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Supporting Information

Domain Swapping in Abiotic Foldamers

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Table of contents

1. List of Abbreviations

CD	circular dichroism
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DIPEA	*N*,*N*-diisopropylethylamine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DOSY	diffusion ordered spectroscopy
HR-ESI	high resolution electrospray ionization
eq.	equivalent
Fmoc	fluorenylmethoxycarbonyl
HBTU	2-(1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HSQC	heteronuclear single quantum correlation
Me	methyl
MeOH	methanol
min	minutes
MS	mass spectrometry
MW	microwave
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
r. t.	room temperature
SPS	solid phase synthesis
***t*Bu**	*tert*-butyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
UV/Vis	ultraviolet–visible

2. Supplementary figures

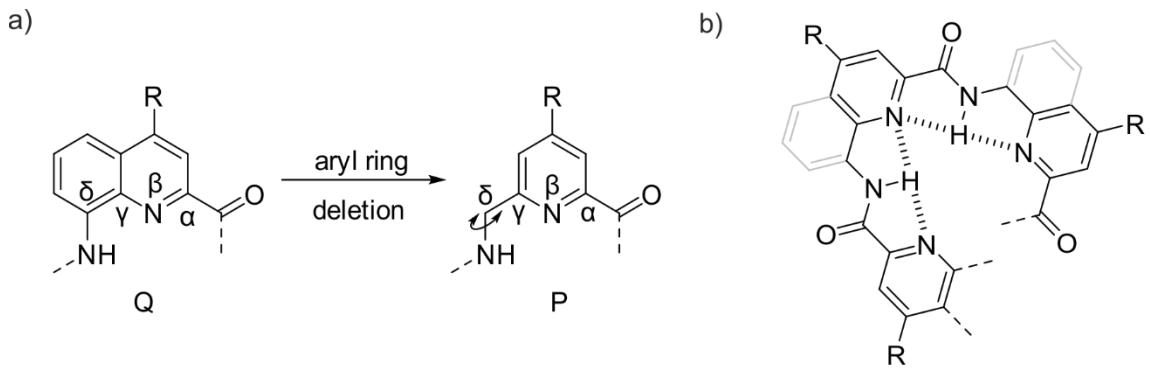


Figure S1. Chemical structure of Q and P units and the folding principle of their oligomers. a) Chemical structure of Q (or X with R = OH) and P (or Y with R = OH). b) Intramolecular H-bonding and helical folding principle of P/Q oligomers. Note that the amide carbonyl groups diverge from the folded structures and thus provide hydrogen bond acceptors.

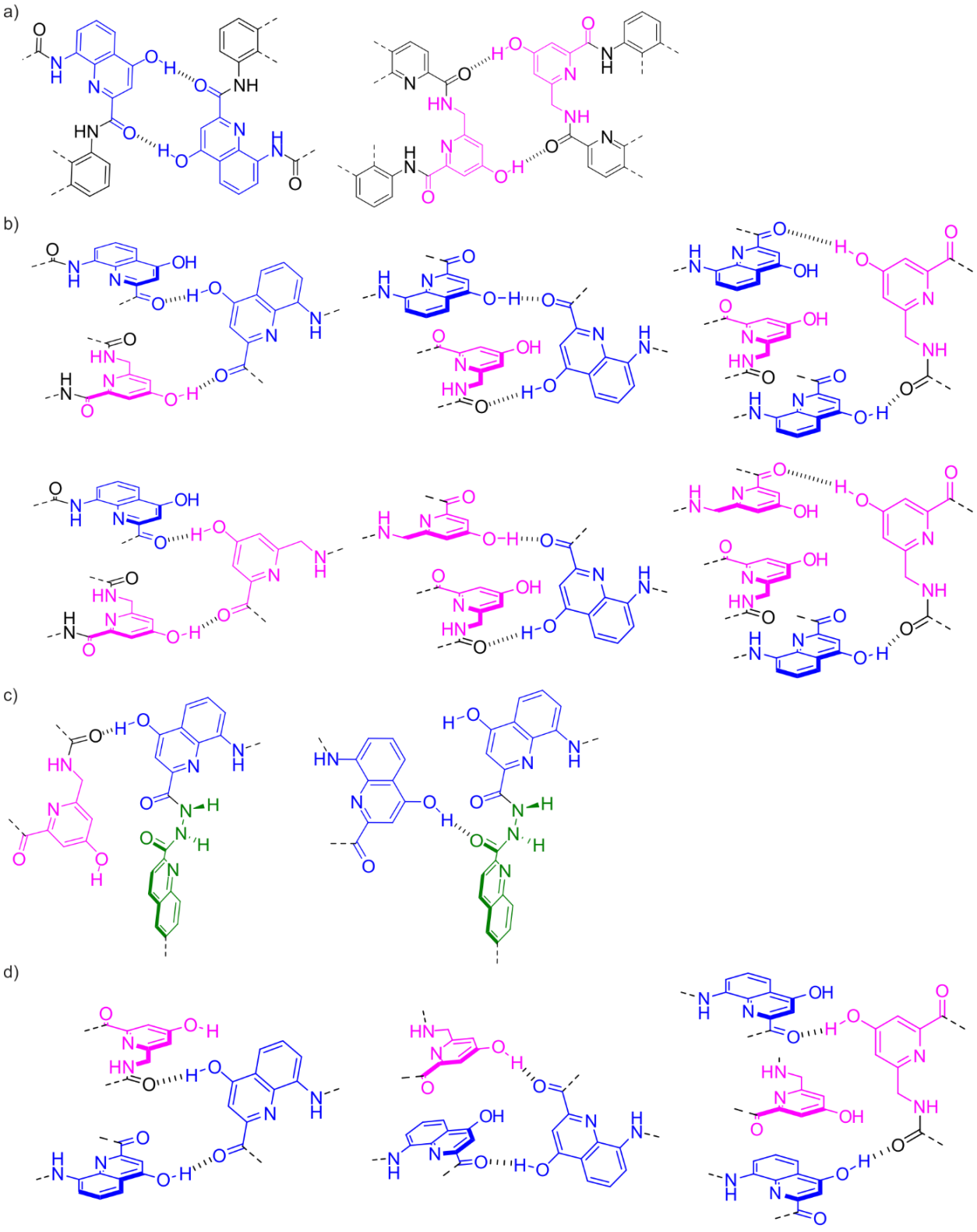


Figure S2. H-bonding patterns involving X and Y units: a) as observed in the helix-turn-helix structure of **1**;[21] b) and c) as observed in the solid state structure of (**3b**)$_2$; d) as observed in clockwise tilted-dimer interfaces.[20]

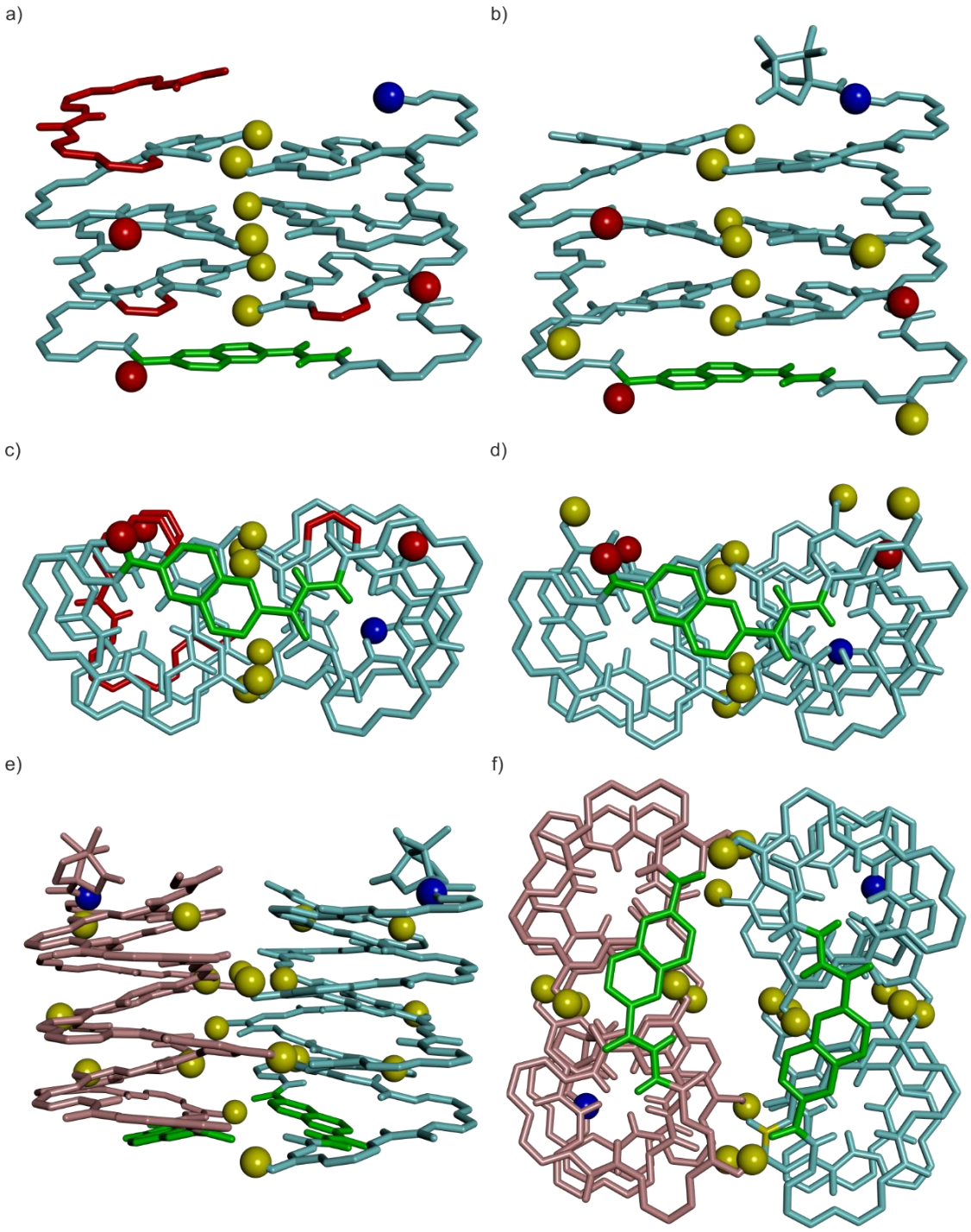


Figure S3. Energy minimized models of dimerized helix-T2-helix structure. The side view (a) and bottom view (c) of the crystal structure of **1**.[21] Parts shown as red tubes highlight aromatic rings that were removed to prevent steric hindrance in the design of **2b** and **3b**. The side view (b) and bottom view (d) of an energy-minimized model of monomeric **2b** in the same (hypothetical) conformation as **1**. The red balls represent H-bond acceptors intended for intermolecular interactions. The yellow balls represent H-bond donors. The side (e) and bottom (f) views of an energy-minimized model of dimerized **2b** maintaining the helix-T2-helix structure of **1**. The T2 linkers are colored in green. The N-termini are shown as blue balls. For clarity, only the outer rim of the helical backbone is shown in tube representation. Side chains of Q and T2 are omitted.

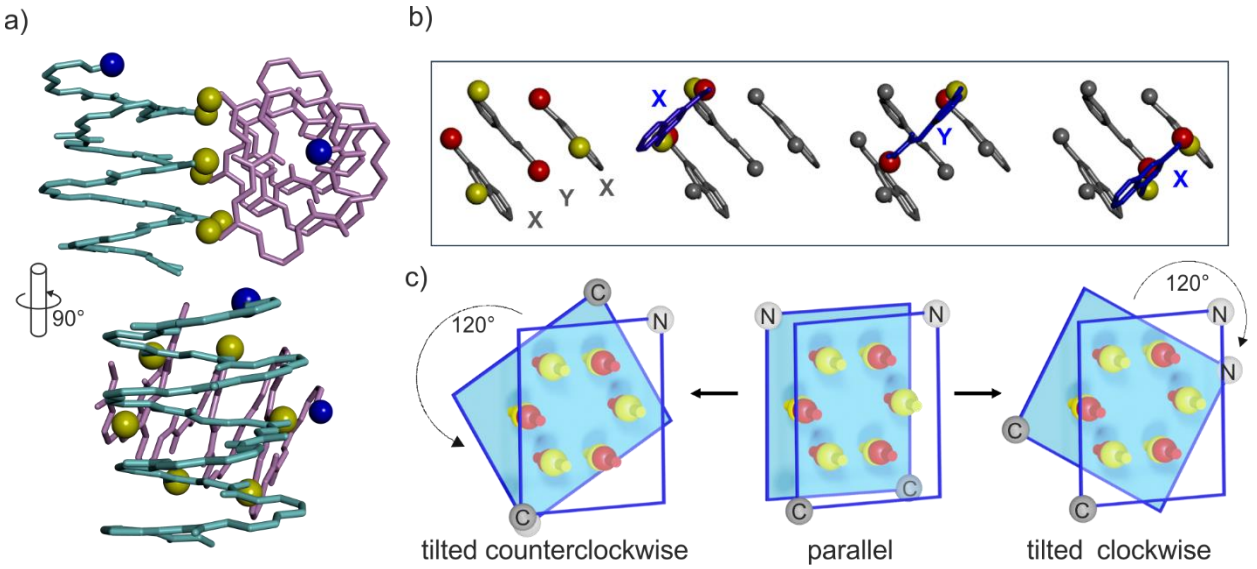


Figure S4. Crystal structure of a clockwise tilted dimer.[20] a) Two views of a clockwise tilted dimer as seen in the crystal. Yellow balls represent the hydrogen bond donors involved in helix-helix interactions. Blue balls highlight the N-terminus of the helix. For clarity, only the outer rim of the helical backbone is shown in tube representation. Side chains are omitted. b) Views of the H-bond patterns of the structure shown in a). c) Schematic representations in stacked view of a hydrogen-bonded parallel head-to-head arrangement and of the related clockwise and counter-clockwise tilted dimers. The top plane is transparent so that one can see the six hydrogen bonds (knobs into cups) and the plane behind.

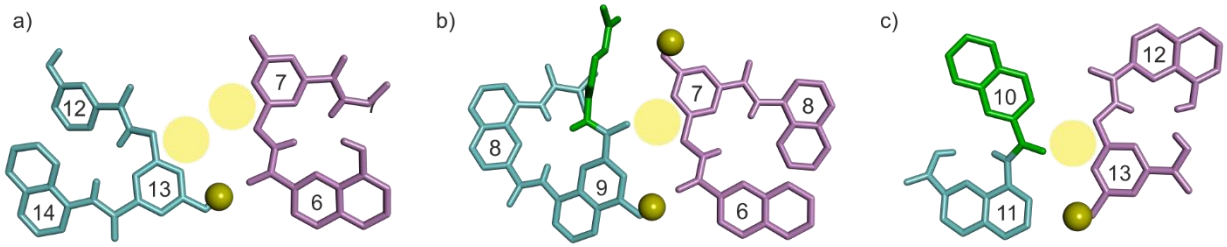


Figure S5. The steric clash avoided by X7Y and Q13Y mutations in the DSD structure. Removing the benzenic rings of the monomers at positions 7 and 13, *i.e.* X7Y and the Q13Y mutations, were intended to prevent steric clashes that could occur in the initially modelled dimerized helix-turn-helix as shown in (a). The crystal structure of the DSD in fact shows that the X7Y (b) and Q13Y (c) mutations also avoid steric clashes in the observed DSD structure.

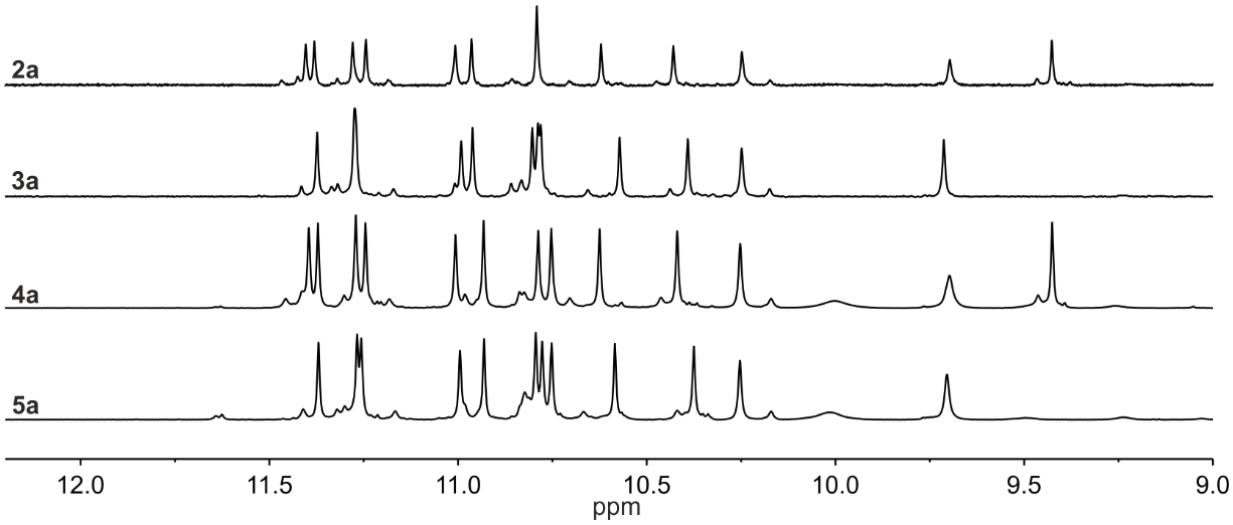


Figure S6. **^{1}H NMR spectra of hydroxy-group-protected precursors.** Extracts of the ^{1}H NMR spectra (500 MHz, $CDCl_3$, 25 °C) of **2a**, **3a**, **4a** and **5a**. A major and a minor species coexist in all cases corresponding to two different conformers.

