

Metal Organic Polyhedra: A Click-and-Clack Approach Toward Targeted Delivery

Supporting Information

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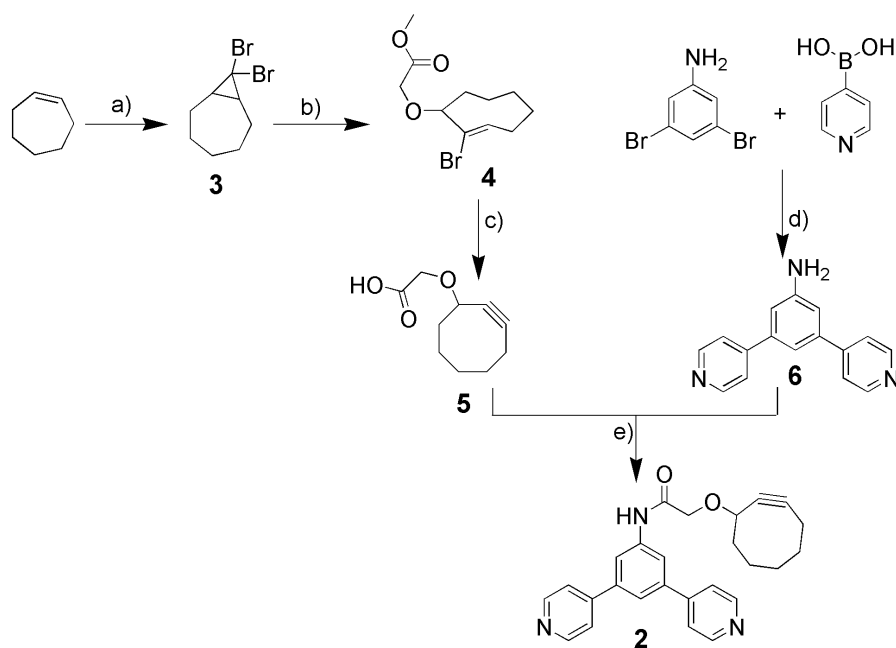
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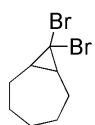
General Procedure

Starting materials were purchased from commercial suppliers and were used without further purification. Melting points were measured on a Meltemp apparatus in open capillary tubes and are uncorrected. IR spectra were measured on a Thermo Nicolet NEXUS 670 FT/IR spectrometer by attenuated total reflectance (ATR) and are reported in cm^{-1} . NMR spectra were measured on commercial spectrometers operating at 400, 500, or 600 MHz for ^1H and 100, 125 or 150 MHz for ^{13}C using deuterated water (D_2O), deuterated chloroform (CDCl_3), or deuterated dimethyl sulfoxide ($\text{DMSO}-d_6$) as solvent. Chemical shifts (δ) are referenced relative to the residual resonances for HOD (4.79 ppm), CHCl_3 (7.26 ppm for ^1H , 77.16 ppm for ^{13}C), and $\text{DMSO}-d_6$ (2.50 ppm for ^1H , 39.51 ppm for ^{13}C). Mass spectrometry was performed using a JEOL AccuTOF electrospray instrument. TEM was performed on a JEOL JEM 2100. Molecular modeling (MMFF) was performed using Spartan '08 on a personal computer.

Synthetic Procedures and Characterization Data

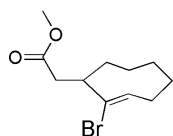


Scheme S11. Synthesis of **2**. Conditions: a) CHBr_3 , *t*-BuOK, dry pentane, 12 h, 88%, b) AgClO_4 , methylglycolate, dry toluene, 70%, c) NaOMe in MeOH, dry DMSO, 1 M HCl, d) $\text{Pd}(\text{PPh}_3)_4$, K_3PO_4 , THF- H_2O -MeOH, 80 °C, 4 days, 72%, e) 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide, DMAP, DCM, 40%.



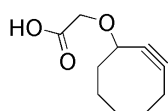
Compound 3: Bromoform (1.35 mL, 15.6 mmol) was added dropwise to a vigorously stirred creamy yellow mixture of cycloheptene (1.0 g, 10.4 mmol) and potassium *t*-butoxide (2.33 g, 20.8 mmol) in anhydrous pentane (10.0 mL) at -10 °C under nitrogen.

The resulting mixture turned brown and was then allowed to warm to room temperature and stirred overnight. The reaction mixture was treated with water (50 mL) and then neutralized with 1 M HCl. Then aqueous phase was extracted with pentane (3 x 50 mL), and the organic phase was dried over MgSO₄ and concentrated in vacuo. The resulting yellowish liquid was purified by filtration on silica gel, eluting with hexane:EtOAc (98:2) to afford compound **3** as a colorless oil (2.45 g, 88%). The ¹H NMR spectral data are identical to those reported previously.¹



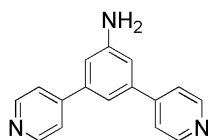
Compound 4: Compound **3** (610 mg, 2.27 mmol) and methyl glycolate (2.10 mL, 27.2 mmol) were dissolved in dry toluene (4 mL) in a flame-dried, aluminum foil wrapped flask under N₂ and then treated with Silver perchlorate (1.42 g, 6.81 mmol).

The reaction mixture was stirred for 2 h at room temperature, diluted with pentane (10 mL) and filtered to remove insoluble silver salts. The solvents were evaporated to give a yellow liquid. The crude yellow liquid was loaded onto a SiO₂ gel column and eluted with hexane:EtOAc (95:5) to give compound **4** as colorless oil (970 mg, 70%). The ¹H NMR spectral data are identical to those reported previously.¹

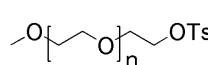


Compound 5: A solution of sodium methylate (3.8 M in MeOH, 5 mL, 20 mmol) in anhydrous DMSO (2 mL) under N₂ was treated with compound **4** (290 mg, 1.05 mmol). The reaction mixture was stirred at room temperature for 1 h,

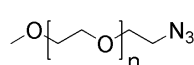
followed by addition of 3.8 M sodium methylate in MeOH (1.0 mL). After 30 minutes, the solvent was removed under high vacuum to give a yellow oil. The yellow oil was treated with 1 M aqueous HCl (40 mL) and then the aqueous phase was extracted with CH₂Cl₂ (3 x 30 mL). The organic fractions were combined, dried over anhydrous MgSO₄, and evaporated to dryness. The crude material was loaded onto a silica gel column and eluted using 8% MeOH/CH₂Cl₂ to afford compound **5** as yellow liquid (140 mg, 75%). The ¹H NMR spectral data are identical to those reported previously.¹



Compound 6: In a three-necked round bottomed flask equipped with a condenser was charged with 3,5-dibromaniline (500 mg, 1.99 mmol), pyridine-4-boronic acid (612 mg, 4.98 mmol) and anhydrous potassium phosphate (3.40 g, 16.0 mmol) under nitrogen. Degassed (twice by freeze-pump-thaw) solvent (H₂O:1,4-dioxane, 1:1, 30 mL) was transferred into the flask and then Pd(PPh₃)₄ (230 mg, 0.199 mmol) was added to the solution. The reaction mixture was heated at 80 °C for 4 days. The solvent mixture was evaporated under reduced pressure. The solid was redissolved in chloroform (100 mL) and washed with water (3 x 100 mL). The organic fractions were combined, dried over anhydrous MgSO₄ and evaporated to dryness. The solution was loaded onto a silica gel column and eluted using ethyl acetate (*R_f* = 0.30) to give compound **6** as pale yellow solid (354 mg, 72%). M.p. 270–271 °C, IR (ATR, cm⁻¹): 3404 (m), 3293 (m), 3172 (m), 3023 (w), 1627 (m), 1589 (s), 1545 (s), 1401 (s), 1362 (m), 1218 (m), 1068 (m), 996 (m), 863 (m), 811 (s). ¹H NMR (600 MHz, CDCl₃): δ = 8.67 (d, *J* = 6.0 Hz, 4H), 7.51 (d, *J* = 6.0 Hz, 4H), 7.23 (t, *J* = 1.8 Hz, 1H), 6.99 (d, *J* = 1.8 Hz, 2H), 3.96 (s, 2H) ppm. ¹³C NMR (150 MHz, CDCl₃) δ = 148.7, 124.6, 122.3, 122.3, 118.5, 116.7, 113.9 ppm. MS: (ESI, positive) *m/z* 248 (100%, [M+H]⁺).

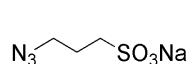


PEG₃₅₀-OTs: Poly(ethylene glycol) monomethyl ether (Alfa Aesar AA41560-22, *M_n* = 750, 1.5 g, 2.0 mmol) and *p*-toluenesulfonyl chloride (3.8 g, 20 mmol) were dissolved in dichloromethane (10 mL) under nitrogen and cooled to 0 °C in an ice-bath. Triethylamine (3.0 mL, 21.5 mmol) was added and the reaction mixture was stirred for 24 h. The reaction mixture was diluted with CH₂Cl₂ (100 mL), washed with aqueous HCl solution (1 M, 2 × 100 mL) and water (2 × 100 mL), the organic layer was dried over anhydrous MgSO₄, and then the solvent was removed to give the crude product. The crude product was loaded onto a silica gel column and eluted with MeOH:CHCl₃ (1:1) to give **PEG₃₅₀-OTs** as a colorless liquid (1.0 g, 57%). The ¹H NMR spectral data matches that reported in the literature.²



PEG₃₅₀-N₃: A solution of PEG₃₅₀-OTs (470 mg, 0.52 mmol) and sodium azide (676 mg, 10.4 mmol) in DMF (6.0 mL) was stirred vigorously at room temperature for 24 h under a N₂ atmosphere. The solvent was removed under high vacuum pressure and the crude product was redissolved in CH₂Cl₂ (30 mL). The organic solution was washed with water (10 × 100 mL) to remove DMF completely. The organic fractions were

combined, dried over MgSO_4 and evaporated to afford $\text{PEG}_{350}\text{-N}_3$ as brown semi-solid (360 mg, 90%). ^1H NMR (600 MHz, CDCl_3): $\delta = 3.70\text{--}3.60$ (m, 59H), 3.55–3.50 (m, 2H), 3.38 (t, $J = 5.2$ Hz, 2H), 3.37 (s, 3H) ppm. ^{13}C NMR (150 MHz, CDCl_3) $\delta = 71.9, 70.7, 70.7, 70.6, 70.5, 70.5, 70.0, 59.0, 50.7$ ppm. MS: (ESI, positive) m/z 780 ($[\text{M}+\text{H}_3\text{O}]^+$).



Sodium-3-Azido-propanesulfonate: A solution of 1,3-propane sultone (5.64 g, 46.2 mmol) in water-1,4-dioxane (1:1 v:v, 50 mL) was treated with a solution of sodium azide (6.0 g, 92.4 mmol) in water (5.0 mL) and the resulting mixture was stirred at room temperature for 12 h. The white precipitate was collected by filtration. The crude solid was recrystallized from water/ethanol (1:1), isolated by filtration, and then washed with ethanol and dried under vacuum to afford the title compound (7.34 g, 85 %). M.p. 240 °C. IR (ATR, cm^{-1}) 2937 (w), 2882 (w), 2173 (w), 2097 (s), 1287 (w), 1207 (s), 1177 (s), 1054 (s), 914 (s), 727 (s). ^1H NMR (600 MHz, D_2O): $\delta = 3.47$ (t, $J = 7.2$ Hz, 2H), 2.98 (m, 2H), 2.00 (m, 2H) ppm. ^{13}C NMR (150 MHz, D_2O , RT, 1,4-dioxane as internal standard) $\delta = 49.1, 47.6, 23.3$ ppm.

Characterization of MOP 4^R

MOP 4^{PEG}: ^1H NMR (600 MHz, D_2O) $\delta = 9.01$ (br s), 8.04 (br s), 7.93 (br s), 6.79 (s), 5.79-5.69 (m), 5.52-5.43 (m), 4.35-4.15 (m), 4.11 (s), 3.69-3.59 (m), 3.47 (br s), 3.35 (m), 2.95 (s), 1.69 (br s), 1.25 (br s) ppm.

MOP 4^{sulfo}: ^1H NMR (600 MHz, D_2O) $\delta = 9.03$ (br s), 8.05 (br s), 6.79 (s), 5.74-5.69 (m), 5.52-5.47 (m), 4.27-4.15 (m), 4.10 (s), 3.36 (s), 3.18 (br s), 2.94 (s), 2.87 (br s), 2.33 (s), 1.90 (s), 1.69 (br s), 1.25 (br s) ppm.

MOP 4^{biotin}: ^1H NMR (600 MHz, D_2O) $\delta = 9.02$ (br s), 8.05 (br s), 7.92 (br s), 6.80 (s), 5.78-5.69 (m), 5.53-5.44 (m), 4.71 (br s), 4.57 (br s), 4.38 (br s), 4.33-4.16 (m), 4.10 (s), 3.70-3.63 (m), 3.56 (br s), 3.34 (br s), 3.32 (br s), 3.18 (br s), 2.96 (s), 2.76 (br s), 2.21 (br s), 1.91 (s), 1.69 (br s), 1.68-1.26 (m) ppm.

MOP 4^{RGD}: ^1H NMR (600 MHz, DMSO-d_6) $\delta = 9.31$ (br s), 8.10 (br s), 7.24-7.22 (m), 7.18-7.16 (m), 7.13-7.12 (m), 6.59 (s), 5.67-5.57 (m), 5.36-5.27 (m), 4.58-4.56 (m), 4.47-4.44 (m), 3.89-3.87 (m), 3.26 (s), 3.24 (s), 3.19-3.17 (m), 3.12 (m), 3.09-3.0 (m), 2.90-2.86 (m), 2.81-2.77

(m), 2.70-2.66 (m), 2.61 (br s), 2.40-2.36 (m), 1.74-1.70 (m), 1.54-1.46 (m), 1.40-1.33 (m), 1.06-1.00 (m) ppm.

MOP 4^{cyan}: ¹H NMR (600 MHz, DMSO-d₆) δ = 8.88 (brs), 8.48-8.44 (m), 8.26-8.25 (m), 8.09-8.05 (m), 7.82-7.80 (m), 7.76-7.72 (m), 7.69-7.66 (m), 7.53-7.50 (m), 6.64-6.58 (m), 6.38-6.31 (m), 5.65-5.59 (m), 5.47-5.35 (m), 4.24-4.08 (m), 3.98 (br s), 3.73 (s), 3.27-3.25 (m), 3.05-2.99 (m), 2.79-2.77 (m), 2.65 (s), 2.42 (s), 2.38 (br s), 2.06-2.04 (m), 1.76-1.72 (m), 1.57-1.53 (m), 1.39-1.34 (m), 1.23 (s), 0.9-0.84 (m) ppm.

MOP 4^{Fluor}: ¹H NMR (600 MHz, DMSO-d₆) δ = 9.50 (br s), 8.88-8.86 (t, ³J = 5.4 Hz), 8.46 (s), 8.24 (d, ³J = 1.6 Hz), 8.23 (d, ³J = 1.6 Hz), 7.37 (d, ³J = 8.0 Hz), 6.68 (d, ³J = 2.3 Hz), 6.58 (s), 6.57 (s), 6.55 (d, ³J = 2.3 Hz), 6.53 (d, ³J = 2.3 Hz), 5.71-5.57 (m), 5.48-5.35 (m), 4.24-4.14 (m), 3.98 (br s), 2.78 (s), 2.08 (br s), 2.07 (br s), 1.90 (s), 1.83-1.79 (m), 1.23 (br s), 1.10 (s) ppm.

Synthesis of MOP 6. An aqueous solution of **MOP 3** (20 μ M, 500 μ L) sample was treated with 6 equiv. of aqueous solution of **Ad-FITC** (conc. of stock solution = 500 μ M). The mixture was sonicated for 10 min to afford **MOP 6 = MOP 3•(Ad-FITC)₆**. The sample was characterized by ¹H NMR.

References

- 1) Bernardin, A.; Cazet, A.; Guyon, L.; Delannoy, P.; Vinet, F.; Bonnaffe, D.; Texier, I. *Bioconjugate Chem.* **2010**, *21*, 583.
- 2) Hua, C.; Peng, S.-M.; Dong, C.-M. *Macromolecules* **2008**, *41*, 6686.

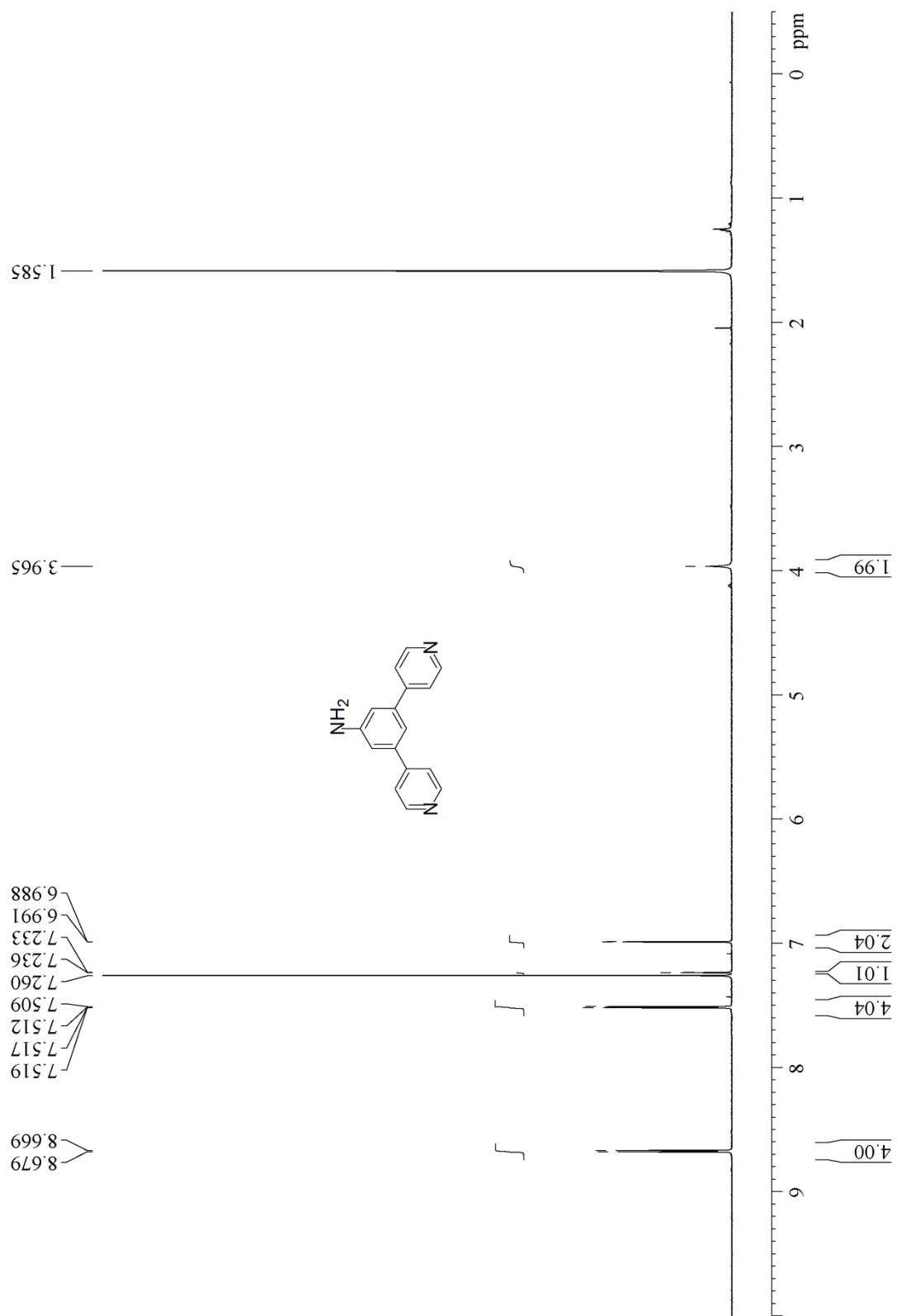


Figure S1. ^1H NMR recorded (600 MHz, CDCl_3 , RT) for compound 6.

