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Supplementary information

Rational design of a supramolecular gel based on a Zn(II)-salophen bis-dipeptide derivative

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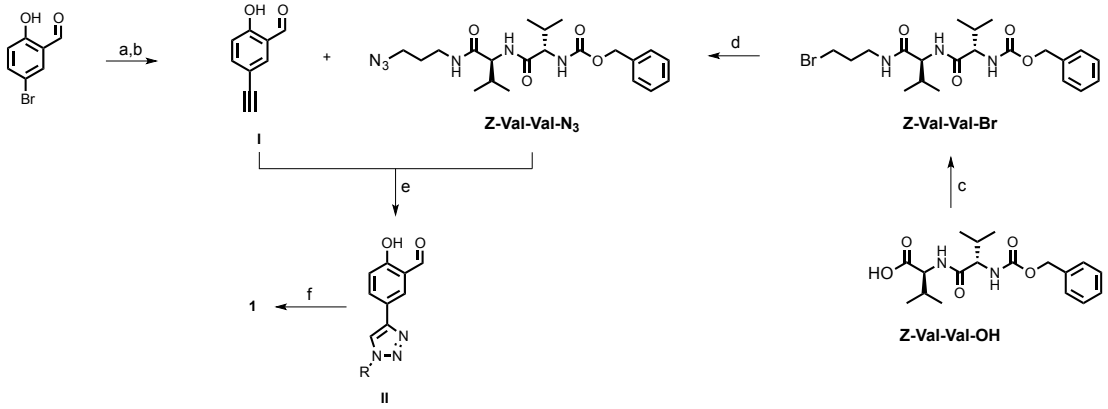
1. Experimental section

General methods and Instrumentation

Reagents and solvents were obtained from commercial suppliers and used without further purification. The ^{1}H and ^{13}C NMR spectra were recorded at 300, 400, or 500 MHz and 75, 100, or 125 MHz, respectively. The chemical shifts (δ) for ^{1}H and ^{13}C are given in ppm relative to residual signals of the solvents ($CHCl_3$, δ = 7.26 ppm for $_1H$ NMR, δ = 77.16 ppm for ^{13}C NMR or DMSO, δ = 2.50 ppm for ^{1}H NMR, δ = 39.52 ppm for ^{13}C NMR). When necessary, ^{1}H and ^{13}C signals were assigned by means of COSY, HSQC, NOESY, and ROESY 2D NMR spectroscopic sequences. High-resolution mass spectra (HRMS) were obtained with a MicroTOF II from Bruker Daltonics (HPLC-MS-TOF) with the positive ionization mode (ESI+) and AutoFlex (Bruker Daltonics) for MALDI-TOF-MS. UV/Vis measurements were carried out with a Shimadzu UV-2401PC spectrophotometer equipped with a photomultiplier detector, double beam optics, and D2 and W light sources. Dynamic light scattering (DLS) analysis were performed on a Zetasizer Nano particle analyser (Malvern Instruments). The sample was prepared diluting 50 µl of the stock DMSO solution containing **1** with 10 mL of acetonitrile (or acetonitrile + 20% of DMSO). The resulting suspension was filtered before the analysis and transferred into a glass cuvette.

Synthesis and Characterization



Scheme S1. Synthetic pathway for the preparation of **1**.

a) Synthesis of 2-hydroxy-5-((trimethylsilyl)ethynyl)benzaldehyde. 5-bromo-2-hydroxybenzaldehyde (0.5 g, 2.5 mmol), $Pd(PPh_3)_2Cl_2$ (52 mg, 0.08 mmol) and CuI (24 mg, 0.12 mmol) were added in a dry Schlenk and vacuum/Argon cycles were performed. Dry Et_3N (8 mL) was added and stirred at 80ºC. Lastly, Ethynyltrimethylsilane (0.53 mL, 3.73 mmol) was added and the reaction was capped under Argon atmosphere and stirred at 80º for 24h. The reaction was transferred in a round bottom flask and the solvent was evaporated under vacuum. The crude was

plugged on silica with EtOAc and then purified on silica column (Hex/EtOAc 99:1). Yield 89%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.12 (s, 1H), 9.88 (s, 1H), 7.73 (d, J = 2.1 Hz, 1H), 7.63 (dd, J = 8.7, 2.1 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 0.28 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.01, 161.52, 140.14, 137.36, 120.34, 117.96, 115.13, 103.13, 93.82, -0.08.

b) Synthesis of 5-ethynyl-2-hydroxybenzaldehyde (I). 2-hydroxy-5-((trimethylsilyl)ethynyl)benzaldehyde 0.94 g, 4.3 mmol) was partially solubilized in 15 mL of MeOH and TBAF 1M in THF (15 mL, 15 mmol) was added. The reaction was stirred at room temperature for 2 hours. Then water and DCM were added to the reaction mixture. The organic layers were combined and dried over Na_2SO_4 and the solvent was evaporated. The crude was purified on silica column (eluent: Hex/EtOAc 95:5). Yield 70%.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.14 (s, 1H), 9.88 (s, 1H), 7.74 (d, J = 2.1 Hz, 1H), 7.64 (dd, J = 8.7, 2.1 Hz, 1H), 6.98 (d, J = 8.7, 1H), 3.06 (s, 1H).

