Supplementary information for:

Glycoligand-Targeted Core-Shell Nanospheres with Tunable Drug Release Profiles from Calixarene-Cyclodextrin Heterodimers.

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General methods. Reagents and solvents were purchased from commercial sources and used without further purification. Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with Sílica Gel 60 F_{254}Merck (0.25 mm), with visualization by UV light (λ 254 nm) and by charring with 10% H_2SO_4, ninhydrin (0.1% in ethanol), or Mostain (20 g of ammonium molibdate·$4H_2O$, 0.4 g of $Ce(SO_4)_2 \cdot H_2O$ and 10% H_2SO_4 in 400 mL of H_2O) and heating at 300 ºC. With preparative purposes, column chromatography was carried out on Sílice 60 A.C.C. Chromagel (SDS, E. Merck, 230-400 mesh). Optical rotations were measured at 20 ± 2 ºC in 1-cm or 1-dm tubes on a Jasco P-2000 polarimeter using Na D line (λ 589 nm), 0.2-1% (w/v) solutions and 1-cm cells. Elemental analyses were performed at the Instituto de Investigaciones Químicas (Seville, Spain) using an elemental analyser Leco CHNS-932 or LecoTruSpec CHN. IR spectra were recorded on a Jasco FT/IR-4100 (ATR) spectrometer. UV spectra were recorded on a Jasco UV-630 spectrometer at 25 ºC. ^{1}H (and ^{13}C NMR) spectra were recorded at 500 (125.7), 400 (100.6) and 300 (75.5) MHz with, respectively, Bruker AVANCE DRX 500 (500 MHz), Bruker AVANCE DRX 400 (400 MHz) and Bruker AVANCE 300 (300 MHz) spectrometers. 2D COSY, 1D TOCSY and HMQC experiments were used to assist on NMR assignments. $CDCl_3$, and CD_3OD have been used as solvents. Electrospray mass spectra were obtained for samples dissolved in MeCN, MeOH or H_2O-MeOH mixtures at low μm concentrations. 25,26,27,28-Tetrakis(*n*-hexyloxy)calix[4]arene (**4**),[1] 25,26,27,28-tetrakis(*n*-docecyloxy)calix[4]arene (**11**),[2] $2^{I–VII}$,$3^{I–VII}$,$6^{II–VII}$-icosa-*O*-methyl-6^{I}-*p*-toluenesulfonylcyclomaltoheptaose (**18**),[3] α-amino-ω-azidotetra(ethyleneglycol)[4] and tris(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl-oxymethyl)methyl isothiocyanate[5] were prepared according to reported procedures.

Preparation of unloaded (blank) nanospheres from the amphiphilic CA_4-βCD heterodimers 1 and 2. Nanosphere suspensions were prepared using the nanoprecipitation technique,[6] taking advantage of the spontaneous self-assembling capabilities of **1** and **2** when dispersed into an aqueous phase. Briefly, the corresponding amphiphilic derivative was dissolved in anhydrous acetone or methanol to a final concentration of 0.5 mM. This solution was incorporated dropwise for 5 min into an equal volume of distilled water with magnetic stirring (500 rpm) at 25 ºC. Nanoparticles were formed spontaneously and the organic solvent was removed under reduced pressure at 35 ºC. The aqueous suspension was characterized, and stored in closed vials.

Preparation of docetaxel (DXT)-loaded nanospheres. DXT-loaded nanosphere suspensions were prepared from acetone solutions containing both the corresponding CA_4-βCD heterodimer **1** or **2** (0.5 mM) and docetaxel (2 mM), following the above described procedure but adding Polysorbate 80 to the aqueous phase at a concentration of 1 mg·mL^{-1} before nanoprecipitation. Unloaded Docetaxel was eliminated by centrifugation (5000 rpm, 15 min). The nanoparticle suspensions were prepared in duplicate and were stored in closed vials at +4 ºC. The amount of encapsulated drug in the formulations was determined spectrophotometrically at 230 nm following solubilization of a known volume of the DXT-loaded nanosphere suspension in methanol. The encapsulation efficiency was 95% and 93% for nanospheres formulated with compounds **1** and **2**, respectively.

Determination of the hydrodynamic diameter and ζ-potential of the nanospheres. The average sizes of the nanopartricles were measured in distilled water using a Zetasizer Nano ZS (Malvern Instruments) with the following specification: sampling time, automatic; number of measurements, 3 per sample; medium viscosity, 1.054 cP; refractive index, 1.33; scattering angle, 173º; λ= 633 nm; temperature, 25 ºC. Data were analyzed using the multimodal number distribution software included in the instrument. Results are presented in Tables S1-S3 as volume distribution of the major population by the mean diameter with its standard deviation (SD) and the corresponding polydispersity index (PI) with its standard deviation (SD). No significant differences were encountered when the data were expressed in intensity or number distributions. This is consistent with a spherical topology of the nanospheres. ζ-Potentials were determined using the "mixed-mode measurement" phase analysis light scattering (M3-PALS) (Tables S1-S3). Before each series of experiments, the performance of the instruments was checked with either a 90 nm monodisperse latex beads (Coulter) for DLS or with DTS 50 standard solution (Malvern) for ζ-potentials.

Table S1. Hydrodynamic diameter (nm), polydispersity index (PI) and ζ Potential (mV) of blank nanospheres prepared from **1** and **2** in distilled water.

Compound	Size (nm)±SD	PI ±SD	ζ Potential (mV) ±SD
1	129 ± 1	0.041 ± 0.028	-31 ± 2
2	189 ± 1	0.054 ± 0.004	-14.2 ± 0.1

Table S2. Hydrodynamic diameter (nm), polydispersity index and ζ-potential (mV) of DXT-loaded nanospheres prepared from **1** and **2** in distilled water.

Compound	Size (nm)±SD	PI ±SD	ζ Potential (mV) ±SD
1-DXT	35 ± 1	0.283 ± 0.019	-13.3 ± 0.4
2-DXT	19.8 ± 0.3	0.231 ± 0.011	-12.7 ± 0.7

Table S3. Hydrodynamic diameter (nm) and polydispersity index of blank nanospheres prepared from **1** and **2** after supramolecular surface post-modification with 30% or 60% of **3** in distilled water.

Compound	Size (nm)±SD	PI	ζ Potential (mV) ±SD
1 + 3 (30%)	136 ± 1	0.040 ± 0.026	-29 ± 1
1 + 3 (60%)	138 ± 1	0.053 ± 0.023	-27 ± 2
2 + 3 (30%)	198 ± 2	0.052 ± 0.006	-13 ± 2
2 + 3 (60%)	201 ± 2	0.056 ± 0.006	-9 ± 1

Nanosphere imaging by Atomic Force Microscopy (AFM). A 20 µL droplet of blank nanosphere suspensions, prepared as described above, was deposited onto freshly-cleaved ruby mica (Ted Pella, Redding, CA) for 2 h and the mica disk was dried under reduced pressure. AFM imaging was performed on the dried sample with a Nanoscope IIIA Microscope (Digital Instruments Inc. Santa Barbara, CA) operating in tapping mode. Commercial diving board silicon cantilevers (NSC-15 Micromash Corp., Estonia) were

used. Images of 512×512 pixels were collected with a scan size of 5 µm at a scan rate of 3 lines per second and were flattened after recording using Nanoscope software.

For DXT-loaded nanospheres, 50 µL of 3-aminopropyltriethoxysilane solution (10% in water) was deposited onto freshly-cleaved ruby mica (SPI, V-4) for 40 min and the mica was washed with Milli-Q water. Then, a 50 µL droplet of nanosphere solution was deposited onto the mica for 20 min. The mica was washed with Milli-Q water and dried at rt for 30 min. AFM imaging was performed on the dried sample with a Molecular Imaging PicoPlus 2500 Microscope (Agilent Technologies) operating in tapping mode. Commercial diving board silicon cantilevers (Pointprobe-Plus Silicon-SPM-Sensor, Nanosensors; resonance frequency 204-497 kHz) were used. Images of 256×256 pixels were collected with a scan size of 5 µm at a scan rate of 1 line per second and were flattened after recording using PicoView 1.14.3 software.

As examples, AFM images of blank nanospheres obtained from **2** (up) and of the DXT-loaded nanospheres prepared from **1** (down left) and the corresponding heigth in the Z-axis (dwon right), which actually represent the diameter of the particles (about 30 nm) are given in Figure S1.

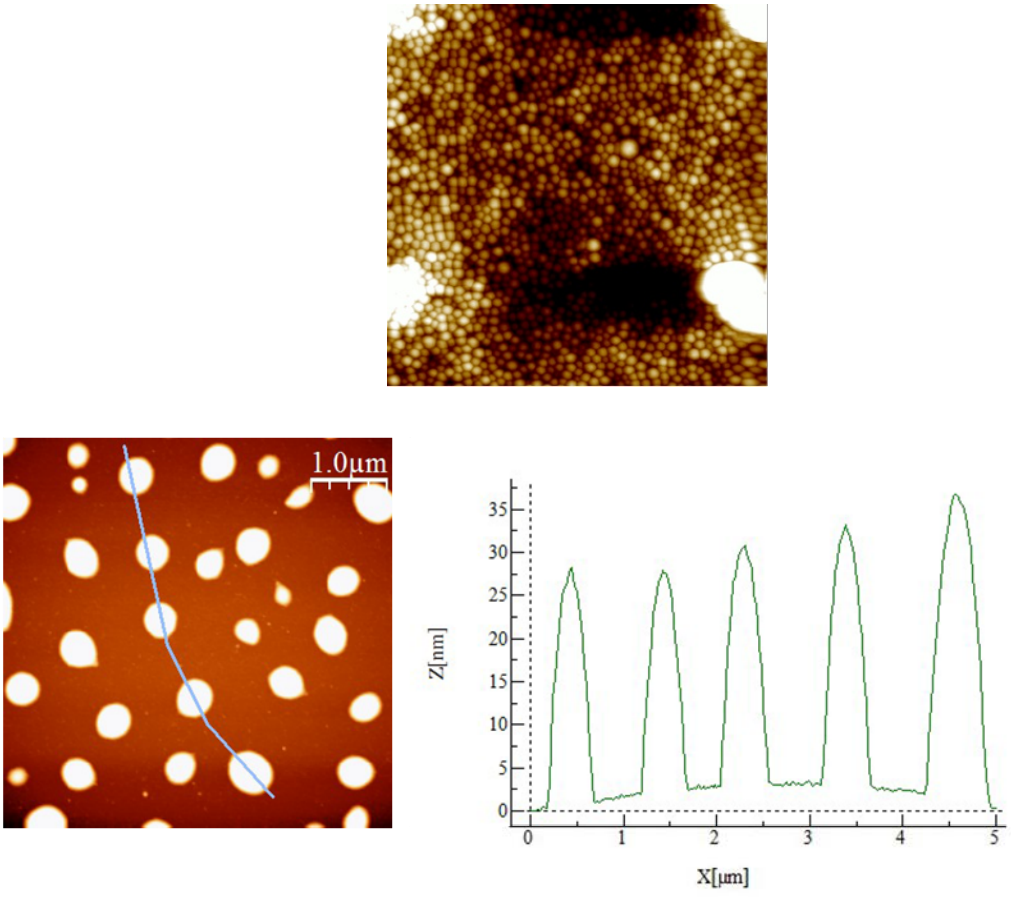


Figure S1. Tapping mode AFM image (5 x 5 µm) of nanospheres obtained from **2** (up) of the DXT-loaded nanospheres obtained by self-assembling of **1** in the presence of the drug (down left) and projection of their height in the Z-axis (down right; the blue line represent the trajectory in the XY plane).

DXT release kinetics from nanospheres. In vitro release kinetics studies were performed by dialysis (cutoff of 12 kDa, Sigma), in phosphate buffer saline medium (PBS, 0.01 M, pH 7.3) at 37 °C. 5 mL of drug-loaded nanospheres were dialyzed against 125 mL of PBS with smooth stirred. Aliquots were withdrawn at 1 h intervals, measured spectrophotometrically at 230 nm and then returned to system. Concentration of docetaxel in the PBS medium was determined by absorbance interpolation in a PBS calibration curve.

Evaluation of the binding affinity of nanospheres modified with the mannosyl dendron 3 towards the human macrophage mannose receptor by modified enzyme-linked lectin assay (ELLA). Nunc-Inmuno plates (MaxiSorp™) were coated overnight with yeast mannan at 100 μL/well diluted from a stock solution of 10 $\mu g \cdot mL^{-1}$ in 10 mm phosphate buffer saline (PBS, pH 7.3 containing 0.1 mm Ca^{2+} and 0.1 mm Mn^{2+}) at rt. The wells were then washed three times with 300 μL of washing buffer (containing 0.05% (v/v) Tween 20) (PBST). The washing procedure was repeated after each of the incubations throughout the assay. The wells were then blocked with 150 μL/well of 1% BSA/PBS for 1 h at 37 ºC.

For determination of recombinant human MMR (rhMMR) binding affinity, the wells were filled with 100 μL of serial dilutions of rhMMR from a 10 $\mu g \cdot mL^{-1}$ stock solution in PBS (pH 7.3 containing 0.1 mm Ca^{2+} and 0.1 mm Mn^{2+}), and incubated at 37 ºC for 1 h. The plates were washed three times with PBST as described above and 100 μL of a solution of biotinylated anti-human MMR antibody (0.2 $mg \cdot mL^{-1}$, R&D Systems) in PBS was added in each well, and the plates were further incubated for 1 h at 37 ºC. The complex NeutrAvidin®-biotinylated HRP was preformed separately by successively adding to Tris buffer (9.6 mL, 50 mM, pH 7.6) a solution of Neutravidin® (100 □$g \cdot mL^{-1}$ in Tris buffer, 1.2 mL, Thermo Scientific) and a solution of biotin-conjugated HRP (25 $\mu g \cdot mL^{-1}$ in Tris buffer, 1.2 mL, Thermo Scientific). The mixture was shaken for 30 min at rt and the solution was immediately transferred into the plates (60 μL/well). After 1 h at 37 ºC, these plates were washed twice with Tris (250 μL/well) and ABTS (0.25 $mg \cdot mL^{-1}$, 50 μL/well) in citrate buffer (0.2 m, pH 4.0 with 0.015% H_2O_2) was added. After 5 min at rt, the optical density was measured at 415 nm. Blank wells were processed with anti-human MMR antibody as well as NeutrAvidin®-biotinylated HRP. The concentration of rhMMR that displayed an absorbance between 0.8 and 1.0 was used for inhibition experiments. For the competitive lectin binding inhibition experiment, the adamantane-armed mannosyl dendron **3** or the nanospheres formulated from heterodimers **1** and **2** and post-modified with 10, 30 or 60% of **3** were mixed in a serial of 2-fold dilutions (60 mL per well) in HEPES buffer (20 mm, pH 7.4) with 60 mL of the appropriate rhMMR concentration in PBS buffer on Nunclon® (Delta) microtitre plates and incubated for 1 h at 37 ºC. The above solutions (100 μL) were then transferred to the mannan-coated titer plates, which were incubated for 1 h at 37 ºC. The plates were washed and the solution of biotinylated anti-human MMR antibody in PBS (100 μL) was added in each well, and the plates were further incubated for 1 h at 37 ºC. Then the NeutrAvidin solution was transferred into the plates (60 μL/well). After 1 h at 37 ºC, these plates were washed twice with Tris (250 μL/well) and ABTS was added (50 μL/well). Optical density at 415 nm was determined after 5 min.

The percentage of inhibition was calculated as follows:

$$\% \text{ Inhibition} = [A_{(\text{no inhibitor})} - A_{(\text{with inhibitor})}]/A_{(\text{no inhibitor})} \times 100$$

Results in triplicate were used for plotting the inhibition curves for each individual ELLA experiment. Typically, the IC_{50} values (concentration required to achieve 50% inhibition of the lectin association to the coating polysaccharide) obtained from several independently performed tests were in the range of ± 15%. Nevertheless, the relative inhibition values calculated from independent series of data were highly reproducible.

Competitive ELLA experiments in the presence of adamantane 1-carboxylate sodium salt. To nanosphere formulations obtained from **1** or **2** decorated with 30% of **3** at 31.25μM (based on **3**), adamantine 1-carboxylate sodium salt (AC) was added so as to have a final concentration of 312.5 μM (10-fol excess with respect to **3**). The capacity of these new formulations to inhibit the association of human MMR to immobilized yeas mannan according to the above ELLA experimental setup was next determined in comparison with the corresponding formulations before addition of AC. A strong decrease in the inhibition potency, meaning a significant weakening of the biniding affinity of the nanospheres towards the lectin, was observed (Figure). As a control, the effect of a 10-fold excess of AC on the inhibition potency of **3** under identical conditions was found to be negligible.

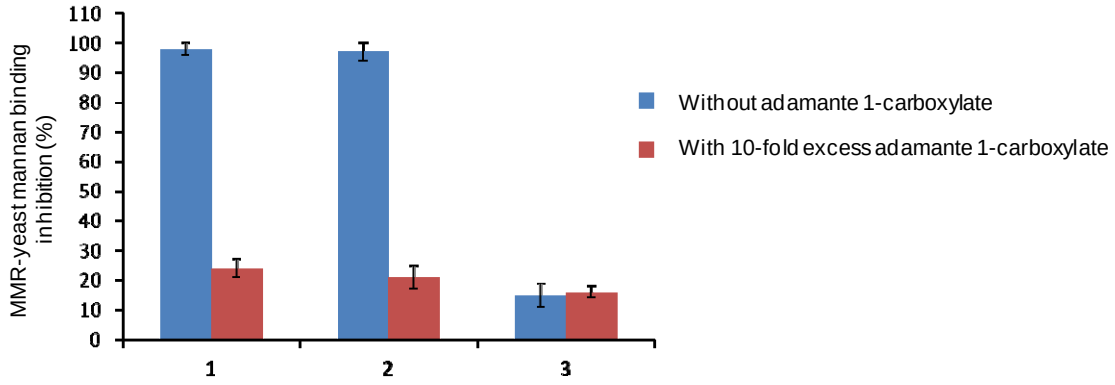
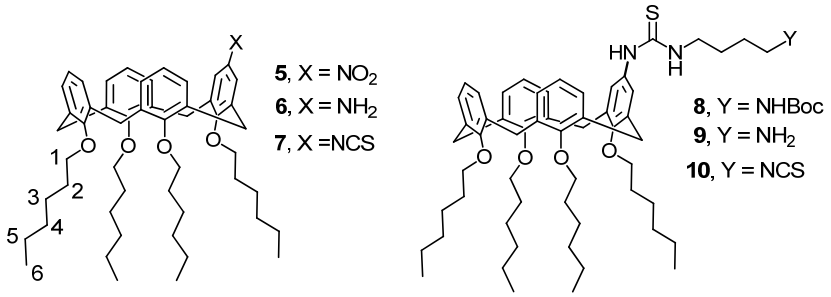


Figure S2. Inhibition (%) of the association of human MMR to immobilized yeast mannan by nanospheres obtained from CD-CA heterodimers **1** and **2** decorated with 30% of the mannosyl dendron **3** at 31.25 mM concentration (base don **3**) as well as by pure **3** in the absence (blue bars) or in the presence of adamantane 1-carboxylate sodium salt at 312.5 mM (10-fold excess). Data are expressed as averages of three independent determinations ± SD.

Preparation of calix[4]arene derivatives 5-10.



