Supplementary Information

for

Multi-target macrocycles: pyrogallol derivatives to control multiple pathological factors associated with Alzheimer's disease

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Materials and Methods. All chemical reagents were purchased from commercial suppliers and used as received unless otherwise stated. Compounds **4**–**6** [4-methylpyrogallol (**4**), 4-methylresorcinol (**5**), and toluene (**6**)] were purchased from Toronto Research Chemicals (North York, ON, Canada), Sigma-Aldrich (St. Louis, MO, USA), and Alfa Aesar (Ward Hill, MA, USA), respectively. Compounds **1**–**3** [pyrogallol[4]arene (**1**), resorcin[4]arene (**2**),[1] and calix[4]arene (**3**)[2]] were prepared following previously reported procedures. $A\beta_{40}$ (DAEFRHDSGYEVHHQKLVFFAE-DVGSNKGAIIGLM-VGGVV) and $A\beta_{42}$ (DAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVG-GVVIA) were obtained from Peptide Institute, Inc. (Osaka, Japan). HEPES (2-[4-(2-hydroxyethyl)piperazin1-yl]ethanesulfonic acid) was purchased from Sigma-Aldrich (St. Louis, MO, USA). The buffered solution was prepared in doubly distilled water [ddH_2O; a Milli-Q Direct 16 system (18.2 MΩ·cm; Merck KGaA, Darmstadt, Germany)]. Trace metal contamination was removed from the solutions by treating with Chelex (Sigma-Aldrich) overnight. ^1H and ^{13}C NMR spectra of compounds were recorded on a Bruker AV400 NMR spectrometer (Bruker BioSpin, Rheinstetten, Germany; Department of Chemistry, KAIST, Daejeon, Republic of Korea). High-resolution mass spectrometric analysis of compounds was carried out by micrOTOF-QII [Bruker Daltonics, Bremen, Germany; KAIST Analysis Center for Research Advancement (KARA), Daejeon, Republic of Korea]. Absorbance values for biological assays were measured on a Molecular Devices SpectraMax M5e microplate reader (Sunnyvale, CA, USA). Optical spectra were recorded on an Agilent 8453 UV–Vis spectrophotometer (Santa Clara, CA, USA). Images gained through gel/Western blot were visualized by a ChemiDoc MP imaging system (Bio-Rad, Hercules, CA, USA). Morphologies of Aβ aggregates produced from the aggregation experiments were taken on a Tecnai F20 transmission electron microscope (FEI Company, Eindhoven, Netherlands; KARA). Mass spectrometric analysis of the interactions of the compounds with $A\beta_{40}$ in the absence and presence of Cu(II) was conducted by a Waters Xevo G2-XS quadrupole time-of-flight (Q-TOF) mass spectrometry (MS). The human neuroblastoma SH-SY5Y (5Y) cell line was purchased from the American Type Culture Collection (ATCC, Manassas, VA, USA). MTT [3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2*H*-tetrazolium bromide] was purchased from Sigma-Aldrich.

Synthesis of compounds 1–3

1 [1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^4,1^5,1^6,3^4,3^5,3^6,5^4,5^5,5^6,7^4,7^5,7^6-dodecaol]. Compound **1** was synthesized following previously reported procedures with slight modifications.[1] 1,2,3-Trihydroxybenzene (0.35 g, 2.8 mmol) was dissolved in an aqueous solution of sodium

hydroxide (NaOH; 0.4 M, 20 mL) at room temperature. The reaction mixture was stirred in an ice bath, and paraformaldehyde (0.08 g, 2.8 mmol) was added. After 2 h, the ice bath was removed, and the reaction mixture was stirred at room temperature for 22 h. A solution of HCl (37% w/w, aq, 0.5 mL) was added dropwise to the mixture, and the precipitates were filtered off using a bottle top vacuum filter (pore size 0.22 μm, Corning, NY, USA), washed with H_2O (x2), and concentrated. The solid was dissolved in CH_3OH (0.1 L), and then H_2O (0.1 L) was added. The precipitates were filtered off and washed with H_2O to obtain compound **1** [beige powder; 94 mg, 0.17 mmol (yield = 24%)]. ^{1}H NMR [400 MHz, DMSO-d_6, δ (ppm)]: 8.26 (12H, s), 6.01 (4H, s), 3.49 (8H, s). ^{13}C NMR [100 MHz, DMSO-d_6, δ (ppm)]: 141.04, 133.19, 120.18, 119.58, 28.43. HRMS: *m/z* Calcd. for $C_{28}H_{23}O_{12}$ $[M - H]^-$: 551.4800; found: 551.1200.

2 [1,3,5,7(1,3)-tetrabenzenacyclooctaphan-1^4,1^6,3^4,3^6,5^4,5^6,7^4,7^6-octaol]. Compound **2** was prepared following previously reported procedures with minor modifications.[1] 1,3-Dihydroxybenzene (0.34 g, 3.1 mmol) was dissolved in an aqueous solution of NaOH (0.4 M, 20 mL) at room temperature. Paraformaldehyde (90 mg, 3.1 mmol) was added to the solution at 0 °C. The solution was gradually warmed up to room temperature over 24 h. The reaction was quenched with HCl (37% w/w, aq, 0.5 mL), and the precipitates were filtered, washed with H_2O, and dried. The crude product was purified by column chromatography (SiO_2; CH_3OH:CH_2Cl_2 = 1:9). Compound **2** was obtained by recrystallization using a mixture of diethyl ether (Et_2O) and CH_3OH [R_f = 0.3; light beige powder; 62 mg, 0.13 mmol (yield = 17%)]. ^{1}H NMR [400 MHz, DMSO-d_6, δ (ppm)]: 8.88 (8H, s), 6.29 (8H, d, J = 4.5 Hz), 3.43 (8H, s). ^{13}C NMR [100 MHz, DMSO-d_6, δ (ppm)]: 153.30, 131.23, 118.46, 102.63, 27.92. HRMS: *m/z* Calcd. for $C_{28}H_{23}O_8$ $[M - H]^-$: 487.1398; found: 487.1361.

3b [octaethyl(1^5,3^5,5^5,7^5-tetra-*tert*-butyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane1^2,3^2, 5^2,7^2-tetrayl) tetrakis(phosphate)]. Compound **3b** was produced with slight modifications of the previously reported procedures.[2] 1^5,3^5,5^5,7^5-Tetra-*tert*-butyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane-1^2,3^2,5^2,7^2-tetraol (0.38 g, 0.6 mmol), diethyl phosphorochloridate (1.1 mL, 7.5 mmol), and tetrabutylammonium bromide (40 mg, 0.1 mmol) were dissolved in a mixture of NaOH (50% w/w, aq, 19 mL) and CH_2Cl_2 (38 mL) and refluxed at 48 °C. After 6 h, the reaction mixture was extracted with CH_2Cl_2. The organic layer was collected, washed with brine, dried with sodium sulfate ($NaSO_4$), filtered, concentrated, and cooled down at 4 °C for 1 h. The crude product was washed with petroleum ether, dried, and purified by column chromatography (SiO_2; acetone:hexanes = 1:1) to yield compound **3b** [R_f = 0.6; white powder; 185 mg, 0.16 mmol (yield = 26%)]. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 6.88 (8H, s), 4.81 (4H, d, J = 13.6 Hz), 4.32–4.22 (16H, m), 3.28 (4H, d, J = 13.7 Hz), 1.31 (24H, t, J = 7.0 Hz), 1.09 (36H, s). ^{13}C NMR [100 MHz, $CDCl_3$, δ (ppm)]:

146.58, 143.02, 133.72, 125.73, 64.74, 64.68, 34.10, 31.51, 31.20, 16.41, 16.34. HRMS: *m/z* Calcd. for $C_{60}H_{92}O_{16}P_4Na_2$ $[M + 2Na]^{2+}$: 619.2548; found: 619.2585.

3c [1^5,3^5,5^5,7^5-tetra-*tert*-butyl-1,3,5,7(1,3)-tetrabenzenacyclooctaphane]. Compound **3c** was synthesized according to previously reported procedures with minor modifications.[2] Potassium metal (0.72 g, 18 mmol) was dissolved in liquid ammonia (9.0 mL) at –60 °C. A solution of compound **3b** (90 mg, 0.1 mmol) in dried Et_2O (1.0 mL) was added dropwise to the stirred blue solution, followed by the addition of potassium metal (90 mg, 2.3 mmol). After 15 min, ammonium chloride (1.1 g, 21 mmol) was added dropwise until the color of solution changed from blue to white. The reaction mixture was mixed with Et_2O (9 mL), warmed to room temperature, and treated with hot diethyl ether (30°C; 18 mL). The crude product was filtered, concentrated, and further purified by column chromatography (SiO_2; EtOAc:petroleum ether = 1:19) to yield compound **3c** [R_f = 0.8; white powder; 24 mg, 0.04 mmol (yield = 38%)]. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 7.09 (8H, s), 6.50 (4H, s), 3.85 (8H, s), 1.30 (36H, s). ^{13}C NMR [100 MHz, $CDCl_3$, δ (ppm)]: 151.08, 141.01, 126.04, 123.72, 42.43, 34.51, 31.44. HRMS: *m/z* Calcd. for $C_{44}H_{56}Na$ $[M + Na]^+$: 607.4280; found: 607.4294.

3 [1,3,5,7(1,3)-tetrabenzenacyclooctaphane]. Compound **3** was prepared following previously reported procedures with modifications.[2] Compound **3c** (0.23 mg, 0.39 mmol) and aluminum chloride (4.2 g, 32 mmol) were dissolved in dried toluene (18 mL) and stirred at –5 °C. After 1 h, the reaction mixture was quenched with HCl (2.0 M, aq, 10 mL). The organic layer was collected, washed with brine, and concentrated. Compound **3** was obtained by recrystallization using a mixture of $CHCl_3$, CH_3OH, and acetone [white powder; 33 mg, 0.09 mmol (yield = 23%)]. ^{1}H NMR [400 MHz, $CDCl_3$, δ (ppm)]: 7.19 (4H, t, J = 8.4, 7.7 Hz), 7.07 (8H, d, J = 7.6 Hz), 6.69 (4H, s), 3.84 (8H, s). ^{13}C NMR [100 MHz, $CDCl_3$, δ (ppm)]: 141.51, 128.92, 128.42, 126.72, 41.90. HRMS: *m/z* Calcd. for $C_{28}H_{24}Na$ $[M + Na]^+$: 383.1776; found: 383.1765.

Calculation of Redox Potentials. All calculations were performed based on the density functional theory (DFT)[3] with the Jaguar 9.1 suite[4] at the B3LYP[5–7] level of theory. The optimization of compounds' structures was carried out with the 6-31G** basis set.[8–10] Following the geometry optimization, electronic energies of the optimized structures were recalculated with a high quality triple-ζ basis set cc-pVTZ(-f).[11] Vibrational frequencies for the optimized structures were calculated at the same level of theory as the geometry optimization procedure. Vibrational entropy correction, along with the zero-point vibrational energies, was considered for proper thermodynamic approximations. Based on the optimized gas phase geometries, solvation correction energies were deduced. Self-consistent reaction field (SCRF)[12–14] approximations were

used to calculate the linearized Poisson-Boltzmann equations with the dielectric constant ε. The solvation energy used in the system was treated with CH_3OH (ε = 32.7). The Gibbs free energies in the solution phase were computed as the following equations:

$$G(Sol) = G(gas) + G(solv)$$
$$G(gas) = H(gas) – TS(gas)$$
$$H(Gas) = E(SCF) + ZPE$$

G(Sol) represents the Gibbs free energy with solvation corrections, G(solv), from the gas phase free energy, G(gas); H(gas) is the enthalpy of the molecule in the gas phase; T is the temperature (298.15 K); S(gas) is the entropy of the molecule in the gas phase; E(SCF) is the self-consistent field-converged electronic energy; ZPE represents the vibrational zero-point energy. To calculate the redox potential, the free energy of the one-electron oxidized form of the compound was deduced by the free energy of its neutral form.

Cyclic Voltammetry. Cyclic voltammograms were recorded under N_2 (g) on a CHI620E potentiostat (CH Instruments, Inc., Bee Cave, TX, USA) with a three-electrode setup: a glassy carbon working electrode (ALS Co., Ltd, Tokyo, Japan), an Ag/Ag(I) reference electrode (RE-7 non-aqueous reference electrode; ALS Co., Ltd), and a Pt wire auxiliary electrode (ALS Co., Ltd). The redox potentials of compounds **1**, **4**, **5** (1 mM; 1% v/v DMSO) and compound **2** (1 mM; 2% v/v DMSO) were obtained in CH_3CN containing 0.1 M tetrabutylammonium hexafluorophosphate ($TBAPF_6$) with the Ag/Ag(I) reference filled with a mixture of 0.1 M $TBAPF_6$ and 0.01 M $AgNO_3$. Measurements were taken at various scan rates (25, 50, 100, 150, 200, and 250 mV/s) at room temperature. All samples were withdrawn from a N_2-filled glove box immediately before each experiment, and they were freshly prepared. Prior to each measurement, N_2 (g) was purged into the solution.

TEAC Assay. The free radical scavenging capacity of compounds, relative to that of the vitamin E analog Trolox, known as an antioxidant,[15] was determined by the TEAC assay based on the decolorization of ABTS [2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)diammonium salt] cation radicals. The TEAC assay was conducted in CH_3OH following previously reported methods.[16,17] Blue $ABTS^{+\bullet}$ cation radicals were generated by dissolving ABTS (7.0 mM) with potassium persulfate (2.5 mM) in H_2O (5 mL) and incubating the solution for 16 h at room temperature in the dark. The solution was diluted with CH_3OH to achieve an absorbance value of

ca. 0.7 at 745 nm. The resultant $ABTS^{+\bullet}$ solution (200 μL) was added into a clear 96-well plate. Various concentrations of the compounds were added into the 96-well plate and incubated at 25 °C for 1, 3, and 5 min. The final concentrations of the compounds were as follows: Trolox, **1**, **4**, and **5** (0.99, 2.48, 4.95, 7.43, 9.90, 14.85, and 19.80 μM); **2** (0.05, 0.10, 0.30, 0.59, 1.19, 2.48, 3.27, and 4.95 μM); **3** and **6** (0.22, 0.45, 0.89, 1.34, 1.78, 2.23, 3.27, and 4.95 μM). Percent inhibition was calculated based on the measured absorbance at 745 nm [% inhibition = 100 x (A_0 – A)/A_0; A_0 = absorbance of the control well without compounds; A = absorbance of the wells treated with compounds] and plotted as a function of the compounds' concentration. The TEAC values of each time point were calculated as the ratio between the slope of the compounds and the slope of Trolox. All measurements were carried out in triplicate.

Docking Studies. Flexible ligand docking studies using AutoDock Vina 1.5.6 software[18] were conducted for the compounds against monomeric $A\beta_{40}$, whose structure was previously determined by NMR spectroscopy in aqueous solution (PDB 2LFM).[19] The MMFF94 energy minimization in ChemBio3D Ultra 11.0 was used to optimize the structures of the compounds for docking studies. The structural files of the molecules and the peptides were prepared in AutoDock Tools, imported into PyRx,[20] and used to run AutoDock Vina.[18] The exhaustiveness for the docking runs was set at 1,024. Docked models of the compounds with monomeric $A\beta_{40}$ were visualized using Pymol 2.0.7.

