Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting information

Piperazine-1,4-diol (PipzDiol): Synthesis, Stereodynamics and Assembly of Supramolecular Hydrogen-Bonded 2D Networks

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General information and instrumentation

All reactions were carried out in oven-dried (150°C) glassware. CH_2Cl_2, $CHCl_3$, pyridine and DMF were distilled over CaH_2; ether and methanol were distilled without drying agents. Piperazine, anhydrous dibenzoyl peroxide, Luperox® LP (Lauroyl peroxide), organic acids and all inorganic reagents were commercial grade and used as received.

NMR spectra were recorded at indicated temperatures with a Bruker Avance 300 and 600 spectrometers with residual solvent peaks as internal standards.[1] Multiplicities are indicated by s (singlet), d (doublet), m (multiplet), and br (broad). Data acquisition and processing were performed with Topspin 4.1.3 and Mestrenova 12.0.0 software, respectively.

Melting points were determined on a Kofler heating stage and were not corrected. HRMS experiments were performed on a mass-spectrometer with electrospray ionization and a time-of-flight (TOF) detector. Peaks in FT-IR spectra data are reported in cm^{-1} with the following relative intensities: s (strong), m (medium), w (weak), br (broad), sh (shoulder). Elemental analysis is average of two combustions. Analytical thin-layer chromatography was performed on silica gel plates with QF 254. Visualization was accomplished with UV light, solution of ninhydrin in ethanol, Dragendorff's reagent solution and iodine absorbed on silica gel.

For details of other methods see corresponding sections.

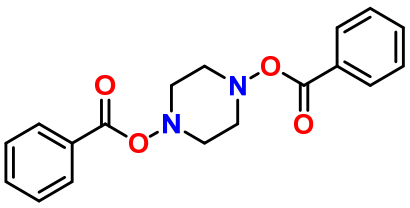
[1] Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR Chemical Shifts of Trace Impurities: Common Laboratory Solvents, Organics, and Gases in Deuterated Solvents Relevant to the Organometallic Chemist. *Organometallics* **2010**, *29* (9), 2176–2179.

Synthesis and characterization of products

Reaction of piperazine with dibenzoyl peroxide

Into the Schlenk tube were placed Cs_2CO_3 (6 equiv., 69.7 mmol, 22.7 g), anhydrous Bz_2O_2 (4 equiv., 46.4 mmol, 11.3 g) and CH_2Cl_2 (112 mL) under argon atmosphere and the mixture was stirred for 15 min. Then, a solution of piperazine (1 equiv., 11.6 mmol, 1.0 g) in CH_2Cl_2 (44 mL) was added. The mixture was stirred under reflux 8 hours (TLC control). After cooling to rt, 95 mL of water was added and the mixture was stirred for additional 15 min. Organic phase was separated, aqueous layer was washed with CH_2Cl_2 (2×155 mL). Combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was triturated with Et_2O to remove most of unreacted dibenzoyl peroxide. The residual solid was dissolved in CH_2Cl_2, pre-adsorbed on silica gel and subjected to a column chromatography on silica gel (eluent EtOAc–hexane, 1 : 9 → 1 : 3) to give 2.3 g (61 %) of product **3a**. Further elution with EtOAc–hexane (1 : 1) gave 0.32 g (9 %) of side product **4a**.

1,4-Dibenzoyloxypiperazine (3a)



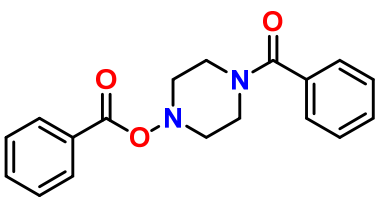
White powder. R_f = 0.5 (hexane–EtOAc, 1:1). Mp 143 – 144 °C.

^{1}H NMR (300 MHz, $CDCl_3$, 300 K, HSQC, mixture of conformers/invertomers): δ 8.03 (d, *J* = 7.5 Hz, 4H, 2 *o*-Ph), 7.59 (t, *J* = 7.5 Hz, 2H, 2 *p*-Ph), 7.46 (t, *J* = 7.5 Hz, 4H, 2 *m*-Ph), 3.56 and 3.36 (2 br m, 8H, 4 CH_2).

^{13}C NMR (75 MHz, $CDCl_3$, 300 K, HSQC, mixture of conformers/invertomers): δ 164.6 (2 C=O), 133.4 (2 *p*-Ph), 129.6 (4 *o*-Ph), 129.1 (2 *i*-Ph), 128.6 (4 *m*-Ph), 54.4 and 53.0 (2 br, 4 CH_2).

ESI-HRMS m/z: $[M+H]^+$ Calcd for $[C_{18}H_{19}N_2O_4]^+$ 327.1339; Found 327.1336.

1-(Benzoyl)-4-(benzoyloxy)piperazine (4a)



White powder. R_f = 0.32 (hexane–EtOAc, 1:1). Mp 132 – 135 °C.

^{1}H NMR (300 MHz, $CDCl_3$, 300 K, HSQC, mixture of conformers/invertomers): δ 8.04 – 7.99 (m, 3H, *p*-Bz_N and *o*-Bz_O), 7.61 – 7.56 (m, 1H, *p*-Bz_O), 7.49 – 7.43 (m, 6H, *o*-Bz_N, *m*-Bz_N and *m*-Bz_O), 3.54, 3.37 and 2.99 (3 br m, 8H, 4 CH_2).

^{13}C NMR (75 MHz, $CDCl_3$, 300 K, HSQC, mixture of conformers/invertomers): δ 170.4 (O–C=O), 164.5 (N–C=O), 135.1 and 133.4 (2 *p*-Ph), 130.1 and 128.9 (2 *i*-Ph), 129.5, 128.6, 128.5 and 127.1 (4 *o*-Ph and 4 *m*-Ph), 56.0 (4 CH_2N).

ESI-HRMS m/z: $[M+H]^+$ Calcd for $[C_{18}H_{19}N_2O_3]^+$ 311.1390; Found 311.1390.

Synthesis of adamantane-1-carboxylic peroxyanhydride (adamatoyl peroxide)[2]

Adamantane-1-carboxylic acid (1 equiv., 5.55 mmol, 1.0 g) was dissolved in 22 mL of dry DMF and cooled under stirring on ice-bath. Oxalyl chloride (3 equiv., 16.64 mmol, 2.11 g) was added dropwise while the temperature of mixture was below 35˚C. After addition the mixture was stirred additional hour at rt. The solvent was removed under reduced pressure and the residual was re-dissolved in 10 mL of ether and cooled under stirring on ice-bath. Hydrogen peroxide (27%, 0.75 equiv., 4.23 mmol, 533 mg) and pyridine (1.2 equiv., 6.76 mmol, 0.545 mL) were consequently added dropwise while the temperature of mixture was below 30˚C. After addition the mixture was stirred additional 1 hour at rt. Then, the mixture was diluted with 10 mL of ether, washed with 20 mL of 3.5% solution of HCl in distilled water, 3 × 20 mL sat. $NaHCO_3$ solution, and then with water until the neutral pH was achieved. Organic phase was dried by Na_2SO_4. Crude product was obtained by solvent evaporation with 86% yield (2.42 mmol, 0.87 g) and was used in the next step without further purification due to instability.

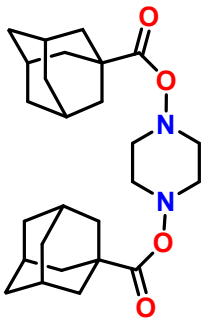
Reaction of piperazine with adamatoyl peroxide

Into the Schlenk tube were placed Cs_2CO_3 (6 equiv, 2.51 mmol, 817 mg) and a solution of adamatoyl peroxide (4 equiv., 1.67 mmol, 600 mg) in CH_2Cl_2 (6 mL) under argon atmosphere. Then, a solution of piperazine (1 equiv., 0.42 mmol, 36 mg) in CH_2Cl_2 (2 mL) was added. The mixture was stirred at rt for overnight (TLC control). Then, 6 mL of water was added and the mixture was stirred additional 10 min. Organic phase was separated, aqueous layer was washed with CH_2Cl_2 (2×12

[2] Beckwith, A. L. J., Cross, R. T., Gream, G. E. The mechanism of lead tetraacetate decarboxylation. I. Tertiary carboxylic acids. *Australian J. Chem.*, **1974**, *27* (8), 1673–1692.

mL). Combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was subjected to a column chromatography on silica gel (eluent EtOAc-hexane, 1 : 9 → 1 : 5 → 1 : 1) to give 108 mg (58 %) of product **3b**. Further elution with EtOAc–MeOH (7 : 1) gave 12 mg (7 %) of side product **4b**.

1,4-(1-Adamantoyl)oxypiperazine (3b)



White powder. R_f = 0.5 (hexane : EtOAc, 1:1). Mp > 250 °C (without decomposition).

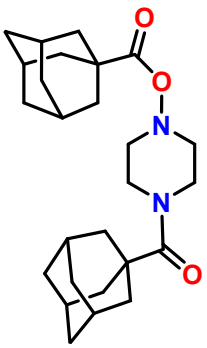
^{1}H NMR (300 MHz, $CDCl_3$, 298 K, HSQC): δ 3.63 (s, 8H, 4 CH_2N), 2.01 (s, 6H, CH), 1.95 (br s, 12H, CH_2), 1.69 (br s, 12H, CH_2).

^{13}C NMR (75 MHz, $CDCl_3$, 298 K, HSQC): δ 176.1 (2 C=O), 45.5 (4 CH_2N), 41.8 (2 C), 39.1 (6 CH_2), 36.6 (6 CH_2), 28.4 (6 CH).

FT-IR (KBr): 2907 (s), 2849 (s), 2676 (w), 2656 (w), 1725 (w), 1614 (s, C=O), 1547 (w), 1447 (m), 1416 (s), 1365 (w), 1343 (w), 1316 (w), 1280 (m), 1260 (m), 1226 (s), 1181 (m), 1163 (w), 1100 (w), 1045 (w), 1011 (s), 975 (w), 943 (w), 806 (w), 723 (w), 648 (w), 575 (w), 481 (w), 458 (w).

ESI-HRMS m/z: $[M+H]^+$ Calcd for $[C_{26}H_{39}N_2O_4]^+$ 443.2904; Found 443.2895.

1-(1-Adamantoyl)-4-(1-adamantoyl)oxypiperazine (4b)



Pale-yellow semi-solid.

^{1}H NMR (300 MHz, $CDCl_3$, 298 K, HSQC): δ 3.67 (s, 8H, CH_2N), 2.04 (br m, 6H, 6 CH), 1.99 and 1.91 (2 br m, 12H and 12H, 6 CH_2), 1.72 (br m, 24H, 6 CH_2).

^{13}C NMR (75 MHz, $CDCl_3$, 298 K, HSQC): δ 176.3 (C=O), 45.7 (4 CH_2N), 41.9 (C), 40.6 (C), 39.2 (3 CH_2), 38.7 (3 CH_2), 36.7 (3 CH_2), 36.6 (3 CH_2), 28.6 (3 CH), 28.0 (3 CH) (amide carbon is not observed).

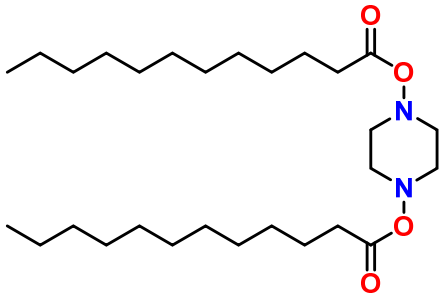
FT-IR (KBr): 2927 (s), 2853 (s sh), 2659 (m br), 2635 (m sh), 2248 (w), 1696 (s, sh, C=O), 1609 (s, sh, C=O), 1452 (s), 1416 (s), 1345 (w), 1320 (w), 1280 (s), 1245 (s), 1219 (s), 1180 (s), 1103 (m), 1081 (m), 1046 (m), 1011 (s), 975 (m), 916 (s), 816 (w sh), 732 (s), 661 (w, sh), 552 (w), 530 (w), 508 (w), 454 (w).

ESI-HRMS m/z: $[M+H]^+$ Calcd for $[C_{26}H_{39}N_2O_3]^+$ 427.2955; Found 427.2962.

Reaction of piperazine with lauroyl peroxide

Into the Schlenk tube were placed Cs_2CO_3 (6 equiv., 1.02 mmol, 332 mg), dodecanoic peroxyanhydride (4 equiv., 0.68 mmol, 270 mg) and CH_2Cl_2 (2.5 mL) under argon atmosphere and the mixture was stirred for 15 min. Then, a solution of piperazine (1 equiv., 0.17 mmol, 15 mg) in CH_2Cl_2 (0.5 mL) was added. The mixture was stirred at rt overnight (TLC control). Then, 1.5 mL of water was added and the mixture was stirred additional 15 min. Organic phase was separated, aqueous layer was washed with CH_2Cl_2 (2×2.5 mL). Combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was subjected to a column chromatography on silica gel (eluent EtOAc–hexane, 1 : 7) to give 28 mg (34 %) of product **3c**. Further elution with EtOAc–hexane (1 : 3) gave 11 mg (13 %) of side product **4c**.

Piperazine-1,4-diyl didodecanoate (3c)



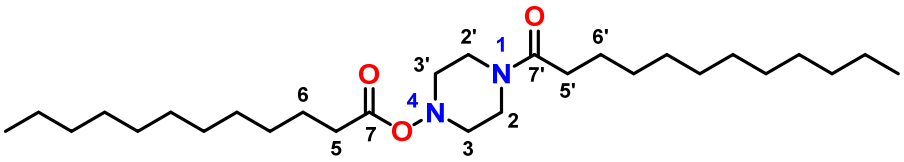
Pale-yellow semi-solid. R_f = 0.7 (hexane : EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$, 300 K, HSQC, mixture of conformers/invertomers): δ 3.32 and 3.09 (2 br m, 8H, 4 CH_2N), 2.27 (t, *J* = 7.5 Hz, 4H, 2 CH_2-C(O)), 1.62 (br q, *J* = 7.3 Hz, 4H, 2 CH_2), 1.26 (br m, 32H, 16 CH_2), 0.87 (t, *J* = 6.5 Hz, 6H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, 300 K, HSQC, mixture of conformers/invertomers): δ 171.8 (2 C=O), 54.4 and 52.6 (2 br, 4 CH_2N), 33.1 (2 CH_2-C(O)), 32.0, 29.7, 29.6, 29.5, 29.3, 29.2, 25.2 and 22.8 (18 CH_2), 14.2 (2 CH_3).

ESI-HRMS m/z: $[M+H]^+$ Calcd for $[C_{28}H_{54}N_2O_4Na]^+$ 505.3976; Found 505.3974.

1-(Dodecanoyl)-4-(dodecanoyloxy)piperazine (4c)



Pale-yellow oil. R_f = 0.5 (hexane : EtOAc, 1:1).

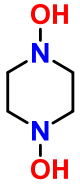
^{1}H NMR (300 MHz, $CDCl_3$, 301 K, HSQC, COSY, mixture of conformers/invertomers): δ 4.44, 3.78, 3.48 and 3.13 (4 br m, 4H, CH_2N-2 and CH_2N-2'), 3.34 and 2.74 (2 br m, 4H, CH_2N-3 and CH_2N-3'), 2.34 – 2.24 (m, 4H, CH_2-5 and CH_2-5'), 1.65 – 1.60 (br m, 4H, CH_2-6 and CH_2-6'), 1.25 (br s, 32H, CH_2), 0.88 (t, *J* = 6.4 Hz, 6H, 2 CH_3).

^{13}C NMR (75 MHz, $CDCl_3$, HSQC, 298 K, mixture of conformers/invertomers): δ 171.81 and 171.78 (2 C=O), 56.1 and 55.8 (CH_2N-3 and CH_2N-3'), 43.8 and 40.0 (CH_2N-2 and CH_2N-2'), 33.3 and 33.1 (CH_2-5 and CH_2-5'), 32.0 (2 CH_2), 29.8 (2 CH_2), 29.7 (2 CH_2), 29.6 (CH_2), 29.6 (CH_2), 29.6 (2 CH_2), 29.5 (2 CH_2), 29.3 (CH_2), 29.2 (CH_2), 25.4 and 25.1 (CH_2-6 and CH_2-6'), 22.8 (2 CH_2), 14.3 (2 CH_3).

FT-IR (KBr): 2957 (m), 2920 (s), 2851 (s), 2387 (br, w), 2348 (w), 2292 (br, w), 1752 (m, C=O), 1645 (s, C=O), 1468 (m), 1455 (m), 1375 (w), 1278 (w), 1246 (w), 1219 (w), 1194 (w), 1143 (w), 1112 (w), 1081 (w), 1029 (s), 721 (w), 660 (br, w), 584 (br, w), 494 (br, w), 419 (w).

ESI-HRMS m/z: $[M+H]^+$ Calcd for $[C_{28}H_{55}N_2O_4]^+$ 467.4207; Found 467.4200.

Synthesis of 1,4-dihydroxypiperazine (PipzDiol 2)



Standard procedure. To a solution of 1,4-dibenzoyloxypiperazine **3a** (1.0 equiv, 772 mg, 2.37 mmol) in dry $CHCl_3$ (40 mL) was added hydrazine hydrate (10 equiv, 1.18 g, 23.6 mmol) under inert atmosphere. Reaction was refluxed until full

conversion of substrate **3a** was achieved (4 h, TLC control). Then, volatiles were removed under reduced pressure, and the residue was dried at ca. 0.5 Torr until constant weight to remove water and hydrazine. The resulting solid was triturated with $CHCl_3$ (7×10 mL) and dried in vacuum. In result, 235 mg (84 %) of PipzDiol **2** was obtained.

Larger scale synthesis. To a solution of 1,4-dibenzoyloxypiperazine **3a** (1 equiv, 1.84 g, 5.64 mmol) in dry $CHCl_3$ (94 mL) was added hydrazine hydrate (10 equiv, 2.82 g, 56.4 mmol) under inert atmosphere. Reaction was refluxed until full conversion of substrate **3a** was achieved (6 h, TLC control). Then, volatiles were removed under reduced pressure, and the residue was dried at ca. 0.5 Torr until constant weight to remove water and hydrazine. The resulting solid was triturated with $CHCl_3$ (7×20 mL) and dried in vacuum. In result, 235 mg (84 %) of PipzDiol **2** was obtained. In result, 396 mg (60 %) of PipzDiol **2** was obtained.

Pale grey solid. Mp = 205–207 °C (with decomposition).

At room temperature in solution (DMSO-d_6 or D_2O), a dynamic mixture of *trans*-**2**/*cis*-**2** stereoisomers (ratio 2.2 : 1) is observed by NMR. Upon heating a coalescence of signals is observed (see section Dynamic NMR for details).

*Major isomer (trans-***2***):*

^{1}H NMR (300 MHz, DMSO-d_6, 300 K, HSQC): δ 7.93 (br s, 2H, OH), 2.95 (br d, 4H, CH_2N), 2.51 (br d, 4H, CH_2N).

^{13}C NMR (75 MHz, DMSO-d_6, 300 K): δ 56.9 (CH_2N).

^{1}H NMR (300 MHz, D_2O, 298 K, HSQC, COSY, NOESY): δ 3.21 (br d, *J* = 7.4 Hz, 4H, CH_2N), 2.72 (br d, *J* = 7.5 Hz, 4H, CH_2N).

^{13}C NMR (75 MHz, D_2O, 300 K): δ 55.8 (CH_2N).

*Minor isomer (cis-***2***):*

^{1}H NMR (300 MHz, DMSO-d_6, 300 K, HSQC): δ 7.93 (br s, 2H, OH), 2.75 (br m, 8H, CH_2N).

^{1}H NMR (300 MHz, D_2O, 298 K, HSQC, COSY, NOESY): 3.14 – 3.01 (br m, 4H, CH_2N), 3.00 – 2.95 (br m, 4H, CH_2N).

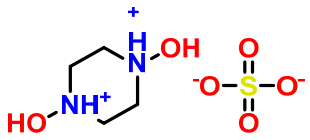
^{13}C NMR (75 MHz, D_2O, 300 K): 52.3 (br, CH_2N).

FT-IR: 3434 (br, w), 3244 (br, w), 3055 (w), 2976 (w), 2907 (w), 2863 (m), 1616 (br, w), 1463 (s), 1412 (m), 1359 (m), 1267 (s), 1106 (s), 1078 (w), 1062 (s), 953 (s), 819 (s), 778 (s), 622 (s), 464 (s).

Anal. calcd for **2**•(1/6)H_2O: C, 39.66; H, 8.60; N, 23.13. Found: C, 39.59; H, 8.50; N, 23.24.

ESI-HRMS m/z: $[M-H]^+$ Calcd for $[C_4H_{11}N_2O_2]^+$ 119.0815; Found 119.0819.

1,4-Dihydroxypiperazine-1,4-diium sulfate $[H_2(2)]^{2+}[SO_4]^{2-}$



Into a round bottom flask were placed 1.4-dihydroxypiperazine **2** (1 equiv, 20 mg, 0.17 mmol), H_2O (1 mL) and MeOH (1 mL). Sulfuric acid (2 equiv, 94 %, 35 mg, 0.02 mL, 0.34 mmol) was added dropwise. After the addition of H_2SO_4 the precipitate immediately formed. The mixture was heated to reflux (most of the precipitate dissolved) and filtered. The solution was kept at ca. 5 °C, and the resulting crystals of salt $[H_2(\mathbf{2})]^{2+}[SO_4]^{2-}$ were collected (27 mg, 74 % yield). The crystals were used for X-Ray analysis (see section X-Ray analysis for details).

Colorless crystals. Mp = 191–192 °C ($MeOH/H_2O$, with decomposition).

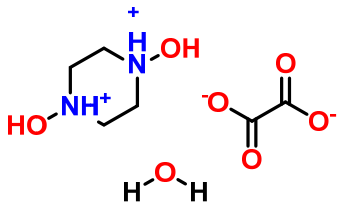
At room temperature in D_2O solution a dynamic mixture of *trans*/*cis* stereoisomers is observed (ratio 1 : 1.2).

Major isomer (trans):
^{1}H NMR (300 MHz, D_2O, 300 K, HSQC): δ 3.70 – 3.62 (br m, 8H).
^{13}C NMR (75 MHz, D_2O, 298 K): δ 50.7 (CH_2N).

Minor isomer (cis):
^{1}H NMR (300 MHz, D_2O, 300 K, HSQC): δ 4.02 (br d, *J* = 10.4 Hz, 4H, CH_2N), 3.51 (br d, *J* = 10.4 Hz, 4H, CH_2N).
^{13}C NMR (75 MHz, D_2O, 298 K): δ 48.9 (br CH_2N).

FT-IR (KBr): 3437 (br w), 3026 (w), 2987 (w), 2608 (br w), 2511 (br), 1639 (br), 1549 (m), 1482 (m), 1458 (m), 1383 (w), 1332 (w), 1297 (w), 1236 (m), 1198 (s), 1110 (s), 1035 (s), 1001 (s), 957 (s), 877 (m), 829 (m), 703 (w), 638 (s), 596 (s), 494 (w), 452 (w), 433 (m).

1,4-Dihydroxypiperazine-1,4-diium oxalate monohydrate $[H_2(2)]^{2+}[Ox]^{2-}\bullet H_2O$



Into a round bottom flask were placed 1.4-dihydroxypiperazine **2** (1 equiv, 15 mg, 0.127 mmol), H_2O (0.5 mL) and MeOH (0.5 mL). Then, a solution of oxalic acid dihydrate (1 equiv, 16 mg, 0.127 mmol) in MeOH/H_2O (0.5 mL/0.5 mL) was added. The precipitate was immediately formed. The mixture was heated to reflux (most of the precipitate dissolved) and filtered. The solution was kept at ca. 5 °C, and the resulting crystals of salt $[H_2(\mathbf{2})]^{2+}[Ox]^{2-}\bullet H_2O$ were collected (13 mg, 45 % yield). The crystals were used for X-Ray analysis (see section X-Ray analysis for details).

Colorless crystals. Mp = 182–183°C (MeOH/H_2O, with decomposition).

At room temperature in D_2O solution a dynamic mixture of *trans*/*cis* stereoisomers is observed (ratio 1.1 : 1.0).

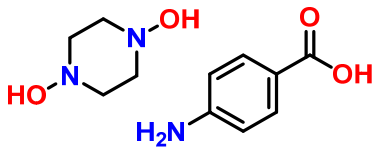
Major isomer (cis):
^{1}H NMR (300 MHz, D_2O, 298 K, HSQC): δ 3.57 – 3.50 (br m, 4H, CH_2N), 3.45 – 3.39 (br m, 4H, CH_2N).

^{13}C NMR (75 MHz, D_2O, 298 K): δ 165.6 (CO), 51.2 (br CH_2N).

Minor isomer (trans):
^{1}H NMR (300 MHz, D_2O, 298 K, HSQC): δ 3.72 (br d, *J* = 10.1 Hz, 4H, CH_2N), 3.21 (br d, *J* = 10.1 Hz, 4H, CH_2N).

^{13}C NMR (75 MHz, D_2O, 298 K): δ 165.6 (CO), 51.2 (br CH_2N).

Adduct of 1,4-dihydroxypiperazine and 4-aminobenzoic acid 2•2PABA

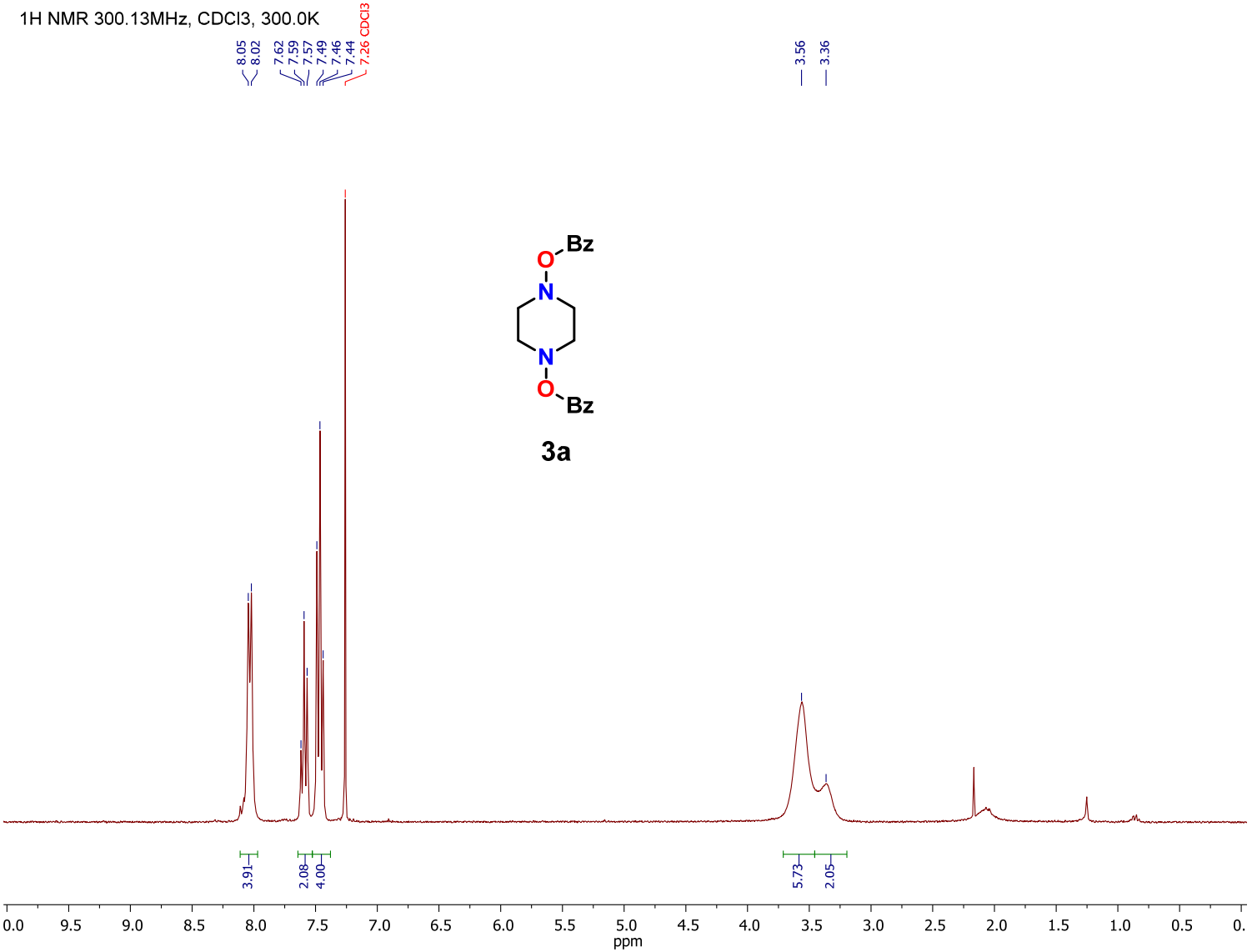


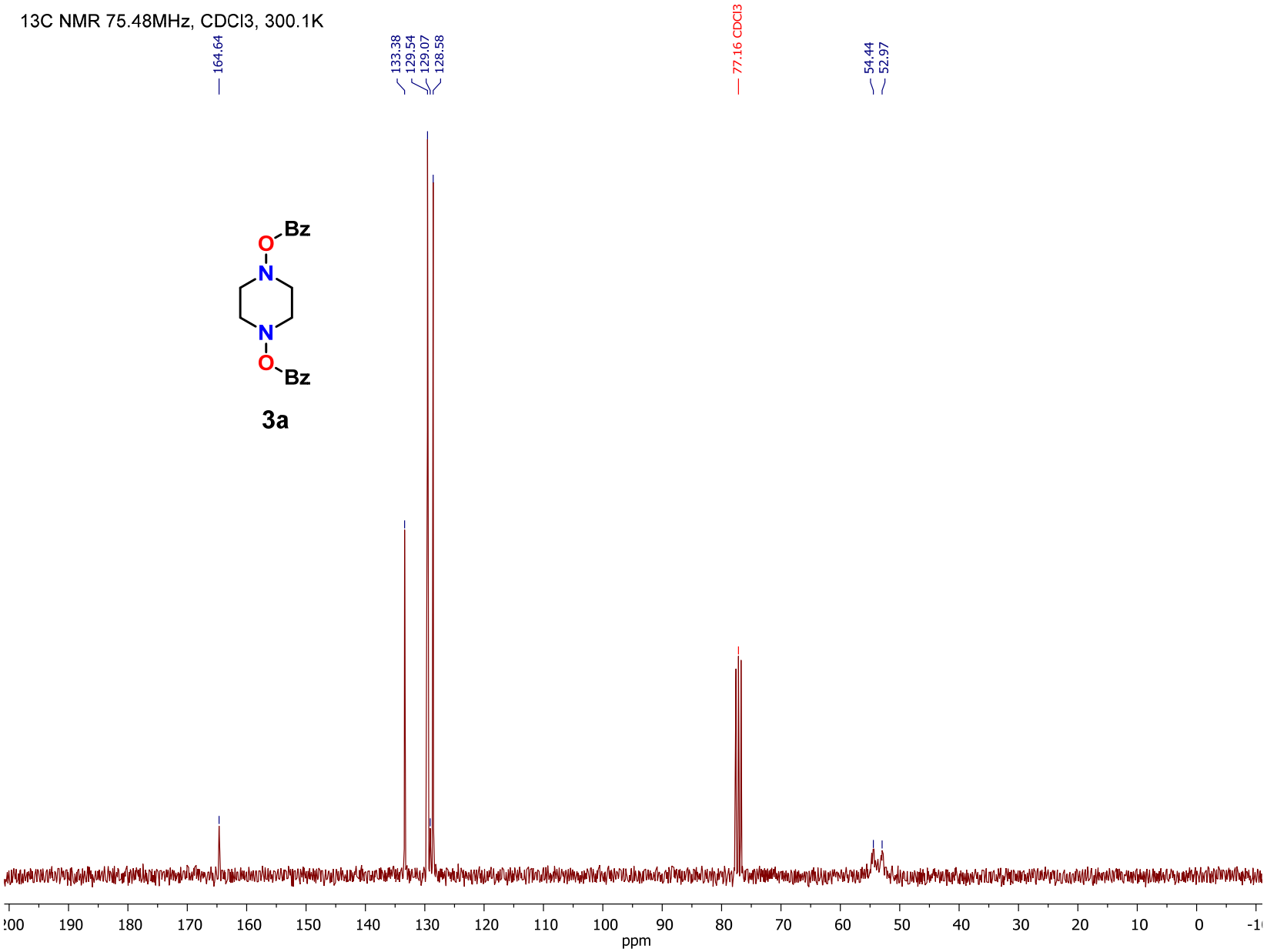
Into a round bottom flask were placed 1.4-dihydroxypiperazine **2** (1 equiv, 20 mg, 0.17 mmol), H_2O (0.5 mL) and MeOH (0.5 mL). Then, a solution of 4-aminobenzoic acid (2 equiv, 46 mg, 0.34 mmol) in MeOH/H_2O (0.5 mL/0.5 mL) was added. The mixture was heated to reflux and filtered. The solution was kept at ca. 5 °C, and the resulting needle crystals of adduct **2**•2PABA were collected (41 mg, 62 %). The crystals were used for X-Ray analysis (see section X-Ray analysis for details).

