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

Electronic Supplementary Information

Saccharin Guanidination via Facile Three-Component "Two Saccharins–One Dialkylcyanamide" Integration

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Experimental section

1. Materials and Instruments. Saccharin, disubstituted cyanamides, and organic solvents were obtained from commercial sources (Acros, Sigma–Aldrich) and used as received. Melting points were measured on a Stuart SMP30 apparatus in capillaries and are not corrected. Electrospray ionization mass spectra were obtained on a Bruker micrOTOF spectrometer equipped with an electrospray ionization (ESI) source. The instrument was operated both in negative and in positive ion mode using an *m/z* range of 50−3000. The nebulizer gas flow was 0.4 bar, and the drying gas flow was 4.0 L/min. For ESI-MS, the clusters were dissolved in MeOH. In the isotopic pattern, the most intensive peak is reported. Infrared spectra (3600−500 cm^{-1}) were recorded on a Shimadzu IR Prestige-21 instrument in KBr pellets. ^{1}H, $^{13}C\{^{1}H\}$ NMR spectra were measured on a Bruker Avance 400 in dmso-d_6 at ambient temperature; the residual solvent signal was used as the internal standard. ^{13}C CP/MAS NMR spectrum for **5** was measured on a Bruker WB Avance III 400 at ambient temperature.

2. X-ray structure determinations. Crystals of **1**•$NCNMe_2$, **2**•$NCNEt_2$, and **4**•$2NCNC_5H_{10}$ were obtained directly from the reaction mixtures upon their evaporation almost to dryness in an open vial at RT for approx. 2 d. These species were obtained as large transparent colorless crystals under a yellow solution (ca. 0.5 mL). All X-ray diffraction (XRD) experiments were performed at 100 K. For **1**•$NCNMe_2$ and **4**•$2NCNC_5H_{10}$, XRD experiments were carried out using SuperNova, Dual, Cu at zero, Atlas diffractometer with monochromated Cu Kα radiation (λ = 1.54184). For **2**•$NCNEt_2$, XRD experiments was carried out using Xcalibur, Eos diffractometer with monochromated Mo Kα radiation (λ = 0.7107). Using Olex2,[1] the structures were solved with SHELXT[2] structure solution program and refined with SHELXL[3] refinement. For **2**•$NCNEt_2$, the second crystallographically independent $NCNEt_2$ molecule was deleted by SQUEEZE in Platon program due to disorder. CCDC numbers 1917245, 1917248, and 1917249 contain the supplementary crystallographic data for this paper. These data can be obtained free of

charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Table S1. Crystallographic parameters for structures **1**•$NCNMe_2$, **2**•$NCNEt_2$, and **4**•$2NCNC_5H_{10}$.

Identification code	**1**•$NCNMe_2$	**2**•$NCNEt_2$	**4**•$2NCNC_5H_{10}$
CCDC number	1917245	1917248	1917249
Empirical formula	$C_{20}H_{22}N_6O_6S_2$	$C_{43}H_{50}N_{10}O_{12}S_4$	$C_{32}H_{40}N_8O_6S_2$
Formula weight	506.55	1027.17	696.84
Temperature/K	100(2)	100(2)	100(2)
Crystal system	monoclinic	triclinic	triclinic
Space group	$P2_1/c$	P-1	P-1
a/Å	7.8690(5)	8.0019(4)	8.4094(5)
b/Å	18.8106(12)	15.8441(8)	13.2878(8)
c/Å	15.5694(12)	20.2939(9)	16.0580(6)
α/°	90	84.309(4)	89.298(4)
β/°	99.693(7)	84.453(4)	78.292(4)
γ/°	90	80.817(4)	72.505(5)
Volume/$Å^3$	2271.7(3)	2518.9(2)	1673.47(16)
Z	4	2	2
$\rho_{calc}g/cm^3$	1.481	1.354	1.383
μ/mm^{-1}	2.573	0.257	1.918
F(000)	1056.0	1076.0	736.0
Crystal size/mm^3	0.19 × 0.17 × 0.14	0.20 × 0.18 × 0.15	0.15 × 0.14 × 0.10
Radiation	Cu Kα (λ = 1.54184)	Mo Kα (λ = 0.7107)	CuKα (λ = 1.54184)
2Θ range for data collection/°	7.434 to 152.518	5.4 to 62.31	6.984 to 152.324
Index ranges	$-9 \le h \le 9$, $-23 \le k \le 22$, $-19 \le l \le 13$	$-10 \le h \le 11$, $-21 \le k \le 21$, $-28 \le l \le 29$	$-10 \le h \le 9$, $-16 \le k \le 14$, $-17 \le l \le 20$
Reflections collected	8462	47338	14698
Independent reflections	4484 [R_{int} = 0.0436, R_{sigma} = 0.0531]	14394 [R_{int} = 0.0355, R_{sigma} = 0.0387]	6847 [R_{int} = 0.0440, R_{sigma} = 0.0521]
Data/restraints/parameters	4484/0/311	14394/2/638	6847/8/451
Goodness-of-fit on F^2	1.040	1.028	1.028
Final R indexes [I≥2σ (I)]	R_1 = 0.0437, wR_2 = 0.1054	R_1 = 0.0489, wR_2 = 0.1143	R_1 = 0.0455, wR_2 = 0.1170
Final R indexes [all data]	R_1 = 0.0560, wR_2 = 0.1154	R_1 = 0.0643, wR2 = 0.1218	R_1 = 0.0559, wR_2 = 0.1259
Largest diff. peak/hole / e·$Å^{-3}$	0.36/–0.49	0.61/–0.41	0.54/–0.77

3. Synthetic work

Synthesis of **1**–**5**. Saccharin (91.6 mg, 0.5 mmol) was dissolved on stirring in the corresponding cyanamide (0.5 mL) at 60 °C. After 30–60 min, a colorless precipitate was formed and the reaction mixture was then stirred for 2 h at 60 °C. After cooling the reaction mixture to RT, the colorless precipitate was filtered off, washed twice with ethyl acetate (two 3-mL portions) and dried *in vacuo* (4 mbar) on a boiling water bath for 5 h.