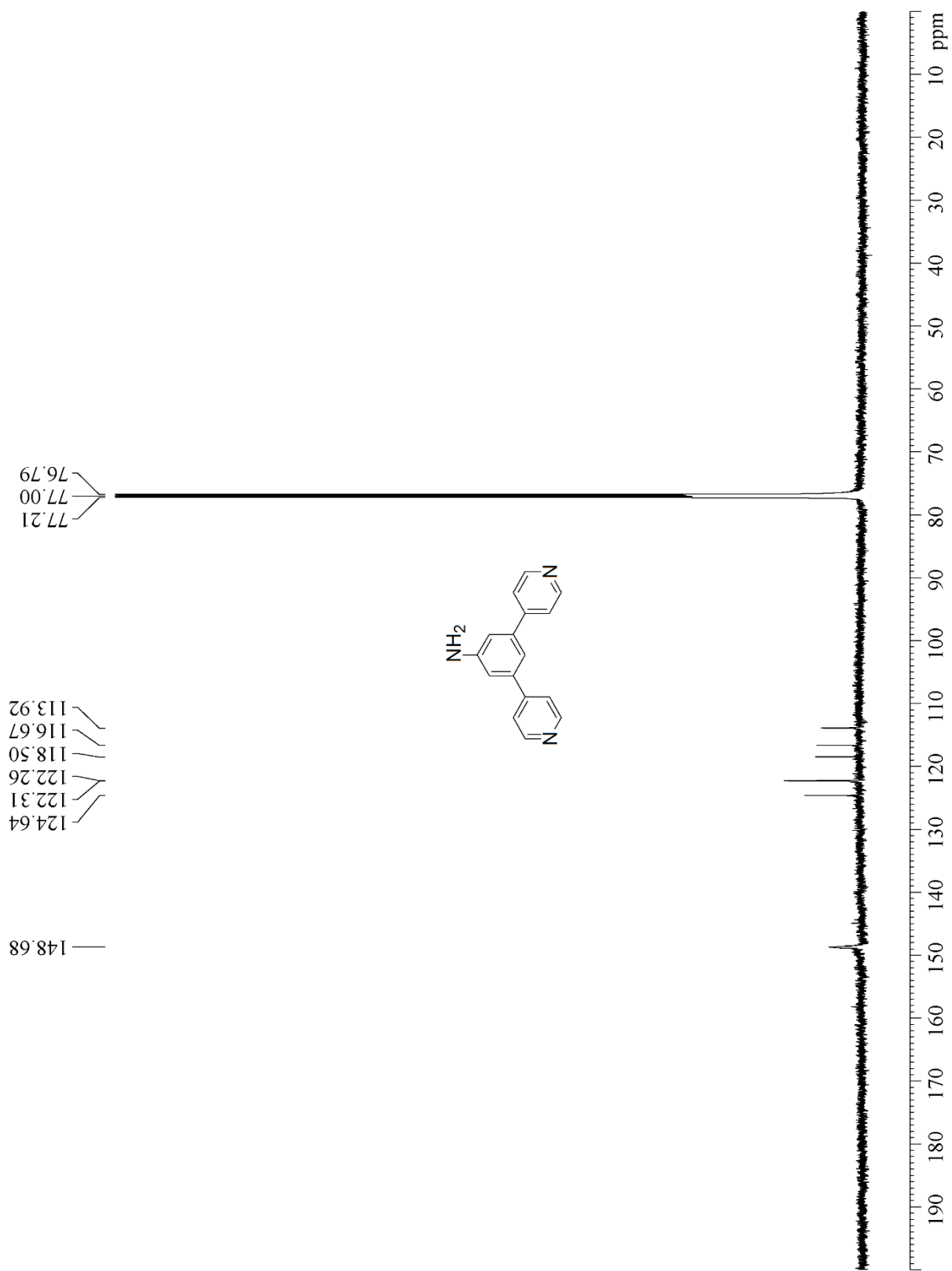


Figure S2. ^{13}C NMR recorded (150 MHz, CDCl_3 , RT) for compound 6.

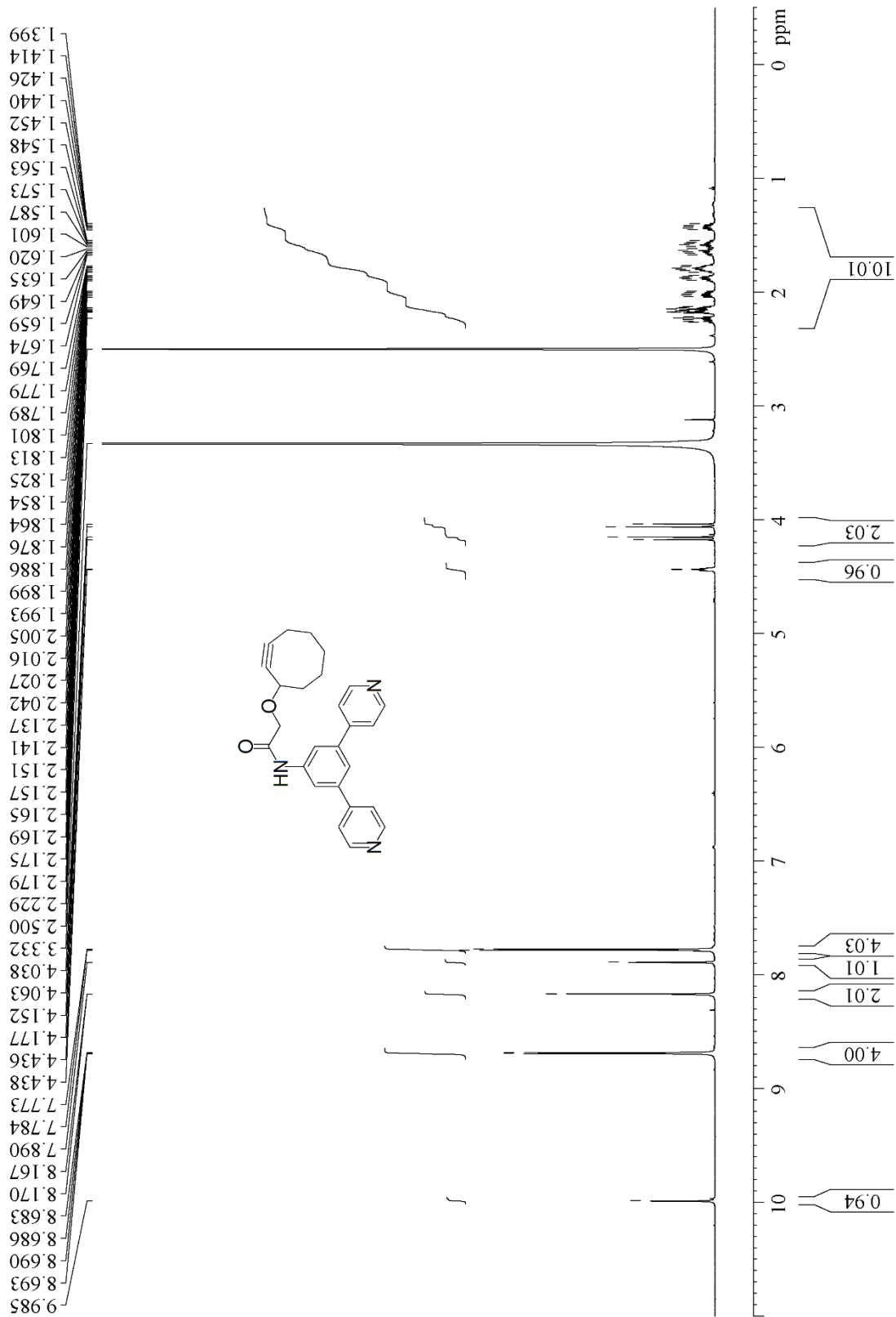


Figure S3. ^1H NMR recorded (600 MHz, $\text{DMSO-}d_6$, RT) for compound 2.

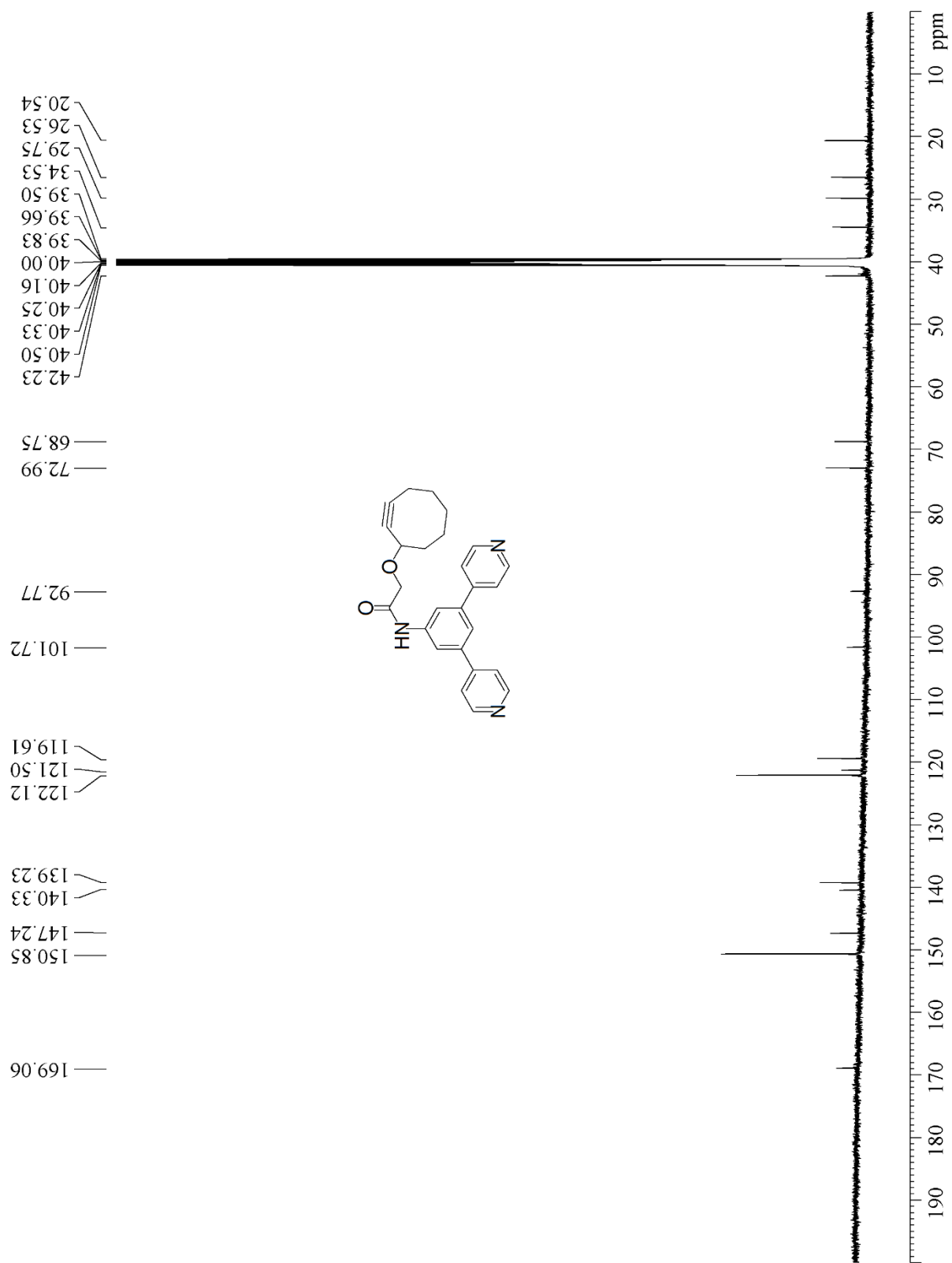


Figure S4. ¹³C NMR recorded (125 MHz, DMSO-*d*₆, RT) for compound 2.

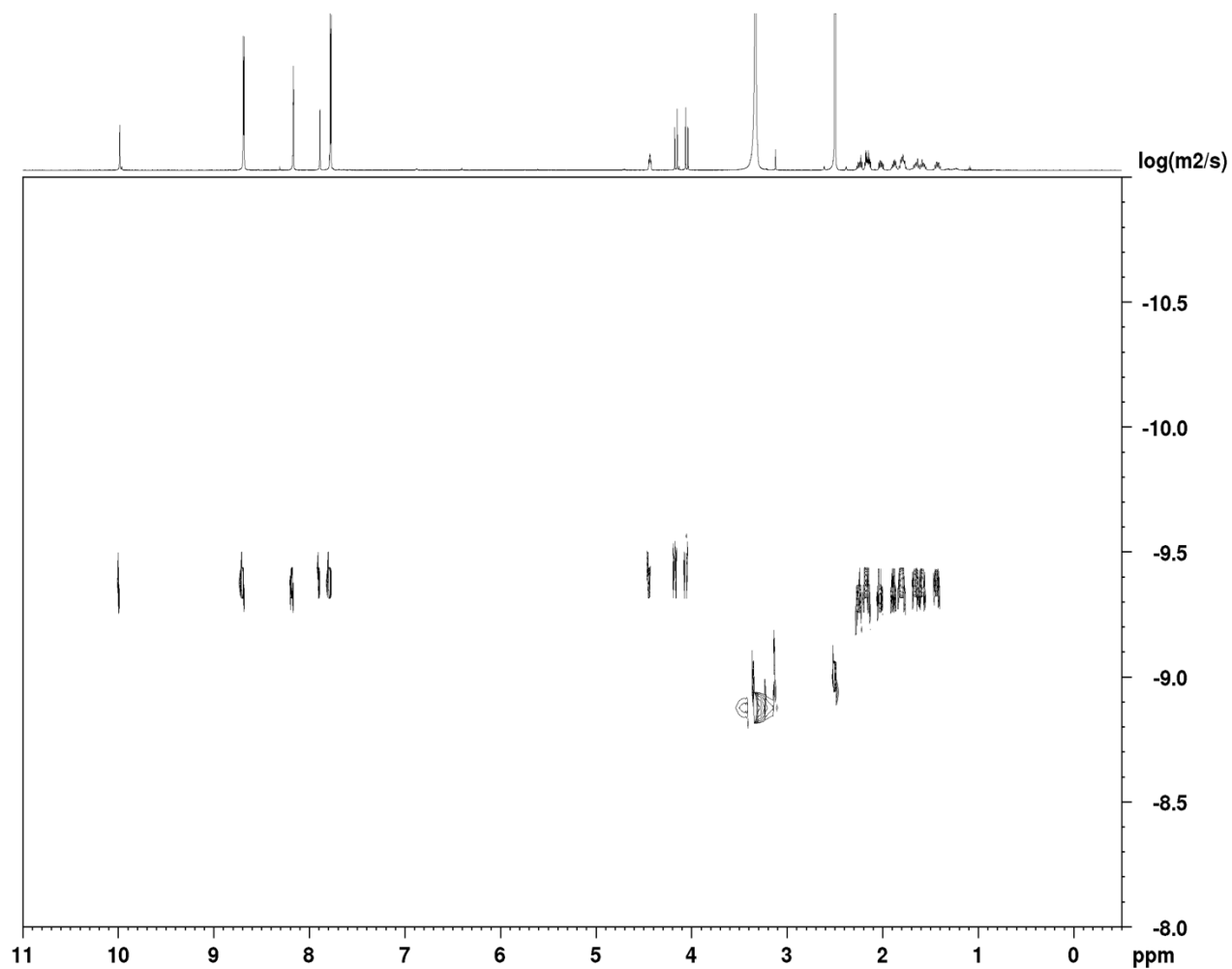


Figure S5. DOSY NMR recorded (600 MHz, DMSO-*d*₆, 300 K) for compound 2.

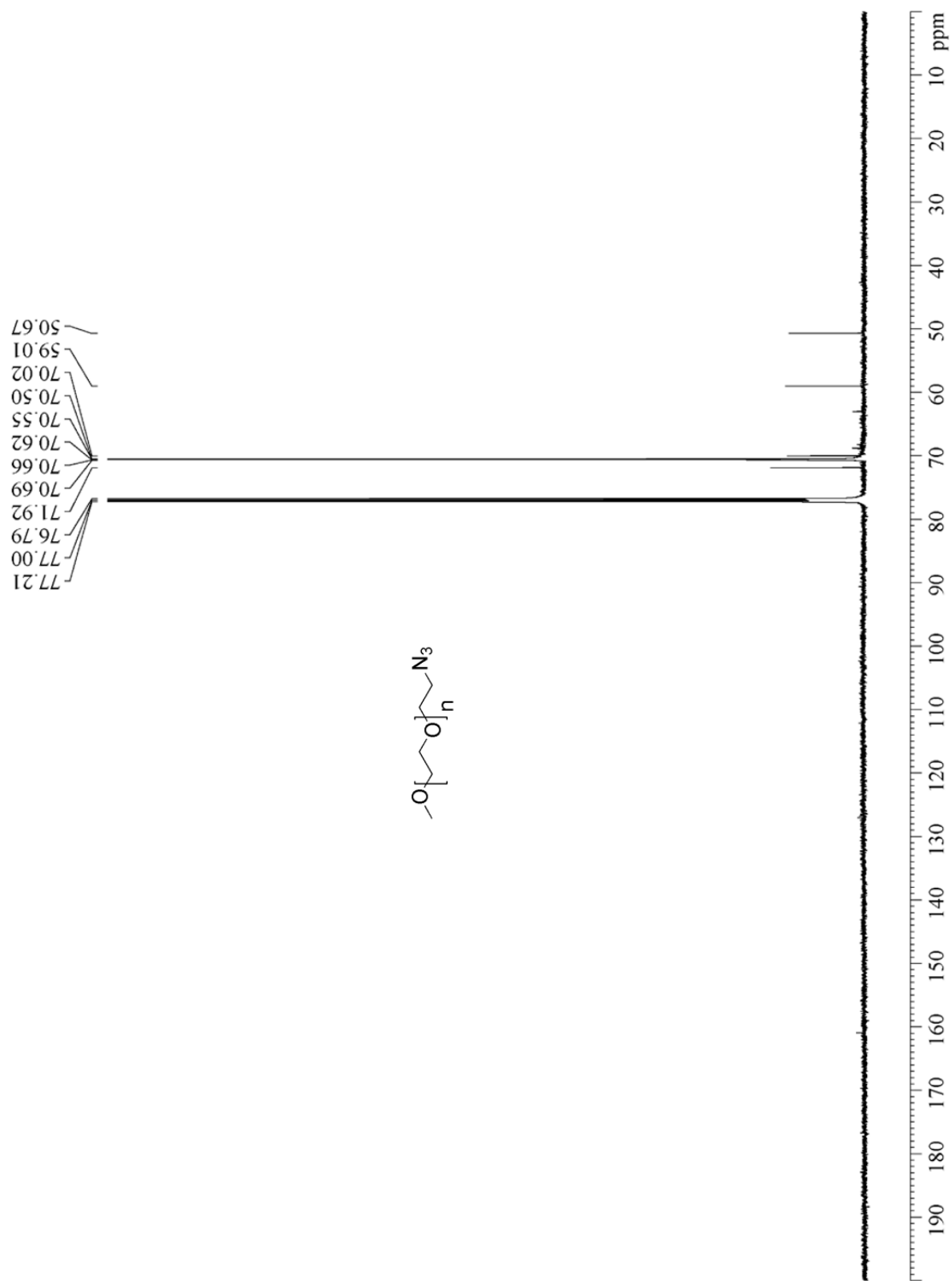


Figure S7. ^{13}C NMR recorded (125 MHz, CDCl_3 , RT) for compound $\text{PEG}_{350}\text{-N}_3$.