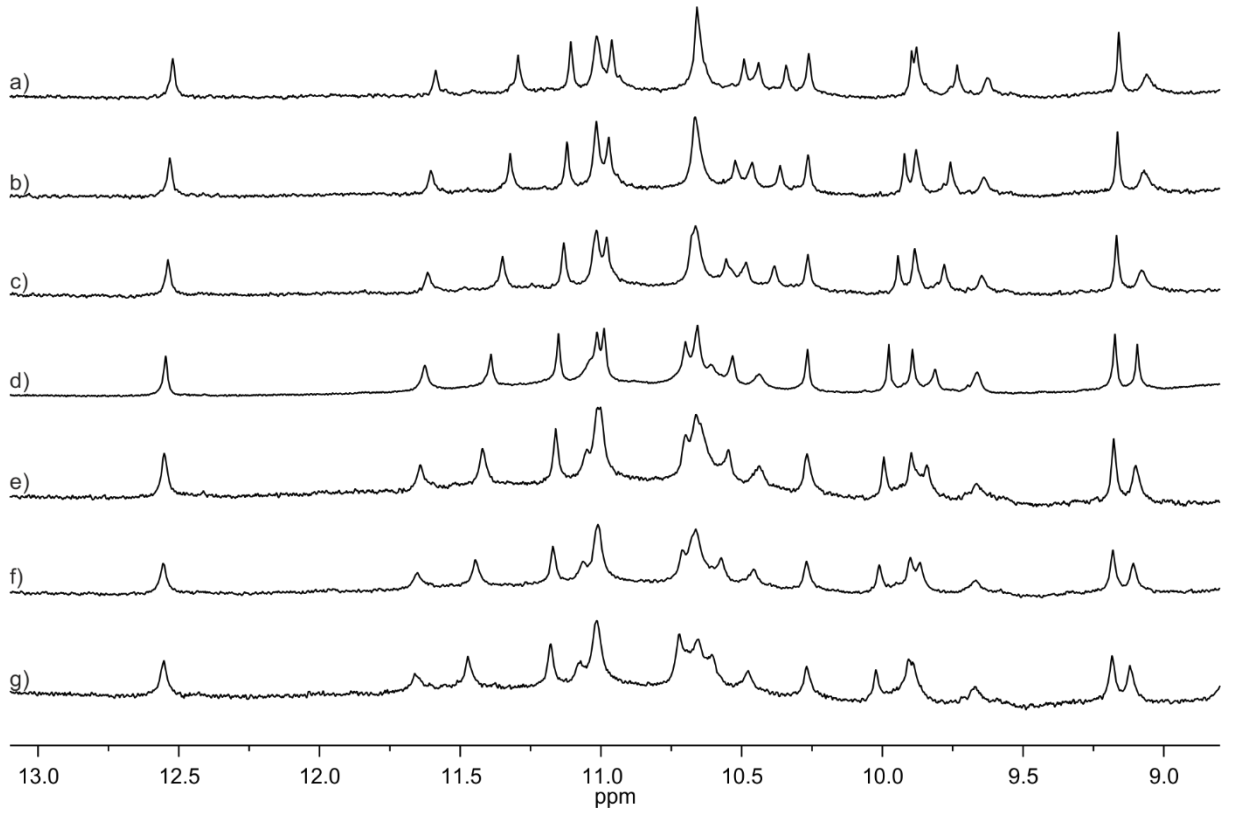


Figure S7. ^{1}H NMR spectra of 2b at different temperatures. Extracts of the ^{1}H NMR spectra (400 MHz, $CDCl_3$) of **2b** at 328 K (a), 318 K (b), 308 K (c), 298 K (d), 283 K (e), 273 K (f) and 263 K (g).

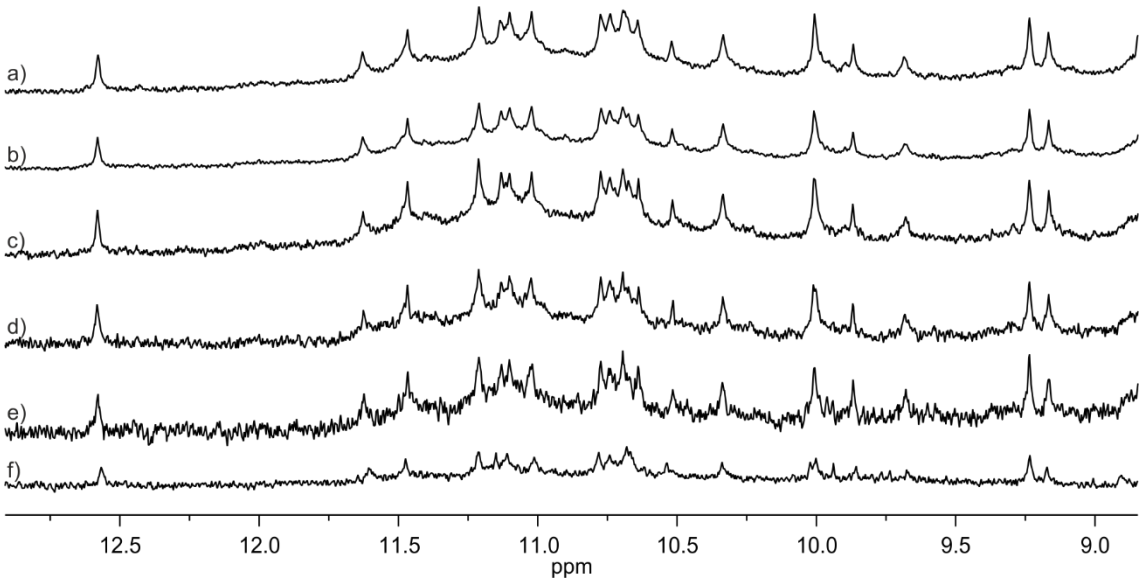


Figure S8. ^{1}H NMR spectra of 2b at different concentrations. Extracts of the ^{1}H NMR spectra (500 MHz, $CDCl_3$, 25 °C) of **2b** at 1.0 mM (a), 0.5 mM (b), 0.25 mM (c), 0.1 mM (d), 0.05 mM (e) and 0.02 mM (f).

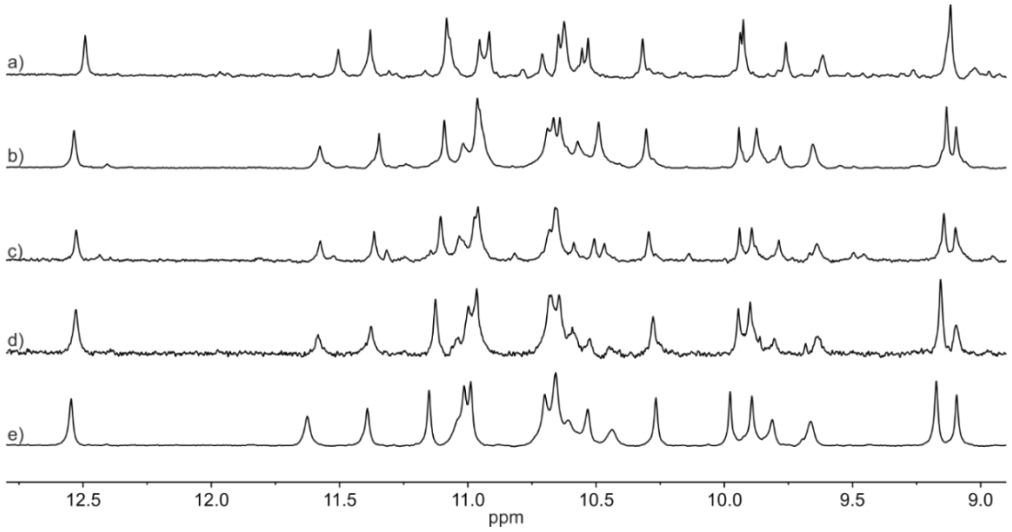


Figure S9. ^{1}H NMR spectra of 2b in varying $CDCl_3$/CD_2Cl_2 mixtures. Extracts of the ^{1}H NMR spectra (500 MHz, 25 °C) of **2b** in $CDCl_3$/CD_2Cl_2 mixtures showing the amide and hydroxy proton resonances. The vol% of CD_2Cl_2 are 100 (a), 75 (b), 50 (c), 25 (d), and 0 (e). With other sequences, aggregation behaviour or conformation has been observed to change radically between $CDCl_3$ and CD_2Cl_2. [20,30]

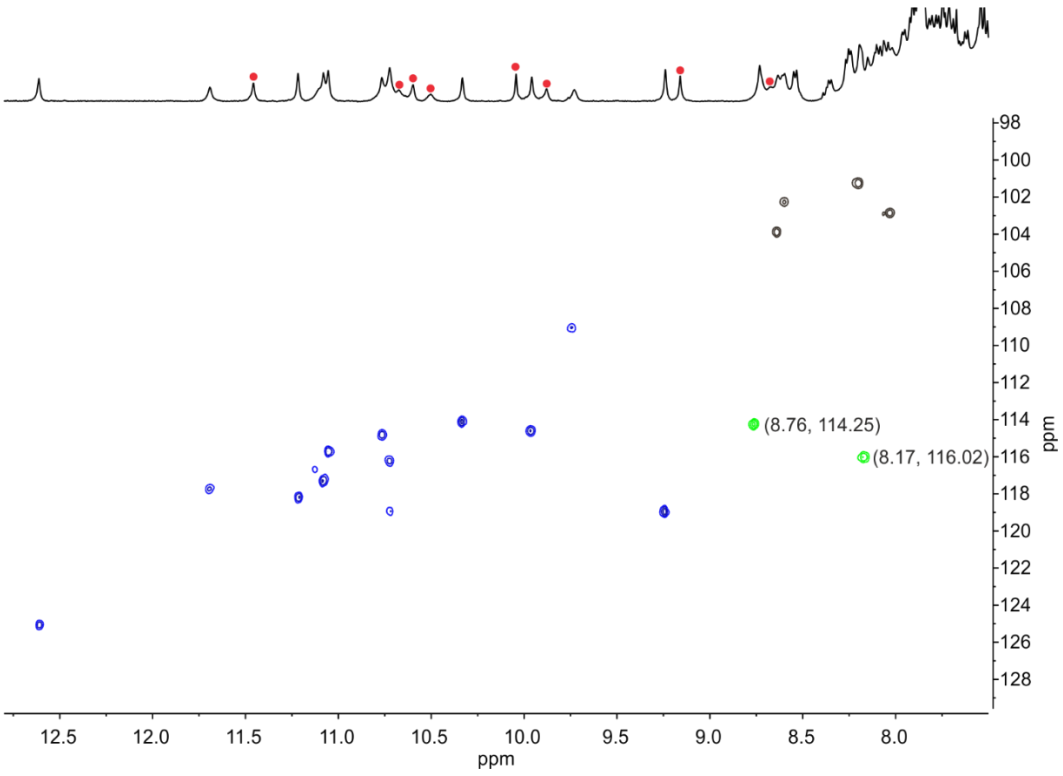


Figure S10. **Identification of the signals of hydrogen-bonded OH protons of 2b in $CDCl_3$.** Extract of the $^{1}H^{15}N$ HSQC NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of **2b**. Only NH resonances correlate, red dots indicate the signals of H-bonded O<u>H</u> protons. The grey correlations are assigned to NH signals of the pyridine-based (Y) monomers. The green correlations are assigned to the NH-NH signals of T2 unit.

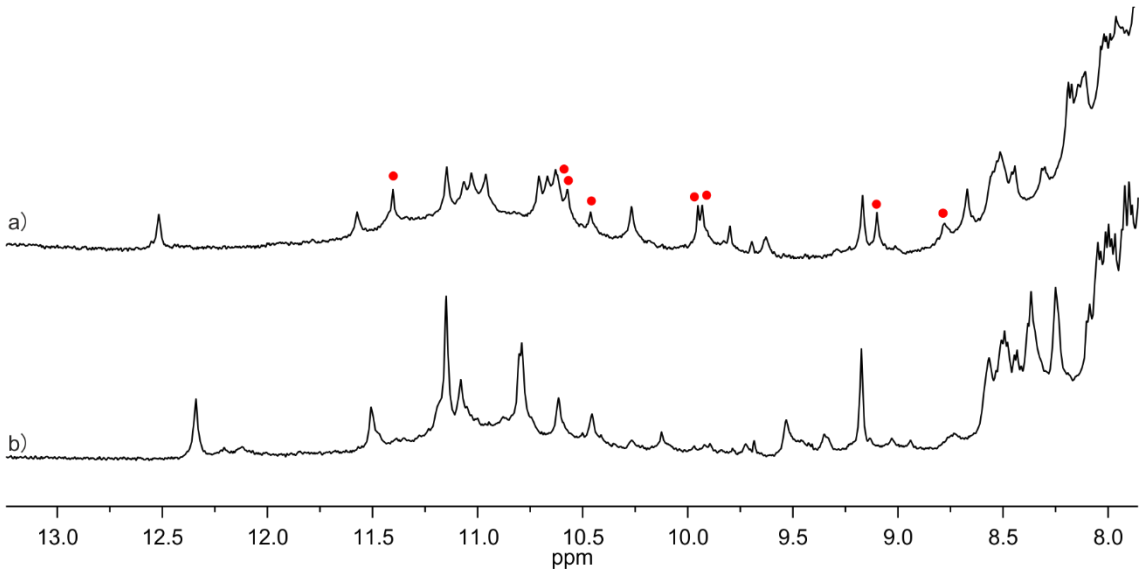


Figure S11 Deuterium exchange experiment of 2b. a) Extract of the ^{1}H NMR of **2b** (500 MHz, $CDCl_3$, 25 °C). The signals assigned to OH protons are marked with a red dot. b) Extract of the ^{1}H NMR of **2b** (500 MHz, 5% $CD_3OD/CDCl_3$, 25 °C).

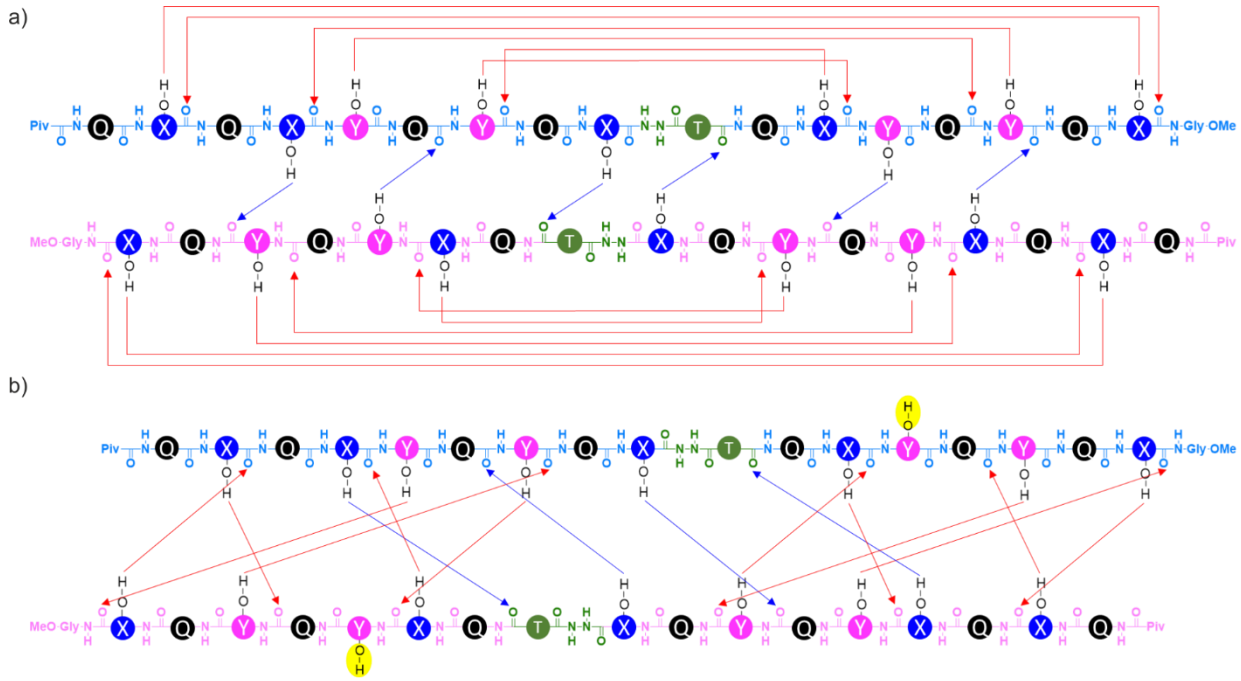


Figure S12. Hydrogen bonding patterns: a) in the initially designed dimer of **3b** based on the structure of **1** (see Figure S3 e, f). Red and blue arrows indicate intramolecular and intermolecular H-bonds, respectively. b) in the crystal structure of (**3b**)$_2$. Red and blue arrows involve the same H-bond donors as in a). Two orphan H-bond donors are highlighted in yellow.

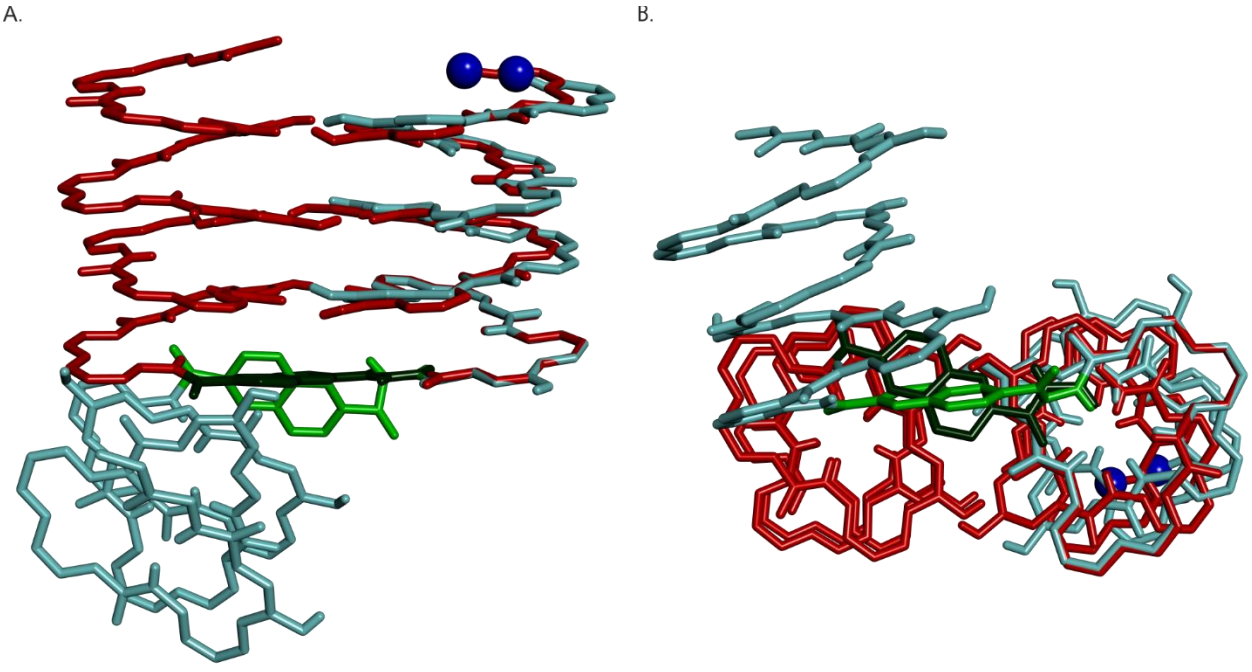


Figure S13. Overlay of the structures of 1 and 3b in the solid state. Compound **1** is shown in red tube representation with a dark green T2 linker. Compound **3b** is shown in light blue tube representation with a light green T2 linker. The N-termini are shown as blue balls. Only the outer rim of the helical backbone is shown in tube representation. Side chains are omitted for clarity.

