Supporting Information

Bio-based chemicals: 1,2,4-benzenetriol, selective deuteration and dimerization to bifunctional aromatic compounds

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Contents

1. General Materials and Methods

Chemicals were obtained from either TCI or Aldrich at highest available purity and used as received. Solvents were obtained from Macron Fine Chemicals or Boom B.V. 1,2,4-benzenetriol (BTO) for the stability experiments was obtained from either TCI or Aldrich showing different levels of **1** in the obtained white solids (3.3 mol% and <1 mol% respectively see Figure S9-S12 for ^{1}H- and ^{13}C-NMR spectra). Double distilled water was used for all experiments. NMR spectra were recorded on an Agilent Technologies 400/54 Premium shielded spectrometer, a Varian Oxford Mercury AS 300 or a Bruker Ascend 600. All chemical shifts (δ) are given in part per million (ppm) with the solvent peak used as reference. Multiplicities are: s = singlet, d = doublet, dd = double doublet. UV-Vis spectra were recorded using a ThermoSpectronic Aquamate. Orbitrap XL mass spectrometer (Thermo Fisher Scientific) equipped with an ESI ionisation source used in negative or positive mode for exact mass and LC-MS (ES) analysis. The samples were measured by direct injection of the sample (flow injection analysis or FIA). When reactions were performed in deoxygenated conditions Schlenk techniques were applied under argon atmosphere.

2. UV-Vis data for BTO and derivatives

Additional data BTO and derivative species

Monomeric BTO is easily distinguishable from the dimeric products as it is a beige to white powder, and clear to slightly golden in aqueous solution, which could be due to the small impurities present in the commercial samples. Both dimeric products are black in

color, and form dark, opaque solutions. Figure S1 displays the UV-Vis spectrums of BTO, dimer **1**, and dimer **3** in THF.
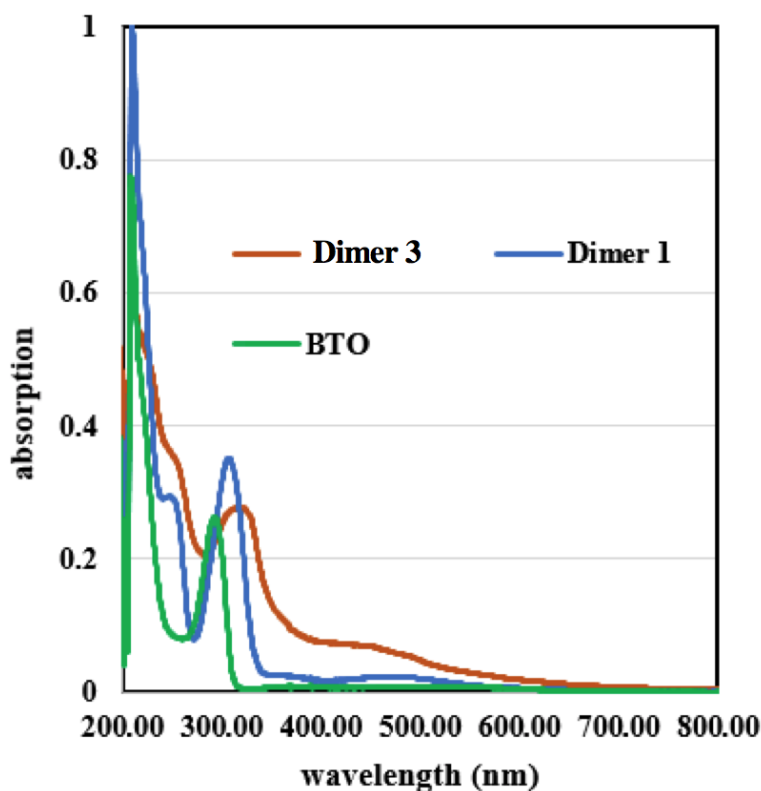

Figure S1. UV-Vis spectrum of BTO, dimer **1**, and dimer **3**. Taken in tetrahydrofuran, 0.5 cm quartz cuvette, 200-800nm.

Figure S1 shows dimer **1** and **3** have a characteristic hump in their absorption spectrum around 250 nm, and large absorptions spanning the entire visible spectrum (400-700 nm). BTO shows ultraviolet (200-320 nm) absorption as do dimer **1** and **3**, but no absorption throughout the visible spectrum. This is why BTO appears clear whilst dimer **1** and **3** appear very dark.

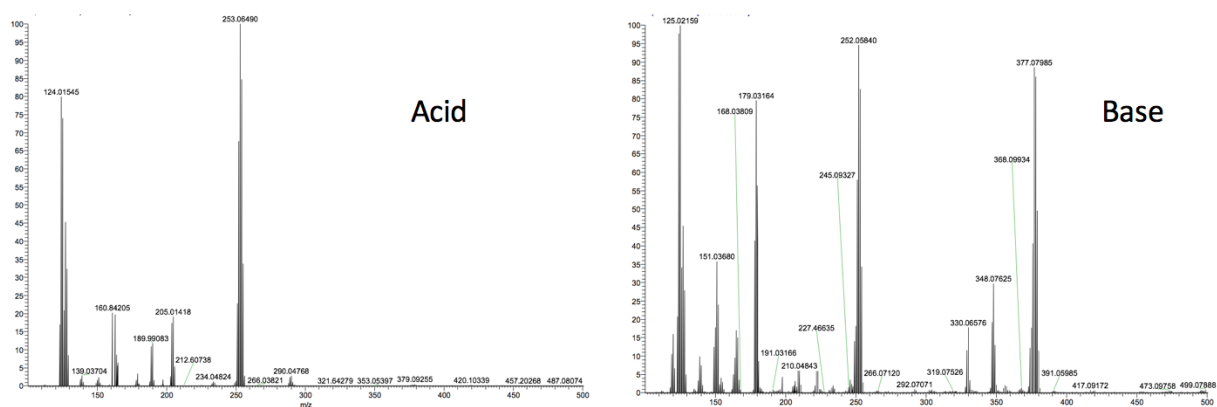### 3. Mass spectroscopy data for BTO reaction in D₂O

Figure S2. LC-MS (ES+) of the solutions obtained from 1,2,4-benzenetriol obtained in acidic (pH = 1, H₂SO₄) and basic (pH = 10, NaOH) conditions showing trimer formation in the latter.