5-Nitro-25,26,27,28-tetrakis(*n*-hexyloxy)calix[4]arene (5). To a solution of 25,26,27,28-tetrakis(*n*-hexyloxy)calix[4]arene[1] (**4**, 1 g, 1.32 mmol) in dry DCM (20 mL), glacial AcOH (1.7 mL, 39.60 mmol) was added. Then, 99.5% HNO_3 (356 μL, 7.92 mmol) was added and the mixture was stirred 40 min at rt. After addition of H_2O (20 mL), the organic layer was separated, washed with sat. $NaHCO_3$ (20 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (1:6 → 1:2 DCM-cyclohexane). Yield: 811 mg (76%); R_f = 0.29 (1:15 EtOAc-cyclohexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (s, 2 H, Ar), 6.94 (t, *J* = 6.9 Hz, 4 H, Ar), 6.83 (t, *J* = 7.2 Hz, 2 H, Ar), 6.23 (bs, 3 H, Ar), 4.47 (d, *J* = 13.6 Hz, 2 H, ArC*H*$_{ax}$Ar), 4.39 (d, *J* = 13.6 Hz, 2 H, ArC*H*$_{ax}$Ar), 4.05-3.84 (m, 6 H, CH_2-1$_{Hex}$), 3.76 (t, *J* = 6.9 Hz, 2 H, CH_2-1$_{Hex}$), 3.21 (d, *J* = 11.7 Hz, 2 H, ArC*H*$_{eq}$Ar), 3.16 (d, *J* = 11.7 Hz, 2 H, ArC*H*$_{eq}$Ar), 1.95-1.82 (m, 8 H, CH_2-2$_{Hex}$), 1.55-1.27 (m, 24 H, CH_2-3$_{Hex}$, CH_2-4$_{Hex}$, CH_2-5$_{Hex}$), 0.99-0.83 (m, 12 H, CH_3-6$_{Hex}$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.4-121.7 (Ar), 75.5, 75.2 (C-1$_{Hex}$), 32.1, 31.9 (C-3$_{Hex}$), 31.1, 30.9 (ArCH_2Ar), 30.4, 30.3 (C-2$_{Hex}$), 26.1, 26.0 (C-4$_{Hex}$), 22.9, 22.8 (C-5$_{Hex}$), 14.1, 14.2 (C-6$_{Hex}$). ESI-MS: *m/z* 828.5 $[M + Na]^+$, 844.4 $[M + K]^+$. Anal. calcd for $C_{52}H_{71}NO_6$: C 77.48, H 8.88, N 1.74. Found: C 77.57, H 9.03, N 1.65.

5-Amino-25,26,27,28-tetrakis(*n*-hexyloxy)calix[4]arene (6). To a solution of **5** (429 mg, 0.53 mmol) in EtOH (20 mL), hydrazine monohydrate (518 μL, 10.6 mmol) and Pd/C (43 mg, 10% w/w) were added. The mixture was refluxed for 6 h, the catalyst was filtrated off and the solvent was removed under reduced pressure. Yield: 381 mg (93%); R_f = 0.41 (DCM). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.68-6.53 (m, 9 H, Ar), 5.95 (s, 2 H, NH_2), 4.46 (d, *J* = 13.2 Hz, 2 H, ArC*H*$_{ax}$Ar), 4.37 (d, *J* = 13.2 Hz, 2 H, ArC*H*$_{ax}$Ar), 3.90-3.84 (m, 6 H, CH_2-1$_{Hex}$), 3.79 (m, 2 H, CH_2-1$_{Hex}$), 3.15 (d, *J* = 13.2 Hz, 2 H, ArC*H*$_{eq}$Ar), 3.03 (d, *J* = 13.2 Hz, 2 H, ArC*H*$_{eq}$Ar), 1.98-1.81 (m, 8 H, CH_2-2$_{Hex}$), 1.46-1.28 (m, 24 H, CH_2-3$_{Hex}$, CH_2-4$_{Hex}$, CH_2-5$_{Hex}$), 0.98-0.85 (m, 12 H, CH_3-6$_{Hex}$).^{13}C NMR (75.5 MHz, $CDCl_3$) δ 156.8-121.6 (Ar), 75.3, 75.2 (C-1$_{Hex}$), 32.1 (C-3$_{Hex}$), 31.1, 31.0 (ArCH_2Ar), 30.3 (C-2$_{Hex}$), 25.9 (C-4$_{Hex}$), 22.9 (C-5$_{Hex}$), 14.2 (C-6$_{Hex}$). ESI-MS: *m/z* 798.6 $[M + Na]^+$, 814.5 $[M + K]^+$. Anal. calcd for $C_{52}H_{73}NO_4$: C 80.47, H 9.48, N 1.80. Found: C 80.55, H 9.40, N 1.71.

5-Isothiocyanato-25,26,27,28-tetrakis(*n*-hexyloxy)calix[4]arene (7). To a solution of **6** (382 mg, 0.49 mmol) in dry toluene (30 mL), Et_3N (412 μL, 2.95 mmol) and Cl_2CS (113 μL, 1.47 mmol) were added. The reaction mixture was stirred for 5 h at rt. Then, the solvent was removed under reduced pressure, DCM was added (15 mL) and the organic layer was washed with H_2O (15 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (1:3 DCM-cyclohexane). Yield: 362 mg

(90%); R_f = 0.67 (1:3 DCM-cyclohexane). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (dd, J_1 = 7.5 Hz, J_2 = 1.6 Hz, 2 H, Ar), 6.87 (dd, J_1 = 7.5 Hz, J_2 = 1.6 Hz, 2 H, Ar), 6.81 (t, J = 7.2 Hz, 2 H, Ar), 6.49 (t, J = 7.2 Hz, 1 H, Ar), 6.32 (d, J = 7.5 Hz, 2 H, Ar), 6.12 (s, 2 H, Ar), 4.44 (d, J = 12.7 Hz, 2 H, ArCH_{ax}Ar), 4.40 (d, J = 12.7 Hz, 2 H, ArCH_{ax}Ar), 4.05-3.85 (m, 4 H, CH_2-1_{Hex}), 3.80-3.73 (m, 4 H, CH_2-1_{Hex}), 3.17 (d, J = 13.7 Hz, 2 H, ArCH_{eq}Ar), 3.09 (d, J = 13.7 Hz, 2 H, ArCH_{eq}Ar), 1.97-1.79 (m, 8 H, CH_2-2_{Hex}), 1.60-1.13 (m, 24 H, CH_2-3_{Hex}, CH_2-4_{Hex}, CH_2-5_{Hex}), 0.99-0.76 (m, 12 H, CH_3-6_{Hex}).^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.2-133.9 (Ar), 131.1 (CS), 129.0-121.8 (Ar), 75.2, 75.1, 75.0 (C-1_{Hex}), 32.0, 31.9, 31.8 (C-3_{Hex}), 30.9, 30.8 (ArCH_2Ar), 30.3, 30.2, 30.0 (C-2_{Hex}), 26.0, 25.9, 25.6 (C-4_{Hex}), 22.8, 22.7, 22.6 (C-5_{Hex}), 14.0, 13.9 (C-6_{Hex}). ESI-MS: *m/z* 840.5 $[M+Na]^+$, 856.5 $[M+K]^+$. Anal. calcd for $C_{53}H_{71}NO_4S$: C 77.80, H 8.75, N 1.71, S 3.92. Found: C 77.86, H 8.66, N 1.50, S 3.68.

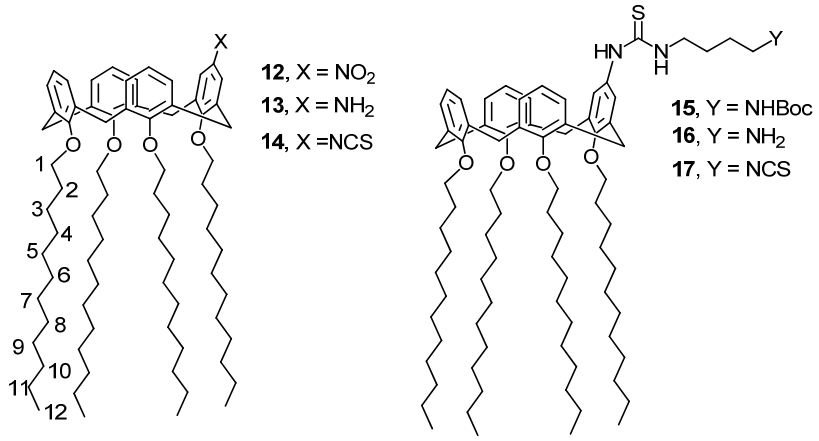
5-[*N'*-(4-(*tert*-Butoxycarbonylamino)butyl)thioureido]-25,26,27,28-tetrakis(*n*-hexyloxy)-calix[4]arene (8). To a solution of **7** (335 mg, 0.41 mmol) in dry DCM (5 mL), Et_3N (228 μL, 1.64 mmol) and a solution of commercial *N'*-[4-(*tert*-butoxycarbonylamino)]butylamine (154 mg, 0.82 mmol) in dry DCM (2 mL) was added. The mixture was stirred overnight at rt under Ar atmosphere. The solvent was eliminated under vacuum and the residue was purified by column chromatography (1:5 → 1:3 EtOAc-cyclohexane). Yield: 411 mg (99%). R_f = 0.27 (1:3 EtOAc-cyclohexane). ^{1}H NMR (500 MHz, CD_3OD) δ 6.99-6.70 (m, 4 H, Ar), 6.83-6.76 (m, 2 H, Ar), 6.37 (bs, 3 H, Ar), 6.22 (bs, 2 H, Ar), 4.49 (d, J = 13.2 Hz, 2 H, ArCH_{ax}Ar), 4.48 (d, J = 13.2 Hz, 2 H, ArCH_{ax}Ar), 4.07-3.95 (m, 4 H, CH_2-1_{Hex}), 3.83-3.75 (m, 4 H, CH_2-1_{Hex}), 3.44 (t, J = 6.7 Hz, 2 H, CH_2NHCS), 3.19 (d, J = 13.2 Hz, 2 H, ArCH_{eq}Ar), 3.17 (d, J = 13.3 Hz, 2 H, ArCH_{eq}Ar), 3.08 (t, J = 6.5 Hz, 2 H, CH_2NHBoc), 2.03-1.88 (m, 8 H, CH_2-2_{Hex}), 1.63-1.31 (m, 37 H, CH_2-3_{Hex}, CH_2-4_{Hex}, CH_2-5_{Hex}, CH_2CH_2CH$_2$NHCS, CMe_3), 0.98-0.88 (m, 12 H, CH_3-6_{Hex}). ^{13}C NMR (125.7 MHz,CD_3OD) δ 180.8 (CS), 158.5 (CO), 158.4-122.8 (Ar), 76.6 (*C*Me_3), 76.4, 76.3 (C-1_{Hex}), 45.4 (*C*H_2NHCS), 41.1 (*C*H_2NHBoc), 33.5, 33.3 (C-3_{Hex}), 31.9, 31.8 (Ar*C*H_2Ar), 31.4 (C-2_{Hex}), 28.8 (C*Me*$_3$), 28.3 (*C*H_2CH$_2$NHCS), 27.6, 27.5 (C-4_{Hex}), 27.2 (*C*H_2CH$_2$CH$_2$NHCS), 24.0, 23.9 (C-5_{Hex}), 14.6, 14.5 (C-6_{Hex}). ESI-MS: *m/z* 1028.7 $[M+Na]^+$, 1044.6 $[M+K]^+$. Anal. calcd for $C_{62}H_{91}N_3O_6S$: C 73.99, H 9.11, N 4.18, S 3.19. Found: C 74.05, H 9.20, N 4.09, S 2.98.

5-[*N'*-(4-(Amino)butyl)thioureido]-25,26,27,28-tetrakis(*n*-hexyloxy)calix[4]arene (9). A solution of **8** (342 mg, 0.34 mmol) in TFA-DCM (1:10, 5 mL) was stirred at rt for 1 h. The solvent was evaporated under reduced pressure and coevaporated several times with water. The residue was dissolved in 0.1 M HCl solution and freeze-dried to obtain **9** as the corresponding hydrochloride salt. Yield: 320 mg (99%). ^{1}H NMR (400 MHz, CD_3OD) δ 6.90 (t, J = 7.6 Hz, 4 H, Ar), 6.74 (t, J = 7.4 Hz, 2 H, Ar), 6.38 (s, 3 H, Ar), 6.24 (s, 2 H, Ar), 4.46 (d, J = 13.1 Hz, 2 H, ArCH_{ax}Ar), 4.45 (d, J = 13.1 Hz, 2 H, ArCH_{ax}Ar), 4.09-3.92 (m, 4 H, CH_2-1_{Hex}), 3.87-3.73 (m, 4 H, CH_2-1_{Hex}), 3.52 (t, J = 6.9 Hz, 2 H, CH_2NHCS), 3.15 (d, J = 13.3 Hz, 2 H, ArCH_{eq}Ar), 3.14 (d, J = 13.3 Hz, 2 H, ArCH_{eq}Ar), 3.01 (t, J = 6.9 Hz, 2 H, CH_2NH$_2$), 2.05-1.84 (m, 8 H, CH_2-2_{Hex}), 1.63-1.50 (m, 4 H, CH_2CH_2CH$_2$NHCS), 1.48-1.30 (m, 24 H, CH_2-3_{Hex}, CH_2-4_{Hex}, CH_2-5_{Hex}), 1.03-0.88 (m, 12 H, CH_3-6_{Hex}). ^{13}C NMR (100.6 MHz, CD_3OD) δ 181.2 (CS), 158.4-122.8 (Ar), 76.5, 76.3 (CH_2-1_{Hex}), 44.5 (*C*H_2NHCS), 40.4 (*C*H_2NH$_2$), 33.5, 33.3 (C-3_{Hex}), 31.9, 31.7 (Ar*C*H_2Ar), 31.4 (C-2_{Hex}), 27.5

(CH_2CH_2NHCS), 27.3, 27.2 (C-4_{Hex}), 25.6 ($CH_2CH_2CH_2NHCS$), 24.1, 24.0 (C-5_{Hex}), 14.5 (C-6_{Hex}). ESI-MS: *m/z* 906.7 $[M + H]^+$. Anal. calcd for $C_{57}H_{84}ClN_3O_4S$: C 72.61, H 8.98, N 4.46, S 3.40. Found: C 72.54, H 9.00, N 4.26, S 3.19.

5-[*N'*-(4-(Isothiocyanato)buthyl)thioureido]-25,26,27,28-tetrakis(*n*-hexyloxy)-calix[4]arene (10). To a solution of **9** (364 mg, 0.40 mmol) in absolute EtOH (10 mL), CS_2 (242 μL, 4.02 mmol) and Et_3N (168 μL, 1.22 mmol) were added. The reaction mixture was stirred for 2 h at rt and then cooled on an ice bath. A solution of Boc_2O (83.3 mg, 0.38 mmol) in absolute EtOH (3 mL) was added followed by the immediate addition of a catalytic amount of DMAP (1 mg, 8 μmol). The reaction mixture was kept in an ice bath for 15 min, and then it was allowed to reach rt and stirred for further 2 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (1:3 → 1:1 DCM-cyclohexane). Yield: 381 mg (quantitative); R_f = 0.37 (DCM). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (d, *J* = 6.6 Hz, 2 H, Ar), 7.00 (d, *J* = 6.6 Hz, 2 H, Ar), 6.92-6.89 (m, 3 H, Ar, NH), 6.30 (t, *J* = 7.6 Hz, 1 H, Ar), 6.22 (d, *J* = 7.5 Hz, 2 H, Ar), 5.95 (s, 2 H, Ar), 5.43 (bt, 1 H, NH), 4.44 (d, *J* = 13.3 Hz, 4 H, ArCH_{ax}Ar), 4.12-3.95 (m, 4 H, CH_2-1_{Hex}), 3.78-3.69 (m, 4 H, CH_2-1_{Hex}), 3.61 (t, *J* = 6.2 Hz, 2 H, CH_2NCS), 3.53 (q, *J* = 6.6 Hz, 2 H, CH_2NHCS), 3.17 (d, *J* = 13.3 Hz, 2 H, ArCH_{eq}Ar), 3.11 (d, *J* = 13.3 Hz, 2 H, ArCH_{eq}Ar), 1.98-1.81 (m, 8 H, CH_2-2_{Hex}), 1.75-1.68 (m, 2 H, CH_2CH_2NCS), 1.66-1.60 (m, 2 H, CH_2CH_2NHCS), 1.58-1.45 (m, 6 H, CH_2-3_{Hex}, CH_2-4_{Hex}, CH_2-5_{Hex}), 1.42-1.19 (m, 18 H, CH_2-3_{Hex}, CH_2-4_{Hex}, CH_2-5_{Hex}), 0.98-0.84 (m, 12 H, CH_3-6_{Hex}). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 180.0 (HNCS), 157.5-133.7 (Ar), 129.3 (NCS), 129.2-121.3 (Ar), 75.6, 75.5, 75.1 (CH_2-1_{Hex}), 44.8 (CH_2NCS), 44.1 (CH_2NHCS), 32.2, 32.0, 31.9 (C-3_{Hex}), 31.1, 31.0 (ArCH_2Ar), 30.5, 30.4, 30.0 (C-2_{Hex}), 27.2 (CH_2CH_2NCS), 26.4 ($CH_2CH_2CH_2NCS$), 26.2, 26.1, 25.7 (C-4_{Hex}), 22.9, 22.7 (C-5_{Hex}), 14.1, 14.0 (C-6_{Hex}). ESI-MS: *m/z* 970.4 $[M + Na]^+$, 986.5 $[M + K]^+$. Anal. calcd for $C_{58}H_{81}N_3O_4S_2$: C 73.45, H 8.61, N 4.43, S 6.76. Found: C 73.13, H 8.87, N 4.13, S 6.44.

Preparation of calix[4]arene derivatives 12-17.



5-Nitro-25,26,27,28-tetrakis(*n*-dodecyloxy)calix[4]arene (12). To a solution of 25,26,27,28-tetrakis(*n*-dococyloxy)calix[4]arene[2] (**11**, 1.24 g, 1.13 mmol) in dry DCM (24 mL), glacial AcOH (1.36 mL, 33.9 mmol) was added. Then, 99.5% HNO_3 (305 μL, 6.78 mmol) was added. The mixture was stirred 30 min at rt. Then, H_2O was added (24 mL) and the organic layer was separated, washed with sat. $NaHCO_3$ (24 mL),

dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (1:6 → 1:2 DCM-Hex). Yield: 968 mg (75%); R_f = 0.52 (1:15 EtOAc-Hex). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (s, 2 H, Ar), 6.93 (t, *J* = 6.8 Hz, 3 H, Ar), 6.82 (t, *J* = 7.3 Hz, 3 H, Ar), 6.22 (bs, 3 H, Ar), 4.46 (d, *J* = 13.4 Hz, 2 H, ArC*H*$_{ax}$Ar), 4.41 (d, *J* = 13.4 Hz, 2 H, ArC*H*$_{ax}$Ar) 4.03-3.83 (m, 6 H, CH_2-1$_{Dod}$), 3.74 (t, *J* = 6.8 Hz, 2 H, CH_2-1$_{Dod}$), 3.19 (d, *J* = 11.9 Hz, 2 H, ArC*H*$_{eq}$Ar), 3.15 (d, *J* = 11.9 Hz, 2 H, ArC*H*$_{eq}$Ar), 1.92-1.83 (m, 8 H, CH_2-2$_{Dod}$), 1.58-1.08 (m, 74 H, CH_2-3$_{Dod}$, CH_2-4$_{Dod}$, CH_2-5$_{Dod}$, CH_2-6$_{Dod}$, CH_2-7$_{Dod}$, CH_2-8$_{Dod}$, CH_2-9$_{Dod}$, CH_2-10$_{Dod}$, CH_2-11$_{Dod}$), 0.89-0.85 (m, 10 H, CH_3-12$_{Dod}$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 161.5-121.7 (Ar), 75.5, 75.2, 75.1 (C-1$_{Dod}$), 32.0, 31.1, 31.0, 30.5-29.5 (Ar*C*H_2Ar and C-2 to C-9$_{Dod}$) 26.6, 26.4, 26.1 (C-10$_{Dod}$), 22.7 (C-11$_{Dod}$), 14.1 (C-12$_{Dod}$). ESI-MS: *m/z* 1164.67 $[M + Na]^+$. Anal. calcd for $C_{76}H_{119}NO_6$: C 79.88, H 10.50, N 1.23. Found: C 80.11, H 10.64, N 1.32.