1. Yield 81% (88.4 mg). mp 240–241 °C. ^{1}H NMR, δ: 8.92 (br. d, J = 6.1 Hz, 1H, NH), 8.40 (d, J = 7.8 Hz, 1H, Ar), 8.37 (br. d, J = 6.6 Hz, 1H, NH), 8.18–8.12 (m, 1H, Ar), 8.06–8.02 (m, 2H, Ar), 7.81 (d, J = 6.4 Hz, 1H, Ar), 7.63 (td, J = 7.6, 1.4 Hz, 1H, Ar), 7.57 (td, J = 7.5, 1.4 Hz, 1H, Ar), 7.44 (d, J = 6.1 Hz, 1H, Ar), 3.24 (s, 3H, Me), 2.95 (s, 3H, Me); ^{13}C NMR, δ: 158.5, 157.3, 155.8, 144.0, 137.1, 137.0, 135.7, 131.0, 130.0, 126.8, 126.7, 126.2, 125.9, 124.9, 121.7, 40.2, 37.6; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{17}H_{16}N_4NaO_6S_2^+$: 459.0403; found: 459.0404. IR spectrum in KBr, selected bands, cm^{-1}: 1768, s ν(C=O), 1674, s and 1646, s ν(C=N), 1308, s, 1230, s, and 1193, s ν_{as+s}(S=O).

2. Yield 85% (98.7 mg). mp 228–229 °C. ^{1}H NMR, δ: 9.02 (br. d, J = 6.2 Hz, 1H, NH), 8.40 (d, J = 7.8 Hz, 1H, Ar), 8.36 (br. d, J = 6.7 Hz, 1H, NH), 8.18–8.12 (m, 1H, Ar), 8.06–8.01 (m, 2H, Ar), 7.82 (d, J = 6.4 Hz, 1H, Ar), 7.63 (td, J = 7.5, 1.3 Hz, 1H, Ar), 7.56 (td, J = 7.5, 1.4 Hz, 1H, Ar), 7.42 (d, J = 6.2 Hz, 1H, Ar), 3.75–3.68 (m, 1H, CH_2), 3.56–3.49 (m, 1H, CH_2), 3.41–3.26 (m, 2H, CH_2), 1.25 (t, J = 7.1 Hz, 3H, Me), 0.91 (t, J = 7.1 Hz, 3H, Me); ^{13}C NMR, δ: 157.5, 157.3, 155.8, 143.9, 137.11, 137.07, 135.7, 130.9, 129.9, 126.8, 126.4, 126.2, 125.9, 124.9, 121.6, 44.4, 42.3, 12.7, 11.5; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{19}H_{20}N_4NaO_6S_2^+$: 487.0716; found: 487.0707. IR spectrum in KBr, selected bands, cm^{-1}: 1768, s ν(C=O), 1670, s and 1642, s ν(C=N), 1303, s, 1234, s, and 1185, s ν_{as+s}(S=O).

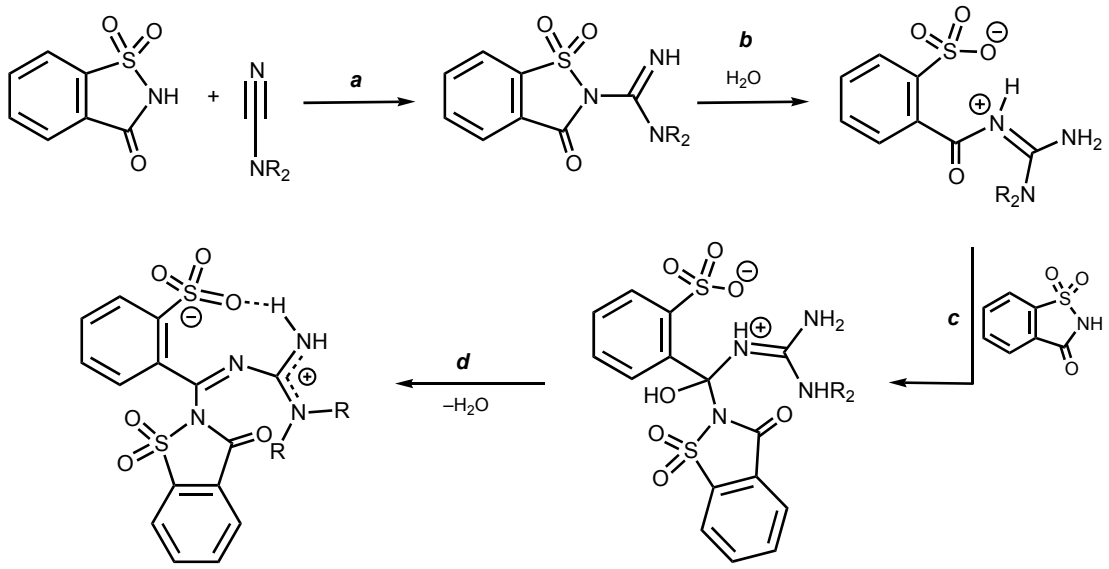
3. Yield 79% (91.3 mg). mp 242–243 °C. ^{1}H NMR, δ: 8.88 (br. s, 1H, NH), 8.40 (d, J = 7.8 Hz, 1H, Ar), 8.26 (br. s, 1H, NH), 8.17–8.13 (m, 1H, Ar), 8.04 (d, J = 4.3 Hz, 2H, Ar), 7.81 (d, J = 7.7 Hz, 1H, Ar), 7.62 (t, J = 7.8 Hz, 1H, Ar), 7.56 (t, J = 7.4 Hz, 1H, Ar), 7.46 (d, J = 7.3

Hz, 1H, Ar), 3.76 (s, 1H, CH_2), 3.64 (s, 1H, CH_2), 3.15 (s, 2H, CH_2), 1.95 (s, 4H, CH_2); CP/MAS ^{13}C NMR (10 kHz), δ: 157.4, 157.2, 155.3, 142.5, 140.3, 138.5, 134.3, 133.6, 132.1, 130.3, 129.0, 126.2, 123.9 (2C), 120.1, 50.1 (2C), 26.7, 24.5; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{19}H_{18}N_4NaO_6S_2^+$: 485.0560; found: 485.0557. IR spectrum in KBr, selected bands, cm^{-1}: 1769, s ν(C=O), 1658, s and 1625, s ν(C=N), 1288, s, 1229, s, and 1197, s ν_{as+s}(S=O).

4. Yield 91% (108.4 mg). mp 209–210 °C. ^1H NMR, δ: 9.01 (br. d, J = 5.8 Hz, 1H, NH), 8.43 (br. d, J = 6.3 Hz, 1H, NH), 8.39 (d, J = 7.7 Hz, 1H, Ar), 8.18–8.12 (m, 1H, Ar), 8.04 (d, J = 4.2 Hz, 2H, Ar), 7.82 (d, J = 5.8 Hz, 1H, Ar), 7.64–7.57 (m, 2H, Ar), 7.43 (d, J = 5.6 Hz, 1H, Ar), 3.76 (s, 1H, CH_2), 3.69 (s, 1H, CH_2), 3.40 (s, 2H, CH_2), 1.64 (s, 5H, CH_2), 1.38 (s, 1H, CH_2); ^{13}C NMR, δ: 157.3, 156.7, 155.8, 143.9, 137.1, 137.05, 135.7, 131.0, 129.8, 126.9, 126.8, 126.1, 125.9, 124.9, 121.6, 47.3, 45.9, 25.2, 24.7, 22.7; HRMS (ESI): *m/z* $[M + Na]^+$ calcd. for $C_{20}H_{20}N_4NaO_6S_2^+$: 499.0716; found: 499.0712. IR spectrum in KBr, selected bands, cm^{-1}: 1763, s ν(C=O), 1650, s and 1630, s ν(C=N), 1284, s, 1259, s, and 1195, s ν_{as+s}(S=O).