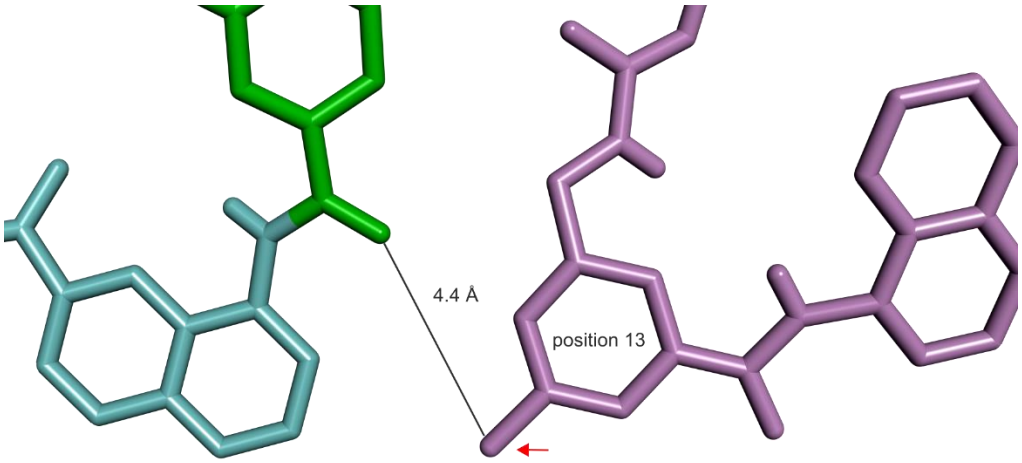


Figure S14. Orphan OH proton in the solid state structure of $(3b)_2$. The distance between the hydroxy group of unit 13 and the nearest carbonyl group is 4.4 Å, which is too far for H-bonding.

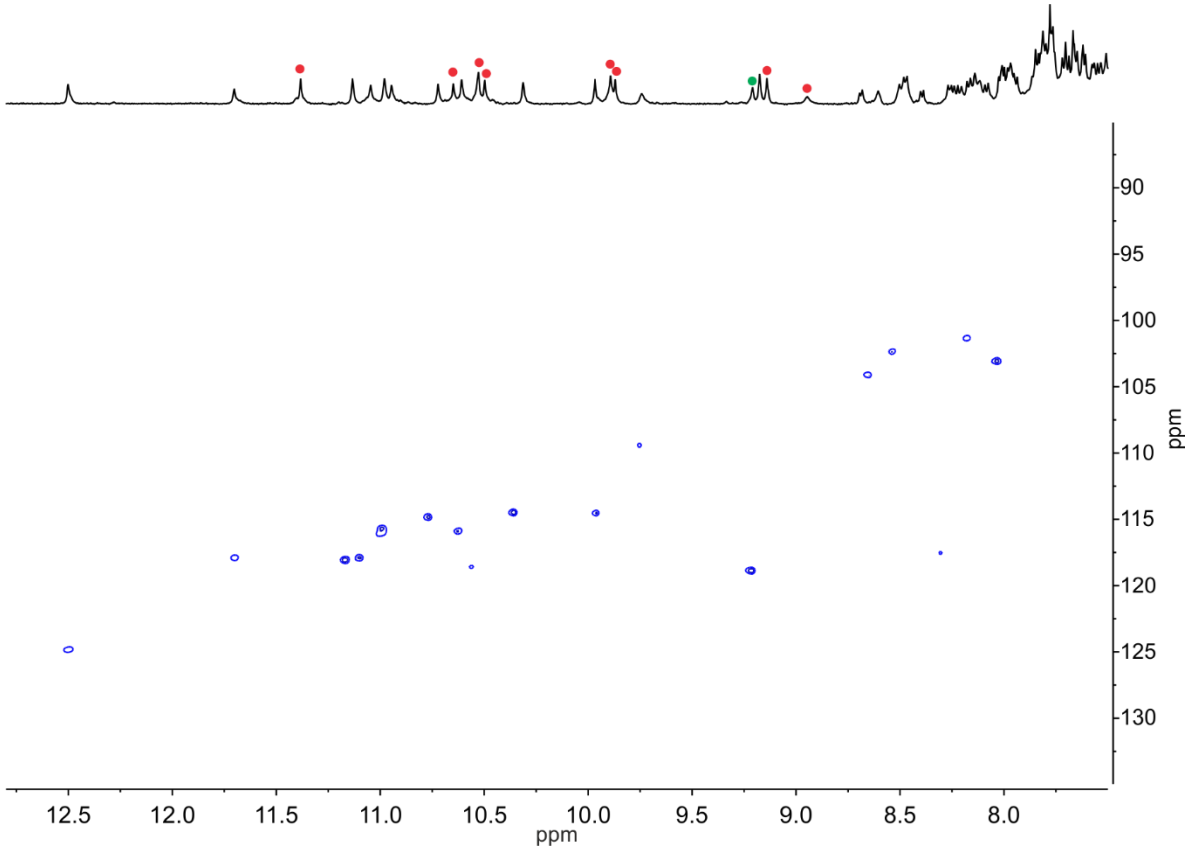


Figure S15. **Identification of free OH that is hydrogen-bonded to DMSO.** Extract of the $^{1}H^{15}N$ HSQC NMR spectrum (500 MHz, in 4% DMSO-d_6/$CDCl_3$, 25 °C) of **2b**. Only NH resonances correlate. Red dots on the ^{1}H trace assign the signals of O<u>H</u> protons hydrogen bonded to carbonyl groups found at similar chemical shift values in the absence of DMSO-d_6. The green dot indicates an O<u>H</u> resonance not visible in this region in the absence of DMSO-d_6 that may be assigned to the O<u>H</u> of Y13.

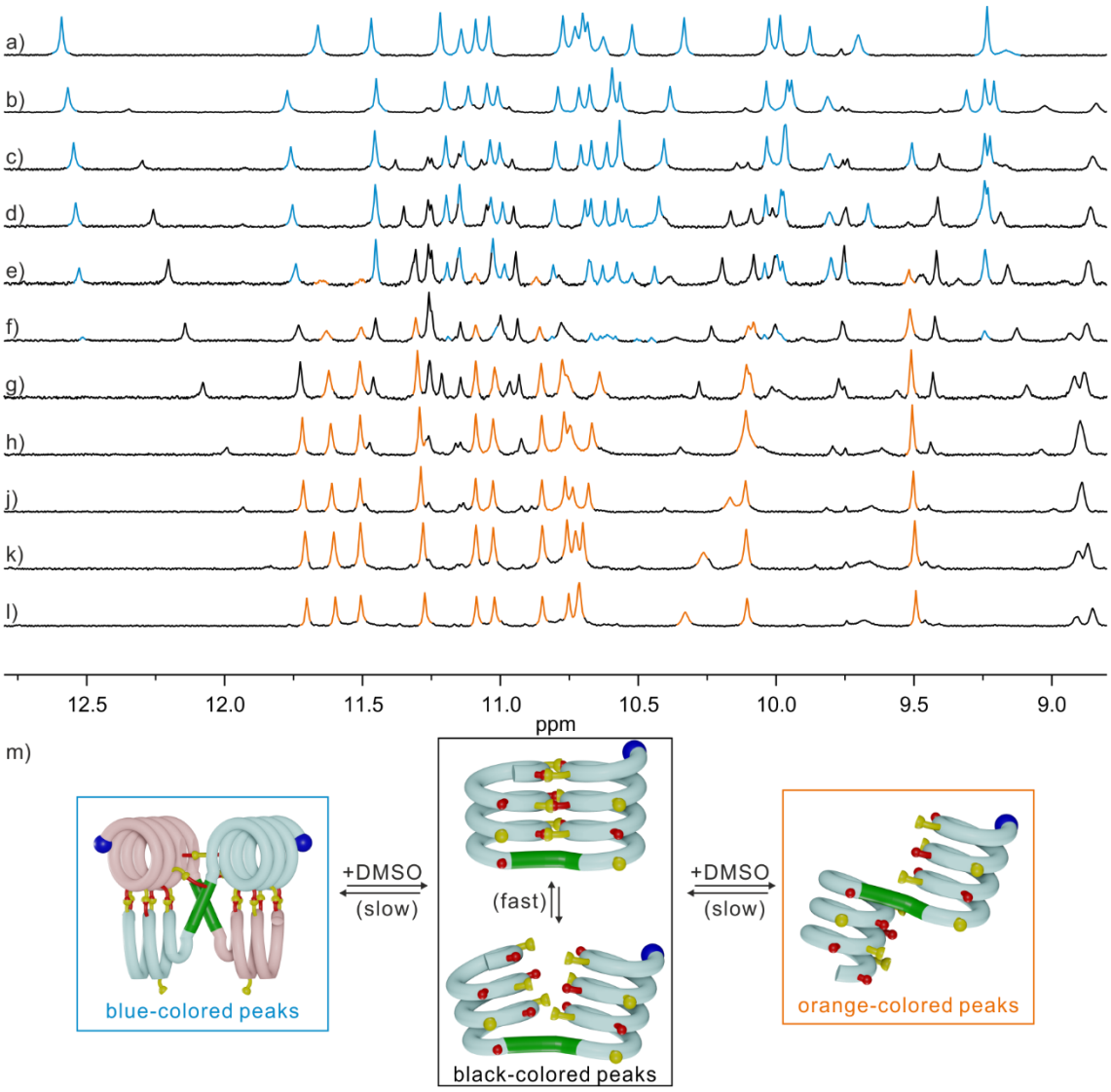


Figure S16. ^{1}H NMR observation of the DMSO-induced dissociation of $(2b)_2$. Extracts of the ^{1}H NMR spectra (500 MHz, 25 °C) showing amide resonances of **2b** in $CDCl_3$/DMSO-d_6 mixture. The vol% of DMSO-d_6 are 0 (a), 4 (b), 6 (c), 8 (d), 10 (e), 12 (f), 14 (g), 16 (h), 18 (j), 20 (k) and 22 (l), respectively. The signals of DSD, helix-T2-helix tertiary structure (*P*-T2-*M*) and disrupted helix-T2-helix tertiary structure (*P*-T2-*P*) are colored in light blue, black and orange, respectively. m) Schematic representation of changes induced by the addition of DMSO to a solution of DSD.

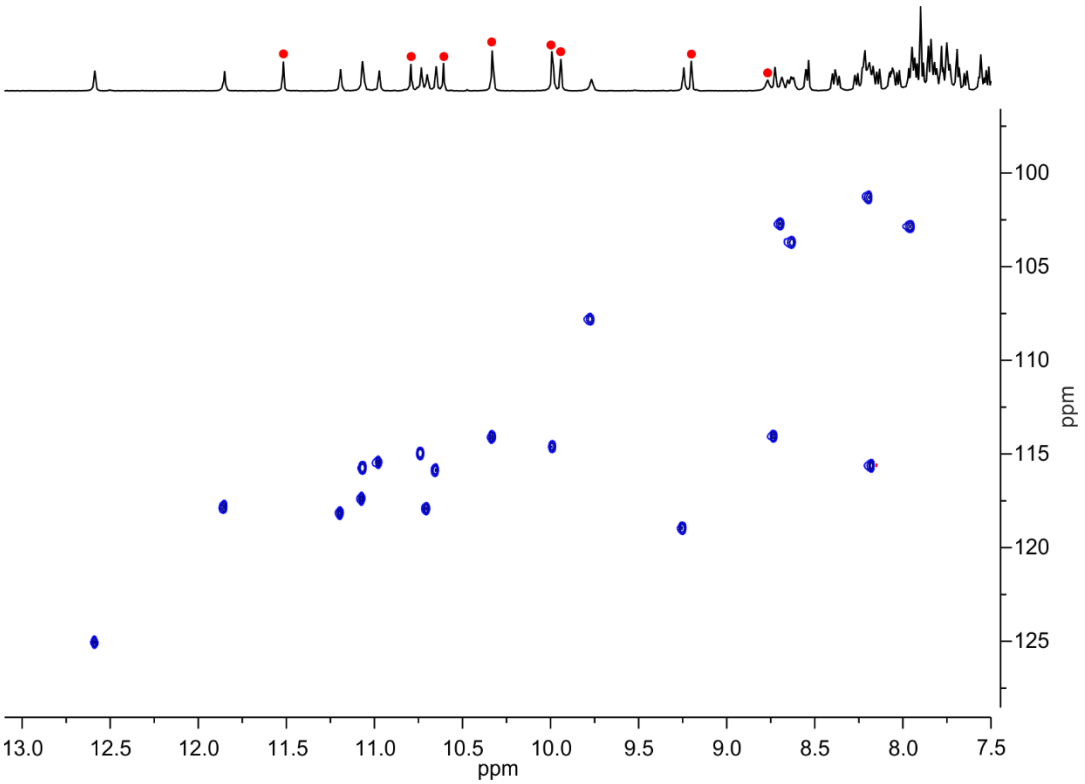


Figure S17. **Identification of the signals of hydrogen-bonded OH protons of 4b in $CDCl_3$.** Extract of the $^{1}H^{15}N$ HSQC NMR spectrum of **4b** (500 MHz, $CDCl_3$, 25 °C). Only NH resonances correlate, red dots indicate the signals of H-bonded O<u>H</u> protons.

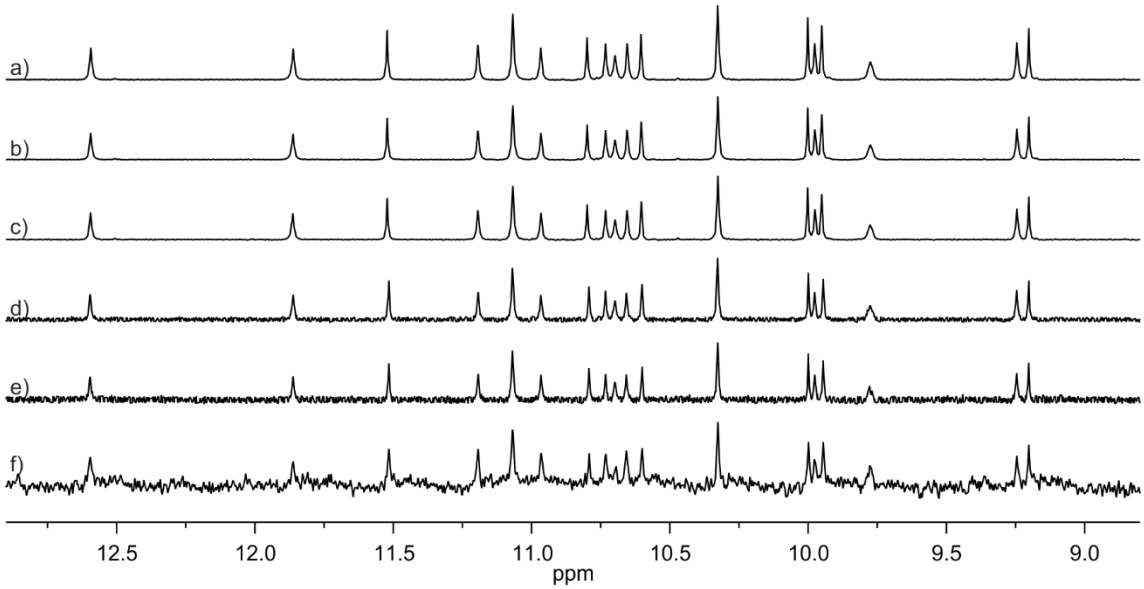


Figure S18. ^{1}H NMR spectra of 4b at different concentrations. a) Extracts of the ^{1}H NMR spectra of **4b** (500 MHz, $CDCl_3$, 25 °C) at 0.8 mM (a), 0.5 mM (b), 0.25 mM (c), 0.1 mM (d), 0.05 mM (e) and 0.02 mM (f).

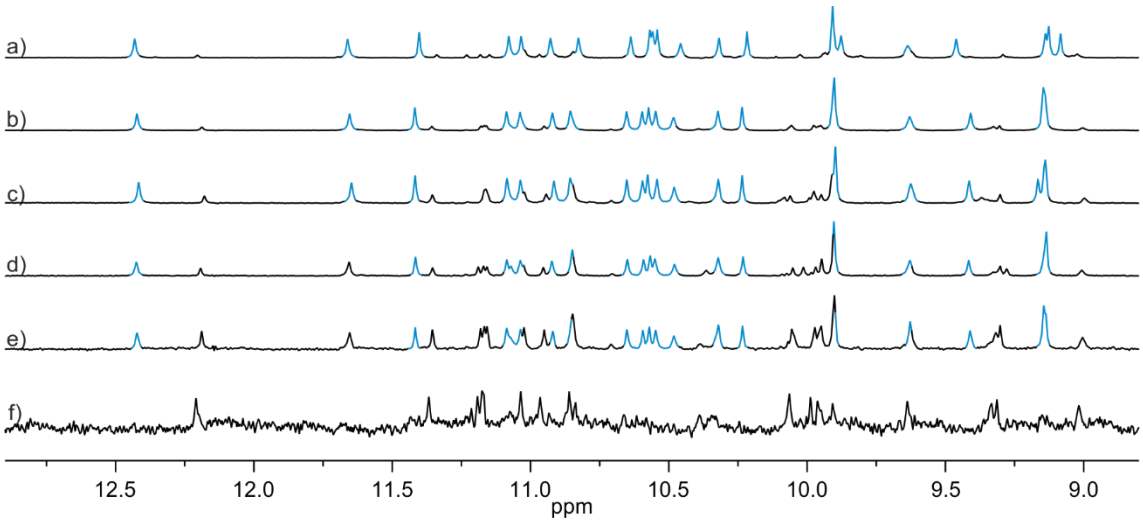


Figure S19. ^{1}H NMR spectra of 4b in 6% DMSO-d_6/$CDCl_3$ at different concentrations. a) Extracts of the ^{1}H NMR spectra of **4b** (500 MHz, 6% DMSO-d_6/$CDCl_3$, 25 °C) at 0.8 mM (a), 0.5 mM (b), 0.25 mM (c), 0.1 mM (d), 0.05 mM (e) and 0.02 mM (f).

