

Supporting Information

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

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Pages S55. Figure 1S. HPLC chromatograms of molecular tongs **3** and **8**. WATERS modular system (quaternary pump + controller E600, UV detector PDA 2996, autosampler 717). Column SUNFIRE, C18, 5 µm, 150 mm x 4.6 mm; mobile phase, a mixture of A (H₂O) and B (AcCN); room temperature; flow rate 1 mL/min; detection at 235 nm.

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, CH₃CN (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-Bromonaphthalene-2,7-diol was synthesized from naphthalene-2,7-diol, according to published methods [24,27-28]. *N*-[3-[[[(2*S*)-2-Amino-3-methyl-butanoyl]amino]carbonyl]-4-methoxy-phenyl]acetamide **40** and *N*-[(1*S*)-1-[(5-acetamido-2-methoxy benzoyl)amino]carbonyl]-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 μ m). TLC analyses were performed on silica gel 60 F₂₅₀ (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 Pharmacy at Châtenay-Malabry, France). NMR spectra were recorded on an ultrafield AVANCE 300 (¹H, 300 MHz, ¹³C, 75 MHz) or a Bruker 400 (¹H, 400 MHz, ¹³C, 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 μ m, 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 μ L, 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, CH₂Cl₂, CH₃OH and Et₂O. After recrystallization from CH₃OH/Et₂O, compound **2** was obtained as an orange solid (174 mg, 50%); mp = 188-194°C; ¹H 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); ¹³C 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; C₅₄H₇₁N₉O₁₄·1H₂O: 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 Et₂O, filtered and washed again successively with saturated aqueous NaHCO₃, distilled H₂O, EtOH, cyclohexane, and Et₂O. Compound **3** was obtained as an orange solid (30 mg, 60%); ¹H 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); ¹³C 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; C₅₁H₆₇N₉O₁₄·2H₂O: 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, CH₂Cl₂, CH₃OH and Et₂O to afford **4** as an orange brown solid (192 mg, 68%); mp = 208-214 °C; ¹H 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); ¹³C 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; C₄₈H₆₁N₉O₁₂·2.5H₂O: 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 H₂O (100 mL), 10% aqueous citric acid (50 mL), 10% aqueous K₂CO₃ (50 mL), H₂O (100 mL), dried over Na₂SO₄ and concentrated under reduced pressure. The crude residue was then purified by flash chromatography on silica gel column (CH₂Cl₂/CH₃OH, 90:10) to afford **6** as a light pink powder (119 mg, 59%); mp = 160-170 °C; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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; C₆₆H₉₃N₁₁O₁₈·2H₂O: 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™ 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 CH₂Cl₂, the filtrate was concentrated under reduced pressure. The residue obtained was purified by flash chromatography on silica gel column (CH₂Cl₂/CH₃OH, 90:10) to afford **7** as white solid (7 mg, 30%); R_f (CH₂Cl₂/CH₃OH, 80/20) = 0.15; ¹H NMR (300 MHz, CD₃OD): 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); ¹³C 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; C₆₃H₈₉N₁₁O₁₈·5H₂O: 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 CH₂Cl₂ (50 mL). After adding water (30 mL) to the organic layer, the precipitate formed was isolated and successively washed with several cycles of H₂O, EtOAc, cyclohexane, and Et₂O. After recrystallization from CH₃OH/Et₂O, compound **8** was obtained as a brown solid (250 mg, 72%); mp = 172-174 °C; R_f (EtOAc/cyclohexane, 80/20) = 0.2; ¹H 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); ¹³C 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; C₆₀H₈₃N₁₁O₁₆·4H₂O: 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 CH₂Cl₂ (50 mL). The organic layer was 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 H₂O, EtOAc, cyclohexane, and Et₂O. After purification by reverse phase preparative HPLC (H₂O/CH₃OH, 47:53 + 0.05% CF₃COOH), the trifluoroacetic salt of **9** was obtained as a white solid (168 mg, 93%); mp = 158-160 °C; R_f (CH₂Cl₂/CH₃OH, 90/10 + 2% NH₄OH) = 0.3; ¹H 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); ¹³C 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} ; $\text{C}_{63}\text{H}_{88}\text{N}_9\text{O}_{12}\cdot 2.5\text{H}_2\text{O}\cdot 2\text{CF}_3\text{COOH}$: 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 $[\text{M}+\text{H}]^+$.

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 $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ to afford **10** as a light yellow solid (217 mg, 61%); mp = 178-180 $^\circ\text{C}$; Rf ($\text{EtOAc}/\text{CH}_2\text{Cl}_2$, 80/20) = 0.3; ^1H 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} ; $\text{C}_{74}\text{H}_{99}\text{N}_{13}\text{O}_{19}\cdot 5\text{H}_2\text{O}$: 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 $[\text{M}+\text{Na}]^+$.

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 $^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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} ; $\text{C}_{66}\text{H}_{93}\text{N}_{13}\text{O}_{17}\cdot 5\text{H}_2\text{O}$: 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 $[\text{M}+\text{H}]^+$.

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 ($\text{H}_2\text{O}/\text{CH}_3\text{OH}$, 47:53 + 0.05% CF_3COOH), the trifluoroacetic salt of **12** was obtained (38 mg, 92%); mp = 158-160 $^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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} ; $\text{C}_{63}\text{H}_{89}\text{N}_{11}\text{O}_{16}\cdot 2\text{CF}_3\text{COOH}\cdot 1\text{H}_2\text{O}$: 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 $[\text{M}+\text{H}]^+$, 1279 $[\text{M}+\text{Na}]^+$.

1.1.1.11. Molecular tong 13. Same procedure as described 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 purified by reverse phase preparative HPLC ($\text{H}_2\text{O}/\text{CH}_3\text{OH}$, 42:58 + 0.1% CF_3COOH). The trifluoroacetic salt of **13** was obtained as a white solid (322 mg, 86%); mp = 168-170 $^\circ\text{C}$; Rf = ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 90/10 + 2% NH_4OH) = 0.3; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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} ; $\text{C}_{65}\text{H}_{93}\text{N}_{11}\text{O}_{16}\cdot 2\text{CF}_3\text{COOH}\cdot 4\text{H}_2\text{O}$: 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 $[\text{M}+\text{H}]^+$.

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 $^\circ\text{C}$ 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 $^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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} ; $\text{C}_{61}\text{H}_{85}\text{N}_{11}\text{O}_{16}\cdot 4\text{H}_2\text{O}$: 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 $[\text{M}+\text{H}]^+$.

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 $^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): 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} ; $\text{C}_{62}\text{H}_{87}\text{N}_{13}\text{O}_{16} \cdot 3.5\text{H}_2\text{O}$: 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 $[\text{M}-\text{H}]^-$.

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 ($\text{H}_2\text{O}/\text{CH}_3\text{OH}$, 30:70 + 0.1% CF_3COOH). Compound **43** was obtained as a yellow solid (322 mg, 86%); mp = 170-172 $^\circ\text{C}$; Rf ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 90/10 + 2% NH_4OH) = 0.3; ^1H 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} ; $\text{C}_{71}\text{H}_{91}\text{N}_{11}\text{O}_{18} \cdot 5\text{H}_2\text{O}$: 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 $[\text{M}+\text{Na}]^+$.

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 ($\text{EtOAc}/\text{CH}_3\text{OH}$, 90:10). to yield **44** as a light yellow solid (198 mg, 65%); mp = 151-153 $^\circ\text{C}$; Rf ($\text{EtOAc}/\text{CH}_3\text{OH}$, 80/20) = 0.5; ^1H 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} ; $\text{C}_{69}\text{H}_{91}\text{N}_{11}\text{O}_{18} \cdot 1.5\text{H}_2\text{O}$: 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 $[\text{M}-\text{H}]^-$.

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 naphthalene-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 H₂O (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 Na₂SO₄, 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%). R_f (EtOAc/cyclohexane: 40/60) = 0.5; mp = 184-186 (lit. 190-191 °C [28]). ¹H 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); ¹³C NMR (75 MHz, CD₃OD): 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), K₂CO₃ (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 K₂CO₃ (50 mL), water (100 mL) and brine (100 mL). The organic layer was dried over Na₂SO₄, 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%). R_f (EtOAc/cyclohexane, 25/75) = 0.3; mp = 61-62 °C. ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CDCl₃): 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; C₃₂H₃₁BrO₆: 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%); R_f (EtOAc/cyclohexane, 30/70) = 0.4; mp = 64-66 °C. ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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; C₂₂H₂₇BrO₆: 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 μ L, 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 and filtered 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%); ^1H 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} ; $\text{C}_{38}\text{H}_{43}\text{NO}_8$: 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 $[\text{M}+\text{H}]^+$.

1.1.2.5. 4-[[6-[(2,2-Dimethyl-1,3-dioxolan-4-yl)methylamino]-7-(4-hydroxy-4-oxo-butoxy)-2-naphthyl]oxy]butanoic acid 21. A solution of **20** (282 mg, 0.44 mmol) in $\text{CH}_3\text{OH}/\text{EtOAc}$ (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; ^1H 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, CD_3OD): 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} ; $\text{C}_{24}\text{H}_{31}\text{NO}_8$: 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 $[\text{M}+\text{H}]^+$.

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 μ mol, 10 mol%), Xantphos (98 mg, 17 μ mol, 20 mol%), and potassium carbonate (2.34 g, 17 mmol). Then, under argon atmosphere, dry dioxane (11.5 mL) and benzophenone imine (213 μ L, 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 $_2$ O (428 mg, 3.54 mmol), and $\text{NH}_2\text{OH}\cdot\text{HCl}$ (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%); R $_f$ = (cyclohexane/EtOAc, 70/30) = 0.3; mp = 87-89 °C; ^1H 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): $\nu = 3367, 1725, 1160. \text{ cm}^{-1}$; $\text{C}_{32}\text{H}_{33}\text{NO}_6 \cdot 0.15\text{H}_2\text{O}$: 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; ¹H NMR (300 MHz, CDCl₃): $\delta = 7.36$ (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); ¹³C NMR (75 MHz, CDCl₃): $\delta = 173.3, 173.2, 154.9, 148.2, 134.7, 134.0, 129.2, 128.2, 126.7, 124.9, 116.2, 109.4, 106.6, 105.4, 67.1, 66.7, 60.5, 60.3, 31.1, 30.9, 29.6, 24.7, 24.6, 14.2$; IR (neat): $\nu = 3454, 3361, 1722, 1616, 1515, 1162. \text{ cm}^{-1}$; $\text{C}_{22}\text{H}_{29}\text{NO}_6 \cdot 0.15\text{H}_2\text{O}$: 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 CH₂Cl₂ (2 mL) was added Et₃N (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 CH₂Cl₂ (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 KHSO₄ (3 x 5 mL), and brine (3 x 5 mL). The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel column (CH₂Cl₂, 100%) to yield **24** as a pink solid (91 mg, 80%); Rf (CH₂Cl₂) = 0.3; mp = 96-98 °C. ¹H NMR (300 MHz, CDCl₃): $\delta = 9.07$ (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); ¹³C NMR (75 MHz, CDCl₃): $\delta = 173.1, 172.9, 163.6, 156.9, 147.5, 131.9, 129.3, 128.6, 128.3, 128.2, 128.1, 124.8, 123.9, 117.0, 116.9, 106.1, 105.3, 67.4, 66.7, 66.5, 66.3, 43.3, 30.9, 30.8, 24.7, 24.5$; IR (neat): $\nu = 3379, 1724, 1672, 1548, 1243, 1156. \text{ cm}^{-1}$; $\text{C}_{34}\text{H}_{34}\text{ClNO}_7 \cdot 0.25\text{H}_2\text{O}$: 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 CH₂Cl₂ (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; ¹H NMR (300 MHz, CDCl₃): $\delta = 9.16$ (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); ¹³C NMR (75 MHz, CDCl₃): $\delta = 173.2, 173.0, 163.5, 156.9, 147.5, 131.9, 129.3, 124.8, 123.9, 116.8, 106.1, 105.2, 67.5, 66.7, 60.6, 60.4, 43.3, 30.8, 30.7, 24.6, 24.4, 14.2$; IR (neat): $\nu = 3378, 1725, 1666, 1543. \text{ cm}^{-1}$; $\text{C}_{24}\text{H}_{30}\text{ClNO}_7$: 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 NH₂CH₃ HCl (304 mg,

4.5 mmol) and Et₃N (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 NaHCO₃ (2 x 5 mL), and brine (10 mL). The organic layer was dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel column (CH₂Cl₂, 100% to CH₂Cl₂/CH₃OH, 100:1) to afford **26** as a yellow solid (105 mg, 60%); Rf (CH₂Cl₂/CH₃OH, 20/1) = 0.23; mp = 80-82 °C; ¹H NMR (300 MHz, CDCl₃): 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, 4H), 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); ¹³C NMR (75 MHz, CDCl₃): 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; C₃₅H₃₈N₂O₇·0.3H₂O: 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 CH₃OH (10 mL) to afford **27** as a white solid (61 mg, 84%); Rf (CH₂Cl₂/CH₃OH, 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, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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; C₃₆H₄₅N₃O₉: 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-Benzoyloxycarbonylpiperazin-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 CH₃OH (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 Et₂O (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 Na₂SO₄ and evaporated under reduced pressure to afford compound **29** as a yellow solid (149 mg, 86%); mp = 92-94 °C; ¹H NMR (300 MHz, CD₃OD): 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): $\delta = 177.0, 158.4, 149.6, 133.9, 129.8, 129.6, 129.2, 129.0, 126.1, 125.2, 118.9, 117.9, 107.3, 106.9, 69.1, 68.6, 68.0, 53.9, 43.9, 31.9, 31.4, 25.8$; IR (neat): $\nu = 2888, 1729, 1692, 1609, 1434, 1235. \text{ cm}^{-1}$; $\text{C}_{32}\text{H}_{37}\text{N}_3\text{O}_6 \cdot 1\text{H}_2\text{O}$: 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 $[\text{M}-\text{H}]^-$.

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), $\text{Pd}(\text{PPh}_3)_4$ (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 $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 20:1) to yield compound **30** as a yellow solid (87 mg, 60%); R_f ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 20/1) = 0.37; mp = 65-67 °C; ^1H NMR (300 MHz, CDCl_3): $\delta = 7.73$ (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): $\delta = 173.0, 157.8, 156.8, 135.9, 135.4, 133.2, 132.1, 132.0, 131.9, 128.9, 128.5, 128.4, 128.2, 123.6, 116.8, 111.7, 105.9, 105.5, 87.9, 81.8, 67.0, 66.7, 66.33, 66.31, 48.7, 44.0, 30.8, 30.7, 29.7, 24.6$; $\text{C}_{37}\text{H}_{39}\text{NO}_6 \cdot 0.5\text{H}_2\text{O}$: 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 $[\text{M}+\text{H}]^+$.

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; ^1H NMR (400 MHz, CD_3OD): $\delta = 7.54$ (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): $\delta = 181.1, 179.6, 158.6, 157.4, 136.6, 129.5, 129.3, 128.9, 125.4, 117.2, 107.1, 106.4, 69.2, 68.4, 58.8, 43.2, 35.6, 33.5, 29.5, 26.8, 26.7, 26.6$; IR (neat): $\nu = 1714, 1632, 1388, 1211, 1147 \text{ cm}^{-1}$; $\text{C}_{23}\text{H}_{31}\text{NO}_6 \cdot 1\text{H}_2\text{O}$: 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 $[\text{M}+\text{H}]^+$.

4.1.2.16. Ethyl 4-[[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%); R_f (cyclohexane/EtOAc, 70/30) = 0.3; ^1H NMR (300 MHz, CDCl_3): $\delta = 7.73$ (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, 4H), 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, CDCl₃) 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; C₄₁H₄₃NO₁₀: 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 CH₃OH/THF (1:1, 5 mL), aqueous NaOH 2N (580 μ L) 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 Et₂O (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 Na₂SO₄ and evaporated under reduced pressure to afford compound **33** as a light brown solid (70 mg, 61%); mp = 92-94 °C; ¹H 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); ¹³C 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 C₂₉H₂₉NO₈Na: 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), K₄[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 Na₂SO₄, 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; R_f (cyclohexane/EtOAc, 70/30) = 0.23; ¹H NMR (400 MHz, CDCl₃): 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); ¹³C NMR (100 MHz, CD₃OD): 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; C₂₃H₂₇NO₆·0.15H₂O: 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 NH₃ 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; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz,

CDCl₃): 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; C₂₃H₃₁NO₆·0.15H₂O : 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 Et₃N (300 μ L, 2.16 mmol) in CH₂Cl₂ (10 mL), was slowly added CbzCl (205 μ L, 1.44 mmol) in CH₂Cl₂ (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 Na₂SO₄, 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 %); R_f (cyclohexane/EtOAc, 70/30) = 0.23; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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; C₃₁H₃₇NO₈ : 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; ¹H 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); ¹³C 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; C₂₇H₂₉NO₈·0.3H₂O: 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 CH₂Cl₂ (5 mL), were successively added Et₃N (202 μ L, 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 temperature for 17 h. After filtration of the suspension through a pad of Celite, the filtrate 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 Na₂SO₄, 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%); R_f (cyclohexane/EtOAc, 60/40) = 0.5; ¹H NMR (300 MHz, CDCl₃): 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); ¹³C NMR (75 MHz, CDCl₃): 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 $[\text{M}+\text{H}]^+$, 682 $[\text{M}+\text{Na}]^+$; HRMS calcd for $\text{C}_{34}\text{H}_{49}\text{N}_3\text{O}_{10}\text{Na}$: 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 $\text{CH}_3\text{OH}/\text{THF}$ (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 $^\circ\text{C}$; ^1H NMR (300 MHz, $\text{DMSO}-d_6$): 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, $\text{DMSO}-d_6$): 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 $[\text{M}+\text{H}]^+$; HRMS calcd for $\text{C}_{20}\text{H}_{25}\text{N}_3\text{O}_6$ $[\text{M}+\text{H}]^+$: 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 $^\circ\text{C}$; ^1H 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 $[\text{M}+\text{H}]^+$

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-11²²) used in this study were expressed and purified as described before¹⁴. 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].

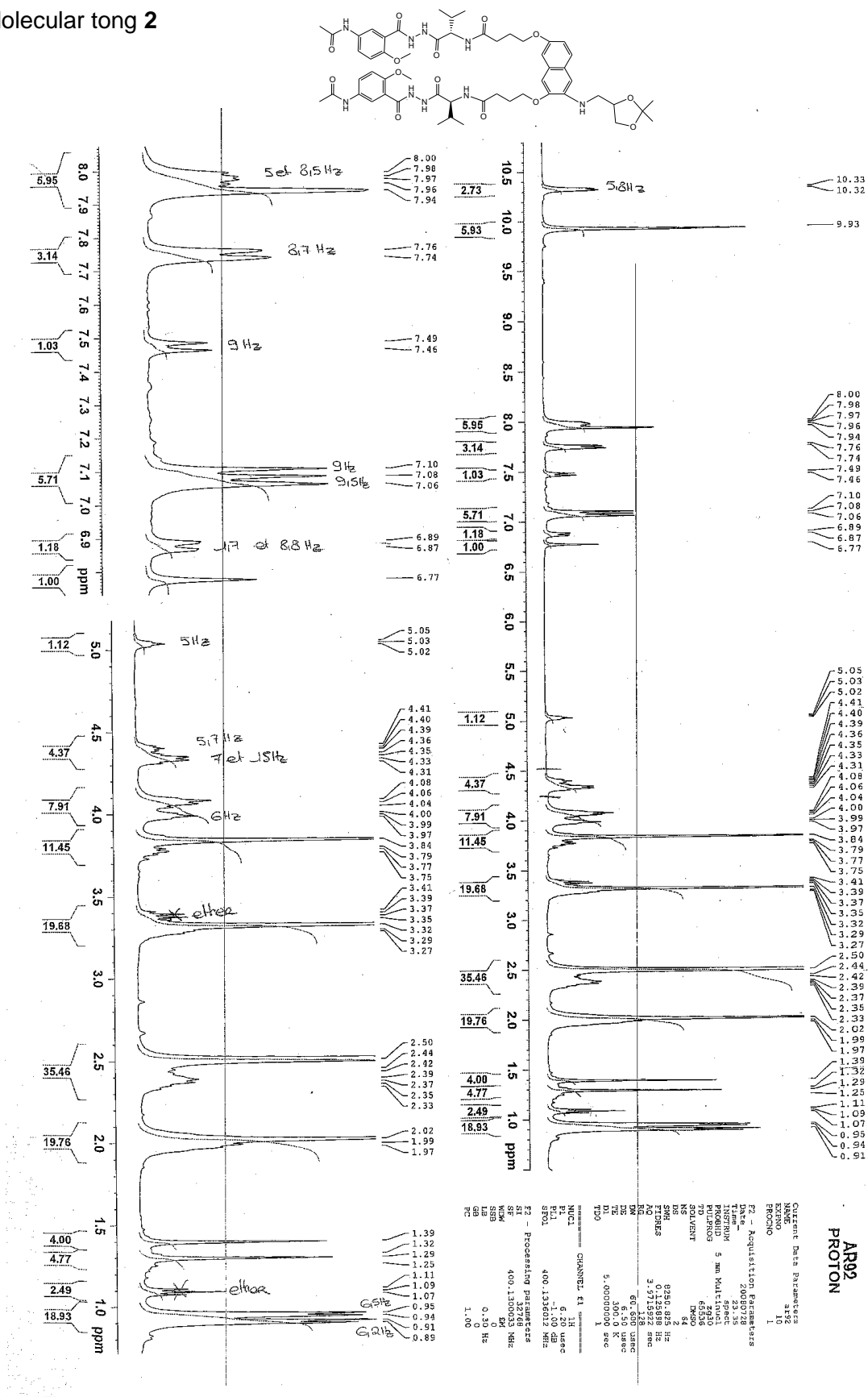
4.2.2. *Enzyme and inhibition assays.* The proteolytic activities of PR and mutated proteases were determined fluorometrically using the fluorogenic substrate DABCYL- α -abu-SQNYPIVQ-EDANS ($\lambda_{\text{ex}} = 340 \text{ nm}$; $\lambda_{\text{em}} = 490 \text{ nm}$) in 100 mM sodium acetate, 1 mM 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 $\log[\text{I}]$ versus time using a minimum of five points [23].

