

Supporting Information: A Wrenchnolol Derivative Optimized for Gene Activation in Cells

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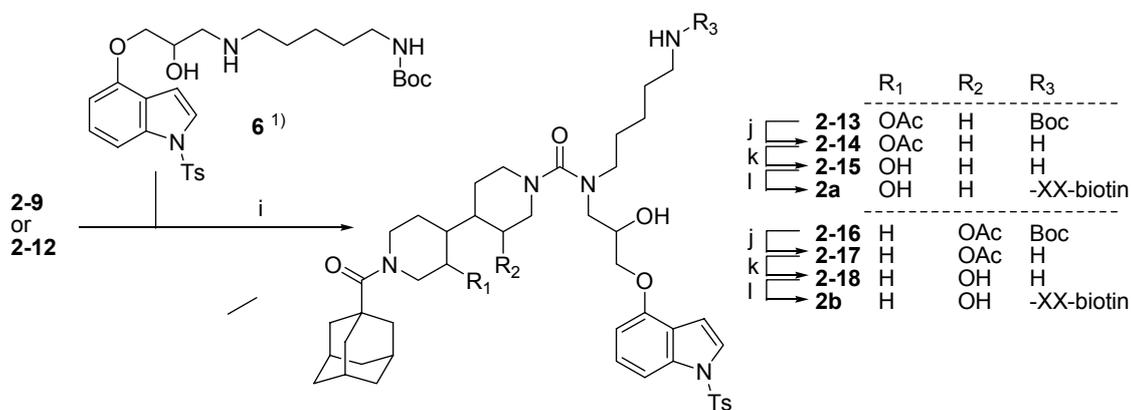
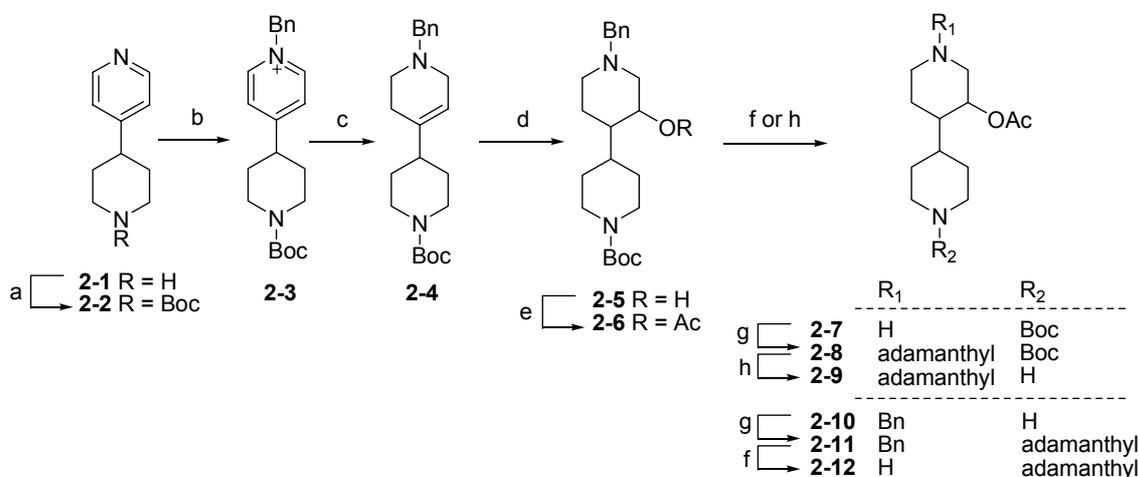
General Procedures.

The solvents used for chemical synthesis were dried prior to use. All other chemicals were used as purchased without purification. All moisture-sensitive reactions were performed in flame-dried and/or oven-dried glassware under a positive pressure of nitrogen unless otherwise noted. Thin-layer chromatography was carried out with glass TLC plates precoated with Merck silica gel 60 F254. Column chromatography was accomplished with Fuji Silysia Chemical silica gel BW820MH. Proton nuclear magnetic resonance spectra were recorded in deuterated solvents at 270 or 600 MHz. High-resolution mass spectra were obtained by Q-star spectrometer (Applied Biosystems) on an ESI mode.

Synthesis of **1c**

To a solution of wrenchnolol¹ (2.0 mg, 2.5 μ mol) and triethylamine (0.05 mL) in DMSO (0.5 mL) was added biotin-NHS (1.0 mg, 3.0 μ mol). This solution was stirred at room temperature for 2h, and purified by reversed-phase HPLC (ODS, 80% MeOH in 0.1% TFA) to give **1c** (2.1 mg, 82%) as a colorless oil.

¹H NMR (CD₃OD, 270 MHz) ¹H NMR (CD₃OD, 270 MHz) δ_{H} 7.76 (d, $J=8.4$ Hz, 2H), 7.57 (m, 2H), 7.32 (d, $J=8.4$ Hz, 2H), 7.23 (m, 1H), 6.77 (m, 2H), 5.32 (br. m, 1H), 4.62-4.54 (m, 3H), 4.34-4.25 (m, 3H), 4.15-3.92 (m, 2H), 3.48 (m, 2H), 3.25-3.05 (m, 2H), 3.02 (m, 2H), 2.91 (dd, $J=7.6, 3.4$ Hz, 1H), 2.85-2.58 (m, 6H), 2.33 (s, 3H), 2.22-2.15 (m, 2H), 2.08-1.92 (m, 9H), 1.79 (s, 6H), 1.90-0.86 (m, 22H); HRMS (ESI) Exact mass calcd for C₅₅H₇₇N₇O₈S₂ + H requires m/z 1028.5353 Found m/z 1028.5351



Conditions: (a) (Boc)₂O, CHCl₃, rt. (b) BnBr, CH₃CN, rt. (c) NaBH₄, CH₃OH, rt. (d) (1) BH₃ dimethylsulfide complex, THF, rt. (2) 30% H₂O₂, 1N NaOHaq, rt. (e) Ac₂O, pyridine, rt. (f) 10% Pd(OH)₂, CH₃OH, rt. (g) adamantanecarbonyl chloride, CHCl₃, rt. (h) TFA, CHCl₃, rt. (i) (1) CDI, THF, reflux (2) CH₃I, CH₃CN, rt. (3) amine **6**, Et₃N, CH₂Cl₂, rt. (j) TFA, CHCl₃, rt. (k) 1N NaOH-MeOH, 45°C (l) biotin-XX-NHS, Et₃N, DMSO, rt.

Scheme S1. Synthesis of 2a, 2b

2-2

To a solution of 4-(4'-piperidyl)pyridine (**2-1**) (1.0 g, 6.2 mmol) in CHCl₃ (10 mL) were added (Boc)₂O (1.6 g, 7.4 mmol) and Et₃N (1 ml). After being stirred at room temperature for 1 h, the reaction mixture was concentrated and purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give **2-2** (1.6 g, quant) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 8.55 (d, *J*=5.4 Hz, 2H), 7.23 (d, *J*=5.4 Hz, 2H), 4.26 (br. d, *J*=13.0 Hz, 2H), 3.26 (br. s, 1H), 2.81 (br. t, *J*=13.0 Hz, 2H), 2.70 (tt, *J*=12.5, 3.5 Hz, 1H), 1.85 (br. d, *J*=13.0 Hz, 2H), 1.70-1.60 (m, 2H), 1.48 (s, 9H); HRMS (ESI) Exact mass calcd for C₁₅H₂₂N₂O₂ + H requires *m/z* 263.1760 Found *m/z* 263.1783

2-3

To a solution of **2-2** (1.5 g, 5.7 mmol) in CH₃CN (10 mL) was added BnBr (1.2 g, 6.8 mmol). After being stirred at room temperature for overnight, the reaction mixture was concentrated and purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give **2-3** (1.9 g, 94 %) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 9.46 (d, *J*=6.8 Hz, 2H), 7.79 (d, *J*=6.8 Hz, 2H), 7.69-7.66 (m, 1H), 7.39-7.35 (m, 4H), 6.26 (s, 2H), 4.25 (br. d, *J*=12.7 Hz, 2H), 2.93 (tt, *J*=12.7, 3.5 Hz, 1H), 2.81 (br. t, *J*=13.2 Hz, 2H), 1.84 (br. d, *J*=12.7 Hz, 2H), 1.61-1.43 (m, 11H); HRMS (ESI) Exact mass calcd for C₂₂H₂₉N₂O₂ (M⁺) requires *m/z* 353.2224 Found *m/z* 353.2231

2-4

To a solution of **2-3** (1.0 g, 2.8 mmol) in MeOH (3 mL) was added NaBH₄ (0.13 g, 3.4 mmol). After being stirred at room temperature for 2 h, the reaction mixture was diluted with brine and extracted with CHCl₃ (3 × 50 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give **2-4** (1.0g, 99%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 7.40 (m, 5H), 5.33 (br. s, 1H), 4.29 (d, *J*=12.7 Hz, 1H), 4.20-4.00 (m, 3H), 3.78 (br. d, *J*=12.7 Hz, 1H), 3.71-3.65 (m, 1H), 3.34 (br. d, *J*=12.7 Hz, 1H), 2.91 (m, 1H), 2.65 (m, 3H), 2.18 (br. d, *J*=15.4 Hz, 1H), 2.02 (br. t, *J*=15.4 Hz, 1H), 1.66 (br. d, *J*=12.7 Hz, 2H), 1.52-1.18 (m, 11H); HRMS (ESI) Exact mass calcd for C₂₂H₃₂N₂O₂ + H requires *m/z* 357.2542 Found *m/z* 357.2540

2-5

To a solution of **2-4** (500 mg, 1.4 mmol) in THF (3 mL) was added a solution of 1.0 M borane dimethyl sulfide complex in methylene chloride (4.2 mmol), and this solution was stirred at room temperature for 4h. 30% H₂O₂ aqueous solution (5 ml) and 1.0 N NaOH aqueous solution (2 ml) were added to the reaction mixture. After being stirred at room temperature for 1 h, the organic solvent in the reaction mixture was evaporated in vacuum. The residual aqueous layer was diluted with brine and extracted with CHCl₃ (3 × 50 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give the **2-5** (450 mg, 86%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 7.28 (m, 5H), 4.10 (br. d, *J*=5.2 Hz, 2H), 3.65-3.40 (m, 3H), 2.95 (m, 1H), 2.76 (m, 1H), 2.75-2.56 (m, 2H), 2.16 (br. s, 1H), 1.98-1.82 (m, 3H), 1.56 (m, 3H), 1.42-0.90 (m, 14H); HRMS (ESI) Exact mass calcd for C₂₂H₃₄N₂O₃ + H requires *m/z* 375.2648 Found *m/z* 375.2655

2-6

Compound **2-5** (400 mg, 1.1 mmol) was dissolved in pyridine (5 mL), and acetic anhydride (2 mL) was added to the solution. After being stirred at room temperature for 1 h, the reaction mixture was concentrated to give **2-6** (440 mg, 99%), which was used without further purification for the next deprotection reaction.

2-7

Compound **2-6** (80 mg, 0.19 mmol) was dissolved in methanol (5 mL), and 20 mol% of Pd(OH)₂ was added to the solution. After 12 h stirring at room temperature under H₂, the resulting solution was filtered through a Celite pad. The filtrate was evaporated to dryness to give **2-7** (72 mg, quant) as a yellow oil.

¹H NMR (CD₃OD, 270 MHz) δ_H 5.05 (m, 1H), 4.10 (br. d, *J*=12.2 Hz, 2H), 3.50-3.29 (m, 2H), 3.10-2.95 (m, 2H), 2.80-2.65 (m, 2H), 2.10 (s, 3H), 1.98 (m, 1H), 1.90-0.90 (m, 16H); HRMS (ESI) Exact mass calcd for C₁₇H₃₀N₂O₃ + H requires *m/z* 327.2284 Found *m/z* 327.2261

2-8

To a solution of **2-7** (70 mg, 0.21 mmol) and triethylamine (0.5 mL) in CHCl₃ (2 mL) was added a solution of 1-adamantanecarbonyl chloride (42 mg, 0.21 mmol) in CHCl₃ (2 mL). The resulting mixture was refluxed for 0.5 h, diluted with water, and extracted with CHCl₃ (3 × 10 mL). The combined extracts were dried over Na₂SO₄ and then concentrated in vacuum. The residue was purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give amide **2-8** (97 mg, 93%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 4.62-4.46 (m, 3H), 4.12 (m, 2H), 2.75-2.49 (m, 4H), 2.10 (s, 3H), 2.09-1.91 (m, 12H), 1.70 (s, 6H), 1.71-0.90 (m, 14H); HRMS (ESI) Exact mass calcd for C₂₈H₄₄N₂O₅ + H requires *m/z* 489.3328 Found *m/z* 489.3318

2-9

To a solution of **2-8** (75 mg, 0.15 mmol) in CHCl₃ (2 mL) was added TFA (2 mL). This solution was stirred at room temperature for 15 min and then concentrated in vacuum to give **2-9** (70 mg, quant) as a colorless oil, which was used without further purification for the next reaction.

¹H NMR (CDCl₃, 270 MHz) δ_H 4.61-4.48 (m, 3H), 3.41 (m, 2H), 2.76-2.46 (m, 4H), 2.25 (br. s, 1H), 2.08 (s, 3H), 2.07-1.93 (m, 12H), 1.70 (s, 6H), 1.71-0.90 (m, 14H); HRMS (ESI) Exact mass calcd for C₂₃H₃₆N₂O₃ + H requires *m/z* 389.2804 Found *m/z* 389.2842

2-10

The deprotection reaction of **2-6** (100 mg, 0.24 mmol) as described for **2-9** gave **2-10** (92 mg, 66%) as a colorless oil, which was used without further purification for the next acylation reaction.

2-11

The acylation reaction of **2-10** (90 mg, 0.28 mmol) as described for **2-8** gave **2-11** (103 mg, 77%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 7.31 (m, 5H), 4.92 (br. m, 1H), 4.67-4.52 (br. m, 2H), 4.55 (br. m, 2H), 3.10 (m, 1H), 2.85 (m, 1H), 2.72-2.56 (br. m, 2H), 2.10 (s, 3H), 2.06-1.91 (m, 12H), 1.70 (s, 6H), 1.71-0.90 (m, 5H); HRMS (ESI) Exact mass calcd for C₃₀H₄₂N₂O₃ + H requires *m/z* 479.3274 Found *m/z* 479.3250

2-12

The deprotection reaction of **2-11** (95 mg, 0.20 mmol) as described for **2-7** gave **2-12** (82 mg, quant) as a colorless oil.

¹H NMR (CD₃OD, 270 MHz) δ_H 5.05 (m, 1H), 4.60-4.50 (br. m, 2H), 3.45-3.40 (br. m, 1H), 3.34-3.20 (br. m, 1H), 3.14 (br. m, 1H), 3.01 (br. m, 1H), 2.96-2.75 (br. m, 2H), 2.11 (s, 3H), 2.06-1.91 (m, 12H), 1.70 (s, 6H), 1.71-0.90 (m, 5H); HRMS (ESI) Exact mass calcd for C₂₃H₃₆N₂O₃ + H requires *m/z* 389.2804 Found *m/z* 389.2802

2-13

To a solution of amide **2-9** (15 mg, 0.039 mmol) in THF (1 mL) was added 1, 1'-carbonyldiimidazole (15 mg, 0.078 mmol). After being refluxed for 4 h, the mixture was diluted with CHCl₃ (10 mL) and washed with water (3 × 10 mL). The organic layer was dried with Na₂SO₄ and concentrated to give a carbamoyl imidazole, which was used without further purification. A solution of the carbamoyl imidazole and MeI (0.5 mL) in MeCN (1 mL) was stirred for 18 h at room temperature. Evaporation of the solvent and excess MeI in vacuum gave the corresponding imidazolium salt. To a solution of the imidazolium salt in CH₂Cl₂ (2 mL) were added amine **6**¹ (32 mg, 0.059 mmol) and Et₃N (0.1 mL). After being stirred at room temperature for over night, the mixture was concentrated and purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give **2-13** (32 mg, 86%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 7.75 (d, *J*=8.1 Hz, 2H), 7.59 (d, *J*=8.4 Hz, 1H), 7.46 (d, *J*=3.4 Hz, 1H), 7.21 (d, *J*=8.1 Hz, 2H), 7.26-7.19 (t, *J*=8.4 Hz, 1H), 6.72 (d, *J*=3.4 Hz, 1H), 6.62 (d, *J*=8.4 Hz, 1H), 5.32 (br. m, 1H), 4.80-4.45 (m, 5H), 4.35-4.01 (m, 2H), 3.50-3.20 (m, 2H), 3.17-2.88 (m, 4H), 2.79-2.52 (m, 4H), 2.34 (s, 3H), 2.11 (s, 3H), 2.03-1.99 (m, 12H), 1.72 (s, 6H), 1.44 (s, 9H), 1.80-0.86 (m, 11H); HRMS (ESI) Exact mass calcd for C₅₂H₇₃N₅O₁₀S + H requires *m/z* 960.5156

Found m/z 960.5129

2-14

To a solution of **2-13** (30 mg, 0.031 mmol) in CHCl_3 (1 mL) was added TFA (2 mL). This solution was stirred at room temperature for 15 min and then concentrated in vacuum to give **2-14** (26 mg) as a colorless oil, which was used without further purification for the next reaction.

^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.76 (d, $J=8.4$ Hz, 2H), 7.55 (m, 2H), 7.30 (d, $J=8.4$ Hz, 2H), 7.22 (m, 1H), 6.77 (m, 2H), 5.32 (br. m, 1H), 4.70-4.32 (m, 5H), 4.25-3.98 (m, 2H), 3.50 (m, 2H), 3.17 (m, 2H), 2.99-2.52 (m, 6H), 2.34 (s, 3H), 2.09 (s, 3H), 2.08-1.92 (m, 12H), 1.70 (s, 6H), 1.90-0.86 (m, 11H); HRMS (ESI) Exact mass calcd for $\text{C}_{47}\text{H}_{65}\text{N}_5\text{O}_8\text{S} + \text{H}$ requires m/z 860.4632 Found m/z 860.4602

2-15

To a solution of **2-14** (15 mg, 0.017 mmol) in EtOH (3 mL) was added a solution of 1.0 N NaOH aqueous solution (1 ml). This solution was stirred at 45 °C for 1h, and the organic solvent in the reaction mixture was evaporated in vacuum. The residual aqueous layer was diluted with brine and extracted with CHCl_3 (3 \times 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by reversed-phase HPLC (ODS, 80% MeOH in 0.1% TFA) to give the **2-15** (5.1 mg, 37%) as a colorless oil.

^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.78 (d, $J=8.4$ Hz, 2H), 7.58 (m, 2H), 7.32 (d, $J=8.4$ Hz, 2H), 7.23 (m, 1H), 6.77 (m, 2H), 5.35 (br. m, 1H), 4.62-4.25 (m, 5H), 4.22-3.95 (m, 2H), 3.45 (m, 2H), 3.11 (m, 2H), 2.93 (t, $J=7.6$ Hz, 2H), 2.85-2.58 (m, 4H), 2.34 (s, 3H), 2.08-1.92 (m, 12H), 1.79 (s, 6H), 1.90-0.86 (m, 11H); HRMS (ESI) Exact mass calcd for $\text{C}_{45}\text{H}_{63}\text{N}_5\text{O}_7\text{S} + \text{H}$ requires m/z 818.4526 Found m/z 818.4542

2a

To a solution of **2-15** (2.8 mg, 3.4 μmol) and triethylamine (0.05 mL) in DMSO (0.5 mL) was added biotin-XX-NHS (2.3 mg, 4.0 μmol). This solution was stirred at room temperature for 2h, and purified by reversed-phase HPLC (ODS, 80% MeOH in 0.1% TFA) to give the **2a** (3.7 mg, 86%) as a colorless oil.

^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.76 (d, $J=8.4$ Hz, 2H), 7.57 (m, 2H), 7.32 (d, $J=8.4$ Hz, 2H), 7.23 (m, 1H), 6.77 (m, 2H), 5.32 (br. m, 1H), 4.62-4.25 (m, 7H), 4.22-3.95 (m, 2H), 3.48 (m, 2H), 3.25-3.05 (m, 8H), 2.91 (dd, $J=7.6, 3.4$ Hz, 1H), 2.85-2.58 (m, 6H), 2.33 (s, 3H), 2.22-2.15 (m, 6H), 2.08-1.92 (m, 12H), 1.79 (s, 6H), 1.90-0.86 (m, 29H); HRMS (ESI) Exact mass calcd for $\text{C}_{67}\text{H}_{99}\text{N}_9\text{O}_{11}\text{S}_2 + \text{H}$ requires m/z 1270.6984 Found m/z 1270.6966

2-16

The reaction of **2-12** (15 mg, 0.039 mmol) as described for **2-13** gave **2-16** (34 mg, 92%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 7.73 (d, *J*=8.1 Hz, 2H), 7.59 (d, *J*=8.4 Hz, 1H), 7.46 (d, *J*=3.4 Hz, 1H), 7.21 (d, *J*=8.1 Hz, 2H), 7.26-7.19 (t, *J*=8.4 Hz, 1H), 6.72 (d, *J*=3.4 Hz, 1H), 6.62 (d, *J*=8.4 Hz, 1H), 5.40-5.20 (br. m, 2H), 4.70-4.42 (m, 2H), 4.40-4.35 (m, 2H), 4.08-3.85 (m, 2H), 3.45-3.40 (m, 2H), 3.15-3.05 (m, 2H), 2.97-2.55 (m, 6H), 2.34 (s, 3H), 2.03-1.99 (m, 15H), 1.73 (s, 6H), 1.44 (s, 9H), 1.80-0.86 (m, 11H); HRMS (ESI) Exact mass calcd for C₅₂H₇₃N₅O₁₀S + H requires *m/z* 960.5156 Found *m/z* 960.5166

2-17

The reaction of **2-16** (30 mg, 0.031 mmol) as described for **2-14** gave **2-17** (22 mg, 82%) as a colorless oil.

¹H NMR (CD₃OD, 270 MHz) δ_H 7.77 (d, *J*=8.4 Hz, 2H), 7.58 (m, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 7.25 (m, 1H), 6.77 (m, 2H), 5.48-5.26 (br. m, 1H), 4.80-4.42 (m, 3H), 4.40-4.35 (m, 2H), 4.08-3.85 (m, 2H), 3.45-3.40 (m, 2H), 3.15-3.05 (m, 2H), 2.97-2.55 (m, 6H), 2.34 (s, 3H), 2.03-1.99 (m, 15H), 1.73 (s, 6H), 1.80-0.86 (m, 11H); HRMS (ESI) Exact mass calcd for C₄₇H₆₅N₅O₈S + H requires *m/z* 860.4632 Found *m/z* 860.4630

2-18

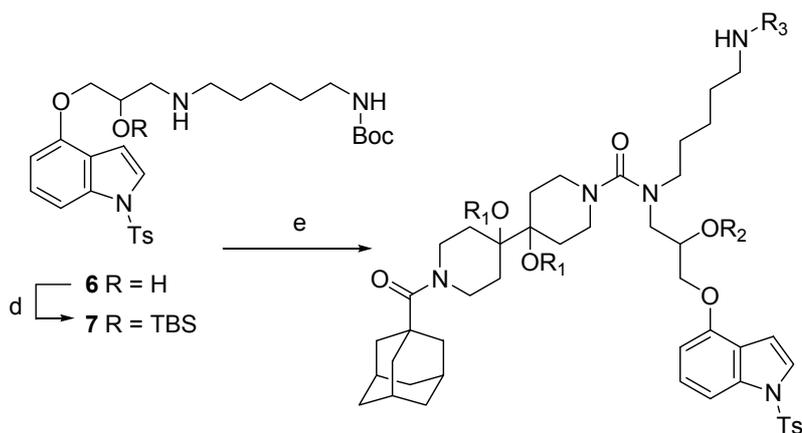
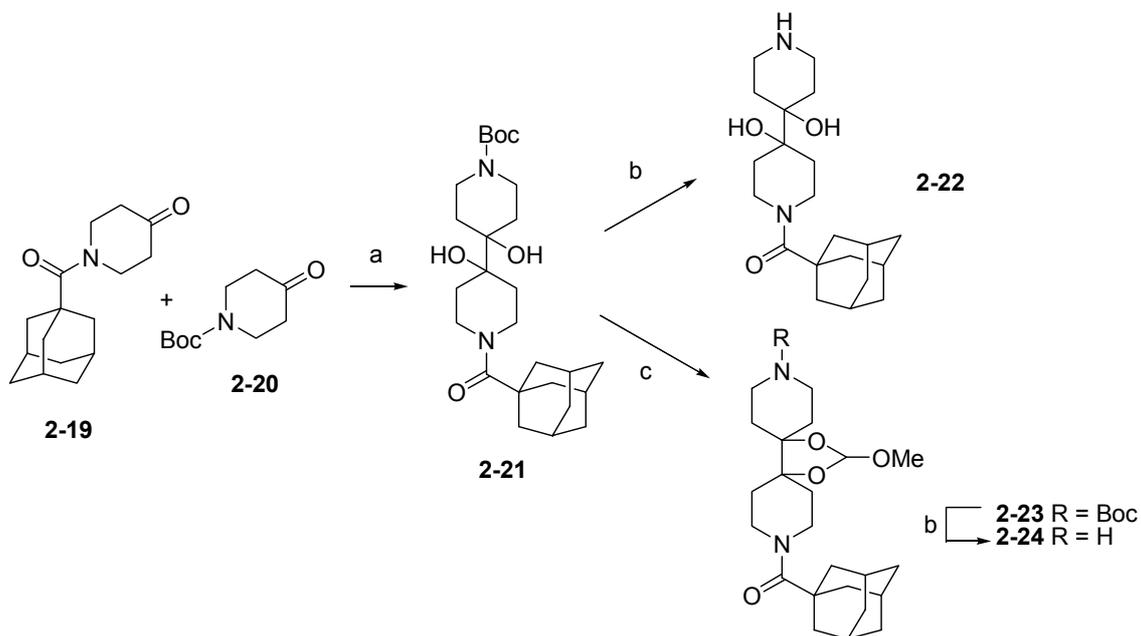
The reaction of **2-17** (15 mg, 0.017 mmol) as described for **2-15** gave **2-18** (1.3 mg, 9.4%) as a colorless oil.

¹H NMR (CD₃OD, 270 MHz) δ_H 7.77 (d, *J*=8.4 Hz, 2H), 7.58 (m, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 7.25 (m, 1H), 6.77 (m, 2H), 5.48-5.26 (br. m, 1H), 4.80-4.42 (m, 2H), 4.40-4.35 (m, 2H), 4.08-3.85 (m, 3H), 3.45-3.40 (m, 2H), 3.15-3.05 (m, 2H), 2.97-2.55 (m, 6H), 2.34 (s, 3H), 2.03-1.99 (m, 12H), 1.73 (s, 6H), 1.80-0.86 (m, 11H); HRMS (ESI) Exact mass calcd for C₄₅H₆₃N₅O₇S + H requires *m/z* 818.4526 Found *m/z* 818.4552

2b

The reaction of **2-18** (1.2 mg, 1.5 μmol) as described for **2a** gave **2b** (1.7 mg, 89%) as a colorless oil.

¹H NMR (CD₃OD, 270 MHz) δ_H 7.76 (d, *J*=8.4 Hz, 2H), 7.57 (m, 2H), 7.32 (d, *J*=8.4 Hz, 2H), 7.23 (m, 1H), 6.77 (m, 2H), 5.45-5.30 (br. m, 1H), 4.62-4.40 (m, 3H), 4.34-4.25 (m, 3H), 4.22-3.85 (m, 3H), 3.48 (m, 2H), 3.25-3.05 (m, 8H), 2.91 (dd, *J*=7.6, 3.4 Hz, 1H), 2.85-2.58 (m, 6H), 2.33 (s, 3H), 2.22-2.15 (m, 6H), 2.08-1.92 (m, 12H), 1.79 (s, 6H), 1.90-0.86 (m, 29H); HRMS (ESI) Exact mass calcd for C₆₇H₉₉N₉O₁₁S₂ + H requires *m/z* 1270.6984 Found *m/z* 1270.6981



	R ₁	R ₂	R ₃
f \rightarrow 2-25	H	TBS	Boc
g \rightarrow 2-26	H	H	Boc
g \rightarrow 2-27	H	H	H
h \rightarrow 2c	H	H	-XX-biotin
f \rightarrow 2-28	methylorthoester	TBS	Boc
g \rightarrow 2-29	methylorthoester	H	Boc
g \rightarrow 2-30	methylorthoester	H	H
h \rightarrow 2d	methylorthoester	H	-XX-biotin

Conditions: (a) Mg, HgCl₂, TiCl₄, THF, rt. (b) TFA, CHCl₃, rt. (c) trimethyl orthoformate, benzoic acid, 150°C (d) TBSCl, Et₃N, THF, rt. (e) (1) CDI, THF, reflux (2) CH₃I, CH₃CN, (3) amine 2-22 or 2-24, Et₃N, CH₂Cl₂, rt. (f) TBAF, CH₂Cl₂, rt. (g) TFA, CHCl₃, rt. (h) biotin-XX-NHS, Et₃N, DMSO, rt.

Scheme S2. Synthesis of 2c, 2d

2-21

To a solution of mercuric chloride (0.11 g, 0.4 mmol) in distilled THF (3 mL) was added mesh magnesium (0.144 g, 6.0 mmol), and the resulting mixture was stirred at room temperature under N₂ flow condition for 1h. This solution was cooled to 0 °C and treated dropwise with titanium tetrachloride (0.88 mL, 8.0 mmol) to give a yellow-green mixture. A solution of *N*-Boc-4-piperidone (**2-20**) (0.40 g, 2.0 mmol) and *N*-adamantyl-4-piperidone (**2-19**) (0.52 g, 2.0 mmol) in THF (5 mL) was added, and the purple reaction mixture was stirred at room temperature for 8 h. The reaction was quenched with saturated K₂CO₃ solution (0.5 mL). The mixture was stirred at room temperature for 0.5 h, diluted with brine, and extracted with CHCl₃ (3 × 50 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give the **2-21** (0.21 g, 23%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 4.42 (br. d, *J*=13.0 Hz, 2H), 4.01 (br. d, *J*=12.4 Hz, 2H), 3.19-2.96 (m, 4H), 2.10-1.90 (m, 11H), 1.70 (s, 6H), 1.65-1.52 (m, 6H), 1.45 (s, 9H); HRMS (ESI) Exact mass calcd for C₂₆H₄₂N₂O₅ + H requires *m/z* 463.3172 Found *m/z* 463.3155

2-22

The reaction of **2-21** (125 mg, 0.27 mmol) as described for **2-9** gave **2-22** (98 mg, quant) as a colorless oil.

¹H NMR (CD₃OD, 270 MHz) δ_H 4.42 (br. d, *J*=13.0 Hz, 2H), 3.28-3.20 (m, 4H), 3.15 (br. t, *J*=13.0 Hz, 2H), 2.10-1.90 (m, 11H), 1.87-1.55 (m, 12H); HRMS (ESI) Exact mass calcd for C₂₁H₃₄N₂O₃ + H requires *m/z* 363.2648 Found *m/z* 363.2618

2-23

Compound **2-21** (50 mg, 0.14 mmol), trimethyl orthoformate (44 mg, 0.41 mmol), and benzoic acid (20 mg, 0.17 mmol) were mixed, and the resulting mixture was stirred at 150 °C under N₂ for 4h. This mixture was cooled to room temperature and purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give **2-23** (20 mg, 28%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 5.64 (s, 1H), 4.55-4.45 (br. d, *J*=12.7 Hz, 2H), 4.12-4.03 (m, 2H), 3.37 (s, 3H), 3.23-2.97 (m, 4H), 2.03 (m, 11H), 2.72 (s, 6H), 1.44 (s, 9H), 1.52-1.30 (m, 6H); HRMS (ESI) Exact mass calcd for C₂₈H₄₄N₂O₆ + H requires *m/z* 505.3278 Found *m/z* 505.3275

2-24

The reaction of **2-23** (15 mg, 0.03 mmol) as described for **2-9** gave **2-24** (12 mg, quant) as a colorless oil, which was used without further purification.

7

To a solution of amine **6** (25 mg, 0.046 mmol) and triethylamine (0.05 mL) in CH₂Cl₂ (2 mL) was added TBS-Cl (21 mg, 0.14 mmol). The resulting mixture was stirred at room temperature for 16 h, diluted with water, and extracted with CHCl₃ (3 × 10 mL). The combined extracts were dried over Na₂SO₄ and then concentrated in vacuum. The residue was purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give **7** (24 mg, 79%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 7.75 (d, *J*=8.1 Hz, 2H), 7.57 (d, *J*=8.4 Hz, 1H), 7.45 (d, *J*=3.5 Hz, 1H), 7.26-7.16 (m, 3H), 6.75 (d, *J*=3.5 Hz, 1H), 6.63 (d, *J*=8.4 Hz, 1H), 4.54 (br. s, 1H), 4.25 (m, 1H), 4.03 (t, *J*=5.4 Hz, 2H), 3.08 (br. m, 2H), 2.88-2.73 (m, 2H), 2.66 (m, 2H), 2.33 (s, 3H), 1.65-1.35 (m, 15H), 0.88 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); HRMS (ESI) Exact mass calcd for C₃₄H₅₃N₃O₆SSi + H requires *m/z* 660.3503 Found *m/z* 660.3497

2-26

The reaction of **7** (10 mg, 15 μmol) and **2-22** (12 mg, 32 μmol) as described for **2-13** to gave the crude **2-25** (7 mg, about 60% purity) as a yellow oil, which was used without further purification.

2-26, 27

To a solution of the crude **2-25** (7 mg, about 60% purity) in CH₂Cl₂ (1 mL) was added 1.0 M tetrabutylammonium fluoride tetrahydrofuran solution (0.1 mL). The resulting mixture was refluxed for 8 h and then concentrated. The residue was purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give the crude **2-26** as a yellow oil. To a solution of this crude oil in CHCl₃ (1 mL) was added TFA (0.5 mL). After being stirred at room temperature for 0.5 h, the reaction mixture was concentrated and purified by reversed-phase HPLC (ODS, 80% MeOH in 0.1% TFA) to give **2-27** (2.5 mg, three steps 10%) as a colorless oil.

¹H NMR (CD₃OD, 270 MHz) δ_H 7.77 (d, *J*=8.4 Hz, 2H), 7.60-7.52 (m, 2H), 7.31 (d, *J*=8.4 Hz, 2H), 7.21 (t, *J*=7.8 Hz, 1H), 6.85 (d, *J*=3.5 Hz, 1H), 6.71 (d, *J*=7.8 Hz, 1H), 4.45-4.35 (m, 2H), 4.14 (m, 1H), 4.05-4.01 (m, 2H), 3.65-3.35 (m, 4H), 3.22-3.02 (m, 6H), 2.89 (t, *J*=6.8 Hz, 2H), 2.34 (s, 3H), 2.08-1.92 (m, 11H), 1.77 (s, 6H), 1.75-1.25 (m, 12H); HRMS (ESI) Exact mass calcd for C₄₅H₆₃N₅O₈S + H requires *m/z* 834.4476 Found *m/z* 834.4451

2c

The reaction of **2-27** (1.2 mg, 1.4 μmol) as described for **2a** gave **2c** (1.3 mg, 72%) as a colorless oil.

¹H NMR (CD₃OD, 270 MHz) δ_H 7.76 (d, *J*=8.4 Hz, 2H), 7.56-7.52 (m, 2H), 7.30 (d, *J*=8.4 Hz, 2H), 7.21 (t, *J*=7.8 Hz, 1H), 6.85 (d, *J*=3.3 Hz, 1H), 6.71 (d, *J*=7.8 Hz, 1H), 4.45-4.35 (m, 3H), 4.28 (m, 1H), 4.14 (m, 1H), 4.05-4.01 (m, 2H), 3.65-3.35 (m, 4H), 3.22-3.02 (m, 12H), 2.95 (m, 1H), 2.75 (m, 2H), 2.34 (s, 3H), 2.25-2.15 (m, 6H), 2.08-1.92 (m, 11H), 1.77 (s, 6H), 1.75-1.25 (m, 30H); HRMS

(ESI) Exact mass calcd for $C_{67}H_{99}N_9O_{12}S + H$ requires m/z 1286.6933 Found m/z 1286.6931

2-28

The reaction of **7** (12 mg, 18 μ mol) and **2-24** (15 mg, 37 μ mol) as described for **2-13** gave the crude **2-28** (10 mg, about 40% purity) as a yellow oil, which was used without further purification.

2-29, 30

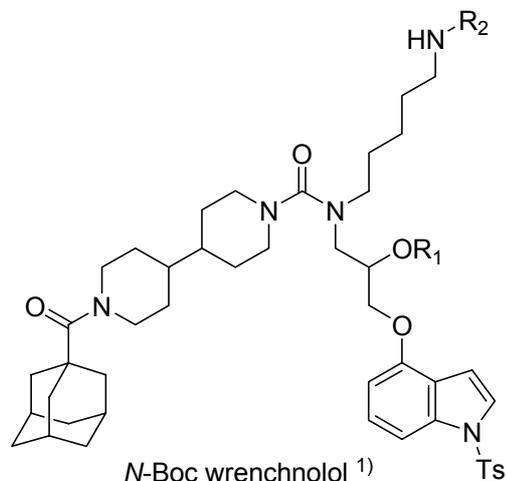
The reaction of **2-28** (10 mg) as described for **2-27** gave **2-30** (2.3 mg, three steps 15%) as a colorless oil.

1H NMR (CD_3OD , 270 MHz) δ_H 7.77 (d, $J=8.4$ Hz, 2H), 7.58-7.52 (m, 2H), 7.31 (d, $J=8.4$ Hz, 2H), 7.21 (t, $J=7.8$ Hz, 1H), 6.85 (d, $J=3.5$ Hz, 1H), 6.71 (d, $J=7.8$ Hz, 1H), 5.66 (s, 1H), 4.45-4.35 (m, 2H), 4.14 (m, 1H), 4.05-4.01 (m, 2H), 3.65-3.35 (m, 4H), 3.34 (s, 3H), 3.22-3.02 (m, 6H), 2.89 (t, $J=6.8$ Hz, 2H), 2.34 (s, 3H), 2.08-1.92 (m, 11H), 1.77 (s, 6H), 1.75-1.25 (m, 12H); HRMS (ESI) Exact mass calcd for $C_{47}H_{66}N_5O_9S + H$ requires m/z 876.4581 Found m/z 876.4575

2d

The reaction of **2-30** (1.1 mg, 1.3 μ mol) as described for **2a** gave **2d** (1.2 mg, 75%) as a colorless oil.

1H NMR (CD_3OD , 270 MHz) δ_H 7.76 (d, $J=8.4$ Hz, 2H), 7.56-7.52 (m, 2H), 7.30 (d, $J=8.4$ Hz, 2H), 7.21 (t, $J=7.8$ Hz, 1H), 6.85 (d, $J=3.3$ Hz, 1H), 6.71 (d, $J=7.8$ Hz, 1H), 5.66 (s, 1H), 4.45-4.35 (m, 3H), 4.28 (m, 1H), 4.14 (m, 1H), 4.05-4.01 (m, 2H), 3.65-3.35 (m, 4H), 3.34 (s, 3H), 3.22-3.02 (m, 12H), 2.95 (m, 1H), 2.75 (m, 2H), 2.34 (s, 3H), 2.25-2.15 (m, 6H), 2.08-1.92 (m, 11H), 1.77 (s, 6H), 1.75-1.25 (m, 30H); HRMS (ESI) Exact mass calcd for $C_{69}H_{101}N_9O_{13}S + H$ requires m/z 1328.7039 Found m/z 1328.7038



		R ₁	R ₂
a	3-1	H	Boc
b	3-2	Ac	Boc
b	3-3	Ac	H
c	3a	Ac	-XX-biotin
d	3-1	H	Boc
e	3-4	CH ₂ COOCH ₃	Boc
f	3-5	CH ₂ COOCH ₃	H
c	3-6	CH ₂ COOH	H
c	3b	CH ₂ COOH	-XX-biotin

Conditions: (a) Ac₂O, pyridine, rt. (b) TFA, CHCl₃, rt. (c) biotin-XX-NHS, Et₃N, DMSO, rt. (d) 2-bromoacetic acid methyl ester, KOH, DMF, rt. (e) TFA, CHCl₃, rt. (f) 1N KOH-MeOH, 45 °C

Scheme S3. Synthesis of 3a, 3b

3-2

N-Boc-wrenchnolol (**3-1**)¹⁾ (5.0 mg, 5.5 μmol) was dissolved in pyridine (1.0 mL), and acetic anhydride (0.1 mL) was added to the solution. After being stirred at room temperature for 1h, the reaction mixture was concentrated to give **3-2** (4.6 mg, 89%)

¹H NMR (CDCl₃, 270 MHz) δ_H 7.75 (m, 2H), 7.59 (m, 1H), 7.46 (m, 1H), 7.26-7.19 (m, 3H), 6.72-6.62 (m, 2H), 5.24 (m, 1H), 4.56 (m, 2H), 4.35-3.95 (m, 4H), 3.85-3.45 (m, 2H), 3.35-3.05 (m, 4H), 2.79-2.62 (m, 4H), 2.34 (m, 3H), 2.17-2.13 (m, 3H), 2.08 (m, 9H), 1.72 (s, 6H), 1.44 (s, 9H), 1.80-1.05 (m, 16H); HRMS (ESI) Exact mass calcd for C₅₂H₇₃N₅O₉S + H requires *m/z* 944.5207 Found *m/z* 944.5216

3-3

To a solution of **3-2** (4.0 mg, 4.7 μmol) in CHCl₃ (1 mL) was added TFA (0.5 mL). After being stirred at room temperature for 0.5 h, the reaction mixture was concentrated and purified by

reversed-phase HPLC (ODS, 80% MeOH in 0.1% TFA) to give **3-3** (3.9 mg, quant) as a colorless oil.

¹H NMR (CD₃OD, 270 MHz) δ_H 7.78 (d, *J*=8.4 Hz, 2H), 7.60-7.53 (m, 2H), 7.30 (d, *J*=8.4 Hz, 2H), 7.24 (m, 1H), 6.79-6.70 (m, 2H), 5.35 (m, 1H), 4.54-4.45 (m, 2H), 4.45-4.18 (m, 2H), 4.15-3.83 (m, 2H), 3.74-3.35 (m, 4H), 2.94 (m, 2H), 2.86-2.56 (m, 4H), 2.34 (s, 3H), 2.14 (s, 1.6H), 2.10 (s, 1.4H), 2.00 (s, 9H), 1.77 (s, 6H), 1.85-0.86 (m, 16H); HRMS (ESI) Exact mass calcd for C₄₇H₆₅N₅O₇S + H requires *m/z* 844.4683 Found *m/z* 844.4665

3a

The reaction of **3-3** (1.8 mg, 2.1 μmol) as described for **2a** gave **3a** (2.3 mg, 85%) as a colorless oil.