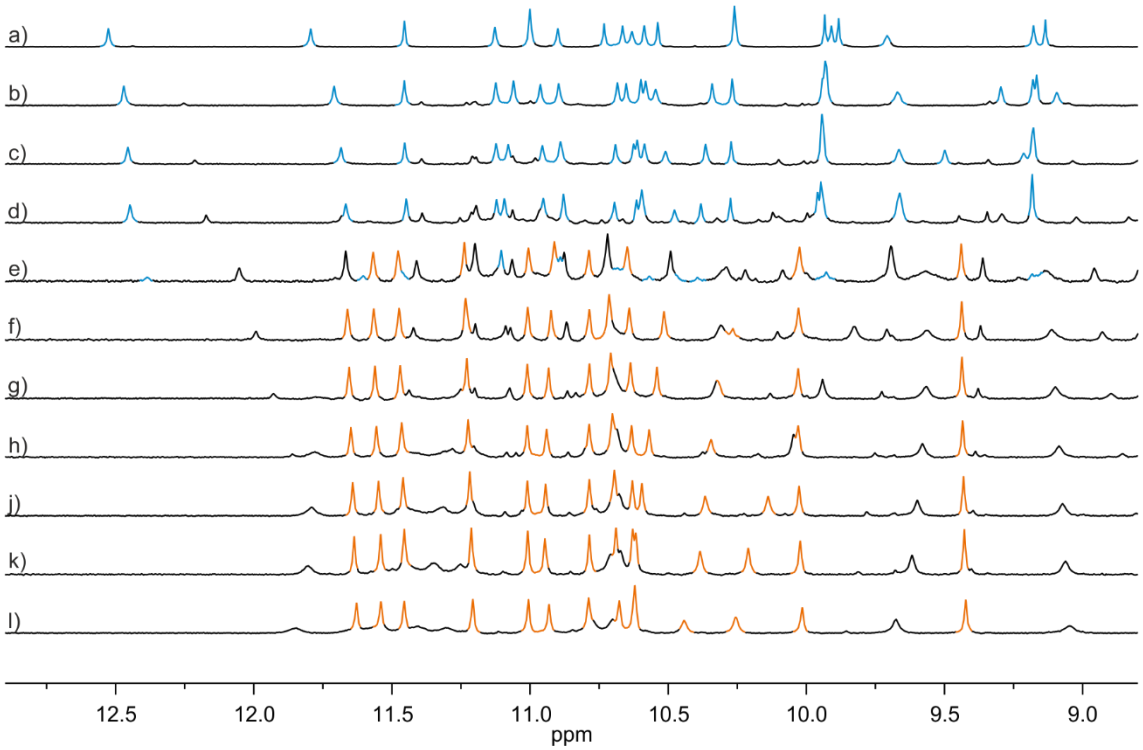


Figure S20. ^{1}H NMR observation of the DMSO-induced dissociation of $(4b)_2$. Extracts of the ^{1}H NMR spectra (500 MHz, 25 °C) showing amide resonances of **4b** in $CDCl_3$/DMSO-d_6 mixture. The vol% of DMSO-d_6 are 0 (a), 4 (b), 6 (c), 8 (d), 10 (e), 12 (f), 14 (g), 16 (h), 18 (j), 20 (k) and 22 (l), respectively. The signals of DSD, helix-T2-helix tertiary structure (*P*-T2-*M*) and disrupted helix-T2-helix tertiary structure (*P*-T2-*P*) are colored in light blue, black and orange, respectively.

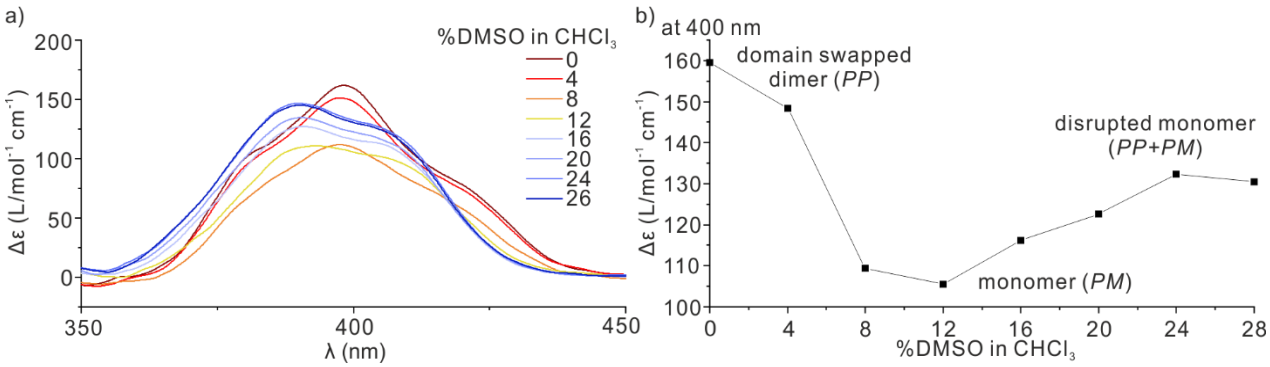


Figure S21. **CD spectra observation of the DMSO-induced dissociation of $(4b)_2$.** a) The CD spectra of **4b**, 0.1 mM in $CHCl_3$ with different proportions of DMSO. b) The Δε values at 400 nm extracted from a) as a function of the vol% of DMSO in $CHCl_3$.

3. Supplementary methods

3.1 LC-MS analyses

LC-MS spectra were recorded on a Bruker microTOF II in positive ionization mode. The instrument was calibrated in positive mode by direct infusion of a calibration solution (Agilent Technologies ESI-L Low Concentration Tuning Mix). The HPLC line was an Ultimate 3000 RP-HPLC system (ThermoFisher Scientific) equipped with a Aeris™ Widepore C4 column (2.1 x 150 mm, 3.6 µm) at a flow rate of 0.25 mL/min. 0.1 % formic acid and 0.025% TFA was added to the aqueous mobile phase (solvent A) and to acetonitrile (solvent B). The gradient is: 0-5 min, 50% to 100% solvent B; 5-14 min, 100% solvent B at 50°C. The column eluent was monitored by UV detection at 214, 254, and 300 nm with a diode array detector. The sample was prepared by adding 10 µL of a solution of the sample in DCM (0.1 mg/mL) to 1 mL acetonitrile containing 0.05-0.1% formic acid.

1.1 Molecular modeling

Models were simulated by using Maestro version 11.5 (Schrödinger Inc.). Energy minimized structures were obtained using MacroModel energy minimization with the following parameters: force field: MMFFs; solvent: none; electrostatic treatment: constant dielectric; dielectric constant: 1.0; charges from: force field; cutoff: normal; Van der Waals: 7.0; electrostatic: 12.0; H-bond: 4.0; mini method: TNCG; maximum iterations: 2500; converge on gradient; convergence threshold: 0.05; constraints: distances. As a starting point, the coordinates of the crystal structure of **1** (CCDC entry # 1955168) was used. Some hydroxyl groups were inserted and some aromatic rings were removed. The modified sequence was first energy-minimized. In a second round, two identical modified helix-turn-helix structures were placed in a plausible arrangement, and distance constraints between plausible hydrogen-bonding partners were set to 1.8 on purpose. While setting the constraints, it was important to match the hydroxy group to their correct hydrogen-bonding carbonyl partner. Then all constraints were removed, and energy minimization was repeated.

3.2 Nuclear magnetic resonance spectroscopy

NMR spectra were recorded on different NMR spectrometers: (I) an Avance III HD NMR spectrometer 500 MHz (Bruker BioSpin) with CryoProbe™ Prodigy for ^{1}H NMR, $^{1}H^{15}N$-HSQC, and DOSY spectra of foldamers. (II) a Bruker HD NMR spectrometer 400 MHz (Bruker BioSpin) for variable temperature measurements. Chemical shifts are described in part per million (ppm, δ) relative to the ^{1}H residual signal of the deuterated solvent used – meaning DMSO-d_6 (δ 2.50 ppm), CD_2Cl_2 (δ 5.32 ppm) and $CDCl_3$ (δ 7.26 ppm). For the DMSO-d_6 and $CDCl_3$ solvent mixture, the chemical shifts were calibrated according to DMSO-d_6 (δ 2.50 ppm). For the CD_2Cl_2 and $CDCl_3$ solvent mixture, the chemical shifts were calibrated according to internal standard tetramethylsilane (δ 0.00 ppm).^{1}H NMR splitting patterns with observed first-order coupling are entitled as singlet (s), doublet (d), triplet (t), quartet (q) or multiplet (m). Coupling constants (*J*) are ported in Hz.

The ^{1}H NMR spectra of each sample were measured at different times respectively until no further change was observed within a week. We generally consider that at this point the compound reached equilibrium. When the sample reached equilibrium, re-dissolving the compound solid results in the equilibrated spectrum immediately without going through the equilibration process again. Complete disruption of the hydrogen bonds was achieved by dissolving the sample in polar solvents (such as DMSO, pyridine or MeOH/chloroform mixture), followed by removal of the solvent. When all of the hydrogen bonds were completely disrupted, it has to go through the equilibrium process again to reach the equilibrium. The equilibrium time (the measurement time gap between two different conditions) of ^{1}H NMR spectra at different temperatures and in different proportions of DMSO-d_6/$CDCl_3$ solvent was usually several minutes. Due to similar properties of $CDCl_3$ and CD_2Cl_2, the individual samples in different proportions of $CDCl_3$/CD_2Cl_2 mixture were prepared and the ^{1}H NMR spectra of all of the samples were measured over time whereas no change was observed.

$^{1}H^{15}N$ HSQC spectra were recorded with a phase-sensitive pulse sequence with sensitivity enhancement using trim pulses in inept transfer (hsqcetgpsi2) from the Bruker pulse program library. Data acquisition was performed utilizing non-uniform sampling (NUS; NUS amount: 50% with an automatically created NUSList) yielding 1024 (F2) x 128 (F1) data points in Echo/Antiecho gradient selection mode. The recycling delay was 2.0 s and 64 transients per increment were applied at a sweep width of 2.5 kHz in F2 and 7 kHz in F1 resulting in an acquisition time of 0.1462 s. NUS processing was performed using the fully automated NUS processing tool provided by MestReNova. Zero filling in F1 has been used to yield a final matrix of 1K x 1K real points.

The DOSY spectrum was recorded applying a pulse sequence with stimulated echo using stimulated echo for diffusion from the Bruker pulse program library (stegp1s). The diffusion delay Δ (big delta) was set to 220 ms and the diffusion gradient pulse length δ (little delta) was set to 1.0 ms. The number of gradient steps were set to 32 with linear spacing starting from 2% reaching 95% of the full gradient strength in the final step. For each of the 32 gradient amplitudes, 256 transients of 65K complex data points were acquired. DOSY processing was performed with the DOSY processing tool from MestReNova (v.12.x64) employing

the “Peak Heights Fit” algorithm including the “overlapped peaks analysis” with 128 points in diffusion dimension and a window of $1.00 \cdot 10^{-16}$ to $1.00 \cdot 10^{+03}$ cm^2 s^{-1}.

3.3 CD studies

The CD spectra of **2b** were recorded on a Jasco J-1500 spectrometer with 1 mm quartz cuvette. The following parameters were used: wavelength range from 460 to 280 nm. Scan speed: 100 nm/min; accumulation: 2; response time: 1.0 s; bandwidth: 2; temperature: 20 °C; sensitivity: standard (100 mdeg); data pitch: 0.5 nm; nitrogen gas flow rate: 500 L/h. The CD spectra of **4b** were recorded on a Jasco J-810 spectrometer with 1 mm quartz cuvette. The following parameters were used: wavelength range from 460 to 280 nm. Scan speed: 200 nm/min; accumulation: 3; response time: 1.0 s; bandwidth: 2; temperature: 20 °C; sensitivity: standard (100 mdeg); data pitch: 0.1 nm; nitrogen gas flow rate: 500 L/h. The sample solution of **2b** and **4b** was prepared in different proportions of DMSO/$CHCl_3$ solvents. The concentration is 0.1 mM. Δε values (in $cm^2 \cdot mol^{-1}$) were obtained by using the formula: $\Delta\varepsilon = m°/(C.l.32980)$ where m = CD value in millidegrees; l = cuvette pathlength in cm; C = sample concentration in mol/L.

3.4 X-ray crystallography

A single crystal of (**3b**)$_2$ used for the X-ray diffraction experiment was obtained by slow liquid/liquid diffusion (layering of acetonitrile on top of a chloroform solution) in an NMR tube. Data were collected at the IECB x-ray facility (CNRS UMS 3033 – INSERM US001) on a Rigaku FRX rotating anode (2.9 kW) diffractometer. CuKα radiation is monochromated with high flux Osmic Varimax HF mirrors. The x-ray source has a Dectris Pilatus 200K detector and partial chi goniometer. The crystal was kept at 100(2) K during data collection. The data were processed with the CrysAlis PRO software[38] with a multiscan absorption correction. The structure was solved using a dual-space algorithm with the ShelXT[39] structure solution program. Crystal model refinement was performed with the ShelXL[40] package using the Least Squares minimization. Both programs are implemented in Olex2.[41]

For some side chains, not all C or O atoms were found. During refinement, anisotropic displacement parameters were used for most atoms of backbone and S atoms of side chains. The C- and N-bound hydrogen atoms were placed in an idealized position. The positions of hydrogen atoms of O-H groups and one H atom of water molecule were based on possible hydrogen bonds. All H atoms were refined in the riding-model approximation, with $U_{iso}(H)=1.2U_{eq}$(CH, CH_2, NH) and $U_{iso}(H)=1.5U_{eq}$ (OH). EADP, DELU, SIMU and RIGU instructions were employed to model temperature parameters. The geometry of the molecules was improved with DFIX, FLAT or AFIX commands.

Wide channels occupying about 33% of the unit cell volume are formed in the structure. These channels are filled with severely disordered solvent molecules removed using the solvent masking procedure implemented in Olex2. The solvent radius was set to 1.2 Å, and the calculated total potential solvent-accessible void volume and electron counts per unit cell were 8674 $Å^3$ and 2737, respectively. Considering the high number of electrons calculated for the channels and the variety of solvents used for crystallization (acetonitrile, water, chloroform), it is impossible to determine the solvent composition reliably. However, structure factors include contributions from the .fab file.

The final cif files were checked using IUCR's checkcif algorithm. Due to the characteristics of the crystal, *i.e.* large volume fractions of disordered solvent molecules, weak diffraction intensity, incompleteness of the data and low resolution, many A - level and B - level alerts remain in the check cif file. These alerts are inherent to the data and refinement procedures and do not reflect errors. They are explicitly listed below and have been divided into two groups. The first group illustrates the poor quality of the data and refinement statistics compared to that expected for small molecule structures from highly diffracting crystals. The second group is connected to decisions made during refinement

GROUP 1

THETM01_ALERT_3_A The value of sine(theta_max)/wavelength is less than 0.550

PLAT023_ALERT_3_A, B Resolution (too) Low [sin(theta)/Lambda < 0.6].

PLAT084_ALERT_3_A, B High wR2 Value (i.e. > 0.25)

PLAT934_ALERT_3_A Number of (Iobs-Icalc)/Sigma(W) > 10 Outliers

PLAT082_ALERT_2_B High R1 Value

PLAT088_ALERT_3_B Poor Data / Parameter Ratio

PLAT241_ALERT_2_B High 'MainMol' Ueq as Compared to Neighbors

PLAT242_ALERT_2_B Low 'MainMol' Ueq as Compared to Neighbors

PLAT340_ALERT_3_B Low Bond Precision on C-C Bonds

GROUP 2

PLAT201_ALERT_2_A Isotropic non-H Atoms in Main Residue(s)

PLAT202_ALERT_3_A Isotropic non-H Atoms in Anion/Solvent

As mentioned above, not all atoms were refined with ADPs

PLAT306_ALERT_2_B Isolated Oxygen Atom (H-atoms Missing)

Unrecognized electron density was introduced to the refinement as dummy oxygen atoms.

PLAT315_ALERT_2_B Singly Bonded Carbon Detected (H-atoms Missing)

Not all H-atoms were localized, but they were used in SFAC calculation[40]

Table S1. Crystal data and refinement details.

Identification code	**$(3b)_2$**
Chemical formula	$2(C_{208}H_{200}N_{36}O_{45}S_7)\cdot H_2O\cdot 2(O)$**, [+solvents]*
Formula weight	8346.91
Crystal system	Triclinic
Space group	*P*-1
Unit cell dimensions (Å)	a= 26.866 (2), b=29.677 (2) c= 31.985 (2)
Volume ($Å^3$)	24326 (3)
Z	2
Radiation type	Cu *K*α
Density (calculated) ($Mg\ m^{-3}$)	1.140
Absorption coefficient (mm^{-1})	1.22
Crystal size (mm)	0.15 × 0.15 × 0.03
Completeness	98.6 (up to 35.42°)
Reflections collected	68886
Reflections observed [$I > 2\sigma(I)$]	11712
R_{int}	0.064
Data/parameters/restrains	21353/2917/ 2518
Goodness-of-fit on F^2	2.17
Final R indices [$I > 2\sigma(I)$]	0.1995, 0.5136
R indices (all data)	0.2558, 0.5551
Largest diff. peak and hole	0.79, -0.45
CCDC #	2337052

* A solvent mask was used to remove severely disordered solvent molecules.