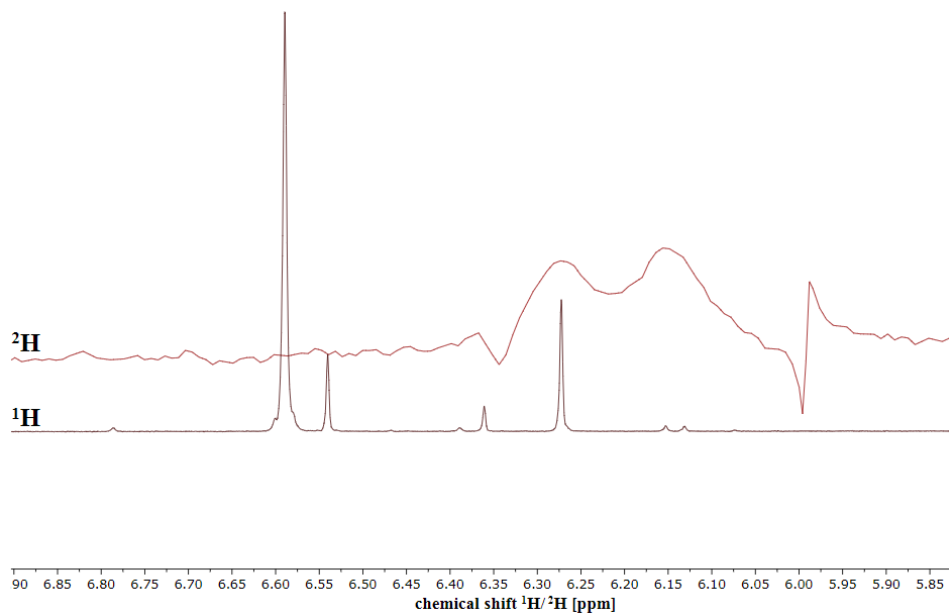### 4. Deuterium exchange

Figure S3. The ²H-NMR spectra and the ¹H-NMR spectra obtained after 140 hours from a BTO solution in D₂O with addition of H₂SO₄ (pH = 1).
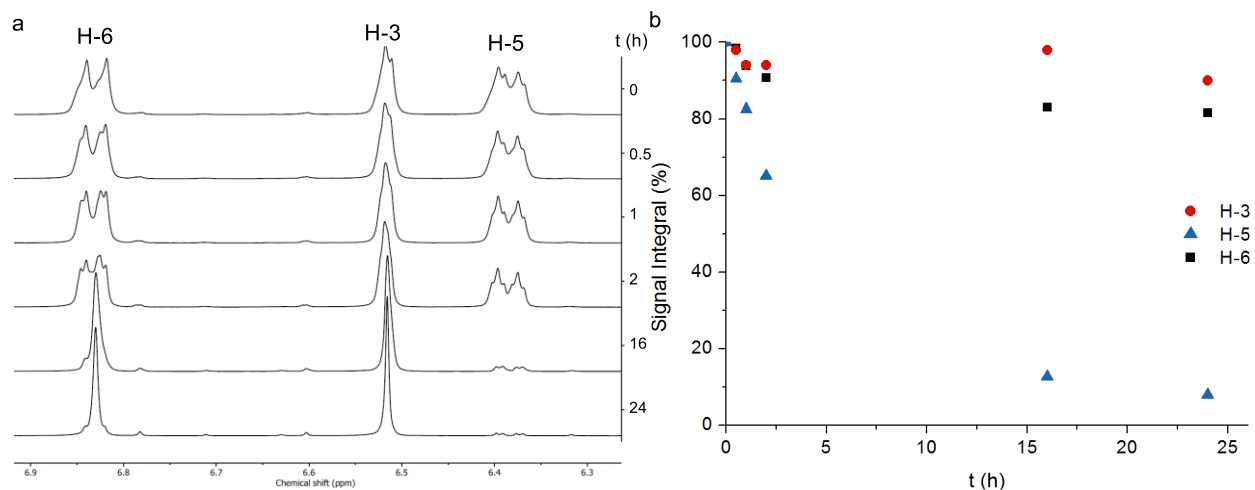
Figure S4. a) Series of ^{1}H-NMR spectra of BTO (Aldrich) in acidic (H_2SO_4) deuterium oxide with exclusion of air by applying degassed solvents and working under nitrogen atmosphere. b) Relative change to signal integrations over time relative to the internal standard.
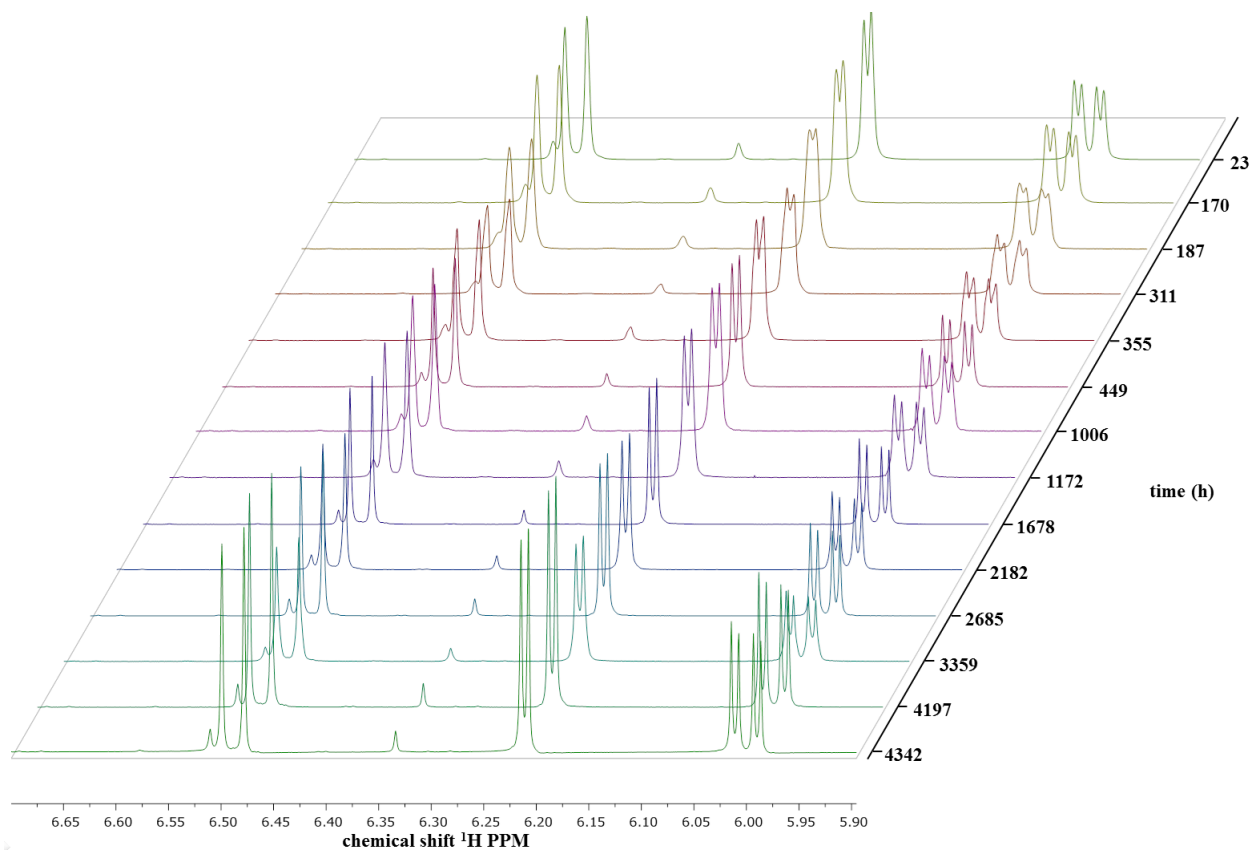
5. BTO stability in H₂O

Figure S5. Series of ¹H-NMR spectrums in DMSO-d6 obtained by sampling an aqueous BTO solution in time showing only 1,2,4-benzenetriol (BTO) and minor amounts of dimer **1**. This spectrum series was used to generate Figure 2a.
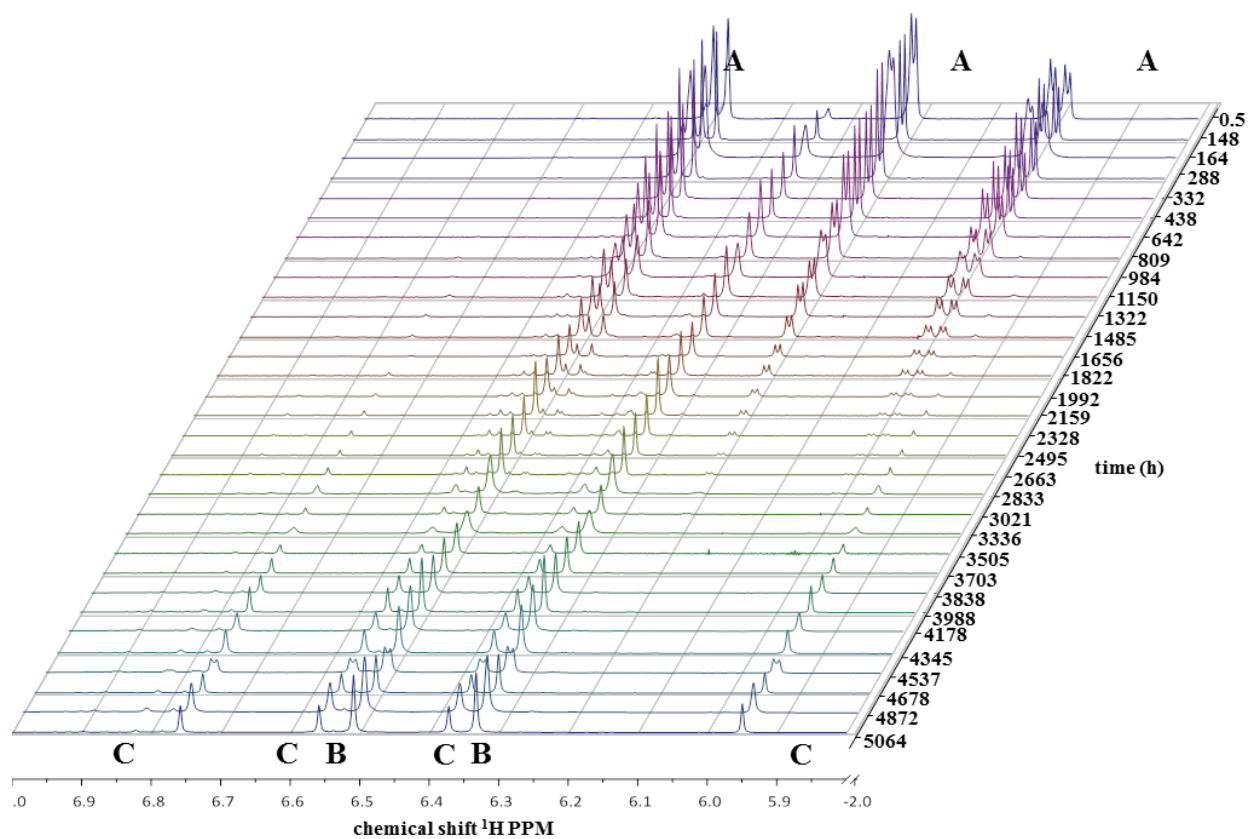
Figure S6. Series of ^{1}H-NMR spectrums in DMSO-d6 obtained by sampling an aqueous BTO in time with exclusion of light. This spectrum series was used to generate Figure 2c.