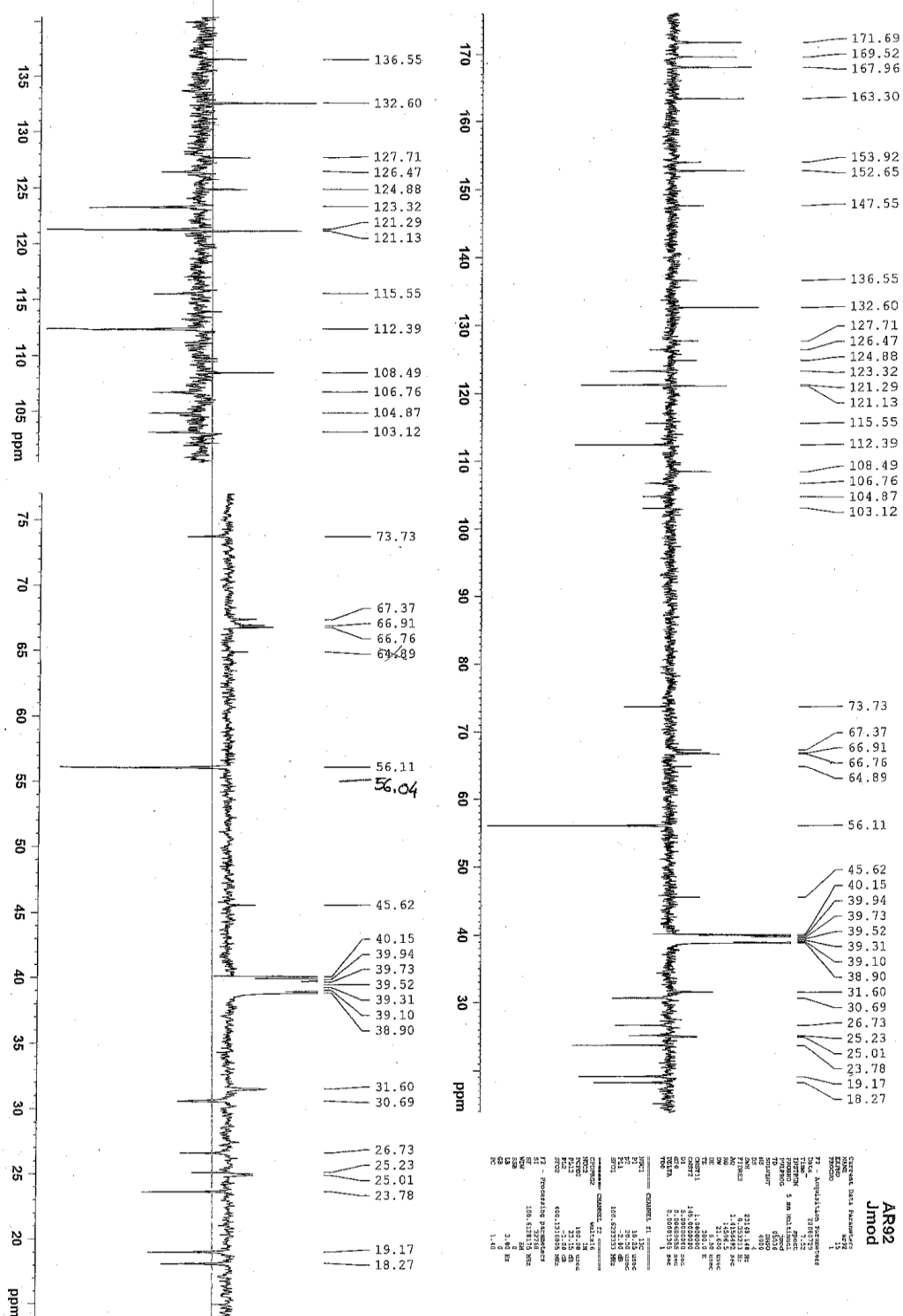
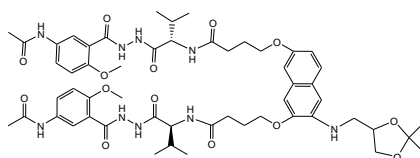
4.3. *Molecular modelling.*

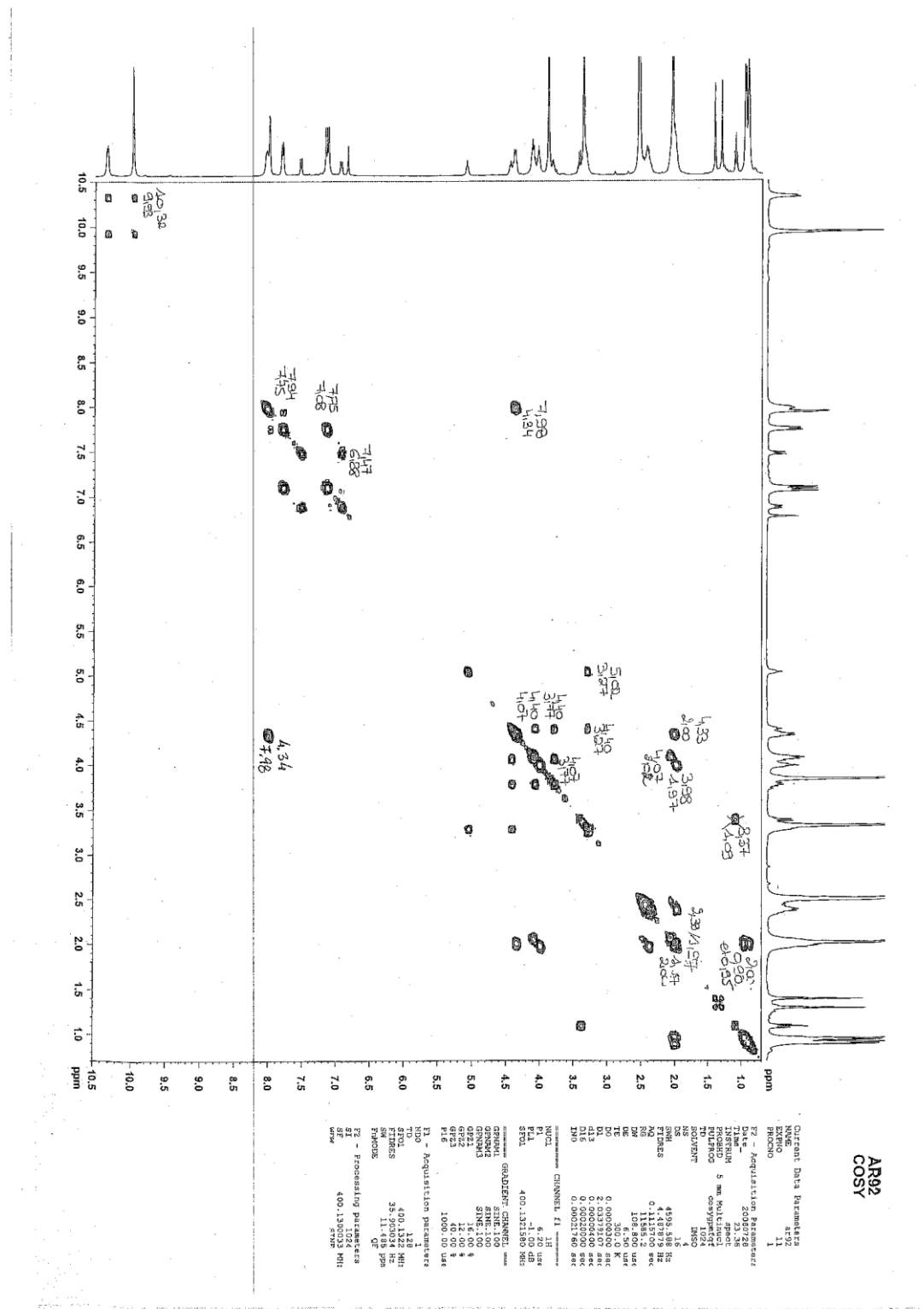
3D coordinates for the likely ionic form at pH 4.7 (i.e. with protonated amines) of compounds **1-15** were generated with CORINA v3.44 software [52] and energy was minimized using OPLS_2005 force field [53] as implemented in MacroModel v9.9 [54] using default parameters from the LigPrep v2.5 interface [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.

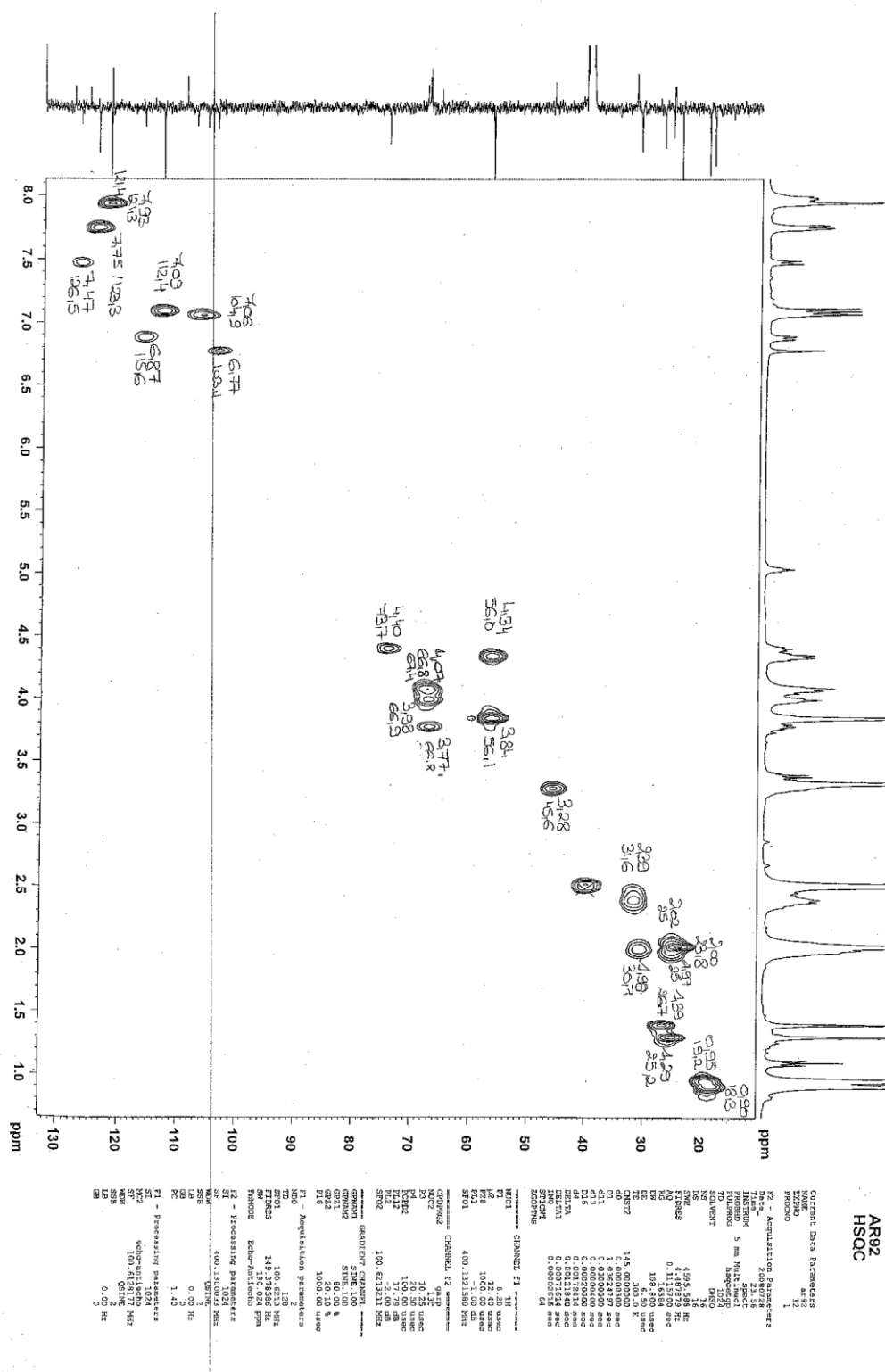
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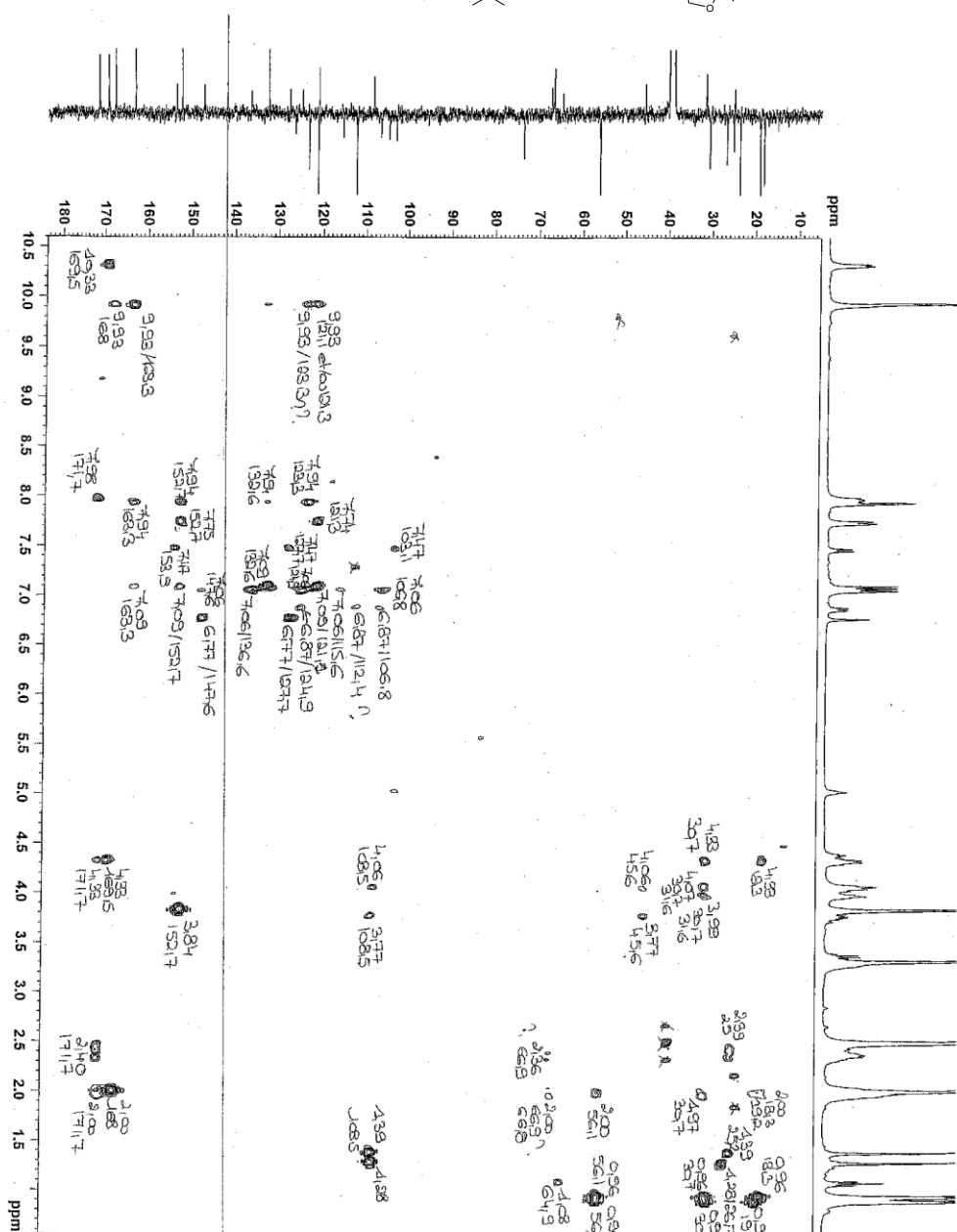


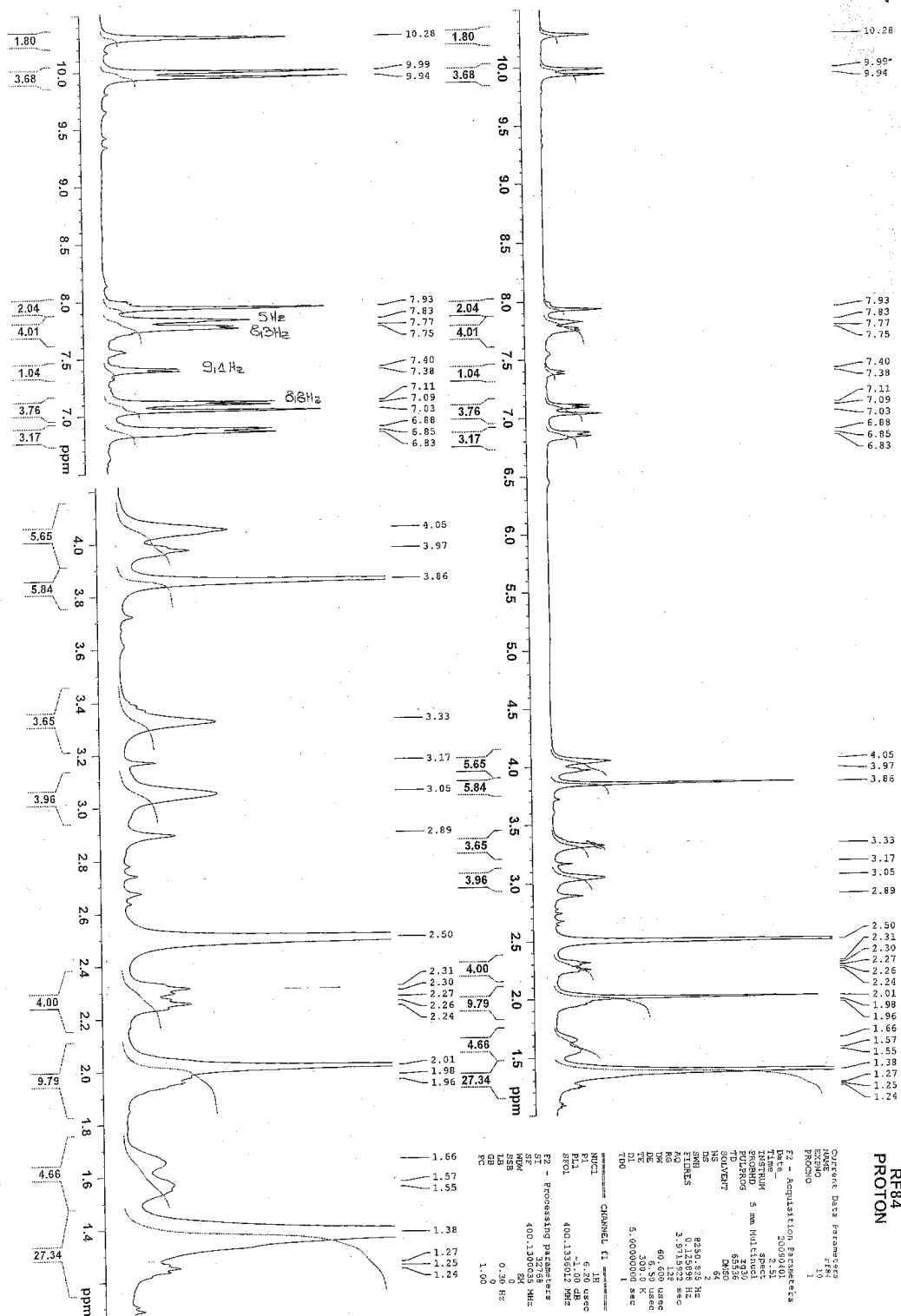
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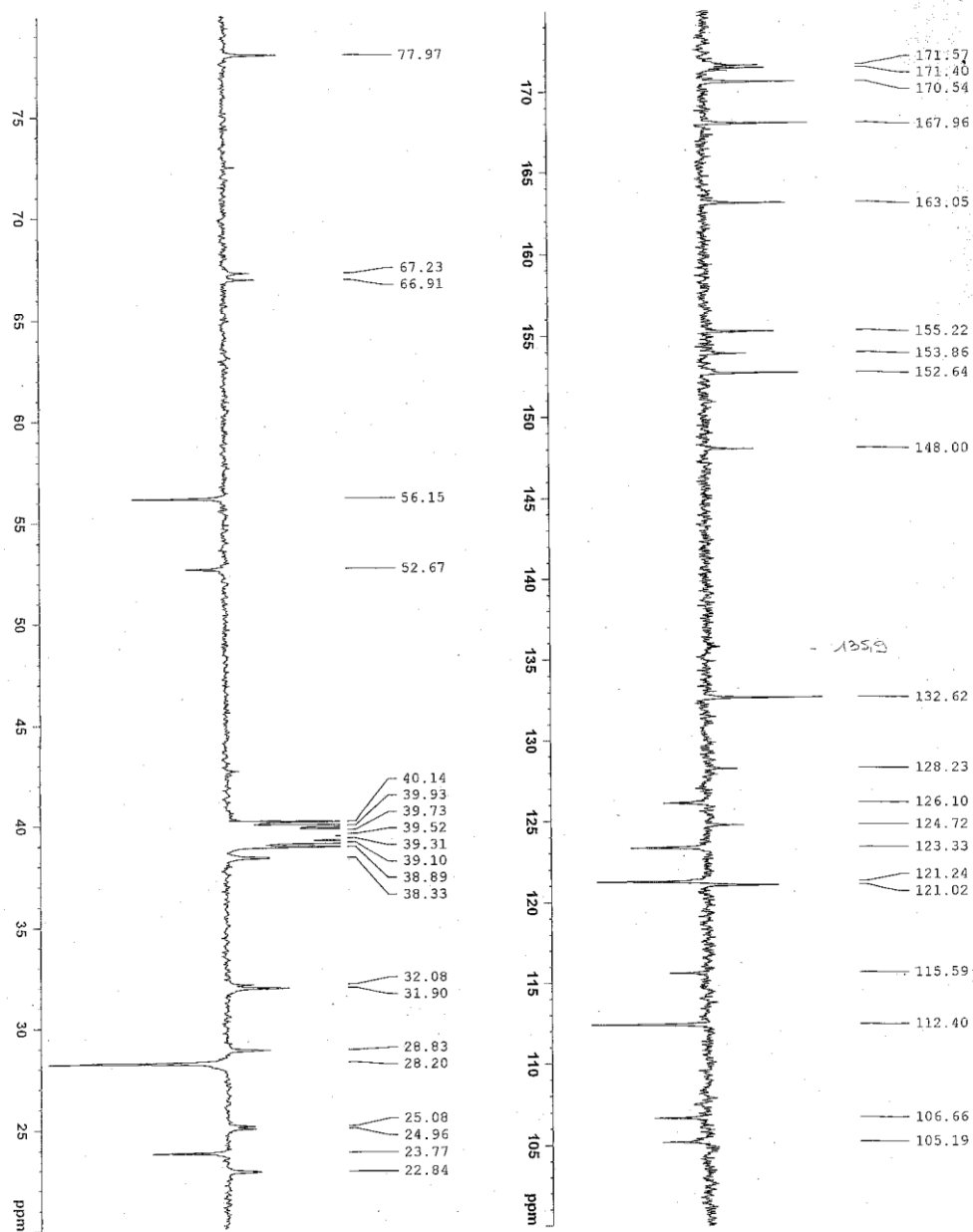
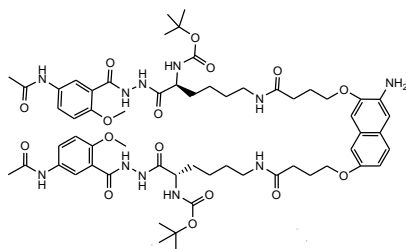




