Electronic Supplementary Information (ESI) for:

Aromatic *β*-sheet foldamers based on tertiary squaramides

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1. ABBREVIATIONS

AcOEt: ethylacetate.

Boc_2O: di-*tert*-butyl dicarbonate.

DCM: dichloromethane.

DIAD: diisopropyl azodicarboxylate.

1,2-DCE: 1,2-dichloroethane.

DIPEA: *N*,*N*-diisopropylethylamine.

DMF: *N*,*N*-dimethylformamide.

ESI: electrospray ionization.

GPC: gel permeation chromatography.

HRMS: high-resolution mass spectrometry.

NMR: nuclear magnetic resonance.

PyBOP: benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate.

1,1,2,2-TCE-d_2: 1,1,2,2-tetrachloroethane-d_2.

TFA: trifluoroacetic acid.

THF: tetrahydrofuran.

TLC: thin layer chromatography.

VT: variable temperature.

2. GENERAL METHODS

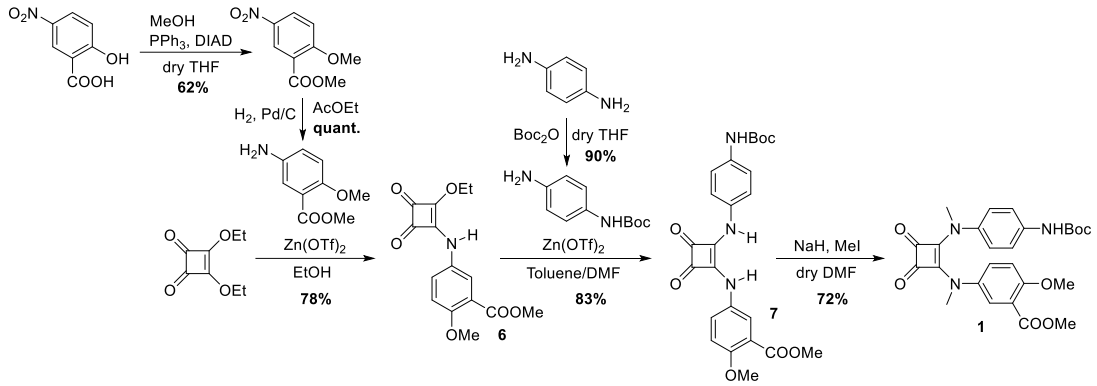
NMR spectroscopic experiments were carried out on six different instruments. NMR instruments at the IECB technology platform: **(1)** Avance II 300 MHz Bruker Biospin (300 MHz for ^{1}H observation) equipped with a BBO H/X probe; **(2)** DPX-400 Bruker Biospin (400 MHz for ^{1}H observation) equipped with a QNP $^{1}H/^{13}C/^{31}P/^{19}F$ probe. NMR instruments of the analytical division at the Faculty for Chemistry and Pharmacy in LMU: **(3)** Avance III HD 400 MHz Bruker BioSpin (400 MHz for ^{1}H observation) equipped with a broadband probe; **(4)** Avance III HD 500 MHz Bruker BioSpin (500 MHz for ^{1}H observation) equipped with a CryoProbe™ Prodigy broadband probe; **(5)** VNMRS 400 Varian (400 MHz for ^{1}H observation) equipped with a room-temperature AutoX Dual Broadband probe; and **(6)** Avance III HD 800 MHz Bruker BioSpin (800 MHz for ^{1}H observation) equipped with a cryogenic probe. Chemical shifts (δ) are reported in parts per million (ppm) relative to trimethylsilane (TMS), and coupling constants (*J*) are reported in Hertz (Hz). ^{1}H NMR splitting patterns are designated as singlet (s), broad singlet (brs), doublet (d), doublet of doublets (dd), triplet (t), quartet (q), multiplet (m) and broad multiplet (brm). Samples were not degassed.

Preparative recycling GPC purifications were performed on a LC-91XXII NEXT series instrument equipped with polymer-based JAIGEL-HR 20 x 600 mm columns (Japan Analytical Industry Co., Ltd.) at a flow rate of 7.5 $mL \cdot min^{-1}$ with a mobile phase composed of 1% EtOH (vol/vol) and 0.5% Et_3N (vol/vol) in HPLC grade chloroform. Monitoring by UV detection was carried out at 254 nm, 280 nm, 300 nm and 360 nm. Collected fractions were washed twice with saturated aqueous NH_4Cl to remove the Et_3N.

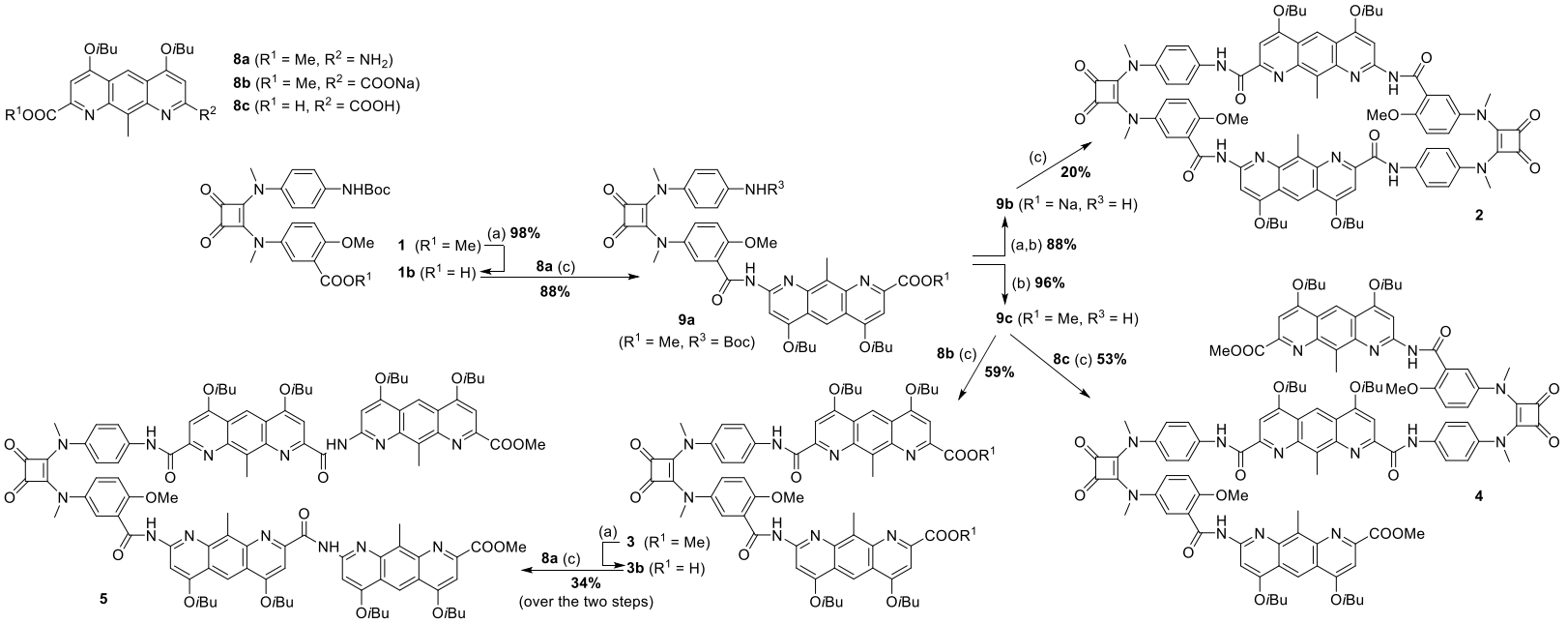
HRMS (ESI+) experiments were performed at the IECB Mass Spectrometry facility, using a Thermo Fisher Scientific Exactive Orbitrap instrument (HESI-II electrospray source operated in positive ion mode).

3. SYNTHETIC PROTOCOLS

3.1. Synthetic schemes



Scheme S1. Synthetic pathway for the synthesis of compound **1**.



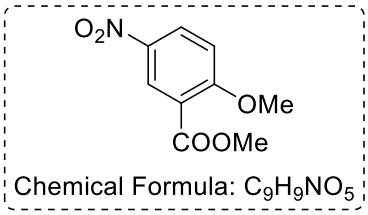
Scheme S2. Synthetic pathway for the synthesis of compounds **2-5**. Reagents and conditions: (a) Me_3SnOH, 1,2-DCE (reflux); (b) TFA/DCM; (c) PyBOP, dry DIPEA, dry $CHCl_3$.

3.2. Materials and methods for chemical synthesis

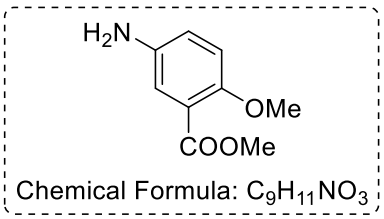
Commercial reagents were purchased from Sigma-Aldrich, TCI Chemicals or Alfa-Aesar and were used without further purification. Tetrahydrofuran was dried over alumina columns (MBRAUN SPS-800 solvent purification system) whereas chloroform and diisopropylethylamine were distilled over CaH_2 prior to use. Reactions were monitored by TLC on Merck silica gel 60 F_{254} plates and observed under UV light. Column chromatography purifications were carried out on Merck GEDURAN Si60 (40-63 µm).

Compounds **8a-c** were synthesized as previously reported [1].

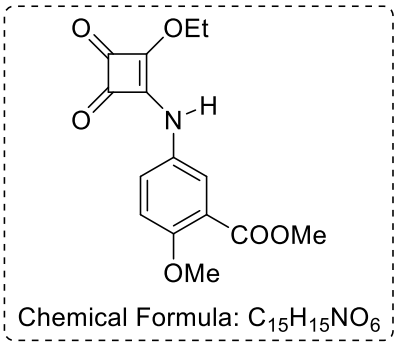
3.3. Synthesis of compound **1**



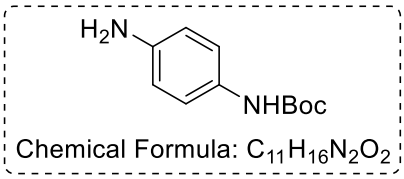
Methyl 2-methoxy-5-nitrobenzoate (CAS: 34841-11-7): Triphenylphosphine (10.17 g, 38.8 mmol) and 2-hydroxy-5-nitrobenzoic acid (3.17 g, 17.3 mmol) were dissolved in dry THF (40 mL) under inert atmosphere of N_2. Then methanol (1.6 mL, 39.6 mmol) was added, followed by the dropwise addition of DIAD (7.6 mL, 38.7 mmol) under stirring. The reaction mixture was stirred at room temperature for 2 hours, then diluted with DCM, washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was washed with methanol and purified by flash chromatography (SiO_2) using AcOEt/cyclohexane as eluent (from 20% to 25% AcOEt) to give 2.26 g (62% yield) of methyl 2-methoxy-5-nitrobenzoate as a white solid. HRMS (ESI+) calcd. for $C_9H_{10}NO_5$ $[M+H]^+$ (m/z): 212.0553, found: 212.0554. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 8.71 (d, *J* = 2.9 Hz, 1H, CH_{Ar}), 8.37 (dd, *J* = 9.3, 2.9 Hz, 1H, CH_{Ar}), 7.07 (d, *J* = 9.2 Hz, 1H, CH_{Ar}), 4.03 (s, 3H, CH_3), 3.94 (s, 3H, CH_3). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 164.6 (1C), 163.8 (1C), 140.8 (1C), 129.1 (1C), 128.0 (1C), 120.6 (1C), 112.1 (1C), 57.0 (1C), 52.7 (1C).



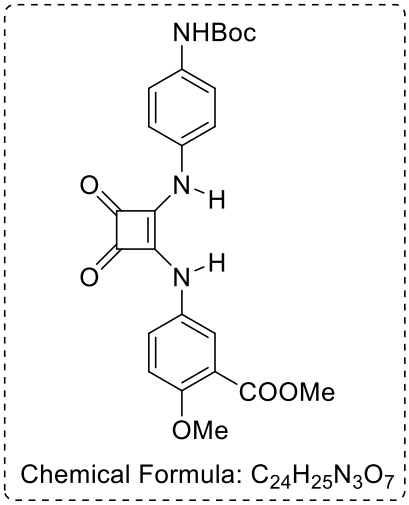
Methyl 5-amino-2-methoxybenzoate (CAS: 22802-67-1): To a solution of methyl 2-methoxy-5-nitrobenzoate (2.26 g, 10.7 mmol) in AcOEt (30 mL), 10% Pd/C (226 mg) was added. The mixture was vigorously stirred at room temperature for 3.5 hours under hydrogen atmosphere, after which complete conversion of the starting material was observed by TLC. The crude mixture was filtered through a bed of Celite® and the filtrate was concentrated to dryness under reduced pressure, obtaining 2.07 g (quant. yield) of methyl 5-amino-2-methoxybenzoate as a white powder. HRMS (ESI+) calcd. for $C_9H_{12}NO_3$ $[M+H]^+$ (m/z): 182.0812, found: 182.0809. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 7.15 (dd, *J* = 2.1, 1.1 Hz, 1H, CH_{Ar}), 6.84 – 6.81 (m, 2H, CH_{Ar}), 3.88 (s, 3H, CH_3), 3.83 (s, 3H, CH_3), 3.49 (brs, 2H, NH_2). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 166.9 (1C), 152.6 (1C), 139.7 (1C), 120.7 (1C), 120.5 (1C), 118.3 (1C), 114.3 (1C), 57.0 (1C), 52.2 (1C).



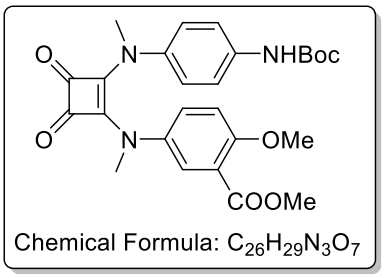
Compound **6**: To a solution of 3,4-diethoxy-3-cyclobutane-1,2-dione (849 mg, 4.99 mmol) in ethanol (10 mL), $Zn(OTf)_2$ (181 mg, 0.499 mmol) was added. The mixture was stirred at room temperature for 5 min and then a solution of methyl 5-amino-2-methoxybenzoate (814 mg, 4.49 mmol) in ethanol (10 mL) was added slowly. After the mixture was stirred at room temperature for 20 hours, the product was filtered off, washed with cold ethanol and dried under reduced pressure, obtaining 1.06 g (78% yield) of compound **6** as a white solid. HRMS (ESI+) calcd. for $C_{15}H_{16}NO_6$ $[M+H]^+$ (m/z): 306.0972, found: 306.0969. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 8.58 (brs, 1H, NH), 7.79 (d, *J* = 2.9 Hz, 1H, CH_{Ar}), 7.62 – 7.39 (m, 1H, CH_{Ar}), 6.99 (d, *J* = 9.0 Hz, 1H, CH_{Ar}), 4.88 (q, *J* = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 3.91 (s, 3H, CH_3), 3.90 (s, 3H, CH_3), 1.50 (t, *J* = 7.1 Hz, 3H, $CH_2C\underline{H}_3$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 183.8 (2C), 178.2 (1C), 168.4 (1C), 166.0 (1C), 156.8 (1C), 130.0 (1C), 125.3 (1C), 123.2 (1C), 120.4 (1C), 113.3 (1C), 70.5 (1C), 56.5 (1C), 52.4 (1C), 15.9 (1C).



tert-butyl (4-aminophenyl)carbamate (CAS: 71026-66-9): A solution of Boc_2O (5.16 g, 23.6 mmol) in dry THF (50 mL) was added to a solution of 1,4-phenylenediamine (5.06 g, 46.8 mmol) in dry THF (50 mL) under inert atmosphere of N_2. After stirring the mixture at room temperature for 25 hours, volatiles were removed *in vacuo*. The crude product was purified by flash chromatography (SiO_2) using AcOEt/cyclohexane as eluent (from 15% to 35% AcOEt) to give 4.42 g (90% yield) of *tert*-butyl (4-aminophenyl)carbamate as a white solid. HRMS (ESI+) calcd. for $C_{11}H_{17}N_2O_2$ $[M+H]^+$ (m/z): 209.1285, found: 209.1285. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 7.13 (d, *J* = 7.4 Hz, 2H, CH_{Ar}), 6.67 – 6.61 (m, 2H, CH_{Ar}), 6.24 (brs, 1H, NH), 3.53 (brs, 2H, NH_2), 1.50 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 153.5 (1C), 142.5 (1C), 129.9 (1C), 121.0 (2C), 115.8 (2C), 80.2 (1C), 28.5 (3C).

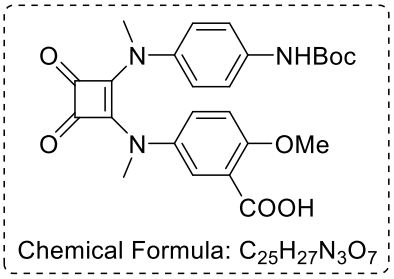


Compound **7**: To a slurry of compound **6** (1.04 g, 3.41 mmol) in 20 mL of toluene/DMF (19:1, vol:vol), $Zn(OTf)_2$ (124 mg, 0.341 mmol) was added. The mixture was stirred at room temperature for 5 min and then a solution of *tert*-butyl (4-aminophenyl)carbamate (782 mg, 3.75 mmol) in 20 mL of toluene/DMF (19:1, vol:vol) was added slowly. After stirring at 90 °C for 5 hours, the reaction mixture was cooled down to room temperature and the product was filtered off, washed with ethanol and dried under reduced pressure, obtaining 1.33 g (83% yield) of compound **7** as a white solid. HRMS (ESI+) calcd. for $C_{24}H_{26}N_3O_7$ $[M+H]^+$ (m/z): 468.1765, found: 468.1768. ^{1}H NMR (400 MHz, DMSO-d_6, 298 K) δ 9.79 (brs, 1H, NH), 9.69 (brs, 1H, NH), 9.33 (brs, 1H, NH), 7.74 – 7.64 (m, 2H, CH_{Ar}), 7.44 (d, J = 8.8 Hz, 2H, CH_{Ar}), 7.34 (d, J = 8.9 Hz, 2H, CH_{Ar}), 7.19 (d, J = 9.0 Hz, 1H, CH_{Ar}), 3.81 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 1.48 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (101 MHz, DMSO-d_6, 298 K) δ 181.5 (1C), 181.4 (1C), 165.7 (1C), 165.2 (1C), 165.0 (1C), 154.4 (1C), 152.8 (1C), 135.4 (1C), 132.9 (1C), 131.5 (1C), 123.7 (1C), 120.9 (1C), 120.3 (1C), 119.1 (2C), 119.0 (2C), 113.8 (1C), 79.0 (1C), 56.2 (1C), 52.1 (1C), 28.1 (3C).

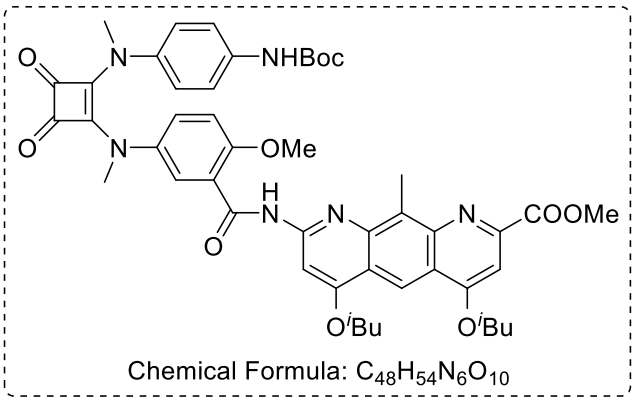


Compound **1**: A commercial mixture of 60% NaH in mineral oil (243 mg, 6.07 mmol) was placed in a round bottom flask and washed twice with 1 mL of dry *n*-pentane under inert atmosphere of N_2. Then 3 mL of dry DMF were added, followed by the slow addition at 0° of a solution of compound **7** (1.29 g, 2.76 mmol) in dry DMF (18 mL). The mixture was stirred at room temperature for 30 min and then iodomethane (618 µL, 9.93 mmol) was added dropwise at 0 °C under stirring. After stirring at room temperature for 16 hours, the reaction mixture was diluted with AcOEt, washed four times with saturated aqueous NH_4Cl, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2) using AcOEt/cyclohexane as eluent (from 50% to 60% AcOEt), and finally crystallized from DCM/Et_2O/cyclohexane, obtaining 986 mg (72% yield) of compound **1** as a white crystalline solid. HRMS (ESI+) calcd. for $C_{26}H_{30}N_3O_7$ $[M+H]^+$ (m/z): 496.2078, found: 496.2076. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 7.00 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 6.96 (d, *J* = 2.9 Hz, 1H, CH_{Ar}), 6.73 (dd, *J* = 8.9, 2.9 Hz, 1H, CH_{Ar}), 6.61 (d, *J* = 8.9 Hz, 1H, CH_{Ar}), 6.50 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 6.34 (brs, 1H, NH), 3.88 (s, 3H, $COOCH_3$), 3.82 (s, 3H, OCH_3), 3.67 (s, 3H, NCH_3), 3.66 (s, 3H, NCH_3), 1.51 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 186.6 (1C, $CH_3NC\underline{C}O$), 186.4 (1C, $CH_3NC\underline{C}O$), 167.4 (1C, $CH_3N\underline{C}CO$), 167.3 (1C, $CH_3N\underline{C}CO$), 165.7 (1C, $\underline{C}OOCH_3$), 156.6 (1C, C_{Ar}), 152.6 (1C, $\underline{C}OO^tBu$), 138.3 (1C, C_{Ar}), 135.9 (1C, C_{Ar}), 135.9 (1C, C_{Ar}), 126.7 (1C, CH_{Ar}), 125.2 (1C, CH_{Ar}), 122.2 (2C, CH_{Ar}), 120.1 (1C, C_{Ar}), 118.9 (2C, CH_{Ar}), 112.5 (1C, CH_{Ar}), 80.9 (1C, $\underline{C}(CH_3)_3$), 56.5 (1C, OCH_3), 52.4 (1C, $COO\underline{C}H_3$), 39.7 (1C, NCH_3), 39.5 (1C, NCH_3), 28.5 (3C, $C(\underline{C}H_3)_3$).

3.4. Synthesis of compound **2**

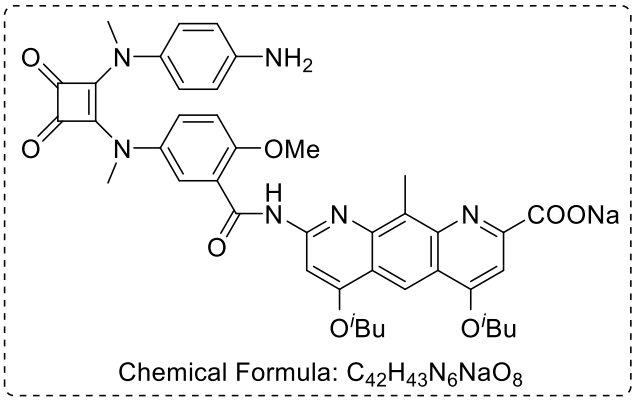


Compound **1b**: $(CH_3)_3SnOH$ (1.45 g, 8.03 mmol) was added to a solution of compound **1** (796 mg, 1.60 mmol) in 1,2-dichloroethane (6 mL). After refluxing for 24 hours, the mixture was diluted with DCM, washed with 5% aqueous citric acid, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was washed twice with Et_2O, obtaining 681 mg (98% yield) of compound **1b** as a white solid. HRMS (ESI+) calcd. for $C_{25}H_{28}N_3O_7$ $[M+H]^+$ (m/z): 482.1922, found: 482.1923. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 10.51 (brs, 1H, COOH), 7.37 (d, *J* = 3.1 Hz, 1H, CH_{Ar}), 7.00 (d, *J* = 8.9 Hz, 2H, CH_{Ar}), 6.85 (dd, *J* = 8.9, 3.1 Hz, 1H, CH_{Ar}), 6.72 (d, *J* = 9.0 Hz, 1H, CH_{Ar}), 6.54 (d, *J* = 9.0 Hz, 2H, CH_{Ar}), 6.36 (brs, 1H, NH), 4.01 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 1.52 (s, 9H, $C(CH_3)_3$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 186.9 (1C), 186.2 (1C), 167.4 (1C), 166.9 (1C), 164.4 (1C), 155.0 (1C), 152.7 (1C), 138.3 (1C), 137.8 (1C), 136.0 (1C), 127.5 (1C), 126.4 (1C), 122.1 (2C), 118.9 (2C), 117.9 (1C), 112.5 (1C), 81.0 (1C), 57.3 (1C), 39.4 (2C), 28.4 (3C).



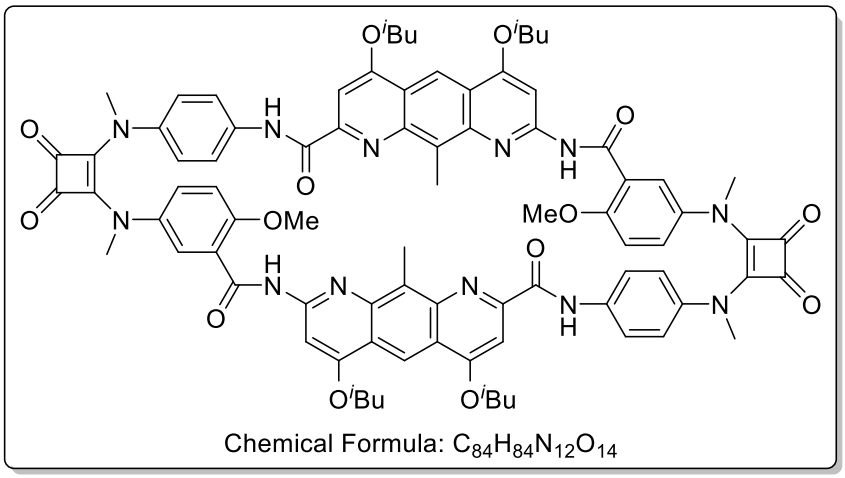
Compound **9a**: Dry DIPEA (164 µL, 0.943 mmol, freshly distilled over CaH_2) was added to a solution of amine **8a** (97 mg, 0.24 mmol), carboxylic acid **1b** (123 mg, 0.255 mmol) and PyBOP (368 mg, 0.707 mmol) in dry chloroform (6 mL, freshly distilled over CaH_2) under inert atmosphere of N_2. After 16 hours stirring at room temperature, volatiles were removed *in vacuo*. Then the residue was dissolved in DCM, washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2) using acetone/DCM as eluent (from 0% to 15% acetone) to give 183 mg (88% yield) of compound **9a** as a yellow solid. HRMS (ESI+) calcd. for $C_{48}H_{55}N_6O_{10}$ $[M+H]^+$ (m/z): 875.3974, found: 875.3971. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 10.60 (brs, 1H, NH), 9.06 (s, 1H, CH_{Ar}), 8.09 (s, 1H, CH_{Ar}), 7.51 (d, *J* = 2.7 Hz, 1H, CH_{Ar}), 7.45 (s, 1H, CH_{Ar}), 7.04 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 6.81 (dd, *J* = 8.7, 2.9 Hz, 1H, CH_{Ar}), 6.73 (d, *J* = 8.9 Hz, 1H, CH_{Ar}), 6.56 (d, *J* = 8.9 Hz, 2H, CH_{Ar}), 6.45 (brs, 1H, NH), 4.16 (d, *J* = 6.3 Hz, 2H, OCH_2), 4.12 (d, *J* = 6.6 Hz, 2H, OCH_2), 4.11 (s, 3H, CH_3), 4.09 (s, 3H, CH_3), 3.73 (s, 3H, CH_3), 3.72 (s, 3H, CH_3), 3.31 (s, 3H, $ArCH_3$), 2.43 – 2.30 (m, 2H, $C\underline{H}(CH_3)_2$), 1.27 (s, 9H, $C(CH_3)_3$), 1.23 – 1.19 (2 x d, 12H, $CH(C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 186.7 (1C), 186.4 (1C), 167.4 (1C), 167.2 (1C), 166.7 (1C), 164.0 (1C), 163.8 (1C), 163.1 (1C), 155.0 (1C), 152.9 (1C), 152.6 (1C), 149.6 (1C), 146.3 (1C), 145.3 (1C), 138.5 (1C), 137.3 (1C), 136.0 (1C), 134.4 (1C), 126.8 (1C), 125.8 (1C), 122.2 (2C), 121.5 (1C), 120.5 (1C), 119.6 (1C), 119.1 (2C), 113.6 (1C), 112.4 (1C), 98.0 (1C), 94.2 (1C), 80.7

(1C), 75.1 (2C), 56.9 (1C), 53.3 (1C), 39.7 (1C), 39.6 (1C), 28.5 (1C), 28.5 (1C), 28.2 (3C), 19.4 (2C), 19.3 (2C), 12.7 (1C).



Chemical Formula: $C_{42}H_{43}N_6NaO_8$

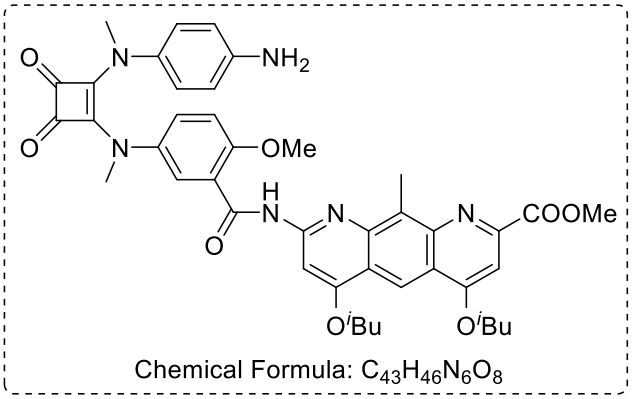
Compound **9b**: $(CH_3)_3SnOH$ (187 mg, 1.03 mmol) was added to a solution of compound **9a** (181 mg, 0.207 mmol) in 1,2-dichloroethane. The mixture was refluxed for 24 hours, after which complete conversion of the starting material was observed by TLC. Then it was diluted with DCM, washed with 5% aqueous citric acid, dried over $MgSO_4$ and concentrated under reduced pressure. The obtained yellow residue (190 mg) was redissolved in DCM (5 mL) and then TFA (2.5 mL) was added. The mixture was stirred at room temperature for 3 hours, after which complete conversion of the starting material was observed by TLC. Volatiles were removed *in vacuo* and then the residue was dissolved in DCM, washed twice with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure, obtaining 142 mg (88% yield) of the sodium salt **9b** as a yellow solid. HRMS (ESI+) calcd. for $C_{42}H_{45}N_6O_8$ $[M+H]^+$ (m/z): 761.3293, found: 761.3297. ^{1}H NMR (300 MHz, $CDCl_3$, 298 K) δ 10.64 (s, 1H, NH), 9.11 (s, 1H, CH_{Ar}), 8.12 (s, 1H, CH_{Ar}), 7.57 (s, 1H, CH_{Ar}), 7.52 (d, J = 2.3 Hz, 1H, CH_{Ar}), 6.87 – 6.78 (m, 2H, CH_{Ar}), 6.46 (d, J = 8.7 Hz, 2H, CH_{Ar}), 6.32 (d, J = 8.7 Hz, 2H, CH_{Ar}), 4.22 – 4.13 (2 x d, 4H, OCH_2), 4.14 (s, 3H, OCH_3), 3.71 (s, 3H, NCH_3), 3.67 (s, 3H, NCH_3), 3.56 (brs, 2H, NH_2), 3.23 (s, 3H, $ArCH_3$), 2.46 – 2.30 (m, 2H, $C\underline{H}(CH_3)_2$), 1.24 – 1.17 (m, 12H, $CH(C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 186.9 (1C), 185.8 (1C), 167.9 (1C), 166.8 (1C), 166.0 (1C), 164.3 (1C), 164.1 (1C), 163.4 (1C), 154.8 (1C), 153.8 (1C), 148.6 (1C), 145.8 (1C), 144.8 (1C), 143.2 (1C), 137.8 (1C), 134.6 (1C), 131.6 (1C), 126.8 (1C), 125.5 (1C), 123.3 (2C), 121.6 (1C), 120.8 (1C), 119.3 (1C), 114.8 (3C), 112.2 (1C), 96.1 (1C), 94.5 (1C), 75.9 (1C), 75.3 (1C), 57.0 (1C), 40.1 (1C), 39.6 (1C), 28.5 (1C), 28.4 (1C), 19.4 (2C), 19.2 (2C), 12.3 (1C).