5. Yield 65% (77.8 mg). mp 208–209 °C. ^1H NMR, δ: 9.17 (br. d, J = 6.3 Hz, 1H, NH), 8.60 (br. d, J = 6.9 Hz, 1H, NH), 8.41 (d, J = 7.8 Hz, 1H, Ar), 8.18–8.11 (m, 1H, Ar), 8.05–7.92 (m, 2H, Ar), 7.85–7.80 (m, 1H, Ar), 7.70–7.59 (m, 2H, Ar), 7.55–7.48 (m, 1H, Ar), 3.88–3.69 (m, 5H, CH_2), 3.45 (s, 3H, CH_2); CP/MAS ^{13}C NMR (10 kHz) δ: 157.6, 157.5, 155.8, 143.9, 137.2, 137.0, 135.7, 131.0, 129.9, 127.0, 126.8, 126.0, 125.9, 124.8, 121.7, 65.6, 64.8, 46.2, 45.1; HRMS (ESI): *m/z* $[M + H]^+$ calcd. for $C_{19}H_{19}N_4O_7S_2^+$: 479.0690; found: 479.0697. IR spectrum in KBr, selected bands, cm^{-1}: 1771, s ν(C=O), 1657, s and 1626, s ν(C=N), 1285, s, 1231, s, and 1195, s ν_{as+s}(S=O).

Scheme S1



Scheme S12. Plausible reaction mechanism of the addition.

X-ray diffraction studies

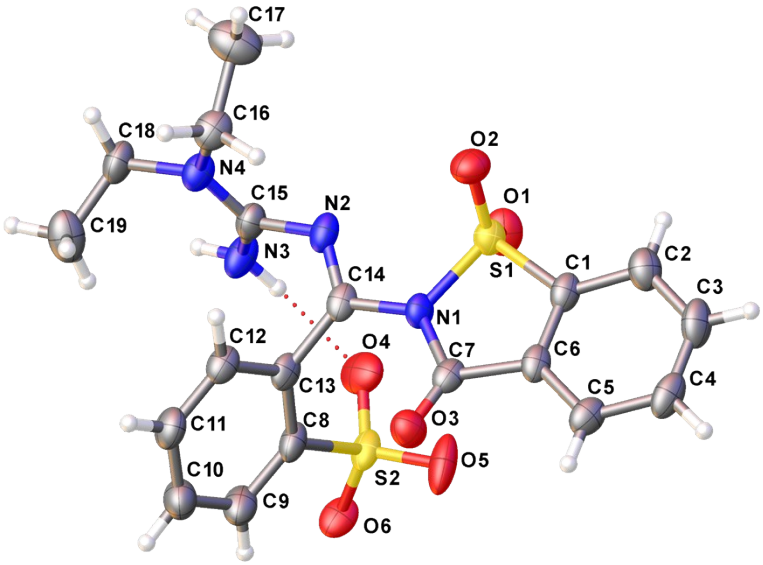


Figure S1. The molecular structure of **2** in **2**•$NCNEt_2$.

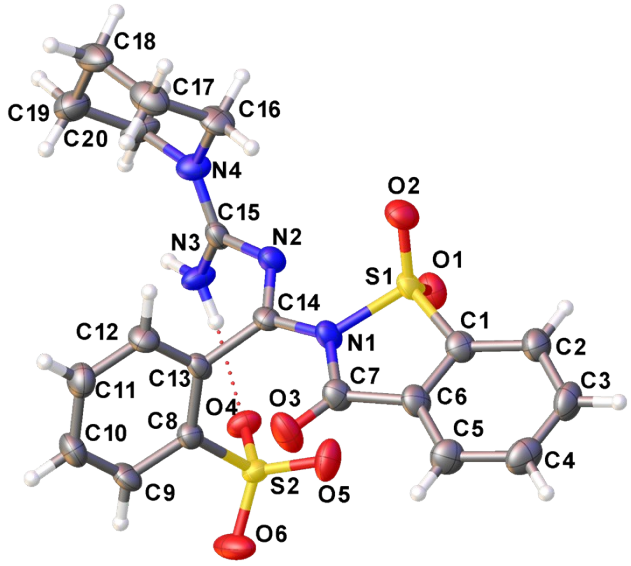


Figure S2. The molecular structure of **4** in **4**•$2NCN(CH_2)_5$.

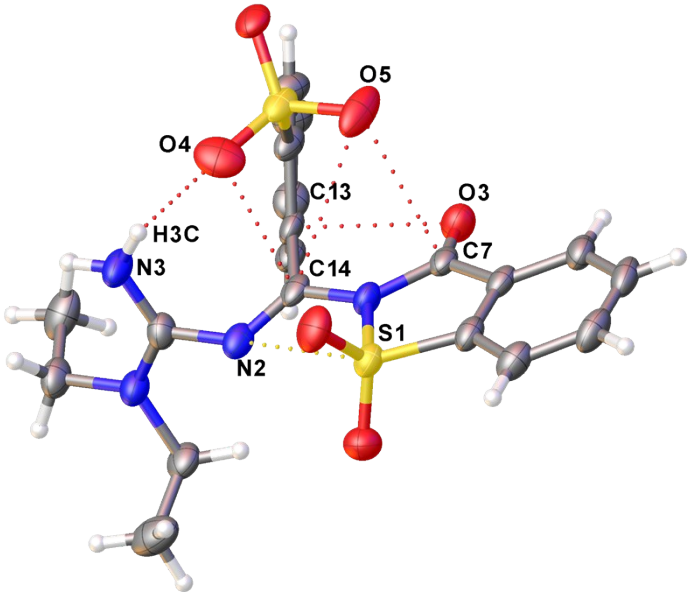


Figure S3. Possible intramolecular weak interactions of **2** in **2**•$NCNEt_2$.