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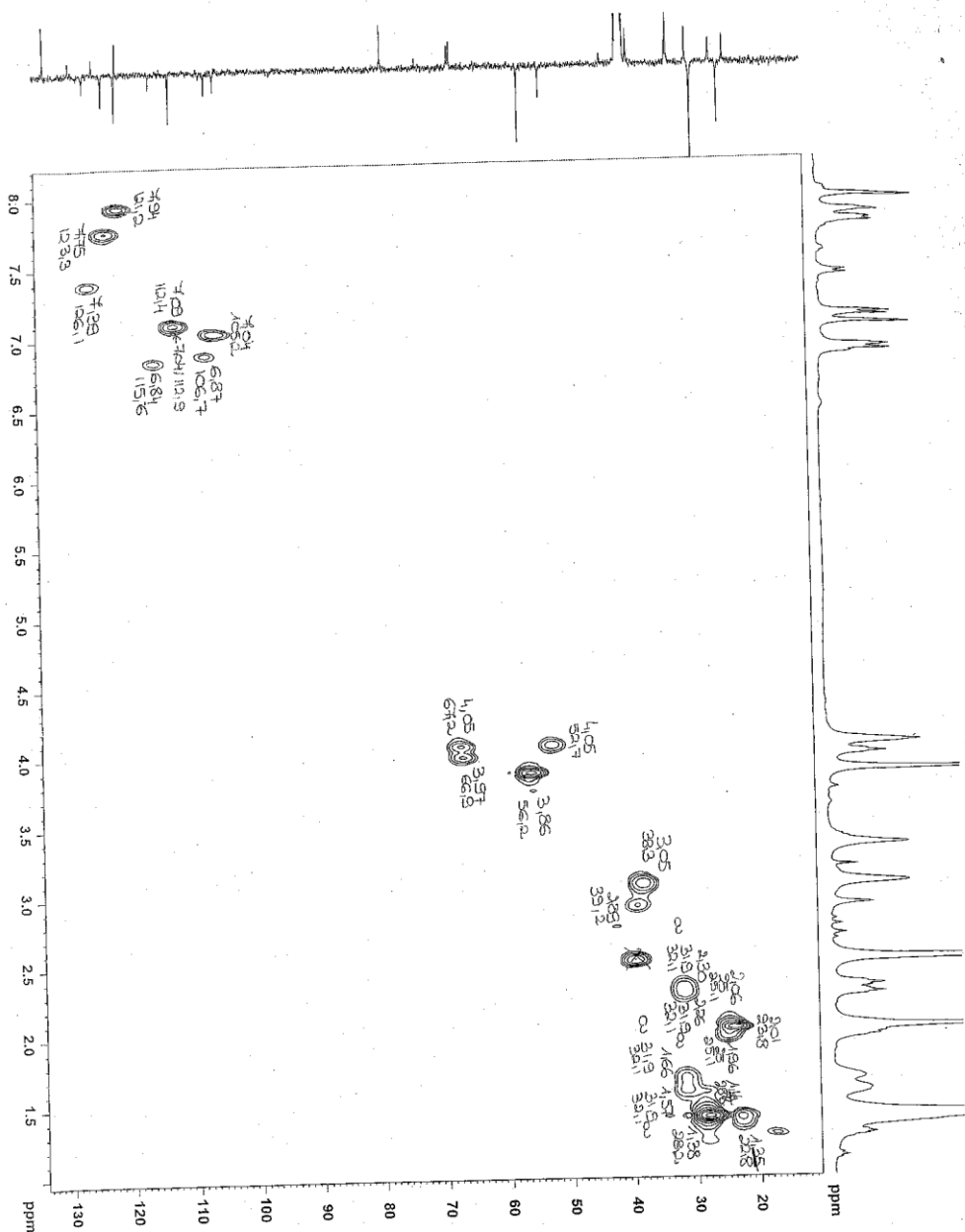
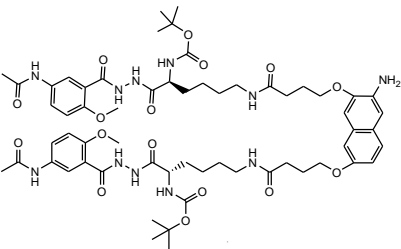


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Molecular tong 8



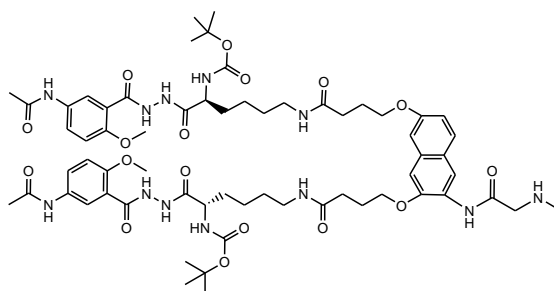
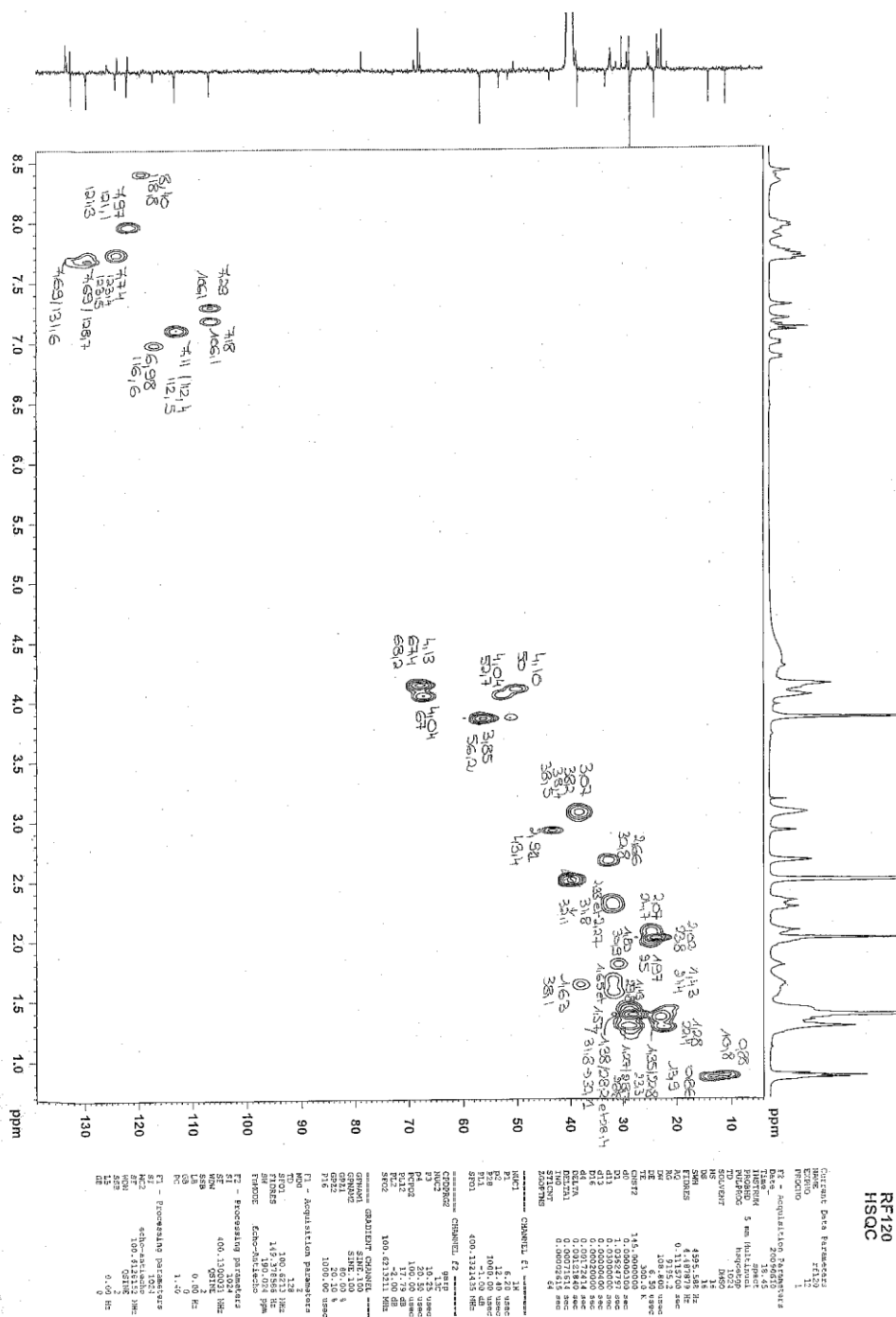
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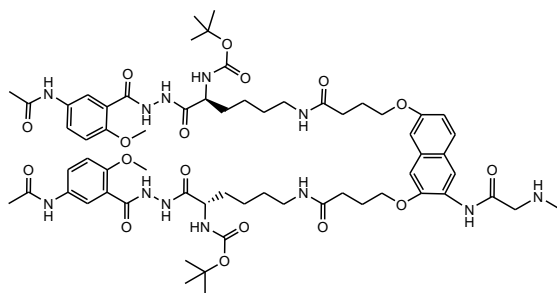
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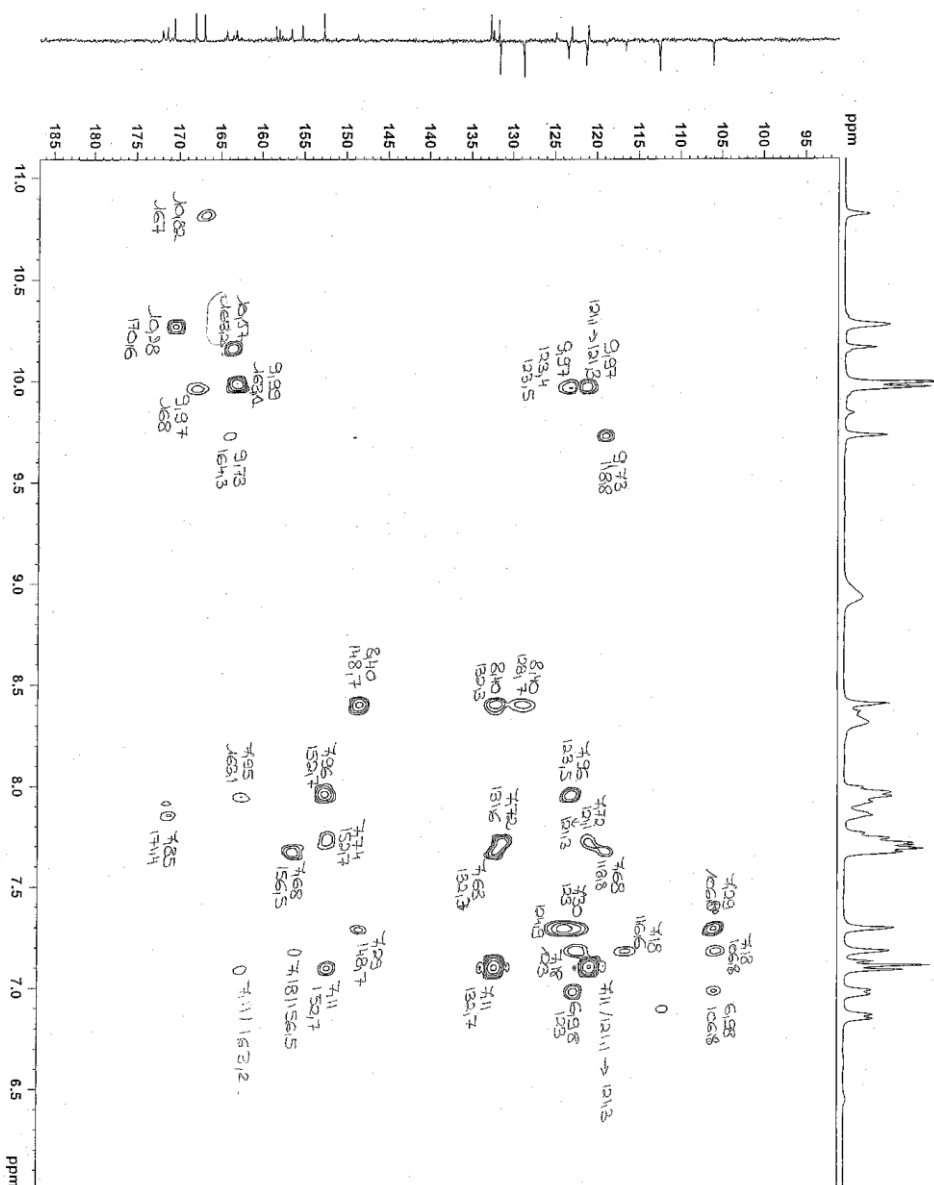


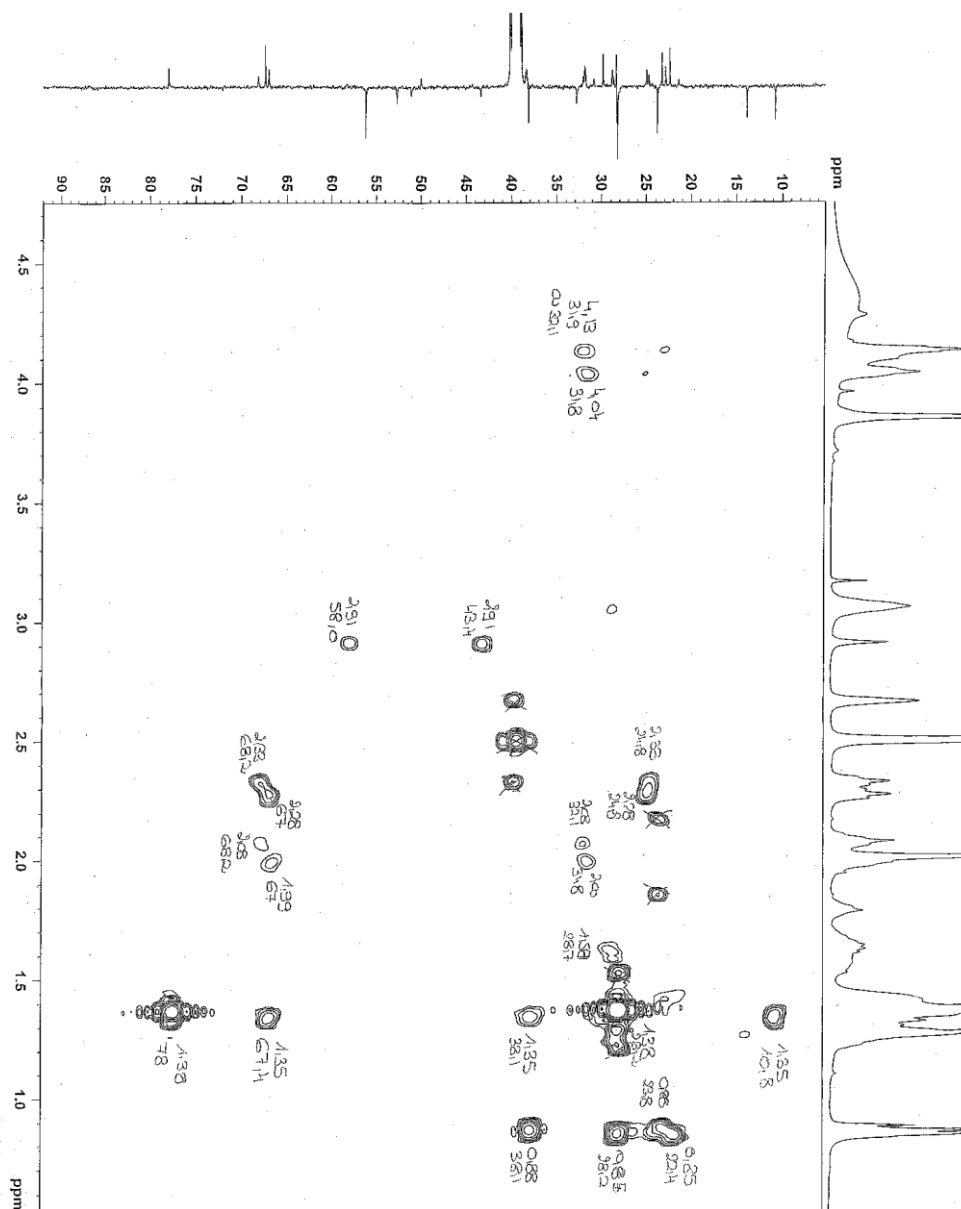
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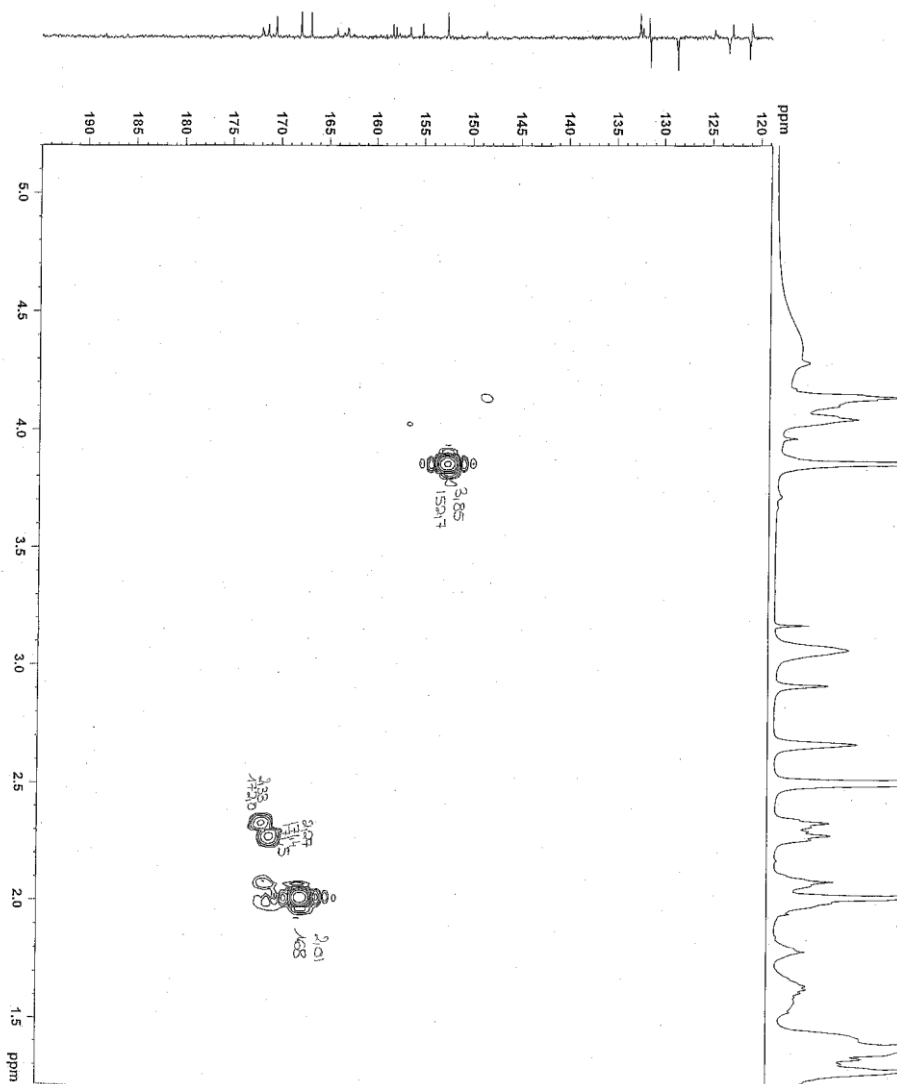
Molecular tong **9**