c) Synthesis of Z-Val-Val-Br. A solution of commercially available Z-Val-Val-OH (1 g, 2.86 mmol) in THF dry (30 mL), was added dropwise to a solution of the 3-Bromopropylamune hydrobromide (688 mg, 3.14 mmol) in THF dry (10 mL) under continuous stirring, nitrogen atmosphere. Then, a dissolution of DIPEA (1.10 mL, 6.30 mmol) and TBTU* (1.08 g, 3.14 mmol) in THF dry (10 mL) was added in the mixture using a pressure-equalizing dropping funnel drop wise. The mixture was stirred at room temperature and nitrogen atmosphere overnight. The solvent was evaporated and the solid obtained was washed with acid water (HCl 0,1 M). The solid obtained was washed again with water to pH = 7, the solid was dried in a vacuum oven at approximately 50 ºC for 4 hours. Finally, the residue was purified by means of column chromatography on silica gel (CH_2Cl_2–MeOH, 95:5) to yield Z-Val-Val-Br (92%) as a white solid.

** O-(Benzotriazol-1yl)-N,N,N´,N´,tetramethyluronium tetrafluoroborate.*

d) Synthesis of Z-Val-Val-N_3: A solution of Z-Val-Val-Br (1.0mmol) in DMF dry and deoxygenated (10 mL), was added quickly the NaN_3 (5.0 mmol) under continuous stirring, nitrogen atmosphere. The mixture was stirred at room temperature and nitrogen atmosphere overnight. Then, water is added very slowly under continuous stirring until forming a white precipitate (10 minutes approximately). To continue, the suspension was filtered under vacuum and precipitate was washed with cold water. Finally, the solid was lyophilized to remove the water to give the azide compound (86%) as a white solid. CAUTION: azide compound is unstable, cannot be warmed or stored for long times. Should be used directly after preparation or stored in freezer for short time.

e) Synthesis of benzyl ((R)-1-(((R)-1-((3-(4-(3-formyl-4-hydroxyphenyl)-1H-1,2,3-triazol-1-yl)propyl)amino)-3-methyl-1-oxobutan-2-yl)amino)-3-methyl-1-oxobutan-

2-yl)carbamate (II). Z-Val-Val-N_3 (76 mg, 0.18 mmol) was solubilized in 1.2 mL of THF and 5-ethynyl-2-hydroxybenzaldehyde I (28 mg, 0.19 mmol) was added. Then 0.6 mL of water were added to the reaction mixture. Lastly $Cu(CH_3CN)_4PF_6$ (32 mg, 0.09 mmol) and TBTA (tris((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)amine, 9 mg, 0.018 mol) were added and the reaction was stirred at room temperature overnight. Then it was diluted with water and extracted with DCM. The organic layers were combined and dried over Na_2SO_4. The solvent was evaporated and the compound was purified by silica column chromatography (eluent: DCM/MeOH 95:5). Yield 50%.

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.07 (s, 1H), 9.98 (s, 1H), 8.13 (d, J = 2.2 Hz, 1H), 7.98 (s, 1H), 7.94 (dd, J = 8.7, 2.2 Hz, 1H), 7.40 - 7.30 (m, 5H), 7.06 (d, J = 8.7 Hz, 1H), 6.76 - 6.71 (m, 1H), 6.52 (d, J = 8.2 Hz, 1H), 5.37 (d, J = 6.5 Hz, 1H), 5.16 (d, J = 12.3 Hz, 1H), 5.08 (d, J = 12.3 Hz, 1H), 4.44 (t, J = 6.6 Hz, 2H), 4.28 - 4.20 (m, 1H), 4.03 (t, J = 6.1 Hz, 1H), 3.34 (m, 1H), 3.21 (m, 1H), 2.31 - 2.12 (m, 4H), 1.02 (d, J = 6.8 Hz, 3H), 0.96 (t, J = 6.9 Hz, 6H), 0.85 (d, J = 6.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.68, 171.65, 171.43, 161.33, 156.94, 146.19, 135.92, 134.29, 130.70, 128.62, 128.57, 128.40, 127.96, 123.07, 120.71, 120.08, 118.16, 67.38, 61.32, 59.02, 47.49, 36.15, 30.39, 30.14, 29.80, 29.70, 19.48, 19.31, 17.88, 17.76.