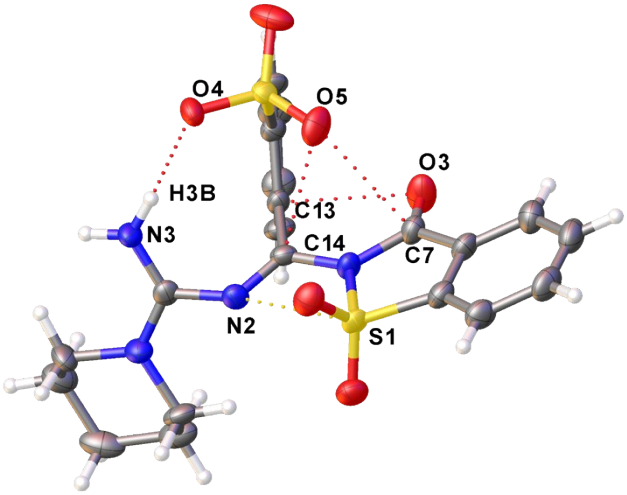


Figure S4. Possible intramolecular weak interactions of **4** in **4**•$2NCN(CH_2)_5$.

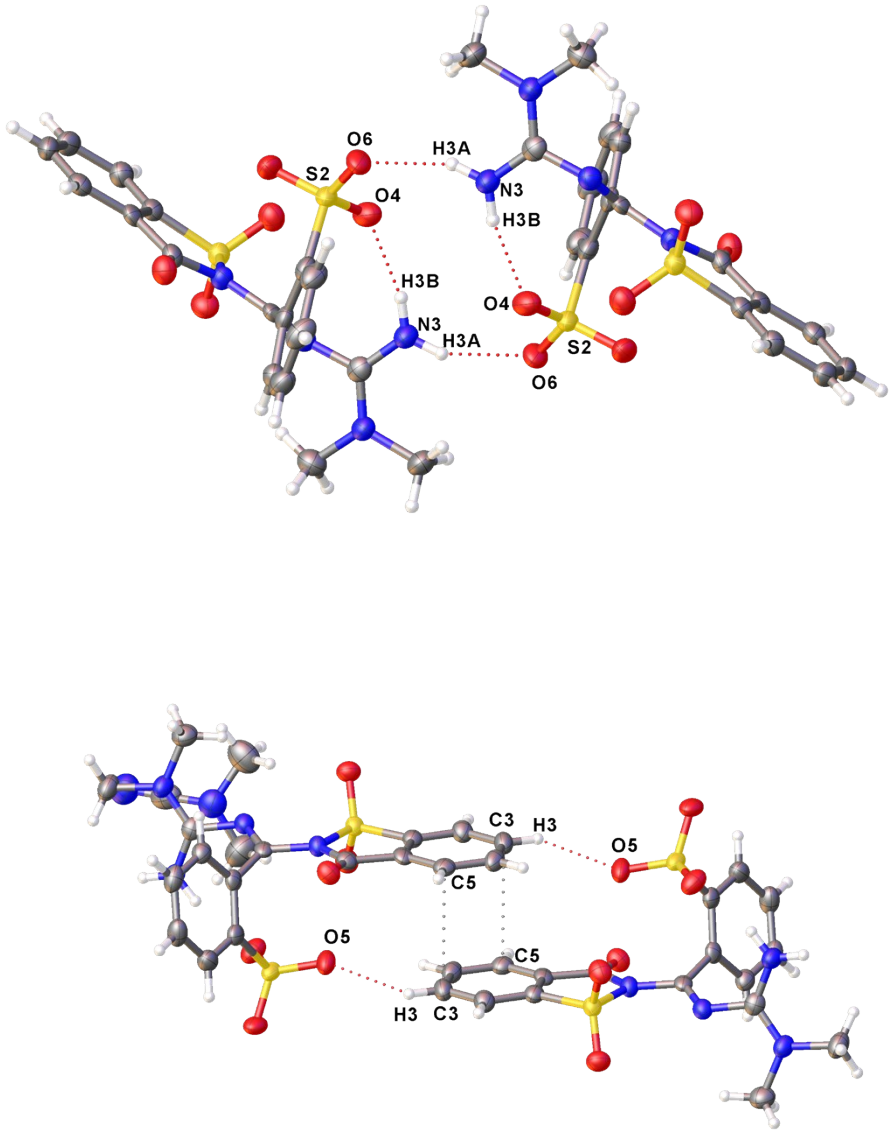


Figure S5. Weak intermolecular interactions in crystal structure of **1**•$NCNMe_2$.

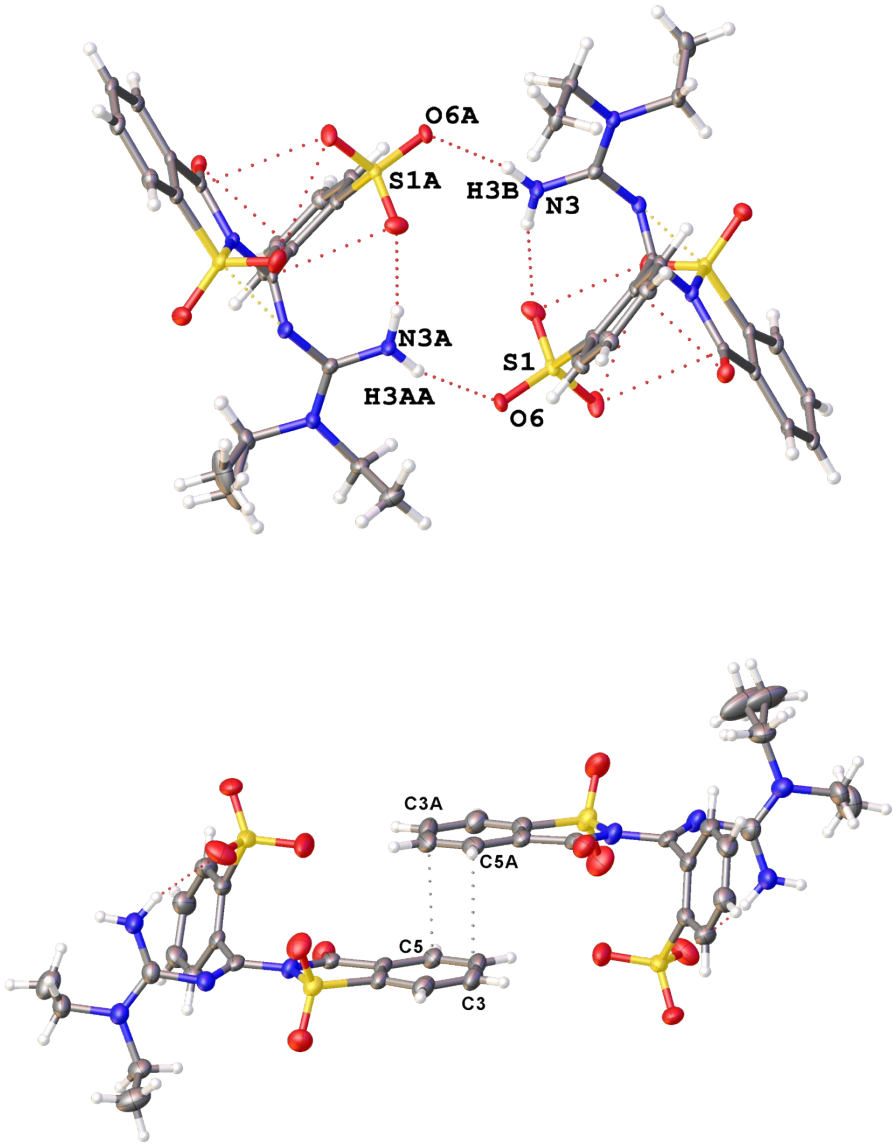


Figure S6. Weak intermolecular interactions in crystal structure of **2**•$NCNEt_2$.