Chemical Formula: $C_{84}H_{84}N_{12}O_{14}$

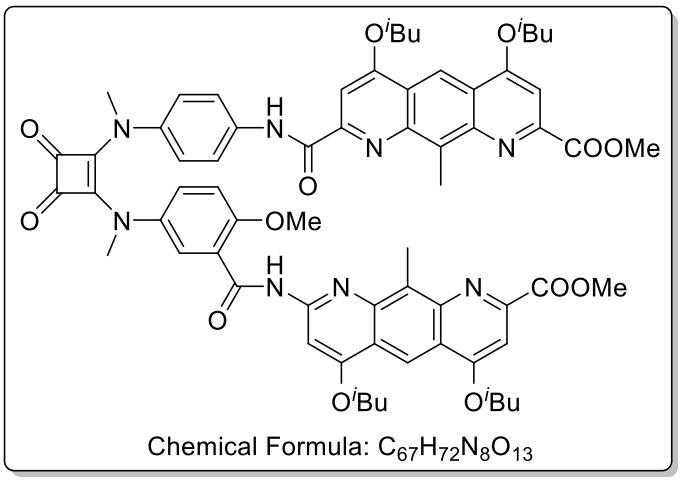
Compound **2**: Dry DIPEA (125 µL, 0.715 mmol, freshly distilled over CaH_2) was added to a solution of compound **9b** (140 mg, 0.179 mmol) and PyBOP (279 mg, 0.537 mmol) in dry chloroform (60 mL, freshly distilled over CaH_2), under inert atmosphere of N_2. After 22 hours stirring at room temperature, volatiles were removed *in vacuo*. Then the residue was dissolved in $CHCl_3$, washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2) using acetone/DCM as eluent (from 0% to 30% acetone), and also by GPC, to give 53 mg (20% yield) of compound **2** as a yellow solid. HRMS (ESI+) calcd. for $C_{84}H_{85}N_{12}O_{14}$ $[M+H]^+$ (m/z): 1485.6303, found: 1485.6310. UV-Vis λ_{max} ($CHCl_3$, 298 K) = 265 nm and 322 nm. ^{1}H NMR (400 MHz, $CDCl_3$, 298 K) δ 10.65 (s, 2H, NH), 10.54 (s, 2H, NH), 8.58 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 8.36 (s, 2H, CH_{Ar}), 7.62 – 7.58 (m, 2H, CH_{Ar}), 7.52 (s, 2H, CH_{Ar}), 7.42 (s, 2H, CH_{Ar}), 6.88 – 6.76 (m, 6H, CH_{Ar}), 6.63 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 6.52 (d, *J* = 8.4 Hz, 2H, CH_{Ar}), 4.28 (s, 6H, OCH_3), 4.25 – 4.18 (2 x d, 2H, OCH_2), 4.05 – 3.98 (2 x d, 2H, OCH_2), 3.95 – 3.88 (2 x d, 2H, OCH_2), 3.78 (s, 6H, NCH_3), 3.77 (s, 6H, NCH_3), 3.71 – 3.63 (2 x d, 2H, OCH_2), 3.15 (s, 6H, $ArCH_3$), 2.45 – 2.22 (m, 4H, $C\underline{H}(CH_3)_2$), 1.25 – 1.19 (2 x d, 12H, $CH(C\underline{H}_3)_2$), 1.18 – 1.11 (2 x d, 12H, $CH(C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 186.6 (2C, $CH_3NC\underline{C}O$), 186.4 (2C, $CH_3NC\underline{C}O$), 167.4 (4C, $CH_3N\underline{C}CO$), 164.3 (2C, C_{Ar}), 162.6 (2C, C_{Ar}), 162.3 (2C, CO), 162.1 (2C, CO), 155.3 (2C, C_{Ar}), 152.5 (2C, C_{Ar}), 150.2 (2C, C_{Ar}), 144.0 (2C, C_{Ar}), 143.7 (2C, C_{Ar}), 138.6 (2C, C_{Ar}), 138.0 (2C, C_{Ar}), 136.5 (2C, C_{Ar}), 131.9 (2C, C_{Ar}), 127.7 (2C, CH_{Ar}), 127.7 (2C, CH_{Ar}), 124.2 (2C, CH_{Ar}), 122.7 (2C, CH_{Ar}), 121.7 (2C, C_{Ar}), 118.9 (2C, C_{Ar}), 118.8 (2C, CH_{Ar}), 118.4 (2C, CH_{Ar}), 118.2 (2C, C_{Ar}), 113.2 (2C, CH_{Ar}), 112.2 (2C, CH_{Ar}), 94.6 (2C, CH_{Ar}), 93.0 (2C, CH_{Ar}), 75.2 (2C, OCH_2), 74.8 (2C, OCH_2), 57.2 (2C, OCH_3), 40.2 (2C, NCH_3), 39.8 (2C, NCH_3), 28.6 (2C, $C\underline{H}(CH_3)_2$), 28.6 (2C, $C\underline{H}(CH_3)_2$), 19.5 (2C, $CH(C\underline{H}_3)_2$), 19.3, (2C, $CH(C\underline{H}_3)_2$), 19.2, (2C, $CH(C\underline{H}_3)_2$), 19.2, (2C, $CH(C\underline{H}_3)_2$), 12.1, (2C, $CH(C\underline{H}_3)_2$).

3.5. Synthesis of compound **3**



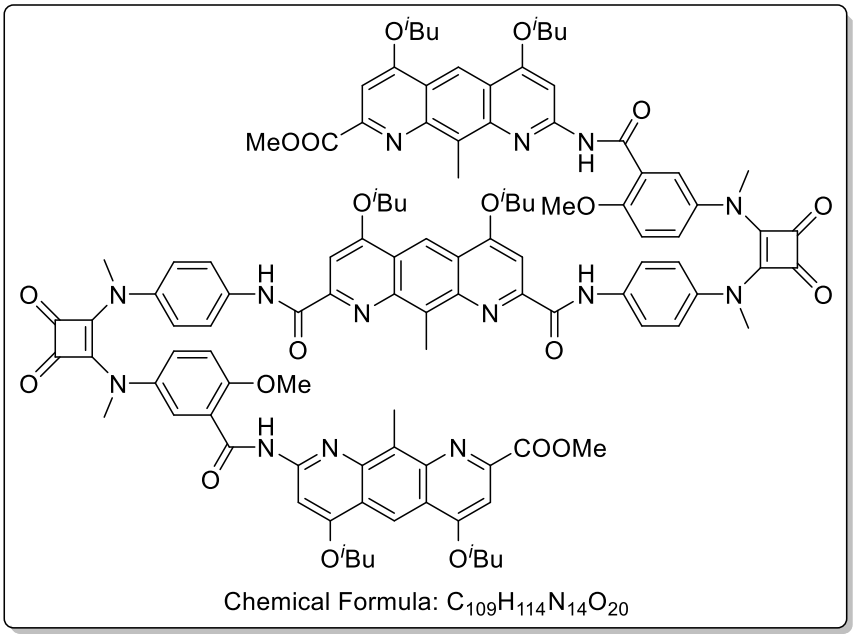
Chemical Formula: $C_{43}H_{46}N_6O_8$

Compound **9c**: TFA (3 mL) was added to a solution of compound **9a** (156 mg, 0.178 mmol) in DCM (6 mL). The mixture was stirred at room temperature for 2 hours, after which complete conversion of the starting material was observed by TLC. Volatiles were removed *in vacuo* and then the residue was dissolved in DCM, washed twice with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure, obtaining 132 mg (96% yield) of compound **9c** as a yellow solid. HRMS (ESI+) calcd. for $C_{43}H_{47}N_6O_8$ $[M+H]^+$ (m/z): 775.3450, found: 775.3473. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 10.58 (s, 1H, NH), 9.07 (s, 1H, CH_{Ar}), 8.07 (s, 1H, CH_{Ar}), 7.50 (d, *J* = 2.6 Hz, 1H, CH_{Ar}), 7.45 (s, 1H, CH_{Ar}), 6.82 (dd, *J* = 8.8, 2.7 Hz, 1H, CH_{Ar}), 6.79 (d, *J* = 8.9 Hz, 1H, CH_{Ar}), 6.44 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 6.31 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 4.16 (d, *J* = 6.4 Hz, 2H, OCH_2), 4.14 – 4.11 (m, 5H, 2 x OCH_2, 3 x CH_3), 4.10 (s, 3H, CH_3), 3.70 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 3.58 (brs, 2H, NH_2), 3.32 (s, 3H, $ArCH_3$), 2.43 – 2.31 (m, 2H, $C\underline{H}(CH_3)_2$), 1.22 – 1.19 (m, 12H, $CH(C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 186.9 (1C), 185.8 (1C), 167.9 (1C), 166.8 (1C), 166.7 (1C), 164.1 (1C), 163.8 (1C), 163.4 (1C), 154.8 (1C), 153.0 (1C), 149.6 (1C), 146.3 (1C), 145.3 (1C), 144.8 (1C), 137.7 (1C), 134.6 (1C), 134.2 (1C), 126.7 (1C), 125.5 (1C), 123.3 (2C), 121.8 (1C), 120.5 (1C), 119.6 (1C), 114.8 (2C), 113.7 (1C), 112.1 (1C), 98.1 (1C), 94.1 (1C), 75.1 (2C), 57.0 (1C), 53.3 (1C), 40.1 (1C), 39.7 (1C), 28.5 (1C), 28.5 (1C), 19.4 (2C), 19.3 (2C), 12.7 (1C).



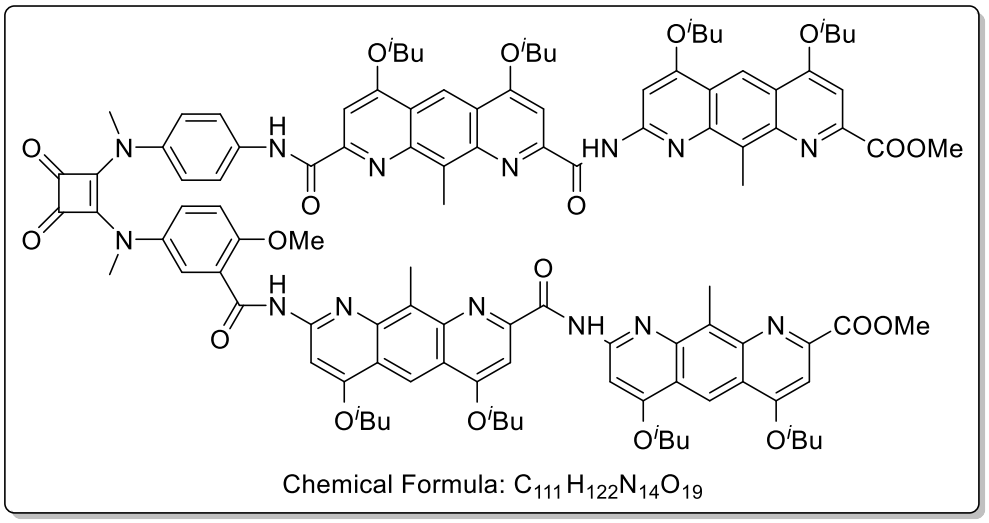
Compound **3**: Dry DIPEA (127 µL, 0.729 mmol, freshly distilled over CaH_2) was added to a solution of compound **9c** (141 mg, 0.182 mmol), compound **8b** (93 mg, 0.20 mmol) and PyBOP (285 mg, 0.547 mmol) in dry chloroform (18 mL, freshly distilled over CaH_2), under inert atmosphere of N_2. After 16 hours stirring at room temperature, volatiles were removed *in vacuo*. Then the residue was dissolved in $CHCl_3$, washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2) using acetone/DCM as eluent (from 8% to 20% acetone), and then precipitated from DCM/MeOH (slow evaporation of DCM), to give 129 mg (59% yield) of compound **3** as a yellow solid. HRMS (ESI+) calcd. for $C_{67}H_{73}N_8O_{13}$ $[M+H]^+$ (m/z): 1197.5292, found: 1197.5267. UV-Vis λ_{max} ($CHCl_3$, 298 K) = 260 nm and 311 nm. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 10.55 (s, 1H, NH), 10.35 (s, 1H, NH), 8.46 (s, 1H, CH_{Ar}), 8.29 (s, 1H, CH_{Ar}), 7.66 – 7.57 (m, 4H, CH_{Ar}), 7.36 (s, 1H, CH_{Ar}), 7.34 (s, 1H, CH_{Ar}), 7.14 (s, 1H, CH_{Ar}), 6.85 (dd, *J* = 8.6, 2.9 Hz, 1H, CH_{Ar}), 6.78 (d, *J* = 8.8 Hz, 1H, CH_{Ar}), 6.68 (d, *J* = 9.0 Hz, 2H, CH_{Ar}), 4.20 (s, 3H, OCH_3), 4.15 (s, 3H, $COO\underline{C}H_3$), 4.10 (s, 3H, $COO\underline{C}H_3$), 4.05 (d, *J* = 6.4 Hz, 2H, OCH_2), 3.95 (d, *J* = 6.5 Hz, 2H, OCH_2), 3.85 (d, *J* = 6.5 Hz, 2H, OCH_2), 3.79 (s, 3H, NCH_3), 3.79 (s, 3H, NCH_3), 3.69 (d, *J* = 6.7 Hz, 2H, OCH_2), 3.30 (s, 3H, $ArCH_3$), 3.06 (s, 3H, $ArCH_3$), 2.36 – 2.24 (m, 2H, $C\underline{H}(CH_3)_2$), 2.22 – 2.13 (m, 1H, $C\underline{H}(CH_3)_2$), 2.11 – 2.01 (m, 1H, $C\underline{H}(CH_3)_2$), 1.20 – 1.13 (2 x d, 12H, $CH(C\underline{H}_3)_2$), 1.08 (d, *J* = 6.5 Hz, 6H, $CH(C\underline{H}_3)_2$), 1.01 (d, *J* = 6.7 Hz, 6H, $CH(C\underline{H}_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 186.6 (1C, $CH_3NC\underline{C}O$), 186.5 (1C, $CH_3NC\underline{C}O$), 167.4 (1C, $CH_3N\underline{C}CO$), 167.2 (1C, $CH_3N\underline{C}CO$), 166.8 (1C, $\underline{C}OOCH_3$), 166.3 (1C, $\underline{C}OOCH_3$), 163.7 (1C, C_{Ar}), 163.3 (1C, C_{Ar}), 162.8 (1C, C_{Ar}), 162.7 (1C, C_{Ar}), 162.5 (1C, CO), 162.1 (1C, CO), 155.3 (1C, C_{Ar}), 152.3 (1C, C_{Ar}), 150.7 (1C, C_{Ar}), 149.4 (1C, C_{Ar}), 148.9 (1C, C_{Ar}), 145.5 (1C, C_{Ar}), 145.3 (1C, C_{Ar}), 144.3 (1C, C_{Ar}), 143.9 (1C, C_{Ar}), 139.1 (1C, C_{Ar}), 137.6 (1C, C_{Ar}), 136.9 (1C, C_{Ar}), 135.9 (1C, C_{Ar}), 134.2 (1C, C_{Ar}), 127.5 (1C, CH_{Ar}), 127.1 (1C, CH_{Ar}), 122.9 (2C, CH_{Ar}), 121.8 (1C, C_{Ar}), 120.8 (1C, C_{Ar}), 120.7 (1C, C_{Ar}), 119.3 (3C, 2 x CH_{Ar} + 1 x C_{Ar}), 118.7 (1C, C_{Ar}), 113.2 (1C, CH_{Ar}), 112.6 (1C, CH_{Ar}), 112.3 (1C, CH_{Ar}), 98.2 (1C, CH_{Ar}), 97.6 (1C, CH_{Ar}), 95.6 (1C, CH_{Ar}), 93.5 (1C, CH_{Ar}), 75.0 (1C, OCH_2), 75.0 (1C, OCH_2), 75.0 (1C, OCH_2), 74.5 (1C, OCH_2), 57.1 (1C, OCH_3), 53.2 (1C, $COO\underline{C}H_3$), 53.1 (1C, $COO\underline{C}H_3$), 40.0 (1C, NCH_3), 39.7 (1C, NCH_3), 28.5 (1C, $\underline{C}H(CH_3)_2$), 28.5 (1C, $\underline{C}H(CH_3)_2$), 28.4 (1C, $\underline{C}H(CH_3)_2$), 28.3 (1C, $\underline{C}H(CH_3)_2$), 19.3 (4C, $CH(\underline{C}H_3)_2$), 19.2 (2C, $CH(\underline{C}H_3)_2$), 19.1 (2C, $CH(\underline{C}H_3)_2$), 12.9 (1C, $ArCH_3$), 12.4 (1C, $ArCH_3$).

3.6. Synthesis of compound **4**



Compound **4**: Dry DIPEA (133 µL, 0.762 mmol, freshly distilled over CaH_2) was added to a solution of compound **9c** (155 mg, 0.200 mmol), compound **8c** (41 mg, 95 µmol) and PyBOP (297 mg, 0.571 mmol) in dry chloroform (8 mL, freshly distilled over CaH_2), under inert atmosphere of N_2. After 42 hours stirring at room temperature, volatiles were removed *in vacuo*. Then the residue was dissolved in $CHCl_3$, washed with 5% aqueous citric acid, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by GPC and then precipitated from DCM/MeOH (slow evaporation of DCM), to give 98 mg (53% yield) of compound **4** as a yellow solid. HRMS (ESI+) calcd. for $C_{109}H_{115}N_{14}O_{20}$ $[M+H]^+$ (m/z): 1939.8407, found: 1939.8491. UV-Vis λ_{max} ($CHCl_3$, 298 K) = 262 nm and 319 nm. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 10.54 (s, 2H, NH), 9.96 (s, 2H, NH), 8.16 (s, 1H, CH_{Ar}), 8.04 (s, 2H, CH_{Ar}), 7.57 (brs, 4H, CH_{Ar}), 7.53 (d, *J* = 2.7 Hz, 2H, CH_{Ar}), 7.45 (s, 2H, CH_{Ar}), 7.20 (s, 2H, CH_{Ar}), 7.19 (s, 2H, CH_{Ar}), 6.86 (dd, *J* = 8.6, 2.8 Hz, 2H, CH_{Ar}), 6.82 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 6.69 (d, *J* = 8.9 Hz, 4H, CH_{Ar}), 4.19 (s, 6H, OCH_3), 3.93 (d, *J* = 6.4 Hz, 4H, OCH_2), 3.88 – 3.81 [m, 16H, (6H, $COOCH_3$ + 4H, OCH_2 + 6H, NCH_3)], 3.78 (s, 6H, NCH_3), 3.41 (d, *J* = 6.7 Hz, 4H, OCH_2), 3.04 (s, 6H, $ArCH_3$), 2.73 (s, 3H, $ArCH_3$), 2.28 – 2.13 (m, 4H, C<u>H</u>$(CH_3)_2$), 1.89 – 1.78 (m, 2H, C<u>H</u>$(CH_3)_2$), 1.13 (d, *J* = 6.7 Hz, 12H, CH(C<u>H</u>$_3)_2$), 1.08 (d, *J* = 6.7 Hz, 12H, CH(C<u>H</u>$_3)_2$), 0.85 (d, *J* = 6.7 Hz, 12H, CH(C<u>H</u>$_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 186.7 (2C, $CH_3NC\underline{C}O$), 186.5 (2C, $CH_3NC\underline{C}O$), 167.8 (2C, $CH_3N\underline{C}CO$), 167.3 (2C, $CH_3N\underline{C}CO$), 166.3 (2C, $\underline{C}OOCH_3$), 163.1 (2C), 163.0 (2C), 162.7 (2C), 162.4 (2C), 161.8 (2C), 155.3 (2C, C_{Ar}), 152.4 (2C, C_{Ar}), 150.5 (2C, C_{Ar}), 148.9 (2C, C_{Ar}), 145.5 (2C, C_{Ar}), 144.3 (2C, C_{Ar}), 143.3 (2C, C_{Ar}), 138.9 (2C, C_{Ar}), 137.4 (2C, C_{Ar}), 135.9 (2C, C_{Ar}), 134.8 (1C, C_{Ar}), 133.5 (2C, C_{Ar}), 127.6 (2C, CH_{Ar}), 126.8 (2C, CH_{Ar}), 122.6 (4C, CH_{Ar}), 121.7 (2C, C_{Ar}), 120.0 (2C, C_{Ar}), 119.3 (2C, C_{Ar}), 119.2 (4C, CH_{Ar}), 118.5 (2C, C_{Ar}), 113.1 (1C, CH_{Ar}), 112.5 (2C, CH_{Ar}), 112.2 (2C, CH_{Ar}), 97.7 (2C, CH_{Ar}), 95.1 (2C, CH_{Ar}), 93.4 (2C, CH_{Ar}), 74.9 (2C, OCH_2), 74.8 (2C, OCH_2), 74.3 (2C, OCH_2), 57.2 (2C, OCH_3), 53.0 (2C, $COO\underline{C}H_3$), 39.9 (2C, NCH_3), 39.7 (2C, NCH_3), 28.4 (2C, $\underline{C}H(CH_3)_2$), 28.4 (2C, $\underline{C}H(CH_3)_2$), 28.2 (2C, $\underline{C}H(CH_3)_2$), 19.2 (4C, CH($\underline{C}H_3)_2$), 19.2 (4C, CH($\underline{C}H_3)_2$), 19.0 (4C, CH($\underline{C}H_3)_2$), 12.5 (2C, $ArCH_3$), 12.3 (1C, $ArCH_3$).

3.7. Synthesis of compound **5**



Compound **5**: $(CH_3)_3SnOH$ (70 mg, 0.39 mmol) was added to a solution of compound **3** (57 mg, 49 µmol) in 1,2-dichloroethane. After refluxing for 3 days, the mixture was diluted with DCM/AcOEt (1:1, vol:vol), washed with 0.1 M HCl and saturated aqueous NaCl, and concentrated under reduced pressure. The residue was then washed twice with CH_3CN/H_2O (1:2, vol:vol) and lyophilized, to obtain 52 mg of intermediate **3b** as a yellow/orange solid. HRMS (ESI+) calcd. for $C_{65}H_{69}N_8O_{13}$ $[M+H]^+$ (m/z): 1169.4979, found: 1169.4980. In the same flask, intermediate **3b** (48 mg, 41 µmol)) was mixed with compound **8a** (51 mg, 0.124 mmol) and PyBOP (129 mg, 0.248 mmol), followed by 9 mL of dry $CHCl_3$/DMF (1:2, vol:vol, $CHCl_3$ freshly distilled over CaH_2) and dry DIPEA (58 µL, 0.33 mmol, freshly distilled over CaH_2) under inert atmosphere of N_2. After 27 hours stirring at 45 °C, volatiles were removed *in vacuo*. Then the residue was dissolved in $CHCl_3$, washed with 0.1 M HCl, saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried over $MgSO_4$ and concentrated under reduced pressure. The crude product precipitated from DCM/MeOH (slow evaporation of DCM) and then purified by GPC, to give 30 mg (34% yield over the two steps) of compound **5** as a yellow solid. HRMS (ESI+) calcd. for $C_{111}H_{123}N_{14}O_{19}$ $[M+H]^+$ (m/z): 1955.9083, found: 1955.9191. UV-Vis λ_{max} ($CHCl_3$, 298 K) = 263 nm and 313 nm. ^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 10.70 (s, 1H, NH), 10.67 (s, 1H, NH), 10.36 (s, 1H, NH), 10.13 (s, 1H, NH), 8.80 (s, 1H, CH_{Ar}), 8.73 (s, 1H, CH_{Ar}), 8.12 (s, 1H, CH_{Ar}), 7.96 (s, 1H, CH_{Ar}), 7.88 (s, 1H, CH_{Ar}), 7.75 (s, 1H, CH_{Ar}), 7.57 (s, 1H, CH_{Ar}), 7.45 (d, *J* = 2.6 Hz, 1H, CH_{Ar}), 7.41 – 7.38 (m, 3H, CH_{Ar}), 7.30 (s, 1H, CH_{Ar}), 6.87 (d, *J* = 8.6 Hz, 1H, CH_{Ar}), 6.81 (dd, *J* = 8.5, 2.7 Hz, 1H, CH_{Ar}), 6.69 (s, 1H, CH_{Ar}), 4.29 (s, 3H, OCH_3), 4.16 (s, 3H, $COOCH_3$), 4.00 (s, 3H, $COOCH_3$), 4.26 – 3.28 (brm, 16H, OCH_2), 3.78 (s, 3H, NCH_3), 3.70 (s, 3H, NCH_3), 3.56 (s, 3H, $ArCH_3$), 3.44 (s, 3H, $ArCH_3$), 2.98 (s, 3H, $ArCH_3$), 2.81 (s, 3H, $ArCH_3$), 2.47 – 2.19 (m, 5H, $CH(CH_3)_2$), 2.16 – 2.07 (m, 2H, $CH(CH_3)_2$), 2.05 – 1.98 (m, 1H, $CH(CH_3)_2$), 1.32 – 1.14 (7 x d, 42H, $CH(CH_3)_2$), 1.07 (d, *J* = 6.6 Hz, 6H, $CH(CH_3)_2$). ^{13}C NMR (126 MHz, $CDCl_3$, 298 K) δ 186.6 (2C, CH_3NCCO), 168.0 (1C, CH_3NCCO), 167.5 (1C, CH_3NCCO), 166.5 (1C, $COOCH_3$), 166.3 (1C, $COOCH_3$), 163.6 (1C), 163.4 (1C), 163.2 (1C), 163.1 (1C), 163.1 (1C), 163.0 (1C), 162.9 (1C), 162.5 (1C), 162.3 (2C), 162.2 (1C), 162.1 (1C), 155.3 (1C, C_{Ar}), 152.5 (1C, C_{Ar}), 151.2 (1C, C_{Ar}), 150.9 (1C,

C_{Ar}), 150.9 (1C, C_{Ar}), 150.0 (1C, C_{Ar}), 149.6 (1C, C_{Ar}), 148.6 (1C, C_{Ar}), 148.6 (1C, C_{Ar}), 145.7 (1C, C_{Ar}), 145.6 (1C, C_{Ar}), 145.1 (1C, C_{Ar}), 144.5 (1C, C_{Ar}), 144.5 (1C, C_{Ar}), 144.3 (1C, C_{Ar}), 144.0 (1C, C_{Ar}), 143.8 (1C, C_{Ar}), 138.2 (1C, C_{Ar}), 136.9 (1C, C_{Ar}), 136.2 (1C, C_{Ar}), 135.6 (1C, C_{Ar}), 134.6 (1C, C_{Ar}), 134.3 (1C, C_{Ar}), 133.1 (1C, C_{Ar}), 127.5 (1C, CH_{Ar}), 126.7 (1C, CH_{Ar}), 121.9 (1C, C_{Ar}), 120.6 (1C, C_{Ar}), 120.5 (1C, C_{Ar}), 119.8 (1C, C_{Ar}), 119.5 (1C, C_{Ar}), 119.2 (1C, C_{Ar}), 118.8 (1C, C_{Ar}), 118.4 (1C, C_{Ar}), 118.3 (1C, C_{Ar}), 113.1 (1C, CH_{Ar}), 112.5 (1C, CH_{Ar}), 112.4 (1C, CH_{Ar}), 112.3 (1C, CH_{Ar}), 111.6 (1C, CH_{Ar}), 97.7 (1C, CH_{Ar}), 96.6 (1C, CH_{Ar}), 95.9 (1C, CH_{Ar}), 95.4 (1C, CH_{Ar}), 94.9 (1C, CH_{Ar}), 92.7 (1C, CH_{Ar}), 92.6 (1C, CH_{Ar}), 92.5 (1C, CH_{Ar}), 75.2 (1C, OCH_2), 75.1 (1C, OCH_2), 75.0 (2C, OCH_2), 74.9 (1C, OCH_2), 74.5 (1C, OCH_2), 74.2 (2C, OCH_2), 57.3 (1C, OCH_3), 53.1 (1C, $COO\underline{C}H_3$), 53.0 (1C, $COO\underline{C}H_3$), 39.7 (1C, NCH_3), 39.2 (1C, NCH_3), 28.7 (1C, $\underline{C}H(CH_3)_2$), 28.6 (3C, $\underline{C}H(CH_3)_2$), 28.5 (3C, $\underline{C}H(CH_3)_2$), 28.3 (1C, $\underline{C}H(CH_3)_2$), 19.5 (2C, $CH(\underline{C}H_3)_2$), 19.4 (8C, $CH(\underline{C}H_3)_2$), 19.3 (4C, $CH(\underline{C}H_3)_2$), 19.2 (2C, $CH(\underline{C}H_3)_2$), 12.9 (1C, $ArCH_3$), 12.5 (1C, $ArCH_3$), 12.4 (1C, $ArCH_3$), 12.0 (1C, $ArCH_3$). Note: Due to internal dynamics at 298 K, the four CH_{Ar} of the *para*-phenylenediamine ring show very broad NMR signals that are difficult to distinguish from the baseline. For that reason, in the ^{1}H and ^{13}C spectra described above, the signals of this aromatic system are not mentioned. See VT-NMR experiments for compound **5** in section 5.3.

4. NMR SPECTRA

4.1. Intermediates (compounds **1b**, **6**,**7** and **9a-c**)

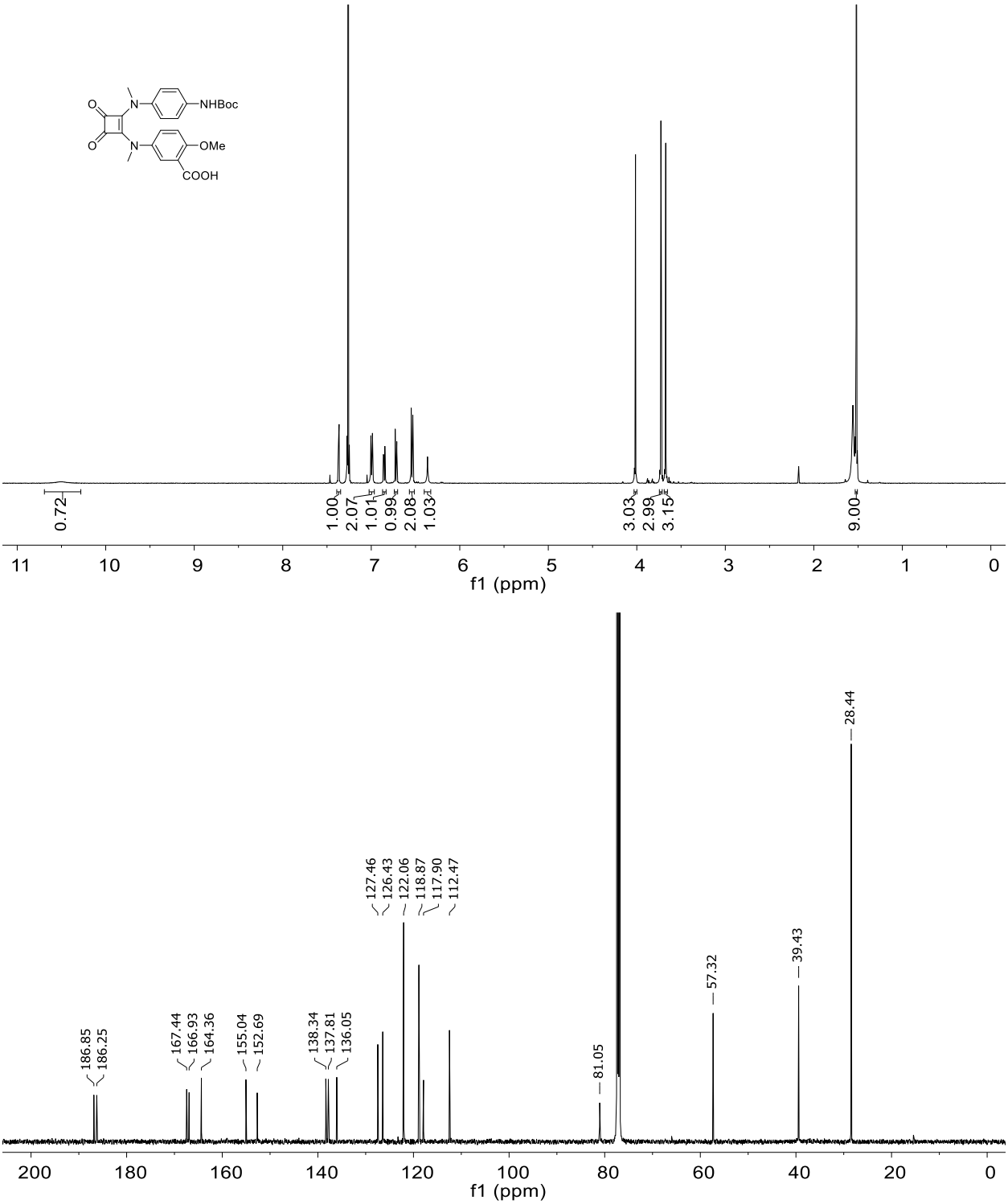


Figure S1. ^{1}H (500 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **1b**.