HRMS-ESI+ *calc* for [M+Na^+]: 601.2738, found: 601.2745.

f) Synthesis of 1. II (58 mg, 0.1 mmol) was solubilized in 1 mL of DCM and a solution of benzene-1,2-diamine (5.42 mg, 0.05 mmol) in 0.5 mL of MeOH and $ZnCl_2$ (7.51 mg, 0.05 mmol) were added. Finally 14 µL of Et_3N were added and the reaction was stirred 3 hours at room temperature. Then, the reaction was transferred in an Eppendorf and centrifuged. The solvent was removed and the solid was washed with DCM and MeOH. Yield 40%.

^{1}H NMR (500 MHz, DMSO-d_6) δ 9.13 (s, 2H), 8.30 (s, 2H), 8.17 – 8.12 (m, 2H), 7.99 (d, *J* = 2.5 Hz, 2H), 7.96 (dd, *J* = 6.2, 3.5 Hz, 2H), 7.75 (d, *J* = 8.6 Hz, 2H), 7.68 (dd, *J* = 8.8, 2.5 Hz, 2H), 7.42 (dd, *J* = 6.2, 3.5 Hz, 2H), 7.40 – 7.29 (m, 12H), 6.81 (d, *J* = 8.8 Hz, 2H), 5.04 (s, 4H), 4.40 (m, 4H), 4.13 – 4.09 (m, 2H), 3.93 (dd, *J* = 9.0, 7.0 Hz, 2H), 3.12 (m, 4H), 1.98 (m, 8H), 0.95 – 0.80 (m, 24H).

^{13}C NMR (125 MHz, DMSO) δ 172.55, 171.53, 171.37, 163.34, 156.55, 147.15, 139.84, 137.53, 133.07, 132.37, 128.77, 128.20, 128.08, 128.04, 127.95, 124.04, 119.76, 119.64, 117.11, 116.45, 65.82, 60.78, 58.41, 47.58, 36.16, 30.98, 30.67, 30.26, 19.68, 18.84, 18.63.

HRMS-MALDI+ *calc* for [M+Na^+]: 1313.5209; found: 1313.5223

2. NMR Spectra

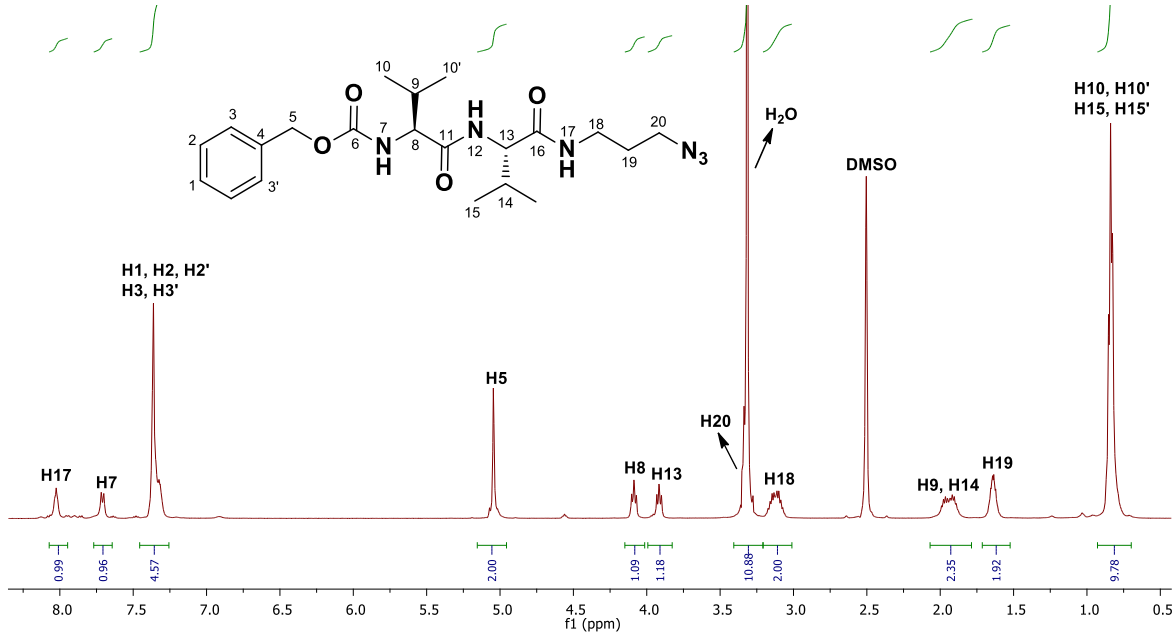


Figure S1. ^{1}H NMR (303 K, 300 MHz, DMSO-d_6) of compound **Z-Val-Val-N$_3$**.