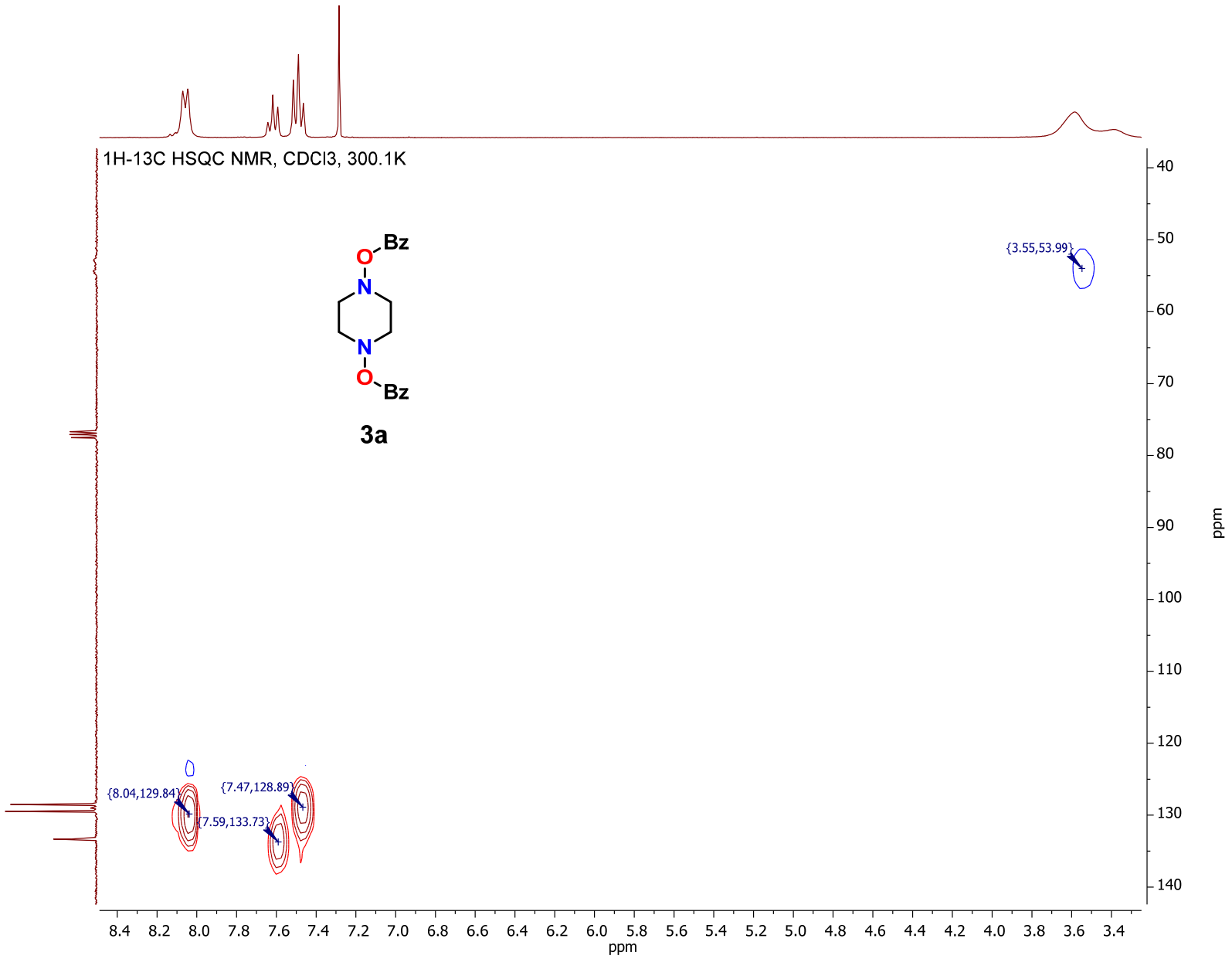
Colorless crystals. Mp = 159–160 °C ($MeOH/H_2O$, with decomposition).

Upon dissolution of **2**•2PABA in DMSO-d_6, dissociation to 1,4-dihydroxypiperazine and *p*-aminobenzoic acid was observed by ^{1}H and ^{13}C NMR.

Spectra of products




13C NMR 75.48MHz, CDCl3, 300.1K
164.64
133.38
129.54
129.07
128.58
77.16 CDCl3
54.44
52.97
Bz
O
N
N
O
Bz
3a
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


1H-13C HSQC NMR, CDCl3, 300.1K
Bz
O
N
N
O
Bz
3a
{3.55,53.99}
{8.04,129.84}
{7.47,128.89}
{7.59,133.73}
40
50
60
70
80
90
100
110
120
130
140
ppm
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
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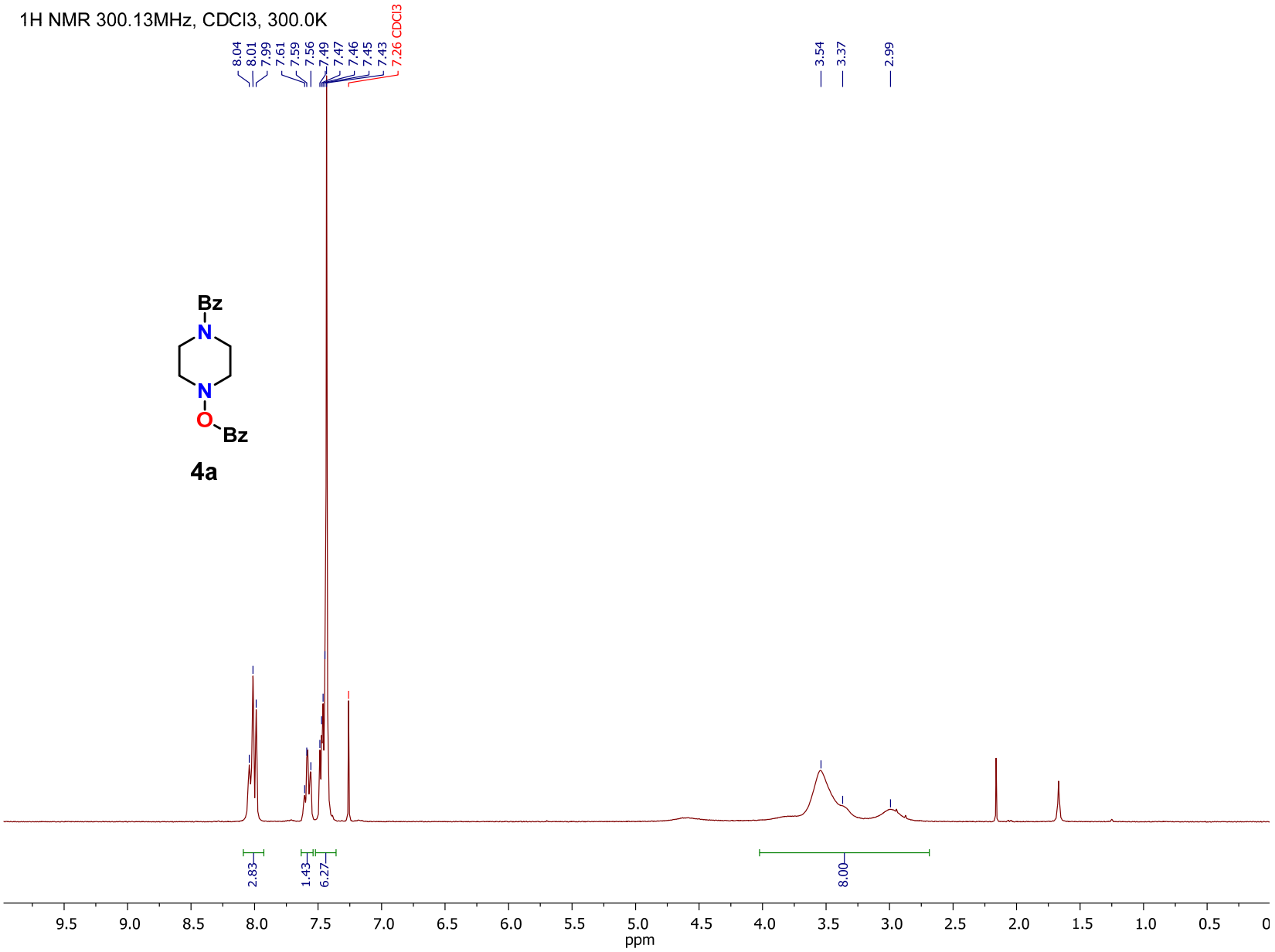
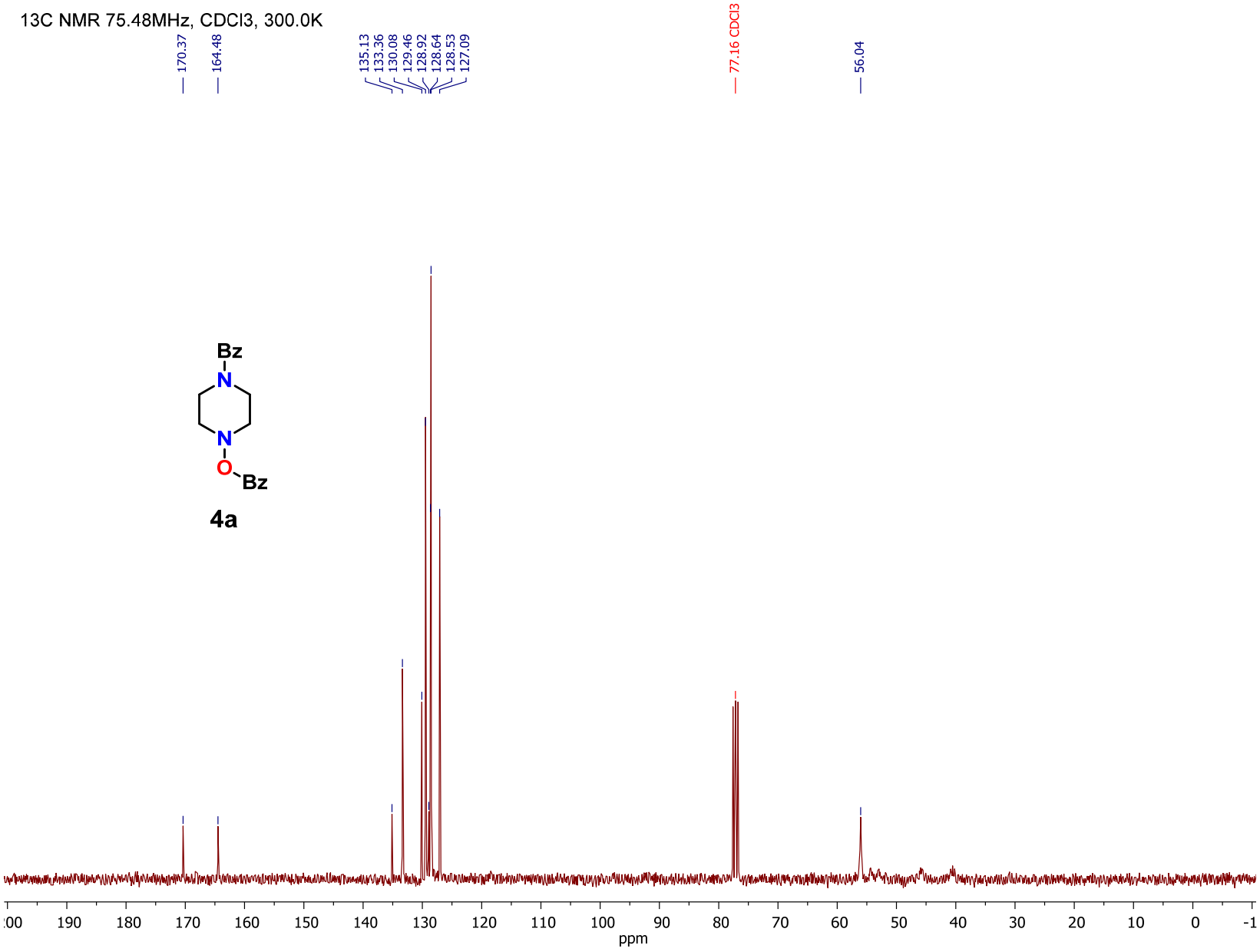
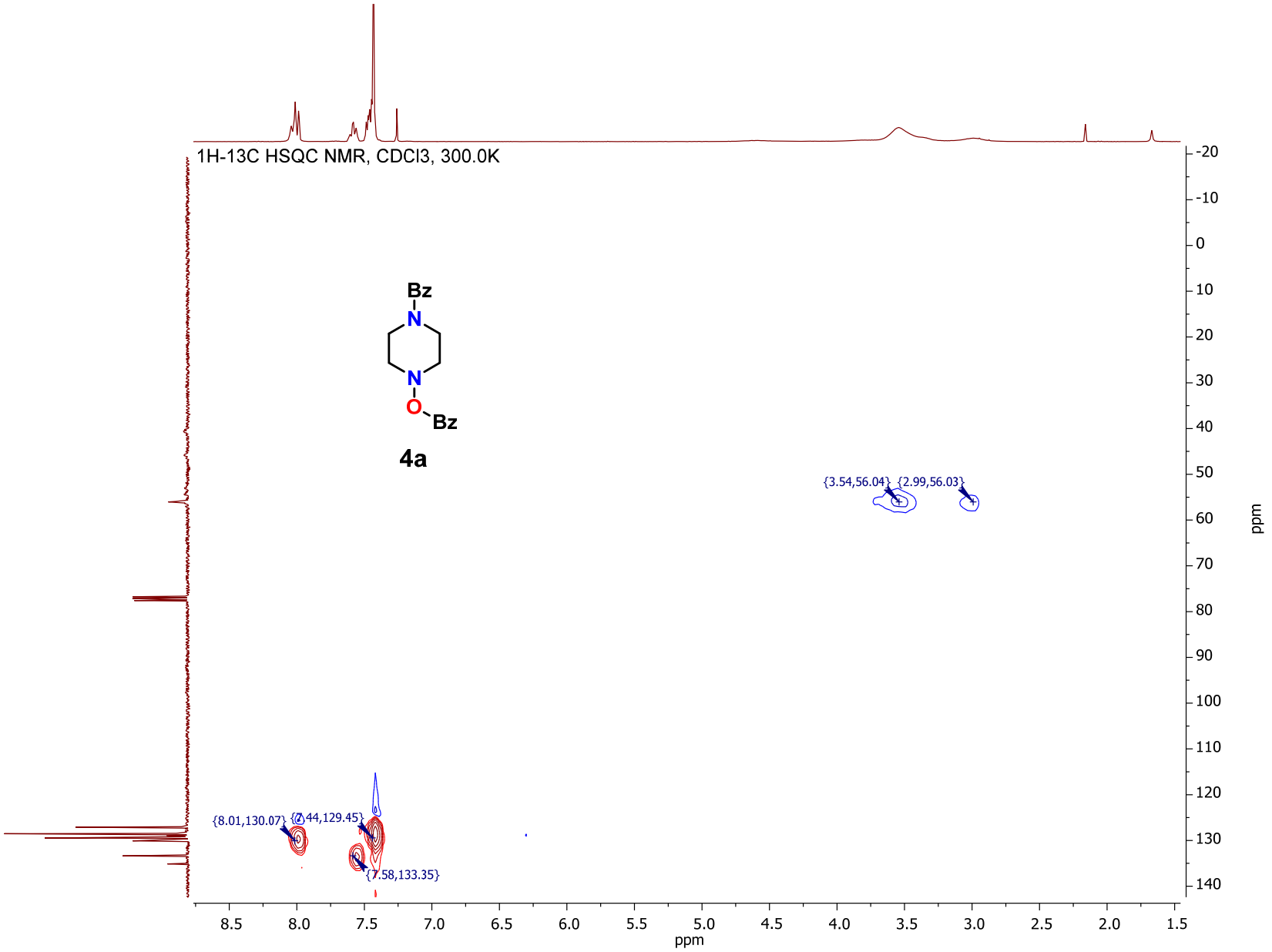
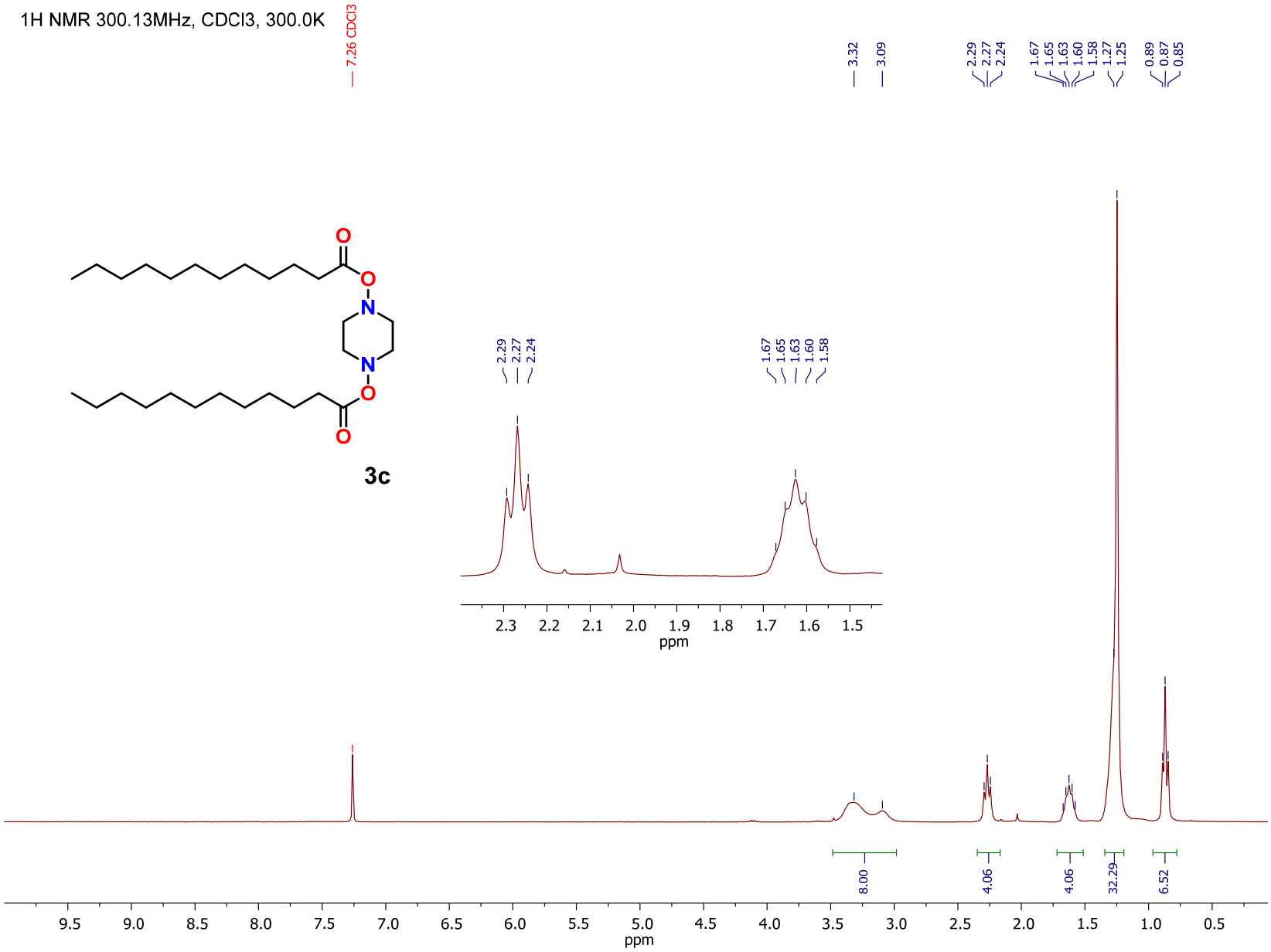
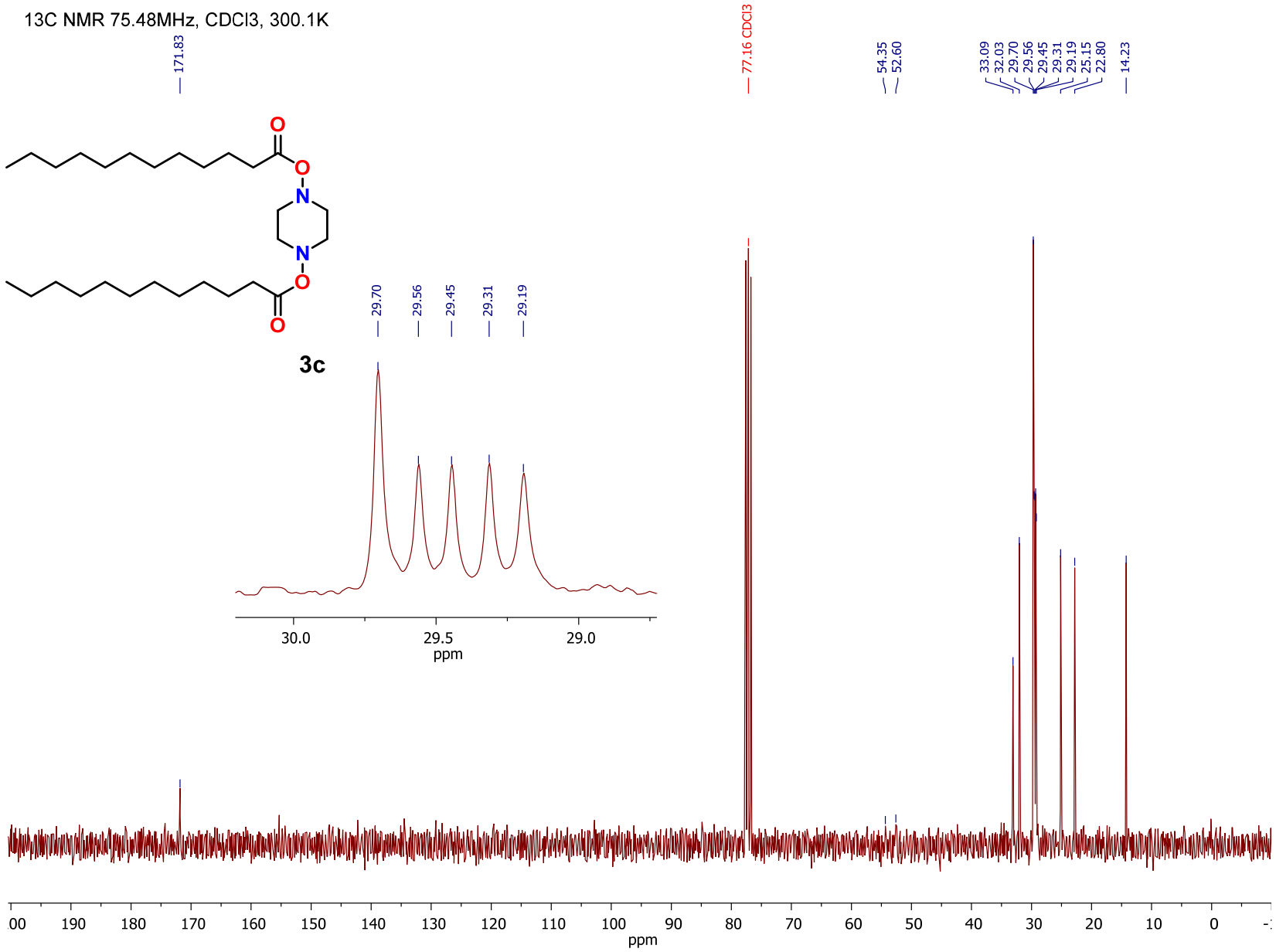
5.0
4.8
4.6
4.4
4.2
4.0
3.8
3.6
3.4
ppm

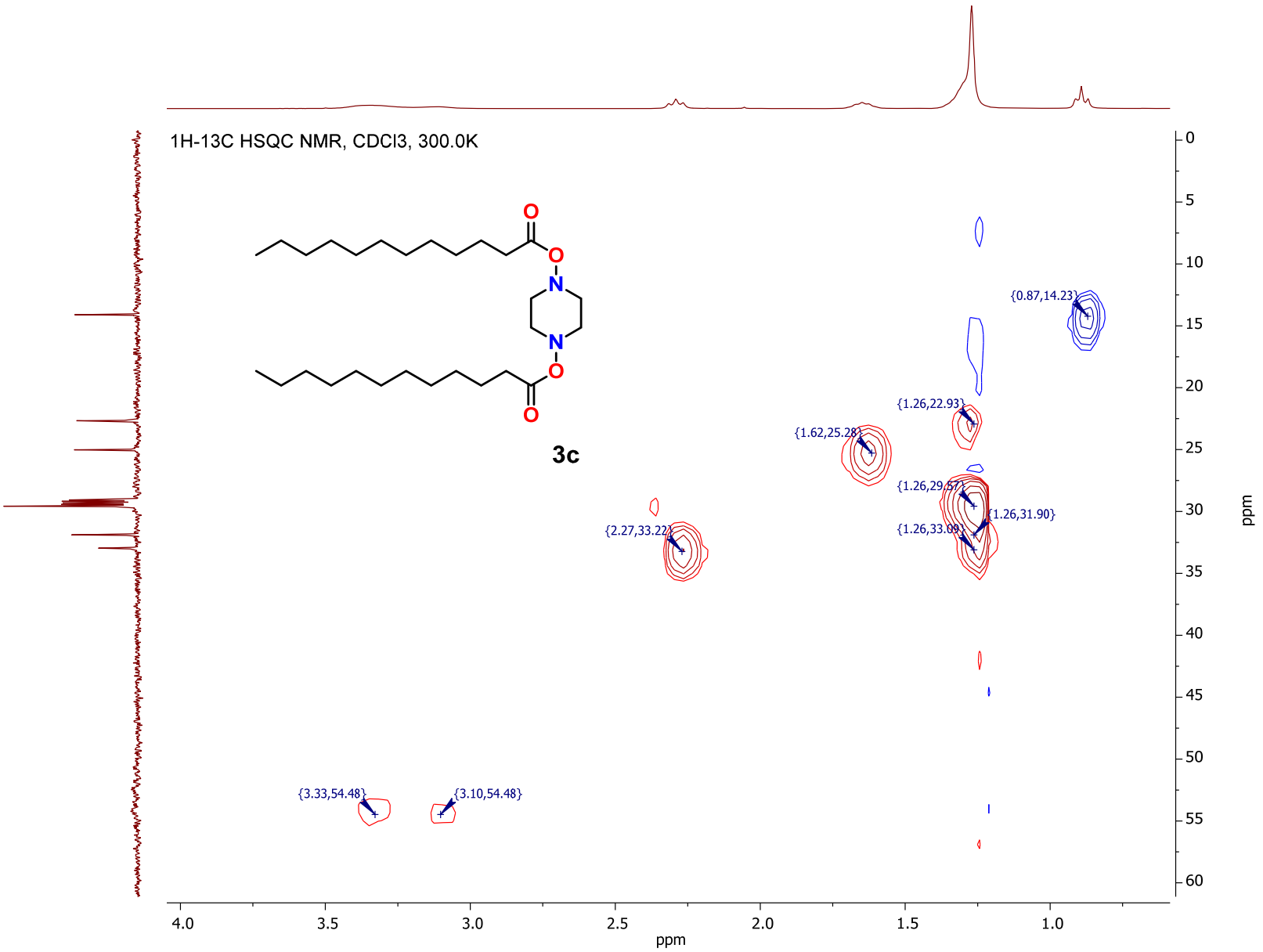

1H NMR 300.13MHz, CDCl3, 300.0K
8.04
8.01
7.99
7.61
7.59
7.56
7.49
7.47
7.46
7.45
7.43
7.26 CDCl3
3.54
3.37
2.99
Bz
N
N
O
Bz
4a
2.83
1.43
6.27
8.00
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0
ppm