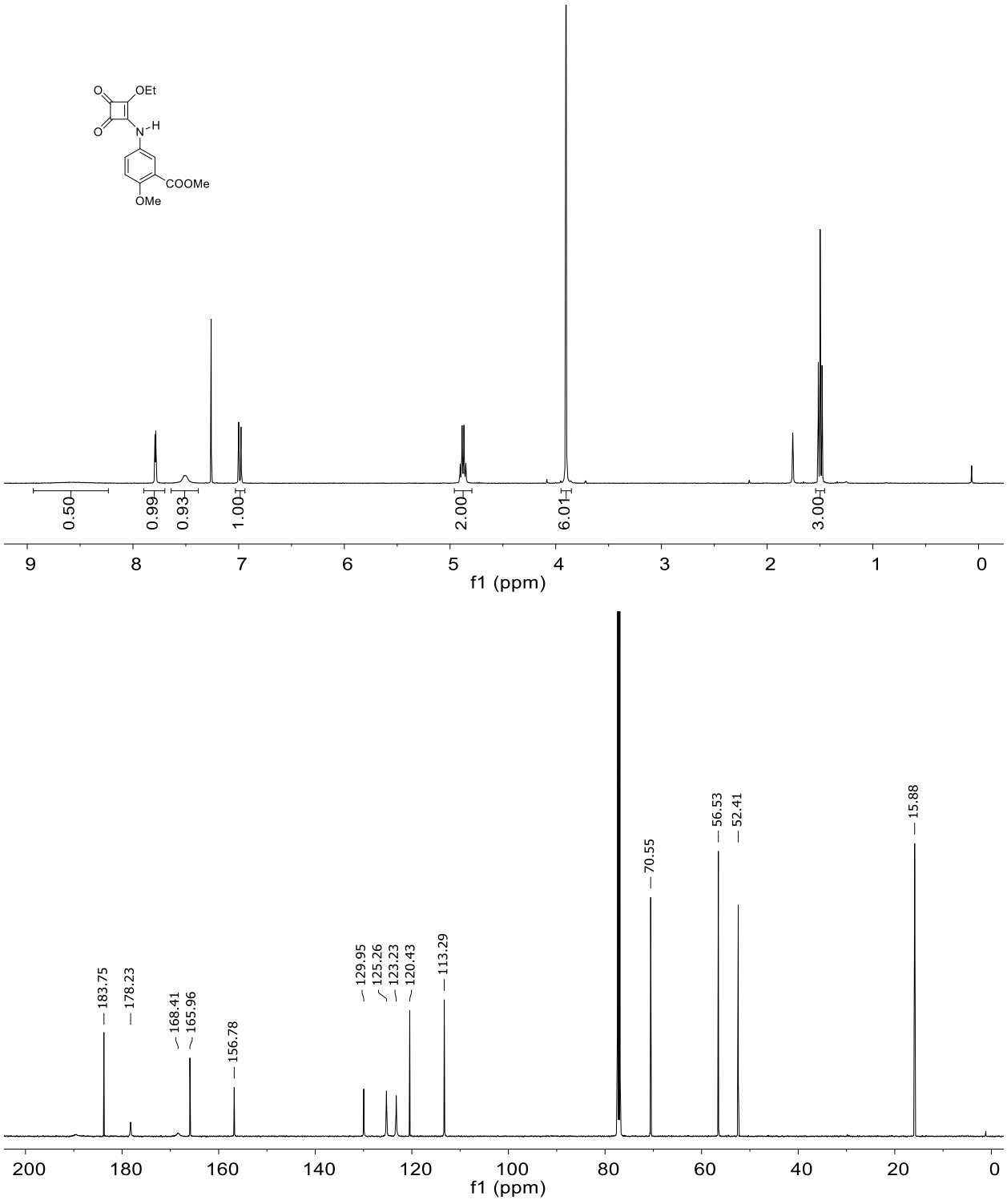


Figure S2. ^{1}H (400 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **6**.

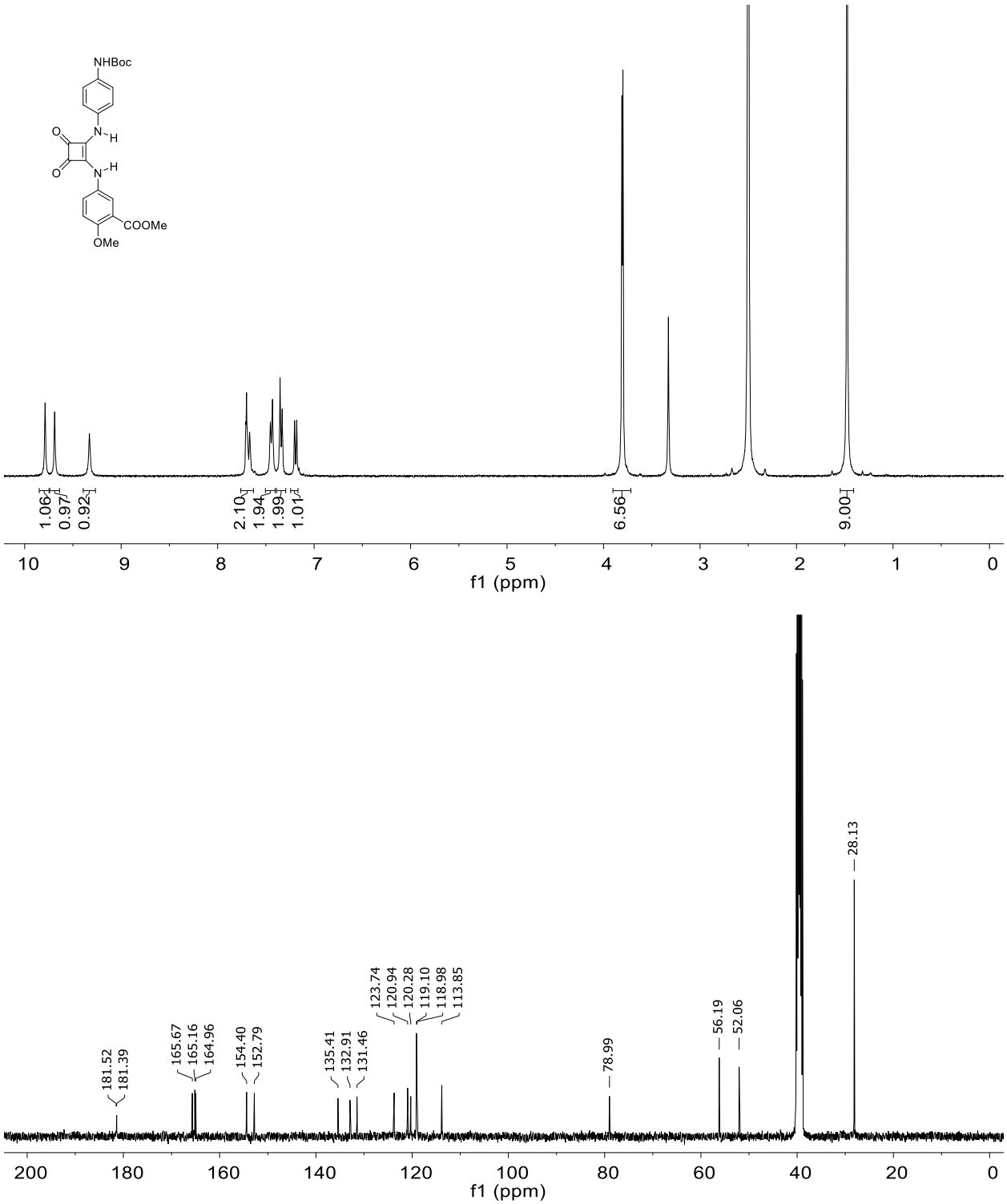


Figure S3. ^{1}H (400 MHz, DMSO-d_6, 298 K) and ^{13}C (101 MHz, DMSO-d_6, 298 K) NMR spectra of compound **7**.

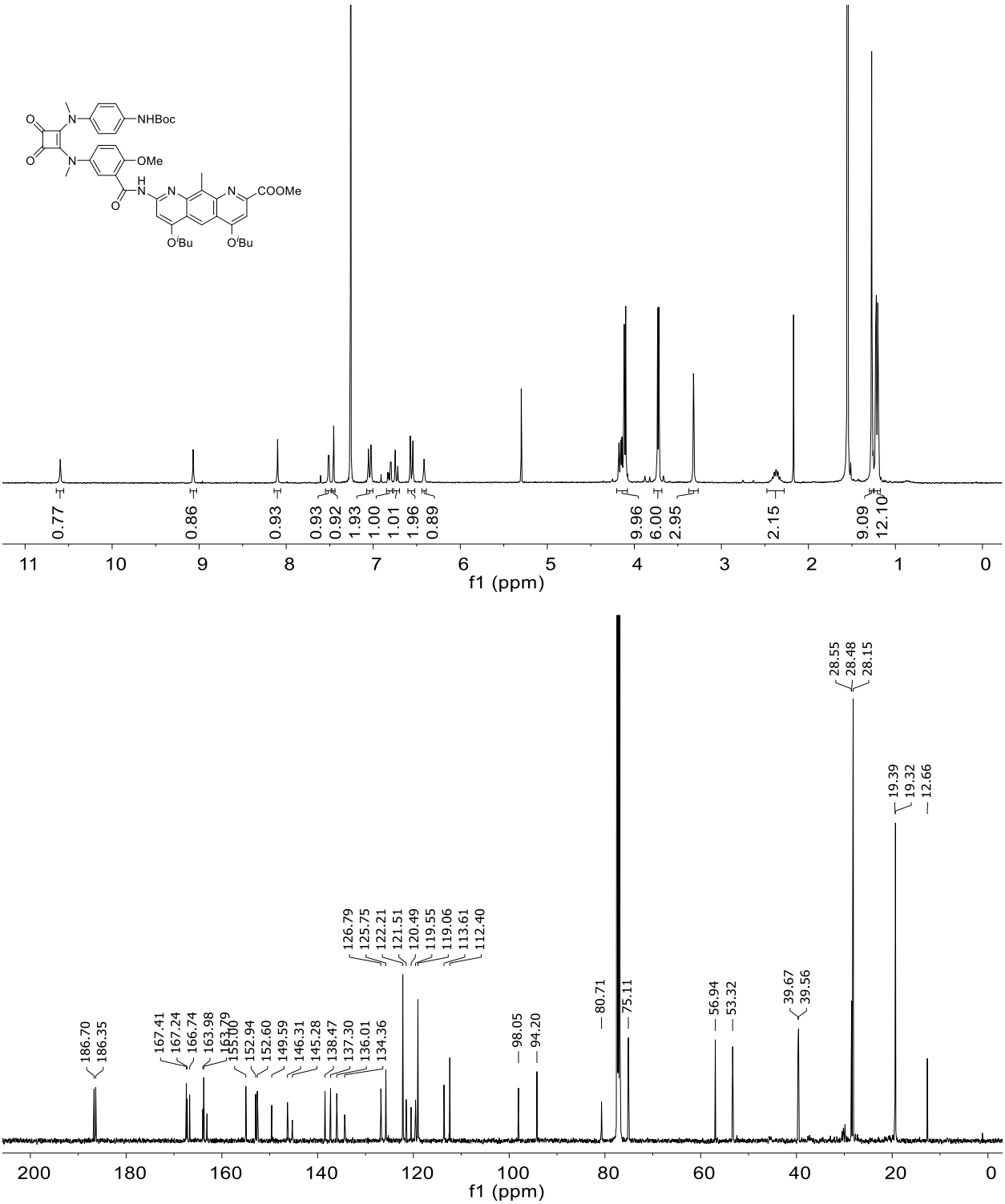


Figure S4. ^{1}H (500 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **9a**.

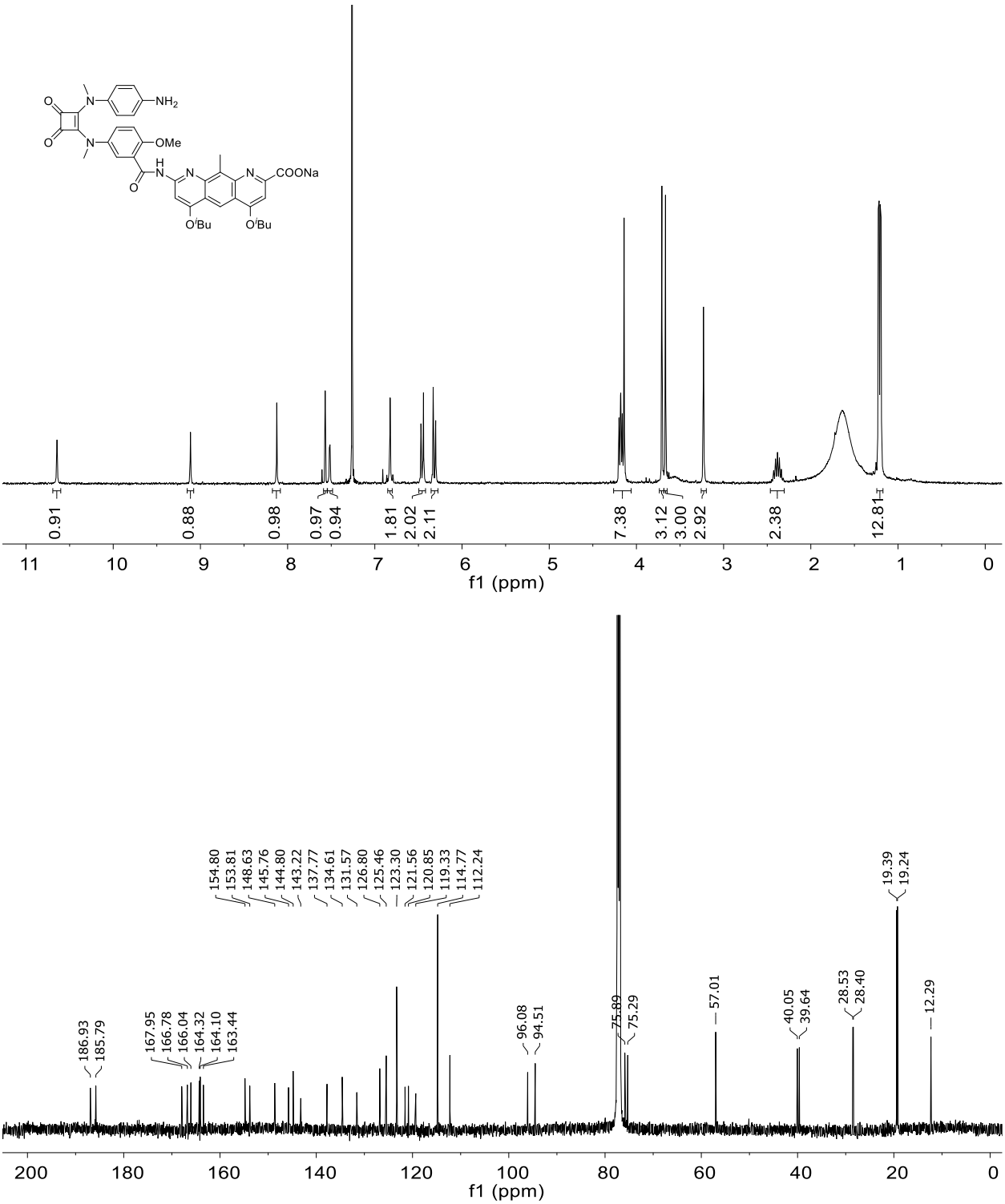


Figure S5. ^{1}H (300 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **9b**.

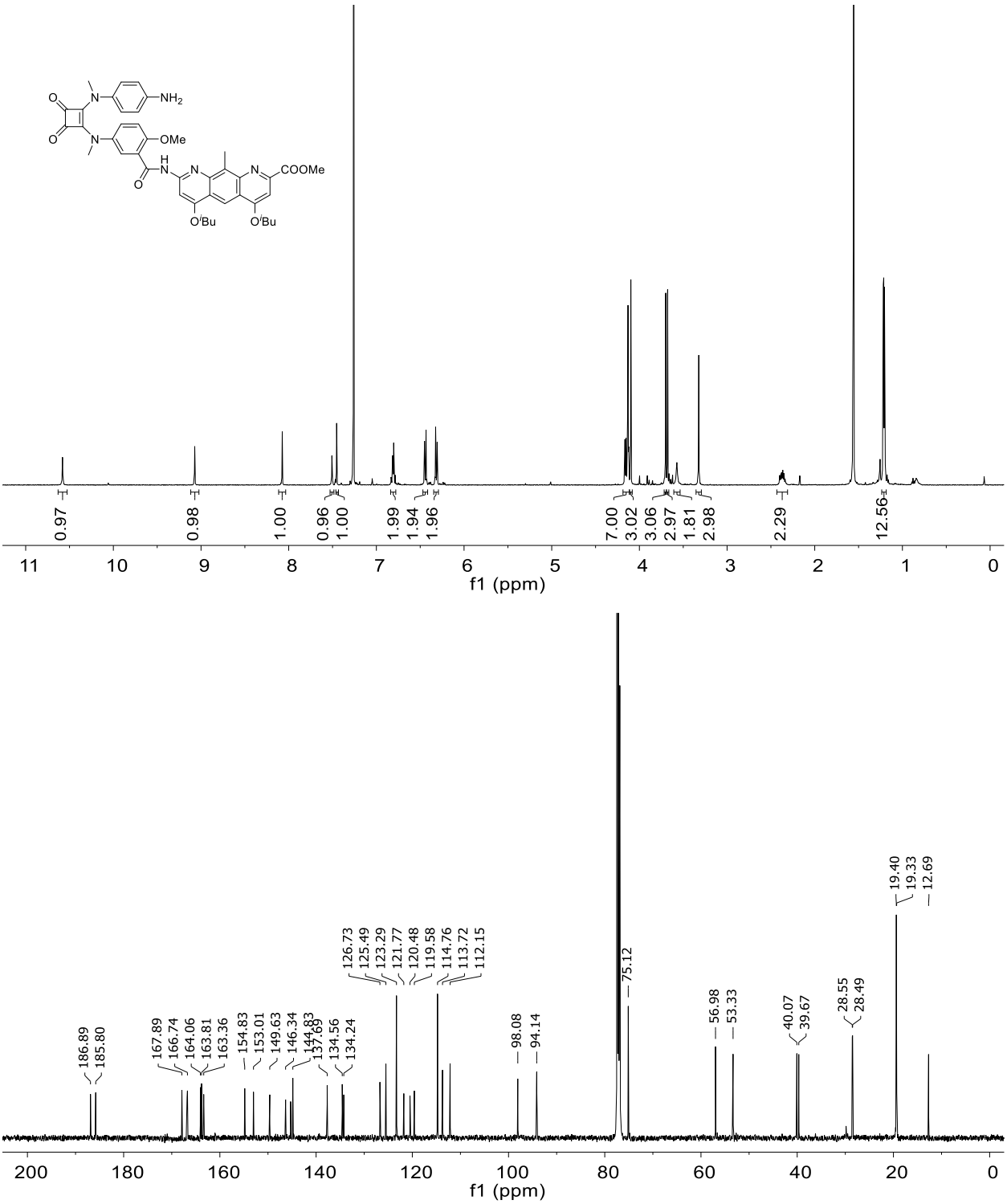


Figure S6. ^{1}H (500 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **9c**.

4.2. Final products (compounds **1-5**)

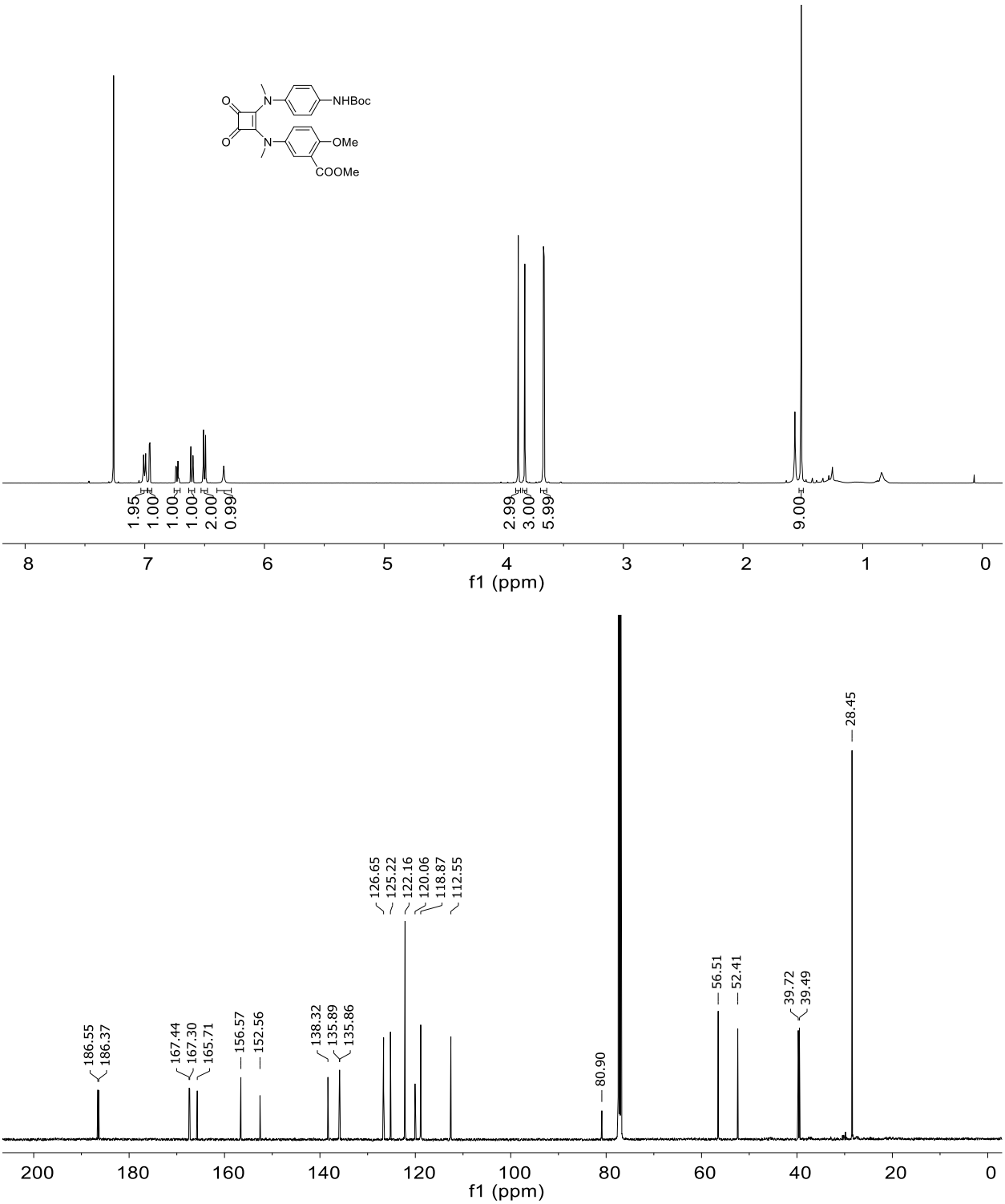


Figure S7. ^{1}H (500 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **1**.

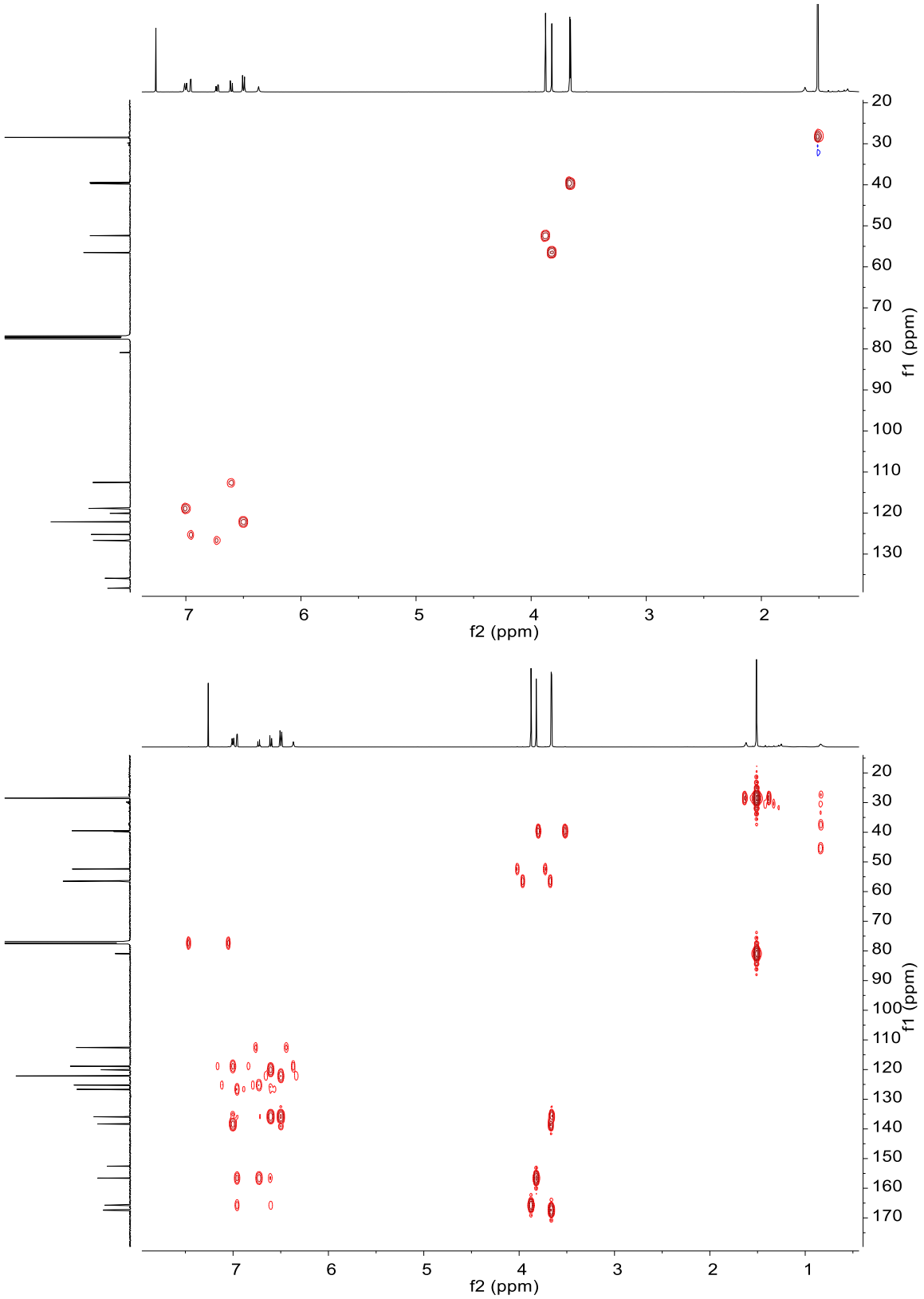


Figure S8. ^{1}H-^{13}C gHSQC (500 MHz, $CDCl_3$, 298 K) and ^{1}H-^{13}C gHMBC (500 MHz, $CDCl_3$, 298 K) NMR spectra of compound **1**.

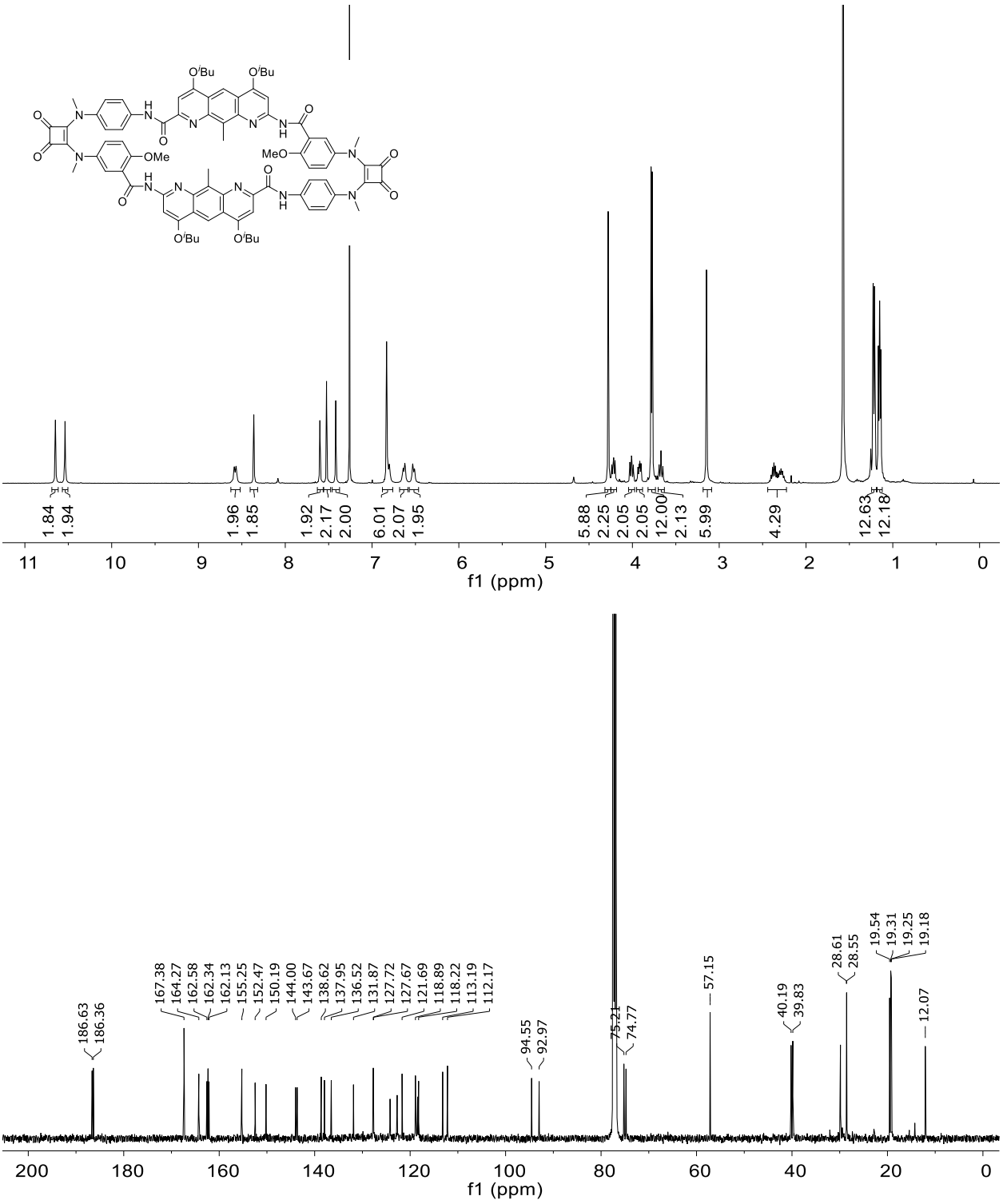


Figure S9. ^{1}H (400 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **2**.

