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Hexacoordinate germanium compounds with BIS-TRIS and amino acid ligands

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Experimental Section

Materials and methods

Reagents for synthesis compounds **1a-c, 2a-c** were purchased from Sigma-Aldrich (BIS-TRIS (≥98 %)) and 'Vekton' (Russia), (germanium(IV) oxide (≥99.9%), glycine (≥99%), L-*α*-alanine (≥98%), L-valine (≥97%)) and used without purification.

The FTIR spectra (Figs. S1-S6) were recorded with a FSM 2202 (INFRASPEK) FTIR spectrometer, using pressed KBr pellets. The percentage content of water was measured on a PE-9210 coulometric Fischer titrator (cell with a membrane) (Ekroskhim, Russia). Elemental analysis was performed on a Euro EA3028-NT elemental analyzer for the simultaneous determination of C, H, and N. ^{1}H and ^{13}C NMR spectra (Figs. S7-S18) of the compounds in D_2O were recorded on a Bruker Avance III spectrometer [400.13 (^{1}H), 100.613 MHz (^{13}C)]. The chemical phenomena presented below refer to a static D_2O signal (4.79 ppm for ^{1}H).[S1] Thermogravimetric analysis (TGA), and differential scanning calorimetry (DSC) curves (Figs. S19-S21) were recorded using the simultaneous thermal analyzer NETZSCH STA 449 C in the temperature range 40–900°C under an air (the air flow was 50 $cm^3\,min^{-1}$) using a heating rate of 10 K min^{-1}.

Synthesis

Germanium glycinate **1a**, was obtained by adding an aqueous solution (20 ml) of glycine (1.1 mmol, 0.08 g) to an aqueous suspension (70 ml) of germanium dioxide (1.1 mmol, 0.11 g) with constant stirring and heating (90°C). During the reaction, germanium oxide was dissolved. The reaction mixture was kept under constant heating and stirring for 2 hours. After the reaction was completed, the water was removed at reduced pressure. The reaction product was isolated as a white powder with a yield of 90.9% (0.2 g). IR spectrum, cm^{-1}: 3166, 3006, 2966, 2891, 2609, 2526, 2273, 2166, 1594, 1504, 1440, 1410, 1331, 1125, 1109, 1034, 962, 901,885, 837, 690, 583, 551, 519. ^{1}H NMR spectrum (D_2O, δ, ppm, J, Hz): 3.43 s (2H, -CH_2-). ^{13}C NMR spectrum (D_2O, δ, ppm): 41.42 (-CH_2-), 172.40 (-C=O).

Germanium L-*α*-alaninate, **1b**, was obtained similarly to **1a**, using aqueous solution (20 ml) of L-α-alanine (2.4 mmol, 0.21 g) and an aqueous suspension (70 ml) of germanium dioxide (2.4

mmol, 0.25 g). The product yield was 92.2% (0.47 g). IR spectrum, cm^{-1}: 3088, 2938, 2815, 2732, 2604, 2510, 2294, 2247, 2114, 1624, 1587, 1507, 1457, 1413, 1360, 1307, 1233, 1150, 1113, 1013, 920, 849, 773. ^{1}H NMR spectrum (D_2O, δ, ppm, J, Hz): 1.34-1.35 d (3H, -CH_3, 7.2), 3.62-3.68 m (1H, -CH-). ^{13}C NMR spectrum (D_2O, δ, ppm): 16.13 (-CH_3), 50.52 (-CH-), 175.79 (-C=O).

Germanium L-valinate, **1c**, was obtained similarly to **1a**, using aqueous solution (20 ml) of L-valine (4.2 mmol, 0.49 g) and an aqueous suspension (70 ml) of germanium dioxide (4.2 mmol, 0.44 g). The product yield was 90.0% (0.9 g). IR spectrum, cm^{-1}: 3151, 3055, 2978, 2885, 2838, 2761, 2694, 2630, 2421, 2290, 2112, 1616, 1585, 1512, 1475, 1426, 1395, 1352, 1327, 1271, 1177, 1140, 1106, 1064, 1030, 942, 922, 888, 855, 823, 775, 752, 713, 665, 586, 543, 477, 429. ^{1}H NMR spectrum (D_2O, δ, ppm, J, Hz): 0.89 dd (6H, -CH_3, 20.8), 2.11-2.19 m (1H, -CH-), 3.48 d (1H, -CH-, 4.2). ^{13}C NMR spectrum (D_2O, δ, ppm): 16.58, 17.91 (-CH_3-), 29.04 (-<u>C</u>H-CH_3), 60.37 (-CH-), 174.24 (-C=O).

Compound **2a** {GlyGe(BIS-TRIS)}·$2H_2O$ was obtained by adding an aqueous solution (5 ml) of BIS-TRIS (1.0 mmol, 0.21 g) to an aqueous suspension (10 ml) of **1a** (1.0 mmol, 0.20 g) with constant stirring. After complete dissolution of **1a**, the reaction mixture was heated (up to 90 ºC) with constant stirring for 2 hours. After the reaction was completed, the solution was left in the open air to slowly evaporate the solvent. The reaction product was isolated as a white powder, washed with ethanol and dried in air. The product yield was 84 % (0.33 g). IR spectrum, cm^{-1}: 3441 (br); 3012; 2941; 2894; 2863; 2735; 2611; 2537; 2424; 2274; 2221; 2141; 1683; 1610; 1526; 1501; 1410; 1386; 1334; 1310; 1273; 1259; 1233; 1206; 1163; 1141; 1119; 1089; 1026; 990; 944; 931; 913; 899; 890; 866; 833; 743; 704; 610; 589; 565; 519; 506; 476; 449; 433; 420. *w*(H_2O) = 9.9 ± 1.5 %. Elemental analysis: calculated for $C_{10}H_{24}GeN_2O_9$, %: C-30.88, H-6.22, N-7.20; experimental C-32.05, H-6.80, N-7.66. ^{1}H NMR spectrum (D_2O, δ, ppm, J, Hz): 2.88-2.94 m (2H, C<u>H</u>$_2$O); 3.40-3.46 m (2H C<u>H</u>$_2$O); 3.55 s (2H, C<u>H</u>$_2$$NH_2$), 3.65-3.80 m (4H, NC<u>H</u>$_2$), 3.78 s (6H, OC<u>H</u>$_2$C). ^{13}C NMR spectrum (D_2O, δ, ppm): 41.37 (-CH_2-), 48.29 (-CH_2OH), 57.88 (-NCH_2), 59.00 (-OCH_2), 66.24 (-C-), 172.34 (-C=O).

Compound **2b** was obtained similarly to **2a**, using aqueous solution (10 ml) of BIS-TRIS (0.5 mmol, 0.10 g) and an aqueous suspension (10 ml) of **1b** (0.5 mmol, 0.11 g). The product yield was 83 % (0.15 g). IR spectrum, cm^{-1}: 3392 (br), 3090; 2941; 2888; 2732; 2604; 2508; 2294; 2250; 2114; 2032; 1623; 1593; 1494; 1456; 1412; 1362; 1302; 1236; 1199; 1155; 1110; 1069; 1020; 983; 924; 893; 847; 772; 644; 594; 541. *w*(H_2O) = 5.9 ± 0.3 %. Elemental analysis: calculated for $C_{11}H_{24}GeN_2O_8$, %: C-34.32, H-6.28, N-7.28; experimental C-35.22; H-6.91; N-7.55. ^{1}H NMR spectrum (D_2O, δ, ppm, J, Hz): 1.38 d (3H, C<u>H</u>$_3$); 2.97-3.04 m (2H, C<u>H</u>$_2$O); 3.50-3.56 m (2H, C<u>H</u>$_2$O); 3.75-3.90 m (4H, NCH_2), 3.79 s (6H, OCH_2C), 4.79 s (1H, CH;

overcrowded with D_2O). ^{13}C NMR spectrum (D_2O, δ, ppm): 16.09 (-$\underline{C}H_3$-), 48.32 (-$\underline{C}H_2OH$), 50.47 (-CH-), 57.88 (-N$\underline{C}H_2$), 59.07 (-O$\underline{C}H_2$), 66.21 (-$\underline{C}$-), 175.74 (-$\underline{C}$=O).

Compound **2c** was obtained similarly to **2a**, using aqueous solution (10 ml) of BIS-TRIS (0.5 mmol, 0.11 g) and an aqueous suspension (10 ml) of **1c** (0.5 mmol, 0.12 g). The product yield was 83.0% (0.19 g). IR spectrum, cm^{-1}: 3378; 3270; 3160; 3061; 2975; 2948; 2885; 2713; 2627; 2415; 2290; 2109; 1614; 1588; 1512; 1424; 1395; 1352; 1327; 1271; 1226; 1166; 1140; 1081; 1044; 1024; 979; 942; 928; 897; 835; 775; 744; 715; 642; 614; 543; 430. $w(H_2O) = 7.0 \pm 0.9$ %. Elemental analysis: calculated for $C_{13}H_{30}GeN_2O_9$, %: C-36.23, H-7.02, N-6.50; experimental C-37.38; H-7.81; N-6.33. ^1H NMR spectrum (D_2O, δ, ppm, J, Hz): 1.00 dd (6H, C$\underline{H}_3$); 2.22-2.30 m (1H, -C$\underline{H}$-); 2.97-3.03 m (2H, C$\underline{H}_2$O); 3.51-3.59 m (2H, C$\underline{H}_2$O); 3.60 d (1H, -C$\underline{H}$-); 3.75-3.88 m (4H, C$\underline{H}_2$N); 3.78 s (6H, CC$\underline{H}_2$O). ^{13}C NMR spectrum (D_2O, δ, ppm): 16.57, 17.89 (-$\underline{C}H_3$-), 29.02 (-$\underline{C}$H-), 48.27 (-$\underline{C}H_2OH$), 57.89 (-N$\underline{C}H_2$), 58.93 (-O$\underline{C}H_2$), 60.31 (-CH-), 66.27 (-$\underline{C}$-), 174.20 (-$\underline{C}$=O).