¹H NMR (CD₃OD, 270 MHz) δ_H 7.78 (d, *J*=8.4 Hz, 2H), 7.60-7.53 (m, 2H), 7.30 (d, *J*=8.4 Hz, 2H), 7.24 (m, 1H), 6.79-6.70 (m, 2H), 5.35 (m, 1H), 4.54-4.45 (m, 3H), 4.45-4.18 (m, 3H), 4.15-3.83 (m, 2H), 3.74-3.54 (m, 2H), 3.25-3.13 (m, 8H), 2.91 (dd, *J*=7.6, 3.4 Hz, 1H), 2.86-2.56 (m, 6H), 2.34 (s, 3H), 2.25-2.05 (m, 9H), 2.03 (s, 9H), 1.77 (s, 6H), 1.85-0.86 (m, 34H); HRMS (ESI) Exact mass calcd for C₆₉H₁₀₁N₉O₁₁S₂ + H requires *m/z* 1296.7140 Found *m/z* 1296.7137

3-4, 5, 6

To a solution of **3-1** (11 mg, 12 μmol) in DMF (1 mL) were added a piece of potassium hydroxide and methyl 2-bromoacetate (1.7 mg, 11 μmol). The resulting mixture was stirred at room temperature for 0.5 h, diluted with brine, and extracted with CHCl₃ (3 × 10 mL). The combined organic layers were dried with Na₂SO₄ and concentrated to give a crude yellow oil (13 mg). To a solution of this crude oil in CHCl₃ (1 mL) was added TFA (0.5 mL). After being stirred at room temperature for 0.5 h, the reaction mixture was concentrated to give a crude yellow oil (14 mg). This crude yellow oil was dissolved in MeOH (1 mL), and a solution of 1.0 N NaOH aqueous solution (0.5 ml) was added. This solution was stirred at 45 °C for 1h, and the organic solvent in the reaction mixture was evaporated in vacuum. The residual aqueous layer was diluted with brine and extracted with CHCl₃ (3 × 10 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. The residue was purified by reversed-phase HPLC (ODS, 80% MeOH in 0.1% TFA) to give **3-6** (3.3 mg, three steps 32%) as a colorless oil.

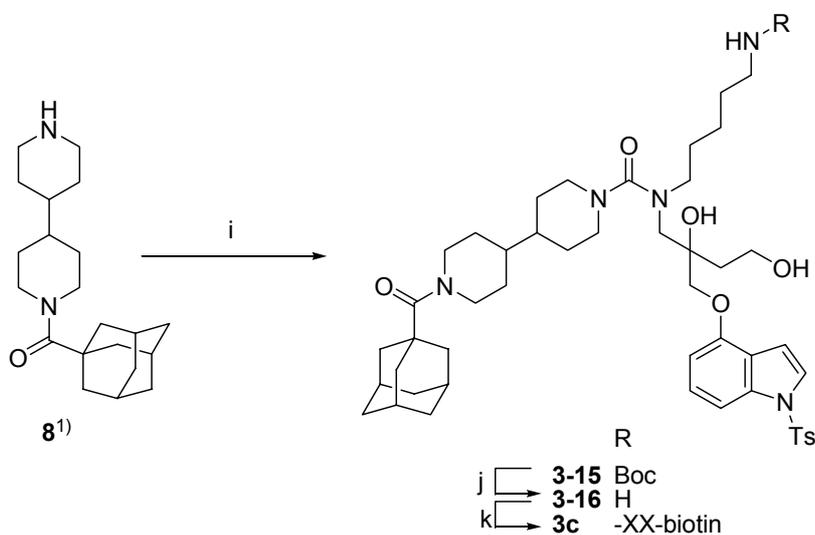
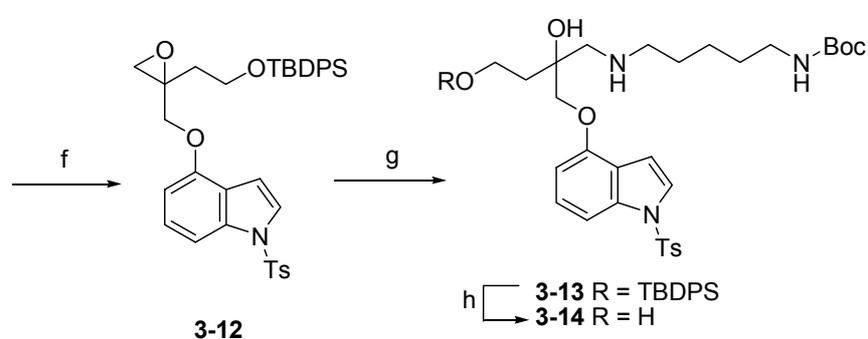
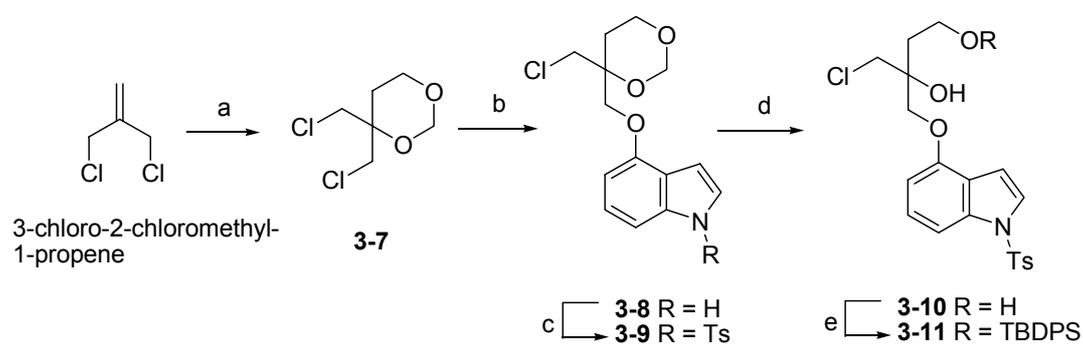
¹H NMR (CD₃OD, 270 MHz) δ_H 7.79 (d, *J*=8.6 Hz, 2H), 7.61-7.56 (m, 2H), 7.31 (d, *J*=8.6 Hz, 2H), 7.27 (m, 1H), 6.79-6.70 (m, 2H), 5.46 (m, 1H), 4.52-4.48 (m, 2H), 4.32 (m, 2H), 4.15-3.83 (m, 4H), 3.85-3.65 (m, 2H), 3.25-3.20 (m, 2H), 2.67 (m, 2H), 2.86-2.56 (m, 4H), 2.35 (s, 3H), 2.00 (s, 9H), 1.77 (s, 6H), 1.85-0.86 (m, 16H); HRMS (ESI) Exact mass calcd for C₄₇H₆₅N₅O₈S + H requires *m/z* 860.4632 Found *m/z* 860.4622

3b

The reaction of **3-6** (1.5 mg, 1.7 μmol) as described for **2a** gave **3b** (2.1 mg, 94%) as a colorless oil.

^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.79 (d, $J=8.1$ Hz, 2H), 7.62-7.57 (m, 2H), 7.31 (d, $J=8.1$ Hz, 2H), 7.24 (m, 1H), 6.82-6.76 (m, 2H), 5.50 (m, 1H), 4.60-4.45 (m, 3H), 4.38-4.30 (m, 3H), 4.25 (m, 2H), 4.22-3.95 (m, 2H), 3.90-3.60 (m, 2H), 3.25-3.13 (m, 8H), 2.89 (dd, $J=7.5, 3.4$ Hz, 1H), 2.86-2.63 (m, 6H), 2.35 (s, 3H), 2.25-2.05 (m, 6H), 2.03 (s, 9H), 1.77 (s, 6H), 1.85-0.86 (m, 34H); HRMS (ESI)

Exact mass calcd for $\text{C}_{69}\text{H}_{101}\text{N}_9\text{O}_{12}\text{S}_2 + \text{H}$ requires m/z 1312.7089 Found m/z 1312.7085



Conditions: (a) paraformaldehyde, H₂SO₄, CH₂Cl₂, rt. (b) 4-hydroxyindole, KOH, DMF, 120 °C (c) NaH, TsCl, THF, 0 °C (d) H₂SO₄, CH₃OH, 60 °C (e) TBDPSCI, imidazole, DMF, rt. (f) NaH, THF, reflux (g) *N*-Boc 1,5-diaminopentane, CH₃OH, reflux (h) TBAF, CH₂Cl₂, rt. (i) (1) CDI, THF, reflux (2) CH₃I, CH₃CN, rt. (3) amine **3-14**, Et₃N, CH₂Cl₂, rt. (j) TFA, CHCl₃, rt. (k) biotin-XX-NHS, Et₃N, DMSO, rt.

Scheme S4. Synthesis of 3c

3-7

To a solution of 3-chloro-2-chloromethyl-1-propene (0.40 g, 3.2 mmol) in dichloromethane (10 mL) were added paraformaldehyde (0.30 g) and then concentrated sulfuric acid (0.20 ml, 3.7 mmol). After being stirred at room temperature for 8 h, the reaction mixture was diluted with water (100 mL) and extracted with CHCl₃ (3 × 100 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with hexane/ethylacetate mixtures to give **3-7** (0.16 g, 18%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 4.86 (s, 2H), 3.89 (t, *J*=5.4 Hz, 2H), 3.81 (d, *J*=11.9 Hz, 2H), 3.69 (d, *J*=11.9 Hz, 2H), 1.88 (t, *J*=5.4 Hz, 2H); HRMS (ESI) Exact mass calcd for C₆H₁₀Cl₂O₂ + H requires *m/z* 185.0136 Found *m/z* 185.0121

3-8

To a solution of 4-hydroxyindole (0.47 g, 3.5 mmol) in dimethylsulfoxide (10 mL) were added potassium hydroxide (0.60 g, 11 mmol) and then **3-7** (2.5 g, 14 mmol). After being stirred at 120 °C for 14 h, the reaction mixture was diluted with a saturated solution of NH₄Cl (100 mL) and extracted with diethyl ether (3 × 100 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with benzene/acetone mixtures to give **3-8** (0.10 g, 10%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 8.20 (s, 1H), 7.16-7.05 (m, 3H), 6.64-6.57 (m, 2H), 5.04 (d, *J*=6.8 Hz, 1H), 4.98 (d, *J*=6.8 Hz, 1H), 4.38 (d, *J*=9.5 Hz, 1H), 4.25 (d, *J*=9.5 Hz, 1H), 4.04-3.99 (m, 3H), 3.89 (d, *J*=11.3 Hz, 1H), 2.16-2.00 (m, 2H); HRMS (ESI) Exact mass calcd for C₁₄H₁₆ClNO₃ + H requires *m/z* 282.0897 Found *m/z* 282.0877

3-9

A solution of **3-8** (50 mg, 0.18 mmol) in THF (3 mL) was cooled to 0 °C, and sodium hydride in mineral oil (60%, 8.3 mg, 0.21 mmol) and tosyl chloride (34 mg, 0.18 mmol) were added. After being stirred at this temperature for 10 min, the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was diluted with water and extracted with CHCl₃ (3 × 50 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with benzene/acetone mixtures to give the **3-9** (73 mg, 93%) as a white solid.

¹H NMR (CDCl₃, 270 MHz) δ_H 7.65 (d, *J*=8.4 Hz, 2H), 7.53 (d, *J*=8.4 Hz, 1H), 7.38 (d, *J*=3.8 Hz, 1H), 7.16-7.10 (m, 3H), 6.63-6.58 (m, 2H), 4.87 (d, *J*=6.8 Hz, 1H), 4.83 (d, *J*=6.8 Hz, 1H), 4.18 (d, *J*=9.7 Hz, 1H), 4.03 (d, *J*=9.7 Hz, 1H), 3.89-3.85 (m, 3H), 3.71 (d, *J*=11.6 Hz, 1H), 2.34 (s, 3H), 1.93-1.85 (m, 2H); HRMS (ESI) Exact mass calcd for C₂₁H₂₂ClNO₅S + H requires *m/z* 436.0985 Found *m/z* 436.0992

3-10

A solution of **3-9** (80 mg, 0.18 mmol) in methanol (10 mL) was added conc. H₂SO₄ (one drop). This solution was stirred at 60 °C for 48 h and then concentrated to about 3 mL at room temperature in vacuum. The reaction mixture was diluted with brine (50 ml) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried with Na₂SO₄, and concentrated. The residue was purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give **3-10** (75 mg, 98%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 7.75 (d, *J*=8.4 Hz, 2H), 7.62 (d, *J*=8.4 Hz, 1H), 7.48 (d, *J*=3.8 Hz, 1H), 7.25-7.20 (m, 3H), 6.73-6.67 (m, 2H), 4.12 (s, 2H), 3.95 (t, *J*=5.7 Hz, 2H), 3.79 (s, 2H), 2.34 (s, 3H), 2.05 (t, *J*=5.7 Hz, 2H); HRMS (ESI) Exact mass calcd for C₂₀H₂₂ClNO₅S + H requires *m/z* 424.0985 Found *m/z* 424.0980

3-11

To a solution of **3-10** (72 mg, 0.17 mmol) and imidazole (23 mg, 0.34 mmol) in DMF (2 mL) was added TBDPS-Cl (56 mg, 0.20 mmol). The resulting mixture was stirred at room temperature for 0.5 h, diluted with water, and extracted with CHCl₃ (3 × 10 mL). The combined extracts were dried over Na₂SO₄ and then concentrated in vacuum. The residue was purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give **3-11** (110 mg, 98%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 7.75 (d, *J*=8.4 Hz, 2H), 7.67-7.63 (m, 5H), 7.46-7.33 (m, 7H), 7.25-7.18 (m, 3H), 6.70-6.63 (m, 2H), 4.17 (d, *J*=9.5 Hz, 1H), 4.08 (d, *J*=9.5 Hz, 1H), 3.95 (t, *J*=6.0 Hz, 2H), 3.82 (d, *J*=11.0 Hz, 1H), 3.75 (d, *J*=11.0 Hz, 1H), 2.34 (s, 3H), 2.05 (t, *J*=6.0 Hz, 2H), 1.05 (s, 9H); HRMS (ESI) Exact mass calcd for C₃₆H₄₀ClNO₅SSi + H requires *m/z* 662.2163 Found *m/z* 662.2142

3-12

A solution of **3-11** (60 mg, 91 μmol) in THF (5 mL) was cooled to 0 °C, and sodium hydride in mineral oil (60%, 5.5 mg, 0.14 mmol) was added. After being stirred at this temperature for 10 min, the reaction mixture was allowed to warm to reflux and stirred for 8 h. The reaction mixture was diluted with water and extracted with CHCl₃ (3 × 20 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give **3-12** (55 mg, 97%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 7.74 (d, *J*=8.4 Hz, 2H), 7.62-7.58 (m, 5H), 7.44-7.28 (m, 7H), 7.21-7.14 (m, 3H), 6.70 (d, *J*=3.8 Hz, 1H), 6.56 (d, *J*=7.8 Hz, 1H), 4.20 (d, *J*=10.5 Hz, 1H), 4.02 (d, *J*=10.5 Hz, 1H), 3.84 (m, 2H), 2.86 (m, 2H), 2.33 (s, 3H), 2.25 (m, 1H), 1.86 (m, 1H), 1.00 (s, 9H); HRMS (ESI) Exact mass calcd for C₃₆H₃₉NO₅SSi + H requires *m/z* 626.2396 Found *m/z* 626.2389

3-13

To a solution of **3-12** (55 mg, 88 μmol) in methanol (2 mL) was added *N*-Boc-1,5-pentanediamine (36 mg, 0.18 mmol). The solution was stirred at reflux for 4 h and then concentrated in vacuum. The residue was purified by column chromatography on silica gel with CHCl_3 /methanol mixtures to give **3-13** (73 mg, quant) as a colorless oil.

^1H NMR (CDCl_3 , 270 MHz) δ_{H} 7.76 (d, $J=8.4$ Hz, 2H), 7.62-7.56 (m, 5H), 7.44-7.28 (m, 7H), 7.21-7.14 (m, 3H), 6.70-6.57 (m, 2H), 4.52 (br. s, 1H), 4.09-3.89 (br. m, 4H), 3.18-3.02 (br. m, 2H), 2.92 (d, $J=11.4$ Hz, 1H), 2.78 (d, $J=11.4$ Hz, 1H), 2.64 (d, $J=3.5$ Hz, 2H), 2.34 (s, 3H), 1.98 (m, 2H), 1.55-1.26 (m, 15H), 1.02 (s, 9H); HRMS (ESI) Exact mass calcd for $\text{C}_{46}\text{H}_{61}\text{N}_3\text{O}_7\text{SSi} + \text{H}$ requires m/z 825.4078 Found m/z 825.4076

3-14

To a solution of **3-13** (73 mg, 88 μmol) in CH_2Cl_2 (5 mL) was added 1.0 M tetrabutylammonium fluoride tetrahydrofuran solution (0.13 mL). The resulting mixture was stirred at room temperature for 0.5 h, concentrated, and purified by column chromatography on silica gel with CHCl_3 /methanol mixtures to give **3-14** (54 mg, quant) as a colorless oil.

^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.74 (d, $J=8.4$ Hz, 2H), 7.58 (d, $J=8.4$ Hz, 1H), 7.53 (d, $J=3.5$ Hz, 1H), 7.27-7.19 (m, 3H), 6.86 (d, $J=3.5$ Hz, 1H), 6.74 (d, $J=8.4$ Hz, 1H), 4.03 (s, 2H), 3.83 (m, 1H), 3.73 (m, 1H), 3.16-2.97 (m, 4H), 2.84 (m, 2H), 2.30 (s, 3H), 1.97 (m, 2H), 1.62 (m, 2H), 1.49-1.33 (m, 13H); HRMS (ESI) Exact mass calcd for $\text{C}_{30}\text{H}_{43}\text{N}_3\text{O}_7\text{S} + \text{H}$ requires m/z 590.2900 Found m/z 590.2923

3-18

The reaction of amine **8**¹⁾ (15 mg, 45 μmol) and **3-14** (32 mg, 54 μmol) as described for **2-13** gave **3-18** (22 mg, 52%) as a colorless oil.

^1H NMR (CDCl_3 , 270 MHz) δ_{H} 7.75 (d, $J=8.1$ Hz, 2H), 7.58 (d, $J=8.4$ Hz, 1H), 7.46 (d, $J=3.8$ Hz, 1H), 7.25-7.15 (m, 3H), 6.75 (d, $J=3.8$ Hz, 1H), 6.63 (d, $J=8.4$ Hz, 1H), 4.55 (m, 2H), 4.29 (m, 2H), 4.40-3.80 (br. m, 2H), 4.01 (s, 2H), 3.66 (d, $J=6.8$ Hz, 2H), 3.01 (m, 2H), 2.97-2.42 (m, 6H), 2.34 (s, 3H), 2.00 (m, 11H), 1.72-1.63 (m, 8H), 1.49-1.33 (m, 23H); HRMS (ESI) Exact mass calcd for $\text{C}_{52}\text{H}_{75}\text{N}_5\text{O}_9\text{S} + \text{H}$ requires m/z 946.5364 Found m/z 946.5381

3-16

The reaction of **3-15** (20 mg, 21 μmol) as described for **3-3** gave **3-16** (18 mg, quant) as a colorless oil.

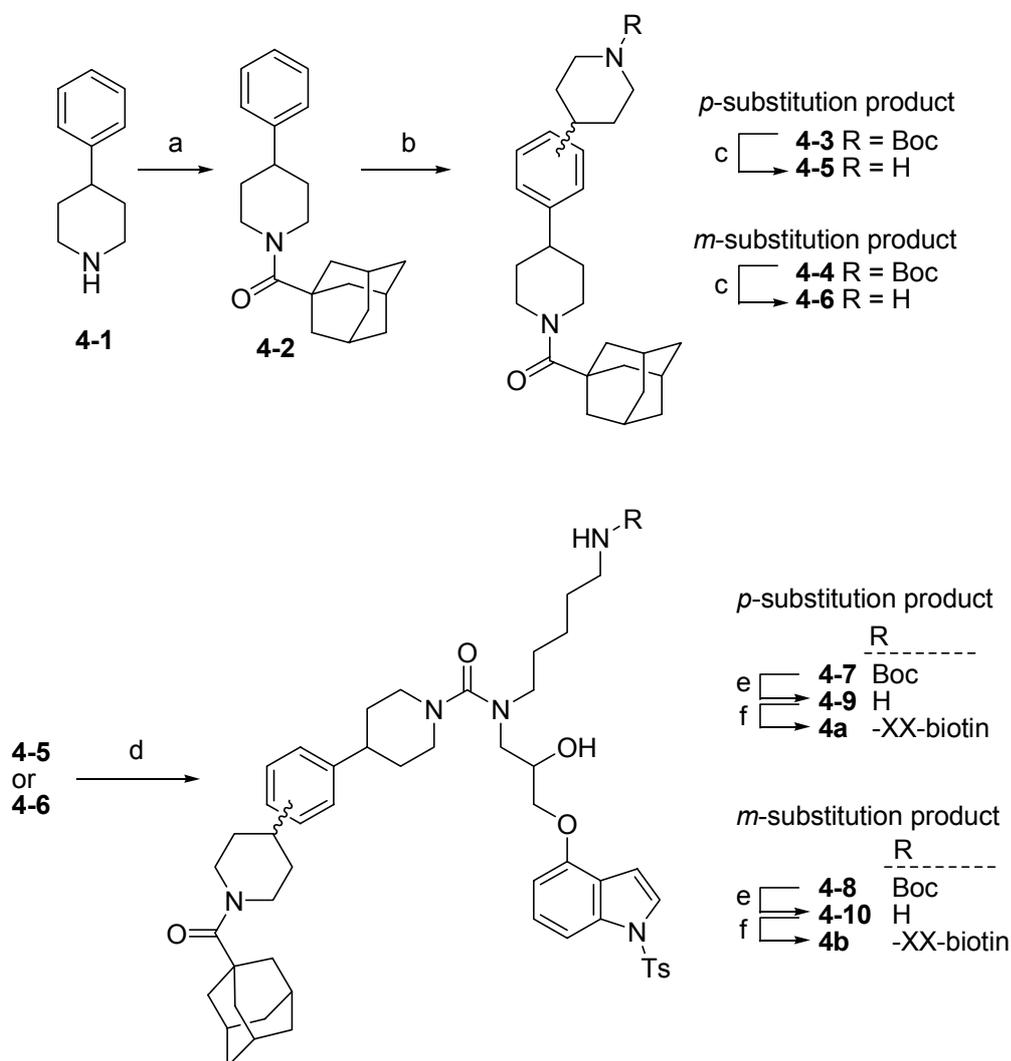
^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.79 (d, $J=8.1$ Hz, 2H), 7.63-7.58 (m, 2H), 7.33-7.22 (m, 3H), 6.85

(d, $J=3.8$ Hz, 1H), 6.74 (d, $J=8.1$ Hz, 1H), 4.54 (m, 2H), 4.42-4.15 (m, 2H), 4.07 (br. m, 2H), 3.85 (m, 1H), 3.56 (m, 1H), 3.16 (m, 1H), 3.03 (m, 2H), 2.90 (m, 2H), 2.75 (m, 2H), 2.34-2.25 (m, 5H), 2.02 (m, 11H), 1.78 (m, 6H), 1.75-0.84 (m, 16H); HRMS (ESI) Exact mass calcd for $C_{47}H_{67}N_5O_7S + H$ requires m/z 846.4839 Found m/z 846.4852

3c

The reaction of **3-16** (8 mg, 9.5 μ mol) as described for **2a** gave **3c** (11 mg, 87%) as a colorless oil.

1H NMR (CD_3OD , 270 MHz) δ_H 7.79 (d, $J=8.4$ Hz, 2H), 7.63-7.58 (m, 2H), 7.33-7.22 (m, 3H), 6.86 (d, $J=3.5$ Hz, 1H), 6.74 (d, $J=8.4$ Hz, 1H), 4.56-4.45 (m, 3H), 4.43-4.22 (m, 3H), 4.08 (m, 2H), 3.85 (m, 1H), 3.56 (m, 1H), 3.16-3.11 (m, 8H), 3.10 (m, 2H), 2.91 (dd, $J=7.5, 3.4$ Hz, 1H), 2.85-2.62 (m, 4H), 2.35 (m, 3H), 2.34-2.10 (m, 8H), 2.01 (m, 11H), 1.78-0.84 (m, 40H); HRMS (ESI) Exact mass calcd for $C_{69}H_{103}N_9O_{11}S_2 + H$ requires m/z 1298.7297 Found m/z 1298.7301



Conditions: (a) adamantanecarbonyl chloride, Et₃N, CHCl₃, rt. (b) (1)4-bromopiperidine, AlCl₃, 120 °C (2) (Boc)₂O, CHCl₃, rt. (c) TFA, CHCl₃, rt. (d) (1) CDI, THF, reflux (2) CH₃I, CH₃CN, rt. (3) amine **6**, Et₃N, CH₂Cl₂, rt. (e) TFA, CHCl₃, rt. (f) biotin-XX-NHS, Et₃N, DMSO, rt.

Scheme S5. Synthesis of 4a, 4b

4-2

To a solution of 4-phenylpiperidine (**4-1**) (150 mg, 0.93 mmol) and triethylamine (0.5 mL) in CHCl₃ (5 mL) was added a solution of 1-adamantanecarbonyl chloride (220 mg, 1.1 mmol) in CHCl₃ (2 mL). The resulting mixture was stirred at room temperature for 0.5 h, diluted with water, and extracted with CHCl₃ (3 × 20 mL). The combined extracts were dried over Na₂SO₄ and then concentrated in vacuum. The residue was purified by column chromatography on silica gel with methanol/CHCl₃ mixtures to give **4-2** (300 mg, quant) as a colorless oil.

IR (thin film) 2911, 2849, 1622 cm⁻¹

¹H NMR (CDCl₃, 270 MHz) δ_H 7.34-7.18 (m, 5H), 4.68 (br. d, *J*=13.0 Hz, 2H), 2.86 (br. t, *J*=13.0 Hz, 2H), 2.77 (tt, *J*=4.1, 12.4 Hz, 1H), 2.05 (s, 9H), 1.93-1.88 (m, 2H), 1.74 (s, 6H), 1.74-1.55 (m, 2H); HRMS (ESI) Exact mass calcd for C₂₂H₂₉NO + H requires *m/z* 324.2327. Found *m/z* 324.2349.

4-3, 4

A mixture of **4-2** (100 mg, 0.31 mmol), 4-bromopiperidine hydrobromide (60 mg, 0.25 mmol), and AlCl₃ (83 mg, 0.62 mmol) was heated for 2 h at 120 °C, diluted with 1N NaOH aq., and extracted with CHCl₃ (3 × 20 mL). The combined organic layers were dried with NaSO₄ and concentrated, which gave the mixture of *m*, *p*-substitution product. To a solution of this *m*, *p*-mixture in CHCl₃ (5 mL) was added Boc-ON (74 mg, 0.3 mmol). After being stirred at room temperature for 2 h, the reaction mixture was washed with water (3 × 20 mL). The organic layer was dried with NaSO₄ and concentrated. The residue was purified by column chromatography on silica gel (CHCl₃/methanol) and reversed-phase HPLC (Phenyl, 80%MeOH) to give the *N*-Boc-*p*-substitution product **4-3** (22 mg, 14%) and *N*-Boc-*m*-substitution product **4-4** (32 mg, 20%) as a colorless oil, respectively.

4-3

IR (thin film) 3447, 1636 cm⁻¹

¹H NMR (CDCl₃, 270 MHz) δ_H 7.14 (s, 4H), 4.67 (br. d, *J*=13.2 Hz, 2H), 4.23 (br. d, *J*=13.2 Hz, 2H), 2.89-2.74 (m, 4H), 2.62 (tt, *J*=4.1, 12.4 Hz, 2H), 2.04 (s, 9H), 1.91-1.75 (m, 4H), 1.74 (s, 6H), 1.73-1.47 (m, 4H), 1.48 (s, 9H); HRMS (ESI) Exact mass calcd for C₃₂H₄₆N₂O₃ + H requires *m/z* 507.3587. Found *m/z* 507.3585.

4-4

IR (thin film) 3443, 1681, 1632 cm⁻¹

¹H NMR (CDCl₃, 270 MHz) δ_H 7.25 (t, *J*=7.6 Hz, 1H), 7.06-7.03 (m, 3H), 4.67 (br. d, *J*=13.0 Hz, 2H), 4.25 (br. d, *J*=13.0 Hz, 2H), 2.89-2.74 (m, 4H), 2.62 (tt, *J*=4.1, 12.1 Hz, 2H), 2.04 (s, 9H), 1.90-1.75 (m, 4H), 1.74 (s, 6H), 1.73-1.54 (m, 4H), 1.49 (s, 9H); HRMS (ESI) Exact mass calcd for C₃₂H₄₆N₂O₃ + H requires *m/z* 507.3587. Found *m/z* 507.3602.

4-5

To a solution of **4-3** (20 mg, 0.04 mmol) in CHCl₃ (3 mL) was added TFA (3 mL). This solution was stirred at room temperature for 15 min, diluted with 1N NaOH aq., and extracted with CHCl₃ (3 × 20 mL). The combined organic layers were dried with NaSO₄ and concentrated to give **4-5** (16 mg, quant) as a colorless oil, which was used without further purification for the next reaction.

IR (thin film) 3446, 1688, 1636 cm⁻¹

¹H NMR (CDCl₃, 270 MHz) δ_H 7.16 (s, 4H), 4.68 (br. d, *J*=13.5 Hz, 2H), 3.59 (br. d, *J*=11.3 Hz, 2H), 3.08 (m, 2H), 2.91 (t, *J*=12.7 Hz, 2H), 2.78 (m, 2H), 2.04 (s, 9H), 1.94-1.90 (m, 4H), 1.74 (s, 6H), 1.73-1.55 (m, 4H); HRMS (ESI) Exact mass calcd for C₂₇H₃₈N₂O + H requires *m/z* 407.3062. Found

m/z 407.3059.

4-6

The reaction of **4-4** (30 mg, 0.06 mmol) as described for **4-5** gave **4-6** (24 mg, quant) as a colorless oil.

IR (thin film) 3451, 1680, 1644 cm^{-1}

^1H NMR (CDCl_3 , 270 MHz) δ_{H} 7.28 (t, $J=7.6$ Hz, 1H), 7.11-7.05 (m, 3H), 4.68 (br. d, $J=13.5$ Hz, 2H), 3.60 (br. d, $J=12.2$ Hz, 2H), 3.10 (m, 2H), 2.92 (t, $J=12.7$ Hz, 2H), 2.79 (m, 2H), 2.07 (s, 3H), 2.04 (s, 6H), 1.99-1.90 (m, 4H), 1.74 (s, 6H), 1.73-1.55 (m, 4H); HRMS (ESI) Exact mass calcd for $\text{C}_{27}\text{H}_{38}\text{N}_2\text{O} + \text{H}$ requires m/z 407.3062. Found m/z 407.3059.

4-7

The reaction of **4-5** (7.0 mg, 17 μmol) and amine **6** (11 mg, 21 μmol) as described for **2-13** gave **4-7** (8.2 mg, 49%) as a colorless oil.

^1H NMR (CDCl_3 , 270 MHz) δ_{H} 7.75 (d, $J=8.4$ Hz, 2H), 7.57 (d, $J=8.4$ Hz, 1H), 7.44 (d, $J=3.1$ Hz, 1H), 7.26-7.12 (m, 7H), 6.75 (d, $J=3.1$ Hz, 1H), 6.66 (d, $J=8.4$ Hz, 1H), 5.21 (br. m, 1H), 4.67 (m, 2H), 4.35-4.26 (m, 4H), 3.17-3.02 (m, 4H), 2.92-2.58 (m, 8H), 2.34 (s, 3H), 2.10 (s, 9H), 1.95-1.20 (m, 29H); HRMS (ESI) Exact mass calcd for $\text{C}_{56}\text{H}_{75}\text{N}_5\text{O}_8\text{S} + \text{H}$ requires m/z 978.5415 Found m/z 978.5425

4-8

The reaction of **4-6** (3.0 mg, 7.4 μmol) and amine **6** (4.8 mg, 8.8 μmol) as described for **2-13** gave **4-8** (4.2 mg, 58%) as a colorless oil.

^1H NMR (CDCl_3 , 270 MHz) δ_{H} 7.74 (m, 2H), 7.62 (m, 1H), 7.48 (m, 1H), 7.26-7.20 (m, 4H), 7.07-6.99 (m, 3H), 6.74 (m, 1H), 6.66 (d, $J=8.4$ Hz, 1H), 5.35 (br. m, 1H), 4.67 (m, 2H), 4.45-4.06 (m, 4H), 3.75-3.25 (m, 2H), 3.12 (m, 2H), 2.92-2.58 (m, 8H), 2.33 (s, 3H), 2.04 (s, 9H), 1.95-1.20 (m, 29H); HRMS (ESI) Exact mass calcd for $\text{C}_{56}\text{H}_{75}\text{N}_5\text{O}_8\text{S} + \text{H}$ requires m/z 978.5415 Found m/z 978.5430

4-9

The reaction of **4-7** (7.0 mg, 7.2 μmol) as described for **3-3** gave **4-9** (7.0 mg, quant) as a colorless oil.

^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.76-7.53 (m, 4H), 7.28-7.14 (m, 7H), 6.86-6.76 (m, 2H), 5.45 (br. m, 1H), 4.65 (m, 2H), 4.36-4.07 (m, 4H), 3.48 (m, 2H), 3.29 (m, 2H), 3.13-2.80 (m, 7H), 2.60 (m, 1H), 2.30 (s, 3H), 2.04 (s, 9H), 1.95-1.40 (m, 20H); HRMS (ESI) Exact mass calcd for $\text{C}_{51}\text{H}_{67}\text{N}_5\text{O}_6\text{S} + \text{H}$ requires m/z 878.4890 Found m/z 878.4880

4-10

The reaction of **4-8** (4.0 mg, 4.1 μmol) as described for **3-3** gave **4-10** (3.6 mg, quant) as a colorless oil.

^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.76-7.54 (m, 4H), 7.28-7.18 (m, 4H), 7.18-6.94 (m, 3H), 6.81 (m, 2H), 5.41 (br. m, 1H), 4.65 (m, 2H), 4.37-4.03 (m, 4H), 3.48 (m, 2H), 3.12 (m, 2H), 3.13-2.80 (m, 7H), 2.60 (m, 1H), 2.29 (s, 3H), 2.04 (s, 9H), 1.95-1.40 (m, 20H); HRMS (ESI) Exact mass calcd for $\text{C}_{51}\text{H}_{67}\text{N}_5\text{O}_6\text{S} + \text{H}$ requires m/z 878.4890 Found m/z 878.4895

4a

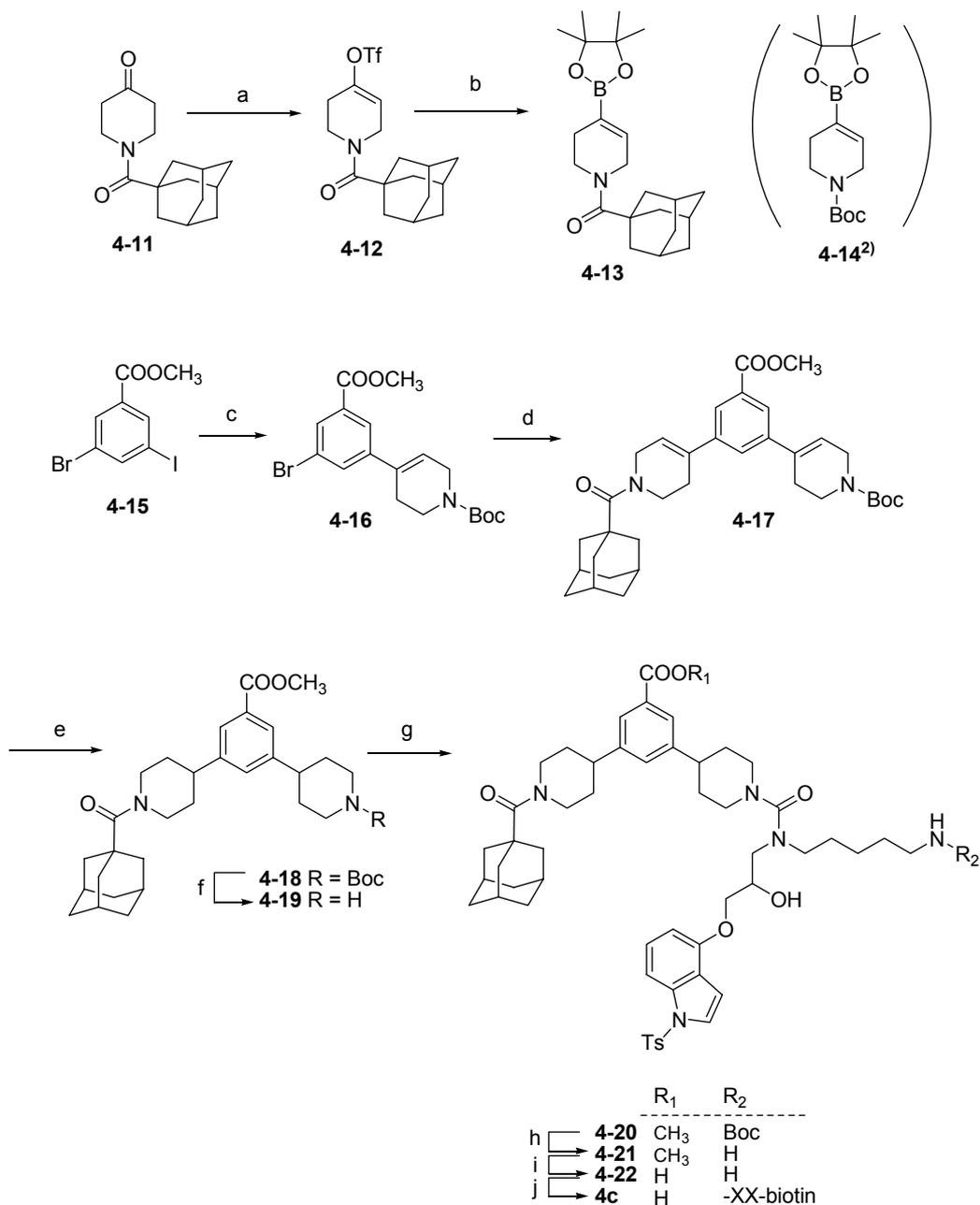
The reaction of **4-9** (3.0 mg, 3.4 μmol) as described for **2a** gave **4a** (3.9 mg, 86%) as a colorless oil.

^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.76-7.53 (m, 4H), 7.28-7.12 (m, 7H), 6.86-6.76 (m, 2H), 5.45 (br. m, 1H), 4.65 (m, 2H), 4.60-4.07 (m, 6H), 3.48 (m, 2H), 3.20-3.06 (m, 8H), 2.93-2.52 (m, 9H), 2.30 (s, 3H), 2.20-2.13 (m, 6H), 2.04 (s, 9H), 1.95-1.40 (m, 38H); HRMS (ESI) Exact mass calcd for $\text{C}_{73}\text{H}_{103}\text{N}_9\text{O}_{10}\text{S}_2 + \text{H}$ requires m/z 1330.7348 Found m/z 1330.7371

4b

The reaction of **4-10** (1.7 mg, 1.9 μmol) as described for **2a** gave **4b** (2.3 mg, 89%) as a colorless oil.

^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.85-7.52 (m, 4H), 7.35-7.18 (m, 4H), 7.11-6.94 (m, 3H), 6.81 (m, 2H), 5.42 (br. m, 1H), 4.65 (m, 2H), 4.52-4.05 (m, 6H), 3.48 (m, 2H), 3.20-3.06 (m, 8H), 2.93-2.58 (m, 9H), 2.32 (s, 3H), 2.20-2.13 (m, 6H), 2.07 (s, 9H), 1.95-1.40 (m, 38H); HRMS (ESI) Exact mass calcd for $\text{C}_{73}\text{H}_{103}\text{N}_9\text{O}_{10}\text{S}_2 + \text{H}$ requires m/z 1330.7348 Found m/z 1330.7346



Conditions: (a) (1) LDA, DME, -78 °C (2) Ph-N(Tf)₂, 0 °C (b) bis(pinacolato)diboron, PdCl₂(dppf), dppf, KOAc, dioxane, 80 °C (c) **4-14**, PdCl₂(dppf), K₂CO₃, DME, rt. (d) **4-13**, PdCl₂(dppf), K₂CO₃, DME, 80 °C (e) Pd-C, H₂, EtOAc, rt. (f) TFA, CHCl₃, rt. (g) (1) CDI, THF, reflux (2) CH₃I, CH₃CN, rt. (3) amine **6**, Et₃N, CH₂Cl₂, rt. (h) TFA, CHCl₃, rt. (i) 1N KOH-MeOH, rt. (j) biotin-XX-NHS, Et₃N, DMSO, rt.

Scheme S6. Synthesis of 4c

4-12

To a freshly prepared solution of LDA in DME (5 mL), from diisopropylamine (0.21 mL, 1.5 mmol) and *n*-BuLi (2 M in hexane, 0.76 mL, 1.5 mmol) at -78 °C, was added a solution of *N*-adamantyl-4-piperidone (**4-11**) (330 mg, 1.3 mmol) in DME (5 mL). After the resulting mixture was stirred at -78 °C for 1 h, a solution of *N*-phenyltrifluoromethanesulfonimide (350 mg, 1.39 mmol) in DME (5 mL) was added dropwise. After stirring for an additional 1 h, the solution was allowed to slowly warm to room temperature. The solvent was removed, and the residue was purified by column chromatography on silica gel with methanol/CHCl₃ mixtures to give **4-12** (360 mg, 73%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 5.80 (m, 1H), 4.25 (dd, *J*=5.7, 2.7 Hz, 2H), 3.87 (t, *J*=5.7 Hz, 2H), 2.49 (m, 2H), 2.06 (s, 3H), 1.99 (m, 6H), 1.73 (s, 6H); HRMS (ESI) Exact mass calcd for C₁₇H₂₂NO₄S + H requires *m/z* 394.1300 Found *m/z* 394.1321

4-13

To a solution of bis(pinacolate)diboron (180 mg, 0.70 mmol), KOAc (190 mg, 1.9 mmol), dppf* (11 mg, 0.019 mmol), PdCl₂dppf (16 mg, 0.019 mmol) in dioxane (5 mL) was added a solution of **4-12** (250 mg, 0.64 mmol) in dioxane (5 mL). The resulting mixture was stirred under N₂ at 80 °C for 5 h, and solvent was removed. The residue was diluted with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give **4-13** (220 mg, 93%) as a colorless oil.