5-Amino-25,26,27,28-tetrakis(*n*-dodecyloxy)calix[4]arene (13). To a solution of **12** (112 mg, 0.098 mmol) in EtOH (14 mL), hydrazine monohydrate (95 μL, 1.96 mmol) and Pd/C (12 mg, 10% w/w) were added. The mixture was refluxed overnight. The catalyst was filtrated off and the solvent was removed under reduced pressure. Yield: 105 mg (97%); R_f = 0.38 (DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75-6.49 (m, 9 H, Ar), 5.97-5.92 (m, 2 H, Ar), 4.47 (d, *J* = 12.8 Hz, 2 H, ArC*H*$_{ax}$Ar), 4.39 (d, *J* = 12.8 Hz, 2 H, ArC*H*$_{ax}$Ar), 3.98-3.76 (m, 8 H, CH_2-1 $_{Dod}$), 3.16 (d, *J* = 13.2 Hz, 2 H, ArC*H*$_{eq}$Ar), 3.04 (d, *J* = 13.2 Hz, 2 H, ArC*H*$_{eq}$Ar), 2.01-1.83 (m, 8 H, CH_2-2$_{Dod}$), 1.56-1.83 (m, 72 H, CH_2-3$_{Dod}$, CH_2-4$_{Dod}$, CH_2-5$_{Dod}$, CH_2-6$_{Dod}$, CH_2-7$_{Dod}$, CH_2-8$_{Dod}$, CH_2-9$_{Dod}$, CH_2-10$_{Dod}$, CH_2-11$_{Dod}$), 0.97-0.81 (m, 12 H, CH_3-12$_{Dod}$).^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.7-113.1 (Ar), 75.3 (C-1$_{Dod}$), 32.1, 31.3, 31.2, 30.4-29.5 (Ar*C*H_2Ar and C-2 to C-9$_{Dod}$), 26.5 (C-10$_{Dod}$), 22.8 (C-11$_{Dod}$), 14.2 (C-12$_{Dod}$). ESI-MS: *m/z* 1112.73 $[M + H]^+$, 1134.56 $[M + Na]^+$. Anal. calcd for $C_{76}H_{121}NO_4$: C 82.03, H 10.96, N 1.26. Found: C 82.18, H 11.10, N 1.13.

5-Isothiocyanato-25,26,27,28-tetrakis(*n*-dodecyloxy)calix[4]arene (14). To a solution of **13** (215 mg, 0.19 mmol) in dry toluene (10 mL), Et_3N (161 μL, 1.16 mmol) was added. Then, Cl_2CS (44 μL, 0.58 mmol) was added and the mixture was stirred at rt, under N_2, overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in DCM (15 mL), washed with H_2O (15 mL) and the organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography (1:3 DCM-Hex). Yield: 201 mg (92%); R_f = 0.63 (1:3 DCM-Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 (d, *J* = 7.2 Hz, 2 H, Ar), 6.88 (d, *J* = 6.4 Hz, 2 H, Ar), 6.82 (t, *J* = 7.2 Hz, 2 H, Ar), 6.51 (t, *J* = 7.6 Hz, 1 H, Ar), 6.34 (d, *J* = 7.6 Hz, 2 H, Ar), 6.13 (s, 2 H, Ar), 4.46 (d, *J* = 12.4 Hz, 2 H, ArC*H*$_{ax}$Ar), 4.42 (d, *J* = 12.4 Hz, 2 H, ArC*H*$_{ax}$Ar), 4.03-3-89 (m, 4 H, CH_2-1$_{Dod}$), 3.80-3.76 (m, 4 H, CH_2-1$_{Dod}$), 3.18 (d, *J* = 13.6 Hz, 2 H, ArC*H*$_{eq}$Ar), 3.10 (d, *J* = 13.6 Hz, 2 H, ArC*H*$_{eq}$Ar), 1.93-1.84 (m, 8 H, CH_2-2$_{Dod}$), 1.59-1.20 (m, 72 H, CH_2-3$_{Dod}$, CH_2-4$_{Dod}$, CH_2-5$_{Dod}$, CH_2-6$_{Dod}$, CH_2-7$_{Dod}$, CH_2-8$_{Dod}$, CH_2-9$_{Dod}$, CH_2-10$_{Dod}$, CH_2-11$_{Dod}$), 0.91 (t, *J* = 6.6 Hz, 12 H, CH_3-12$_{Dod}$). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 157.3-134.1 (Ar), 131.4 (NCS), 129.1-122.0 (Ar), 75.3, 75.2 (C-1$_{Dod}$), 32.0, 31.0, 30.9, 30.5-29.5 (Ar*C*H_2Ar and C-2 to C-9$_{Dod}$), 26.6, 26.5, 26.1 (C-10$_{Dod}$), 22.8 (C-11$_{Dod}$), 14.2 (C-12$_{Dod}$). ESI-MS: *m/z* 1176.50 $[M + Na]^+$, 1193.46 $[M + K]^+$. Anal. calcd for $C_{77}H_{119}NO_4S$: C 80.08, H 10.39, N 1.21, S 2.78. Found: C 80.24, H 10.60, N 1.30, S 2.56.

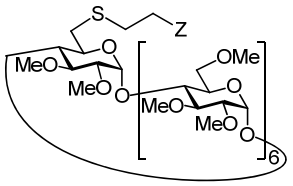
5-[*N'*-(4-(*tert*-Butoxycarbonylamino)butyl)thioureido]-25,26,27,28-tetrakis(*n*-dodecyloxy)calix[4]arene (15). To a solution of **14** (160 mg, 0.14 mmol) in dry DCM (6 mL), Et_3N (77 μL, 0.56 mmol) was added. Then, a solution of commercial *N'*-[4-(*tert*-butoxycarbonylamino)]butylamine (52 mg, 0.28 mmol) in dry DCM (2 mL) was added. The mixture was stirred overnight at rt, under N_2 atmosphere. The solvent was evaporated under reduced pressure and the residue was purified by column cromatography (1:3 → 1:1 EtOAc-Hex). Yield: 188 mg (99%); R_f = 0.32 (1:3 EtOAc-Hex). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, *J* = 7.6 Hz, 2 H, Ar), 6.97 (d, *J* = 7.2 Hz, 2 H, Ar), 6.89 (t, *J* = 7.2 Hz, 3 H, Ar), 6.30 (t, *J* = 7.6 Hz, 1 H, NH), 6.20 (d, *J* = 7.6 Hz, 2 H, Ar), 5.94 (s, 2 H, Ar), 5.43 (m, 1 H, NH), 4.64 (m, 1 H, NH), 4.42 (d, *J* = 13.2 Hz, 4 H, ArCH_{ax}Ar), 4.08-3.95 (m, 4 H, CH_2-1_{Dod}), 3.73-3.68 (m, 4 H, CH_2-1_{Dod}), 3.52-3.45 (m, 2 H, CH_2NHCS), 3.21-3.04 (m, 6 H, ArCH_{eq}Ar, CH_2NHBoc), 1.94-1.85 (m, 8 H, CH_2-2_{Dod}), 1.57-1.19 (m, 85 H, CH_2CH_2CH$_2$NHBoc, CMe_3, CH_2-3_{Dod}, CH_2-4_{Dod}, CH_2-5_{Dod}, CH_2-6_{Dod}, CH_2-7_{Dod}, CH_2-8_{Dod}, CH_2-9_{Dod}, CH_2-10_{Dod}, CH_2-11_{Dod}), 0.93-0.84 (m, 12 H, CH_3-12_{Dod}). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.7 (CS), 157.5 (CO), 156.0-121.4 (Ar), 79.1 (*C*Me_3), 75.6, 75.4, 75.1 (C-1_{Dod}), 44.8 (NHCS*C*H_2), 40.1 (*C*H_2NHBoc), 32.0 (C-3_{Dod}), 31.1, 31.0 (Ar*C*H_2Ar), 31.9-29.4 (C-2_{Dod}, C-4_{Dod}, C-5_{Dod}, C-6_{Dod}, C-7_{Dod}, C-8_{Dod}), 29.8 (C*Me*$_3$), 28.5-26.5 (C-9_{Dod}), 26.4 (CSNHCH$_2$*C*H$_2$), 26.2 (NHCH$_2$CH$_2$*C*H$_2$), 26.1 (C-10_{Dod}), 22.7 (C-11_{Dod}), 14.1 (C-12_{Dod}). ESI-MS: *m/z* 1344.19 $[M + H]^+$, 1366.04 $[M + Na]^+$.Anal. calcd for $C_{86}H_{139}N_3O_6S$: C 76.91, H 10.43, N 3.13, S 2.39. Found: C 76.78, H 10.39, N 2.99, S 2.58.

5-[*N'*-(4-Aminobuthylthioureido]-25,26,27,28-tetrakis(*n*-dodecyloxy)calix[4]-arene (16). To a solution of **15** (140 mg, 0.10 mmol) TFA-DCM (1:1, 5 mL) was stirred for 1 h at rt. The solvent was evaporated under reduced pressure and coevaporated several times with H_2O to give **16** as the corresponding trifluoroacetate salt. Yield: 134 mg (99%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (m, 2 H, NH), 7.35 (BS, 1 H, NH), 7.07 (d, *J* = 7.2 Hz, 2 H, Ar), 7.00 (d, *J* = 7.2 Hz, 2 H, Ar), 6.87 (t, *J* = 6.8 Hz, 2 H, Ar), 6.21 (s, 3 H, Ar), 6.01 (s, 2 H, Ar), 5.46 (m, 1 H, NH), 4.46 (d, *J* = 12.3 Hz, 2 H, ArCH_{ax}Ar), 4.43 (d, *J* = 13.3 Hz, 2 H, ArCH_{ax}Ar), 4.09-3.99 (m, 4 H, CH_2-1_{Dod}), 3.71 (bs, 4 H, CH_2-1_{Dod}), 3.53-3.43 (m, 2 H, CH_2NHCS), 3.17 (d, *J* = 13.3 Hz, 2 H, ArCH_{eq}Ar), 3.12 (d, *J* = 13.3 Hz, 2 H, ArCH_{eq}Ar), 1.99-1.83 (m, 8 H, CH_2-2_{Dod}), 1.71 (m, 2 H, CH_2CH$_2$CH$_2$NH$_2$), 1.60-1.20 (m, 74 H, CH$_2$CH_2CH$_2$NH$_2$, CH_2-3_{Dod}, CH_2-4_{Dod}, CH_2-5_{Dod}, CH_2-6_{Dod}, CH_2-7_{Dod}, CH_2-8_{Dod}, CH_2-9_{Dod}, CH_2-10_{Dod}, CH_2-11_{Dod}), 0.88-0.87 (m, 12 H, CH_3-12_{Dod}). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 179.0 (CS), 162.1-121.4 (Ar), 75.7, 75.5, 75.2 (C-1_{Dod}), 43.6 (*C*H_2NHCS), 39.5 (*C*H_2NH$_2$), 32.0, 31.0, 30.6, 30.2-29.4 (Ar*C*H_2Ar and C-2 to C-9_{Dod}), 26.6, 26.1 (C-10_{Dod}), 25.9 (CSNHCH$_2$*C*H$_2$), 23.9 (CSNHCH$_2$CH$_2$*C*H$_2$), 22.7 (C-11_{Dod}), 14.1 (C-12_{Dod}). ESI-MS: *m/z* 1243.06 $[M + H]^+$, 1265.02 $[M + Na]^+$, 1280.93 $[M + K]^+$. Anal. calcd for $C_{83}H_{132}F_3N_3O_6S$: C 73.46, H 9.80, N 3.10, S 2.36. Found: C 73.32, H 9.67, N 2.96, S 2.09.

5-[*N'*-(4-Isothiocyanatobutylthioureido]-25,26,27,28-tetrakis(*n*-dodecyloxy)calix[4]arene (17). To a solution of **16** (134 mg, 0.108 mmol) in absolute EtOH (8 mL), CS_2 (390 μL, 6.48 mmol) and Et_3N (451 μL, 3.24 mmol) were added. The reaction mixture was stirred for 1 h at rt and then cooled on an ice bath. A solution of Boc_2O (22.3 mg, 0.103 mmol) in absolute EtOH (6 mL) was added followed by the immediate addition of a catalytic amount of DMAP (0.3 mg, 3 μmol). The reaction mixture was kept in the ice bath for

30 min. Then it was allowed to reach rt and stirred for 2 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography (5:1 DCM-Hex → DCM). Yield: 128 mg (93%); R_f = 0.47 (DCM). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 6.4 Hz, 2 H, Ar), 7.00 (d, *J* = 6.4 Hz, 2 H, Ar), 6.94-6.88 (m, 3 H, Ar), 6.29 (t, *J* = 8.0, 1 H, NH), 6.21 (d, *J* = 7.2 Hz, 2 H, Ar), 5.94 (s, 2 H, Ar), 5.41 (t, *J* = 5.6, 1 H, NH), 4.43 (d, *J* = 13.2 Hz, 4 H, ArC*H*$_{ax}$Ar), 4.09-3.96 (m, 4 H, CH_2-1_{Dod}), 3.74-3.69 (m, 4 H, CH_2-1_{Dod}), 3.60 (t, *J* = 6.4 Hz, 2 H, C*H*$_2$NCS), 3.54 (q, *J* = 6.4 Hz, 2 H, C*H*$_2$NHCS), 3.16 (d, 2 H, *J* = 13.2 Hz, ArC*H*$_{eq}$Ar), 3.11 (d, 2 H, *J* = 13.2 Hz, ArC*H*$_{eq}$Ar), 1.95-1.83 (m, 8 H, CH_2-2_{Dod}), 1.72-1.65 (m, 4 H, C*H*$_2$*C*H$_2$CH$_2$NH$_2$), 1.60-1.20 (m, 72 H, CH_2-3_{Dod}, CH_2-4_{Dod}, CH_2-5_{Dod}, CH_2-6_{Dod}, CH_2-7_{Dod}, CH_2-8_{Dod}, CH_2-9_{Dod}, CH_2-10_{Dod}, CH_2-11_{Dod}), 0.89-0.85 (m, 12 H, CH_3-12_{Dod}). ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 180.1 (HNCS), 155.9-133.8 (Ar), 130.4 (NCS), 129.4-121.5 (Ar), 75.8, 75.7, 75.3 (C-1_{Dod}), 45.0 (NHCS*C*H$_2$), 44.3 (*C*H$_2$NCS), 32.2, 32.2, 31.3, 31.2-29.6 (Ar*C*H$_2$Ar and C-2 to C-9_{Dod}), 26.7 (CSNHCH$_2$*C*H$_2$), 26.6 (CSNHCH$_2$CH$_2$*C*H$_2$), 26.3 (C-10_{Dod}), 22.9 (C-11_{Dod}), 14.3 (C-12_{Dod}). ESI-MS: *m/z* 1307.12 $[M + Na]^+$, 1323.08 $[M + K]^+$. Anal. calcd for $C_{82}H_{129}N_3O_4S_2$: C 76.64, H 10.12, N 3.27, S 4.99. Found: C 76.29, H 9.93, N 3.33, S 5.11.

Preparation of β-cyclodextrin derivatives 19 and 20.



19; Z = NHBoc

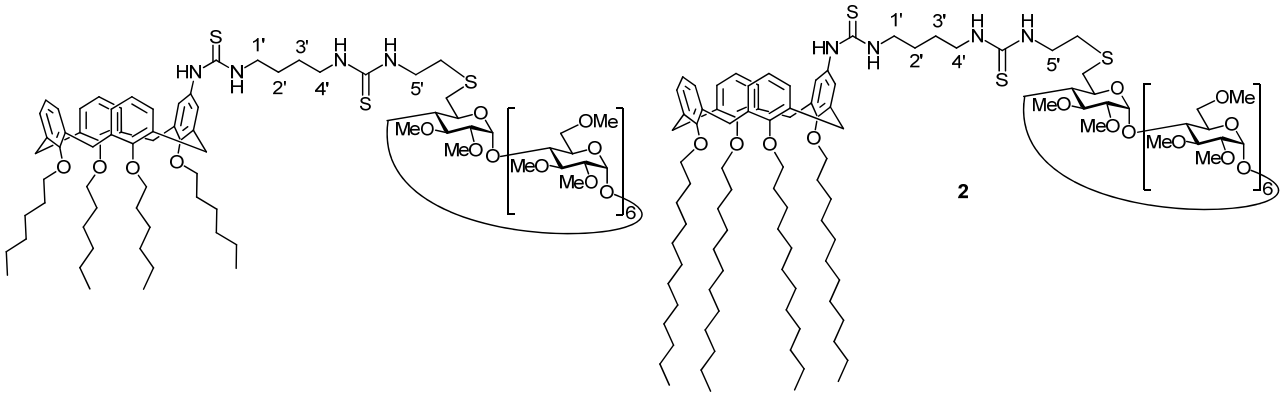
20; Z = NH_3Cl

6^I-[2-(*tert*-Butoxycarbonylamino)ethylthio]-6^I-deoxy-6^{II-VII}-hexa-*O*-methyl-heptakis-(2,3-di-*O*-methyl)cyclomaltoheptaose (19). To a suspension of 6^{II-VII}-hexa-*O*-methyl-6^I-p-toluensulfonyl-heptakis-(2,3-di-*O*-methyl)cyclomaltoheptaose[3] (**18**, 534 mg, 0.34 mmol) and Cs_2CO_3 (142 mg, 0.44 mmol) in dry DMF (6 mL), *tert*-butyl *N*-(2-mercaptoethyl)carbamate (75 μL, 0.44 mmol) was added. The suspension was stirred, under Ar atmosphere, at 70 ºC for 24 h. Solvents were evaporated and DCM (15 mL) was added. The organic phase was washed with water (2 x 10 mL), and dried (Na_2SO_4). The residue was purified by column chromatography (25:1 → 20:1 DCM-MeOH) to give **19**. Yield: 519 mg (97%); R_f = 0.52 (9:1 DCM-MeOH); $[\alpha]_D$ = +148.8 (*c* 1.0 in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.18-5.12 (m, 7 H, H-1^{I-VII}), 4.19 (m, 13 H, H-5^{I-VII}, H-6a^{II-VII}), 3.67 (m, 21 H, OMe), 3.66-3.54 (m, 20 H, H-3^{I-VII}, H-4^{I-VII}, H-6b^{II-VII}), 3.53 (m, 21 H, OMe), 3.41 (m, 18 H, OMe), 3.32 (m, 2 H, CH_2N_{Cyst}), 3.21 (m, 7 H, H-2^{I-VII}), 3.09 (dd, 1 H, $J_{6a,6b}$ = 13.6 Hz, $J_{5,6a}$ = 2.9 Hz, H-6a^I), 3.02 (dd, 1 H, $J_{5,6b}$ = 6.0 Hz, H-6b^I), 2.73 (t, 2 H, $^3J_{H,H}$ = 6.3 Hz, CH_2S_{Cyst}), 1.48 (s, 9 H, CMe_3). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 162.4 (CO), 99.0-98.2 (C-1^{I-VII}), 83.1 (C-4^I), 83.0-81.4 (C-2^{I-VII}, C-3^{I-VII}), 80.4-80.0 (C-4^{II-VII}), 79.0 (*C*Me$_3$), 71.5-70.7 (C-5^{I-VII}, C-6^{II-VII}), 61.4-61.3 (OMe), 59.0-58.0 (OMe), 39.5 (CH_2N_{Cyst}), 33.6 (CH_2S_{Cyst}), 33.2 (C-6^I), 28.3 (C*Me*$_3$); ESI-MS: *m/z* 809.9 $[M + 2 Na]^{2+}$, 1596.7 $[M + Na]^+$. Anal. Calcd. for $C_{69}H_{123}NO_{36}S$: C 52.63, H 7.87, N 0.89. Found: C 52.55, H 7.79, N 0.79.