Computational Details

The fully local meta-GGA correlation functional (M06-L), developed by Truhlar's group[S2] was used. This method provides satisfactory results in the description of numerous systems, especially for those with noncovalent interactions.[S2-S5] The basis set used was the Dunning correlation-consistent aug-cc-pVDZ set.[S6,S7]

***In silico* ADME and PASS analysis**

The SwissADME web tool provided by the Swiss Institute of Bioinformatics, Lausanne, Switzerland[S8] was used to predict the physicochemical and pharmacokinetic properties of germanium-containing derivatives of BIS-TRIS and TEA.

Profiles of the pharmacological activity were predicted using the PASS software.[S9,S10] PASS is a web-based program used to predict the biological activity spectrum based on the structural formula of a substance.

Table S1. Experimental and estimated at the M06L/Aug-CC-pVDZ level of theory IR vibrational spectra of compound **2a**

Experiment (cm^{-1})	Harmonic frequencies (cm^{-1})	Intensities(km mol^{-1})	Assignment
2141 s		533	ν NH_2
1683 s			δ H_2O, ν C=O
1610 s	1633	23	δ NH_2
1526 s	1517	4	δ CH_2
	1512	5	
1501 s	1497	4	δ CH_2(OH)

	1493	6	
	1485	1	
	1469	13	δ CH_2
1410 w	1453	2	
	1445	3	
	1444	8	δ $CH_2(NH_2)$
	1438	10	ρ CH_2
1386 ms	1391	5	
	1387	10	
	1374	8	
	1370	2	
1334 ms	1368	75	ρ $CH_2(NH_2)$
	1350	5	
	1335	2	ρ CH_2
	1327	3	
	1299	0	w $CH_2(NH_2)$
1310 ms	1295	176	ν OC(O)
	1292	37	w CH_2
1273 ms	1287	68	w $CH_2(NH_2)$
	1273	6	
	1264	3	w CH_2
1259 mw	1260	14	
	1249	5	
1233 ms	1243	24	w $CH_2(NH_2)$
1206 ms	1207	35	w CH_2
	1186	4	
	1170	70	ν NC_3
	1148	11	
1163 ms	1156	164	ν CO(Ge)
	1146	11	ρ CH_2-NH_2
1141 w sh	1134	70	ν CO(Ge)
1119 mw	1110	66	
	1107	6	ν CO(H)
	1082	6	ν $CN(H_2)$
1089 s	1077	125	ν CO(H)
	1070	15	ν CC
1026 ms	1056	80	ν $CH_2(OH)$
	1047	7	w CH_2
	1018	15	w $CH_2(OH)$
990 s	996	210	w NH_2
	957	12	ν CC
944 m	948	10	
931 ms	920	32	δ OCO
913 w	904	30	w $CH_2(OH)$
899 w sh	898	111	w CH_2-NH_2
890 s	893	20	w CH_2-NH_2
866 mw	874	2	w CH_2
833 w	842	12	ν CC(OH)
	760	6	w CH_2
743 mw	725	40	δ GeOC

704 ms	686	71	δ GeOC
	635	3	
610 m	600	29	ν CC
589 w sh	596	45	δ GeOC
565 w sh	586	92	w NH_2
519 w sh	558	19	
506 m	554	15	ν CC
449 w sh	540	28	
	498	9	w CH_2
476 w sh	494	27	δ OCC
449 w sh	474	6	
433 m	459	16	δ CNC
	425	7	
407 w	423	2	δ CCO(H)
	411	15	δ CCN (ν Ge···N)

Table S2. IR bands of compounds **2b** and **2c** and their assignment

2b	**2c**	Assignment
2114	2109	ν(NH_2)
1623	1614	ν(C=O)
1593	1588	δ(NH_2)
1494	1512	
1456	1424	δ(C-H)
1412	1395	
1362	1352	ρ(C-H)
	1327	ρ(C-H)
1302		ν(OC(O))
	1271	w(C-H)
1236	1226	w(C-H)
1199		w(C-H)
1155	1166	ν(CO(Ge))
	1140	ν(CO(Ge))
1110		
1069	1081	ν(CO(H))
	1044	ν(CC)
1020	1024	ν(CH_2(OH))
	979	w(NH_2)
938	942	ν(CC)
924	928	δ(OCO)
893	897	w(C-H)
847		w(C-H)
	835	ν(CC(OH))
772	775	w(C-H)
	744	δ(GeOC)

644	642	δ(GeOC)
	614	ν(CC)
594		δ(GeOC)
541	543	w(NH_2)

Table S3. Some pharmacological activity (PASS) of 1-germatranol hydrate, {GlyGe(TEA)}, and compounds **2a-c** (Pa – probabilities of the compound to be active; P_i – probabilities of the compound to be inactive)

Probability, P_a/P_i	Predicted pharmacological activity
[OHGe(TEA)]H_2O	
0.991/0.000	Systemic lupus erythematosus treatment
0.988/0.002	Rheumatoid arthritis treatment
0.989/0.003	Autoimmune disorders treatment
0.977/0.001	Gastrointestinal disorders treatment
0.969/0.003	Analgesic
0.890/0.007	Phobic disorders treatment
0.796/0.001	Antiviral (Hepatitis B)
{GlyGe(TEA)}	
0.916/0.004	Phobic disorders treatment
0.887/0.002	Antihypoxic
2a	
0.943/0.004	Apoptosis agonist
0.869/0.012	Phobic disorders treatment
0.822/0.004	Antihypoxic
2b	
0.901/0.004	Apoptosis agonist
0.810/0.004	Antihypoxic
0.764/0.048	Phobic disorders treatment
2c	
0.881/0.005	Apoptosis agonist
0.819/0.027	Phobic disorders treatment
0.746/0.005	Antihypoxic