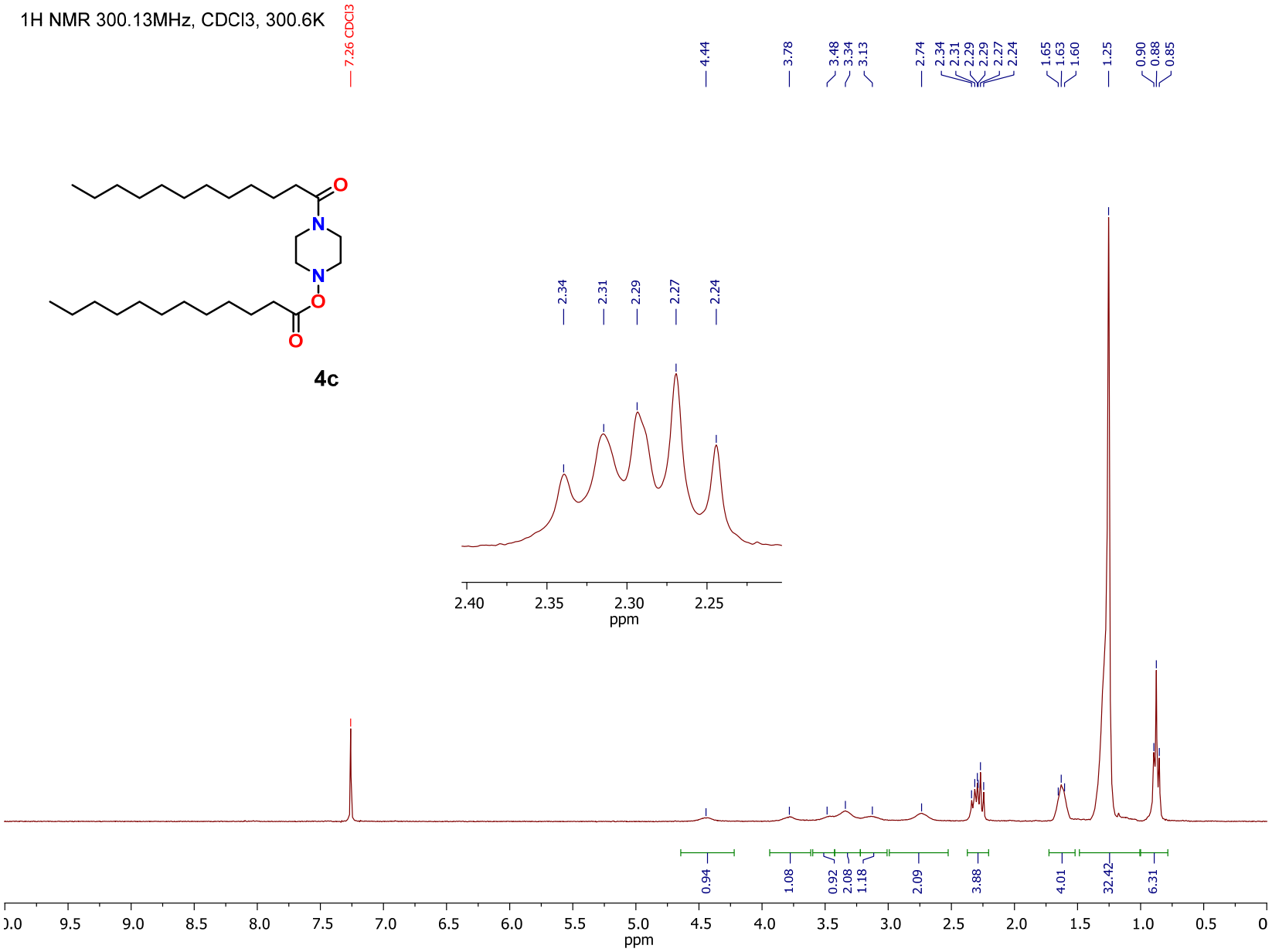

13C NMR 75.48MHz, CDCl3, 300.0K
170.37
164.48
135.13
133.36
130.08
129.46
128.92
128.64
128.53
127.09
77.16 CDCl3
56.04
Bz
N
N
O
Bz
4a
ppm

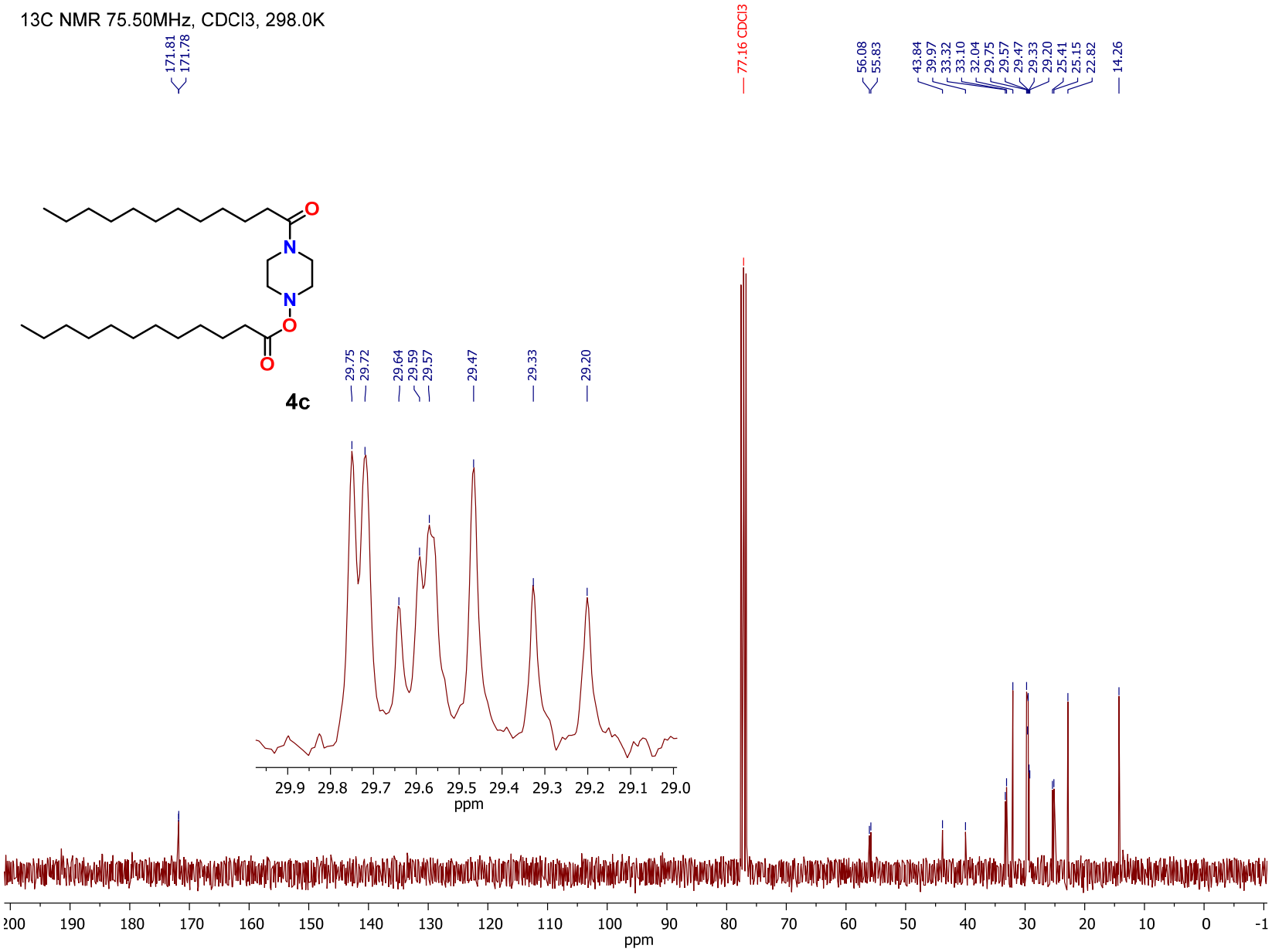

1H-13C HSQC NMR, CDCl3, 300.0K
Bz
N
N
O
Bz
4a
{3.54,56.04}
{2.99,56.03}
{8.01,130.07}
{7.44,129.45}
{7.58,133.35}
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
-20
-10
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
ppm

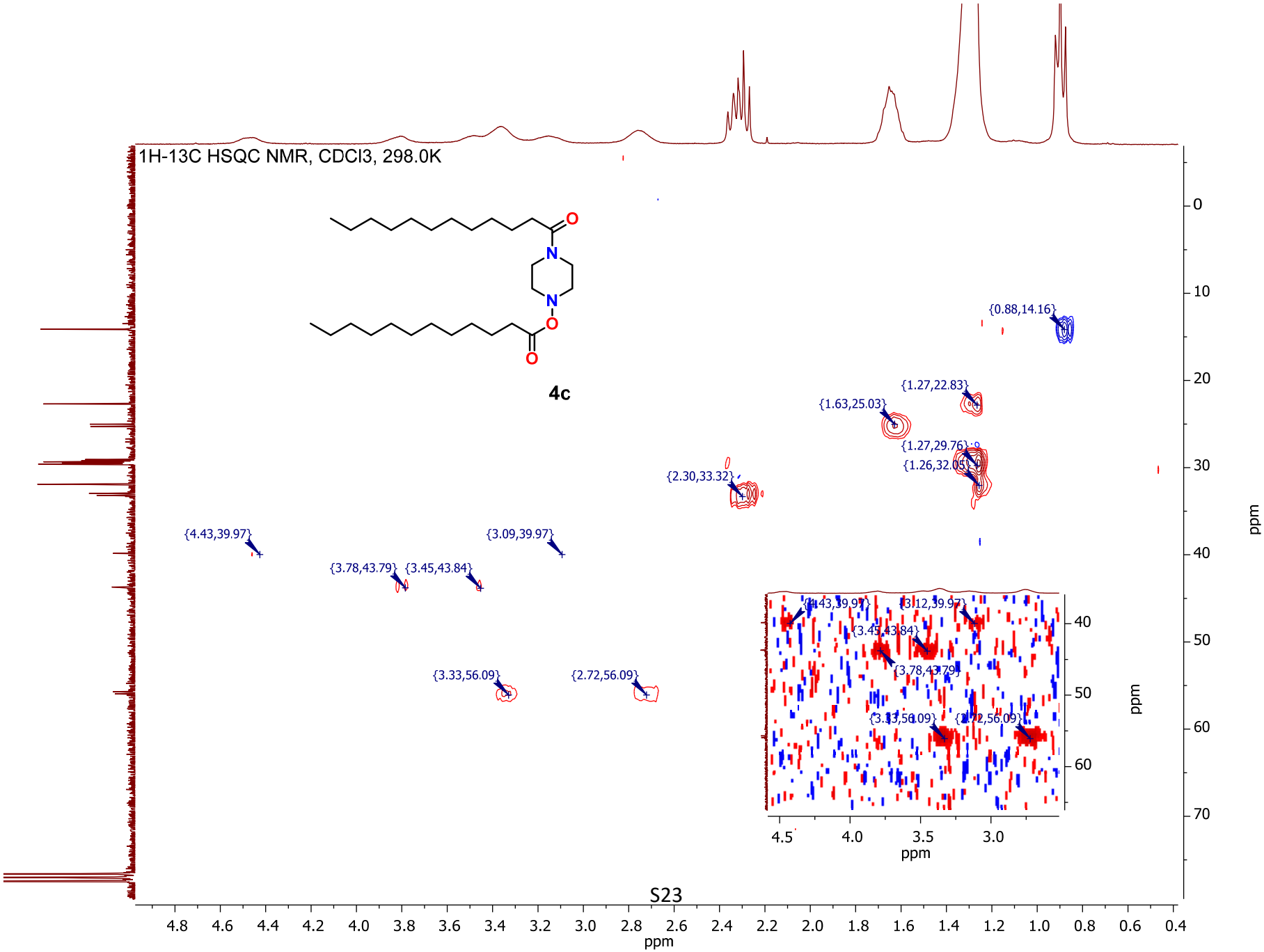

1H NMR 300.13MHz, CDCl3, 300.0K
7.26 CDCl3
3.32
3.09
2.29
2.27
2.24
1.67
1.65
1.63
1.60
1.58
1.27
1.25
0.89
0.87
0.85
O
O
N
N
O
O
O
3c
ppm
8.00
4.06
4.06
32.29
6.52
ppm

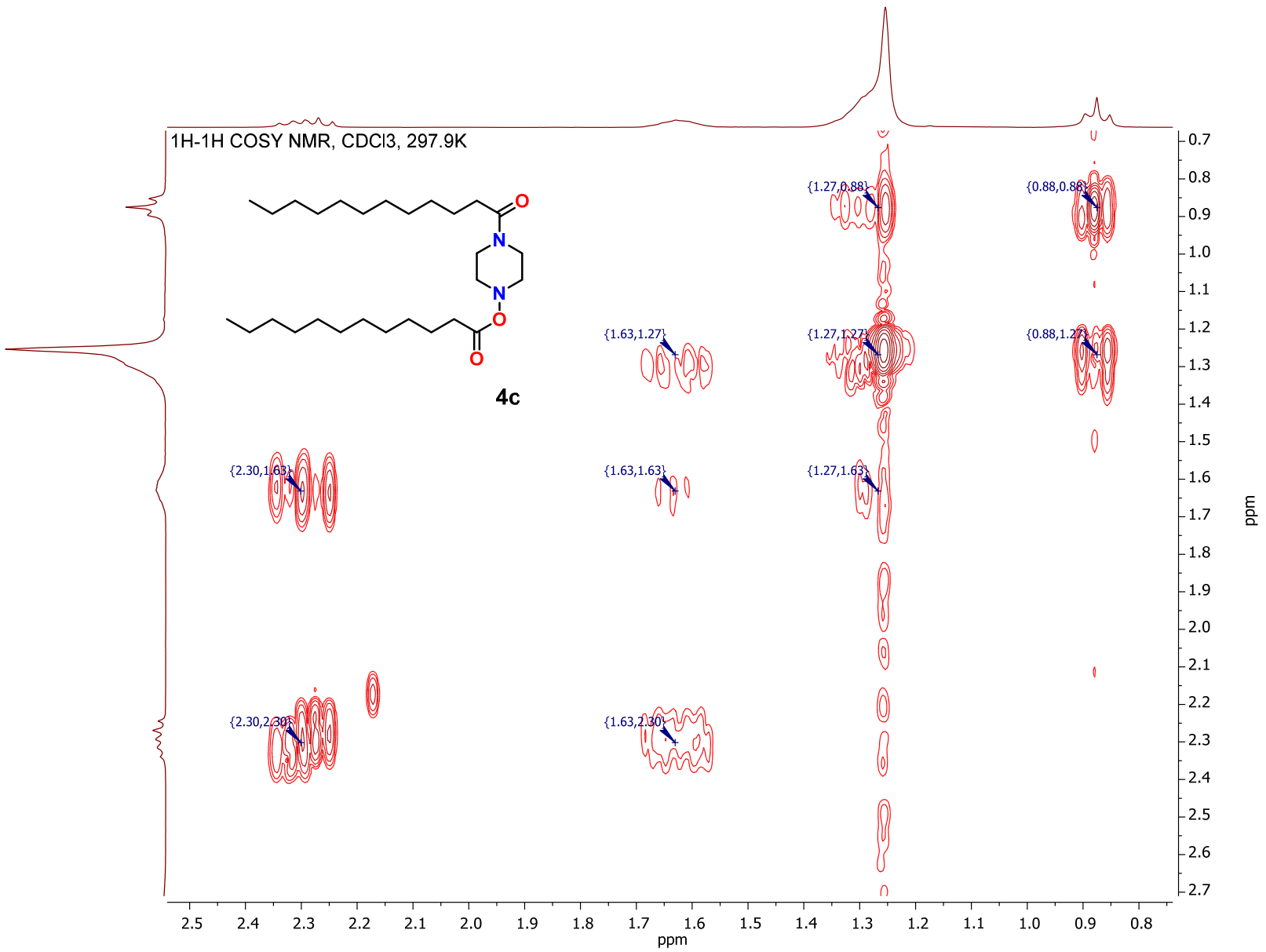

13C NMR 75.48MHz, CDCl3, 300.1K
171.83
77.16 CDCl3
54.35
52.60
33.09
32.03
29.70
29.56
29.45
29.31
29.19
25.15
22.80
14.23
3c
29.70
29.56
29.45
29.31
29.19
30.0
29.5
29.0
ppm
ppm


1H-13C HSQC NMR, CDCl3, 300.0K
3c
{0.87,14.23}
{1.26,22.93}
{1.62,25.28}
{1.26,29.57}
{1.26,31.90}
{1.26,33.09}
{2.27,33.22}
{3.33,54.48}
{3.10,54.48}
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0
5
10
15
20
25
30
35
40
45
50
55
60
ppm

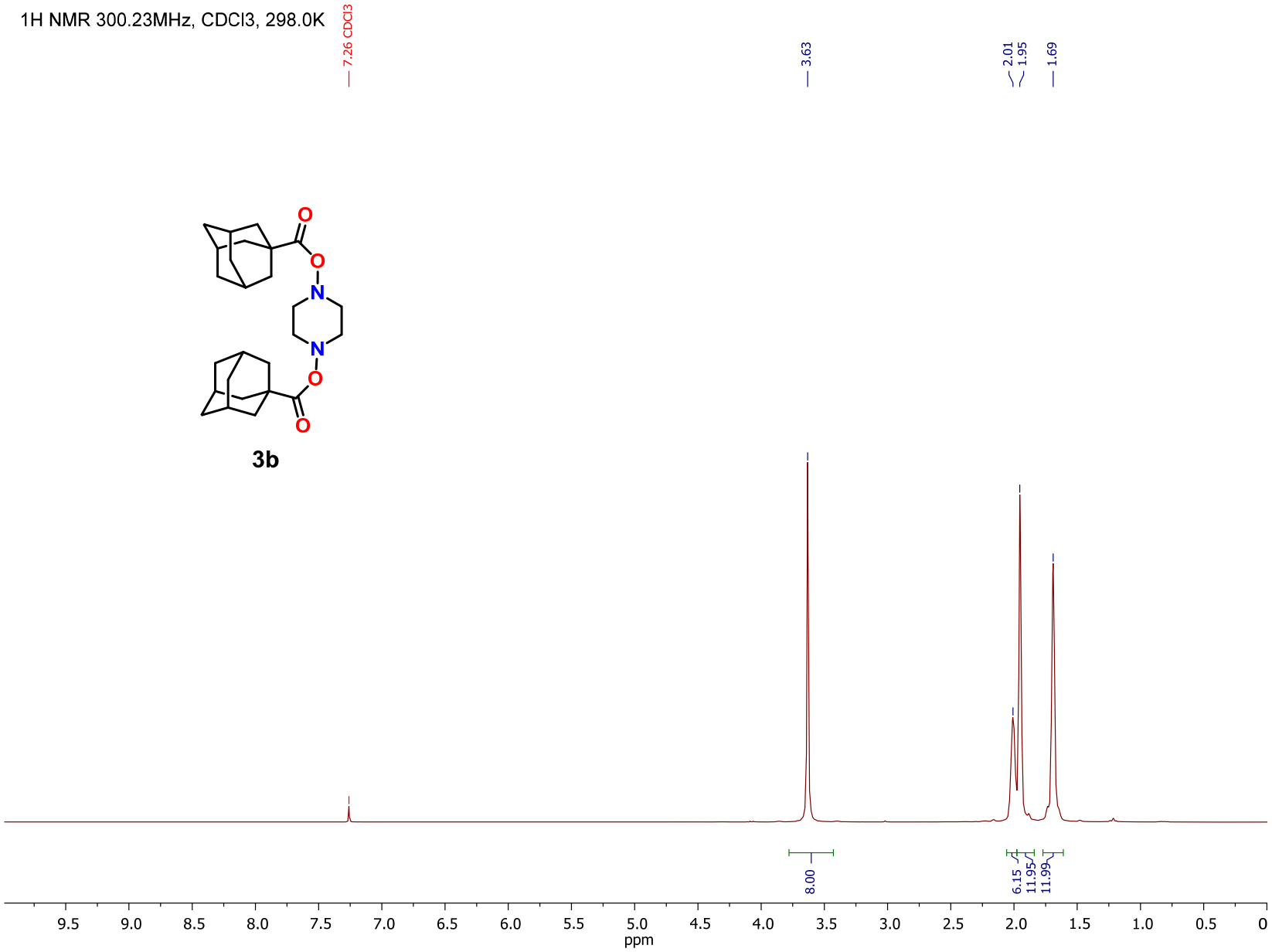

1H NMR 300.13MHz, CDCl3, 300.6K
7.26 CDCl3
4.44
3.78
3.48
3.34
3.13
2.74
2.34
2.31
2.29
2.27
2.24
1.65
1.63
1.60
1.25
0.90
0.88
0.85
O
N
N
O
O
4c
2.40
2.35
2.30
2.25
ppm
0.94
1.08
0.92
2.08
1.18
2.09
3.88
4.01
32.42
6.31
ppm


13C NMR 75.50MHz, CDCl3, 298.0K
171.81
171.78
77.16 CDCl3
56.08
55.83
43.84
39.97
33.32
33.10
32.04
29.75
29.57
29.47
29.33
29.20
25.41
25.15
22.82
14.26
O
N
N
O
O
O
4c
29.75
29.72
29.64
29.59
29.57
29.47
29.33
29.20
29.9 29.8 29.7 29.6 29.5 29.4 29.3 29.2 29.1 29.0
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
ppm


1H-13C HSQC NMR, CDCl3, 298.0K
4c
{0.88,14.16}
{1.27,22.83}
{1.63,25.03}
{1.27,29.76}
{1.26,32.05}
{2.30,33.32}
{4.43,39.97}
{3.09,39.97}
{3.78,43.79}
{3.45,43.84}
{3.33,56.09}
{2.72,56.09}
ppm
ppm
ppm
ppm

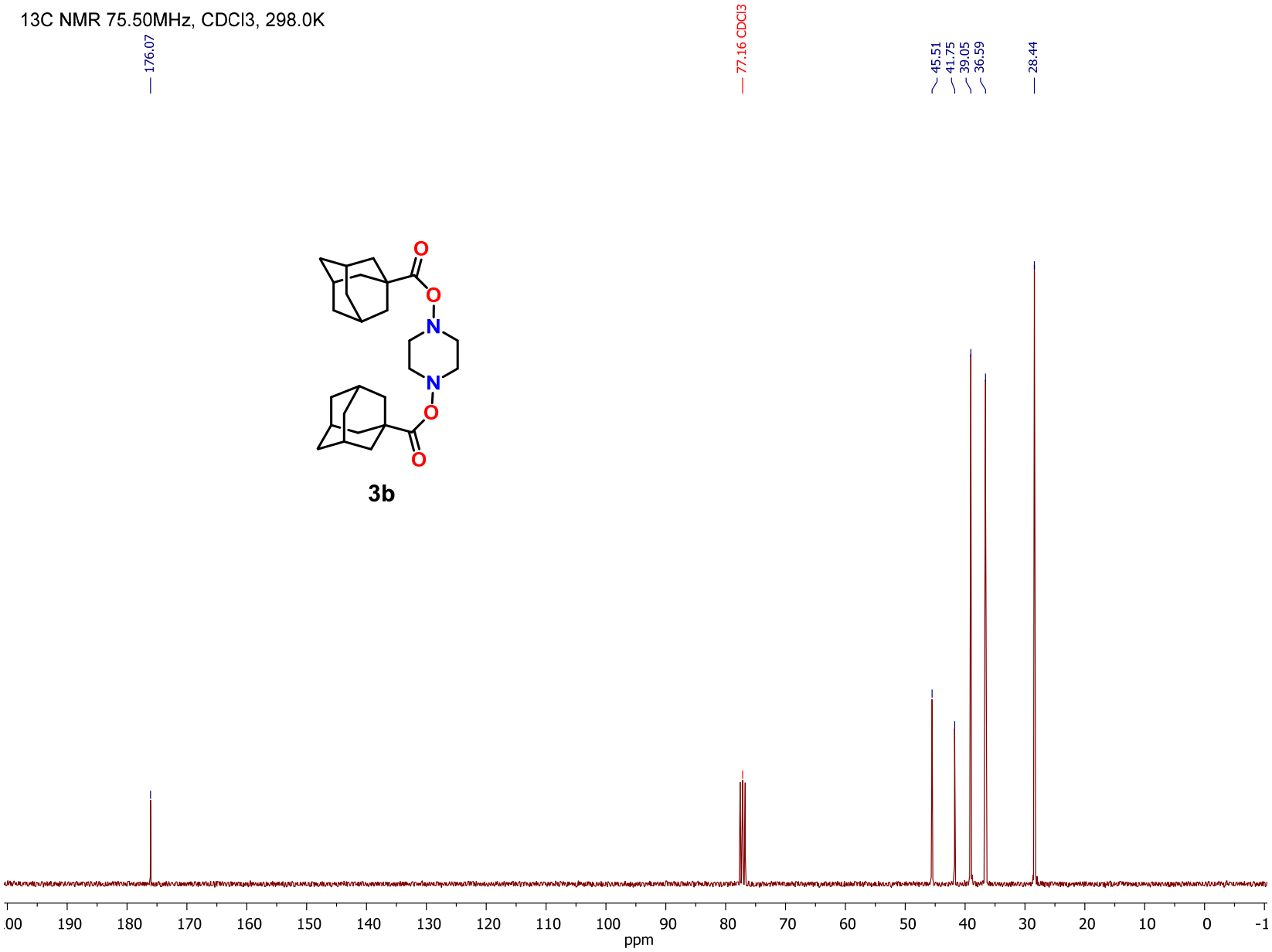

1H-1H COSY NMR, CDCl3, 297.9K
4c
{1.27,0.88}
{0.88,0.88}
{1.63,1.27}
{1.27,1.27}
{0.88,1.27}
{2.30,1.63}
{1.63,1.63}
{1.27,1.63}
{2.30,2.30}
{1.63,2.30}
ppm
ppm