Electronic Abs Spectroscopy. Compound **4** (250 μM; 1% v/v DMSO) was added to H_2O in the absence and presence of $CuCl_2$ (250 or 500 μM). Abs spectra of the samples were collected for 1 h at 37 °C.

Aβ Aggregation Experiments. Aβ was dissolved in ammonium hydroxide [1% w/w NH_4OH (aq)], and the resulting solution was aliquoted, lyophilized overnight, and stored at –80 °C. A stock solution of Aβ was then prepared by dissolving the lyophilized peptide with NH_4OH (1% w/w, aq; 10 μL) and diluting it with ddH_2O. All Aβ samples were prepared following previously reported procedures.[21,22] The concentration of the peptide solution was determined by measuring its absorbance at 280 nm (ε = 1,450 $M^{-1}cm^{-1}$ for $A\beta_{40}$; ε = 1,490 $M^{-1}cm^{-1}$ for $A\beta_{42}$). A buffered solution [20 mM HEPES, pH 6.8 or 7.4, 150 mM NaCl] was used for preparing the samples of Aβ. For the inhibition studies, compounds (final concentration, 25 or 100 μM; 1% v/v DMSO) were added to the samples of Aβ (25 μM) in the absence and presence of $CuCl_2$ or $ZnCl_2$ (25 μM) followed by

incubation for 24 h at 37 °C with constant agitation. For the disaggregation studies, Aβ (25 μM) was incubated with and without $CuCl_2$ or $ZnCl_2$ (25 μM) for 24 h at 37 °C with constant agitation to generate preformed Aβ aggregates. The resulting Aβ aggregates were then treated with the compounds (25 or 100 μM; 1% v/v DMSO) and incubated for additional 24 h with constant agitation.

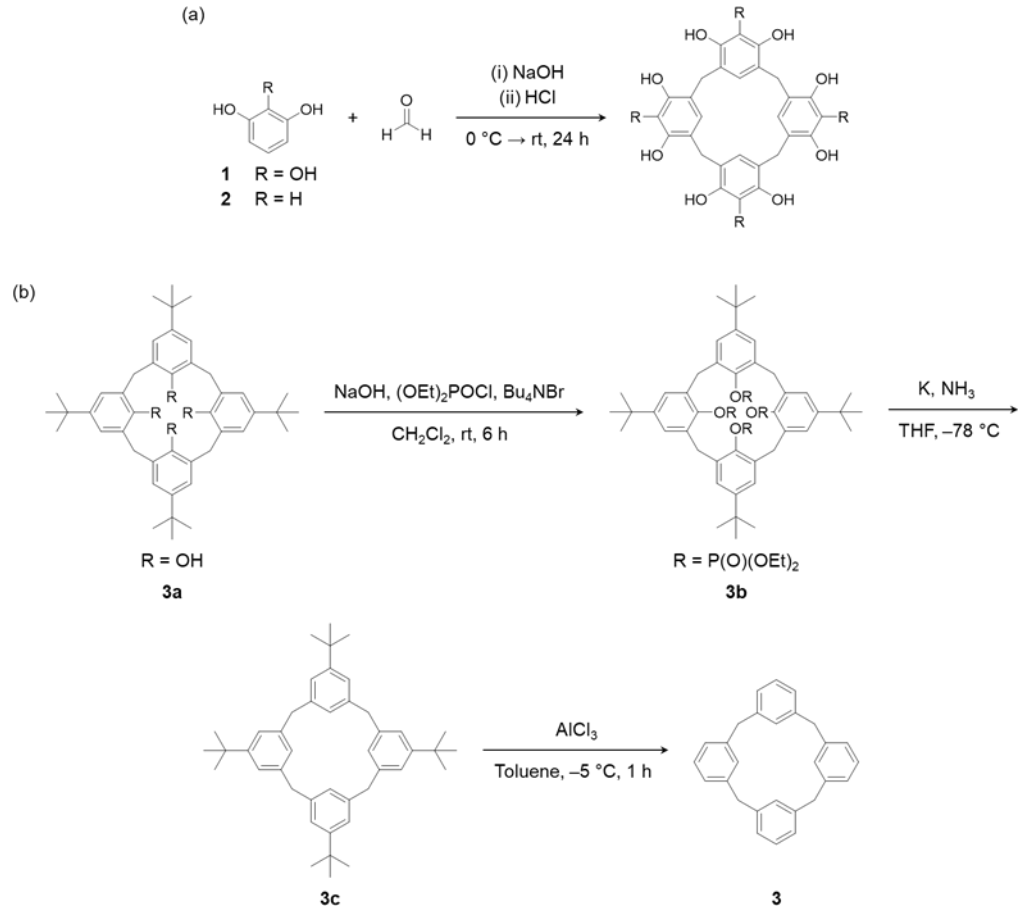
Gel/Western Blot. The resultant Aβ species from the aggregation experiments were analyzed by gel/Western blot using anti-Aβ antibodies [6E10 (Covance, Princeton, NJ, USA); anti-Aβ 22-35 (Sigma-Aldrich)].[21–23] Each sample (10 μL) was separated on a 10-20% tricine gel (Invitrogen, Carlsbad, CA, USA). Following separation, the proteins were transferred onto nitrocellulose membranes and blocked with bovine serum albumin (BSA, 3% w/v; Sigma-Aldrich) in Tris-buffered saline (TBS) containing 0.1% v/v Tween-20 (Sigma-Aldrich) (TBS-T) overnight at 4 °C. The membranes were incubated with 6E10 (1:2,000; Covance) or anti-Aβ 22-35 (1:10,000; Sigma-Aldrich) in a solution of BSA (2% w/v in TBS-T) for 4 h at room temperature. After washing with TBS-T (3x, 10 min), a horseradish peroxidase (HRP)-conjugated goat anti-mouse secondary antibody (for 6E10; 1:5,000 in 2% w/v BSA in TBS-T; Cayman Chemical Company, Ann Arbor, MI, USA) or HRP-conjugated goat anti-rabbit secondary antibody (for anti-Aβ 22-35; 1:5,000 in 2% w/v BSA in TBS-T; Invitrogen) was added for 2 h at room temperature. A homemade ECL kit[21,22,24] was used to visualize gel/Western blots on a ChemiDoc MP Imaging System (Bio-Rad).

TEM. Samples for TEM were prepared following previously reported methods.[22,25] Glow discharged grids (Fromvar/Carbon 300-mesh; Electron Microscopy Sciences, Hatfield, PA, USA) were treated with Aβ samples (25 μM; 5 μL) for 2 min at room temperature. Excess sample was removed using filter paper, followed by washing with ddH_2O (3x). Each grid was incubated with uranyl acetate (1% w/v ddH_2O; 5 μL) for 2 min, blotted off, and dried overnight at room temperature. Images for each sample were taken on a TEM (200 kV; 29,000x magnification). The locations of samples on the grids were randomly picked for taking more than 20 images per each grid.

ESI–MS and ESI–MS^2. $Aβ_{40}$ (25 μM) was incubated with compounds (25 μM; 1% v/v DMSO) in the presence and absence of $CuCl_2$ (25 μM) in 20 mM ammonium acetate, pH 6.8 or 7.4 at 37 °C with constant agitation. The incubated samples were diluted 25-fold with H_2O and then injected into the mass spectrometer. The capillary voltage, sampling cone voltage, and desolvation

temperature were set to 2.0 kV, 40 V, and 250 °C, respectively. The ESI parameters and experimental conditions of ESI–MS^2 were the same as above. Collision-induced dissociation was carried out by applying the collision energy in the trap ranging from 57 to 61 V. More than 200 spectra were obtained for each sample and averaged for the analysis. For the experiments under anaerobic conditions, all samples were prepared following the same procedure described above for the aerobic samples in a N_2-filled glove box.

Cell Viability Studies. 5Y cells were maintained in a media containing 50% v/v minimum essential medium (GIBCO, Grand Island, NY, USA) and 50% v/v F12 (GIBCO), supplemented with 10% v/v fetal bovine serum (Sigma-Aldrich) and 100 U/mL penicillin with 100 mg/mL streptomycin (GIBCO). The cells were grown and maintained at 37 °C in a humidified atmosphere with 5% CO_2. Cell viability was determined by the MTT assay. Cells were seeded in a 96-well plate (15,000 cells/100 μL) and treated with the samples ([compound] = 25, 50, and 100 μM; 1% v/v DMSO). After 24 h of incubation, 5Y cells were washed with phosphate buffered saline (PBS; GIBCO). MTT [5 mg/mL in PBS (pH 7.4, GIBCO); 25 μL] was added to each well, and the plate was incubated for 4 h at 37 °C. The formazan produced by the cells was solubilized using an acidic solution of dimethylformamide (pH 4.5, 50% v/v, aq) and sodium dodecyl sulfate (20% w/v) overnight at room temperature in the dark. Absorbance was measured at 600 nm by a microplate reader (Molecular Devices). Cell viability was calculated relative to that of the cells containing an equivalent amount of DMSO. The measurements were conducted in triplicate.



Scheme S1 Synthetic routes to (a) compounds **1**, **2**[1], and (b) **3**[2].

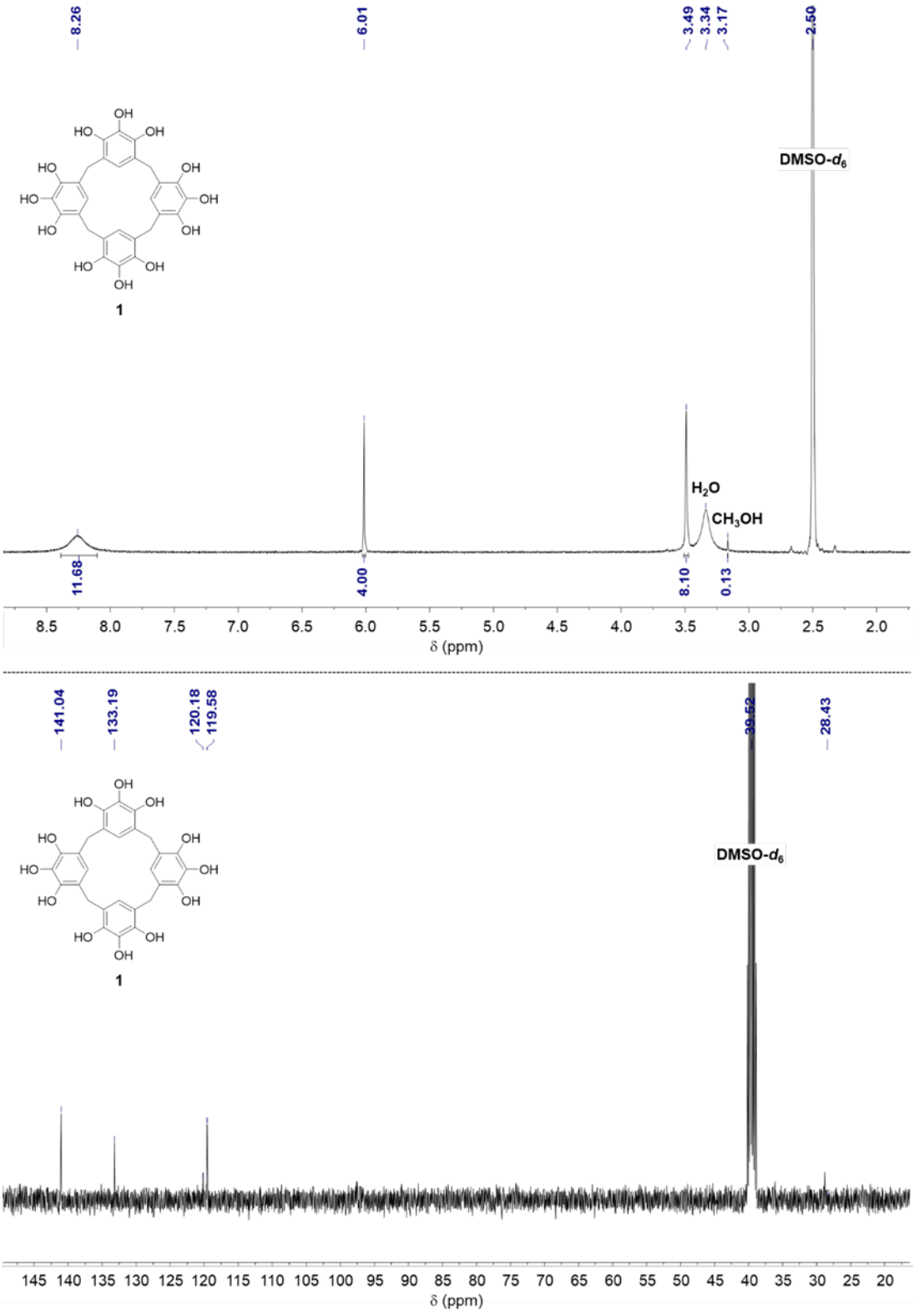


Fig. S1 ^{1}H (400 MHz, top) and ^{13}C (100 MHz, bottom) NMR spectra of compound **1** in DMSO-d_6.

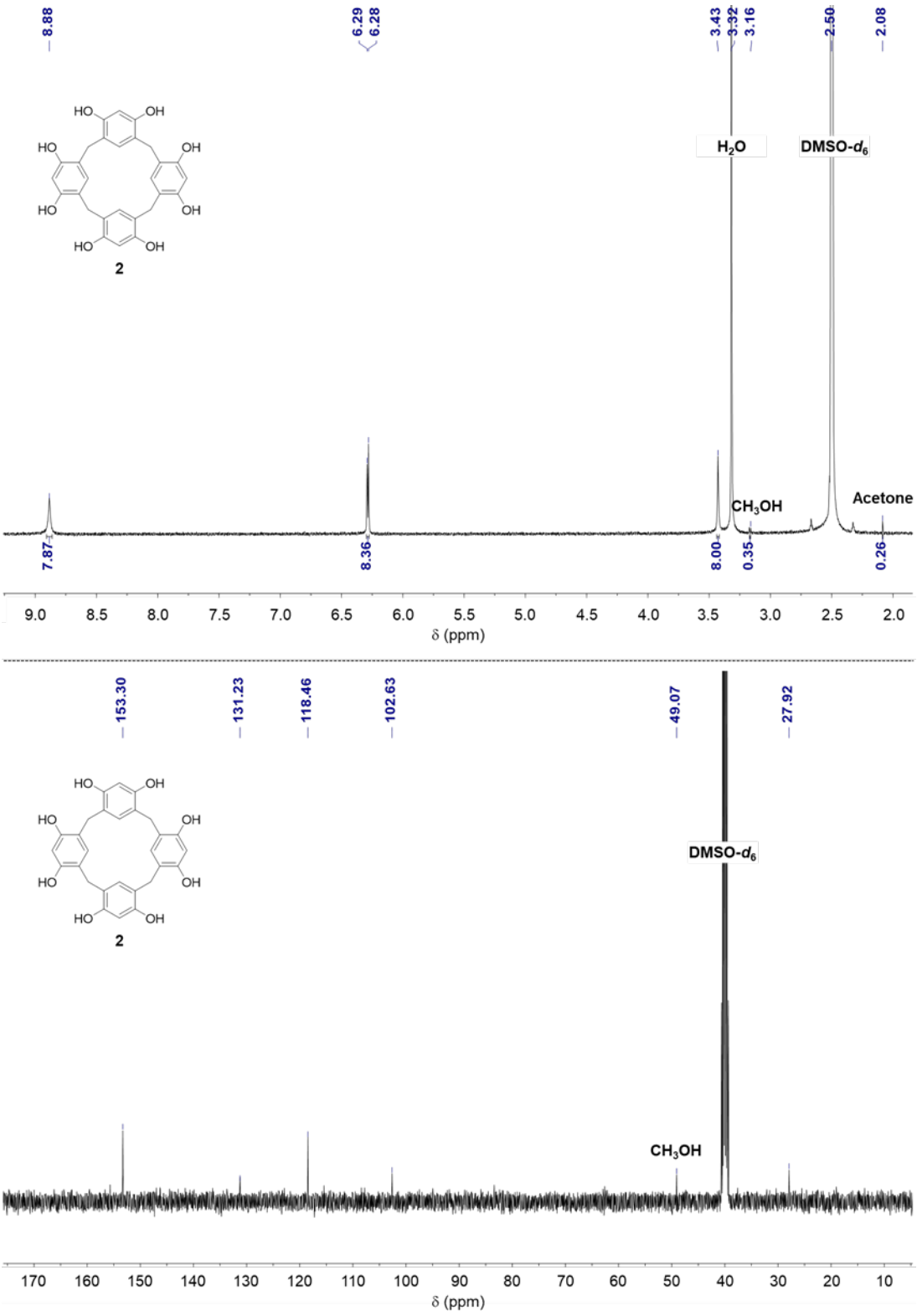


Fig. S2 ^{1}H (400 MHz, top) and ^{13}C (100 MHz, bottom) NMR spectra of compound **2** in DMSO-d_6.