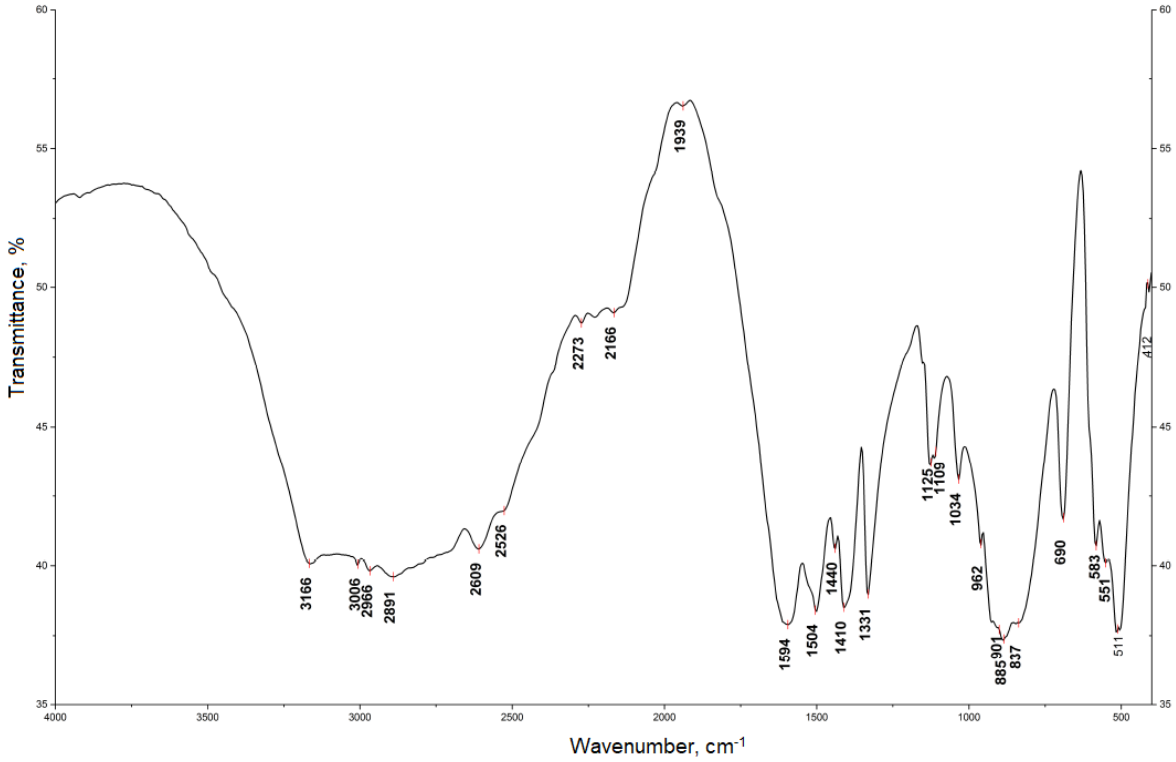

Figure S1. FTIR spectrum of **1a**

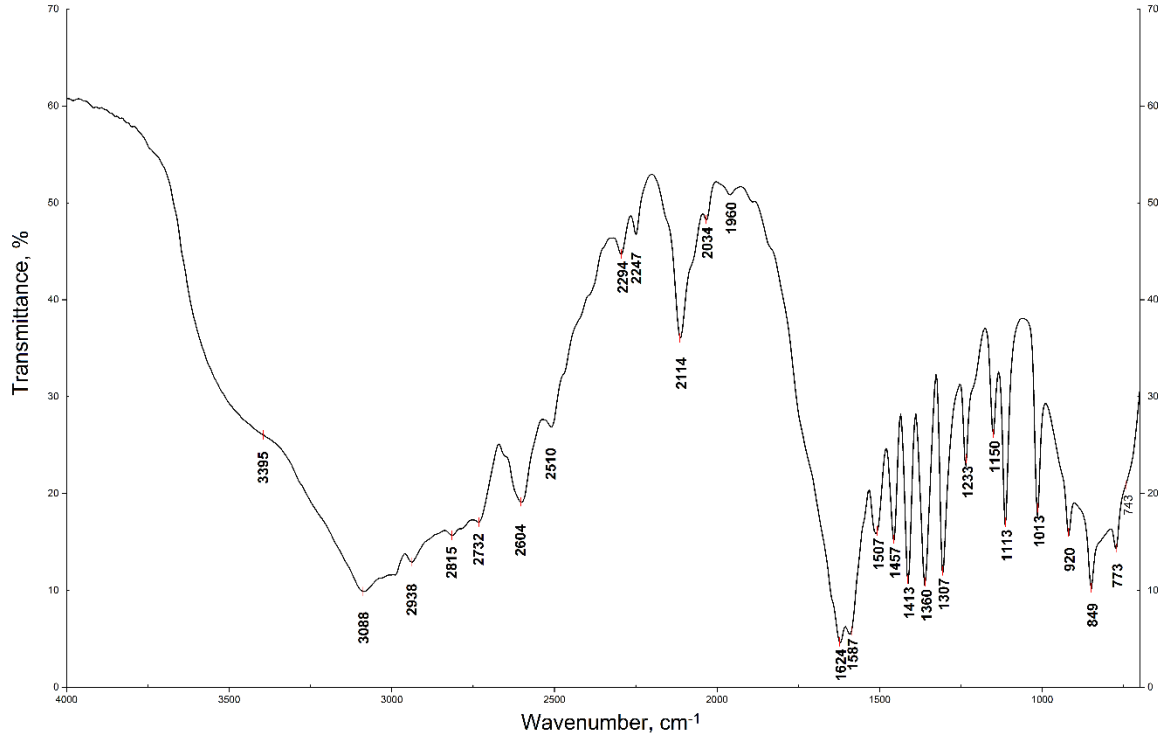

Figure S2. FTIR spectrum of **1b**

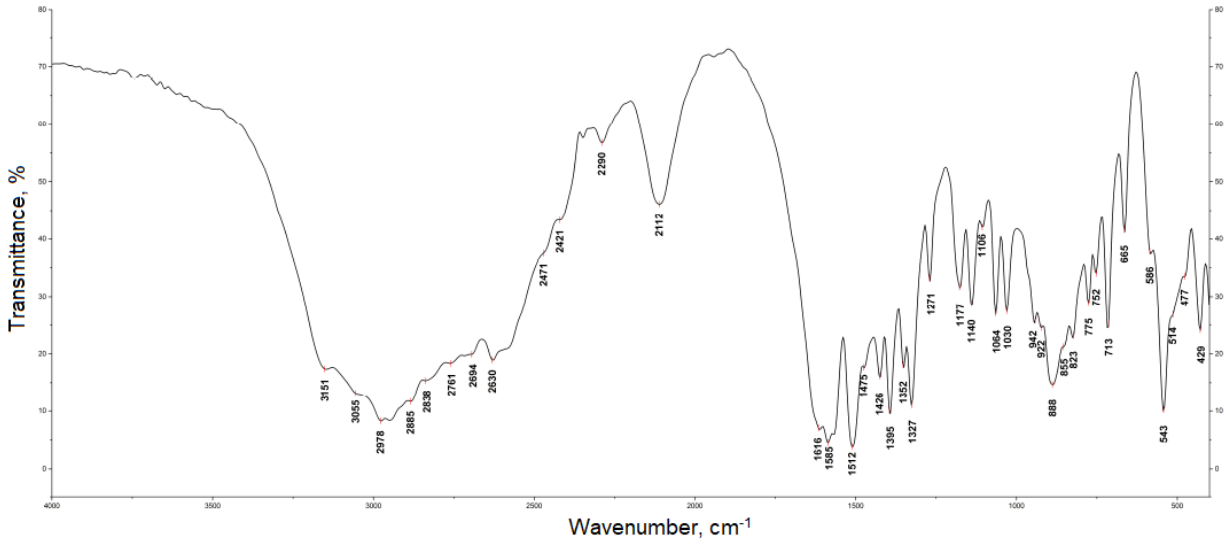

Figure S3. FTIR spectrum of **1c**

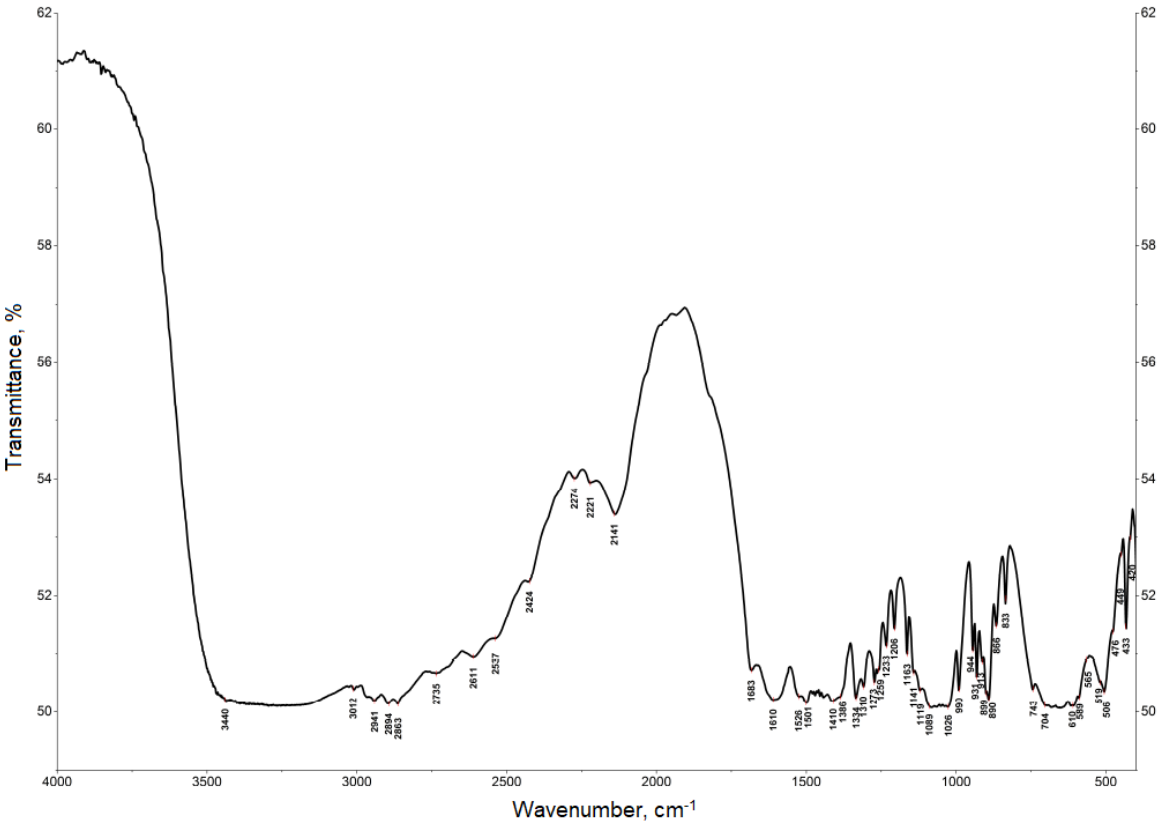

Figure S4. FTIR spectrum of **2a**

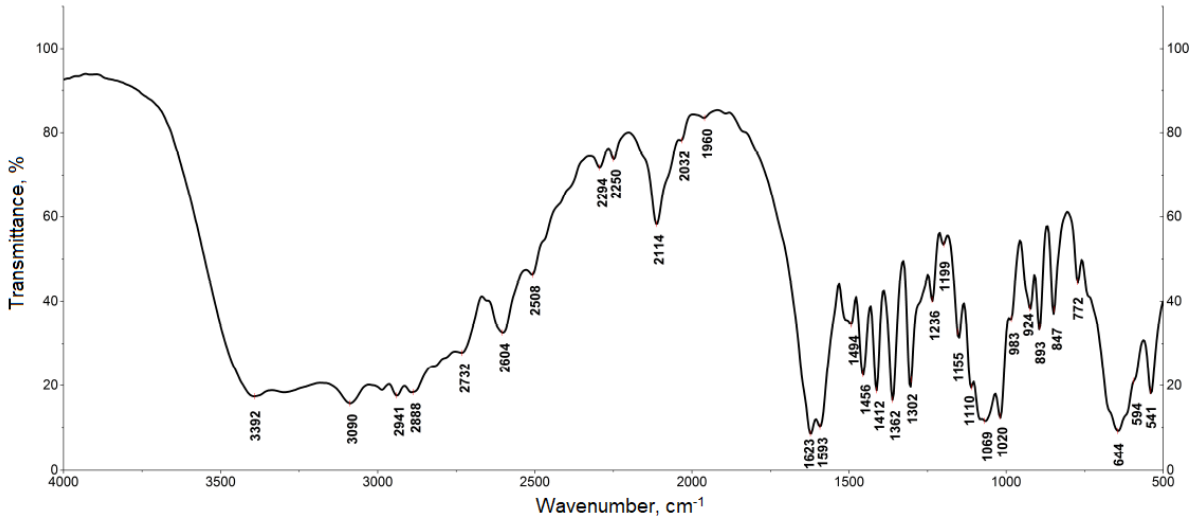