Molecular tong 9

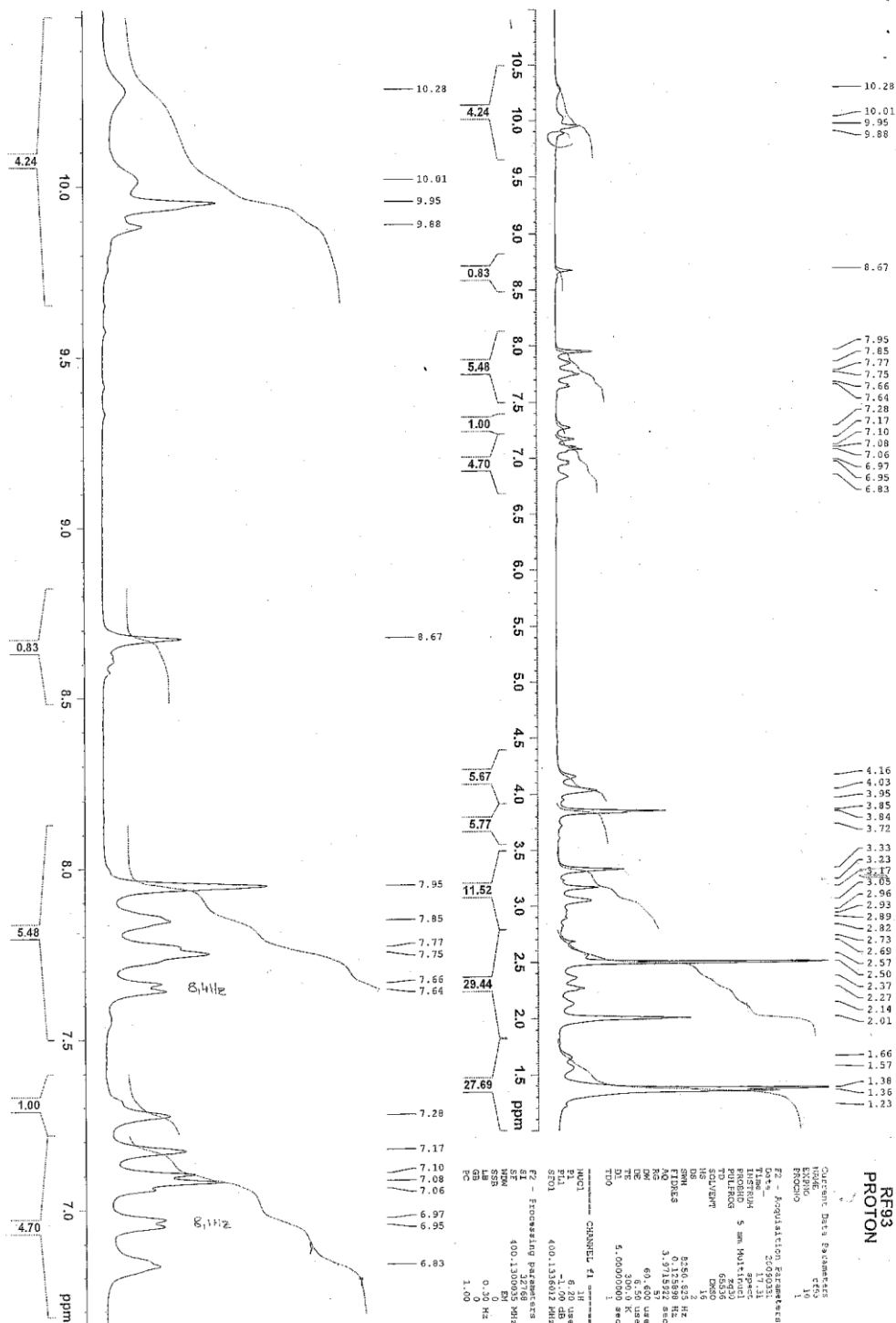
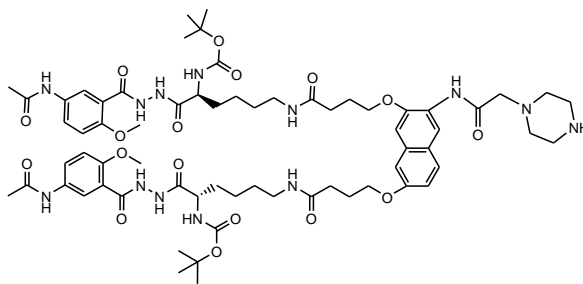
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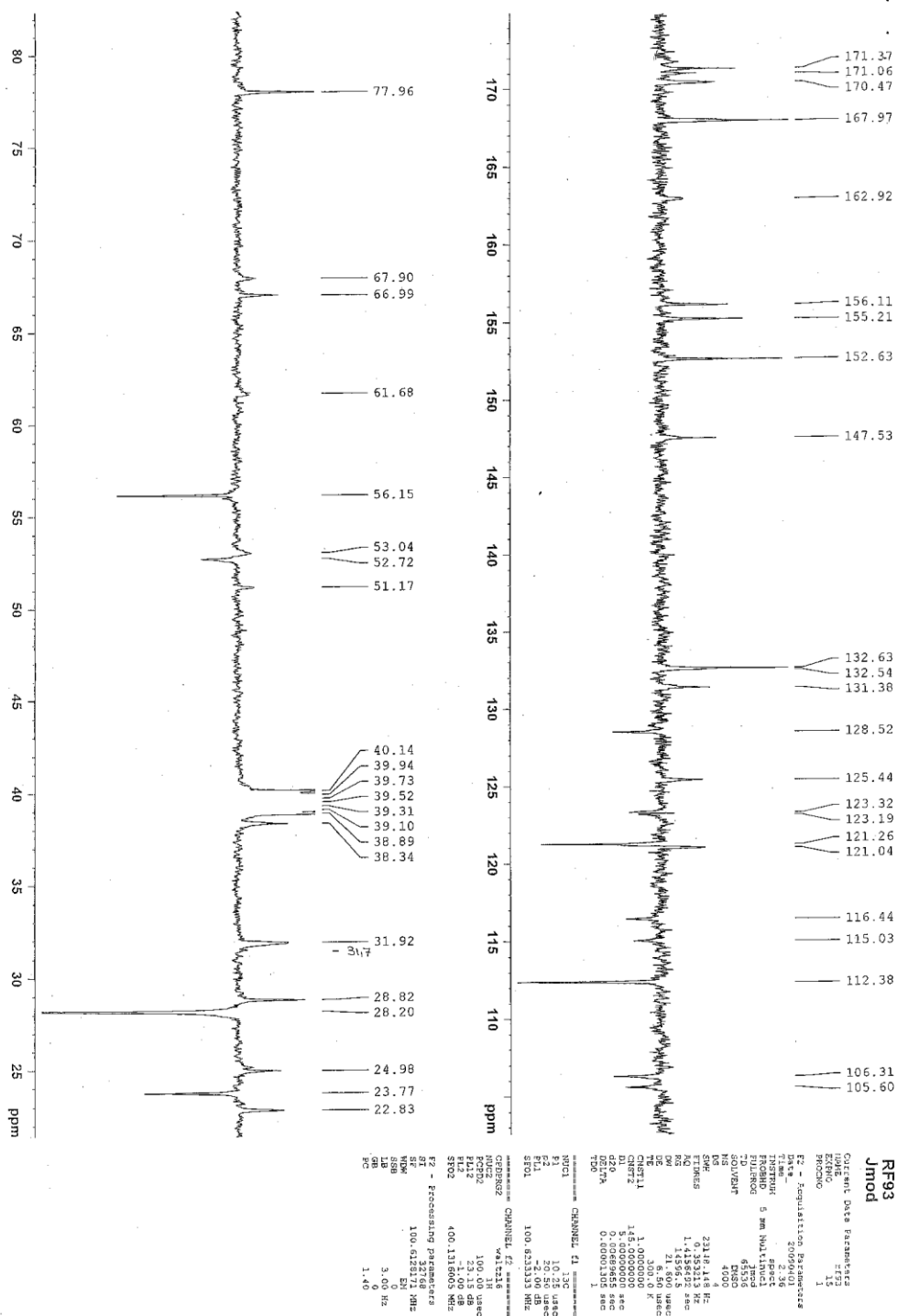
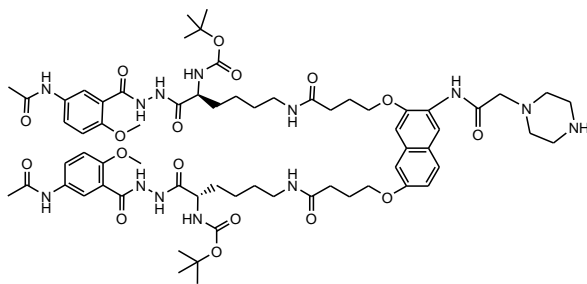
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HMBC

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W3	1.0	1.0
W4	1.0	1.0
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W8	1.0	1.0
W9	1.0	1.0
W10	1.0	1.0
W11	1.0	1.0
W12	1.0	1.0
W13	1.0	1.0
W14	1.0	1.0
W15	1.0	1.0
W16	1.0	1.0
W17	1.0	1.0
W18	1.0	1.0
W19	1.0	1.0
W20	1.0	1.0
W21	1.0	1.0
W22	1.0	1.0
W23	1.0	1.0
W24	1.0	1.0
W25	1.0	1.0
W26	1.0	1.0
W27	1.0	1.0
W28	1.0	1.0
W29	1.0	1.0
W30	1.0	1.0
W31	1.0	1.0
W32	1.0	1.0
W33	1.0	1.0
W34	1.0	1.0
W35	1.0	1.0
W36	1.0	1.0
W37	1.0	1.0
W38	1.0	1.0
W39	1.0	1.0
W40	1.0	1.0
W41	1.0	1.0
W42	1.0	1.0
W43	1.0	1.0
W44	1.0	1.0
W45	1.0	1.0
W46	1.0	1.0
W47	1.0	1.0
W48	1.0	1.0
W49	1.0	1.0
W50	1.0	1.0
W51	1.0	1.0
W52	1.0	1.0
W53	1.0	1.0
W54	1.0	1.0
W55	1.0	1.0
W56	1.0	1.0
W57	1.0	1.0
W58	1.0	1.0
W59	1.0	1.0
W60	1.0	1.0
W61	1.0	1.0
W62	1.0	1.0
W63	1.0	1.0
W64	1.0	1.0
W65	1.0	1.0
W66	1.0	1.0
W67	1.0	1.0
W68	1.0	1.0
W69	1.0	1.0
W70	1.0	1.0
W71	1.0	1.0
W72	1.0	1.0
W73	1.0	1.0
W74	1.0	1.0
W75	1.0	1.0
W76	1.0	1.0
W77	1.0	1.0
W78	1.0	1.0
W79	1.0	1.0
W80	1.0	1.0
W81	1.0	1.0
W82	1.0	1.0
W83	1.0	1.0
W84	1.0	1.0
W85	1.0	1.0
W86	1.0	1.0
W87	1.0	1.0
W88	1.0	1.0
W89	1.0	1.0
W90	1.0	1.0
W91	1.0	1.0
W92	1.0	1.0
W93	1.0	1.0
W94	1.0	1.0
W95	1.0	1.0
W96	1.0	1.0
W97	1.0	1.0
W98	1.0	1.0
W99	1.0	1.0
W100	1.0	1.0
W101	1.0	1.0
W102	1.0	1.0
W103	1.0	1.0
W104	1.0	1.0
W105	1.0	1.0
W106	1.0	1.0
W107	1.0	1.0
W108	1.0	1.0
W109	1.0	1.0
W110	1.0	1.0
W111	1.0	1.0
W112	1.0	1.0
W113	1.0	1.0
W114	1.0	1.0
W115	1.0	1.0
W116	1.0	1.0
W117	1.0	1.0
W118	1	

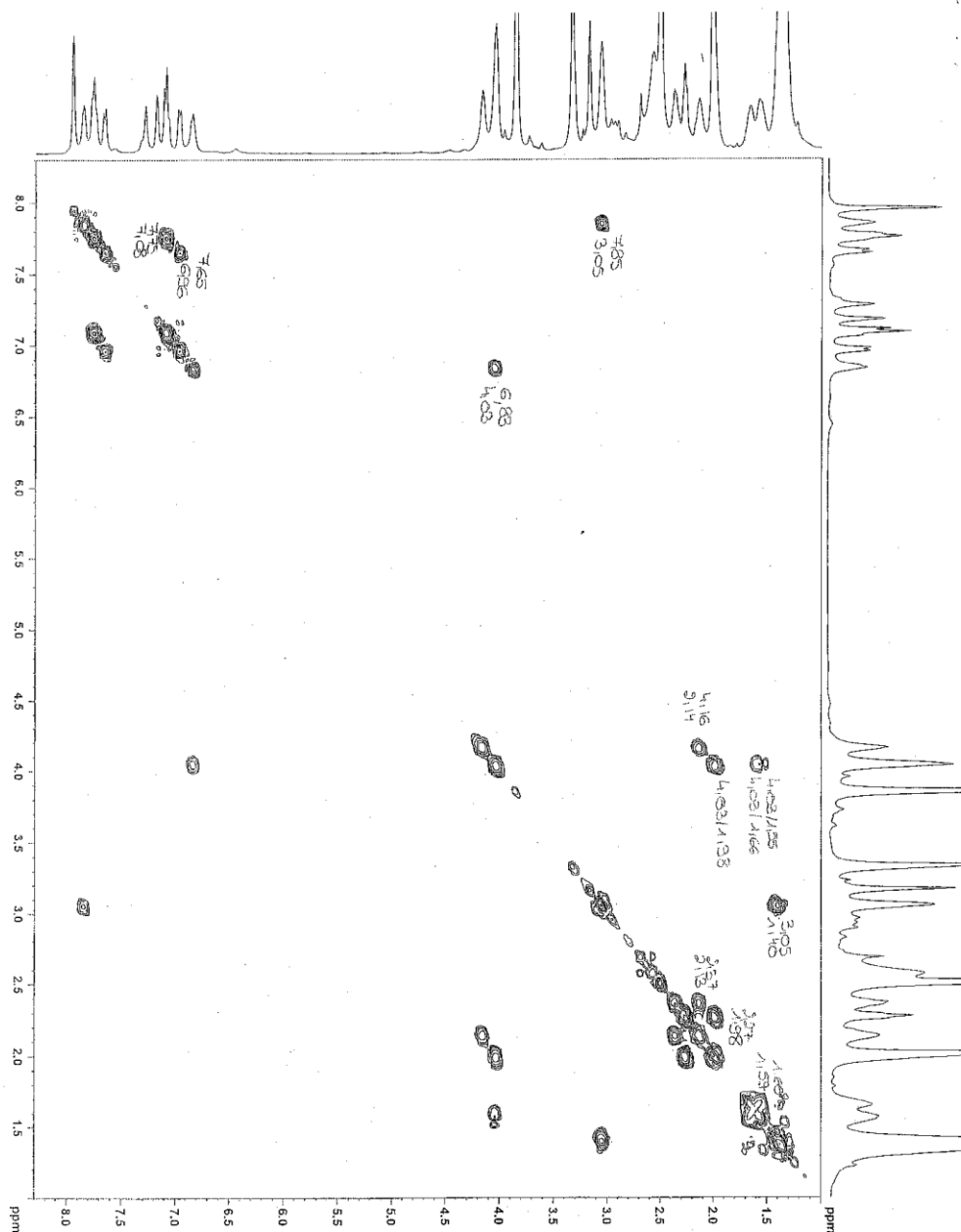
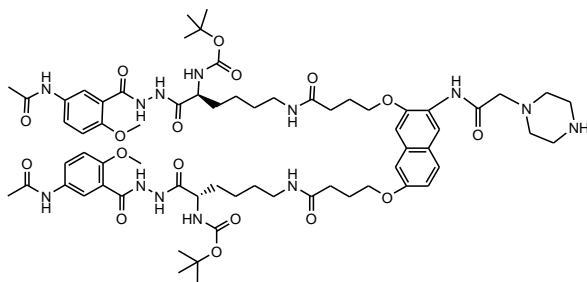
Molecular tong 11



Molecular tong 11



Molecular tong 11



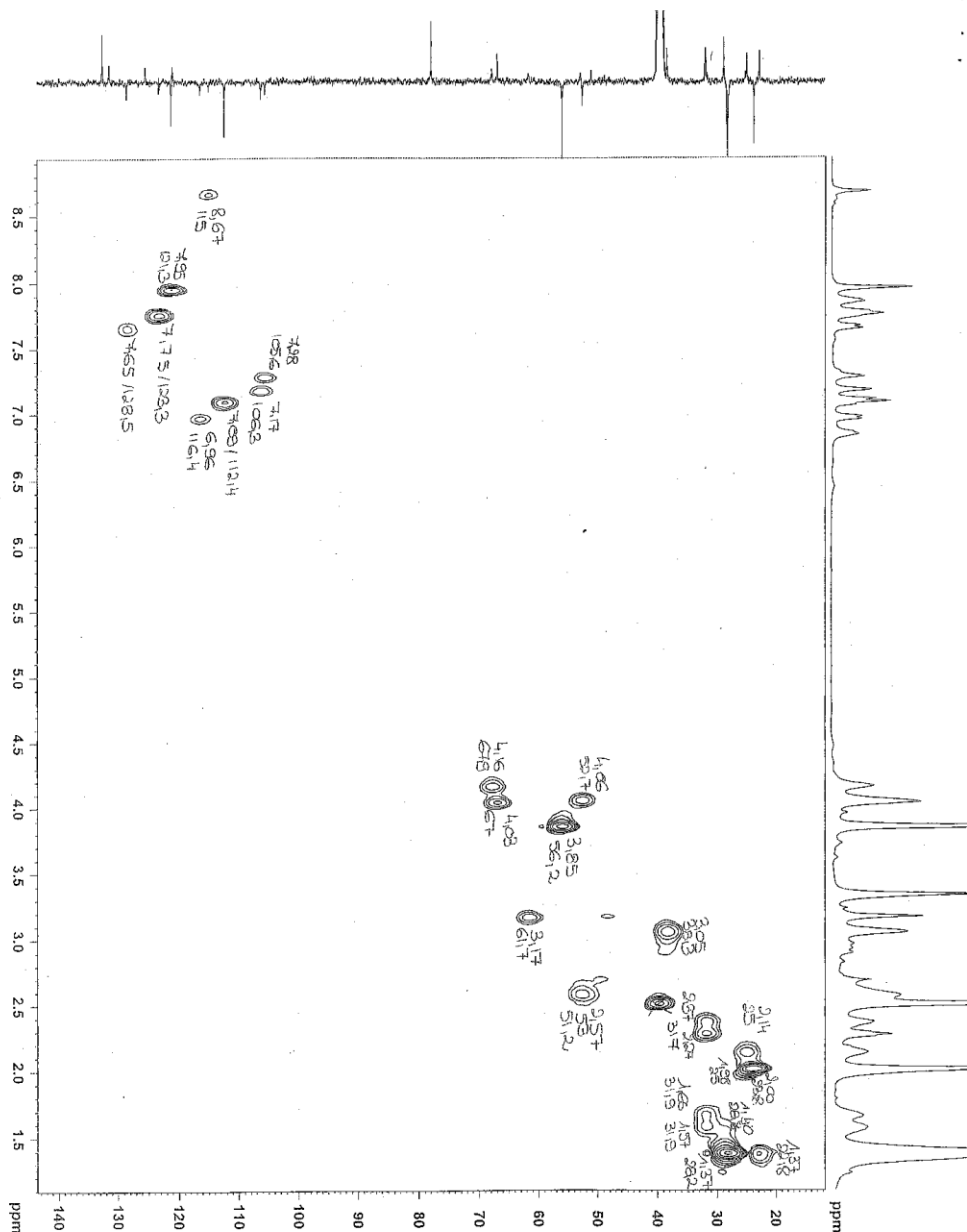
RF93
COSY

Current Data Parameters
Name: RF93
Date: 11/13/2010
Time: 11:13
Pulse: zgpg30
F2 - Acquisition Parameters
Date_UTC: 11/13/2010
Time: 11:13
F2 - Processing parameters
SI: 32768
SF: 400.1300615 MHz
WDW: EM
SSB: 0
LB: 0.60 Hz
GB: 0
PC: 1.10

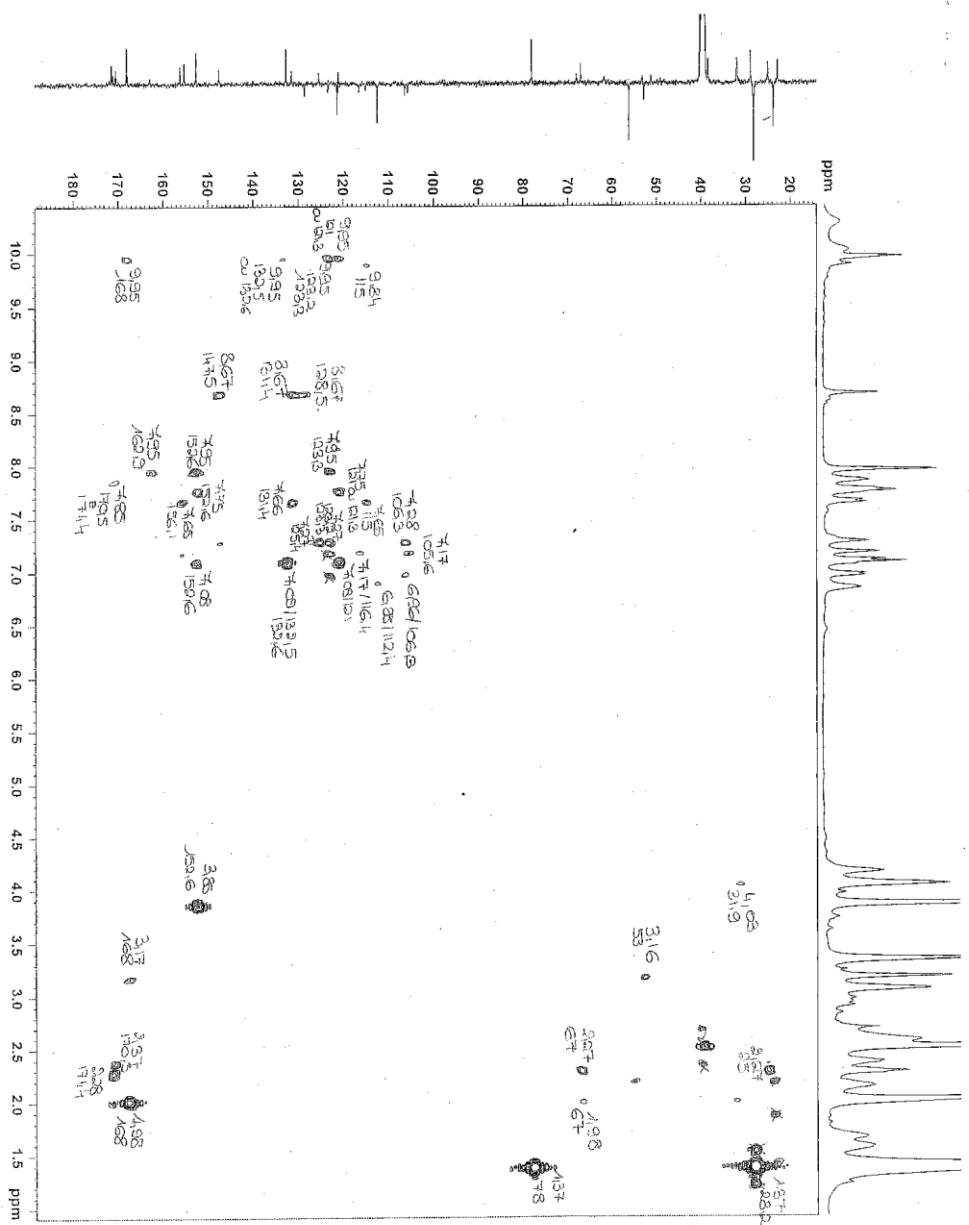
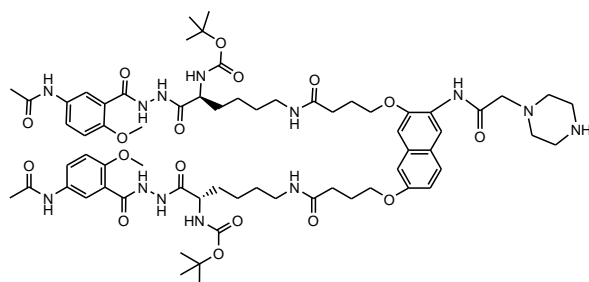
F1 - Processing parameters
SI: 32768
SF: 400.1300615 MHz
WDW: EM
SSB: 0
LB: 0.60 Hz
GB: 0
PC: 1.10

F2 - Acquisition Parameters
Date_UTC: 11/13/2010
Time: 11:13
F2 - Processing parameters
SI: 32768
SF: 400.1300615 MHz
WDW: EM
SSB: 0
LB: 0.60 Hz
GB: 0
PC: 1.10