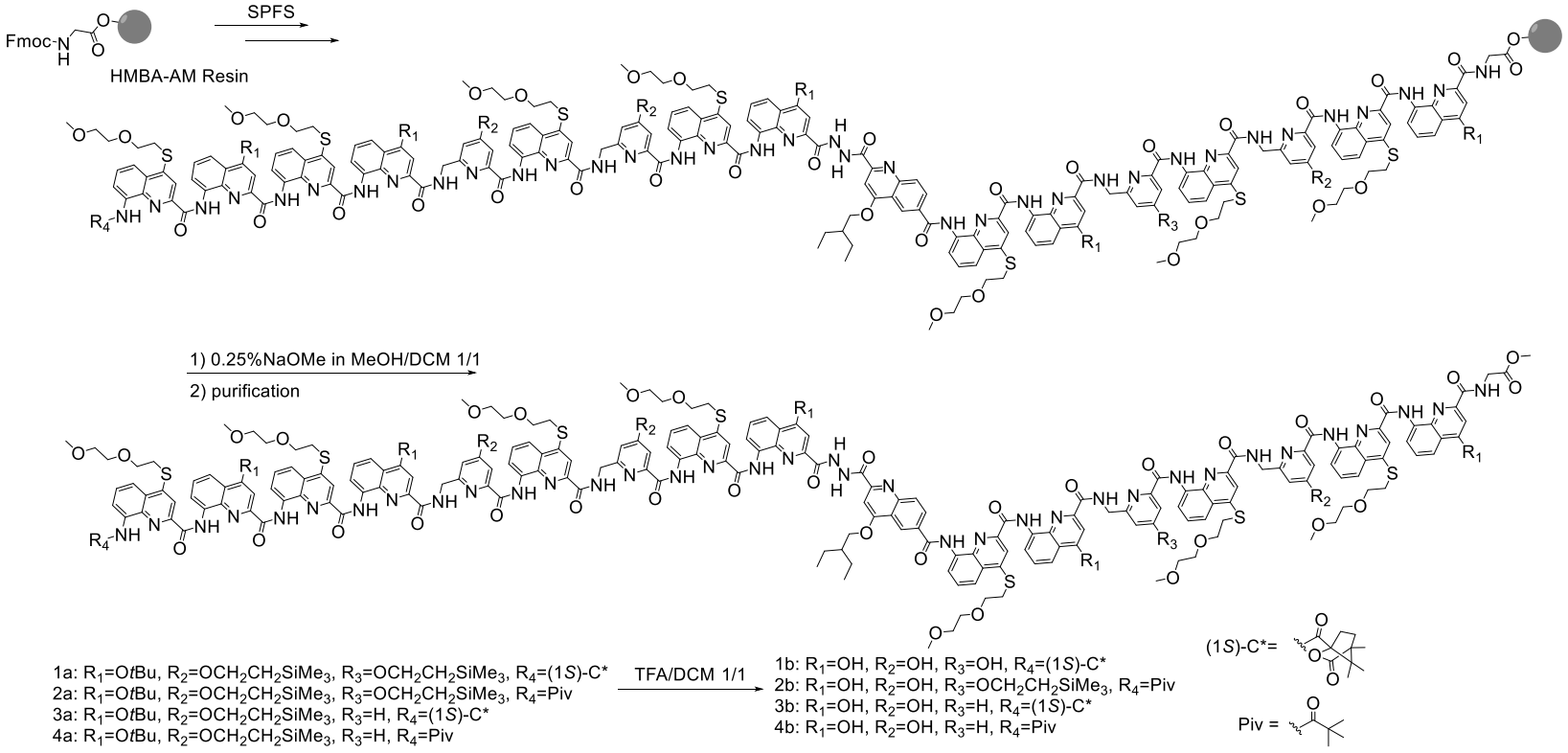
** Unrecognized electron density was introduced to the refinement as dummy oxygen.

Table S2. Hydrogen-bond geometry. Atoms are named as in the cif.

D—H···*A*	*D*—H (Å)	H···*A* (Å)	*D*···*A* (Å)	*D*—H···*A* (°)
First group				
O18D—H18D···O3C	0.84	1.74	2.57 (2)	169
O1D—H1D···O16G	0.84	1.82	2.62 (2)	161
O3D—H3D···O19G	0.84	1.82	2.65 (3)	175
O15D—H15D···O5C	0.84	1.73	2.57 (2)	171
O17D—H17D···O8C	0.84	1.81	2.64 (3)	168
O4D—H4D···O14G	0.84	1.86	2.69 (2)	168
Second group				
O9D—H9D···O3G	0.84	1.84	2.66 (3)	165
O10D—H10D···O16C	0.84	1.88	2.72 (3)	177
O12D—H12D···O19C	0.84	1.78	2.62 (2)	174
O6D—H6D···O5G	0.84	1.90	2.74 (3)	173
O8D—H8D···O8G	0.84	1.80	2.63 (3)	176
O13D—H13D···O14C	0.84	2.01	2.80 (2)	156
Third group				
O14D—H14D···O7C	0.84	1.78	2.63 (3)	174
O5D—H5D···O7G	0.84	1.82	2.65 (3)	168
O12D—H12D···O19C	0.84	1.78	2.62 (2)	174
O1D—H1D···O16G	0.84	1.82	2.62 (2)	161

Symmetry code(s): (i) -*x*+2, -*y*+2, -*z*; (ii) -*x*+2, -*y*+2, -*z*+1

4. Synthetic Scheme of foldamer synthesis



Scheme 1. Solid phase synthesis of aromatic oligomers.

5. Experimental Procedures

5.1 General methods

Commercially available reagents were purchased from Sigma-Aldrich, Alfa-Aesar or TCI and were used without further purification unless specified. HMBA-AM resin (200-400 mesh, loading 0.8–1.2 mmol/g) was purchased from Iris-biotech. THF, DCM and toluene were dried over alumina columns (MBRAUN SPS-800 solvent purification system). *N*,*N*-Diisopropylethylamine and chloroform were distilled over CaH_2 prior to use. Extra dry DMF was purchased from Sigma-Aldrich. Ultrapure water was obtained via a Stakpure OmniaPure-T UV-TOC ultrapure water system.

Analytical reversed phase (RP) high performance liquid chromatography (HPLC) was performed on a Thermo Fisher Scientific Ultimate 3000 HPLC System using Macherey-Nagel Nucleodur C8 Gravity columns (4 × 50 mm, 5 µm). UV absorbance was monitored at 300 nm and 254 nm, if not stated otherwise. The semi-preparative HPLC was performed on a Waters system equipped with a 2545 Quaternary Gradient Module with automated fraction collector system on a XBridge® Prep C8 OBD™ column (19 × 150 mm, 5 µm) at a flow rate of 25 mL/min. 0.1 % TFA was added to the aqueous mobile phase (referred to as mobile phase A) and to acetonitrile (referred to as mobile phase B). The gradient is: 0-5 min, 90% to 100% solvent B; 5-25 min, 100% solvent B at r.t.. The column eluent was monitored by UV detection at 254 and 300 nm with a diode array detector.

The ultraviolet–visible (UV/Vis) absorbance measurements were done with a Thermo Fisher Scientific Nanodrop One instrument using a 1 cm path length quartz cuvette. Circular dichroism (CD) spectra were measured on Jasco J-810 or Jasco J-1500 spectrometers. Measurements were performed at 20 °C if not stated otherwise.

Solid phase synthesis (SPS) was performed manually under MW-irradiation on a CEM Discover (Liberty Bio) microwave oven using a reaction vessel and an internal fiber optic probe for temperature control, or with a fully automated synthesizer followed by previously reported protocol.[42]

5.2 Synthesis of monomers

The Fmoc-<u>Y</u>-OH,[21] Fmoc-T2-OH,[21] Fmoc-Q^{Deg}-OH,[30] Fmoc-<u>X</u>-OH[30] and Fmoc-P-OH[43] were synthesized according to literature. All of the Fmoc-protected monomers was ≥ 98% pure before used in the solid phase synthesis.

5.3 Solid phase synthesis general methods

5.3.1 Loading of the resin via HBTU activation

HMBA-AM resin (500 mg, 0.4-0.6 mmol, 1 eq.) was swollen in 5 mL DCM for 1 h, transferred to the microwave vessel and washed 3 times with extra dry DMF. DIPEA (170 µL, 1.0 mmol, 2 eq.) was added to a mixture of Fmoc-Gly-OH (134 mg; 0.45 mmol, 0.9 eq.) and HBTU (228 mg, 1.2 eq.) in extra dry DMF (5 mL) and the resulting solution was shaken for 30 s before to be poured to the resin-containing reaction

vessel. The reaction mixture was subjected to treatment in a microwave oven (50 °C, 20 min, 25 W). The resin was filtered and washed with DMF (5 x 2 mL) and DCM (10 x 2 mL). Capping was performed by adding a mixture of DCM/pyridine/benzoyl chloride (3:1:1 (v/v/v), 5 mL) to the resin followed by shaking for 30 min at r.t., and subsequent washing with DCM (20 x 2 mL). For monitoring the efficiency of the 1st loading, small amount of resin (around 2 mg) was taken and dried under vacuum. The loading was estimated at this scale.

5.3.2 Estimation of the loading

To a small amount of resin-bound Fmoc-Gly (1–2 mg), a freshly prepared solution of DMF/piperidine (8:2 (v/v), 3.0 mL) was added. The mixture was shaken and incubated for 5 min. Then the absorption was measured at 301 nm using a NanoDrop One Microvolume UV-Vis Spectrophotometer and a Hellma quartz glass cuvette 104 (path length 10 mm). Three replicates were measured, then the loading was calculated with the following equation:

$$\text{loading}\left(\text{in}\ \frac{\text{mmol}}{\text{g}}\right) = \frac{\text{Abs}_{301\ \text{nm}} \times \text{V}}{\varepsilon_{301\text{nm}} \times l \times \text{m}}$$

$$\varepsilon_{301\text{nm}} = 7800\ \text{L/mol/cm}^{[44]}$$

5.3.3 Solid Phase Synthesis via in-situ-activation[42]

Fmoc-Gly-HMBA-AM resin (100 mg, loading 0.3 mmol/g, 30 µmol) was first swollen in DCM (3 mL) for 1 h, the resin was transferred into the microwave vessel and washed 3 times with DMF and 3 times with NMP.

The deprotection of the Fmoc group was performed by adding a solution of 2% DBU in NMP (3 mL) to the resin and incubation for 3 min. The resin was next filtered off and the deprotection step was repeated once. After filtration, the resin was washed with DCM (3 x 2 mL) and then with anhydrous THF (5 x 2 mL). This deprotection step was performed after each aromatic monomer coupling.

The resin was next suspended in anhydrous THF (1 mL) and 2,3,5-collidine (5 eq. with respect to the resin-loading) was added to the resin supernatant. The Fmoc-protected monomer (2 eq. with respect to the resin-loading) and PPh_3 (4 eq. with respects to the resin-loading) were successively added in a vial to be solubilized in freshly distilled $CHCl_3$ (1 mL).

Trichloroacetonitrile (4.5 eq. with respect to the resin loading) was next added to the vial and the resulting acid chloride solution was shaken for 30 s before to be poured to the resin-containing reaction vessel. The reaction vessel was then placed in the microwave oven and subjected to MW irradiation for 15 min (50°C, 50 W). The resin was then washed 3 times with anhydrous THF. This entire coupling step was then repeated once more. For the coupling of Fmoc-T2-OH, the same acid chloride activation process was followed but the coupling was, this time, performed at r.t. by shaking the resin for 2 h. Then the resin was washed with anhydrous THF (3 x 2 mL).

For the final coupling of pivaloyl- (Piv-) or (1*S*)-camphanic ((1*S*)-C*-) amides, the resin was suspended in anhydrous THF (1 mL) and 2,3,5-collidine (5 eq. with respect to the resin-loading) was added to the resin suspensions. A solution of pivaloyl chloride (2 eq. with respect to the resin-loading) or (1*S*)-camphanic chloride (2 eq. with respect to the resin-loading, purchased from Sigma-Aldrich, 98%, ee: 99%) in freshly distilled $CHCl_3$ (1 mL) was added to the supernatant and the resin was shaken at r.t. for 2 h. The resin was filtered off, washed 3 times with dry THF, and the same process was repeated once. After coupling, the resin was vigorously washed 3 times with DMF and 3 times with DCM.

5.3.4 Mini-Cleavage

To perform a mini cleavage, the resin (1–2 mg) was swollen in 1 mL MeOH/DCM (1:1, v/v) solution followed by addition of 10 µL NaOMe (25% (m/m)) and incubated at r.t. for 10 min. The cleavage solution was diluted with DCM, washed with aqueous citric acid solution (5%), dried over $MgSO_4$, filtered and the solvent was finally removed under reduced pressure.

5.3.5 Full Cleavage[45]

Preparation of cleavage solution: 200 mL dry MeOH was added to 200 mL dry DCM under N_2 atmosphere. 2 mL NaOMe (25% (m/m)) in methanol was added and the mixture was well-mixed by magnetic stirring. Sufficient amount of cleavage solution (at least 400 mL cleavage solution for 100 mg resin) was important to avoid the formation of oligomer acid as the side-product.

The resin (around 100 mg) was dried under vacuum and slowly added to 400 mL cleavage solution under N_2 atmosphere. The mixture was stirred under N_2 atmosphere for 2 h before it was added to 100 mL aqueous citric acid solution (5%). The aqueous layer was extracted with DCM(3 x 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated under reduced pressure. The crude was recovered as solid.

5.4 Synthesis of oligomers

(1*S*)-Camph-Q^D<u>X</u>Q^D<u>XY</u>Q^D<u>Y</u>Q^D<u>X</u>-T2-Q^D<u>XY</u>Q^D<u>Y</u>Q^D<u>X</u>-Gly-OMe (**2a**): Compound **2a** was synthesized using the SPS procedures reported in paragraph 5.3 on Fmoc-Gly-HMBA AM resin. The crude product was obtained after full cleavage and purification by RP-HPLC. (15 mg, 12%). **^{1}H NMR** (500 MHz, chloroform-*d*) δ 11.40 (s, 1H), 11.38 (s, 1H), 11.28 (s, 1H), 11.24 (s, 1H), 11.01 (s, 1H), 10.96 (s, 1H), 10.79 (s, 2H), 10.62 (s, 1H), 10.43 (s, 1H), 10.25 (s, 1H), 9.70 (s, 1H), 9.43 (s, 1H), 8.52 (t, *J* = 3.3 Hz, 1H), 8.27 (s, 1H), 8.26 (s, 1H), 8.20 (d, *J* = 7.3 Hz, 1H), 8.14–8.11 (m, 2H), 8.05 (t, *J* = 3.3 Hz, 1H), 8.02 (s, 1H), 7.78 (s, 2H), 7.76 (s, 2H), 7.74 (s, 2H), 7.73–7.70 (m, 6H), 7.66–7.61 (m, 4H), 7.59 (s, 1H), 7.56 (s, 2H), 7.54 (s, 3H), 7.47 (s, 2H), 7.45 (s, 2H), 7.42–7.40 (m, 2H), 7.39 (s, 3H), 7.32–7.29 (m, 4H), 7.15 (s, 1H), 7.12 (s, 2H), 7.11 (s, 2H), 7.10 (s, 1H), 7.08 (s, 1H), 7.07 (s, 2H), 7.05 (s, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.69 (s, 1H), 6.67 (s, 1H), 6.61 (s, 1H), 6.50 (s, 1H), 6.41 (s, 1H), 6.40 (s, 1H), 6.37 (s, 1H), 6.33 (s, 1H), 6.29 (s, 1H), 6.26 (s, 1H), 6.18 (s, 1H), 5.93 (s, 1H). 4.33–4.27 (m, 1H), 4.26–4.13 (m, 4H), 4.08–3.95 (m, 9H), 3.93–3.90 (m, 4H), 3.89–3.77 (m, 12H), 3.76–3.66 (m, 13H), 3.65–3.58 (m, 8H), 3.57 (s, 3H), 3.54 (s, 3H), 3.52–3.49 (m, 4H), 3.47 (s, 3H), 3.46–3.44 (m, 6H), 3.43 (s, 3H), 3.42 (s, 4H), 3.37 (t, *J* = 6.5 Hz,

3H), 3.33–3.18 (m, 12H), 3.16 (s, 3H), 3.01 (d, *J* = 16.0 Hz, 1H), 2.90 (t, *J* = 8.4 Hz, 1H), 2.80 (d, *J* = 15.3 Hz, 1H), 2.58 (d, *J* = 14.6 Hz, 1H), 2.33 (d, *J* = 15.0 Hz, 1H), 2.03–1.99 (m, 3H), 1.95–1.85 (m, 2H), 1.67 (s, 9H), 1.66 (s, 9H), 1.64 (s, 9H), 1.47 (s, 9H), 1.32–1.24 (m, 5H), 1.09 (s, 10H), 1.05–0.99 (m, 4H), 0.91–0.82 (m, 2H), 0.70 (d, *J* = 7.2 Hz, 6H), 0.57–0.49 (m, 6H), 0.33 (s, 9H), 0.26 (s, 9H), 0.17 (s, 9H), 0.13–0.04 (m, 2H), -0.03 (s, 9H). (mixture of two conformers in a ratio of 1:0.3, only the major peaks are reported.) **HRMS** (ESI+) calcd. for $C_{253}H_{292}N_{36}O_{47}S_7Si_4$ $[M+2H]^{2+}$ 2461.9417, found 2461.8227.

(1*S*)-Camph-Q^{D}XQ^{D}XYQ^{D}YQ^{D}X-T2-Q^{D}XYQ^{D}YQ^{D}X-Gly-OMe (**2b**): Compound **2a** was treated with a solution of TFA/DCM (1:1 (v/v), 2 mL) at r.t. overnight. The solvent was removed under vacuum. The solid was precipitated from MeOH, was subsequently filtered and washed 2 times with MeOH to yield the desired product as a yellow solid. (13 mg, quant.) **^{1}H NMR** (500 MHz, chloroform-*d*) δ 12.61 (s, 1H), 11.69 (s, 1H), 11.46 (s, 1H), 11.22 (s, 1H), 11.11 (s, 1H), 11.08 (s, 1H), 11.05 (s, 2H), 10.77 (s, 1H), 10.72 (s, 2H), 10.68 (s, 1H), 10.60 (s, 1H), 10.50 (s, 1H), 10.33 (s, 1H), 10.04 (s, 1H), 9.96 (s, 1H), 9.88 (s, 1H), 9.74 (s, 1H), 9.24 (s, 1H), 9.16 (s, 1H), 8.73 (s, 1H), 8.68 (s, 1H), 8.64–8.59 (m, 2H), 8.54 (d, *J* = 8.0 Hz, 1H), 8.39–8.34 (m, 1H), 8.27–8.23 (m, 3H), 8.20–8.18 (m, 2H), 8.15 (s, 1H), 8.11 (s, 1H), 8.10 (d, *J* = 2.9 Hz, 1H), 8.08 (s, 1H), 8.07–8.05 (m, 1H), 8.04 (s, 1H), 8.02 (s, 1H), 7.96 (d, *J* = 7.0 Hz, 2H), 7.93–7.89 (m, 3H), 7.88 (s, 1H), 7.86 (s, 2H), 7.84 (s, 2H), 7.81 (d, *J* = 7.3 Hz, 2H), 7.78 (d, *J* = 6.7 Hz, 2H), 7.75 (s, 2H), 7.73 (s, 1H), 7.71 (s, 2H), 7.69 (s, 1H), 7.67 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 2H), 7.56 (s, 1H), 7.54 (s, 2H), 7.52 (s, 1H), 7.51 (s, 1H), 7.47 (s, 2H), 7.45 (s, 1H), 7.43 (s, 1H), 7.37–7.30 (m, 3H), 7.25–7.20 (m, 2H), 7.14–7.11 (m, 1H), 7.09 (s, 1H), 6.98 (s, 1H), 6.94 (s, 1H), 6.90 (s, 1H), 6.83 (s, 1H), 6.76 (s, 1H), 6.54–6.51 (m, 2H), 6.31 (s, 1H), 6.15 (s, 1H), 4.31–4.18 (m, 7H), 4.16–4.06 (m, 10H), 4.05–3.98 (m, 8H), 3.97–3.95 (m, 5H), 3.94–3.90 (m, 4H), 3.85–3.78 (m, 10H), 3.78–3.71 (m, 4H), 3.70 (s, 3H), 3.68–3.63 (m, 6H), 3.61 (s, 3H), 3.56–3.48 (m, 6H), 3.46 (s, 6H), 3.42–3.32 (m, 5H), 3.30 (s, 6H), 3.24 (d, *J* = 6.2 Hz, 3H), 3.15–3.00 (m, 4H), 2.85–2.80 (m, 2H), 1.53 (m, 2H), 1.27 (d, *J* = 15.6 Hz, 12H), 0.87 (dd, *J* = 16.1, 9.4 Hz, 10H). **HRMS** (ESI+) calcd. for $C_{213}H_{204}N_{36}O_{47}S_7$ $[M+2K]^{2+}$ 2159.5994, found 2159.5140.