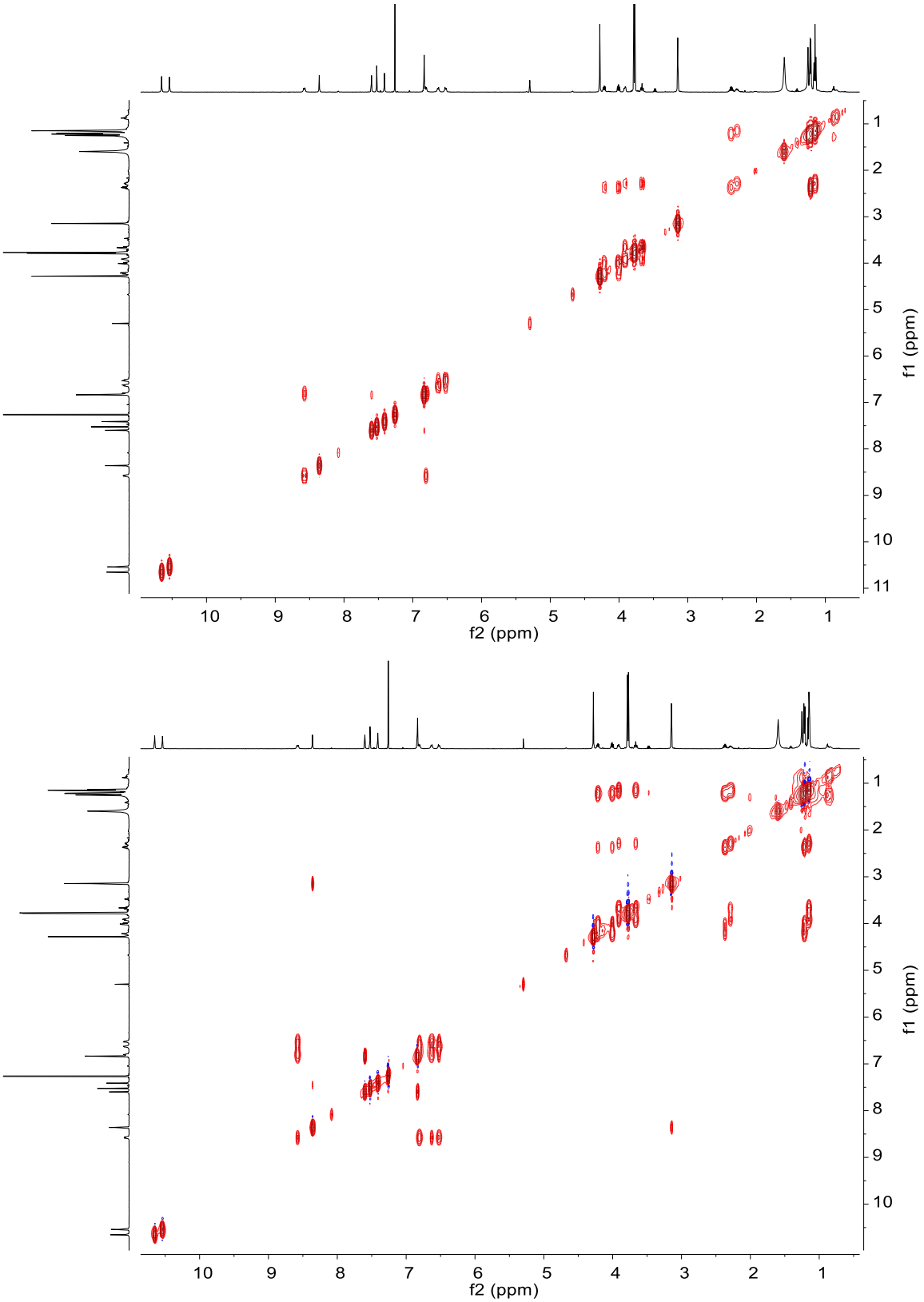


Figure S10. ^{1}H-^{1}H gCOSY (500 MHz, $CDCl_3$, 298 K) and ^{1}H-^{1}H gTOCSY (500 MHz, $CDCl_3$, 298 K) NMR spectra of compound **2**.

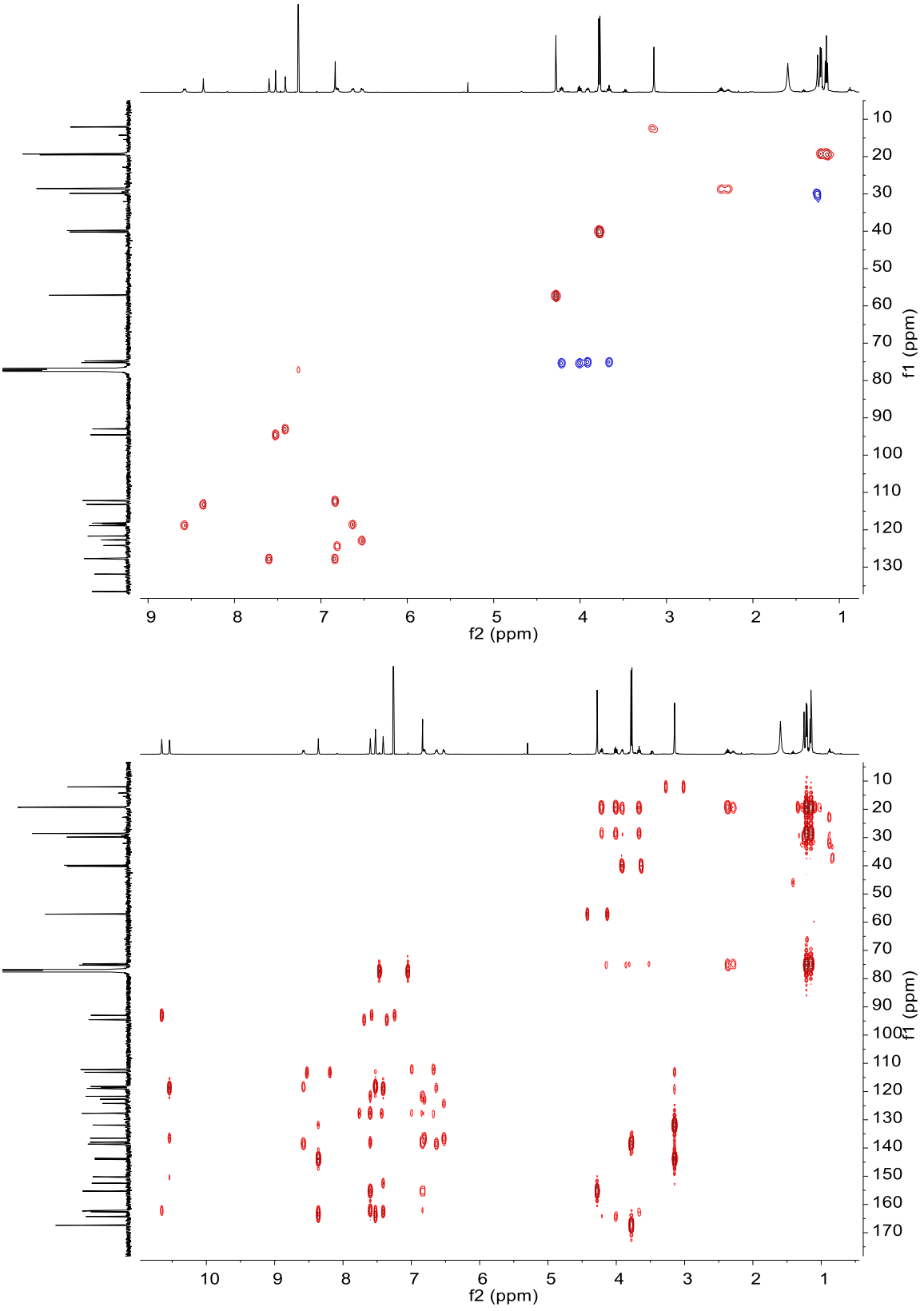


Figure S11. ^{1}H-^{13}C gHSQC (500 MHz, $CDCl_3$, 298 K) and ^{1}H-^{13}C gHMBC (500 MHz, $CDCl_3$, 298 K) NMR spectra of compound **2**.

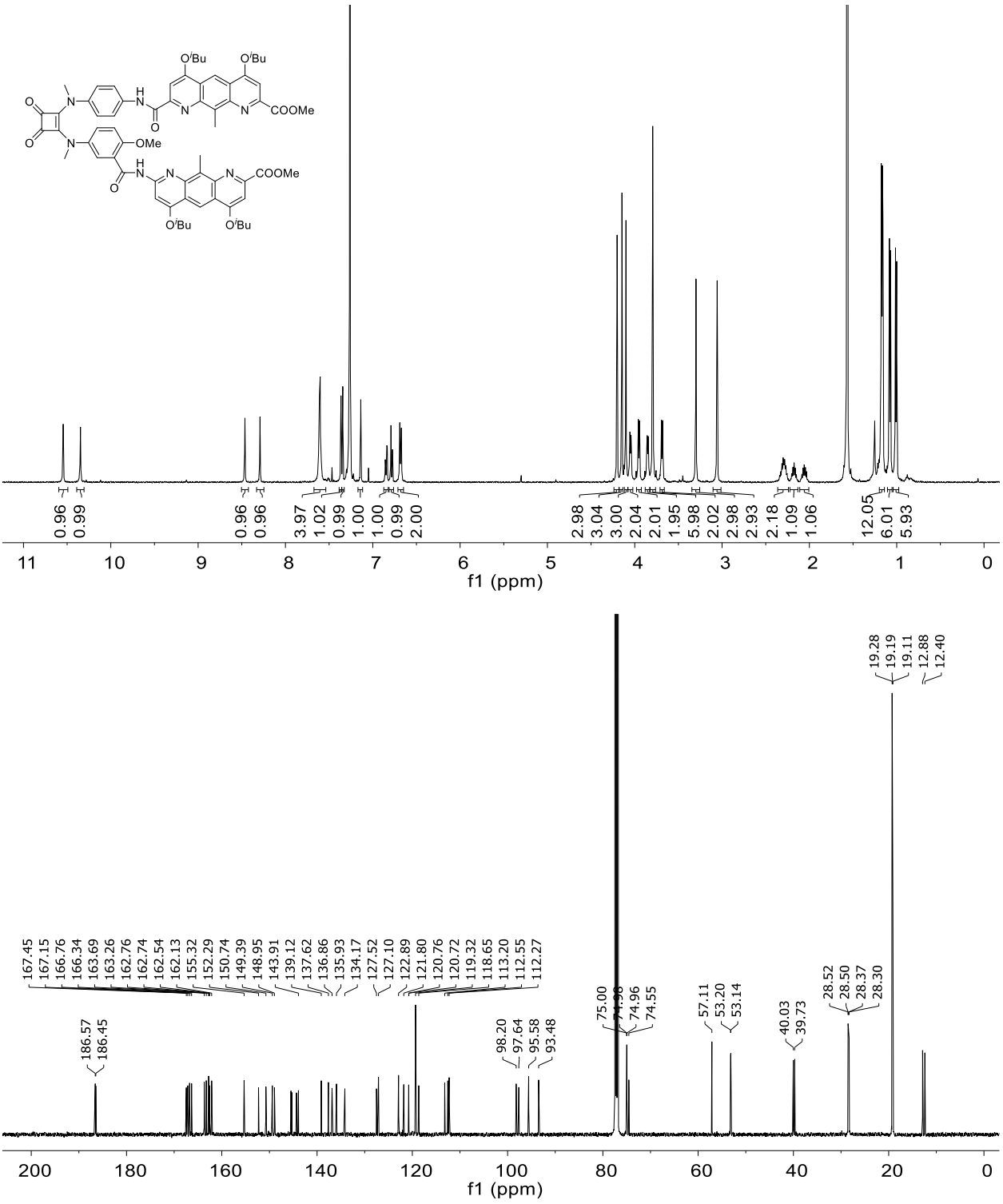


Figure S12. ^{1}H (500 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **3**.

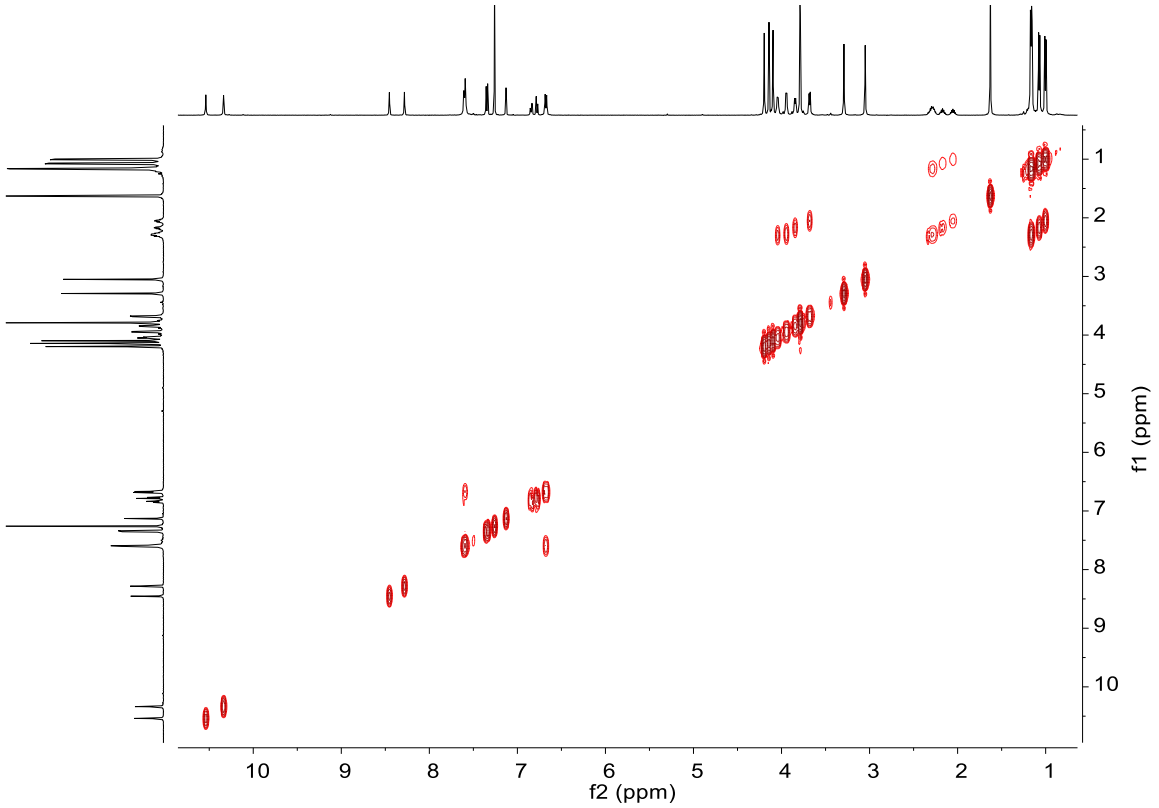


Figure S13. ^{1}H-^{1}H gCOSY (500 MHz, $CDCl_3$, 298 K) NMR spectrum of compound **3**.

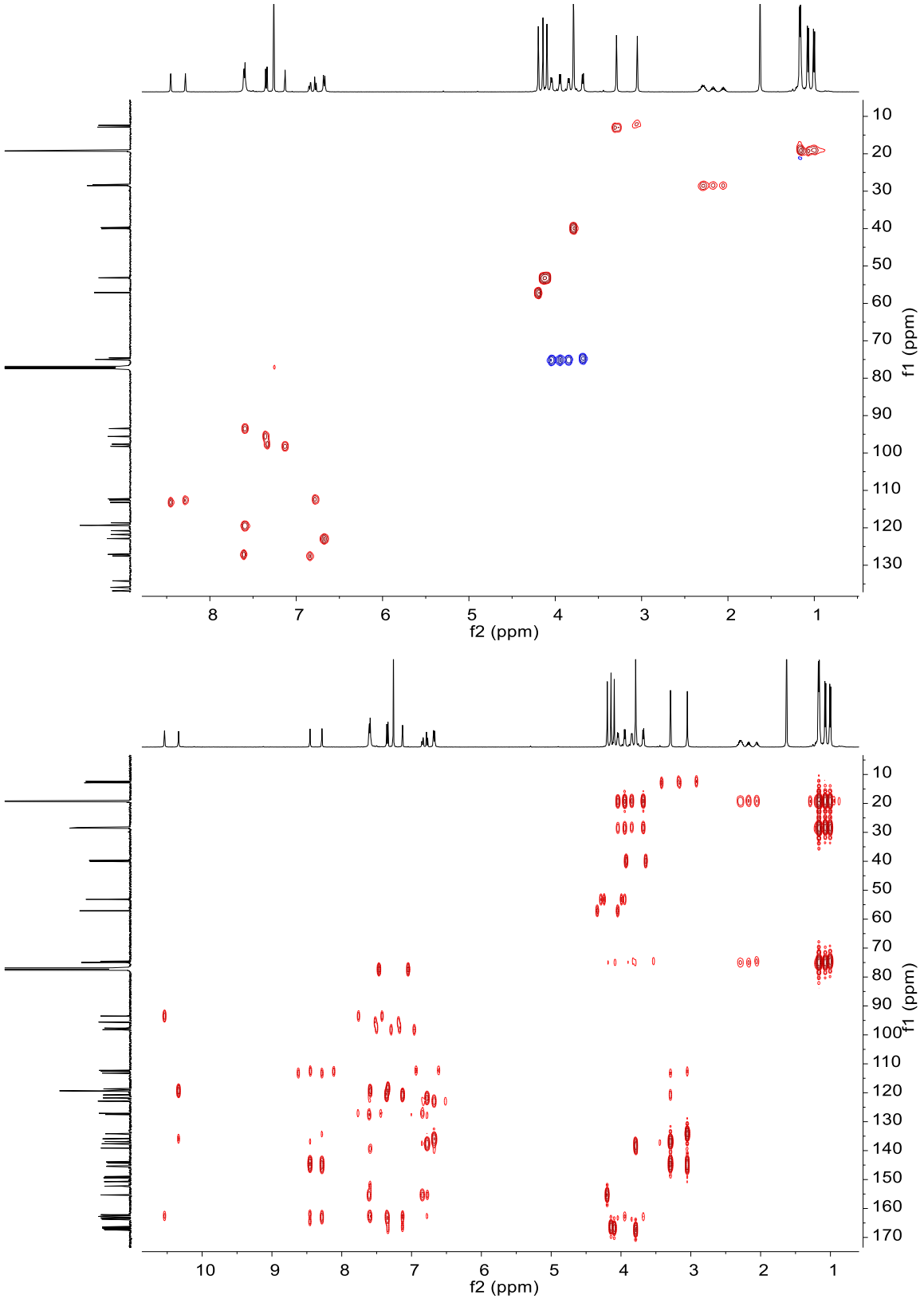


Figure S14. ^{1}H-^{13}C gHSQC (500 MHz, $CDCl_3$, 298 K) and ^{1}H-^{13}C gHMBC (500 MHz, $CDCl_3$, 298 K) NMR spectra of compound **3**.

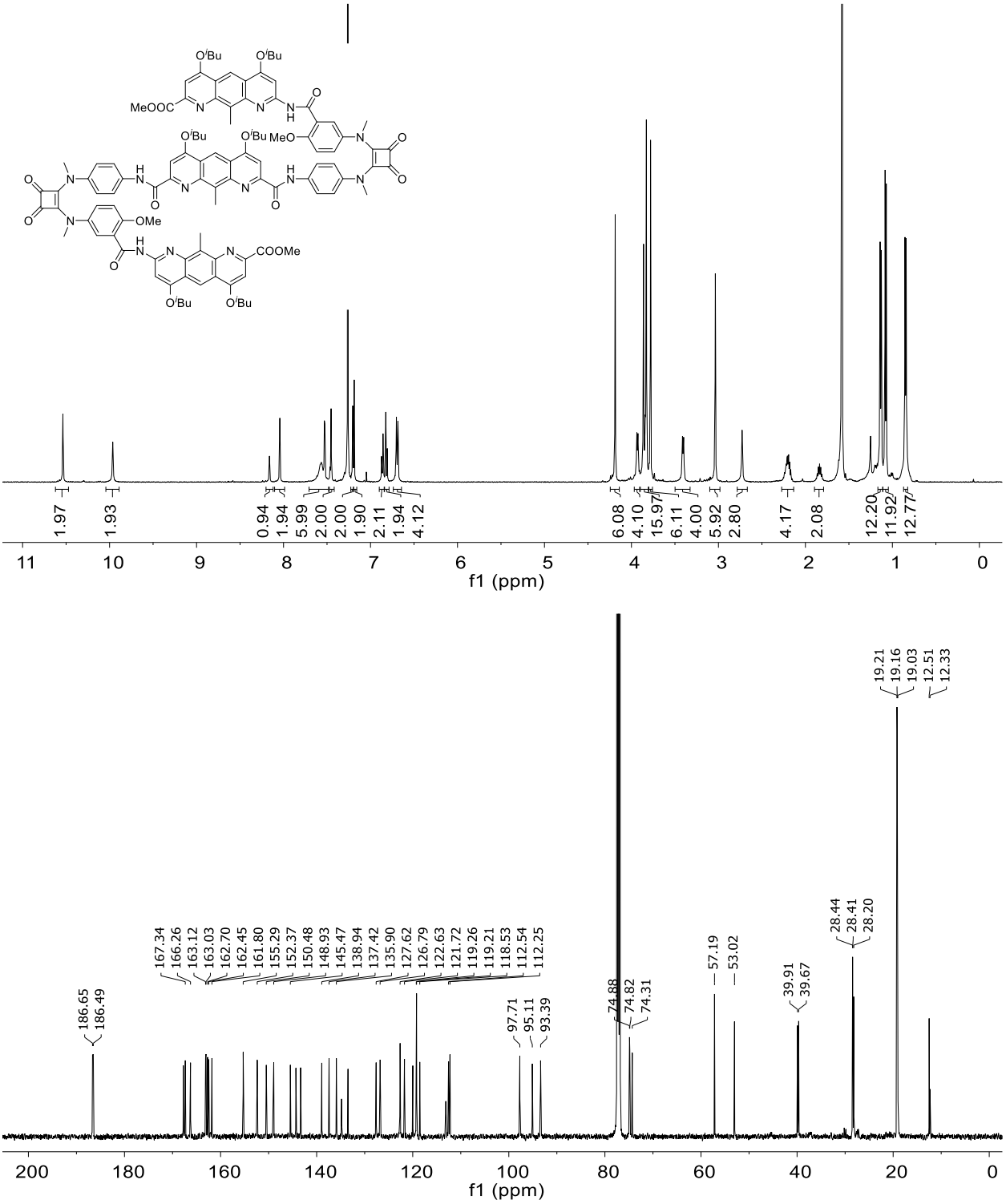


Figure S15. ^{1}H (500 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **4**.

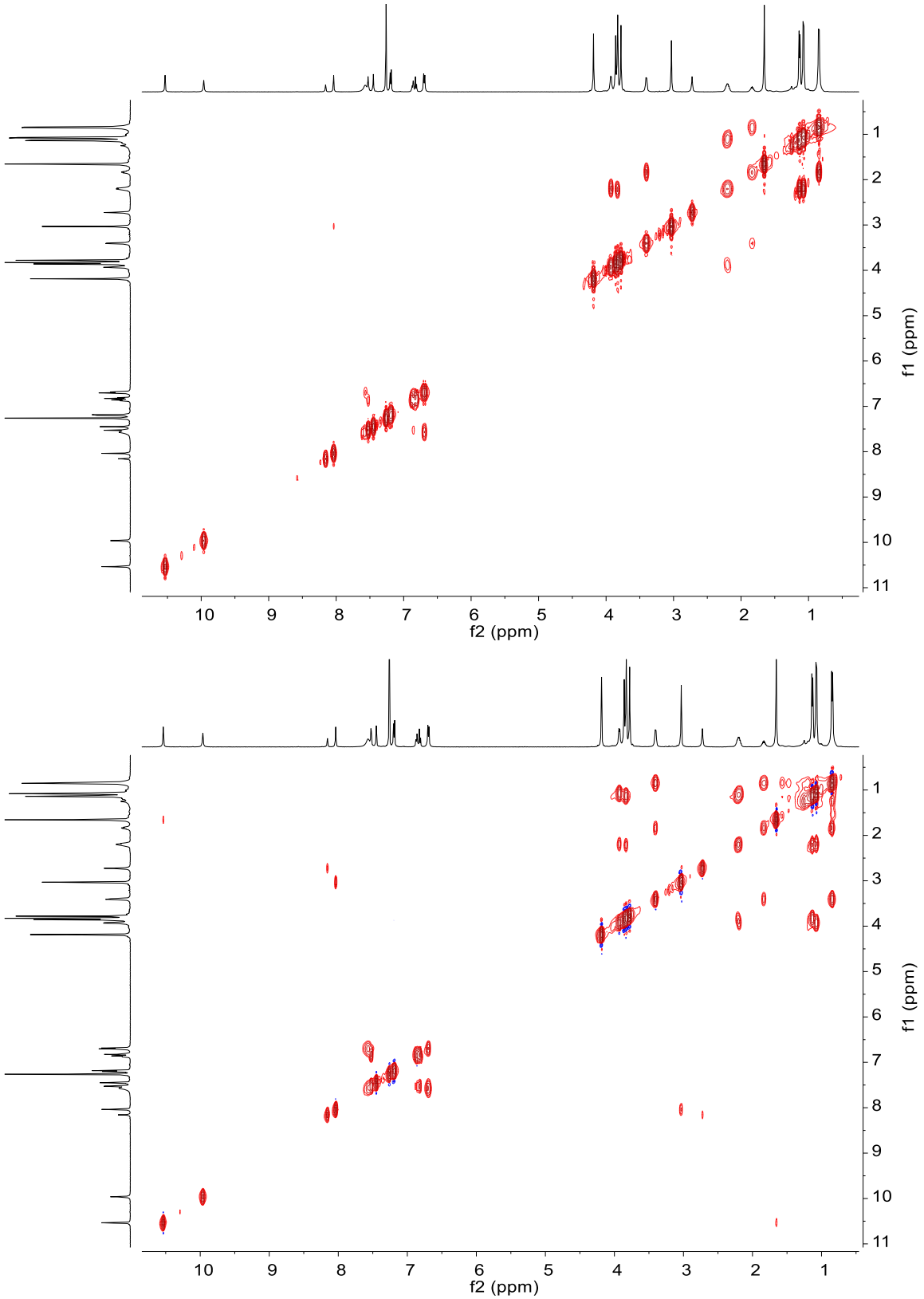


Figure S16. ^{1}H-^{1}H gCOSY (500 MHz, $CDCl_3$, 298 K) and ^{1}H-^{1}H gTOCSY (500 MHz, $CDCl_3$, 298 K) NMR spectra of compound **4**.

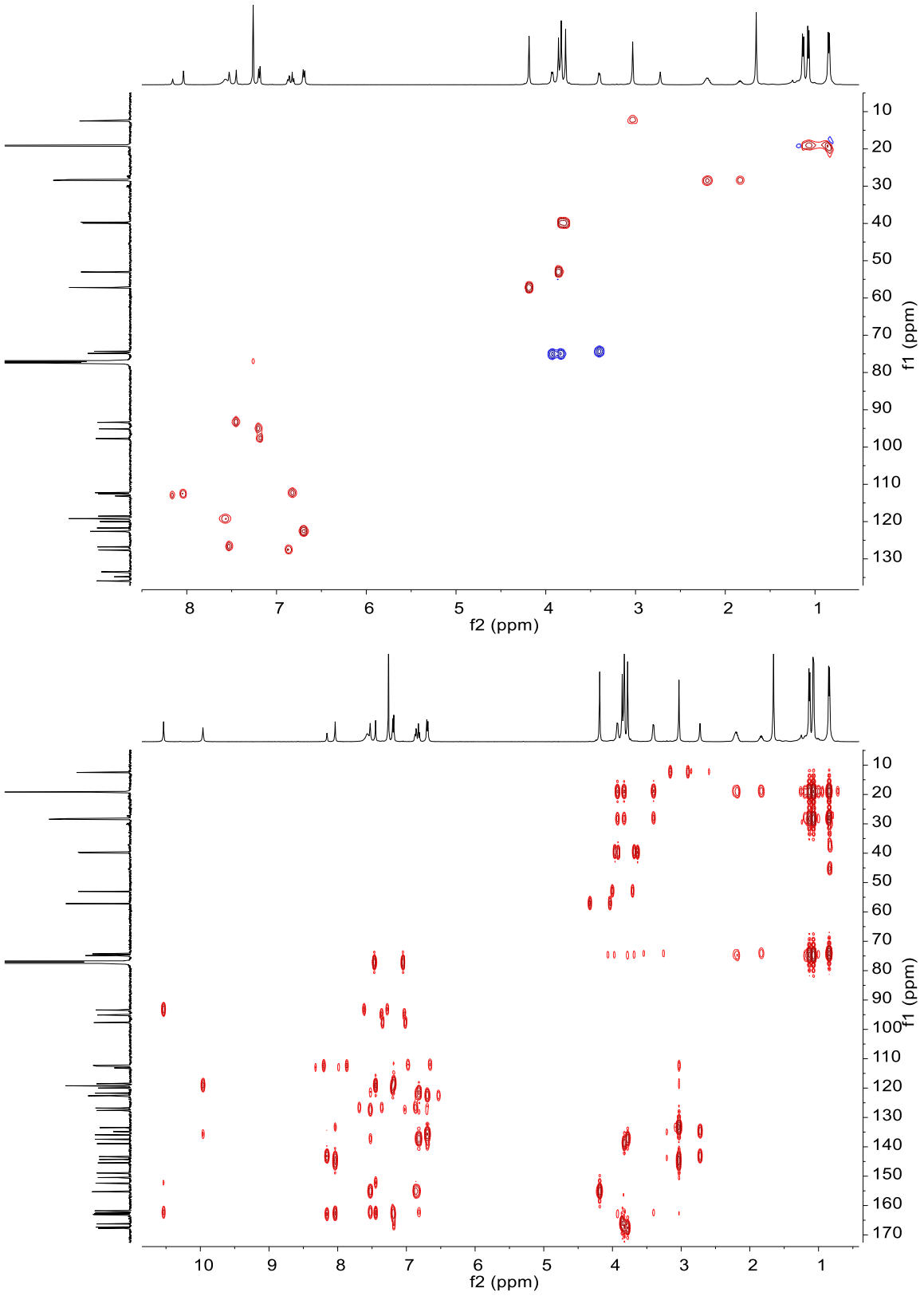


Figure S17. ^{1}H-^{13}C gHSQC (500 MHz, $CDCl_3$, 298 K) and ^{1}H-^{13}C gHMBC (500 MHz, $CDCl_3$, 298 K) spectra of compound **4**.

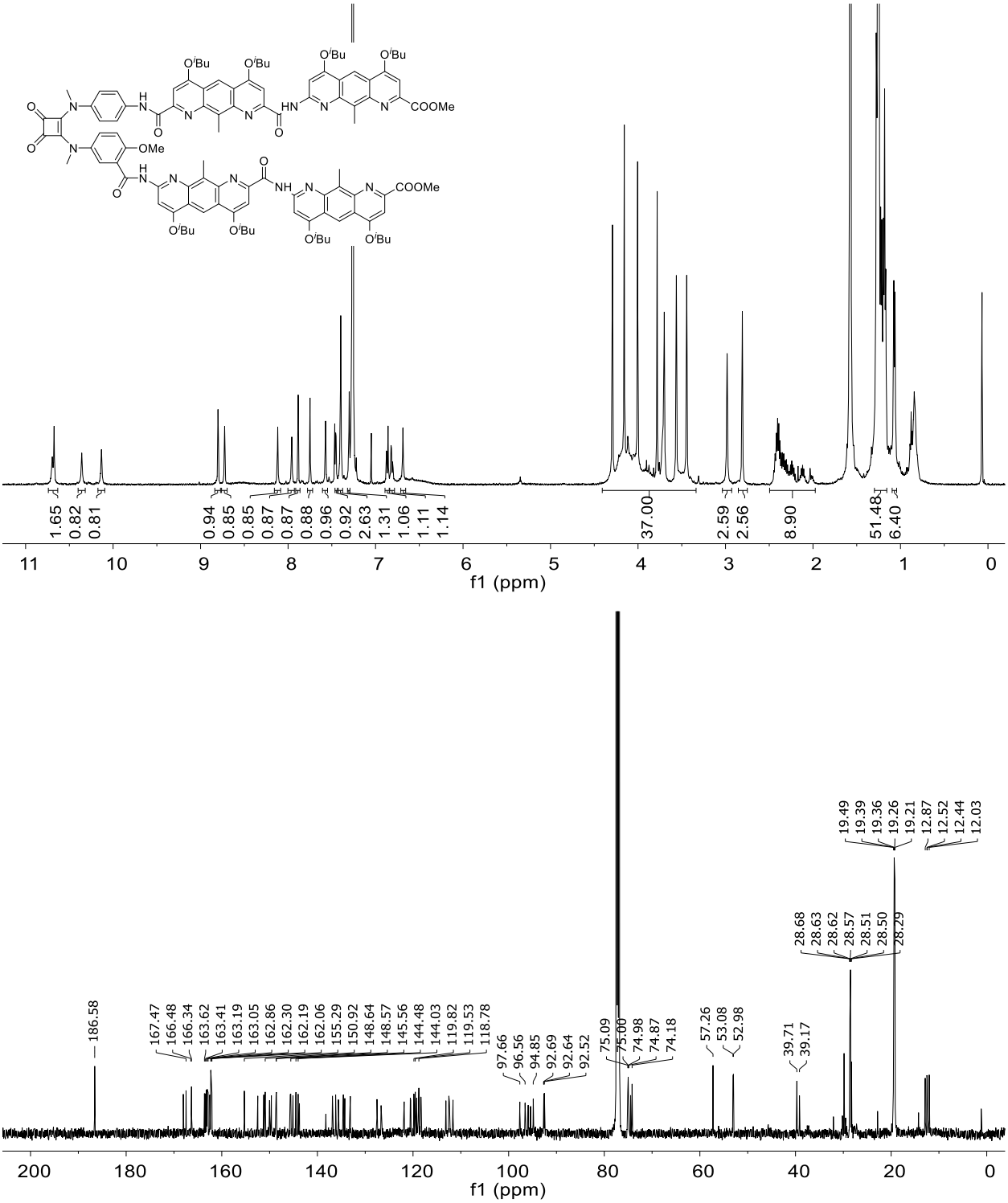


Figure S18. ^{1}H (500 MHz, $CDCl_3$, 298 K) and ^{13}C (126 MHz, $CDCl_3$, 298 K) NMR spectra of compound **5**.