Figure S5. FTIR spectrum of **2b**

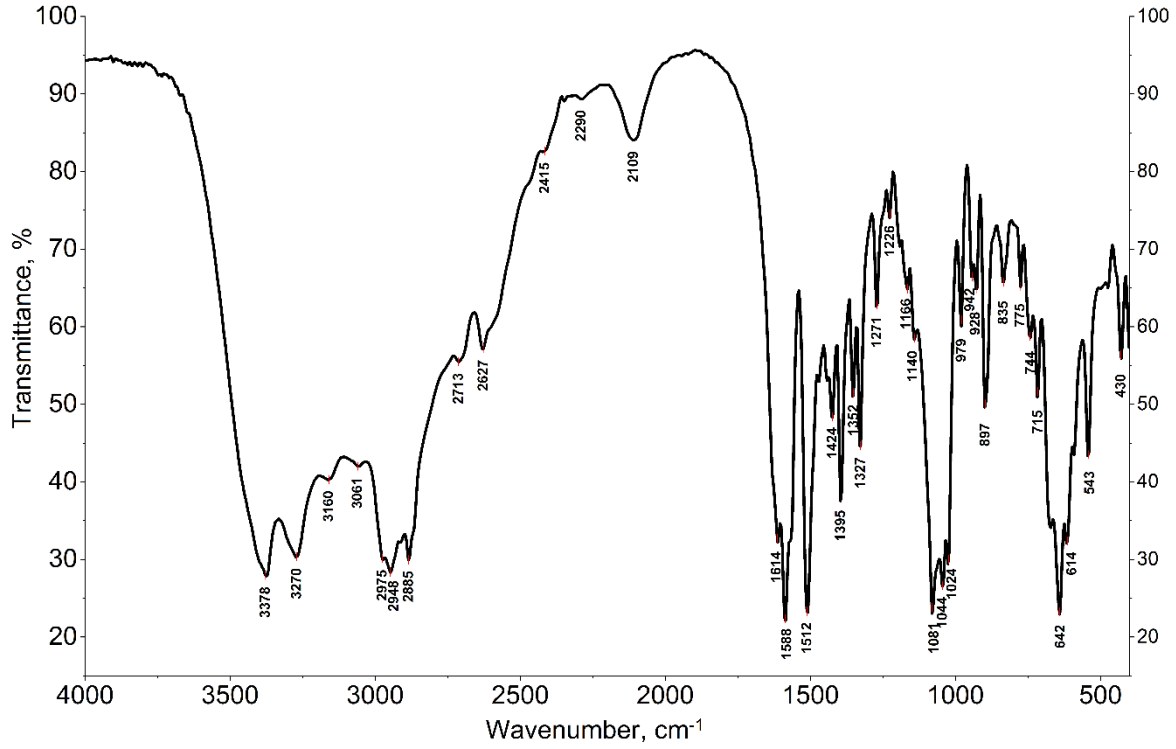

Figure S6. FTIR spectrum of **2c**

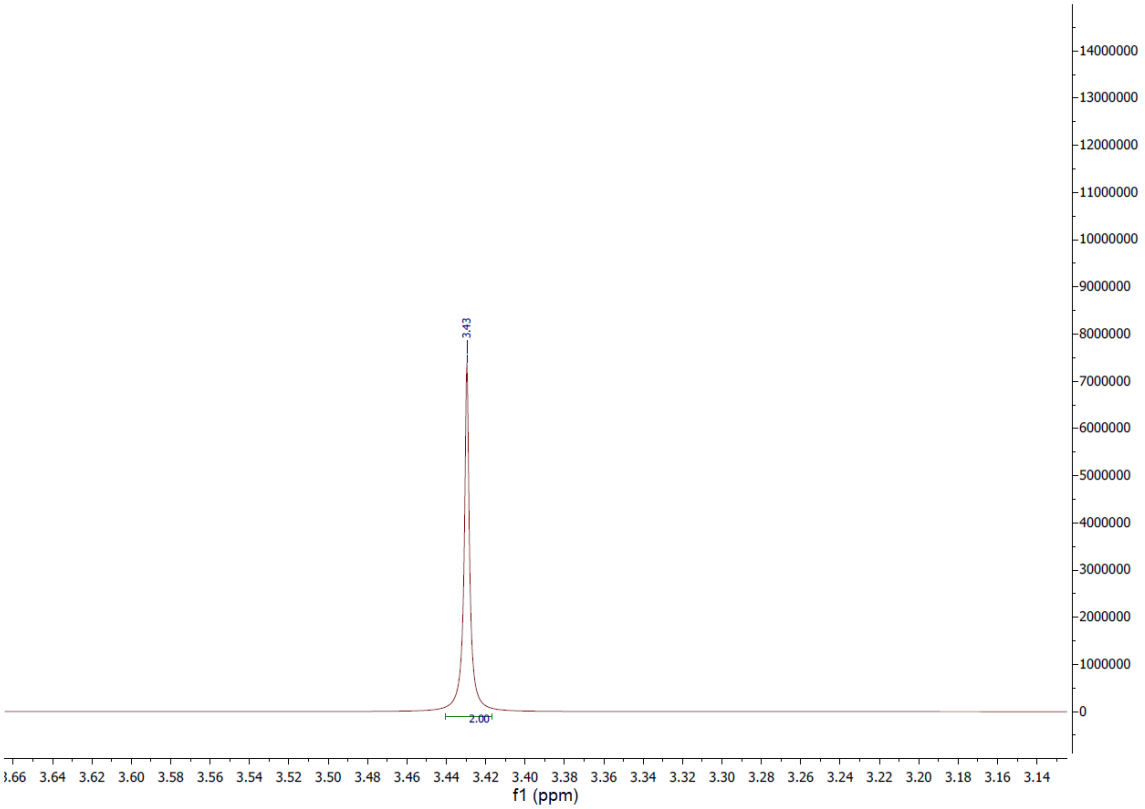

Figure S7. ^{1}H NMR spectrum of **1a** (D_2O, δ, ppm, J, Hz)

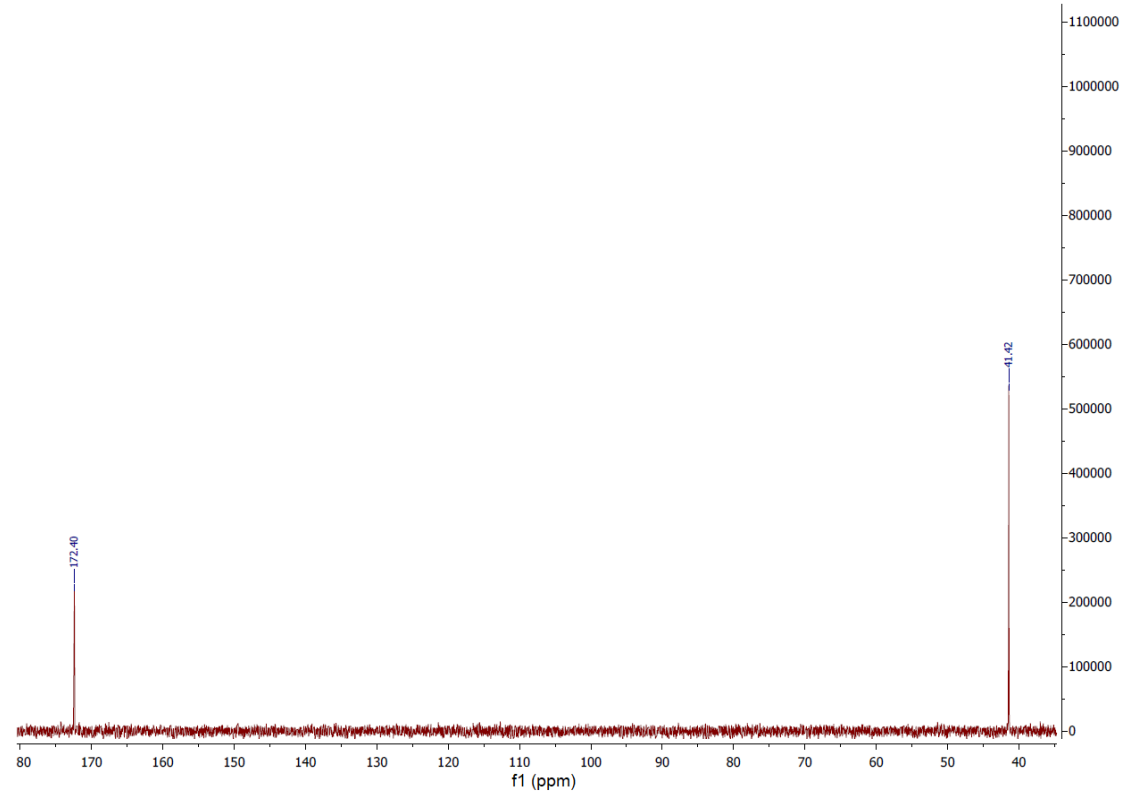

Figure S8. ^{13}C NMR spectrum of **1a** (D_2O, δ, ppm)