Piv-Q^D<u>X</u>Q^D<u>XY</u>Q^D<u>Y</u>Q^D<u>X</u>-T2-Q^D<u>XY</u>Q^D<u>Y</u>Q^D<u>X</u>-Gly-OMe (**3a**): Compound **3a** was synthesized using the SPS procedures reported in 5.3 on Fmoc-Gly-HMBA AM resin. The crude product was obtained after full cleavage and purified by RP-HPLC. (11 mg, 9%). **^{1}H NMR** (500 MHz, chloroform-*d*) δ 11.37 (s, 1H), 11.28 (s, 2H), 10.99 (s, 1H), 10.96 (s, 1H), 10.80 (s, 1H), 10.79 (s, 1H), 10.78 (s, 1H), 10.57 (s, 1H), 10.39 (s, 1H), 10.25 (s, 1H), 9.71 (s, 1H), 8.69 (s, 1H), 8.54 (t, *J* = 3.3 Hz, 1H), 8.35 (d, *J* = 3.3 Hz, 1H), 8.27 (s, 1H), 8.25 (s, 1H), 8.21 (d, *J* = 3.3 Hz, 1H), 8.16–8.11 (m, 4H), 8.04–8.01 (m, 3H), 7.93–7.88 (m, 5H), 7.82–7.77 (m, 3H), 7.76–7.75 (m, 2H), 7.75–7.73 (m, 2H), 7.71 (dd, *J* = 7.6, 4.8 Hz, 2H), 7.63 (s, 1H), 7.62–7.59 (m, 3H), 7.58 (s, 1H), 7.55 (d, *J* = 8.1 Hz, 3H), 7.46–7.43 (m, 2H), 7.42–7.37 (m, 4H), 7.32 (d, *J* = 7.5 Hz, 2H), 7.30 (s, 2H), 7.21 (s, 1H), 7.20 (s, 1H), 7.19–7.16 (m, 2H), 7.15 (s, 1H), 7.13 (s, 1H), 7.12 (s, 1H), 7.10–7.09 (m, 2H), 7.06 (s, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.68–6.67 (m, 1H), 6.62 (s, 1H), 6.60 (s, 1H), 6.48 (s, 1H), 6.46 (s, 1H), 6.42 (s, 1H), 6.36 (s, 1H), 6.34 (s, 1H), 6.31 (d, *J* = 2.4 Hz, 1H), 6.26 (s,

1H), 6.19 (s, 1H), 5.93–5.91 (m, 1H). 4.32–4.14 (m, 5H), 4.08–3.91 (m, 9H), 3.89–3.77 (m, 18H), 3.76–3.66 (m, 12H), 3.65–3.59 (m, 16H), 3.57 (s, 3H), 3.54 (s, 3H), 3.50 (s, 4H), 3.47 (s, 3H), 3.44 (s, 5H), 3.43 (s, 3H), 3.42 (s, 3H), 3.40–3.17 (m, 7H), 3.16 (s, 3H), 2.97 (s, 2H), 2.90 (s, 2H), 2.80 (d, *J* = 14.6 Hz, 1H), 2.54 (d, *J* = 15.5 Hz, 1H), 1.72 (s, 9H), 1.66 (s, 9H), 1.65 (s, 9H), 1.63 (d, *J* = 2.4 Hz, 2H), 1.60 (s, 2H), 1.50 (s, 2H), 1.47 (s, 9H), 1.38–1.20 (m, 4H), 1.12 (s, 9H), 1.07 (s, 9H), 1.05–0.97 (m, 1H), 0.86–0.81 (m, 1H), 0.71–0.67 (m, 1H), 0.57 (s, 9H), 0.50 (t, *J* = 7.4 Hz, 2H), 0.32 (d, *J* = 2.3 Hz, 9H), 0.25 (s, 9H), 0.17 (s, 9H) (mixture of two conformers in a ratio of 1:0.3, only the major peaks are reported). **HRMS** (ESI+) calcd. for $C_{248}H_{288}N_{36}O_{45}S_7Si_4$ $[M+2H]^{2+}$ 2413.9311, found 2413.8372.

Piv-Q^{D}XQ^{D}XYQ^{D}YQ^{D}X-T2-Q^{D}XYQ^{D}YQ^{D}X-Gly-OMe (**3b**): Compound **3a** was treated with a solution of TFA/DCM (1:1 (v/v), 2 mL) at r.t. overnight. The solvent was removed under vacuum. The solid was precipitate from MeOH and recovered by filtration. The solid was washed with MeOH for another 2 times. The compound was obtained as a yellow solid. (9.5 mg, quant.) **^{1}H NMR** (500 MHz, chloroform-*d*) δ 12.43 (s, 1H), 11.60 (s, 1H), 11.22 (s, 1H), 11.09 (s, 1H), 11.06 (s, 1H), 11.04 (s, 1H), 10.97 (s, 1H), 10.80 (s, 1H), 10.79 (s, 1H), 10.76 (s, 0H), 10.69 (s, 1H), 10.64 (s, 1H), 10.36 (s, 1H), 9.99 (s, 1H), 9.98 (s, 1H), 9.78 (s, 1H), 9.75 (s, 1H), 9.16 (s, 1H), 8.93 (s, 1H), 8.76 (s, 1H), 8.64 (s, 1H), 8.63–8.60 (m, 3H), 8.60 (s, 2H), 8.58–8.57 (m, 1H), 8.52–8.49 (m, 2H), 8.39 (d, *J* = 8.0 Hz, 1H), 8.31 (d, *J* = 8.0 Hz, 1H), 8.28–8.25 (m, 2H), 8.22 (s, 1H), 8.18 (s, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 8.09–8.05 (m, 3H), 8.04 (s, 1H), 8.02 (s, 1H), 8.00 (s, 1H), 7.96 (s, 2H), 7.94 (s, 1H), 7.92 (s, 1H), 7.91–7.90 (m, 2H), 7.90 (s, 1H), 7.89 (s, 2H), 7.87 (s, 1H), 7.87–7.86 (m, 2H), 7.85–7.83 (m, 2H), 7.82 (s, 1H), 7.79–7.77 (m, 2H), 7.75–7.73 (m, 2H), 7.72–7.71 (m, 2H), 7.70 (d, *J* = 7.3 Hz, 1H), 7.67 (s, 1H), 7.66 (s, 1H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.54 (s, 1H), 7.52 (s, 1H), 7.48 (s, 1H), 7.45 (d, *J* = 2.7 Hz, 1H), 7.44–7.42 (m, 1H), 7.36–7.34 (m, 2H), 7.19 (s, 1H), 7.18 (s, 1H), 7.08 (s, 1H), 6.97 (s, 1H), 6.94 (s, 1H), 6.91 (s, 1H), 6.85 (s, 1H), 6.72 (s, 1H), 6.55 (d, *J* = 7.2 Hz, 2H), 6.28 (d, *J* = 1.3 Hz, 2H), 6.04 (s, 1H), 5.77 (s, 1H), 5.49 (s, 1H), 4 4.30–4.18 (m, 2H), 4.21–4.14 (m, 3H), 4.13–4.05 (m, 3H), 4.06–3.88 (m, 18H), 3.88–3.77 (m, 12H), 3.79–3.71 (m, 6H), 3.69 (s, 3H), 3.69–3.60 (m, 10H), 3.61 (s, 3H), 3.60 (s, 3H), 3.54 (s, 3H), 3.54–3.47 (m, 3H), 3.46 (s, 3H), 3.46 (s, 3H), 3.29 (s, 3H), 3.28–3.22 (m, 3H), 3.13 (s, 3H), 3.08–3.03 (m, 3H), 3.00–2.94 (m, 2H), 2.89–2.82 (m, 1H), 2.62–2.57 (m, 1H), 2.38–2.33 (m, 1H), 2.02–1.99 (m, 1H), 1.28 (s, 9H), 1.26–1.22 (m, 10H). **HRMS** (ESI+) calcd. for $C_{208}H_{200}N_{36}O_{45}S_7$ $[M+2H]^{2+}$ 2073.6329, found 2073.6093.

(1*S*)-Camph-Q^{D}XQ^{D}XYQ^{D}YQ^{D}X-T2-Q^{D}XPQ^{D}YQ^{D}X-Gly-OMe (**4a**): Compound **4a** was synthesized using the SPS procedures reported in 5.3 on Fmoc-Gly-HMBA AM resin. The crude product was obtained after full cleavage and purified by RP-HPLC. (18 mg, 15%). **^{1}H NMR** (500 MHz, chloroform-*d*) δ 11.40 (s, 1H), 11.37 (s, 1H), 11.27 (s, 1H), 11.25 (s, 1H), 11.01 (s, 1H), 10.93 (s, 1H), 10.79 (s, 1H), 10.75 (s, 1H), 10.63 (s, 1H), 10.42 (s, 1H), 10.25 (s, 1H), 9.70 (s, 1H), 9.43 (s, 1H), 8.48 (t, *J* = 3.3 Hz, 1H), 8.28–8.24 (m, 2H), 8.22–8.19 (m, 2H), 8.14 (d, *J* = 7.4 Hz, 1H), 8.04–8.01 (m, 3H), 7.96 (d, *J* = 7.3 Hz, 1H), 7.88 (s, 2H), 7.86 (s, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.77–7.74 (m, 3H), 7.73–7.72 (m, 2H), 7.71–7.70 (m, 2H), 7.69–7.67 (m, 2H), 7.65 (s, 1H), 7.63 (s, 2H), 7.61 (s, 1H), 7.60 (s, 1H), 7.58 (s, 1H), 7.57–7.55 (m, 1H),

7.54 (s, 2H), 7.49 (dd, *J* = 12.7, 7.7 Hz, 2H), 7.45 (s, 1H), 7.39 (d, *J* = 8.0 Hz, 2H), 7.34 (s, 3H), 7.30 (s, 3H), 7.28 (s, 2H), 7.25 (s, 1H), 7.16–7.14 (m, 2H), 7.14–7.13 (m, 1H), 7.12–7.10 (m, 2H), 7.10 (s, 1H), 7.08 (s, 1H), 7.07–7.06 (m, 2H), 6.95–6.91 (m, 2H), 6.68 (s, 1H), 6.63 (s, 1H), 6.49 (s, 1H), 6.41 (s, 1H), 6.39 (d, *J* = 4.8 Hz, 2H), 6.33 (s, 1H), 6.27 (s, 1H), 6.17 (s, 1H), 5.93 (s, 1H), 5.87 (d, *J* = 7.8 Hz, 1H), 4.29 (d, *J* = 8.3 Hz, 1H), 4.23–4.13 (m, 4H), 4.06–4.02 (m, 4H), 4.01–3.96 (m, 6H), 3.93–3.90 (m, 4H), 3.89–3.76 (m, 16H), 3.76–3.73 (m, 2H), 3.73–3.66 (m, 8H), 3.64–3.58 (m, 9H), 3.57 (s, 3H), 3.54 (s, 2H), 3.52 (s, 1H), 3.50 (s, 3H), 3.47 (s, 2H), 3.44 (s, 5H), 3.43 (s, 3H), 3.42 (s, 3H), 3.38–3.18 (m, 14H), 3.16 (s, 2H), 3.14 (s, 1H), 3.00 (d, *J* = 16.4 Hz, 1H), 2.90 (t, *J* = 8.4 Hz, 1H), 2.77 (d, *J* = 14.9 Hz, 1H), 2.61 (d, *J* = 14.9 Hz, 1H), 2.32 (d, *J* = 13.8 Hz, 1H), 1.86–1.75 (m, 1H), 1.66 (s, 9H), 1.66 (s, 9H), 1.63 (s, 9H), 1.46 (s, 9H), 1.35–1.22 (m, 9H), 1.09 (s, 9H), 1.05–0.99 (m, 1H), 0.86–0.78 (m, 2H), 0.70 (t, *J* = 7.2 Hz, 2H), 0.55 (s, 3H), 0.52 (s, 3H), 0.32 (t, *J* = 7.4 Hz, 4H), 0.25 (s, 9H), 0.17 (s, 9H), -0.03 (s, 9H). (mixture of two conformers in a ratio of 1:0.3, only the major peaks are reported.) **HRMS** (ESI+) calcd. for $C_{248}H_{280}N_{36}O_{46}S_7Si_3$ $[M+2H]^{2+}$ 2403.9088, found 2403.8301.

(1*S*)-Camph-Q^{D}XQ^{D}XYQ^{D}YQ^{D}X-T2-Q^{D}XPQ^{D}YQ^{D}X-Gly-OMe (**4b**): Compound **4a** was treated with a solution of TFA/DCM (1:1 (v/v), 2 mL) at r.t. overnight. The solvent was removed under vacuum. The solid was precipitate from MeOH and recovered by filtration. The solid was washed by MeOH for another 2 times. The compound was obtained as a yellow solid. (15.8 mg, quant.) **^{1}H NMR** (500 MHz, chloroform-*d*) δ 12.59 (s, 1H), 11.86 (s, 1H), 11.52 (s, 1H), 11.19 (s, 1H), 11.07 (s, 2H), 10.97 (s, 1H), 10.80 (s, 1H), 10.73 (s, 1H), 10.70 (s, 1H), 10.65 (s, 1H), 10.61 (s, 1H), 10.33 (s, 2H), 10.00 (s, 1H), 9.98 (s, 1H), 9.95 (s, 1H), 9.77 (s, 1H), 9.24 (s, 1H), 9.20 (s, 1H), 8.77 (s, 1H), 8.73 (s, 1H), 8.69 (s, 1H), 8.66–8.61 (m, 2H), 8.56–8.53 (m, 2H), 8.41–8.35 (m, 2H), 8.26 (d, *J* = 8.0 Hz, 1H), 8.23–8.18 (m, 4H), 8.17 (s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 8.08–8.05 (m, 3H), 8.03 (d, *J* = 7.0 Hz, 1H), 7.97–7.93 (m, 3H), 7.92–7.88 (m, 2H), 7.86–7.81 (m, 5H), 7.79–7.77 (m, 2H), 7.76–7.74 (m, 2H), 7.73 (s, 1H), 7.69 (t, *J* = 4.1 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.57–7.54 (m, 3H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.50–7.44 (m, 5H), 7.42–7.35 (m, 4H), 7.33–7.27 (m, 2H), 7.25–7.20 (m, 3H), 7.14 (s, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.94 (s, 1H), 6.87 (d, *J* = 13.8 Hz, 2H), 6.80 (s, 1H), 6.58 (d, *J* = 8.1 Hz, 1H), 6.51 (s, 1H), 6.48 (s, 1H), 6.31 (d, *J* = 1.6 Hz, 1H), 6.17 (s, 1H), 4.33–4.28 (m, 1H), 4.26–4.20 (m, 4H), 4.14 (dd, *J* = 10.1, 4.4 Hz, 8H), 4.08–3.90 (m, 16H), 3.85–3.82 (m, 3H), 3.81–3.76 (m, 9H), 3.74–3.71 (m, 5H), 3.69–3.64 (m, 10H), 3.62 (s, 3H), 3.57 (s, 3H), 3.54–3.51 (m, 3H), 3.48 (s, 3H), 3.46 (s, 3H), 3.46 (s, 3H), 3.43–3.35 (m, 6H), 3.29 (s, 3H), 3.24 (s, 3H), 3.09 (dd, *J* = 18.5, 4.2 Hz, 2H), 3.05–3.00 (m, 1H), 2.89–2.80 (m, 2H), 2.42–2.38 (m, 1H), 1.63–1.44 (m, 1H), 1.25 (s, 10H, overlap with impurities), 0.92–0.79 (m, 8H, overlap with impurities), 0.67 (s, 3H), 0.60 (s, 2H). **HRMS** (ESI+) calcd. for $C_{213}H_{204}N_{36}O_{46}S_7$ $[M+2H]^{2+}$ 2113.6460, found 2113.6315.