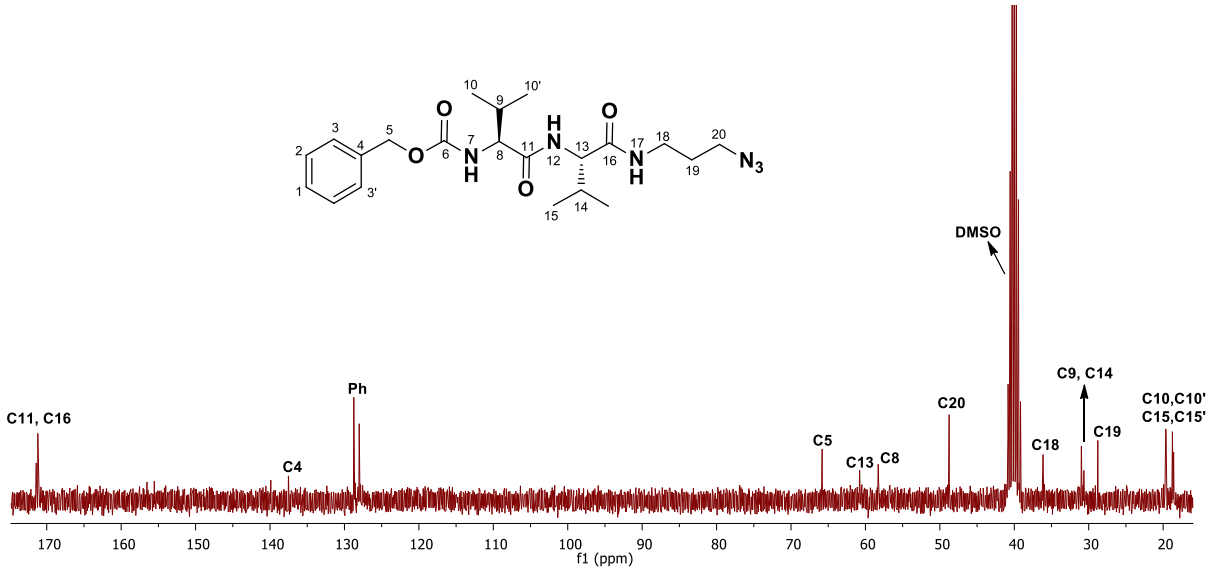


Figure S2. ^{13}C NMR (303 K, 75 MHz, DMSO) of compound **Z-Val-Val-N$_3$**.

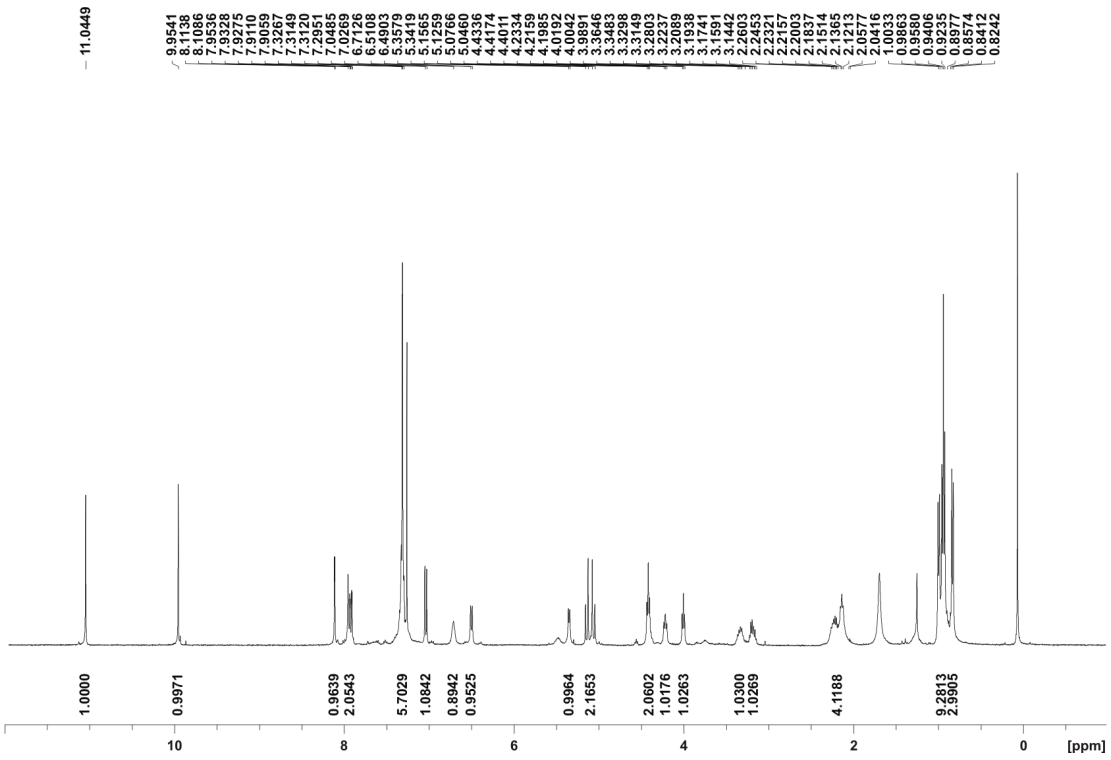


Figure S3. ^{1}H NMR (298 K, 400 MHz, $CDCl_3$) of compound **II**.