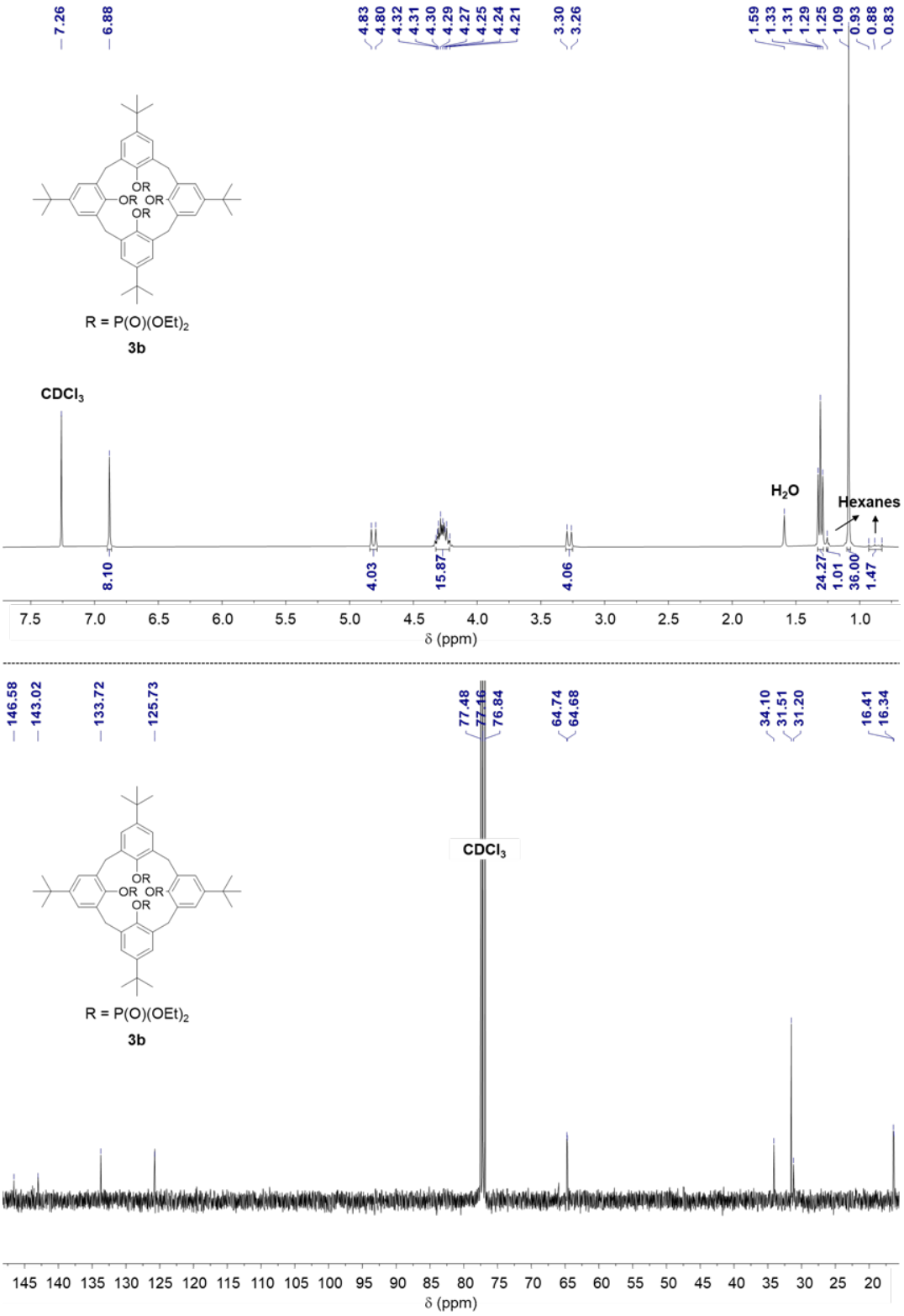


Fig. S3 ^{1}H (400 MHz, top) and ^{13}C (100 MHz, bottom) NMR spectra of compound **3b** in $CDCl_3$.

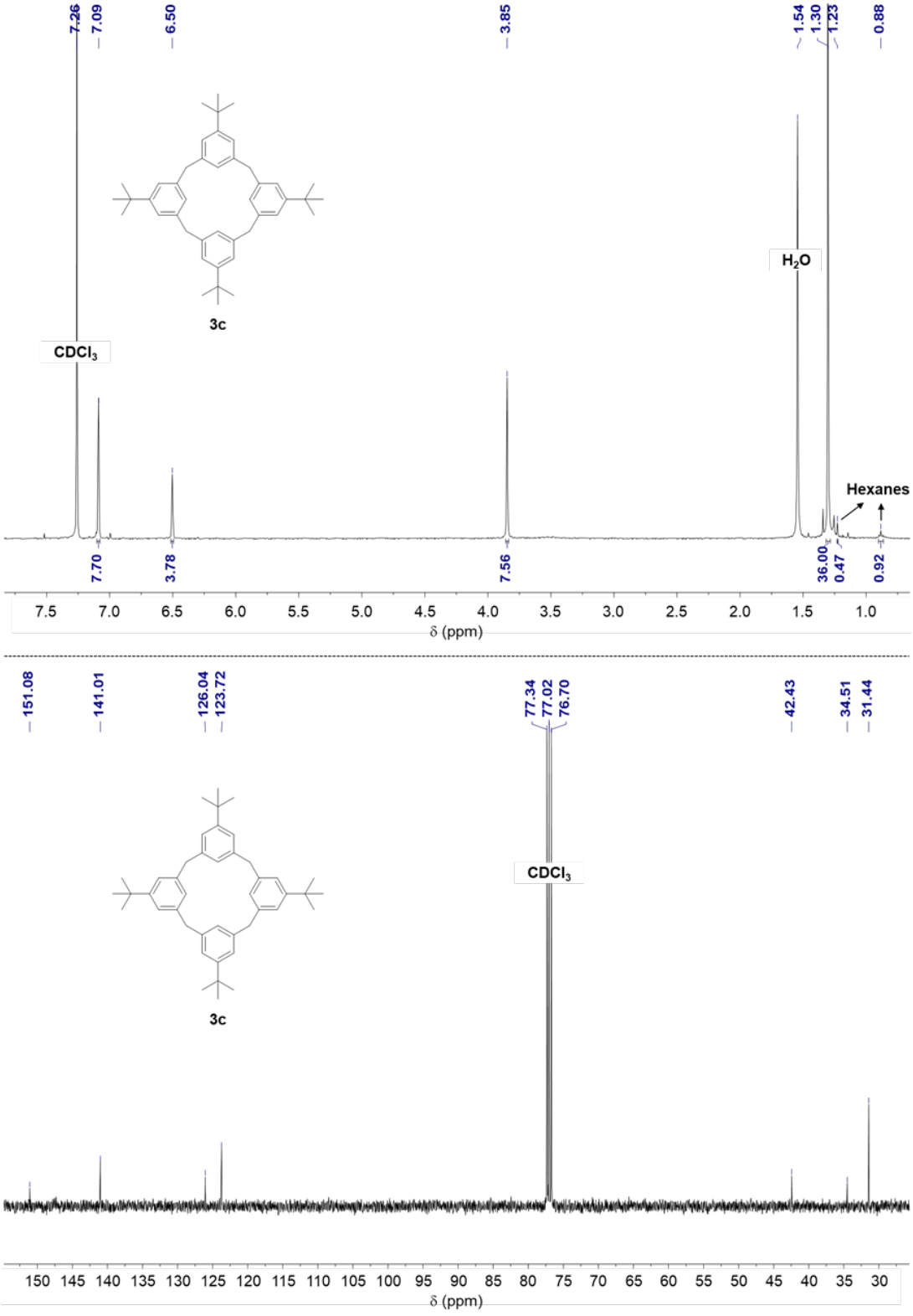


Fig. S4 ^{1}H (400 MHz, top) and ^{13}C (100 MHz, bottom) NMR spectra of compound **3c** in $CDCl_3$.

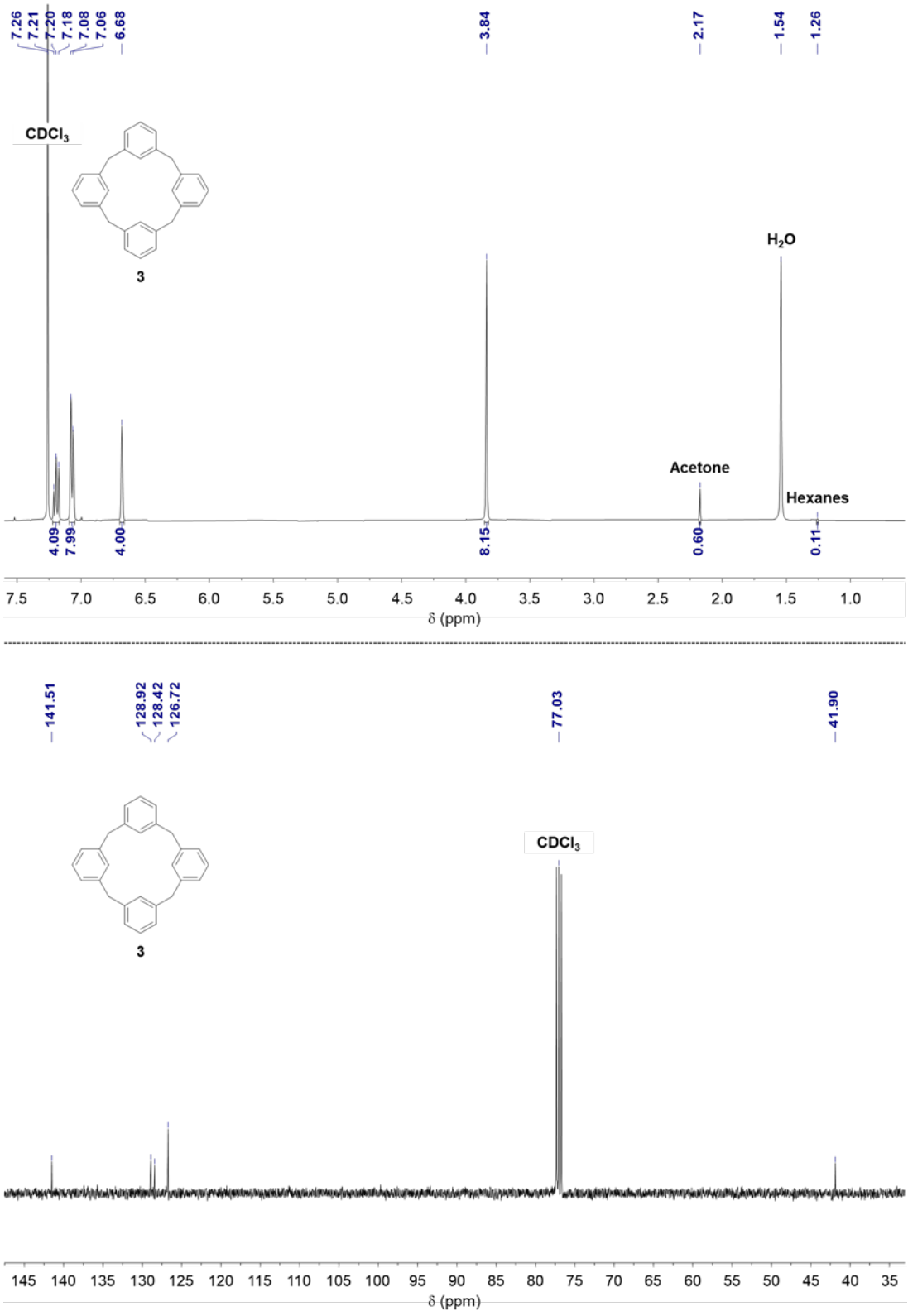


Fig. S5 ^{1}H (400 MHz, top) and ^{13}C (100 MHz, bottom) NMR spectra of compound **3** in $CDCl_3$.