1H NMR 300.23MHz, CDCl3, 298.0K

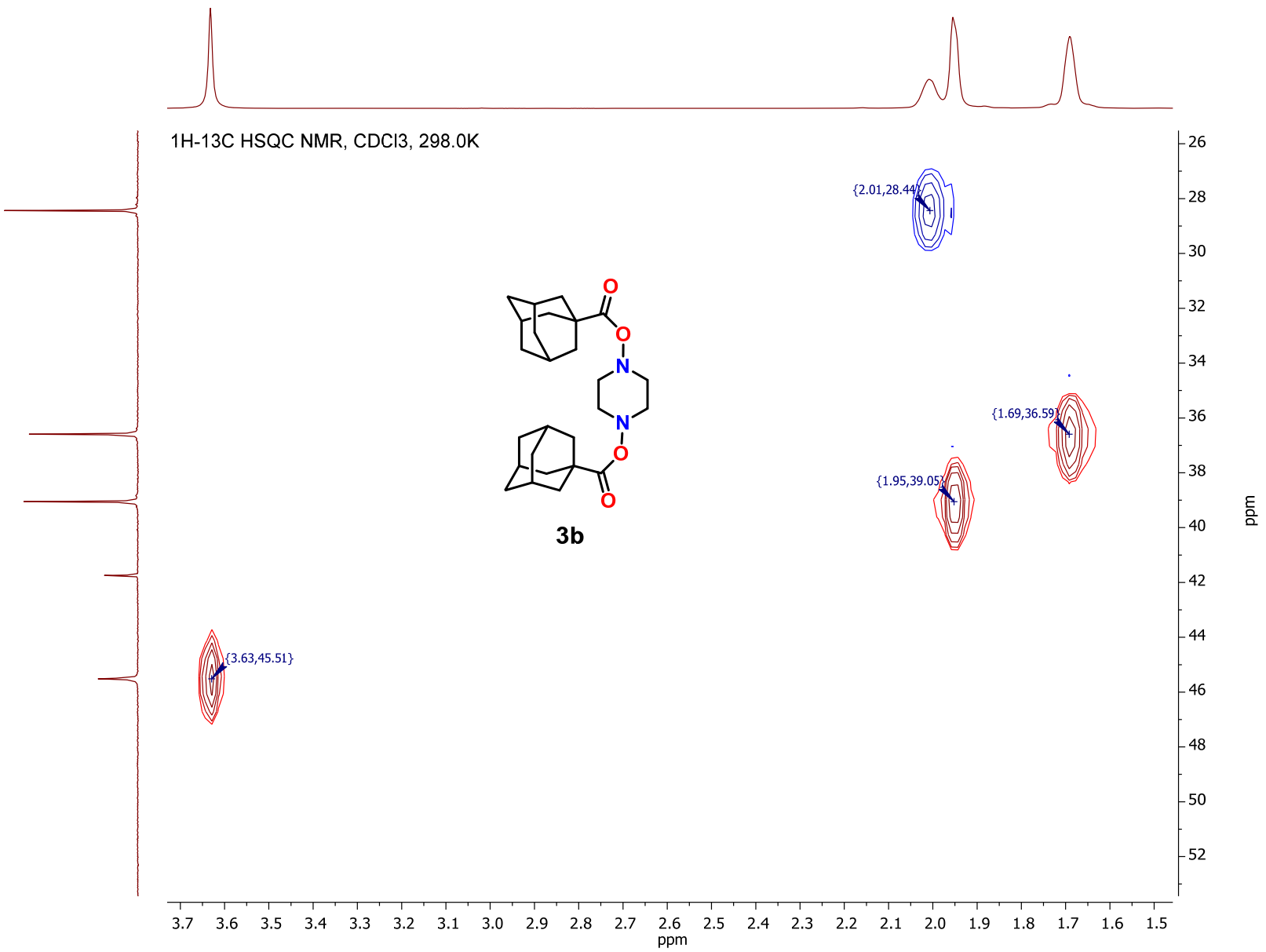


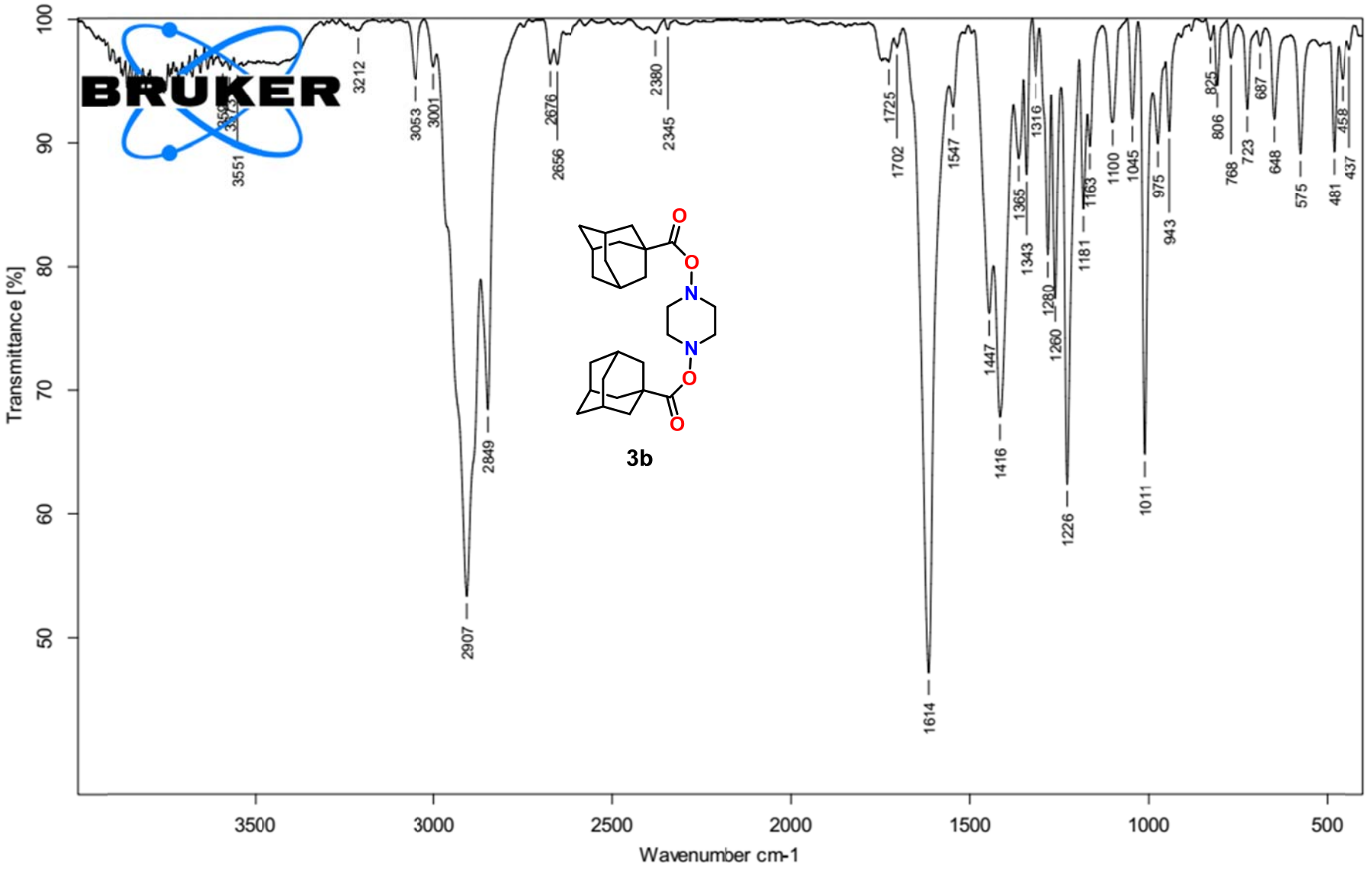
3b

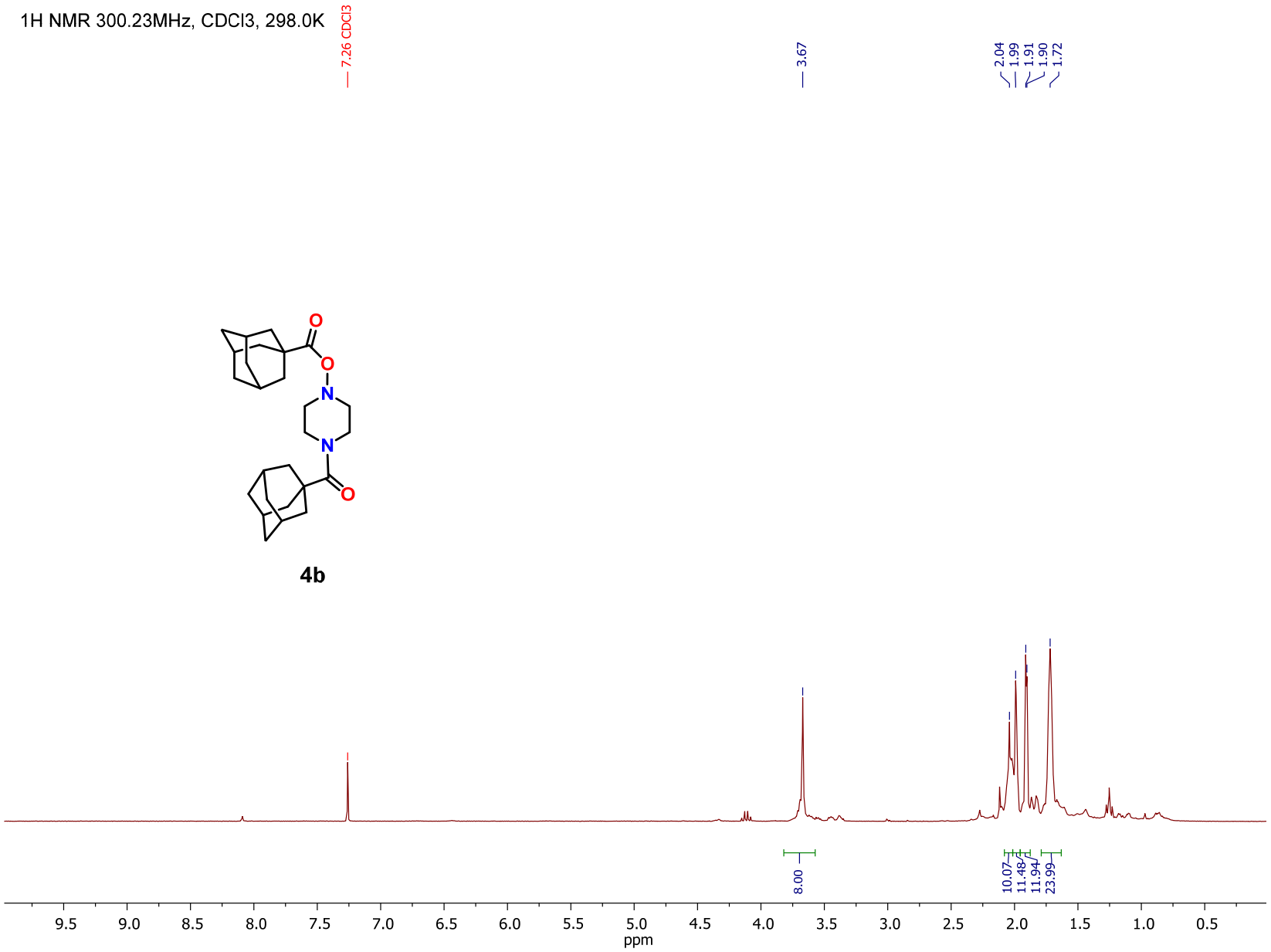
13C NMR 75.50MHz, CDCl3, 298.0K

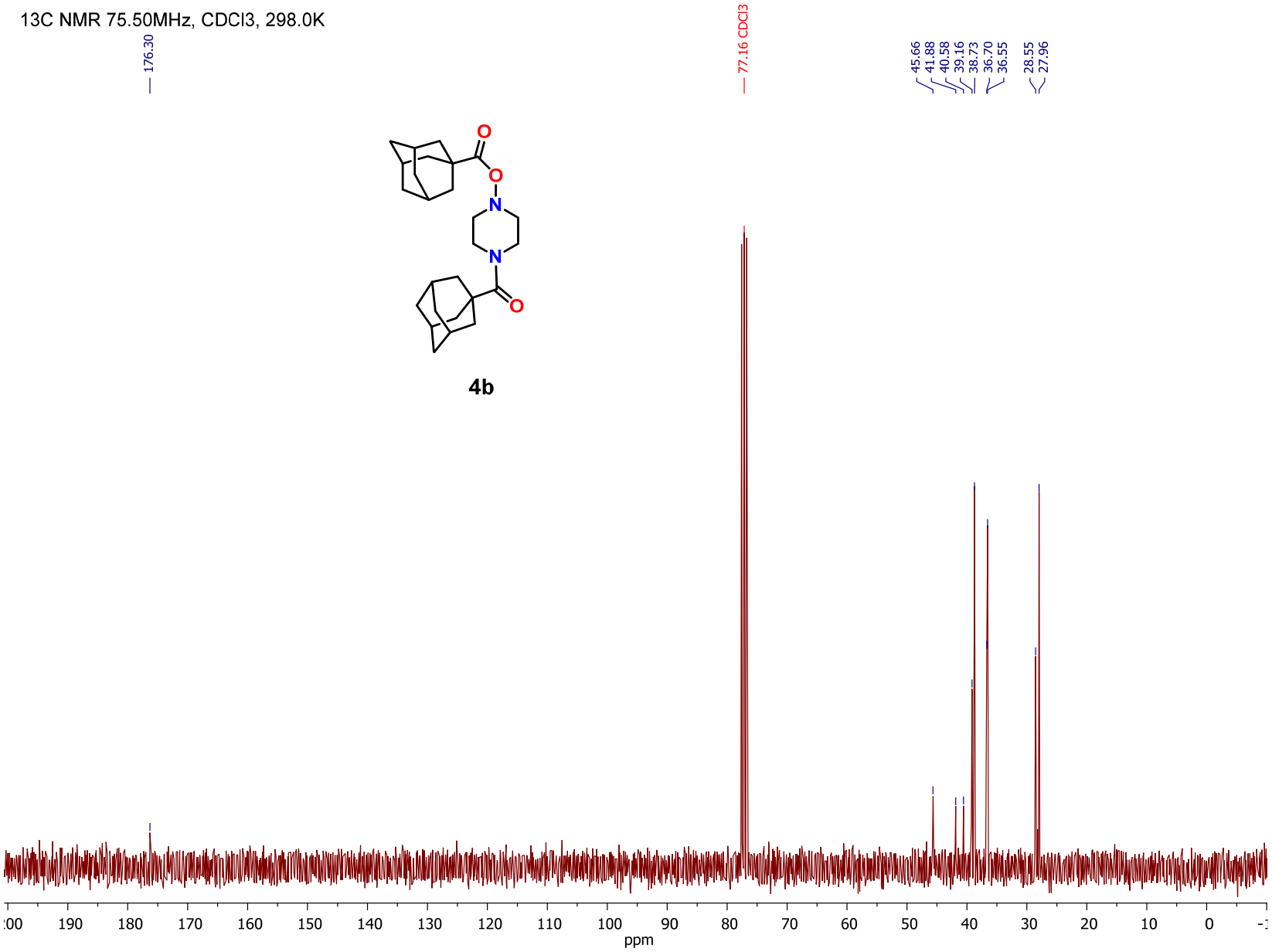


3b

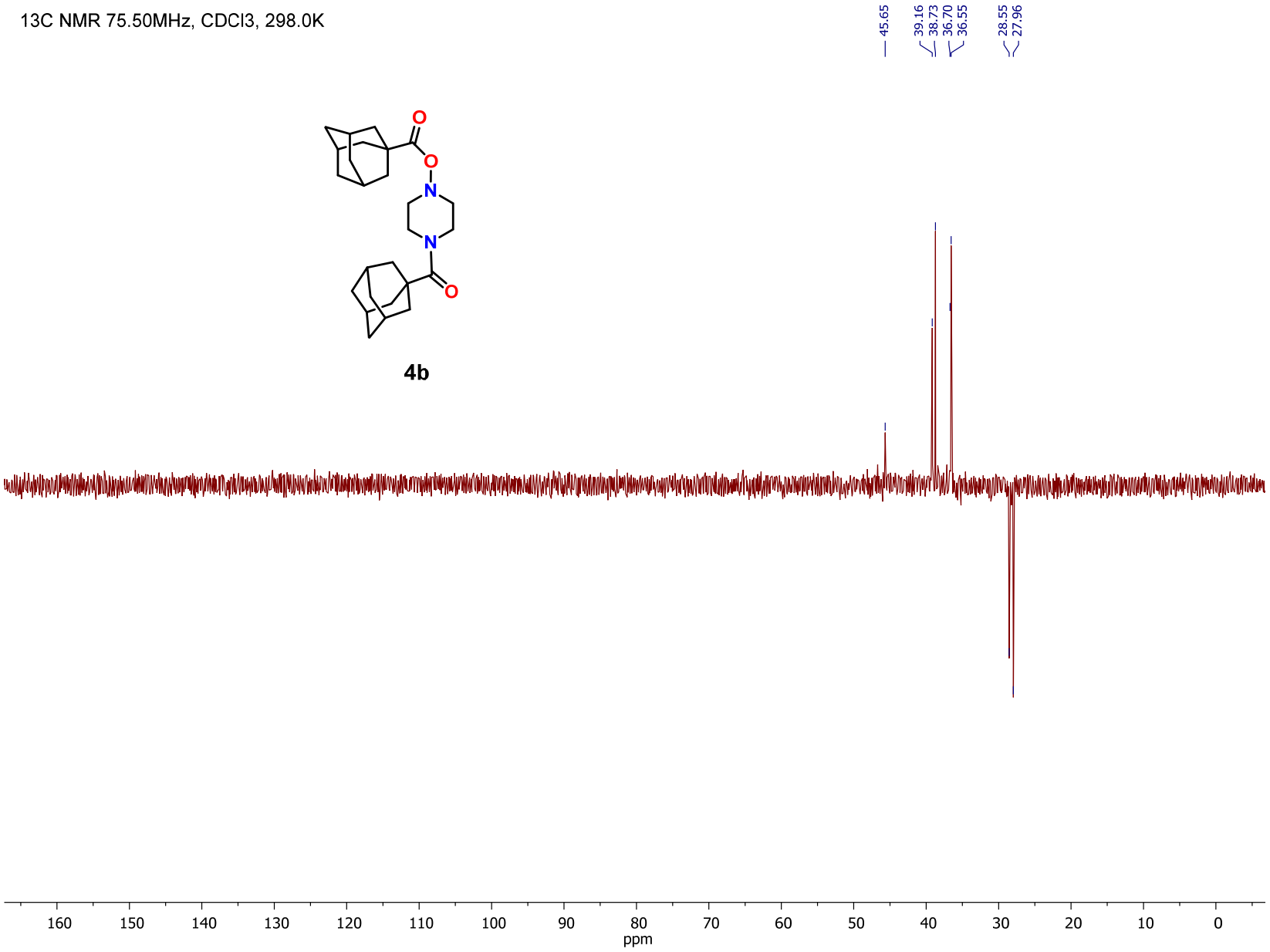

1H-13C HSQC NMR, CDCl3, 298.0K
{2.01,28.44}
{1.69,36.59}
{1.95,39.05}
{3.63,45.51}
O
O
N
N
O
O
3b
26
28
30
32
34
36
38
40
42
44
46
48
50
52
ppm
3.7
3.6
3.5
3.4
3.3
3.2
3.1
3.0
2.9
2.8
2.7
2.6
2.5
2.4
2.3
2.2
2.1
2.0
1.9
1.8
1.7
1.6
1.5
ppm


BRUKER
Transmittance [%]
Wavenumber cm-1
3500
3000
2500
2000
1500
1000
500
100
90
80
70
60
50
3551
3212
3053
3001
2907
2849
2676
2656
2380
2345
1725
1702
1614
1547
1447
1416
1365
1343
1316
1280
1260
1226
1181
1163
1100
1045
1011
975
943
825
806
768
723
687
648
575
481
458
437
3b

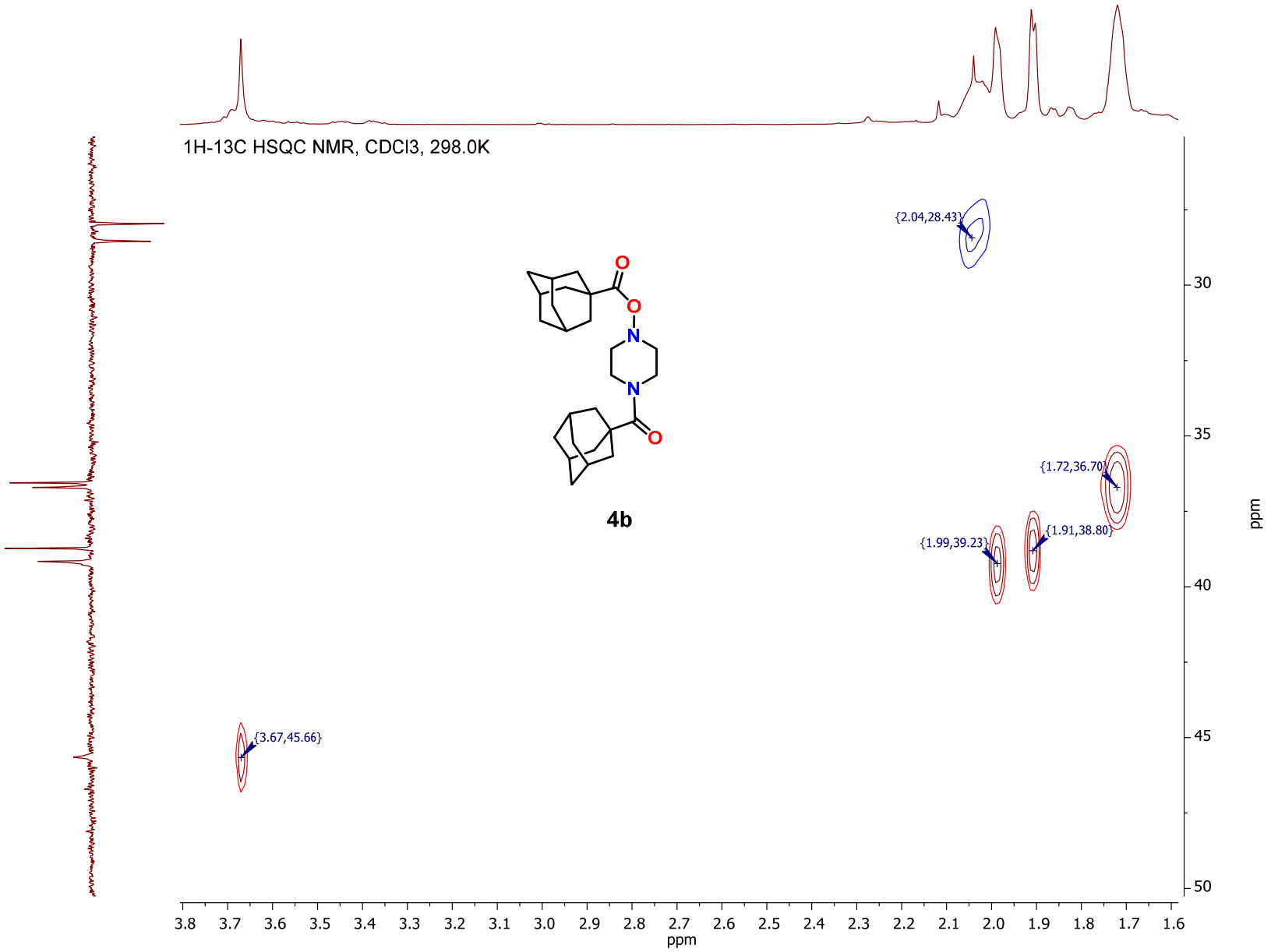

1H NMR 300.23MHz, CDCl3, 298.0K
7.26 CDCl3
3.67
2.04
1.99
1.91
1.90
1.72
O
O
N
N
O
4b
8.00
10.07
11.48
11.94
23.99
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

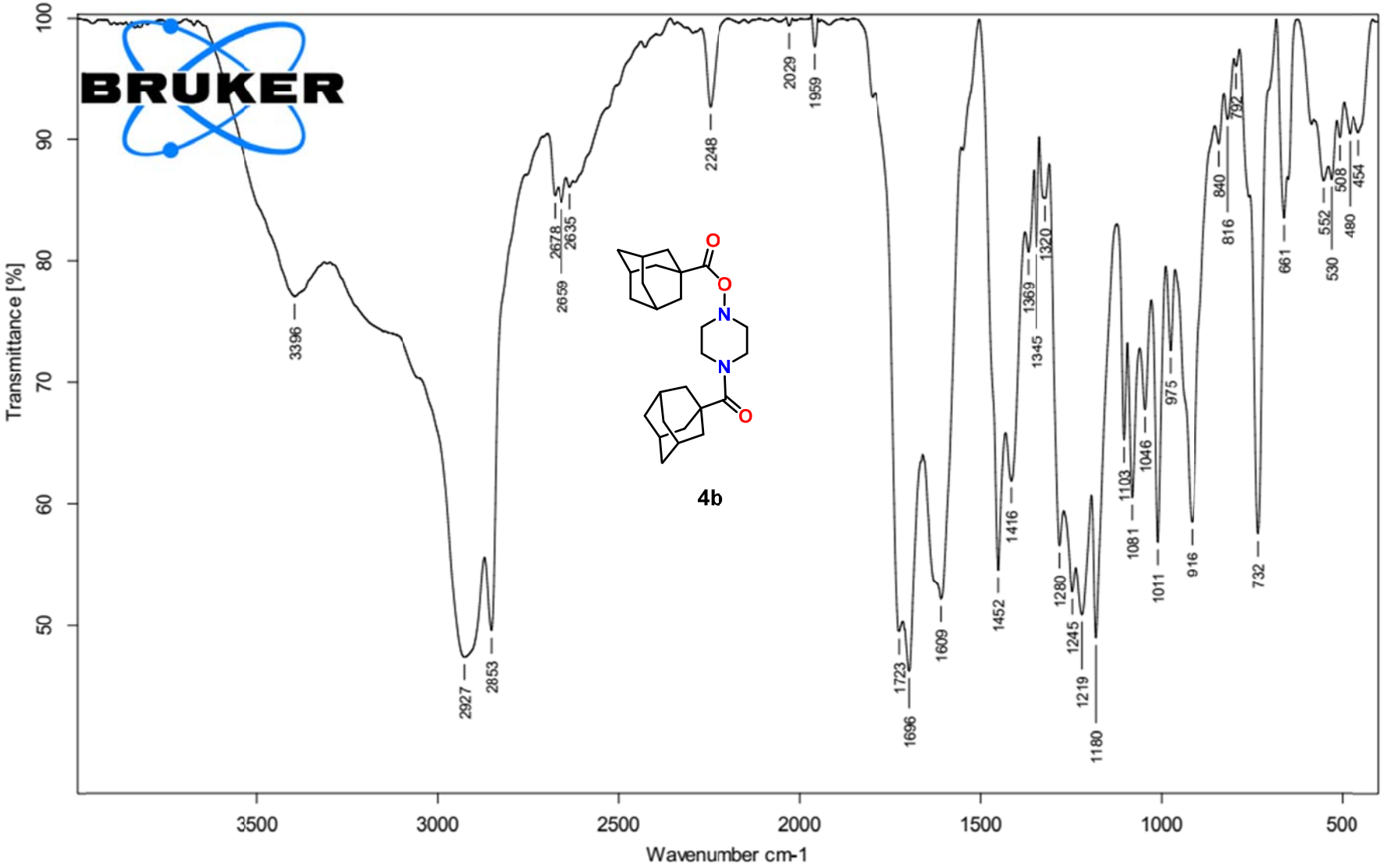

13C NMR 75.50MHz, CDCl3, 298.0K
176.30
77.16 CDCl3
45.66
41.88
40.58
39.16
38.73
36.70
36.55
28.55
27.96
O
O
N
N
O
4b
ppm

13C NMR 75.50MHz, CDCl3, 298.0K

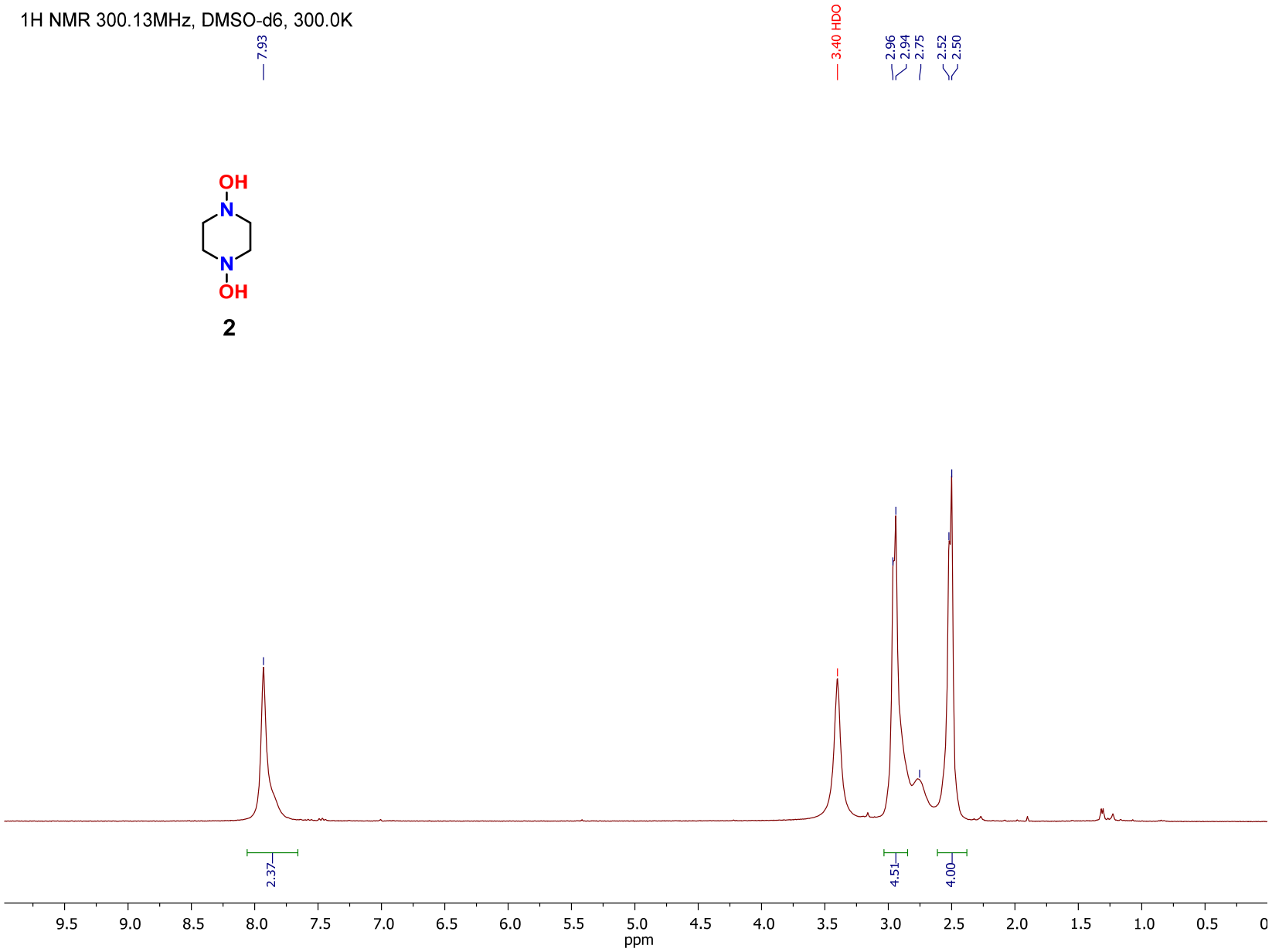


4b

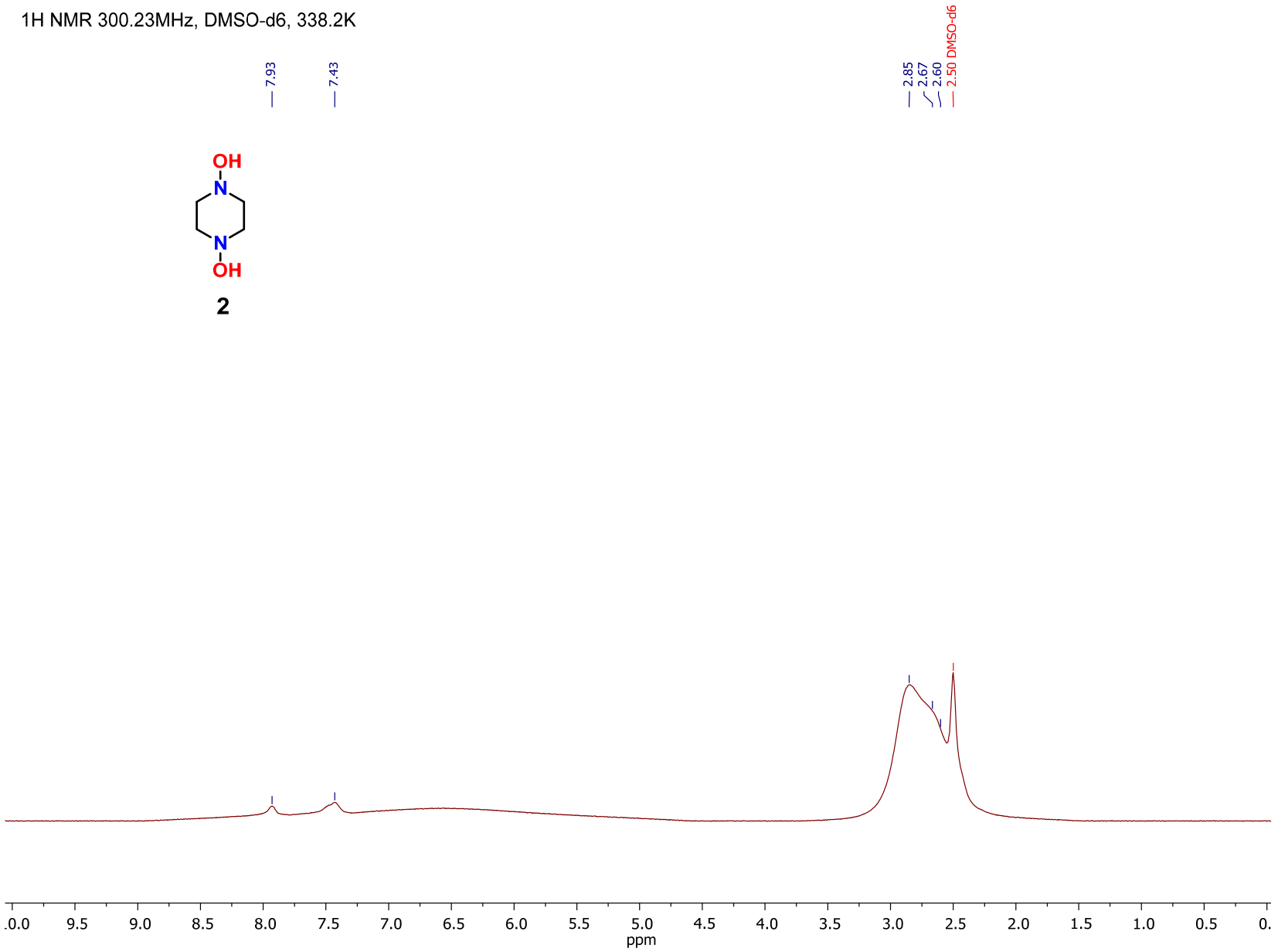

1H-13C HSQC NMR, CDCl3, 298.0K
{2.04,28.43}
{1.72,36.70}
{1.91,38.80}
{1.99,39.23}
{3.67,45.66}
O
O
N
N
O
4b
30
35
40
45
50
ppm
3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5 2.4 2.3 2.2 2.1 2.0 1.9 1.8 1.7 1.6
ppm