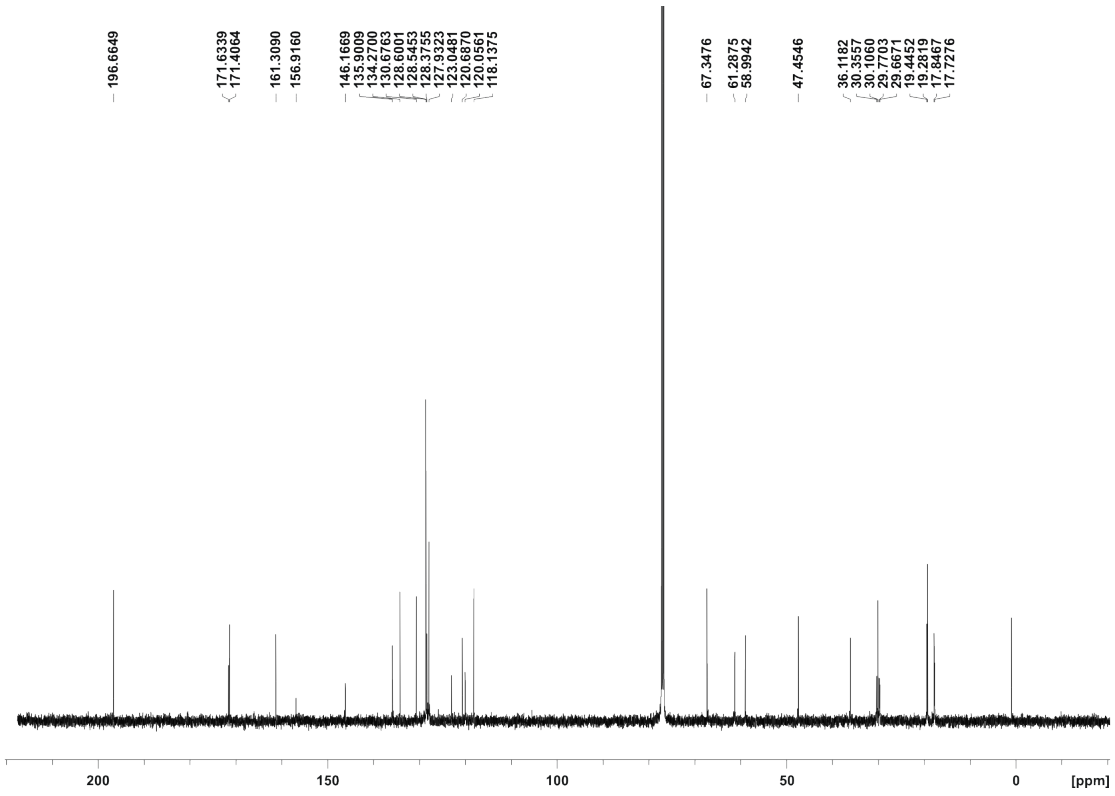


Figure S4. ^{13}C NMR (298 K, 126 MHz, $CDCl_3$) of compound **II**.