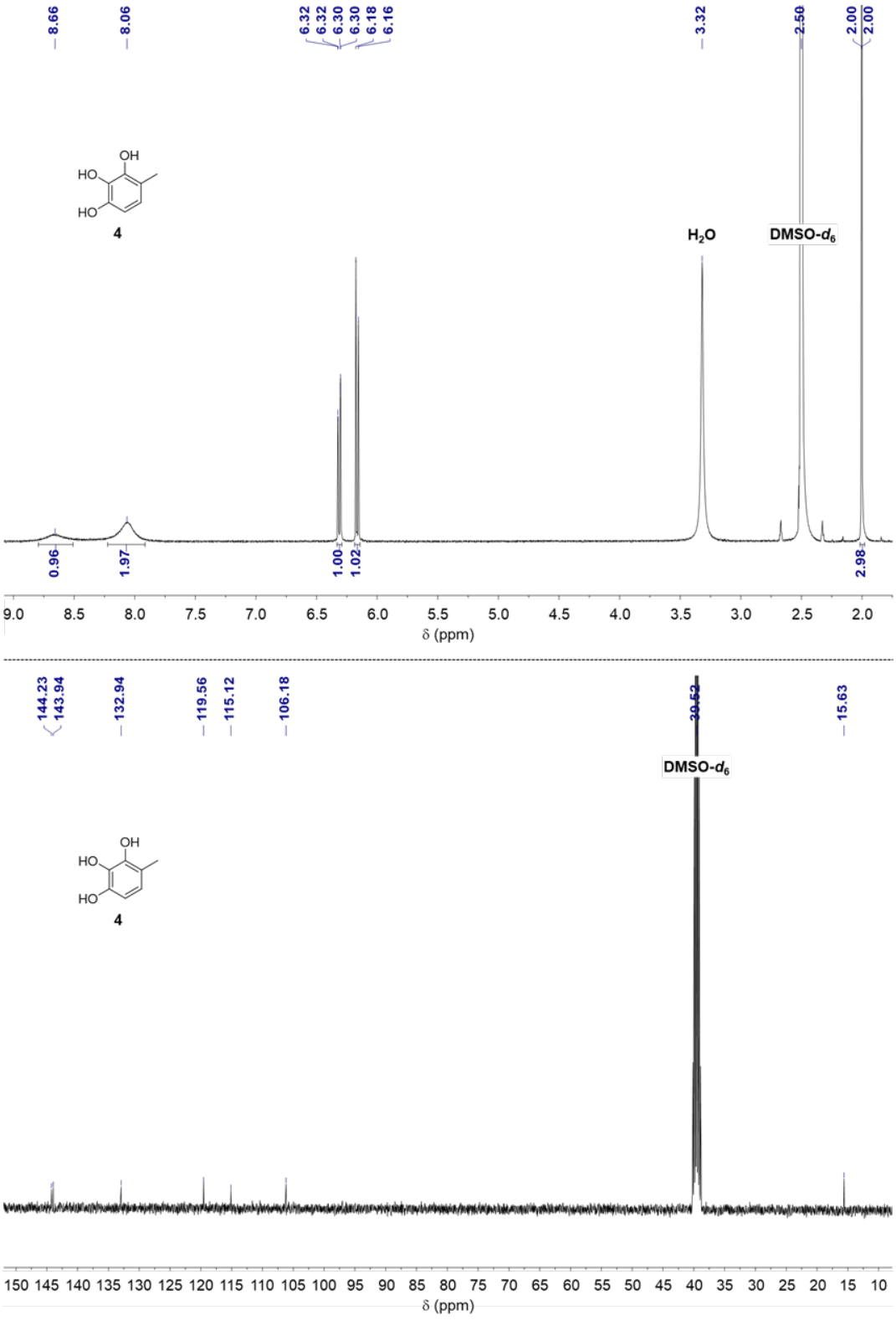


Fig. S6 ^{1}H (400 MHz, top) and ^{13}C (100 MHz, bottom) NMR spectra of compound **4** in DMSO-d_6.

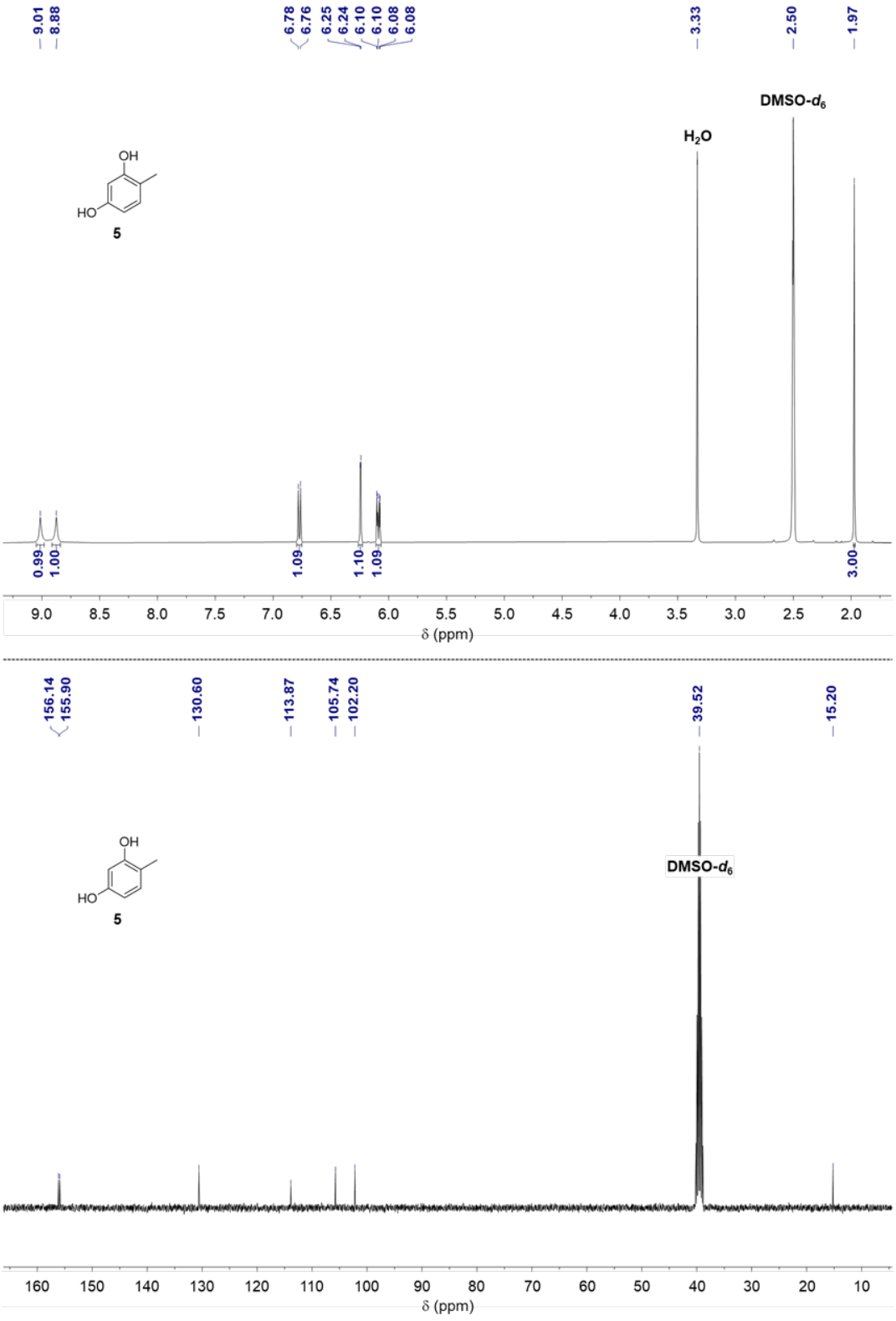


Fig. S7 ^{1}H (400 MHz, top) and ^{13}C (100 MHz, bottom) NMR spectra of compound **5** in DMSO-d_6.

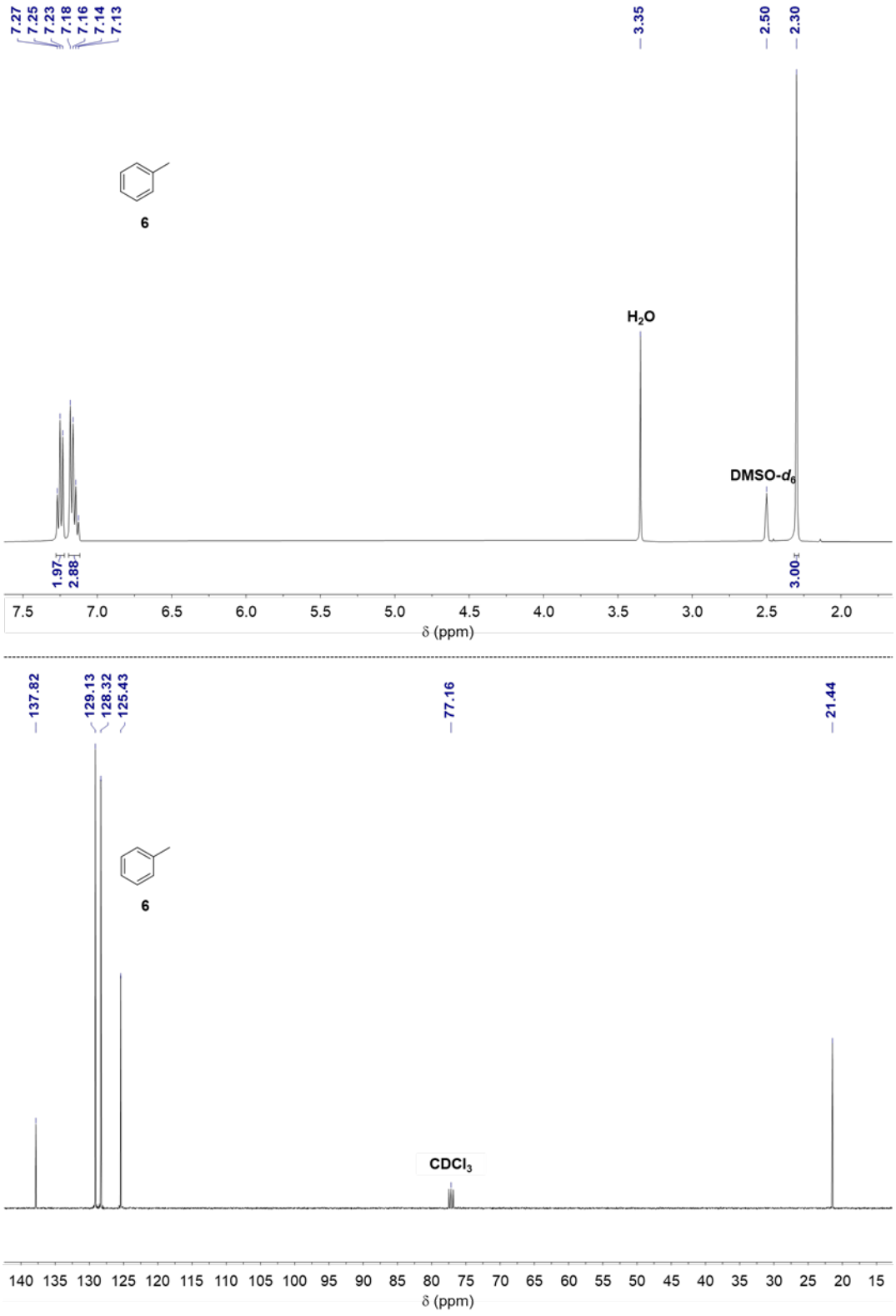
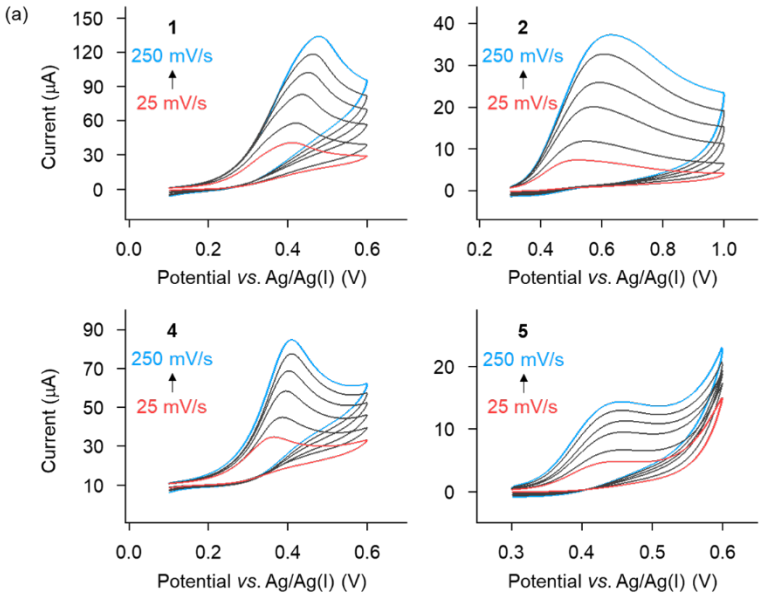


Fig. S8 ^{1}H (400 MHz, top) and ^{13}C (100 MHz, bottom) NMR spectra of compound **6** in DMSO-d_6 and $CDCl_3$, respectively.

(a)

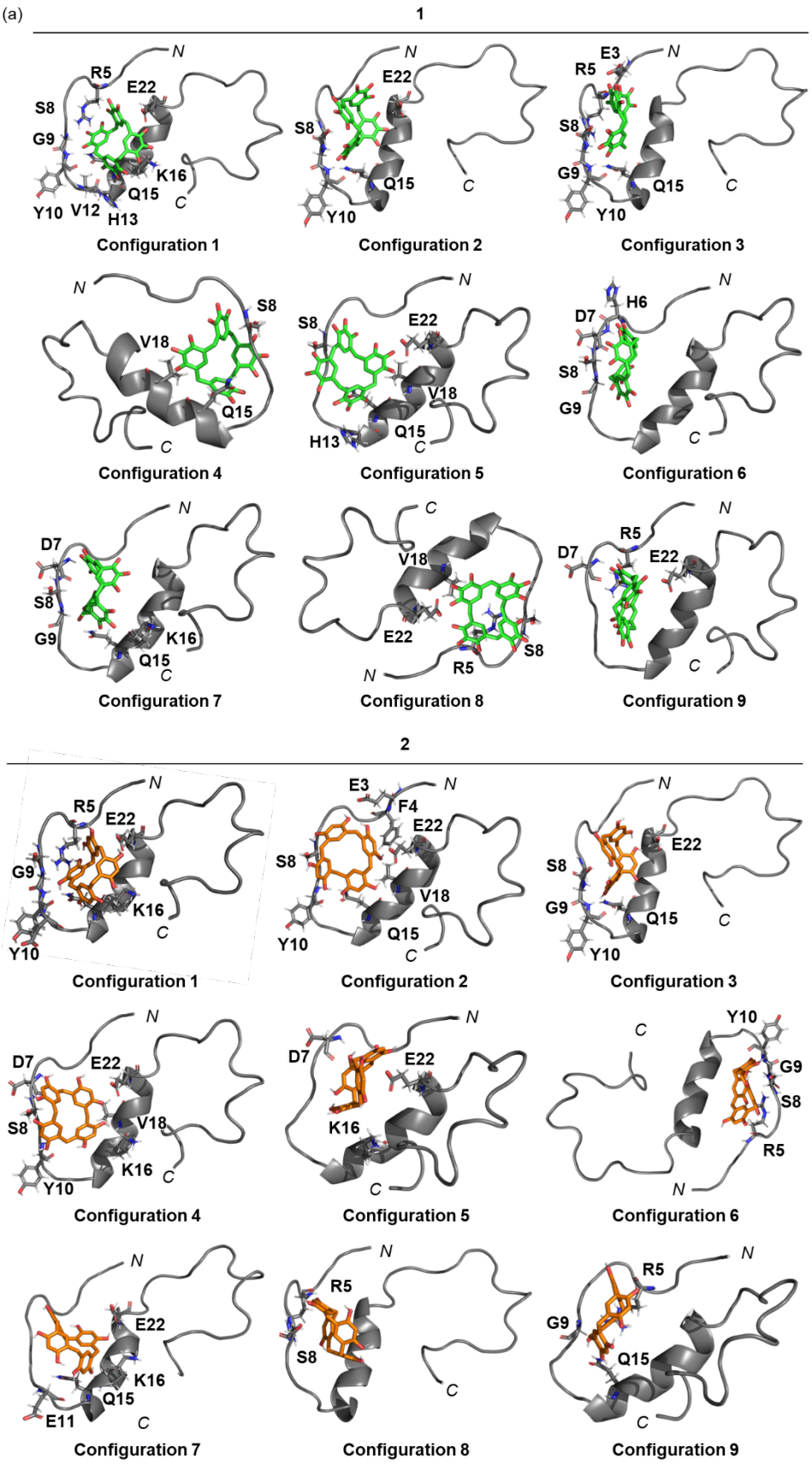


(b)

Compound	E_{pa} (V) *vs.* Ag/Ag(I)
1	0.47
2	0.63
4	0.41
5	0.45

Fig. S9 Redox potentials of compounds **1**, **2**, **4**, and **5** measured by cyclic voltammetry. (a) Cyclic voltammograms of compounds **1**, **2**, **4**, and **5** in CH_3CN. (b) E_{pa} values of compounds **1**, **2**, **4**, and **5** at the scan rate of 250 mV/s. Conditions: [compound] = 1 mM (for **1**, **4**, and **5**, 1% v/v DMSO; for **2**, 2% v/v DMSO); [$TBAPF_6$] = 0.1 M (for supporting electrolyte and reference electrode); [$AgNO_3$] = 0.01 M (for reference electrode); N_2 (g); scan rates = 25, 50, 100, 150, 200, and 250 mV/s; three electrodes: glassy carbon working electrode, Ag/Ag(I) reference electrode, and platinum counter electrode; room temperature. All samples were withdrawn from a N_2-filled glove box immediately before each experiment, and they were freshly prepared. Prior to each measurement, N_2 (g) was purged into the solution.