6^I-(2-Aminoethylthio)-6^{II-VII}-hexa-*O*-methyl-heptakis-(2,3-di-*O*-methyl)cyclomaltoheptaose hydrochloride (20). Compound **20** was obtained by treatment of carbamate **19** (400 mg, 0.25 mmol) with

TFA-DCM (1:1, 3 mL) for 2 h, followed by evaporation of the solvent and purification of the residue by column chromatography DCM-MeOH (20:1 → 9:1). Yield: 365 mg (95%); R_f = 0.41 (9:1 DCM-MeOH); $[\alpha]_D$ = +57.8 (*c* 0.2 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.16-5.05 (m, 7 H, H-1^{I-VII}), 3.94 (m, 1 H, H-5^{I}), 3.91-3.77 (m, 12 H, H-5^{II-VII}, H-$6a^{II-VII}$), 3.64 (m, 21 H, OMe), 3.63-3.53 (m, 22 H, H-3^{I-VII}, H-4^{I-VII}, H-$6b^{II-VII}$, CH_2N_{Cyst}), 3.52 (m, 21 H, OMe), 3.39 (m, 18 H, OMe), 3.20 (m, 7 H, H-2^{I-VII}), 3.17 (m, 1 H, H-$6a^{I}$), 3.09 (m, 1 H, H-$6b^{I}$), 2.91 (bt, 2 H, $^3J_{H,H}$ = 6.6 Hz, CH_2S_{Cyst}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 99.2-98.4 (C-1^{I-VII}), 83.5 (C-4^{I}), 83.4-81.4 (C-2^{I-VII}, C-3^{I-VII}), 81.0-79.6 (C-4^{II-VII}), 71.3-70.9 (C-5^{I-VII}, C-6^{II-VII}), 61.4-61.3 (OMe), 59.2-58.2 (OMe), 38.5 (CH_2N_{Cyst}), 33.6 (CH_2S_{Cyst}), 29.5 (C-6^{I}); ESI-MS: *m/z* 1474.8 $[M + H]^+$. Anal. Calcd. for $C_{64}H_{115}NO_{34}S \cdot HCl$: C 50.87, H 7.74, N 0.93. Found: C 50.80, H 7.57, N 0.87.

Preparation of CA_4-βCD heterodimer derivatives 1 and 2.

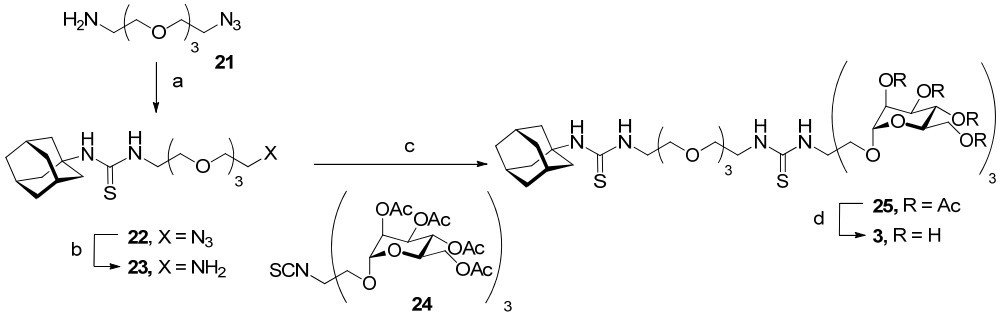


Amphiphilic CA_4-βCD heterodimer 1. To a solution of **20** (45 mg, 0.03 mmol) in DCM (4 mL), under Ar atmosphere, Et_3N (21 μL, 0.16 mmol) and **10** (31.8 mg, 0.03 mmol) were added and the mixture was stirred overnight at rt. The solvent was removed under reduced pressure and the residue was purified by column chromatography (EtOAc → 20:1 DCM-MeOH) to give **1**. Yield: 65 mg (87%); R_f = 0.44 (9:1 DCM-MeOH) ; $[\alpha]_D$ = +85.1 (*c* 0.4 in MeOH). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (bs, 1 H, NH),7.10 (d, 2 H, *J* = 6.7 Hz, Ar), 7.03 (d, 2 H, *J* = 7.1 Hz, Ar), 6.90 (d, 2 H, *J* = 7.1 Hz, Ar), 6.58 (bs, 1 H, NH), 6.42-6.31 (m, 3 H, Ar), 6.04-5.96 (m, 2 H, Ar), 5.42 (bs, 2 H, NH), 5.18-5.03 (m, 7 H, H-1^{I-VII}), 4.44 (d, 4 H, *J* = 13.0 Hz, ArCH_{ax}Ar), 4.11-3.99 (m, 4 H, CH_2-1_{Hex}), 3.98-3.76 (m, 15 H, H-5^{I-VII}, H-$6a^{II-VII}$, CH_2-5'), 3.75-3.68 (m, 4 H, CH_2-1_{Hex}), 3.67-3.55 (m, 36 H, H-4^{I-VII}, H-$6b^{II-VII}$, CH_2-1', OCH_3), 3.54-3.41 (m, 30 H, H-3^{I-VII}, CH_2-4', OCH_3), 3.40-3.29 (m, 18 H, OCH_3), 3.23-3.06 (m, 13 H, H-2^{I-VII}, H-$6a^{I}$, H-$6b^{I}$, ArCH_{eq}Ar), 2.74 (m, 2 H, CH_2S), 2.03-1.80 (m, 8 H, CH_2-2_{Hex}), 1.66-1.46 (m, 4 H, CH_2-2', CH_2-3'), 1.43-1.17 (m, 24 H, , CH_2-3_{Hex}, CH_2-4_{Hex}, CH_2-5_{Hex}), 0.76 (bs, 12 H, CH_3-6_{Hex}). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.5, 179.8 (CS), 157.5-121.5 (Ar), 99.2-98.6 (C-1^{I-VII}), 82.1-81.6 (C-2^{I-VII}, C-3^{I-VII}), 80.5-80.0 (C-4^{I-VII}), 75.8-75.7 (C-1_{Hex}), 71.2-71.7 (C-5^{I-VII}, C-6^{II-VII}), 61.6, 59.5-58.9 (OCH_3), 44.1 (CH_2-1', CH_2-4', CH_2-5'), 37.6 (C-6^{I}), 34.0 (CH_2S), 32.3, 32.1 (C-3_{Hex}), 31.2, 30.5 (ArCH_2Ar), 30.1, 29.8 (C-2_{Hex}), 26.6 (CH_2-2'), 26.2 (CH_2-3'), 25.8, 25.6 (C-4_{Hex}), 23.1, 22.8 (C-5_{Hex}), 14.1 (C-6_{Hex}). ESI-MS: *m/z* 2445.3 $[M + Na]^+$, 1234.2 $[M + 2Na]^{2+}$. Anal. calcd for $C_{122}H_{196}N_4O_{38}S_3$: C 60.47, H 8.15, N 2.31, S 3.97. Found: C

60.11, H 7.98, N 2.06, S 3.64.

Amphiphilic CA_4-βCD heterodimer 2. To a solution of **20** (93 mg, 0.058 mmol) in DCM (4 mL), under Ar atmosphere, Et_3N (32 μL, 0.230 mmol) and a solution of **17** (103 mg, 0.080 mmol) in DCM (4 mL) were added and the mixture was stirred overnight at rt. The solvent was removed under reduced pressure and the residue was purified by column chromatography (1:1 EtOAc-cyclohexane → 20:1 DCM-MeOH) to give **2**. Yield: 135 mg (90%); R_f = 0.36 (15:1 DCM-MeOH); $[\alpha]_D$ = +78.5 (*c* 0.5 in DCM). ^{1}H NMR (500 MHz, $CDCl_3$, 313 K) δ 7.15 (bs, 1 H, NH), 7.07 (d, 2 H, *J* = 6.5 Hz, Ar), 6.99 (d, 2 H, *J* = 7.3 Hz, Ar), 6.87 (t, 2 H, *J* = 7.3 Hz, Ar), 6.51 (bs, 2 H, NH), 6.26-6.20 (m, 3 H, Ar), 5.99 (s, 2 H, Ar), 5.38 (bt, 1 H, NH), 5.17-5.07 (m, 7 H, H-1^{I-VII}), 4.44 (d, 4 H, *J* = 13.3 Hz, ArCH_{ax}Ar), 4.11-3.99 (m, 4 H, CH_2-1_{Dod}), 3.97-3.93 (m, 1 H, H-5^{I}), 3.91-3.76 (m, 14 H, H-5^{II-VII}, H-$6a^{II-VII}$, CH_2-5'), 3.75-3.70 (m, 4 H, CH_2-1_{Dod}), 3.69-3.55 (m, 36 H, H-4^{I-VII}, H-$6b^{II-VII}$, CH_2-1',, OMe), 3.54-3.42 (m, 30 H, CH_2-4', H-3^{I-VII}, OMe), 3.41-3.34 (m, 18 H, OMe), 3.21-3.05 (m, 13 H, H-2^{I-VII}, H-$6a^{I}$, H-$6b^{I}$, ArCH_{eq}Ar), 2.90-2.76 (m, 2 H, CH_2S), 1.98-1.82 (m, 8 H, CH_2-2_{Dod}), 1.67-1.58 (m, 4 H, CH_2-2', CH_2-3'), 1.57-1.22 (m, 72, CH_2-3_{Dod}, CH_2-4_{Dod}, CH_2-5_{Dod}, CH_2-6_{Dod}, CH_2-7_{Dod}, CH_2-8_{Dod}, CH_2-9_{Dod}, CH_2-10_{Dod}, CH_2-11_{Dod}), 0.93-0.84 (m, 12 H, CH_3-12_{Dod}).^{13}C NMR (125.7 MHz, $CDCl_3$, 313 K) δ 182.7, 180.0 (CS), 157.6-121.5 (Ar), 99.3-98.7 (C-1^{I-VII}), 82.2-81.7 (C-2^{I-VII}, C-3^{I-VII}), 80.5-80.0 (C-4^{I-VII}), 75.9-75.2 (C-1_{Dod}), 71.8-71.1 (C-5^{I-VII}, C-6^{II-VII}), 61.6-61.4 (OCH_3), 59.4-58.6 (OCH_3), 44.1-43.7 (CH_2-1', CH_2-4', CH_2-5'), 34.1 (C-6^{I}), 32.8 (CH_2S), 32.1, 31.3, 31.2, 30.6, 30.2-29.9 (ArCH_2Ar, CH_2-2', CH_2-3', C-2 to C-7_{Dod}), 26.7 (C-8_{Dod}), 26.6 (C-9_{Dod}), 25.6 (C-10_{Dod}), 22.8 (C-11_{Dod}), 14.2 (C-12_{Dod}). ESI-MS: *m/z* 1402.6 $[M +2 Na]^{2+}$, 2781.3 $[M + Na]^{+}$. Anal. calcd for $C_{146}H_{244}N_4O_{38}S_3$: C 63.54, H 8.91, N 2.03, S 3.49. Found: C 63.68, H 8.66, N 1.80, S 3.79.

Preparation of the adamantane-armed trimannosyl dendron 3.



Scheme S1. Preparation of trimannosyl-adamantane conjugate **3**. Reagents and conditions*:* (a) 1-adamantyl isothiocyanato, Et_3N, DMF, rt, 3 d, 53%; (b) 1,3-propanedithiol, Et_3N, MeOH, rt, 16 h, 65%. (c) **24**, $NaHCO_3$, acetone-H_2O 5:1, rt, 16 h, 92%. (d) MeONa, MeOH, rt, 2-4 h. quant.

***N*-Adamant-1-yl-*N'*-[ω-azidotetra(ethyleneglycol)]thiourea (22).** A solution of α-amino-ω-azidotetra(ethyleneglycol)[4] (**21**, 121 mg, 0.56 mmol), 1-adamantyl isothiocyanate (161 mg, 0.83 mmol) and Et_3N (0.15 mL, 1.08 mmol) in dry DMF (3 mL) was stirred at room temperature for 3 days. The solvent were evaporated under reduced pressure and the residue was purified by colum chromatography (EtOAc-

petroleum ether 1:1) to give **22** as a colorless oil. Yield: 121 mg (53%). R_f = 0.51 (EtOAc-petroleum ether 3:1). IR (ATR): 2904, 2098 (N_3), 1087 cm^{-1}. UV (DCM): 254 nm (ε_{mM} 12.7). ^{1}H NMR (300 MHz, CD_3OD): δ 3.80-3.62 (m, 14 H, CH_2-1-7), 3.43 (t, 2 H, $^3J_{H,H}$ = 4.7 Hz, CH_2-8), 2.22 (m, 6 H, αH), 2.11 (m, 3 H, βH), 1.76 (m, 6 H, γH). ^{13}C NMR (75.5 MHz, CD_3OD): δ 182.9 (CS), 73.4-71.7 (CH_2-2-7), 52.6 (C_q Ad), 50.0 (CH_2-8), 44.7 (CH_2-1), 43.6 (αC), 38.3 (γC), 31.9 (βC). MS (ESI): *m/z* 424.3 $[M + Na]^+$, 410.2 $[M - H]^-$, 446.1 $[M + Cl]^-$. Anal. Calcd. for $C_{19}H_{33}N_5O_3S$: C 55.45, H 8.08, N 17.02, S 7.79 Found C 55.61, H 8.11, N 16.88, S 7.54.

***N*-adamant-1-yl-*N'*-[ω-aminotetra(ethyleneglycol)]thiourea (23).** A solution of **22** (121 mg, 0.29 mmol), 1,3-propanedithiol (65 μL, 0.65 mmol), and Et_3N (90 μL, 0.65 mmol) in MeOH (4 mL) under Ar atmosphere was stirred overnight at room temperature. 1,3-Propanedithiol (65 μL, 0.65 mmol), and Et_3N (90 μL, 0.65 mmol) were added and the reaction mixture was further stirred for 6 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (CH_3CN-H_2O 10:1 → CH_3CN-H_2O-NH_4OH 10:1:1) to give **23** as colorless oil. Yield: 72 mg (65%). R_f = 0.24 (CH_3CN-H_2O-NH_4OH 10:1:1). IR (ATR): 3298, 2902, 1088 cm^{-1}. UV (DCM): 254 nm (ε_{mM} 14.0). ^{1}H NMR (300 MHz, CD_3OD): δ 3.72-3.60 (m, 12 H, CH_2-1-6), 3.56 (t, 2 H, $^3J_{H,H}$ = 5.4 Hz, CH_2-7), 2.84 (t, 2 H, CH_2-8), 2.23 (d, 6 H, $^3J_{H,H}$ = 2.7 Hz, αH), 2.11 (m, 3 H, βH), 1.76 (t, 6 H, $^3J_{H,H}$ = 2.9 Hz, γH). ^{13}C NMR (75.5 MHz, CD_3OD): δ 182.2 (CS), 73.1 (CH_2-7) 71.6-70.9 (CH_2-1-6) 54.7 (C_q Ad), 45.0 (CH_2-1), 42.9 (αC), 42.0 (CH_2-8), 37.4 (γC), 31.1 (βC). MS(ESI): *m/z* 386.4 $[M + H]^+$. Anal. Calcd. for $C_{19}H_{35}N_3O_3S$: C 59.19, H 9.15, N 10.90, S 8.32 Found C 59.22, H 9.33, N 10.92, S 8.40.

Acetyl-protected adamantane-armed trimannosyl dendron 25. To a solution of **23** (19 mg, 45 μmol) and $NaHCO_3$ (7.6 mg, 90 μmol) in H_2O (0.5 mL), a solution of tris(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxymethyl)methyl isothiocyanate[5] (**24**, 101 mg, 90 μmol) in acetone (2.5 mL) was added, and the reaction mixture was stirred overnight. The solvent was evaporated and the residue was dissolved in DCM (10 mL), then washed with H_2O (3 x 3 mL). The organic layer was dried, filtered and concentrated and the residue was purified by column chromatography (EtOAc-petroleum ether 1:1→2:1) to give **25**. Yield: 64 mg (92%). R_f = 0.34 (DCM-MeOH 30:1).). $[\alpha]_D$ = +17.1 (c 0.9 in DCM). IR: 2915, 1743, 1042 cm^{-1}. UV (MeOH): 254 nm (ε_{mM} 4.8). ^{1}H NMR (500 MHz, $CDCl_3$, 313 K): δ 7.98 (s, 1 H, NH), 6.67 (s, 1 H, NH), 6.36 (t, 1 H, $^3J_{H,H}$ = 4.7 Hz, NH), 6.19 (BS, 1 H, NH), 5.27 (t, 3 H, $J_{3,4}$= $J_{4,5}$ = 9.8 Hz, H-4), 5.20 (dd, 3 H, $J_{2,3}$ = 3.4 Hz, H-3), 5.18 (dd, 3 H, $J_{1,2}$ = 1.2 Hz, H-2), 4.90 (d, 3 H, H-1), 4.37 (d, 3 H, $^3J_{H,H}$ = 10.0 Hz, C*H*H-OMan), 4.31 (dd, 3 H, $J_{6a,6b}$ = 12.4 Hz, $J_{5,6a}$ = 4.7 Hz, H-6a), 4.12 (dd, 1 H, $J_{5,6b}$ = 2.3 Hz, H-6b), 4.04 (ddd, 3 H, H-5), 4.01 (d, 3 H, CH*H*-OMan), 3.75-3.55 (m, 18 H, CH_2-1-8, C*H*$_2$NHCS), 2.12, 2.08, 2.01, 1.96 (4 s, 36 H, COMe), 2.05 (bs, 6 H, αH), 2.04 (s, 3 H, βH), 1.67 (bs, 6 H, γH). ^{13}C NMR (125.7 MHz, $CDCl_3$, 313 K): δ 182.6, 181.0 (CS), 170.8, 170.2, 170.0, 169.5 (CO), 98.2 (C-1), 70.4-69.4 (CH_2-1-8), 69.4 (C-2), 69.3 (C-3), 69.0 (C-5), 66.3 (*C*H_2-OMan), 65.9 (C-4), 62.2 (C-6), 61.0 ($C_{q,Tris}$), 53.9 (C_q Ad), 44.8, 43.8 (*C*H_2NHCS), 42.0 (αC), 36.1 (γC), 29.5 (βC), 20.7, 20.6 (CO*Me*). MS (ESI): *m/z* 1562.2 $[M + Na]^+$. Anal. Calcd. for $C_{66}H_{98}N_4O_{33}S_2$: C 51.49, H 6.42, N 3.64, S 4.17. Found C 51.57, H 6.62, N 3.70, S 3.89.

Adamantane-armed trimannosyl dendron 3. Treatment of **25** (30 mg, 19 μmol) with a solution of MeONa in MeOH (0.1M, 2 mL) followed by stirring for 1 h at rt, and neutralization with ionic exchange resine Amberlite IR-120 (H^+), filtration, evaporation of the solvent gave **3**. The residue was freeze-dried from an aqueous solution to isolate **3** as a white foam. Yield: 19.7 mg (99%). R_f = 0.71 (CH_3CN-H_2O-NH_4OH 6:3:1). $[\alpha]_D$ = +36.9 (c 0.3) in MeOH). IR (ATR): 3306, 2911, 1036 cm^{-1}. UV (MeOH): 246 nm (ε_{mM} 18.3). ^1H NMR (500 MHz, CD_3OD): δ 4.83 (d, 3 H, $J_{6a,5}$ = 1.6 Hz, H-1), 4.10, 4.06 (2 d, 6 H, $^3J_{H,H}$ = 10.0 Hz, C*H*$_2$-OMan), 3.90 (d, 3 H, $J_{6a,6b}$ = 11.9 Hz, H-6a), 3.88 (dd, 3 H, $J_{2,3}$ = 3.3 Hz, H-2), 3.76-3.63 (m, 30 H, H-3, H-4, H-5, H-6b, C*H*$_2$NHCS, CH_2-1-8), 2.23 (bs, 6 H, αH), 2.11 (bs, 3 H, βH), 1.76 (bs, 6 H, γH). ^{13}C NMR (125.7 MHz, CD_3OD): δ 183.6, 181.1 (CS), 103.2 (C-1), 75.9 (C-3), 73.5 (C-5), 72.8 (C-2), 72.5-71.5 (CH_2-1-8), 69.6 (C-4), 68.6 ($CH_{2,tris}$), 63.7 (C-6), 62.9 ($C_{q,tris}$), 55.6 (C_q Ad), 46.3, 45.8 (*C*H_2NHCS), 43.6 (αC), 38.3 (γC), 32.0 (βC). MS (ESI): *m/z* 1058 $[M+Na]^+$, 1073.9 $[M+K]^+$, 1033.8 $[M-H]^-$, 1059.8 [M + Cl]$^-$. Anal. Calcd. for $C_{42}H_{74}N_4O_{21}S_2$: C 48.73, H 7.21, N 5.41, S 6.20 Found C 48.72, H 7.53, N 5.04, S 5.84.