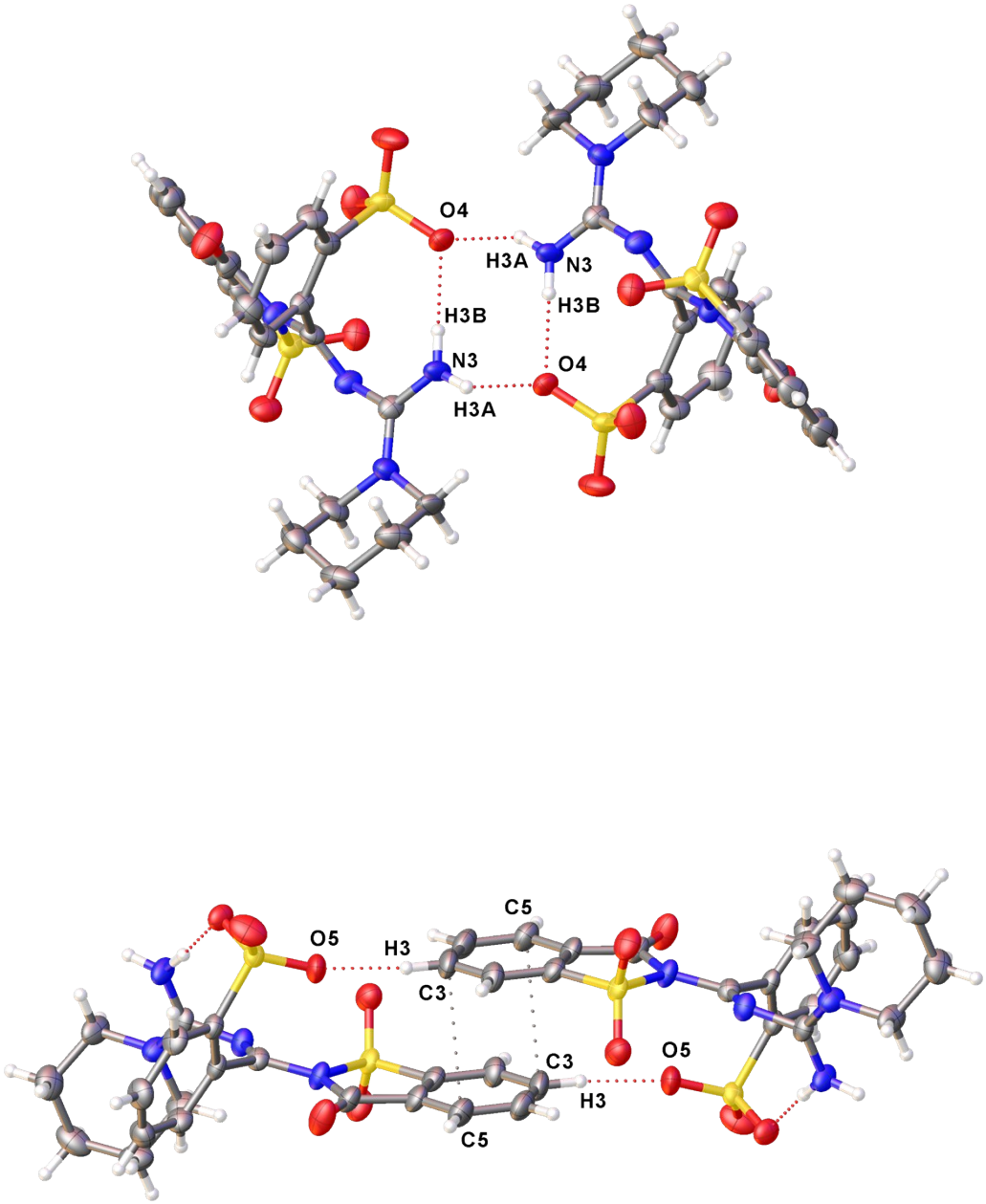


Figure S7. Weak intermolecular interactions in crystal structure of **4**•2NCN$(CH_2)_5$.

Table S1. Bond lengths for different types of C–N bonds in adducts.

Bond	**Order**	**Bond length (Å)**		
		1•$NCNMe_2$	**2**•$NCNEt_2$	**4**•$2NCN(CH_2)_5$
C15–N2	1	1.391(3)	1.396(2)	1.391(2)
C15–N3	1.5	1.319(3)	1.322(2)	1.316(3)
C15–N4	1.5	1.318(3)	1.316(2)	1.320(2)
C14–N2	2	1.279(3)	1.282(2)	1.278(2)

Table S2. The D•••A distances for lp–πh contacts in **1**•$NCNMe_2$, **2**•$NCNEt_2$, and **4**•$2NCN(CH_2)_5$.

	D•••A distance, Å				
Product	N2•••S1	O5•••C7	O3•••C13	O4•••C14	O5•••C14
1•$NCNMe_2$	2.8466(17)	2.923(3)	2.797(2)	2.977(3)	–
2•$NCNEt_2$	2.8277(13) 2.8444(14)	3.008(2) 2.980(2)	2.7827(18) 2.7618(19)	2.905(2) 3.003(2)	– –
4•$2NCN(CH_2)_5$	2.7934(15)	2.985(3)	2.769(2)	–	2.977(3)

The sum of Bondi vdW radii[4] are $R_{vdW}(S) + R_{vdW}(N) = 3.35$ Å and $R_{vdW}(C) + R_{vdW}(O) = 3.22$ Å.

Table S3. Intra- and intermolecular N–H•••O HBs in **1**•$NCNMe_2$, **2**•$NCNEt_2$, and **4**•$2NCN(CH_2)_5$.

