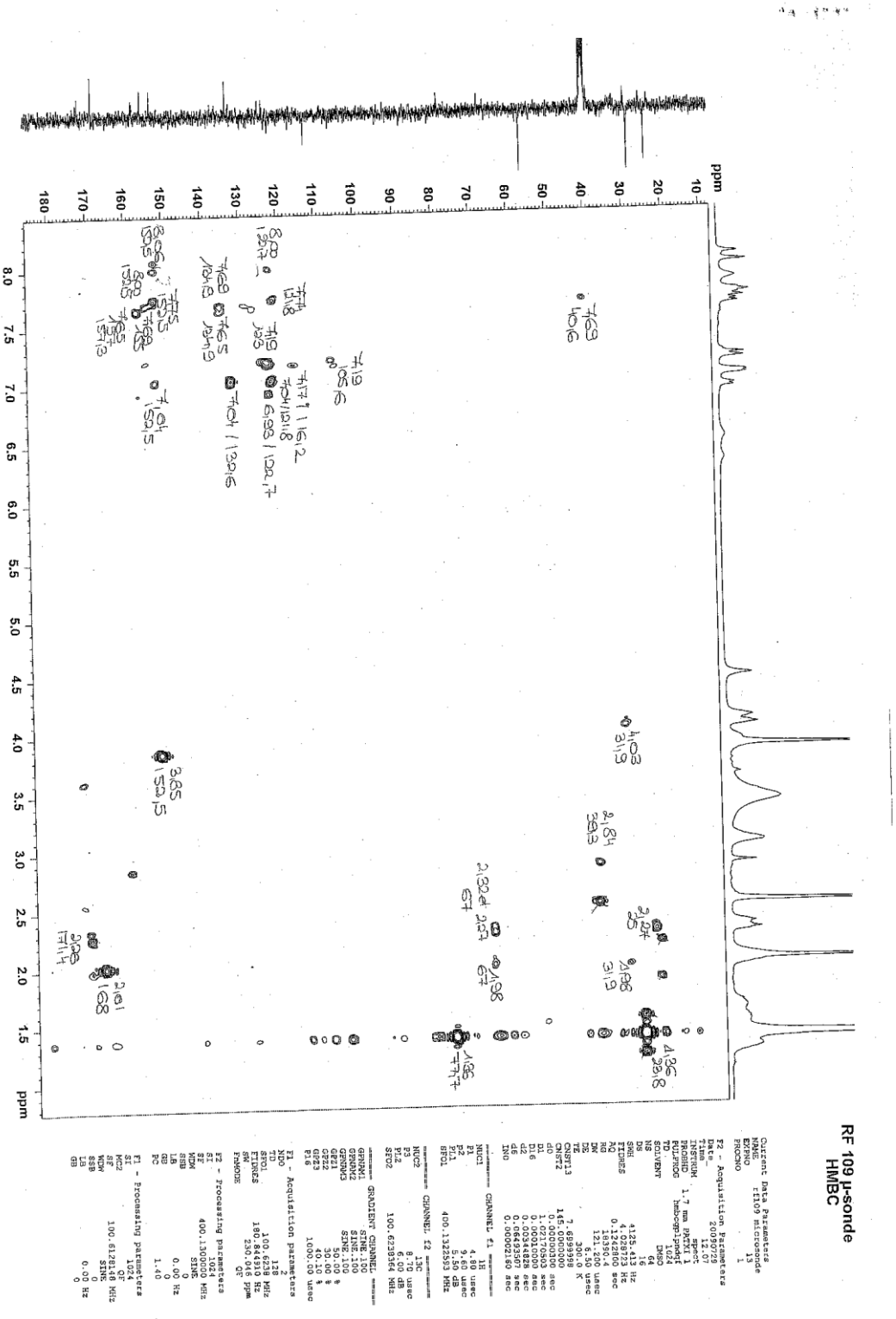

Figure 1S.

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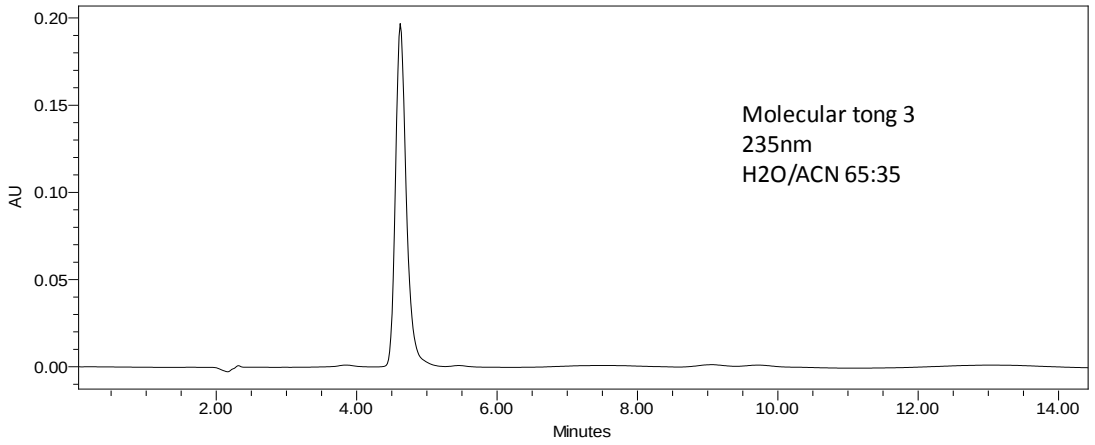