6. Dimer 1 synthesis results

Table S1: Selected results for the synthesis of dimer **1**.[a]

Entry	Reaction time (hours)	Product composition (%)		
		BTO	Dimer **1**	Dimer **3**
1[e]	2	20.2	79.8	-
2[d]	21	29.7	47.4	-
3[bf]	65	40.8	46.8	12.4
4	20	52.9	43.7	3.4
5	45	32.8	29.6	5
6[d]	22	33.1	29.2	7
7[b]	18	78.8	21.2	-
8[cf]	20	93.4	6.6	-

[a] Conditions: around 0.17 M BTO (typically 50-150 mg) in H_2O, reflux, analysis by ^{1}H-NMR
[b] 95 °C instead of reflux
[c] pyridinium p-TsOH as catalyst
[d] Significant amounts of unknown impurities in product
[e] in excess of 140 °C, No solvent used (procedure in SI Section 7)
[f] Extraction with THF and addition of NaCl to the water layer occurred before analysis

7. Solventless synthesis of 1

BTO, which exists as an off-white powder, is weighed into two clean test tubes, labelled T_1 (20.0 mg - test 1) and T_2 (27.7mg - test 2). The BTO containing test tube bottoms are placed into a 163 °C stirred oil bath for 125 minutes. The test tubes were removed from the hot oil bath, affording blacked material in the bottom of the test tube, and additional sublimated material above the hot oil level of the test tubes (Figure S7). The black product (Figure S7.3A) is mostly **1**, whilst the sublimated material (Figure S7.3.B) of less dark appearance is mostly unreacted sublimated BTO. Unreacted BTO can be removed by washing with cold water.
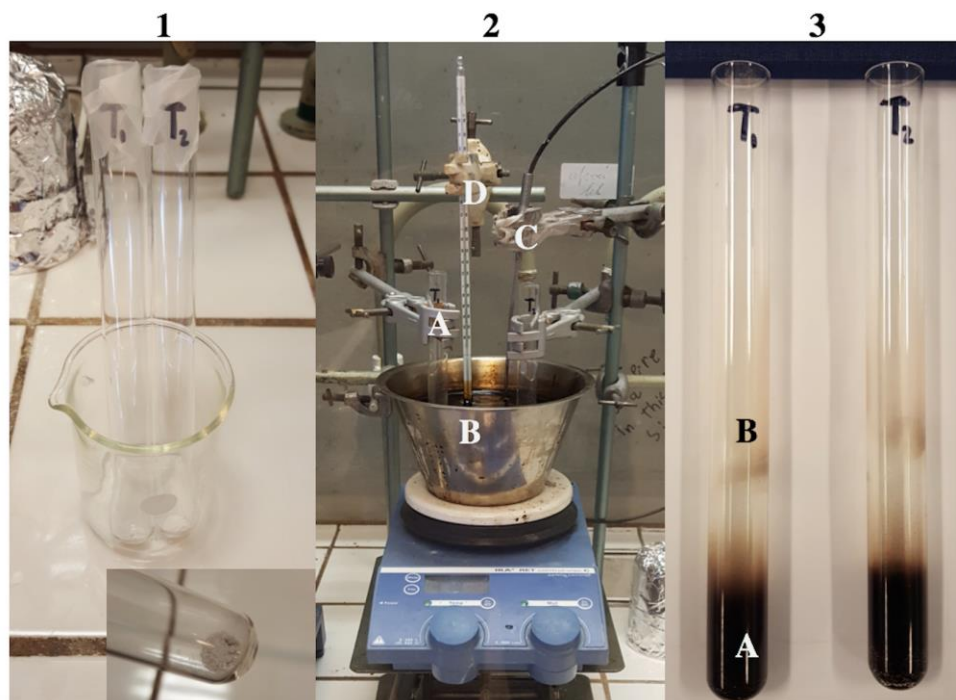

Figure S7. Images of dimer **1** quick synthesis process.

1: Starting material - BTO, seen as a beige to off-white powder.

2: Photo of reaction set up, **A** BTO containing test tube, **B** Oil bath, **C** Temperature probe, **D** thermometer.

3: Final product in test tubes, **A** blackened product, **B** sublimated material above hot oil level.

8. Decomposition of 1 to give a pure sample of 3

When a sample of **1** (190 °C as decomposition temperature) was heated to 355 °C at 95 mbar vacuum in a device with a cold finger a yellowish solid (Figure S8) was obtained which was found to be a pure sample of **3**.
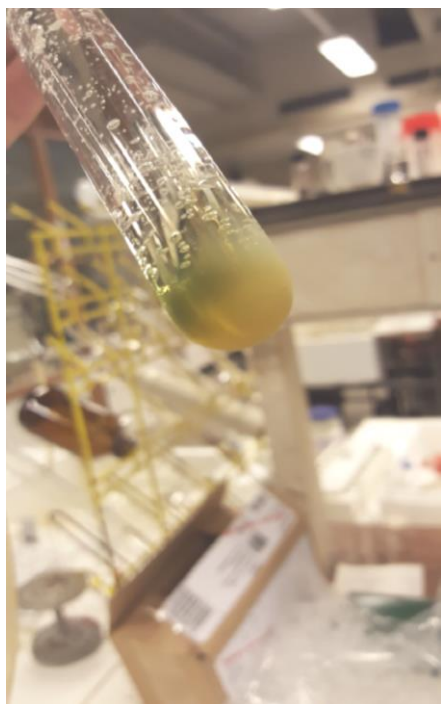

Figure S8. Pure **3**, sublimated after decomposition of **1** upon heating *in vacuo*.

9. PKa calculations

PKa calculations were done using the thermodynamic cycle outlined by Liptak et al.[1] By using experimental values of $G_{gas}(H^+)$ and $\Delta G_s(H^+)$ of -6.82 and -264.61 kcal/mol respectively, they have presented the following equation for the calculation of pKa:

$$pKa = \frac{G_{gas}(A) - G_{gas}(AH^+) - \Delta G_s(A) - \Delta G_s(AH^+) - 269.0}{1.3644} \qquad (Eq.1)$$

G_{gas} values were obtained following the Complete Basis Set (CBS-QB3)[2] method. For the calculation of the free energy of solvation (ΔG_s), the Hartree Fock method with 6-31+G(d) basis set was used both for geometry optimization in gas phase and for the single point calculation using the SMD[3] implicit solvent model. ΔG_s was computed as the sum of total electrostatic (solute polarization, polarized solute-solvent energies) and non-electrostatic (cavitation, dispersion, repulsion energies) contributions. Gaussian16[4] software was used for all calculations.

Table S2: G_{gas} and ΔG_s values for BTO-D3, deuterated BTO-D3 and BTO-D4

	G_{gas} (Hartree)	ΔG_s (kcal/mol)
BTO-D3	-457.967039	-16.66
Deuterated BTO-D3	-458.299272	-71.55
BTO-D4	-457.970358	-16.67

G_{gas} and ΔG_s values were calculated for BTO-D3, deuterated BTO-D3, BTO-D4. Inserting these values in Eq. 1 for the deuterated BTO-D3 with both BTO-D3 and BTO-D4 as its conjugated base pair resulted in pKa values of -4.13 and -5.66 respectively.
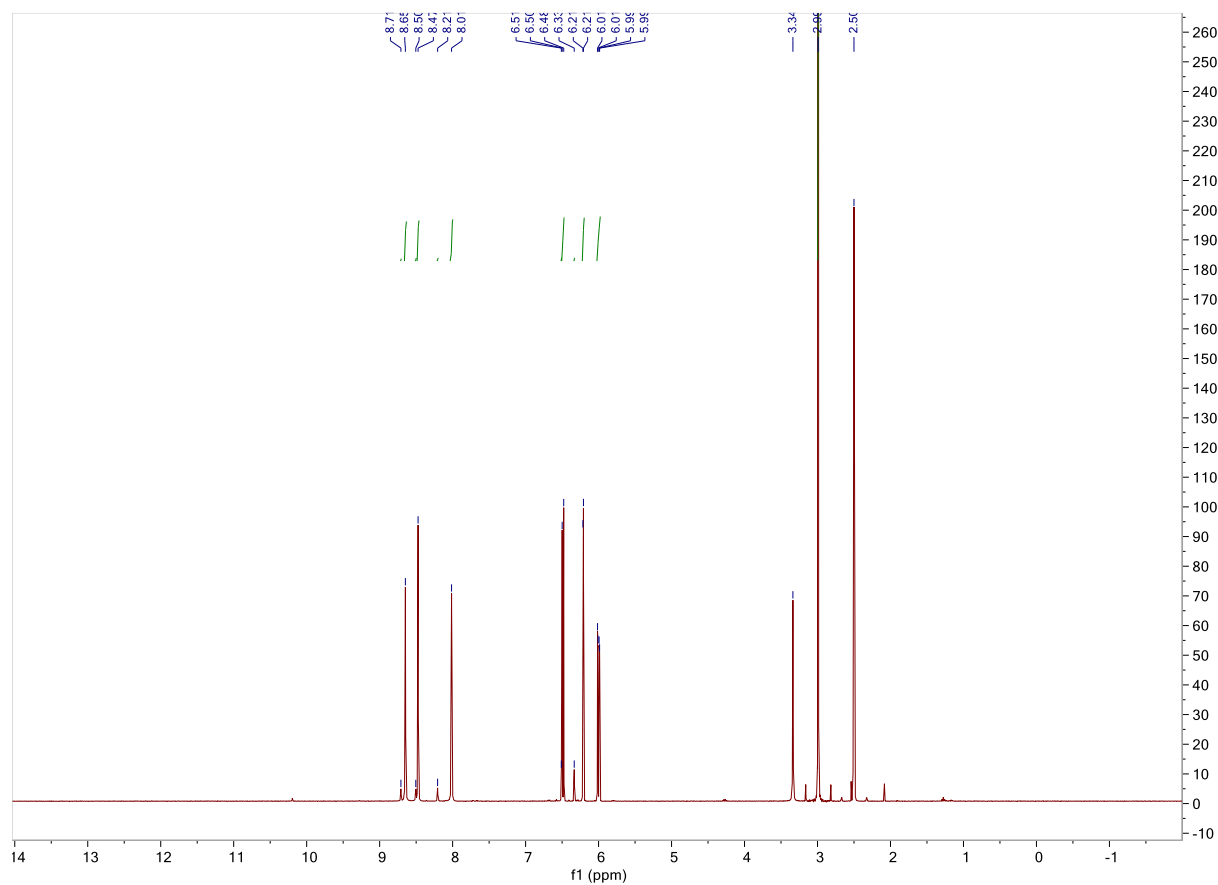
10. NMR spectra