HB	H•••O distance, Å	N–H•••O distance, Å	N–H•••O angle, °	Type of contacts
1•$NCNMe_2$				
N3–H3B•••O4	1.9846(15)	2.826(2)	165.56(14)	intramolecular
N3–H3A•••O6	2.0427(16)	2.829(2)	151.54(13)	intermolecular
2•$NCNEt_2$				
N3–H3C•••O4	1.9967(12)	2.8194(10)	159.72(12)	intramolecular
N3A–H3AB•••O4A	2.0226(15)	2.8587(18)	165.50(11)	intramolecular
N3–H3B•••O6A	2.0427(16)	2.829(2)	164.12(11)	intermolecular
N3A–H3AA•••O6	2.086(11)	2.9153(18)	163.2(1)	intermolecular
4•$2NCN(CH_2)_5$				
N3–H3B•••O4	1.9267(16)	2.783(2)	173.79(10)	intramolecular
N3–H3A•••O4	2.0039 (13)	2.806(2)	154.75(14)	intermolecular

Experimental spectra of 1–5

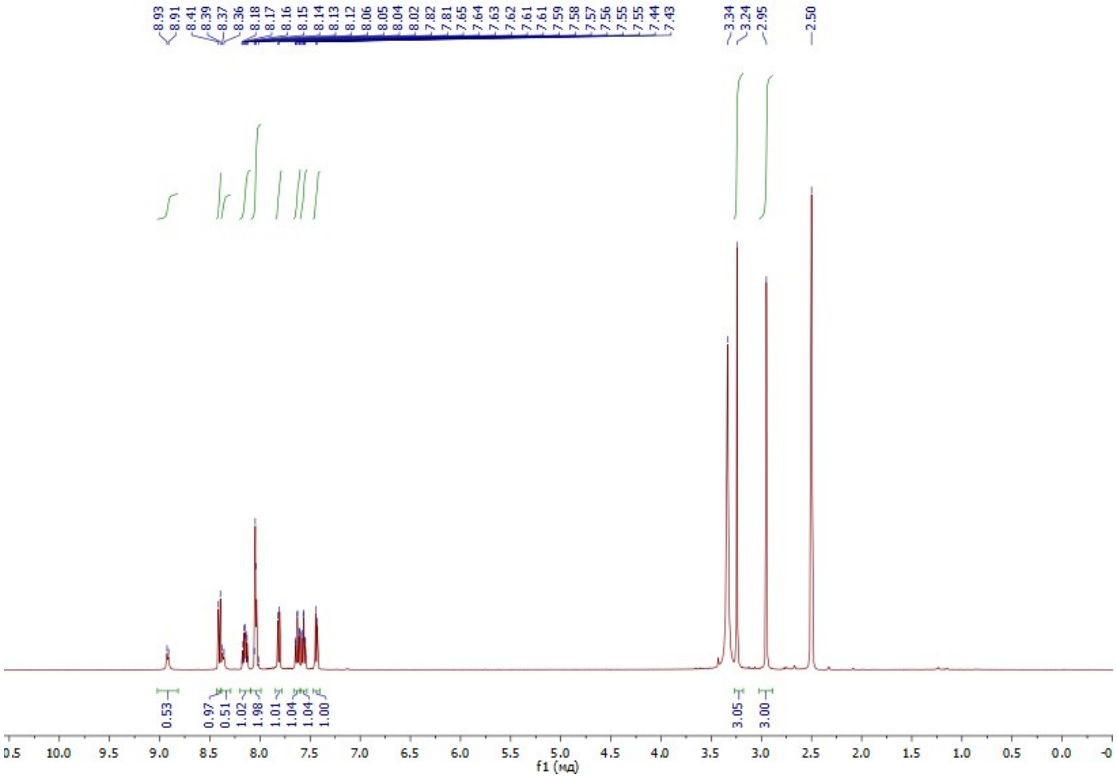


Figure S8. ^{1}H NMR spectrum of **1** in dmso-d_6.

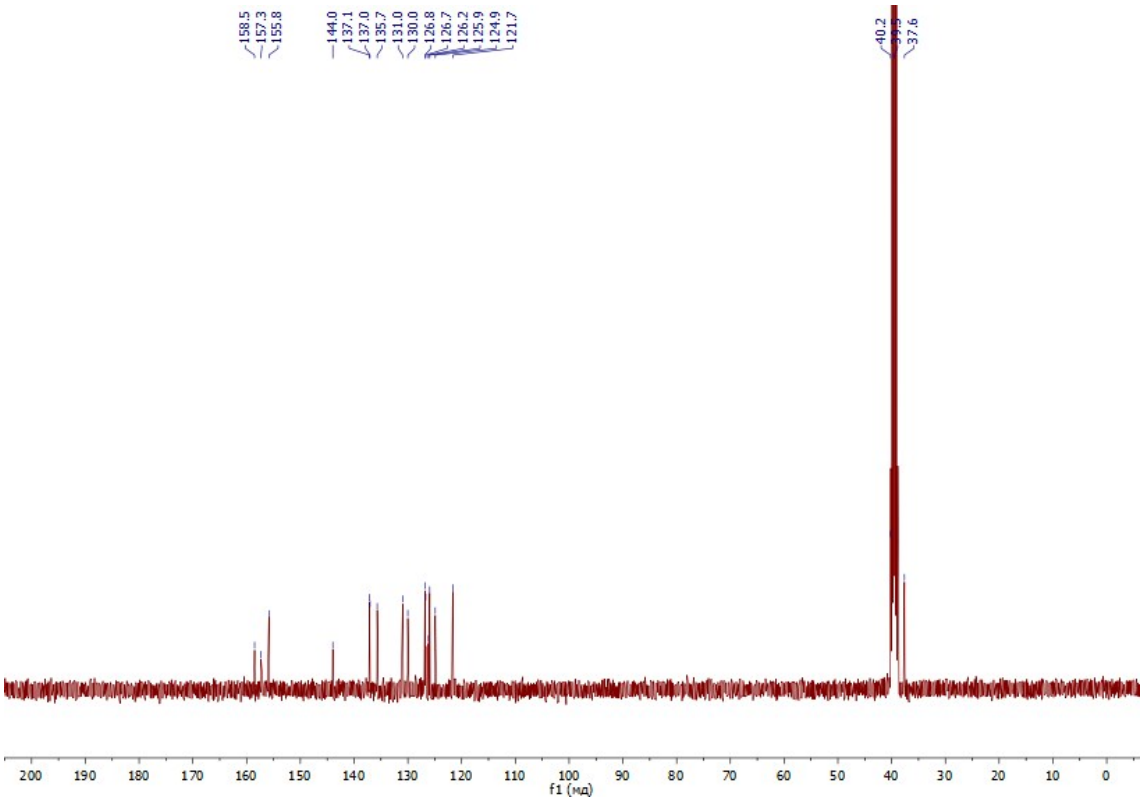


Figure S9. ^{13}C NMR spectrum of **1** in dmso-d_6.