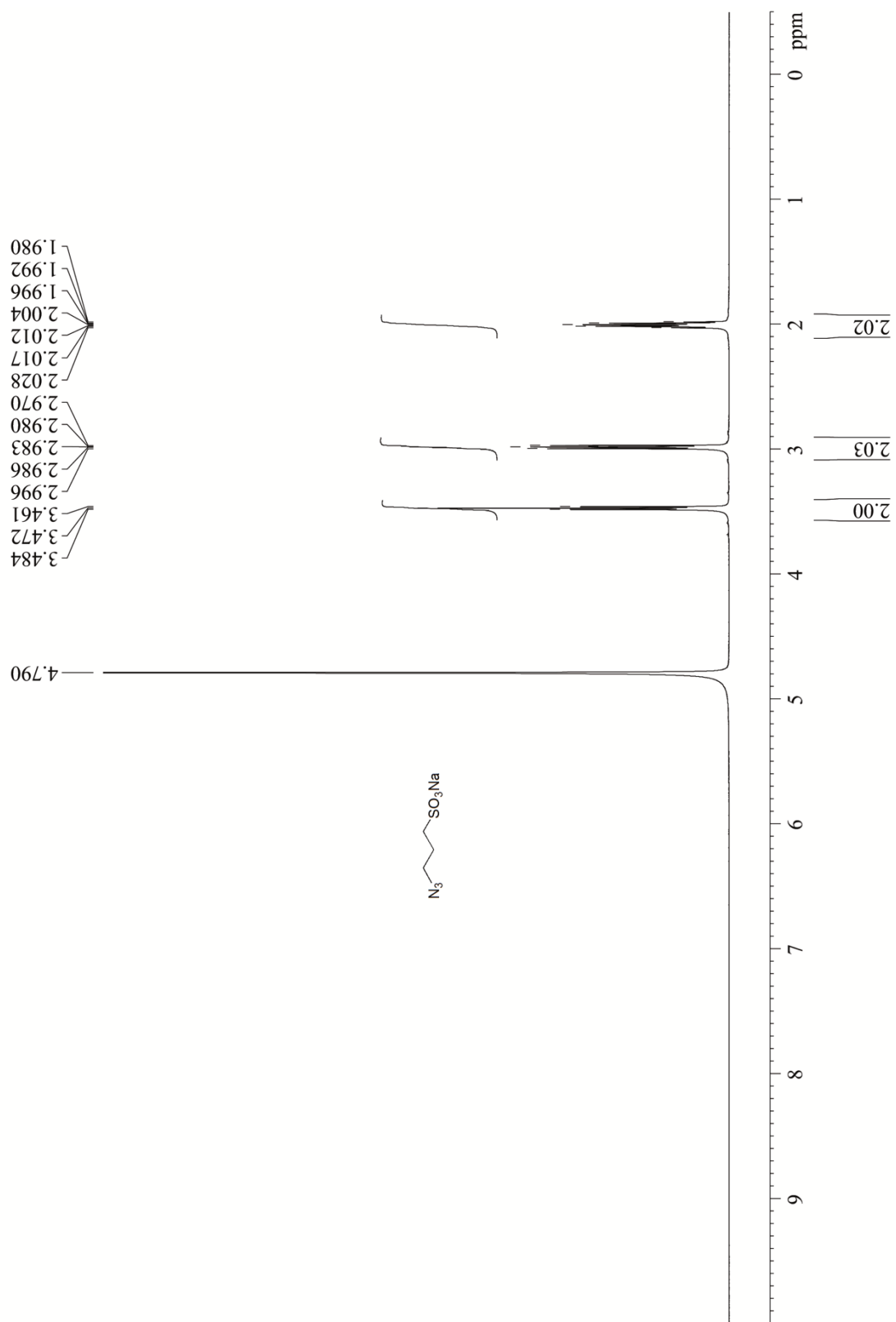


Figure S8. ^1H NMR recorded (600 MHz, CDCl_3 , RT) for sodium-3-azido-propanesulfonate.

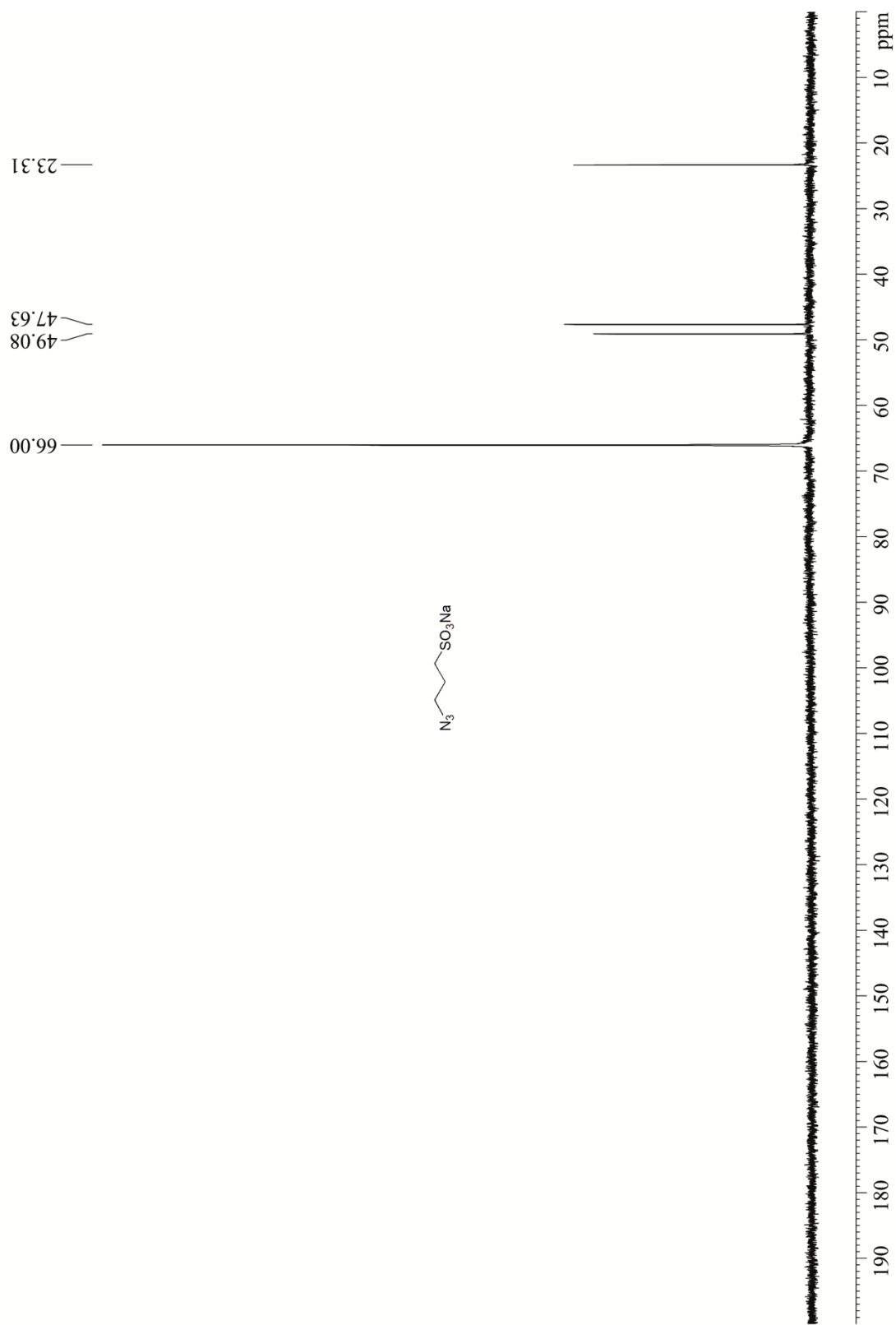


Figure S9. ^{13}C NMR recorded (125 MHz, CDCl_3 , RT) for sodium-3-azido-propanesulfonate.

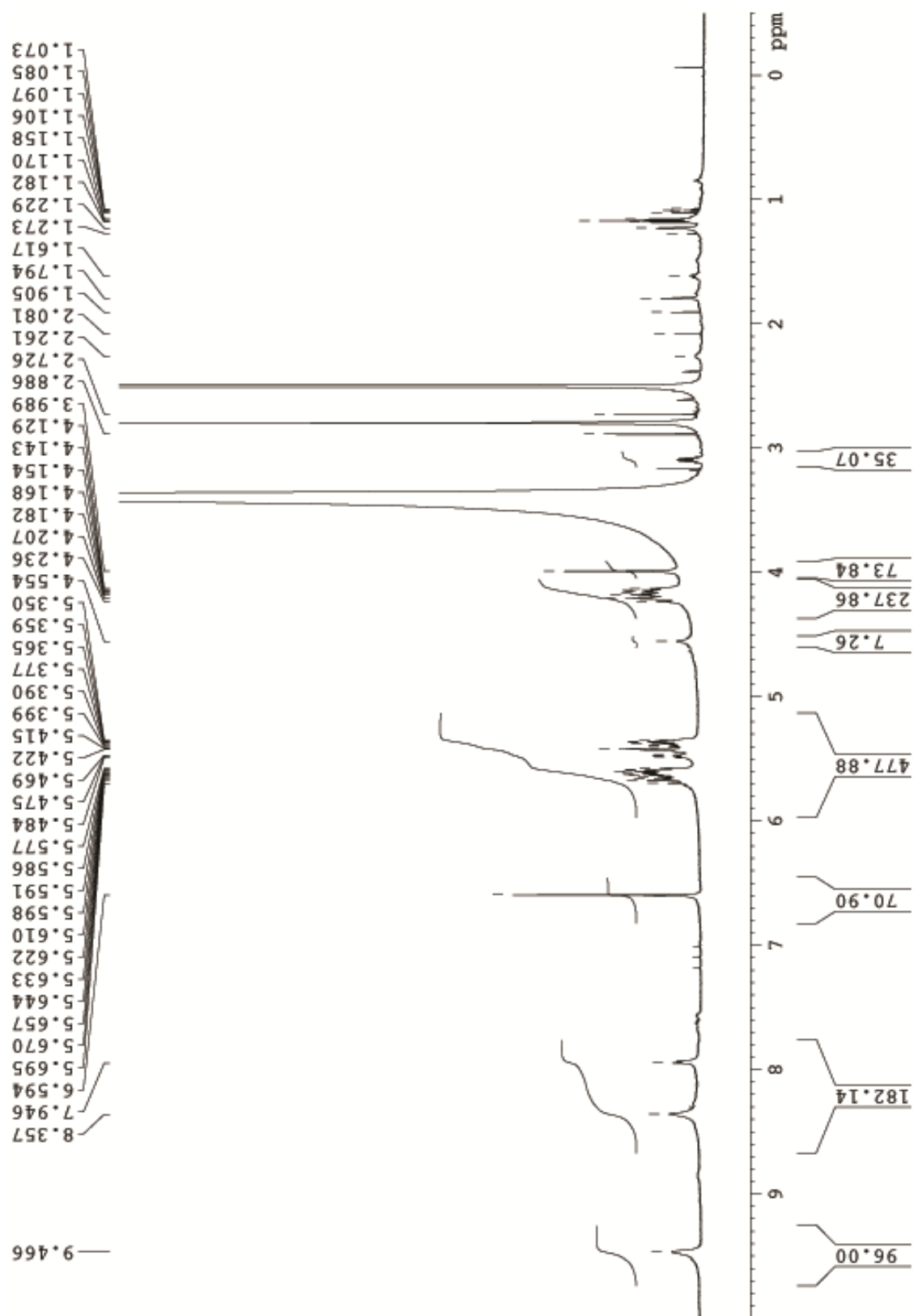


Figure S10. ^1H NMR recorded (600 MHz, DMSO- d_6 , RT) for **MOP 1**.

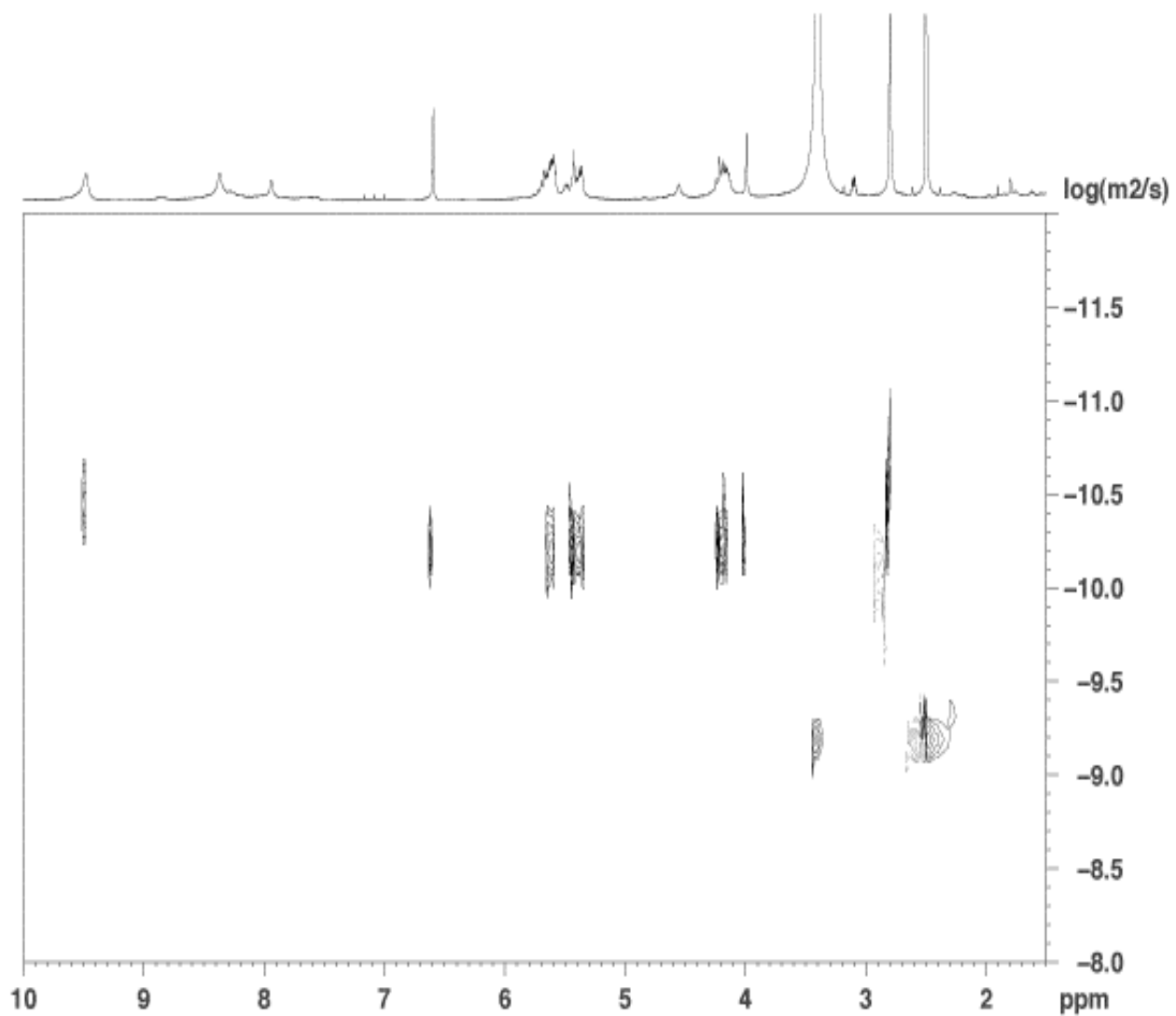


Figure S11. DOSY NMR recorded (600 MHz, DMSO, RT) for **MOP 1**.

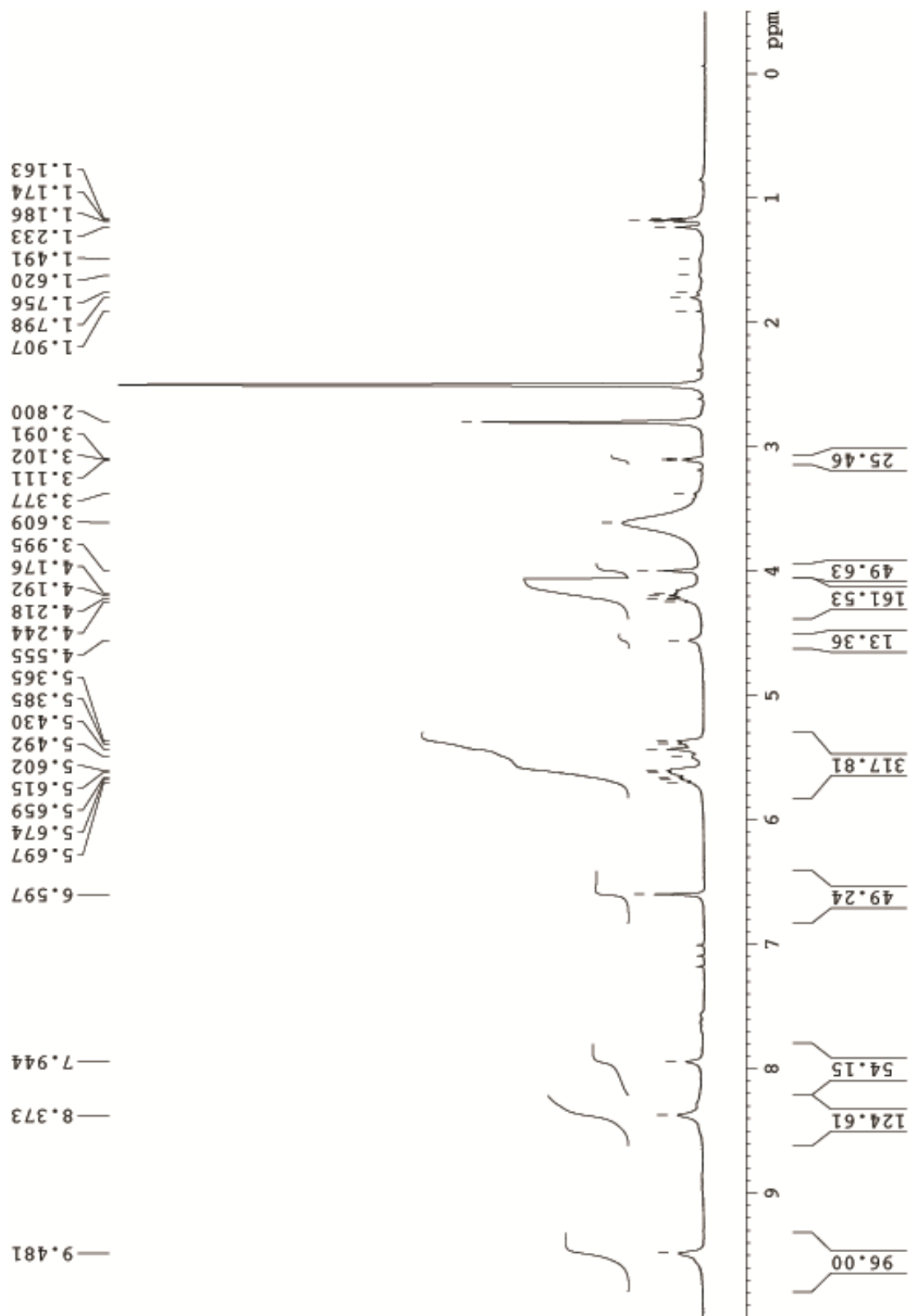


Figure S12. ^1H NMR recorded (600 MHz, $\text{DMSO-}d_6$, RT) for **MOP 2**.