BRUKER
Transmittance [%]
100
90
80
70
60
50
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
3396
2927
2853
2678
2659
2635
2248
2029
1959
1723
1696
1609
1452
1416
1369
1345
1320
1280
1245
1219
1180
1103
1081
1046
1011
975
916
840
816
792
732
661
552
530
508
480
454
O
O
N
N
O
4b

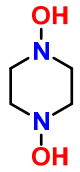
1H NMR 300.13MHz, DMSO-d6, 300.0K



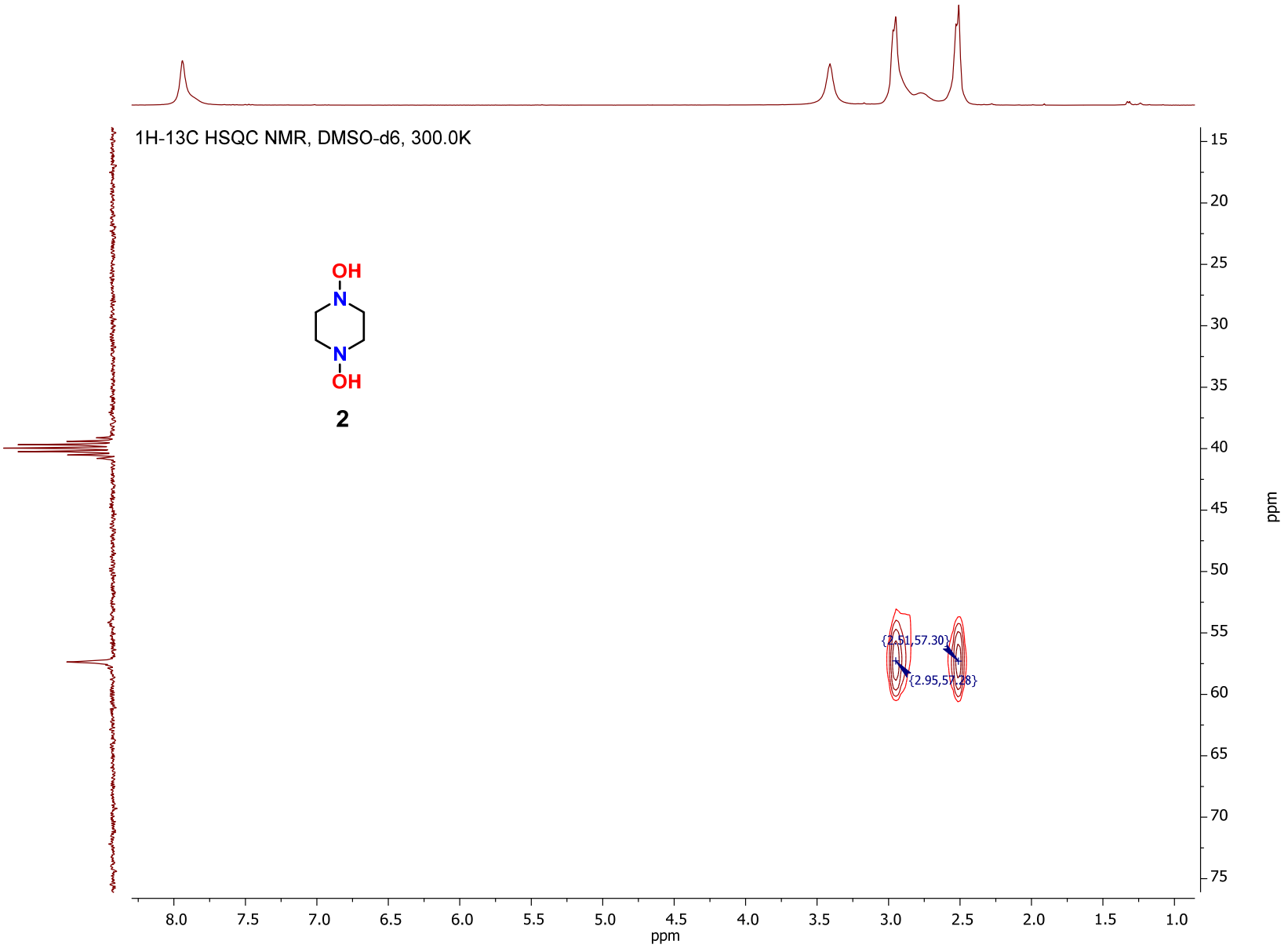
1H NMR 300.23MHz, DMSO-d6, 338.2K



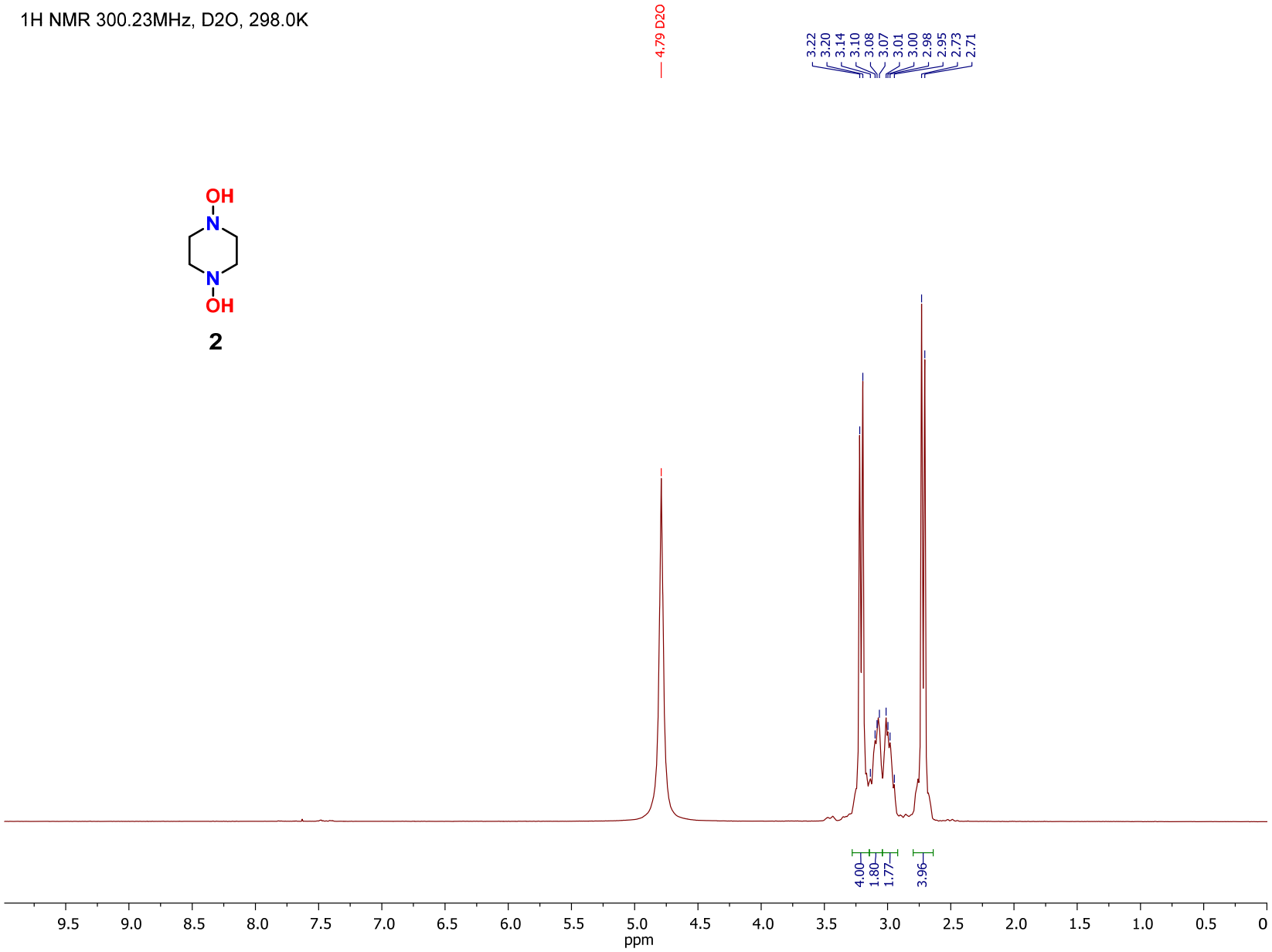
13C NMR 75.48MHz, DMSO-d6, 300.1K



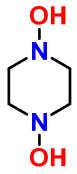
2


1H-13C HSQC NMR, DMSO-d6, 300.0K
OH
N
N
OH
2
{2.51,57.30}
{2.95,57.28}
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
15
20
25
30
35
40
45
50
55
60
65
70
75
ppm

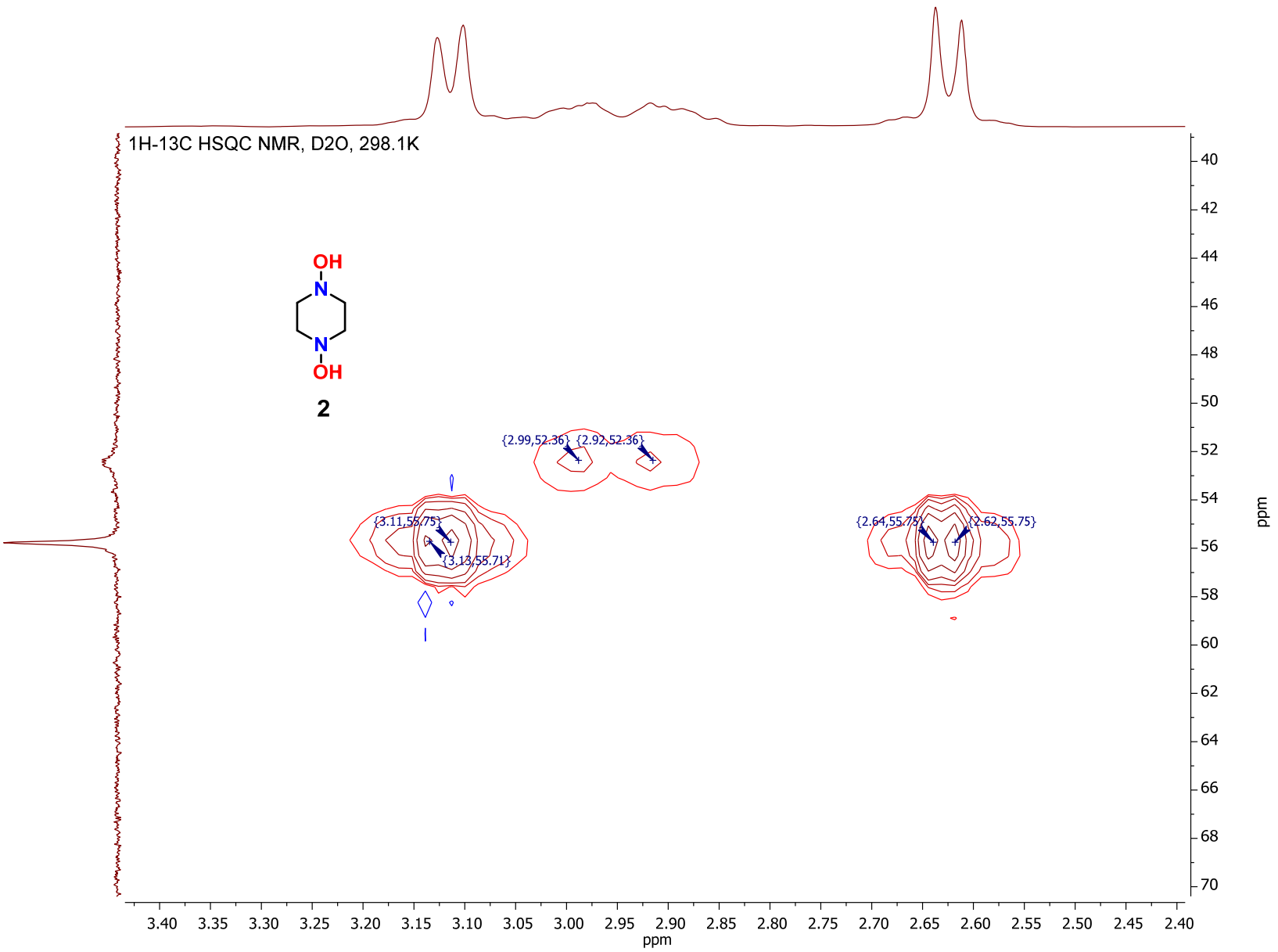
1H NMR 300.23MHz, D2O, 298.0K

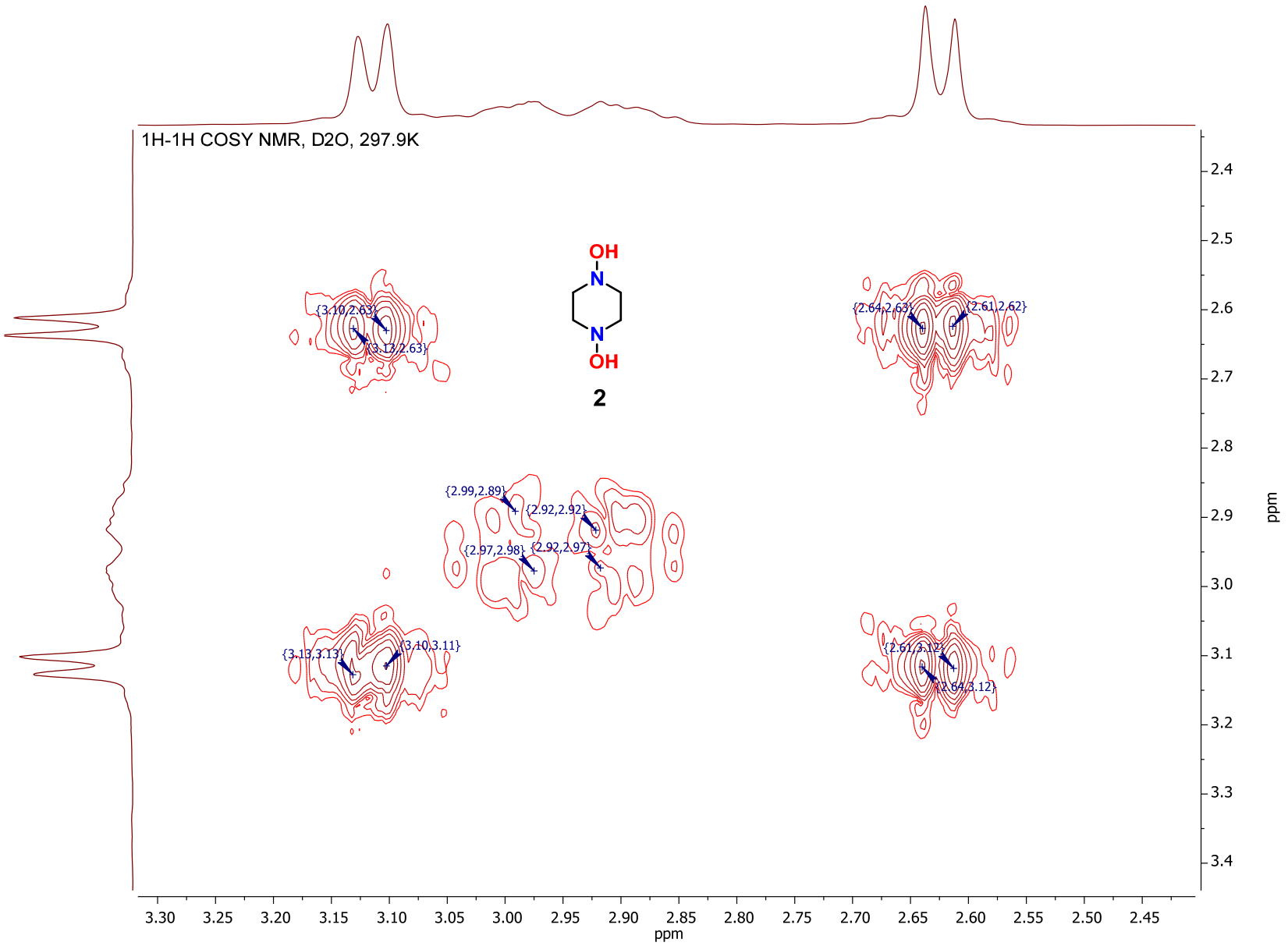


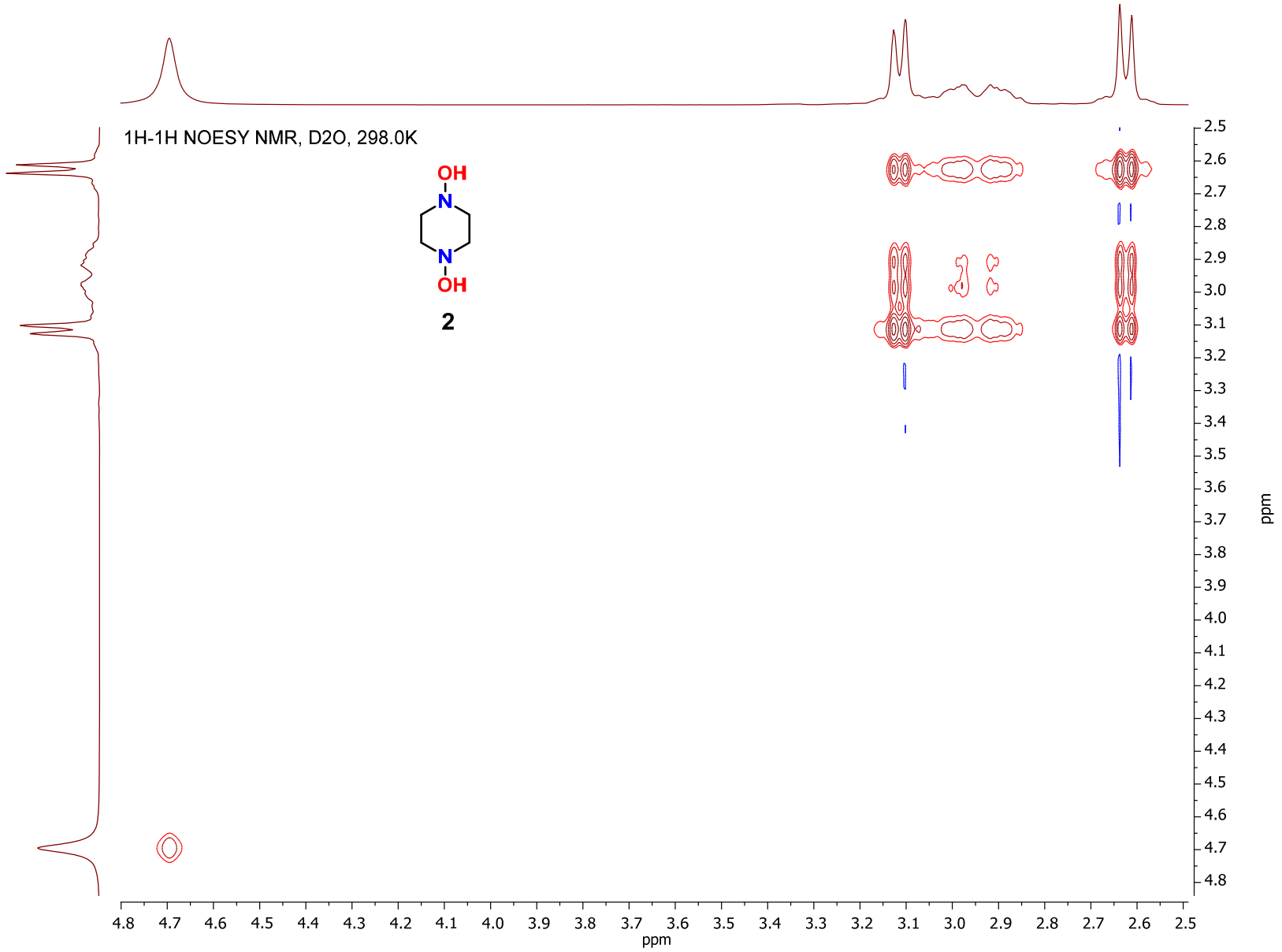
13C NMR 75.48MHz, D2O, 300.1K



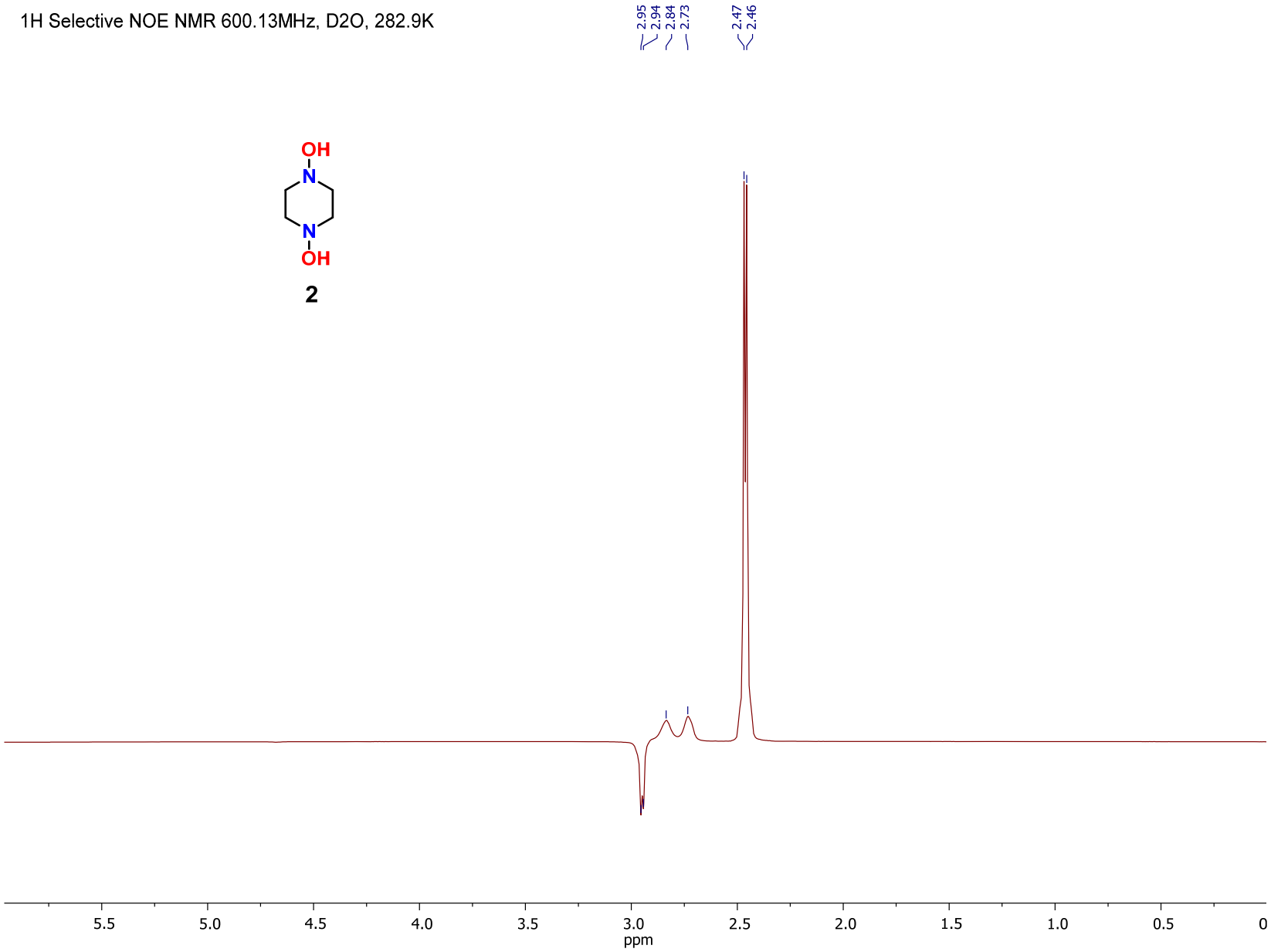
2

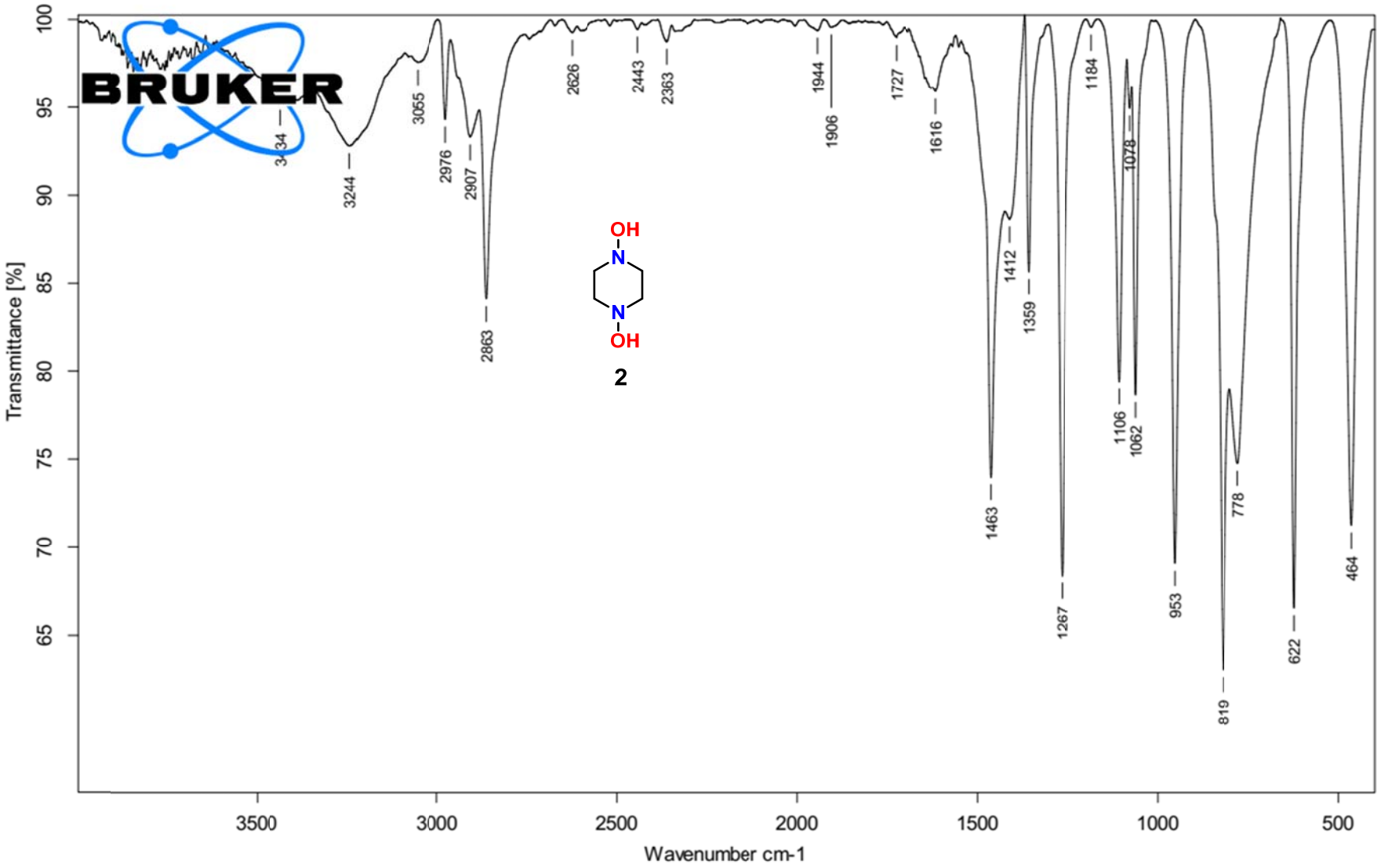

1H-13C HSQC NMR, D2O, 298.1K
OH
N
N
OH
2
{2.99,52.36}
{2.92,52.36}
{3.11,55.75}
{3.13,55.71}
{2.64,55.75}
{2.62,55.75}
3.40 3.35 3.30 3.25 3.20 3.15 3.10 3.05 3.00 2.95 2.90 2.85 2.80 2.75 2.70 2.65 2.60 2.55 2.50 2.45 2.40
ppm
40 42 44 46 48 50 52 54 56 58 60 62 64 66 68 70
ppm


1H-1H COSY NMR, D2O, 297.9K
OH
N
N
OH
2
{3.10,2.63}
{3.12,2.63}
{2.64,2.63}
{2.61,2.62}
{2.99,2.89}
{2.92,2.92}
{2.97,2.98}
{2.92,2.97}
{3.13,3.13}
{3.10,3.11}
{2.61,3.12}
{2.64,3.12}
3.30 3.25 3.20 3.15 3.10 3.05 3.00 2.95 2.90 2.85 2.80 2.75 2.70 2.65 2.60 2.55 2.50 2.45
ppm
2.4 2.5 2.6 2.7 2.8 2.9 3.0 3.1 3.2 3.3 3.4
ppm

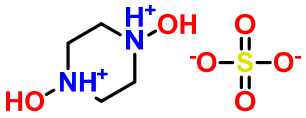

1H-1H NOESY NMR, D2O, 298.0K
OH
N
N
OH
2
4.8 4.7 4.6 4.5 4.4 4.3 4.2 4.1 4.0 3.9 3.8 3.7 3.6 3.5 3.4 3.3 3.2 3.1 3.0 2.9 2.8 2.7 2.6 2.5
ppm
2.5 2.6 2.7 2.8 2.9 3.0 3.1 3.2 3.3 3.4 3.5 3.6 3.7 3.8 3.9 4.0 4.1 4.2 4.3 4.4 4.5 4.6 4.7 4.8
ppm

1H Selective NOE NMR 600.13MHz, D2O, 282.9K



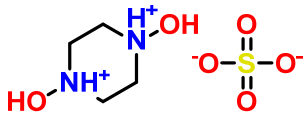

BRUKER
Transmittance [%]
100
95
90
85
80
75
70
65
3500
3000
2500
2000
1500
1000
500
Wavenumber cm-1
3434
3244
3055
2976
2907
2863
2626
2443
2363
1944
1906
1727
1616
1463
1412
1359
1267
1184
1106
1078
1062
953
819
778
622
464
OH
N
N
OH
2