(a)


1
Configuration 1
Configuration 2
Configuration 3
Configuration 4
Configuration 5
Configuration 6
Configuration 7
Configuration 8
Configuration 9
2
Configuration 1
Configuration 2
Configuration 3
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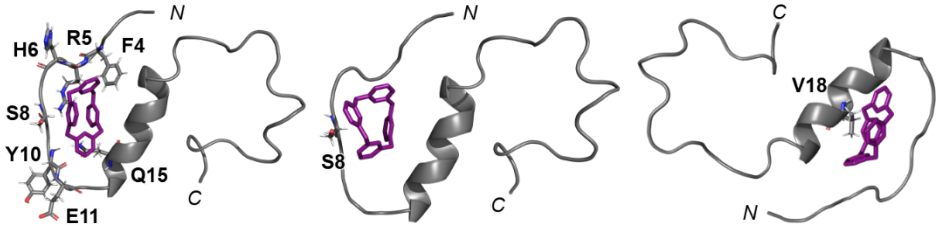
Configuration 5
Configuration 6
Configuration 7
Configuration 8
Configuration 9

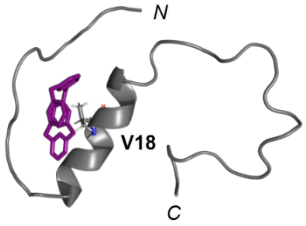
3



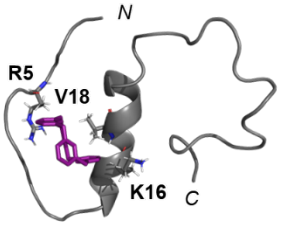
Configuration 1

Configuration 2

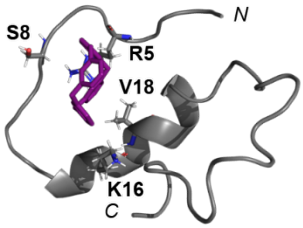
Configuration 3



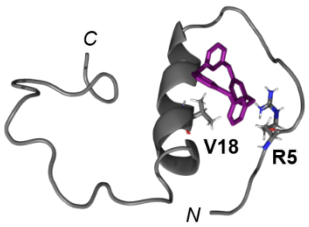
Configuration 4



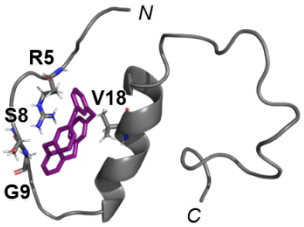
Configuration 5



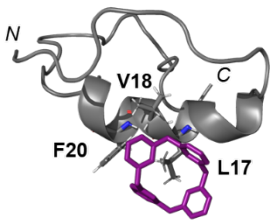
Configuration 6



Configuration 7

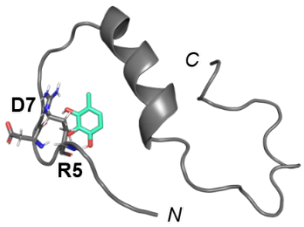


Configuration 8

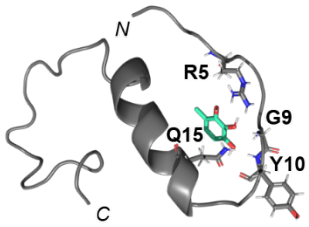


Configuration 9

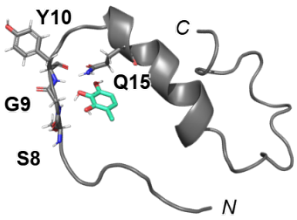
4



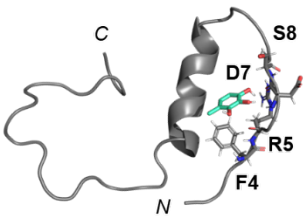
Configuration 1



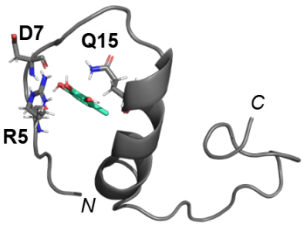
Configuration 2



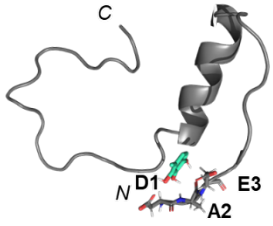
Configuration 3



Configuration 4



Configuration 5



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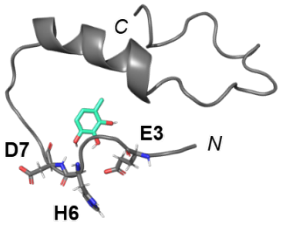
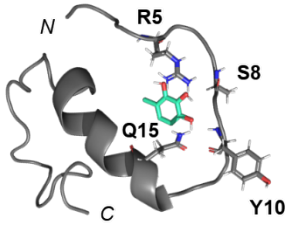
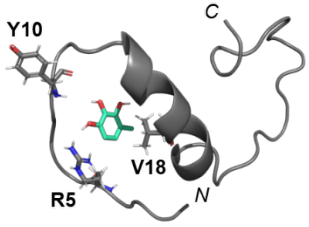


Configuration 7

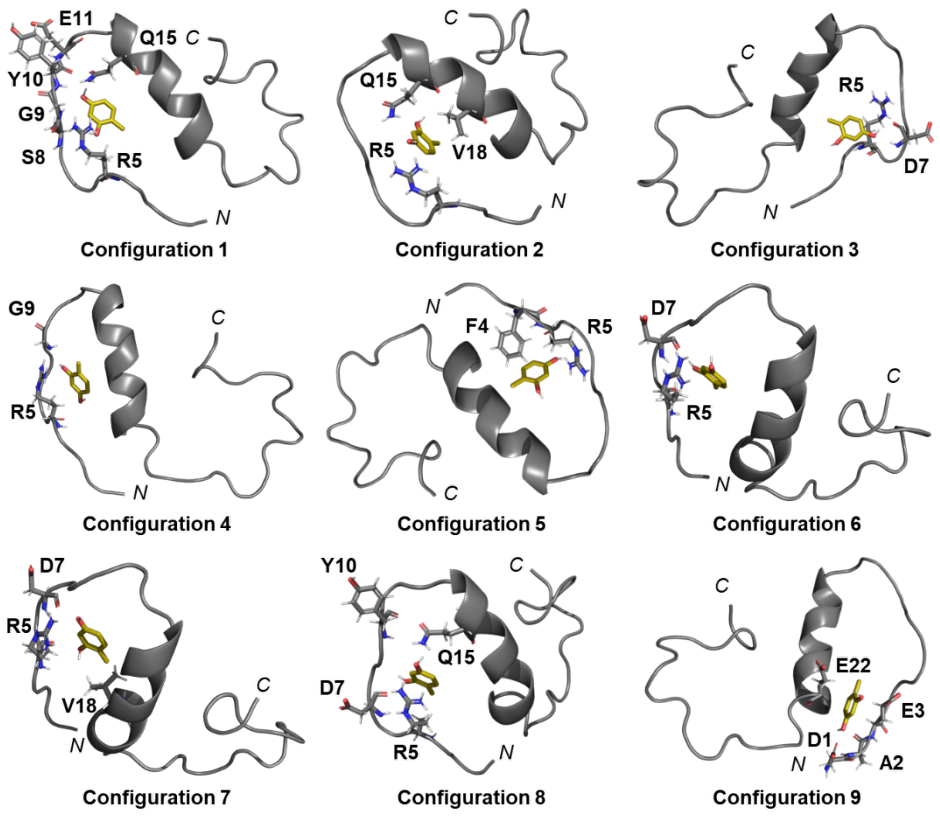


Configuration 8

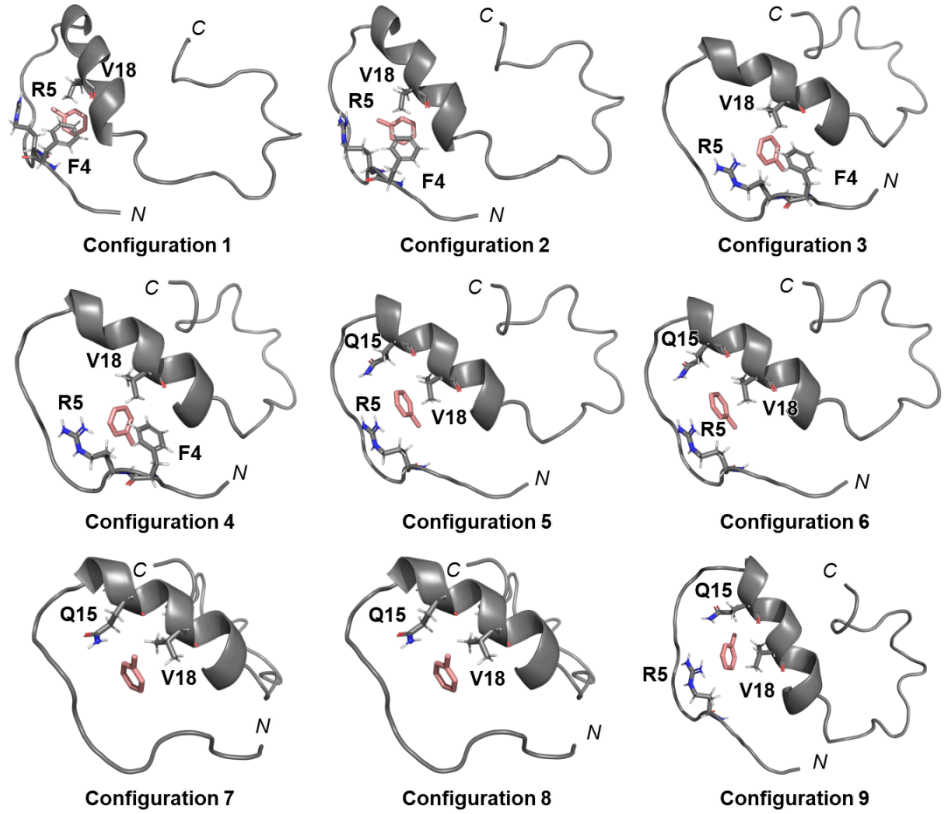


Configuration 9

5


E11
Q15
C
Y10
G9
S8
R5
N
Configuration 1
C
Q15
R5
V18
N
Configuration 2
C
R5
D7
N
Configuration 3
G9
C
R5
N
Configuration 4
N
F4
R5
C
Configuration 5
D7
R5
C
N
Configuration 6
D7
R5
V18
C
N
Configuration 7
Y10
C
Q15
D7
R5
N
Configuration 8
C
E22
E3
D1
N
A2
Configuration 9

6


C
V18
R5
F4
N
Configuration 1
C
V18
R5
F4
N
Configuration 2
C
V18
R5
F4
N
Configuration 3
C
V18
R5
F4
N
Configuration 4
C
Q15
R5
V18
N
Configuration 5
C
Q15
V18
R5
N
Configuration 6
C
Q15
V18
N
Configuration 7
C
Q15
V18
N
Configuration 8
C
Q15
R5
V18
N
Configuration 9

(b)

Configuration	1	2	3	4	5	6
	Energy (kcal/mol)					
1	–10.1	–8.8	–7.6	–4.7	–4.3	–4.0
2	–9.8	–8.6	–7.6	–4.5	–4.2	–4.0
3	–9.5	–8.5	–7.6	–4.5	–4.1	–3.8
4	–9.3	–8.3	–7.6	–4.4	–4.1	–3.8
5	–9.3	–8.3	–7.5	–4.4	–4.0	–3.7
6	–9.2	–8.2	–7.4	–4.3	–4.0	–3.7
7	–9.1	–8.2	–7.4	–4.3	–4.0	–3.7
8	–9.0	–8.2	–7.3	–4.3	–4.0	–3.7
9	–8.9	–8.1	–7.3	–4.3	–4.0	–3.7

Fig. S10 Docking studies of compounds **1**–**6** with Aβ_{40} monomer (PDB 2LFM[19]) by AutoDock Vina. (a) Nine docked models of compounds **1**–**6** with Aβ_{40} monomer. O, H, and N atoms are indicated in red, white, and blue, respectively. (b) Binding energies predicted for compounds **1**–**6** with Aβ_{40} monomer are summarized in the table.

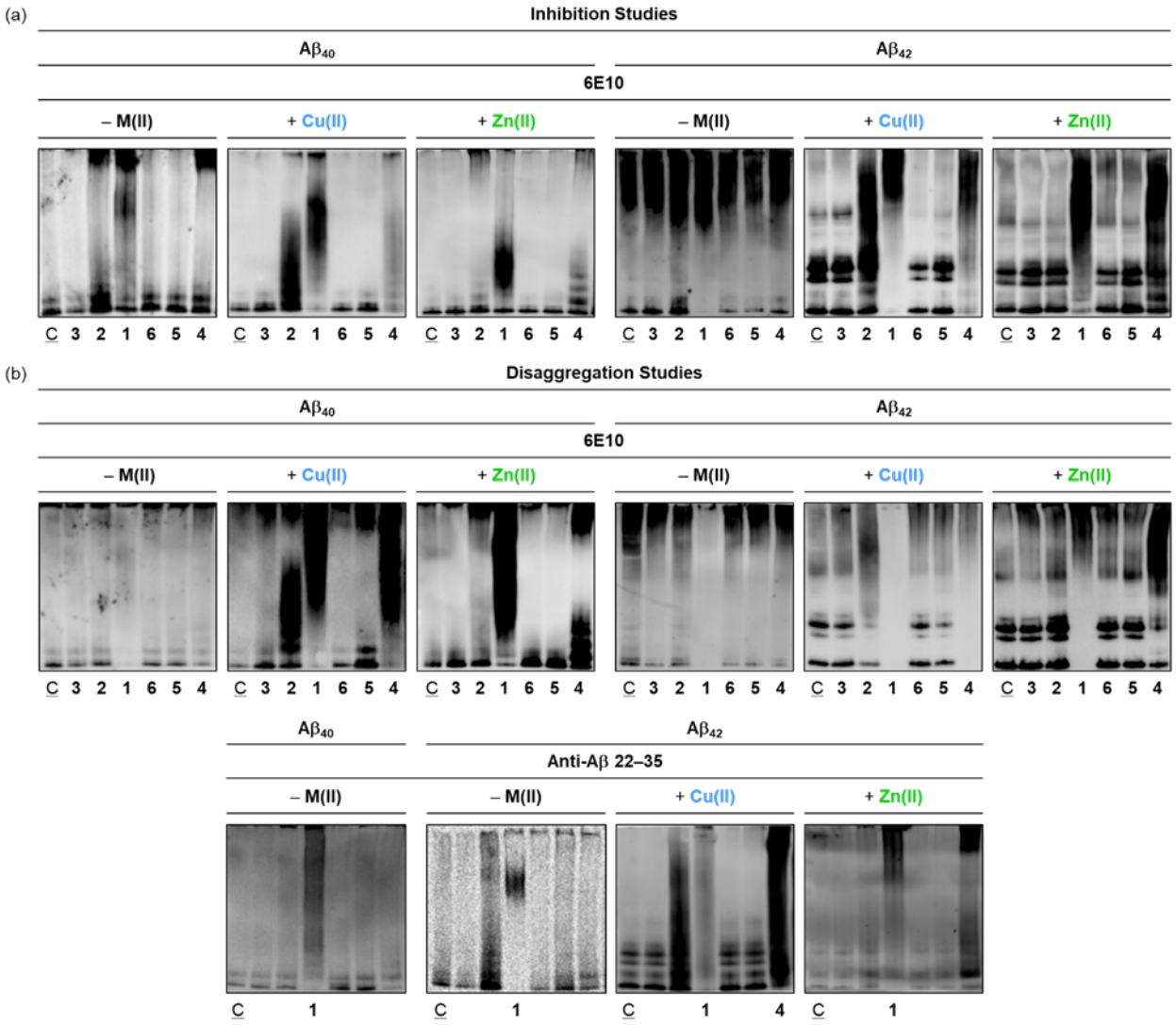


Fig. S11 Original gel images from Fig. 4 and 6.