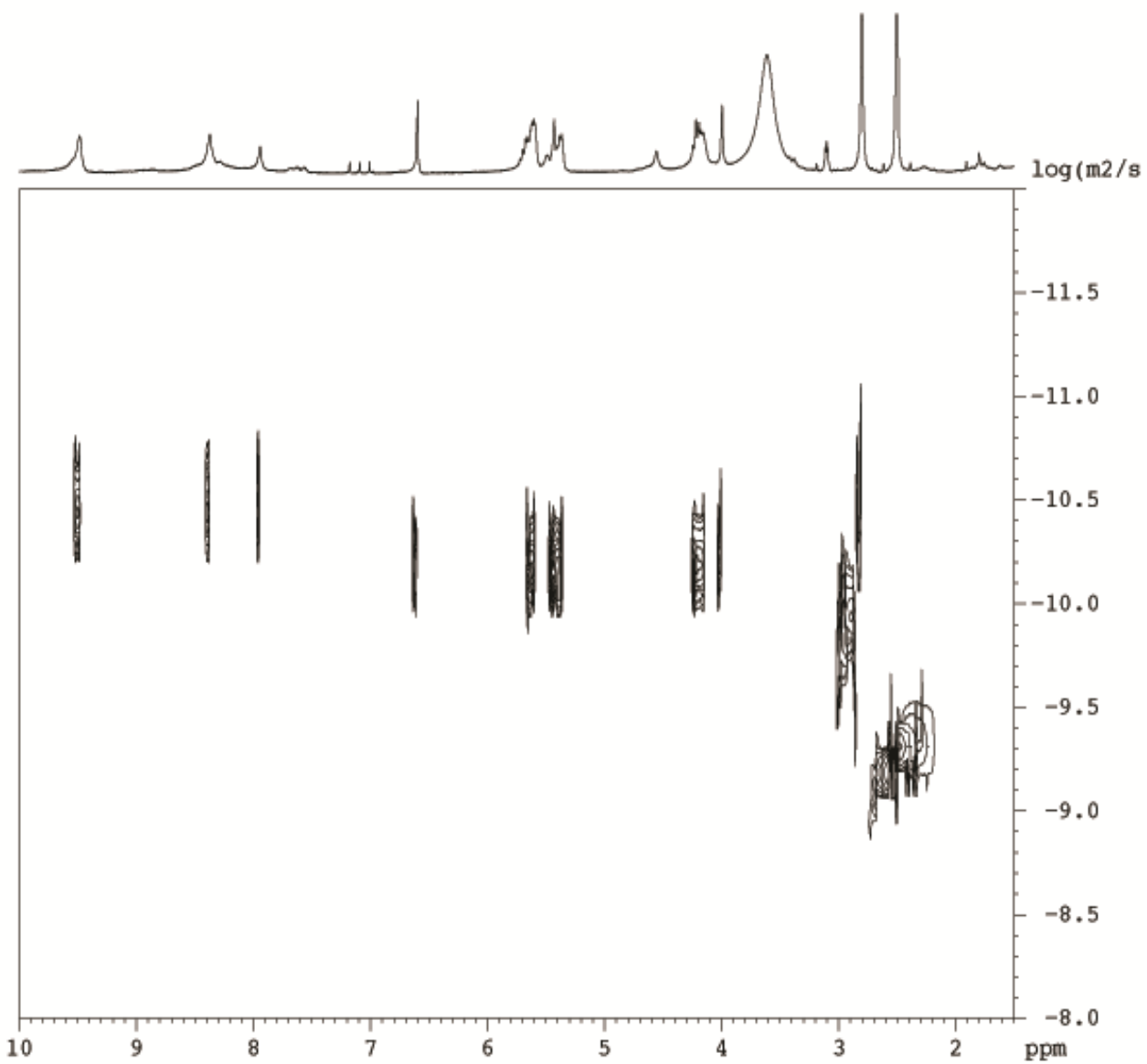


Figure S13. DOSY NMR recorded (600 MHz, DMSO-*d*₆, RT) for **MOP 2**.

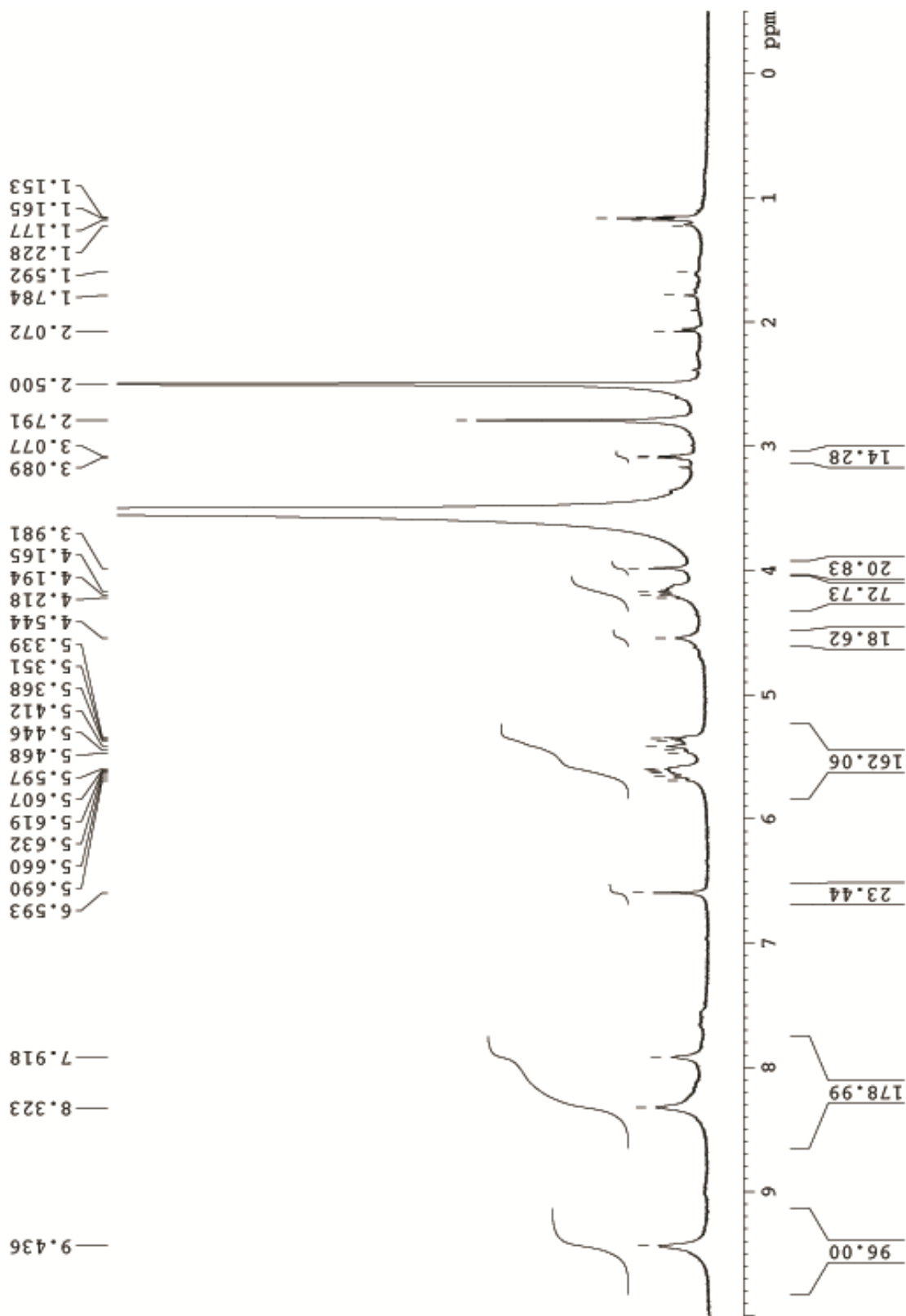


Figure S14. ^1H NMR recorded (600 MHz, $\text{DMSO-}d_6$, RT) for **MOP 3**.

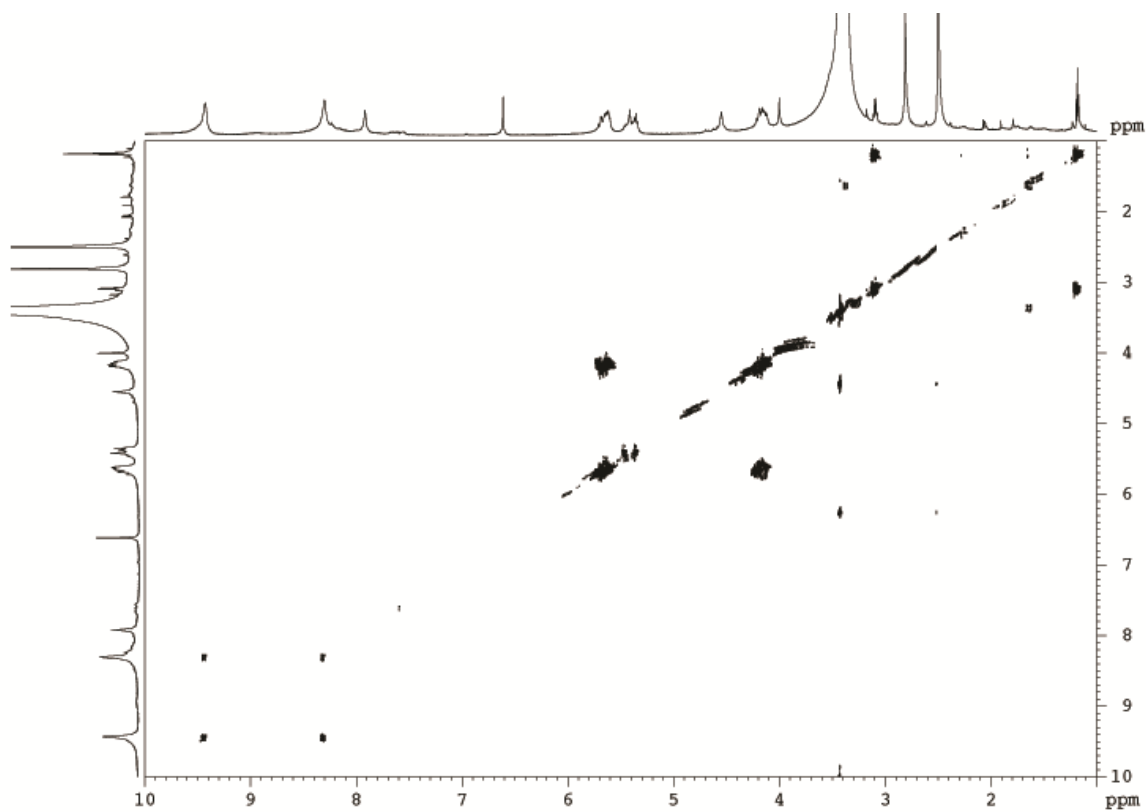


Figure S15. COSY NMR recorded (600 MHz, DMSO, RT) for **MOP 3**.

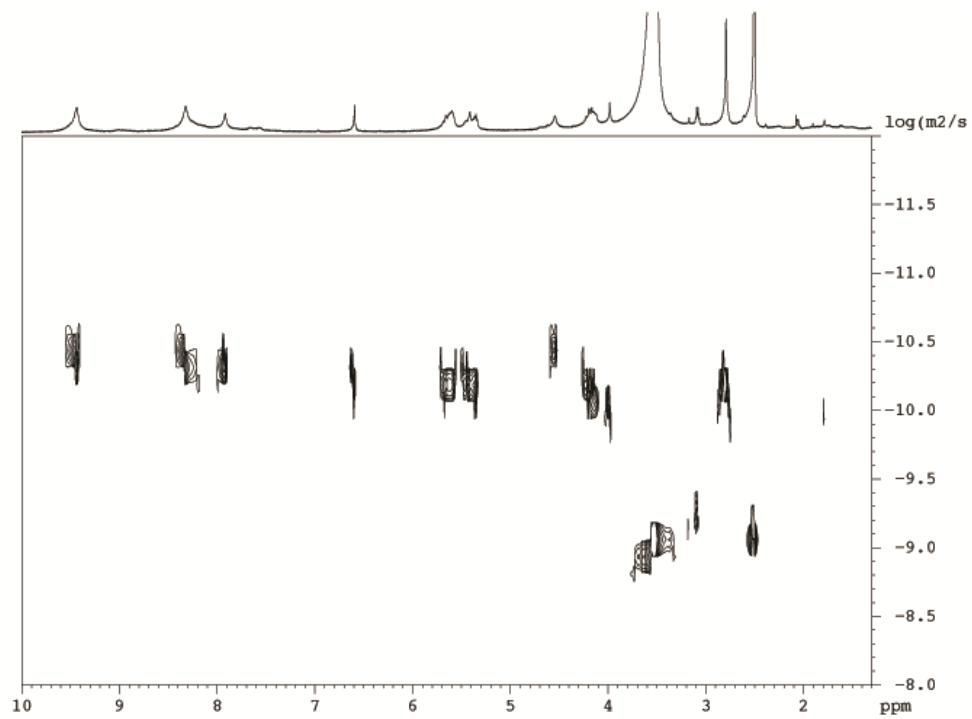


Figure S16. DOSY NMR recorded (600 MHz, DMSO, RT) for **MOP 3**.

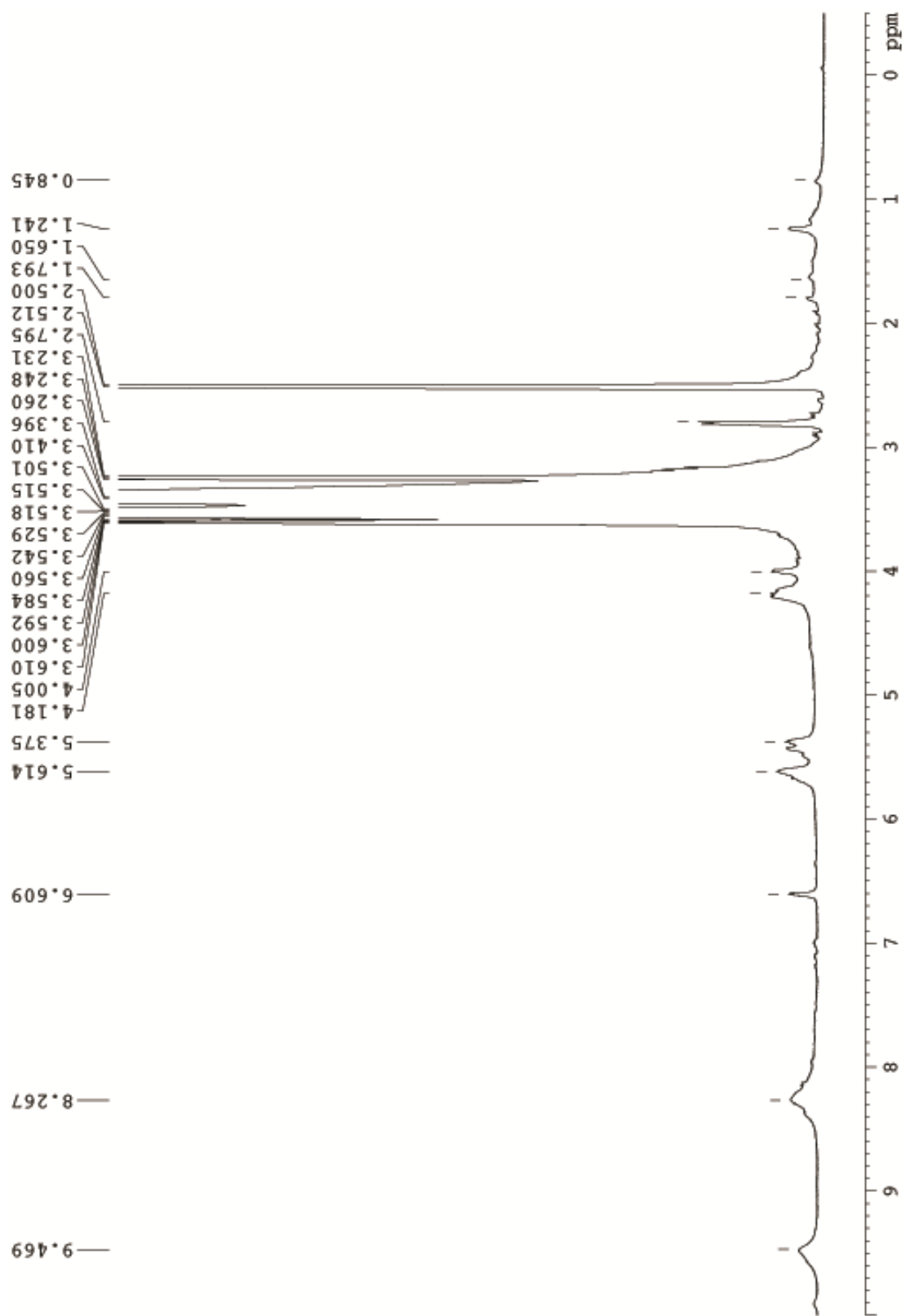


Figure S17. ^1H NMR recorded (600 MHz, DMSO- d_6 , RT) for **MOP 4^{PEG}**.