Figure S9. ^{1}H-NMR spectrum (DMSO, 400 Mhz) of BTO (TCI). Dimethyl sulfoxide was added as internal standard.
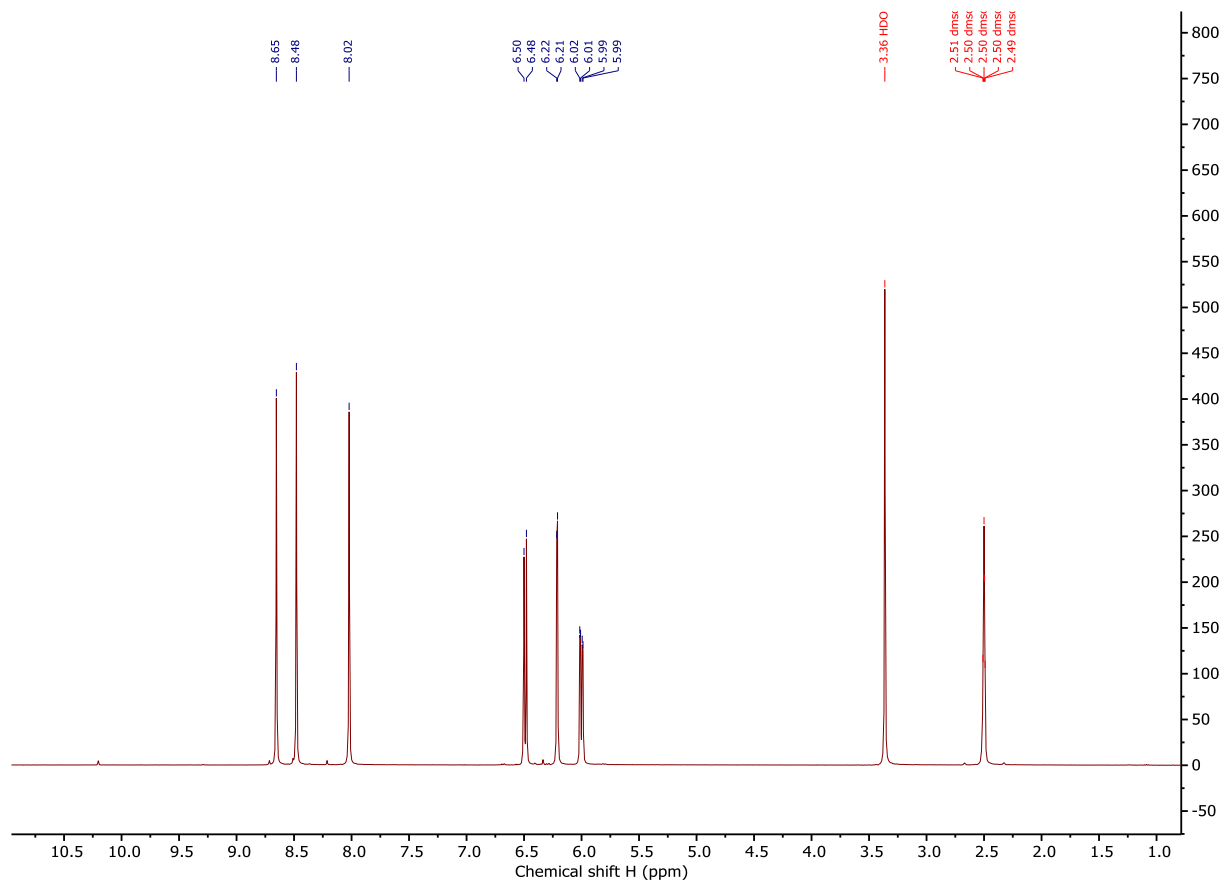
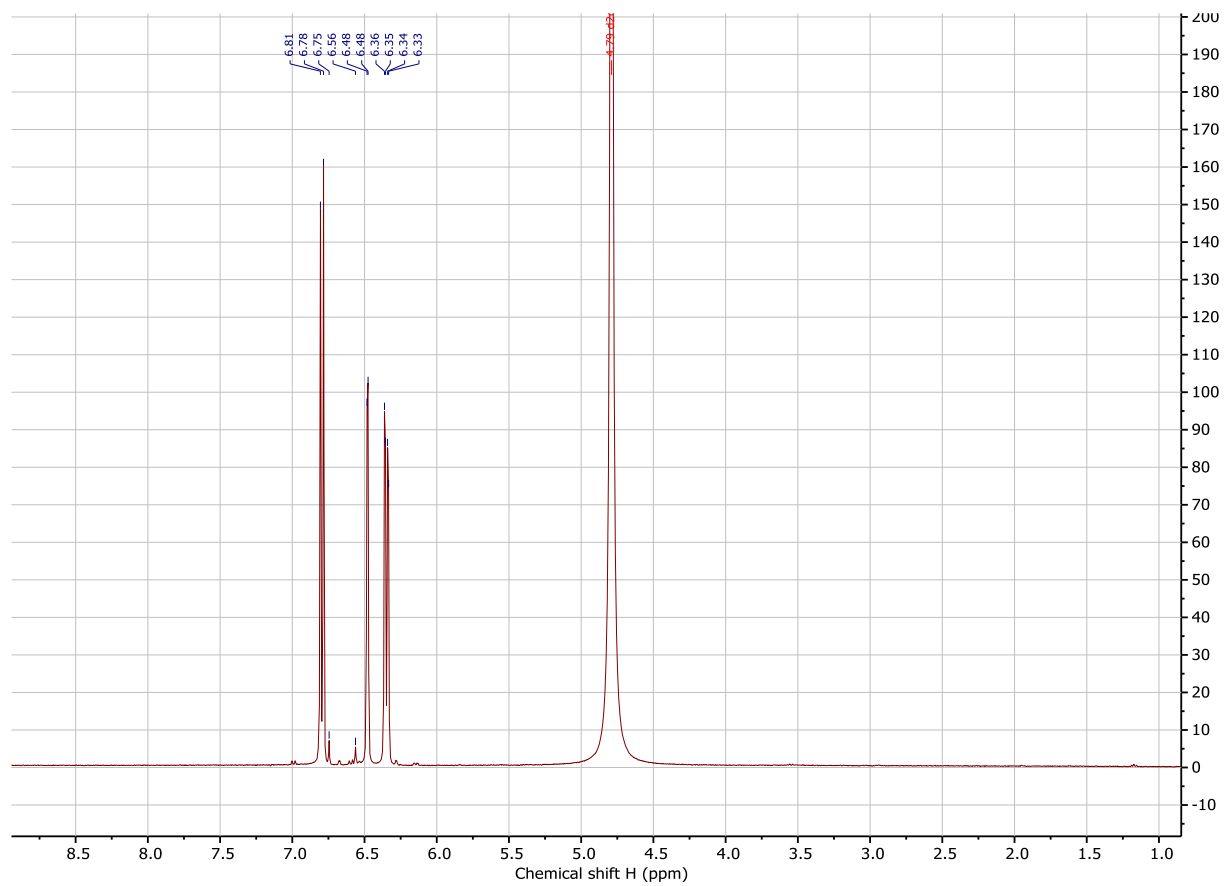**Figure S10.** ^{1}H-NMR spectrum (DMSO-d6, 400 MHz) of BTO (Aldrich).