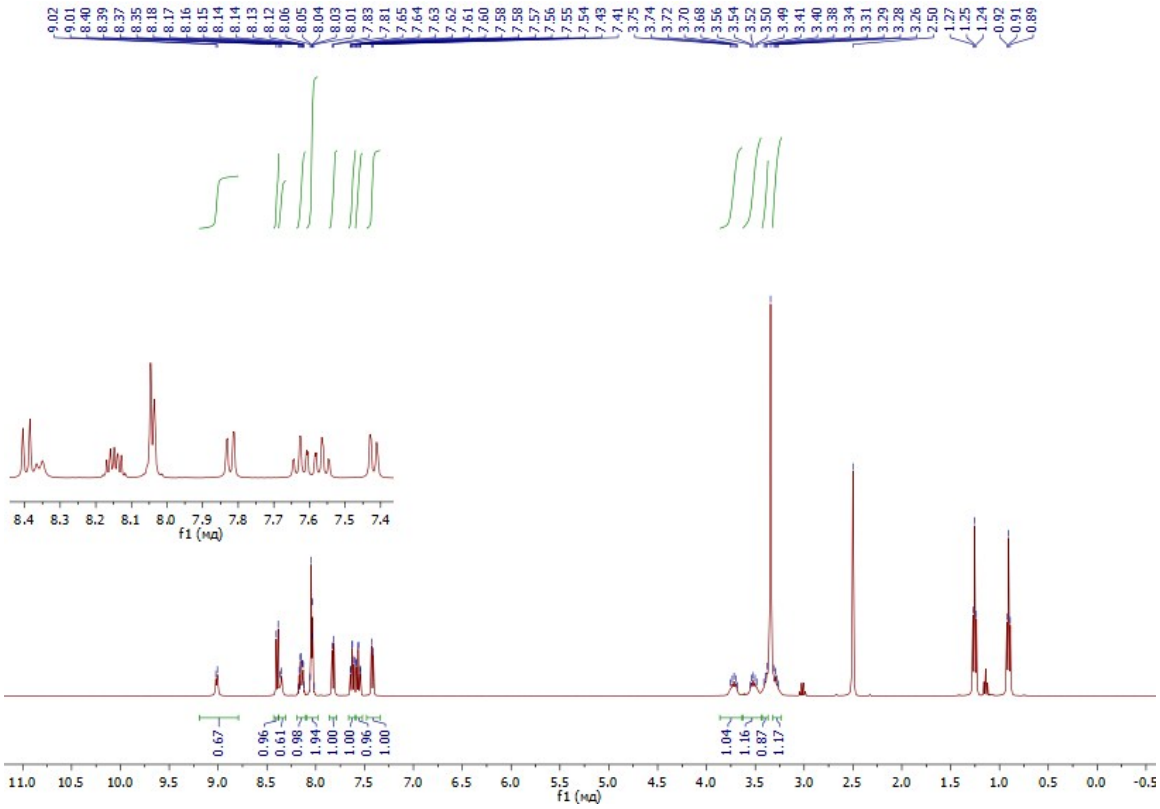


Figure S10. ^{1}H NMR spectrum of **2** in dmso-d_6.

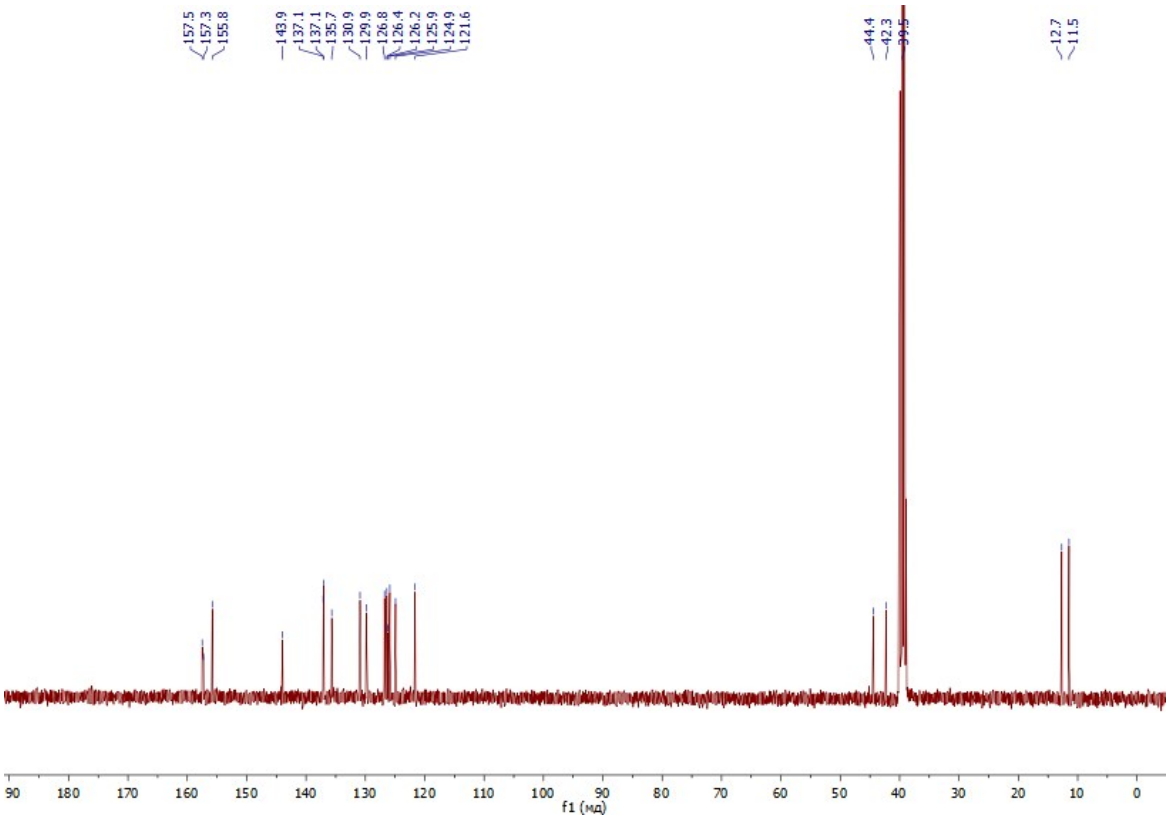


Figure S11. ^{13}C NMR spectrum of **2** in dmso-d_6.