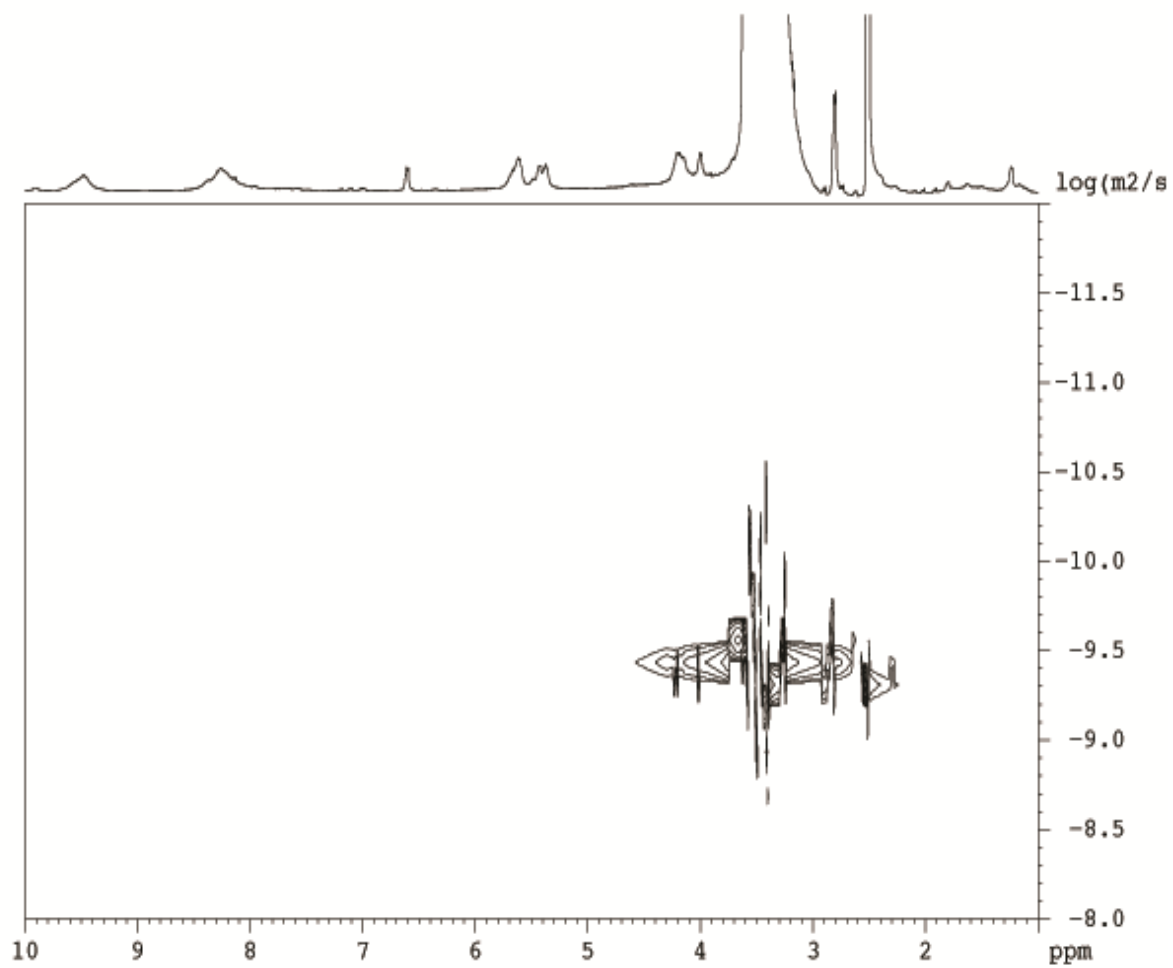


Figure S18. DOSY NMR recorded (600 MHz, DMSO- d_6 , RT) for **MOP 4^{PEG}**.

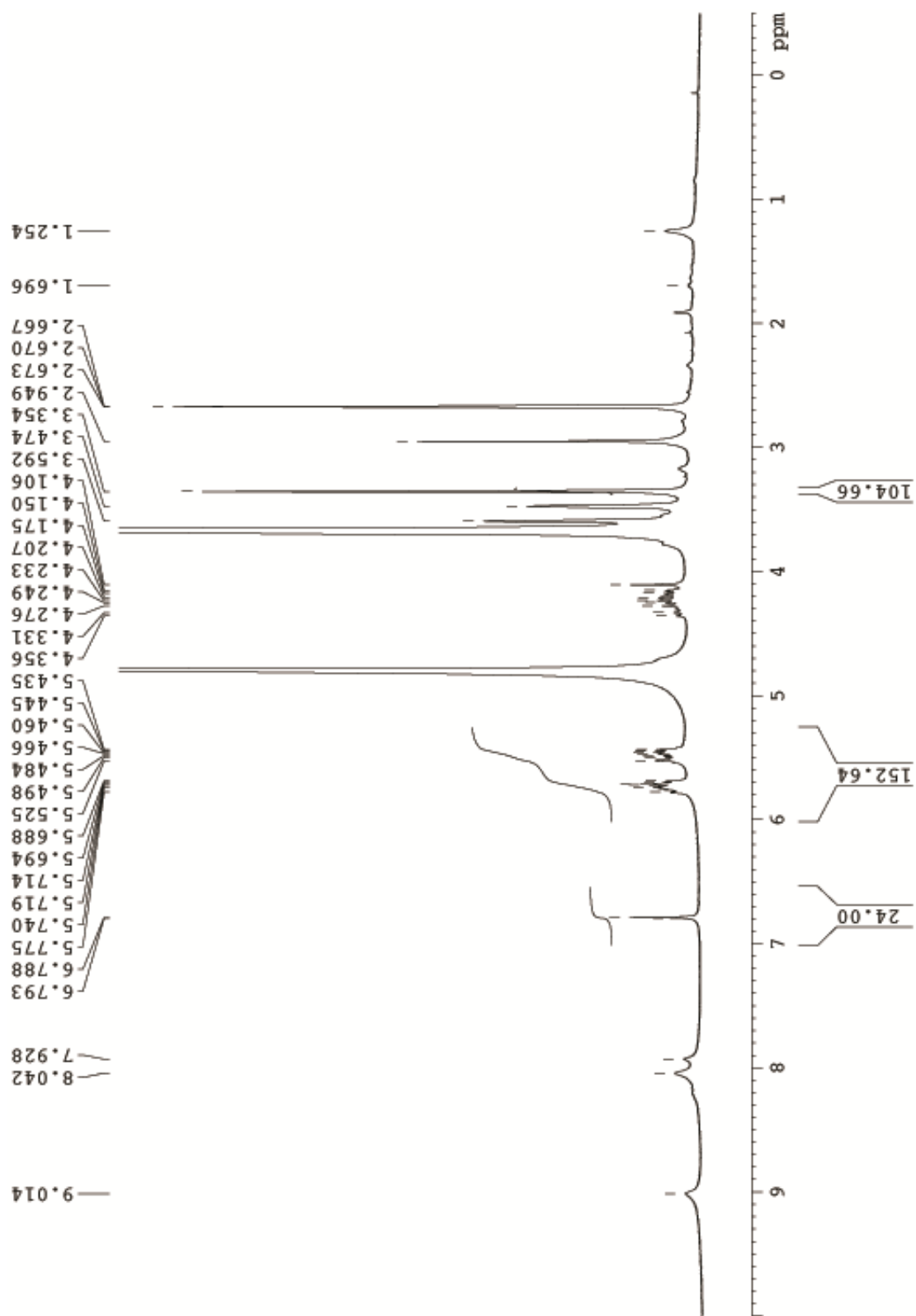


Figure S19. ^1H NMR recorded (600 MHz, D_2O , RT) for **MOP 4^{PEG}**.

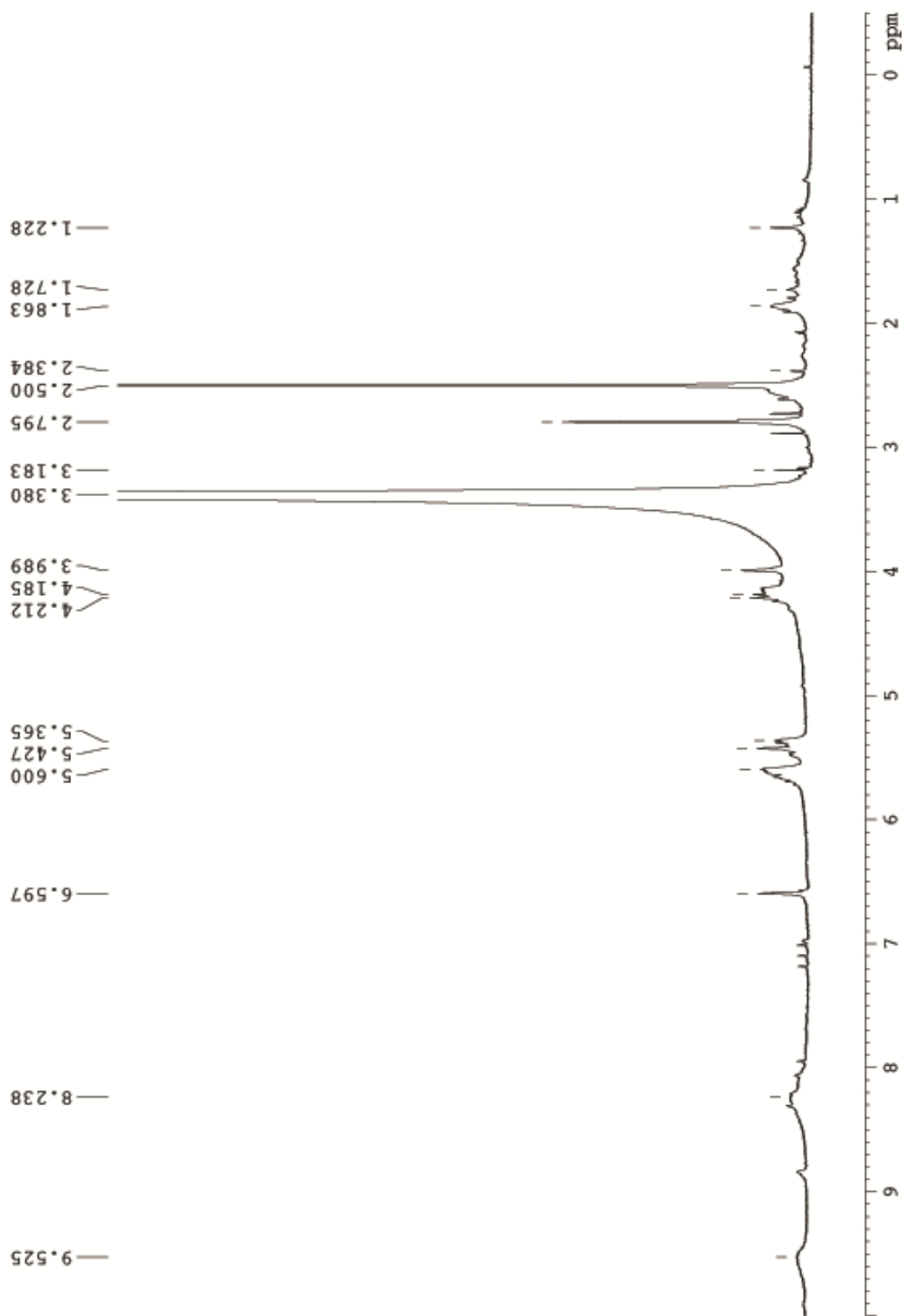


Figure S20. ^1H NMR recorded (600 MHz, $\text{DMSO-}d_6$, RT) for **MOP 4^{sulfo}**.

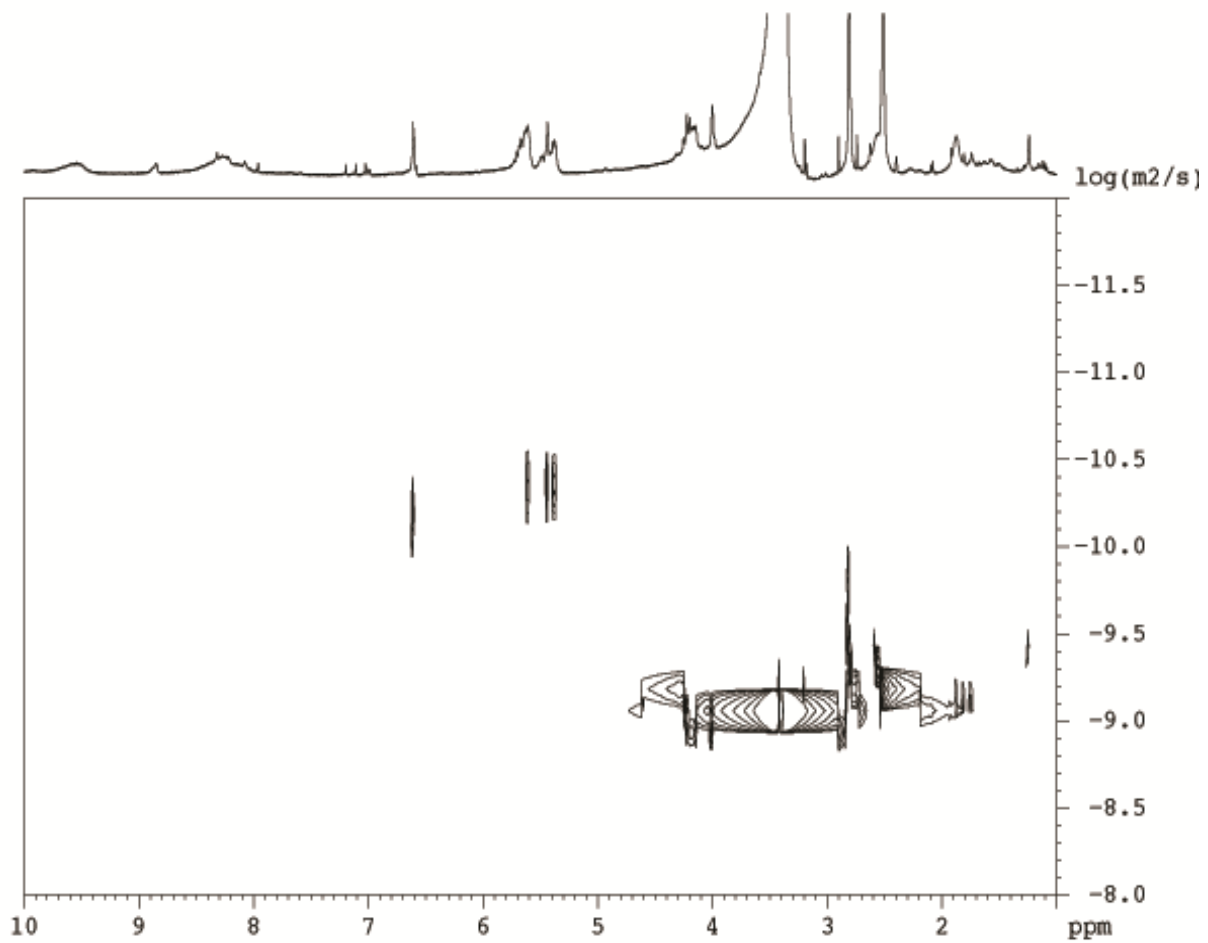


Figure S21. DOSY NMR recorded (600 MHz, DMSO-d₆, RT) for **MOP 4^{sulfo}**.

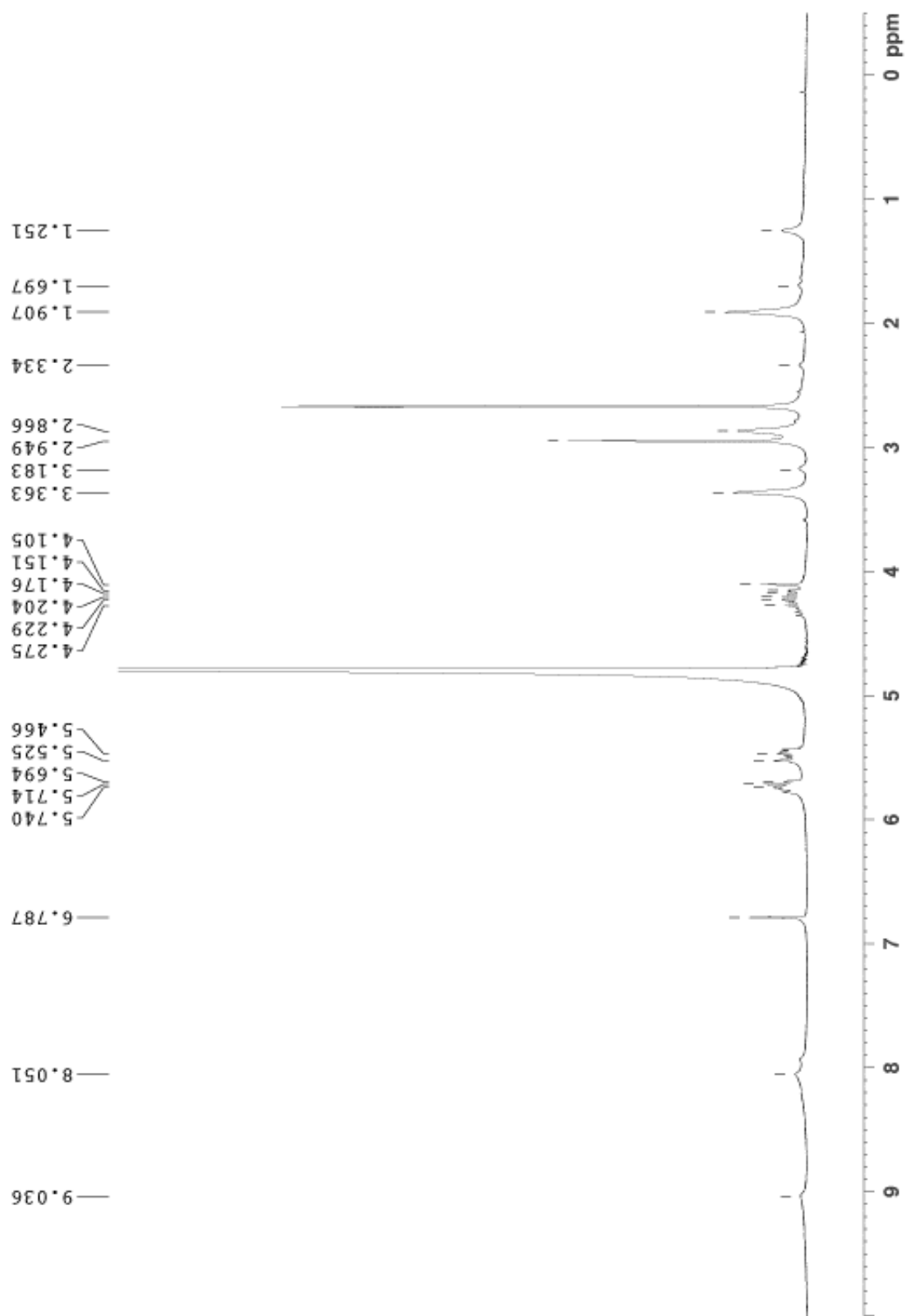


Figure S22. ^1H NMR recorded (600 MHz, D_2O , RT) for **MOP 4^{sulfate}**.