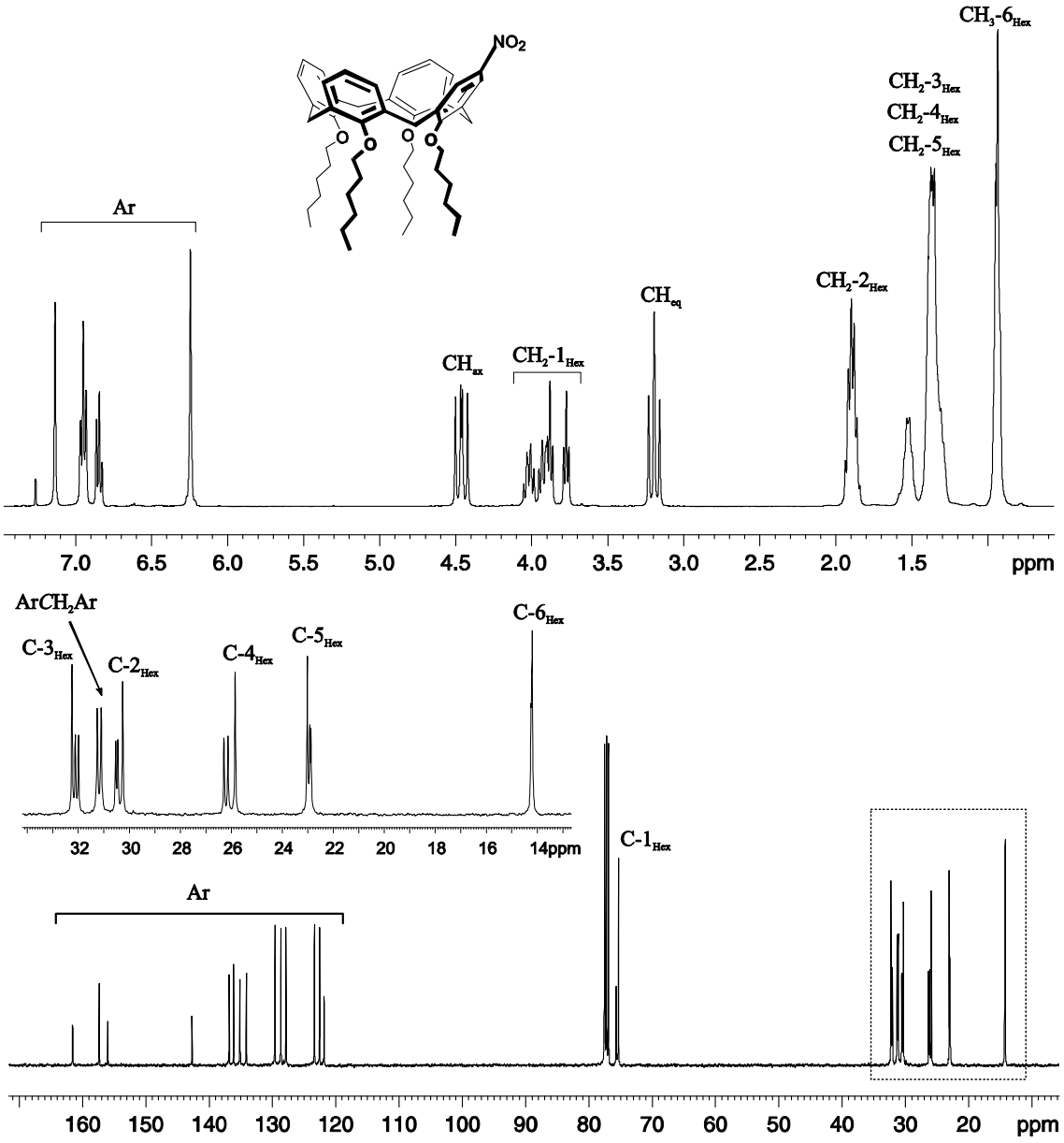


Figure S3. ^{1}H NMR and ^{13}C NMR spectra (300 MHz, 100.6 MHz, $CDCl_3$) of compound **5**.

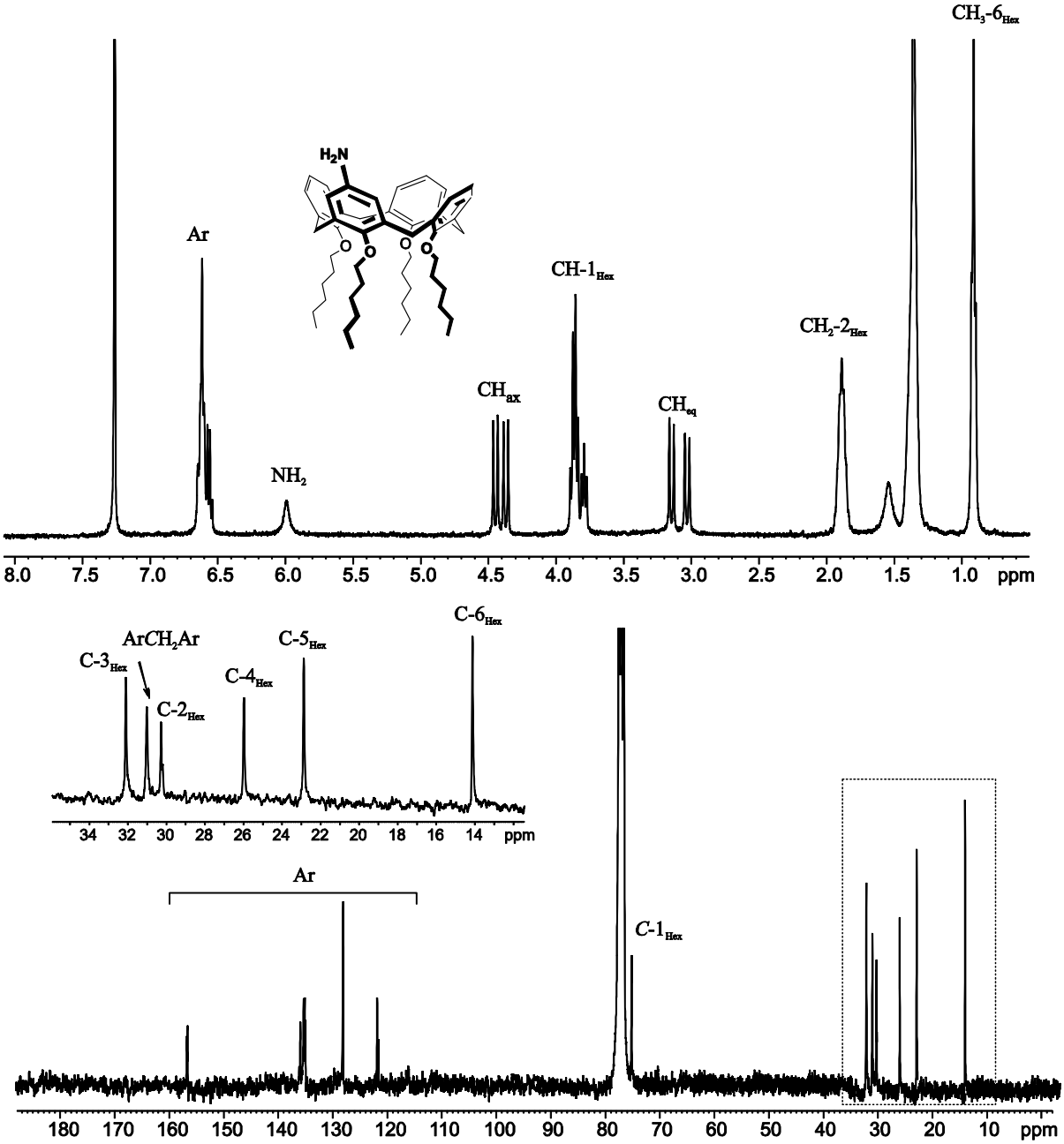


Figure S4. ^{1}H NMR and ^{13}C NMR spectra (400 MHz, 75.5 MHz, $CDCl_3$) of compound **6**.

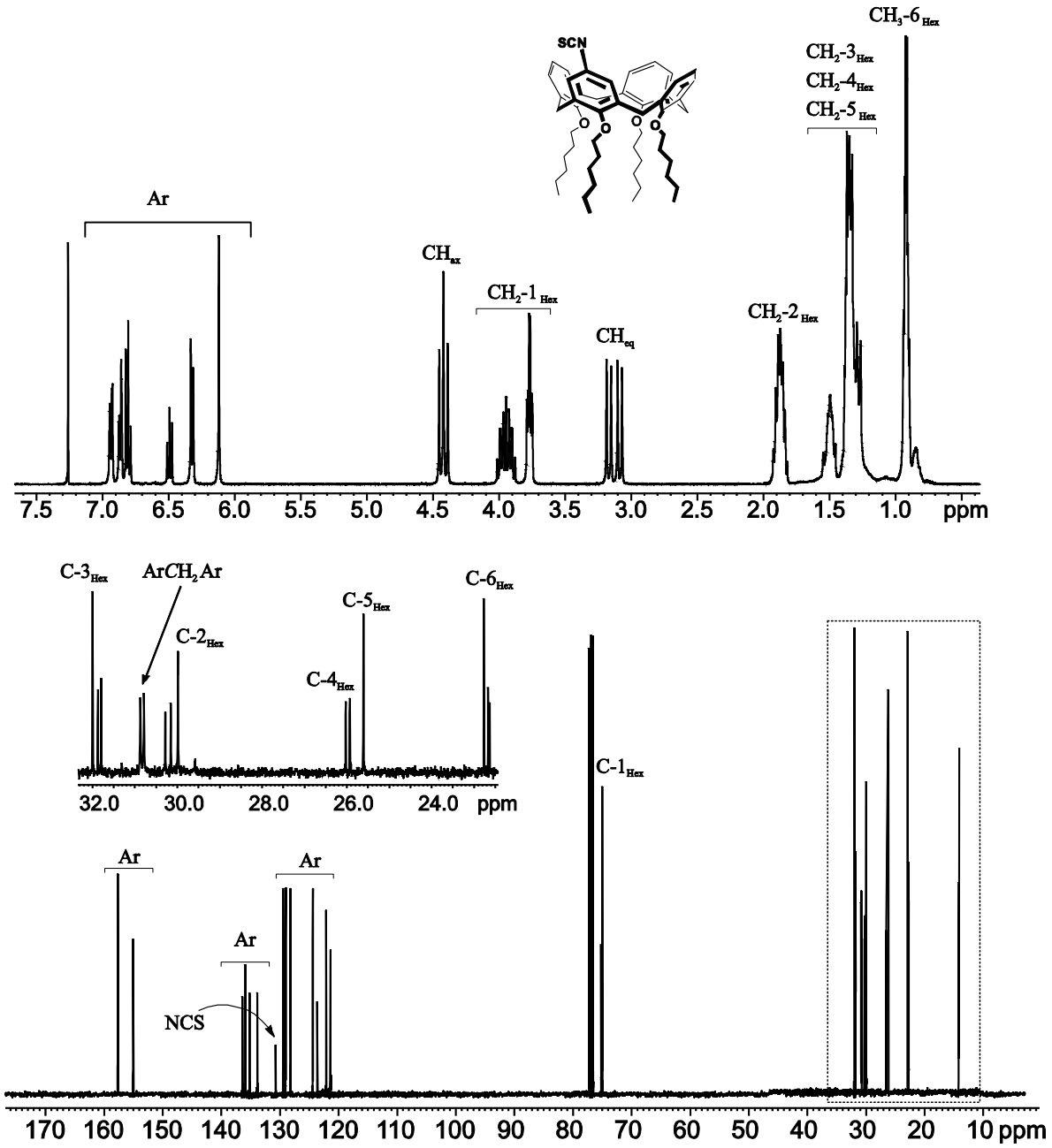


Figure S5. ^{1}H NMR and ^{13}C NMR spectra (400 MHz, 100.6 MHz, $CDCl_3$) of compound **7**.

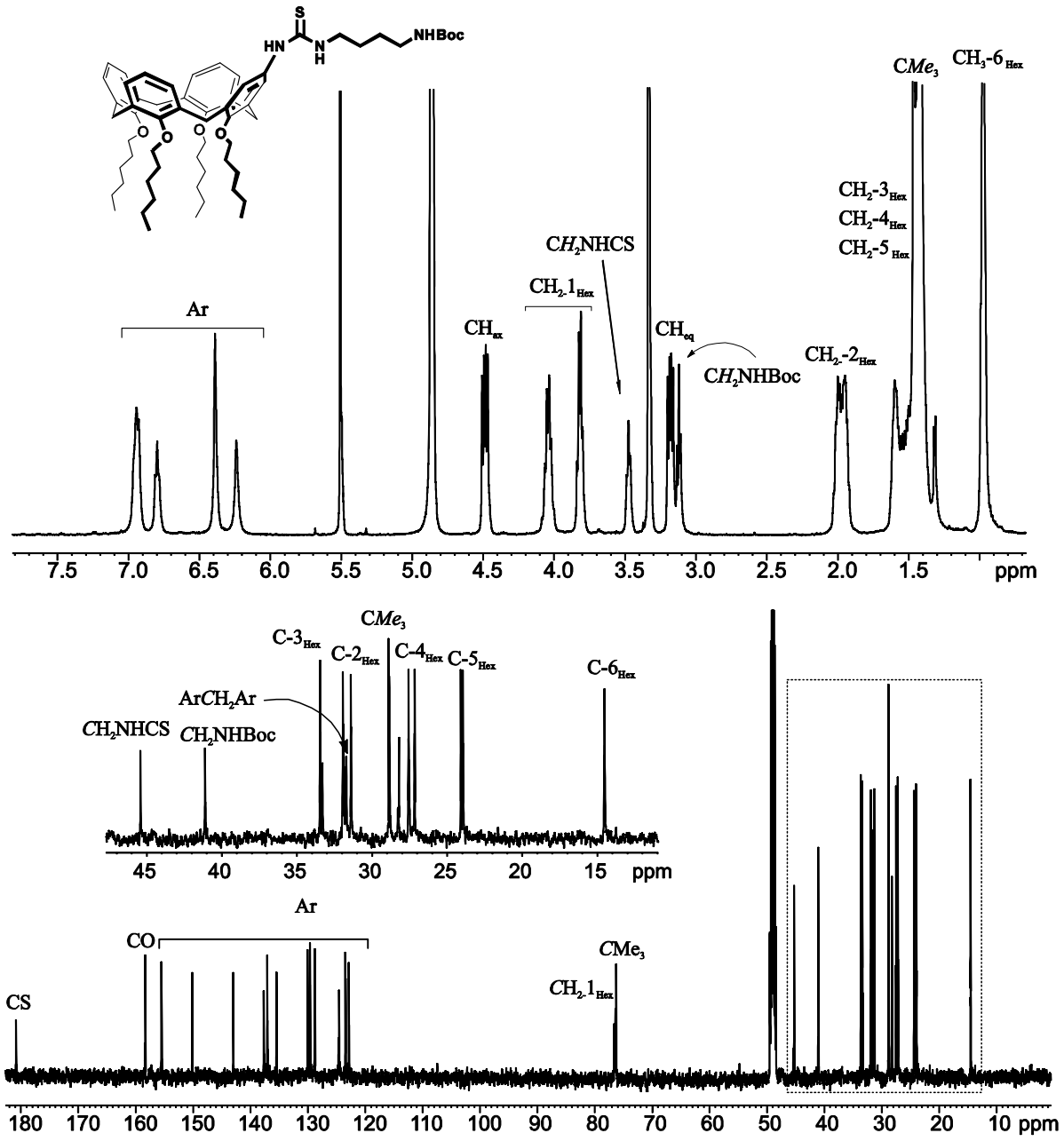


Figure S6. ^{1}H NMR and ^{13}C NMR spectra (500 MHz, 125.7 MHz, CD_3OD) of compound **8**.

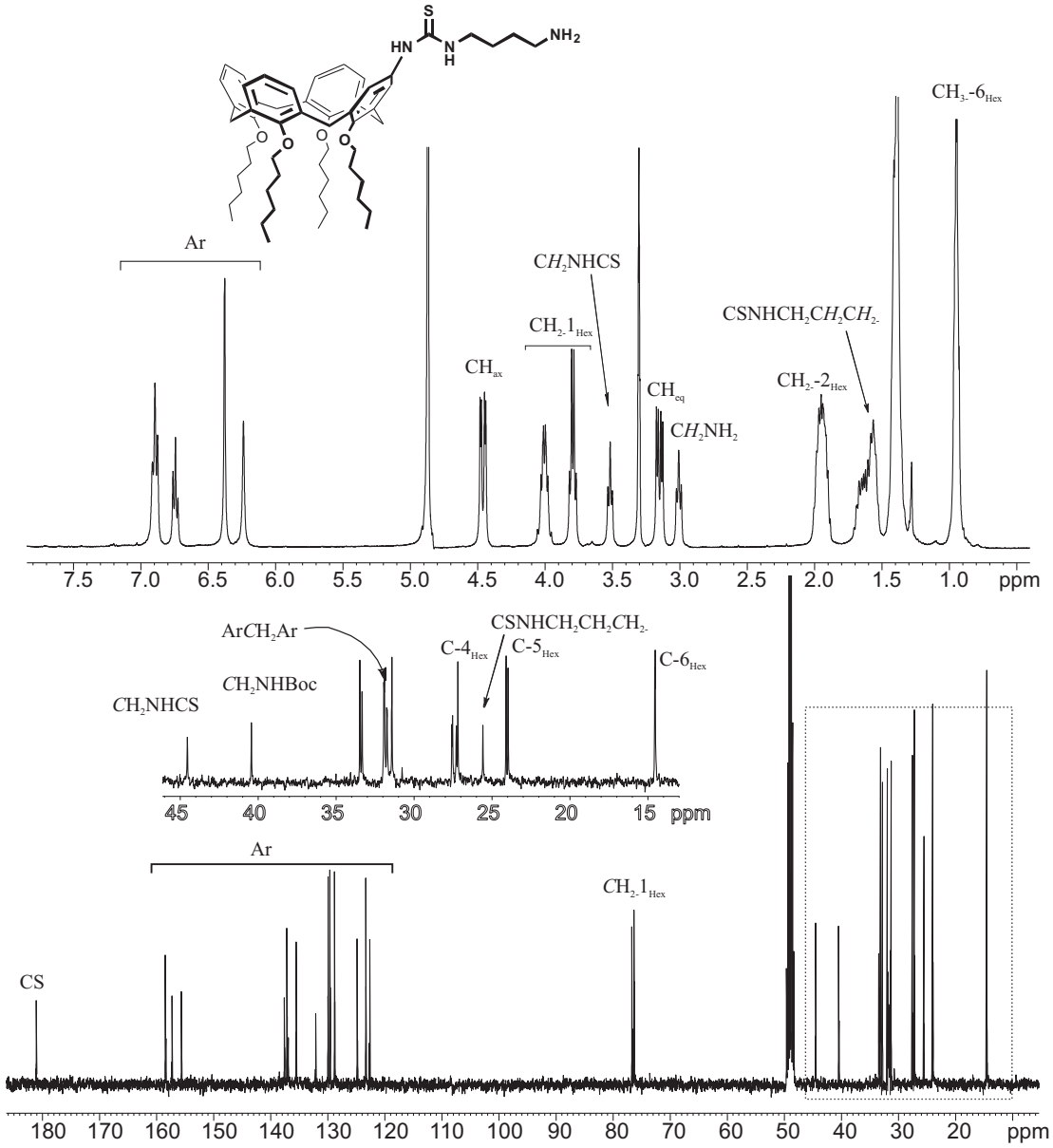


Figure S7. ^{1}H NMR and ^{13}C NMR spectra (400 MHz, 100.6 MHz, CD_3OD) of compound **9**.