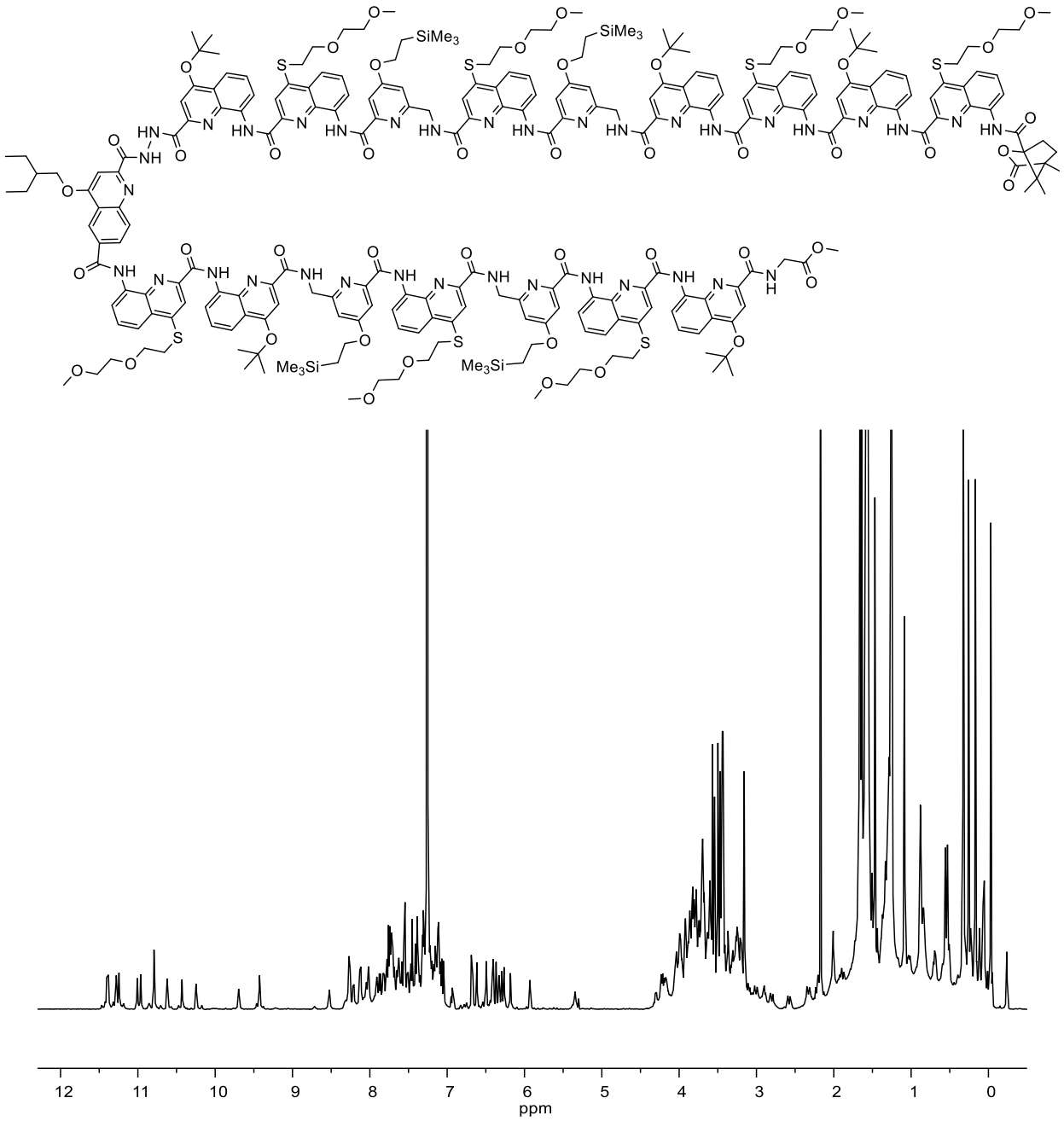
Piv-Q^{D}<u>X</u>Q^{D}<u>XY</u>Q^{D}<u>Y</u>Q^{D}<u>X</u>-T2-Q^{D}<u>X</u>PQ^{D}<u>Y</u>Q^{D}<u>X</u>-Gly-OMe (**5a**): Compound **5a** was synthesized using the SPS procedures reported in 5.3 on Fmoc-Gly-HMBA AM resin. The crude product was obtained after full cleavage and purified by RP-HPLC. (16 mg, 14%). **^{1}H NMR** (500 MHz, chloroform-*d*) δ 11.37 (s, 1H), 11.27 (s, 1H), 11.26 (s, 1H), 10.99 (s, 1H), 10.93 (s, 1H), 10.79 (s, 1H), 10.78 (s, 1H), 10.75 (s, 1H),

10.58 (s, 1H), 10.38 (s, 1H), 10.25 (s, 1H), 9.70 (s, 1H), 8.69 (s, 1H), 8.48 (t, *J* = 3.3 Hz, 2H), 8.26 (t, *J* = 3.3 Hz, 2H), 8.26–8.24 (m, 1H), 8.20 (t, *J* = 3.3 Hz, 1H), 8.17–8.12 (m, 2H), 8.04–8.00 (m, 3H), 7.96 (d, *J* = 7.2 Hz, 1H), 7.92–7.89 (m, 1H), 7.88 (s, 2H), 7.86 (s, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.78–7.75 (m, 2H), 7.75 (s, 2H), 7.73 (s, 1H), 7.71–7.67 (m, 2H), 7.64 (d, *J* = 3.5 Hz, 1H), 7.63 (s, 2H), 7.61 (s, 1H), 7.60–7.59 (m, 2H), 7.58 (s, 1H), 7.56 (s, 2H), 7.55 (d, *J* = 1.8 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.44 (s, 1H), 7.39 (d, *J* = 7.9 Hz, 2H), 7.35 (s, 3H), 7.32 (d, *J* = 6.3 Hz, 2H), 7.30 (s, 2H), 7.24 (s, 1H), 7.19–7.17 (m, 1H), 7.16 (s, 2H), 7.15 (s, 2H), 7.14–7.13 (m, 1H), 7.11 (s, 2H), 7.07–7.06 (m, 2H), 6.95–6.91 (m, 2H), 6.65 (s, 1H), 6.63 (s, 1H), 6.49 (s, 1H), 6.42 (s, 2H), 6.38 (s, 1H), 6.33 (s, 1H), 6.27 (s, 1H), 6.17 (s, 1H), 5.92 (d, *J* = 1.3 Hz, 1H), 4.29 (q, *J* = 8.0 Hz, 1H), 4.17 (dd, *J* = 19.6, 8.8 Hz, 4H), 4.07–4.02 (m, 4H), 4.01–3.94 (m, 5H), 3.93–3.90 (m, 4H), 3.88–3.83 (m, 9H), 3.81–3.77 (m, 9H), 3.76–3.73 (m, 3H), 3.72–3.67 (m, 10H), 3.63–3.59 (m, 7H), 3.57 (s, 3H), 3.54 (s, 3H), 3.52–3.48 (m, 4H), 3.47 (s, 3H), 3.44 (s, 3H), 3.43 (s, 3H), 3.42 (s, 3H), 3.38–3.35 (m, 2H), 3.33–3.29 (m, 2H), 3.28–3.18 (m, 8H), 3.16 (s, 1H), 2.98 (d, *J* = 15.9 Hz, 1H), 2.90 (t, *J* = 8.4 Hz, 1H), 2.77 (d, *J* = 14.7 Hz, 1H), 2.60 (d, *J* = 15.3 Hz, 1H), 2.30 (d, *J* = 13.6 Hz, 1H), 1.83 (d, *J* = 14.0 Hz, 1H), 1.71 (s, 9H), 1.66 (s, 9H), 1.66 (s, 9H), 1.59 (s, 3H), 1.50 (s, 3H), 1.46 (s, 9H), 1.37–1.29 (m, 5H), 1.09 (s, 9H), 0.72–0.68 (m, 2H), 0.56 (s, 9H), 0.52 (d, *J* = 7.4 Hz, 2H), 0.32 (t, *J* = 7.4 Hz, 2H), 0.25 (s, 9H), 0.16 (s, 9H), 0.06 (s, 9H). (mixture of two conformers in a ratio of 1:0.3, only the major peaks are reported.) **HRMS** (ESI+) calcd. for $C_{243}H_{276}N_{36}O_{44}S_7Si_3$ $[M+2H]^{2+}$ 2355.8982, found 2355.8719.

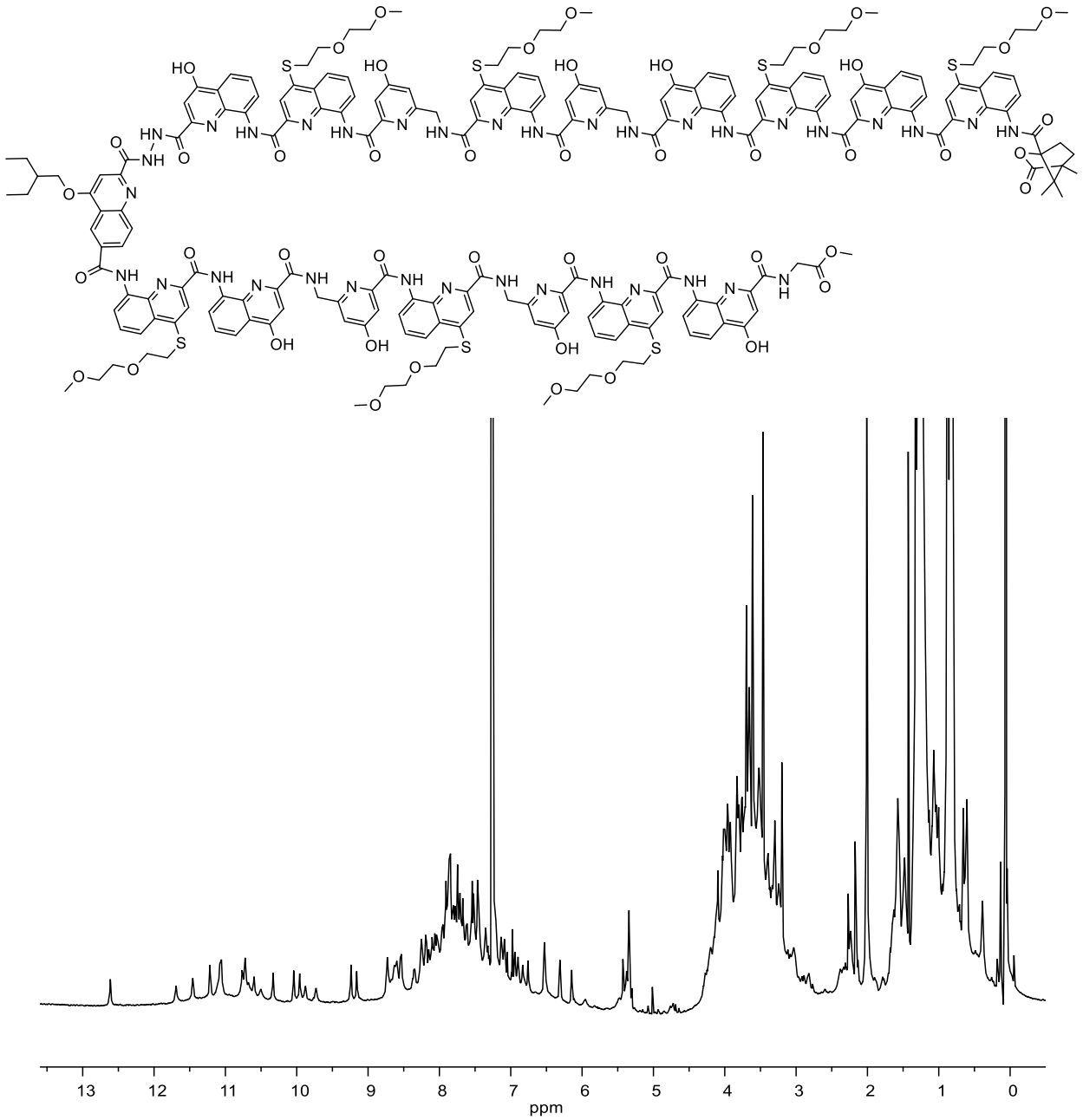
Piv-Q^{D}XQ^{D}XYQ^{D}YQ^{D}X-T2-Q^{D}XPQ^{D}YQ^{D}X-Gly-OMe (**5b**): Compound **5a** was treated with a solution of 50% TFA/DCM (2 mL) at r.t. overnight. The solvent was removed under vacuum. The solid was precipitated from MeOH and recovered by filtration. The solid was washed by MeOH for another 2 times. The compound was obtained as a yellow solid. (14 mg, quant.) **^{1}H NMR** (500 MHz, chloroform-*d*) δ 12.46 (s, 1H), 11.88 (s, 1H), 11.11 (s, 1H), 11.07 (s, 1H), 11.05 (s, 2H), 10.88 (s, 1H), 10.80 (s, 1H), 10.76 (s, 1H), 10.73 (s, 1H), 10.71 (s, 1H), 10.63 (s, 1H), 10.56 (s, 1H), 10.36 (s, 1H), 9.96 (s, 1H), 9.96 (s, 1H), 9.90 (s, 1H), 9.85 (s, 1H), 9.21 (s, 1H), 8.72 (s, 2H), 8.66 (s, 1H), 8.64–8.61 (m, 2H), 8.59 (s, 1H), 8.57 (d, *J* = 7.3 Hz, 1H), 8.54 (d, *J* = 8.4 Hz, 1H), 8.44 (d, *J* = 7.1 Hz, 1H), 8.35 (d, *J* = 8.1 Hz, 1H), 8.29 (d, *J* = 8.2 Hz, 2H), 8.21 (s, 1H), 8.17 (d, *J* = 7.0 Hz, 3H), 8.13 (s, 1H), 8.12–8.06 (m, 3H), 7.97–7.93 (m, 4H), 7.92 (s, 1H), 7.91–7.88 (m, 3H), 7.87–7.84 (m, 2H), 7.84–7.83 (m, 1H), 7.83–7.80 (m, 3H), 7.78 (d, *J* = 7.8 Hz, 2H), 7.76 (s, 2H), 7.71 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.58 (s, 1H), 7.56 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.50–7.44 (m, 5H), 7.42–7.40 (m, 1H), 7.39–7.37 (m, 1H), 7.36 (d, *J* = 2.0 Hz, 1H), 7.34 (s, 1H), 7.33–7.29 (m, 3H), 7.28 (s, 1H), 7.23 (d, *J* = 9.1 Hz, 1H), 7.09–7.05 (m, 2H), 6.95 (s, 1H), 6.90 (s, 2H), 6.79 (s, 1H), 6.53 (s, 1H), 6.48 (s, 1H), 6.45 (d, *J* = 8.0 Hz, 1H), 6.29 (d, *J* = 1.4 Hz, 1H), 6.06 (s, 1H), 5.45 (s, 1H), 4.24 (s, 3H), 4.20–4.09 (m, 4H), 4.07–4.04 (m, 1H), 4.03–3.98 (m, 6H), 3.97–3.95 (m, 4H), 3.94–3.91 (m, 3H), 3.85–3.82 (m, 3H), 3.81–3.76 (m, 8H), 3.73 (d, *J* = 4.4 Hz, 3H), 3.71 (s, 3H), 3.69 (s, 1H), 3.68–3.67 (m, 2H), 3.67 (s, 2H), 3.66 (s, 1H), 3.66 (s, 3H), 3.65–3.63 (m, 3H), 3.62 (s, 3H), 3.61–3.58 (m, 2H), 3.57 (s, 3H), 3.56–3.49 (m, 8H), 3.49 (s, 3H), 3.47 (s, 3H), 3.45 (s, 3H), 3.42 (d, *J* = 4.0 Hz, 2H), 3.41–3.38 (m, 3H), 3.38–3.35 (m, 1H), 3.29 (s, 3H), 3.20 (s, 3H), 3.19–3.17 (m, 1H), 3.09 (d, *J* = 4.4

Hz, 1H), 3.07–2.99 (m, 2H), 2.87–2.83 (m, 1H), 1.65–1.54 (m, 1H), 1.28 (s, 9H), 1.27–1.22 (m, 10H). **HRMS** (ESI+) calcd. for $C_{208}H_{200}N_{36}O_{44}S_7$ $[M+2H]^{2+}$ 2065.6355, found 2065.6050.