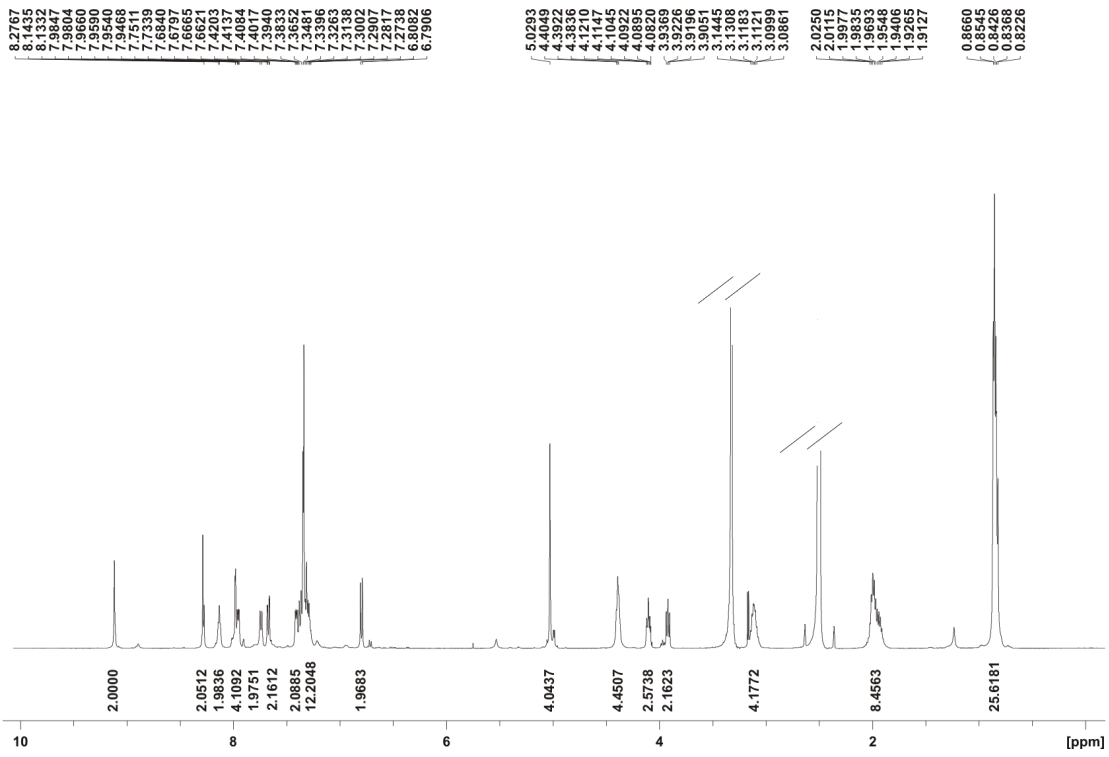


Figure S5. ^{1}H NMR (298 K, 500 MHz, DMSO-d_6) of compound **1**.

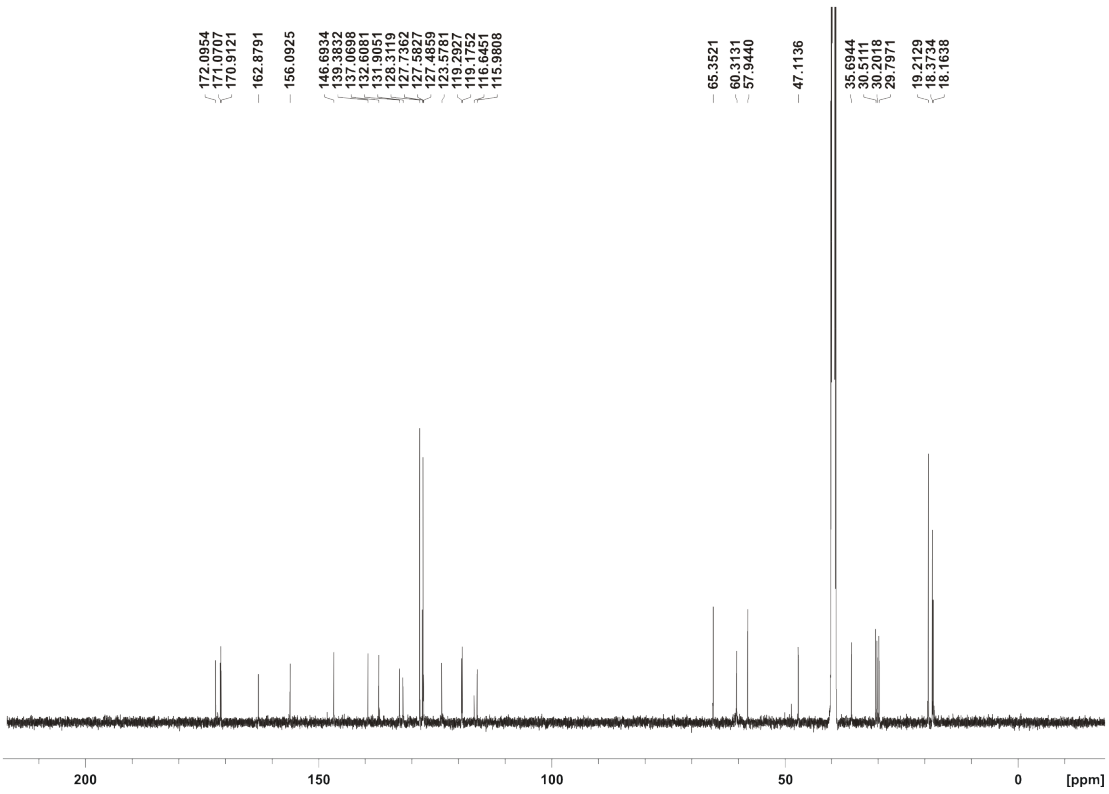


Figure S6. ^{13}C NMR (298 K, 125 MHz, DMSO) of compound **1**.