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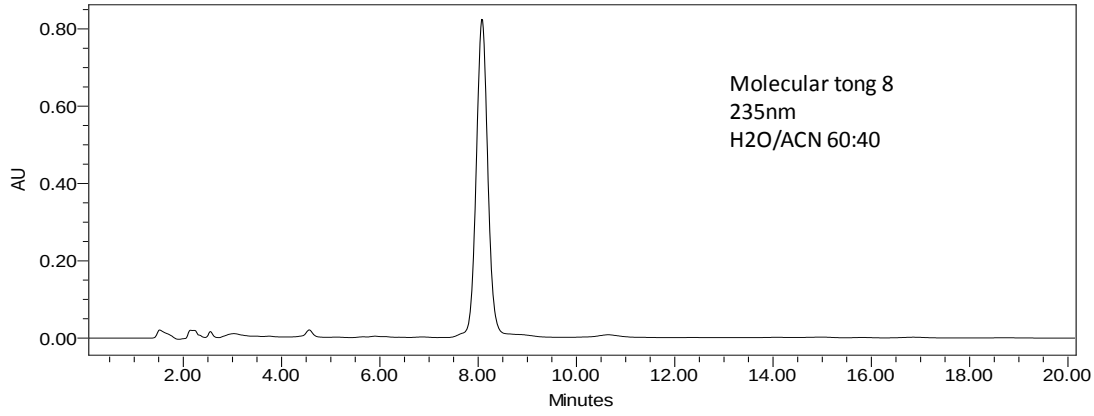
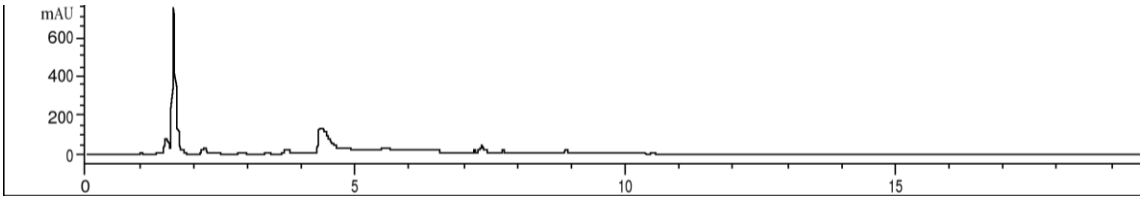


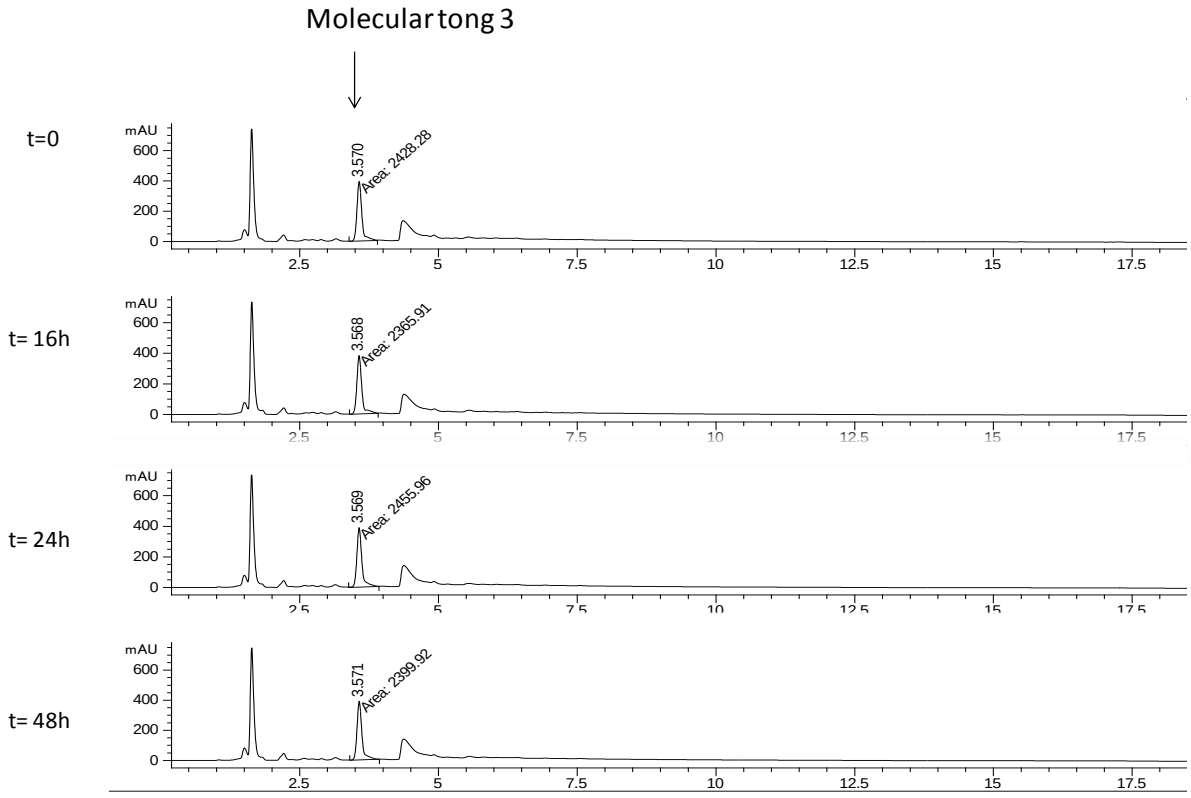
Figure 2S.