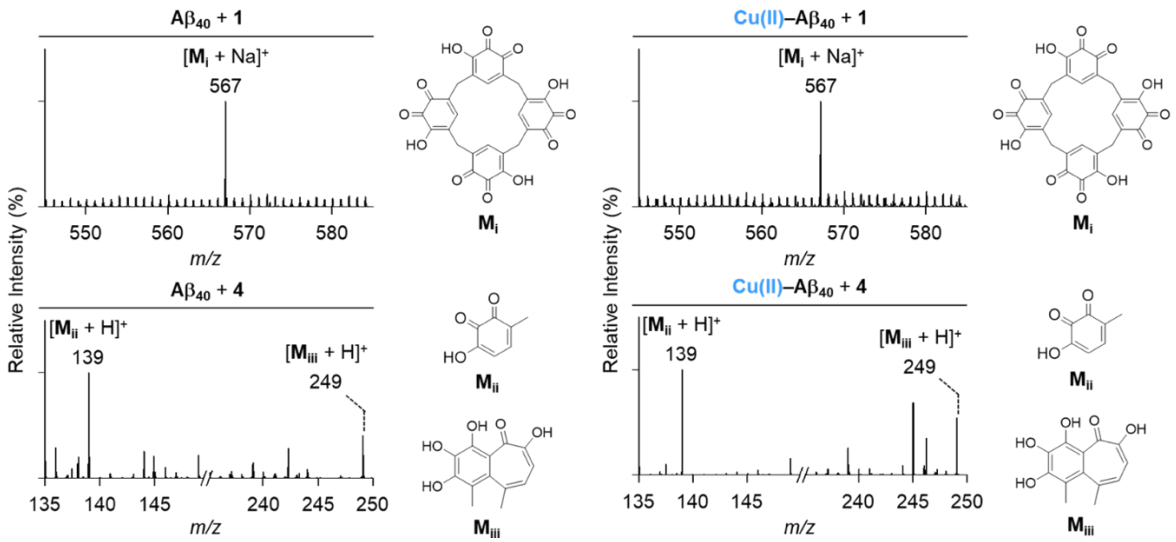


Fig. S12 Chemical transformations of compounds **1** and **4** in the presence of metal-free and Cu(II)-treated Aβ_{40} analyzed by ESI–MS. The graphs depicted for compounds **1** and **4** present 100x or 70x zoom-in spectra from 545 to 585 *m/z* and 135 to 250 *m/z*, respectively. Conditions: [Aβ_{40}] = 25 μM; [Cu(II)] = 25 μM; [compound] = 25 μM (1% v/v DMSO); 20 mM ammonium acetate, pH 7.4 [for metal-free samples] or pH 6.8 [for Cu(II)-treated samples]; 37 °C; 3 h; constant agitation. The samples were diluted 25-fold with H_2O before injection to the mass spectrometer.

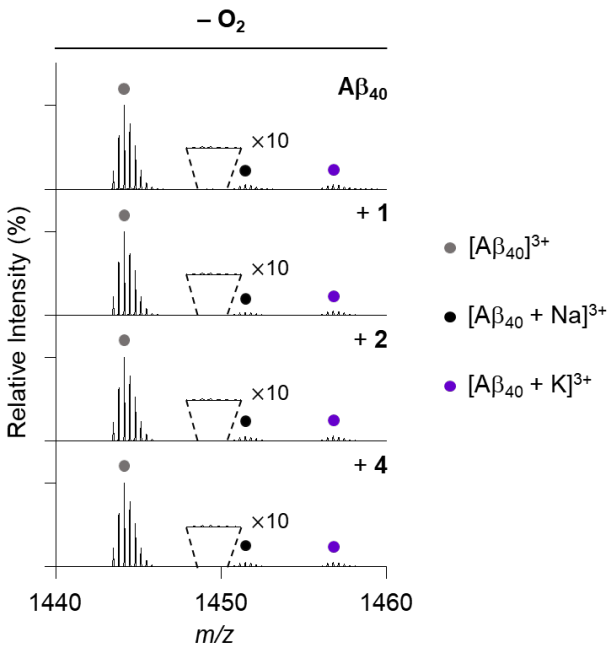


Fig. S13 Interactions of compounds **1**, **2**, and **4** with metal-free $A\beta_{40}$ under anaerobic conditions analyzed by ESI–MS. Conditions: $[A\beta_{40}]$ = 25 μM; [compound] = 25 μM (1% v/v DMSO); 20 mM ammonium acetate, pH 7.4; 37 °C; 3 h; constant agitation. The samples were diluted 25-fold with H_2O before injection to the mass spectrometer.

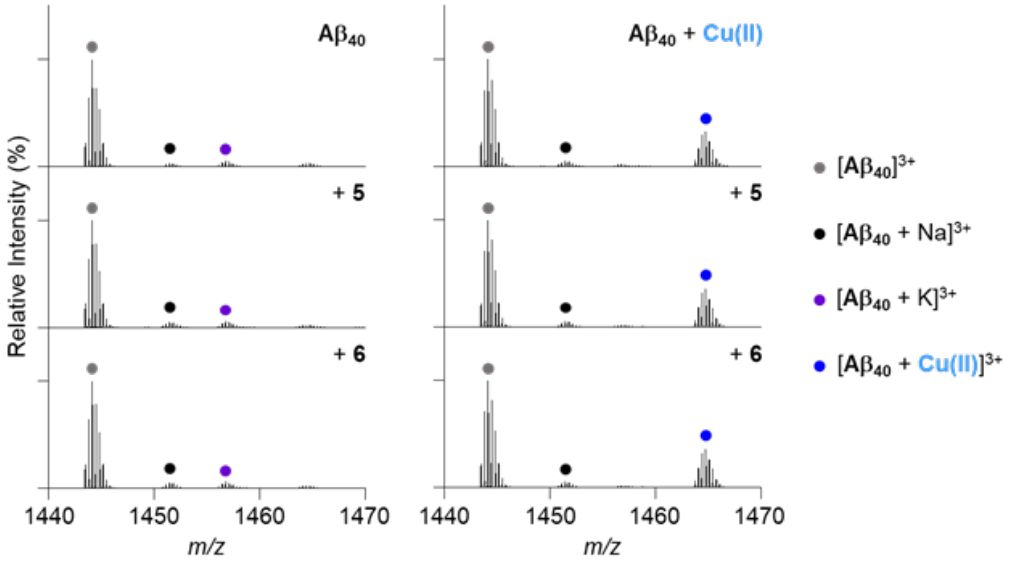


Fig. S14 Interactions of compounds **5** and **6** with metal-free and Cu(II)-treated Aβ$_{40}$ analyzed by ESI–MS. Conditions: [Aβ$_{40}$] = 25 μM; [Cu(II)] = 25 μM; [compound] = 25 μM (1% v/v DMSO); 20 mM ammonium acetate, pH 7.4 [for metal-free samples] or pH 6.8 [for Cu(II)-treated samples]; 37 °C; 3 h; constant agitation. The samples were diluted 25-fold with H_2O before injection to the mass spectrometer

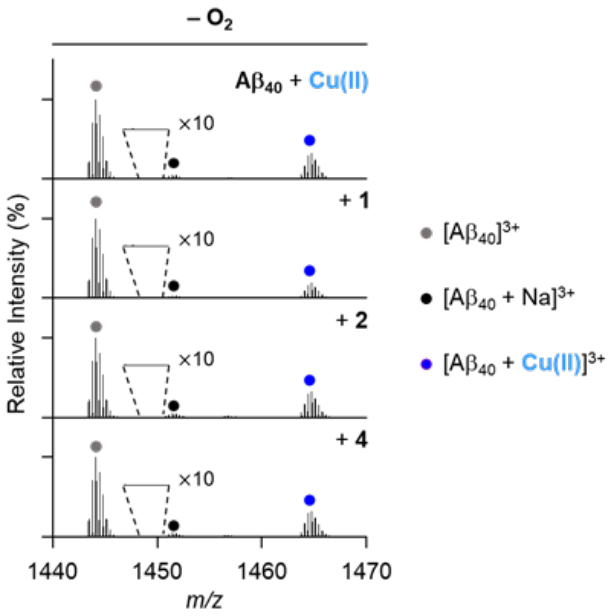


Fig. S15 Interactions of compounds **1**, **2**, and **4** with Cu(II)-treated $A\beta_{40}$ under anaerobic conditions analyzed by ESI–MS. Conditions: [$A\beta_{40}$] = 25 μM; [Cu(II)] = 25 μM; [compound] = 25 μM (1% v/v DMSO); 20 mM ammonium acetate, pH 6.8; 37 °C; 3 h; constant agitation. The samples were diluted 25-fold with H_2O before injection to the mass spectrometer.

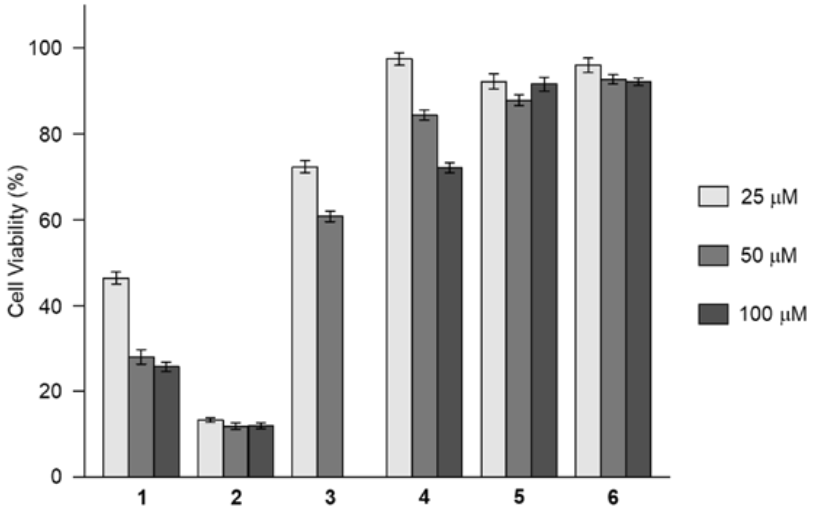


Fig. S16 Toxicity of compounds **1**–**6** in 5Y cells. Viability (%) of cells incubated with various concentrations of compounds was determined by the MTT assay. Cell survival was calculated in comparison to that of the cells treated with an equivalent amount of DMSO (1% v/v). Error bars indicate the standard error from three independent experiments. The cytotoxicity of **3** at 100 μM could not be determined due to its limited solubility in DMSO. Conditions: [compound] = 25, 50, and 100 μM (1% v/v DMSO); 37 °C; 24 h.

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Appendix A Cartesian coordinates of the optimized geometries.

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1

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C	-1.763557553	2.956509352	2.122610807
C	-1.538650513	1.884125233	2.992017746
C	-0.688304543	3.541062832	1.442607045
C	-0.253486425	1.383578300	3.181634188
C	0.595936716	3.020845413	1.657738090
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C	3.356382608	-0.583877742	-3.542580843
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O	-0.636853576	6.934533119	-1.377558827
O	0.026900556	6.582503796	-3.965104103
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O	6.526932240	4.046953201	0.167929739
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2

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C	-0.095524326	3.084159613	-2.121976614
C	-1.697729945	1.496496439	-2.916002035
H	0.192629948	3.849262238	-1.407998681
C	0.826725423	2.717532396	-3.108351707
C	-0.811113417	1.112412930	-3.921343565
C	0.447923332	1.710205913	-4.008884430
C	0.543427944	4.079993725	3.175773621
C	-2.328214407	2.844558239	-0.864087999
C	2.191458464	3.365944862	-3.181631804
C	3.480543852	0.566140831	0.898895442
H	1.393802166	4.779935837	3.134713411
H	0.068846107	4.226694584	4.154092789
H	3.003319025	-0.278314233	0.377961844
H	4.419041157	0.181217104	1.321267605
H	2.051763535	4.456721306	-3.108158350
H	2.611601353	3.172838211	-4.177127838
H	-3.271339417	3.200121880	-1.301480293
H	-2.570351124	1.927014351	-0.305631101
O	2.667960882	-1.201007247	3.041141748
O	-0.111197628	2.085838556	5.078465462
O	-0.413042694	6.782381535	2.768460274
O	-3.048700809	5.574013710	-1.011804581
O	-2.905631304	0.853926837	-2.886404991
O	1.349838734	1.339869261	-4.973913670
O	4.815657139	4.556127548	-2.932892561
O	5.932025433	1.969157577	0.908010483
H	0.167131171	6.400396347	3.438804626
H	-2.007384539	7.222857952	0.838367224
H	-3.228016853	6.521538734	-0.962729692
H	-3.448308945	1.229700089	-2.182149887
H	-1.117883682	0.338529706	-4.620033741
H	0.953908205	0.651971757	-5.523683548
H	4.122172832	4.664182186	-3.595563889
H	6.316441059	3.790067434	-1.029427290
H	6.735352993	2.494560480	0.803822041
H	3.292037964	-1.318862557	2.314272642
H	1.054569244	-0.312790811	4.794484138
H	-0.254492998	1.332263231	5.664793015