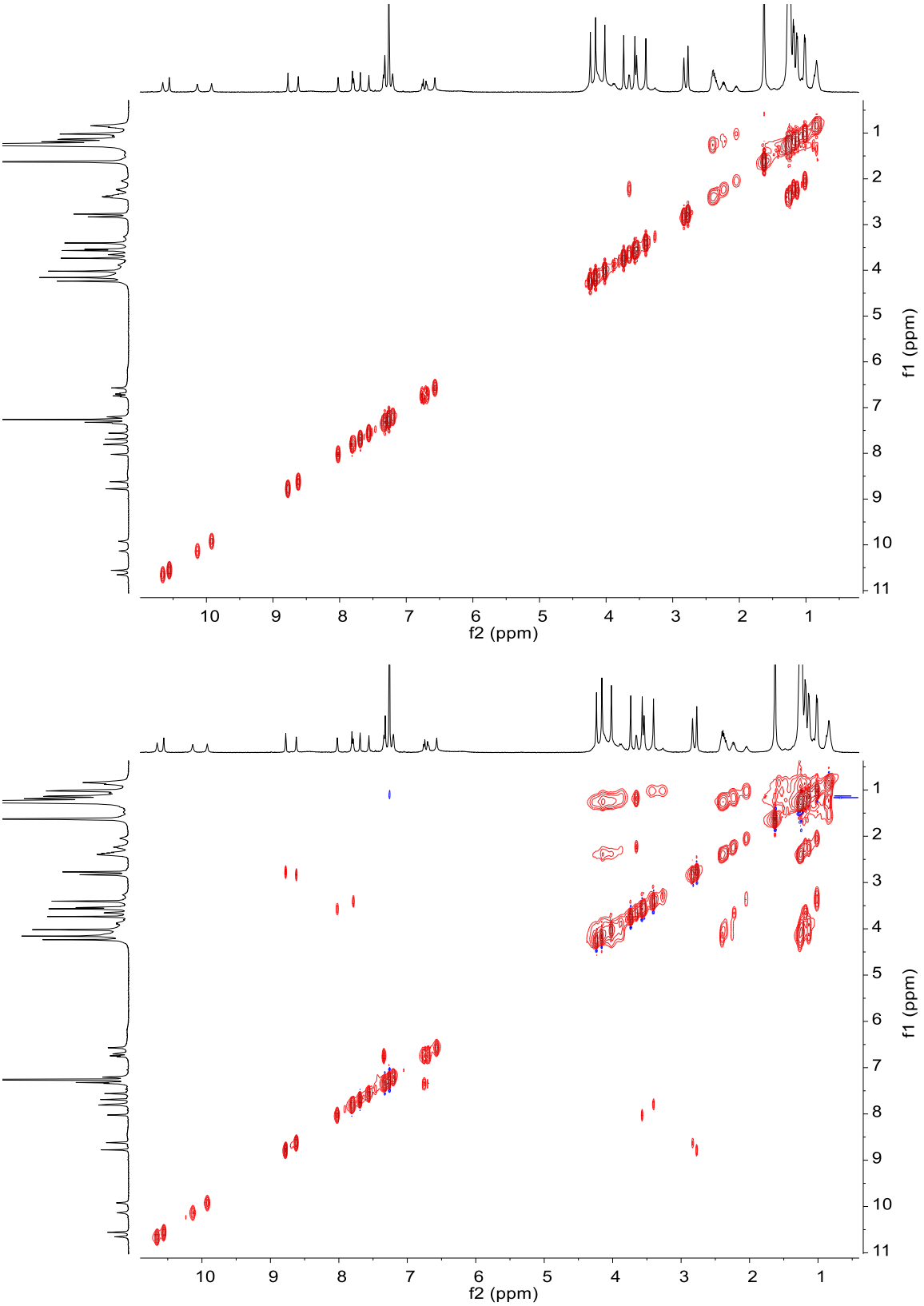


Figure S19. ^{1}H-^{1}H gCOSY (500 MHz, $CDCl_3$, 298 K) and ^{1}H-^{1}H gTOCSY (500 MHz, $CDCl_3$, 298 K) NMR spectra of compound **5**.

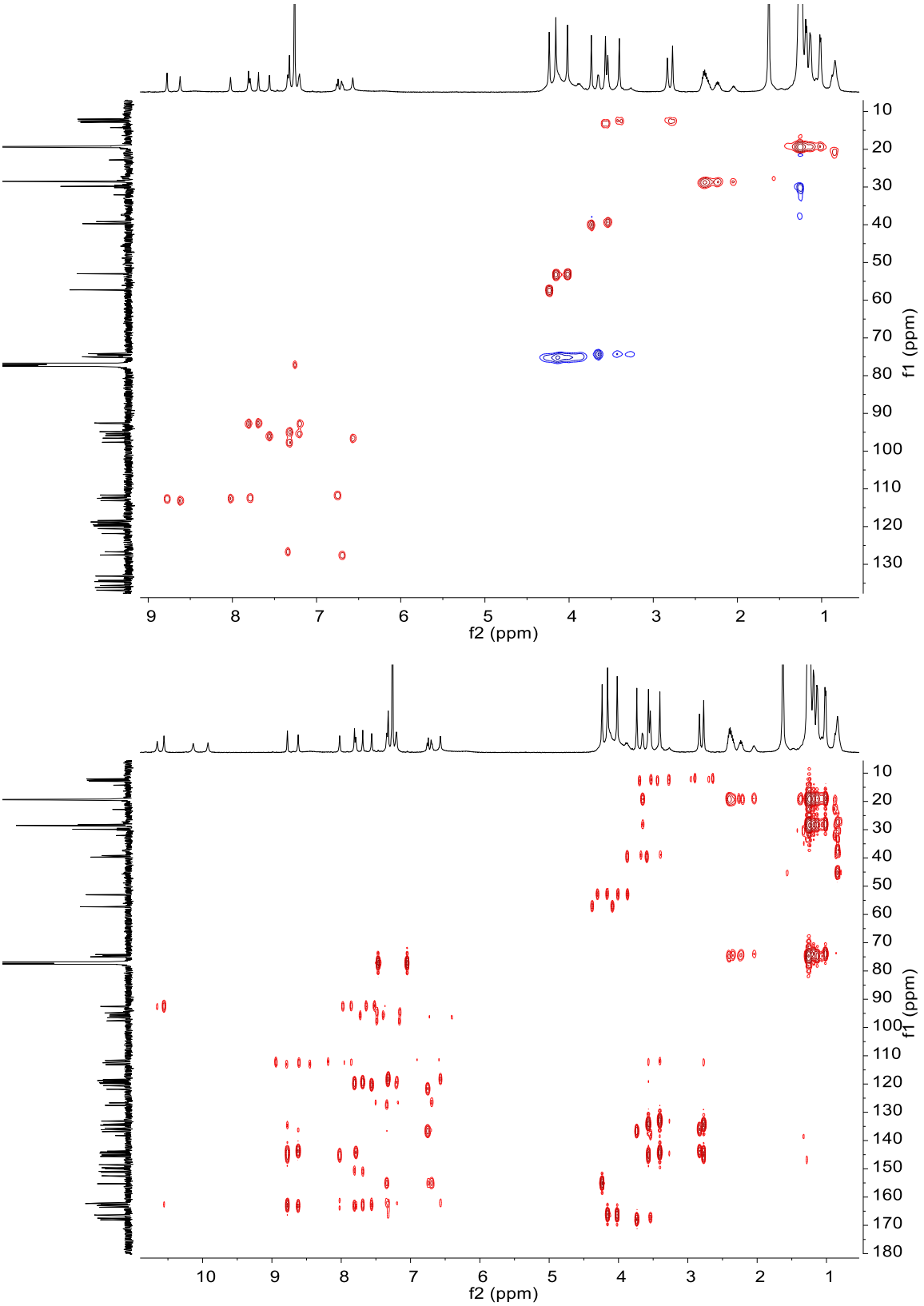


Figure S20. ^{1}H-^{13}C gHSQC (500 MHz, $CDCl_3$, 298 K) and ^{1}H-^{13}C gHMBC (500 MHz, $CDCl_3$, 298 K) NMR spectra of compound **5**.

5. NMR STUDIES

5.1. Color code for the assignment

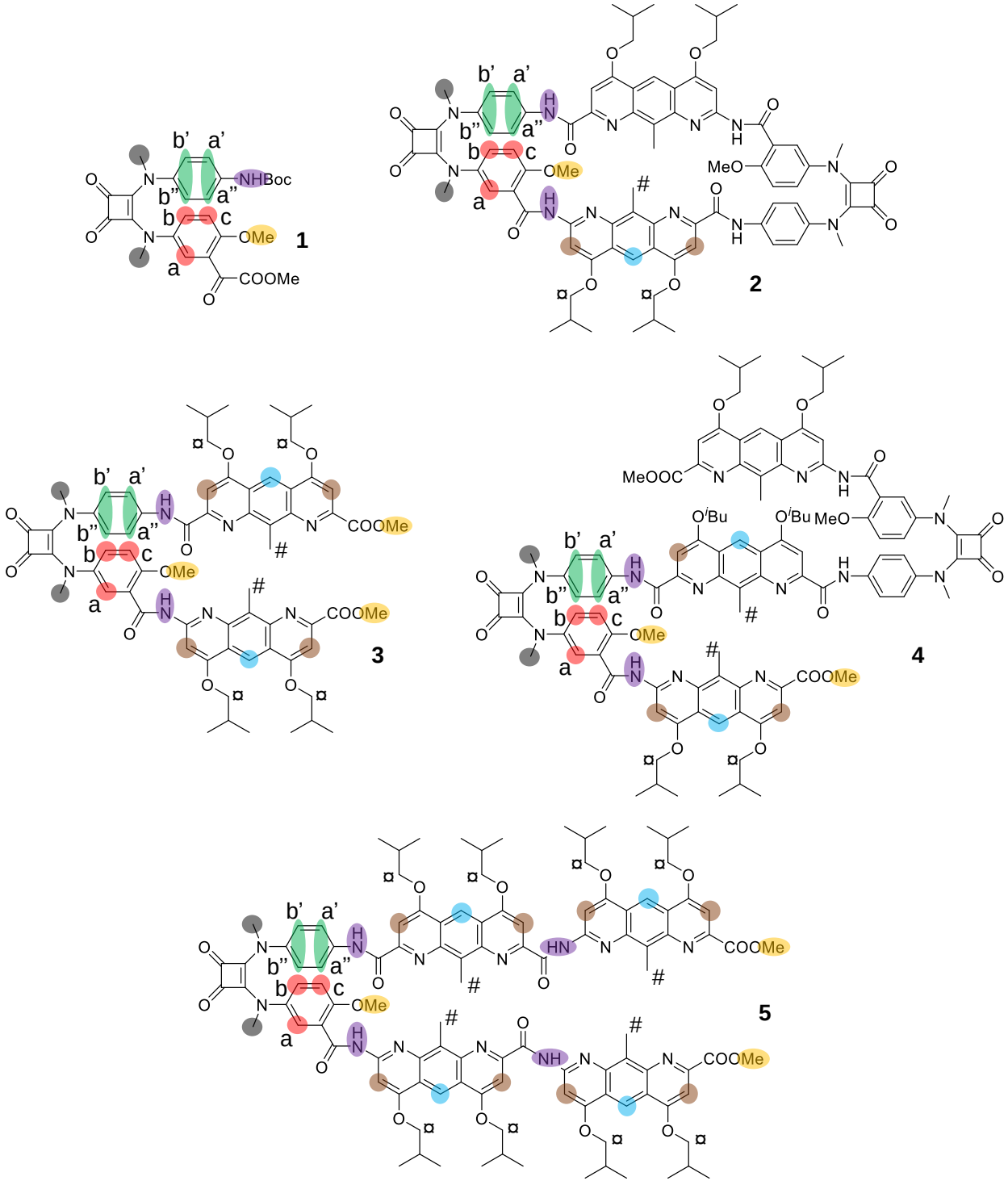


Figure S21. Chemical structure with the color code for the NMR assignment.

5.2. Dilution experiments

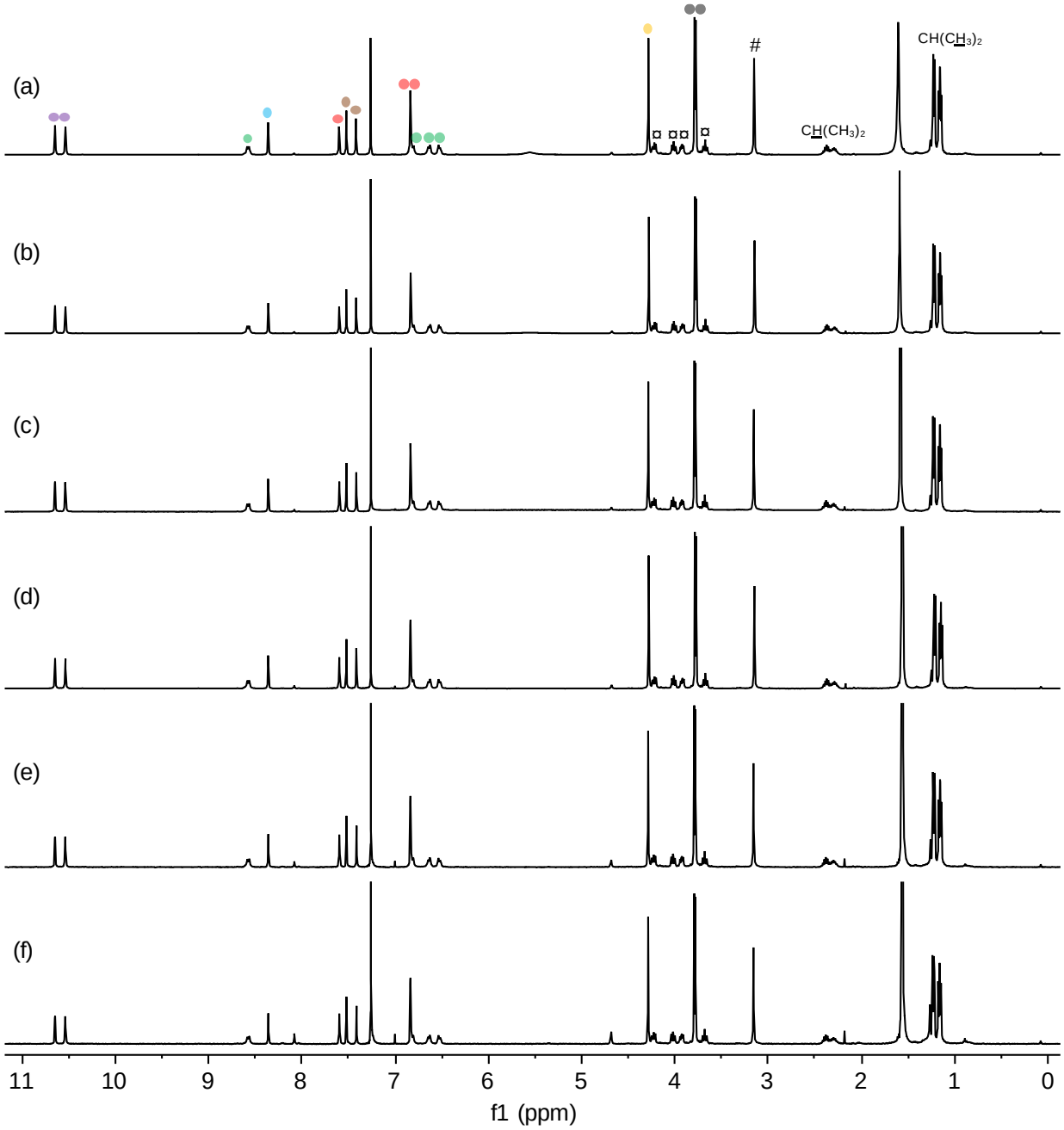


Figure S22. ^{1}H (400 MHz, $CDCl_3$, 298 K) spectra of compound **2** at different concentrations: (a) 4.03 mM; (b) 2.88 mM; (c) 1.83 mM; (d) 1.06 mM; (e) 0.59 mM; (f) 0.26 mM.

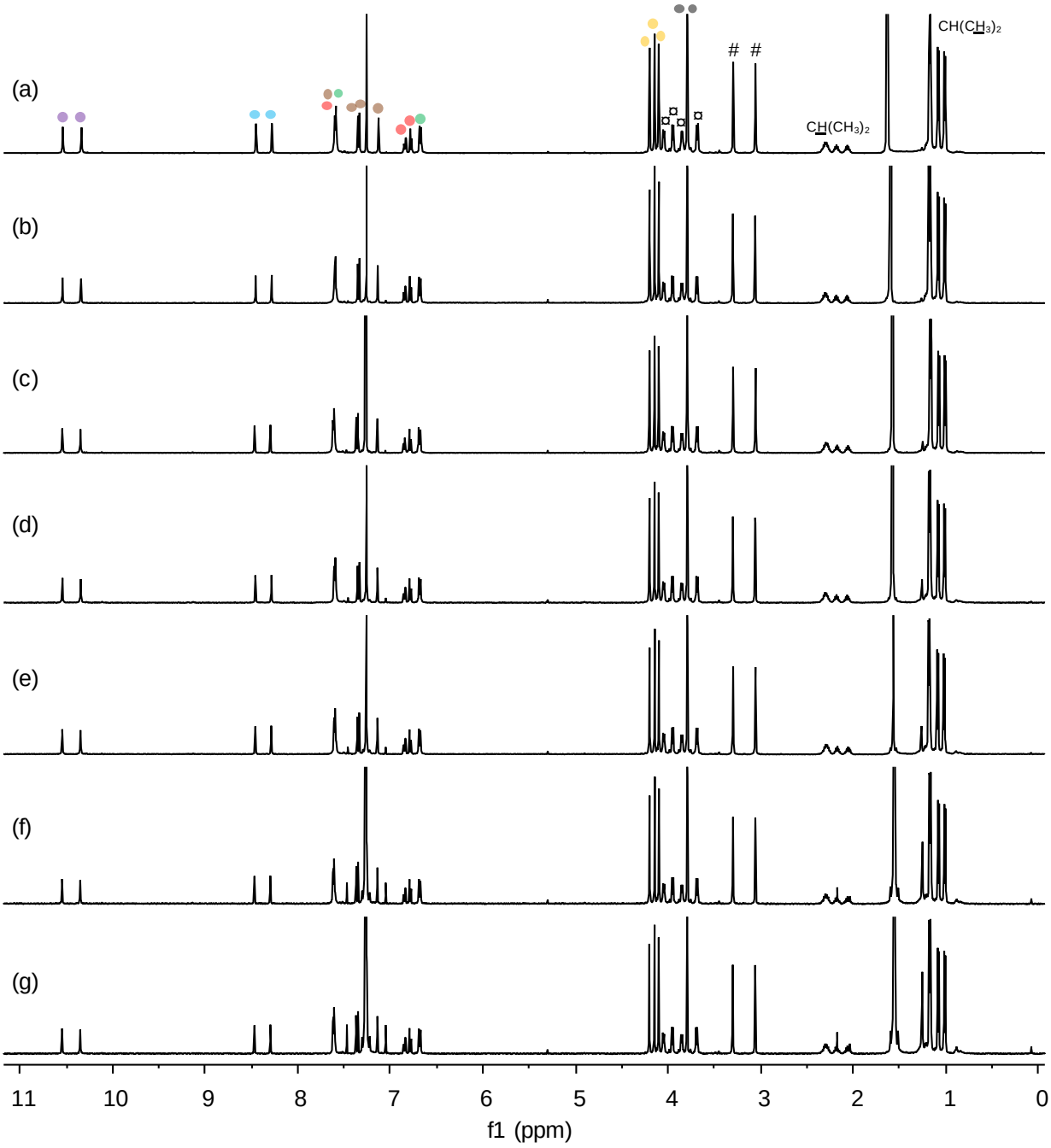


Figure S23. ^{1}H (500 MHz, $CDCl_3$, 298 K) spectra of compound **3** at different concentrations: (a) 11.3 mM; (b) 5.67 mM; (c) 4.05 mM; (d) 2.58 mM; (e) 1.49 mM; (f) 0.62 mM; (g) 0.39 mM.

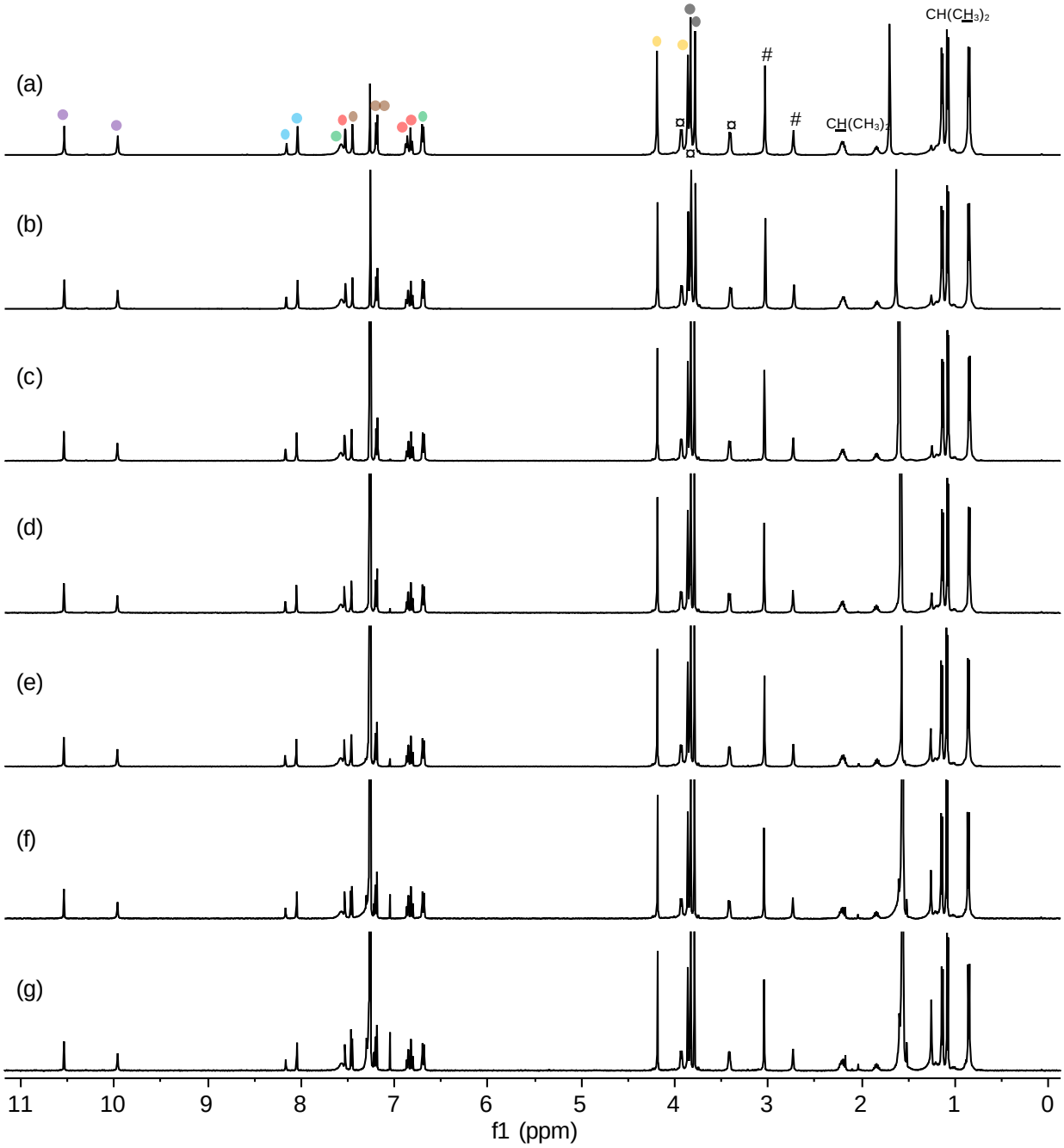


Figure S24. ^{1}H (500 MHz, $CDCl_3$, 298 K) spectra of compound **4** at different concentrations: (a) 11.0 mM; (b) 5.77 mM; (c) 3.54 mM; (d) 2.11 mM; (e) 1.19 mM; (f) 0.55 mM; (g) 0.25 mM.

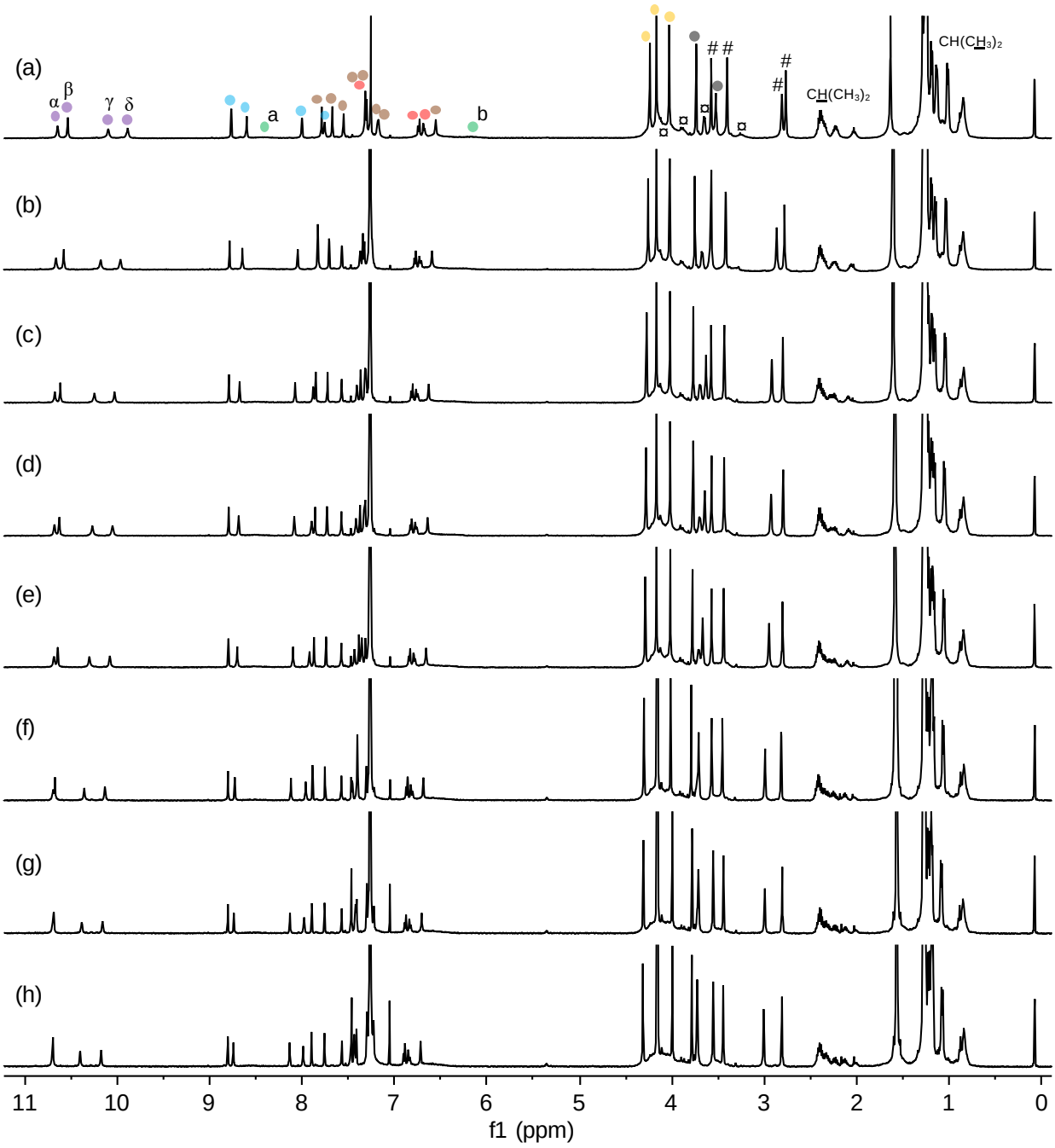


Figure S25. ^{1}H (500 MHz, $CDCl_3$, 298 K) spectra of compound **5** at different concentrations: (a) 7.33 mM; (b) 4.89 mM; (c) 3.19 mM; (d) 2.44 mM; (e) 1.88 mM; (f) 1.34 mM; (g) 0.78 mM; (h) 0.47 mM.

5.3. VT experiments

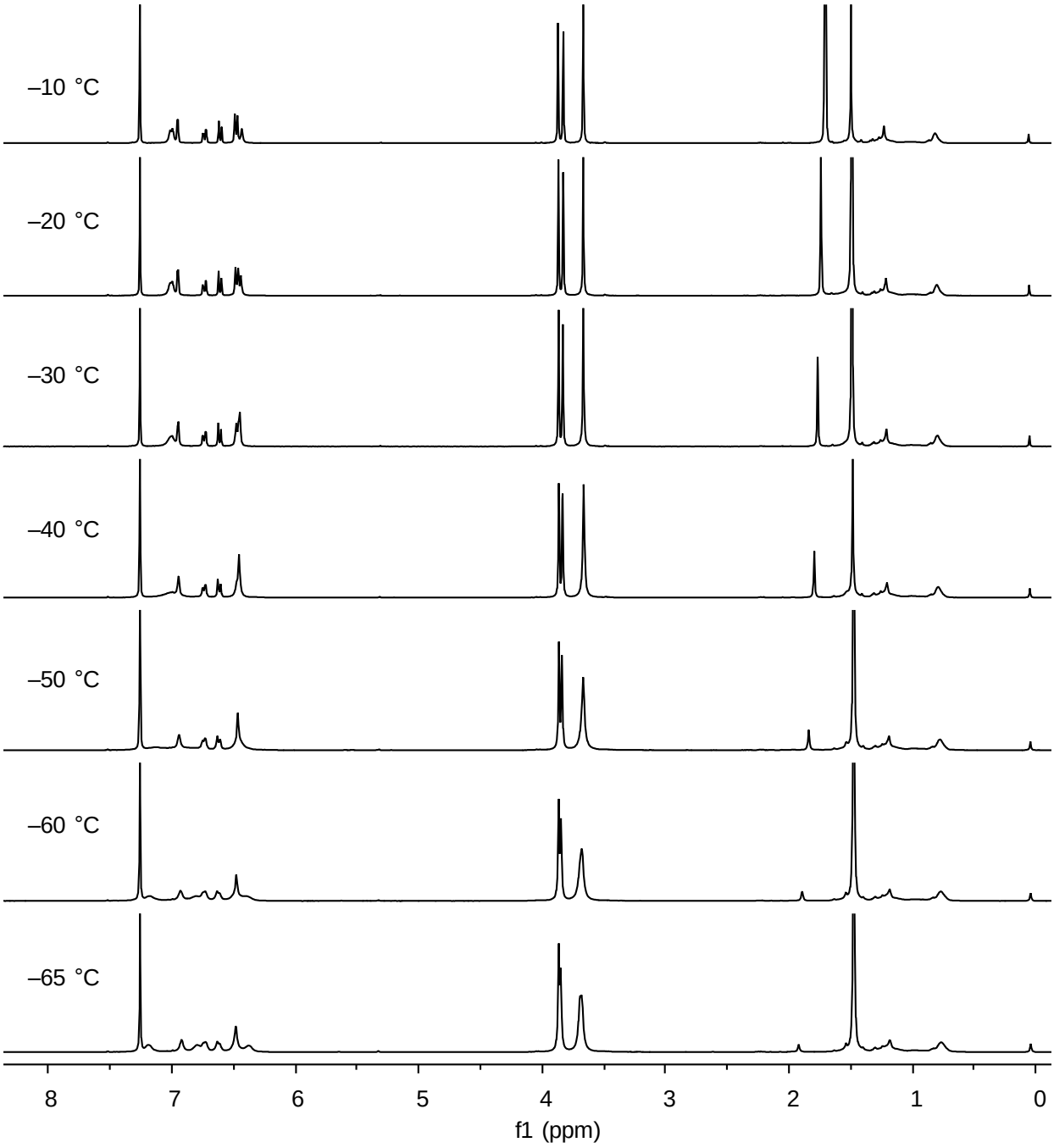


Figure S26. ^{1}H (400 MHz, $CDCl_3$) spectra of compound **1** at different temperatures.