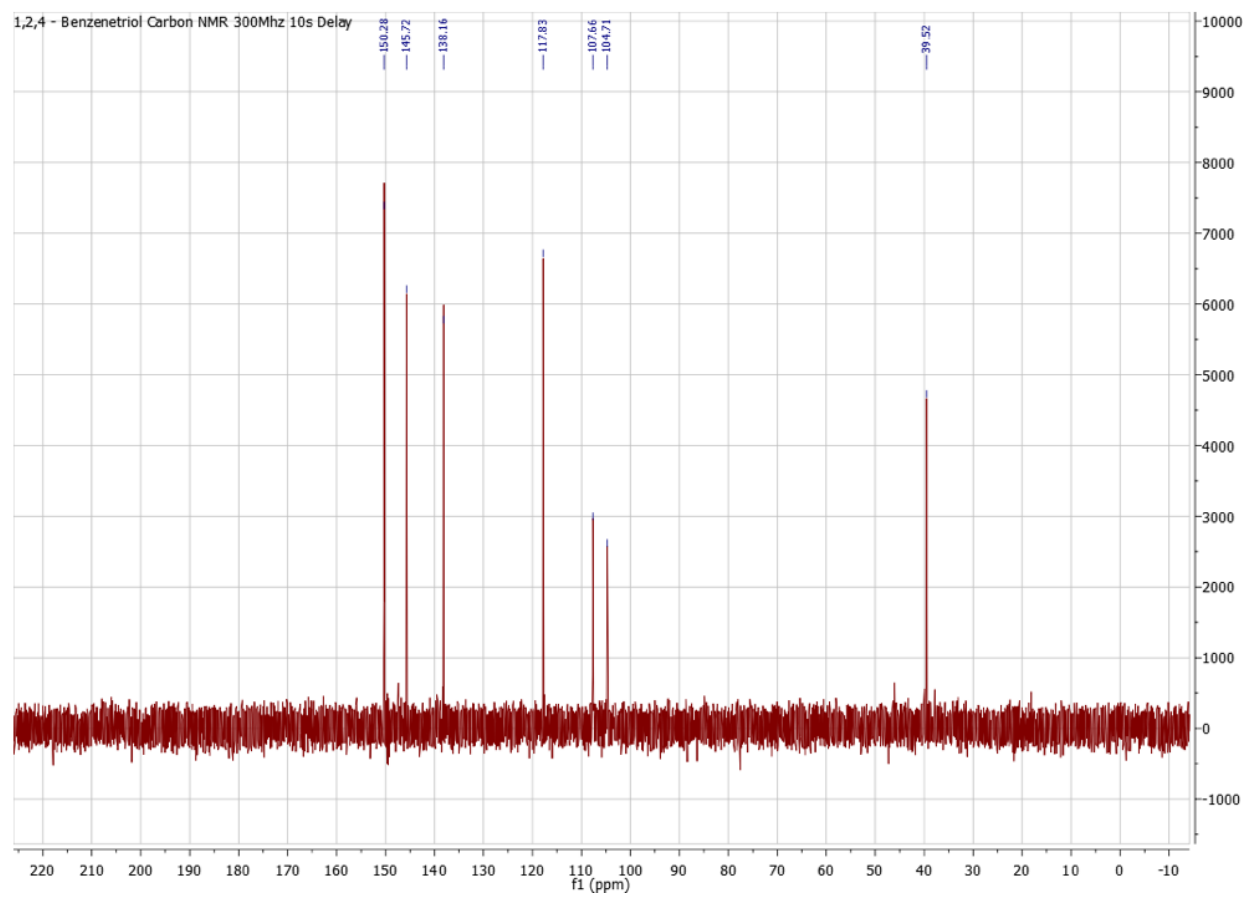**Figure S11.** ^{1}H-NMR spectrum (D$_2$O, 400 MHz) of BTO (Aldrich).

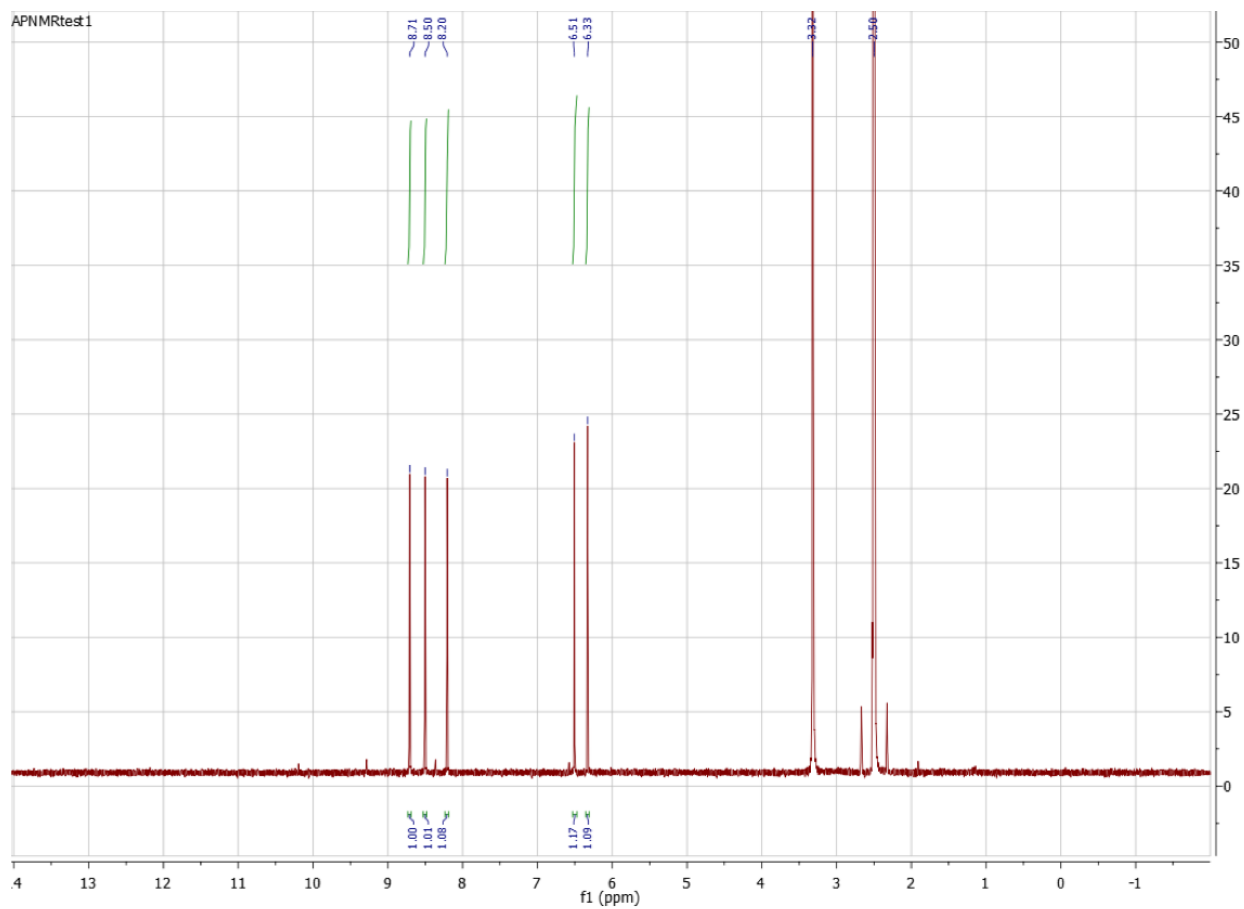**Figure S12.** ^{13}C-NMR spectrum (DMSO-d6, 75 MHz) of BTO.

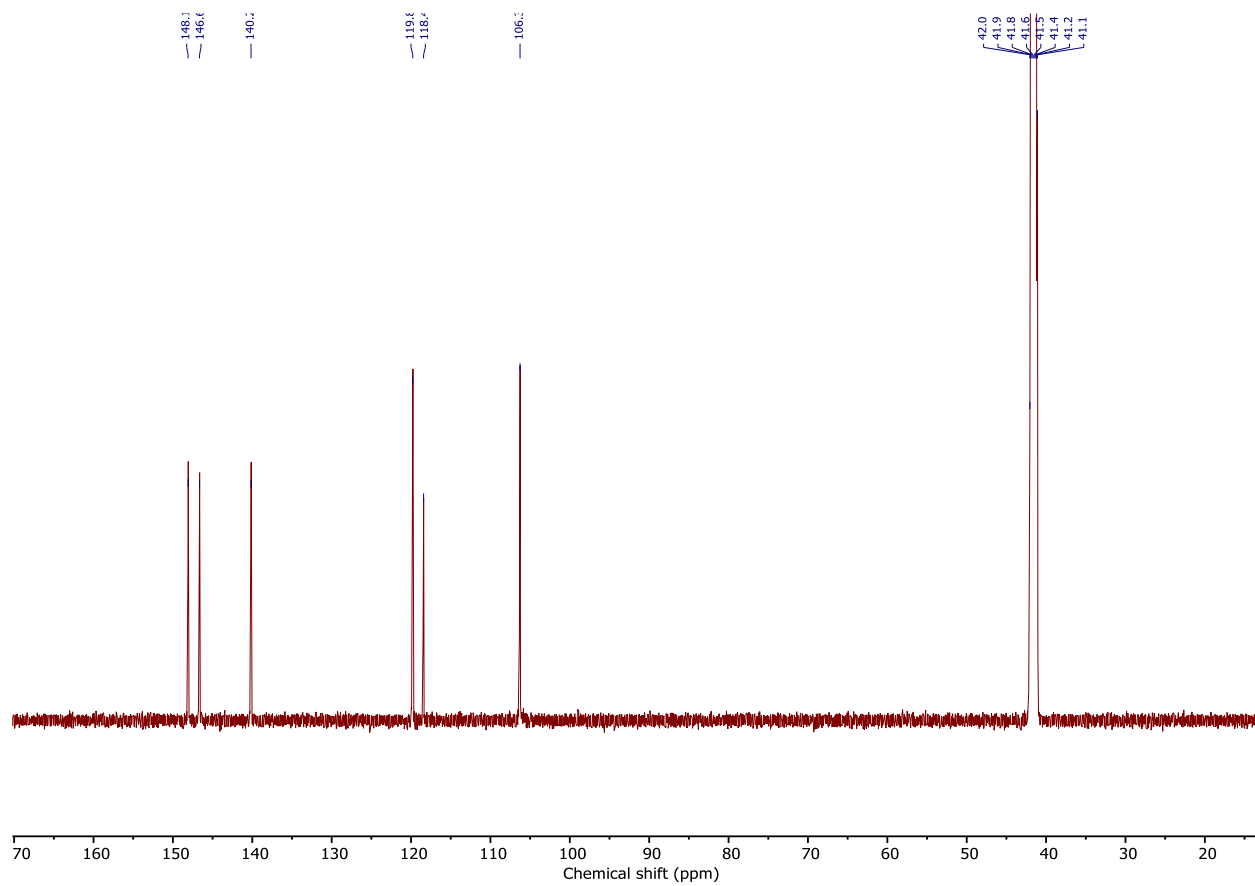**Figure S13.** ¹H-NMR spectrum (DMSO-d6, 400 MHz) of **1**. Dimethyl sulfoxide was added as internal standard.