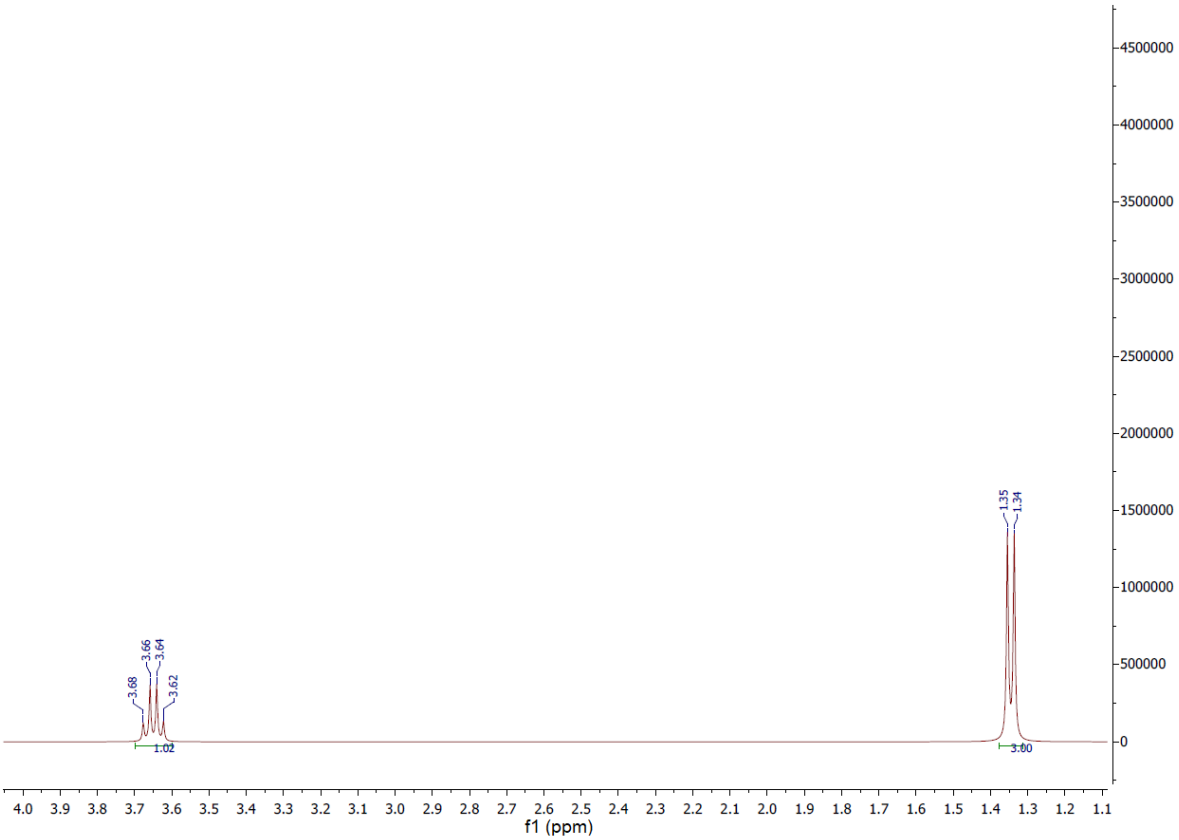

Figure S9. ^{1}H NMR spectrum of **1b** (D_2O, δ, ppm, J, Hz)

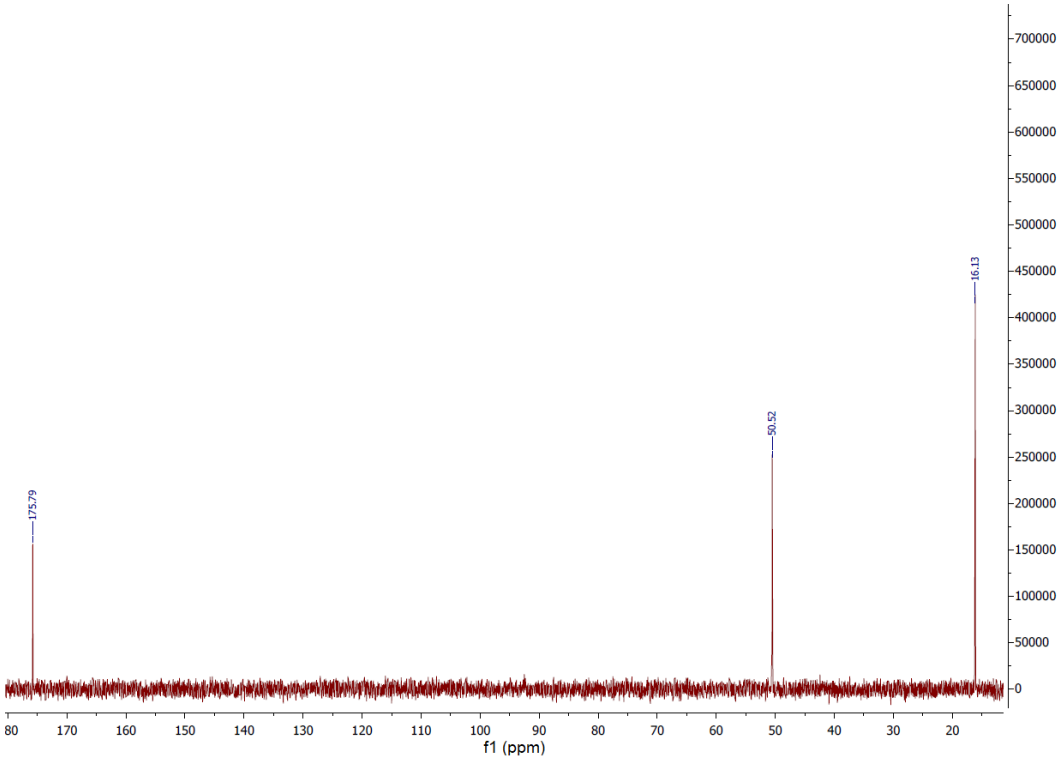

Figure S10. ^{13}C NMR spectrum of **1b** (D_2O, δ, ppm)

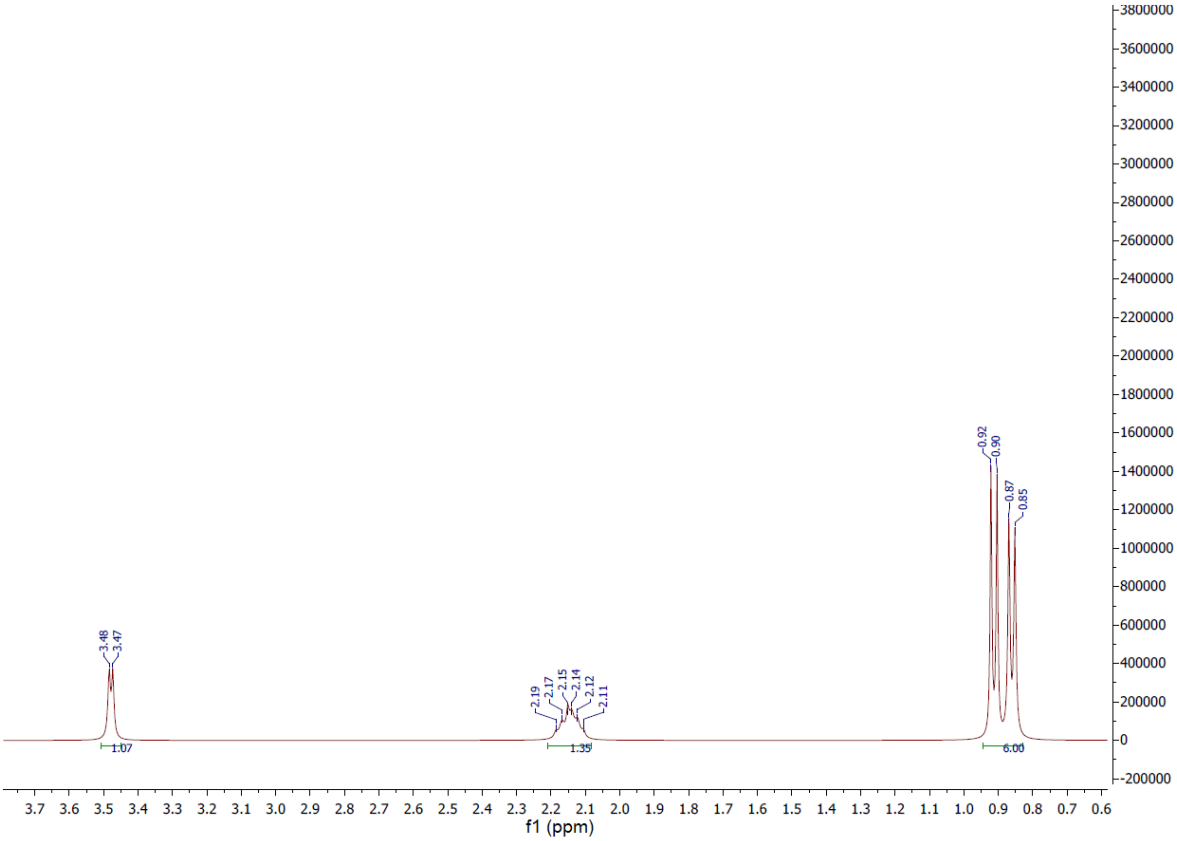

Figure S11. ^{1}H NMR spectrum of **1c** (D_2O, δ, ppm, J, Hz)