1H NMR 300.13MHz, D2O, 300.0K

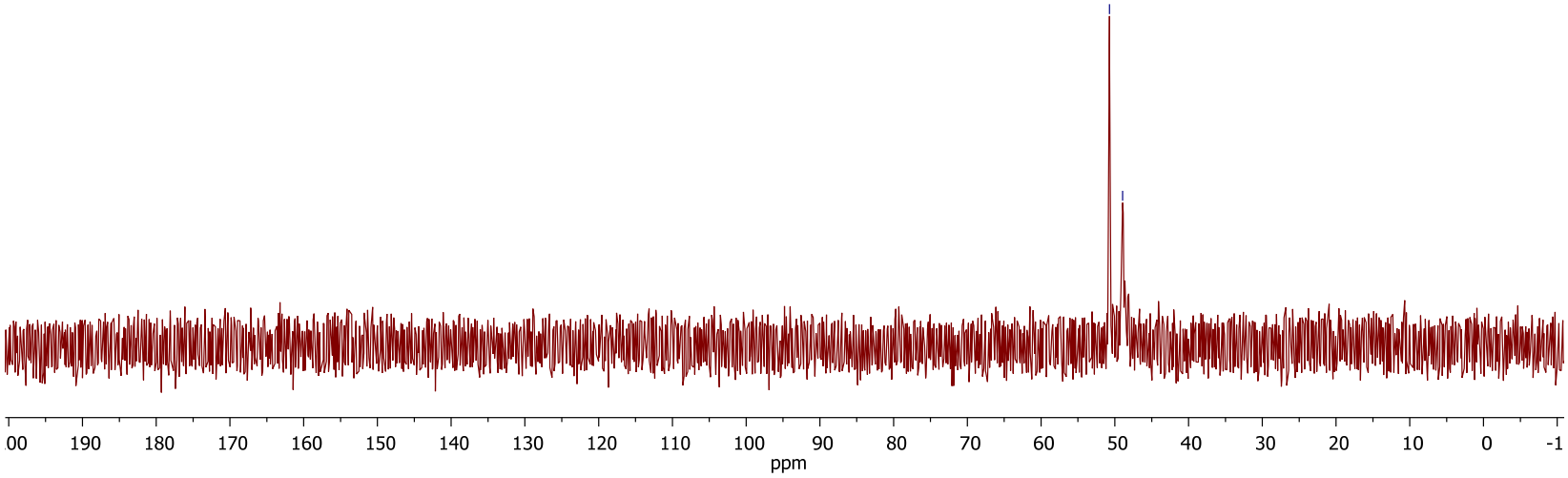


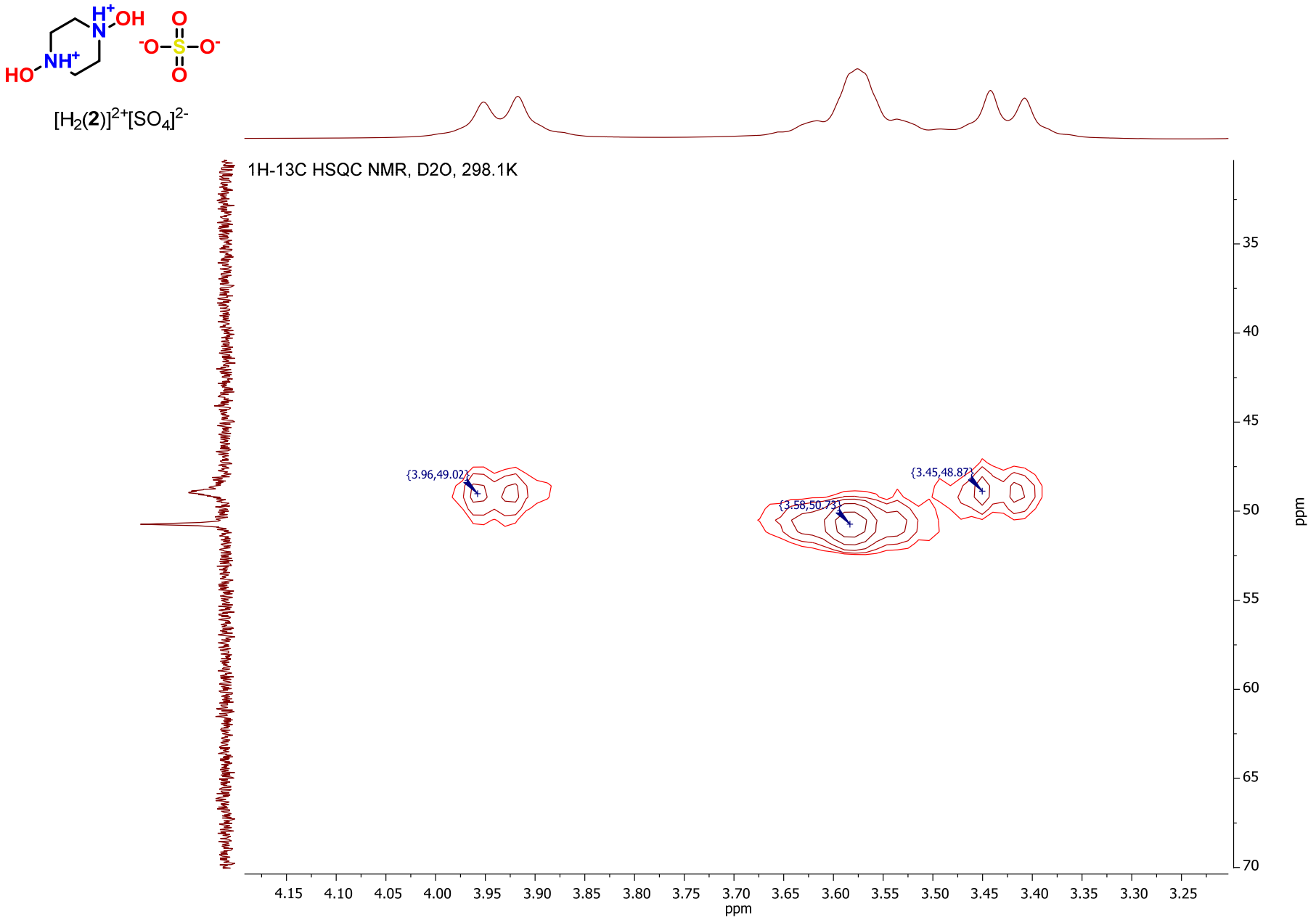
$[H_2(\mathbf{2})]^{2+}[SO_4]^{2-}$

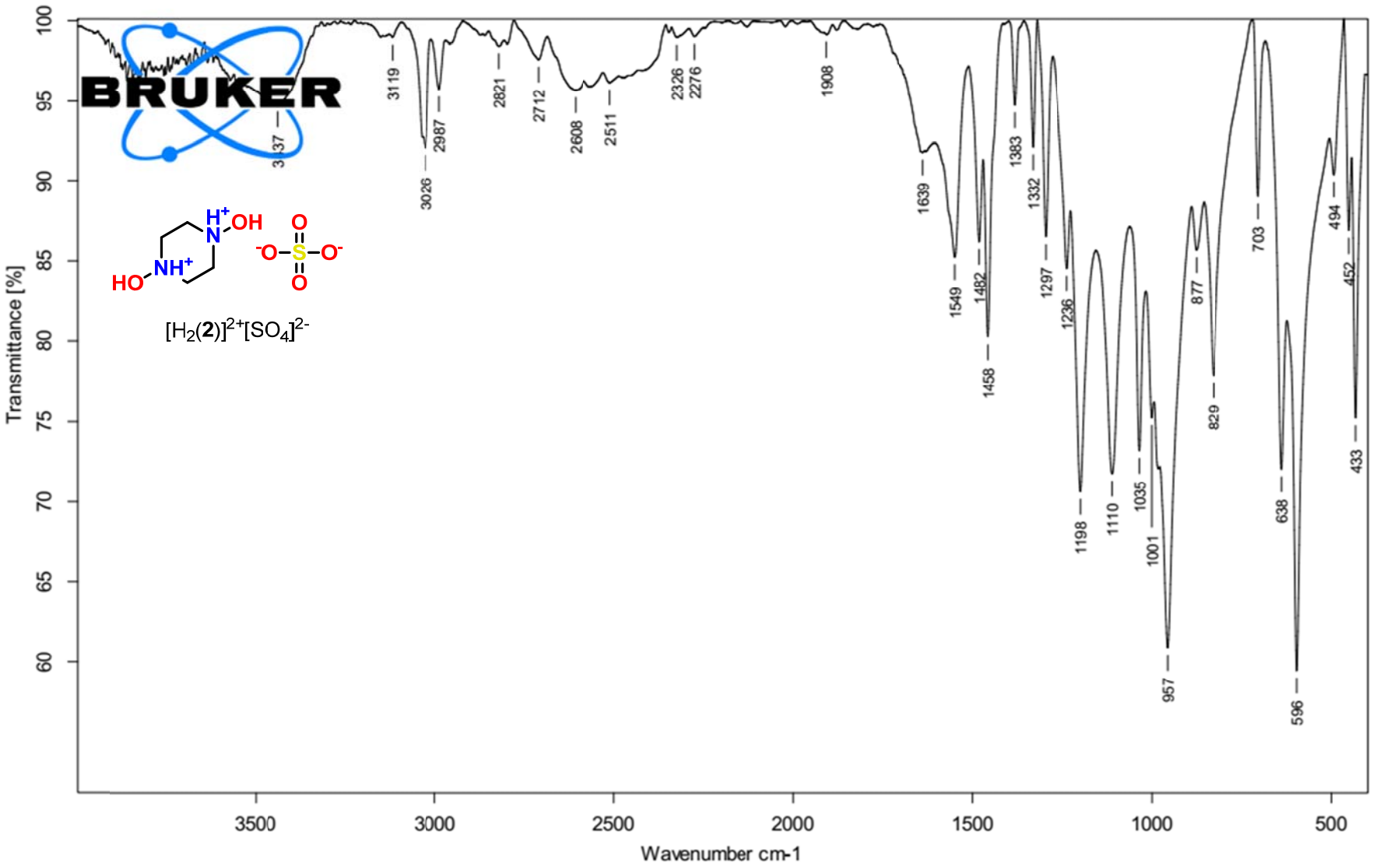
13C NMR 75.50MHz, D2O, 298.0K



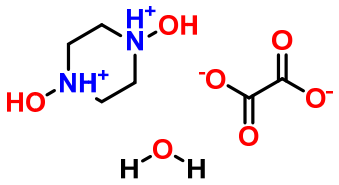
$[H_2(\mathbf{2})]^{2+}[SO_4]^{2-}$




[H2(2)]2+[SO4]2-
1H-13C HSQC NMR, D2O, 298.1K
{3.96,49.02}
{3.58,50.73}
{3.45,48.87}
4.15 4.10 4.05 4.00 3.95 3.90 3.85 3.80 3.75 3.70 3.65 3.60 3.55 3.50 3.45 3.40 3.35 3.30 3.25
ppm
35 40 45 50 55 60 65 70
ppm

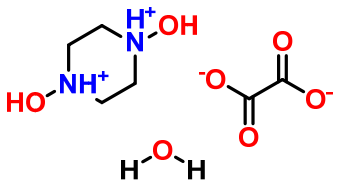

BRUKER
[H2(2)]2+[SO4]2-
Transmittance [%]
Wavenumber cm-1
3337
3119
3026
2987
2821
2712
2608
2511
2326
2276
1908
1639
1549
1482
1458
1383
1332
1297
1236
1198
1110
1035
1001
957
877
829
703
638
596
494
452
433

1H NMR 300.23MHz, D2O, 298.0K

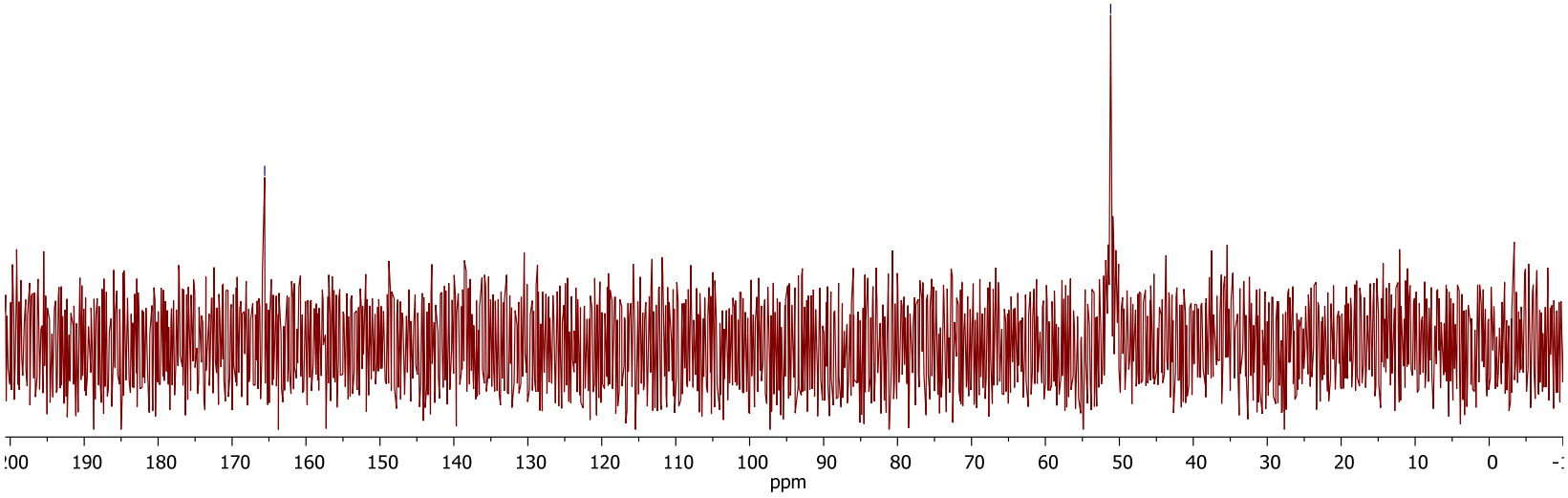


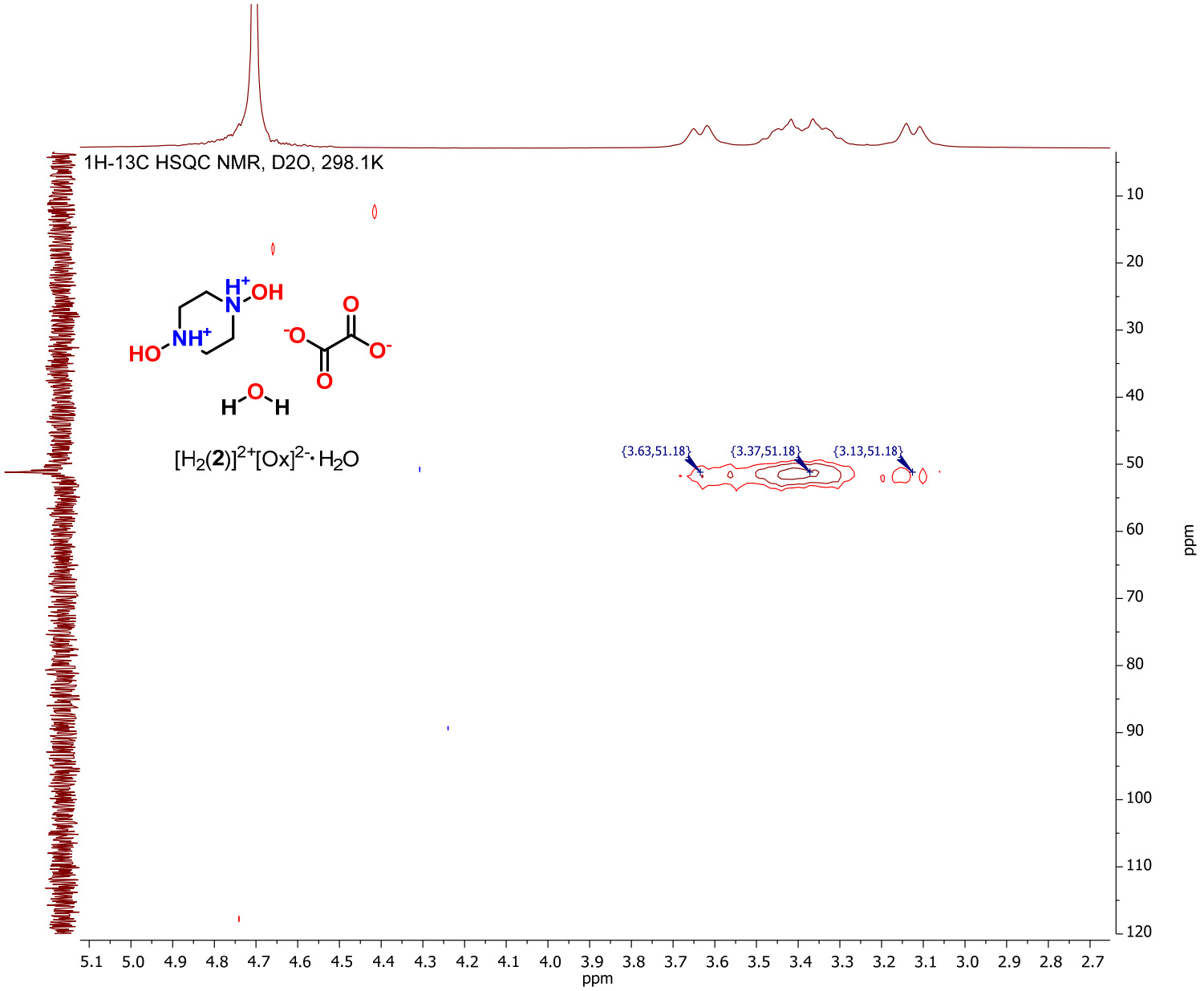
$[H_2(\mathbf{2})]^{2+}[Ox]^{2-}\cdot H_2O$

13C NMR 75.50MHz, D2O, 298.1K

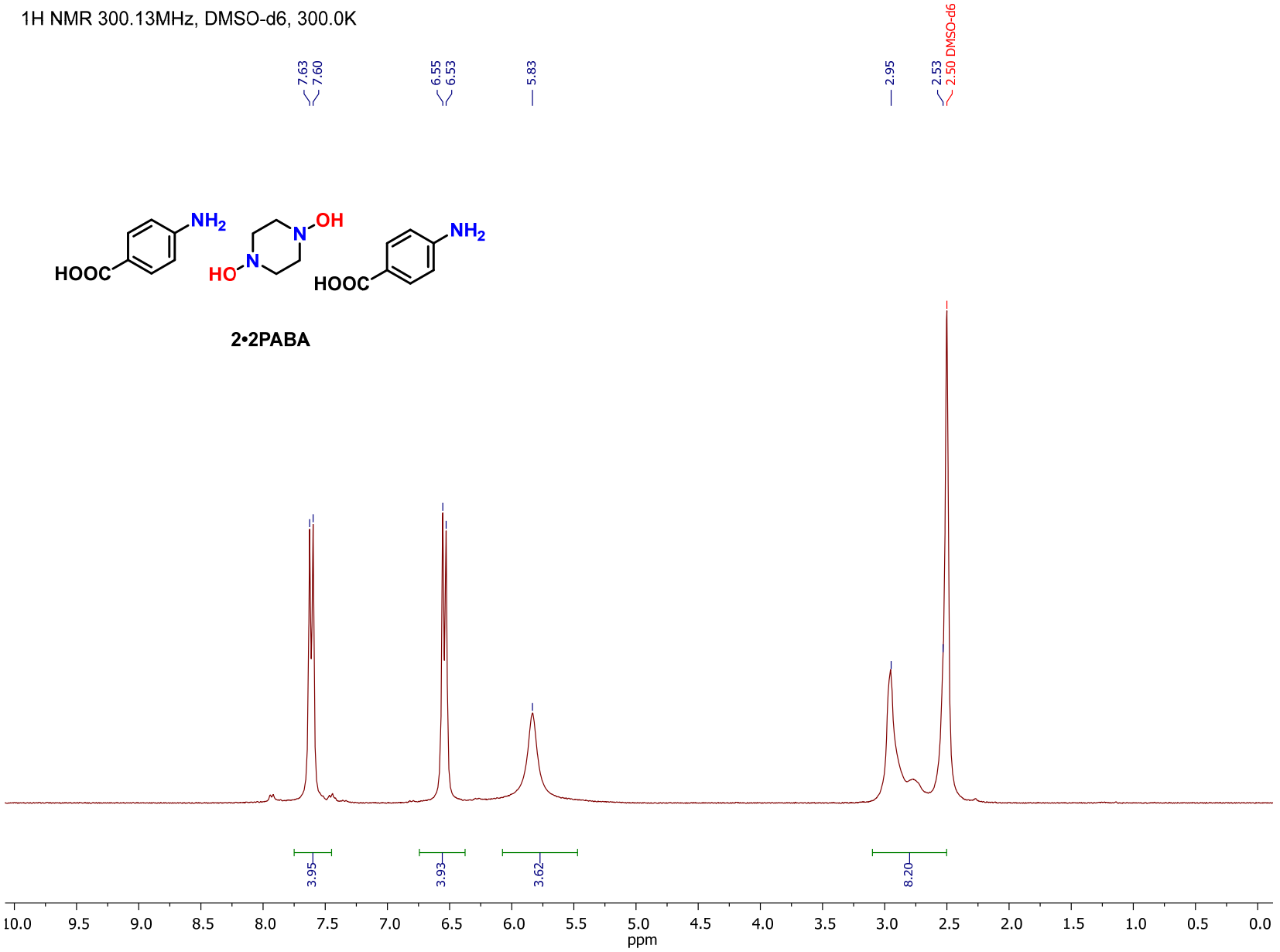


$[H_2(\mathbf{2})]^{2+}[Ox]^{2-}\cdot H_2O$



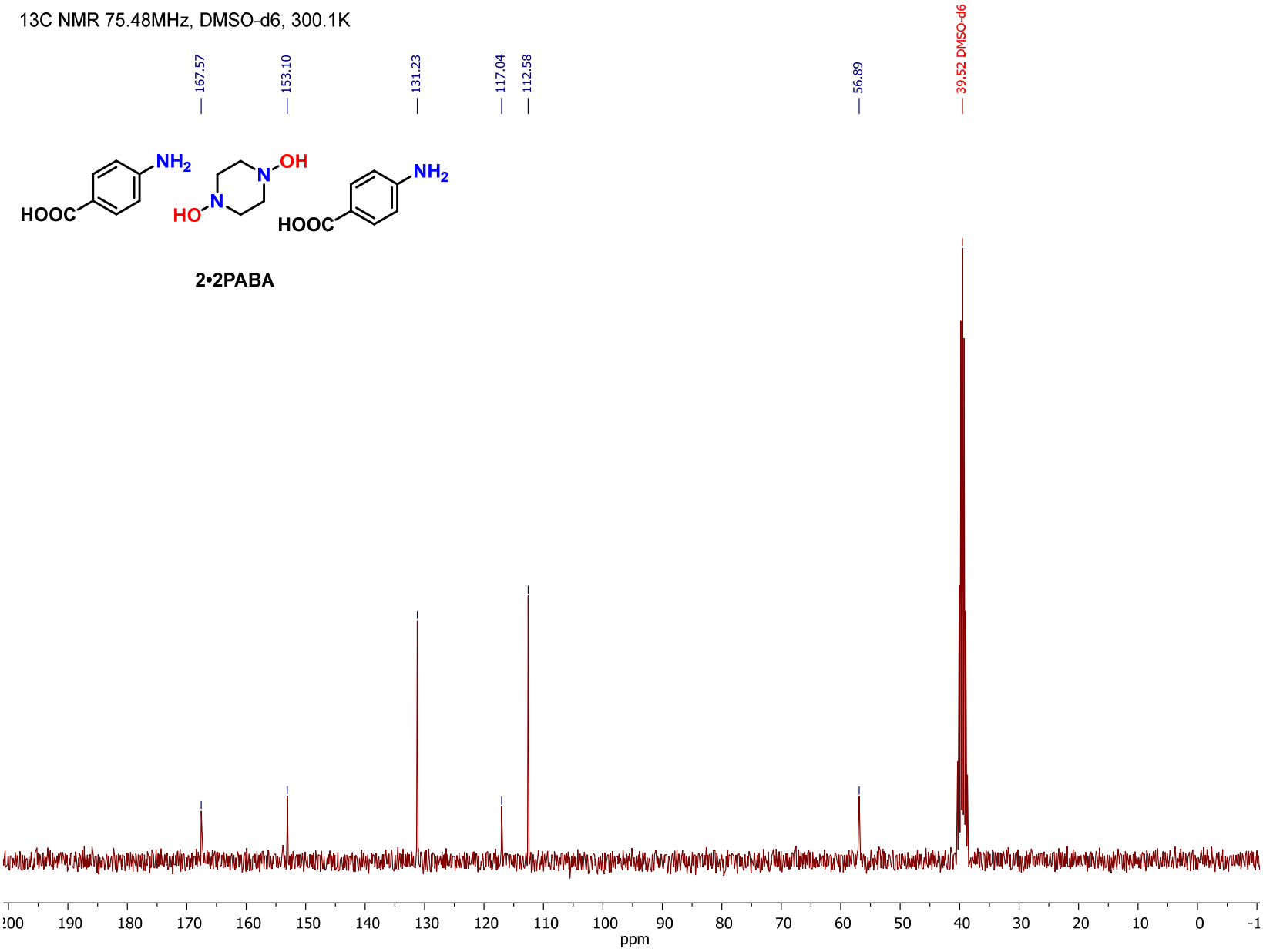

1H-13C HSQC NMR, D2O, 298.1K
{3.63,51.18}
{3.37,51.18}
{3.13,51.18}
[H2(2)]2+[Ox]2-· H2O
ppm
ppm

1H NMR 300.13MHz, DMSO-d6, 300.0K

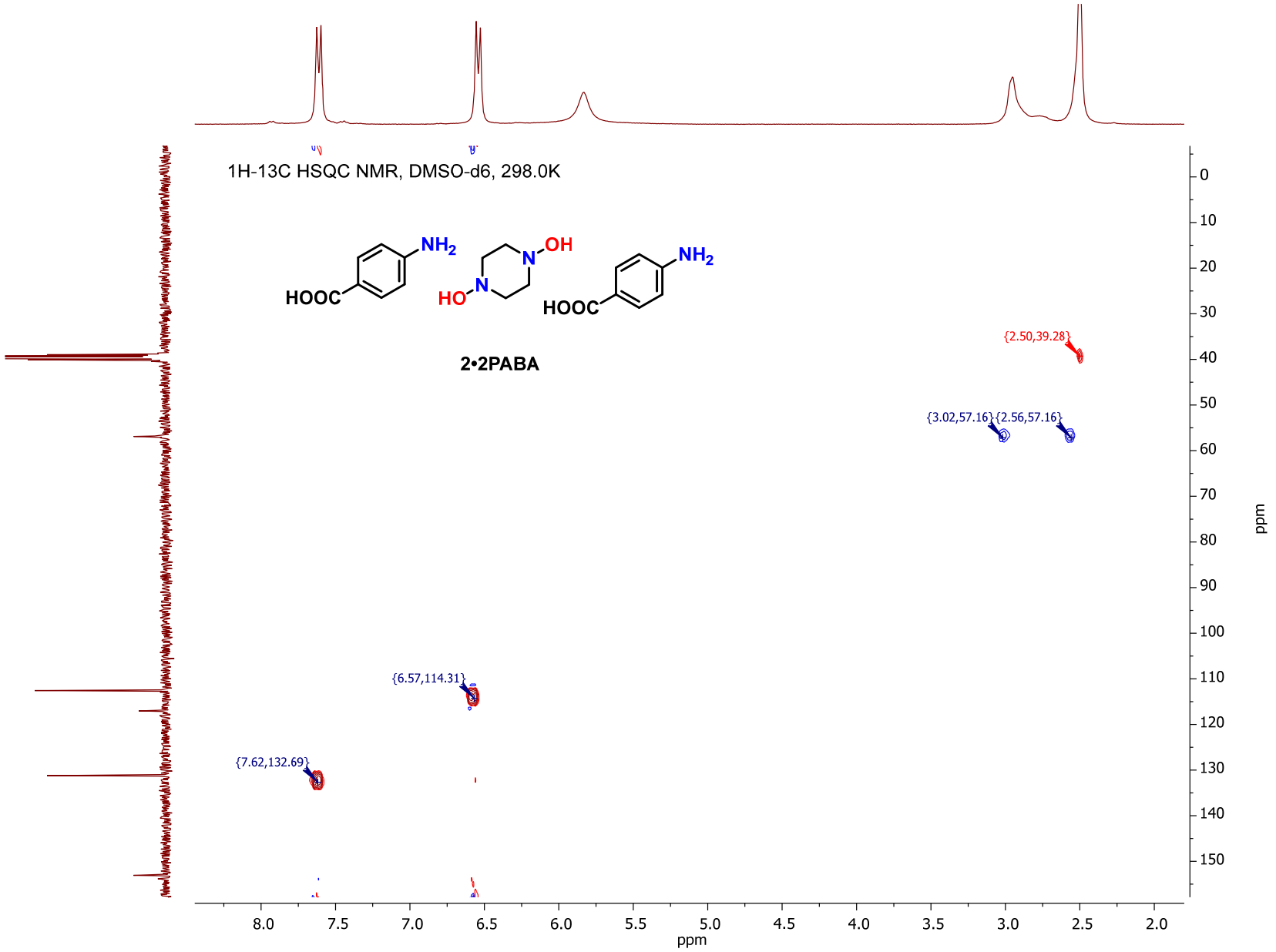


2•2PABA

13C NMR 75.48MHz, DMSO-d6, 300.1K



2•2PABA


1H-13C HSQC NMR, DMSO-d6, 298.0K
NH2
HOOC
OH
N
HO
N
NH2
HOOC
2•2PABA
{2.50,39.28}
{3.02,57.16}{2.56,57.16}
{6.57,114.31}
{7.62,132.69}
ppm
ppm

Dynamic NMR

Full line shape analysis was carried out using TopSpin 4.1.3 DNMR (Dynamic NMR) Lineshape Fitting module. The following model was used with subsequent optimization of the parameters until the best overlap of the simulated and real spectra was achieved by more than 93% (see tables below):