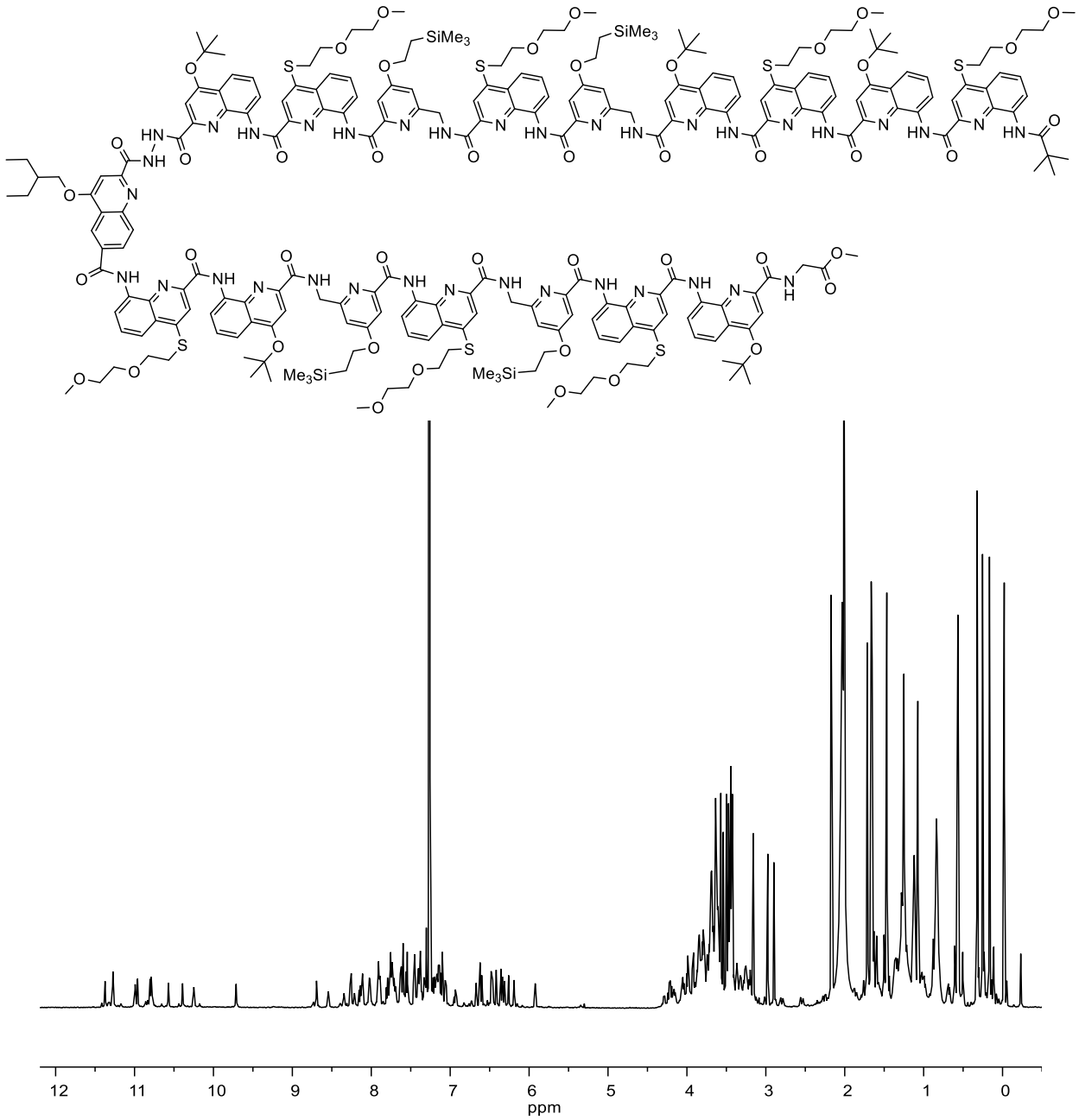
6. NMR spectra of new compounds



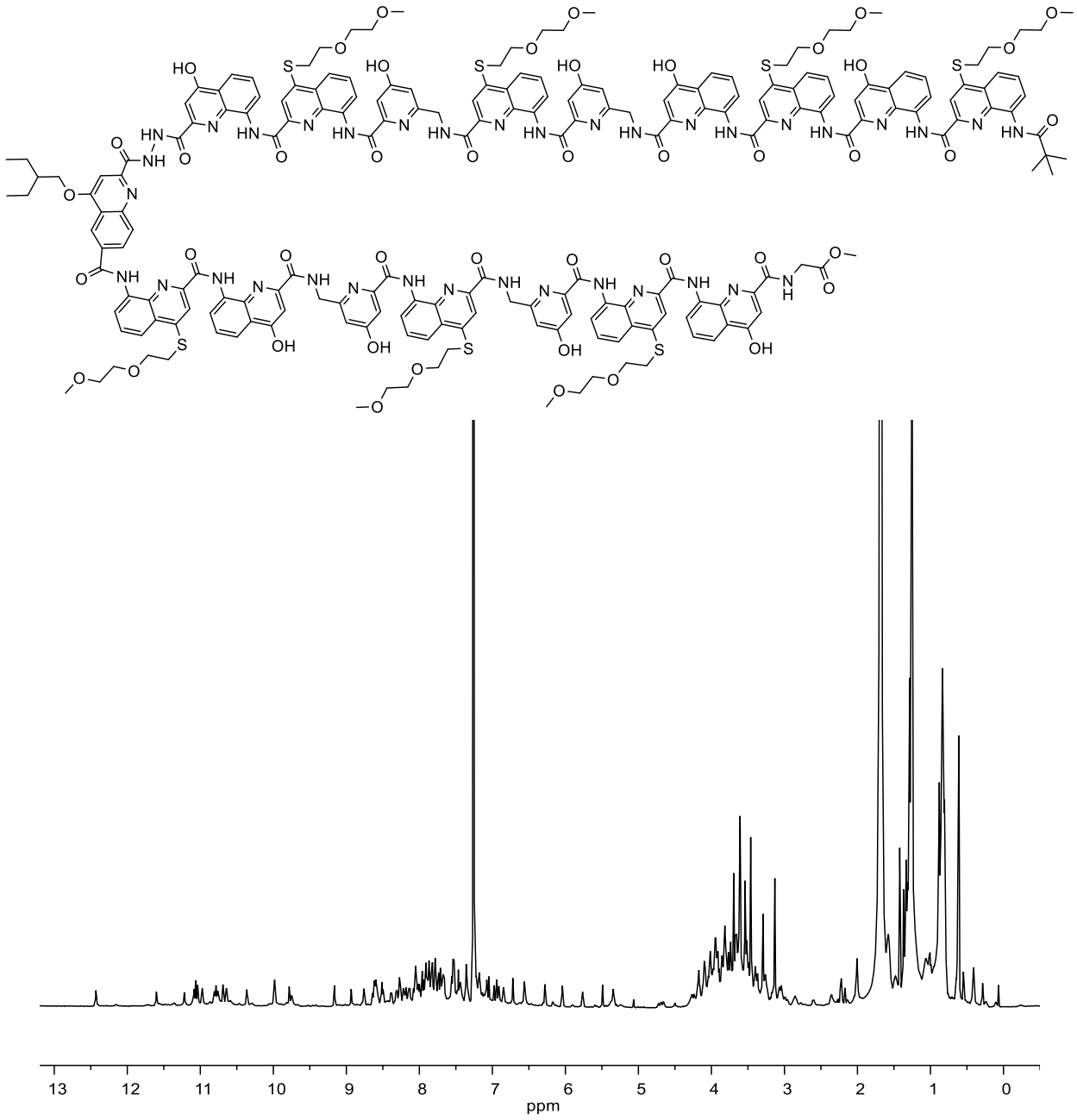
Chemical structure and ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of **2a**.



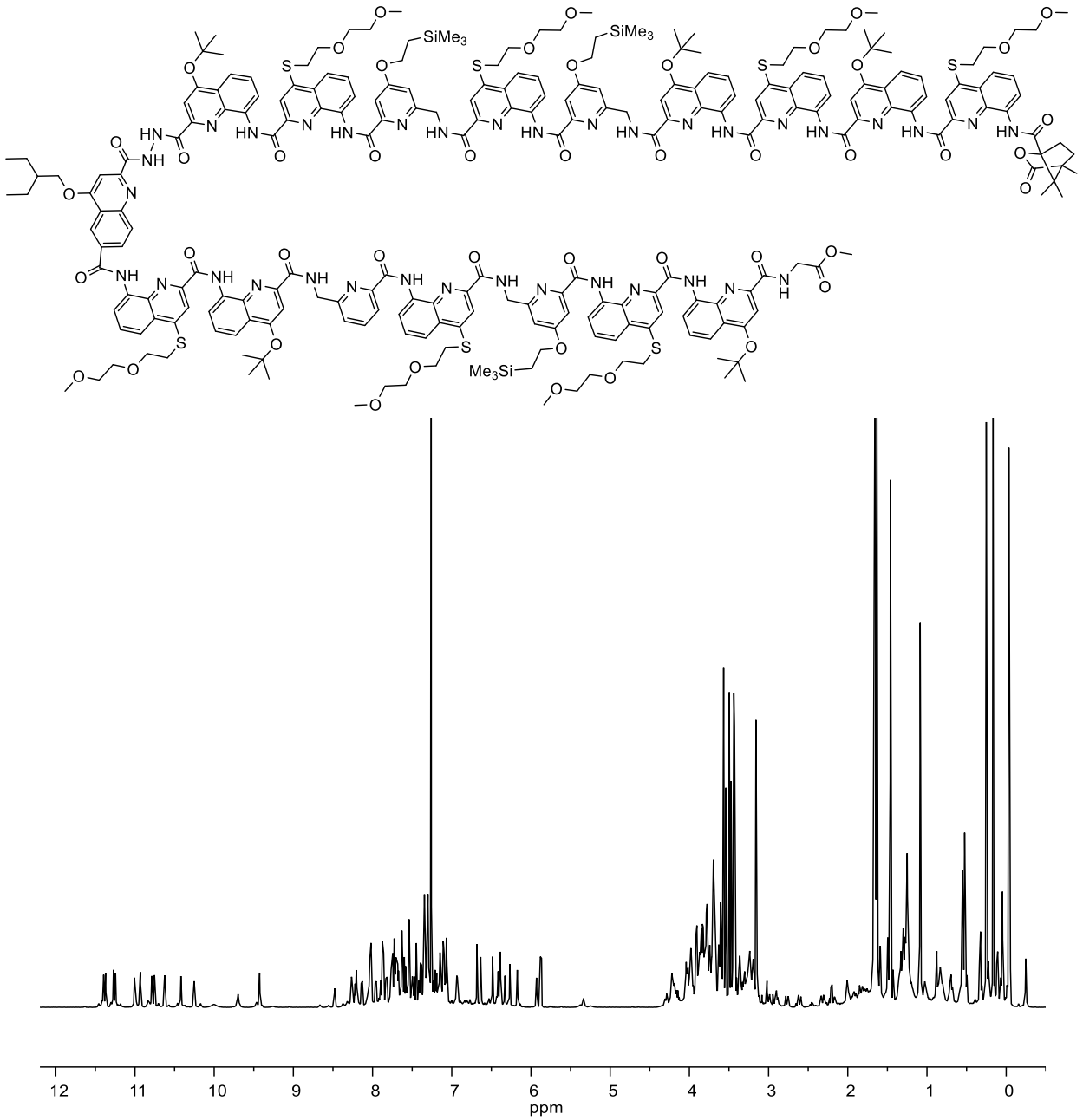
Chemical structure and ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of **2b**.



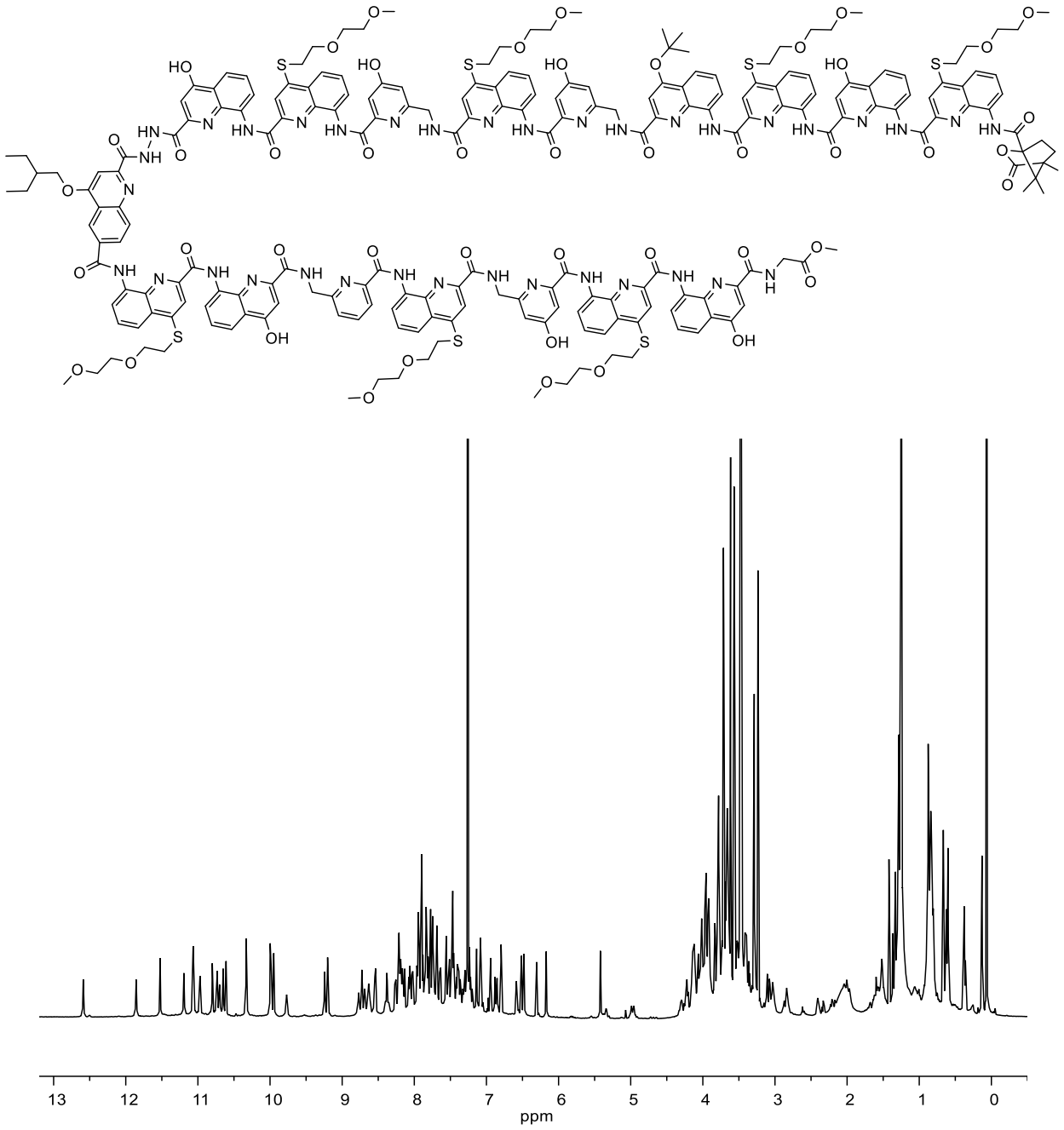
Chemical structure and ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of **3a**.



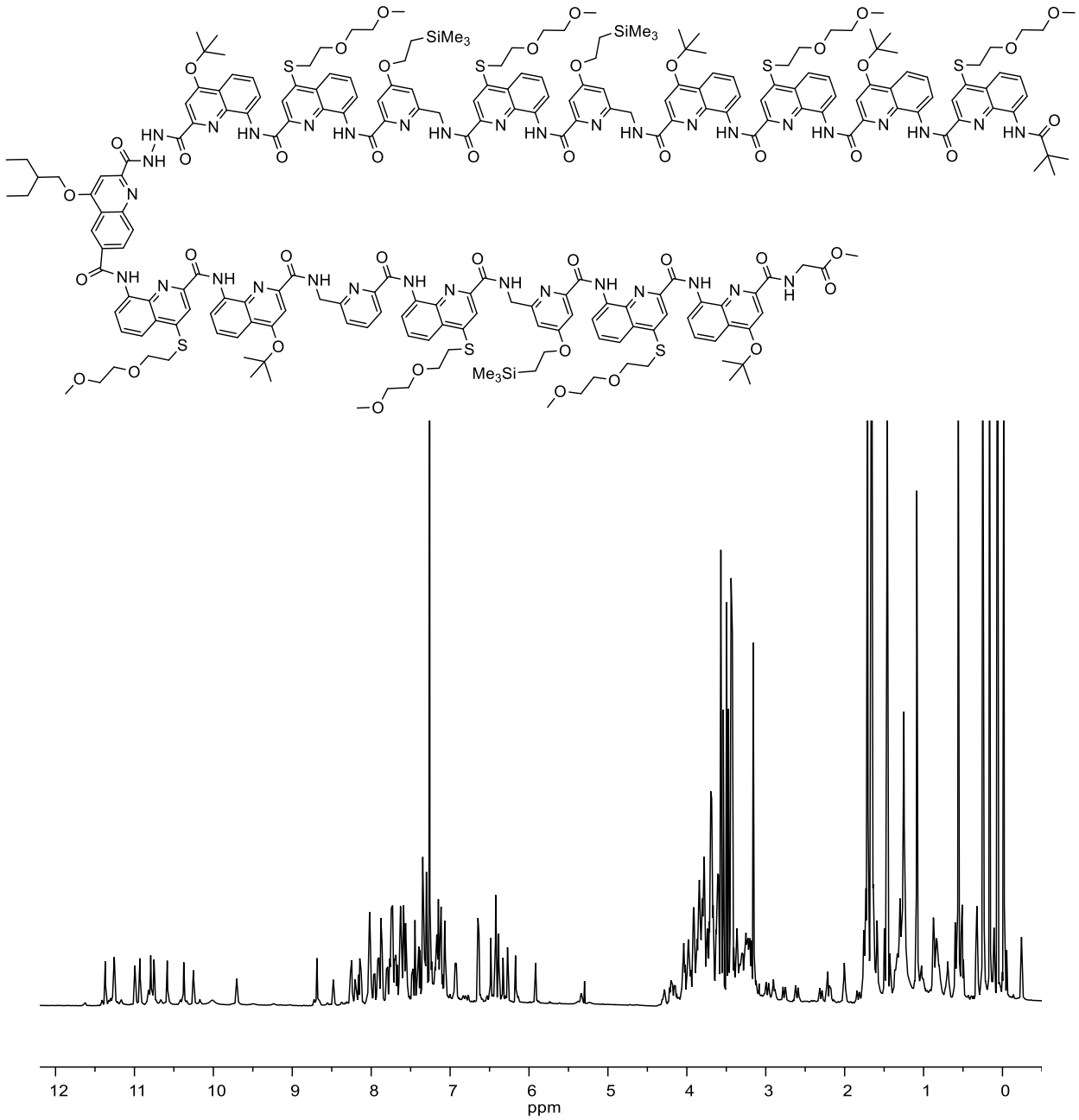
Chemical structure and ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of **3b**.



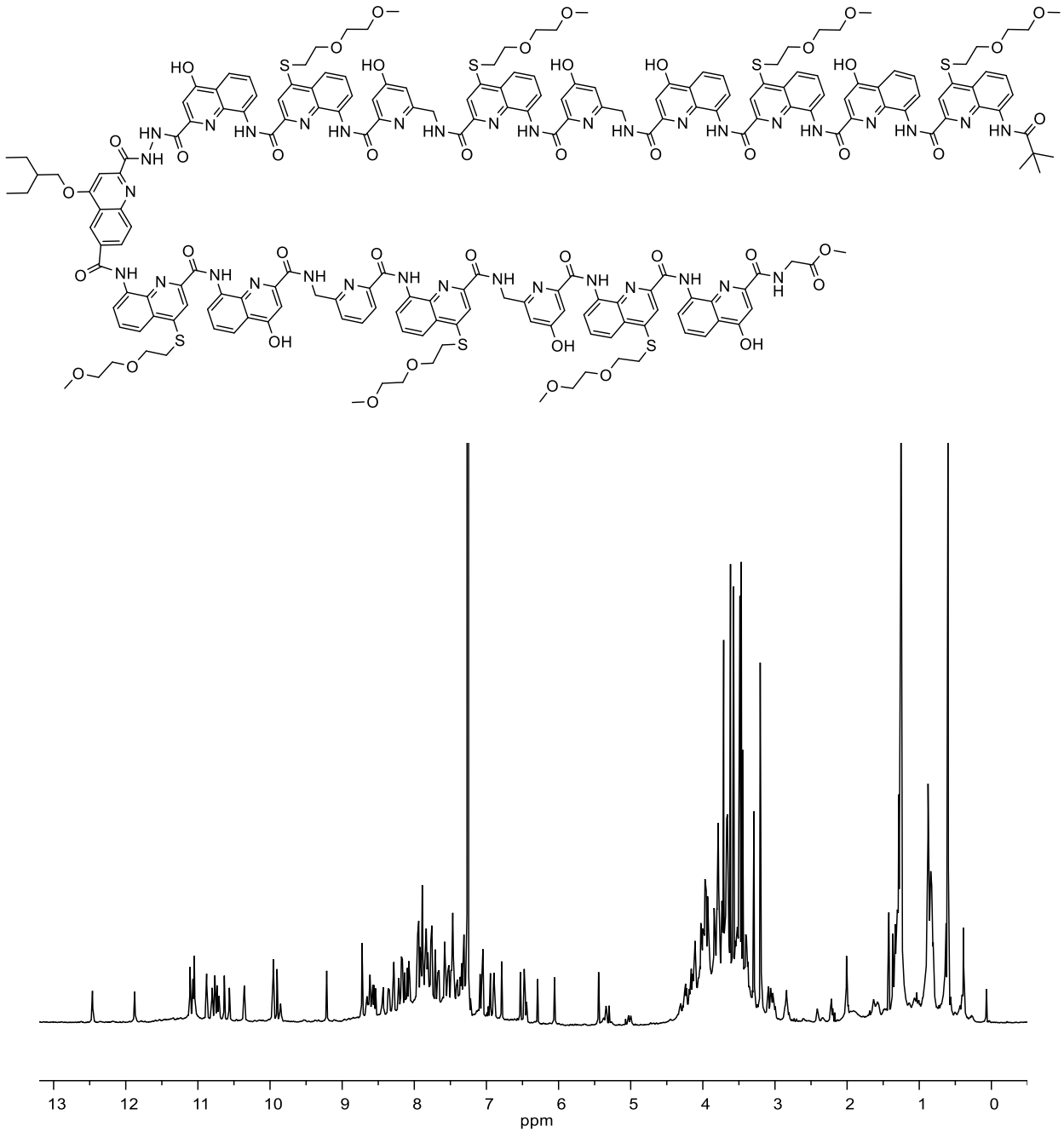
Chemical structure and ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of **4a**.



Chemical structure and ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of **4b**.



Chemical structure and ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of **5a**.



Chemical structure and ^{1}H NMR spectrum (500 MHz, $CDCl_3$, 25 °C) of **5b**.