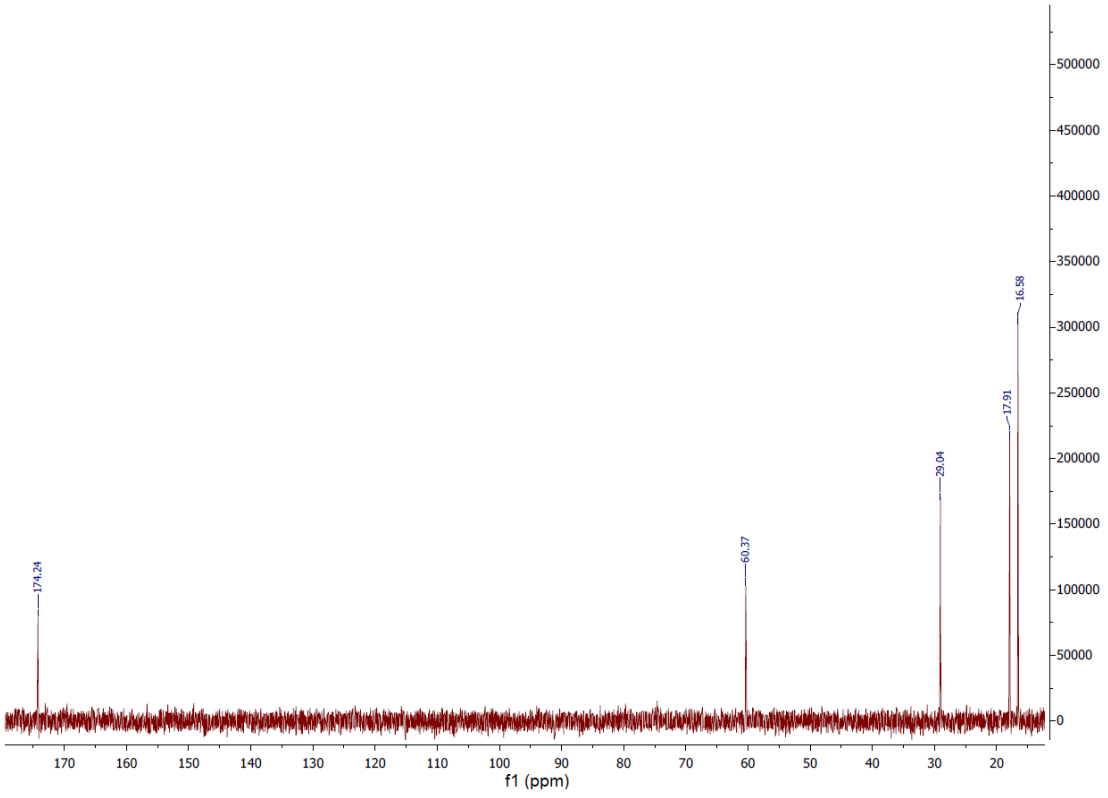

Figure S12. ^{13}C NMR spectrum of **1c** (D_2O, δ, ppm)

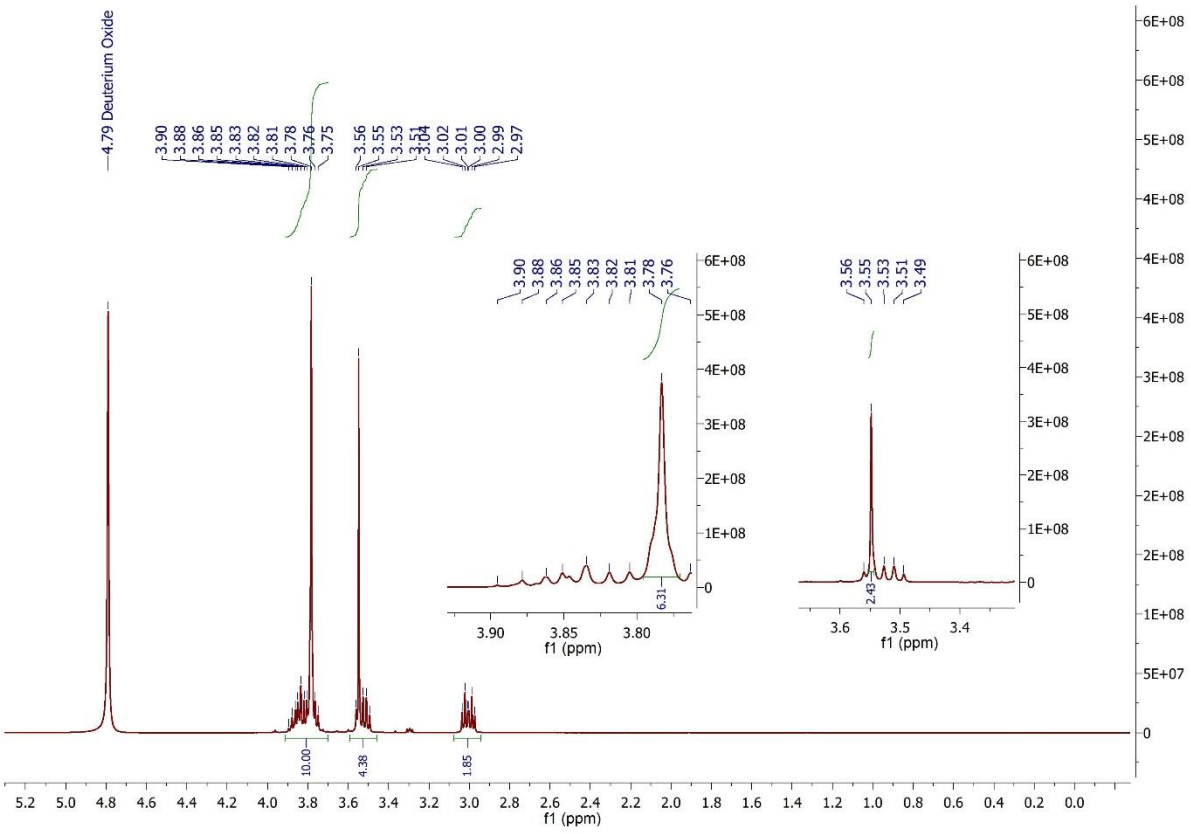

Figure S13. ^{1}H NMR spectrum of **2a** (D_2O, δ, ppm, J, Hz)

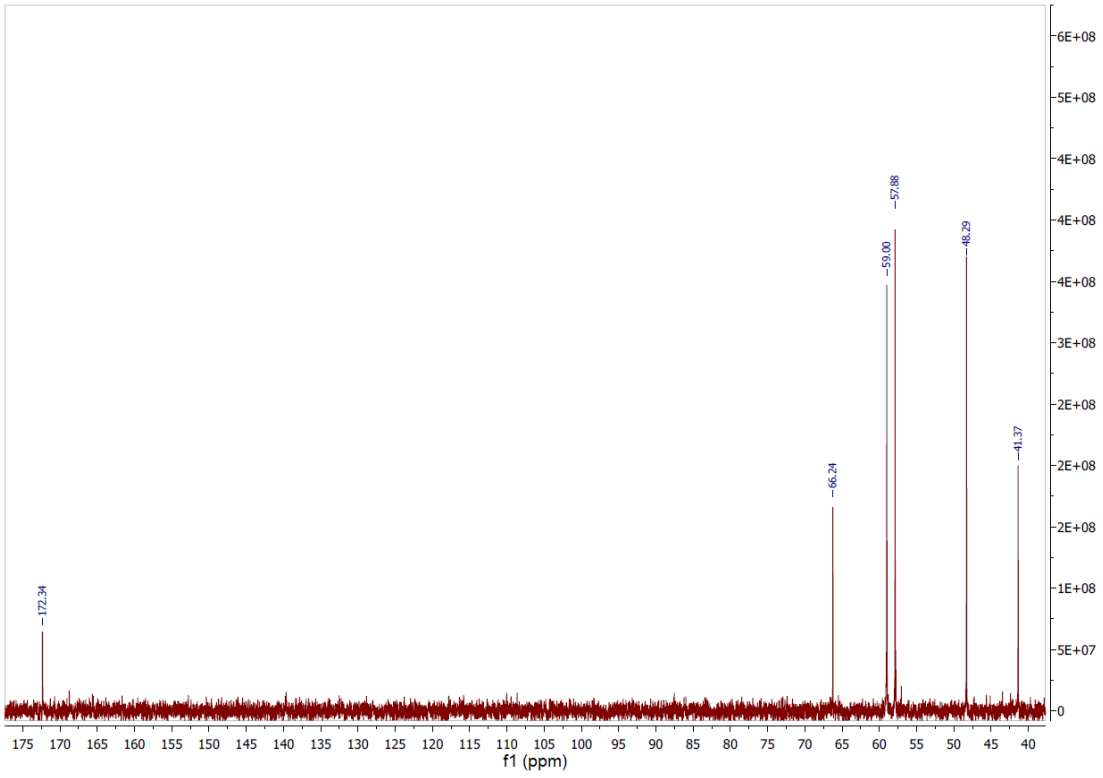

Figure S14. ^{13}C NMR spectrum of **2a** (D_2O, δ, ppm)