F1 - Processing parameters
SI: 32768
SF: 400.1300615 MHz
WDW: EM
SSB: 0
LB: 0.60 Hz
GB: 0
PC: 1.10

[illegible]

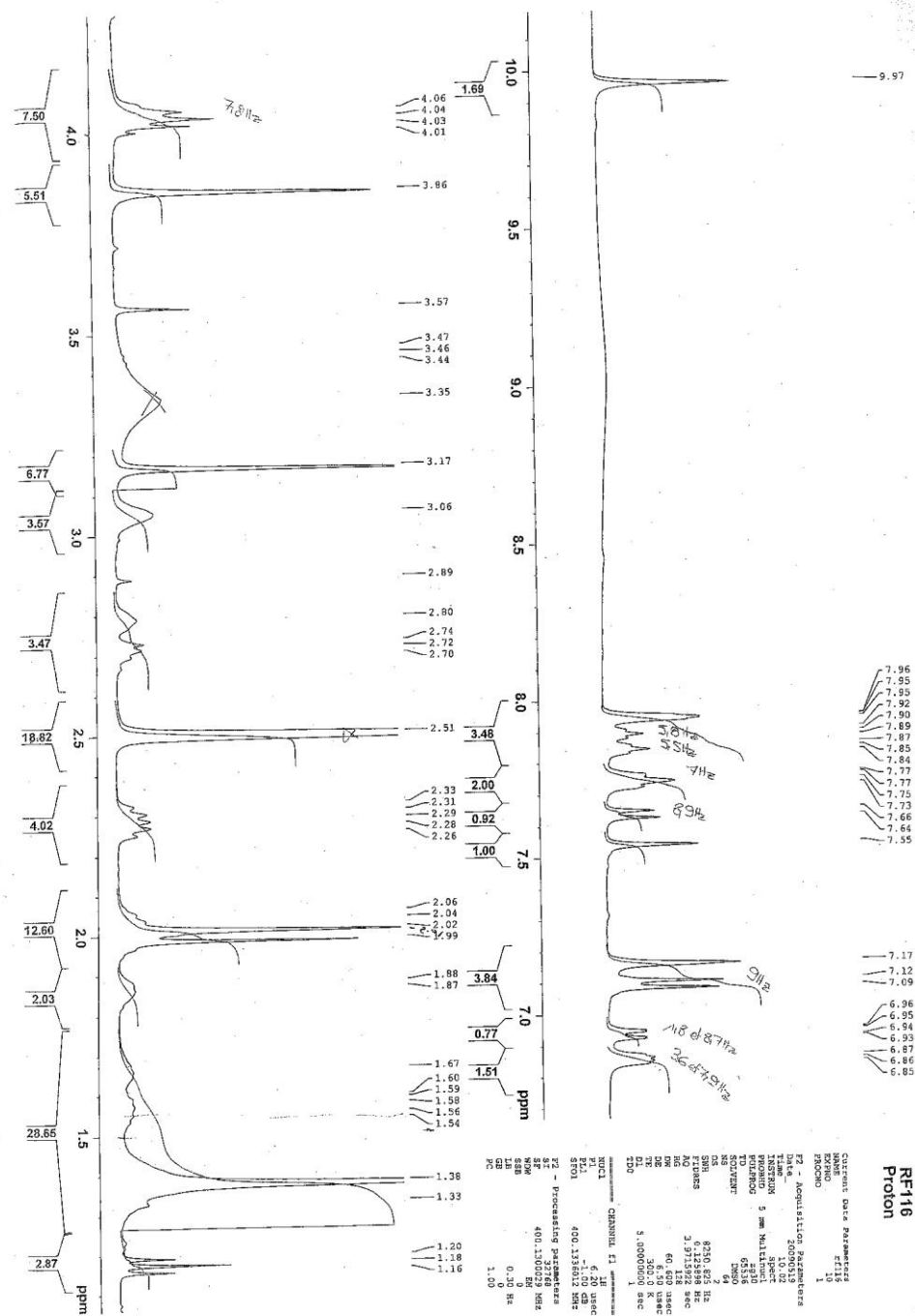
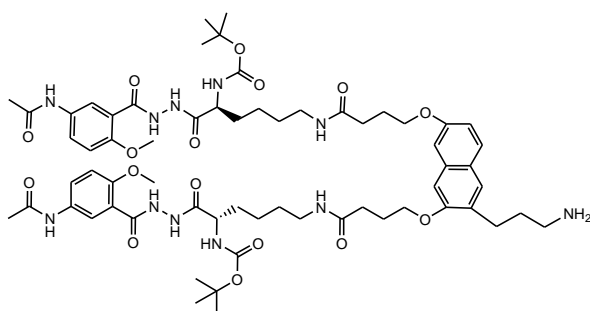
Molecular tong 11



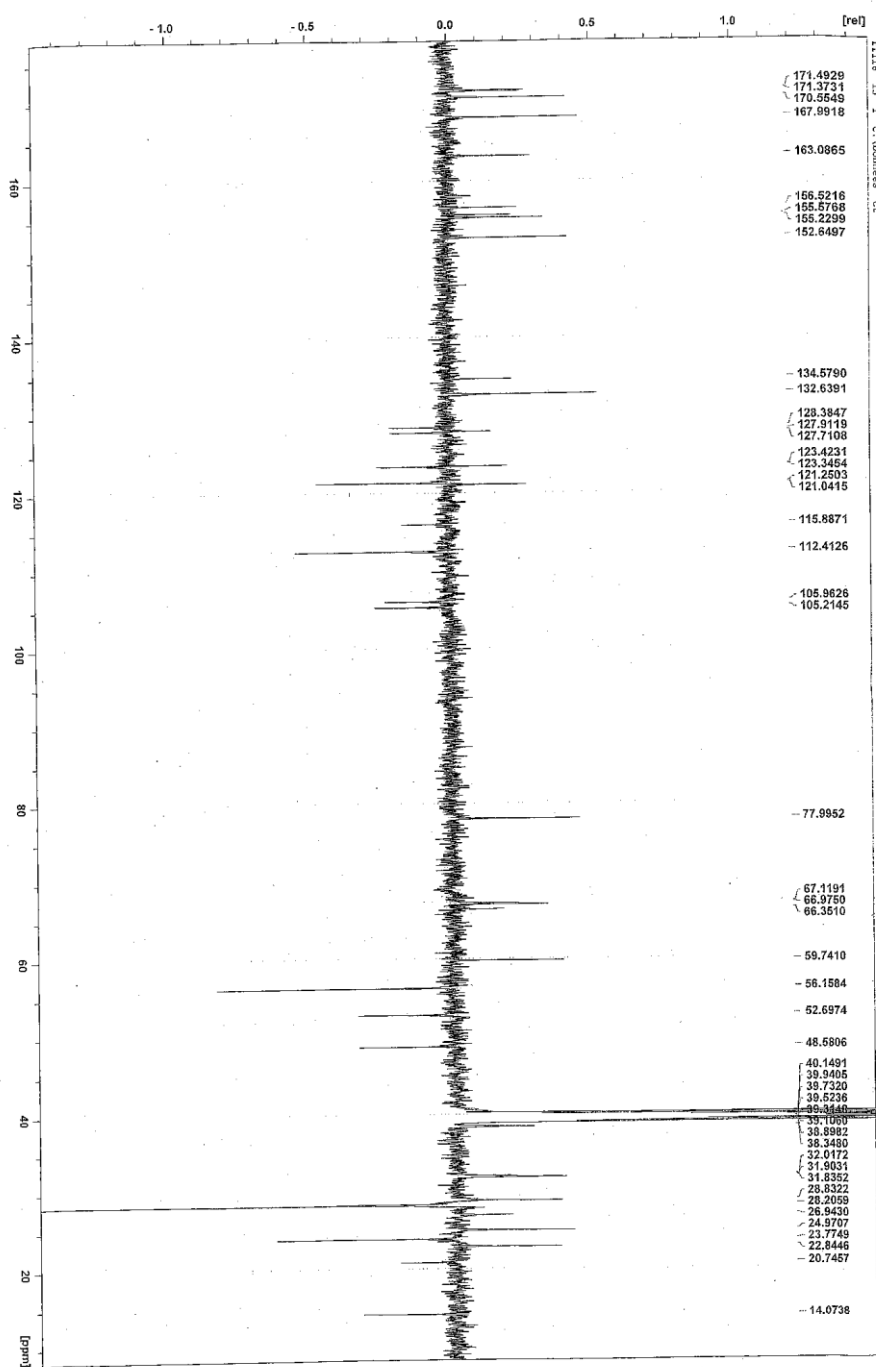
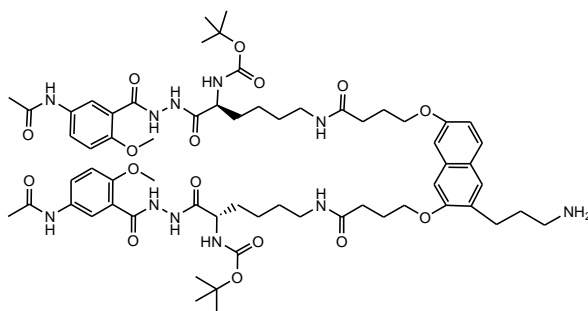
RF83
HMBC

NAME: 11
EXPNO: 1
PROCNO: 1
F2 - Acquisition Parameters
Date_: 20090211
Time: 10.00
INSTRUM: spect
PROBHD: 5 mm HLLHNP1
PULPROG: zgpg30
TD: 65536
SOLVENT: DMSO
NDC: 1
DE: 1.00
FIDRES: 0.114600 Hz
AQ: 4.391002 Hz
RG: 131.200
DM: 6.50
DC: 3.000000 Hz
F2 - Processing parameters
SI: 32768
SF: 400.146000 MHz
WDW: EM
SSB: 0.00 Hz
GB: 0.00
PC: 1.46
F1 - Processing parameters
SI: 32768
SF: 100.626126 MHz
WDW: EM
SSB: 0.00 Hz
GB: 0.00
PC: 1.46

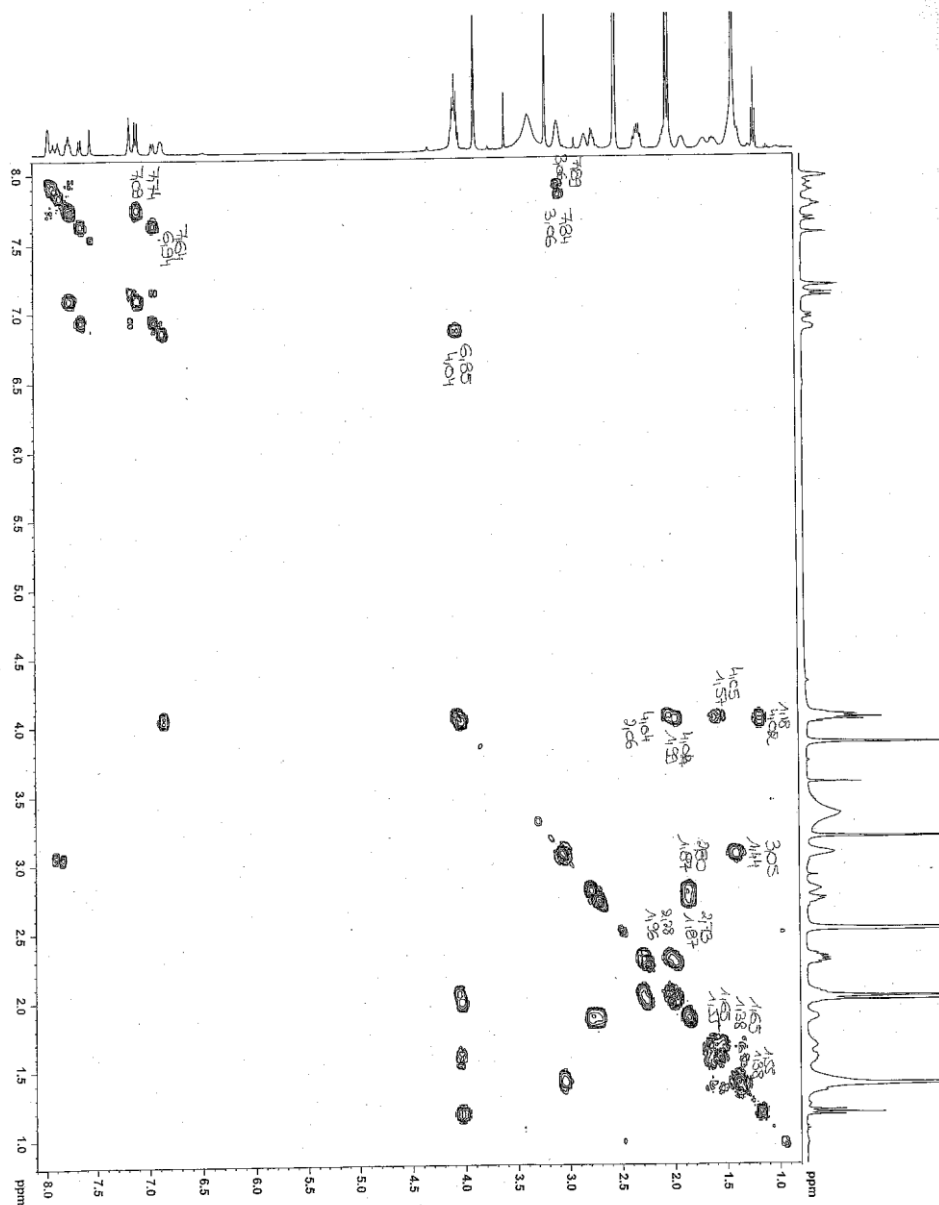
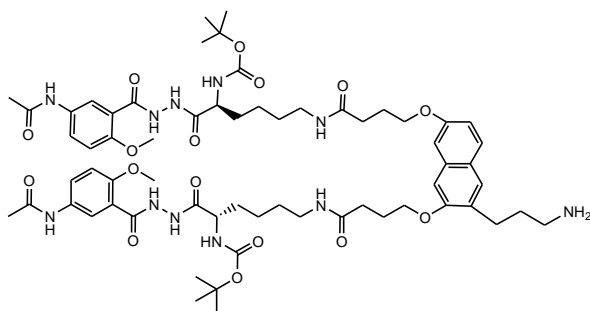
Molecular tong 12



Molecular tong 12

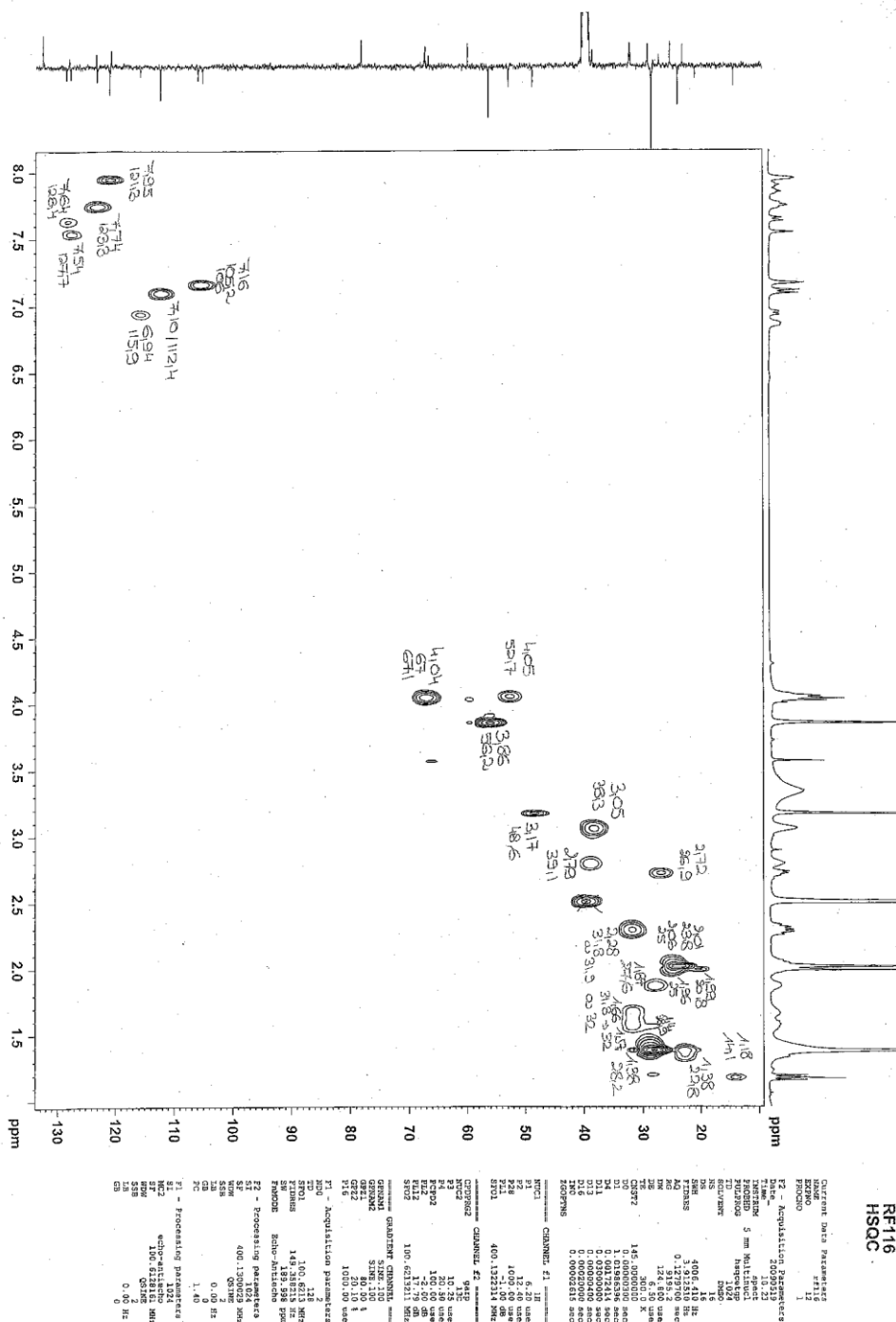


Molecular tong 12



RF116
COSY

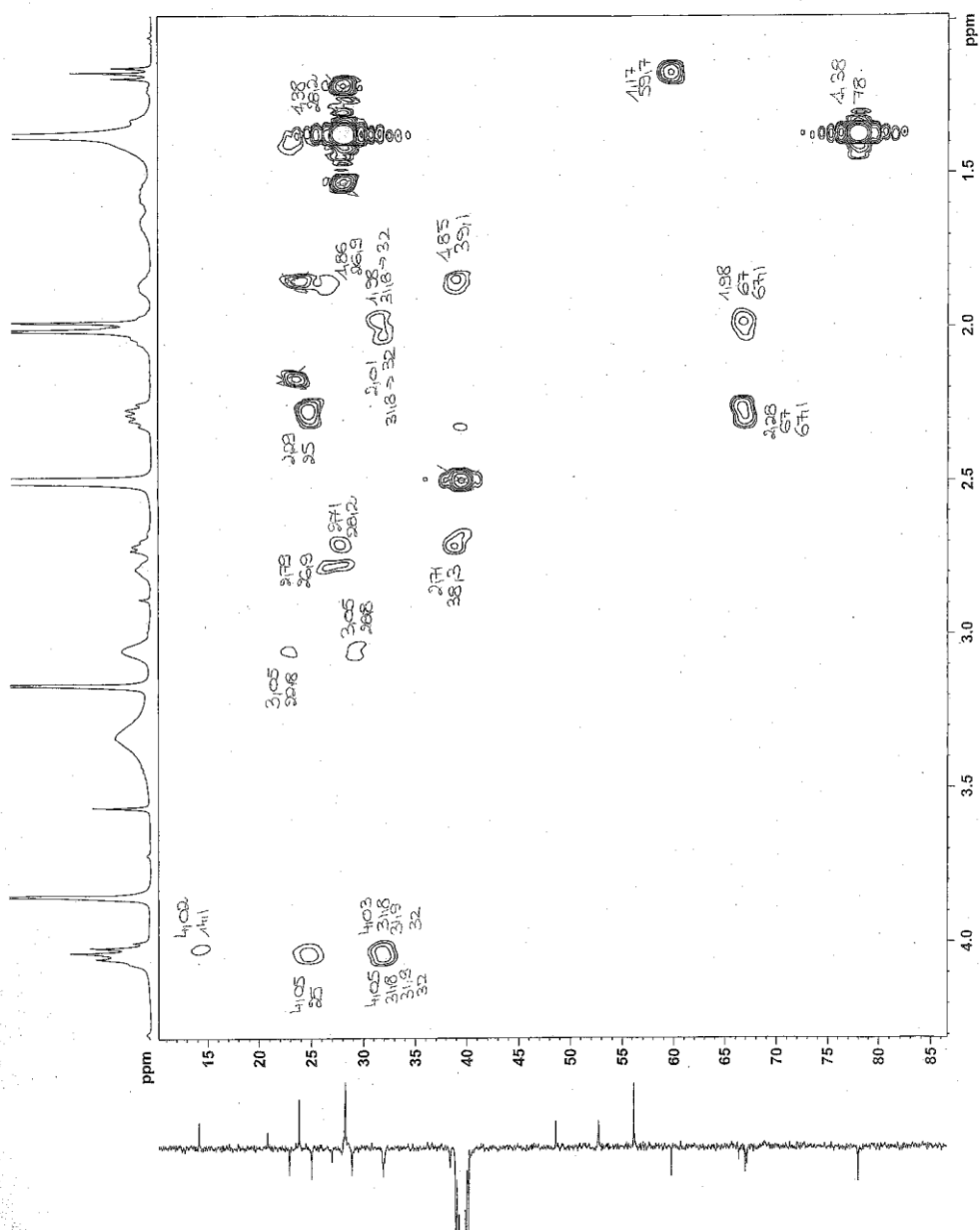
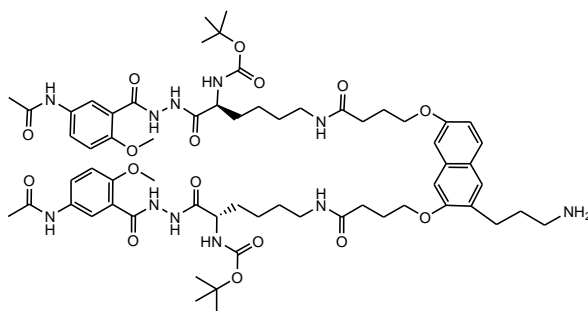
Current Data Parameters
NAME: rf116
EXPNO: 1
PROCNO: 1
Date_: 20080919
Time: 10.00
INSTRUM: spect
PROBHD: 5 mm Maltipul
TD: 65536
SOLVENT: DMSO
DMSO
DS: 4
F2 - Acquisition Parameters
Date_: 20080919
Time: 10.00
INSTRUM: spect
PROBHD: 5 mm Maltipul
TD: 65536
SOLVENT: DMSO
DMSO
DS: 4
F2 - Processing parameters
SI: 32768
SF: 400.136059 MHz
WDW: EM
SSB: 0
GB: 0
PC: 1.10
F2 - Acquisition parameters
SI: 32768
SF: 400.136059 MHz
WDW: EM
SSB: 0
GB: 0
PC: 1.10
F2 - Processing parameters
SI: 32768
SF: 400.136059 MHz
WDW: EM
SSB: 0
GB: 0
PC: 1.10
F2 - Acquisition parameters
SI: 32768
SF: 400.136059 MHz
WDW: EM
SSB: 0
GB: 0
PC: 1.10