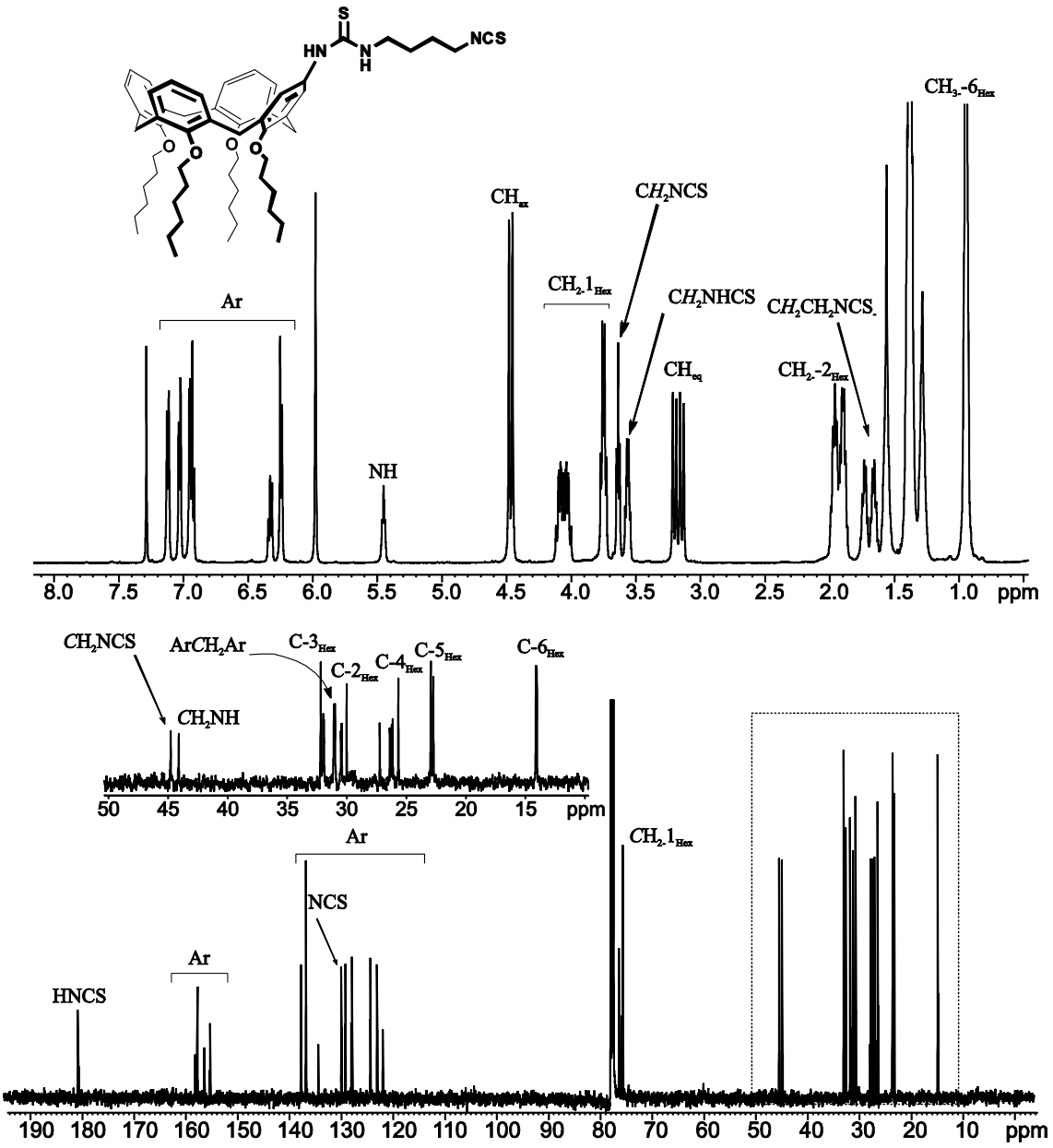


Figure S8. ^{1}H NMR and ^{13}C NMR spectra (500 MHz, 125.7 MHz, $CDCl_3$) of compound **10**.

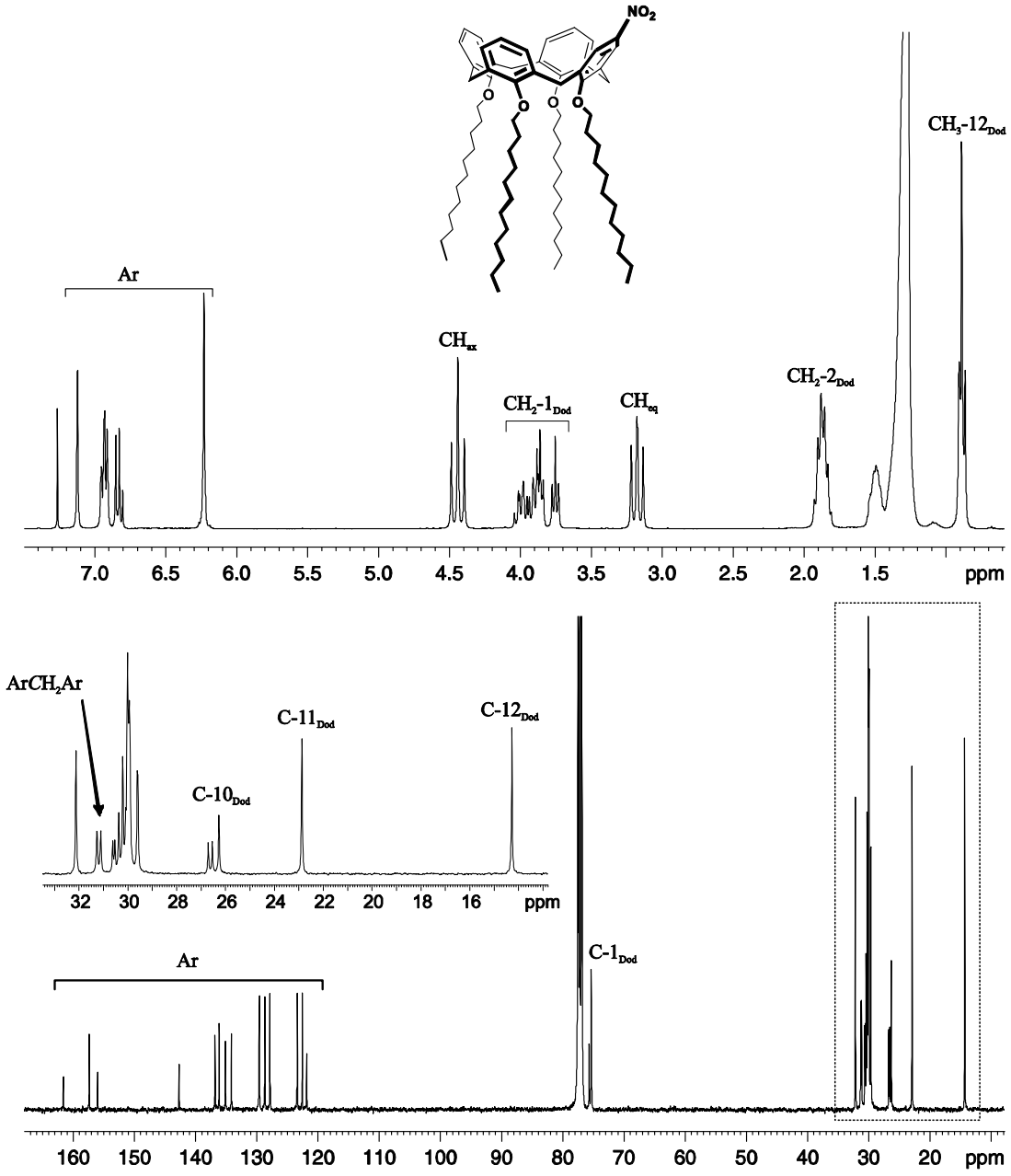


Figure S9. ^{1}H NMR and ^{13}C NMR spectra (300 MHz, 100.6 MHz, $CDCl_3$) of compound **12**.

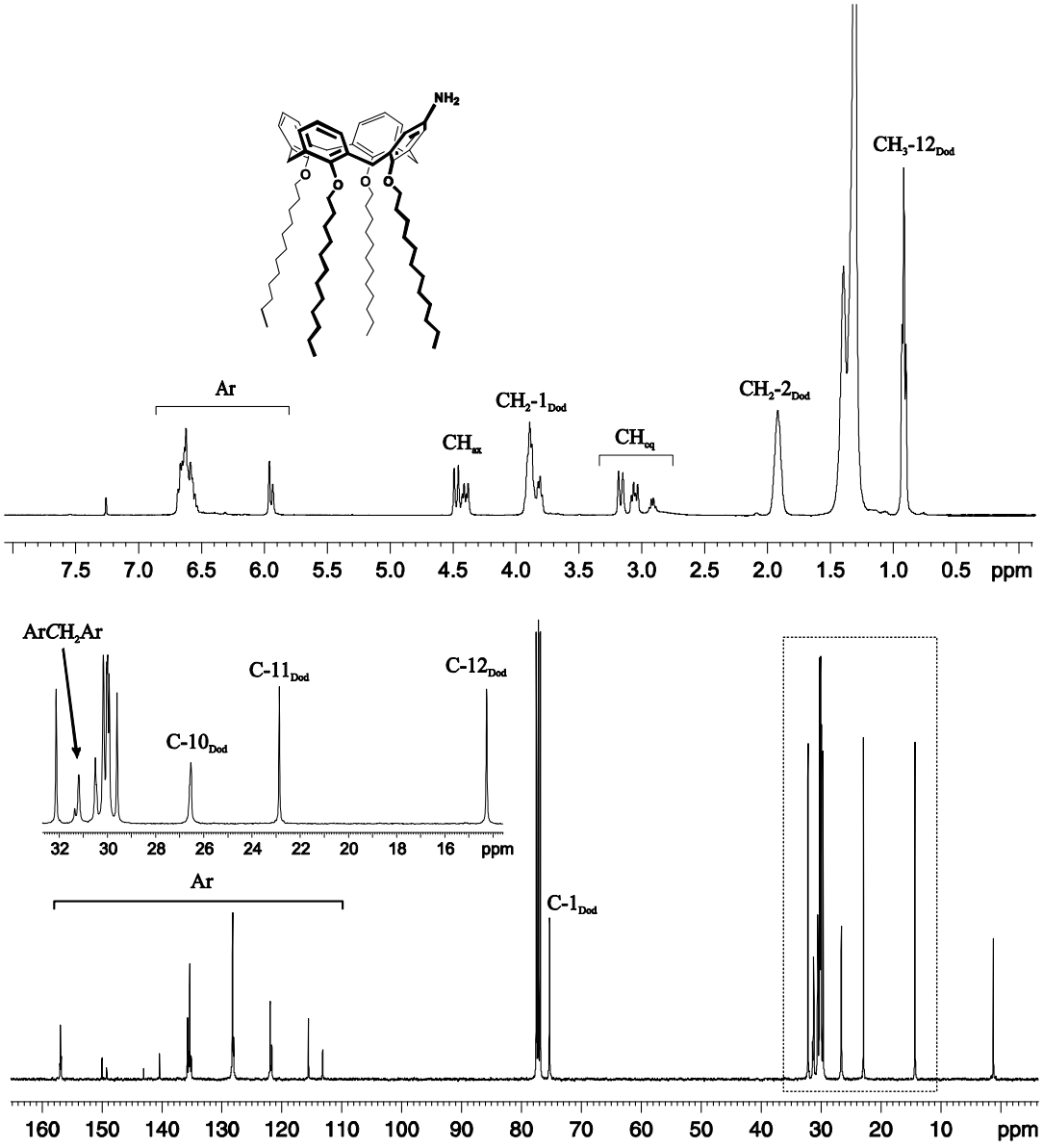


Figure S10. ^{1}H NMR and ^{13}C NMR spectra (400 MHz, 100.6 MHz, $CDCl_3$) of compound **13**.

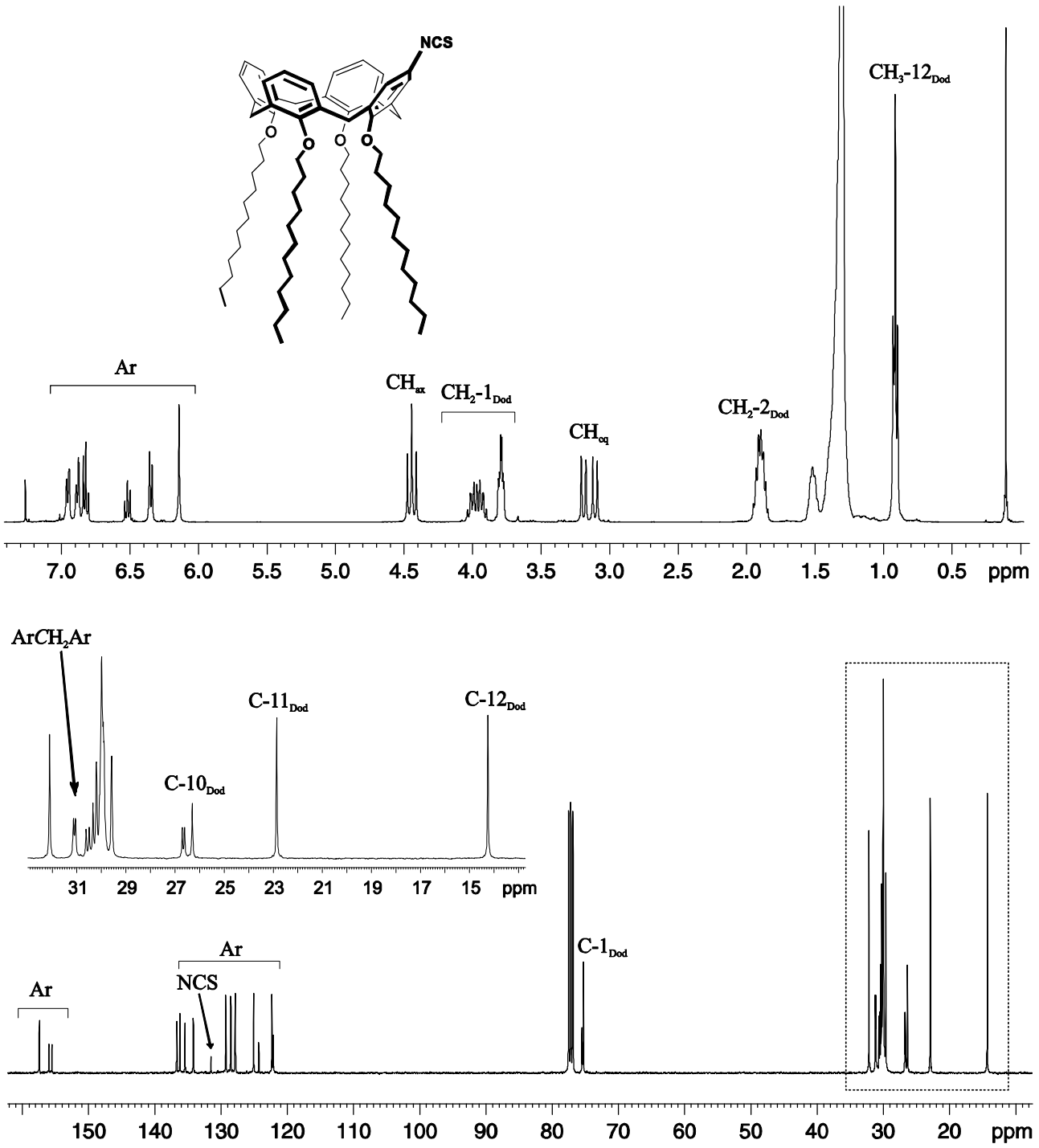


Figure S11. ^{1}H NMR and ^{13}C NMR spectra (400 MHz, 100.6 MHz, $CDCl_3$) of compound **14**.

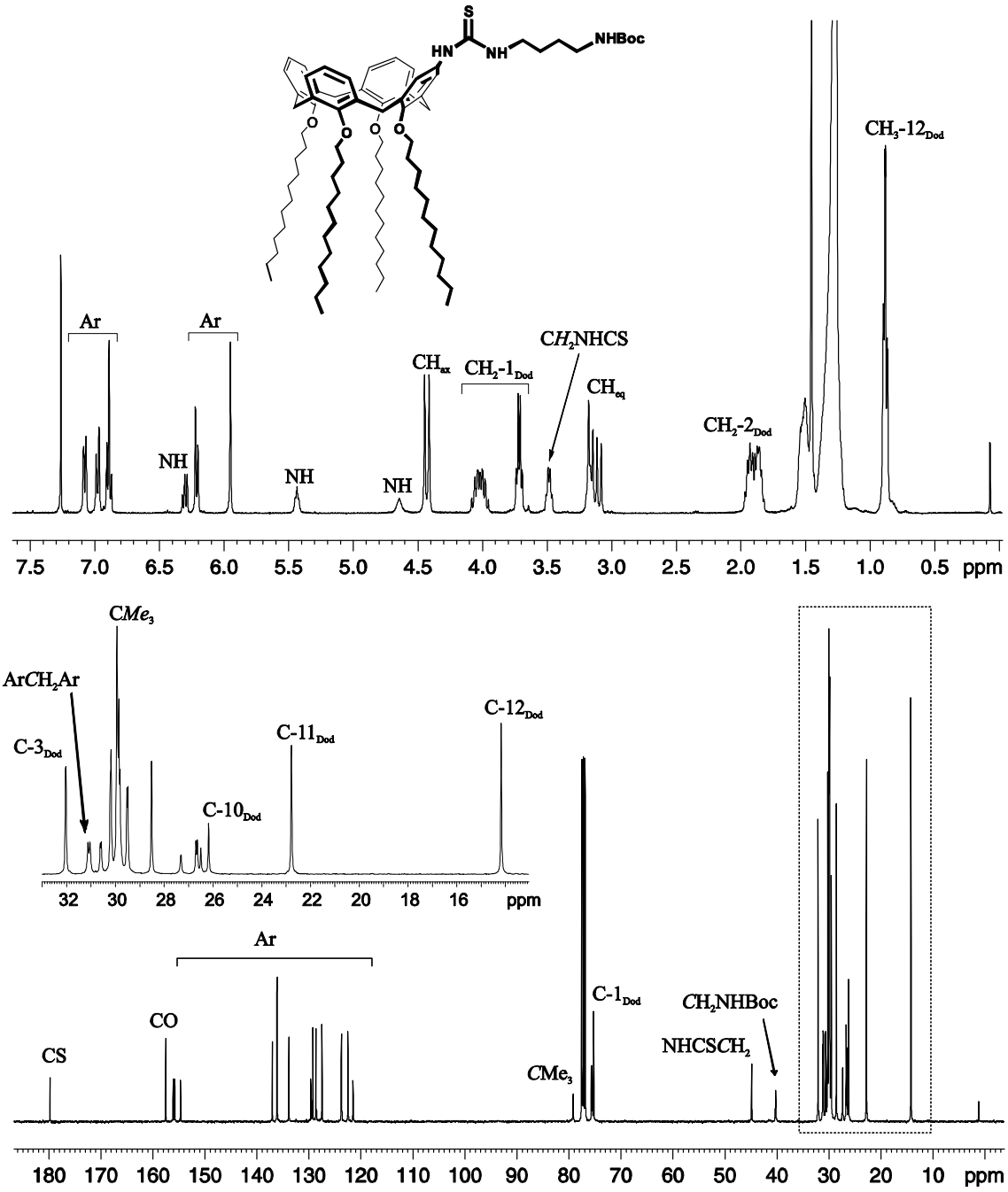


Figure S12. ^{1}H NMR and ^{13}C NMR spectra (400 MHz, 100.6 MHz, $CDCl_3$) of compound **15**.