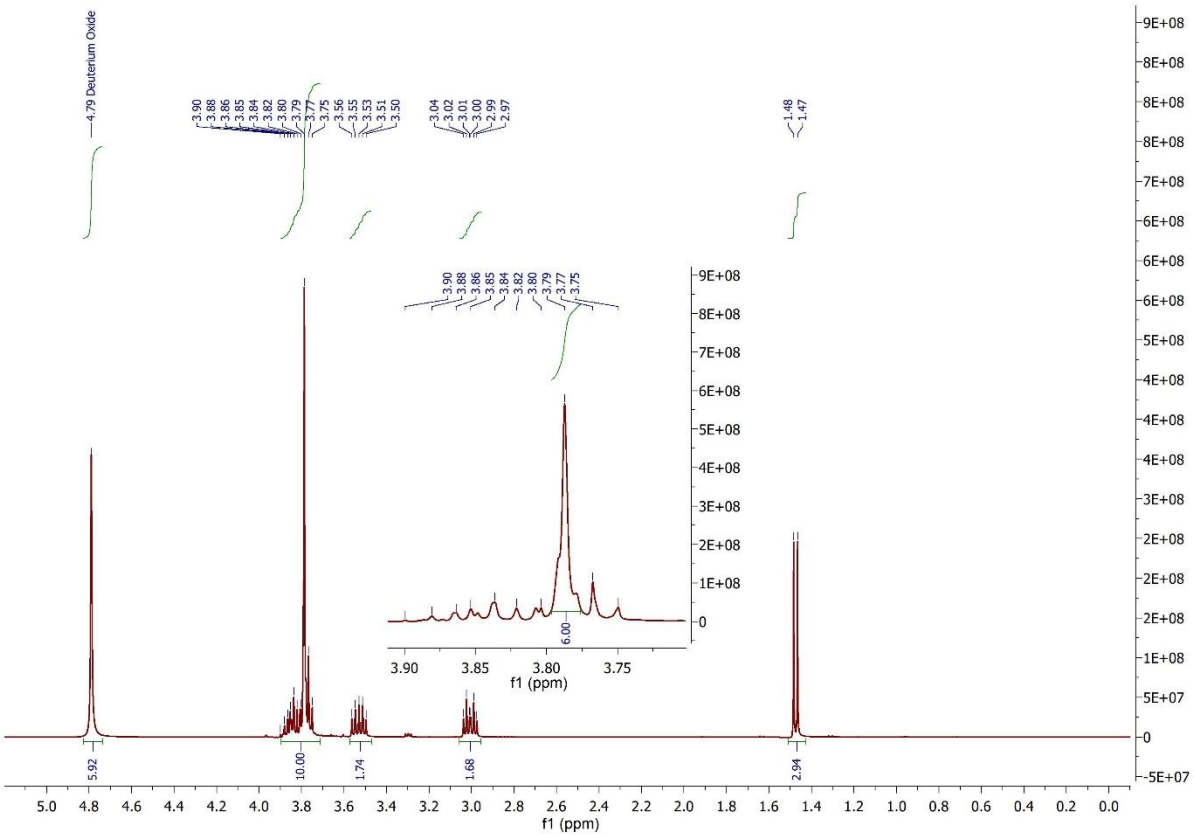

Figure S15. ^{1}H NMR spectrum of **2b** (D_2O, δ, ppm, J, Hz)

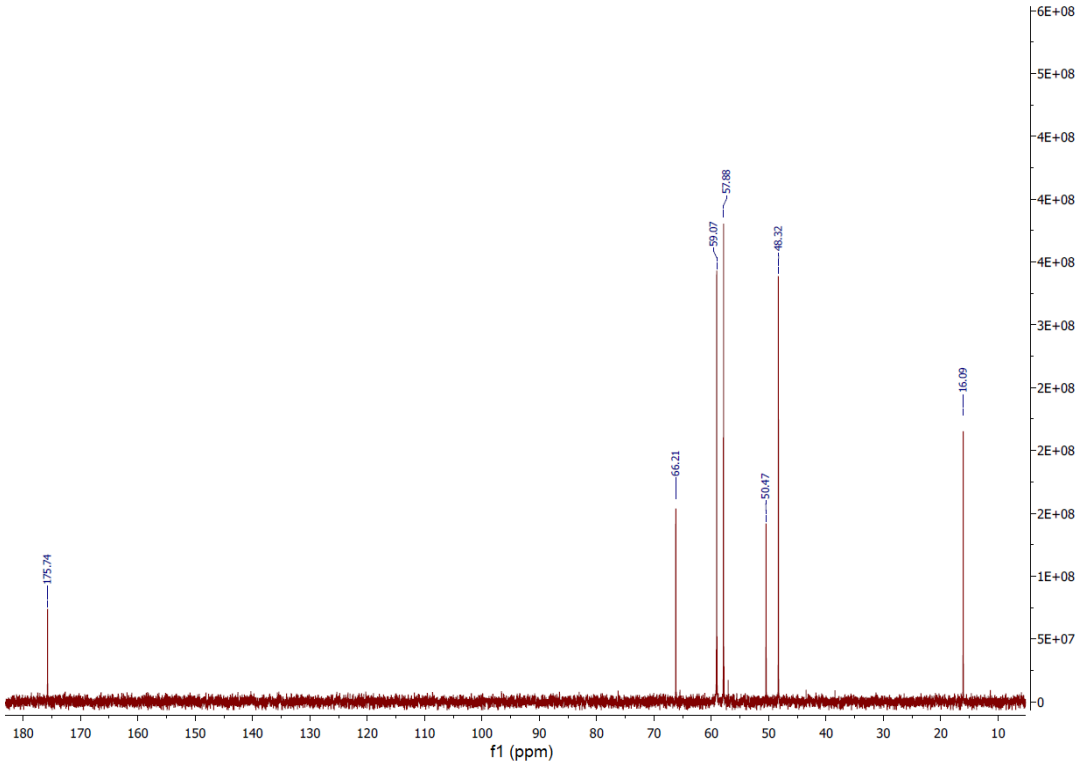

Figure S16. ^{13}C NMR spectrum of **2b** (D_2O, δ, ppm)

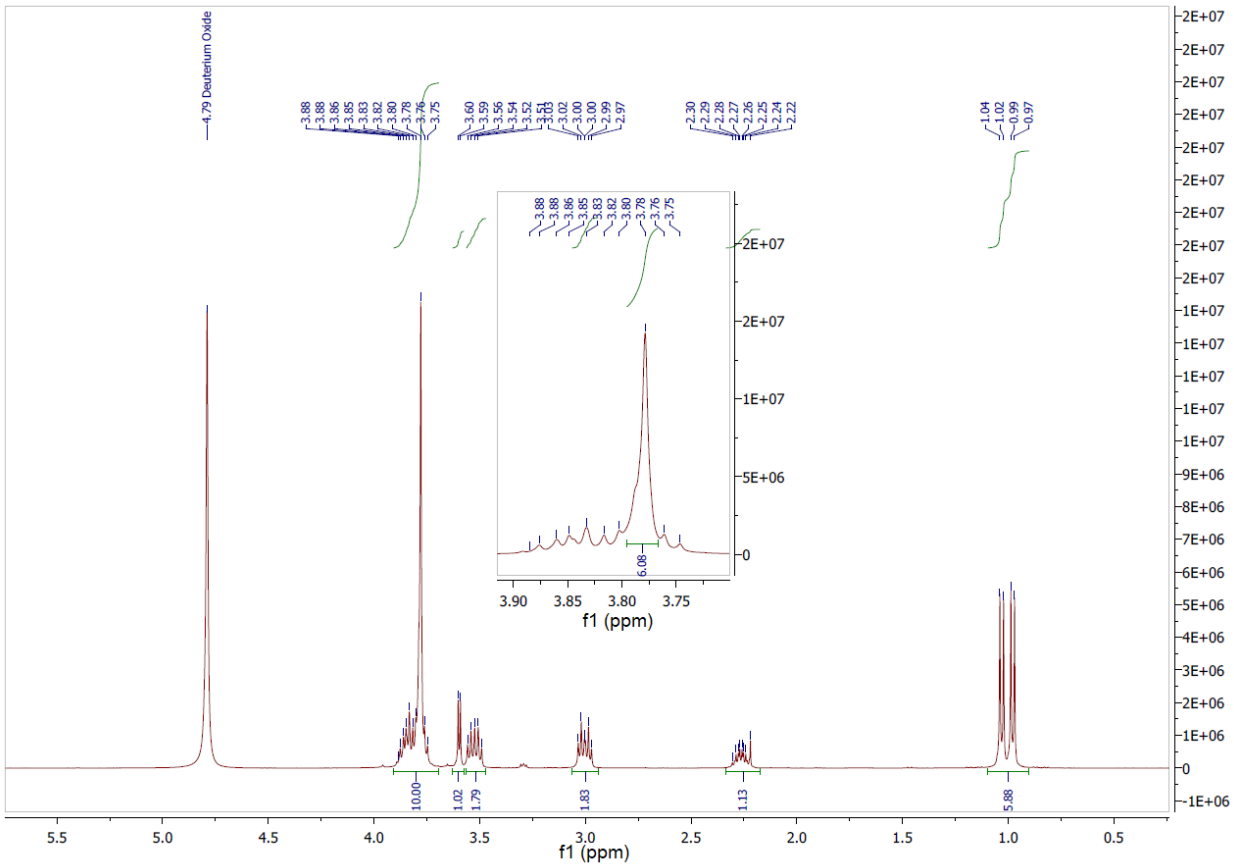

Figure S17. ^{1}H NMR spectrum of **2c** (D_2O, δ, ppm, J, Hz)

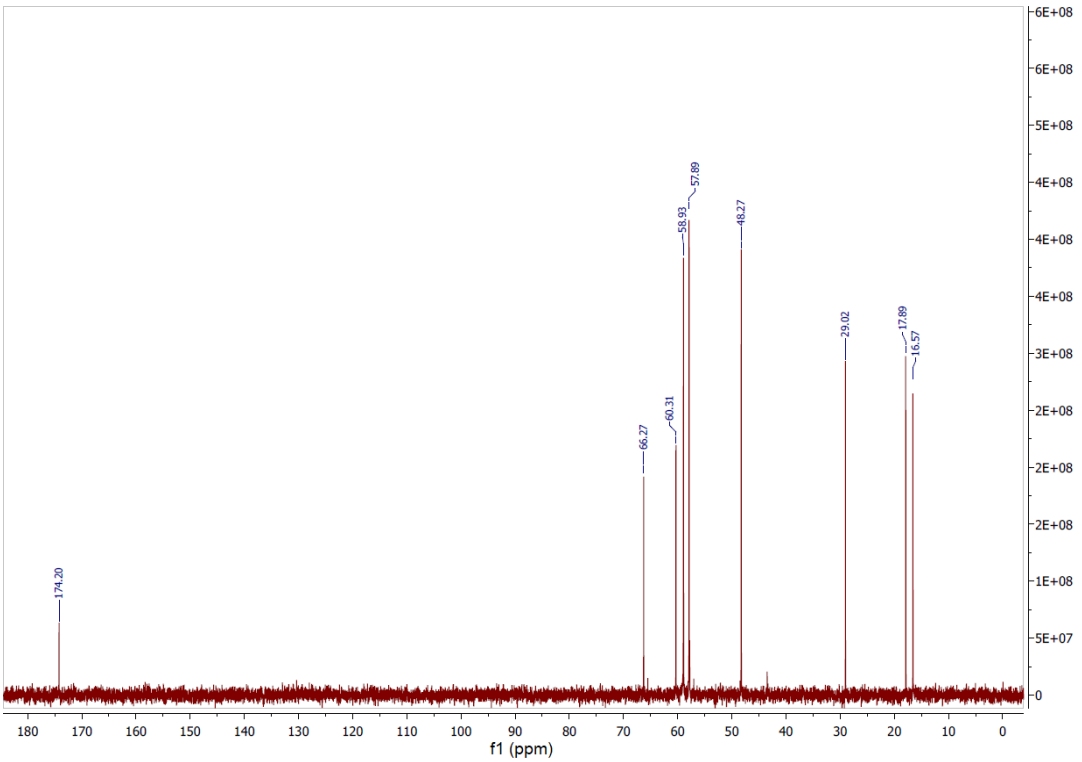

Figure S18. ^{13}C NMR spectrum of **2c** (D_2O, δ, ppm)