CC(=O)Nc1ccc2c(c1)oc(=O)[nH]c2NC(=O)N[C@@H](CCCCNC(=O)CCOC3=CC=CC=C4C(=C3)C=C(C=C4)CCCN)C(=O)OC(C)(C)C

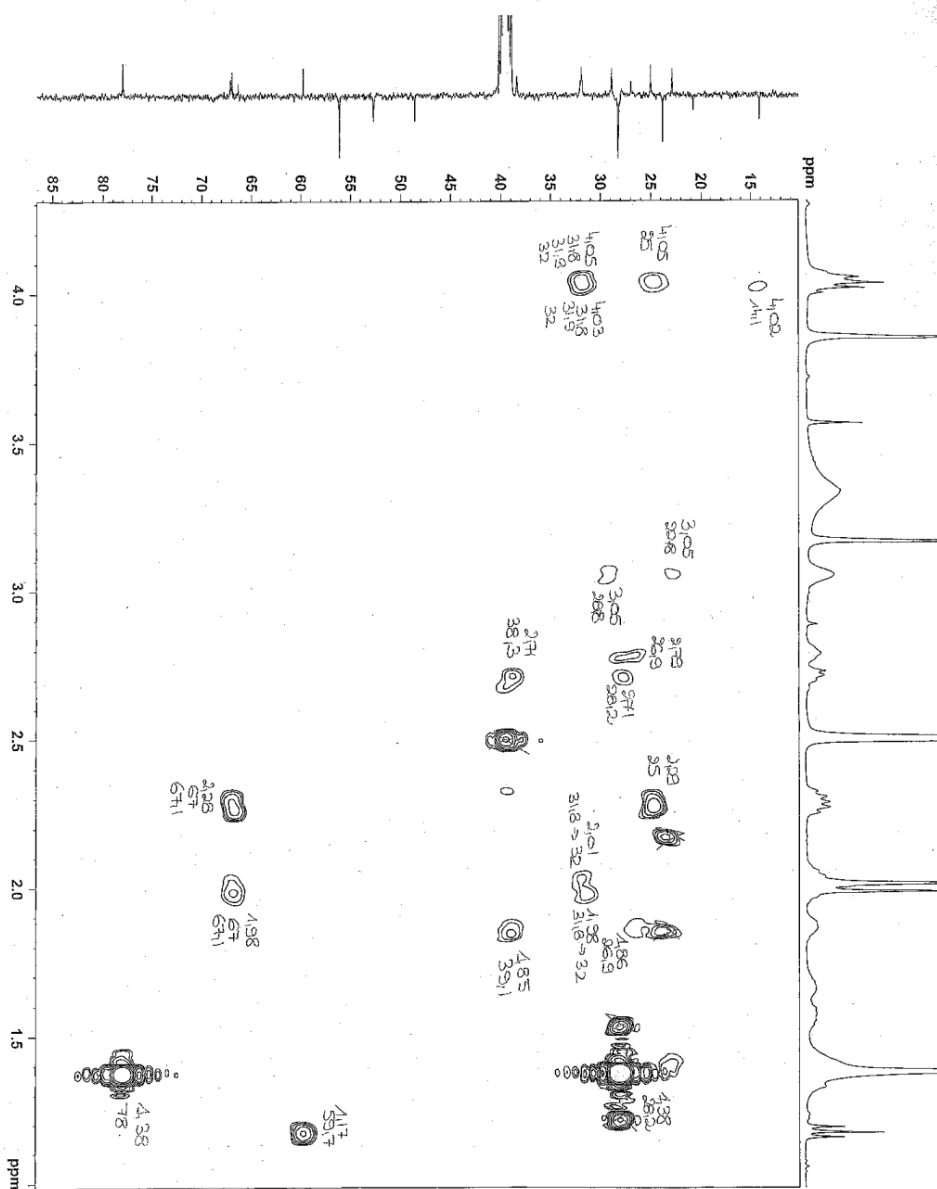
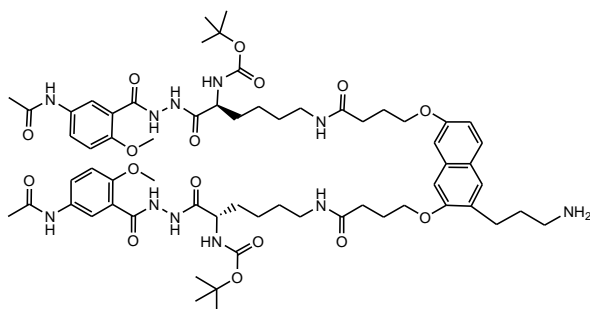
Molecular tong 12

RF116
HMBC

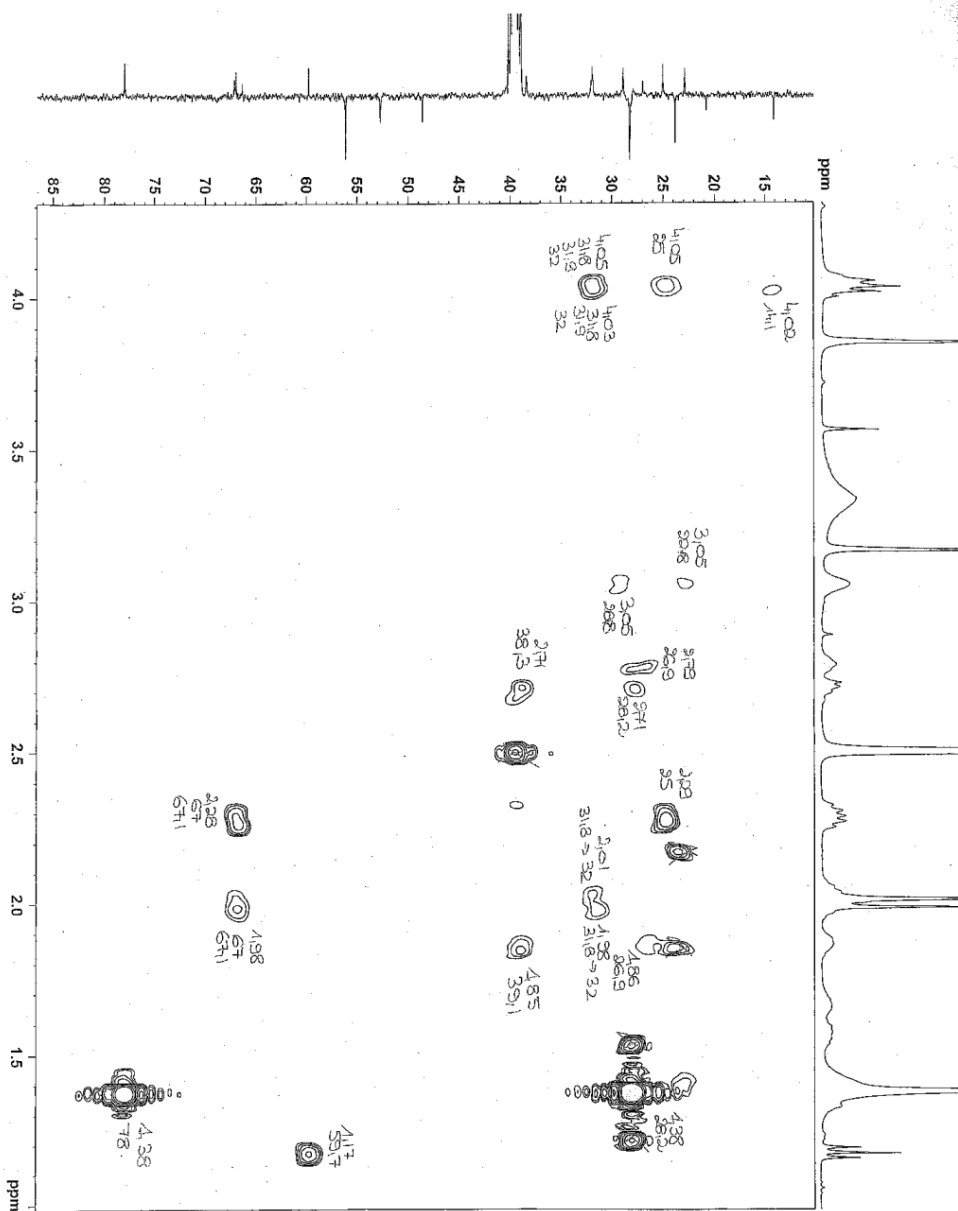
Current Data Parameters
Date_ 20050514
Time_ 11:13
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20050514
Time_ 11:13
INSTRUM spect
PROBHD 5 mm Hainbow
PULPROG zgpg30
FIDRES 1024
AQ 0.129700 sec
RG 327.50
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 1624
SF 400.139000 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40
F2 - Acquisition Parameters
Date_ 20050514
Time_ 11:13
INSTRUM spect
PROBHD 5 mm Hainbow
PULPROG zgpg30
FIDRES 1024
AQ 0.129700 sec
RG 327.50
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40
F1 - Processing parameters
SI 1624
SF 400.139000 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.40



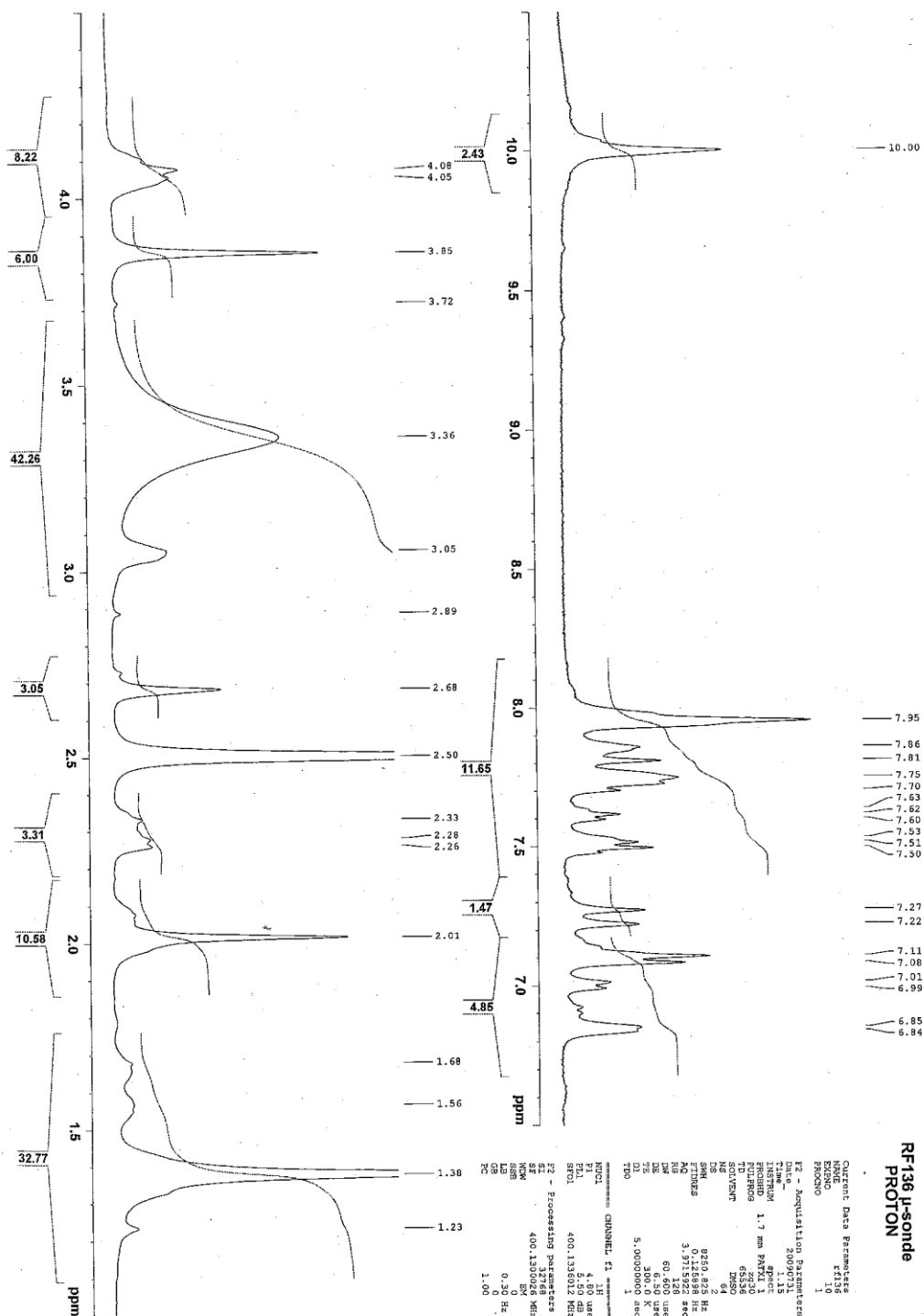
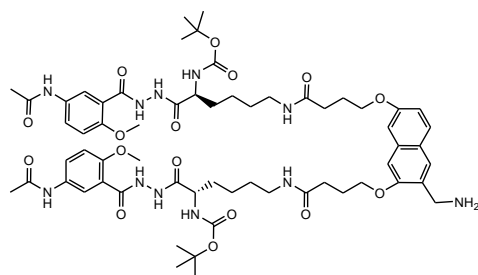
Molecular tong 12

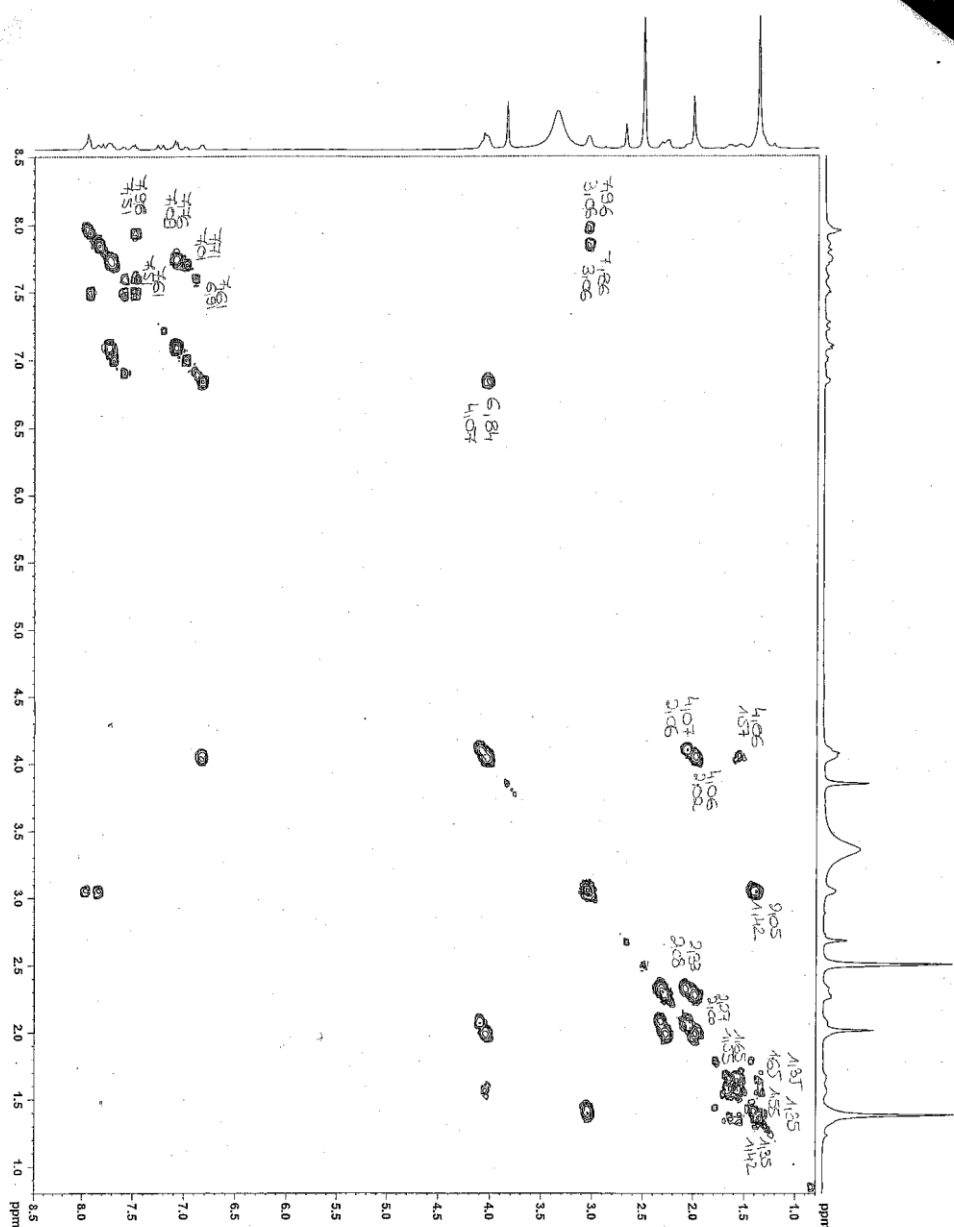


Experiment Data Parameters
NAME: RF116
EXPNO: 1
PROCNO: 1
F2 - Acquisition Parameters
Date_ : 201104
Time : 11.04
PROBHD: 5 mm HX113mm1
PULPROG: hmcgcp-1purg
SOLVENT: DMSO
NS: 16
DS: 16
SWH: 4006.412 Hz
AQ: 0.1279703 sec
RG: 1939.4 Hz
DE: 6.35 umic
TE: 300.2 K
CHRG2: 7.6993998 sec
D1: 0.0034482 sec
D2: 0.0034482 sec
D3: 0.0034482 sec
D16: 0.0002000 sec
D10: 0.0002160 sec
F1 - Acquisition Parameters
Date_ : 201104
Time : 11.04
PROBHD: 5 mm HX113mm1
PULPROG: hmcgcp-1purg
SOLVENT: DMSO
NS: 16
DS: 16
SWH: 4006.412 Hz
AQ: 0.1279703 sec
RG: 1939.4 Hz
DE: 6.35 umic
TE: 300.2 K
CHRG2: 7.6993998 sec
D1: 0.0034482 sec
D2: 0.0034482 sec
D3: 0.0034482 sec
D16: 0.0002000 sec
D10: 0.0002160 sec
F2 - Processing parameters
SI: 16224
SF: 100.613000 MHz
WDW: SINC
SSB: 0.0 Hz
GB: 0

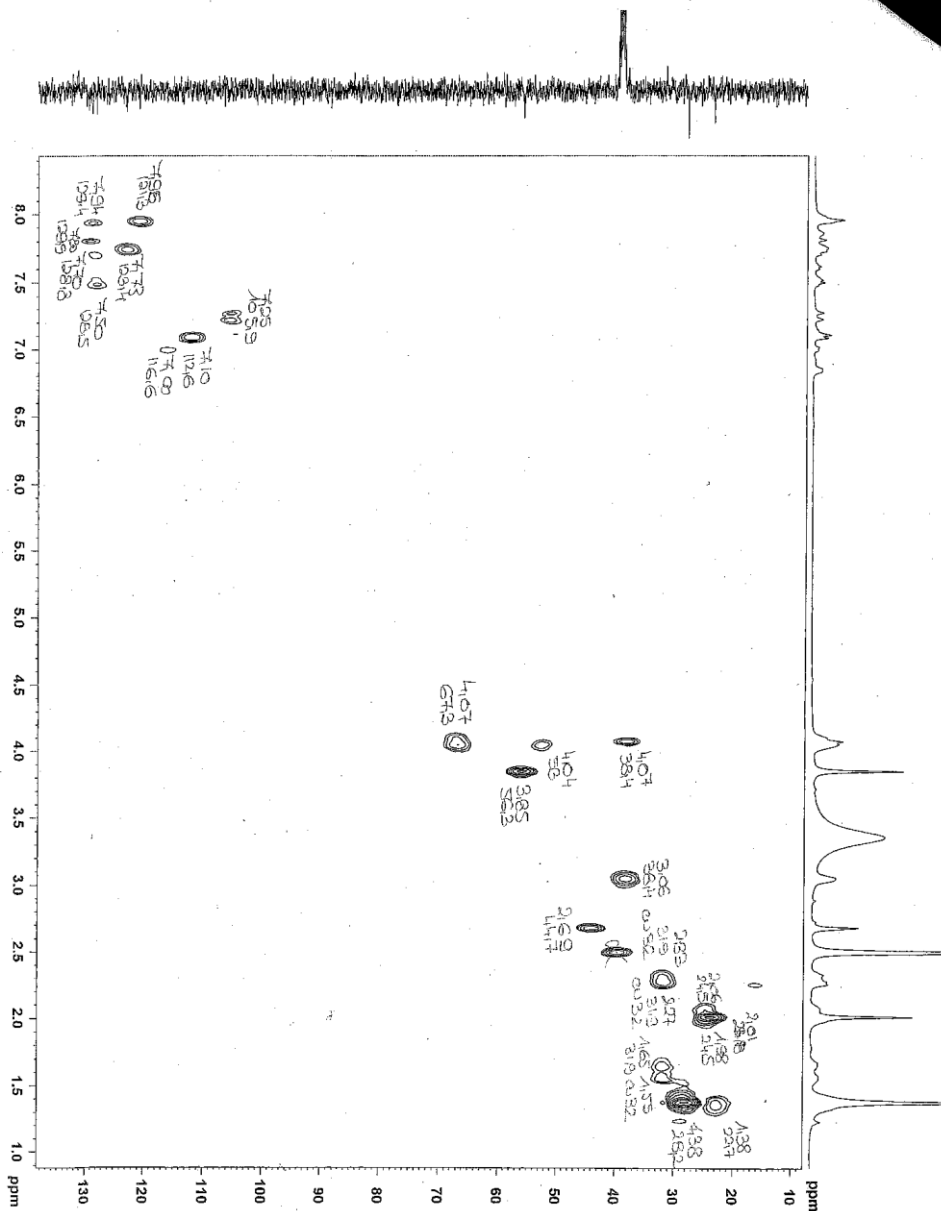
CC(=O)Nc1ccc2c(c1)oc(=O)[nH]c2NC(=O)N[C@@H](CCCCNC(=O)CCOC3=CC=CC=C4C(=C3)C=C(C=C4)CCCN)C(=O)OC(C)(C)C[illegible]