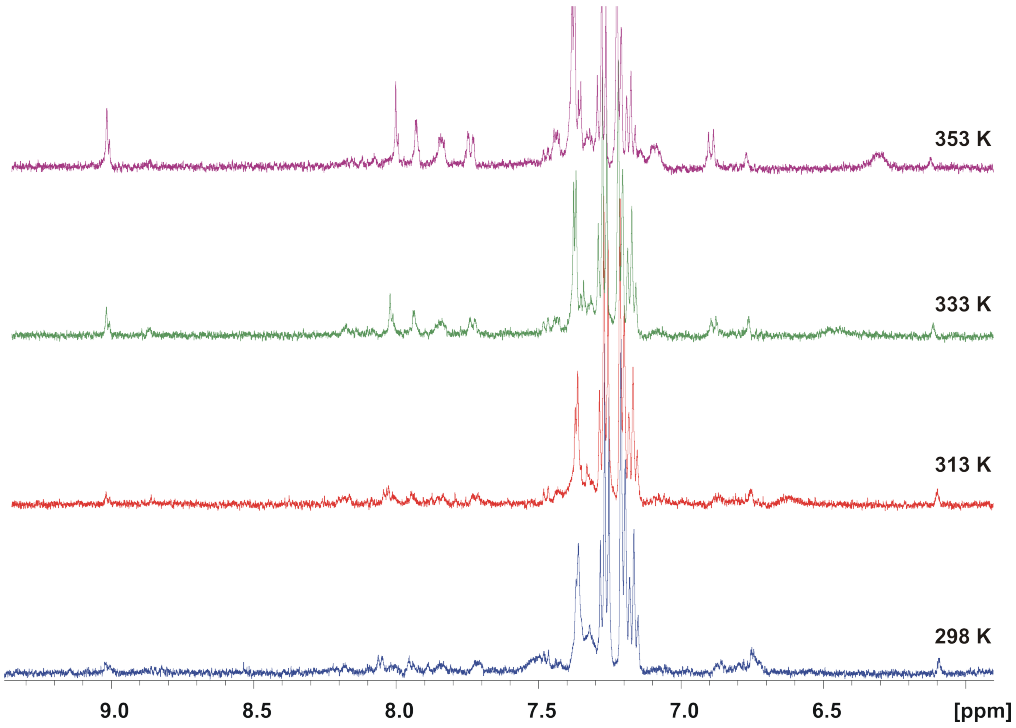


Figure S7. Variable temperature ^{1}H-NMR (500 MHz) experiments. Spectra: [**1**] = 4 mg/mL, solvent ACN-d_3/DMSO-d_6 5:1.

3. Mass Spectra

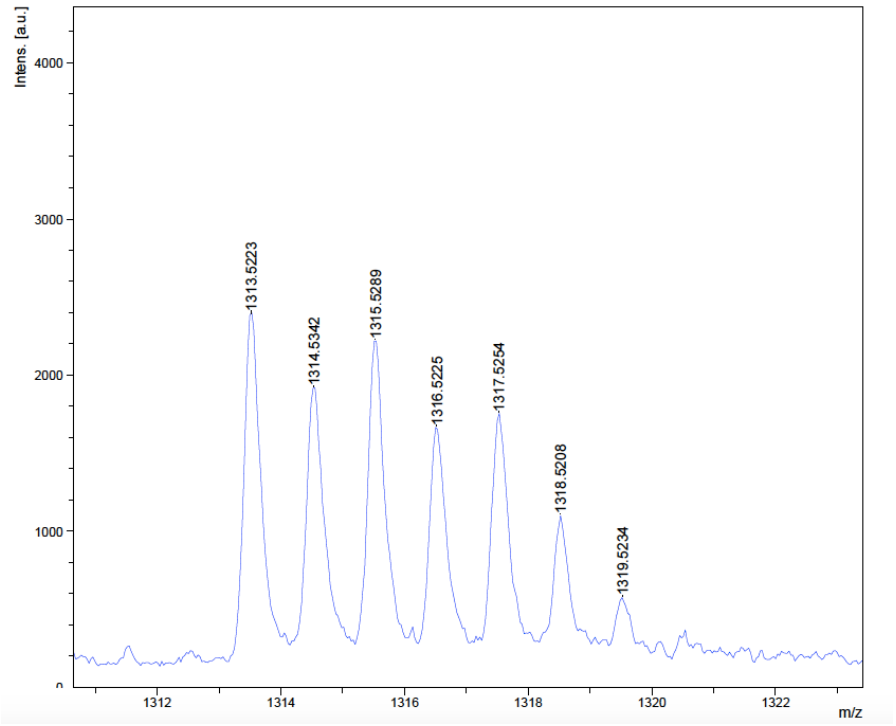


Figure S8. HRMS-MALDI+ of compound **1**, *calc* for [M+Na$^+$]: 1313,5209; found: 1313,5223 (1ppm).