Table S1. *Fitting model for full line shape analysis.*

Fixed Spectroscopic Model Parameters							Refined Spectroscopic Model Parameters							
	DMSO-d_6			D_2O				DMSO-d_6				D_2O		
NEXP	1			1			CONC1	4,6E+11				8,0E+11		
NTASK	3			3			CONCD1	5,9E+09				8,4E+09		
NR	1			1			CONCF1	1				1		
NAT	2	2	1	2	2	1	LB1	0				0		
NMOL	1	1	1	1	1	1	LBD1	0				0		
NREAC	1	1	1	1	1	1	LBF1	1				1		
FORCEX	1	1	1	1	1	1	DISO1	3	3			3	3	
LBGROUP	0	0	0	0	0	0	DISOD1	0	0			0	0	
VL	300			300			DISOF1	1	1			1	1	
O1PSR	6			6			SCJ1	0	-6	-6	0	0	8	8	0
F1P	3			5			SCJD1	0	0	0	0	0	0	0	0
F2P	2			2			SCJF1	0	1	1	0	0	1	1	0
IY	5,3E+09			2,1E+10			DELTAH1	60				10		
B1	1			1			DELTAHD1	1				0		
B2	0			0			DELTAHF1	1				1		
PSPIN1	1	1		1	1		DELTAS1	60				10		
MOAT1	1	1		1	1		DELTASD1	1				0		
NXCHG1	2			2			DELTASS1	1				1		
KGROUP1	0			0			MOLX1	1				1		
KAPPAX1	1			1			MOLXD1	0				0		
XFROM1	1	2		1	2		MOLXF1	0				0		

XTO1	2	1		2	1		CONC2	1,2E+11				3,8E+11			
COEF1	-1			-1			CONCD2	5,4E+08				3,1E+09			
XGROUP1	0			0			CONCF2	1				1			
PSPIN2	1	1		1	1		LB2	10				10			
MOAT2	1	1		1	1		LBD2	0				0			
NXCHG2	2			2			LBF2	1				1			
KGROUP2	0			0			DISO2	3	3			3	3		
KAPPAX2	1			1			DISOD2	0	0			0	0		
XFROM2	1	2		1	2		DISOF2	1	1			1	1		
XTO2	2	1		2	1		SCJ2	0	-3	-3	0	0	10	10	0
COEF2	-1			-1			SCJD2	0	0	0	0	0	0	0	0
XGROUP2	0			0			SCJF2	0	1	1	0	0	1	1	0
PSPIN3	3			1			DELTAH2	123				19			
MOAT3	1			1			DELTAHD2	6				0			
NXCHG3	2			2			DELTAHF2	1				1			
KGROUP3	0			0			DELTAS2	123				19			
KAPPAX3	1			1			DELTASD2	6				0			
XFROM3	1	1		1	1		DELTASS2	1				1			
XTO3	1	1		1	1		MOLX2	1				1			
COEF3	-1			-1			MOLXD2	0				0			
XGROUP3	0			0			MOLXF2	0				0			
END							CONC3	8,0E+08				8,5E+11			
							CONCD3	3,8E+06				7,2E+09			
							CONCF3	1				1			
							LB3	12				10			
							LBD3	0				0			
							LBF3	1				1			
							DISO3	3				5			
							DISOD3	0				0			

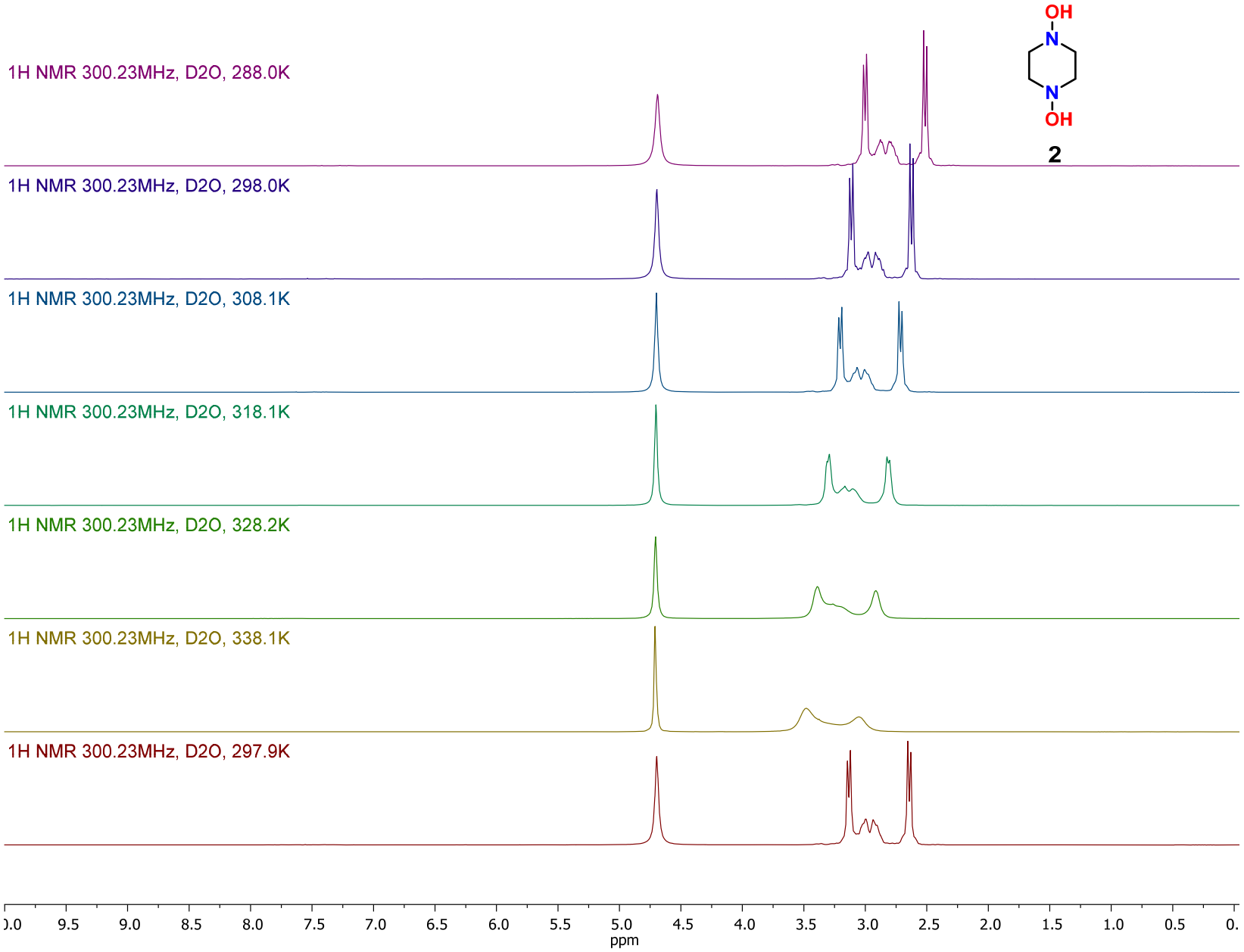
							DISOF3	1				1			
							SCJ3	0				0			
							SCJD3	0				0			
							SCJF3	0				0			
							DELTAH3	50				50			
							DELTAHD3	0				0			
							DELTAHF3	0				0			
							DELTAS3	50				50			
							DELTASD3	0				0			
							DELTASS3	0				0			
							MOLX3	1				1			
							MOLXD3	0				0			
							MOLXF3	0				0			
							END								

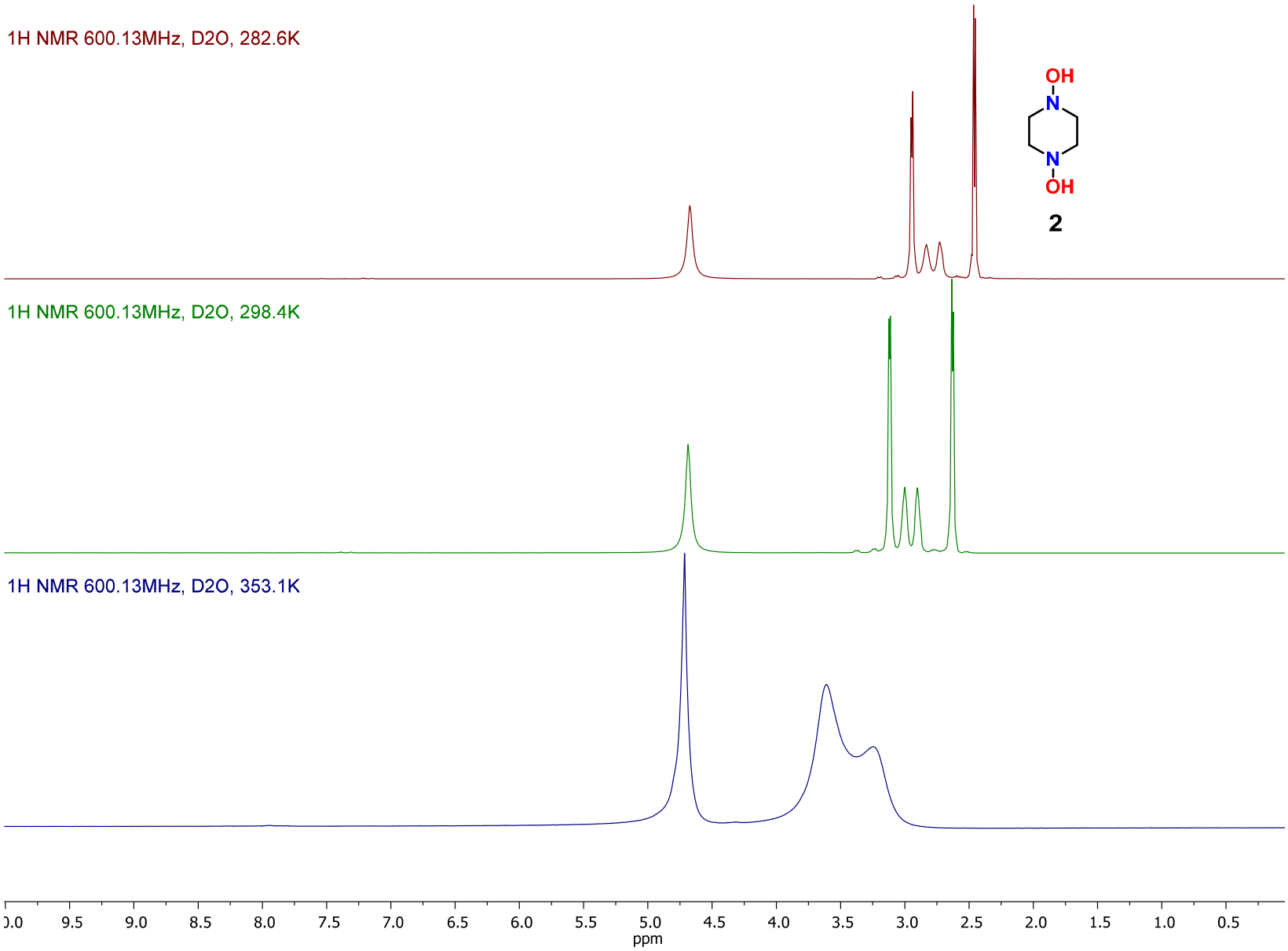
Table S2. *Full line shape analysis for spectra in D_2O*

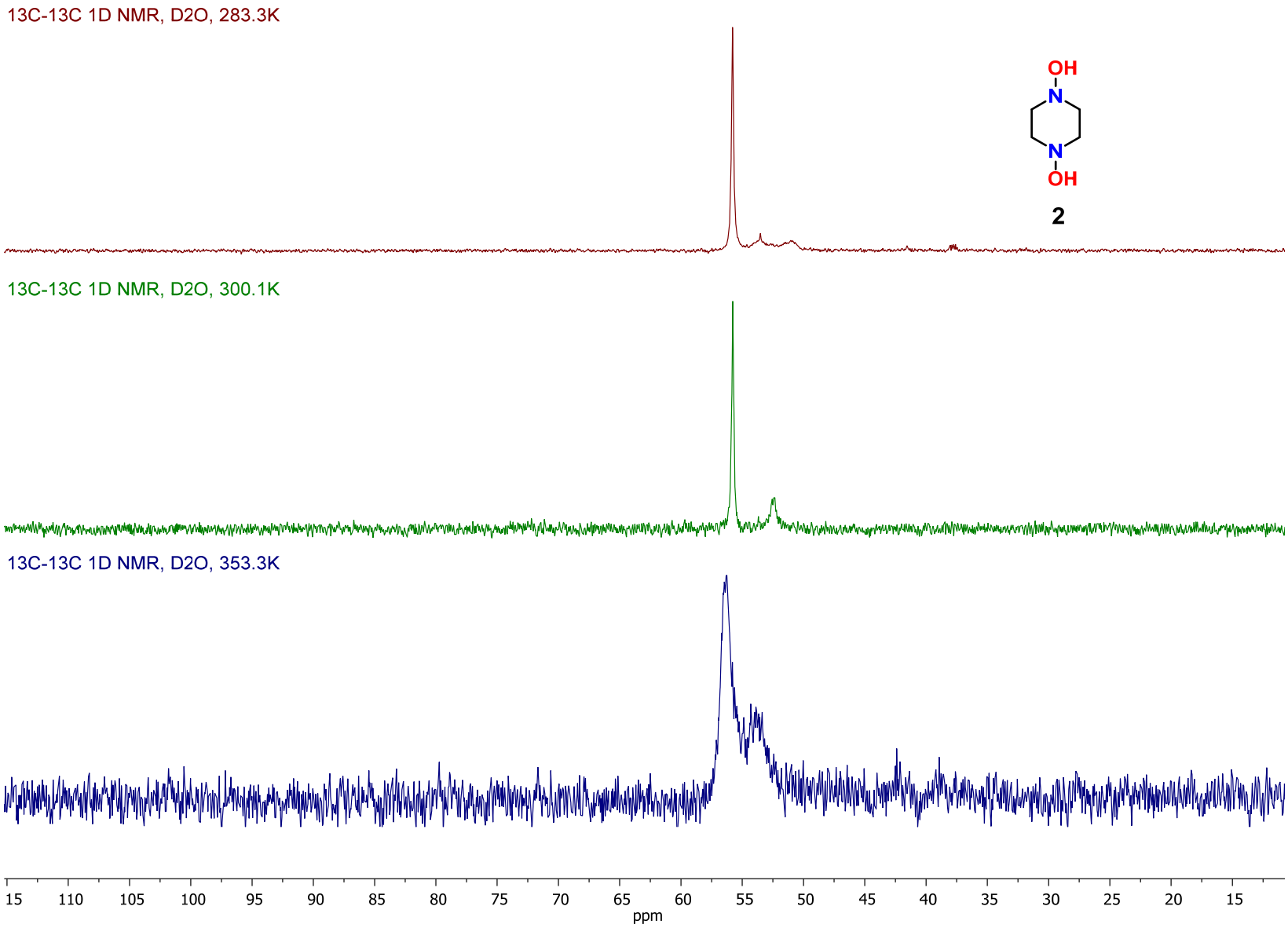
T, K	System 1				System 2				Best overlap, %
	ATOM		k[Hz]	ΔG‡, cal/mol	ATOM		k[Hz]	ΔG‡, cal/mol	
	1	2	1 ↔ 2		1	2	1 ↔ 2		
288,15	3.0021	2.5137	6.73392	15757	2.8948	2.7813	22.778	15059	93,01
298,15	3.1327	2.643	11.4644	16004	3.0281	2.9019	32.8346	15384	95,79
308,15	3.2037	2.7131	17.2686	16311	3.1018	2.9712	46.9927	15699	94,08
318,15	3.3021	2.8109	27.7688	16561	3.2147	3.0599	67.2526	16002	96,71
328,15	3.3962	2.907	57.9362	16623	3.3475	3.1411	124.74	16123	97,14
338,15	3.4974	3.0386	99.2219	16788	3.525	3.2508	152.777	16498	94,37

Table S3. *Full line shape analysis for spectra in DMSO-d_6*

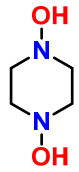
T, K	System 1				System 2				Best overlap, %
	ATOM		k[Hz]	ΔG‡, cal/mol	ATOM		k[Hz]	ΔG‡, cal/mol	
	1	2	1 ↔ 2		1	2	1 ↔ 2		
298,15	2.9667	2.5166	60.1092	15025	2.9749	2.7371	123.307	14599	98.36
338,15	3.0224	2.4841	404.935	15843	3.0647	2.7142	510.819	15687	97.87


1H NMR 300.23MHz, D2O, 288.0K
1H NMR 300.23MHz, D2O, 298.0K
1H NMR 300.23MHz, D2O, 308.1K
1H NMR 300.23MHz, D2O, 318.1K
1H NMR 300.23MHz, D2O, 328.2K
1H NMR 300.23MHz, D2O, 338.1K
1H NMR 300.23MHz, D2O, 297.9K
OH
N
N
OH
2
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


1H NMR 600.13MHz, D2O, 282.6K
OH
N
N
OH
2
1H NMR 600.13MHz, D2O, 298.4K
1H NMR 600.13MHz, D2O, 353.1K
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


13C-13C 1D NMR, D2O, 283.3K
OH
N
N
OH
2
13C-13C 1D NMR, D2O, 300.1K
13C-13C 1D NMR, D2O, 353.3K
15
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
15
ppm

1H NMR 300.23MHz, DMSO-d6, 338.2K



2

1H NMR 300.23MHz, DMSO-d6, 298.0K

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

ppm

DFT calculations

Conformations search

Conformational search was performed with meta-dynamics driven search algorithm CREST v2.11.2[3] using GFN2-xtb semiempirical tight-binding method[4] implemented in XTB v6.4.1 program. Resulting molecular ensemble was sorted using CENSO v.1.2.0 code[5] and ORCA v.5.0.3[6] quantum chemistry package. CENSO routine consisted of:

part0: b97-d3/def2-SV(P) // GFNn-xTB (Input geometry)

part1: r2scan-3c + SMD[chcl3] + GmRRHO(GFN2[alpb]-bhess) // GFNn-xTB (Input geometry)

part2: r2scan-3c + SMD[chcl3] + GmRRHO(GFN2[alpb]-bhess) // r2scan-3c[SMD]

part3: pw6b95-d4/def2-TZVPD + SMD[chcl3] + GmRRHO(GFN2[alpb]-bhess) // r2scan-3c[SMD]

DFT calculation of thermodynamic parameters and nitrogen inversion barrier

DFT calculations were performed with the Gaussian 16 Rev C.01.[7] M11 DFT functional with Def2TZVP basis set was used for geometry optimization, calculations of thermodynamics and kinetics. Calculations were performed in

---

[3] Pracht, P.; Bohle, F.; Grimme, S. Automated Exploration of the Low-Energy Chemical Space with Fast Quantum Chemical Methods. *Phys. Chem. Chem. Phys.* **2020**, *22* (14), 7169–7192.

[4] Bannwarth, C.; Ehlert, S.; Grimme, S. GFN2-XTB - An Accurate and Broadly Parametrized Self-Consistent Tight-Binding Quantum Chemical Method with Multipole Electrostatics and Density-Dependent Dispersion Contributions. *J. Chem. Theory Comput.* **2019**, *15* (3), 1652–1671.

[5] Grimme, S.; Bohle, F.; Hansen, A.; Pracht, P.; Spicher, S.; Stahn, M. Efficient Quantum Chemical Calculation of Structure Ensembles and Free Energies for Nonrigid Molecules. *J. Phys. Chem. A* **2021**, *125* (19), 4039–4054.

[6] Neese, F. Software update: The ORCA program system—Version 5.0. *WIREs Comput Mol Sci*. **2022**, e1606.

[7] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Farkas, O.; Foresman, J. B.; Fox, D. J. Gaussian, Inc., Wallingford CT, **2016**.

water (SMD model), the approach of Martin and co-workers was followed.[8] Cartesian coordinates are given in angstroms; absolute energies for all substances are given in hartrees. Analysis of vibrational frequencies was performed for all optimized structures. All compounds, except transition state structures, were characterized by only real vibrational frequencies. TS was characterized by one imaginary frequency. Wavefunction stability, using stable keyword, was also checked for each molecule

For calculations of optimized geometries, frequencies, thermodynamics and kinetics following keywords were used:

 # opt=(calcfc) freq M11/Def2TZVP scf=xqc scrf=(smd,solvent=water) nosymm pressure=1358 temperature=298.15 test

The same parameters were calculated for transition state structure with keywords:

 # opt=(calcfc,ts,noeigentest) freq M11/Def2TZVP scf=xqc scrf=(smd,solvent=water) nosymm pressure=1358 temperature=298.15 test

IRC calculation was performed for TS and proved that TS connects products and reactants:

 # irc=(forward,calcfc,maxcycle=150,MaxPoints=15,HPC) scf=xqc M11/Def2TZVP

scrf=(smd,solvent=water) geom=checkpoint guess=(read) nosymm pressure=1358 temperature=298.15 test

 # irc=(reverse,calcfc,maxcycle=150,MaxPoints=15,HPC) scf=xqc M11/Def2TZVP

scrf=(smd,solvent=water) geom=checkpoint guess=(read) nosymm pressure=1358 temperature=298.15 test

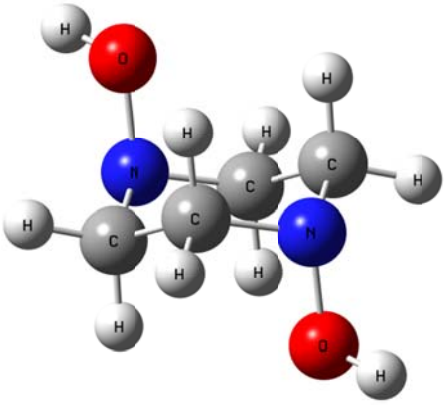
[8] Martin, R. L.; Hay, P. J.; Pratt, L. R. Hydrolysis of Ferric Ion in Water and Conformational Equilibrium. *J. Phys. Chem. A* **1998**, *102*, 3565.

Relative stability of conformers/invertomers of PipzDiol 2

Table S4**. Relative stability of conformers/invertomers of PipzDiol **2

Structure	ΔE_0 Kcal/mol	$\Delta G^o_{298,15K}$ Kcal/mol
ax,*ax*-**2**	+0.6	+1.3
ax,*eq*-**2**	0	0
eq,*eq*-**2**	+0.2	+0.1

ax,*ax*-**2**

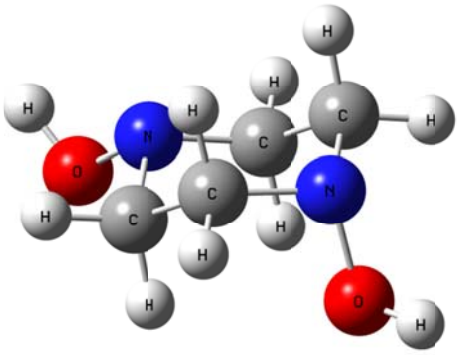


Charge 0; multiplicity 1

C	0.76417300	-0.89302900	0.00692300
C	0.93420500	0.59897700	-0.24391600
N	-0.16932600	1.39855300	0.30230000
C	-1.44610600	0.87790600	-0.20118100
C	-1.61613300	-0.61409800	0.04966500
N	-0.51260500	-1.41366900	-0.49656800
O	-0.16946600	1.18507400	1.72291600
O	-0.51245500	-1.20015600	-1.91717800
H	0.78300300	-1.10163700	1.08137200
H	1.57726800	-1.45319200	-0.46200600
H	0.96286200	0.80188100	-1.31925200
H	1.87055700	0.95467200	0.19381600
H	-1.46494300	1.08650600	-1.27563100
H	-2.25919900	1.43807100	0.26774900
H	-2.55249000	-0.96979400	-0.38805700
H	-1.64477700	-0.81700400	1.12500100
H	-0.04657500	2.06019100	2.10530800
H	-0.63564500	-2.07522100	-2.29959200

DFT M11/Def2TZVP, solvent water, SMD model	
Total electronic energy=	-418.277000 E_0
Sum of electronic and zero-point Energies=	-418.121748 $E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-418.114050 $E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-418.113105 $E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-418.146320 $E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.155252
Number of imaginary vibrational frequencies = 0	

ax,*eq*-**2**

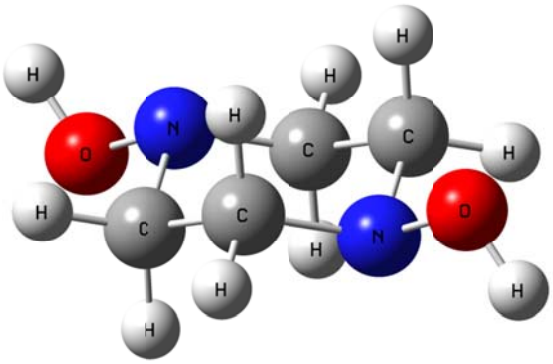


Charge 0; multiplicity 1

C	1.11620900	-0.86463400	0.25137700
C	1.26082400	0.60799300	-0.10196100
N	0.12857900	1.42195300	0.34700700
C	-1.12188100	0.82650900	-0.13022200
C	-1.25502000	-0.64735000	0.22188000
N	-0.11964600	-1.38036500	-0.33632400
O	0.10463500	1.34705500	1.77928800
O	-0.25140300	-2.73194600	0.11651100
H	1.09620600	-1.00008600	1.34396500
H	1.96175800	-1.42662400	-0.15377900
H	1.32040400	0.72705200	-1.18895600
H	2.17538300	1.01174000	0.33816300
H	-1.13395100	0.95320900	-1.21789600
H	-1.95811100	1.38949900	0.29038200
H	-2.17823400	-1.04768900	-0.20508300
H	-1.28697800	-0.78208400	1.31434600
H	0.18966500	2.25914100	2.07686400
H	-0.25899000	-3.27126100	-0.68184100

DFT M11/Def2TZVP, solvent water, SMD model	
Total electronic energy=	-418.277941 E_0
Sum of electronic and zero-point Energies=	-418.123170 $E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-418.115175 $E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-418.114231 $E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-418.148351 $E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.154772
Number of imaginary vibrational frequencies = 0	

eq,eq-**2**

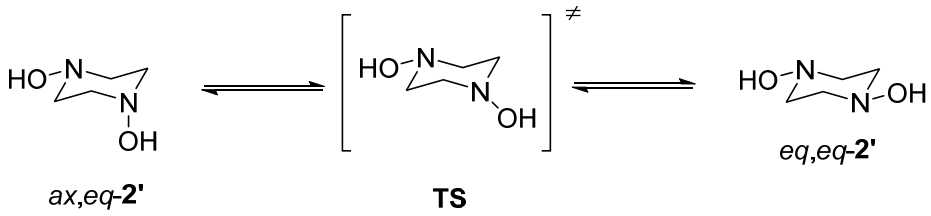


Charge 0; multiplicity 1

C	1.12016200	-0.83384400	0.22162000
C	1.25700200	0.61585500	-0.19807700
N	0.12437400	1.38012200	0.32272800
C	-1.11790600	0.83346700	-0.22201300
C	-1.25474600	-0.61623200	0.19768400
N	-0.12211800	-1.38049800	-0.32312200
O	0.25226500	2.70132900	-0.20624900
O	-0.25000800	-2.70170700	0.20585100
H	1.11473500	-0.91394200	1.32006500
H	1.96079700	-1.41306700	-0.16794600
H	1.28790200	0.69352200	-1.29635200
H	2.18090900	1.03392300	0.20870500
H	-1.11248000	0.91356400	-1.32045800
H	-1.95854100	1.41269000	0.16755300
H	-2.17865400	-1.03430000	-0.20909700
H	-1.28564500	-0.69389900	1.29596000
H	0.27353600	3.28563500	0.55951300
H	-0.27131300	-3.28600700	-0.55991400

DFT M11/Def2TZVP, solvent water, SMD model	
Total electronic energy=	-418.277605 E_0
Sum of electronic and zero-point Energies=	-418.122941 $E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-418.114893 $E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-418.113949 $E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-418.148180 $E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.154664
Number of imaginary vibrational frequencies = 0	

Inversion of nitrogen atom in PipzDiol 2



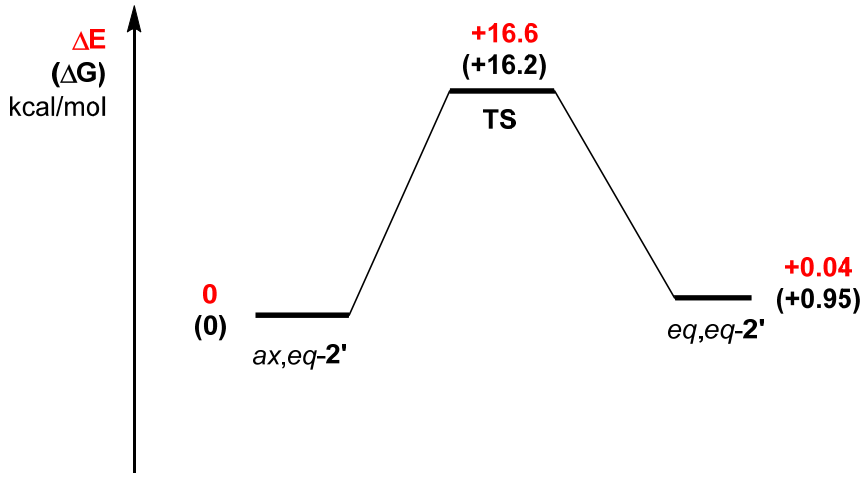
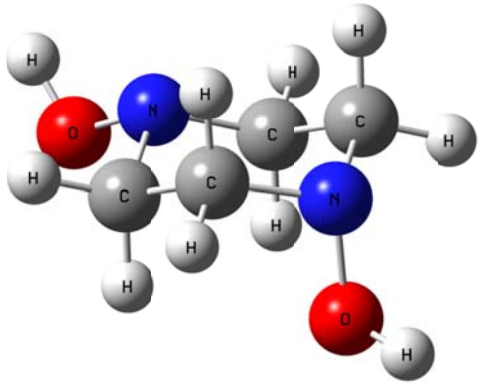