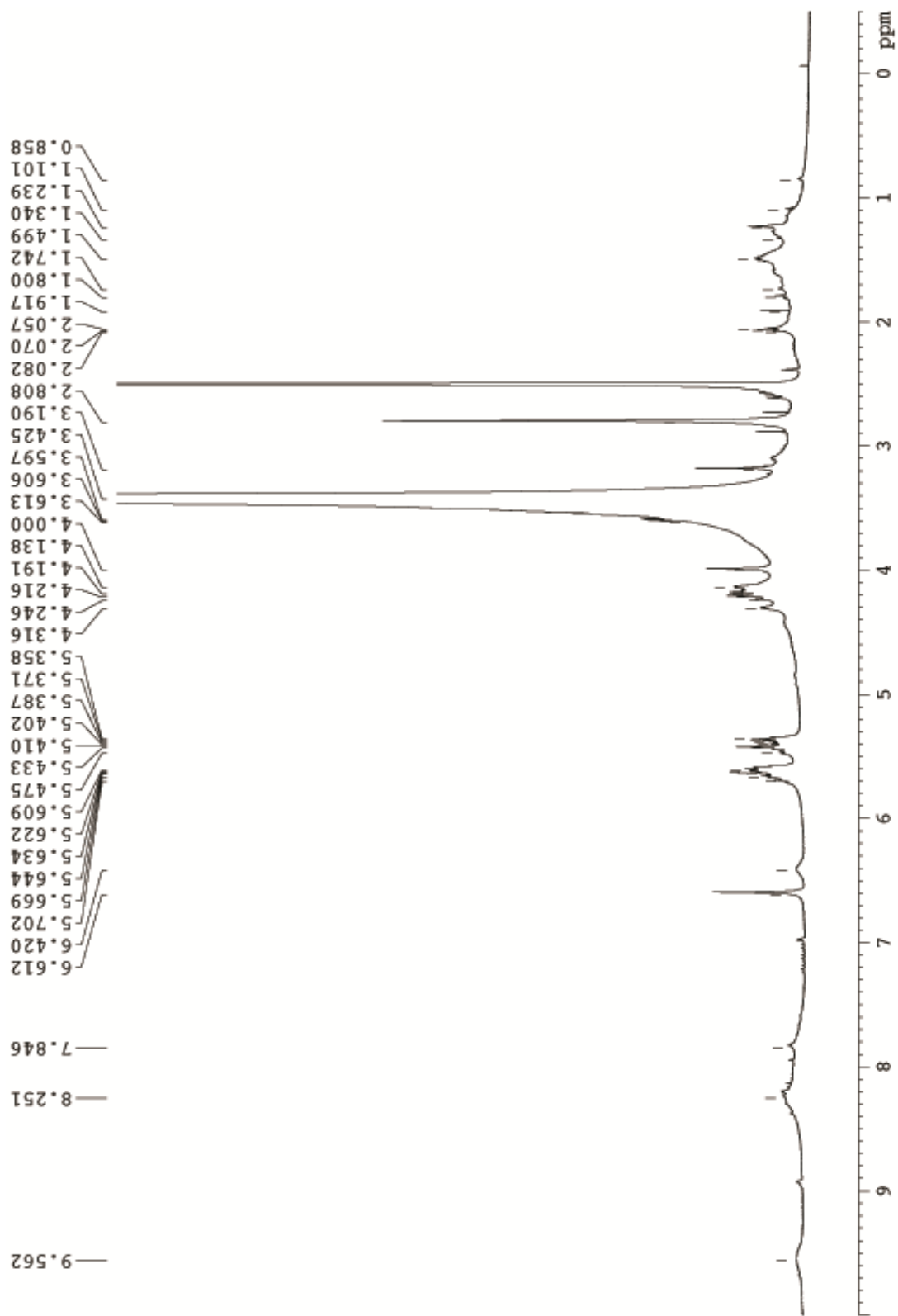


Figure S23. ^1H NMR recorded (600 MHz, $\text{DMSO-}d_6$, RT) for **MOP 4^{biotin}**.

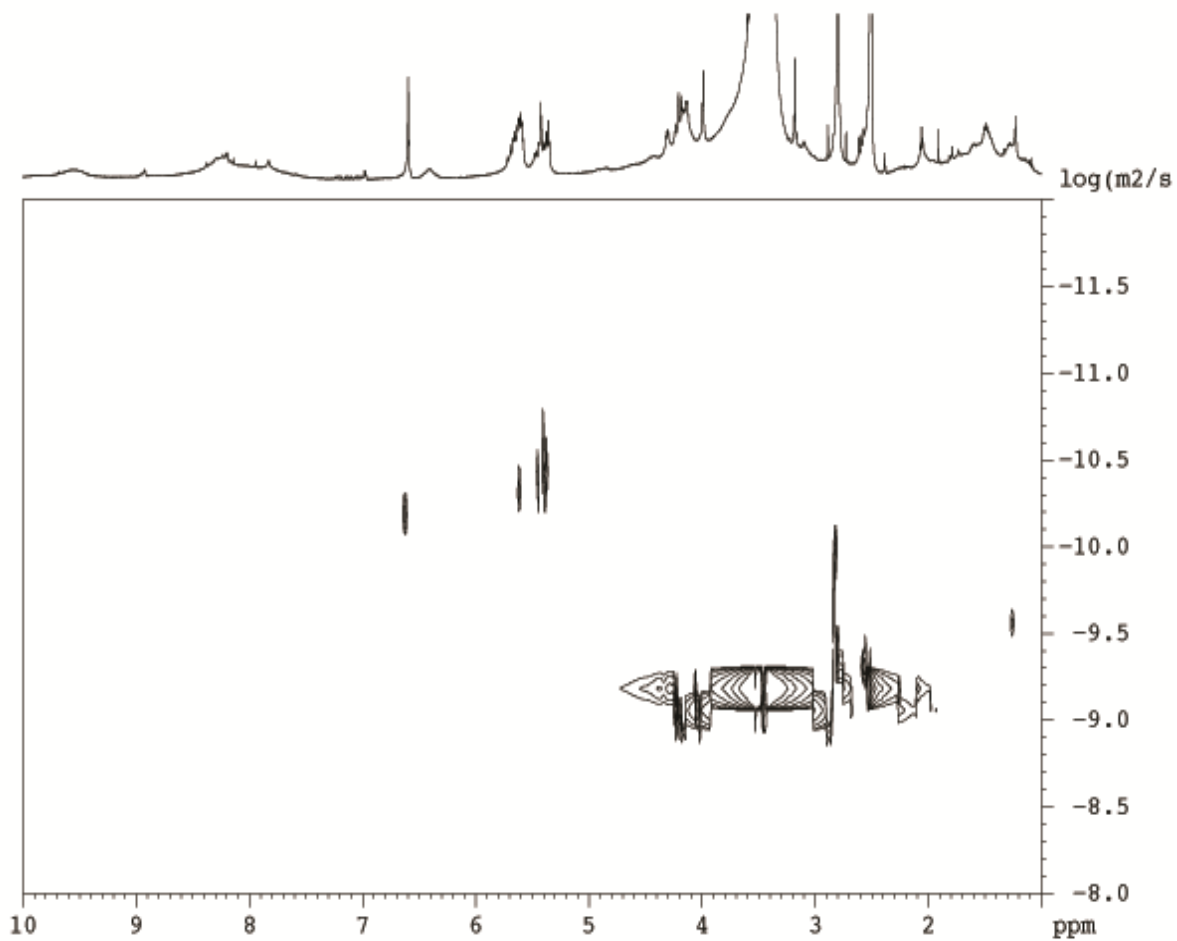


Figure S24. DOSY NMR recorded (600 MHz, DMSO- d_6 , RT) for **MOP 4^{biotin}**.

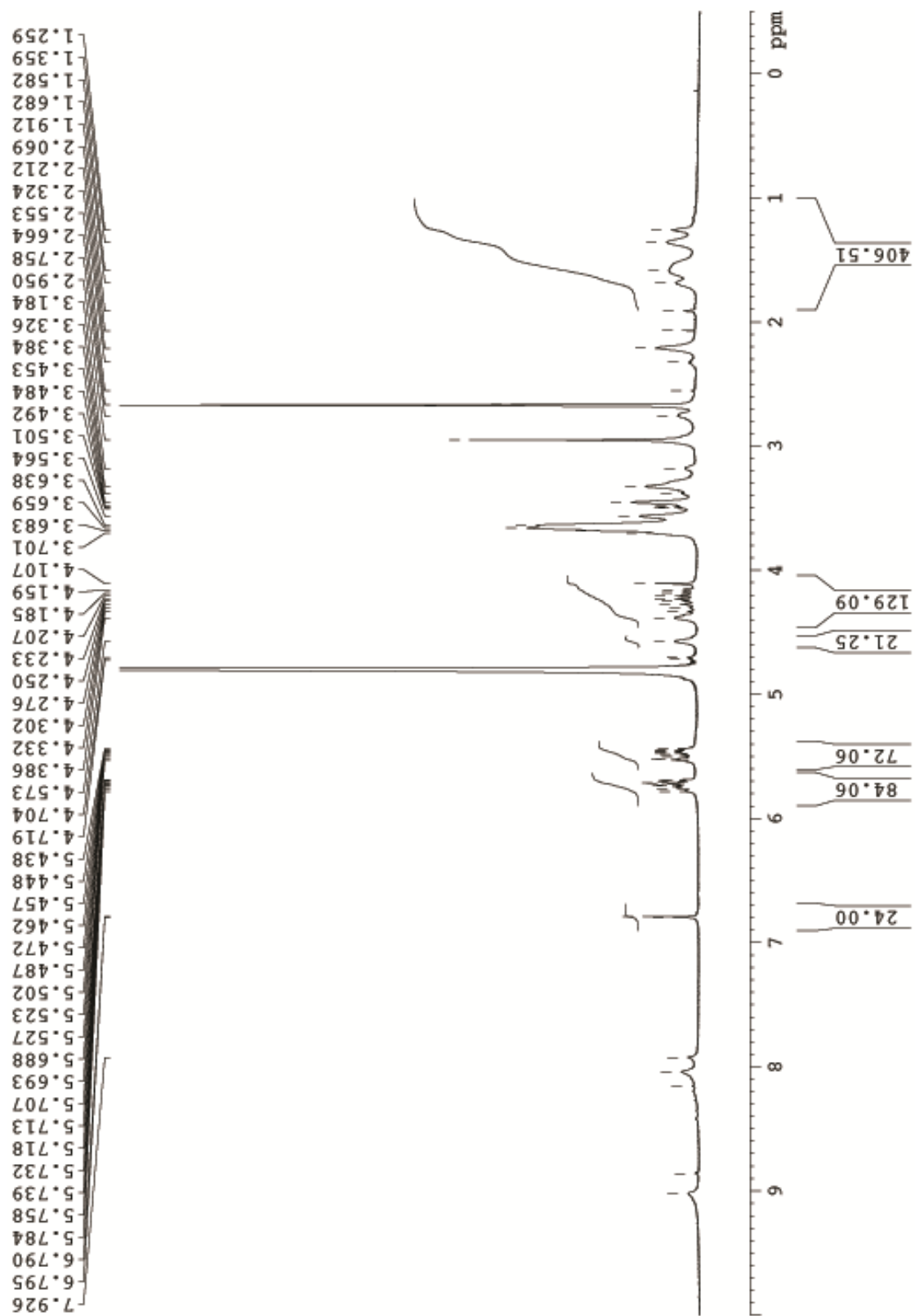


Figure S25. ^1H NMR recorded (600 MHz, D_2O , RT) for **MOP 4^{biotin}**.

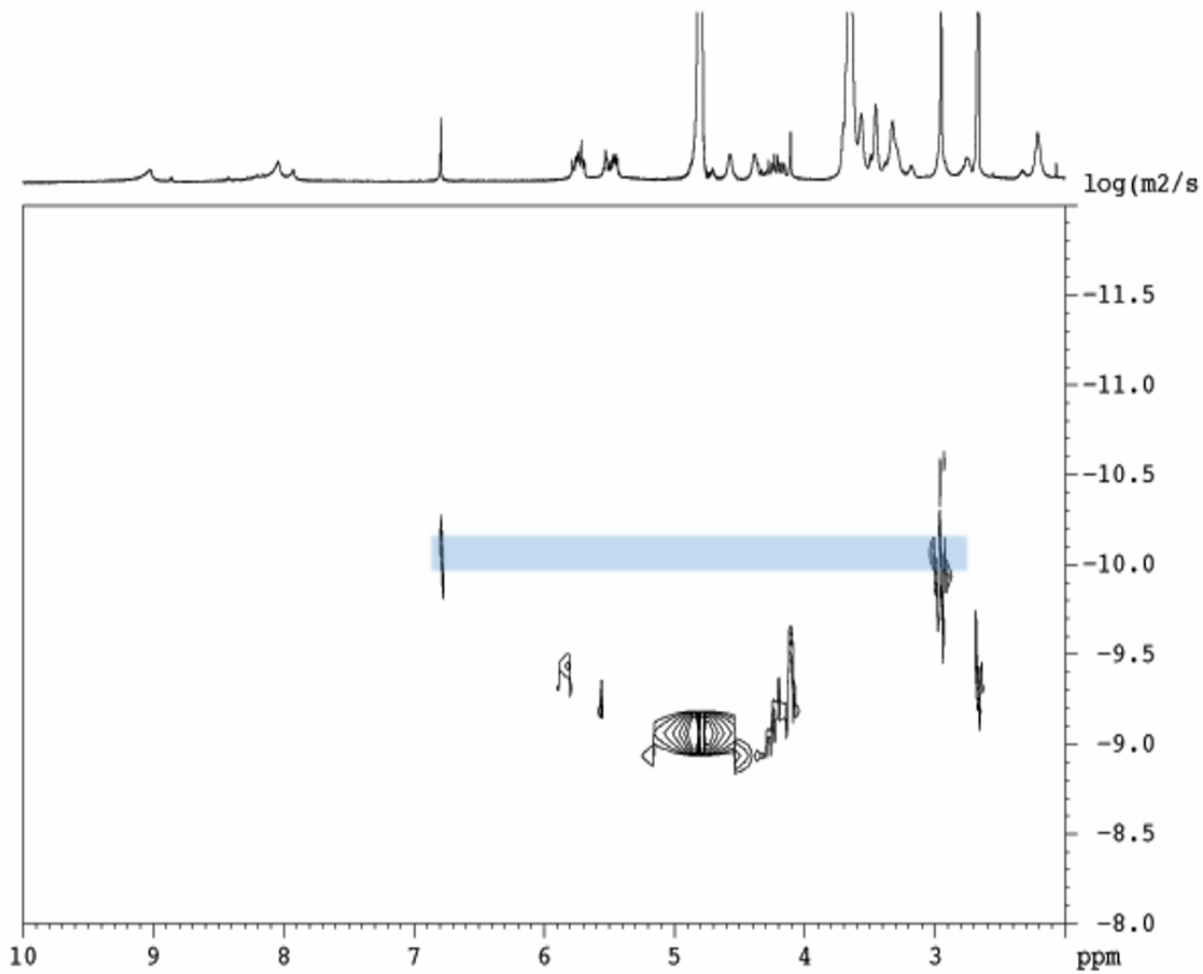


Figure S26. DOSY NMR recorded (600 MHz, D₂O, RT) for **MOP 4^{biotin}**.

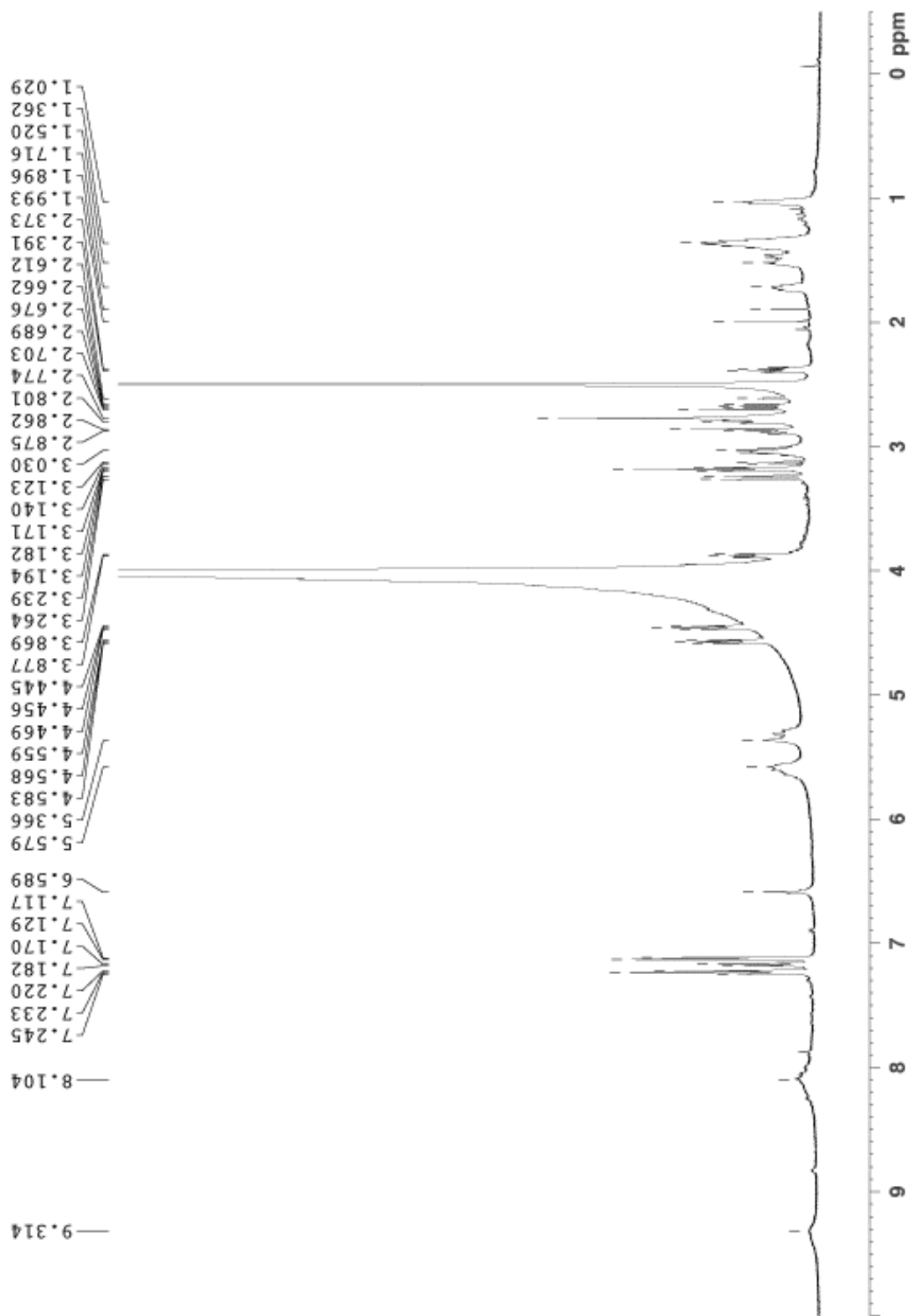


Figure S27. ^1H NMR recorded (600 MHz, $\text{DMSO-}d_6$, RT) for **MOP 4^{RGD}**.

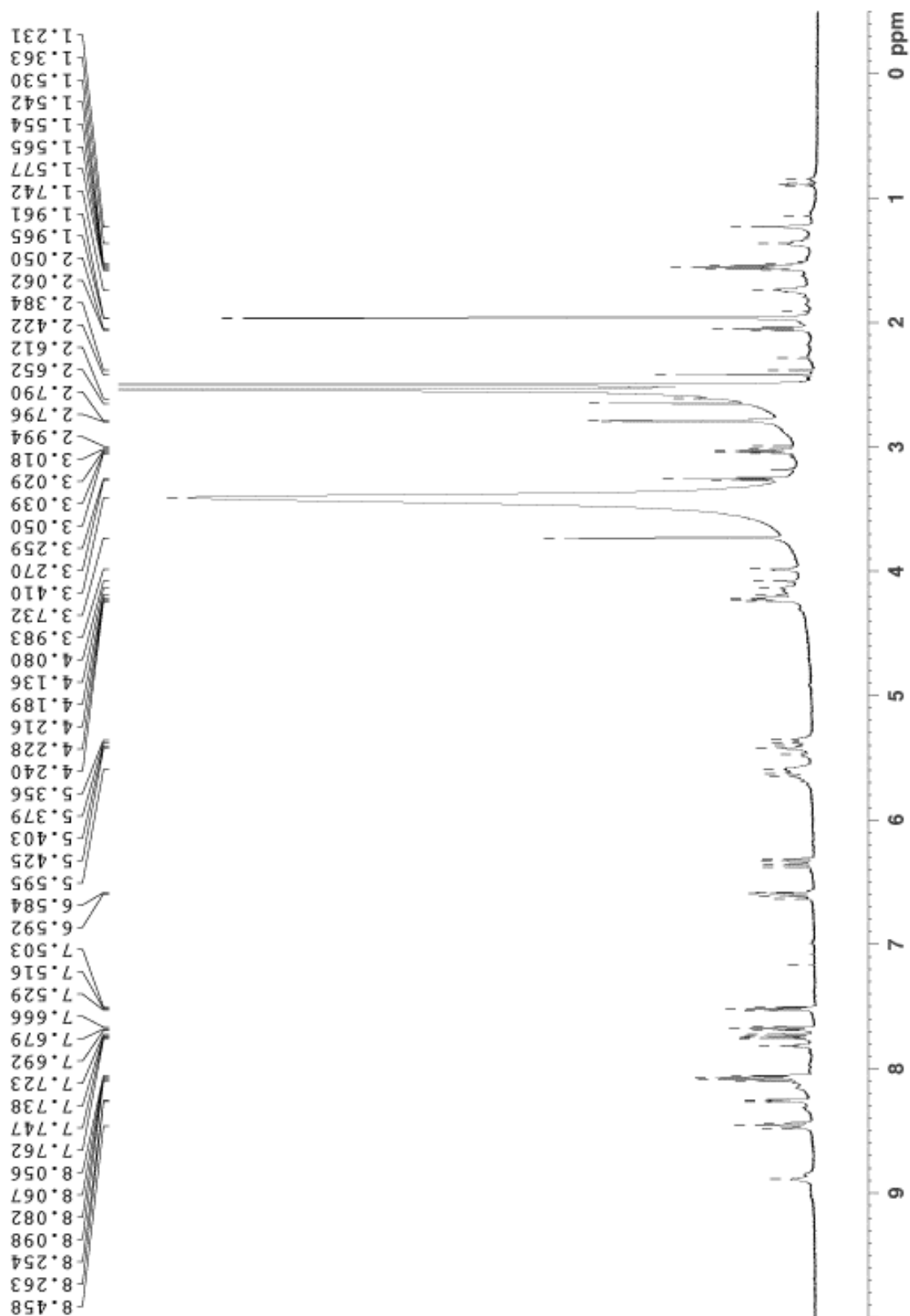


Figure S28. ^1H NMR recorded (600 MHz, $\text{DMSO-}d_6$, RT) for **MOP 4^{cyan}**.