*dppf : 1, 1'-Bis(diphenylphosphino)-ferrocene

¹H NMR (CDCl₃, 270 MHz) δ_H 6.47 (m, 1H), 4.15 (dd, *J*=5.7, 2.7 Hz, 2H), 3.71 (t, *J*=5.7 Hz, 2H), 2.27 (m, 2H), 2.00 (s, 9H), 1.72 (m, 6H), 1.26 (s, 12H); HRMS (ESI) Exact mass calcd for C₂₂H₃₄BNO₃ + H requires *m/z* 372.2710 Found *m/z* 372.2697

4-16

To a solution of methyl 3-bromo-5-iodobenzoate (**4-15**) (290 mg, 0.85 mmol), PdCl₂dppf (35 mg, 0.043 mmol), KOAc (210 mg, 2.1 mmol) in DMF (5 mL) was added a solution of *N*-Boc-1,2,5,6-tetrahydropyridine-4-(pinacolato)boronate (**4-14**)² (220 mg, 0.71 mmol) in DMF (5 mL). The resulting mixture was stirred under N₂ at room temperature for 8 h, diluted with water (100 mL), and extracted with EtOAc/hexane (3 × 100 mL). The combined organic layers were dried with Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel with CHCl₃/methanol mixtures to give **4-16** (210 mg, 75%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 8.05 (t, *J*=1.6 Hz, 1H), 7.96 (t, *J*=1.6 Hz, 1H), 7.68 (t, *J*=1.6 Hz, 1H), 6.13 (m, 1H), 4.10 (m, 2H), 3.93 (s, 3H), 3.64 (t, *J*=5.9 Hz, 2H), 2.51 (m, 2H), 1.50 (s, 9H); HRMS

(ESI) Exact mass calcd for $C_{18}H_{22}BrNO_4 + H$ requires m/z 396.0810 Found m/z 396.0815

4-17

To a solution of **4-16** (180 mg, 0.46 mmol), $PdCl_2dppf$ (22 mg, 0.027 mmol), KOAc (130 mg, 1.4 mmol) in DMF (5 mL) was added a solution of **4-13** (170 mg, 0.46 mmol) in DMF (5 mL). The resulting mixture was stirred under N_2 at 80 °C for 8 h, diluted with water (100 mL), and extracted with EtOAc/hexane (3 × 100 mL). The combined organic layers were dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel with $CHCl_3$ /methanol mixtures to give **4-17** (205 mg, 80%) as a colorless oil.

1H NMR ($CDCl_3$, 270 MHz) δ_H 7.93 (d, $J=1.6$ Hz, 2H), 7.54 (t, $J=1.6$ Hz, 1H), 6.16 (m, 1H), 6.10 (m, 1H), 4.30 (m, 2H), 4.08 (m, 2H), 3.92-3.86 (m, 5H), 3.64 (t, $J=5.9$ Hz, 2H), 2.62-2.51 (m, 4H), 2.05 (s, 9H), 1.74 (s, 6H), 1.50 (s, 9H); HRMS (ESI) Exact mass calcd for $C_{34}H_{44}N_2O_5 + H$ requires m/z 561.3328 Found m/z 561.3306

4-18

Compound **4-17** (200 mg, 0.36 mmol) was dissolved in methanol (50 mL), and 10% Pd-C (20 mg) was added. After 12 h stirring at room temperature under H_2 , the resulting solution was filtered through a Celite pad. The filtrate was evaporated to dryness to give **4-18** (166 mg, 82 %) as a yellow oil.

1H NMR ($CDCl_3$, 270 MHz) δ_H 7.73 (s, 2H), 7.22 (s, 1H), 4.68 (m, 2H), 4.25 (m, 2H), 3.90 (s, 3H), 2.96-2.64 (m, 6H), 2.04 (s, 9H), 1.99-1.61 (m, 14H), 1.48 (s, 9H); HRMS (ESI) Exact mass calcd for $C_{34}H_{48}N_2O_5 + H$ requires m/z 565.3641 Found m/z 565.3640

4-19

The reaction of **4-18** (150 mg, 0.27 mmol) as described for **2-9** gave **4-19** (143 mg, quant) as a yellow oil.

1H NMR (CD_3OD , 270 MHz) δ_H 7.78 (s, 2H), 7.40 (s, 1H), 4.66 (m, 2H), 3.89 (s, 3H), 3.50 (m, 2H), 3.14 (m, 2H), 3.00-2.89 (m, 4H), 2.04 (s, 9H), 1.99-1.61 (m, 14H); HRMS (ESI) Exact mass calcd for $C_{29}H_{40}N_2O_3 + H$ requires m/z 465.3117 Found m/z 465.3101

4-20

The reaction of **4-19** (70 mg, 0.15 mmol) and amine **6** (99 mg, 0.18 mmol) as described for **2-13** gave **4-20** (25 mg, 16%) as a colorless oil.

1H NMR ($CDCl_3$, 270 MHz) δ_H 7.75-7.70 (m, 4H), 7.58 (d, $J=8.4$ Hz, 1H), 7.45 (d, $J=3.5$ Hz, 1H), 7.26-7.20 (m, 4H), 6.75 (d, $J=3.5$ Hz, 1H), 6.69 (d, $J=8.4$ Hz, 1H), 5.20 (m, 1H), 4.67 (m, 2H), 4.45-4.06 (m, 4H), 3.91 (s, 3H), 3.07 (m, 2H), 3.01 (m, 2H), 2.90-2.75 (m, 6H), 2.65 (m, 2H), 2.32

(s, 3H), 2.04 (s, 9H), 1.95-1.20 (m, 29H); HRMS (ESI) Exact mass calcd for $C_{58}H_{77}N_5O_{10}S + H$ requires m/z 1036.5469 Found m/z 1036.5450

4-21

The reaction of **4-20** (12 mg, 12 μ mol) as described for **2-9** gave **4-21** (12 mg, quant) as a yellow oil.

1H NMR (CD_3OD , 270 MHz) δ_H 7.74-7.55 (m, 6H), 7.34-7.25 (m, 3H), 7.12 (d, $J=8.1$ Hz, 1H), 6.79 (m, 2H), 5.40 (m, 1H), 4.67 (m, 2H), 4.40-4.27 (m, 4H), 3.92-3.88 (m, 3H), 3.48 (m, 2H), 3.12 (m, 2H), 2.97-2.91 (m, 6H), 2.72 (m, 2H), 2.27 (s, 3H), 2.04 (s, 9H), 1.92-1.29 (m, 20H); HRMS (ESI) Exact mass calcd for $C_{53}H_{69}N_5O_8S + H$ requires m/z 936.4945 Found m/z 936.4920

4-22

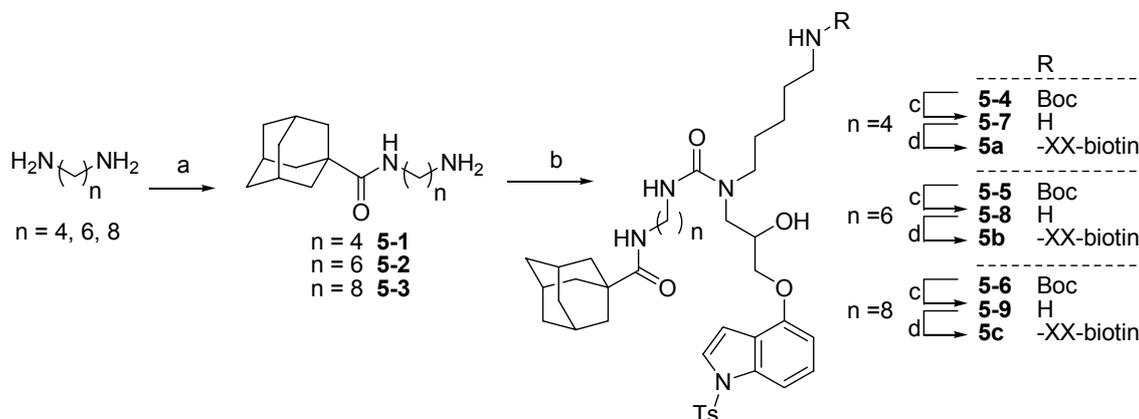
The reaction of **4-21** (5.0 mg, 5.3 μ mol) as described for **2-15** gave **4-22** (4.6 mg, 93%) as a colorless oil.

1H NMR (CD_3OD , 270 MHz) δ_H 7.76-7.53 (m, 6H), 7.35-7.25 (m, 3H), 7.12 (d, $J=8.4$ Hz, 1H), 6.79 (m, 2H), 5.35 (m, 1H), 4.67 (m, 2H), 4.40-4.25 (m, 4H), 3.48 (m, 2H), 3.12 (m, 2H), 2.97-2.91 (m, 6H), 2.72 (m, 2H), 2.25 (s, 3H), 2.03 (s, 9H), 1.92-1.29 (m, 20H); HRMS (ESI) Exact mass calcd for $C_{52}H_{66}N_5O_8S + H$ requires m/z 922.4789 Found m/z 922.4783

4c

The reaction of **4-22** (4.0 mg, 4.3 μ mol) as described for **2a** gave **4c** (3.2 mg, 54%) as a colorless oil.

1H NMR (CD_3OD , 270 MHz) δ_H 7.76-7.53 (m, 6H), 7.35-7.25 (m, 3H), 7.12 (d, $J=8.4$ Hz, 1H), 6.79 (m, 2H), 5.35 (m, 1H), 4.67 (m, 2H), 4.40-4.05 (m, 6H), 3.44 (m, 2H), 3.22-3.05 (m, 8H), 3.01-2.87 (m, 5H), 2.74-2.65 (m, 4H), 2.27 (s, 3H), 2.20-2.13 (m, 6H), 2.05 (s, 9H), 1.92-1.29 (m, 38H); HRMS (ESI) Exact mass calcd for $C_{74}H_{103}N_9O_{12}S_2 + H$ requires m/z 1374.7246 Found m/z 1374.7251



Conditions: (a) adamantanecarbonyl chloride, Et₃N, CHCl₃, rt. (b) (1) CDI, THF, reflux (2) CH₃I, CH₃CN, rt. (3) amine **6**, Et₃N, CH₂Cl₂, rt. (c) TFA, CHCl₃, rt. (d) biotin-XX-NHS, Et₃N, DMSO, rt.

Scheme S7. Synthesis of 5a, 5b and 5c

5-1

To a solution of butane-1,4-diamine (66 mg, 0.76 mmol) and triethylamine (0.1 mL) in CHCl₃ (10 mL) was added a solution of 1-adamantanecarbonyl chloride (50 mg, 0.25 mmol) in CHCl₃ (5 mL). The resulting mixture was refluxed for 0.5 h, diluted with water, and extracted with CHCl₃ (3 × 30 mL). The combined extracts were dried over Na₂SO₄ and then concentrated in vacuum. The residue was purified by column chromatography on silica gel with methanol/aqueous ammonia mixtures to give **5-1** (52 mg, 83%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 5.90 (br. s, 1H), 3.21 (br. q, *J*=5.7 Hz, 2H), 2.70 (br. s, 2H), 2.00 (s, 3H), 1.81 (s, 6H), 1.68 (s, 6H), 1.45-1.25 (m, 4H); HRMS (ESI) Exact mass calcd for C₁₅H₂₆N₂O + H requires *m/z* 251.2123 Found *m/z* 251.2121

5-2

The reaction of hexane-1,6-diamine (88 mg, 0.76 mmol) and 1-adamantanecarbonyl chloride (50 mg, 0.25 mmol) as described for **5-1** gave **5-2** (51 mg, 73%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 5.64 (br. s, 1H), 3.18 (q, *J*=7.0 Hz, 2H), 2.64 (t, *J*=6.5 Hz, 2H), 1.99 (s, 3H), 1.80 (s, 6H), 1.67 (s, 6H), 1.45-1.28 (m, 8H); HRMS (ESI) Exact mass calcd for C₁₇H₃₀N₂O + H requires *m/z* 279.2436 Found *m/z* 279.2435

5-3

The reaction of octane-1,8-diamine (110 mg, 0.76 mmol) and 1-adamantanecarbonyl chloride (50 mg, 0.25 mmol) as described for **5-1** gave **5-3** (54 mg, 70%) as a colorless oil.

¹H NMR (CDCl₃, 270 MHz) δ_H 5.58 (br. s, 1H), 3.18 (q, *J*=6.8 Hz, 2H), 2.64 (t, *J*=6.5 Hz, 2H), 2.00

(s, 3H), 1.81 (s, 6H), 1.69 (s, 6H), 1.40-1.23 (m, 12H); HRMS (ESI) Exact mass calcd for $C_{19}H_{35}N_2O + H$ requires m/z 307.2749 Found m/z 307.2755

5-4

The reaction of **5-1** (8.3 mg, 33 μ mol) and amine **6** (20 mg, 37 μ mol) as described for **2-13** gave **5-4** (23 mg, 85%) as a colorless oil.

1H NMR ($CDCl_3$, 270 MHz) δ_H 7.75 (d, $J=8.4$ Hz, 2H), 7.58 (d, $J=8.4$ Hz, 1H), 7.47 (d, $J=3.5$ Hz, 1H), 7.23-7.17 (m, 3H), 6.73 (d, $J=3.5$ Hz, 1H), 6.66 (d, $J=8.4$ Hz, 1H), 5.87 (br. m, 1H), 5.77 (br. m, 1H), 4.66 (br. m, 1H), 4.25-4.08 (m, 2H), 3.97 (m, 1H), 3.60-3.43 (m, 2H), 3.22-3.06 (m, 8H), 2.33 (s, 3H), 2.00 (s, 3H), 1.82 (m, 6H), 1.67 (m, 6H), 1.62-1.01 (m, 19H); HRMS (ESI) Exact mass calcd for $C_{44}H_{63}N_5O_8S + H$ requires m/z 822.4476 Found m/z 822.4457

5-5

The reaction of **5-2** (16 mg, 59 μ mol) and amine **6** (35 mg, 65 μ mol) as described for **2-13** gave **5-5** (49 mg, 97%) as a colorless oil.

1H NMR ($CDCl_3$, 270 MHz) δ_H 7.75 (d, $J=8.4$ Hz, 2H), 7.58 (d, $J=8.4$ Hz, 1H), 7.47 (d, $J=3.5$ Hz, 1H), 7.26-7.18 (m, 3H), 6.73 (d, $J=3.5$ Hz, 1H), 6.67 (d, $J=8.4$ Hz, 1H), 5.77-5.61 (m, 2H), 4.66 (br. m, 1H), 4.22-4.12 (m, 2H), 3.95 (m, 1H), 3.60-3.43 (m, 2H), 3.26-3.06 (m, 8H), 2.34 (s, 3H), 2.03 (s, 3H), 1.82 (m, 6H), 1.67 (m, 6H), 1.62-1.01 (m, 23H); HRMS (ESI) Exact mass calcd for $C_{46}H_{67}N_5O_8S + H$ requires m/z 850.4789 Found m/z 850.4777

5-6

The reaction of **5-3** (18.3 mg, 60 μ mol) and amine **6** (36 mg, 65 μ mol) as described for **2-13** gave **5-6** (44 mg, 84%) as a colorless oil.

1H NMR ($CDCl_3$, 270 MHz) δ_H 7.75 (d, $J=8.4$ Hz, 2H), 7.58 (d, $J=8.4$ Hz, 1H), 7.47 (d, $J=3.5$ Hz, 1H), 7.23-7.17 (m, 3H), 6.71 (d, $J=3.5$ Hz, 1H), 6.67 (d, $J=8.4$ Hz, 1H), 5.63 (m, 1H), 4.69 (br. m, 1H), 4.14-4.09 (m, 2H), 3.94 (m, 1H), 3.55-3.46 (m, 2H), 3.28-3.07 (m, 8H), 2.33 (s, 3H), 2.02 (s, 3H), 1.83 (m, 6H), 1.65 (m, 6H), 1.57-1.01 (m, 27H); HRMS (ESI) Exact mass calcd for $C_{48}H_{71}N_5O_8S + H$ requires m/z 878.5102 Found m/z 878.5089

5-7

The reaction of **5-4** (20 mg, 24 μ mol) as described for **3-3** gave **5-7** (18 mg, quant) as a colorless oil.

1H NMR (CD_3OD , 270 MHz) δ_H 7.77 (d, $J=8.4$ Hz, 2H), 7.59-7.53 (m, 2H), 7.30 (d, $J=8.1$ Hz, 2H), 7.22 (t, $J=8.1$ Hz, 1H), 6.84 (d, $J=3.5$ Hz, 1H), 6.73 (d, $J=8.4$ Hz, 1H), 4.15 (m, 1H), 4.05 (m, 2H), 3.47 (m, 2H), 3.19-3.08 (m, 6H), 2.90-2.85 (m, 2H), 2.34 (s, 3H), 1.95 (s, 3H), 1.80 (m, 6H), 1.71 (m, 6H), 1.62-1.01 (m, 10H); HRMS (ESI) Exact mass calcd for $C_{39}H_{55}N_5O_6S + H$ requires m/z

722.3951 Found m/z 722.3952

5-8

The reaction of **5-5** (39 mg, 46 μmol) as described for **3-3** gave **5-8** (36 mg, quant) as a colorless oil. ^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.77 (d, $J=8.4$ Hz, 2H), 7.58-7.53 (m, 2H), 7.30 (d, $J=8.0$ Hz, 2H), 7.22 (t, $J=8.1$ Hz, 1H), 6.84 (d, $J=3.5$ Hz, 1H), 6.73 (d, $J=8.4$ Hz, 1H), 4.16 (m, 1H), 4.04 (m, 2H), 3.46 (m, 2H), 3.15-3.04 (m, 6H), 2.90-2.84 (m, 2H), 2.34 (s, 3H), 1.99 (s, 3H), 1.82 (m, 6H), 1.74 (m, 6H), 1.67-1.01 (m, 14H); HRMS (ESI) Exact mass calcd for $\text{C}_{41}\text{H}_{59}\text{N}_5\text{O}_6\text{S} + \text{H}$ requires m/z 750.4264 Found m/z 750.4251

5-9

The reaction of **5-6** (40 mg, 46 μmol) as described for **3-3** gave **5-9** (40 mg, quant) as a colorless oil. ^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.77 (d, $J=8.4$ Hz, 2H), 7.59-7.53 (m, 2H), 7.30 (d, $J=8.0$ Hz, 2H), 7.22 (t, $J=8.1$ Hz, 1H), 6.84 (d, $J=3.5$ Hz, 1H), 6.74 (d, $J=8.4$ Hz, 1H), 4.15 (m, 1H), 4.04 (m, 2H), 3.46 (m, 2H), 3.16-3.03 (m, 6H), 2.90-2.84 (m, 2H), 2.34 (s, 3H), 1.99 (s, 3H), 1.84 (m, 6H), 1.74 (m, 6H), 1.64-1.10 (m, 18H); HRMS (ESI) Exact mass calcd for $\text{C}_{43}\text{H}_{63}\text{N}_5\text{O}_6\text{S} + \text{H}$ requires m/z 778.4577 Found m/z 778.4592

5a

The reaction of **5-7** (5.0 mg, 6.9 μmol) as described for **2a** gave **5a** (7.0 mg, 86%) as a colorless oil. ^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.76 (d, $J=8.4$ Hz, 2H), 7.58-7.53 (m, 2H), 7.29 (d, $J=8.1$ Hz, 2H), 7.22 (t, $J=8.1$ Hz, 1H), 6.84 (d, $J=3.5$ Hz, 1H), 6.74 (d, $J=8.4$ Hz, 1H), 4.47 (dd, $J=8.4, 4.5$ Hz, 1H), 4.28 (dd, $J=8.4, 4.5$ Hz, 1H), 4.15 (m, 1H), 4.04 (m, 2H), 3.48 (m, 2H), 3.19-3.08 (m, 13H), 2.90 (dd, $J=13.0, 4.5$ Hz, 1H), 2.68 (d, $J=13.0$ Hz, 1H), 2.33 (s, 3H), 2.21-2.14 (m, 6H), 1.96 (s, 3H), 1.81 (m, 6H), 1.71 (m, 6H), 1.62-1.01 (m, 28H); HRMS (ESI) Exact mass calcd for $\text{C}_{61}\text{H}_{91}\text{N}_9\text{O}_{10}\text{S}_2 + \text{H}$ requires m/z 1174.6409 Found m/z 1174.6417

5b

The reaction of **5-8** (8.0 mg, 11 μmol) as described for **2a** gave **5b** (12 mg, 94%) as a colorless oil. ^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.77 (d, $J=8.4$ Hz, 2H), 7.58-7.53 (m, 2H), 7.28 (d, $J=8.1$ Hz, 2H), 7.21 (t, $J=8.1$ Hz, 1H), 6.84 (d, $J=3.5$ Hz, 1H), 6.72 (d, $J=8.4$ Hz, 1H), 4.46 (dd, $J=8.4, 4.5$ Hz, 1H), 4.27 (dd, $J=8.4, 4.5$ Hz, 1H), 4.15 (m, 1H), 4.04 (m, 2H), 3.47 (m, 2H), 3.19-3.08 (m, 13H), 2.90 (dd, $J=13.0, 4.5$ Hz, 1H), 2.68 (d, $J=13.0$ Hz, 1H), 2.32 (s, 3H), 2.21-2.14 (m, 6H), 1.98 (s, 3H), 1.83 (m, 6H), 1.73 (m, 6H), 1.62-1.01 (m, 32H); HRMS (ESI) Exact mass calcd for $\text{C}_{62}\text{H}_{95}\text{N}_9\text{O}_{10}\text{S}_2 + \text{H}$ requires m/z 1202.6722 Found m/z 1202.6709

5c

The reaction of **5-9** (7.0 mg, 9.0 μmol) as described for **2a** gave **5c** (11 mg, 99%) as a colorless oil.

^1H NMR (CD_3OD , 270 MHz) δ_{H} 7.77 (d, $J=8.4$ Hz, 2H), 7.58-7.53 (m, 2H), 7.28 (d, $J=8.1$ Hz, 2H), 7.21 (t, $J=8.1$ Hz, 1H), 6.84 (d, $J=3.5$ Hz, 1H), 6.72 (d, $J=8.4$ Hz, 1H), 4.46 (dd, $J=8.4$, 4.5 Hz, 1H), 4.27 (dd, $J=8.4$, 4.5 Hz, 1H), 4.15 (m, 1H), 4.04 (m, 2H), 3.47 (m, 2H), 3.19-3.08 (m, 13H), 2.90 (dd, $J=13.0$, 4.5 Hz, 1H), 2.68 (d, $J=13.0$ Hz, 1H), 2.32 (s, 3H), 2.21-2.14 (m, 6H), 1.98 (s, 3H), 1.83 (m, 6H), 1.73 (m, 6H), 1.62-1.01 (m, 36H); HRMS (ESI) Exact mass calcd for $\text{C}_{64}\text{H}_{99}\text{N}_9\text{O}_{10}\text{S}_2 + \text{H}$ requires m/z 1230.7035 Found m/z 1230.7055

Reference

- 1) Shimogawa, H.; Kwon, Y.; Mao, Q.; Kawazoe, Y.; Choi, Y.; Asada, S.; Kigoshi, H.; Uesugi, M. *J. Am. Chem. Soc.* **2004**, *126*, 3461-3471.
- 2) Paul, R. E. *Tetrahedron lett.* **2000**, *41*, 3705-3708.

- **Complete reference of Reference 11 in the main manuscript**

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Fluorescence polarization assay

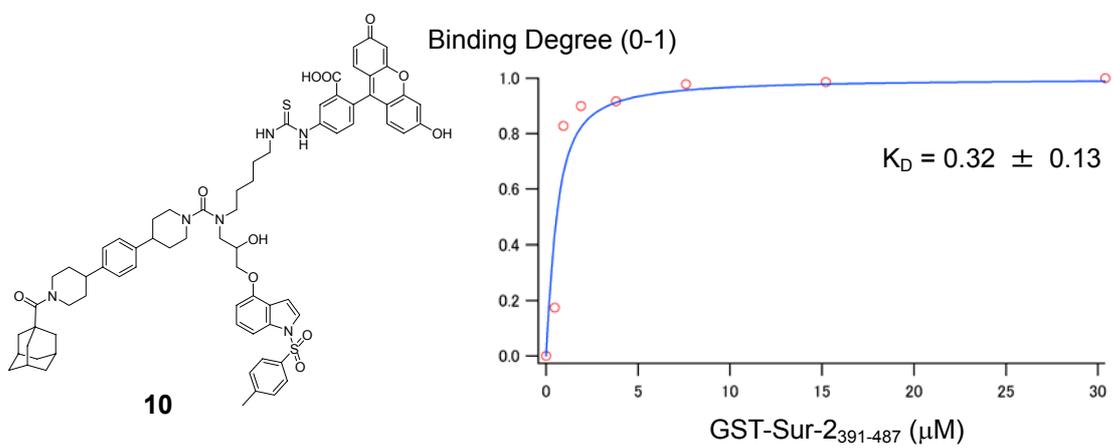
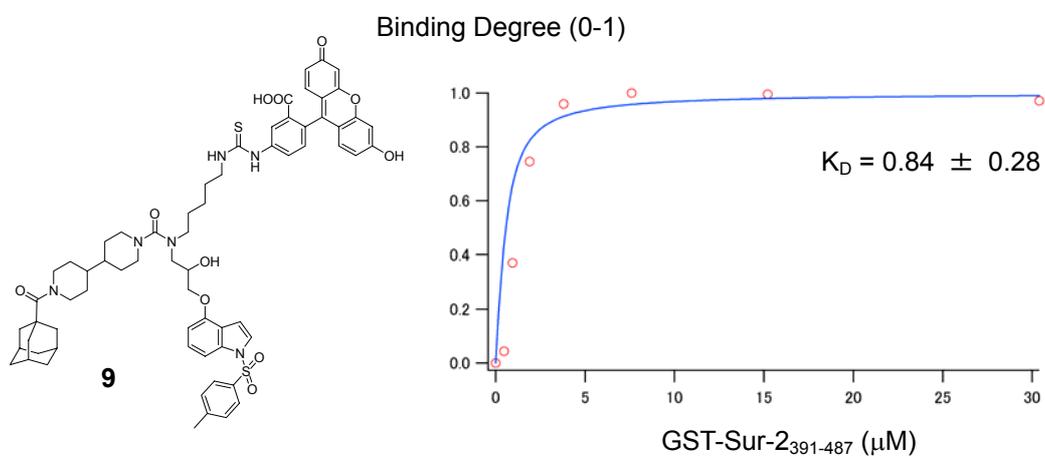
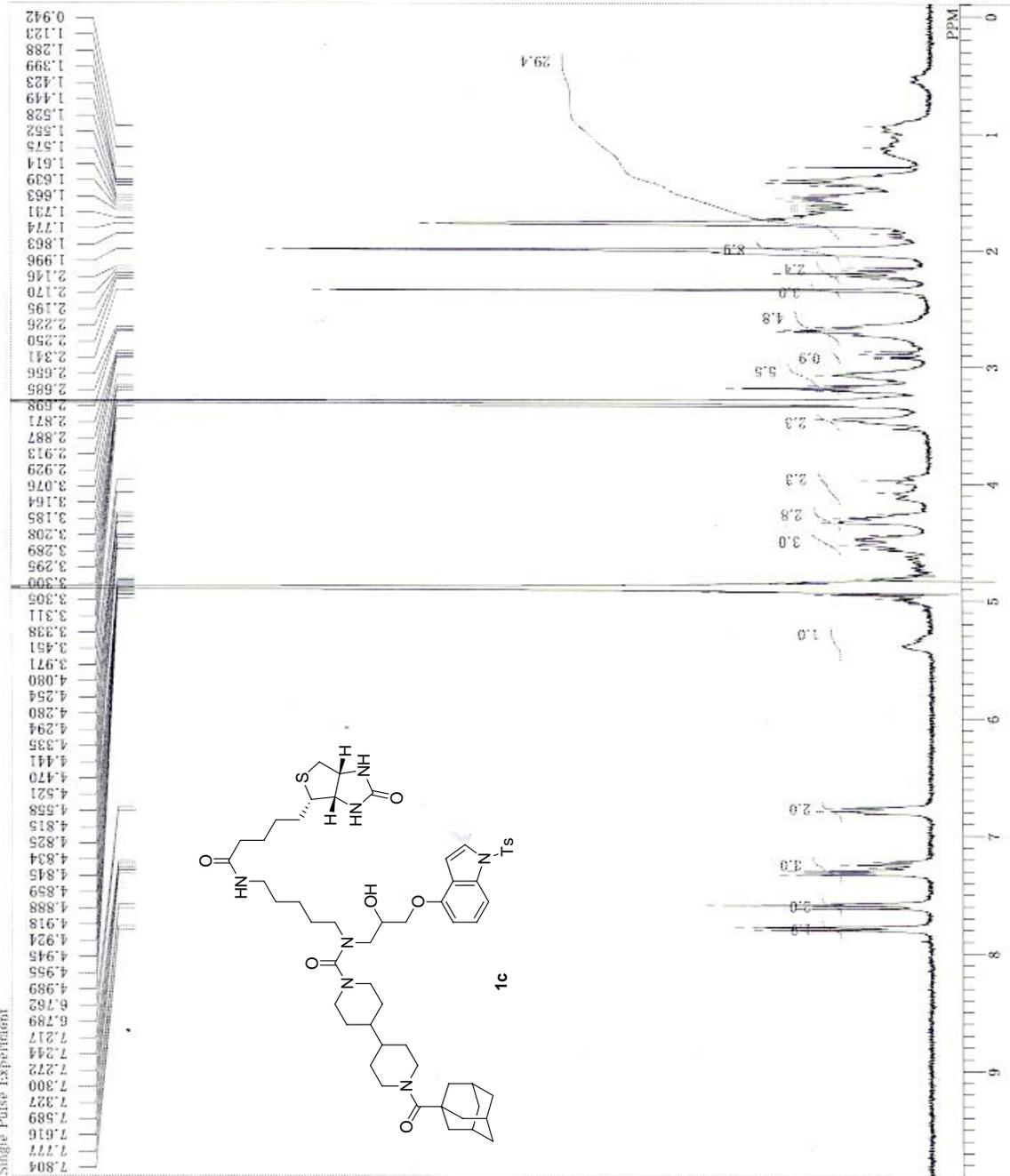
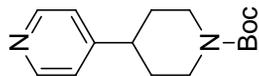


Figure S1

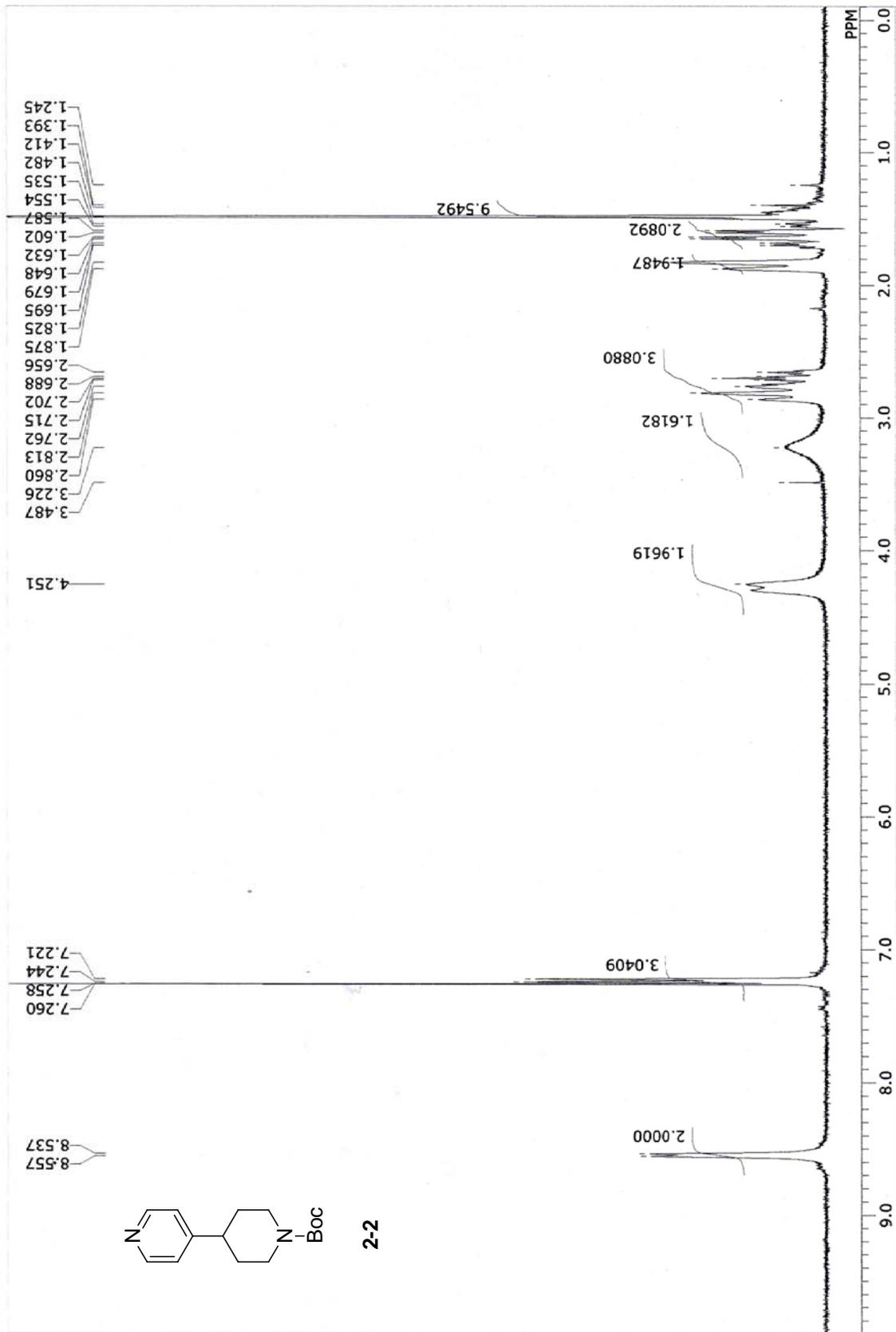
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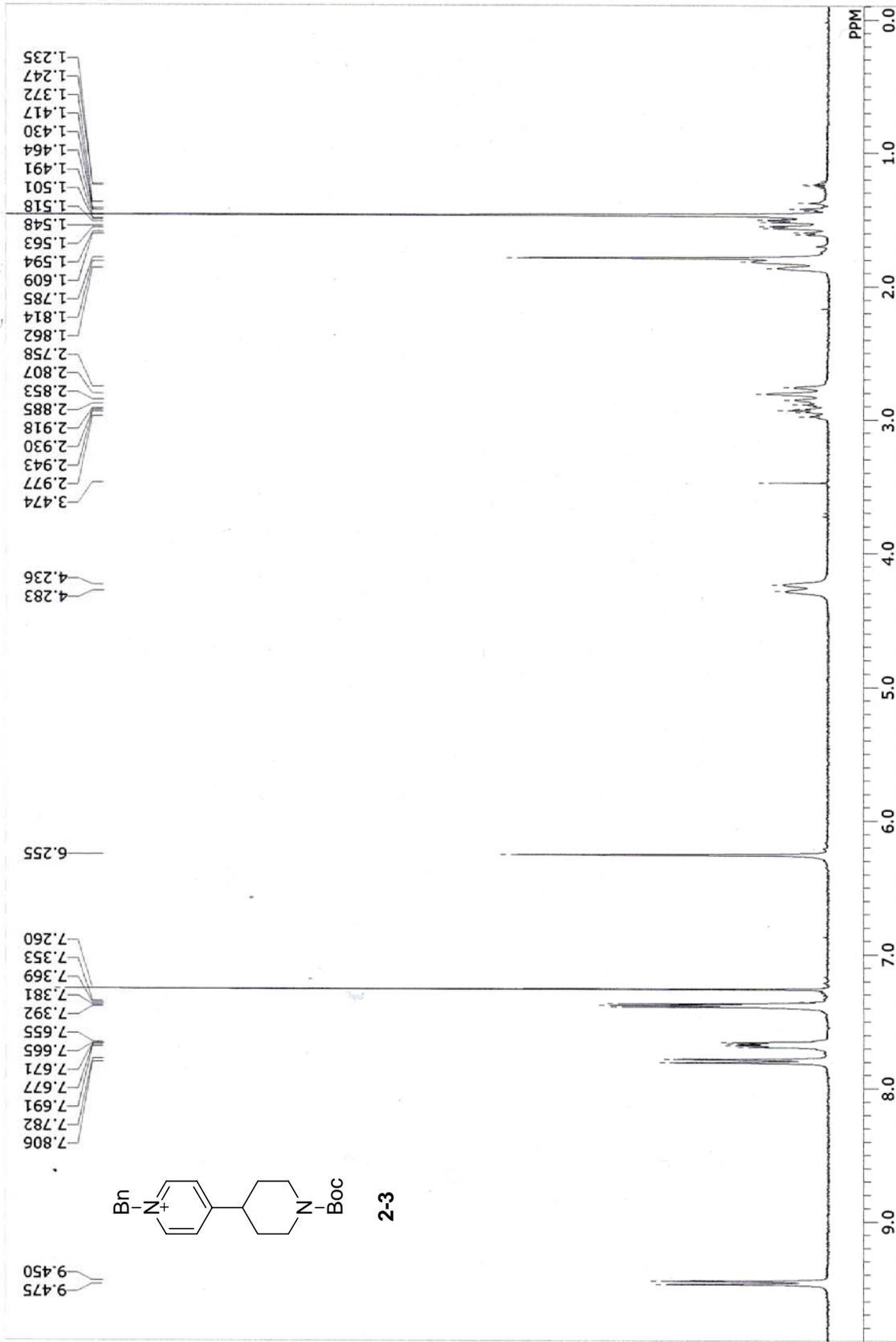
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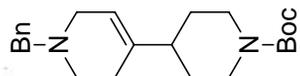
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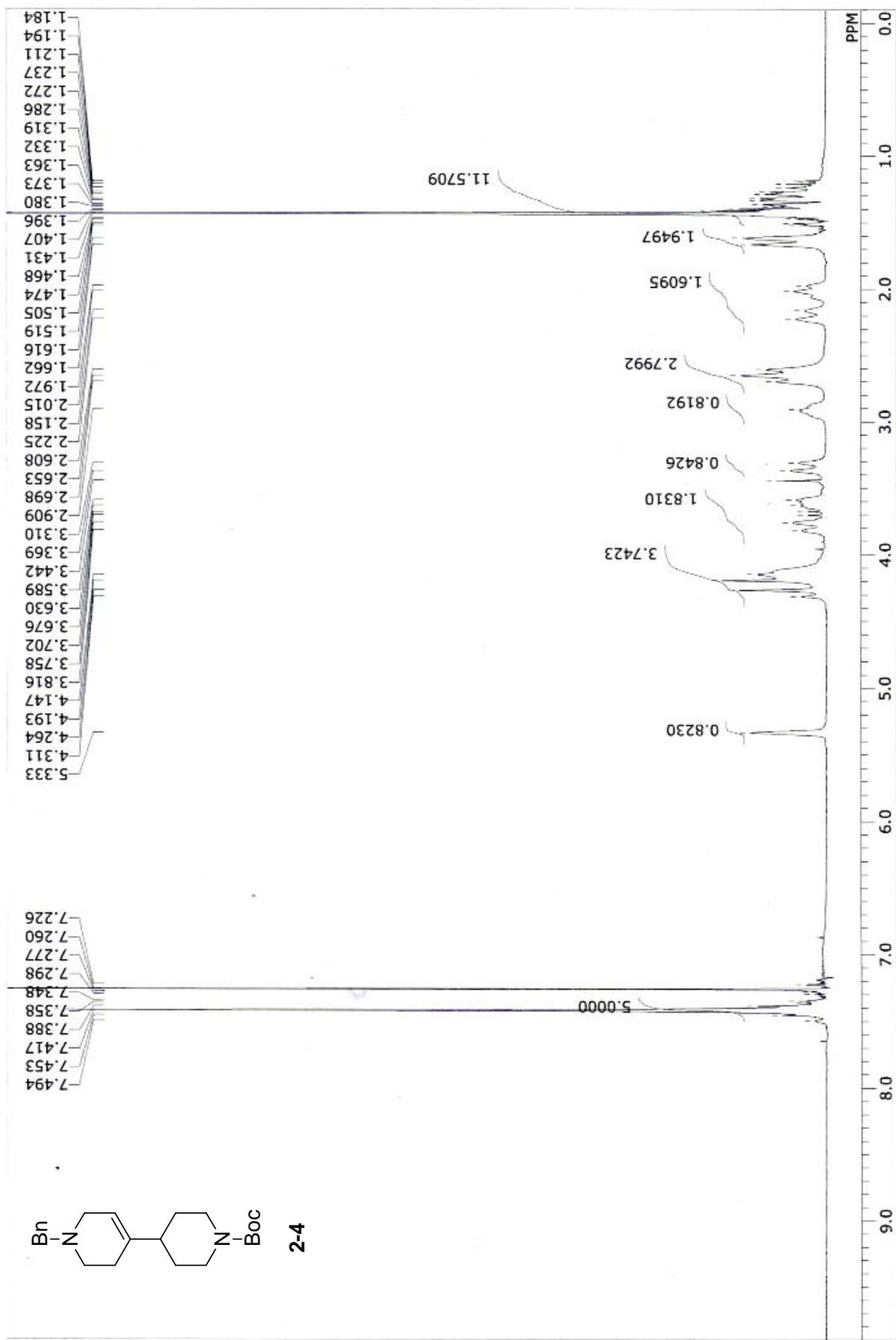
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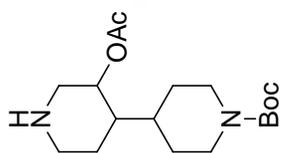
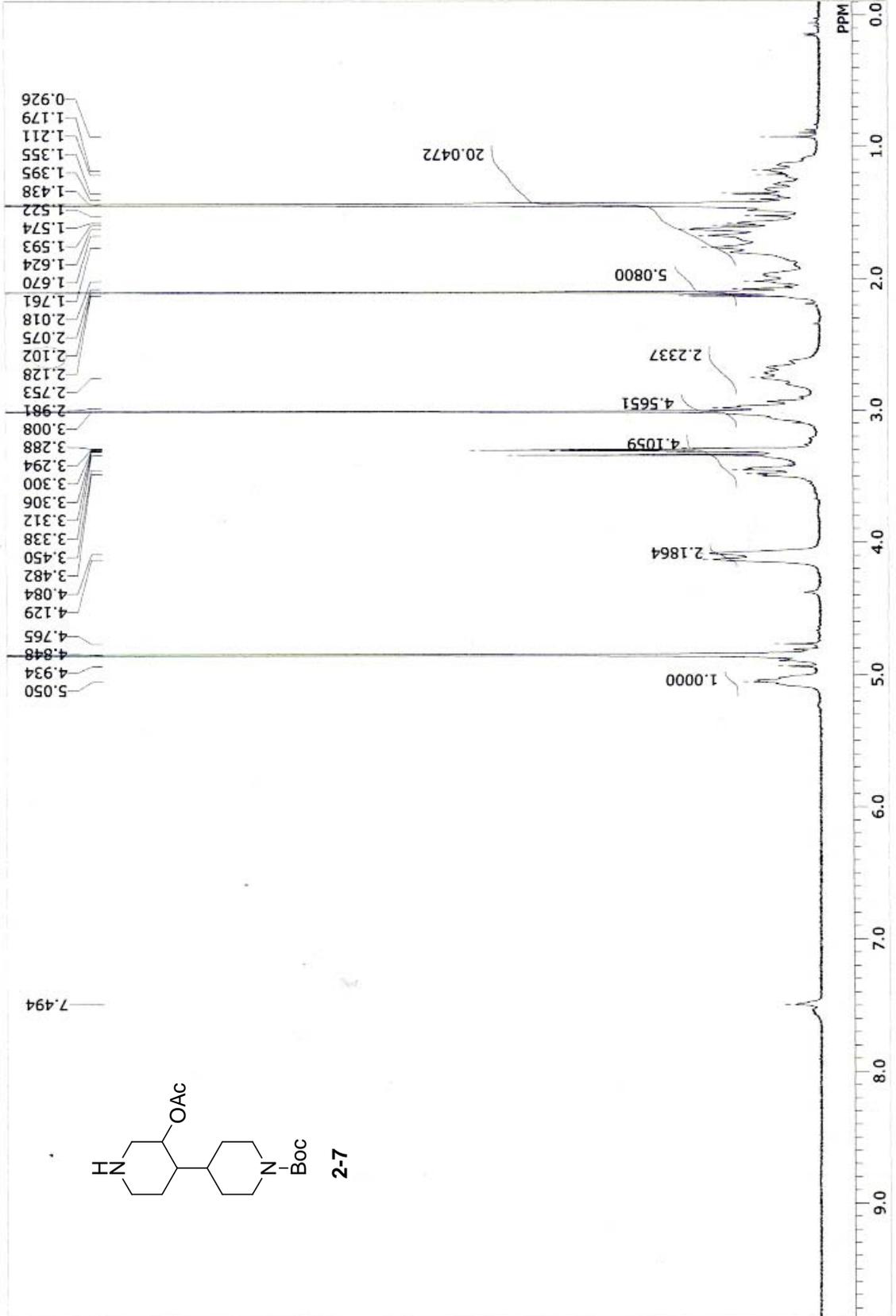