Molecular tong 14

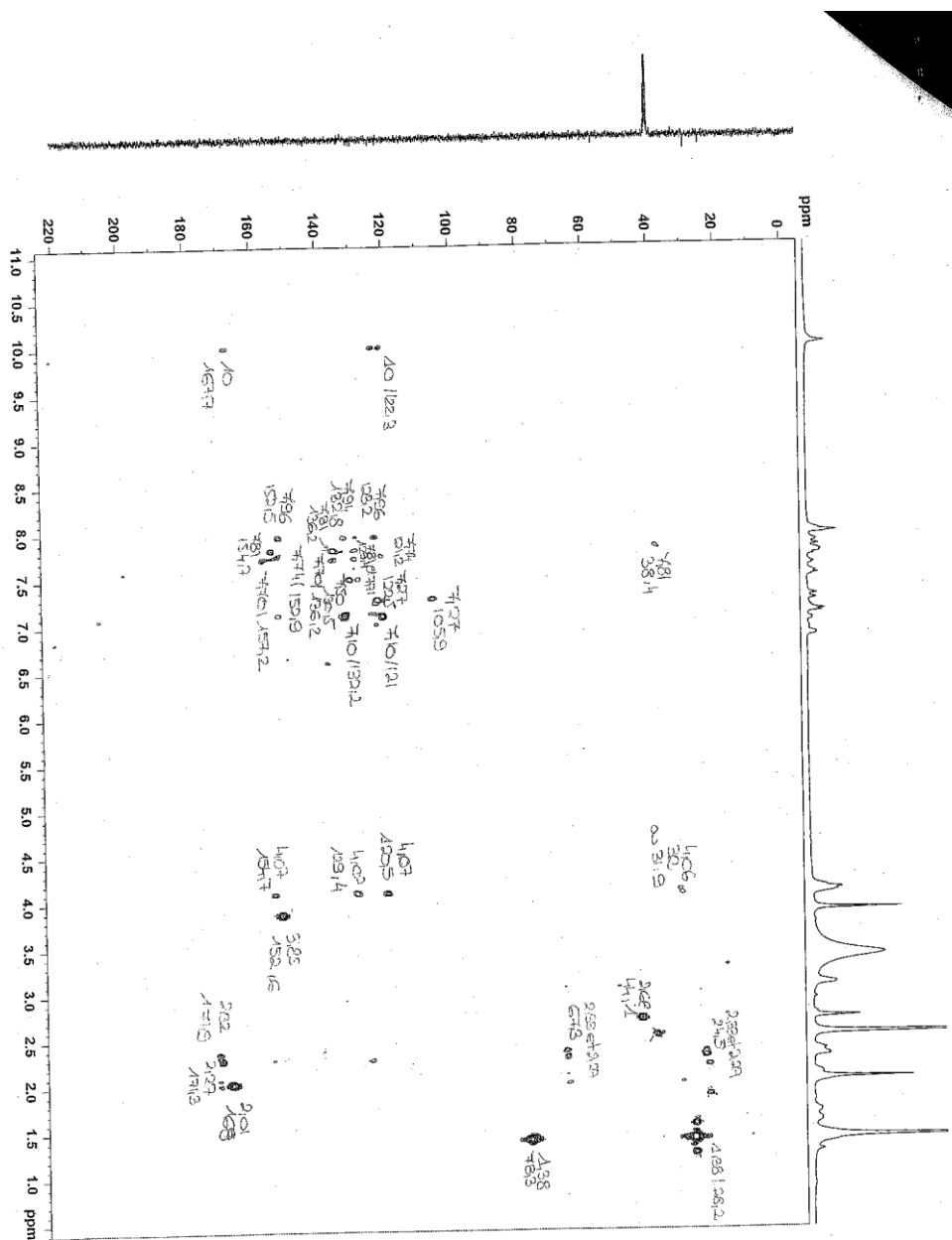
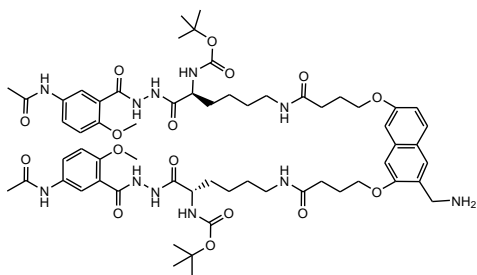


CC(=O)Nc1ccc2c(c1)c(=O)[nH]c2Oc3ccc(NC(=O)N[C@@H](C(C)C)CCCCNC(=O)OCCCCOc4ccc5ccccc5o4)cc3RF136 μ -sonde
COSY

Current Data Parameters		F2 - Acquisition Parameters	
NAME	20090731	NAME	20090731
EXPNO	11	EXPNO	11
PROCNO	1	PROCNO	1
F1 - Processing Parameters		F2 - Acquisition Parameters	
SI - Processing Parameters		NAME	20090731
SI1	400.130024 MHz	EXPNO	11
SI2	1024	PROCNO	1
SI3	400.130024 MHz	NAME	20090731
SI4	SINE	EXPNO	11
SI5	0	PROCNO	1
SI6	0	NAME	20090731
SI7	0	EXPNO	11
SI8	0	PROCNO	1
SI9	0	NAME	20090731
SI10	0	EXPNO	11
SI11	0	PROCNO	1
SI12	0	NAME	20090731
SI13	0	EXPNO	11
SI14	0	PROCNO	1
SI15	0	NAME	20090731
SI16	0	EXPNO	11
SI17	0	PROCNO	1
SI18	0	NAME	20090731
SI19	0	EXPNO	11
SI20	0	PROCNO	1
SI21	0	NAME	20090731
SI22	0	EXPNO	11
SI23	0	PROCNO	1
SI24	0	NAME	20090731
SI25	0	EXPNO	11
SI26	0	PROCNO	1
SI27	0	NAME	20090731
SI28	0	EXPNO	11
SI29	0	PROCNO	1
SI30	0	NAME	20090731
SI31	0	EXPNO	11
SI32	0	PROCNO	1
SI33	0	NAME	20090731
SI34	0	EXPNO	11
SI35	0	PROCNO	1
SI36	0	NAME	20090731
SI37	0	EXPNO	11
SI38	0	PROCNO	1
SI39	0	NAME	20090731
SI40	0	EXPNO	11
SI41	0	PROCNO	1
SI42	0	NAME	20090731
SI43	0	EXPNO	11
SI44	0	PROCNO	1
SI45	0	NAME	20090731
SI46	0	EXPNO	11
SI47	0	PROCNO	1
SI48	0	NAME	20090731
SI49	0	EXPNO	11
SI50	0	PROCNO	1
SI51	0	NAME	20090731
SI52	0	EXPNO	11
SI53	0	PROCNO	1
SI54	0	NAME	20090731
SI55	0	EXPNO	11
SI56	0	PROCNO	1
SI57	0	NAME	20090731
SI58	0	EXPNO	11
SI59	0	PROCNO	1
SI60	0	NAME	20090731
SI61	0	EXPNO	11
SI62	0	PROCNO	1
SI63	0	NAME	20090731
SI64	0	EXPNO	11
SI65	0	PROCNO	1
SI66	0	NAME	20090731
SI67	0	EXPNO	11
SI68	0	PROCNO	1
SI69	0	NAME	20090731
SI70	0	EXPNO	11
SI71	0	PROCNO	1
SI72	0	NAME	20090731
SI73	0	EXPNO	11
SI74	0	PROCNO	1
SI75	0	NAME	20090731
SI76	0	EXPNO	11
SI77	0	PROCNO	1
SI78	0	NAME	20090731
SI79	0	EXPNO	11
SI80	0	PROCNO	1
SI81	0	NAME	20090731
SI82	0	EXPNO	11
SI83	0	PROCNO	1
SI84	0	NAME	20090731
SI85	0	EXPNO	11
SI86	0	PROCNO	1
SI87	0	NAME	20090731
SI88	0	EXPNO	11
SI89	0	PROCNO	1
SI90	0	NAME	20090731
SI91	0	EXPNO	11
SI92	0	PROCNO	1
SI93	0	NAME	20090731
SI94	0	EXPNO	11
SI95	0	PROCNO	1

RF136 μ -sonde
HSQC[illegible]

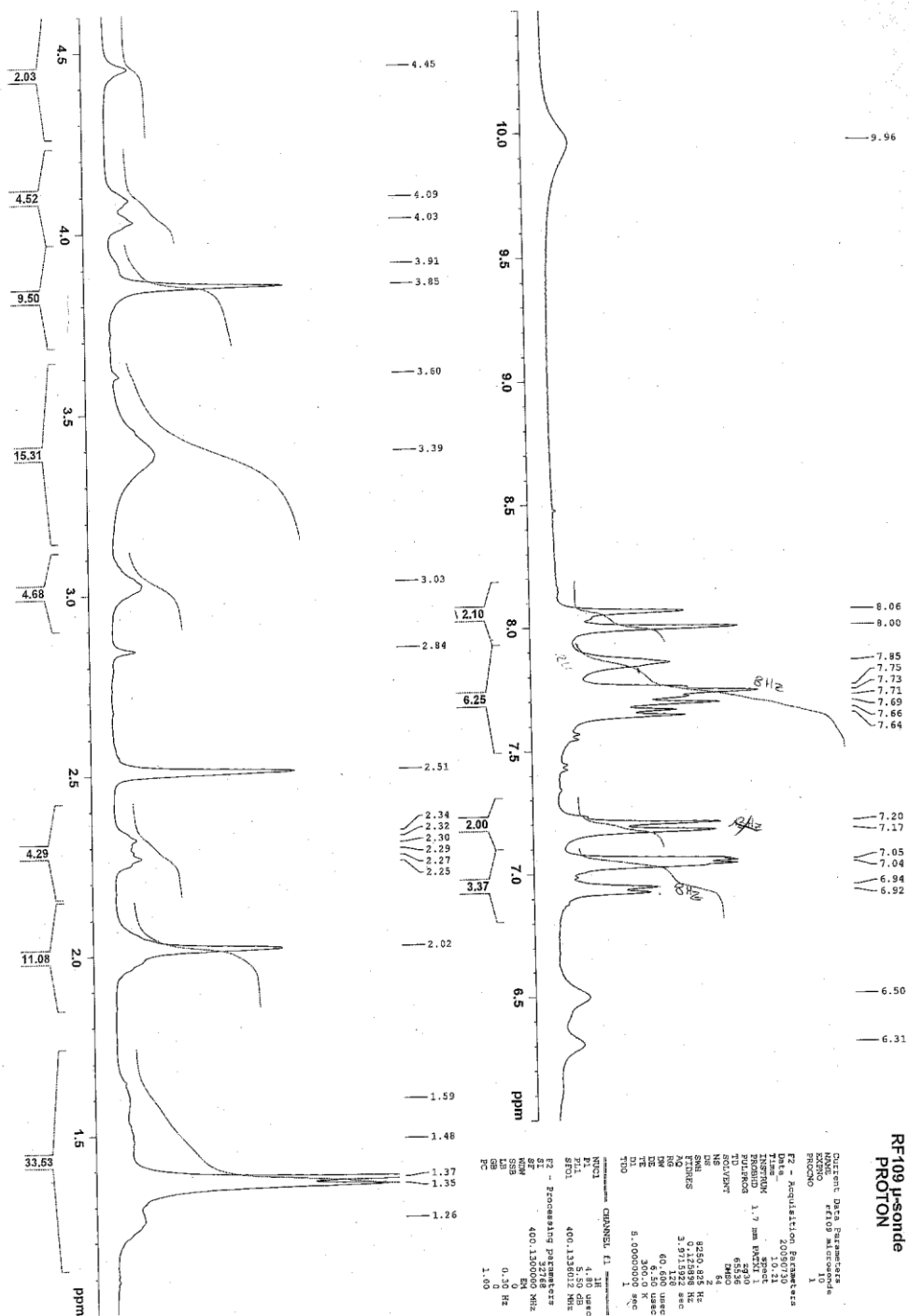
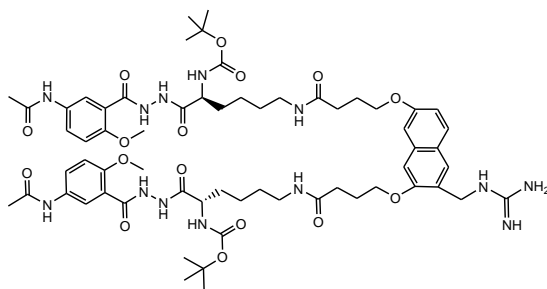
Molecular tong 14

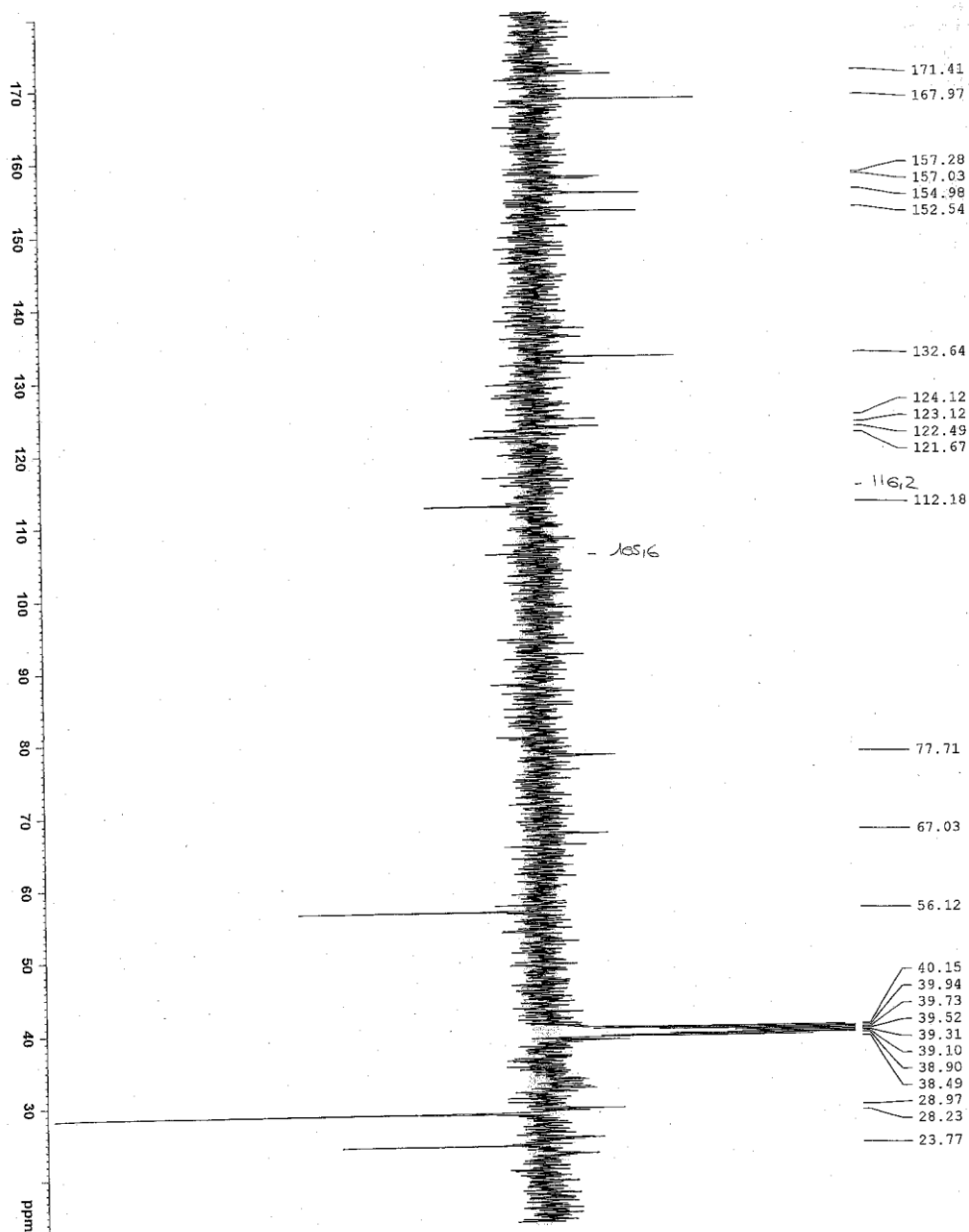


Current Data Parameters

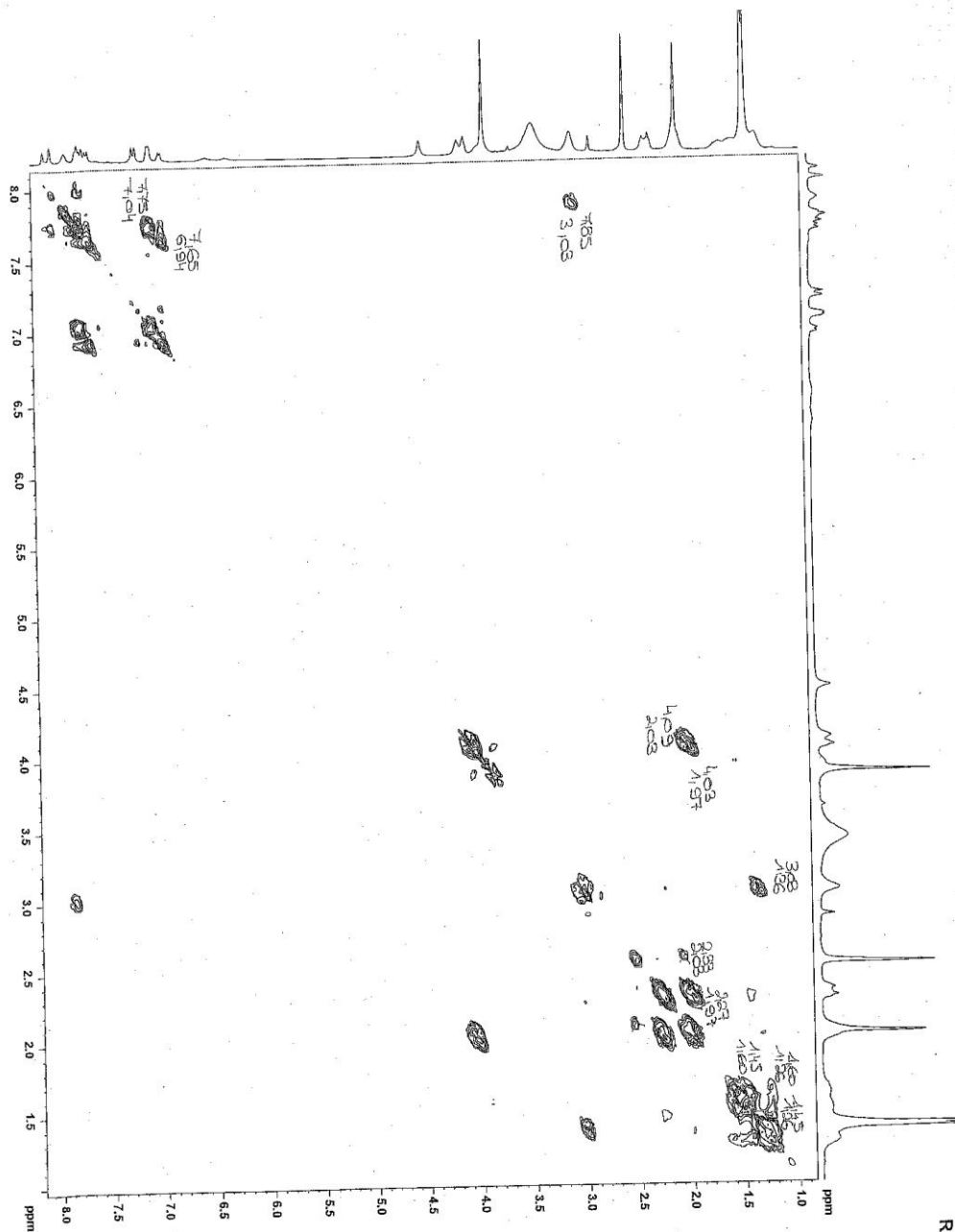
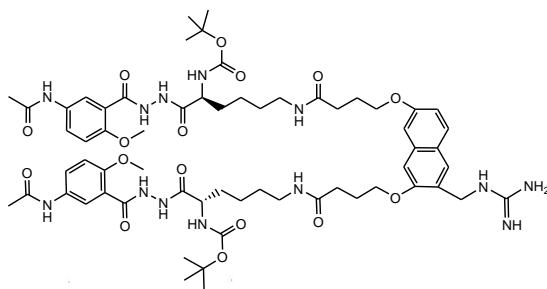
Parameter	Value
NAME	20090731
EXPNO	1
PROCNO	1
PROBHD	5 mm QNP 1H/13
PROBHD2	1.7 mm QNP 1H/13
PROBHD3	1.7 mm QNP 1H/13
PROBHD4	1.7 mm QNP 1H/13
PROBHD5	1.7 mm QNP 1H/13
PROBHD6	1.7 mm QNP 1H/13
PROBHD7	1.7 mm QNP 1H/13
PROBHD8	1.7 mm QNP 1H/13
PROBHD9	1.7 mm QNP 1H/13
PROBHD10	1.7 mm QNP 1H/13
PROBHD11	1.7 mm QNP 1H/13
PROBHD12	1.7 mm QNP 1H/13
PROBHD13	1.7 mm QNP 1H/13
PROBHD14	1.7 mm QNP 1H/13
PROBHD15	1.7 mm QNP 1H/13
PROBHD16	1.7 mm QNP 1H/13
PROBHD17	1.7 mm QNP 1H/13
PROBHD18	1.7 mm QNP 1H/13
PROBHD19	1.7 mm QNP 1H/13
PROBHD20	1.7 mm QNP 1H/13
PROBHD21	1.7 mm QNP 1H/13
PROBHD22	1.7 mm QNP 1H/13
PROBHD23	1.7 mm QNP 1H/13
PROBHD24	1.7 mm QNP 1H/13
PROBHD25	1.7 mm QNP 1H/13
PROBHD26	1.7 mm QNP 1H/13
PROBHD27	1.7 mm QNP 1H/13
PROBHD28	1.7 mm QNP 1H/13
PROBHD29	1.7 mm QNP 1H/13
PROBHD30	1.7 mm QNP 1H/13
PROBHD31	1.7 mm QNP 1H/13
PROBHD32	1.7 mm QNP 1H/13
PROBHD33	1.7 mm QNP 1H/13
PROBHD34	1.7 mm QNP 1H/13
PROBHD35	1.7 mm QNP 1H/13
PROBHD36	1.7 mm QNP 1H/13
PROBHD37	1.7 mm QNP 1H/13
PROBHD38	1.7 mm QNP 1H/13
PROBHD39	1.7 mm QNP 1H/13
PROBHD40	1.7 mm QNP 1H/13
PROBHD41	1.7 mm QNP 1H/13
PROBHD42	1.7 mm QNP 1H/13
PROBHD43	1.7 mm QNP 1H/13
PROBHD44	1.7 mm QNP 1H/13
PROBHD45	1.7 mm QNP 1H/13
PROBHD46	1.7 mm QNP 1H/13
PROBHD47	1.7 mm QNP 1H/13
PROBHD48	1.7 mm QNP 1H/13
PROBHD49	1.7 mm QNP 1H/13
PROBHD50	1.7 mm QNP 1H/13
PROBHD51	1.7 mm QNP 1H/13
PROBHD52	1.7 mm QNP 1H/13
PROBHD53	1.7 mm QNP 1H/13
PROBHD54	1.7 mm QNP 1H/13
PROBHD55	1.7 mm QNP 1H/13
PROBHD56	1.7 mm QNP 1H/13
PROBHD57	1.7 mm QNP 1H/13
PROBHD58	1.7 mm QNP 1H/13
PROBHD59	1.7 mm QNP 1H/13
PROBHD60	1.7 mm QNP 1H/13
PROBHD61	1.7 mm QNP 1H/13
PROBHD62	1.7 mm QNP 1H/13
PROBHD63	1.7 mm QNP 1H/13
PROBHD64	1.7 mm QNP 1H/13
PROBHD65	1.7 mm QNP 1H/13
PROBHD66	1.7 mm QNP 1H/13
PROBHD67	1.7 mm QNP 1H/13
PROBHD68	1.7 mm QNP 1H/13
PROBHD69	1.7 mm QNP 1H/13
PROBHD70	1.7 mm QNP 1H/13
PROBHD71	1.7 mm QNP 1H/13
PROBHD72	1.7 mm QNP 1H/13
PROBHD73	1.7 mm QNP 1H/13
PROBHD74	1.7 mm QNP 1H/13
PROBHD75	1.7 mm QNP 1H/13
PROBHD76	1.7 mm QNP 1H/13
PROBHD77	1.7 mm QNP 1H/13
PROBHD78	1.7 mm QNP 1H/13
PROBHD79	1.7 mm QNP 1H/13
PROBHD80	1.7 mm QNP 1H/13
PROBHD81	1.7 mm QNP 1H/13
PROBHD82	1.7 mm QNP 1H/13
PROBHD83	1.7 mm QNP 1H/13
PROBHD84	1.7 mm QNP 1H/13
PROBHD85	1.7 mm QNP 1H/13
PROBHD86	1.7 mm QNP 1H/13
PROBHD87	1.7 mm QNP 1H/13
PROBHD88	1.7 mm QNP 1H/13
PROBHD89	1.7 mm QNP 1H/13
PROBHD90	1.7 mm QNP 1H/13
PROBHD91	1.7 mm QNP 1H/13
PROBHD92	1.7 mm QNP 1H/13
PROBHD93	1.7 mm QNP 1H/13
PROBHD94	1.7 mm QNP 1H/13
PROBHD95	1.7 mm QNP 1H/13
PROBHD96	1.7 mm QNP 1H/13
PROBHD97	1.7 mm QNP 1H/13
PROBHD98	1.7 mm QNP 1H/13
PROBHD99	1.7 mm QNP 1H/13
PROBHD100	1.7 mm QNP 1H/13