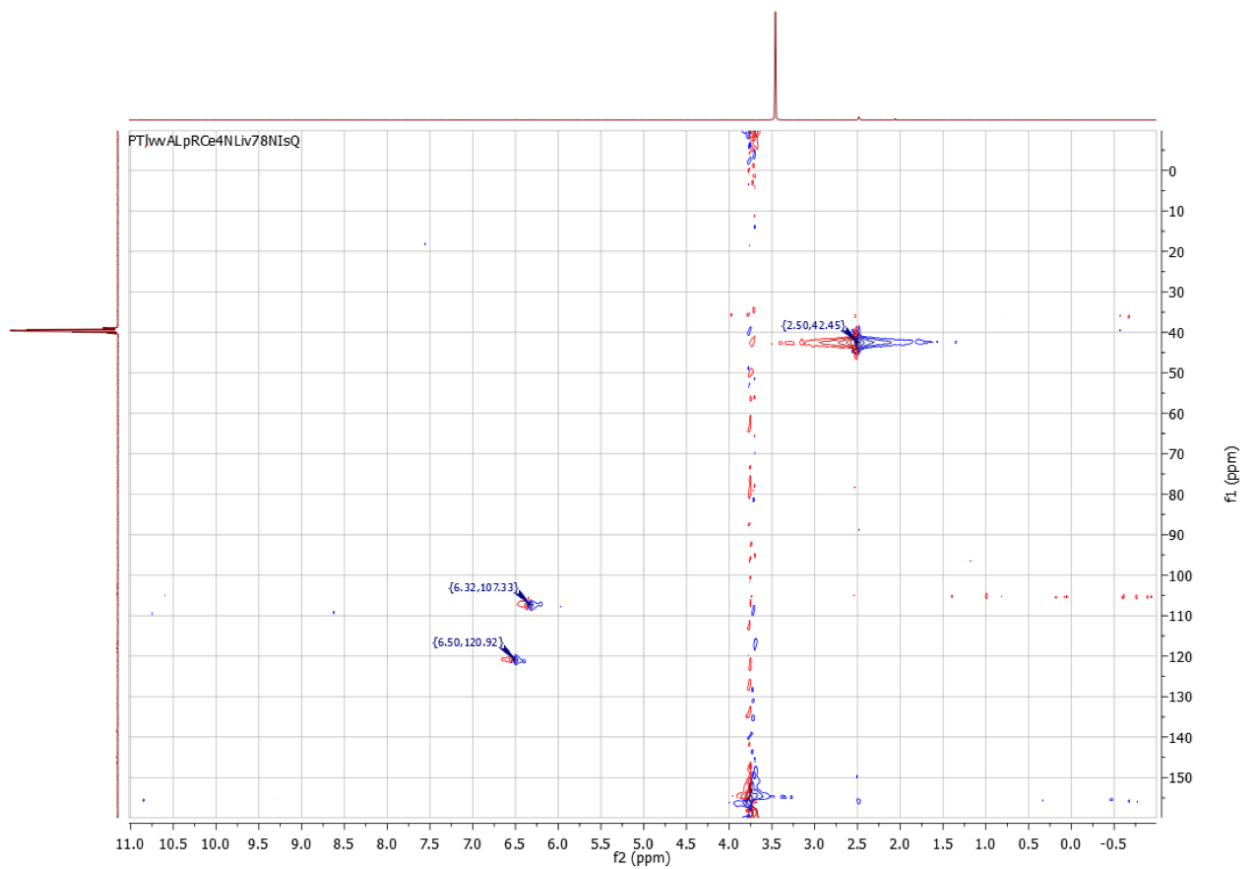**Figure S14.** ^{13}C-NMR spectrum (DMSO-d6, 150 MHz) of **1**.

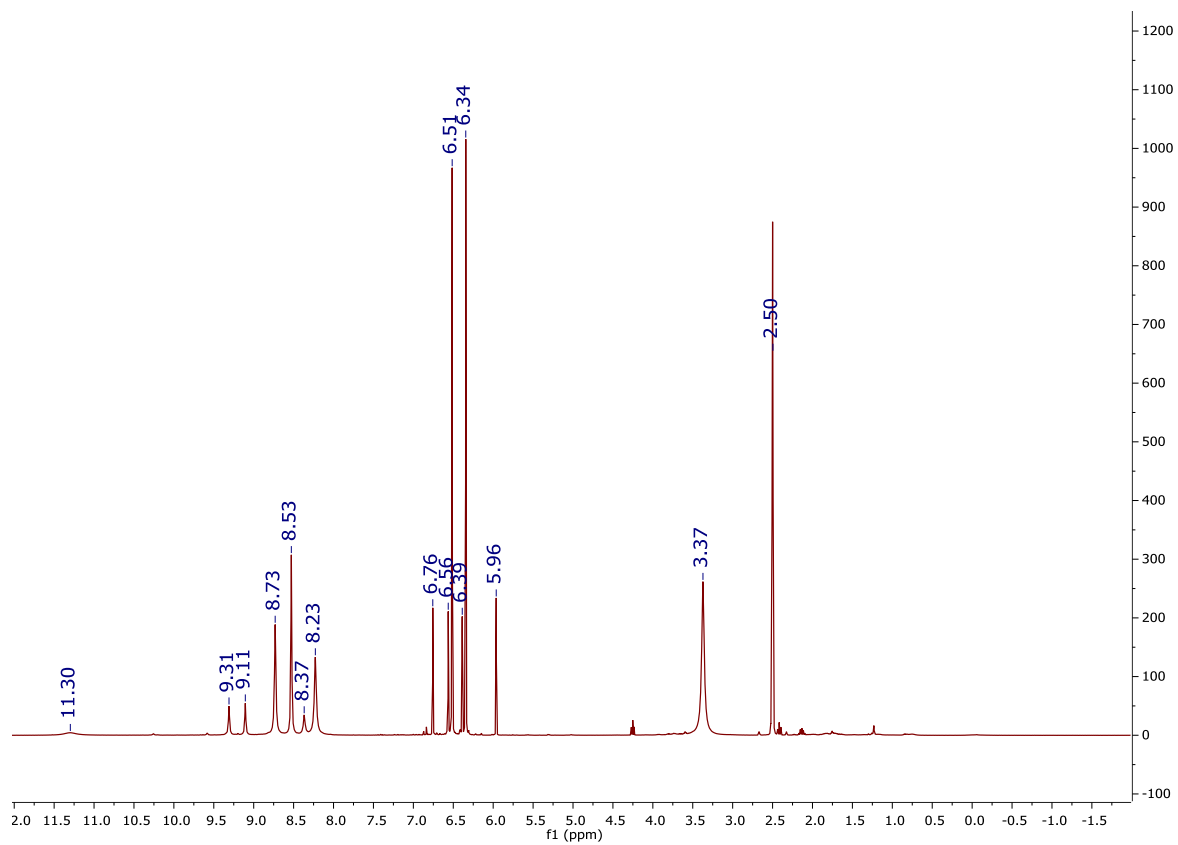**Figure S15.** HSQC-NMR spectrum (DMSO-d6) of **1**.