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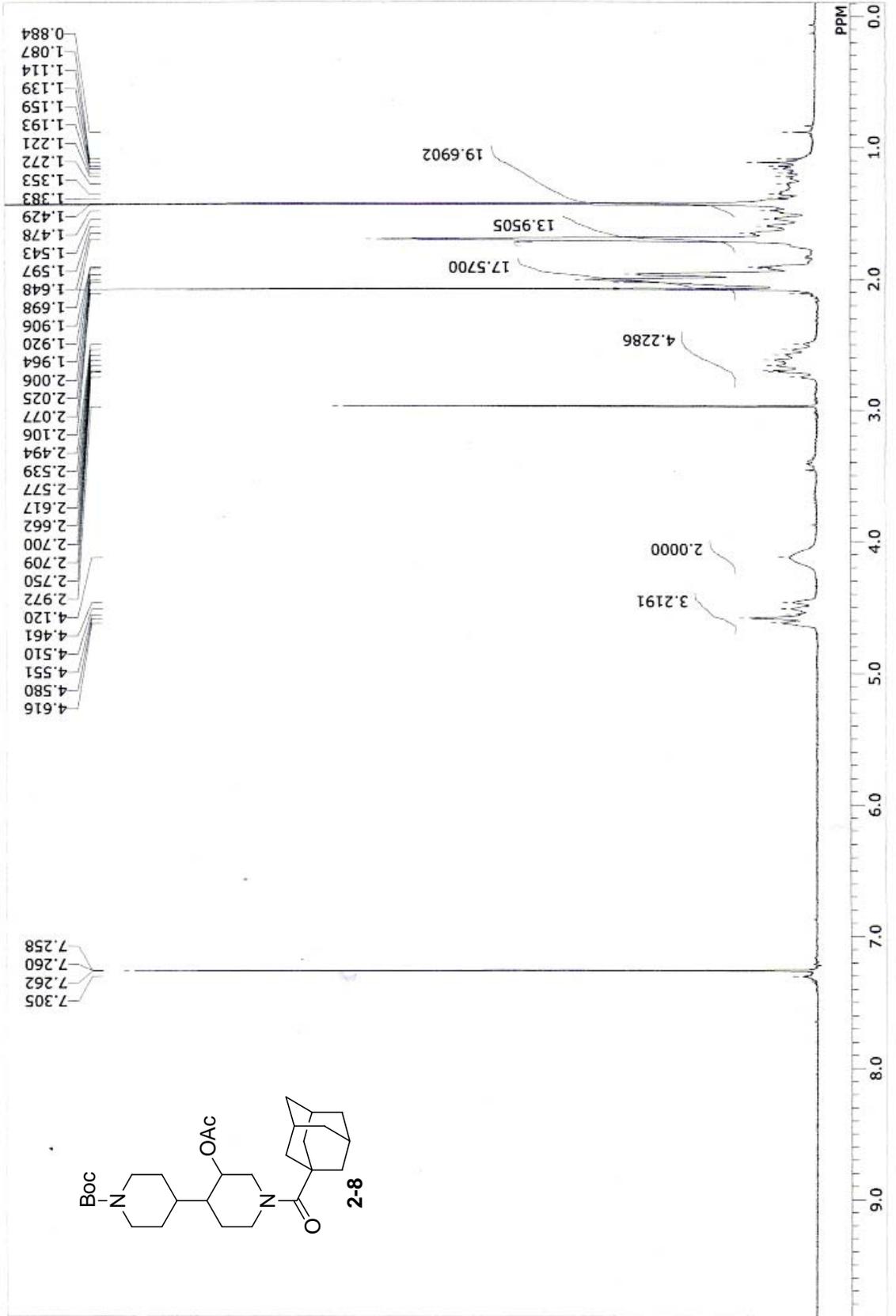
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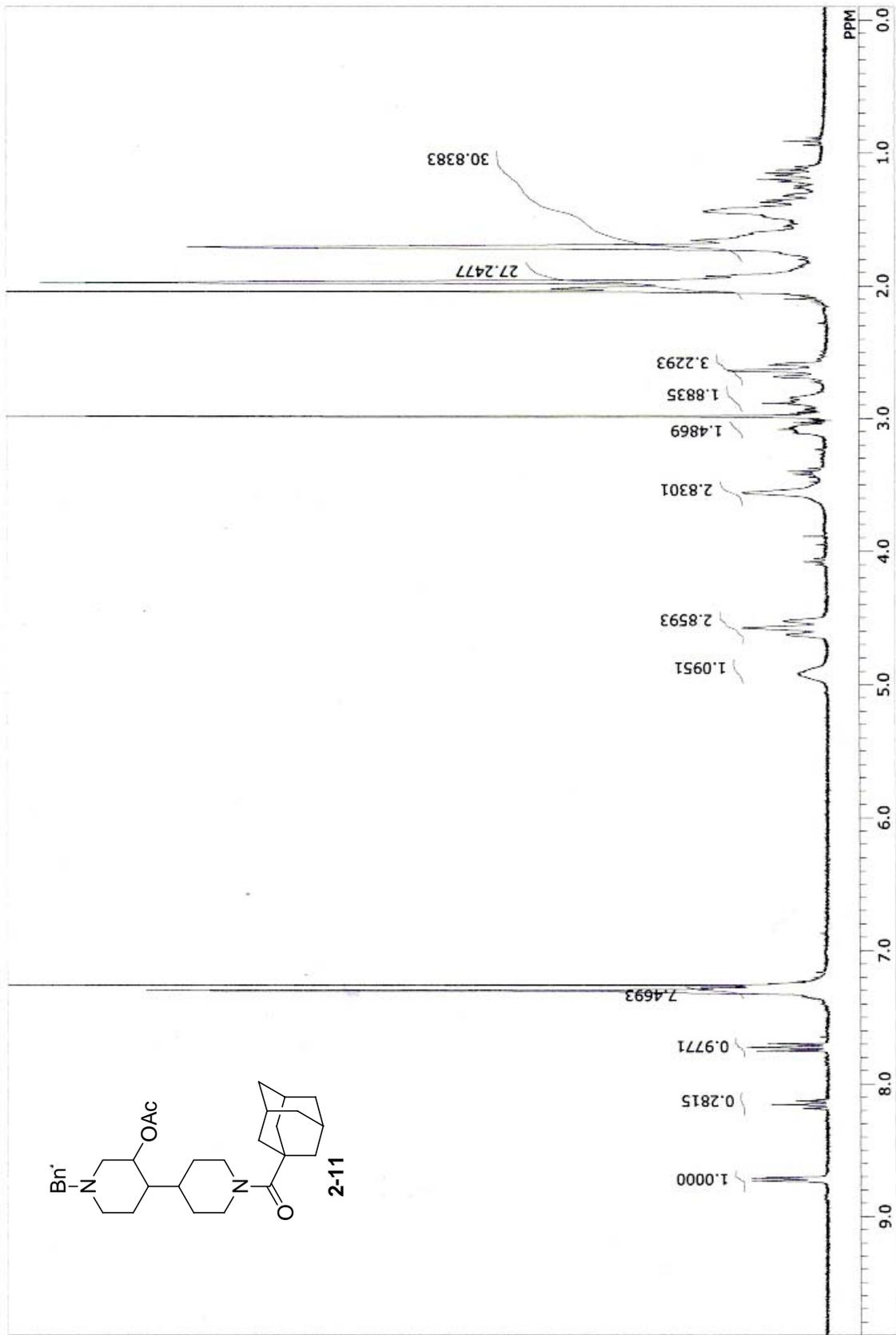


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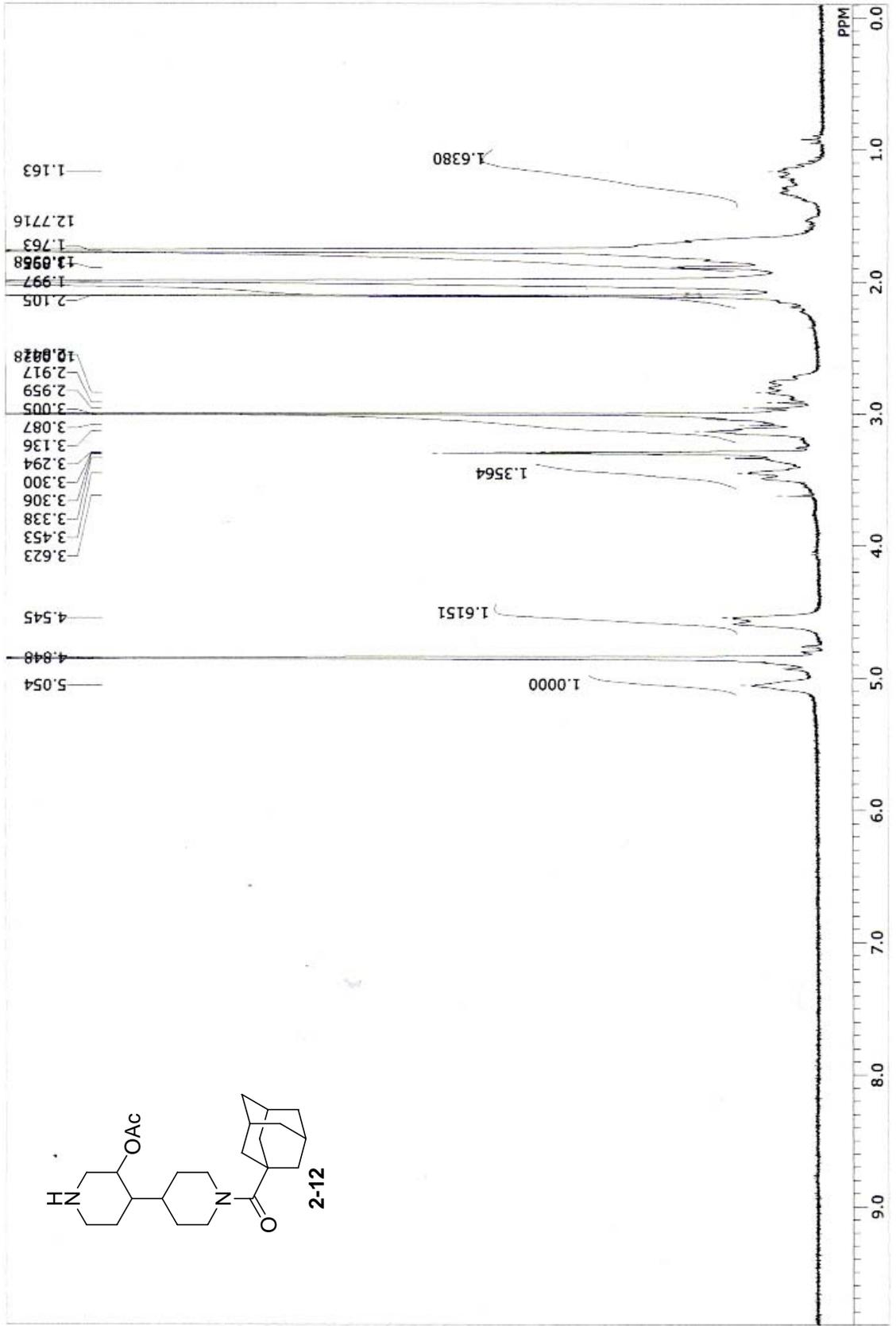
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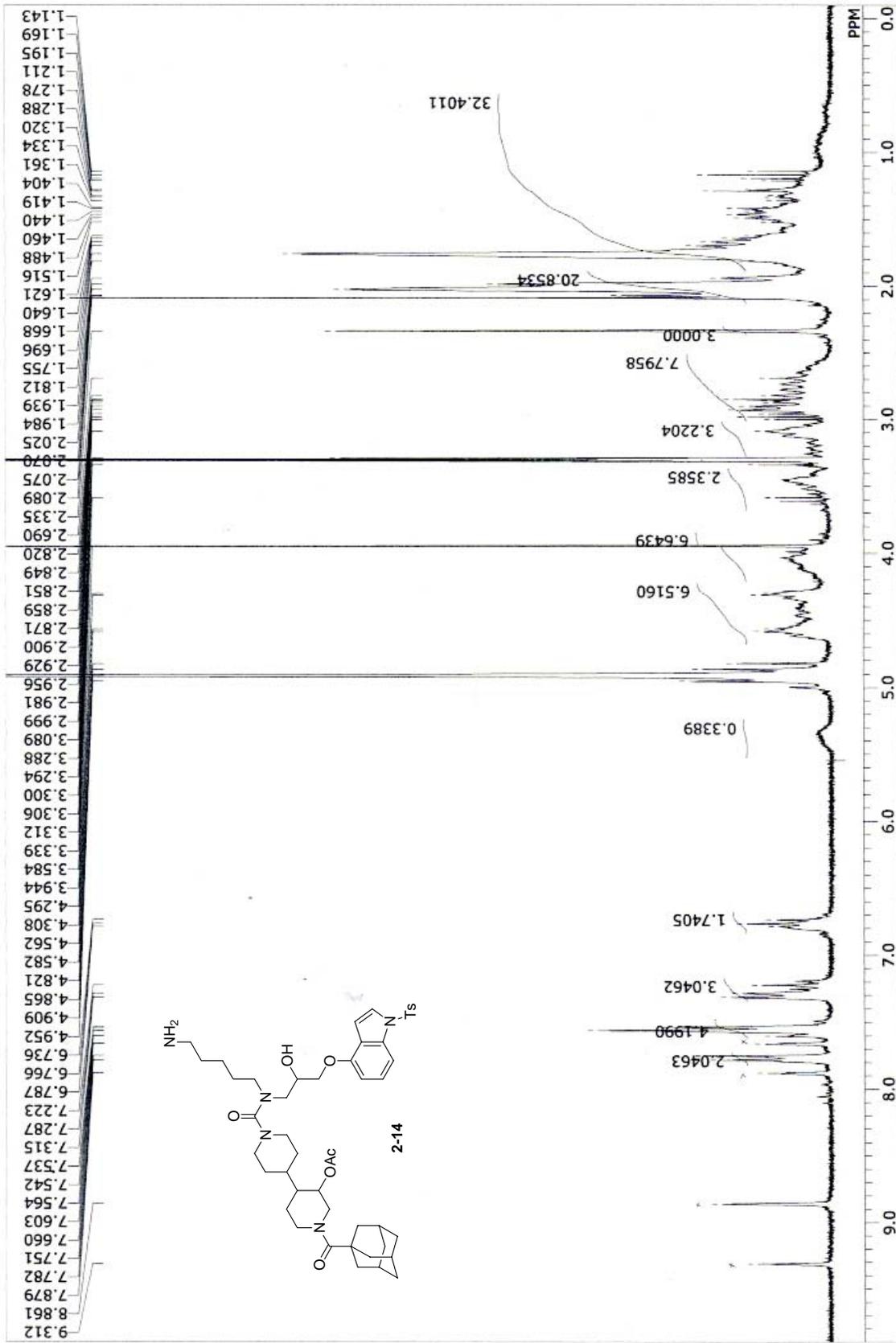
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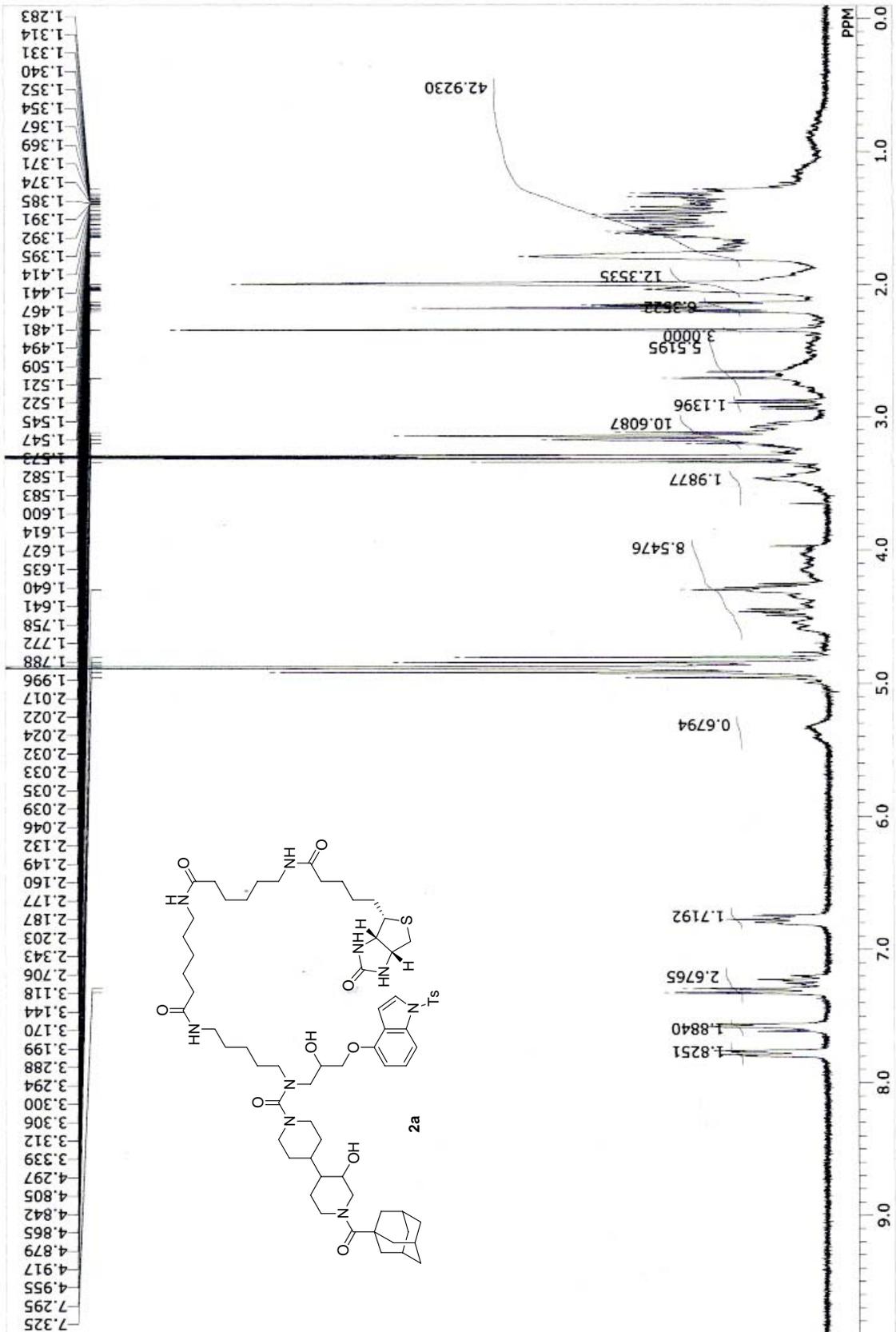
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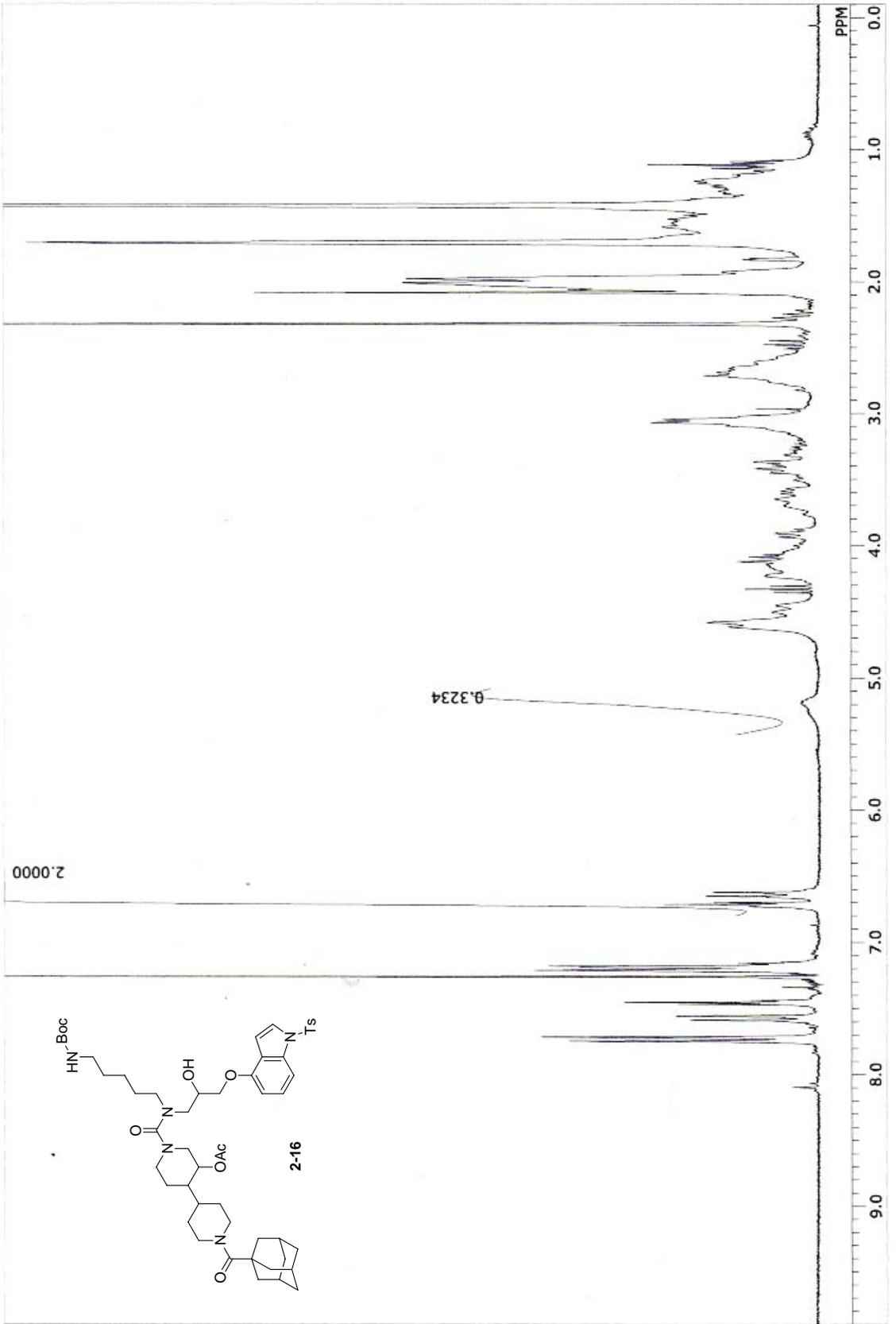
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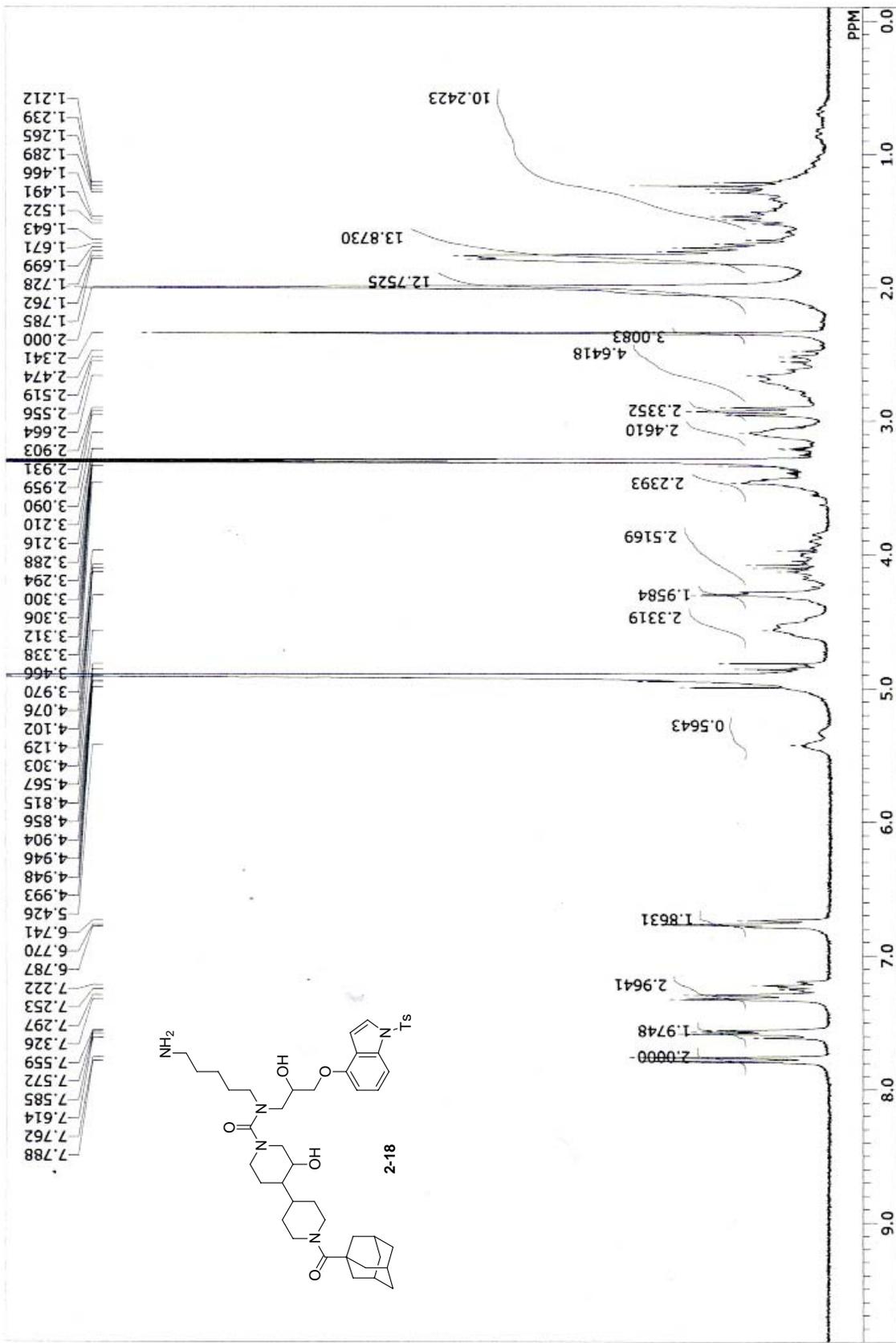


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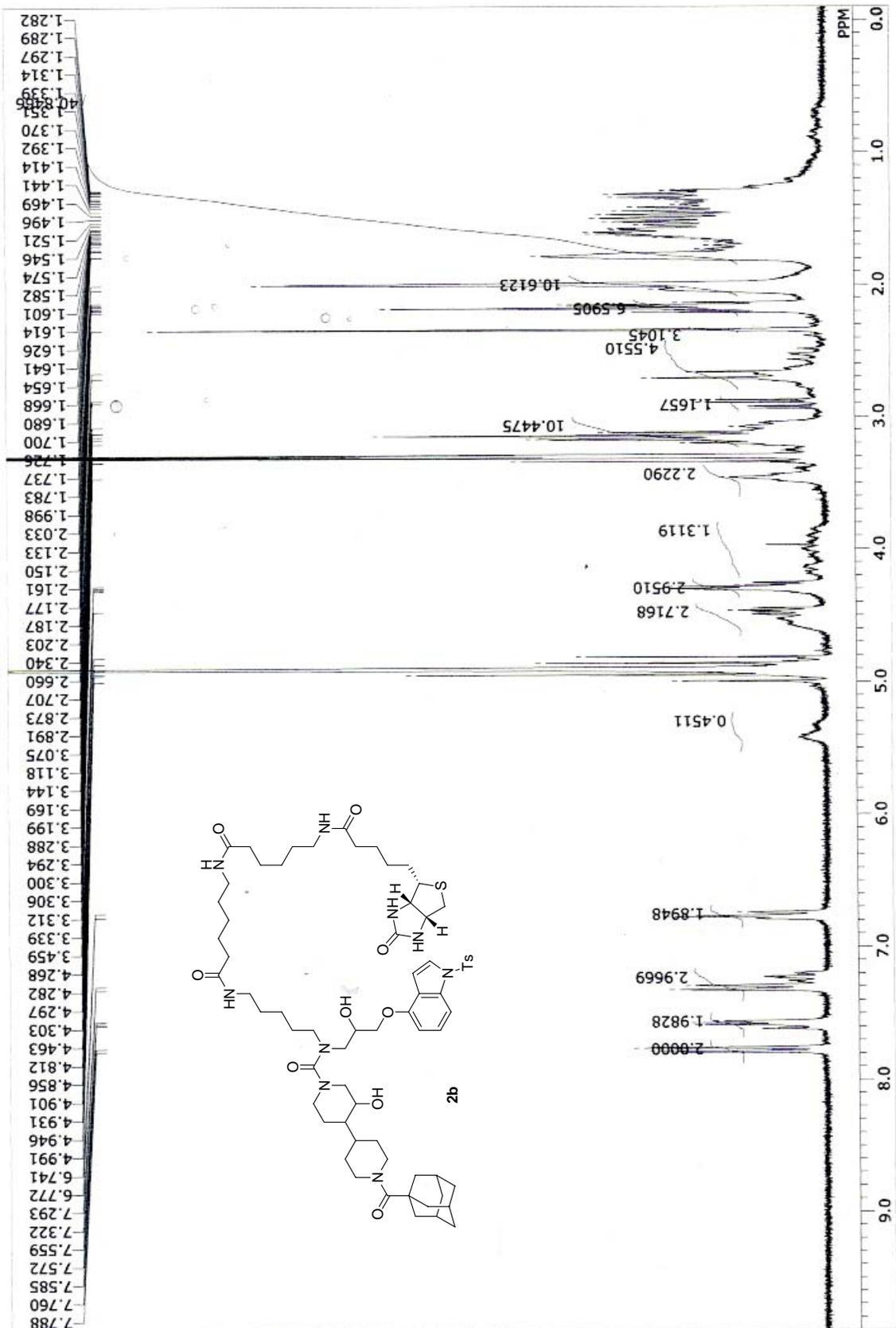


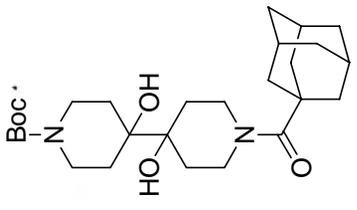
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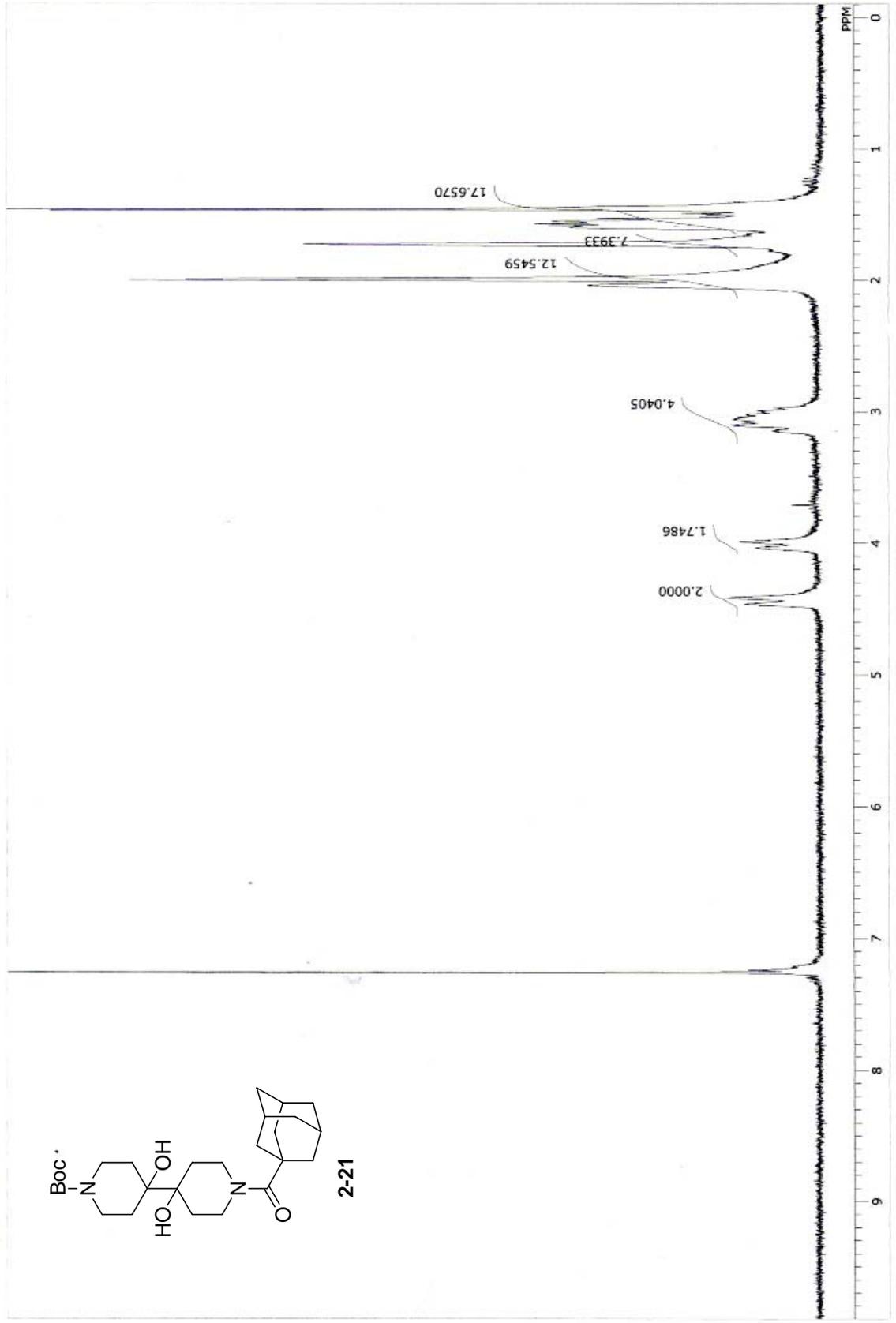


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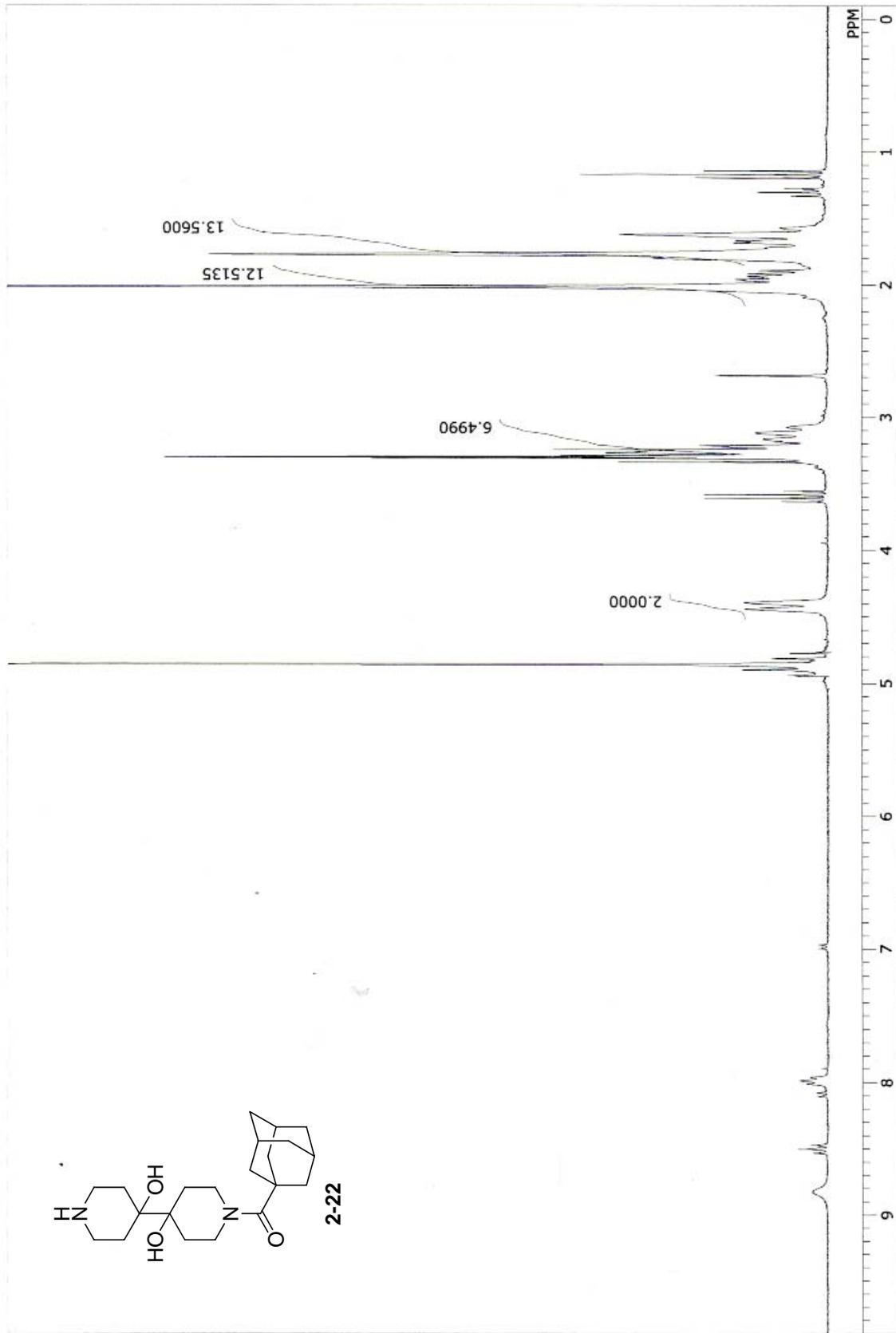
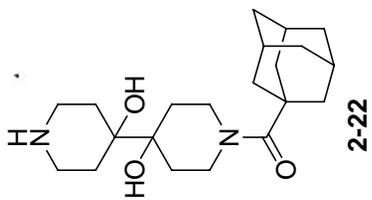