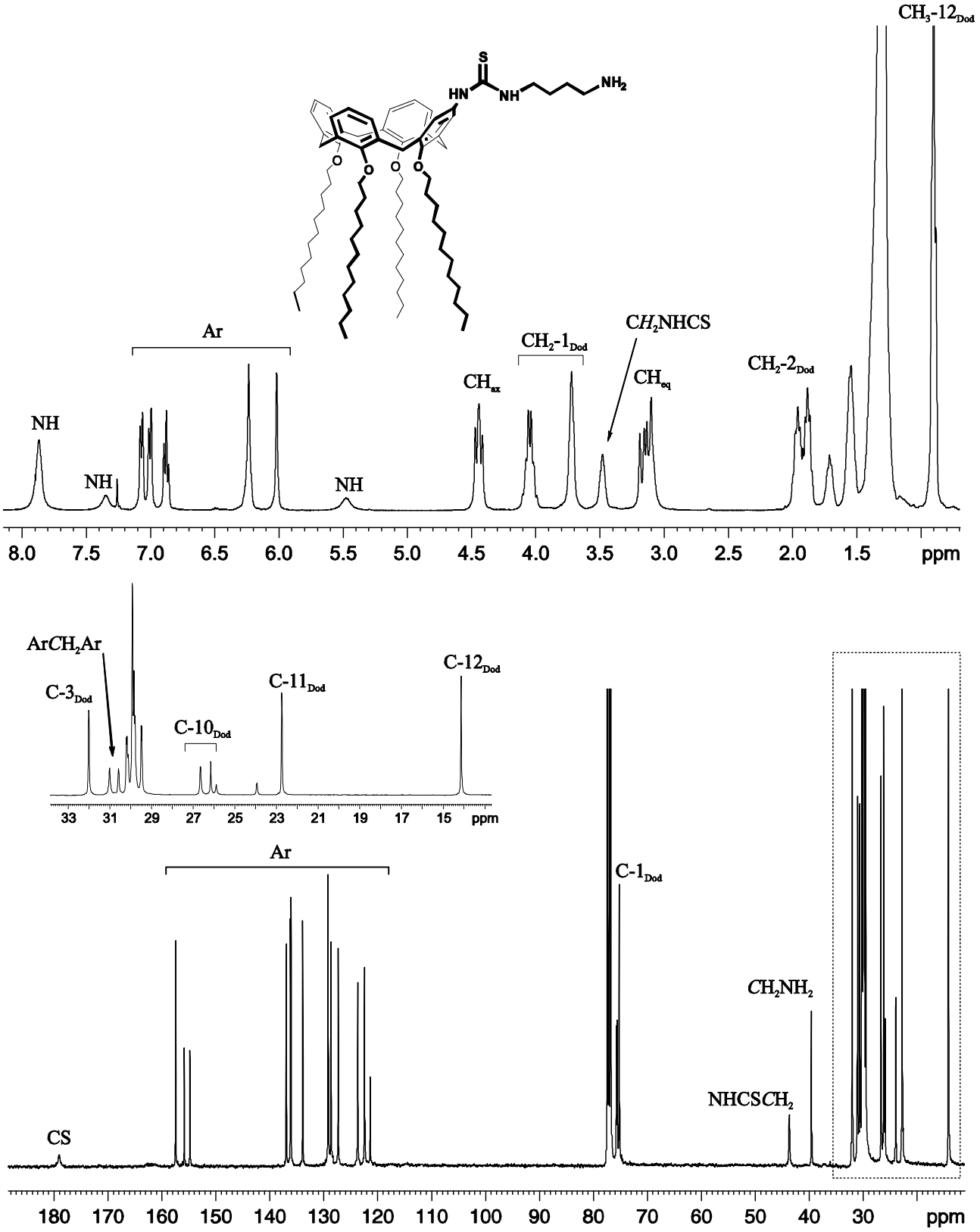


Figure S13. ^{1}H NMR and ^{13}C NMR spectra (400 MHz, 100.6 MHz, $CDCl_3$) of compound **16**.

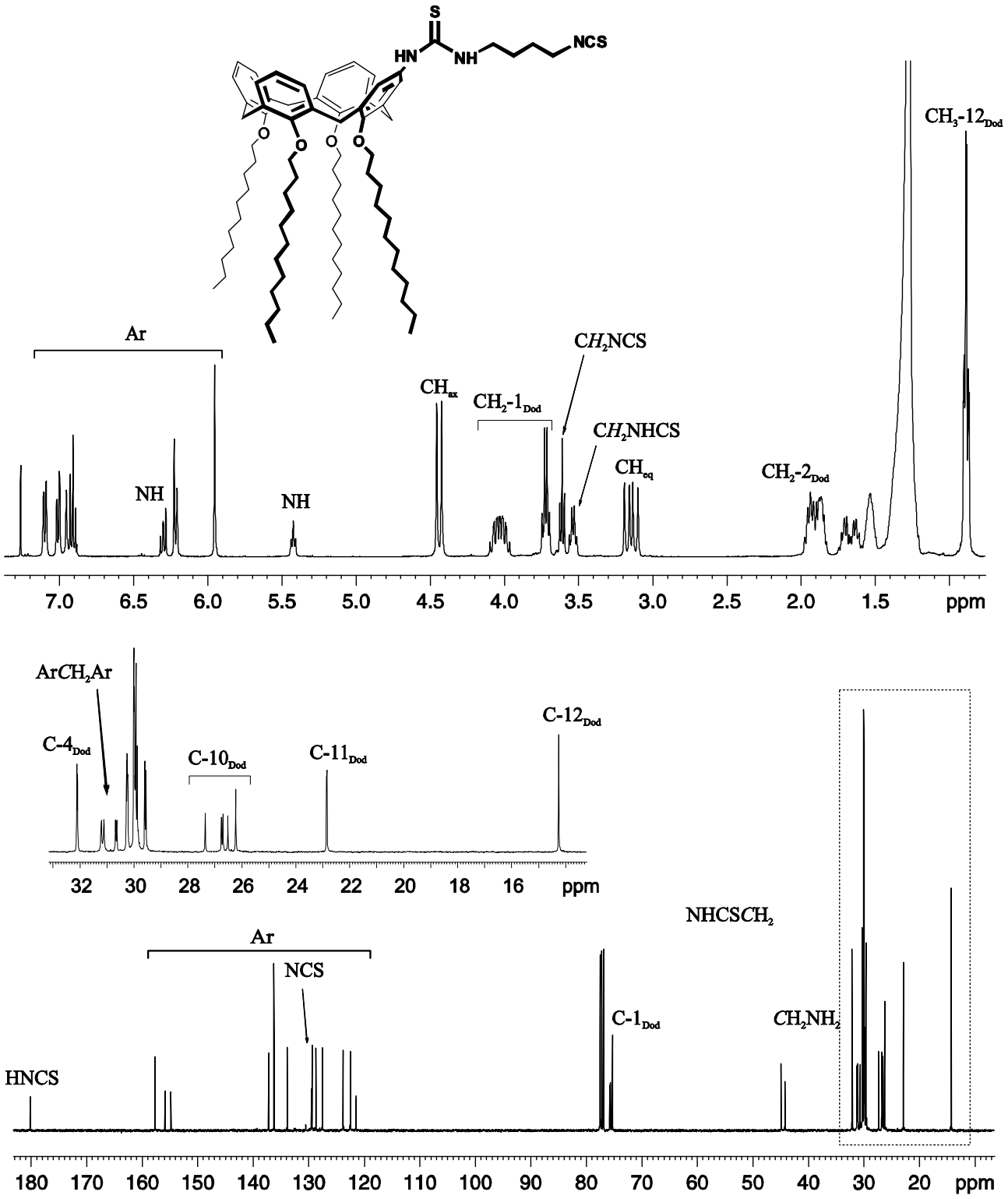


Figure S14. ^{1}H NMR and ^{13}C NMR spectra (400 MHz, 100.6 MHz, $CDCl_3$) of compound **17**.

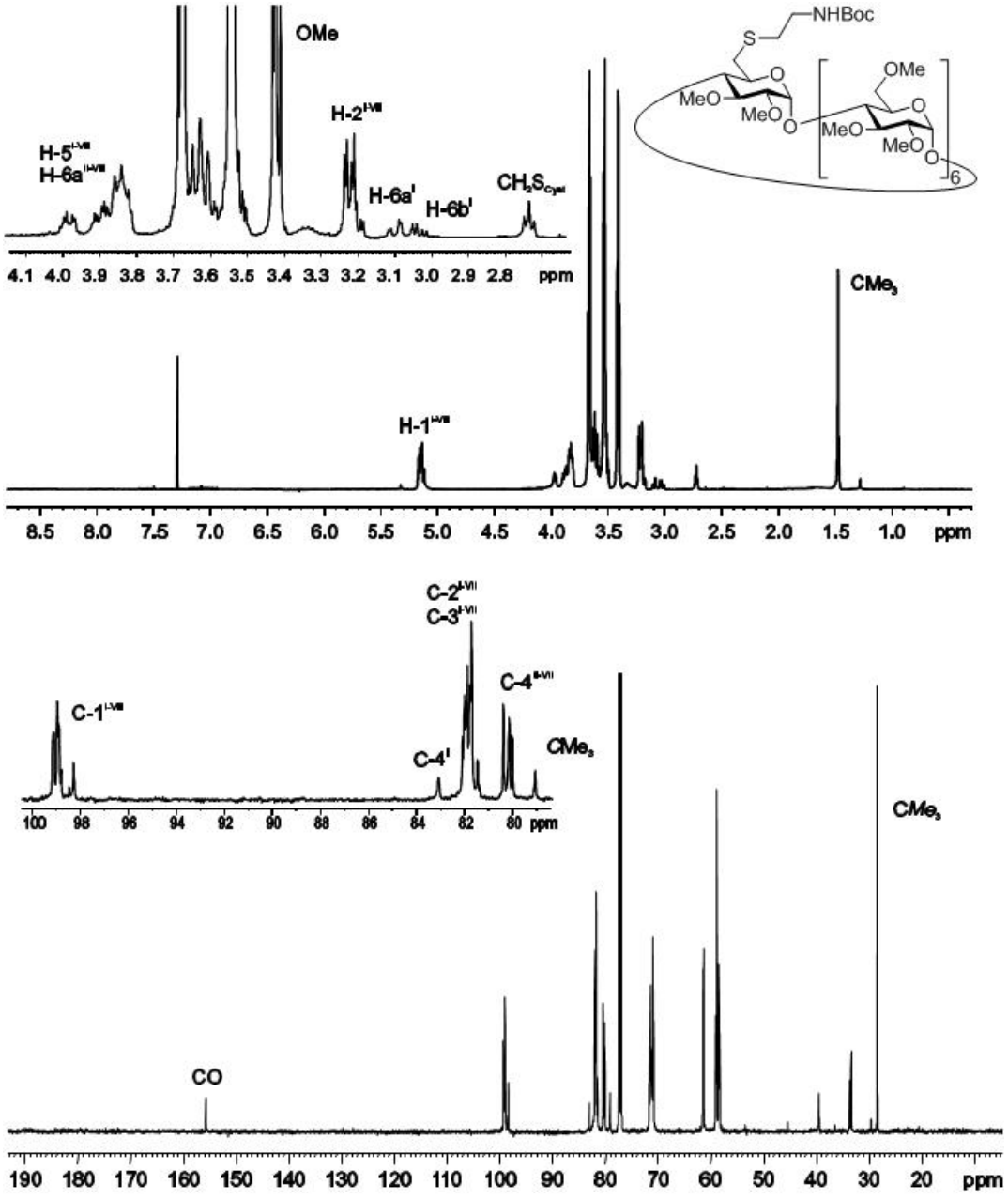


Figure S15. ^{1}H NMR and ^{13}C NMR spectra (500 MHz, 125.7 MHz, $CDCl_3$) of compound **19**.

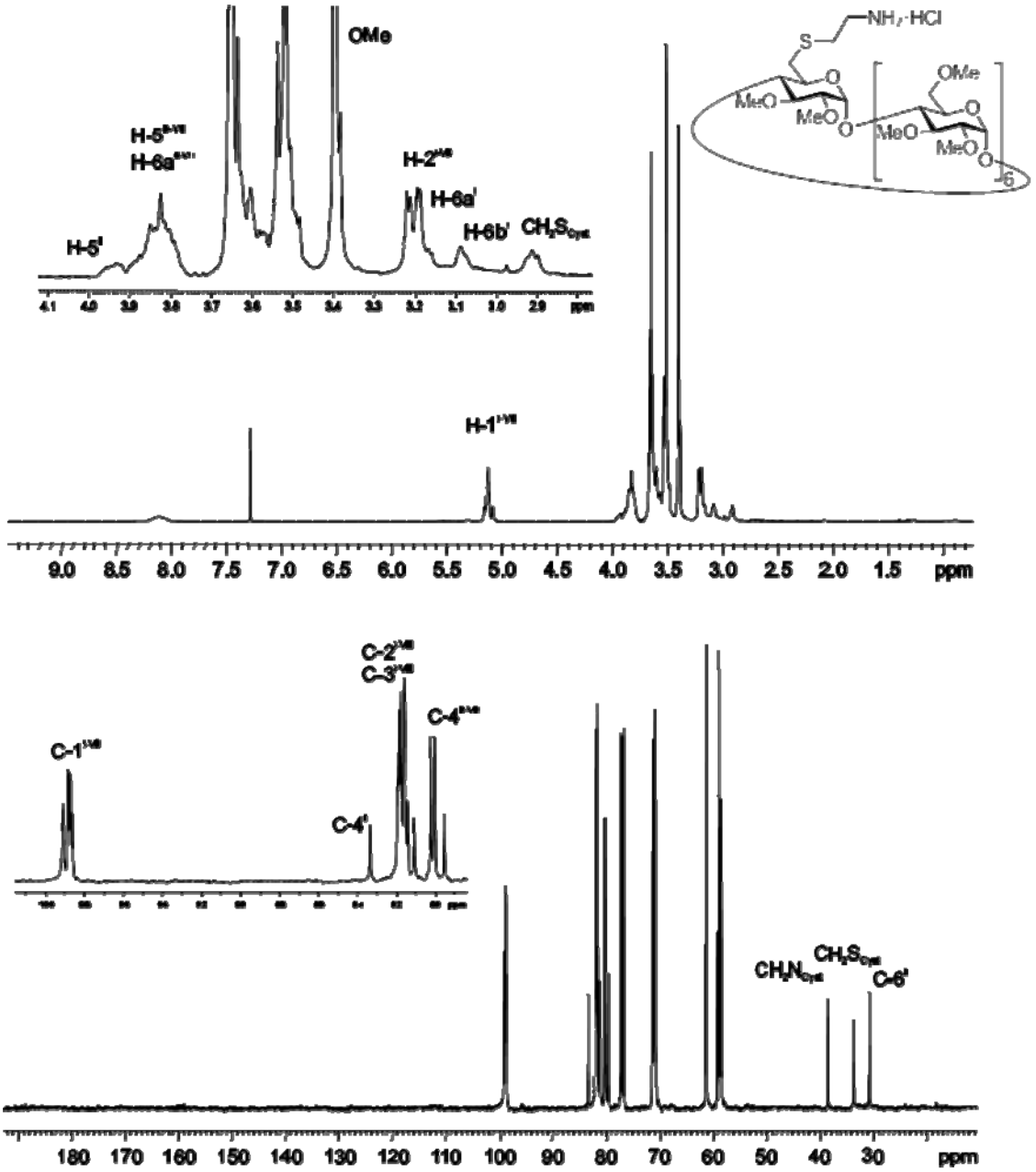


Figure S16. ^{1}H NMR and ^{13}C NMR spectra (400 MHz, 100.6 MHz, $CDCl_3$) of compound **20**.

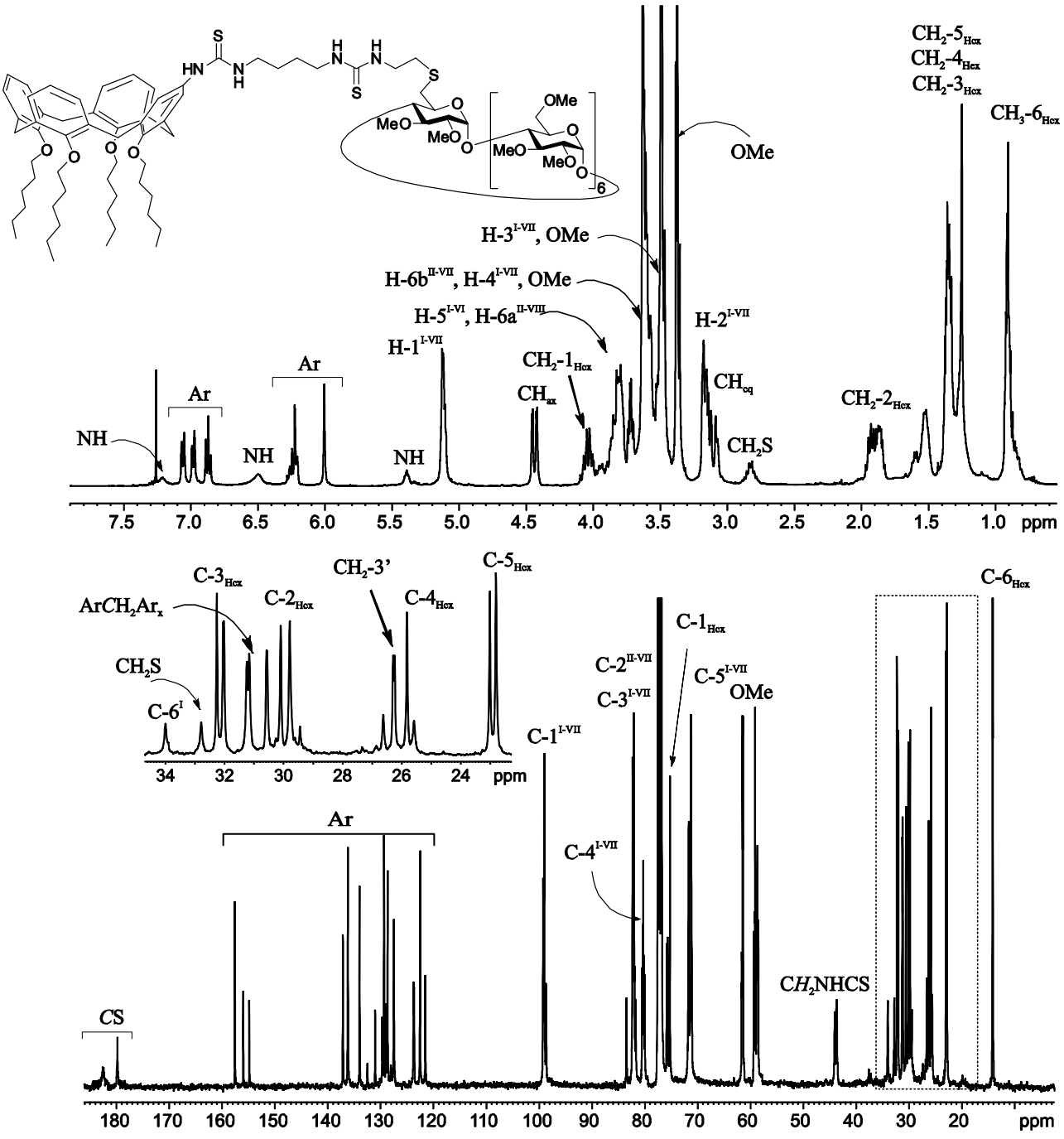


Figure S17. ^{1}H NMR and ^{13}C NMR spectra (500 MHz, 125.7 MHz, $CDCl_3$) of compound **1**.