Figure S1. *Energy profile for the inversion of nitrogen atom in PipzDiol* ***2***

ax,eq-**2'**

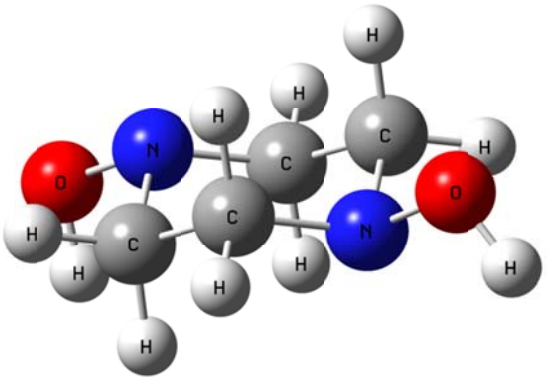


Charge 0; multiplicity 1

C	1.13138200	-0.69687700	-0.00493900
C	1.27390300	0.77898000	-0.34546200
N	0.14052500	1.58743100	0.11061700
C	-1.10904500	0.99440000	-0.37194300
C	-1.24016600	-0.48264000	-0.03262800
N	-0.10375300	-1.20940500	-0.59690200
O	0.11653800	1.49982800	1.54217600
O	-0.23347300	-2.56479700	-0.15501900
H	1.11167300	-0.84176900	1.08644100
H	1.97772900	-1.25409500	-0.41499000
H	1.33329600	0.90762000	-1.43137200
H	2.18790800	1.18013700	0.09818200
H	-1.12114500	1.13050100	-1.45848000
H	-1.94613400	1.55250600	0.05344000
H	-2.16278200	-0.88051500	-0.46318300
H	-1.27215600	-0.62688300	1.05860900
H	0.20136100	2.40920000	1.84802000
H	-0.24342200	-3.09747100	-0.95778000

DFT M11/Def2TZVP, solvent water, SMD model	
Total electronic energy=	-418.277941 E_0
Sum of electronic and zero-point Energies=	-418.123195 $E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-418.115183 $E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-418.114239 $E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-418.148422 $E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.154747
Number of imaginary vibrational frequencies = 0	

eq,eq-**2'**

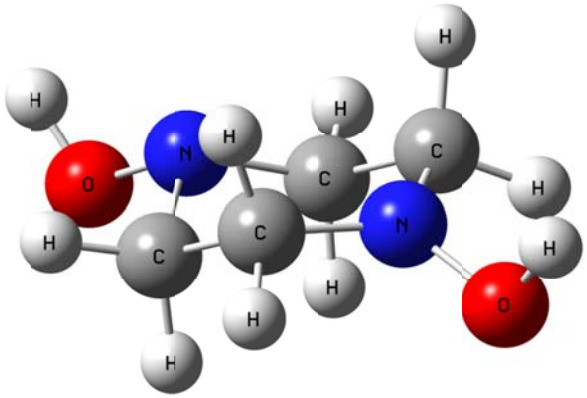


Charge 0; multiplicity 1

C	1.12353700	-0.83645600	-0.03452900
C	1.26090700	0.67041900	0.04595100
N	0.10413100	1.22720700	0.74490700
C	-1.11757400	0.88594900	0.01943800
C	-1.25256600	-0.62083300	-0.06262700
N	-0.09628700	-1.17185200	-0.76814700
O	0.23064600	2.64097400	0.75030200
O	-0.22654900	-2.59311500	-0.70879400
H	1.08413800	-1.26904100	0.97744600
H	1.98068400	-1.25936900	-0.56384100
H	1.32695100	1.09942700	-0.96878700
H	2.16632600	0.93460500	0.59742000
H	-1.08167800	1.31875900	-0.99543000
H	-1.97300300	1.31008800	0.55049300
H	-2.15907700	-0.88230000	-0.61367900
H	-1.31627000	-1.05225200	0.94858900
H	0.24905900	2.93499400	-0.17654700
H	-0.23809700	-2.89029300	-1.62530700

DFT M11/Def2TZVP, solvent water, SMD model	
Total electronic energy=	-418.277872 E_0
Sum of electronic and zero-point Energies=	-418.122345 $E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-418.114787 $E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-418.113843 $E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-418.146915 $E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.155527
Number of imaginary vibrational frequencies = 0	

TS



Charge 0; multiplicity 1

C	1.10966200	-0.99693700	0.26761400
C	1.30554300	0.51185900	0.17416700
N	0.10515100	1.19792300	0.55575300
C	-1.18997600	0.73695100	0.14670000
C	-1.26919600	-0.78235300	0.24152800
N	-0.11556200	-1.37027600	-0.44049700
O	0.18766700	2.22884700	1.48554700
O	-0.24590900	-2.78833800	-0.28528200
H	1.03416500	-1.30682000	1.32239900
H	1.95163500	-1.51521900	-0.19811300
H	1.62017200	0.76885800	-0.85225600
H	2.10737600	0.81429600	0.85289000
H	-1.43151500	1.04399600	-0.88572700
H	-1.93934500	1.17898000	0.80861800
H	-2.18003000	-1.14271400	-0.24321900
H	-1.27337000	-1.09860900	1.29705800
H	0.27085500	3.05780600	0.99635600
H	-0.25787300	-3.14613900	-1.17981800

DFT M11/Def2TZVP, solvent water, SMD model	
Total electronic energy=	-418.251524 E_0
Sum of electronic and zero-point Energies=	-418.097733 $E_0 + E_{ZPE}$
Sum of electronic and thermal Energies=	-418.090164 $E_0 + E_{tot}$
Sum of electronic and thermal Enthalpies=	-418.089220 $E_0 + H_{corr}$
Sum of electronic and thermal Free Energies=	-418.122669 $E_0 + G_{corr}$
Zero-point correction *(unscaled)* =	0.153791
Number of imaginary vibrational frequencies = 1; i378	

X-Ray analysis

X-ray crystallographic data and refinement details

For **2**•2PABA and $[H_2(\mathbf{2})]^{2+}[Ox]^{2-}\bullet H_2O$ X-ray diffraction data were collected at 100K on a four-circle Rigaku Synergy S diffractometer equipped with a HyPix600HE area-detector (kappa geometry, shutterless ω-scan technique), using graphite monochromatized Cu K_α-radiation. The intensity data were integrated and corrected for absorption and decay by the CrysAlisPro program[9]. For $[H_2(\mathbf{2})]^{2+}[SO_4]^{2-}$ intensities of reflections were measured with a Bruker APEXII DUO CCD diffractometer [λ(MoKα) = 0.71073 Å, ω-scans, 2θ<58°], and 2302 independent reflections were used in the further refinement. The structures were solved by direct methods using SHELXT[10] and refined on F^2 using SHELXL-2018[11] (**2**•2PABA and $[H_2(\mathbf{2})]^{2+}[Ox]^{2-}\bullet H_2O$) or Intrinsic Phasing and refined with the XL[10] refinement package using Least-Squares minimization in the OLEX2 program.[12] All non-hydrogen atoms were refined with individual anisotropic displacement parameters. For **2**•2PABA and $[H_2(\mathbf{2})]^{2+}[Ox]^{2-}\bullet H_2O$ locations of amino and hydroxy hydrogen atoms were found from the electron density-difference map; these hydrogen atoms were refined with individual isotropic displacement parameters. For $[H_2(\mathbf{2})]^{2+}[SO_4]^{2-}$ hydrogen atoms of NH and OH groups were located from difference Fourier synthesis. All other hydrogen atoms were placed in ideal calculated positions and refined as riding atoms with relative isotropic displacement parameters.

CCDC 2176251 for **2**•2PABA, CCDC 2176252 for $[H_2(\mathbf{2})]^{2+}[Ox]^{2-}\bullet H_2O$ and CCDC 2175349 for $[H_2(\mathbf{2})]^{2+}[SO_4]^{2-}$ contain the supplementary crystallographic information for this paper.

Graphical materials were prepared using Olex2, Mercury and Crystal explorer software.

[9] CrysAlisPro. Version 1.171.41.106a. *Rigaku Oxford Diffraction*, **2021**.
[10] Sheldrick, G. M. SHELXT - Integrated space-group and crystal-structure determination. *Acta Cryst.* **2015**, A71(1), 3-8.
[11] Sheldrick, G. M. Crystal structure refinement with SHELXL. *Acta Cryst.* **2015**, *C71* (1), 3-8.
[12] Dolomanov, O.V.; Bourhis, L.J.; Gildea, R.J.; Howard, J.A.K.; Puschmann, H. OLEX2: a complete structure solution, refinement and analysis program. *J. Appl. Cryst.* **2009**, *42* (2), 229-341.

Table S5. *Experimental parameters for X-Ray analysis.*

Identification code	**2**•2PABA	$[H_2(\mathbf{2})]^{2+}[SO_4]^{2-}$	$[H_2(\mathbf{2})]^{2+}[Ox]^{2-}\bullet H_2O$
Empirical formula	$C_9H_{12}N_2O_3$	$C_4H_{12}N_2O_6S$	$C_6H_{13.80}N_2O_{6.90}$
Formula weight	196.21	216.22	224.40
Temperature, K	100	120	100
Wavelength, Å	1.54184	0.71073	1.54184
Crystal system	Monoclinic	Triclinic	Monoclinic
Space group	$P2_1/n$	P-1	$P2_1/n$
Unit cell dimensions			
a, Å	10.63990(10) Å	5.7797(4)	9.54180(10)
b, Å	8.49780(10) Å	6.3309(5)	9.76040(10)
c, Å	11.93370(10)	12.8187(10)	10.15310(10)
α, °	90°.	76.647(2)	90
β, °	116.019(2)°	78.320(2)	97.0180(10)
γ, °	90	74.621(2)	90
Volume, $Å^3$	969.64(2)	435.01(6)	938.492(17)
Z	4	2 (Z' = 1)	4
Density (calculated), g/cm^{-3}	1.344	1.651	1.588
Absorption coefficient, mm^{-1}	0.856	0.377	1.275
F(000)	416	228	476
Reflections collected	12736	5422	12301
Independent reflections	2067	2302	1990
Goodness-of-fit on F2	1.062	1,042	1.095
Final R indices [I>2σ(I)]	R1 = 0.0427 wR2 = 0.1176	R1 = 0,0358 wR2 = 0,0912	R1 = 0.0329 wR2 = 0.0918

1,4-Dihydroxypiperazine-1,4-diium sulfate $[H_2(2)]^{2+}[SO_4]^{2-}$

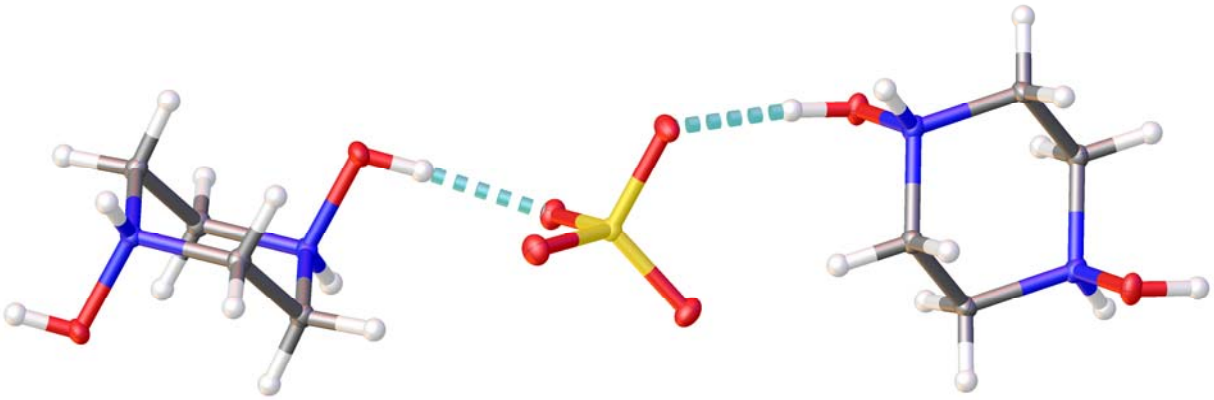


Figure S2. *General view of the compound* $[H_2(\mathbf{2})]^{2+}[SO_4]^{2-}$ *in representation of non-hydrogen atoms as thermal ellipsoids at 30% probability level.*

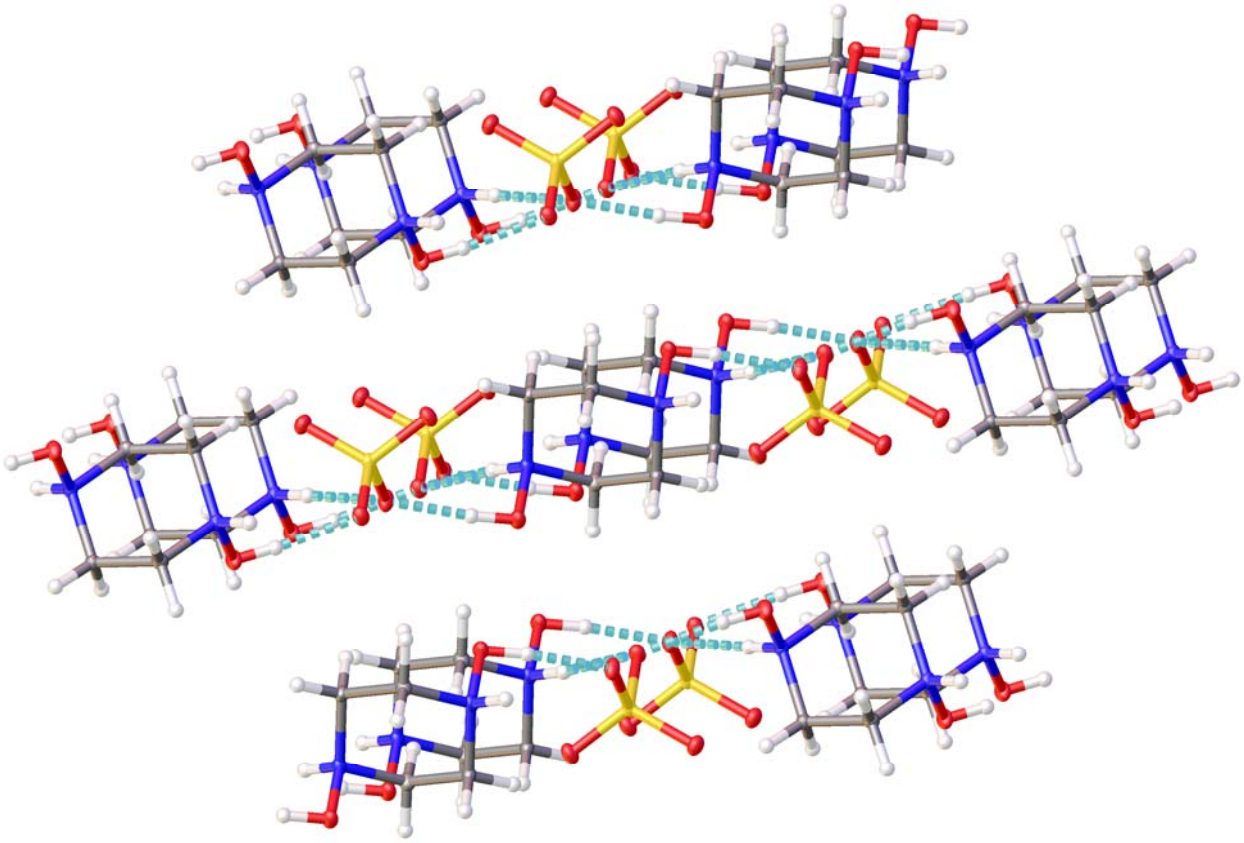


Figure S3. *View of the* $[H_2(\mathbf{2})]^{2+}[SO_4]^{2-}$ *packing in representation of non-hydrogen atoms as thermal ellipsoids at 30% probability level.*

Table S6. *Hydrogen bonds and short contacts of* $[H_2(\mathbf{2})]^{2+}[SO_4]^{2-}$.

:: Resd 0 - Infinite (Type2) 2D-Network					
:: Base Vectors: 1 : [1 0 0], 2 : [0 -1 -1], Plane: (0 1 -1)					
Donor --- H...Acceptor	**[ARU]**	**D – H, Å**	**H...A, Å**	**D...A, Å**	**D - H...A, ˚**
O1--H1 .....O4	[1555.03]	0.8938(16)	1.6966(16)	2.5861(16)	173.05(14)
N1--H1A.....O3	[1655.03]	0.8730(17)	2.4485(17)	2.9707(17)	118.93(13)
N1--H1A.....O6	[1655.03]	0.8730(17)	1.8516(17)	2.7216(17)	174.27(15)
O2--H2 .....O6	[1555.03]	0.8373(16)	1.7576(16)	2.5933(16)	175.73(14)
N2--H2C.....O4	[1455.03]	0.8525(17)	1.8494(17)	2.6971(17)	172.72(15)
N2--H2C.....O5	[1455.03]	0.8525(17)	2.5598(17)	3.1068(17)	122.94(13)
C2--H2A.....O3	[2856.03]	0.990(2)	2.427(2)	3.246(2)	139.80(16)
C2--H2B.....O3	[2756.03]	0.990(2)	2.578(2)	3.173(2)	118.61(13)
C3--H3A.....O3	[1465.03]	0.990(2)	2.384(2)	3.327(2)	158.86(18)
C3--H3A.....O5	[1465.03]	0.990(2)	2.592(2)	3.279(2)	126.57(16)
C4--H4A.....O5	[2567.03]	0.990(2)	2.459(2)	3.322(2)	145.45(14)
C4--H4B.....O5	[2667.03]	0.990(2)	2.581(2)	3.235(2)	123.57(14)
:: Resd 0 - Infinite (Type3) 2D-Network					
:: Base Vectors: 1 : [1 0 0], 2 : [0 -1 -1] , Plane: (0 1 -1)					

1,4-Dihydroxypiperazine-1,4-diium oxalate monohydrate $[H_2(2)]^{2+}[Ox]^{2-}\bullet H_2O$

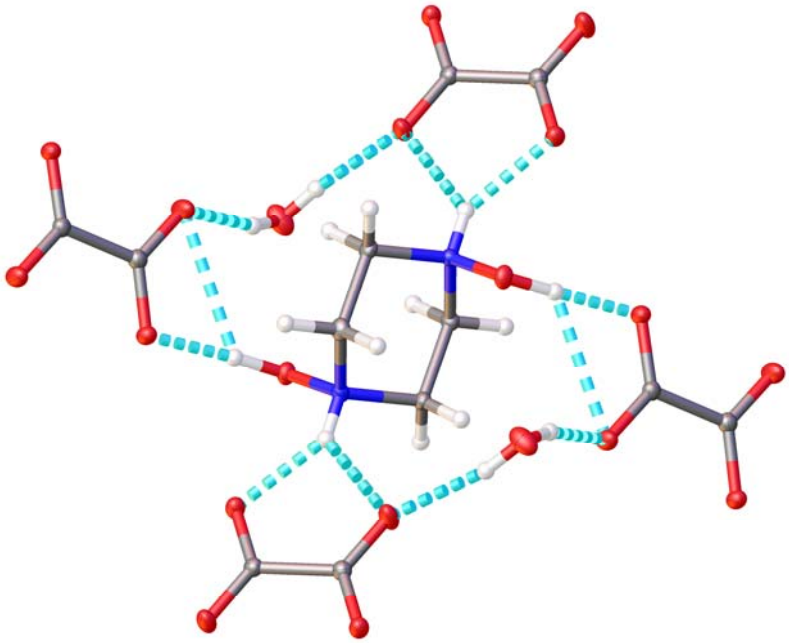


Figure S4. *General view of the compound $[H_2(\mathbf{2})]^{2+}[Ox]^{2-}\bullet H_2O$ in representation of non-hydrogen atoms as thermal ellipsoids at 30% probability level.*

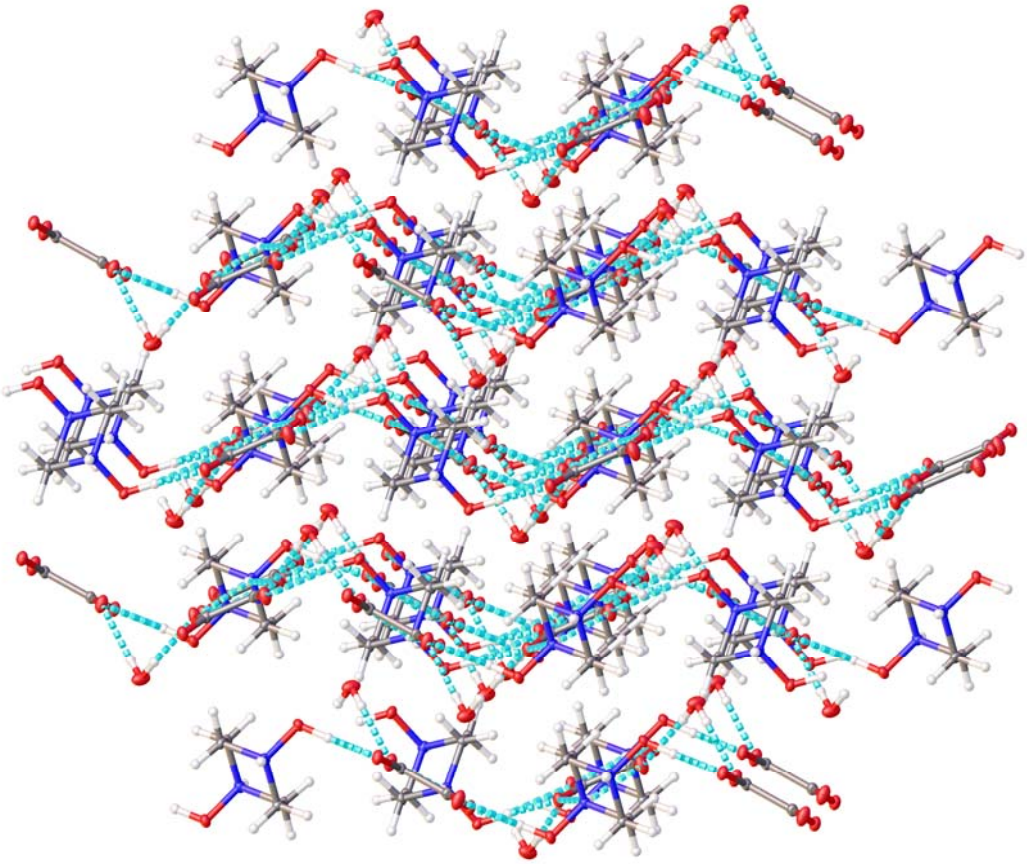


Figure S5. *View of the $[H_2(\mathbf{2})]^{2+}[Ox]^{2-}\bullet H_2O$ packing in representation of non-hydrogen atoms as thermal ellipsoids at 30% probability level.*

Table S7. *Hydrogen bonds and short contacts of* $[H_2(\mathbf{2})]^{2+}[Ox]^{2-}\bullet H_2O$.

:: Resd 0 - Infinite (Type2) 2D-Network					
:: Base Vectors: 1 : [0 0 1], 2 : [1 0 0], Plane: (0 1 0)					
:: Resd 0 - Infinite (Type2) 2D-Network					
:: Base Vectors: 1 : [1 0 0], 2 : [0 0 1], Plane: (0 1 0)					
Donor -H...Acceptor	**[ARU]**	**D – H, Å**	**H...A, Å**	**D...A, Å**	**D - H...A, ˚**
O1--H1.....O5	[1556.02]	1.01(2)	1.57(2)	2.5733(11)	176.4(17)
O1--H1.....O6	[1556.02]	1.01(2)	2.57(2)	3.2371(12)	123.2(14)
N1--H1A.....O4	[4465.02]	0.891(19)	1.955(19)	2.7364(12)	145.5(15)
N1--H1A.....O6	[4465.02]	0.891(19)	2.166(18)	2.8281(13)	130.6(15)
O2--H2.....O4	[1555.02]	0.94(2)	1.62(2)	2.5632(11)	178(2)
N2--H2A.....O3	[4565.02]	0.897(17)	2.115(16)	2.7875(13)	131.1(13)
N2--H2A.....O5	[4565.02]	0.897(17)	1.960(17)	2.7513(12)	146.2(14)
O7--H7A.....O3	[1555.02]	0.82(3)	2.03(3)	2.8295(14)	165(3)
O7--H7B.....O6	[4465.02]	0.84(2)	2.02(2)	2.8454(14)	165.5(18)
C2--H2B.....O1	[3677.01]	0.99	2.55	3.3361(13)	137
C2--H2C.....O3	[1555.02]	0.99	2.48	3.3323(13)	144
C3--H3B.....O7	[3667.03]	0.99	2.28	3.2094(16)	156
C4--H4A.....O6	[1556.02]	0.99	2.50	3.3512(13)	144
C4--H4A.....O3	[4565.02]	0.99	2.57	3.0326(14)	108
C4--H4B.....O5	[2646.02]	0.99	2.59	3.5741(14)	173
:: Resd 0 - Infinite (Type3) 2D-Network					
:: Base Vectors: 1 : [0 0 1], 2 : [1 0 0], Plane: (0 1 0)					
:: Resd 0 - Infinite (Type3) 2D-Network					
:: Base Vectors: 1 : [0 0 1], 2 : [1 0 0], Plane: (0 1 0)					

Co-crystal of 1,4-dihydroxypiperazine and 4-aminobenzoic acid (2•2PABA)

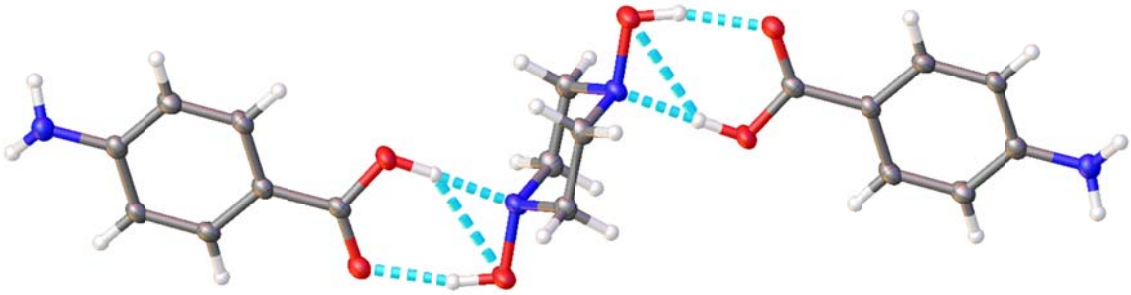


Figure S6. *General view of the compound* ***2****•2PABA in representation of non-hydrogen atoms as thermal ellipsoids at 30% probability level.*

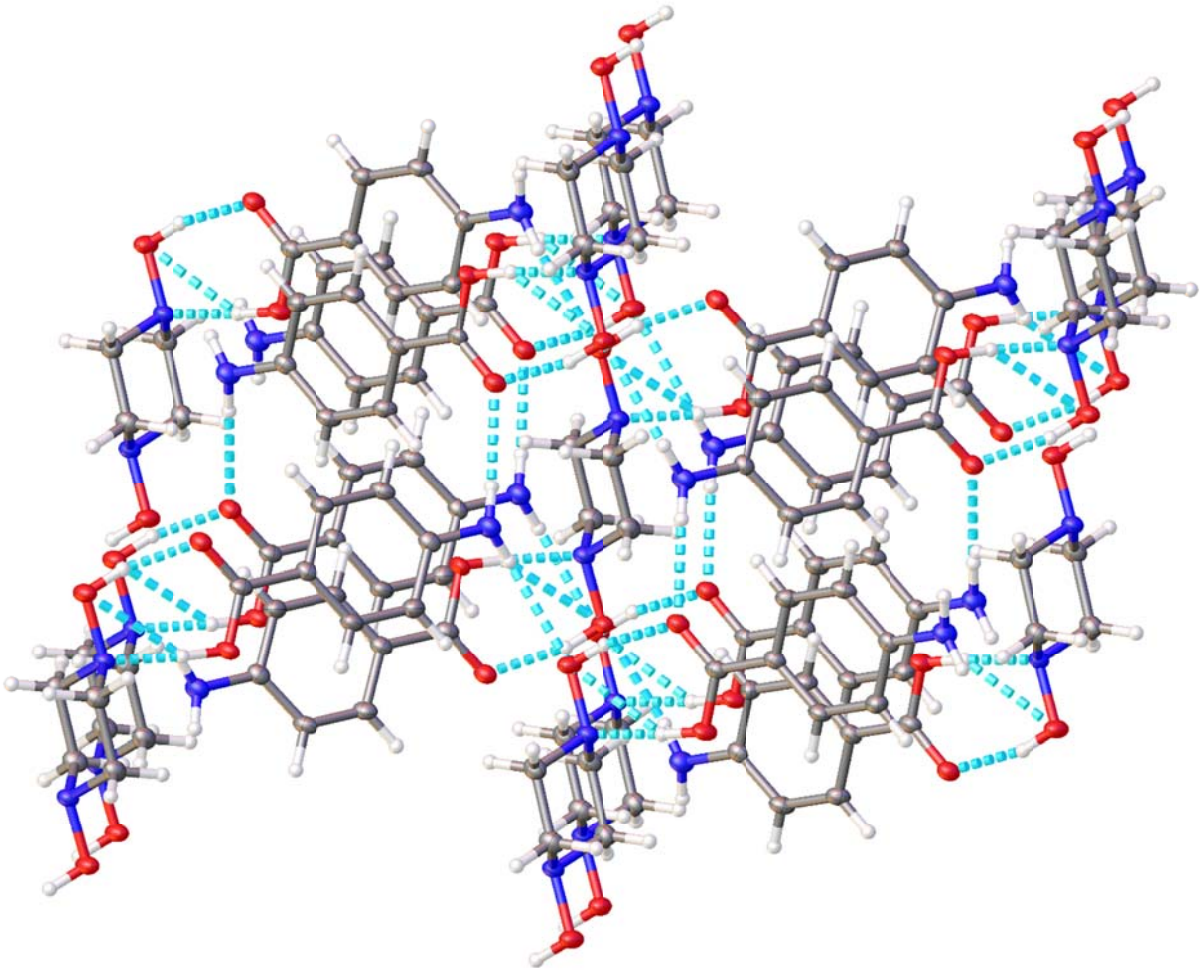


Figure S7. *View of the* ***2****•2PABA packing in representation of non-hydrogen atoms as thermal ellipsoids at 30% probability level.*

Table S8. *Hydrogen bonds and short contacts of* ***2***•*2PABA.*

Donor---H...Acceptor	[ARU]	D - H, Å	H...A, Å	D...A, Å	D - H...A, ˚
O1--H1.....O2	[1555.01]	0.92(2)	1.78(2)	2.6853(15)	167(2)
N2--H2A.....O2	[2555.01]	0.902(19)	2.13(2)	3.0117(15)	166.2(16)
N2--H2B.....O1	[4465.02]	0.89(2)	2.41(2)	3.1824(15)	146.7(15)
O3--H3.....O1	[1555.02]	0.98(3)	2.45(3)	3.2692(14)	141.6(19)
O3--H3.....N1	[1555.02]	0.98(3)	1.65(3)	2.6211(15)	174(2)
C1--H1A.....O2	[2645.01]	0.99	2.53	3.3529(16)	140
:: Resd 0 - Infinite (Type3) 3D-Framework: Det = 2					
:: Base Vectors: 1 : [0 1 0], 2 : [1 0 1], 3 : [1 0 -1]					