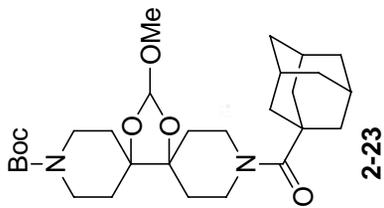
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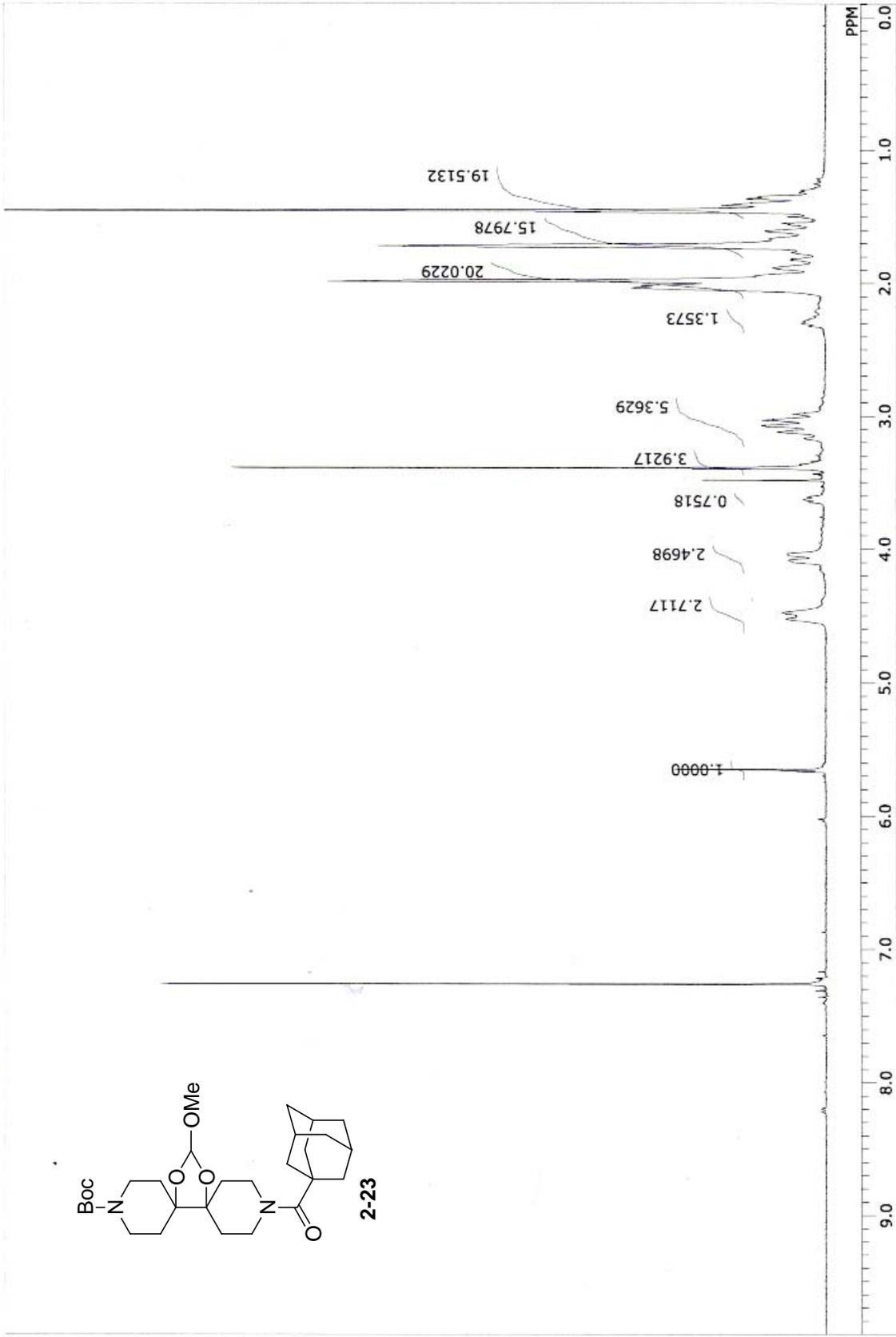
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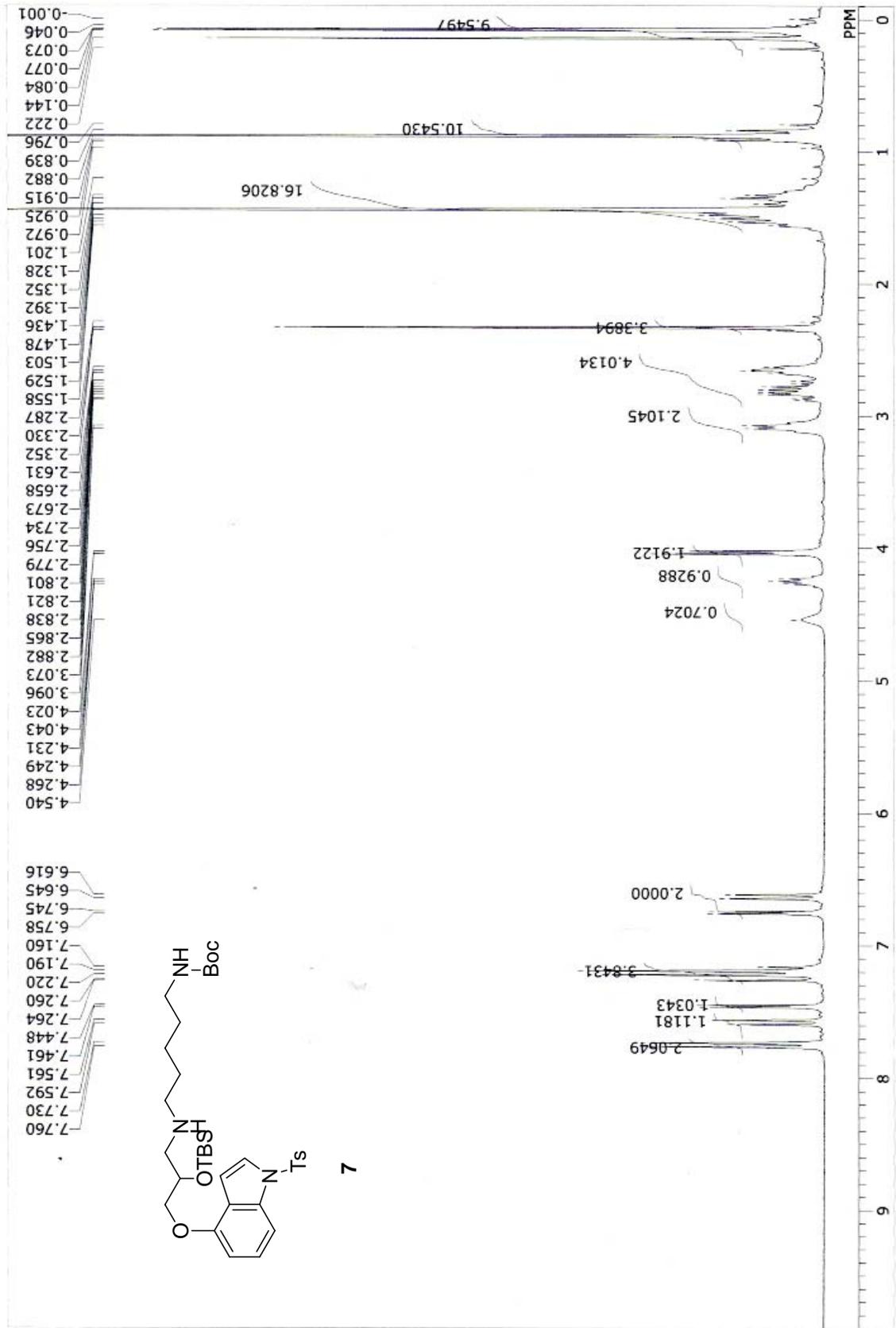


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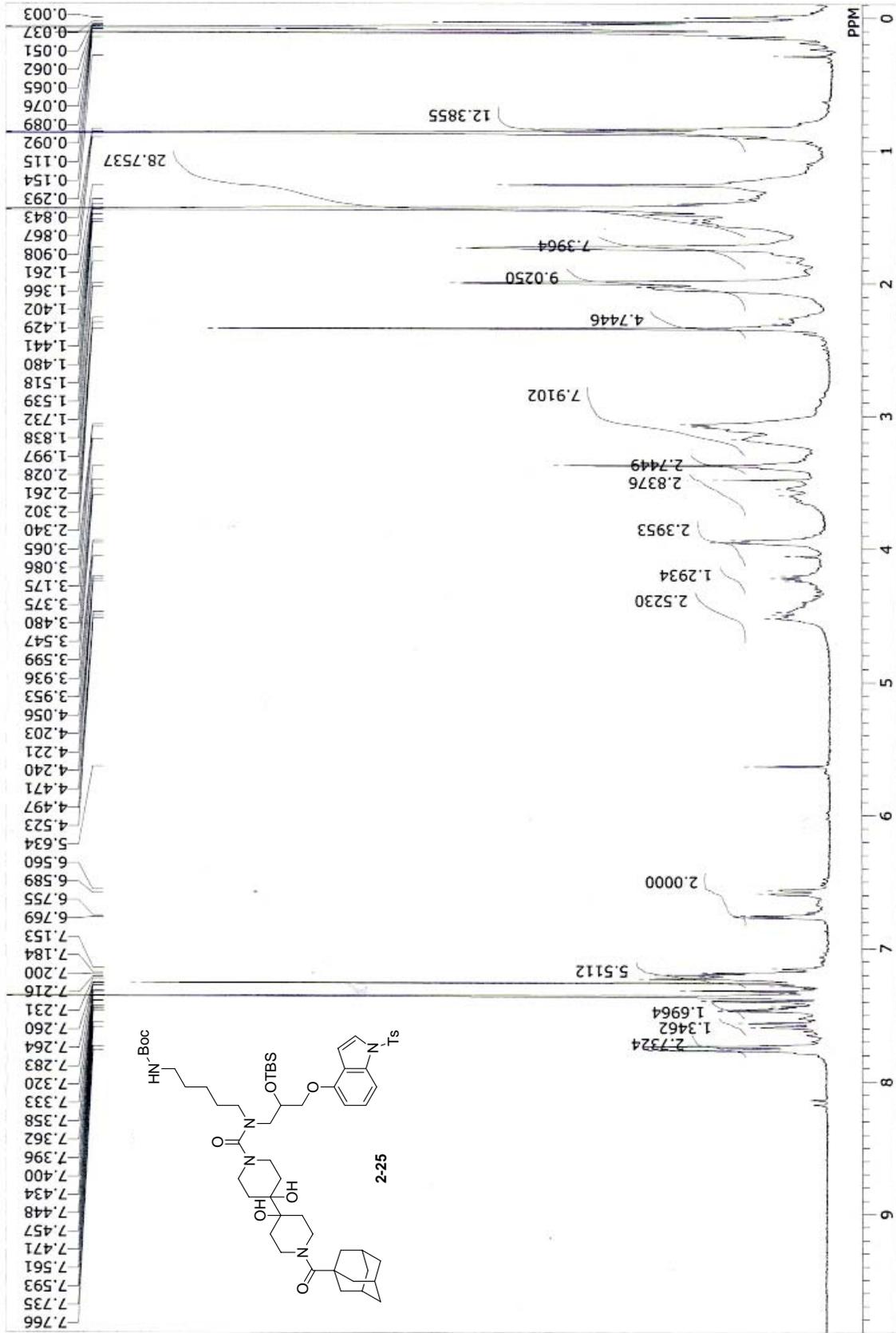


DFILE
COMINT
DATIM
OBNUC
EXMOD
OBFRO
OBSET
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POINT
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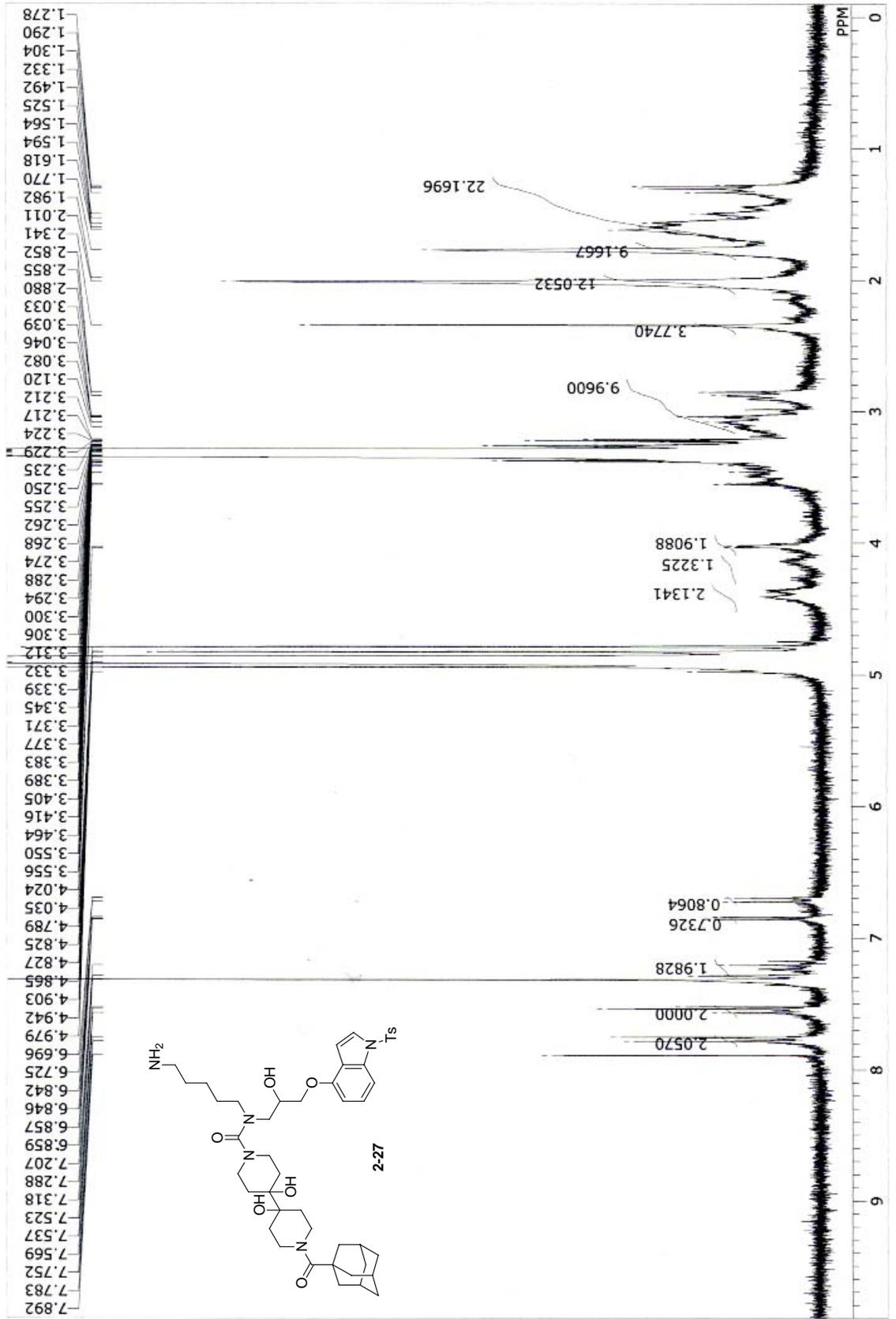




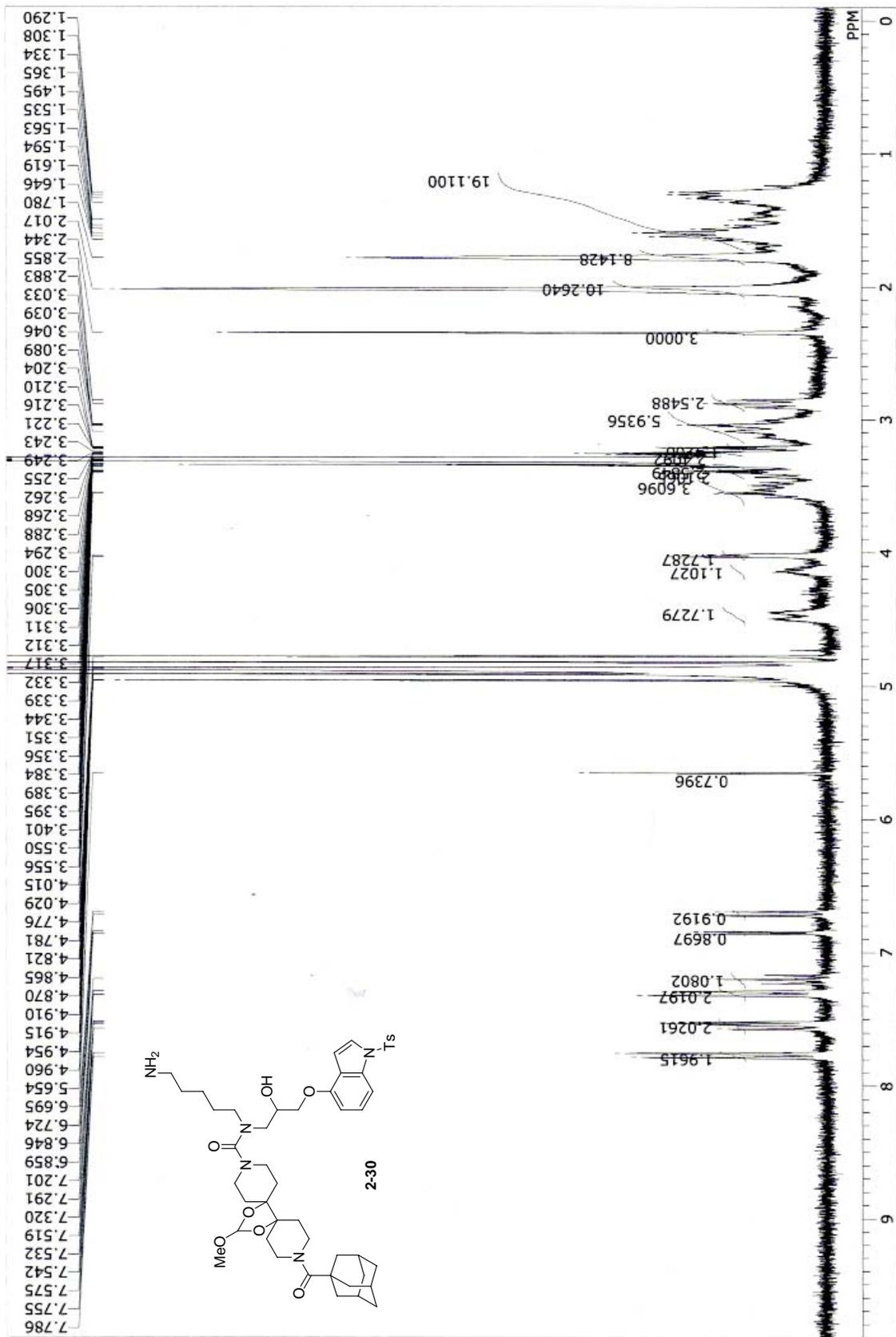
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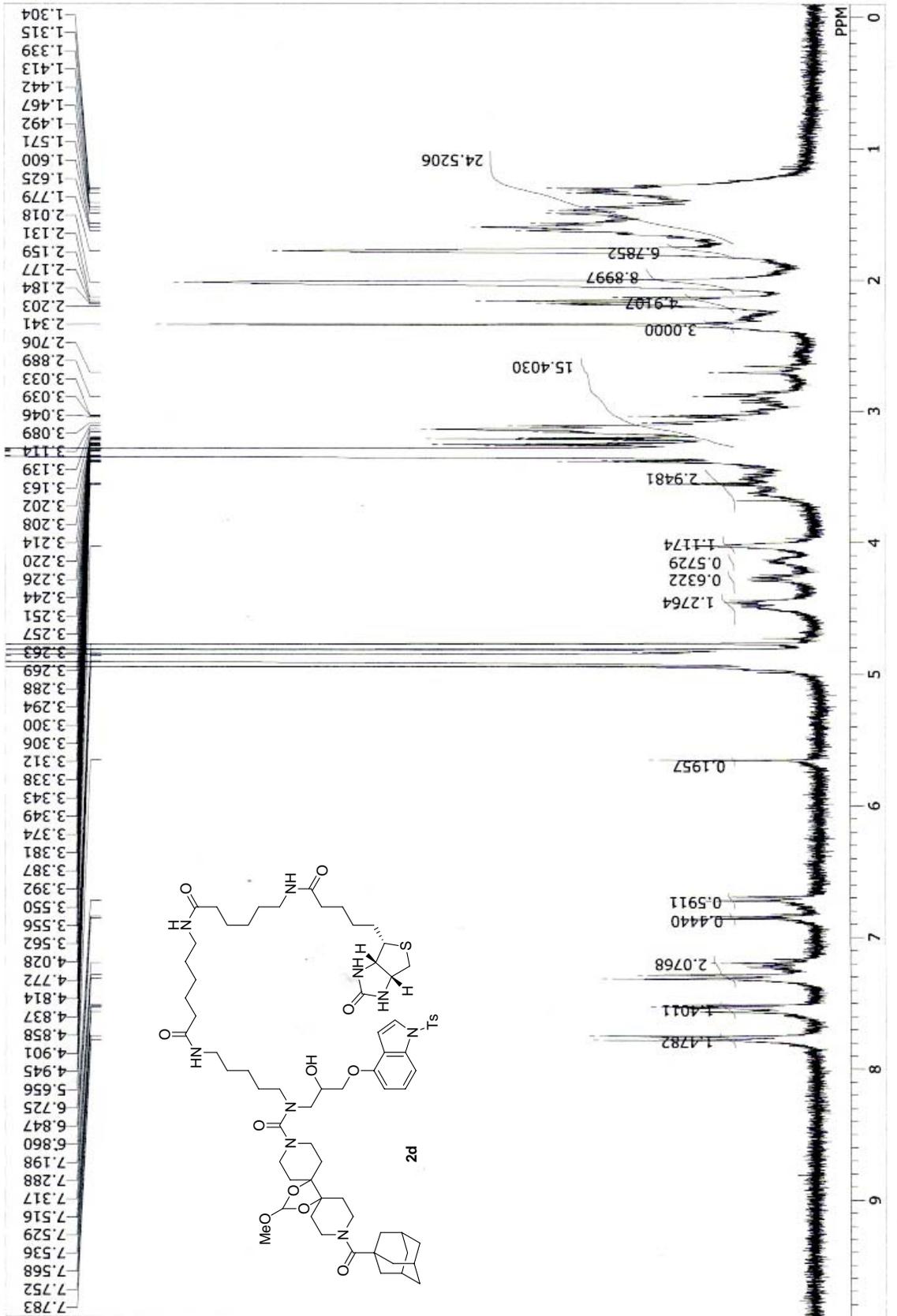
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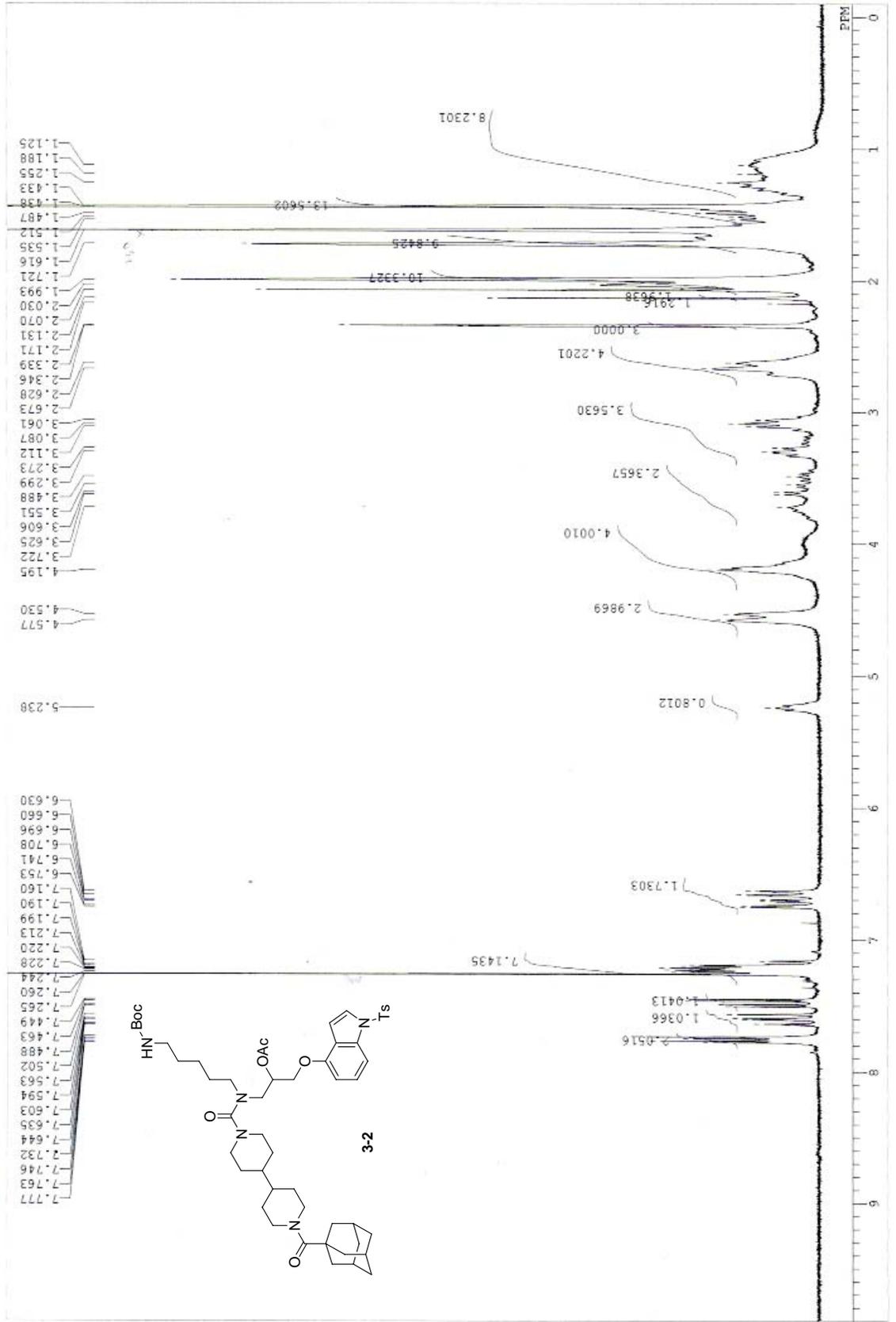
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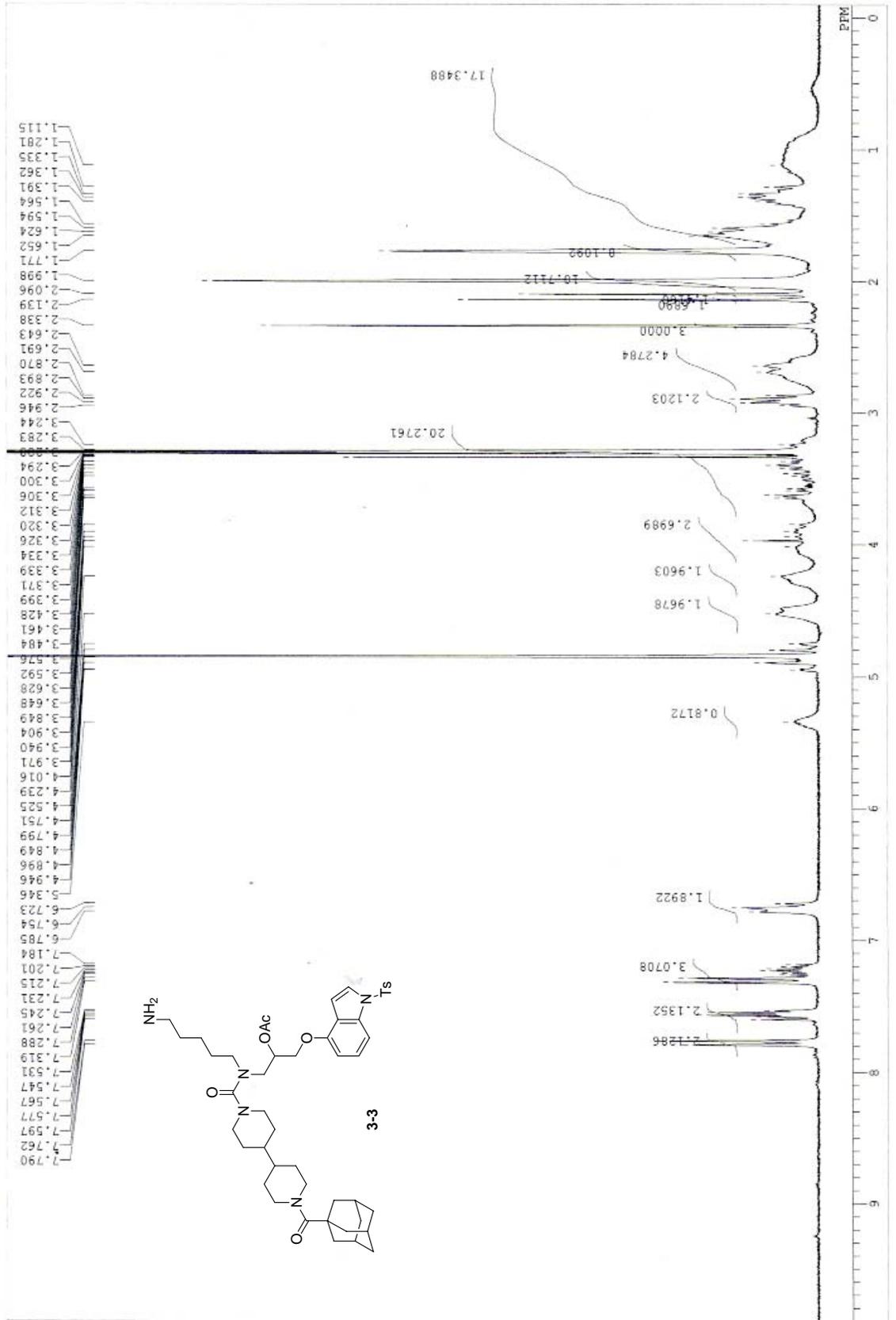


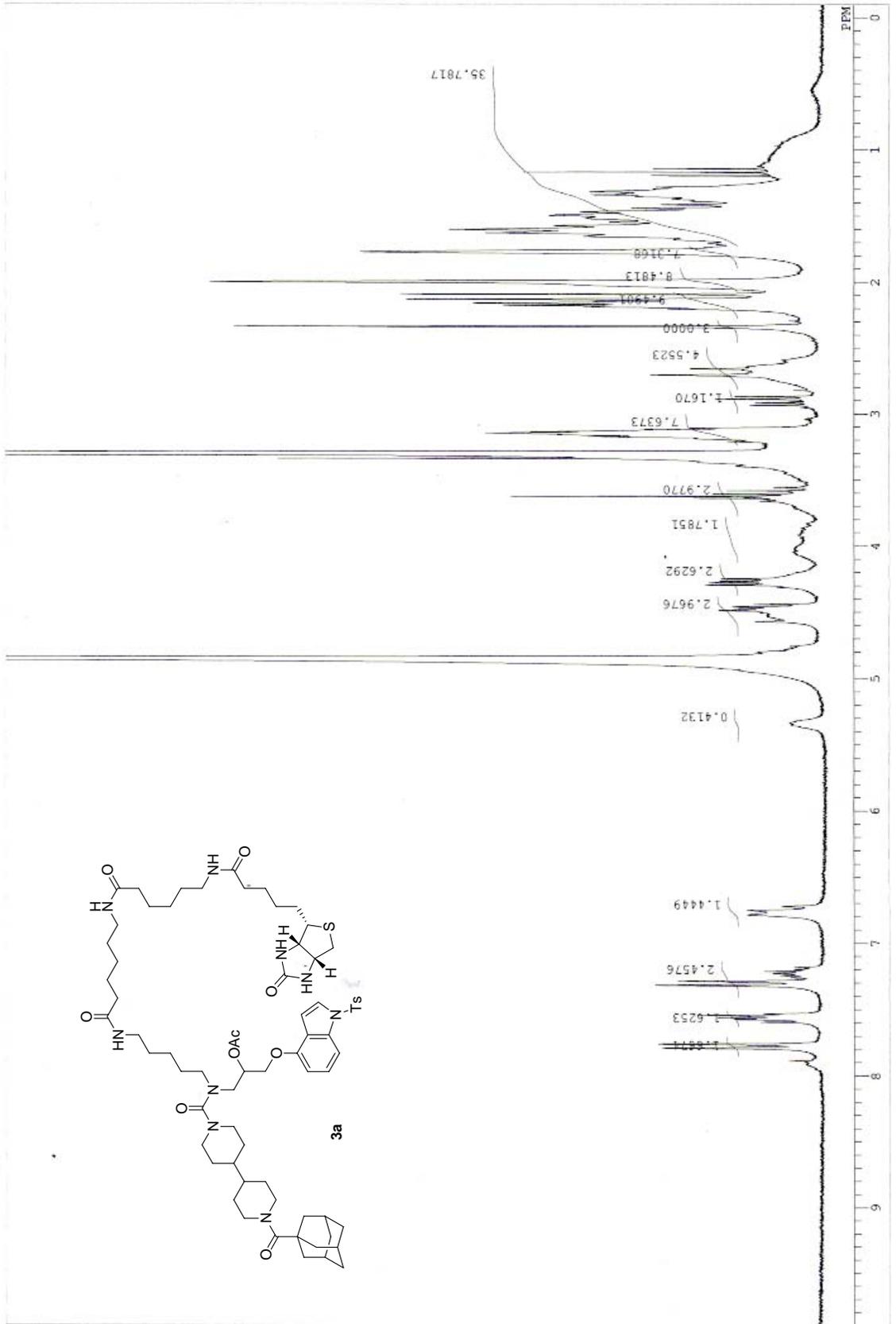
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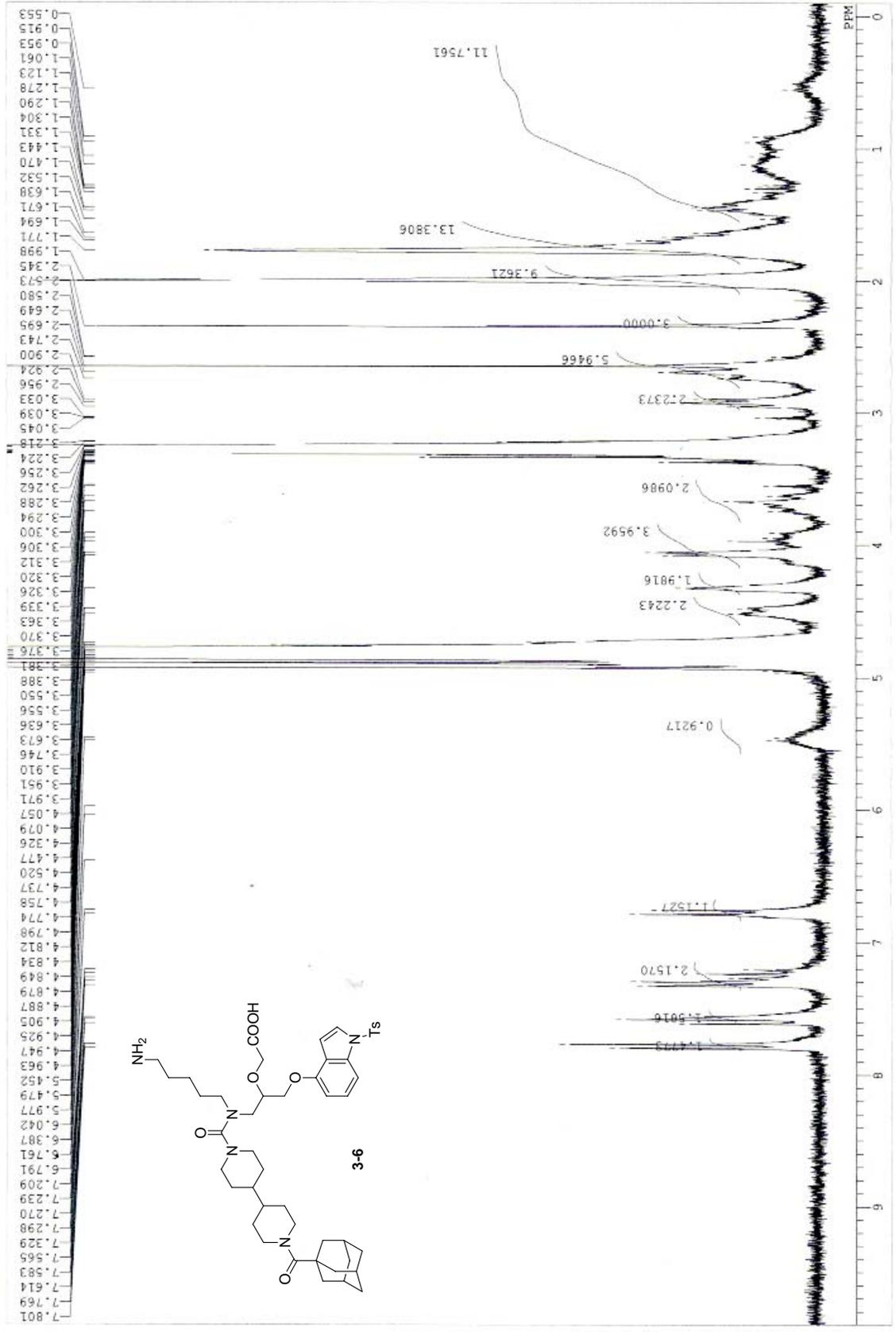
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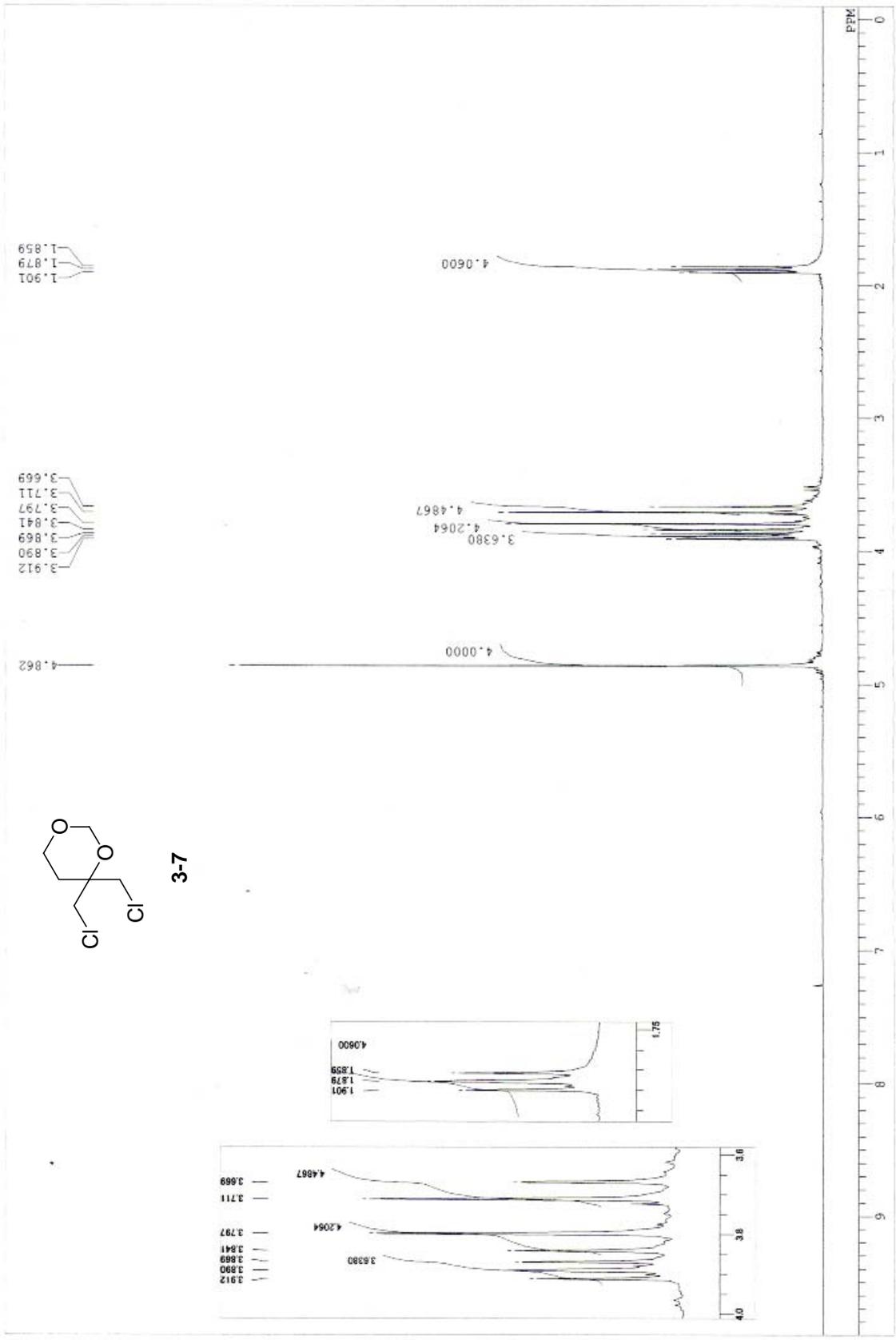




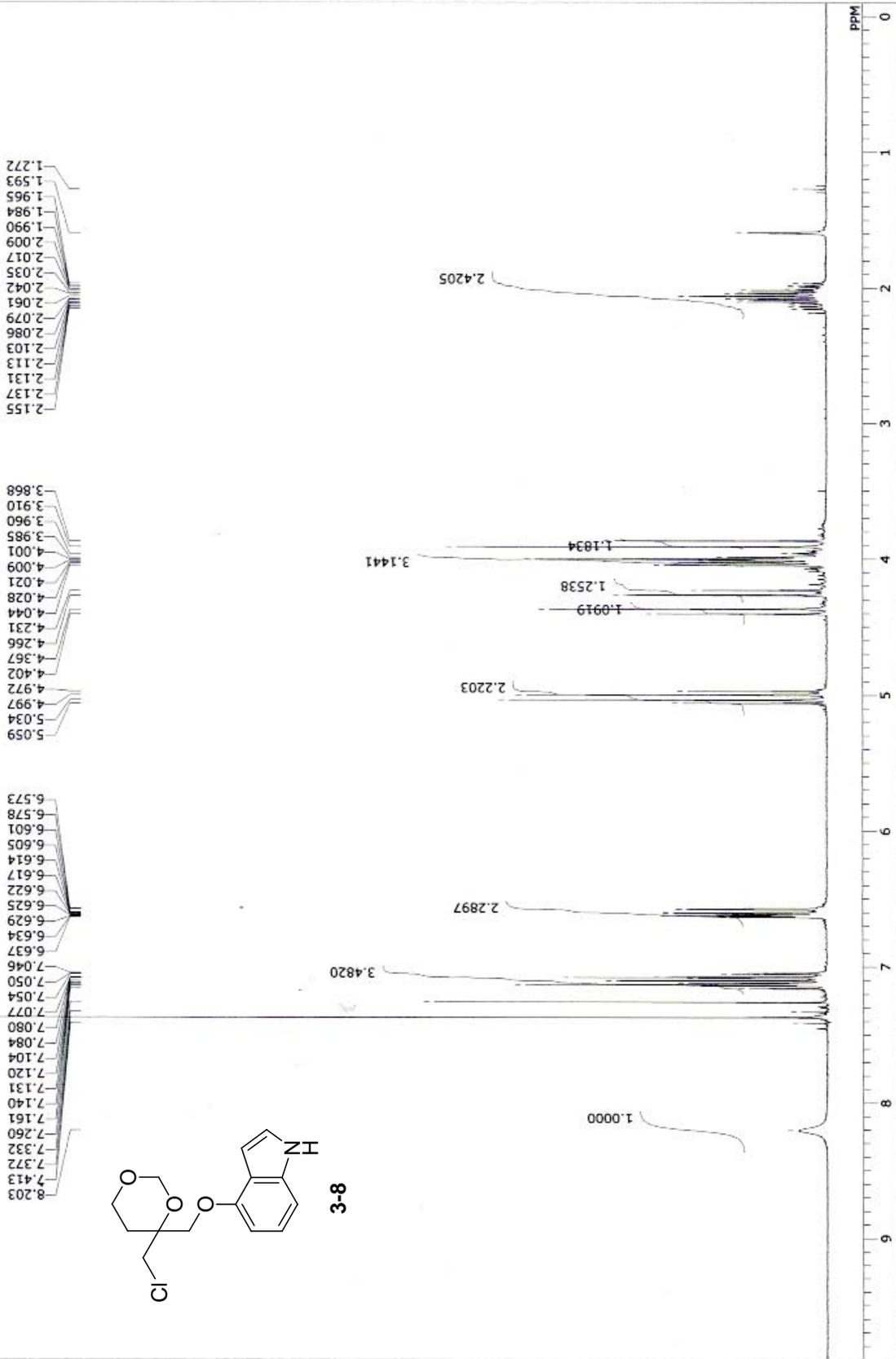
1-0-015-0001 1A

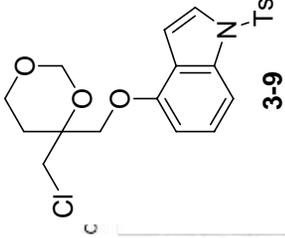
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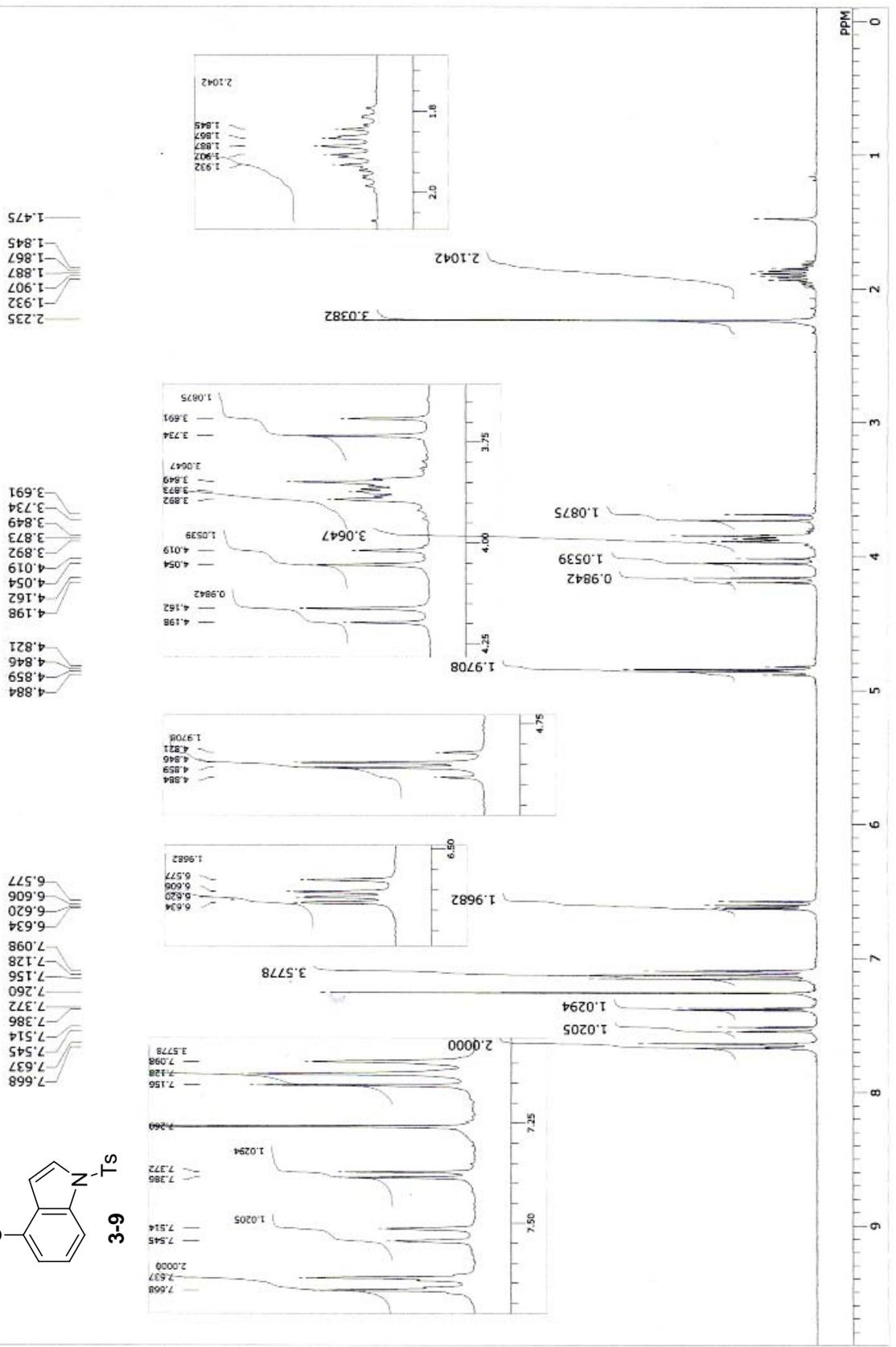