A1

Blank serum

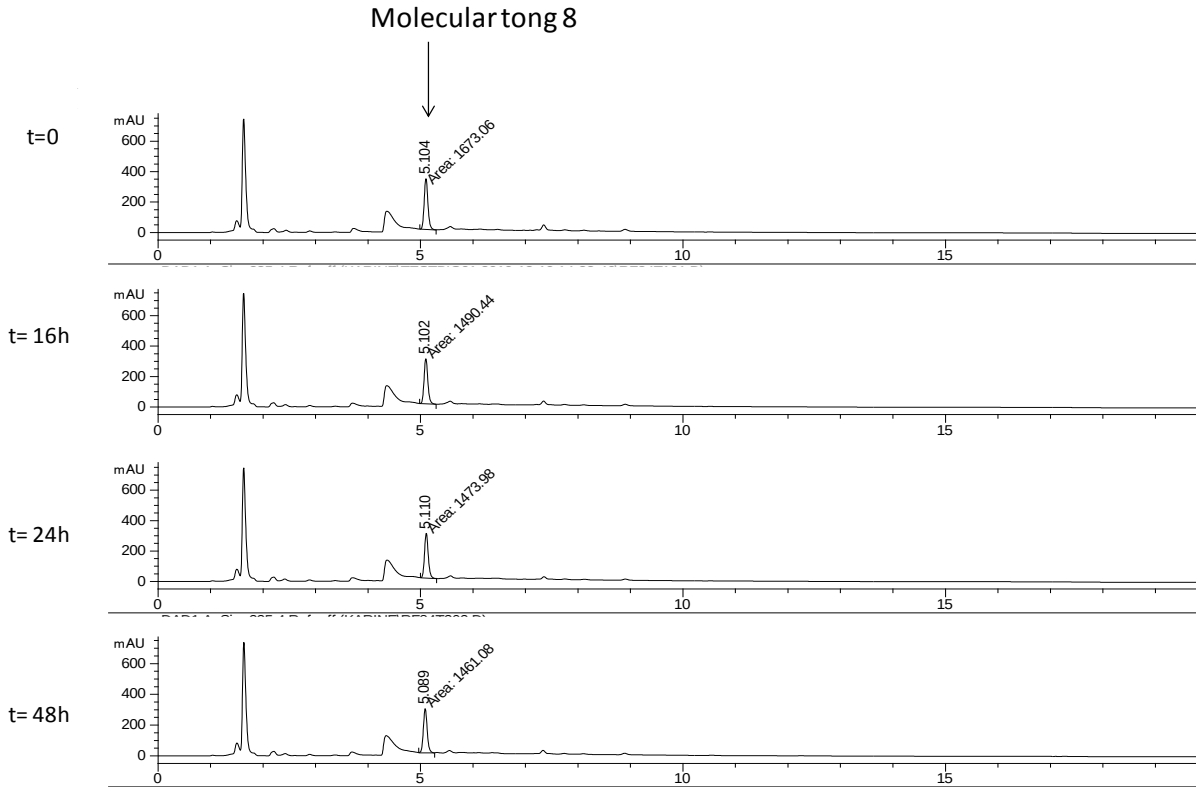


B1



Molecular tong **3** after incubation in the culture medium

B2



Molecular tong **8** after incubation in the culture medium