Figure S16. [^1]H-NMR spectrum (DMSO-d6, 400 MHz) of a mixture of **1** and **2**.
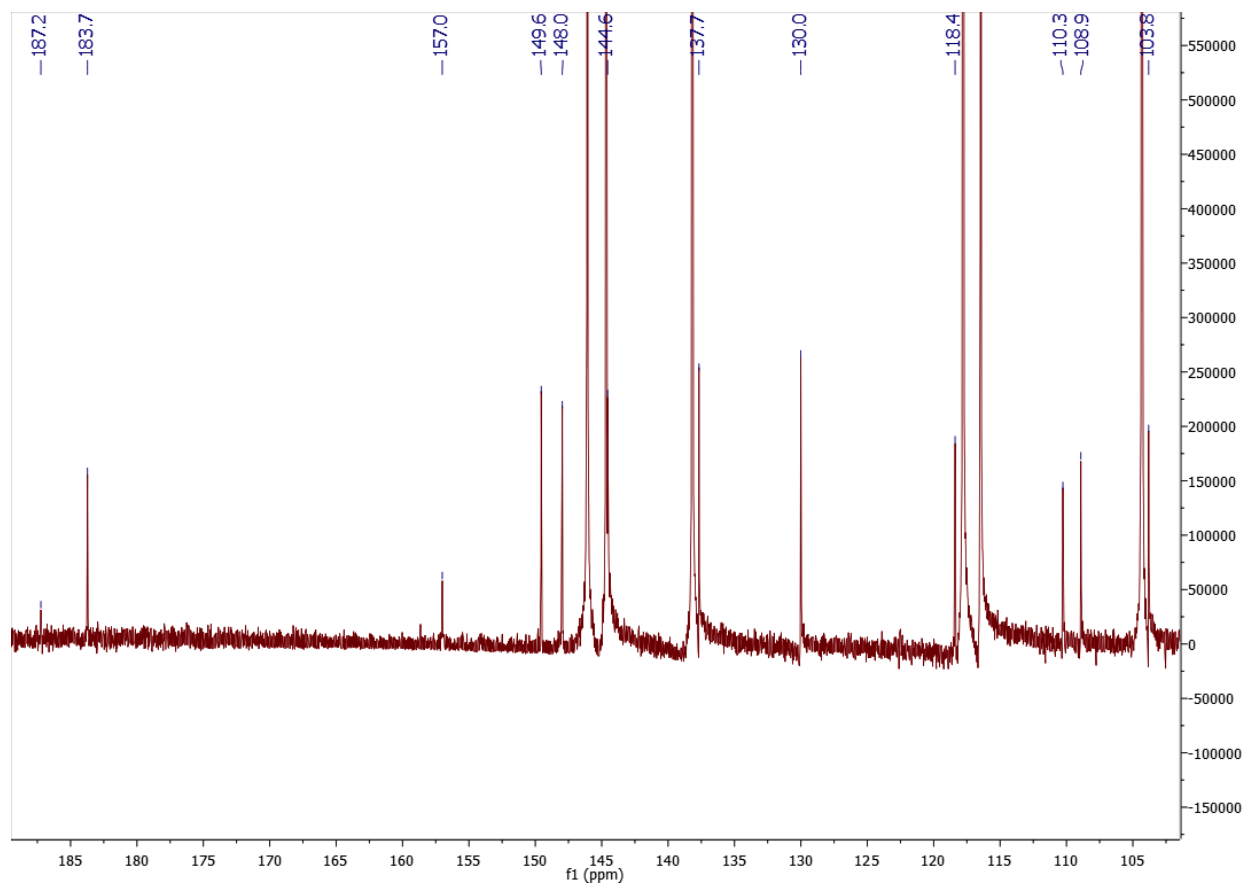
Figure S17. ^{13}C-NMR spectrum (DMSO-d6, 150MHz) of a mixture of **1** and **2** (d1 = 10 s).
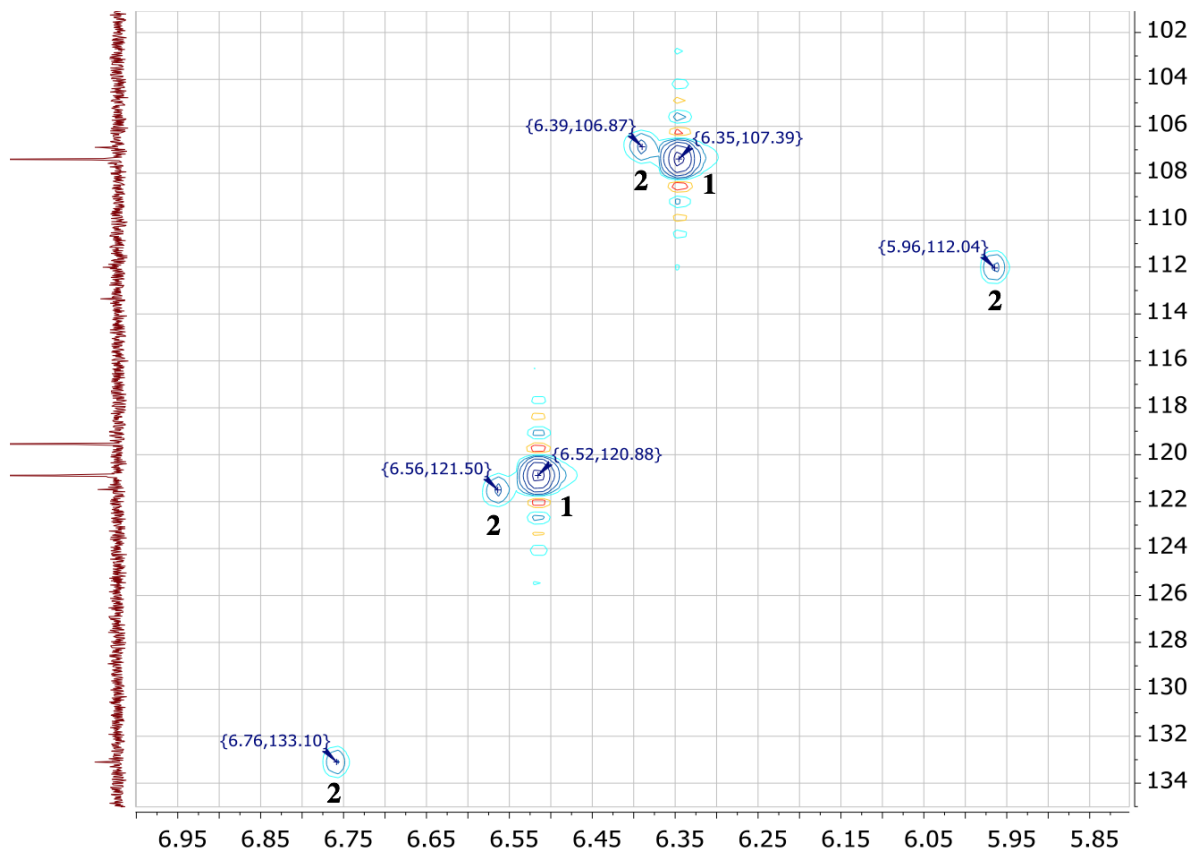
Figure S18. HSCQ-NMR spectrum (DMSO-d6, 400MHz) of a mixture of **1** and **2**.
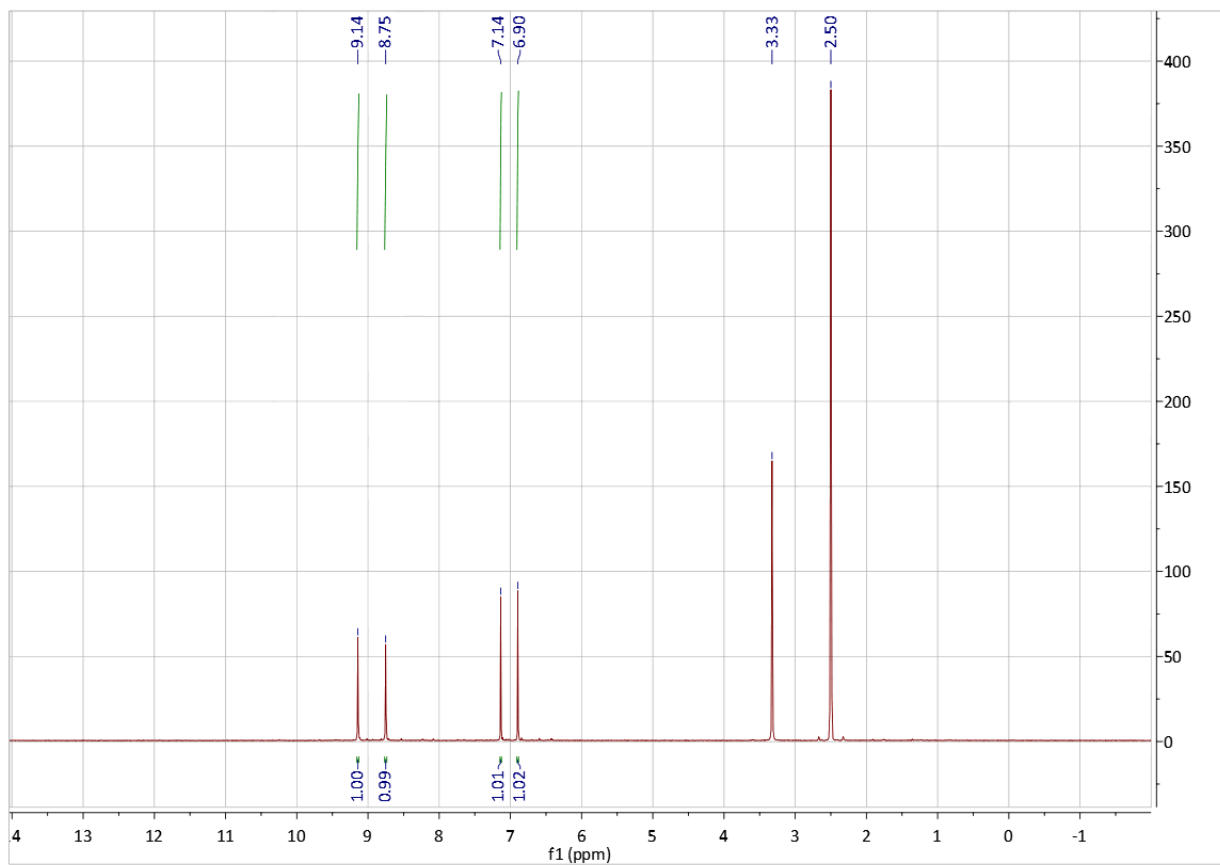
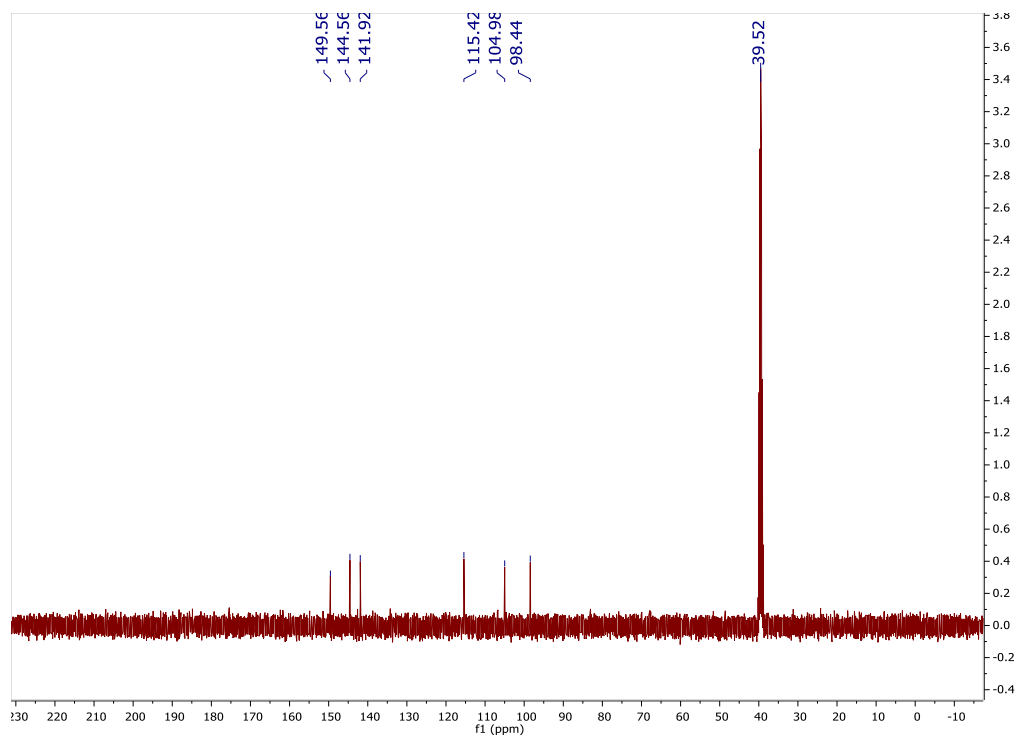**Figure S19.** ^{1}H-NMR spectrum (DMSO-d6, 400 MHz) of **3**.