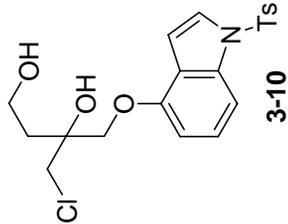
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AULT.ALS



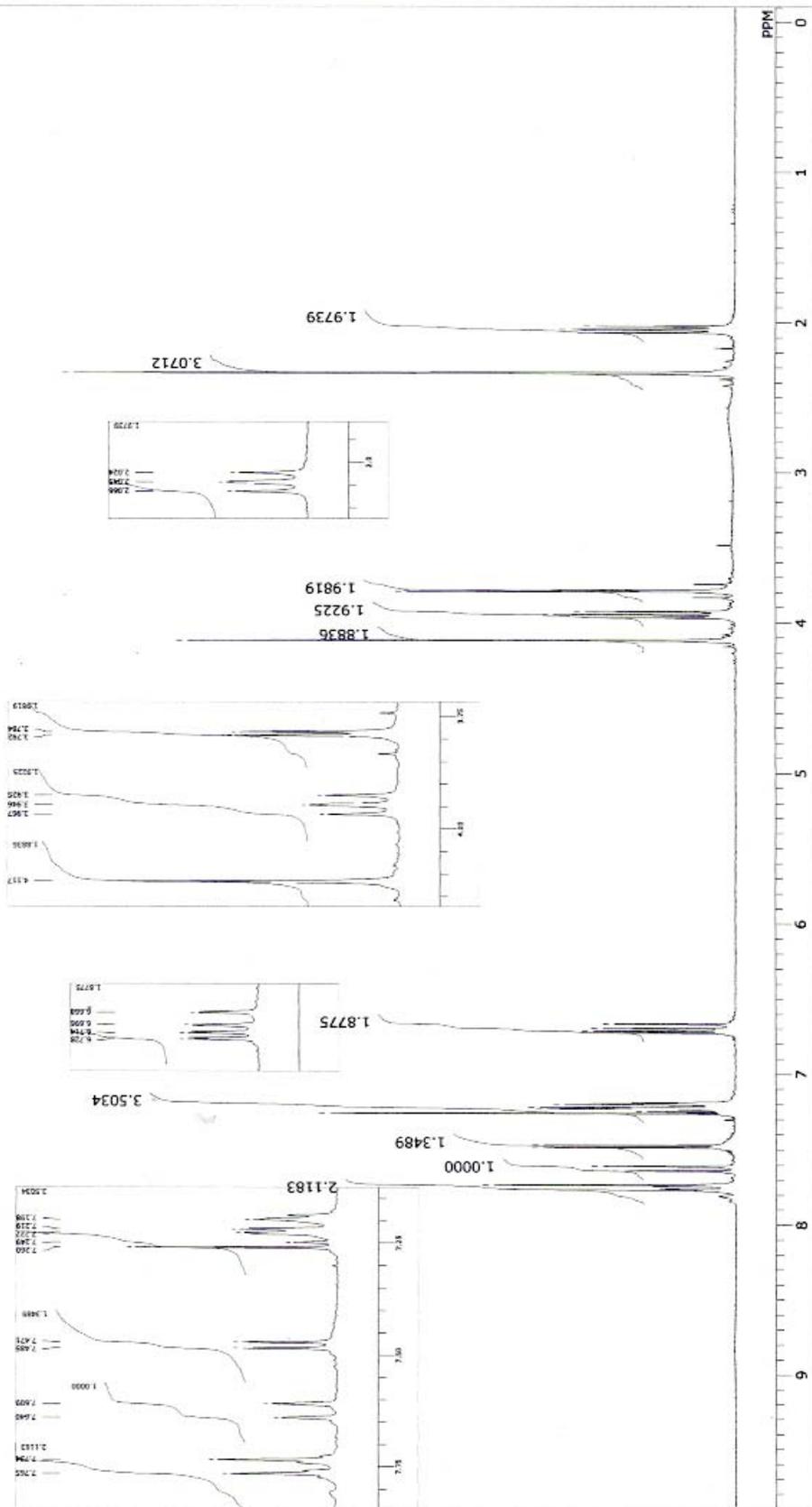


FAULT.ALS

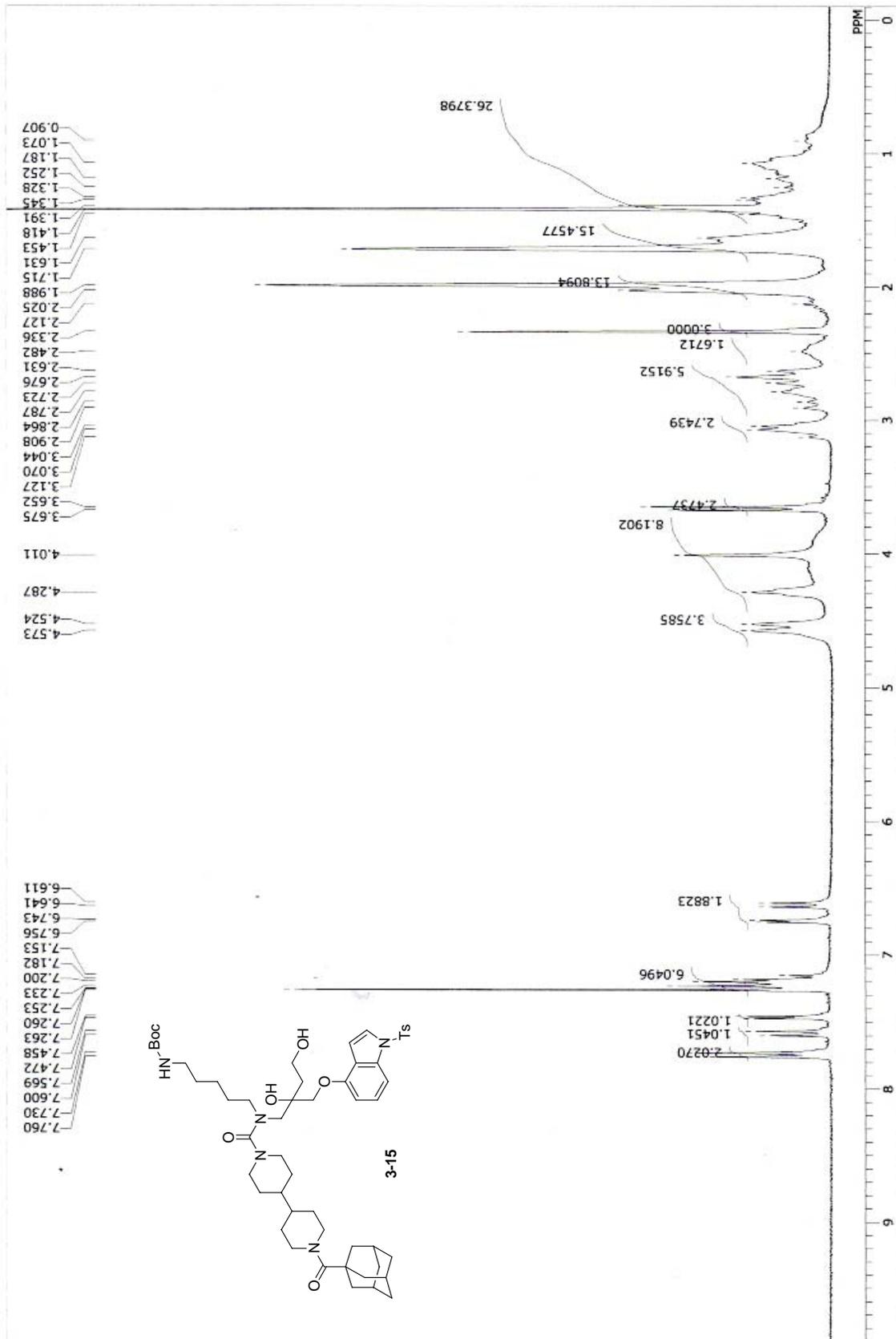
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2.024

4.117
3.967
3.946
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3.792
3.784

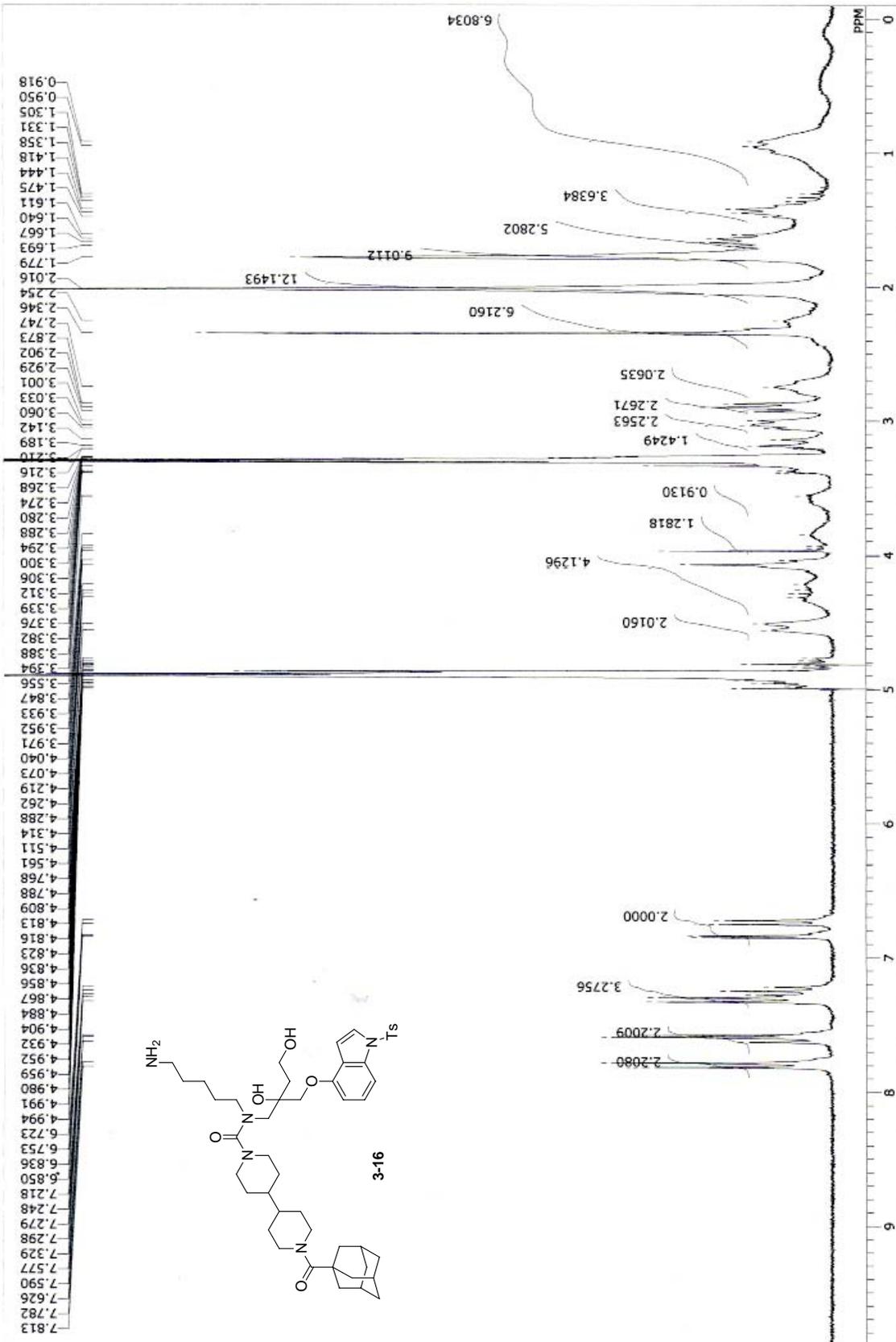
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7.734
7.640
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7.485
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7.249
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7.219
7.198
6.728
6.714
6.696
6.668



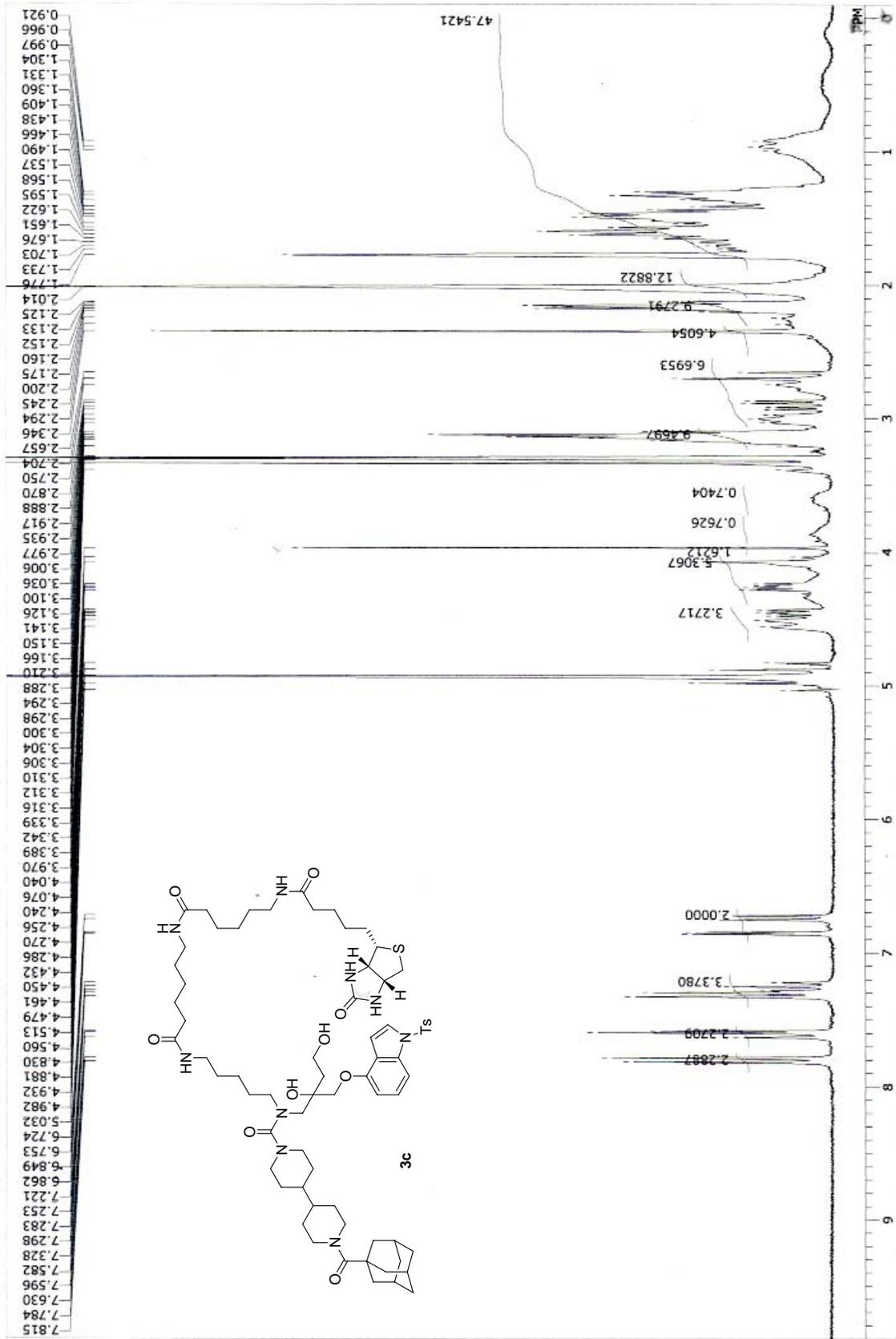
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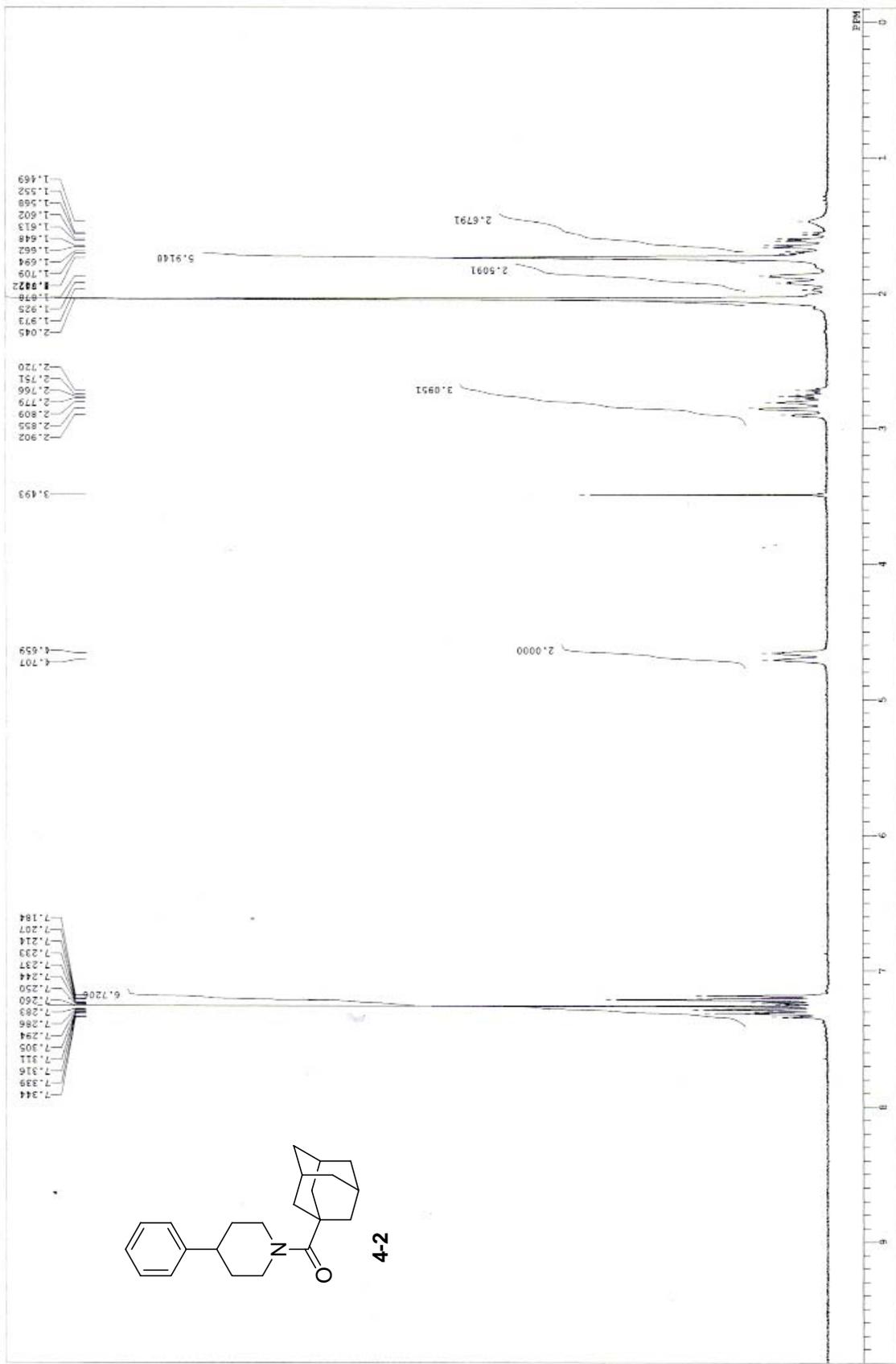
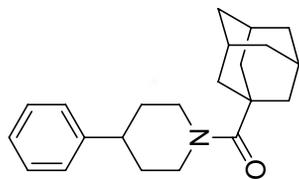


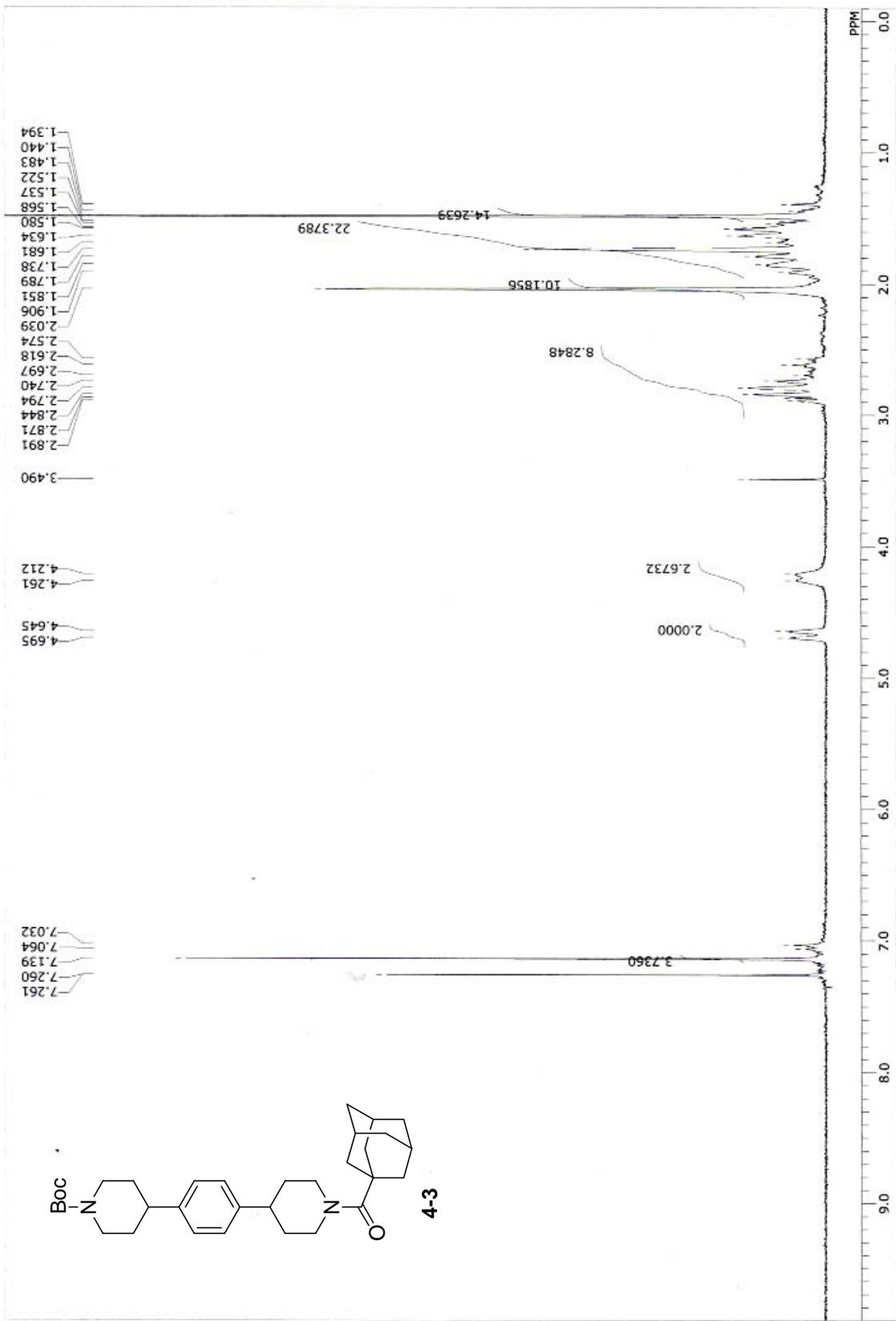
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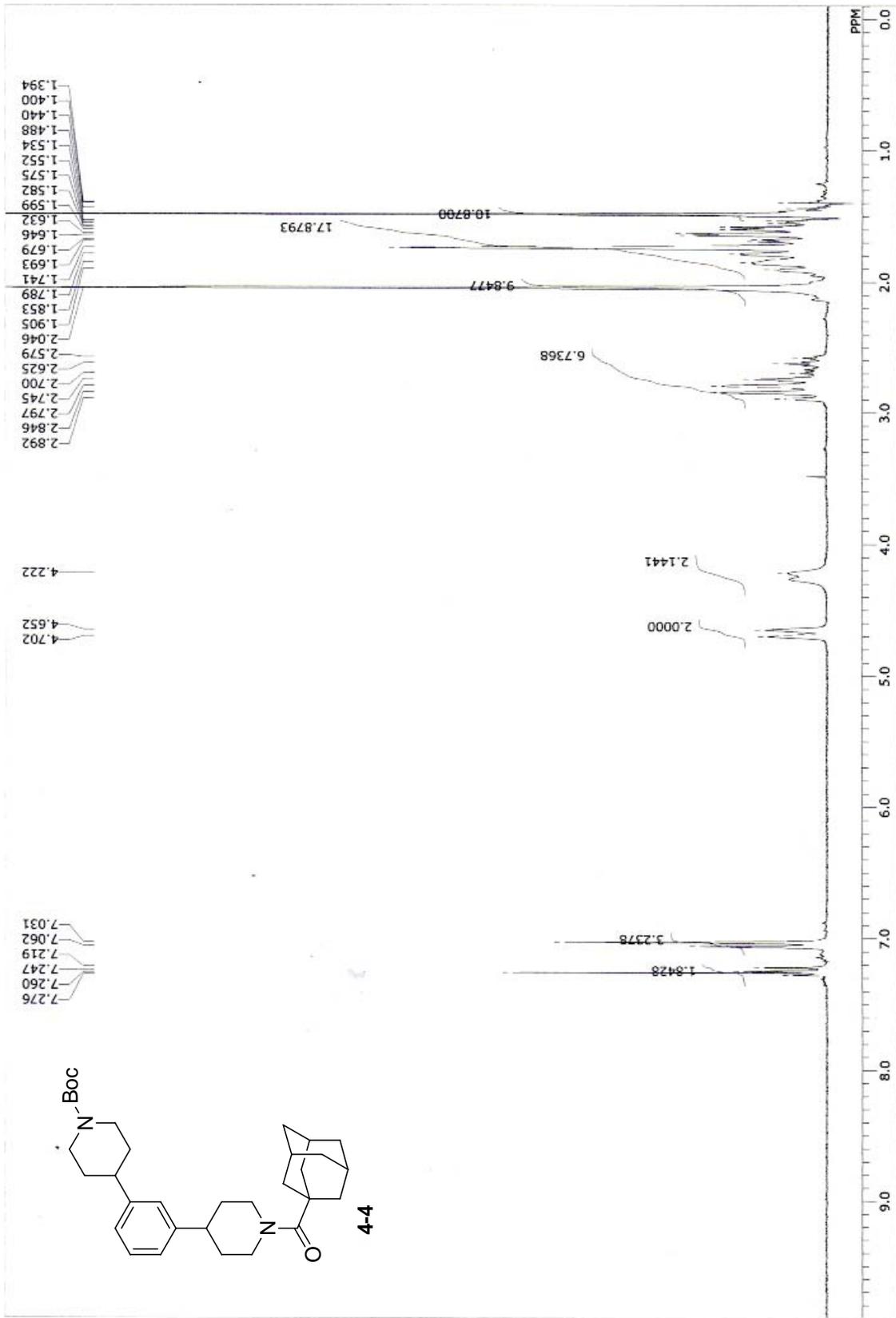




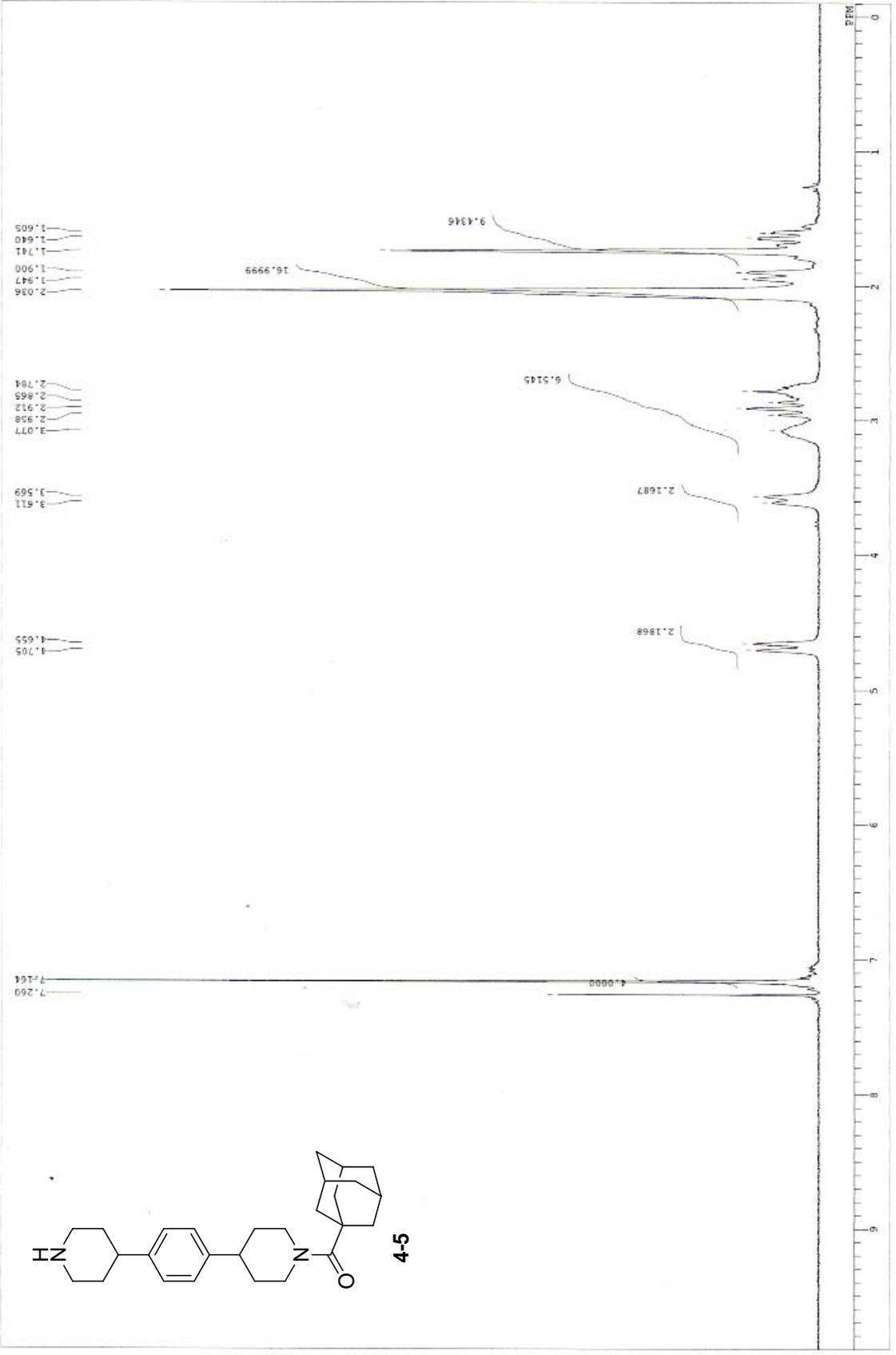
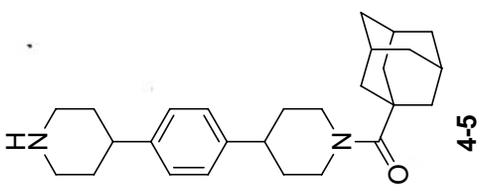


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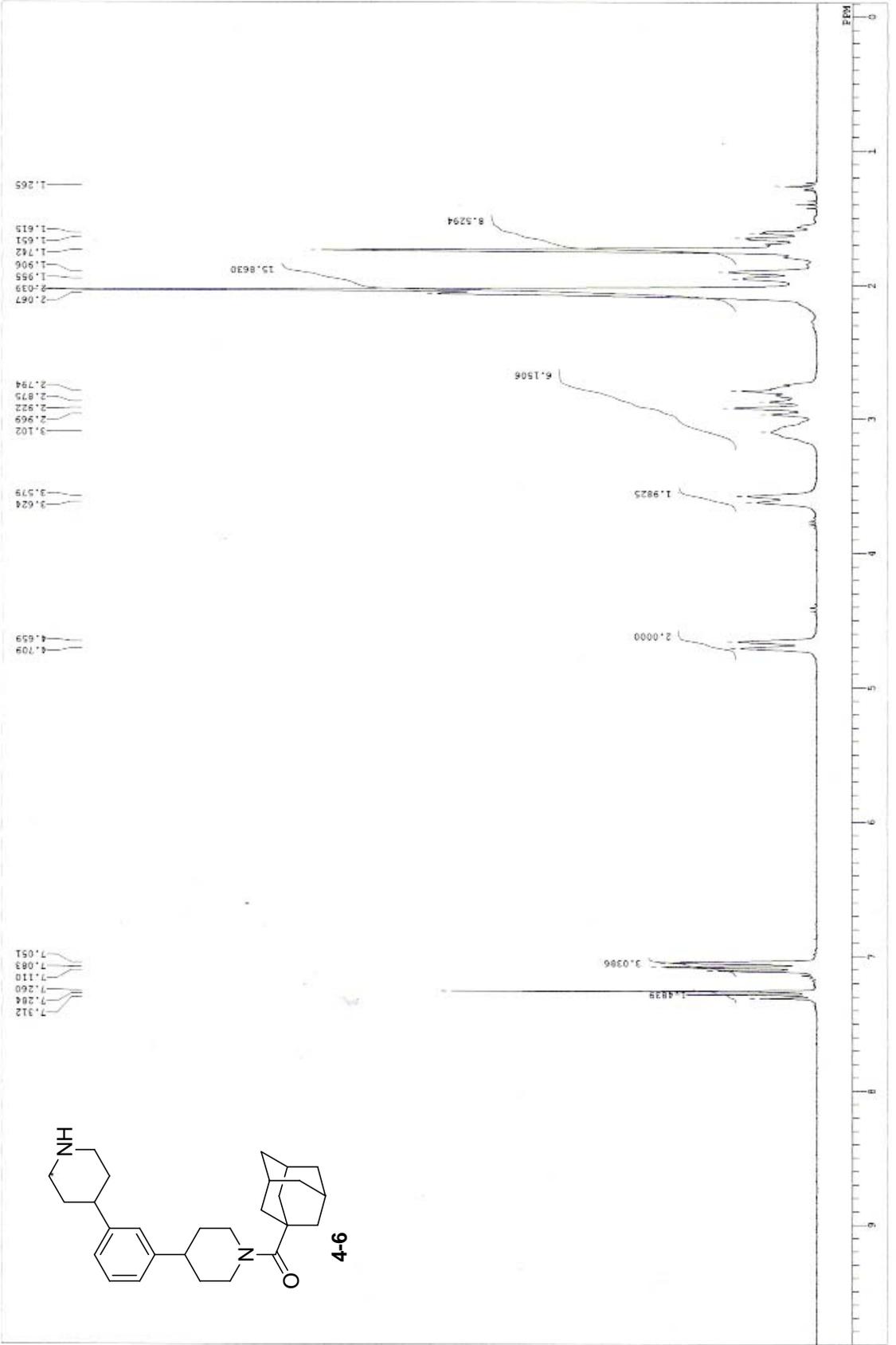
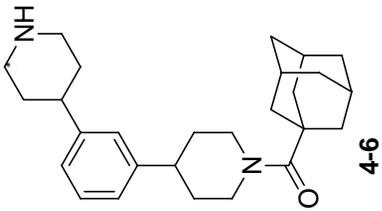
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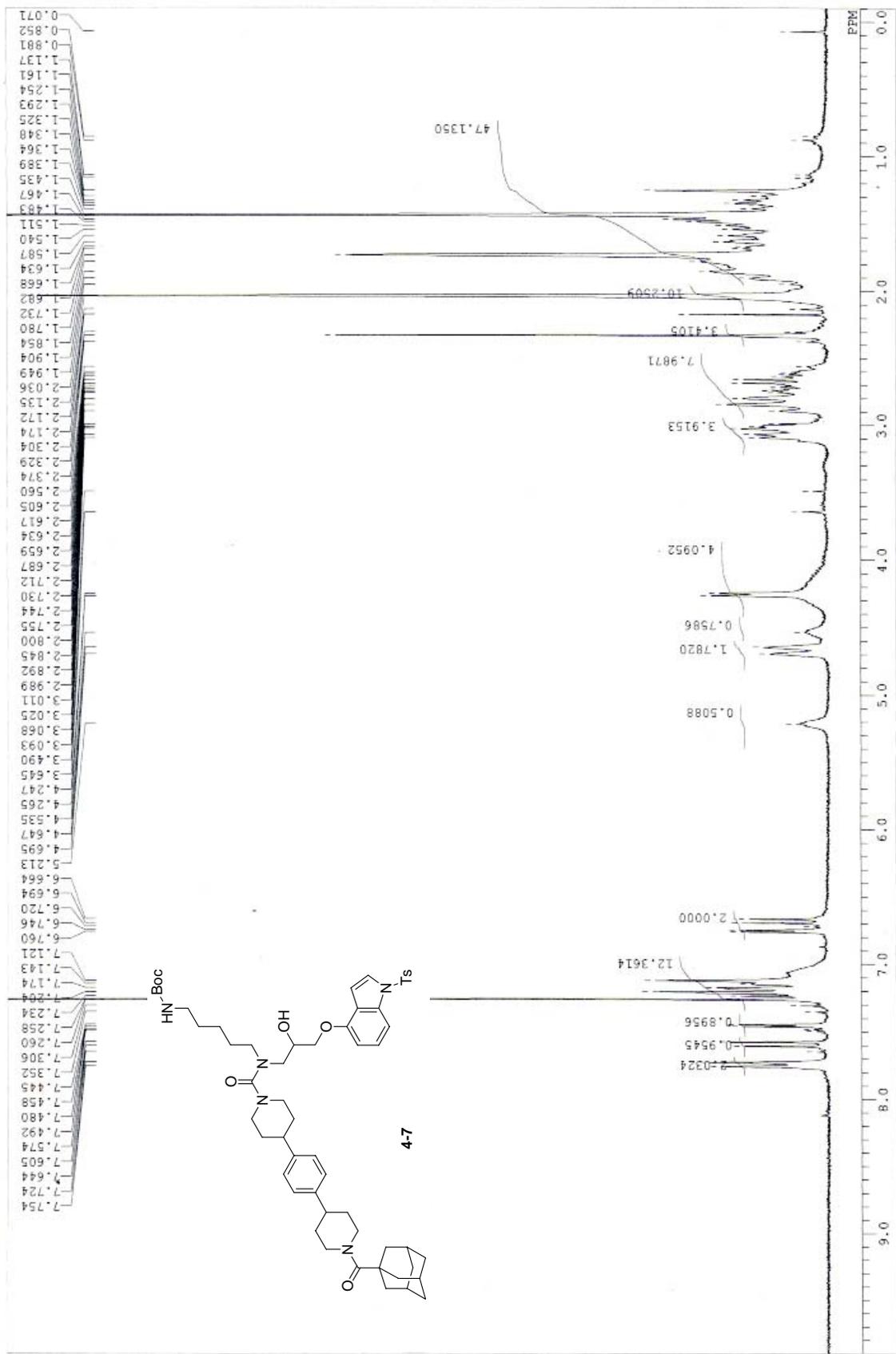
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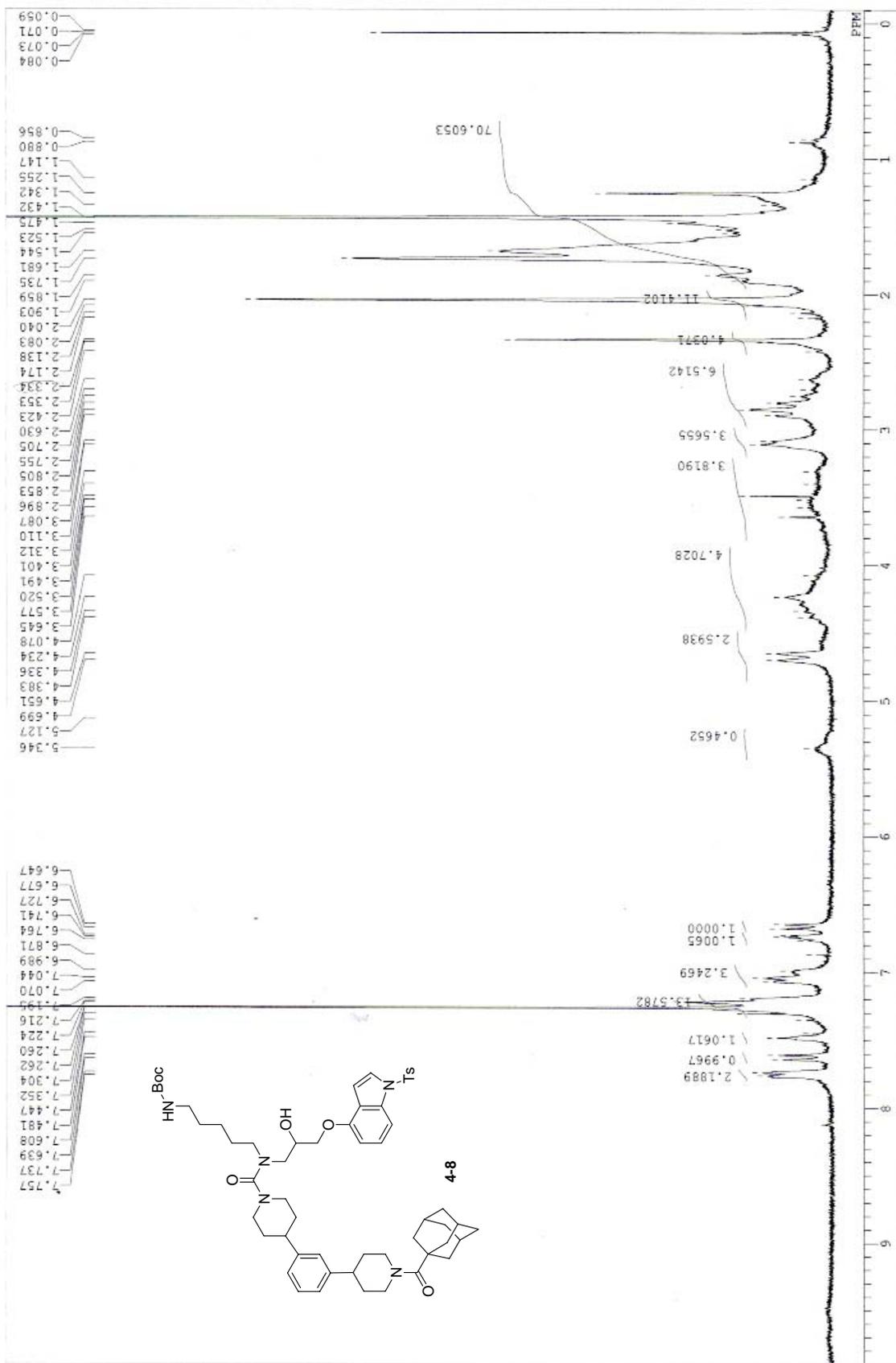
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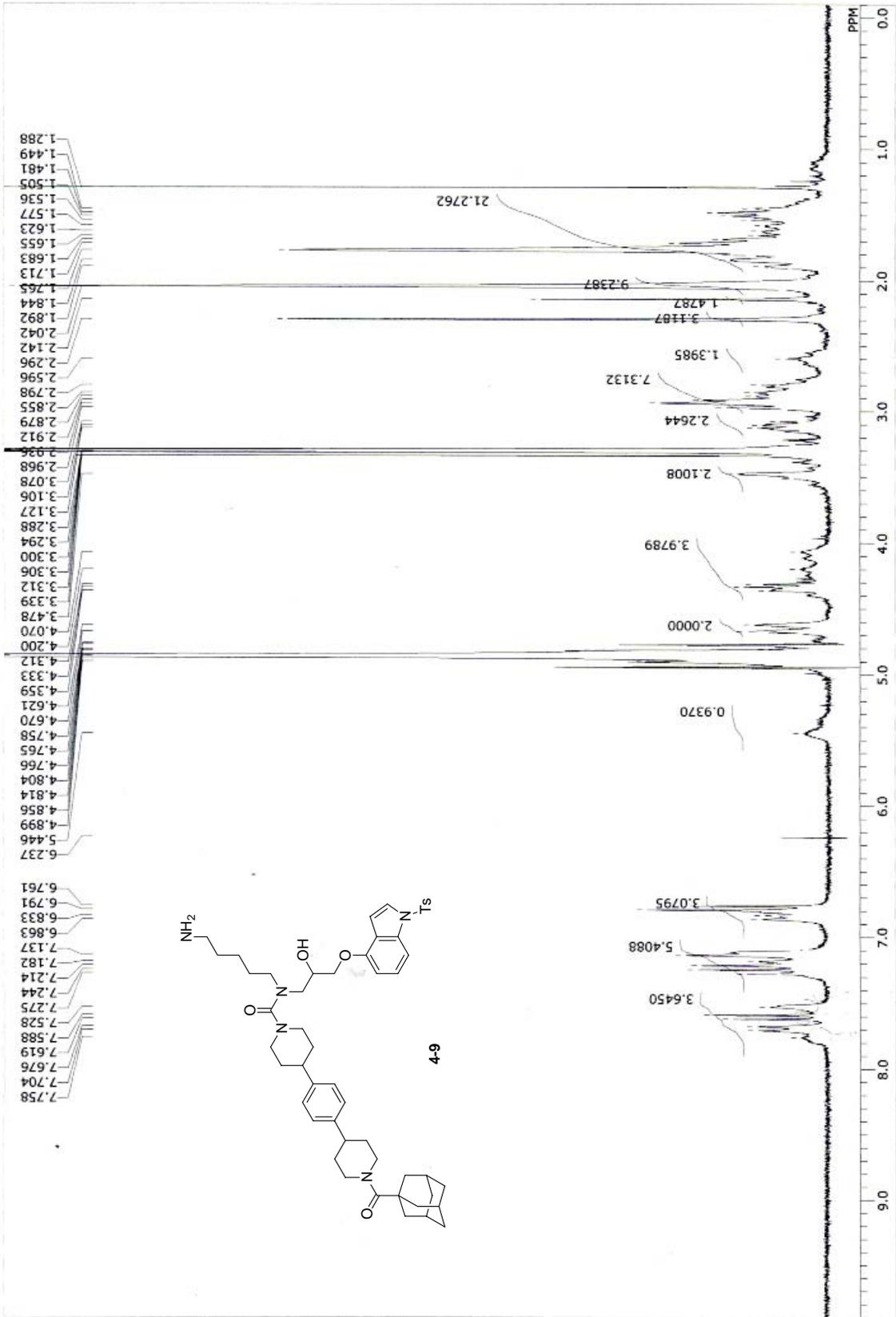