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C	-1.511981964	2.333025932	-1.111463904
C	-1.969443202	3.007567883	0.019727390
C	-0.808023989	1.128538847	-0.987198234
H	-2.510889530	3.943397284	-0.090418734
C	-1.728590012	2.488274813	1.292061090
C	-0.575053751	0.620942891	0.296428859
H	-2.086979389	3.017150164	2.171826363
H	-0.014155490	-0.304478407	0.408295065
C	-1.028169632	1.285280466	1.444001555
H	-1.702194691	2.742738247	-2.100823879
C	1.685457587	1.271146059	2.978494644
C	0.656516612	0.333141834	3.134982347
C	3.014898300	0.960063219	3.288247824
C	0.978594005	-0.942644656	3.612613201
C	3.309824705	-0.324849695	3.762560844
H	0.191799581	-1.683128238	3.737161398
H	4.337959290	-0.584520400	4.004106522
C	2.297832966	-1.269701004	3.924556732
H	2.538271904	-2.265016079	4.288862228
H	1.448055387	2.258659840	2.591380119
C	3.076929808	-1.297171712	-2.697923183
C	1.700066209	-1.096674323	-2.609934807
C	3.956876993	-0.239958689	-2.463566780
H	1.018017650	-1.924100518	-2.790884972
H	5.030129910	-0.404117227	-2.529164076
C	1.186340809	0.166816190	-2.288994551
C	3.470428467	1.031544685	-2.137855768
C	2.083487988	1.216492414	-2.057007551
H	1.695143700	2.195076227	-1.785009861
H	3.467009544	-2.281010866	-2.945237875
C	4.245986938	2.896743298	-0.560437143
C	4.264125347	2.175810337	0.638972878
C	4.061954021	4.284469604	-0.503551602
H	4.382691860	1.094822049	0.606099844
H	4.042314529	4.859783649	-1.426269770
C	4.103093147	2.806777716	1.879235506
C	3.899307489	4.929199219	0.722605467
H	3.751107454	6.005282402	0.754232466
C	3.918644428	4.194767475	1.908436775
H	3.786817074	4.699292660	2.862618208
C	-0.318074942	0.389951527	-2.222080946
C	4.425055504	2.192503691	-1.897951484
C	4.121761322	1.998596311	3.162991762
C	-0.789493620	0.692098856	2.823711157
H	-0.640447974	0.947882414	-3.111296415
H	-0.816575646	-0.586220443	-2.286347389
H	-1.401344180	-0.212547243	2.933892965

H	-1.161273241	1.396319032	3.580336332
H	4.063698292	2.688958645	4.015277863
H	5.088037968	1.487177730	3.259749651
H	4.307641983	2.932165384	-2.700491667
H	5.454210758	1.820143223	-1.981086135

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H	-0.537639856	-0.085455060	-1.697314143
C	1.635536194	-0.041393936	-0.005873866
H	1.789227366	-0.067244932	-1.088172436
H	2.139752150	-0.909856081	0.433214694
H	2.140856981	0.846049070	0.391953677
C	0.165578023	-0.031521816	0.327947080
C	-0.240330249	0.005564197	1.671776175
C	-1.594927907	0.016555423	2.010380030
C	-2.570273876	-0.007701863	1.011754394
C	-2.191511631	-0.045205567	-0.327362567
C	-0.830842674	-0.055759151	-0.651754260
H	-2.947549105	-0.067934133	-1.108267665
O	0.704256594	0.030175738	2.658117533
O	-3.870704174	0.004518854	1.469652414
H	0.236510396	0.062629424	3.506284952
H	-4.476017952	-0.006524979	0.718472719
O	-1.915482044	0.057900555	3.347180605
H	-2.880894661	0.052620880	3.417994499

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H	-0.544514358	-0.073866688	-1.690133810
C	1.634947658	-0.036012113	-0.018973403
H	1.777851939	-0.075360641	-1.102528214
H	2.145558834	-0.898275316	0.424756229
H	2.144243956	0.856972694	0.361137718
C	0.167964876	-0.024225011	0.327175468
C	-0.244462326	0.012961440	1.673847556
C	-1.593294978	0.023472754	2.025770187
C	-2.569880486	0.001307375	1.025672913
C	-2.193192720	-0.032817207	-0.317330271
C	-0.833908260	-0.045920279	-0.642618299
H	-1.905061126	0.049916282	3.066519737
H	-2.947305918	-0.049235661	-1.100626111
O	0.746024311	0.033576265	2.618844032
O	-3.876791000	0.018296668	1.432635069
H	0.343341023	0.066474207	3.495712996
H	-4.445209980	-0.021031538	0.652638793

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H	-0.546877563	-0.011317325	-1.706037045
C	1.627597928	0.010404175	-0.052411448
H	1.800296426	-0.483853370	-1.013218403
H	2.244217157	-0.489835232	0.700441957
H	1.998757482	1.038857698	-0.144973829
C	0.164901957	-0.011940504	0.326395124
C	-0.230179444	-0.014313255	1.670611739
C	-1.579869747	-0.004351875	2.023313046
C	-2.563198805	0.005371444	1.033084631
C	-2.184247017	0.003613293	-0.310044587
C	-0.833070278	-0.006343945	-0.656982780
H	0.529263020	-0.025554476	2.448794603
H	-1.863562107	-0.008868411	3.072073936
H	-3.614627838	0.009494169	1.305491805
H	-2.941362143	0.005344837	-1.089237452

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C	-1.853078127	2.797669649	2.050116539
C	-1.577703476	1.712962151	2.904656410
C	-0.799250782	3.455640554	1.413135886
C	-0.257627547	1.287516952	3.126075745
C	0.510841966	3.003768682	1.650325775
H	1.330638289	3.515615940	1.158974528
C	0.813691437	1.925040364	2.494183779
C	3.696570158	1.753524065	0.687398016
C	3.319701910	2.143712521	1.974410892
C	4.702856541	2.403188467	-0.055374969
C	3.983597040	3.233273506	2.554666042
C	5.365390301	3.473377228	0.555667102
C	5.009877205	3.887277126	1.843921423
H	3.195550680	0.903971791	0.235771731
C	0.230844006	5.575695992	-2.949248791
C	-0.256461531	5.679435730	-1.641525865
C	0.443576187	4.315292358	-3.543944120
C	-0.534290493	4.529105663	-0.896546543
C	0.156378254	3.146557808	-2.824669838
C	-0.330651760	3.282028675	-1.523112893
H	-0.564734519	2.384402990	-0.960686147
C	1.751640916	1.169737697	-3.199555397
C	2.770409584	1.808327079	-2.478929996

C	2.023936510	-0.107744098	-3.698784828
H	2.580345869	2.803107500	-2.091684341
C	4.024373055	1.222700238	-2.227364302
C	3.265325785	-0.718723357	-3.461728096
C	4.267500877	-0.057917617	-2.724026203
C	-1.068411231	4.649085522	0.520090878
C	0.379267514	1.788550496	-3.450072765
C	5.096514225	1.967933536	-1.458150029
C	2.232463598	1.417925358	2.734169483
H	-0.619673848	5.533940315	0.996361017
H	-2.148999691	4.831653595	0.498834819
H	2.277514696	0.353872091	2.464050055
H	2.461716652	1.479717135	3.806884289
H	5.370546341	2.861558676	-2.039022446
H	5.994410992	1.340556145	-1.417169094
H	0.217814803	1.878234148	-4.532871246
H	-0.391794384	1.103739977	-3.071879148
O	-2.636286497	1.116308928	3.504958391
O	-0.154500067	0.220893189	3.976468563
O	-3.135876894	3.197853804	1.864468575
O	-0.406012326	6.972026825	-1.207011819
O	0.507221043	6.666649342	-3.706653595
O	0.909234405	4.240977287	-4.812061310
O	1.150422931	-0.878829598	-4.416600704
O	3.559299946	-1.956851482	-3.929941654
O	5.462792873	-0.668165445	-2.518465757
O	6.374828339	4.213851929	-0.007999313
O	5.634113312	4.916203976	2.471742630
O	3.662013292	3.644725323	3.803270578
H	-0.958838761	7.012339115	-0.417127818
H	0.270116866	7.462301731	-3.203214407
H	1.004066229	5.141373634	-5.162066460
H	0.397283286	-0.357198149	-4.721833706
H	2.805345297	-2.285035849	-4.445940495
H	5.441745281	-1.541820407	-2.939089537
H	6.787985802	3.737841606	-0.738807797
H	6.349252701	5.238338470	1.899435759
H	4.257274628	4.369286060	4.053970814
H	0.766625583	0.047852509	4.208802700
H	-2.312429667	0.406630069	4.082820415
H	-3.719894171	2.625463724	2.386054993

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C	0.605521262	1.446543574	4.015649319
C	1.221217155	0.202706411	3.908983469
C	0.970155299	2.512797356	3.155125380
C	2.200797081	-0.006754251	2.937878609
C	1.953617930	2.265061855	2.190894127
H	2.235080242	3.071897507	1.522352695
C	2.586976767	1.033169866	2.049430132
C	2.991828918	1.938708901	-1.134659886
C	3.856409788	1.817230701	-0.046140008
C	3.154097557	2.897226095	-2.137722015
C	4.946084499	2.718953371	0.035237886
C	4.272075653	3.766650677	-2.032341957
C	5.153108120	3.676597357	-0.953507960
H	2.151244164	1.255403280	-1.205375433
C	-1.306325197	6.296478748	0.836808741
C	-0.604038358	5.799597740	1.936309576
C	-1.841531992	5.418778896	-0.101493128
C	-0.415588379	4.403428078	2.111519814
C	-1.700216532	4.017444134	0.054011211
C	-0.985253990	3.555300474	1.158339500
H	-0.858926058	2.483934879	1.280743003
C	-1.347689033	2.508934021	-1.996639967
C	-0.044059750	2.967216969	-2.168638229
C	-1.791039228	1.460536480	-2.846748829
H	0.313719690	3.765795231	-1.526469588
C	0.828108251	2.444761992	-3.129917383
C	-0.947336137	0.912642002	-3.813575029
C	0.351224273	1.393962860	-3.953446865
C	0.346182227	3.881401300	3.317554951
C	-2.304904699	3.067896843	-0.951928139
C	2.217305183	3.008034468	-3.329189539
C	3.659984350	0.751369059	1.005372047
H	1.165056825	4.580039978	3.551801205
H	-0.305064678	3.874310970	4.198834896
H	3.390903473	-0.178552493	0.480565369
H	4.619208336	0.562574923	1.503856897
H	2.093358517	4.073118687	-3.584663868
H	2.670012712	2.537431002	-4.208951950
H	-3.142758846	3.568095207	-1.453047991
H	-2.733891010	2.223667622	-0.390562147
O	2.749792337	-1.242179036	2.897240162
O	-0.357772648	1.699257612	4.937439919
O	-0.123090453	6.723943233	2.801351309
O	-2.522819996	5.847978115	-1.193568945
O	-3.036013126	0.936571538	-2.771983624
O	1.212673306	0.890618205	-4.873729229
O	4.553972244	4.720633507	-2.951337576
O	5.766935349	2.592904806	1.108473301
H	0.280293643	6.300535679	3.570271254

H	-1.425444603	7.371368885	0.739266396
H	-2.605590343	6.811558247	-1.179084539
H	-3.569800138	1.402559280	-2.115101337
H	-1.325798512	0.111839190	-4.441681862
H	0.775079191	0.210971564	-5.404790878
H	3.945333958	4.670316219	-3.699823141
H	5.994128704	4.362103939	-0.911072671
H	6.504111767	3.215414524	1.040537953
H	3.446784258	-1.290819407	2.229856491
H	0.954540312	-0.619757831	4.565837860
H	-0.500727832	0.921482921	5.494334698

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C	-2.013048887	0.143146962	-0.938006401
C	-2.784016848	-0.074906208	0.084088884
C	-0.676941574	0.534989476	-0.795590043
H	-3.824959755	-0.373901993	-0.000707823
C	-2.246688128	0.082986519	1.445509315
C	-0.134497434	0.686017573	0.459509432
H	-2.814153910	-0.077494793	2.357857466
H	0.872390926	0.975169182	0.747117102
C	-0.884415984	0.481363326	1.598749042
H	-2.548011303	-0.013313855	-1.870468259
C	1.508078694	1.392727017	3.188418865
C	0.401409984	1.053776979	3.797316790
C	2.636684179	1.747859240	3.867885590
C	0.432482243	1.064147353	5.209895611
C	2.642359018	1.740597844	5.264185429
H	-0.466942847	0.788197160	5.753068447
H	3.497716665	2.002032518	5.880761623
C	1.588550925	1.418837786	5.908059597
H	1.588550925	1.418837786	6.994406700
H	1.425411224	1.366368771	2.105542421
C	2.237497091	1.247275352	-5.001128674
C	1.089866996	0.899439931	-4.317502975
C	3.354340553	1.590255737	-4.318053722
H	0.189859569	0.626582563	-4.861273766
H	4.234149456	1.860398173	-4.895210743
C	1.055371404	0.885040343	-2.862318516
C	3.348841667	1.584420800	-2.968268633
C	2.214244366	1.240506172	-2.261901379
H	2.176929235	1.229269266	-1.176253676
H	2.224316597	1.243202686	-6.087388039
C	4.488948345	2.195944786	-0.555198014
C	3.870728970	1.963829160	0.626308620
C	5.860668659	2.638610840	-0.569072425
H	2.837882996	1.628312945	0.597860754
H	6.393160820	2.833018780	-1.495791793
C	4.509412289	2.136755228	1.803378701
C	6.522378922	2.836478233	0.635587871
H	7.552624702	3.180046797	0.609025002
C	5.861284733	2.589710474	1.847521067
H	6.411052227	2.752246380	2.770281792
C	-0.267869294	0.568285286	-2.280922413
C	4.260130882	1.953310847	-1.865425587
C	3.836247206	2.053372145	3.142359018
C	-0.901473999	0.618936300	3.115993738
H	-1.031526923	1.200839996	-2.724486828
H	-0.515469611	-0.472009629	-2.472046137
H	-1.086053848	-0.370424926	3.524823904
H	-1.681512117	1.293695688	3.457004070
H	4.243320465	2.935960054	3.627516031
H	3.910654068	1.209778070	3.822697401
H	4.582774162	2.798847437	-2.466272354
H	5.117808819	1.320323706	-1.656227350

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H	-0.528934956	-0.076993614	-1.661265731
C	1.657071710	-0.045822471	-0.006453720
H	1.793769121	-0.151608452	-1.084019065
H	2.177218199	-0.868241251	0.493903130
H	2.142101049	0.882907033	0.312949747
C	0.195373759	-0.036156118	0.349462509
C	-0.208605275	-0.005746904	1.685971141
C	-1.614892602	0.008822410	2.010844946
C	-2.622083664	-0.007986977	0.981265962
C	-2.215057135	-0.037812624	-0.327247024
C	-0.822209477	-0.051232662	-0.615793228
H	-2.935135841	-0.052872874	-1.138764381
O	0.694664657	0.012410872	2.659455538
O	-3.870162487	0.007478573	1.481699824
H	0.283449650	0.031079868	3.540609598
H	-4.551710129	-0.004548880	0.792600632
O	-1.935842514	0.037897330	3.288169861
H	-2.906945229	0.041528948	3.405128002

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H	-0.547300637	-0.075287089	-1.718099356

C	1.612167954	-0.035791717	-0.009858371
H	1.783044219	-0.083701767	-1.085323215
H	2.117973804	-0.878397882	0.478827208
H	2.096272230	0.864877641	0.392231077
C	0.162187606	-0.031065956	0.316309124
C	-0.263348728	0.010684811	1.713426709
C	-1.602755070	0.025210256	2.067466497
C	-2.563961744	0.004272082	1.051403403
C	-2.175897360	-0.031529874	-0.337172806
C	-0.840976834	-0.048378117	-0.674306691
H	-1.927528977	0.051076807	3.102371693
H	-2.944224358	-0.039772741	-1.105717301
O	0.735489130	0.025911519	2.587681770
O	-3.834807634	0.027465228	1.415648937
H	0.423226744	0.064333580	3.505880594
H	-4.446366787	-0.007516009	0.661773026

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H	-0.546628833	-0.007947815	-1.734960556
C	1.598613381	-0.009558758	-0.044875786
H	1.778848886	-0.468357861	-1.020802021
H	2.230309010	-0.467948079	0.720662415
H	1.927755833	1.043309331	-0.130871028
C	0.167350799	-0.019477610	0.325795710
C	-0.228400007	-0.014168534	1.710769176
C	-1.555563331	0.000747301	2.053261042
C	-2.544981003	0.012633237	1.028361678
C	-2.177295446	0.010083996	-0.348090231
C	-0.850795269	-0.004791672	-0.692986965
H	0.543273985	-0.024416367	2.474068880
H	-1.862941265	0.001308143	3.093681574
H	-3.596776009	0.023658007	1.300686002
H	-2.951016903	0.017669566	-1.108517408

Appendix B Vibrational frequencies of the optimized structures.