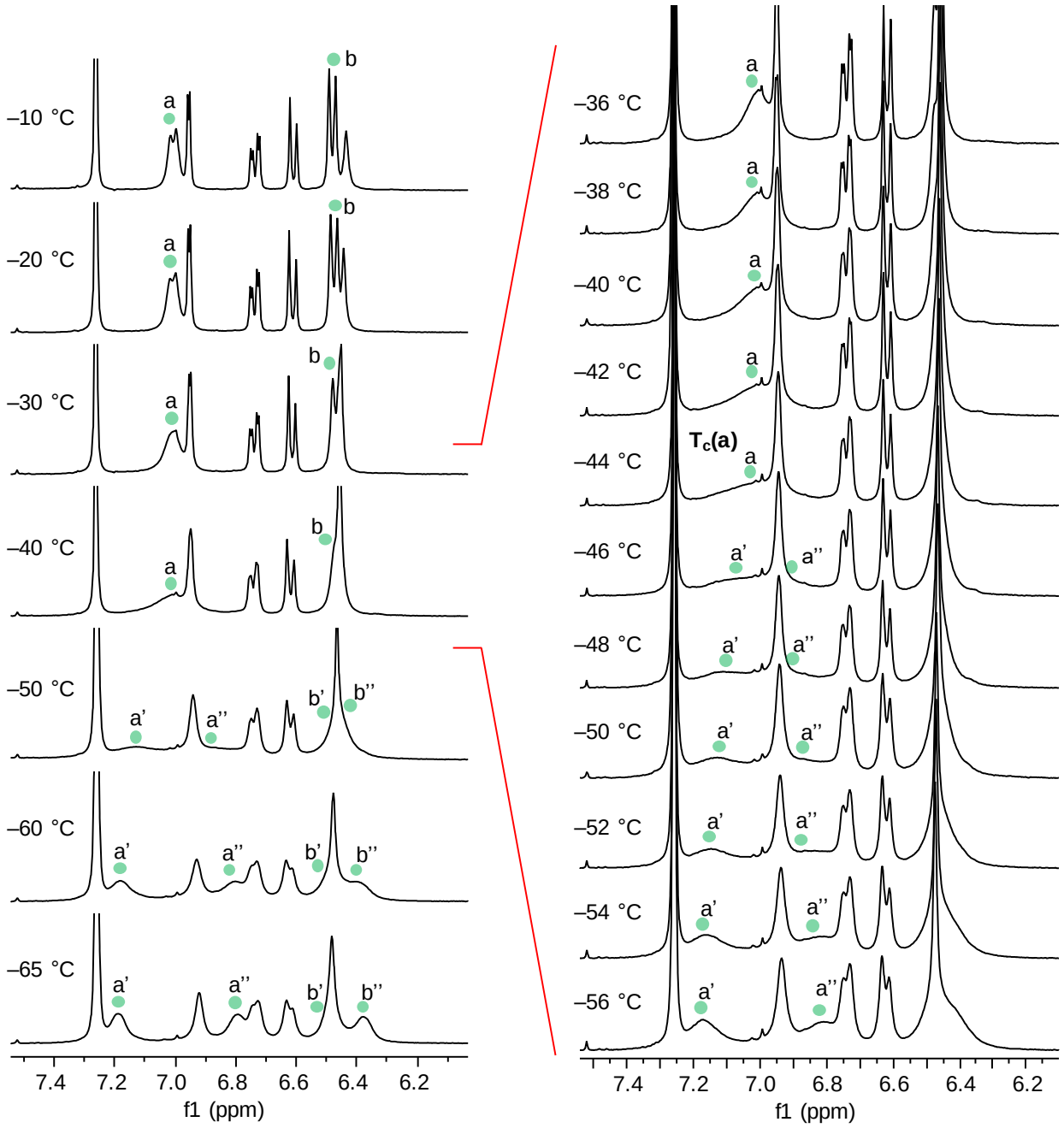


Figure S27. Left: VT ^{1}H (400 MHz, $CDCl_3$) partial spectra (region of CH_{Ar}(a) and CH_{Ar}(b)) of compound **1**. Right: smaller ΔT for the temperature range where the coalescence of CH_{Ar}(a) is observed.

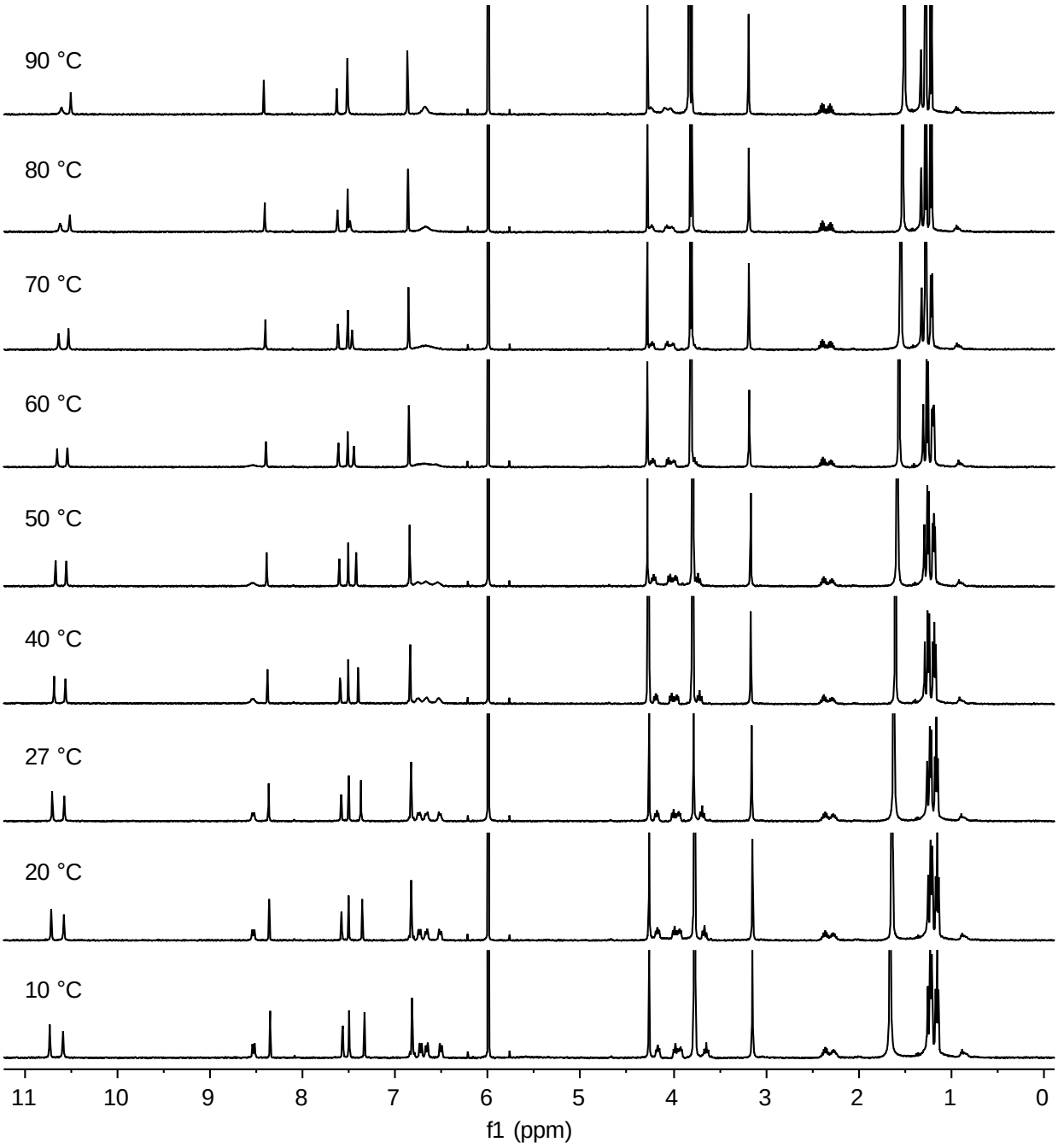


Figure S28. ^{1}H (400 MHz, 1,1,2,2-tetrachloroethane-d_2) spectra of compound **2** at different temperatures.

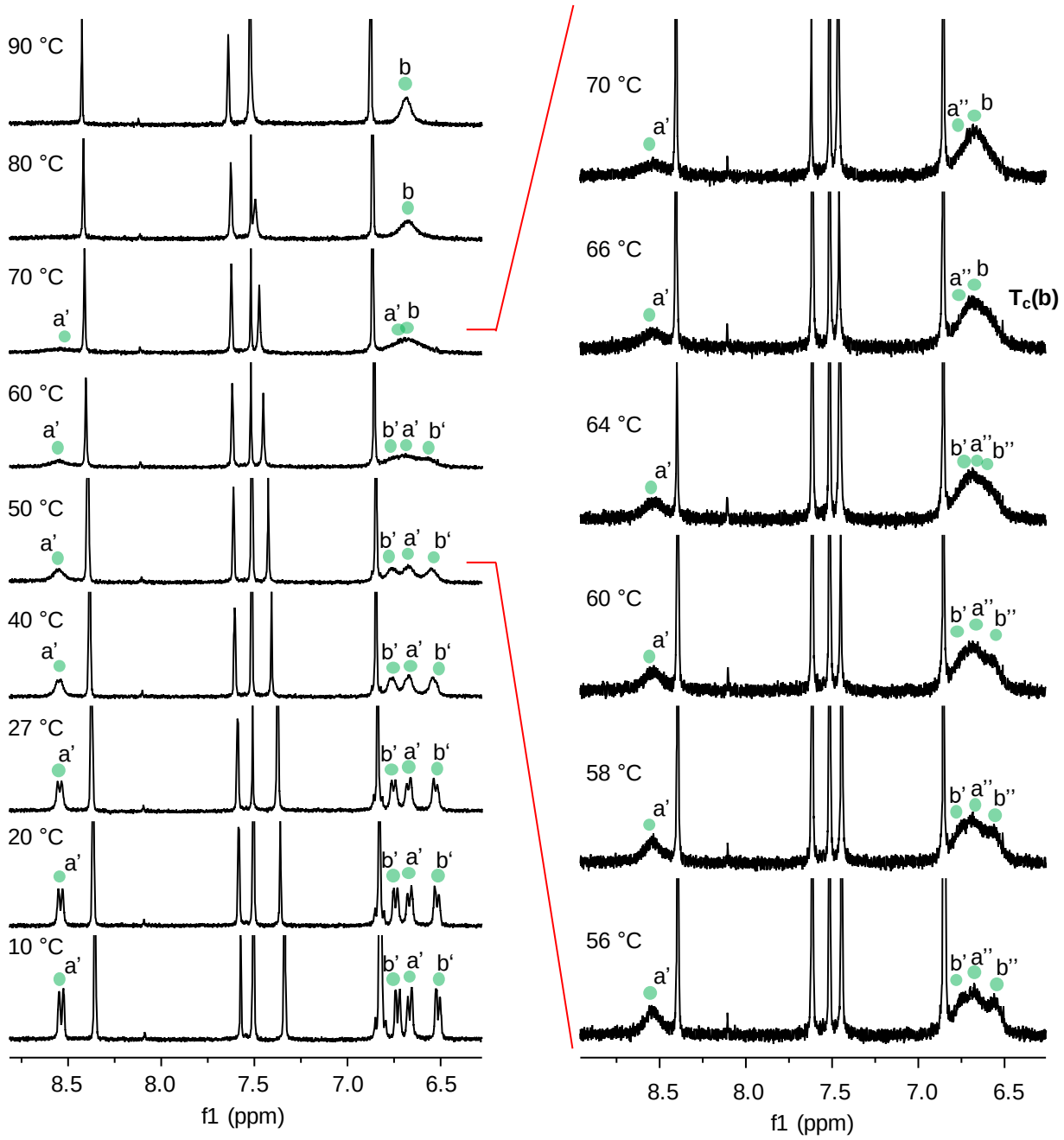


Figure S29. Left: VT ^{1}H (400 MHz, 1,1,2,2-tetrachloroethane-d_2) partial spectra (region of CH_{Ar}(a) and CH_{Ar}(b)) of compound **2**. Right: smaller ΔT for the temperature range where the coalescence of CH_{Ar}(b) is observed.

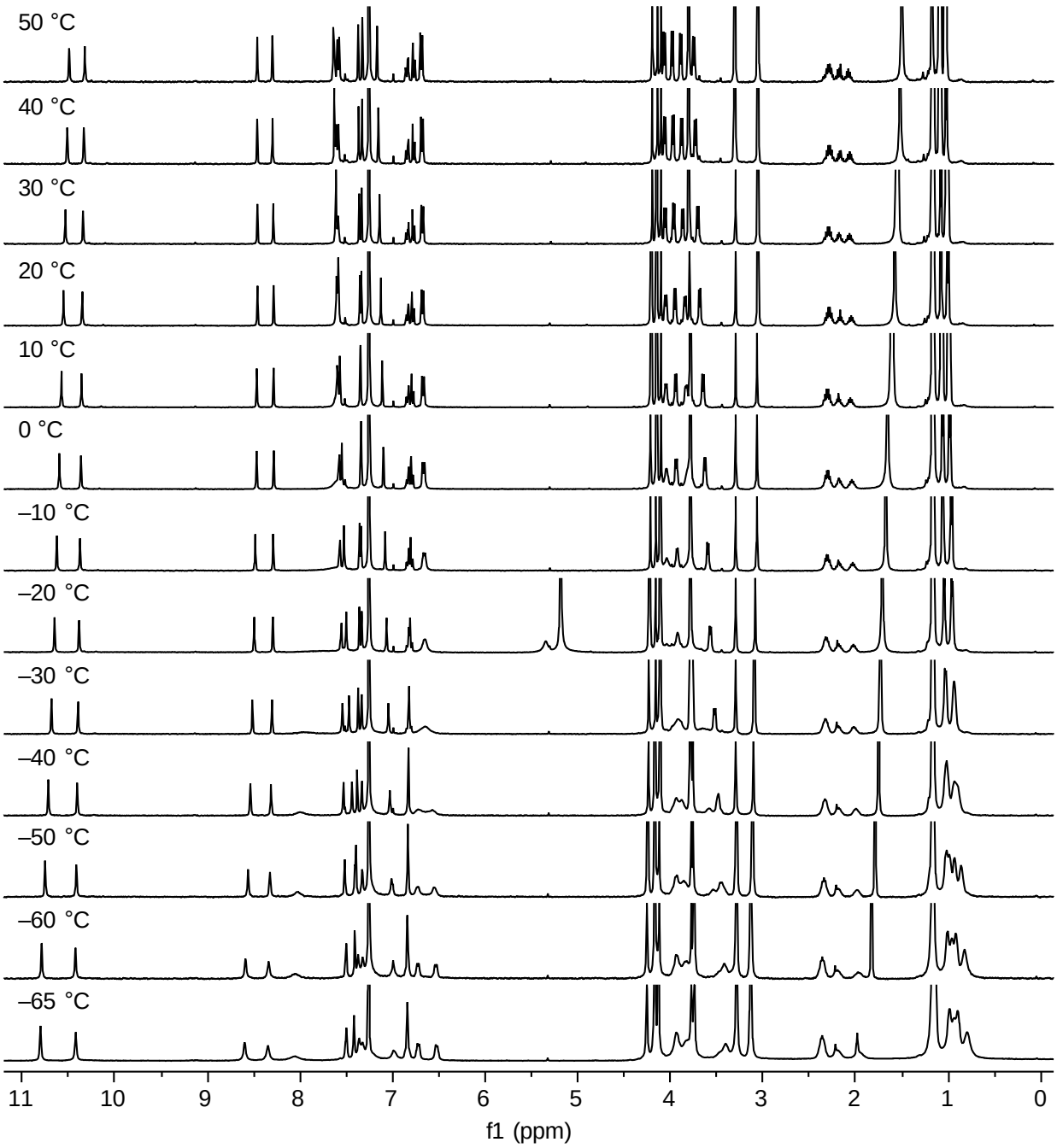


Figure S30. ^{1}H (400 MHz, $CDCl_3$) spectra of compound **3** at different temperatures.

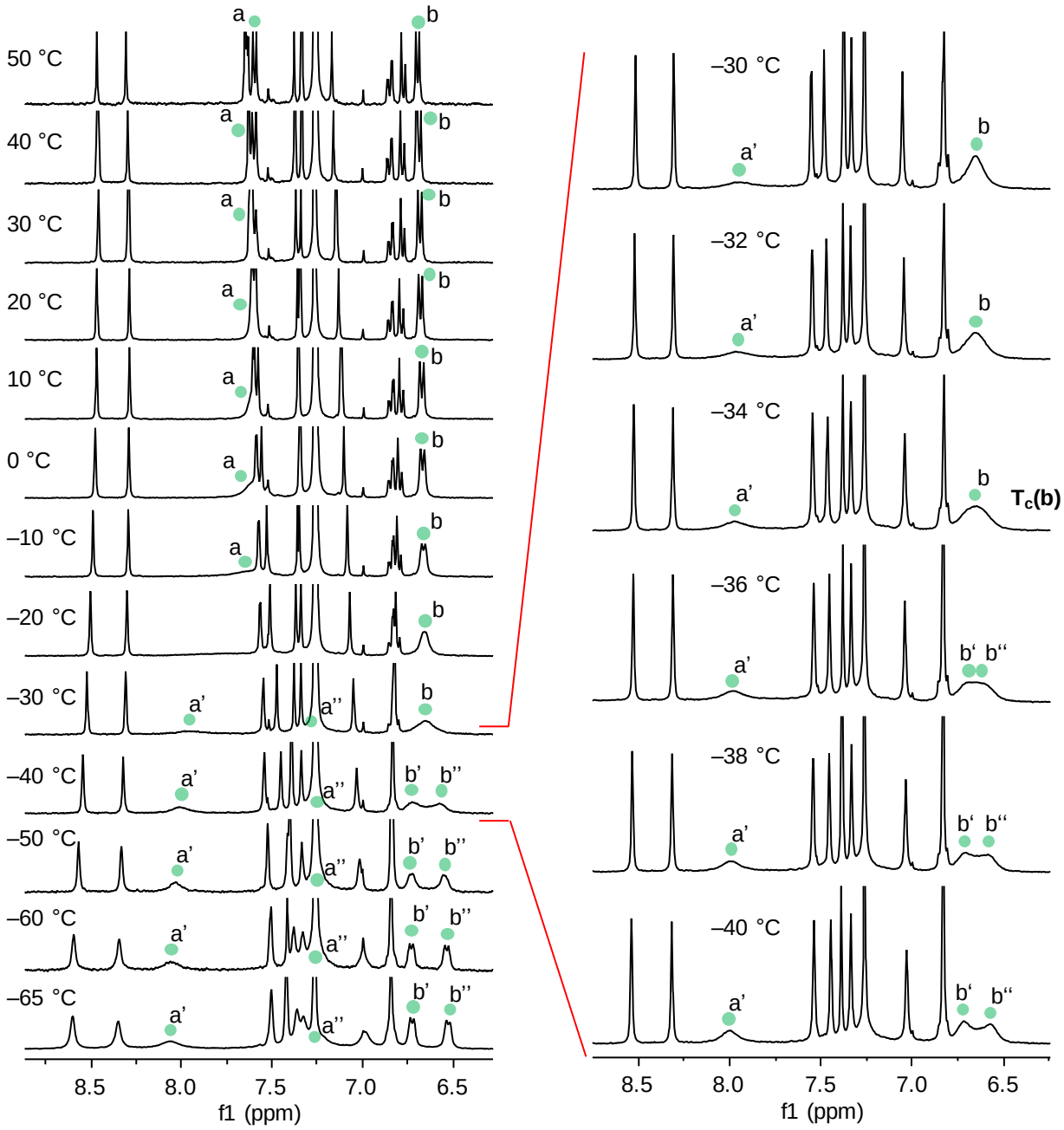


Figure S31. Left: VT ^{1}H (400 MHz, $CDCl_3$) partial spectra (region of CH_{Ar}(a) and CH_{Ar}(b)) of compound **3**. Right: smaller ΔT for the temperature range where the coalescence of CH_{Ar}(b) is observed.

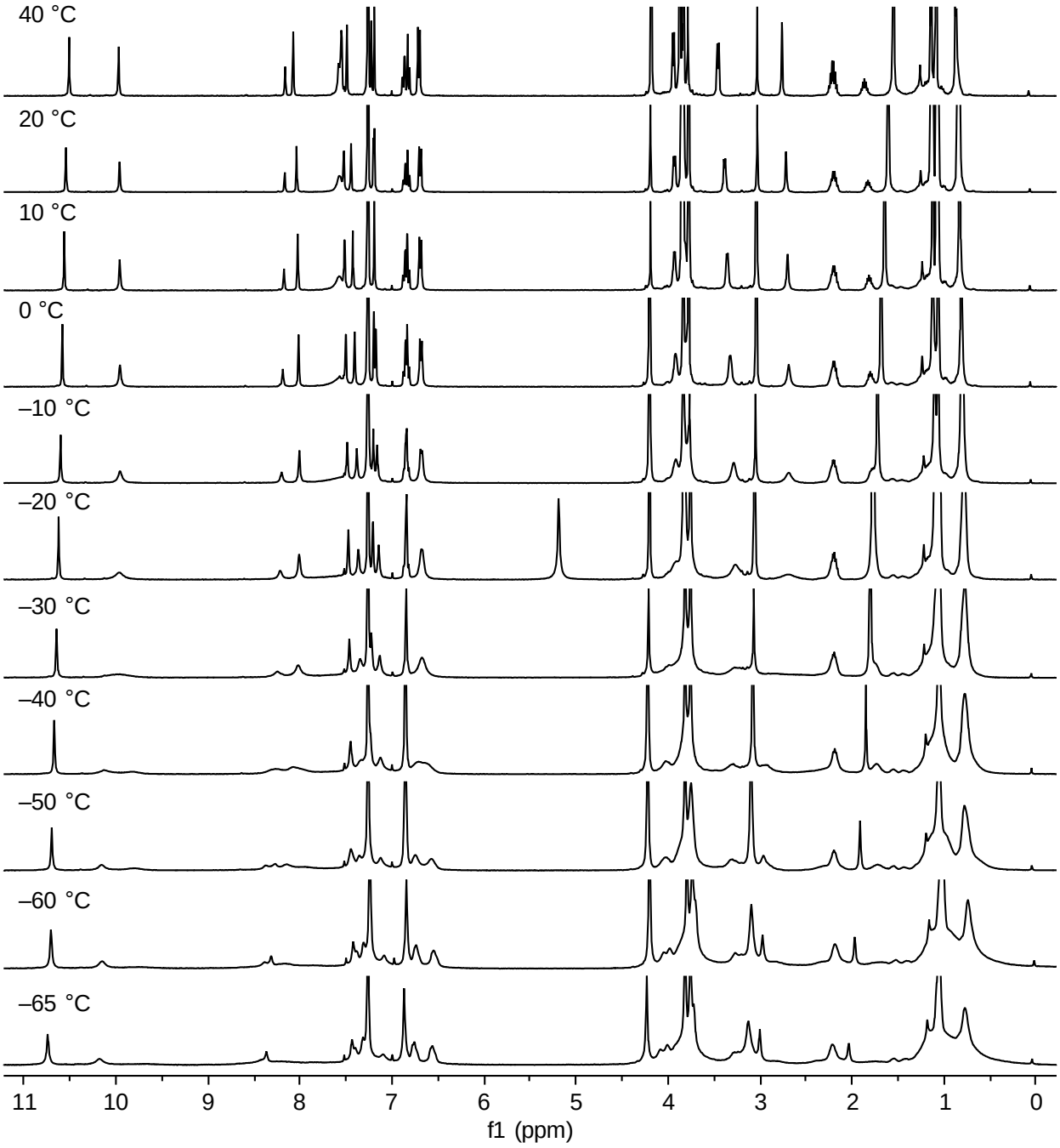


Figure S32. ^{1}H (400 MHz, $CDCl_3$) spectra of compound **4** at different temperatures.

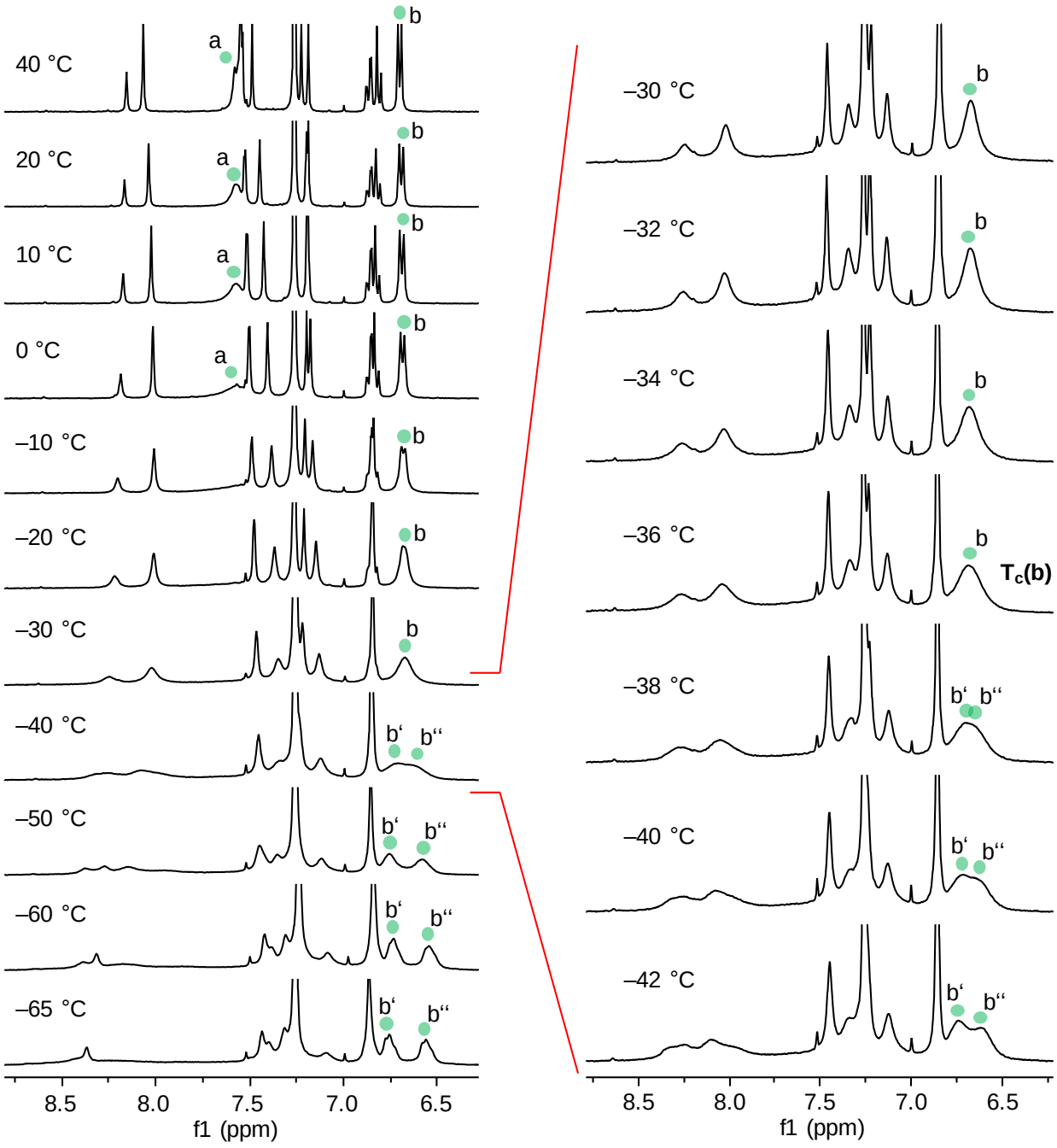


Figure S33. Left: VT ^{1}H (400 MHz, $CDCl_3$) partial spectra (region of CH_{Ar}(a) and CH_{Ar}(b)) of compound **4**. Right: smaller ΔT for the temperature range where the coalescence of CH_{Ar}(b) is observed.

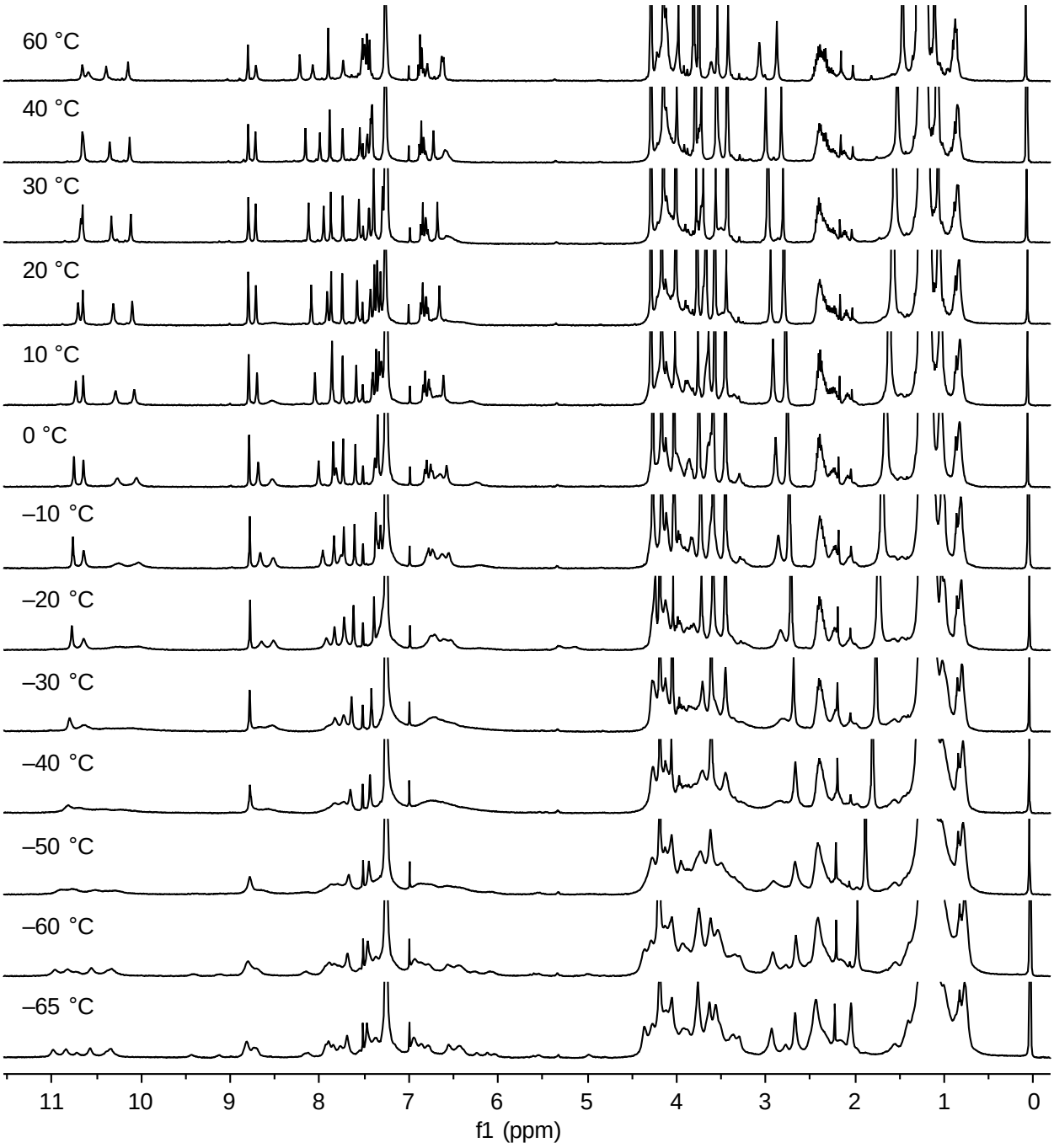


Figure S34. ^{1}H (400 MHz, $CDCl_3$) spectra of compound **5** at different temperatures.