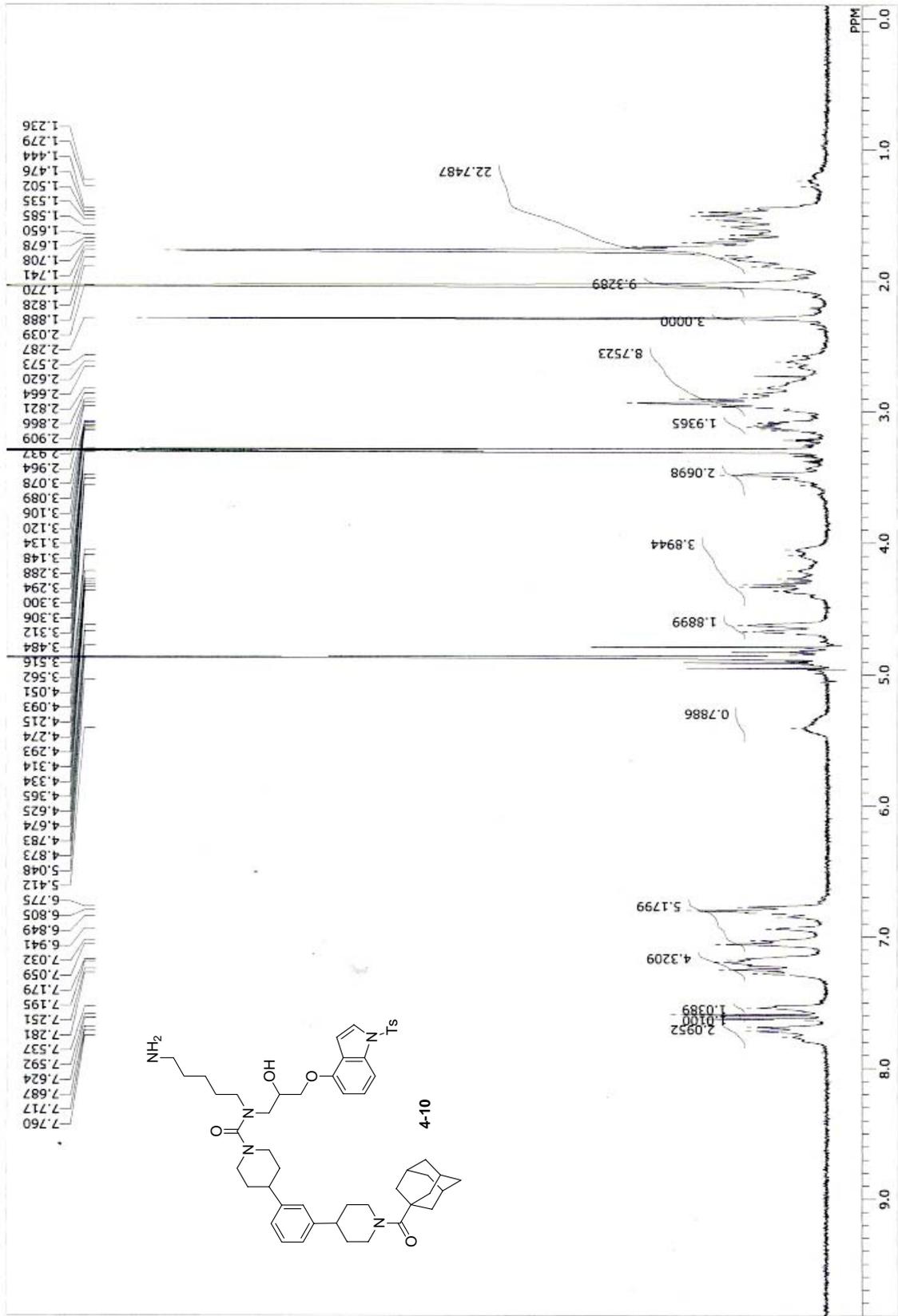
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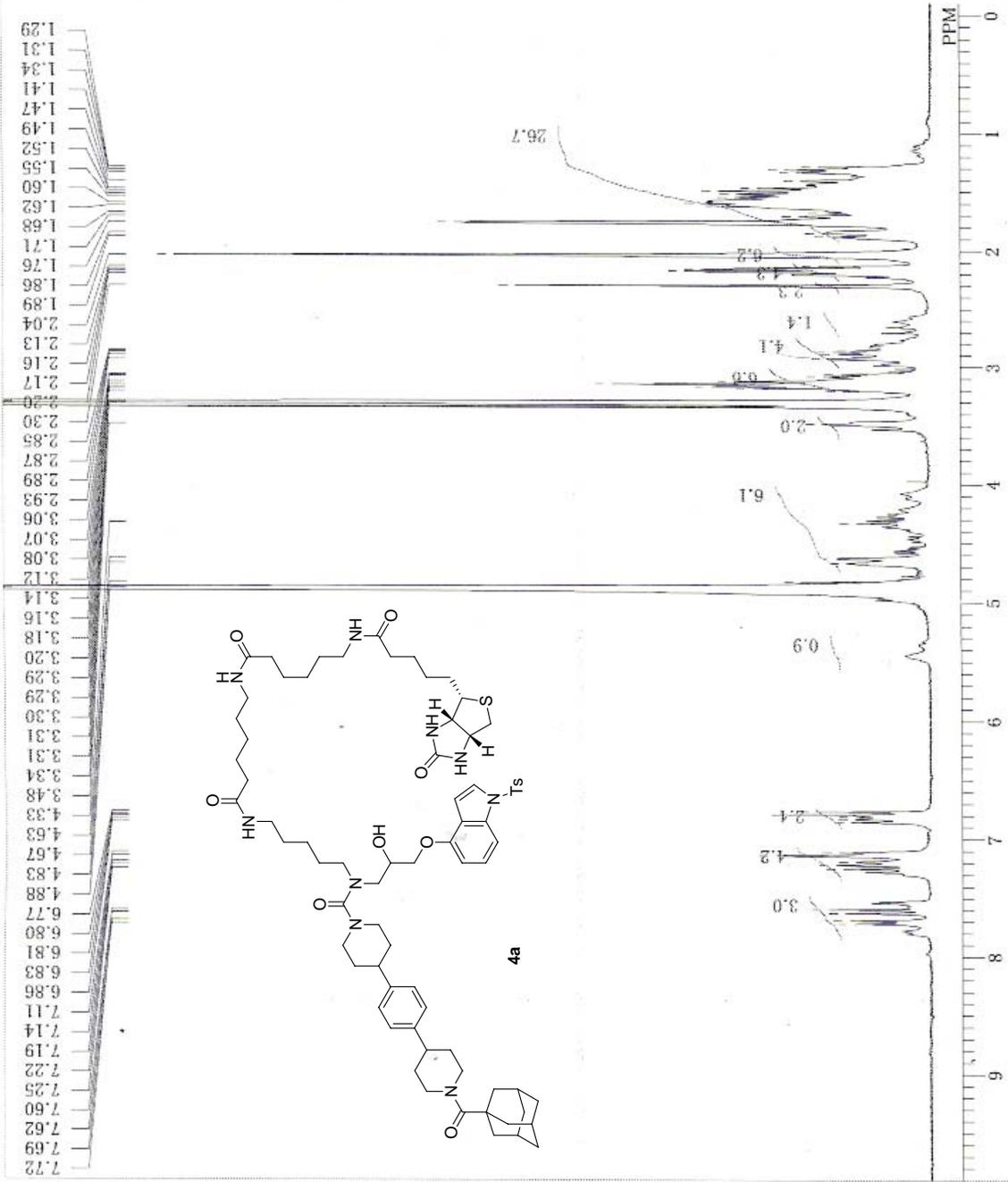




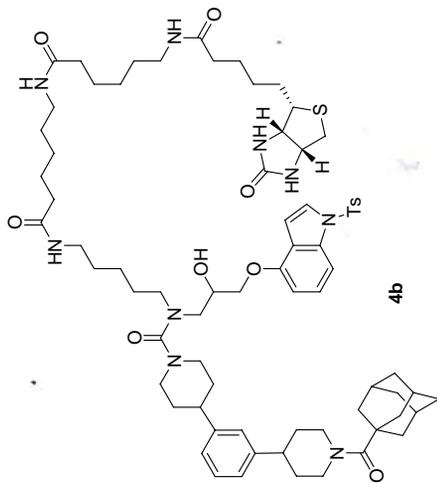
Single Pulse Experiment

DFILE
 COMNT
 DATIM
 OBNUC
 EXMOD
 OBFRQ
 OBSET
 OBFIN
 POINT
 FREQU
 SCANS
 ACQTM
 PD
 PW1
 IRNUC
 CTEMP
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 EXREF
 BF
 RGAIN

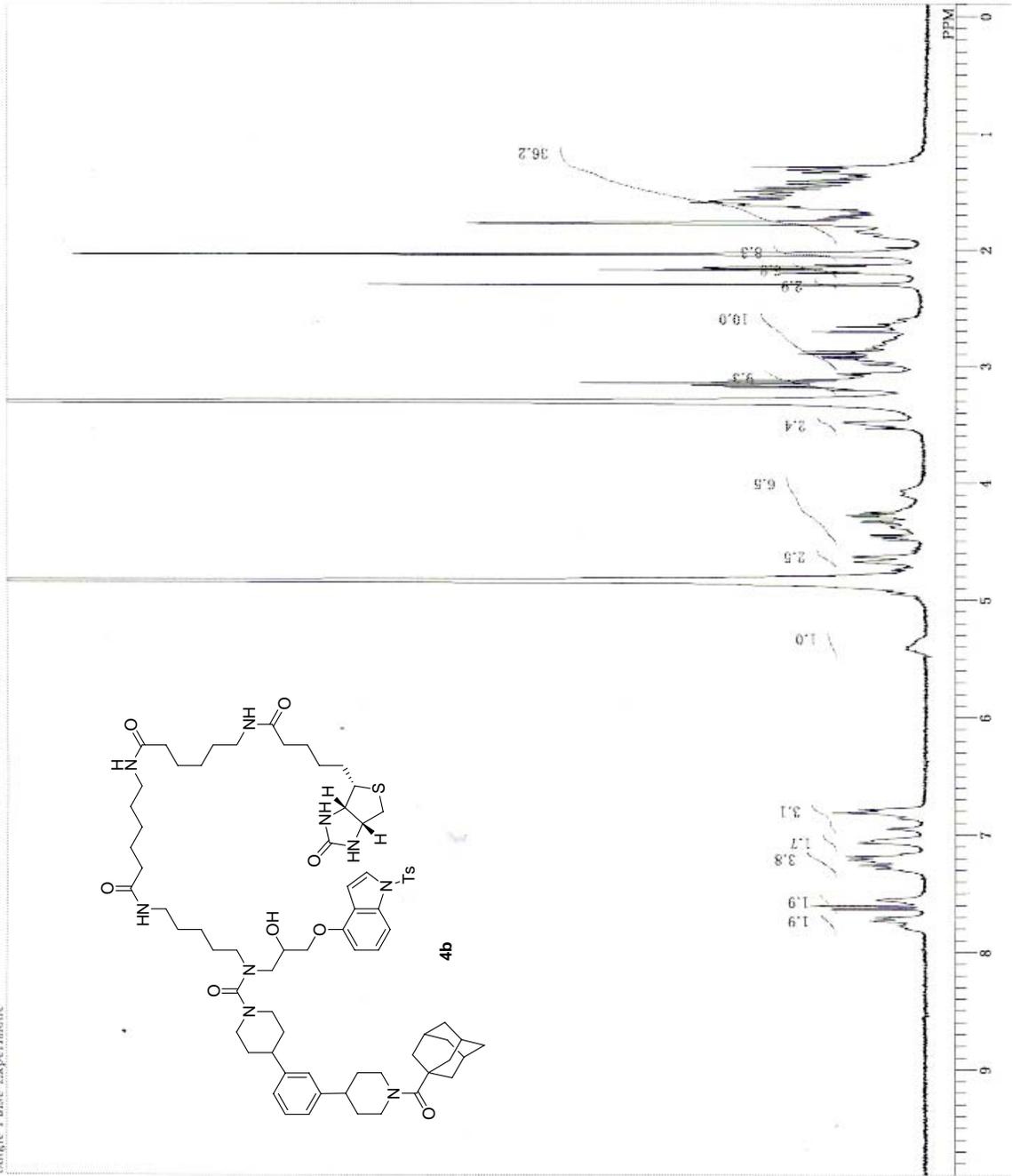
simo080302-1.2
 Single Pulse Experiment
 02-03-2008 13:54:54
 1H
 single_pulse.exp
 300.53 MHz
 1.15 KHz
 8.57 Hz
 16384
 4508.57 Hz
 128
 3.6340 sec
 1.0000 sec
 6.50 usec
 21.0 c
 CD3OD
 3.30 ppm
 0.12 Hz
 17



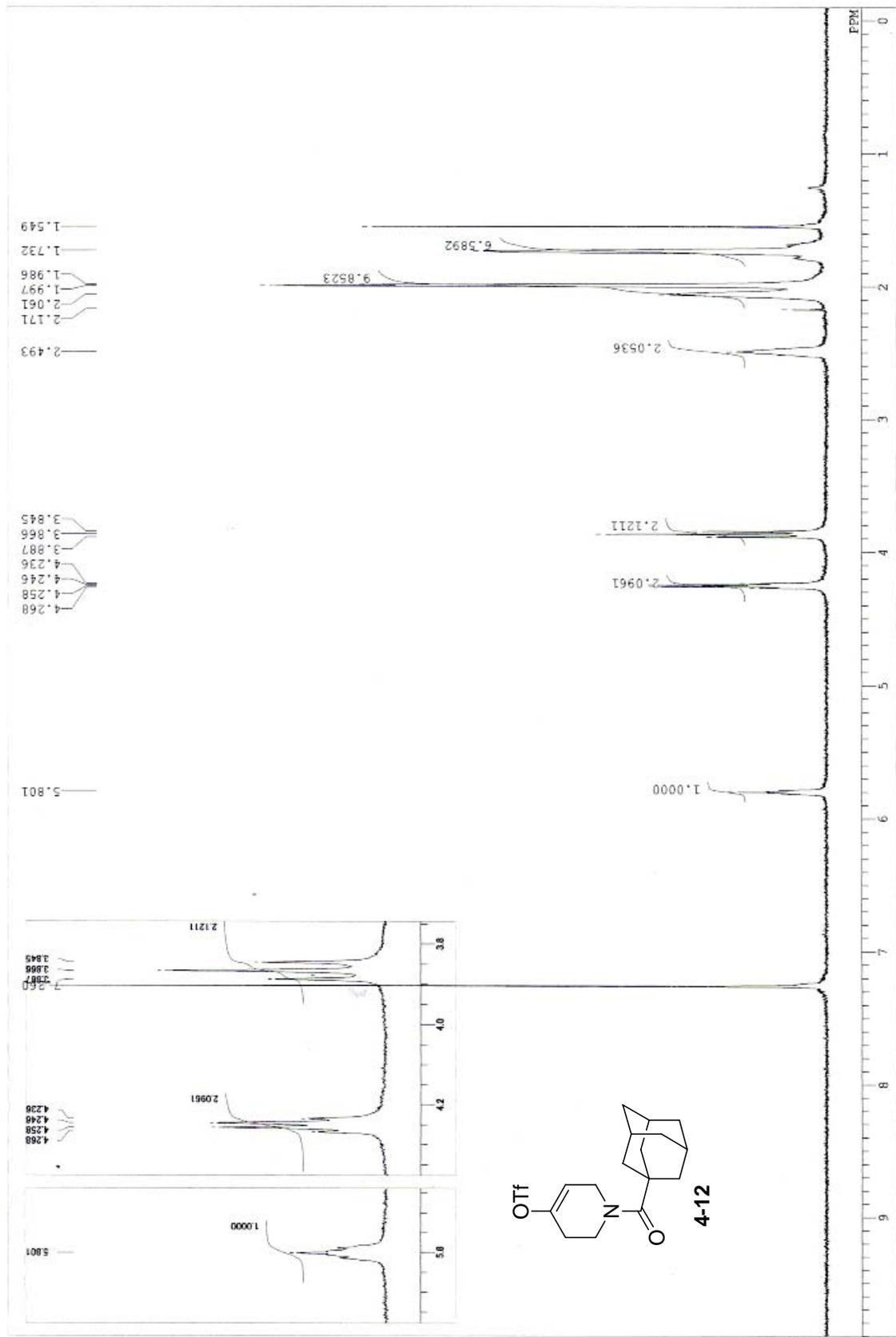
DFILE ophe-wre-biotin.ads
COMNT Single Pulse Experiment
DATIM 19-06-2007 10:10:31
OBNUC 1H
single_pulse.exp
EXMOD 300.53 MHz
OBFREQ 1.15 KHz
OBSET 8.57 Hz
OBFIN 16384
POINT 4508.57 Hz
FREQ/J 128
SCANS 3.6340 sec
ACQTM 1.0000 sec
PD 6.50 usec
PWL 25.3 c
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SLVNT 0.12 Hz
EXREF 19
BF
RGAIN



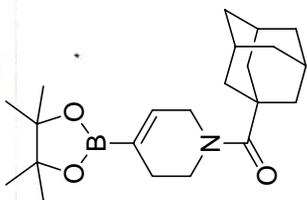
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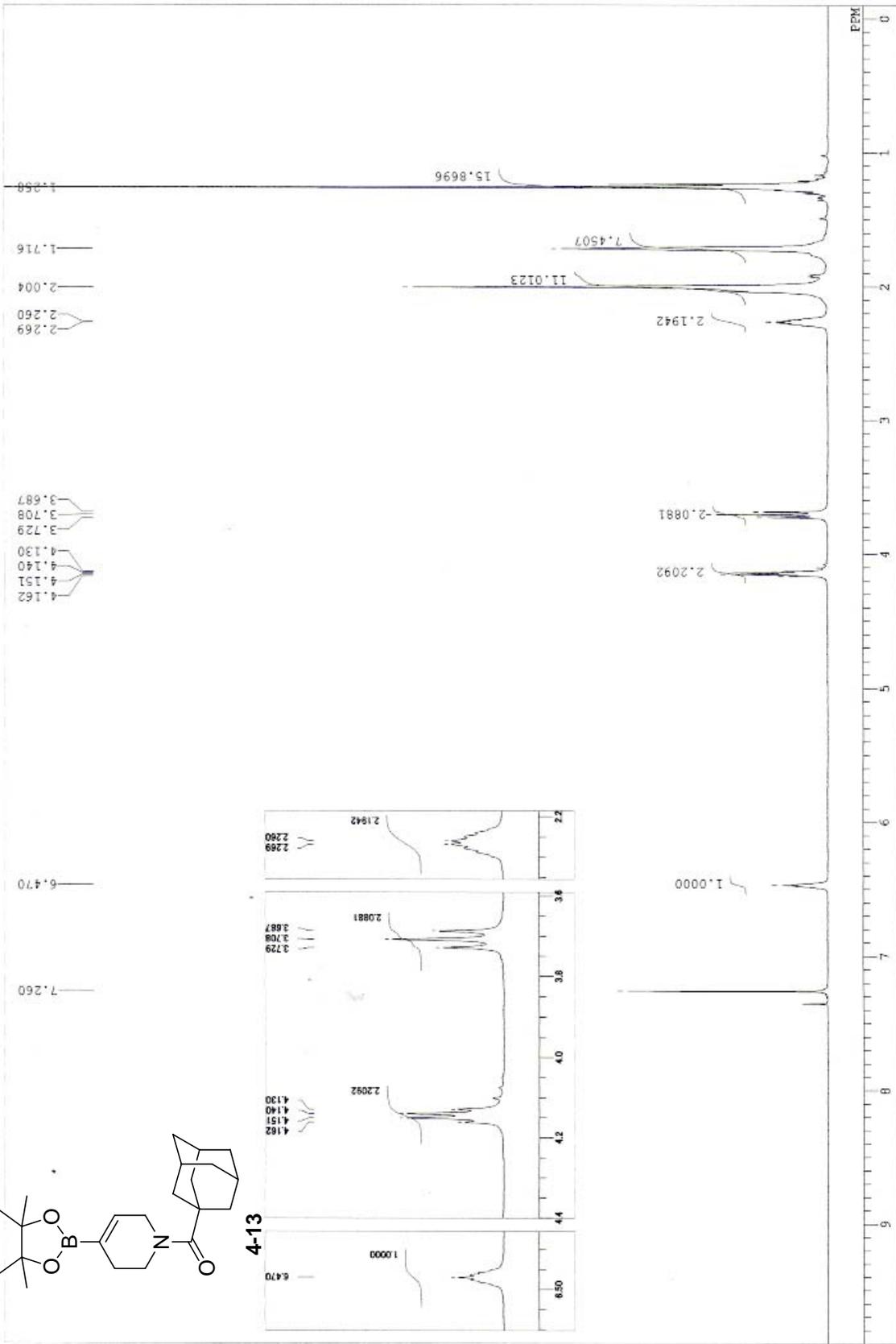
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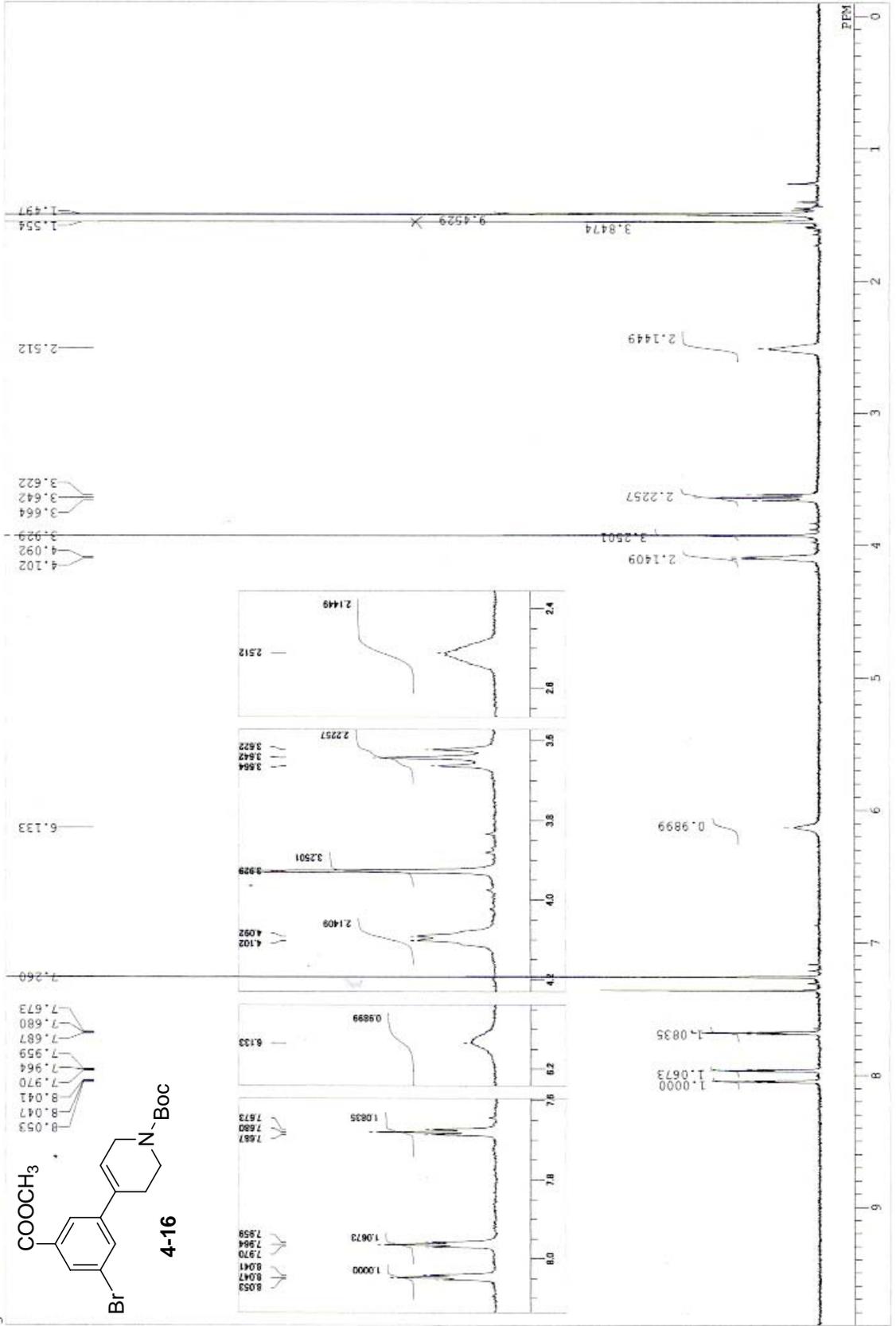
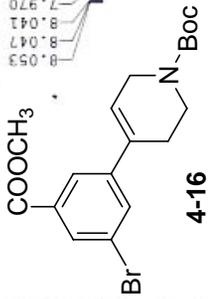


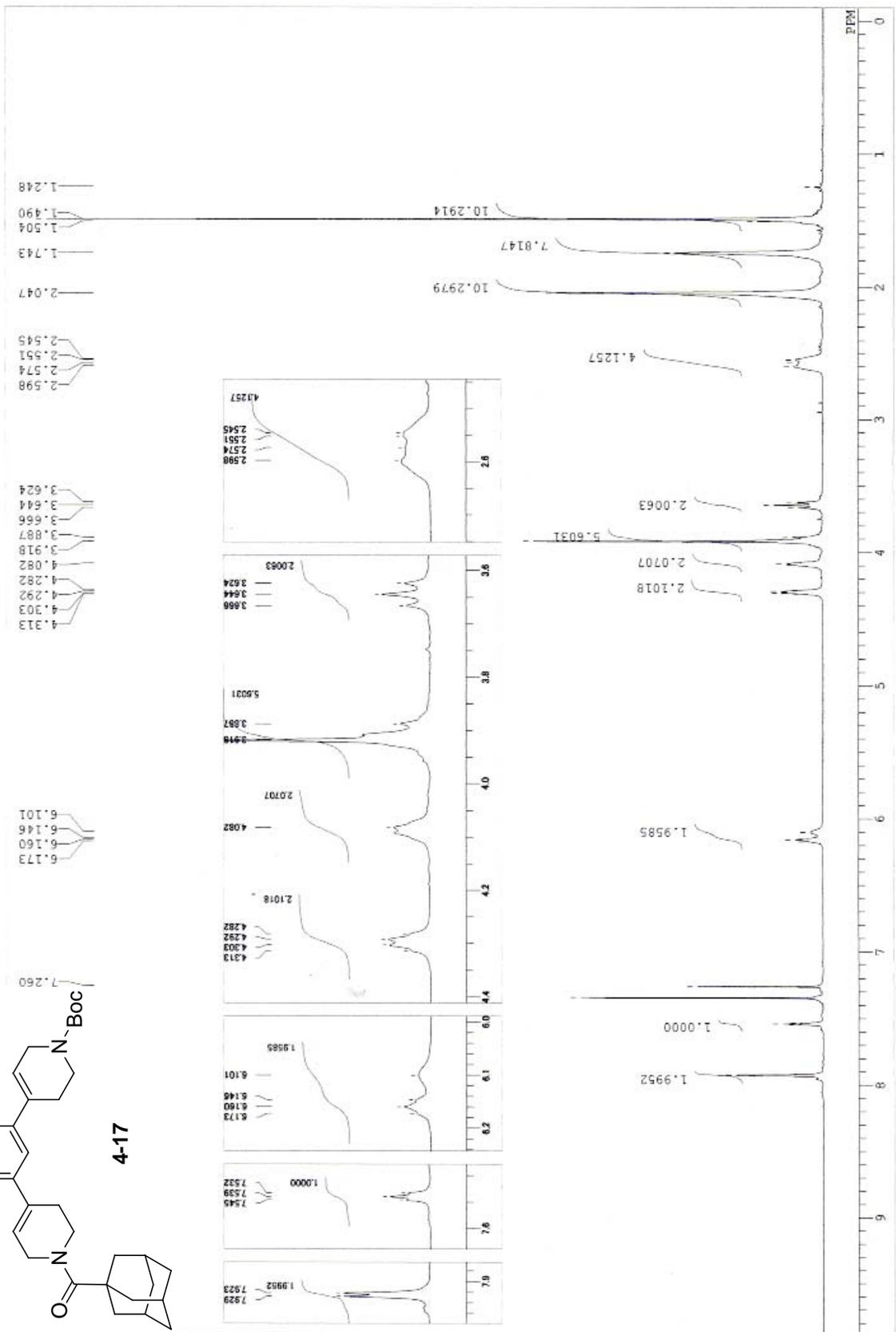
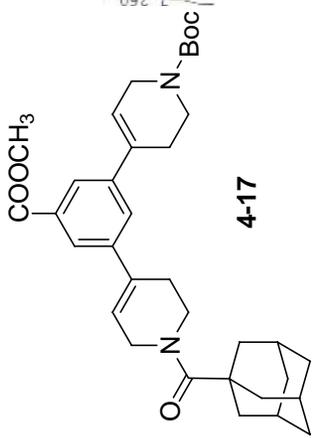
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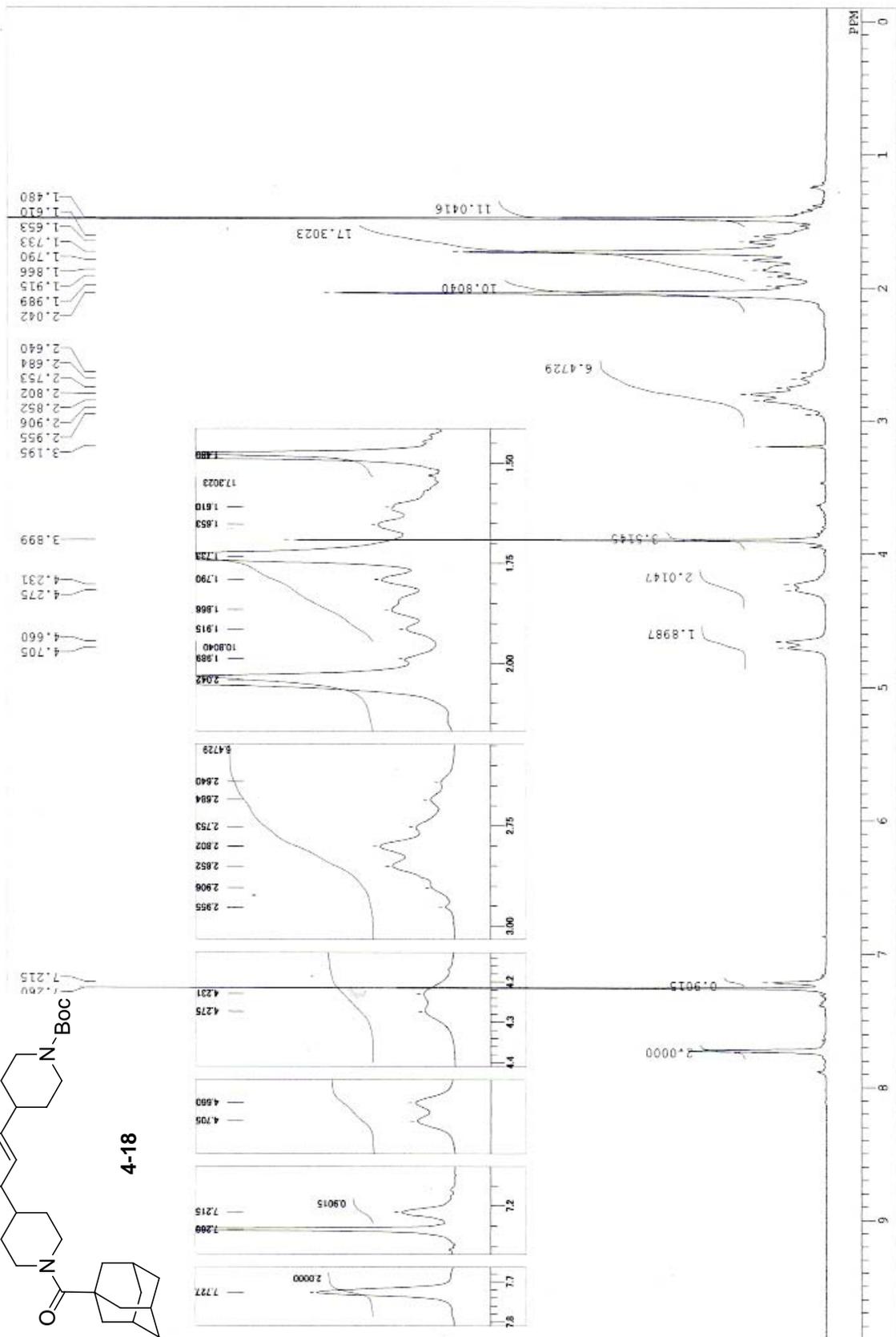
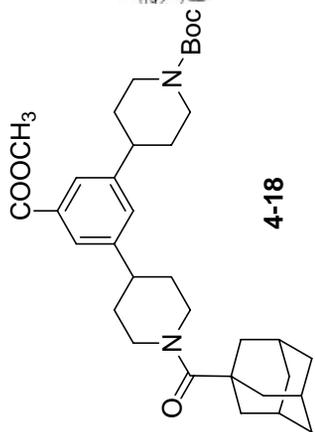


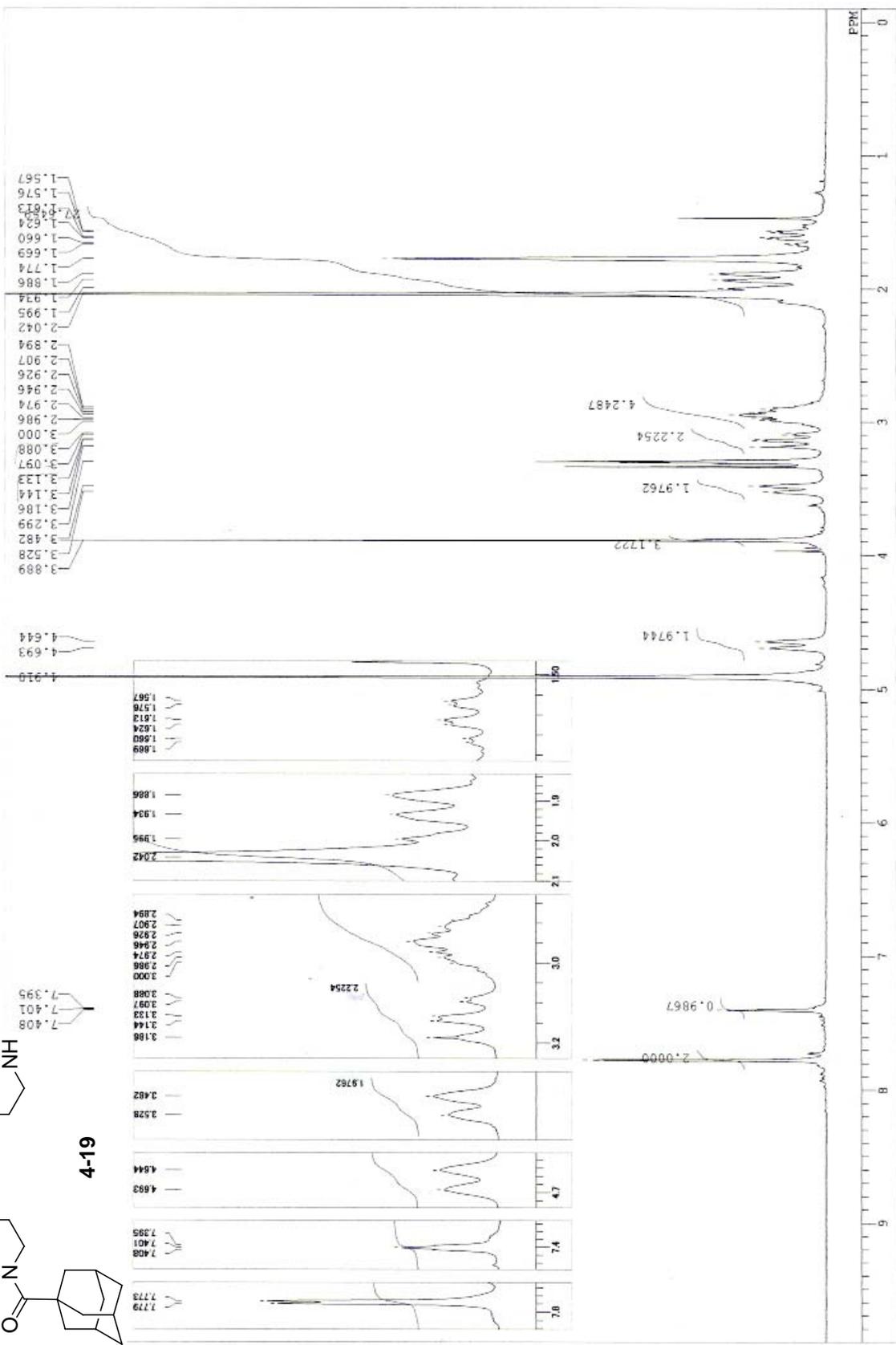
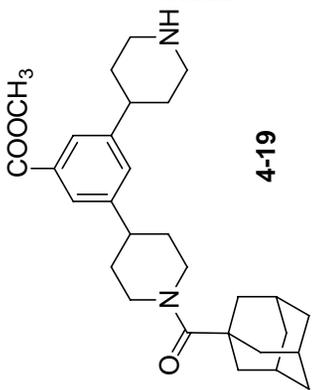
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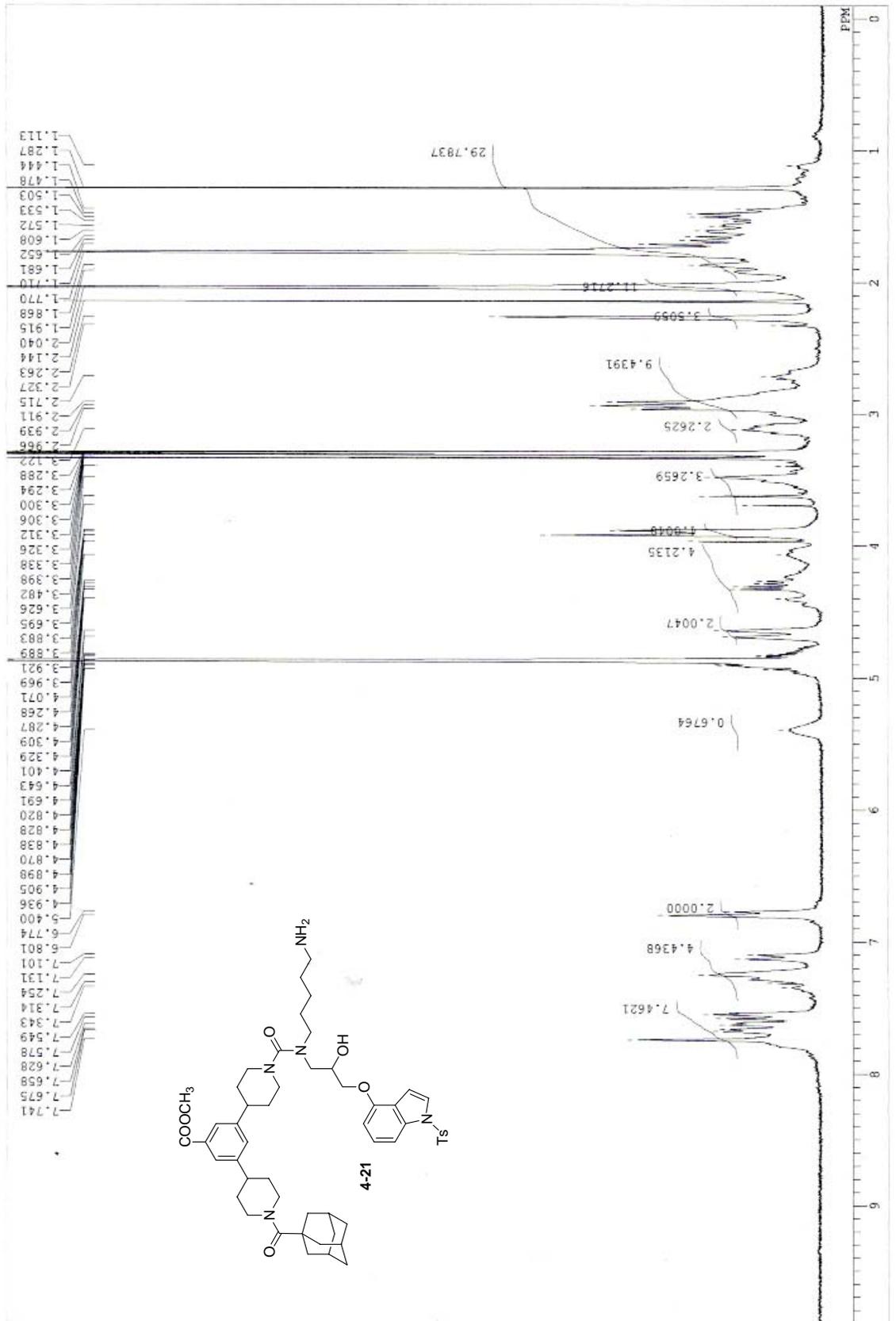