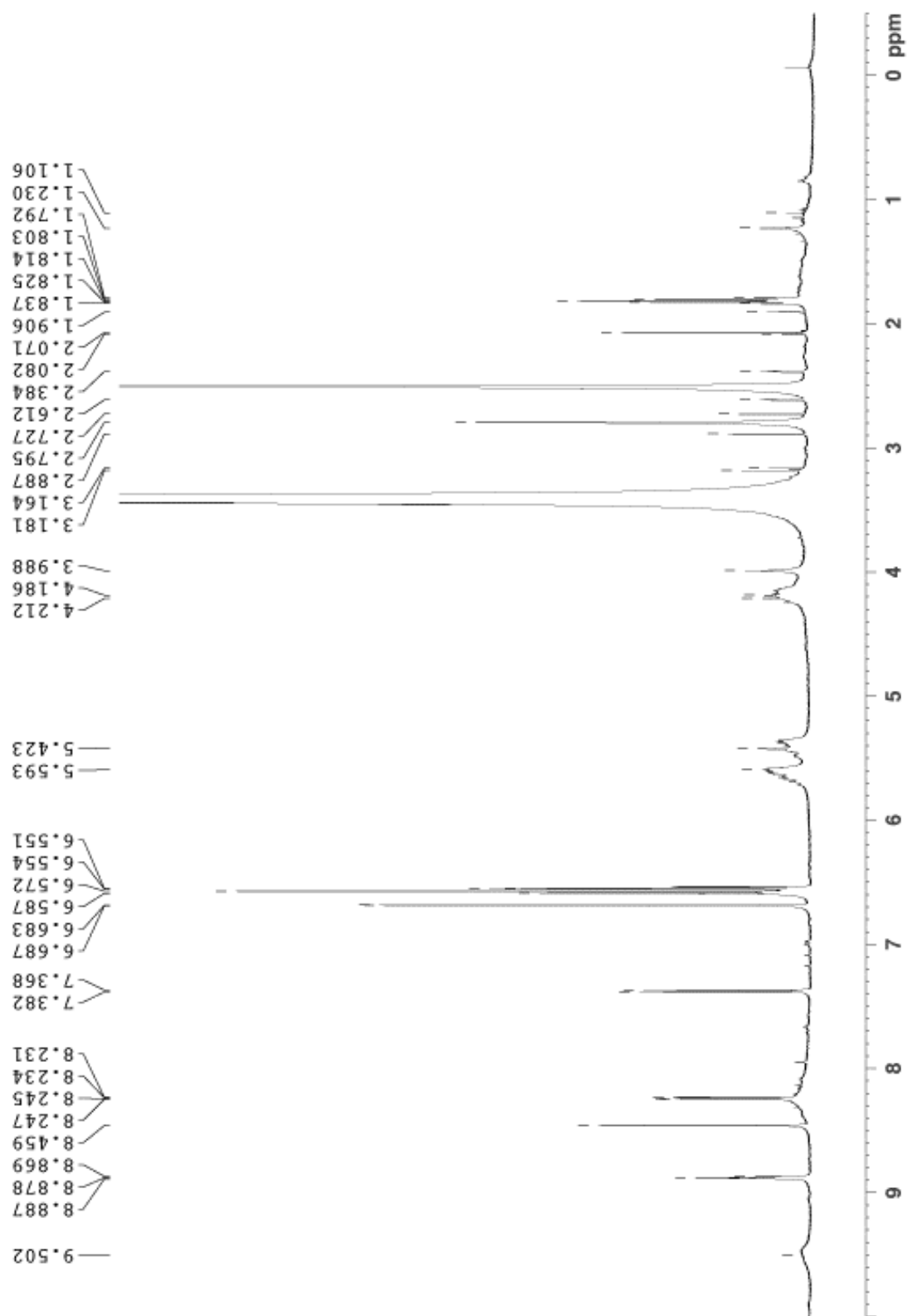


Figure S29. ^1H NMR recorded (600 MHz, $\text{DMSO-}d_6$, RT) for **MOP 4^{Fluor}**.

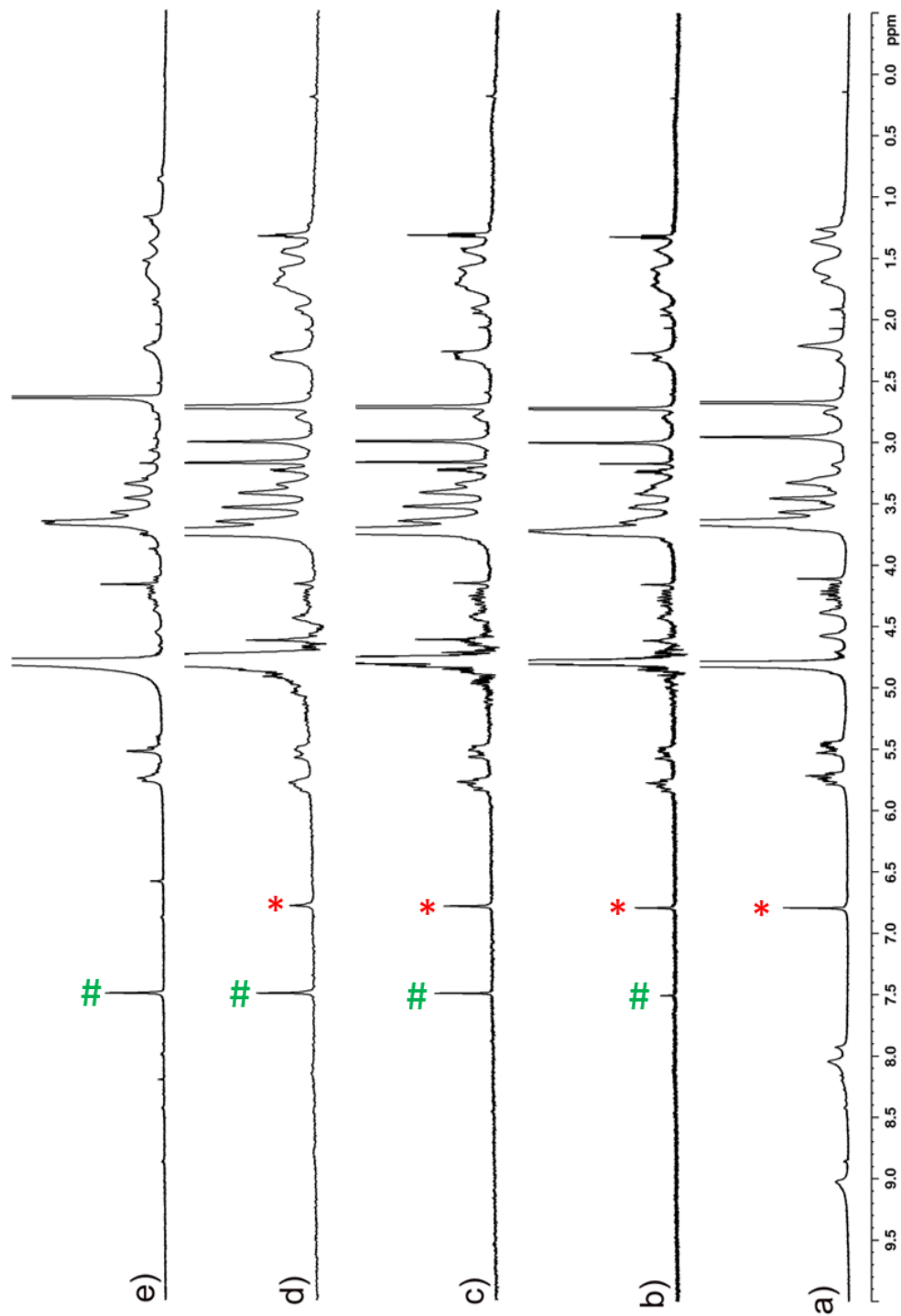


Figure S30. ^1H NMR spectra recorded (600 MHz, D_2O , RT) for (a) $\text{MOP-4}^{\text{biotin}}$ (b) $\text{MOP-4}^{\text{biotin}}$ (20 μM) and Ad-FITC (30 μM) (c) $\text{MOP-4}^{\text{biotin}}$ (20 μM) and Ad-FITC (60 μM), (d) $\text{MOP-4}^{\text{biotin}}$ (20 μM) and Ad-FITC (90 μM) (e) $\text{MOP-4}^{\text{biotin}}$ (20 μM) and Ad-FITC (120 μM). (* bound PXDA, # free PXDA)

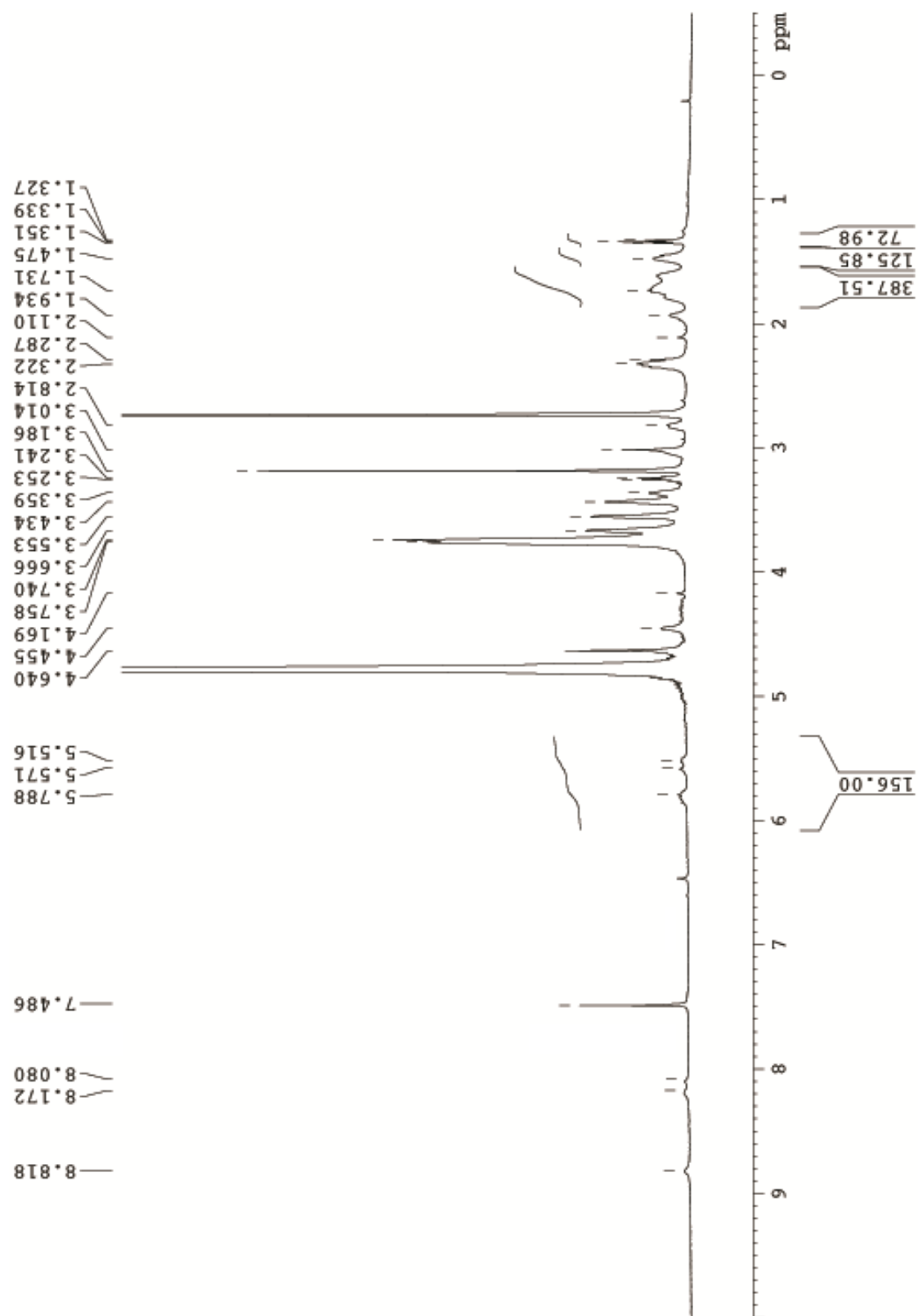


Figure S31. ^1H NMR recorded (600 MHz, D_2O , RT) for **MOP 5^{biotin}•Ad-FITC**.

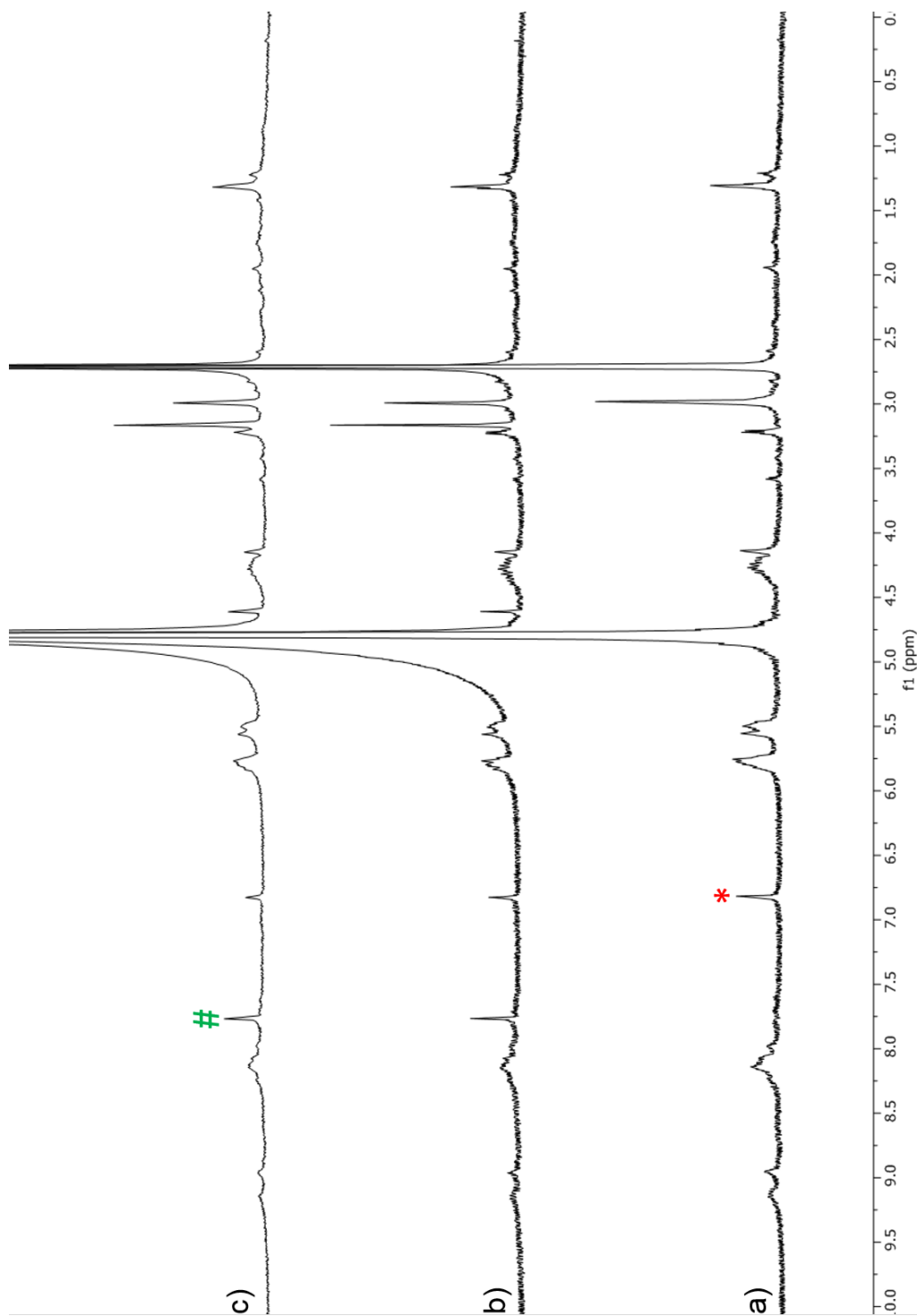


Figure S32. ¹H NMR spectra recorded (600 MHz, D₂O, RT) for (a) **MOP-3** (b) **MOP-3** (20 μM) and **Ad-FITC** (60 μM) (c) **MOP-3** (20 μM) and **Ad-FITC** (120 μM). (* bound PXDA, # free PXDA)

Transmission Electron Microscopy

The samples were prepared on a carbon-coated Cu grid (400 mesh) by adding DMSO solutions of **MOP 1** or **MOP 2**. After evaporation of solvent, TEM images were recorded. Spheres with a size commensurate with that of molecular models of the **MOPs** can be clearly observed.

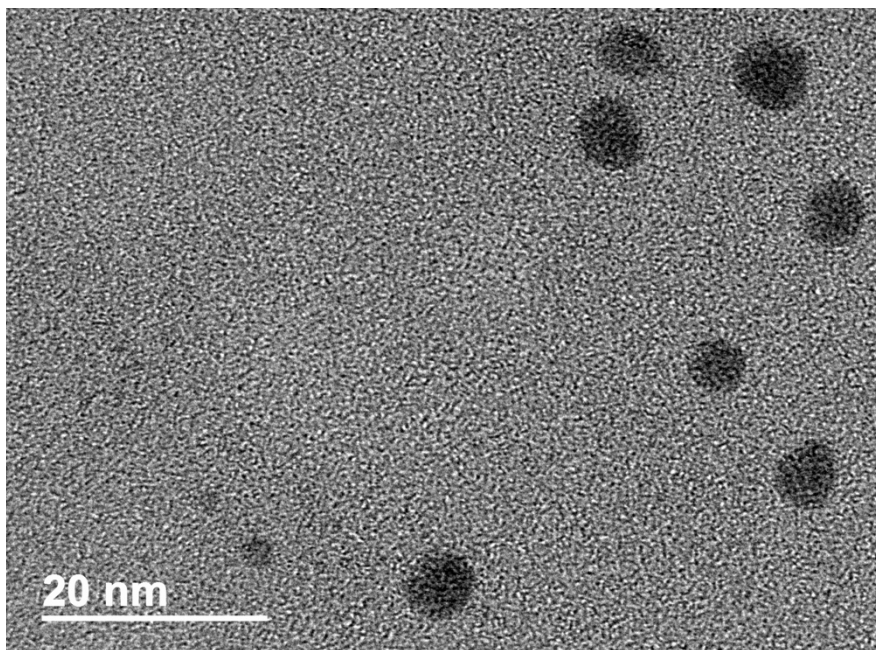


Figure S33. TEM image of **MOP1**.