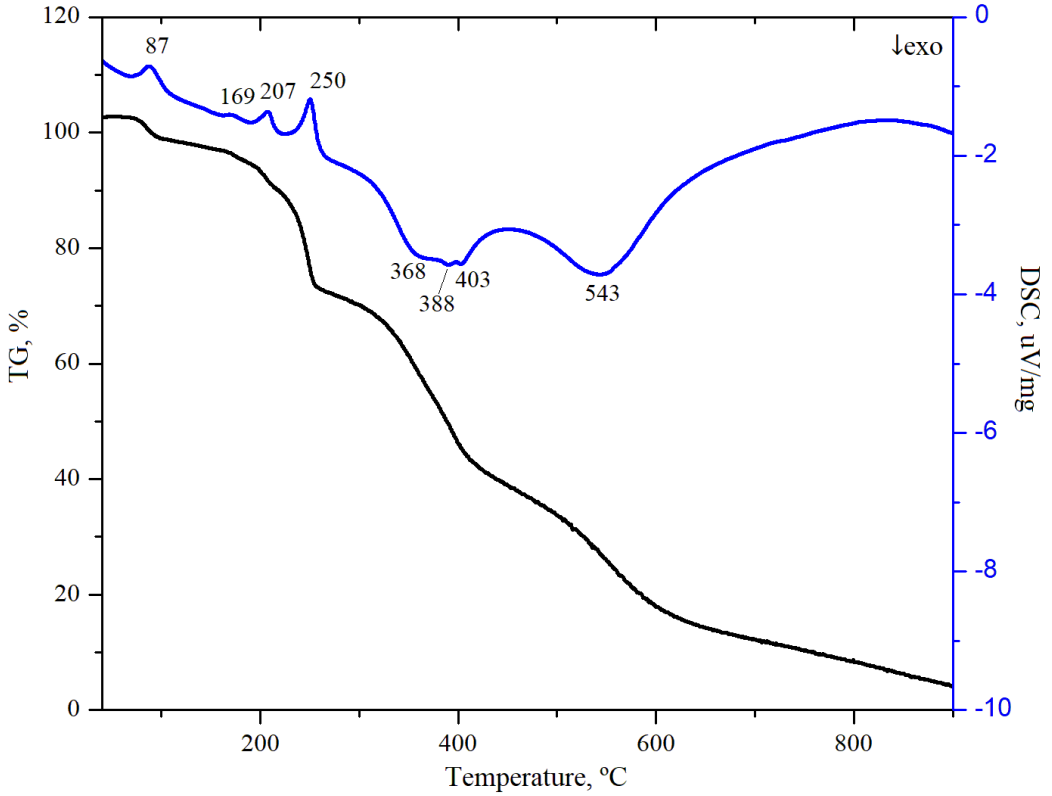

Figure S19. TG and DSC curves of **2a** obtained by heating samples from 40 to 900°C at a heating rate of 10 K min^{-1}

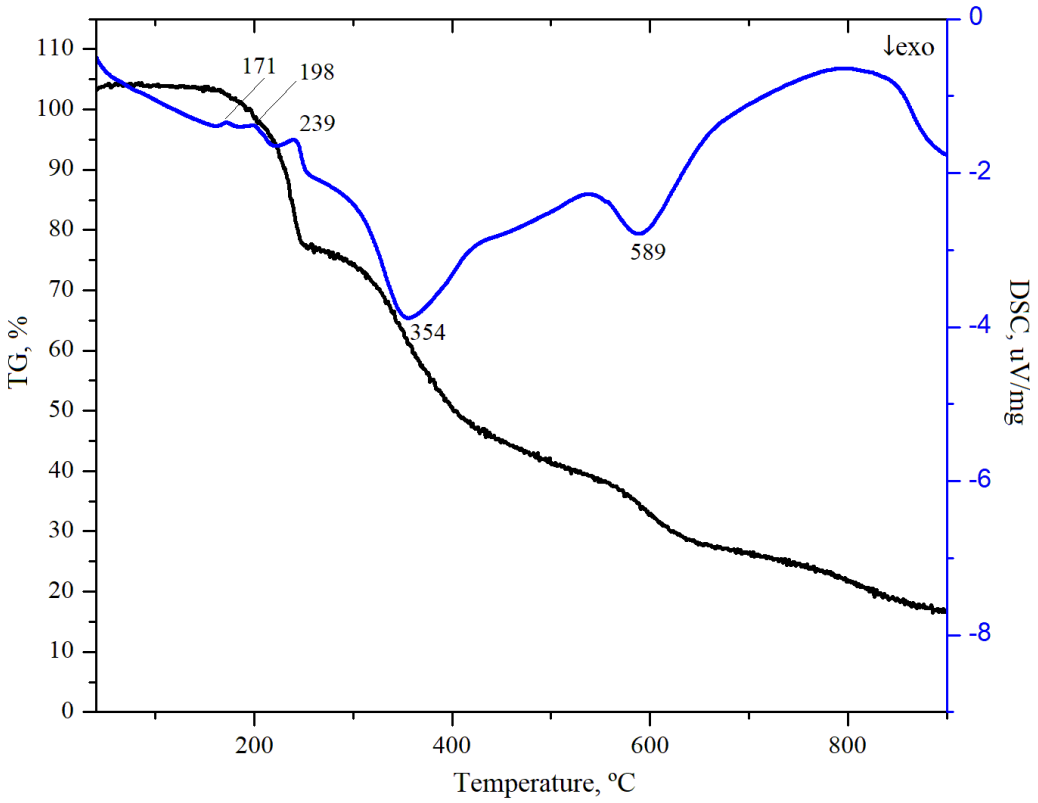

Figure S20. TG and DSC curves of **2b** obtained by heating samples from 40 to 900°C at a heating rate of 10 K min^{-1}

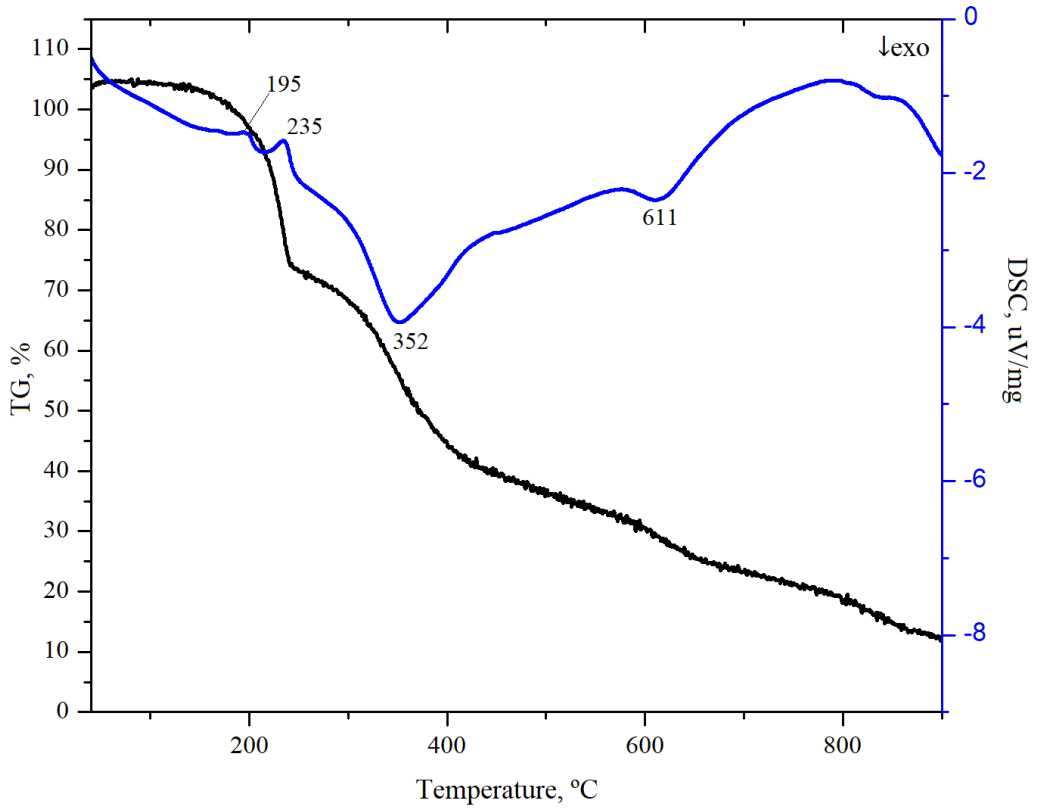

Figure S21. TG and DSC curves of **2c** obtained by heating samples from 40 to 900°C at a heating rate of 10 K min^{-1}

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