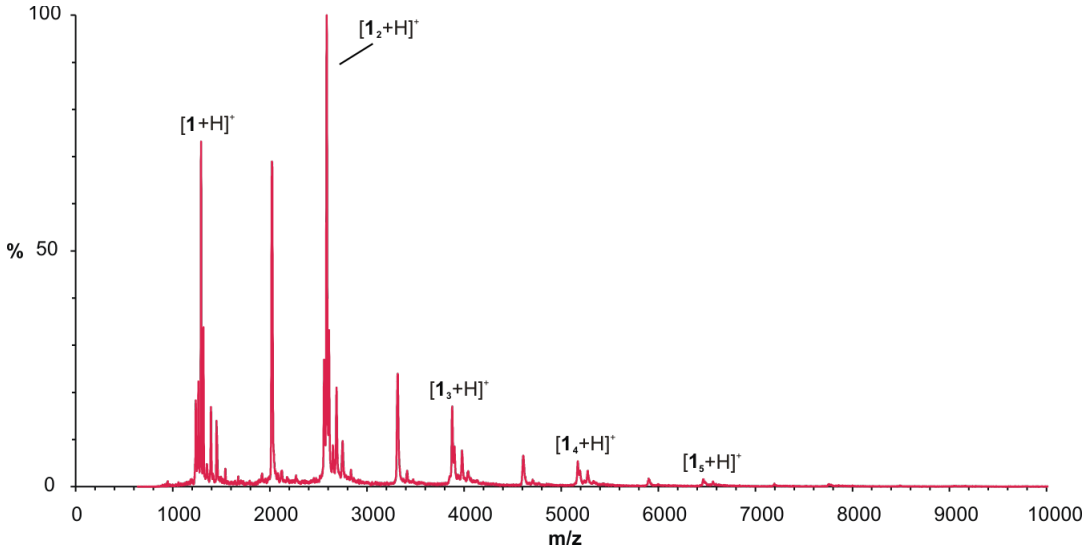


Figure S9. MALDI spectrum of compound **1** and aggregates.

4. Dynamic light scattering experiments

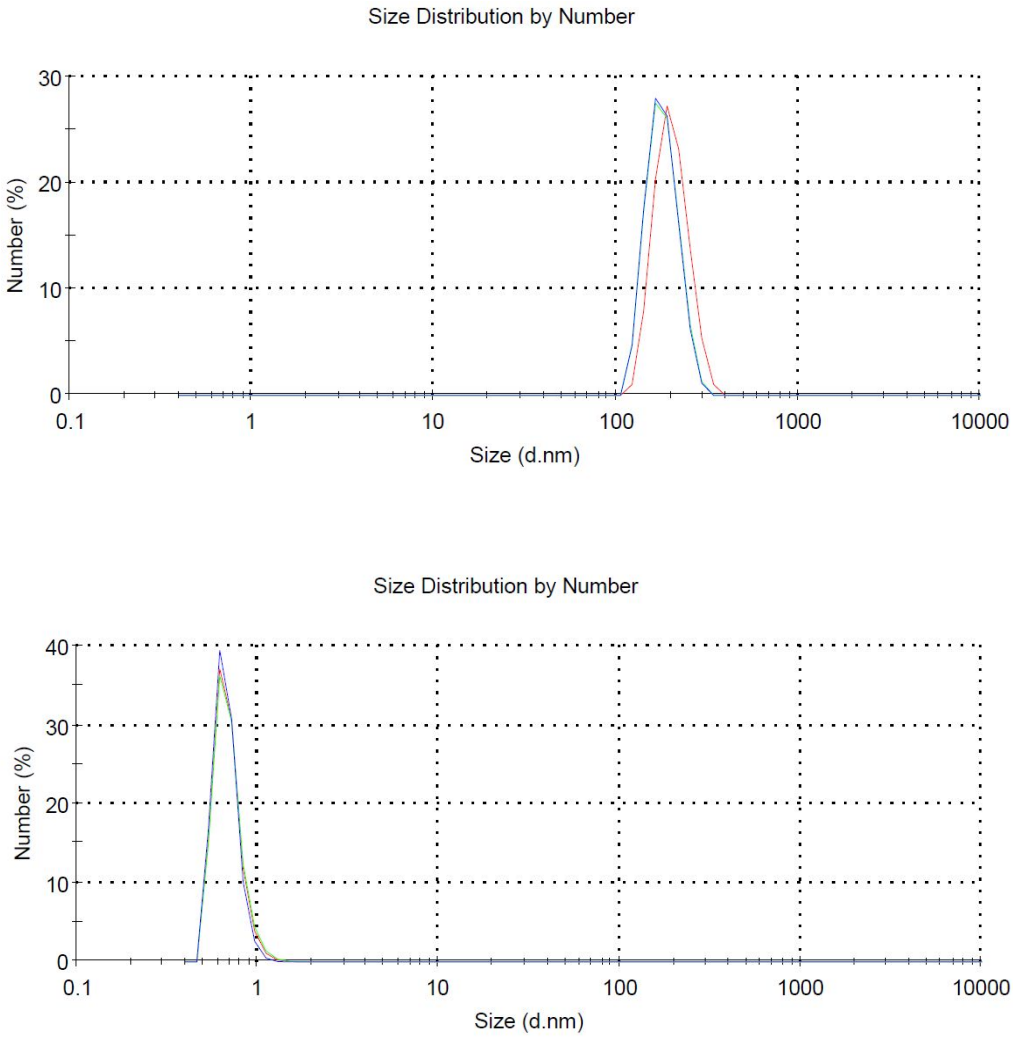


Figure S10. Dynamic light scattering (DLS) analysis of **1** in acetonitrile (top) and acetonitrile + 20% of DMSO (bottom).