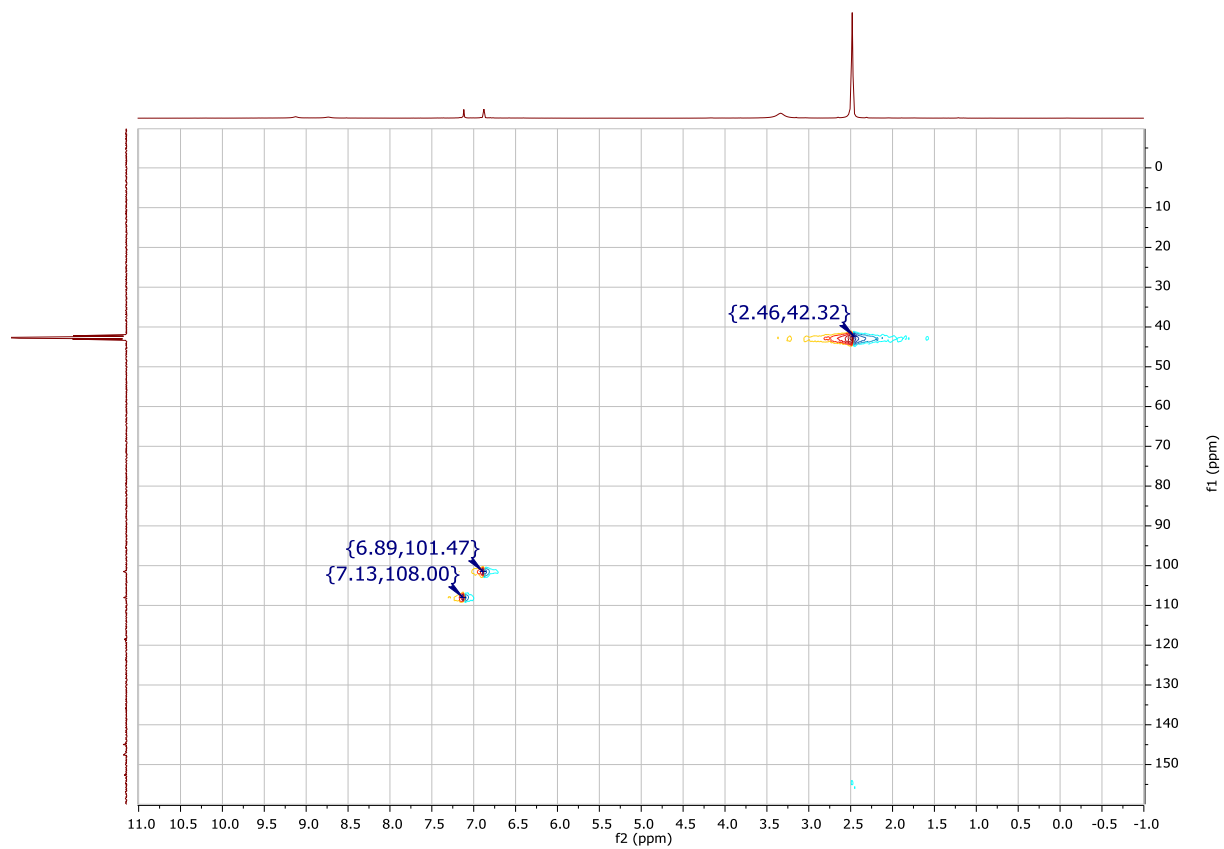**Figure S20.** ^{13}C-NMR spectrum (DMSO-d6, 150MHz) of **3**.

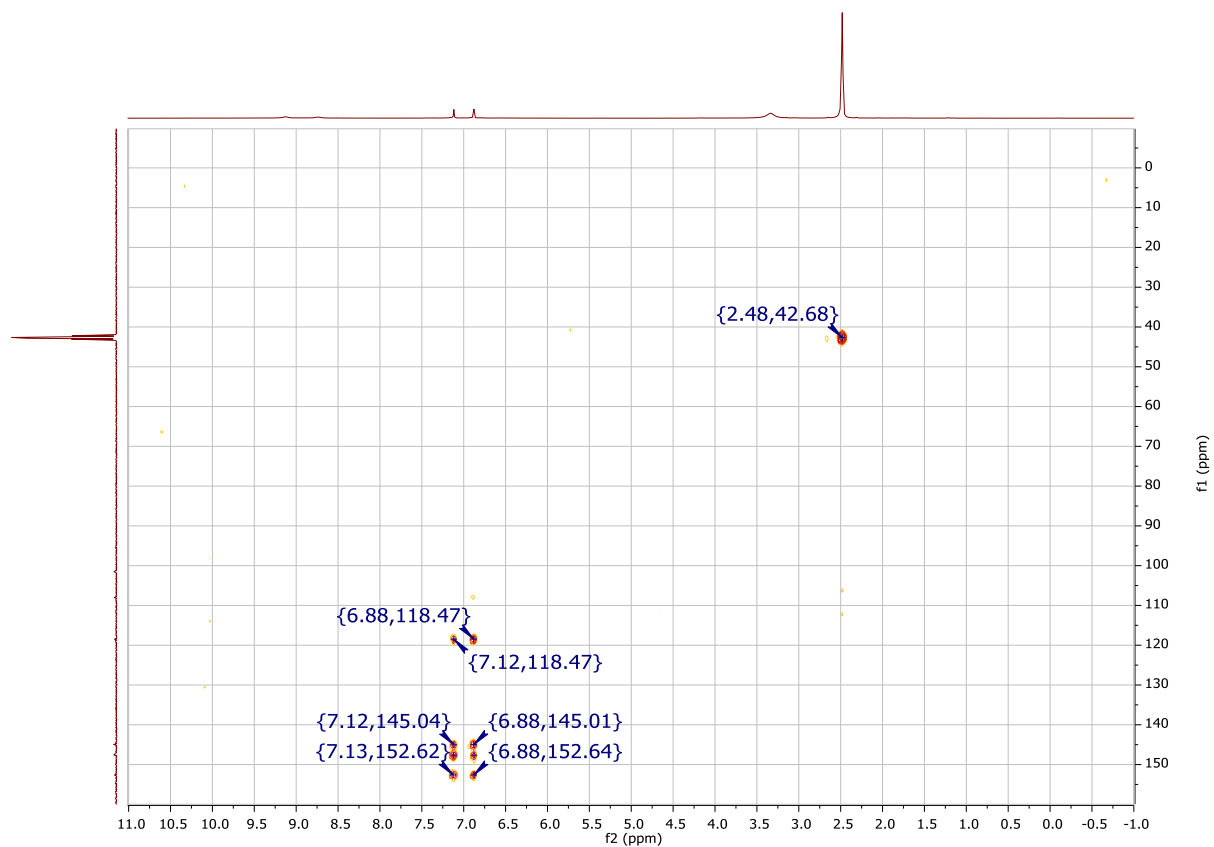**Figure S21.** HSQC-NMR spectrum (DMSO-d6) of **3**.

Figure S22. HMBC-NMR spectrum (DMSO-d6) of **3**.

11. References

1. Liptak, M. D.; Shields, G. C., Accurate pK(a) calculations for carboxylic acids using Complete Basis Set and Gaussian-n models combined with CPCM continuum solvation methods. *J Am Chem Soc* **2001,** *123* (30), 7314-7319.

2. Montgomery, J. A.; Frisch, M. J.; Ochterski, J. W.; Petersson, G. A., A complete basis set model chemistry. VI. Use of density functional geometries and frequencies. *J Chem Phys* **1999,** *110* (6), 2822-2827.

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