Molecular tong 15



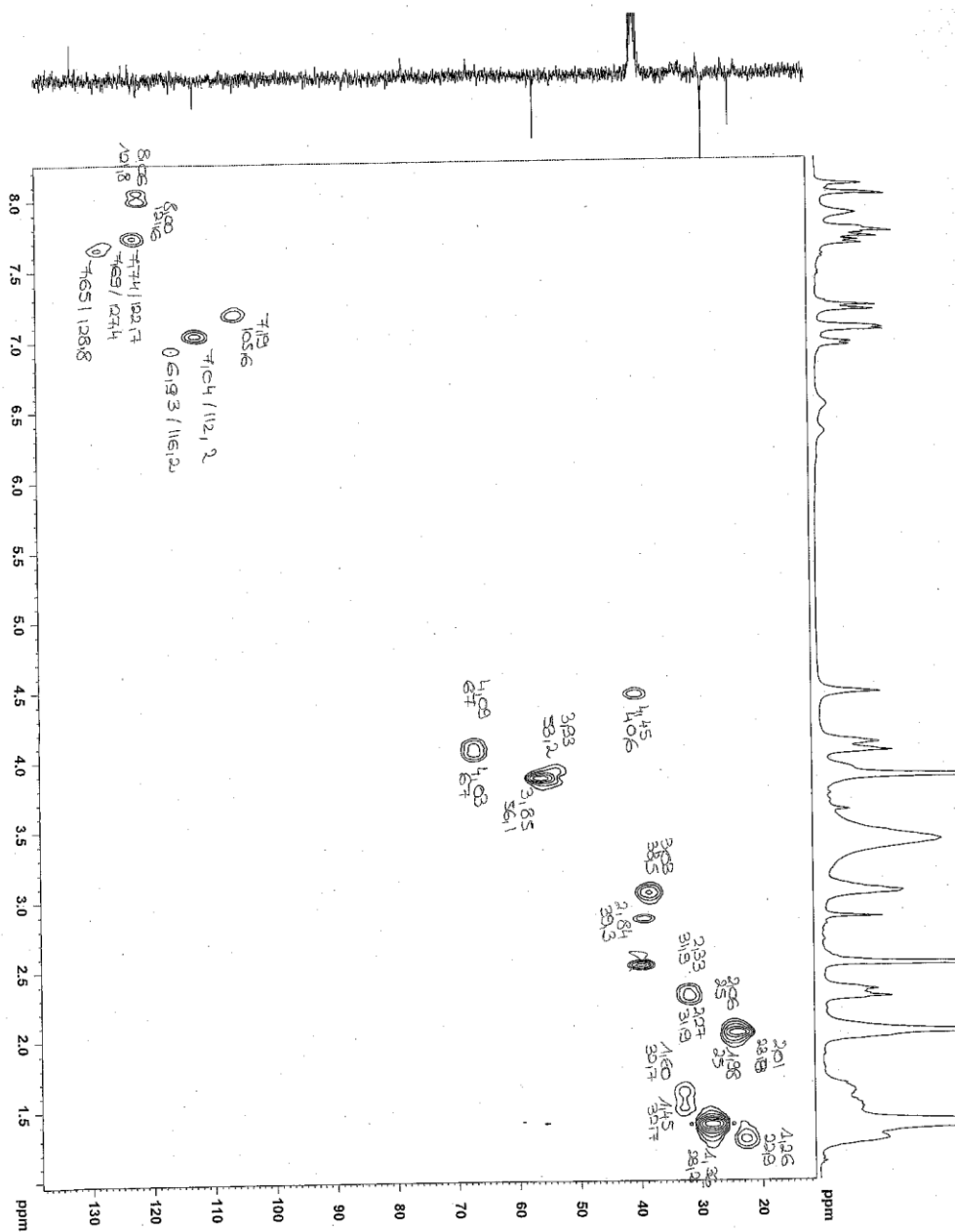
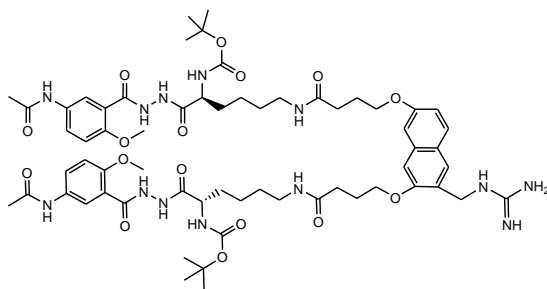
[illegible]RF109 μ -sonde
Jmod[illegible]

Molecular tong 15



RF 109 μ -sonde
COSY

Current Data Parameters
NAME RF109 μ -sonde
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 09092729
Time 11.03
INSTRUM 1.7 mm BBO
PROBHD 1.7 mm BBO
PULPROG zgpg30
TD 65536
SFO 400.136353 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.10
F1 - Processing parameters
SI 32768
SF 400.136353 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.10
F2 - Processing parameters
SI 32768
SF 400.136353 MHz
WDW EM
SSB 0
LB 3.00 Hz
GB 0
PC 1.10



Molecular tong 15

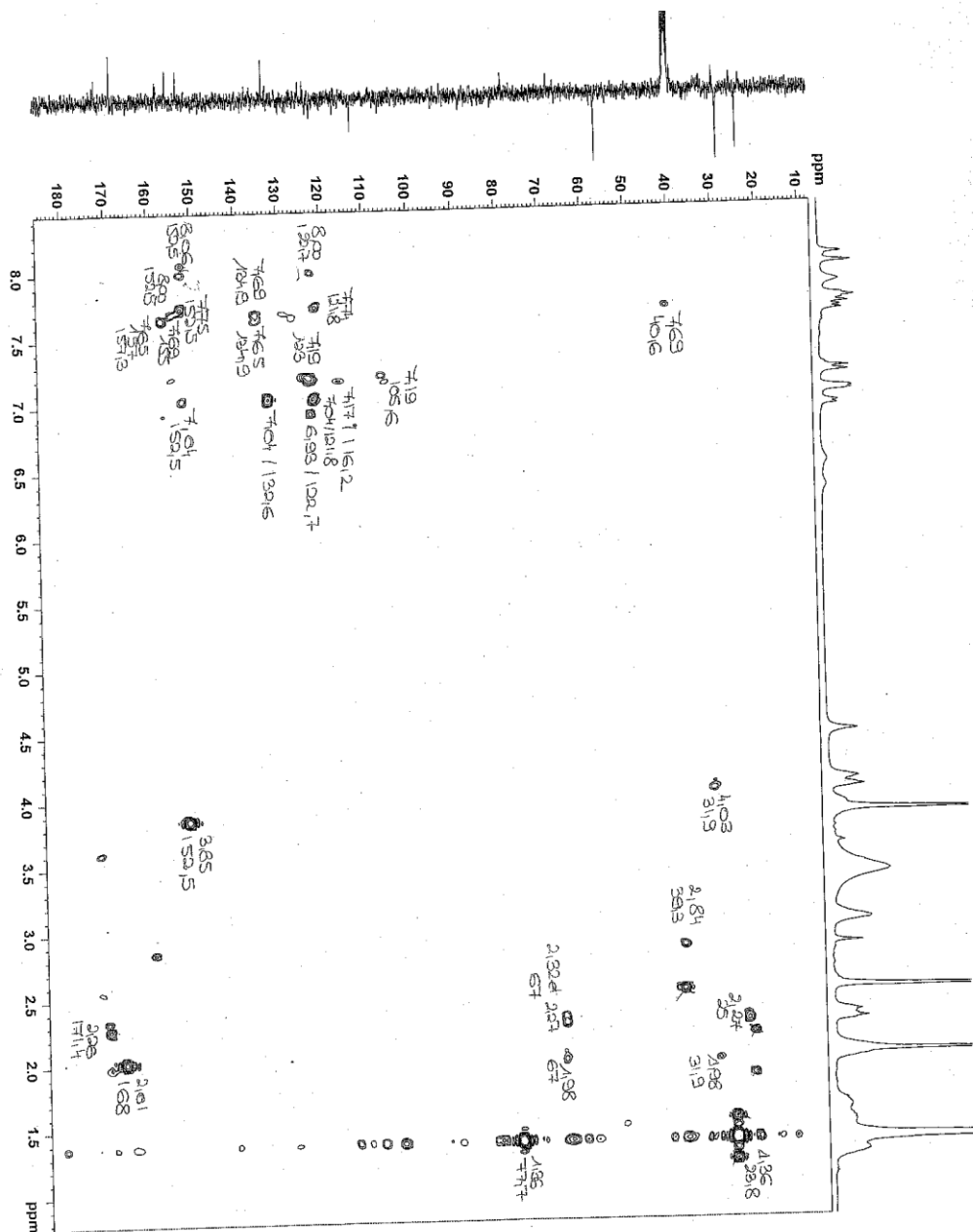
[illegible][illegible]

Figure 1S.

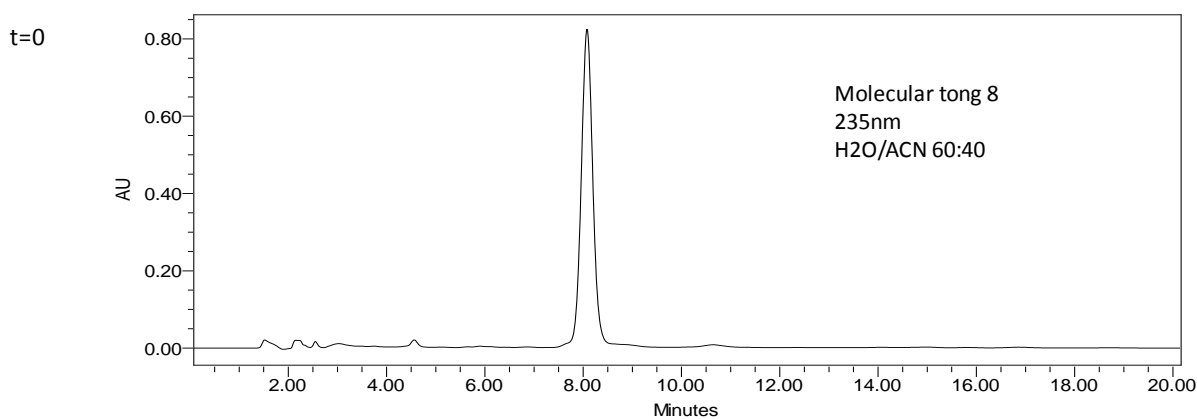
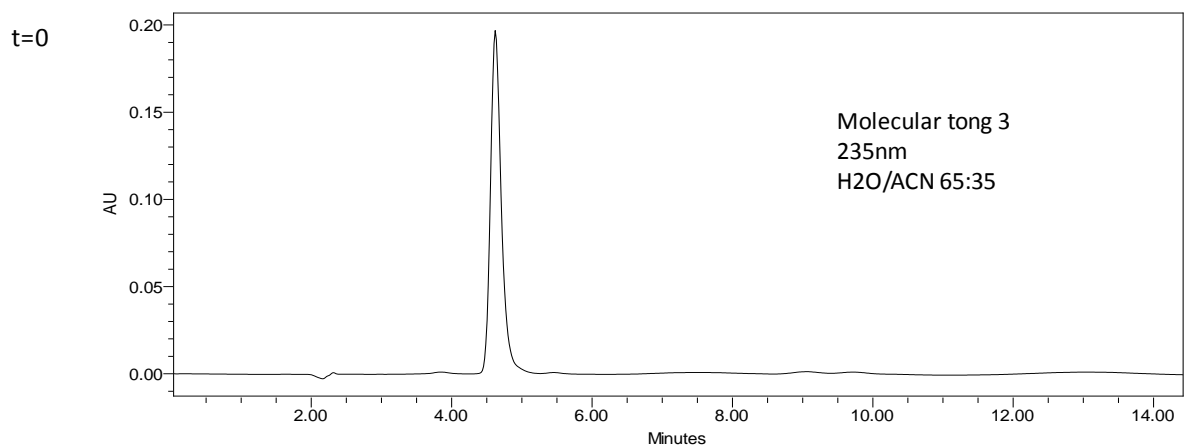
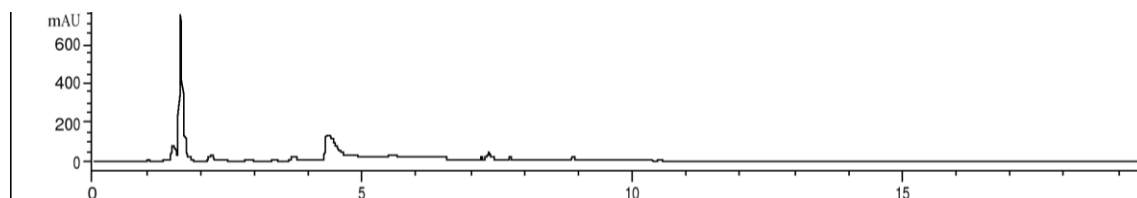


Figure 2S.

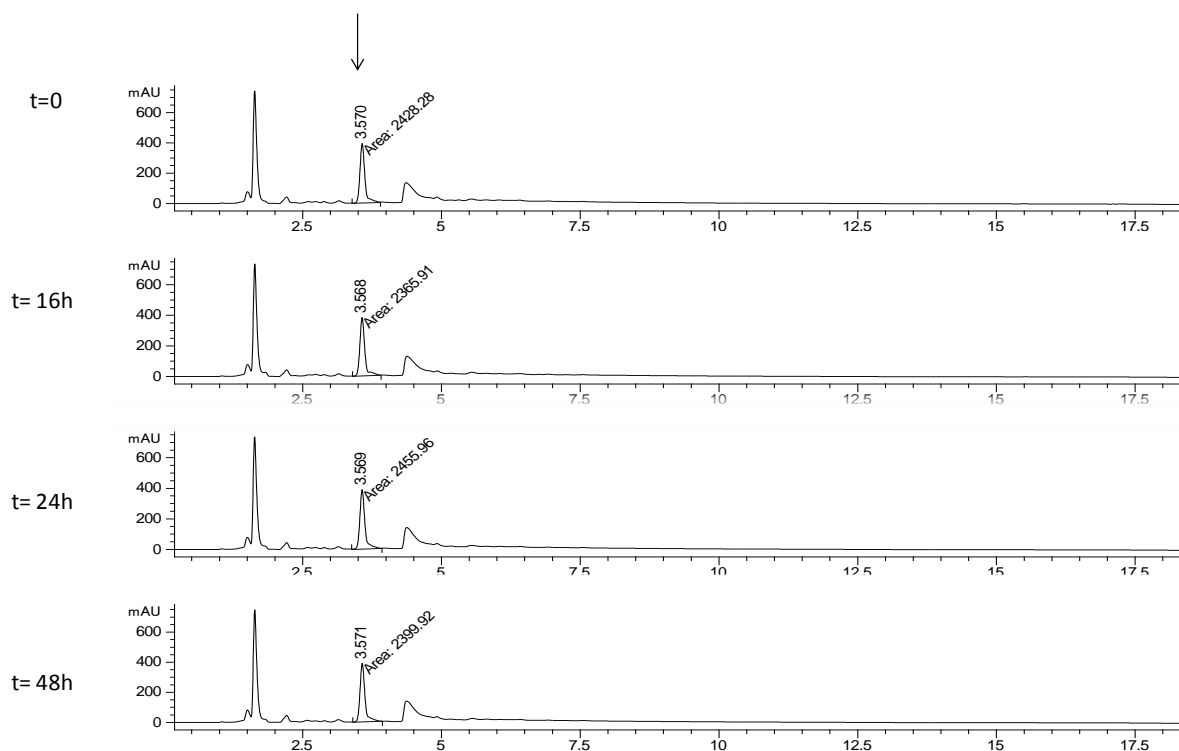
A1

Blank serum



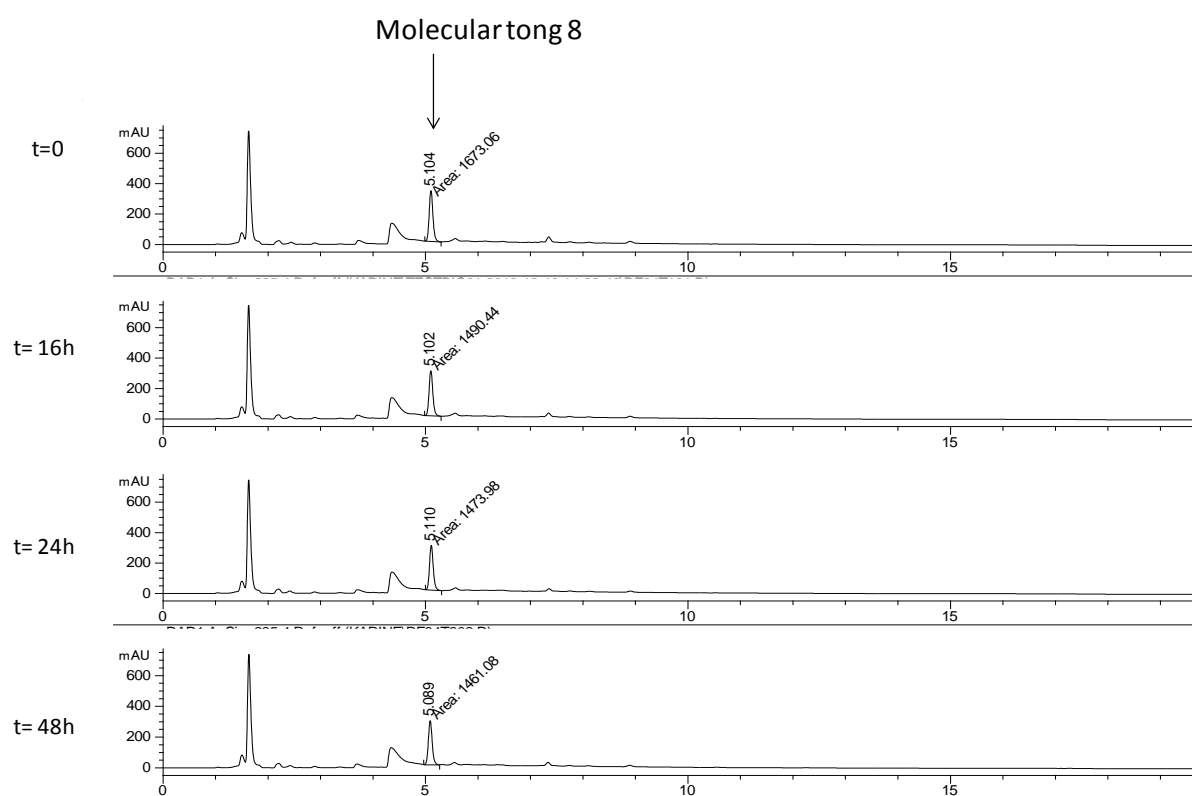
B1

Molecular tong 3



Molecular tong 3 after incubation in the culture medium

B2



Molecular tong 8 after incubation in the culture medium