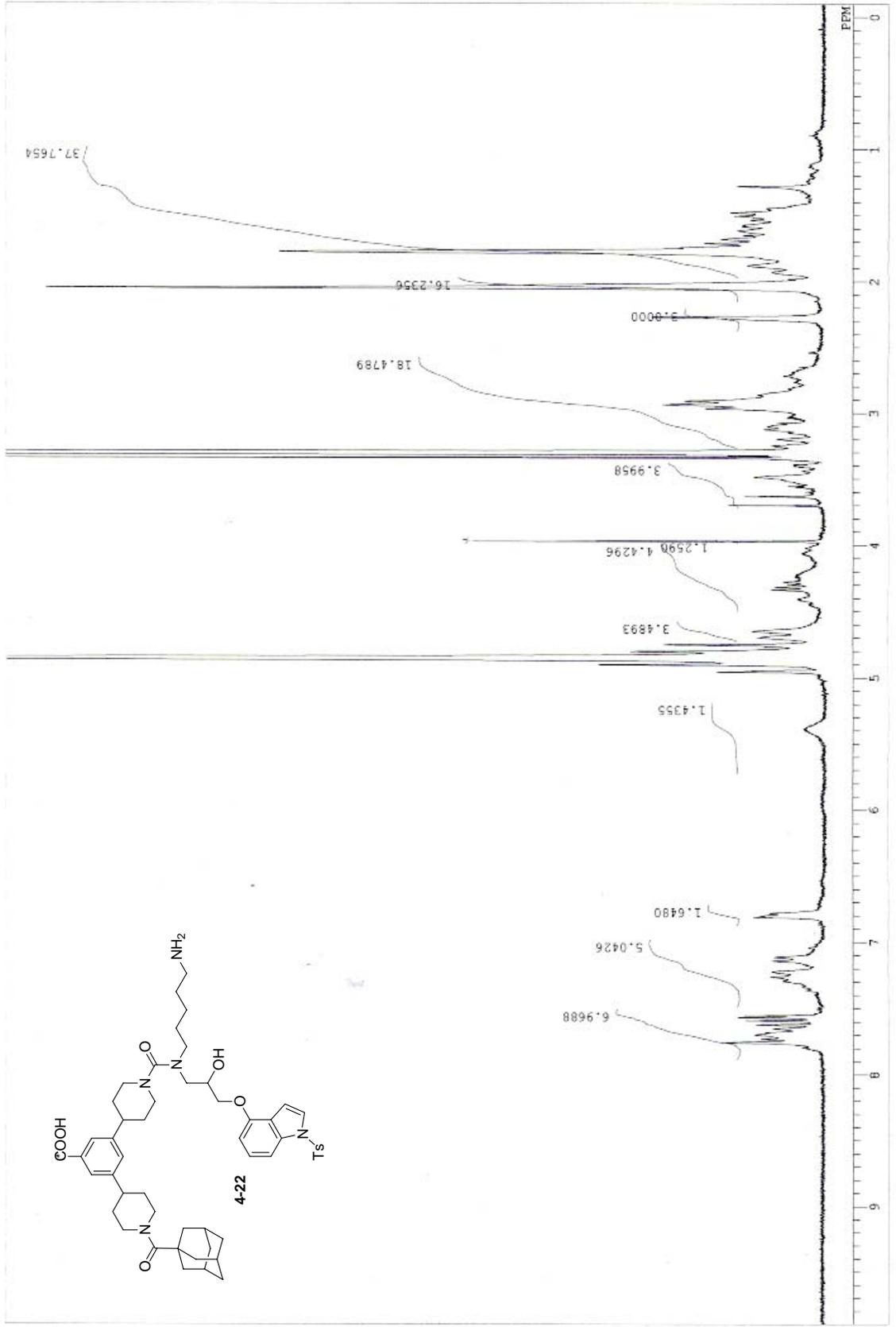




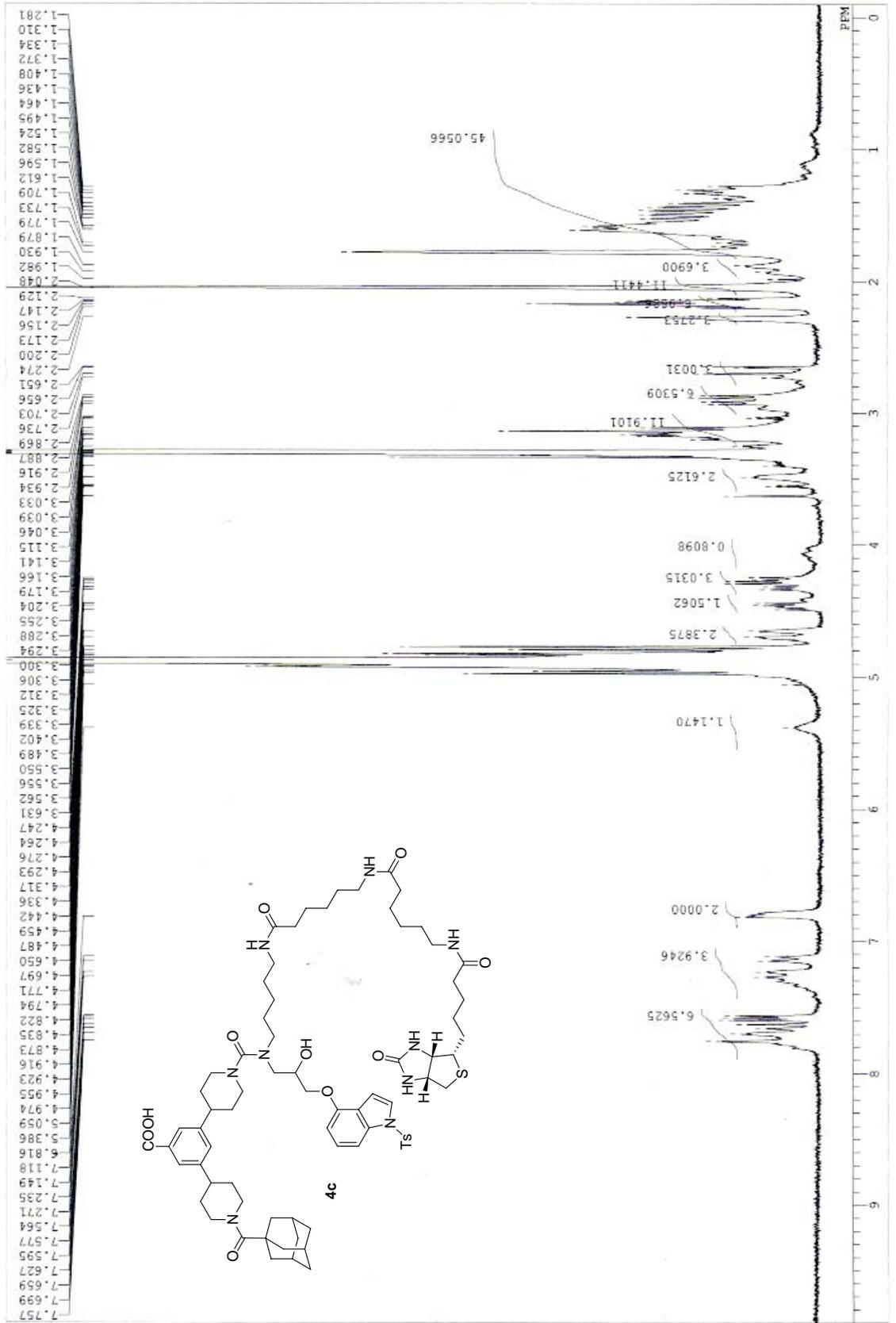
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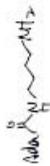


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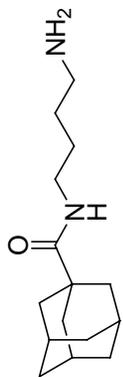


C:\WINNR98\COMMON_DEFAULT_ALS

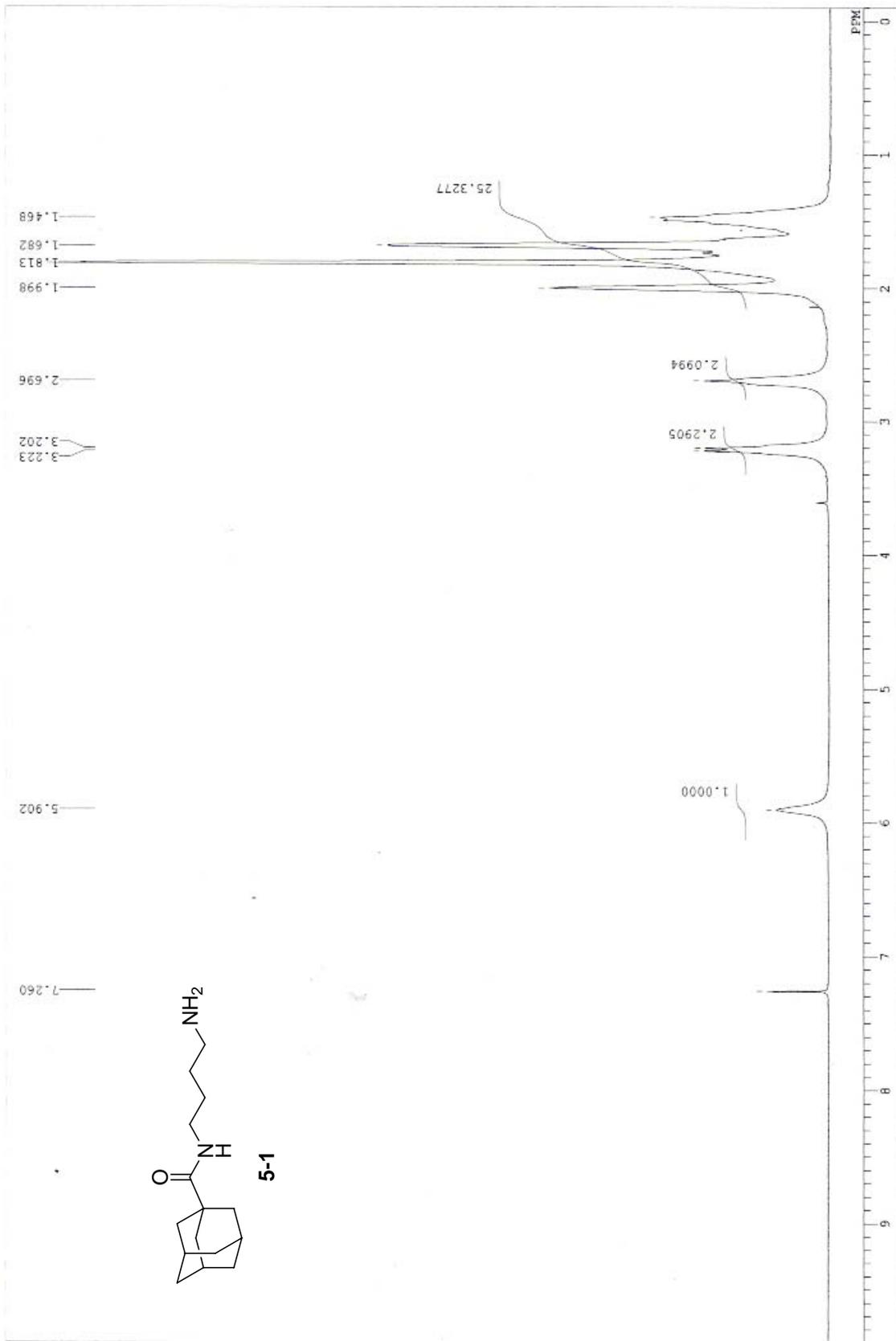




C:\WINNERS8\COMMON\DEFAULT.ALS

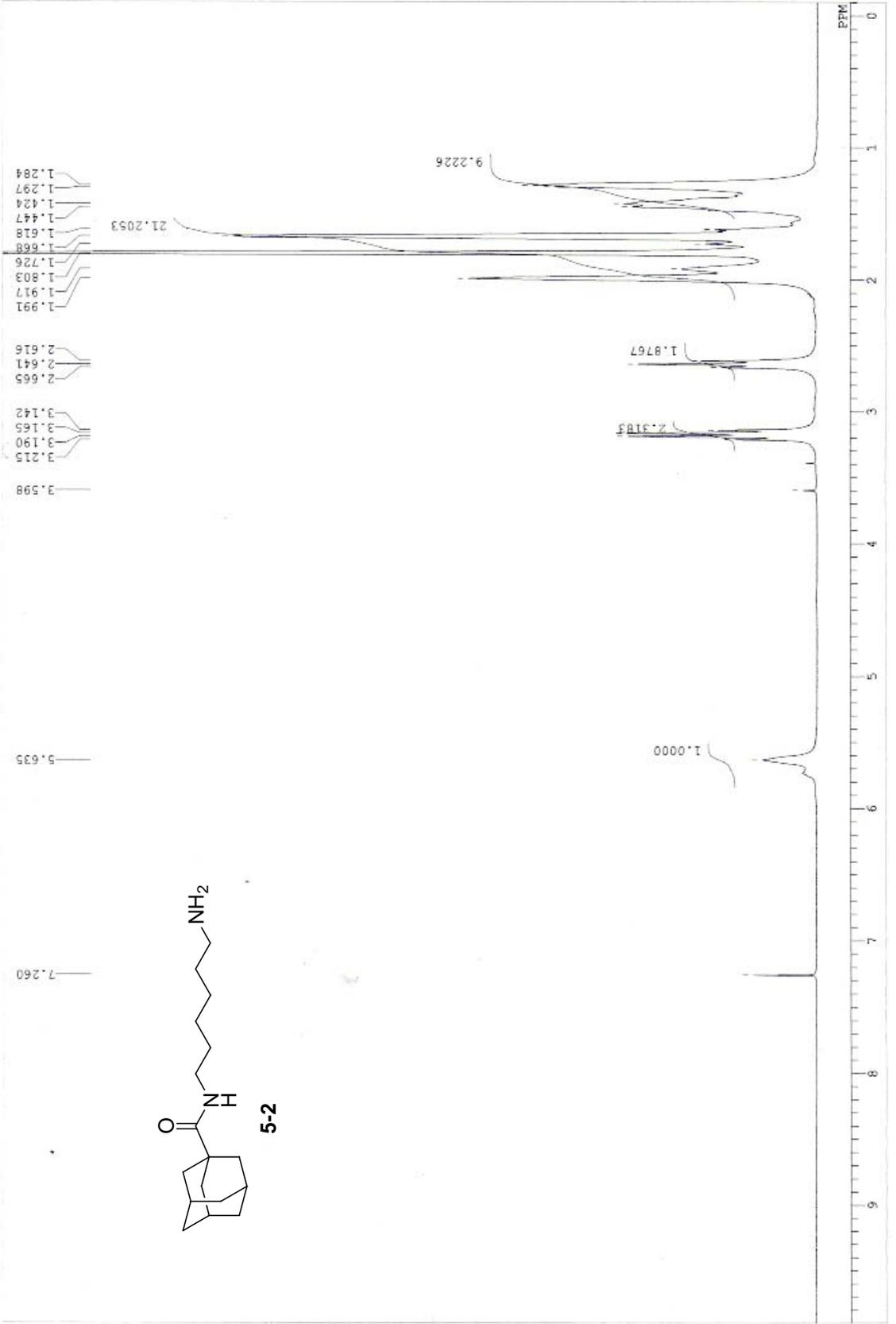
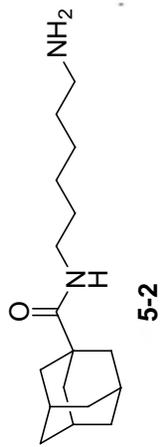


5-1



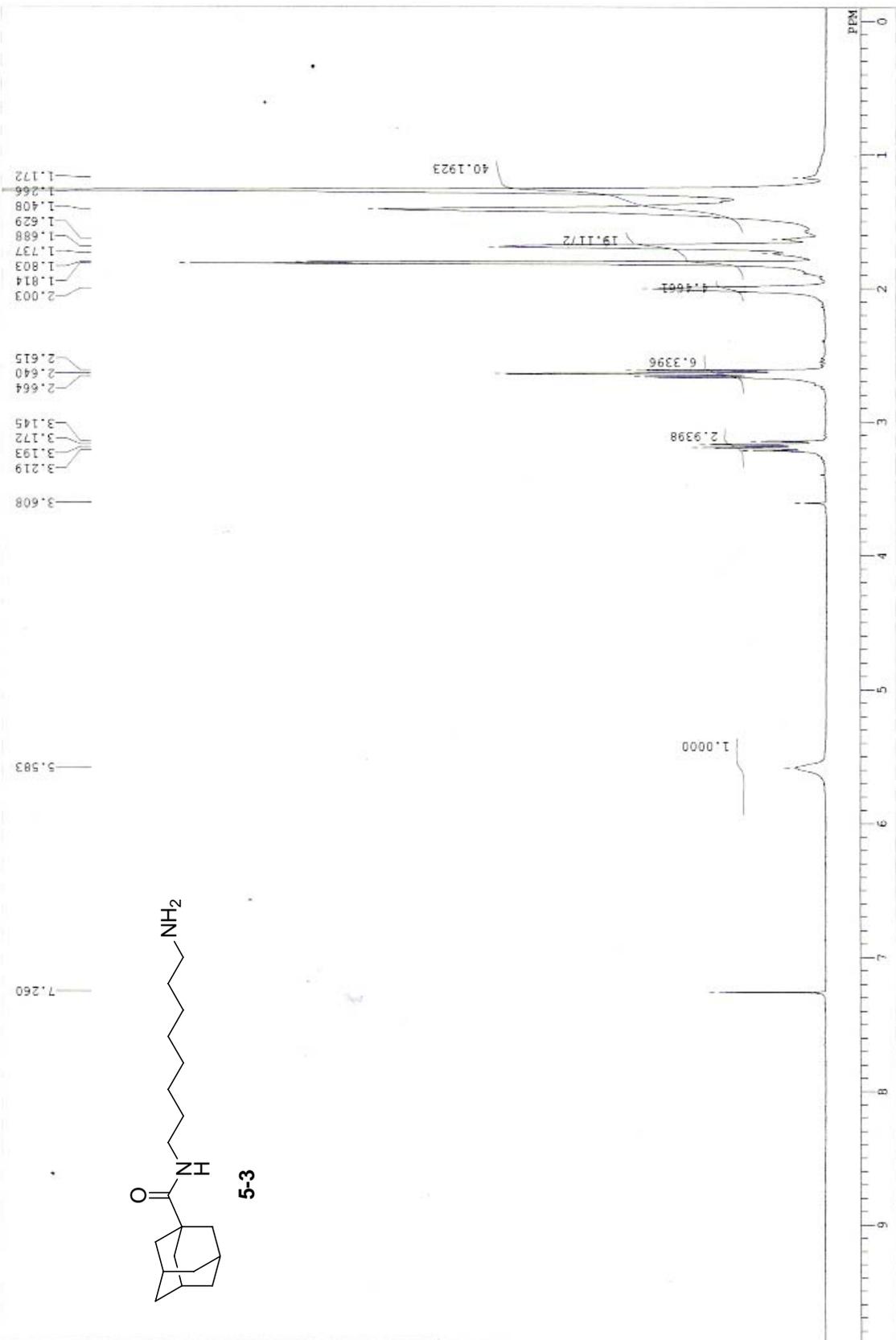
Ada
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C:\WINNR98\COMMON\DEFAULT.ALS

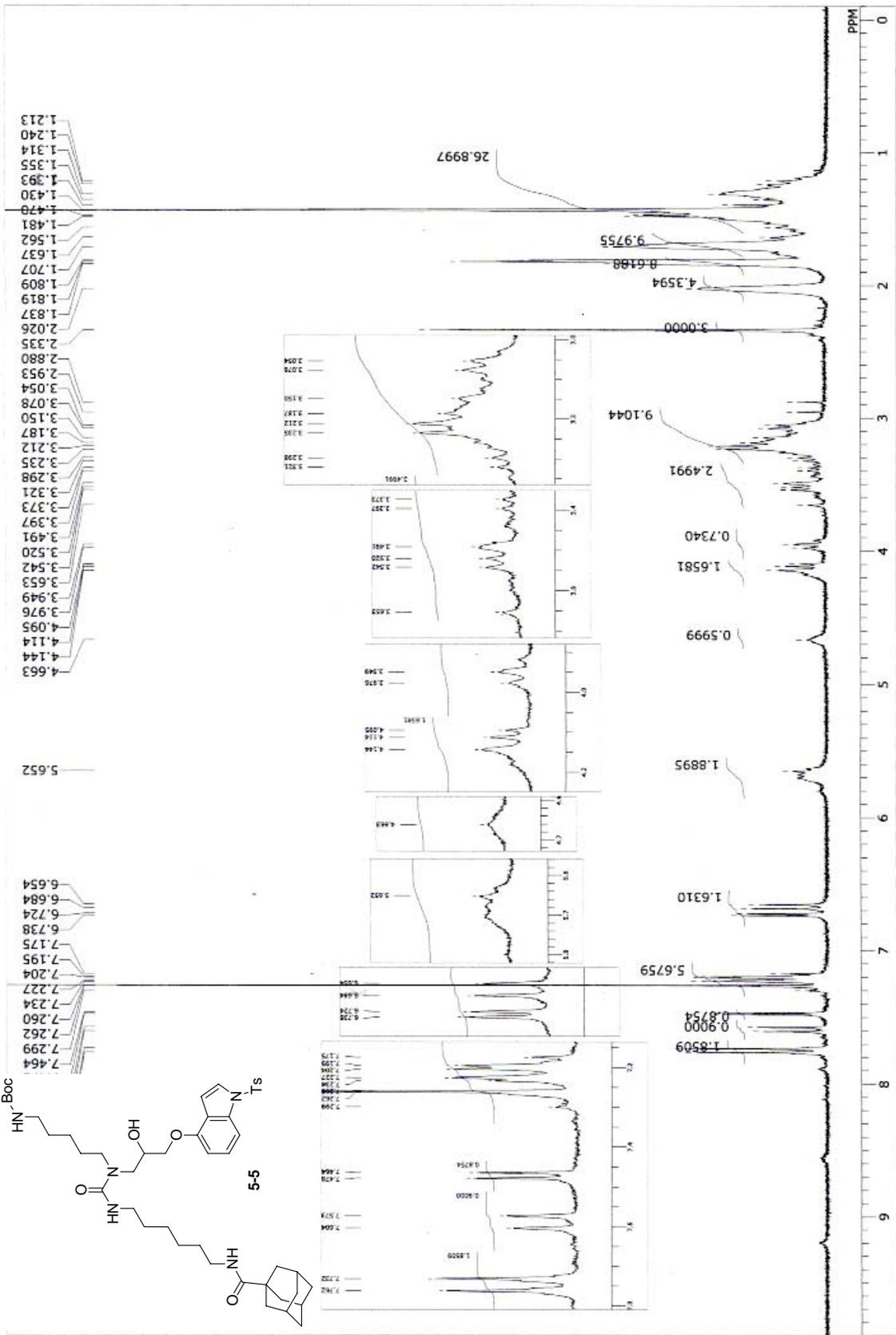
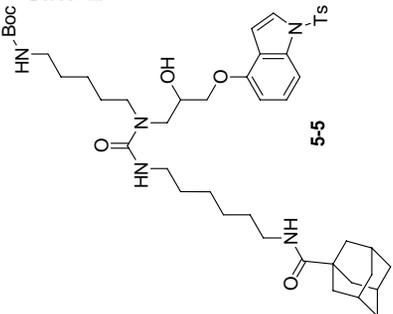


Ada

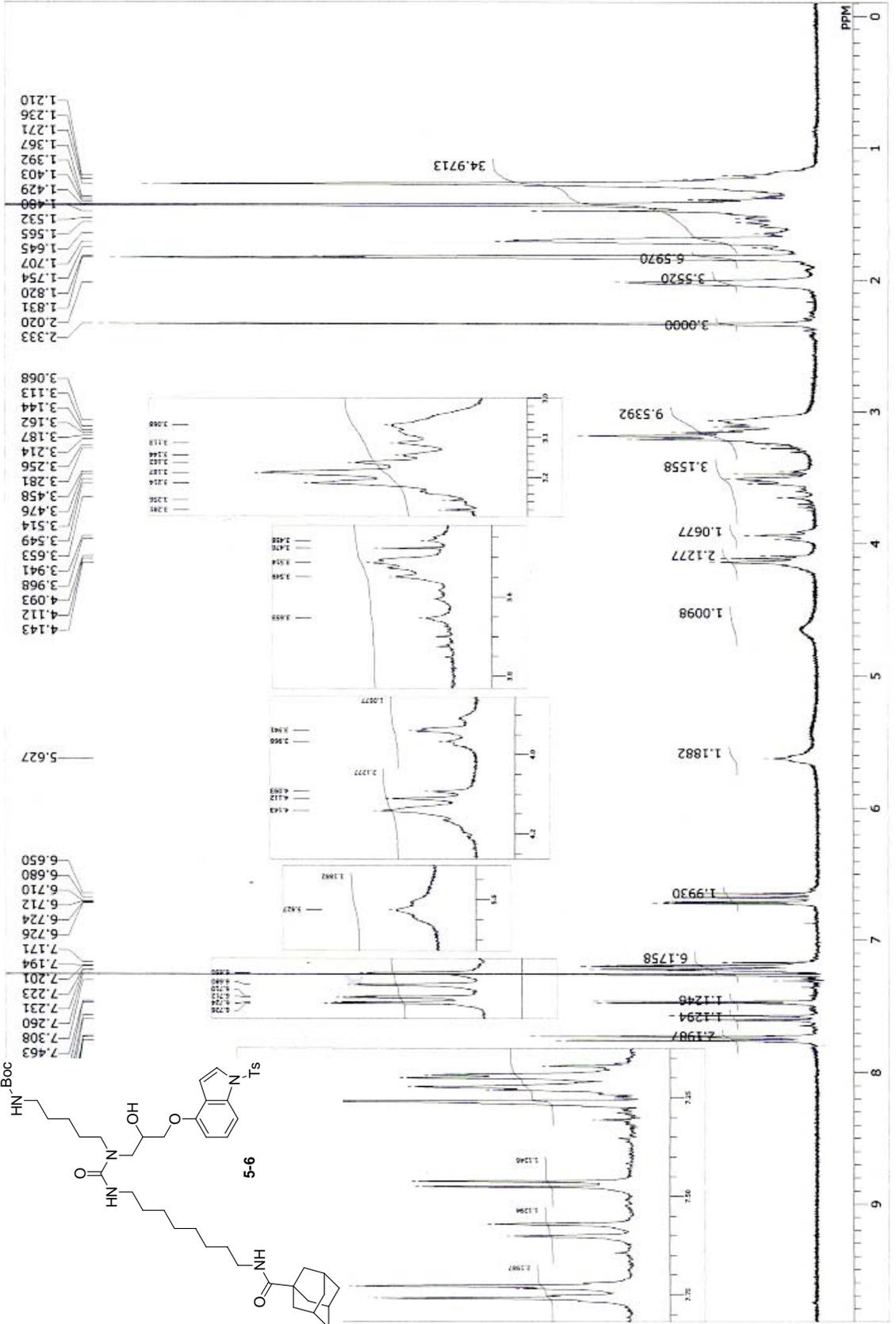
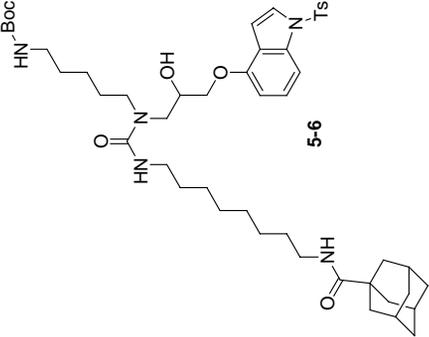
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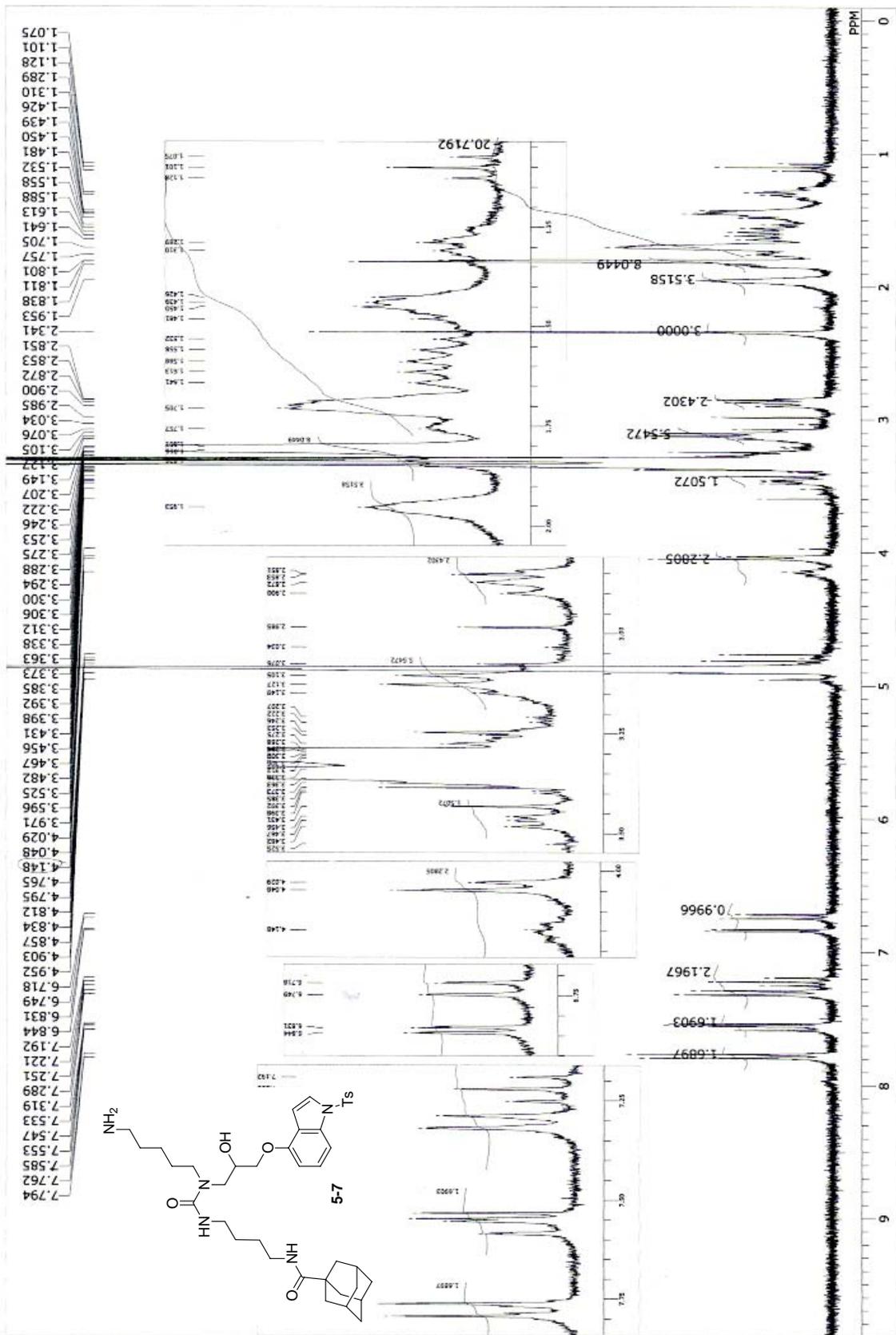


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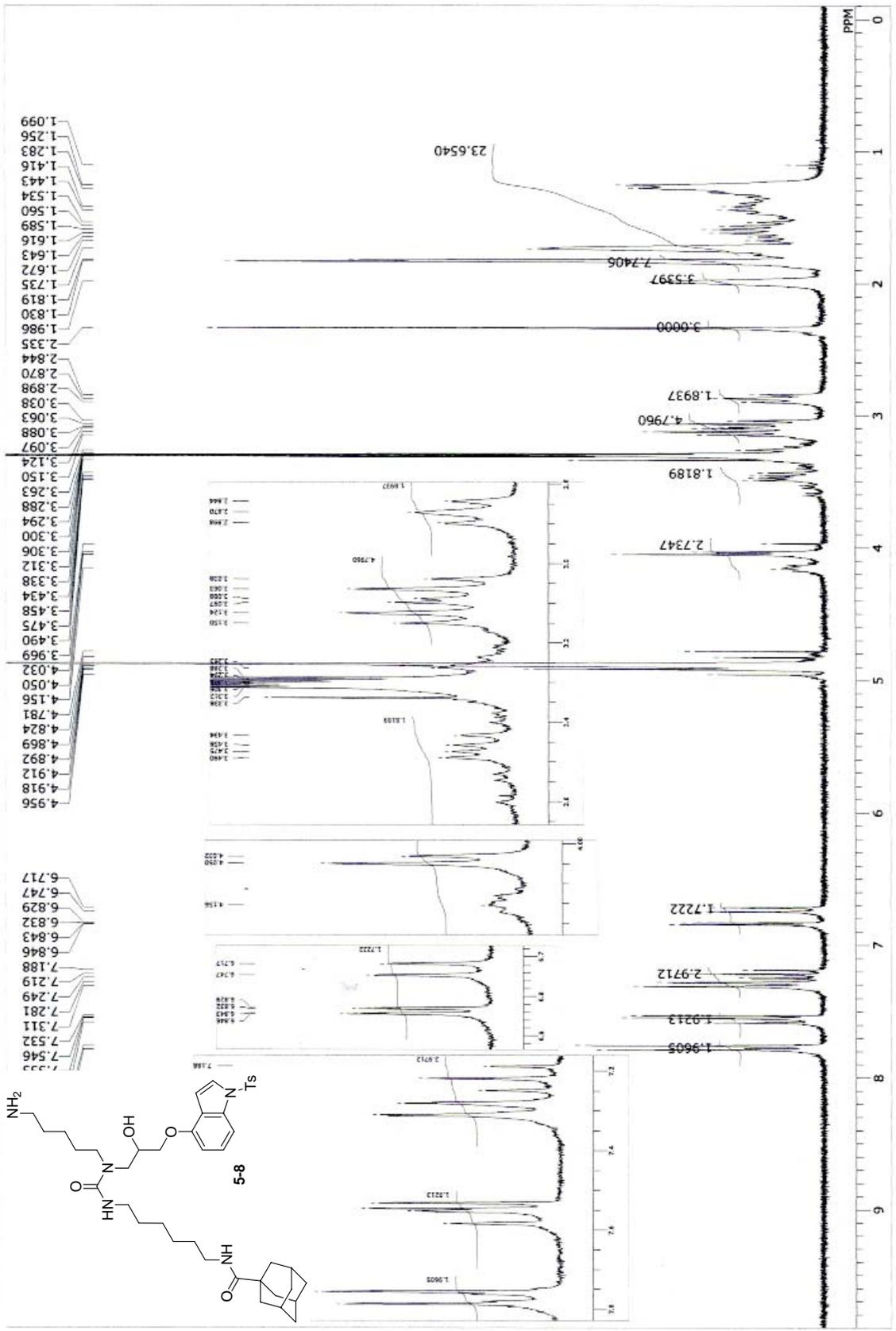
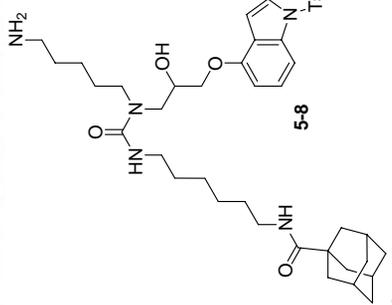
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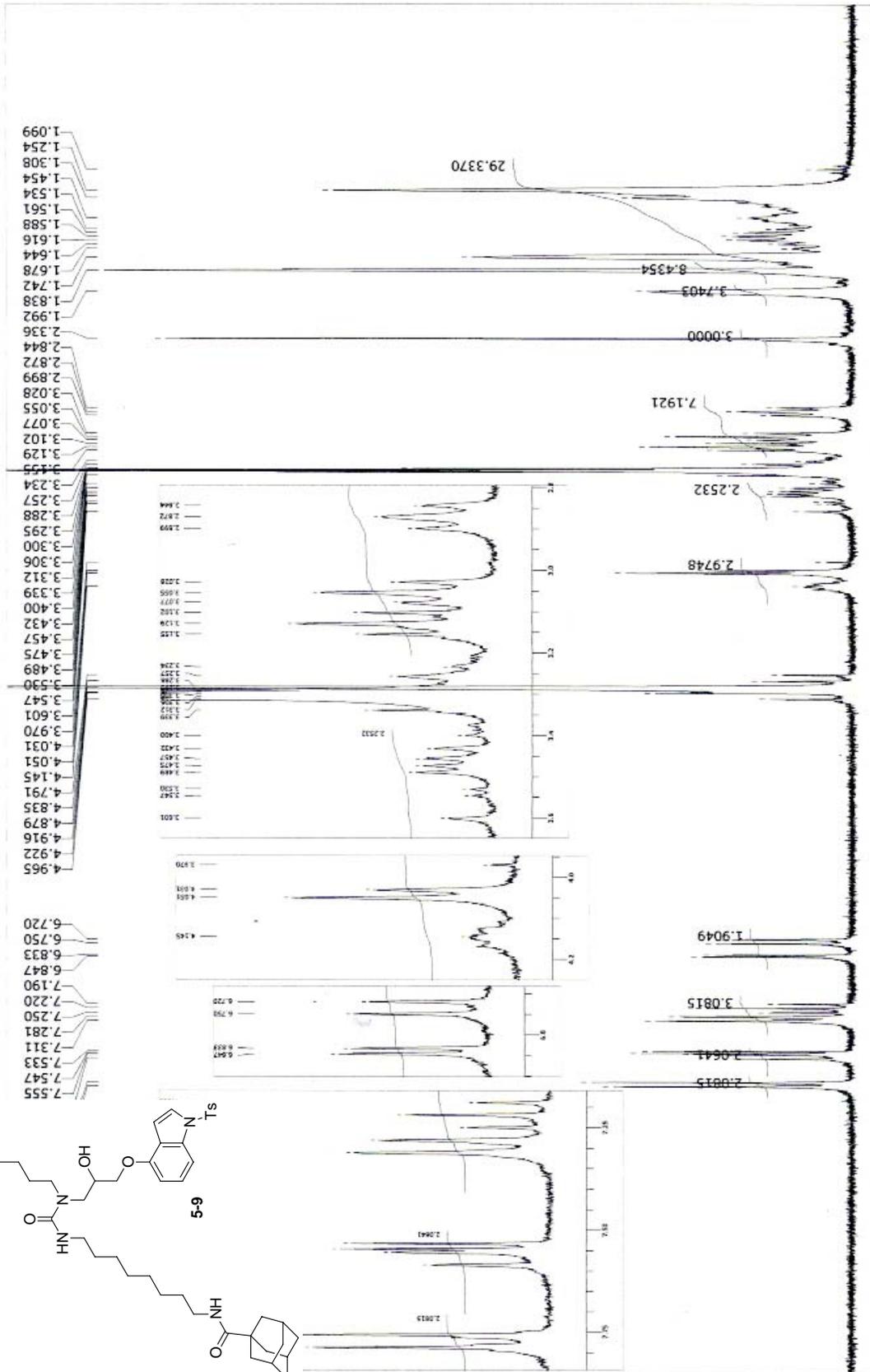


6-408-411

C:\WINNMR98\COMMON_DEFAULT.ALS



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(5-9) 100% (5-9) - NH₂

13-11-06-06 - 0.211

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