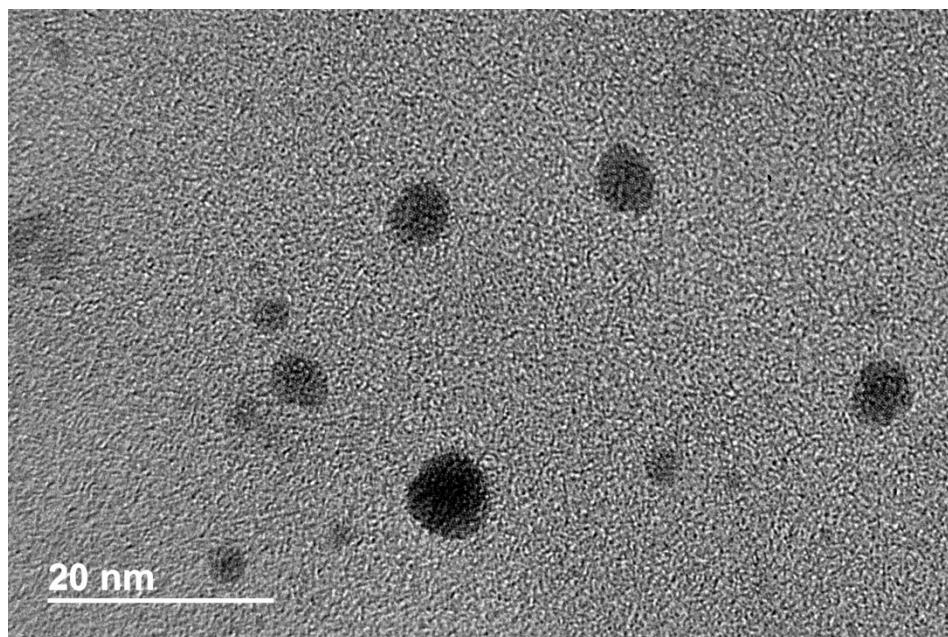


Figure S34. TEM image of **MOP2**.

Infrared Spectroscopy

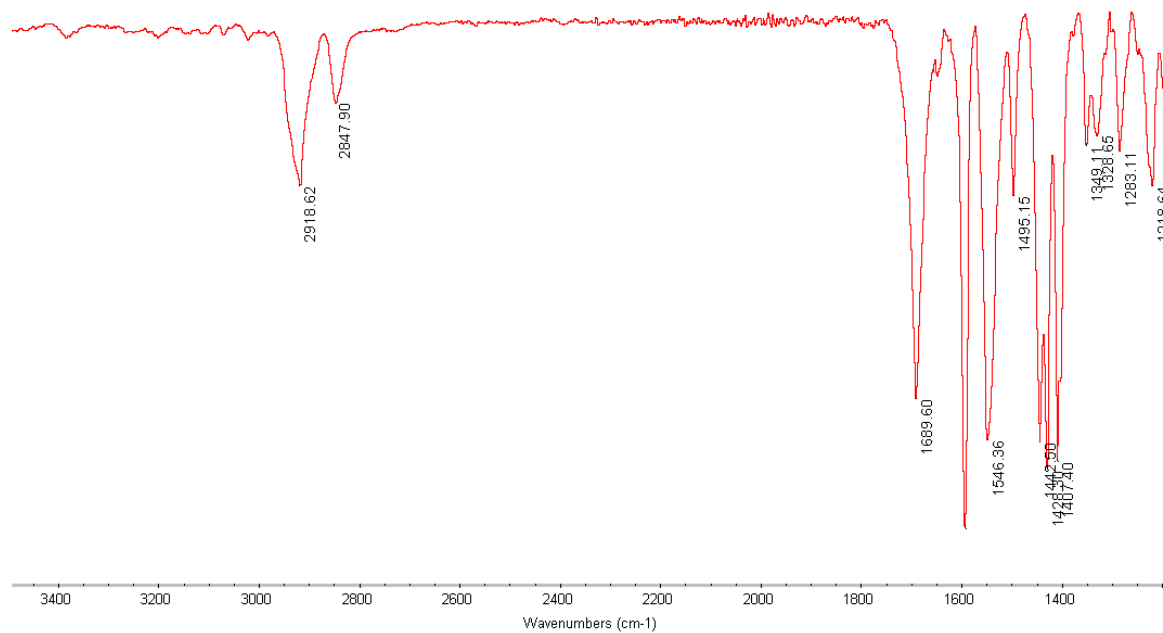


Figure S35. FTIR spectrum recorded for compound 2.

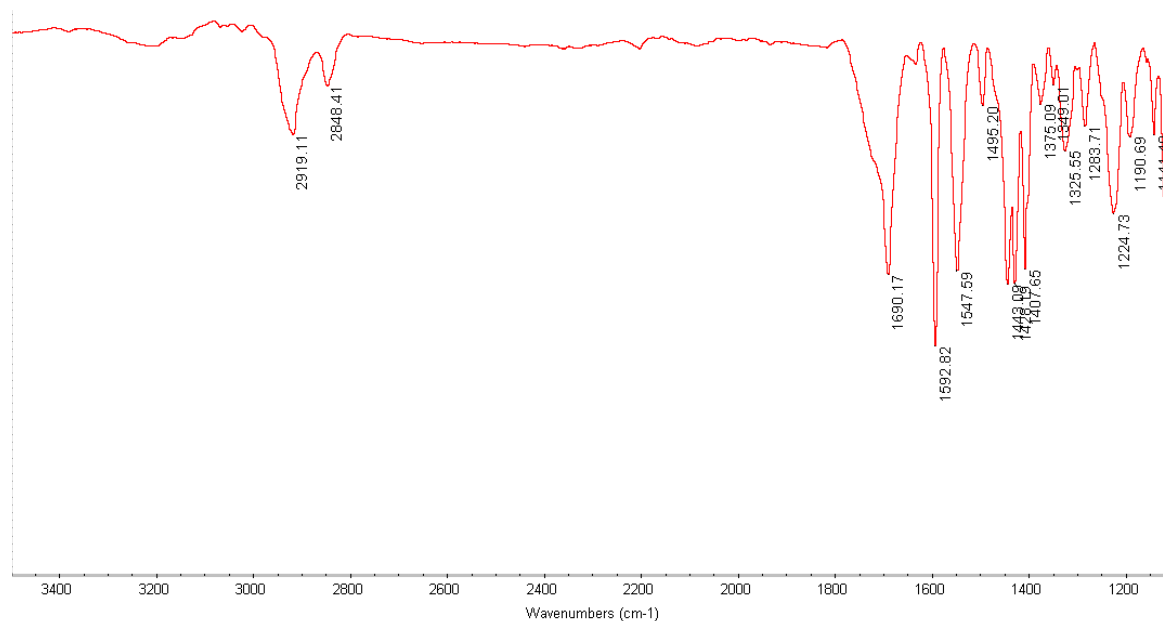


Figure S36. FTIR spectrum recorded for MOP 3.

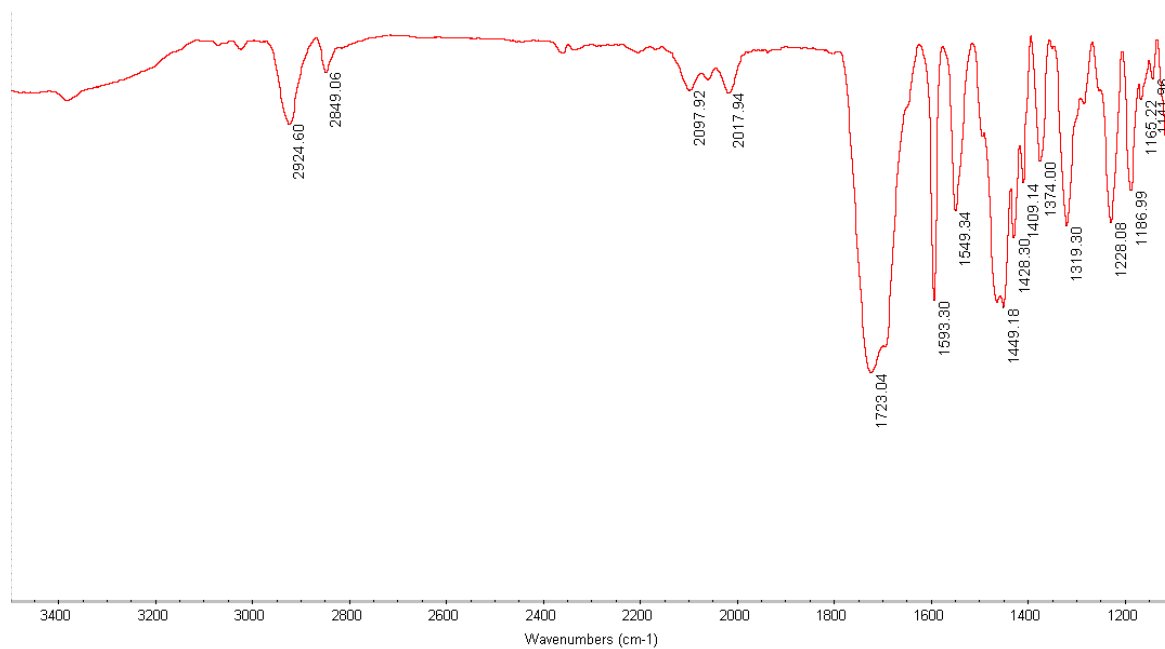


Figure S37. FTIR spectrum recorded for a mixture of **MOP 3** and 18 equiv. of biotin-N₃ before reaction.

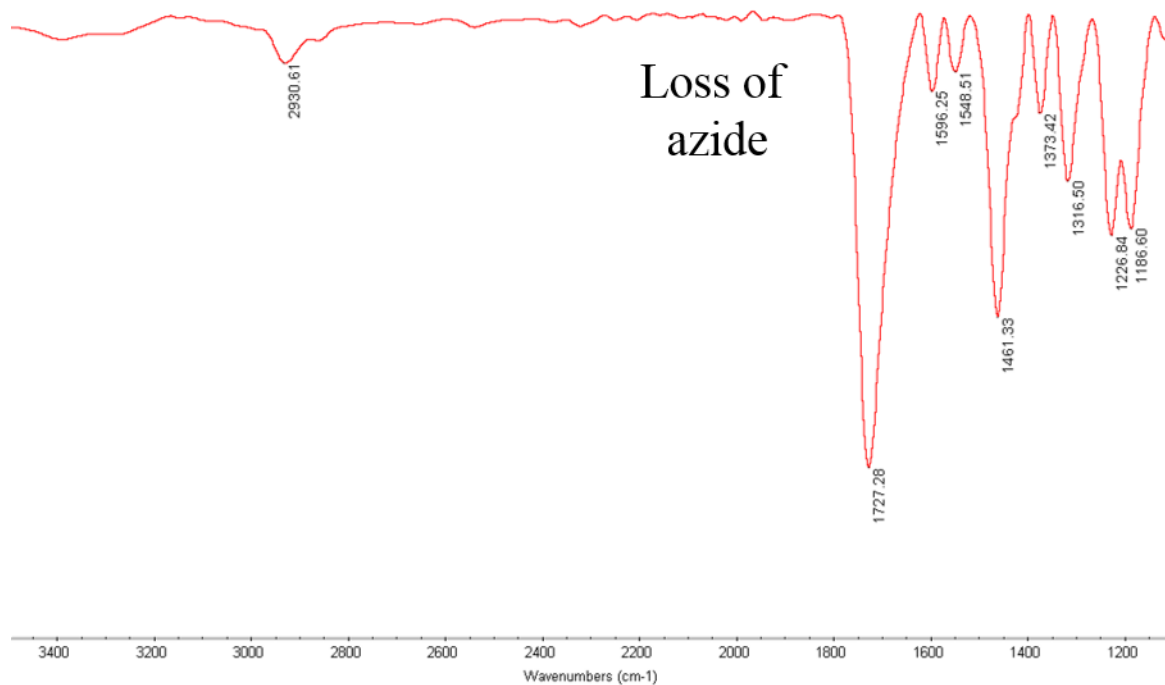


Figure S38. FTIR spectrum recorded for a mixture of **MOP 3** and 18 equiv. of biotin-N₃ after heating at 50 °C for 24 h in DMSO.

Size Measurement using *Stokes-Einstein* Equation:

$$D = K_B T / 6\pi\eta r$$

D = Diffusion Coefficient

K_B = Boltzmann's constant

π = viscosity coefficient

r = hydrodynamic radius

Viscosity coefficient (η) for DMSO- d_6 at 27 °C = 1.99 cps

Viscosity coefficient (η) for D₂O at 27 °C = 0.89 cps

Table S1. Diffusion coefficient (D), experimentally measured diameter and estimated diameter based on MMFF computation.

Sample	Diffusion coefficient (m ² /s)	Measured diameter (nm) from <i>Stokes-Einstein</i> Equation
MOP 1 (in DMSO- d_6)	3.12×10^{-11}	7.0
MOP 2 (in DMSO- d_6)	3.54×10^{-11}	6.2
MOP 3 (in DMSO- d_6)	5.01×10^{-11}	4.4
MOP 4^{biotin} (in DMSO- d_6)	3.55×10^{-11}	6.2
MOP 4^{biotin} (in D ₂ O)	7.94×10^{-11}	6.1
MOP 4^{sulfo} (in DMSO- d_6)	5.13×10^{-11}	4.3
MOP4^{PEG} (in DMSO- d_6)	3.98×10^{-11}	5.5

Molecular Modelling

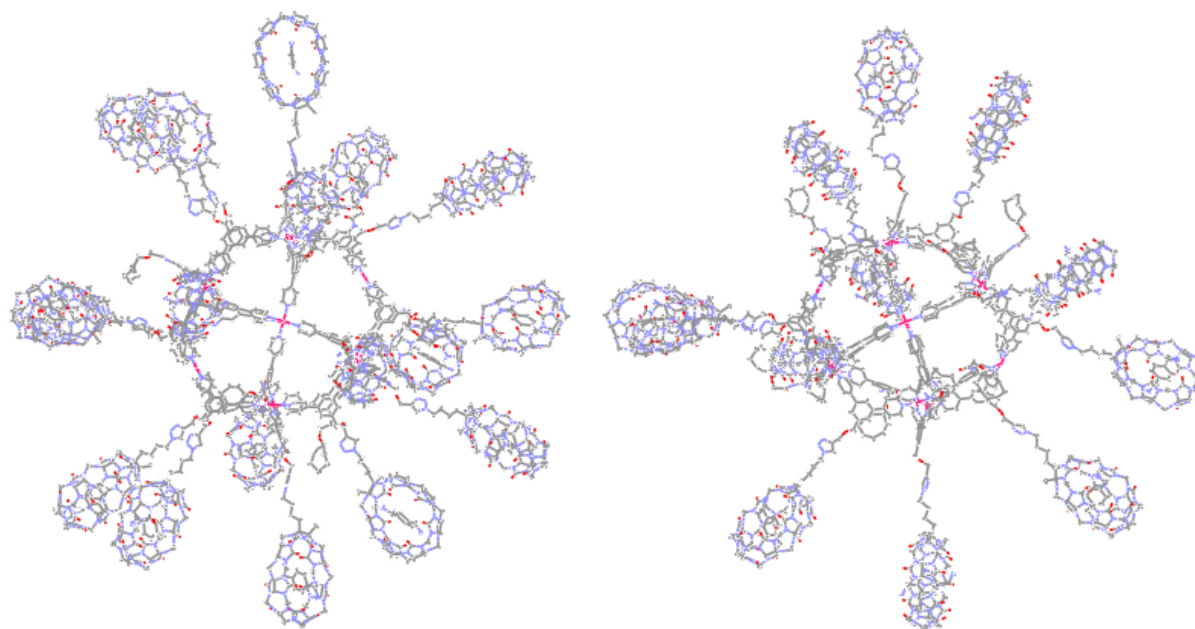


Figure S39. Spartan optimized (MMFF) structure of (left) **MOP 1** and (right) **MOP 2**.

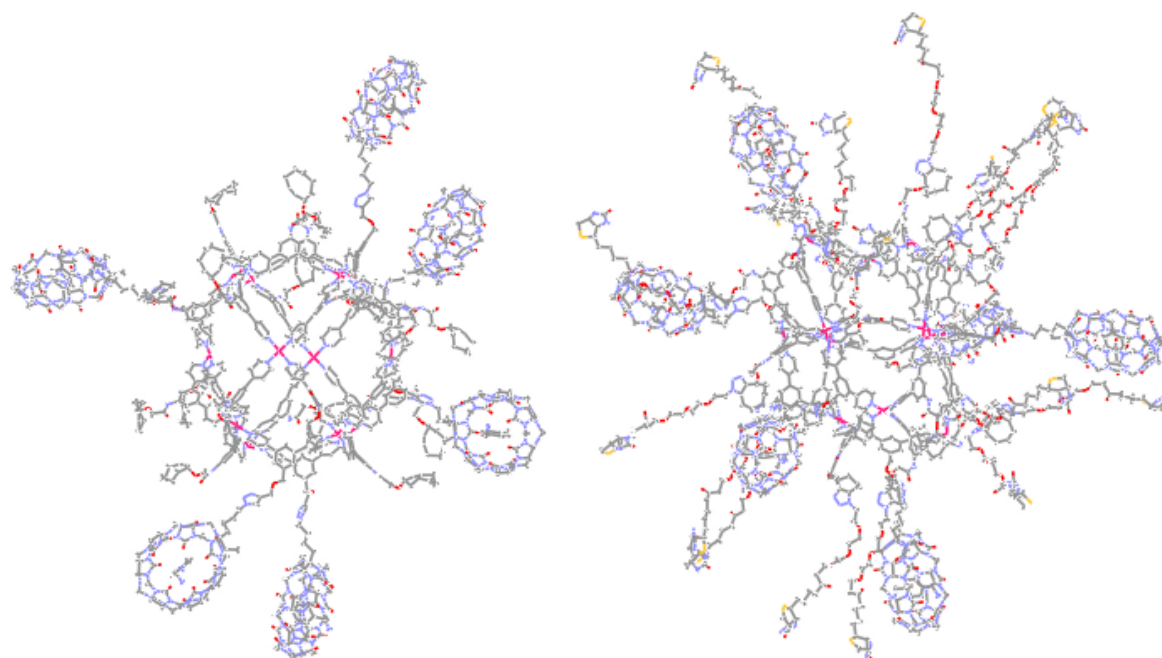


Figure S40. Spartan optimized (MMFF) structure of (left) **MOP 3** and (right) **MOP 4^{biotin}**.