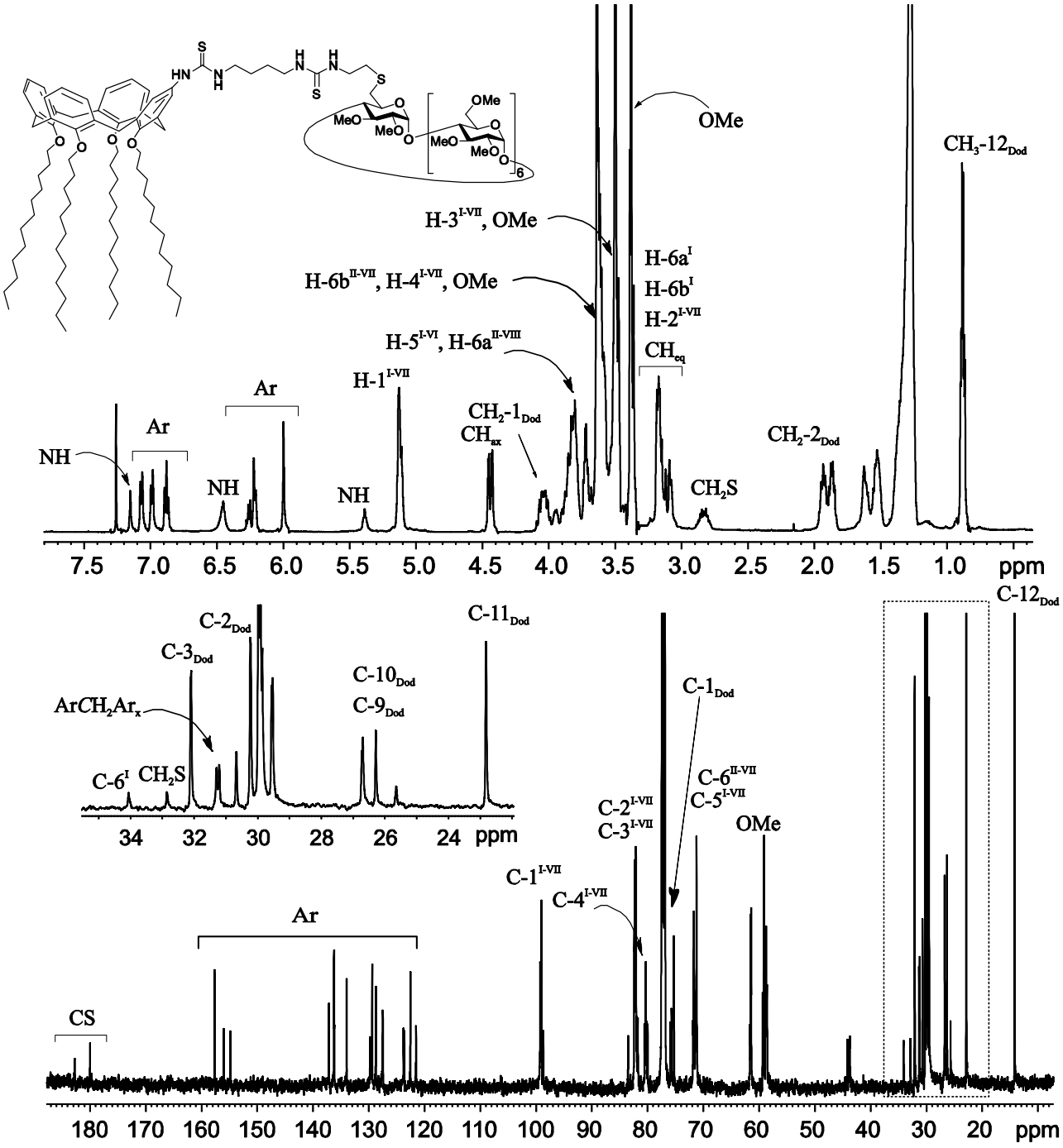


Figure S18. ^{1}H NMR and ^{13}C NMR spectra (500 MHz, 100.6 MHz, 313 K, $CDCl_3$) of compound **2**.

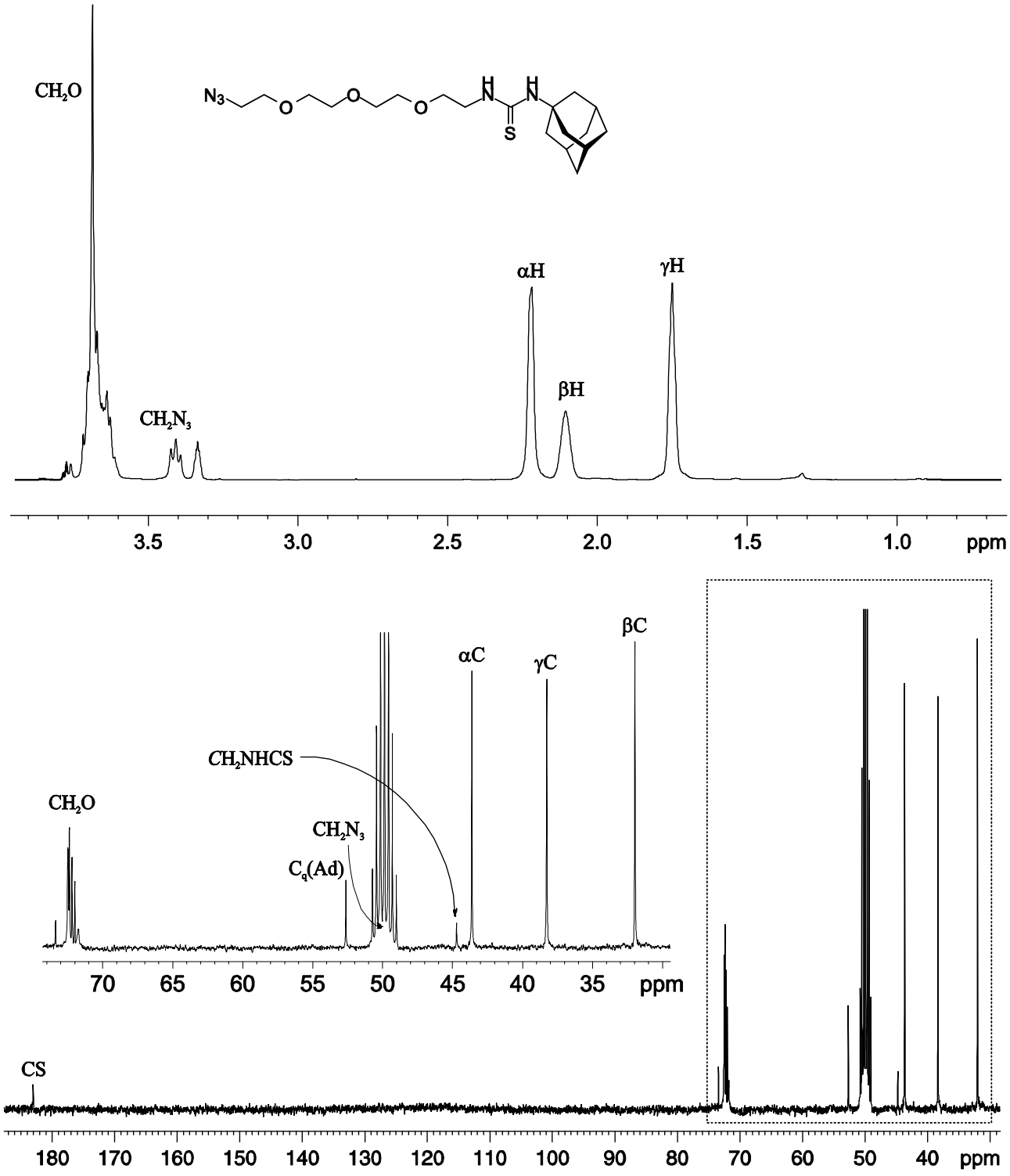


Figure S19. ^{1}H NMR and ^{13}C NMR spectra (300 MHz, 75.5 MHz, CD_3OD) of compound **22**.

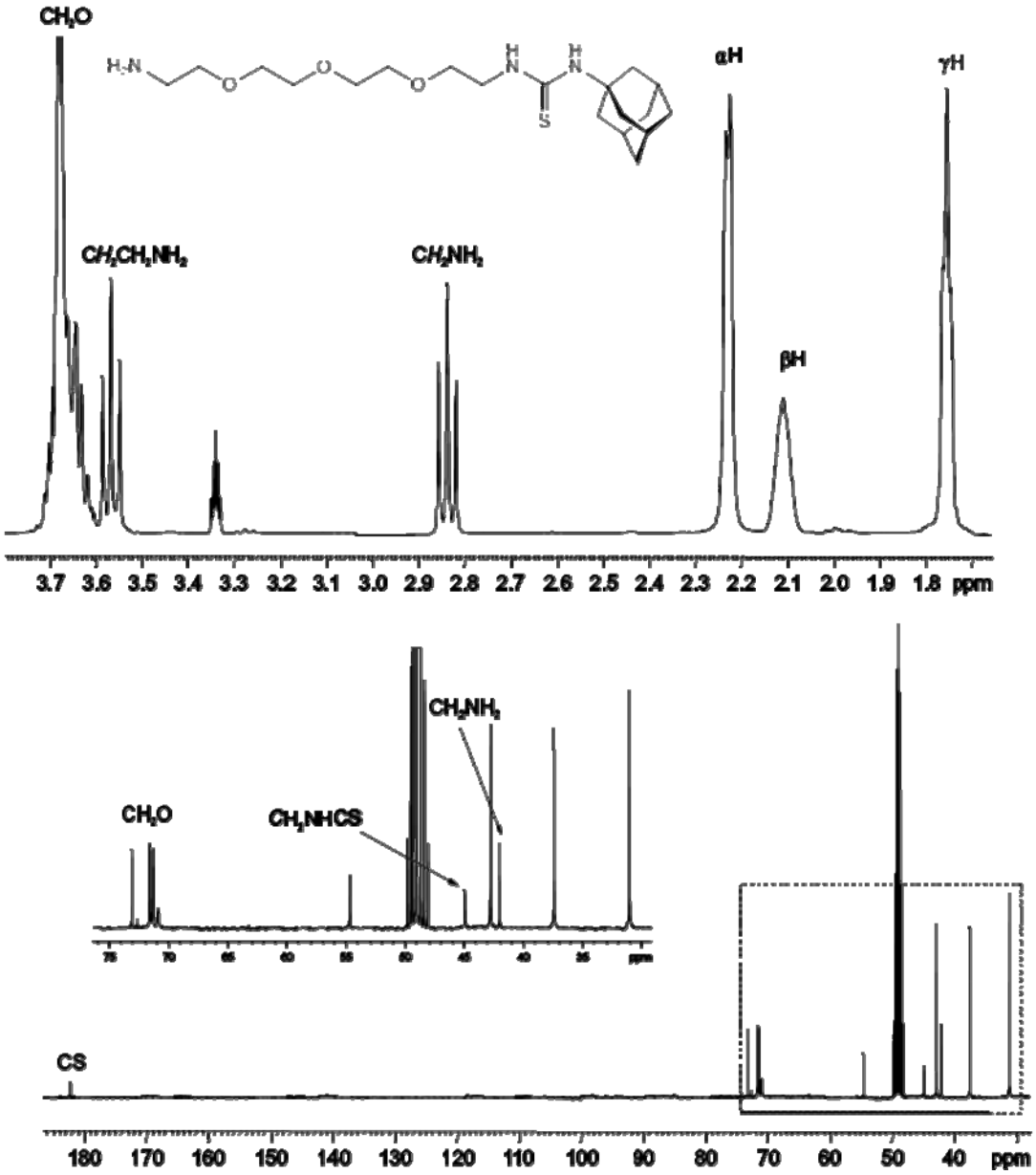


Figure S20. ^{1}H NMR and ^{13}C NMR spectra (300 MHz, 75.5 MHz, CD_3OD) of compound **23**.

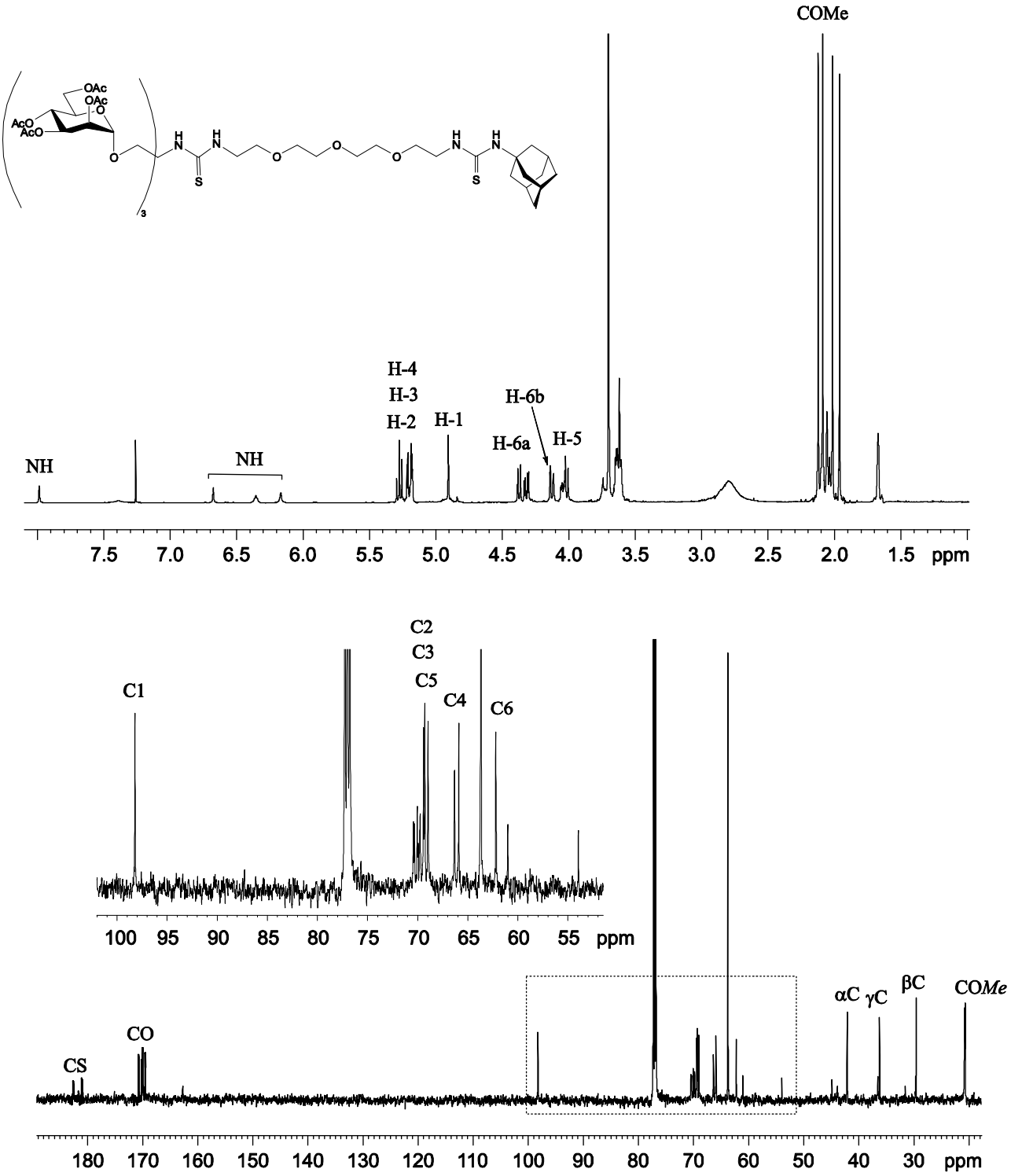


Figure S21. ^{1}H NMR and ^{13}C NMR spectra (500 MHz, 125.7 MHz, 313 K, $CDCl_3$) of **25**.

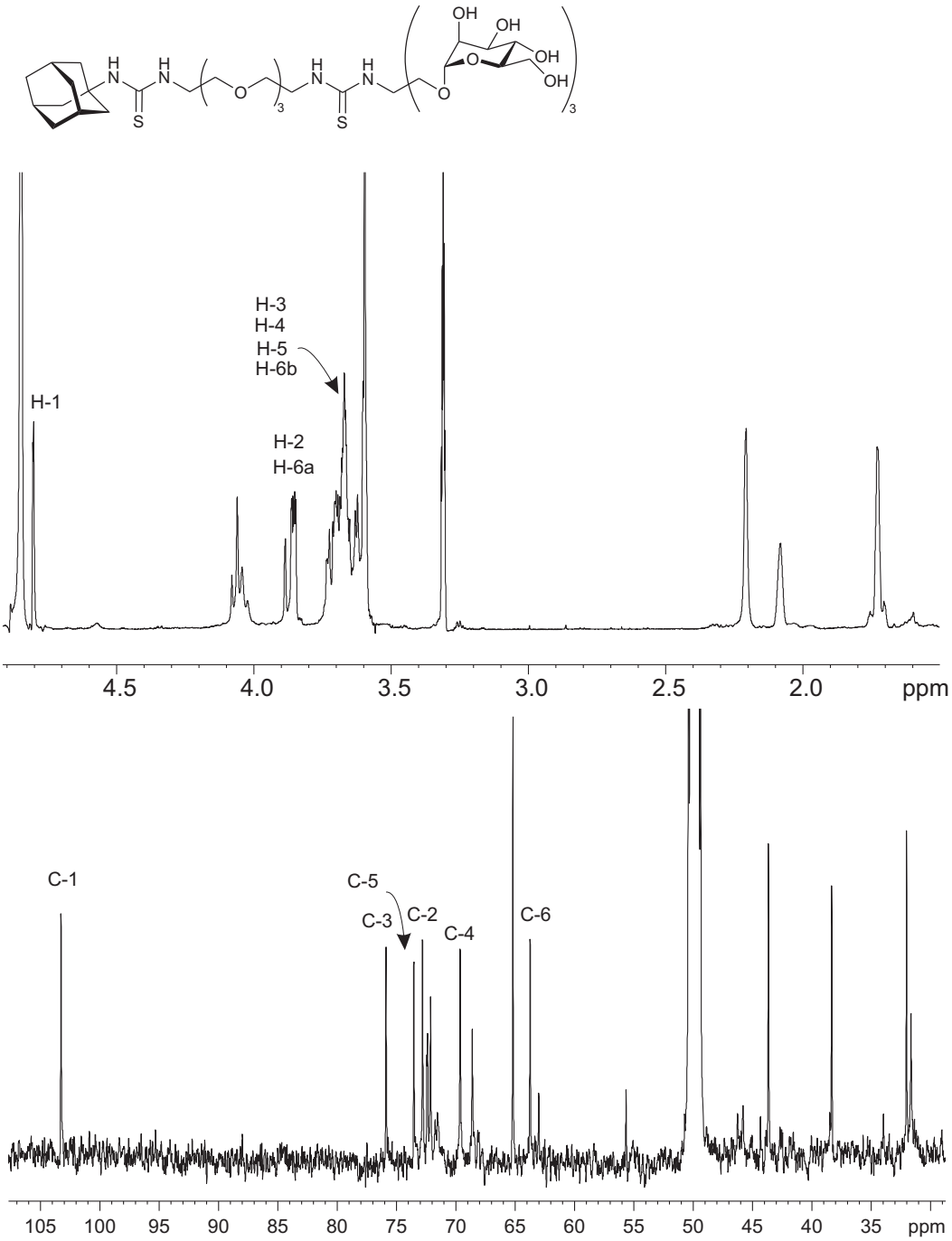


Figure S22. ^{1}H NMR and ^{13}C NMR spectra (500 MHz, 125.7 MHz, CD_3OD) of compound **3**.

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