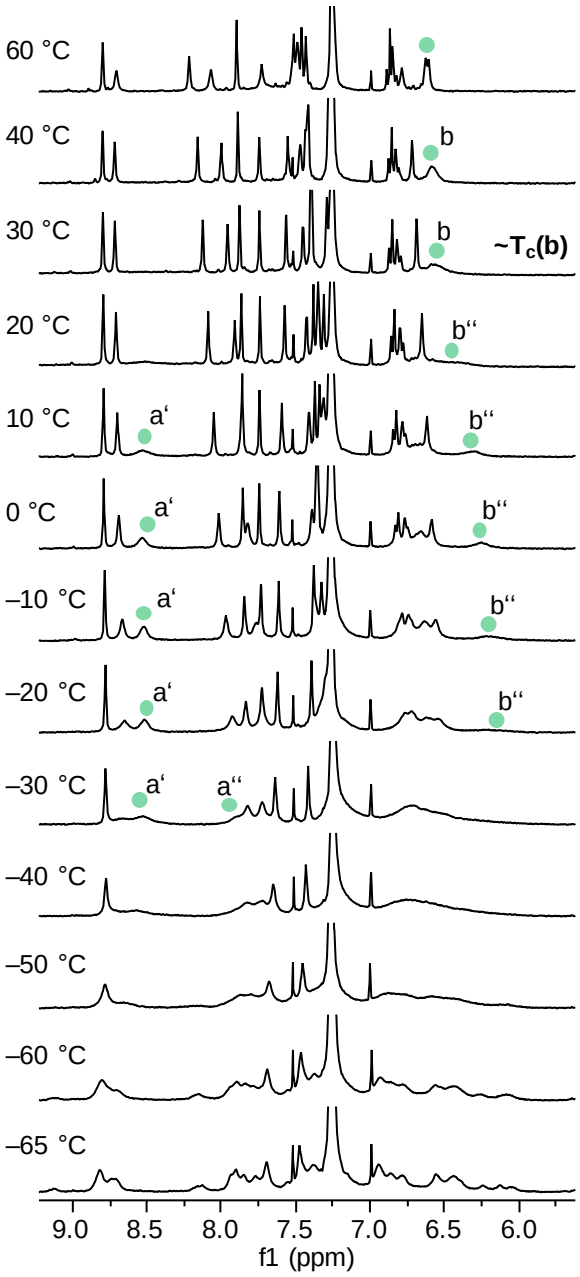


Figure S35. VT ^{1}H (400 MHz, $CDCl_3$) partial spectra (region of CH_{Ar}(a) and CH_{Ar}(b)) of compound **5**. In this particular case the temperature of coalescence could not be determined very precisely because of the peak broadness and the increase of spectra complexity when lowering the temperature.

Table S1. Data from the VT-NMR experiments and calculated values of $\Delta G^{\ddagger}_c$ for the *p*-diaminophenyl ring rotation. Chemical shift frequency difference (δν, Hz), coalescence temperature (T_c, °C) and energetic barrier at T_c ($\Delta G^{\ddagger}_c$, kJ/mol).

Compound	Solvent	^{1}H signal	T_c (°C)	δν (Hz)[a]	$\Delta G^{\ddagger}_c$ (kJ·mol^{-1})[b]
1	$CDCl_3$	CH_{Ar} (a)	–44 ± 2	159	44.4 ± 0.4
2	1,1,2,2-TCE-d_2	CH_{Ar} (b)	+66 ± 2	88	68.5 ± 0.4
3	$CDCl_3$	CH_{Ar} (b)	–34 ± 2	80	47.8 ± 0.4
4	$CDCl_3$	CH_{Ar} (b)	–36 ± 2	78	47.5 ± 0.4
5	$CDCl_3$	CH_{Ar} (b)	+30 ± 10	— [c]	— [c]

[a] The δν values are those corresponding to the ^{1}H NMR recorded at the lowest temperature. [b] The energy barriers were calculated using the approximated formula for $\Delta G^{\ddagger}_c$ at the temperature of coalescence: $\Delta G^{\ddagger}_c = RT_c(22.96 + \ln(T_c/\delta\nu)$.[2] The corresponding errors were estimated by taking into account the error in the determination of T_c (± 2 °C for entries 1-4). [c] These values could not be determined due to the complexity of the ^{1}H NMR spectrum at low temperatures.

5.4. CD_3OH titrations

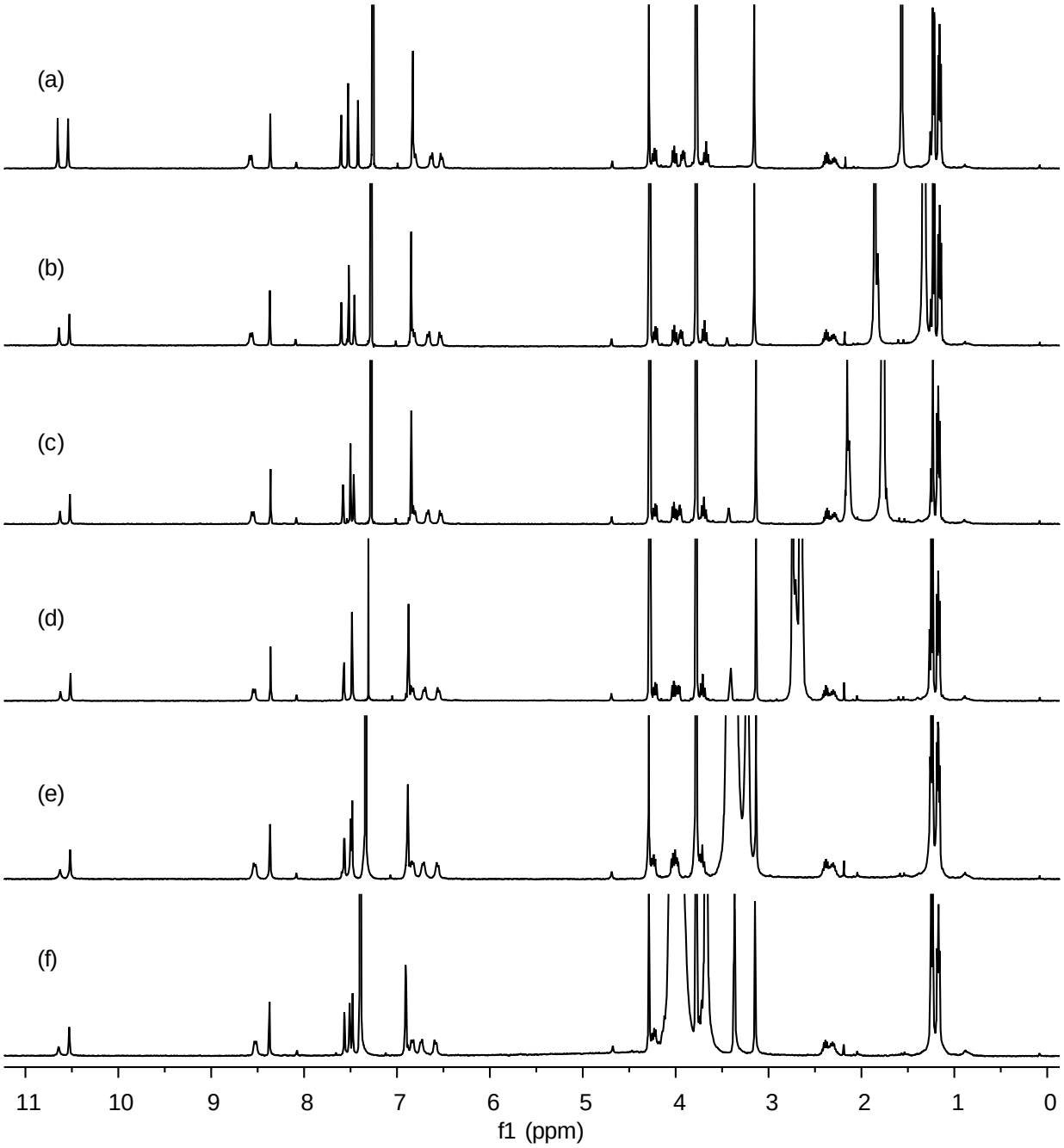


Figure S36. ^1H (400 MHz, 298 K) spectra of compound **2** at different proportions of CD_3OH in $CDCl_3$: (a) 0.0% CD_3OH, 1.06 mM; (b) 1.0% CD_3OH, 1.05 mM; (c) 2.0% CD_3OH, 1.04 mM; (d) 4.8% CD_3OH, 1.01 mM; (e) 10% CD_3OH, 0.95 mM; (f) 20% CD_3OH, 0.85 mM.

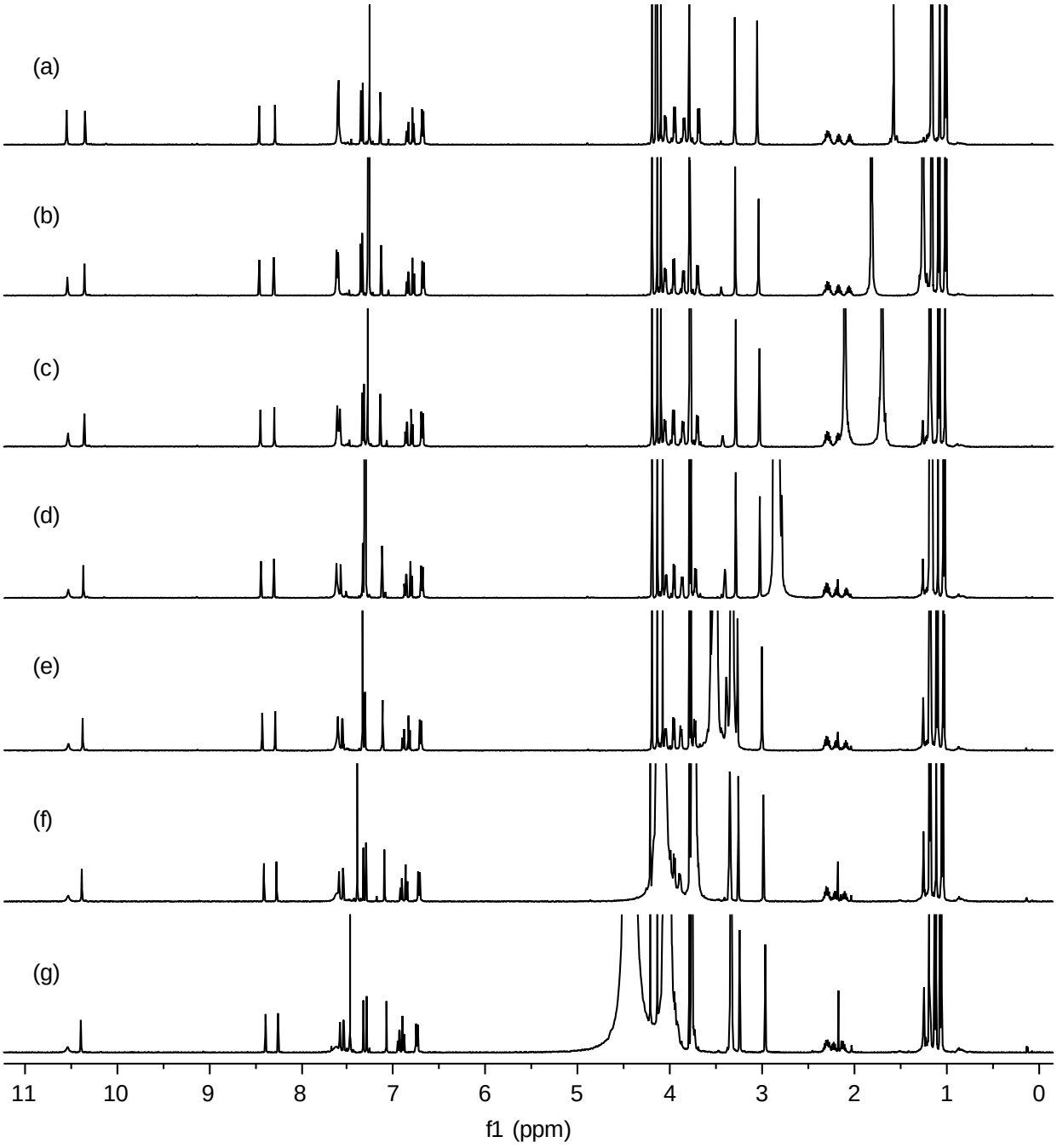


Figure S37. ^{1}H (500 MHz, 298 K) spectra of compound **3** at different proportions of CD_3OH in $CDCl_3$: (a) 0.0% CD_3OH, 2.97 mM; (b) 1.0% CD_3OH, 2.94 mM; (c) 2.0% CD_3OH, 2.91 mM; (d) 5.7% CD_3OH, 2.80 mM; (e) 11% CD_3OH, 2.65 mM; (f) 21% CD_3OH, 2.36 mM; (g) 33% CD_3OH, 1.98 mM.

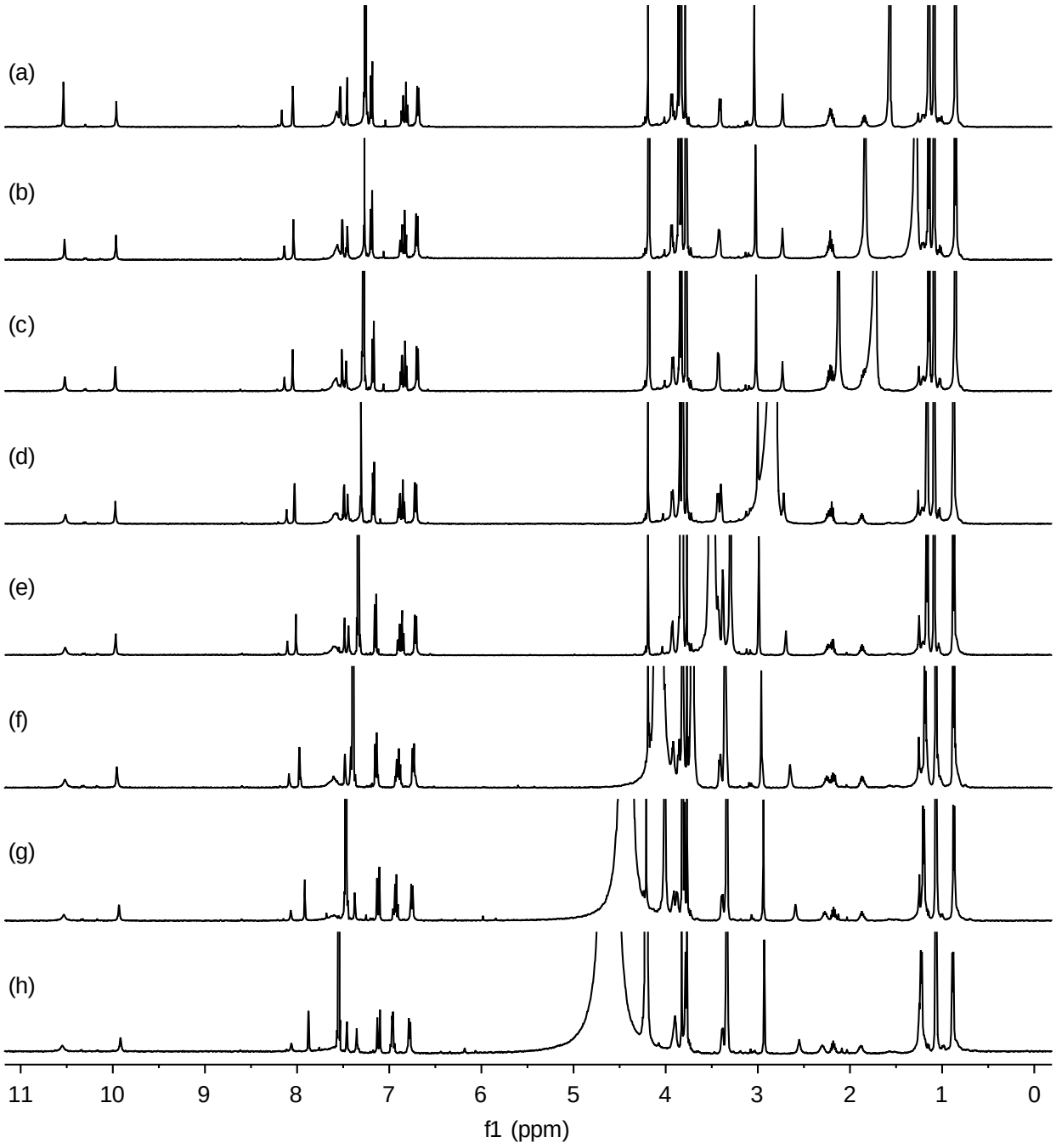


Figure S38. ^{1}H (500 MHz, 298 K) spectra of compound **4** at different proportions of CD_3OH in $CDCl_3$: (a) 0.0% CD_3OH, 2.10 mM; (b) 1.0% CD_3OH, 2.08 mM; (c) 2.0% CD_3OH, 2.06 mM; (d) 5.7% CD_3OH, 1.98 mM; (e) 11% CD_3OH, 1.88 mM; (f) 21% CD_3OH, 1.67 mM; (g) 33% CD_3OH, 1.40 mM; (h) 45% CD_3OH, 1.15 mM.

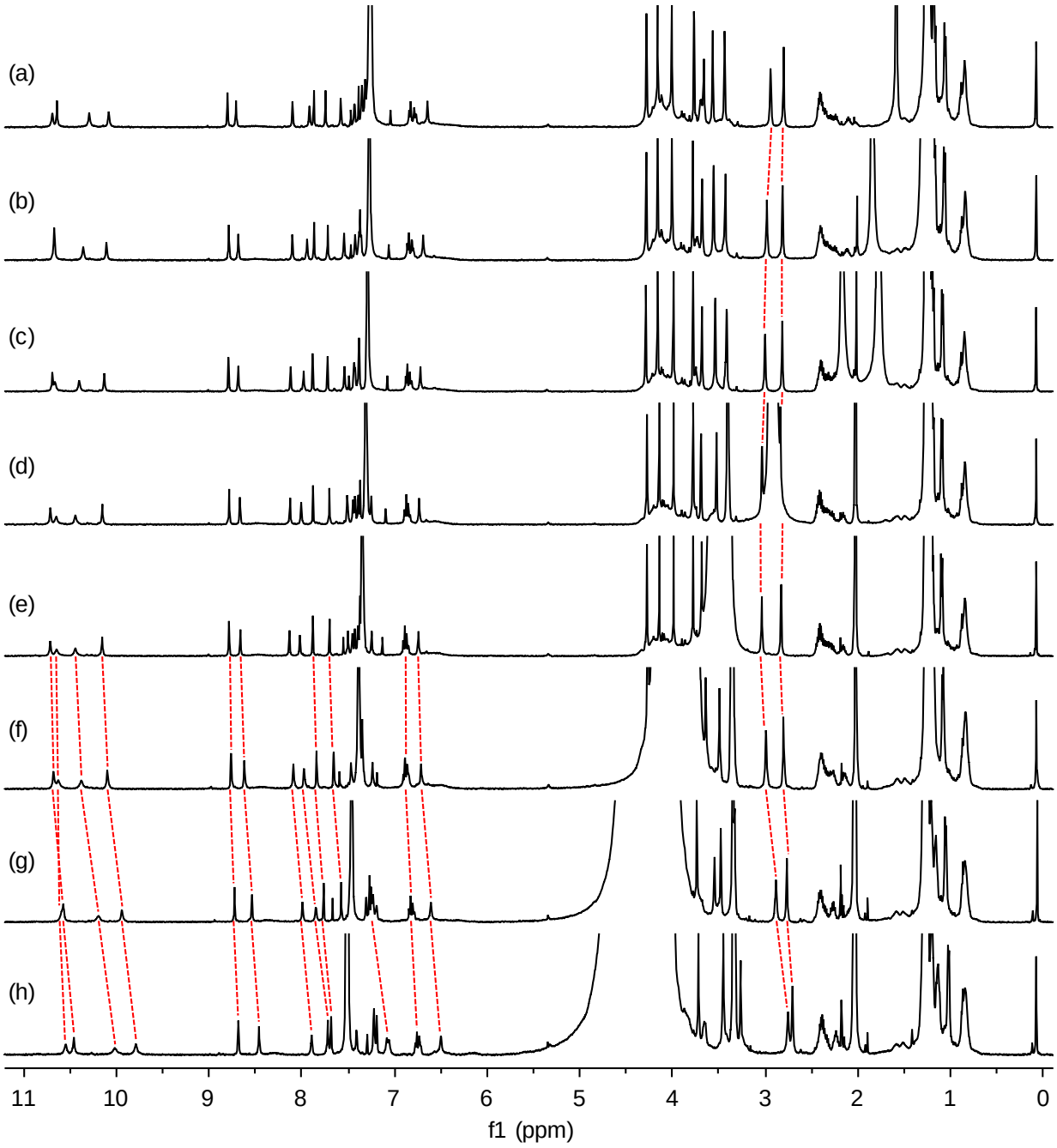


Figure S39. ^{1}H (500 MHz, 298 K) spectra of compound **5** at different proportions of CD_3OH in $CDCl_3$: (a) 0.0% CD_3OH, 2.36 mM; (b) 1.0% CD_3OH, 2.34 mM; (c) 2.0% CD_3OH, 2.31 mM; (d) 5.7% CD_3OH, 2.23 mM; (e) 11% CD_3OH, 2.11 mM; (f) 21% CD_3OH, 1.87 mM; (g) 33% CD_3OH, 1.57 mM; (h) 41% CD_3OH, 1.40 mM. The most relevant shifts are indicated with red dashed lines.

5.5. NOESY and ROESY experiments

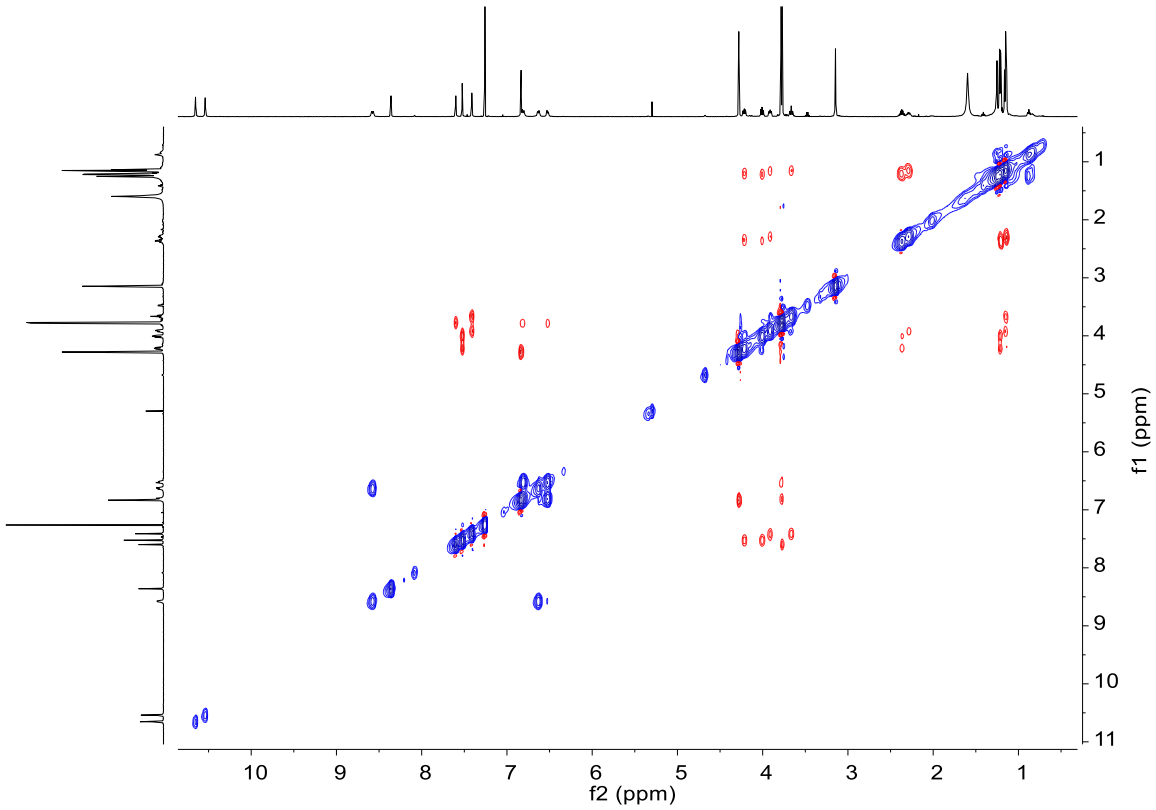


Figure S40. 2D ROESY (500 MHz, $CDCl_3$) spectrum of compound **2**.

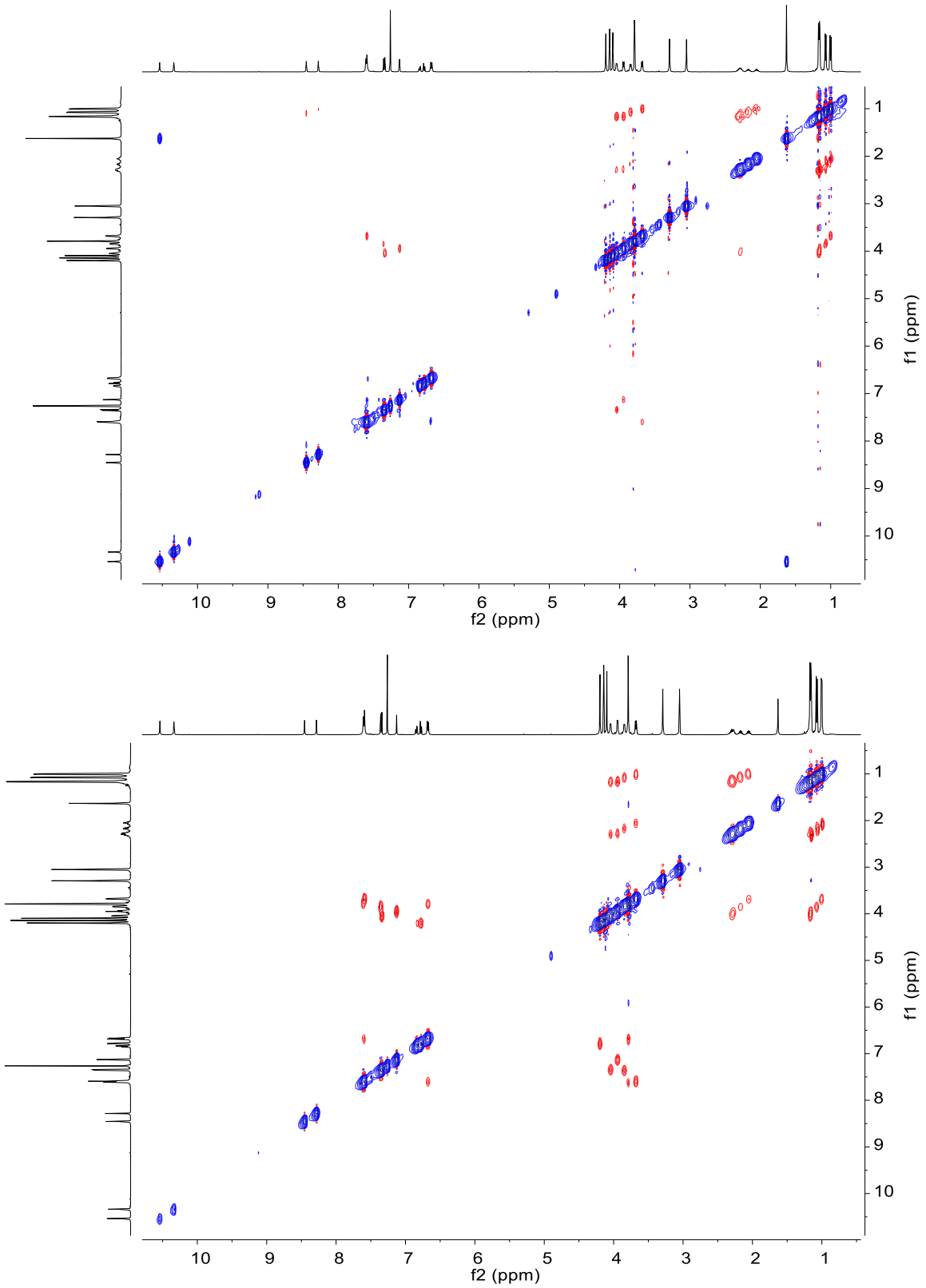


Figure S41. 2D NOESY (500 MHz, $CDCl_3$) and 2D ROESY (500 MHz, $CDCl_3$) spectra of compound **3**.

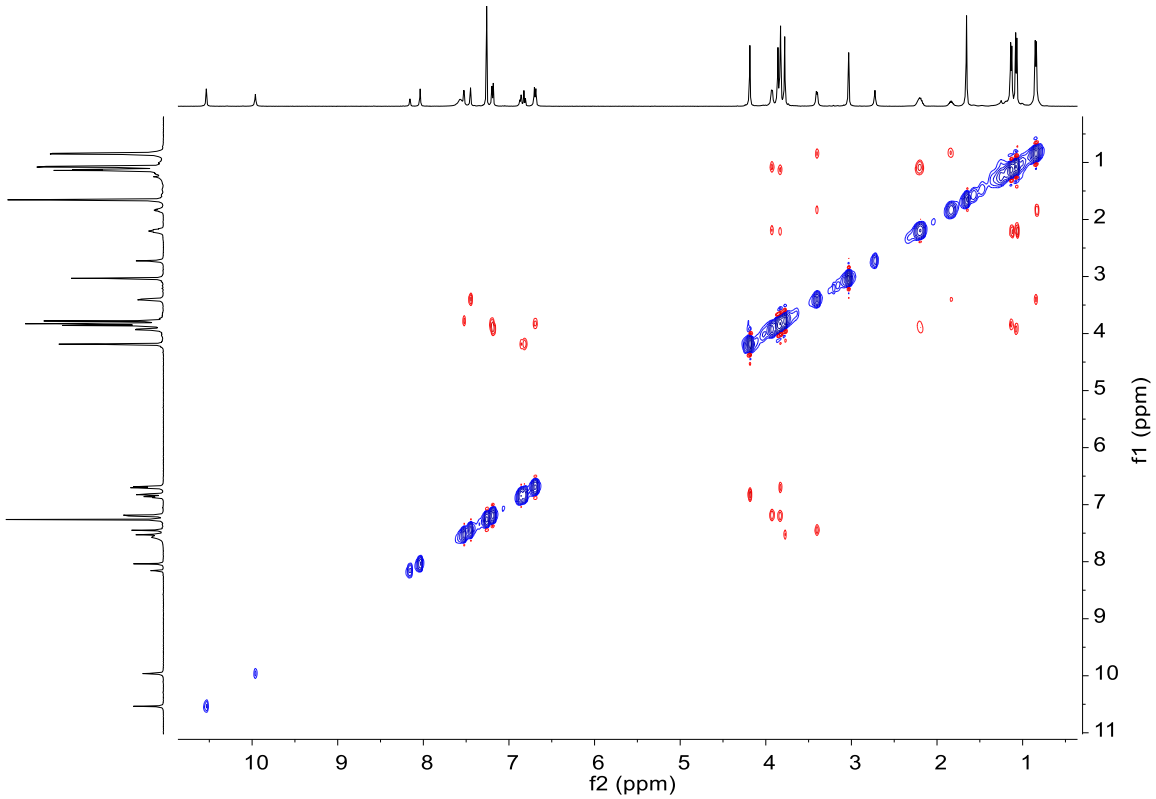


Figure S42. 2D ROESY (500 MHz, $CDCl_3$) spectrum of compound **4**.