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1.92 9.91 26.49 30.87 34.41 52.43
56.94 73.17 80.68 89.01 89.52 95.28
110.01 113.87 122.68 156.72 159.16 160.28
161.19 164.56 167.41 170.17 171.64 201.90
205.99 220.11 264.05 269.06 288.39 291.99
303.24 304.69 305.61 309.39 315.83 317.13
318.60 320.09 327.40 332.11 332.70 335.80
346.56 347.33 348.54 350.02 375.87 378.29
381.65 382.04 425.86 428.80 429.25 429.98
493.96 494.33 499.29 501.16 504.53 510.48
512.99 518.01 554.63 561.76 565.65 571.72
594.65 601.85 607.43 626.88 630.45 636.36
642.11 653.08 673.35 676.53 689.57 689.80
720.23 722.38 723.05 725.25 744.71 751.85
755.52 762.80 870.19 879.59 884.83 896.86
907.94 910.30 911.18 934.16 957.60 960.68
964.66 971.41 1003.30 1016.76 1024.71 1038.43
1092.03 1103.42 1107.56 1115.83 1193.89 1194.10
1195.09 1195.40 1219.13 1220.84 1225.45 1227.14
1251.71 1252.58 1253.04 1253.87 1271.83 1277.38
1280.30 1285.32 1296.63 1300.51 1302.27 1308.94
1327.94 1328.18 1328.92 1329.35 1351.07 1354.54
1357.02 1363.25 1383.90 1384.81 1387.81 1387.94
1420.83 1421.87 1424.43 1425.92 1497.15 1498.32
1501.20 1501.83 1511.98 1515.67 1518.27 1524.05
1556.03 1557.29 1557.93 1558.73 1665.62 1667.49
1669.26 1670.64 1689.25 1690.67 1691.83 1692.98
2980.86 2981.24 2995.49 3000.82 3035.40 3036.05
3059.36 3059.90 3205.15 3205.94 3211.14 3211.95
3777.08 3780.74 3781.11 3781.73 3795.97 3798.13
3799.32 3799.56 3845.60 3846.04 3847.96 3848.54

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17.51 19.97 35.55 37.81 38.74 51.55
84.80 85.88 106.19 109.73 129.79 171.49
172.79 175.18 176.77 206.23 207.07 227.15
243.96 251.28 251.88 252.66 272.30 279.56
280.49 282.57 295.09 301.99 309.47 313.20
315.23 317.41 319.21 319.66 347.68 353.46
354.99 355.65 380.55 382.11 386.08 398.40
460.54 462.80 463.43 464.60 475.65 499.29
502.16 526.44 528.64 541.17 545.71 561.27
597.35 598.12 601.44 608.07 663.13 668.56
669.72 678.13 679.94 703.80 705.37 718.99
731.61 736.48 740.27 741.73 776.87 781.08
783.47 785.33 825.82 826.44 827.40 827.78
869.75 875.71 877.17 880.45 912.29 915.50
926.81 929.11 970.59 973.85 975.88 978.64
1092.80 1106.21 1107.67 1123.01 1152.58 1156.51
1157.55 1158.83 1185.38 1185.73 1186.30 1187.75
1219.98 1221.71 1222.45 1223.31 1238.33 1239.28
1240.37 1242.26 1265.97 1267.05 1267.26 1267.72
1290.38 1306.23 1308.68 1321.55 1345.48 1350.19
1351.77 1352.32 1356.79 1358.82 1360.19 1360.66
1406.10 1407.60 1408.88 1409.50 1475.68 1481.60
1482.52 1490.04 1502.36 1503.04 1504.64 1505.19
1550.94 1552.09 1552.55 1552.90 1652.26 1654.71
1655.89 1659.13 1682.47 1683.83 1684.21 1685.44
2980.35 2983.57 2993.91 2994.18 3039.99 3040.76
3051.02 3057.84 3185.22 3186.10 3186.18 3186.47
3200.05 3200.49 3201.04 3202.01 3830.16 3830.35
3830.64 3830.74 3832.79 3834.43 3835.28 3835.41

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13.93 25.68 41.13 41.89 47.60 68.82
144.04 158.71 188.28 188.43 209.72 215.75
225.75 245.58 275.73 277.22 279.82 284.32
329.41 361.92 369.34 388.30 440.58 444.59
445.06 447.16 491.38 500.38 501.60 537.51
570.85 573.09 573.97 575.62 605.63 643.87
650.62 695.24 697.15 711.26 716.94 717.14
739.54 758.81 761.36 780.43 791.66 811.71
814.57 831.57 896.96 897.37 897.87 899.79
909.38 916.14 917.88 928.64 931.74 936.00
937.66 951.07 959.83 977.45 978.55 980.91
981.71 984.32 986.90 993.43 1004.98 1015.85
1016.17 1016.51 1116.34 1120.92 1122.28 1128.84
1160.87 1170.06 1172.91 1180.43 1197.95 1199.19
1199.90 1201.01 1209.14 1211.05 1211.54 1212.41
1255.42 1256.51 1257.44 1261.49 1290.75 1313.99
1318.96 1346.92 1352.24 1357.35 1357.82 1358.27

1363.41 1368.76 1371.05 1373.17 1474.55 1475.69
1475.85 1477.16 1490.22 1496.12 1496.59 1503.01
1529.95 1530.51 1530.80 1530.97 1637.49 1641.85
1642.33 1647.00 1654.93 1660.55 1660.97 1664.36
3024.99 3025.52 3026.03 3029.39 3060.34 3060.75
3062.02 3065.59 3167.01 3167.05 3168.51 3168.65
3173.99 3174.66 3175.04 3175.60 3176.40 3177.02
3180.17 3185.02 3194.00 3194.22 3195.26 3195.58

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119.10 146.68 160.33 161.40 277.83 291.65
295.98 317.31 324.27 353.89 444.23 472.69
516.98 549.81 585.47 607.90 692.83 693.59
751.75 768.68 900.57 951.68 1003.34 1063.85
1083.27 1170.67 1184.60 1256.05 1283.84 1300.41
1344.88 1371.58 1411.88 1430.42 1490.61 1502.06
1549.62 1561.52 1669.48 1691.04 3041.20 3094.99
3126.11 3174.11 3193.90 3780.79 3802.28 3846.75

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128.99 145.16 229.51 286.45 317.65 335.45
336.36 367.96 455.49 466.90 518.23 578.36
638.75 709.53 747.60 772.37 784.39 827.38
927.30 983.06 1023.58 1065.77 1137.43 1183.69
1192.83 1236.09 1248.84 1333.79 1351.88 1390.91
1430.49 1488.00 1490.74 1520.59 1568.29 1658.75
1682.63 3040.49 3094.12 3124.01 3169.24 3186.23
3188.29 3824.65 3830.90

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27.90 211.20 342.66 417.08 476.86 527.99
636.24 711.30 747.06 800.99 859.94 912.16
971.44 996.54 1006.08 1016.71 1057.75 1065.81
1117.78 1185.94 1208.39 1236.51 1347.34 1363.01
1425.80 1481.40 1501.54 1514.89 1542.24 1643.58
1666.38 3038.20 3097.73 3125.02 3170.73 3172.55
3184.75 3193.41 3205.79

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6.51 14.16 29.26 34.25 36.18 51.06
85.20 86.45 101.02 109.77 110.74 119.41
128.41 148.19 152.06 153.31 155.20 156.39
159.96 174.78 175.96 182.23 190.21 197.66
204.27 220.02 255.90 259.93 290.72 293.87
304.82 305.64 308.57 309.44 327.50 329.98
330.64 333.52 337.03 337.84 344.31 347.19
365.23 372.67 375.01 376.43 411.99 417.65
427.49 435.95 454.61 459.29 469.08 472.82
479.51 484.26 486.14 486.68 491.37 496.31
507.14 512.45 547.20 555.09 559.21 566.73
597.56 602.57 607.39 625.37 630.52 634.89
639.57 653.68 672.34 680.76 688.91 691.44
720.92 721.82 723.80 725.97 743.05 748.52
752.46 763.47 872.14 872.43 880.24 887.72
907.41 909.48 911.00 937.23 941.75 945.06
962.64 968.89 1006.01 1022.54 1033.18 1049.15
1094.86 1105.84 1114.43 1123.39 1184.20 1185.01
1186.16 1188.86 1215.43 1218.51 1219.48 1221.78
1246.65 1249.22 1250.40 1253.42 1266.87 1274.61
1278.67 1284.95 1290.65 1296.80 1297.54 1310.98
1317.66 1326.25 1330.71 1337.53 1353.03 1360.38
1366.41 1372.79 1381.12 1382.02 1392.88 1393.34
1404.32 1406.73 1414.70 1416.82 1477.41 1478.67
1486.07 1491.65 1495.39 1499.63 1503.73 1524.77
1532.53 1535.94 1552.24 1554.31 1580.26 1587.25
1596.70 1601.82 1632.51 1637.48 1640.36 1667.52
3003.09 3005.40 3016.61 3019.23 3052.49 3055.23
3074.65 3074.76 3208.88 3209.29 3215.53 3216.43
3759.17 3760.96 3763.56 3764.04 3764.82 3767.62
3773.31 3774.95 3837.16 3838.16 3846.47 3847.65

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12.40 17.27 32.40 33.72 34.63 52.26
79.64 80.67 102.21 108.28 134.44 167.93
169.61 170.26 179.39 201.21 201.62 224.67
232.94 243.26 244.43 245.44 279.43 284.21
304.99 312.97 317.48 325.42 325.81 331.55
352.39 360.54 363.21 363.52 372.66 378.27
378.46 387.09 409.49 413.40 414.80 418.90
453.90 455.53 455.58 457.01 469.51 492.79
496.31 512.94 521.91 529.00 537.28 560.91
593.77 599.83 602.31 603.12 661.42 663.75
667.30 678.28 680.42 698.10 700.26 714.99
730.50 735.45 741.41 742.90 762.48 776.65

780.49 782.47 838.86 839.60 839.86 840.71
869.49 872.80 874.70 883.09 897.34 906.67
910.47 923.13 950.55 953.66 964.71 966.85
1094.71 1108.30 1114.27 1132.20 1148.30 1155.87
1157.33 1159.98 1178.94 1181.26 1181.29 1188.92
1219.61 1220.22 1221.22 1221.88 1229.11 1234.01
1238.13 1248.99 1257.79 1259.69 1261.63 1265.92
1287.56 1299.27 1303.70 1311.68 1336.28 1344.30
1345.45 1358.13 1362.27 1364.25 1367.52 1376.29
1403.40 1404.74 1408.65 1410.20 1475.02 1476.00
1478.18 1481.58 1486.77 1491.64 1494.81 1501.86
1539.08 1540.46 1541.84 1543.55 1590.97 1598.29
1599.46 1631.33 1642.27 1647.13 1652.84 1657.38
2984.35 2990.75 2996.48 3000.14 3060.50 3063.39
3078.44 3079.89 3197.49 3199.07 3201.97 3202.56
3202.82 3202.95 3203.33 3206.73 3812.15 3812.47
3813.03 3814.56 3823.06 3823.64 3824.00 3825.77

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13.07 32.20 45.18 45.38 48.61 55.30
141.73 160.07 180.12 181.10 197.36 205.94
210.33 217.88 266.32 268.87 285.91 291.74
333.88 378.93 381.97 400.39 424.41 425.60
430.17 431.07 456.52 488.07 489.24 526.60
537.26 546.54 555.79 557.62 590.29 629.49
633.76 683.96 686.52 695.82 697.72 699.36
734.81 755.46 757.98 776.54 801.21 815.15
817.27 828.63 887.04 889.85 891.07 893.31
900.04 900.79 903.97 922.37 935.88 938.37
939.19 939.57 946.26 977.34 978.81 987.90
996.93 997.29 998.18 998.37 1007.22 1007.40
1012.23 1012.26 1106.12 1110.47 1111.64 1116.74
1154.48 1178.24 1180.19 1182.24 1185.56 1185.82
1188.11 1195.01 1197.35 1199.63 1200.77 1201.40
1244.43 1244.92 1247.77 1269.11 1297.74 1318.68
1320.81 1342.85 1351.90 1362.03 1364.14 1369.44
1372.99 1378.60 1379.82 1380.13 1441.99 1448.28
1448.51 1457.10 1477.06 1487.56 1490.88 1493.14
1500.06 1530.15 1535.06 1538.08 1540.71 1543.31
1550.51 1555.34 1623.54 1625.15 1628.19 1656.22
3045.55 3048.30 3049.02 3051.10 3085.74 3088.10
3089.98 3091.63 3184.43 3184.94 3186.69 3188.95
3189.16 3189.48 3189.89 3190.22 3196.19 3196.58
3197.09 3197.43 3211.35 3211.51 3211.78 3212.62

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100.35 132.44 139.23 276.09 278.91 287.81
316.66 341.21 368.50 379.29 472.25 490.21
507.51 583.59 596.53 646.74 679.94 708.08
744.05 835.42 949.01 952.25 1010.57 1062.38
1090.16 1126.94 1169.29 1235.51 1289.99 1332.27
1357.77 1392.63 1401.90 1435.05 1467.99 1485.58
1503.41 1547.03 1591.69 1687.21 3059.97 3122.23
3157.95 3208.97 3221.17 3671.97 3742.68 3798.74

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105.59 126.77 194.82 300.37 306.77 352.08
417.72 429.99 515.33 518.08 538.65 559.35
637.04 688.52 740.09 749.29 800.25 848.74
958.01 967.36 1011.73 1016.08 1159.56 1179.93
1194.07 1246.64 1291.41 1304.79 1394.23 1418.24
1435.70 1455.68 1477.27 1500.67 1551.73 1580.80
1628.62 3033.63 3080.51 3170.35 3201.18 3220.68
3226.74 3765.23 3776.63

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16.16 151.27 346.50 353.24 386.05 500.02
512.94 574.10 743.85 780.14 800.74 939.79
984.59 990.46 994.81 1006.55 1013.84 1026.12
1090.00 1168.11 1218.92 1260.37 1305.29 1367.10
1395.27 1410.72 1438.81 1474.90 1490.88 1544.24
1688.23 2968.99 3092.95 3153.72 3212.50 3216.60
3219.27 3231.35 3234.45