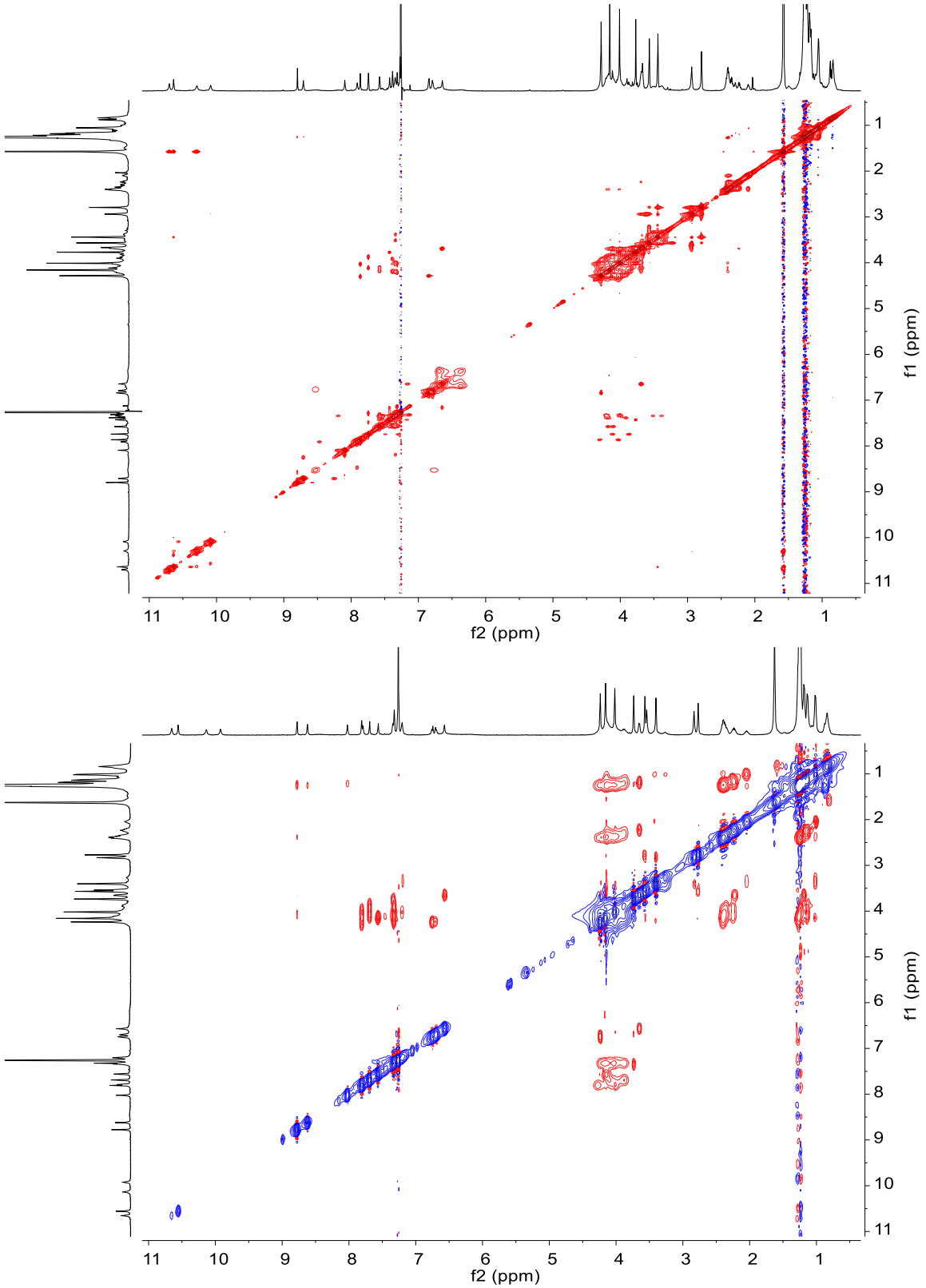


Figure S43. 2D NOESY (800 MHz, $CDCl_3$) and 2D ROESY (500 MHz, $CDCl_3$) spectra of compound **5**.

6. MOLECULAR MODELING

Molecular Modeling calculations were done using MacroModel (Schrödinger Release 2019-2: MacroModel, Schrödinger, LLC, New York, NY, 2019) with the MMFFs force-field as implemented in this software. Energy minimized structures were obtained using 2500 steps of Truncated Newton Conjugate Gradient (TNCG), chloroform as implicit solvent and the extended cutoff option.

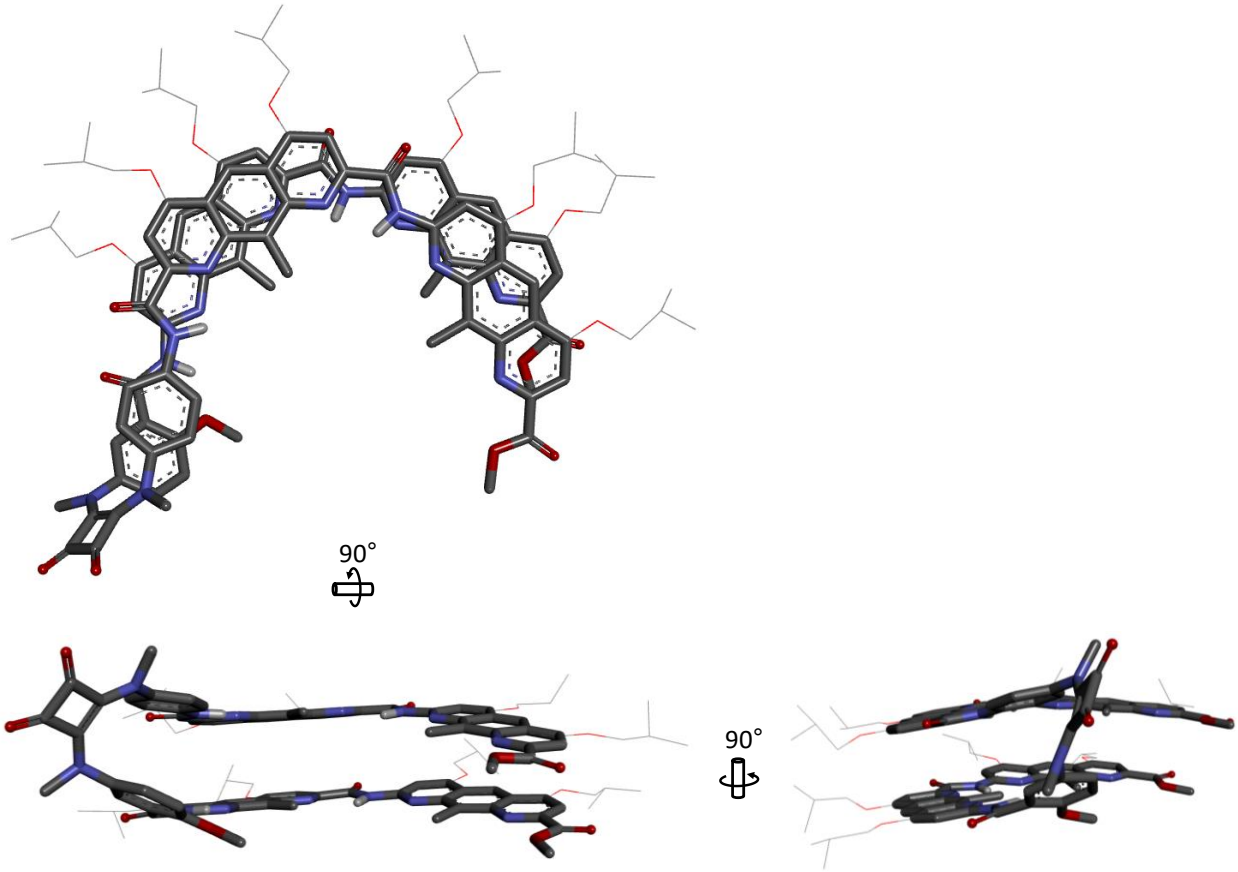


Figure S44. Top, front and side views of the energy minimized structure of compound **5**. Non-polar hydrogen atoms are omitted and *i*Bu side-chains are represented using thiner lines for clarity.

7. CRYSTALLOGRAPHIC DATA

Table S2. Crystallographic data for compounds **2**, **3** and **4**.

	Compound **2** (**wv202**)	Compound **3** (**jau275**)	Compound **4** (**jau290**)
CCDC	1885611	1885612	1885613
net formula	$C_{87}H_{90}Cl_6N_{12}O_{14}$	$C_{68.40}H_{73.40}Cl_{4.21}N_8O_{13}$	$C_{109}H_{114}N_{14}O_{20}$
M_r/g mol^{-1}	1740.40	1364.65	1940.14
crystal size/mm	0.090 × 0.050 × 0.040	0.400 × 0.050 × 0.050	0.300 × 0.200 × 0.010
crystal system	triclinic	triclinic	triclinic
space group	'P -1'	'P -1'	'P -1'
a/Å	13.973(3)	14.9049(3)	11.6470(6)
b/Å	17.045(4)	15.4511(3)	23.8157(6)
c/Å	20.872(4)	18.3390(4)	24.7874(6)
α/°	89.660(7)	86.407(2)	104.064(2)
β/°	85.484(6)	68.494(2)	96.215(4)
γ/°	89.815(7)	84.330(2)	96.776(3)
V/Å^3	4955.5(17)	3908.56(15)	6555.6(4)
Z	2	2	2
calc. density/g cm^{-3}	1.166	1.160	0.983
μ/mm^{-1}	0.235	1.933	0.561
Transm. factor range	0.86–0.99	0.61946–1.00000	0.44980–1.00000
refls. Measured	17359	51374	64400
R_{int}	0.1091	0.0307	0.0956
mean σ(I)/I	0.1791	0.0196	0.0768
θ range	3.157–25.025	3.305–68.242	1.856–74.540
observed refls.	7507	13051	16793
x, y (weight. scheme)	0.1361, 0	0.1498, 1.7284	0.1676, 9.5946
hydrogen refinement	constr	constr	constr
refls in refinement	17359	14131	25205
Parameters	1073	1153	1311
Restraints	0	533	42
$R(F_{obs})$	0.0897	0.0786	0.1200
$R_w(F^2)$	0.2633	0.2414	0.3636
S	0.938	1.031	1.031
shift/error$_{max}$	0.001	0.001	0.001
max electr. dens./e Å^{-3}	0.453	0.518	0.535
min electr. dens./e Å^{-3}	−0.514	−0.370	−0.412

The intensity data of **wv202** were measured at a temperature of 100 K on a Bruker D8 Venture TXS system equipped with a multilayer mirror optics monochromator and a Mo Kα rotating-anode X-ray tube (λ = 0.71073 Å), those of **jau275** and **jau290** at a temperature of 120 K on a Rigaku FRX diffractometer (Cu Kα rotating-anode X-ray tube (λ = 1.54178 Å)). The frames of **wv202** were integrated with the Bruker SAINT software package [3], **jau275** and **jau290** were integrated with CrysAlisPro [4]. Data were corrected for absorption effects using the Multi-Scan method (SADABS [5] for **wv202**, SCALE3 ABSPACK, embedded in [4]). The structures were solved and refined using the Bruker SHELXTL Software Package [6]. All hydrogen atoms were calculated in positions having ideal geometry riding on their parent atoms. In all structures solvent molecules could not be refined properly and have been squeezed out (partly) by means of the SQUEEZE application [7] embedded in PLATON [8]: approximately 4 CH_2Cl_2 per unit cell have been squeezed out in **2** (**wv202**), approximately 2 $CHCl_3$ in **3** (**jau275**), and approximately 15 $CHCl_3$ in **4** (**jau290**).

There are three minor disordered parts in the main moiety of **wv202**. These disordered parts of the structure have been refined isotropically.

In **jau275**, the disorder has been described by a split model including two structure parts. The site occupation factors refined to 0.75 and 0.25. The atoms of the minor part have been refined isotropically. The SAME instruction has been applied to restraint the 1-2 and 1-3 distances of the minor part while the corresponding atoms of the major part served as structure model. The SAME instruction has also been applied in the disorder of C31 - C34 and two disordered chloroform moieties. In order to improve the vibration ellipsoids of a few atoms, SIMU and ISOR restraints have been applied.

In **jau290**, the ISOR instruction has been applied in order to improve the anisotropic displacement parameters of seven atoms.

The figures were drawn at the 50% ellipsoid probability level (ORTEP [9]).

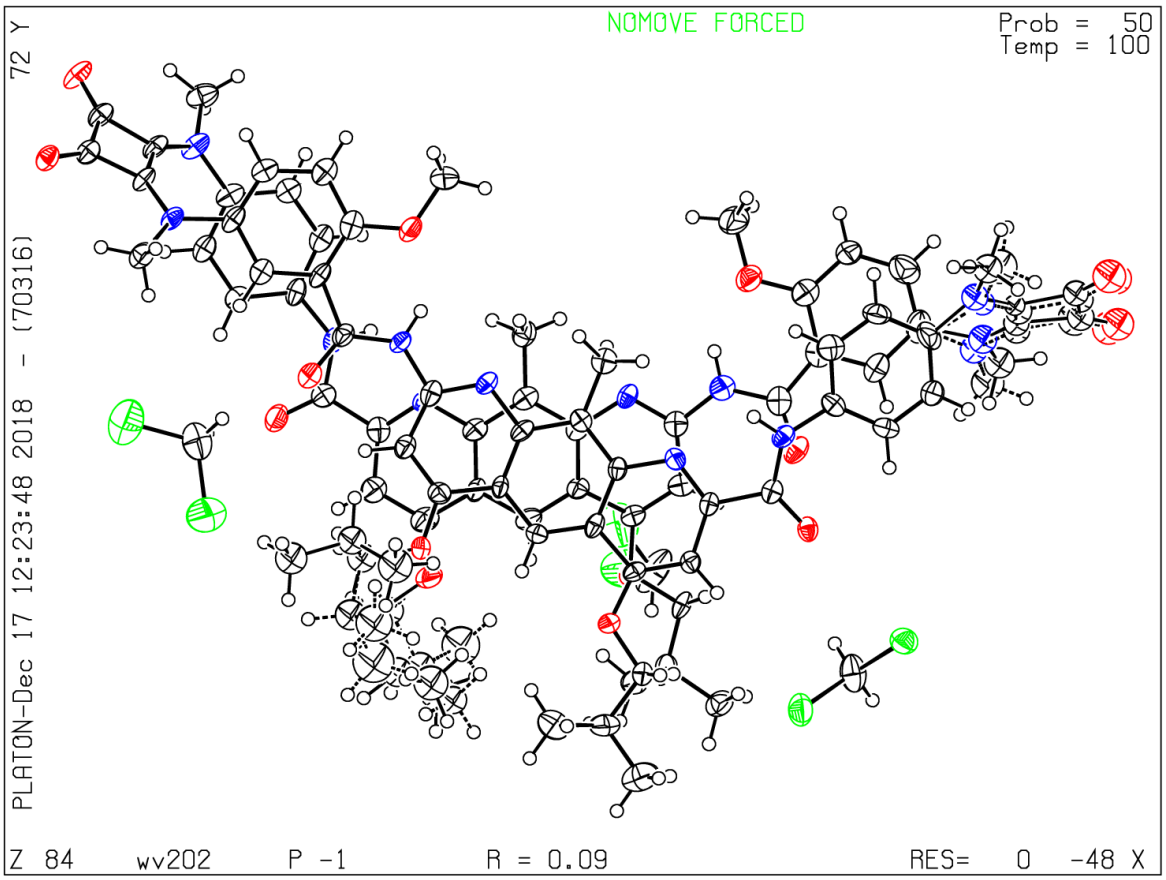


Figure S45. Crystal structure of compound **2** (**wv202**) at the 50% ellipsoid probability level (ORTEP [8]).

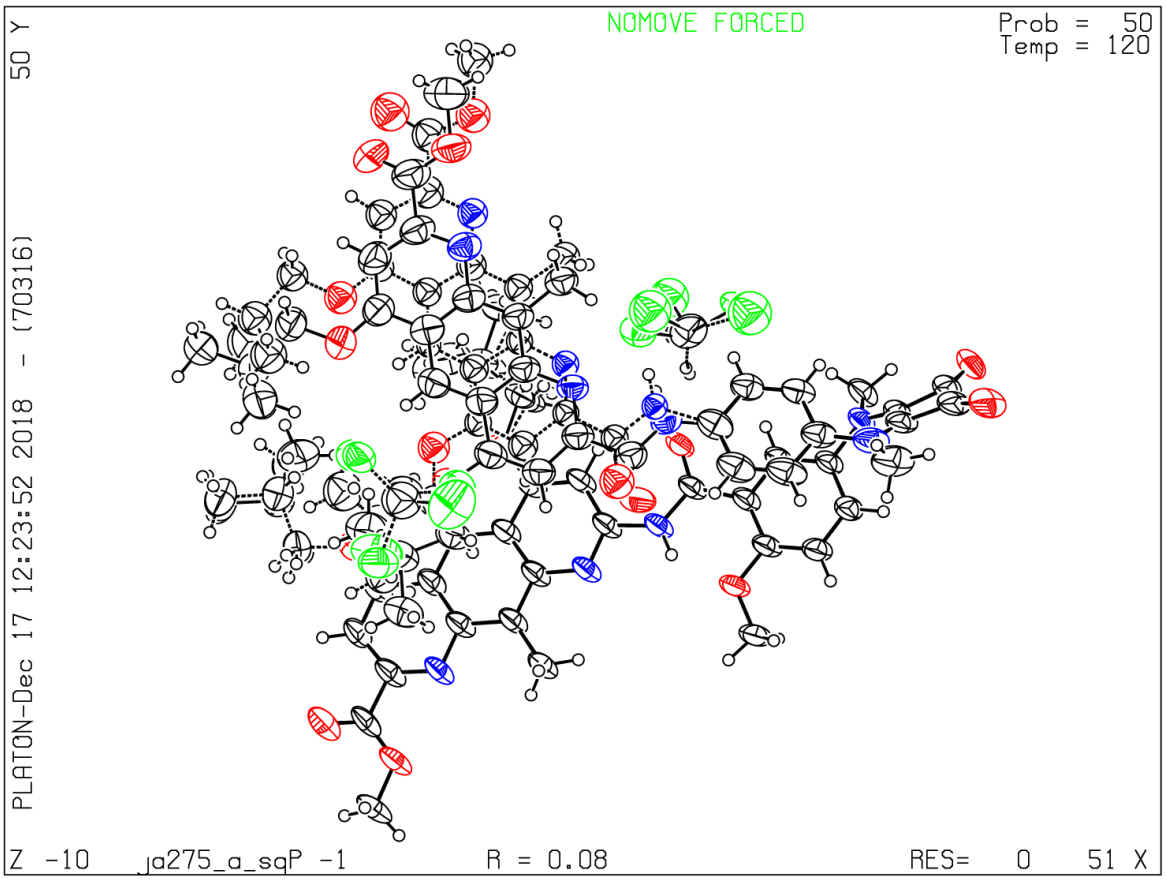


Figure S46. Crystal structure of compound **3** (**jau275**) at the 50% ellipsoid probability level (ORTEP [8]).

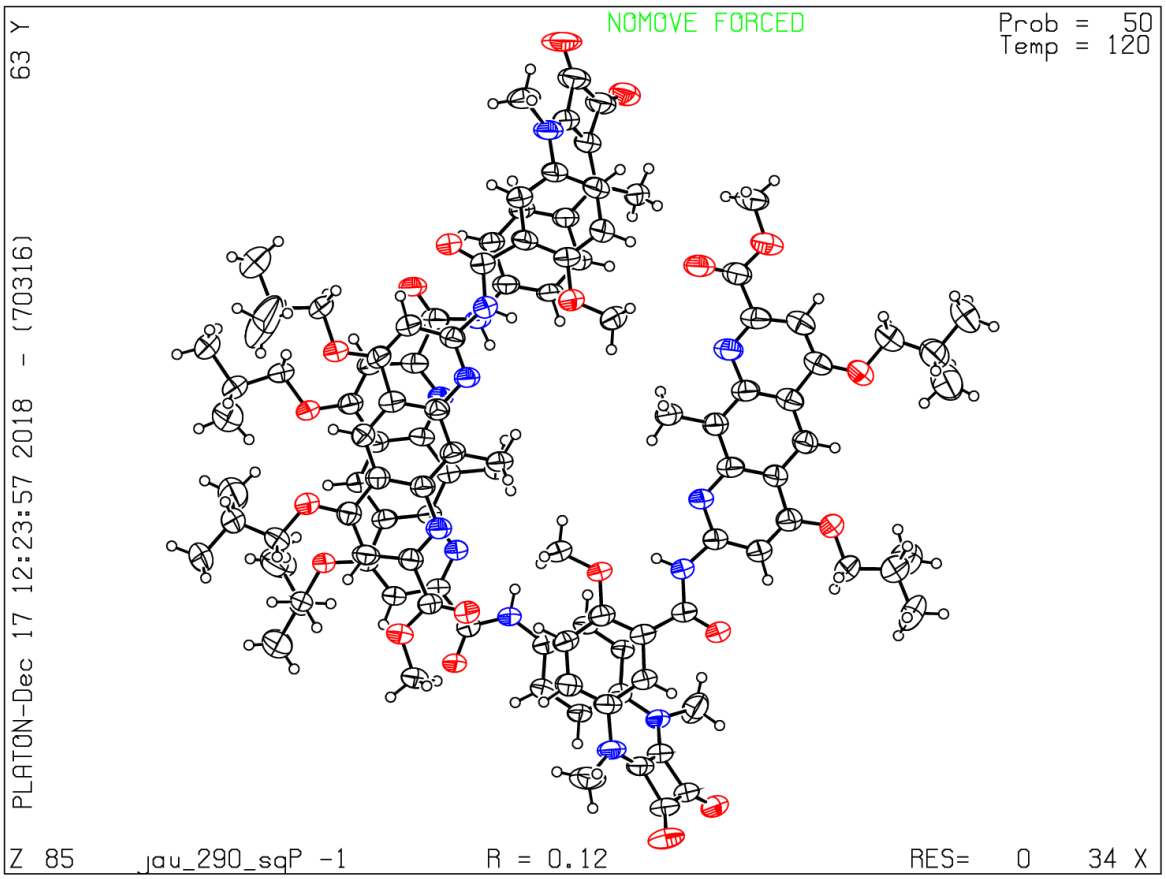


Figure S47. Crystal structure of compound **4** (**jau290**) at the 50% ellipsoid probability level (ORTEP [8]).

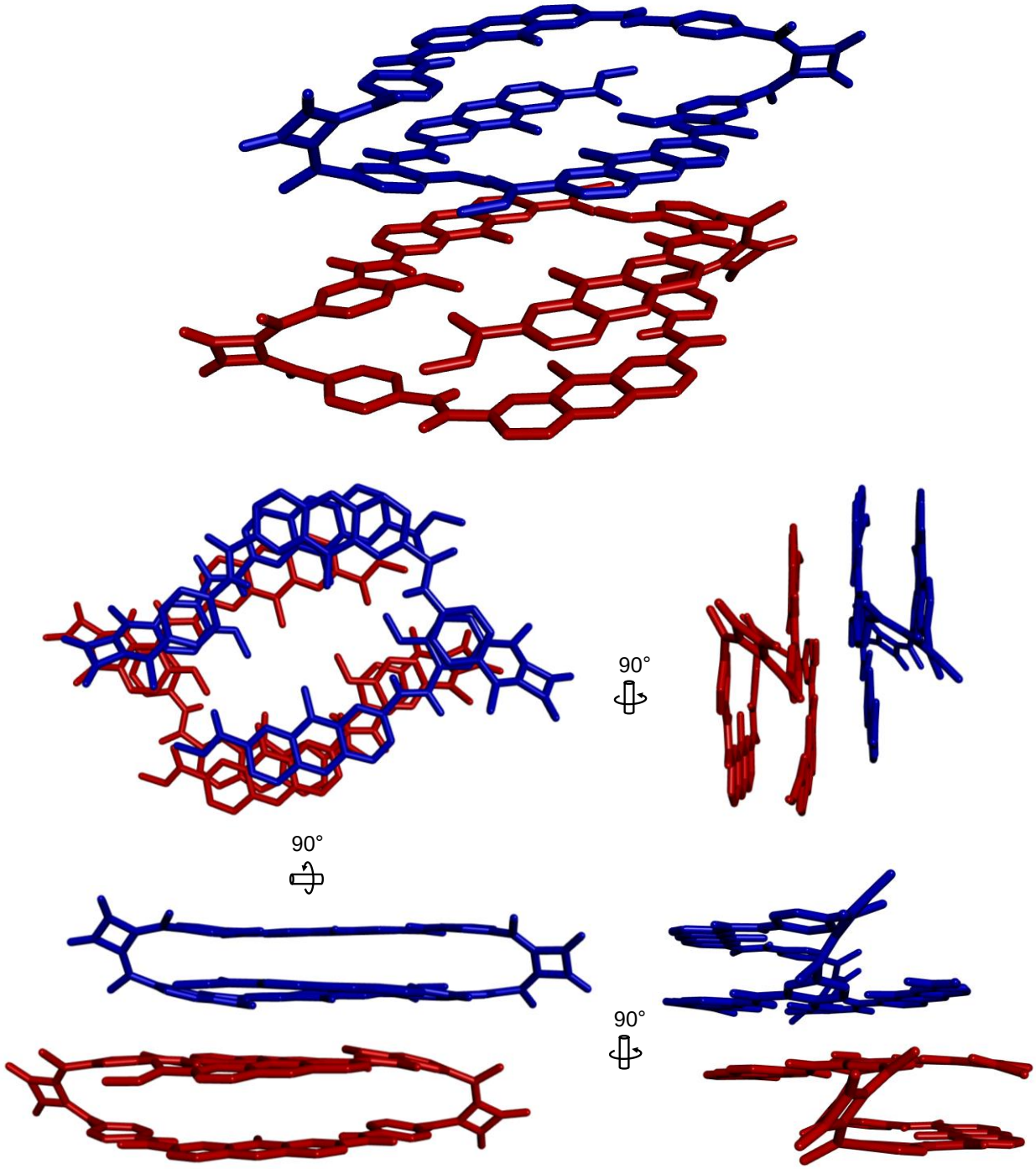


Figure S48. Crystal structure of compound **4** (**jau290**) showing the packing of the two enntiomeric conformers.

8. SPECTROSCOPIC STUDIES

8.1. UV-Vis spectroscopy

UV-Vis measurements were performed on a Cary 60 UV-Vis (Agilent Technologies) instrument using a 1 x 1 cm quartz cuvette and the following settings: single beam, 4800 nm/min scan rate, 0.0125 s averaging time and 1 nm data interval. The $CHCl_3$ used to prepare the solutions was freshly filtered through basic alumina and degassed (freeze-pump-thaw).

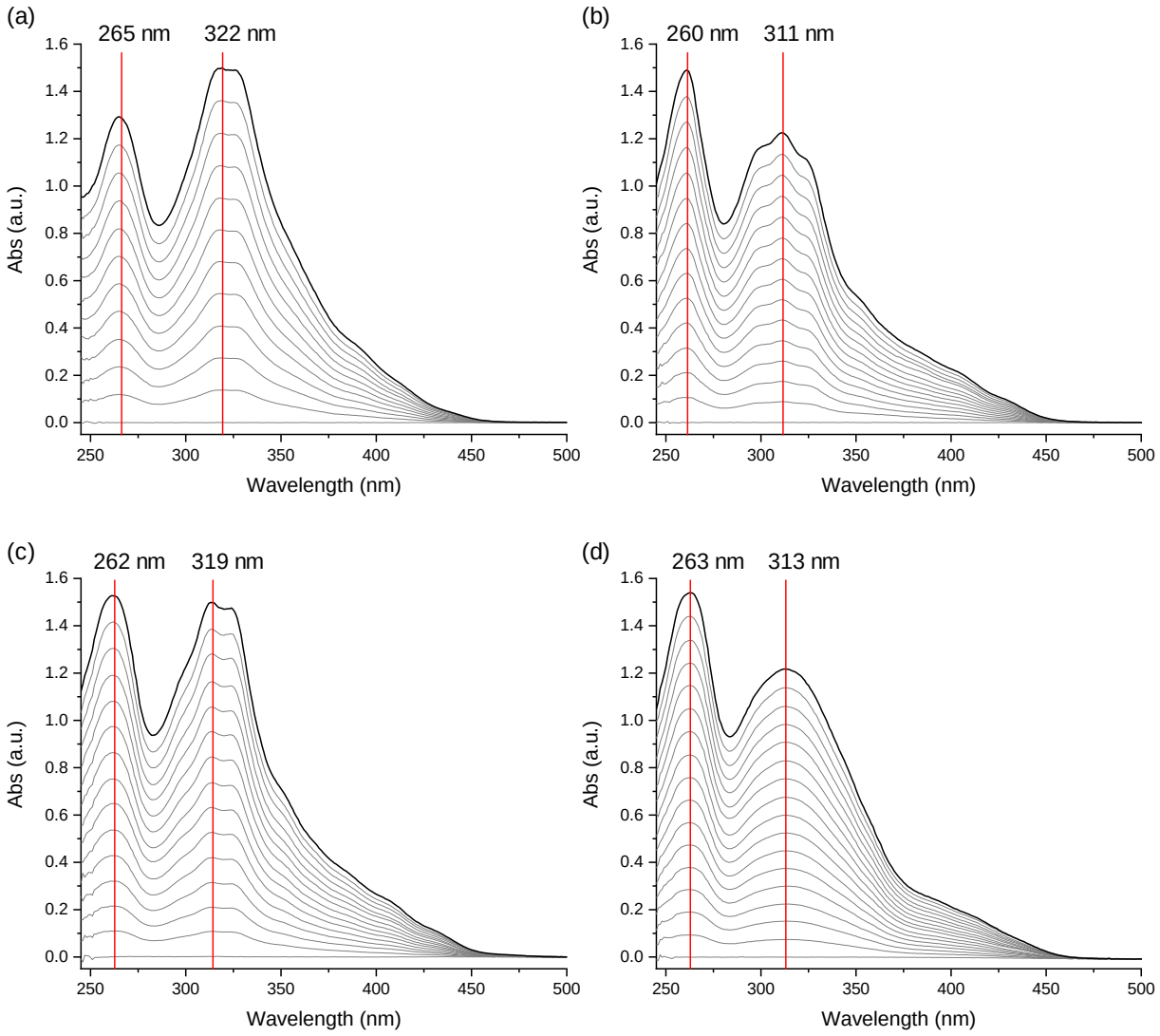


Figure S49. UV-Vis spectra (245-500 nm, 298 K, $CHCl_3$) of (a) compound **2** (1.2-12.9 µM, λ_{max} = 265 nm and 322 nm), (b) compound **3** (1.2-16.1 µM, λ_{max} = 260 nm and 311 nm), (c) compound **4** (0.76-10.5 µM, λ_{max} = 262 nm and 319 nm) and (d) compound **5** (0.69-10.8 µM, λ_{max} = 263 nm and 313 nm) under anaerobic conditions.

8.2. Fluorescence spectroscopy

Fluorescence measurements were performed on a Cary Elipse (Varian) instrument using a 1 x 1 cm quartz cuvette and the following settings: 5 nm slit, 600 nm/min scan rate, 0.1 s averaging time and 1 nm data interval. The $CHCl_3$ used to prepare the solutions was freshly filtered through basic alumina and degassed (freeze-pump-thaw).

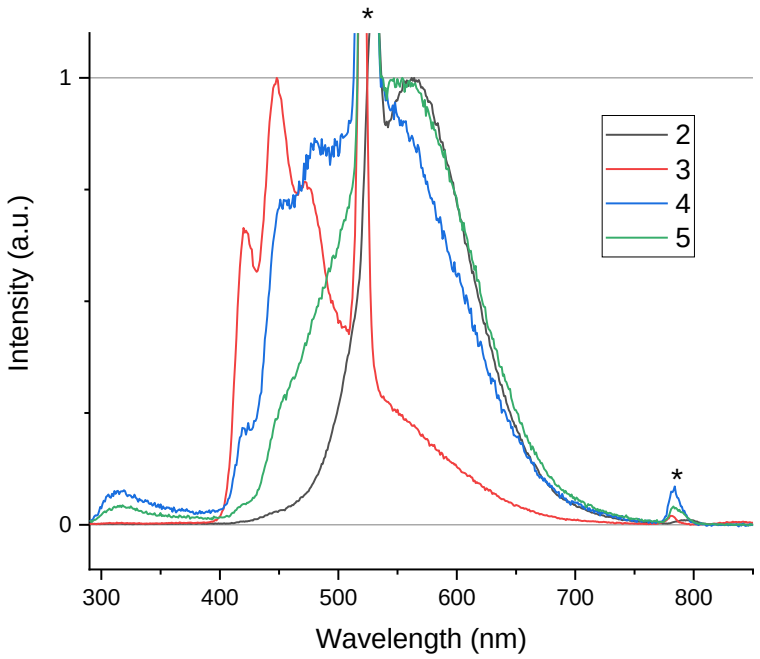


Figure S50. Fluorescence spectra ($CHCl_3$, 298 K, 290-850 nm, normalized) of compounds **2** (black line, 3.2 µM, λ_{ex} = 265 nm), **3** (red line, 3.1 µM, λ_{ex} = 260 nm), **4** (blue line, 2.5 µM, λ_{ex} = 262 nm) and **5** (green line, 2.3 µM, λ_{ex} = 263 nm) under anaerobic conditions. Scattering peak are identified with an asterisk ($\lambda_{em} = 2\lambda_{ex}$ and $3\lambda_{ex}$).

9. REFERENCES

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[9] Farrugia, L. J., *J. Appl. Cryst.* **2012**, *45*, 849.