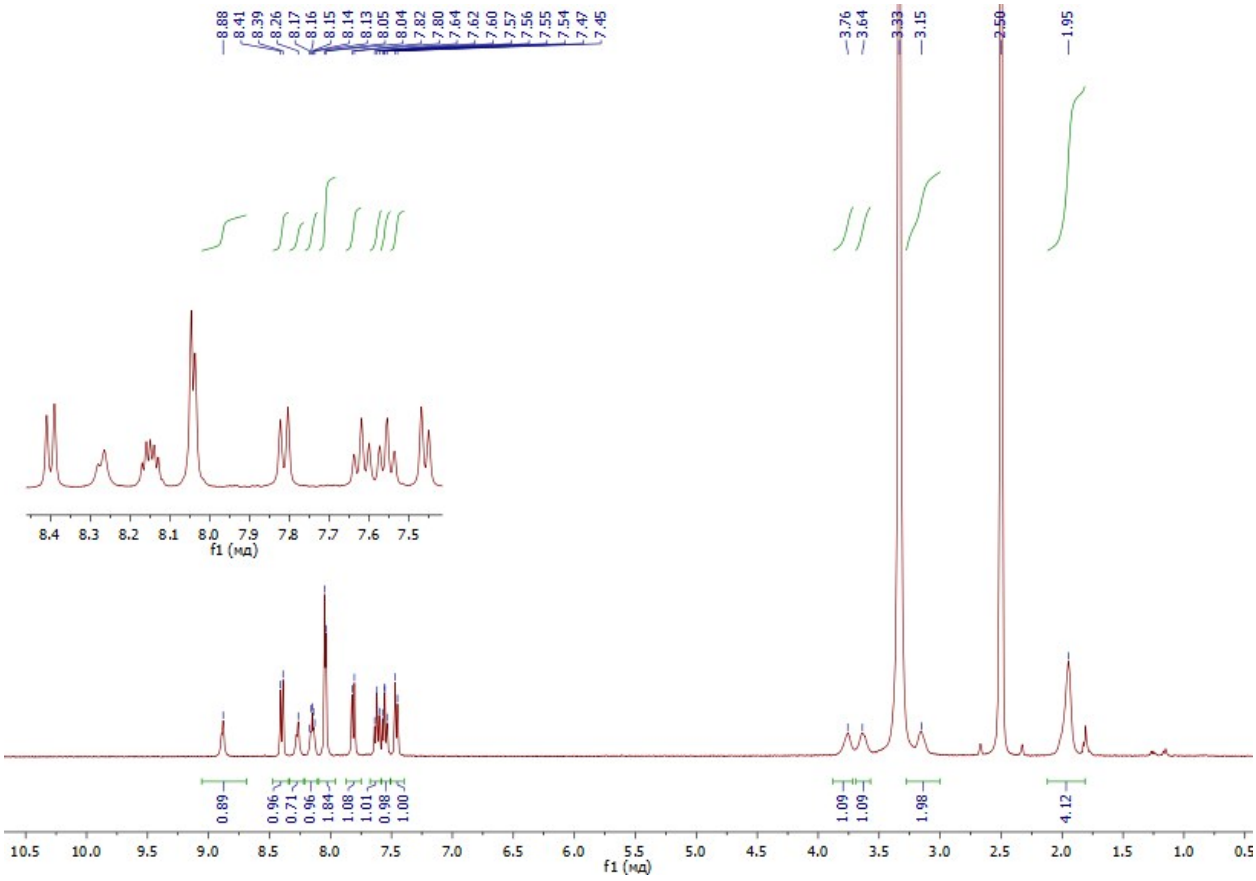


Figure S12. ^{1}H NMR spectrum of **3** in dmso-d_6.

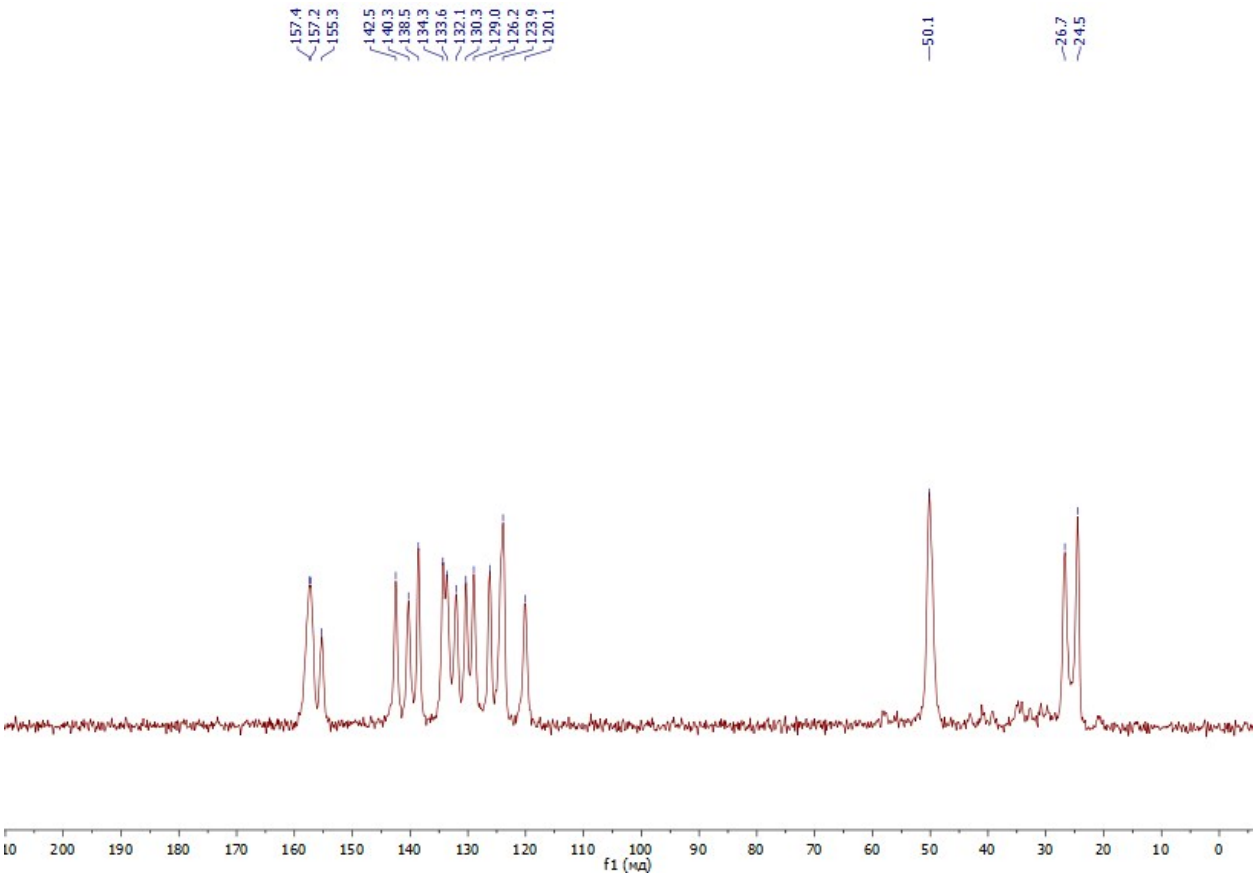


Figure S13. CP/MAS ^{13}C NMR spectrum of **3**.

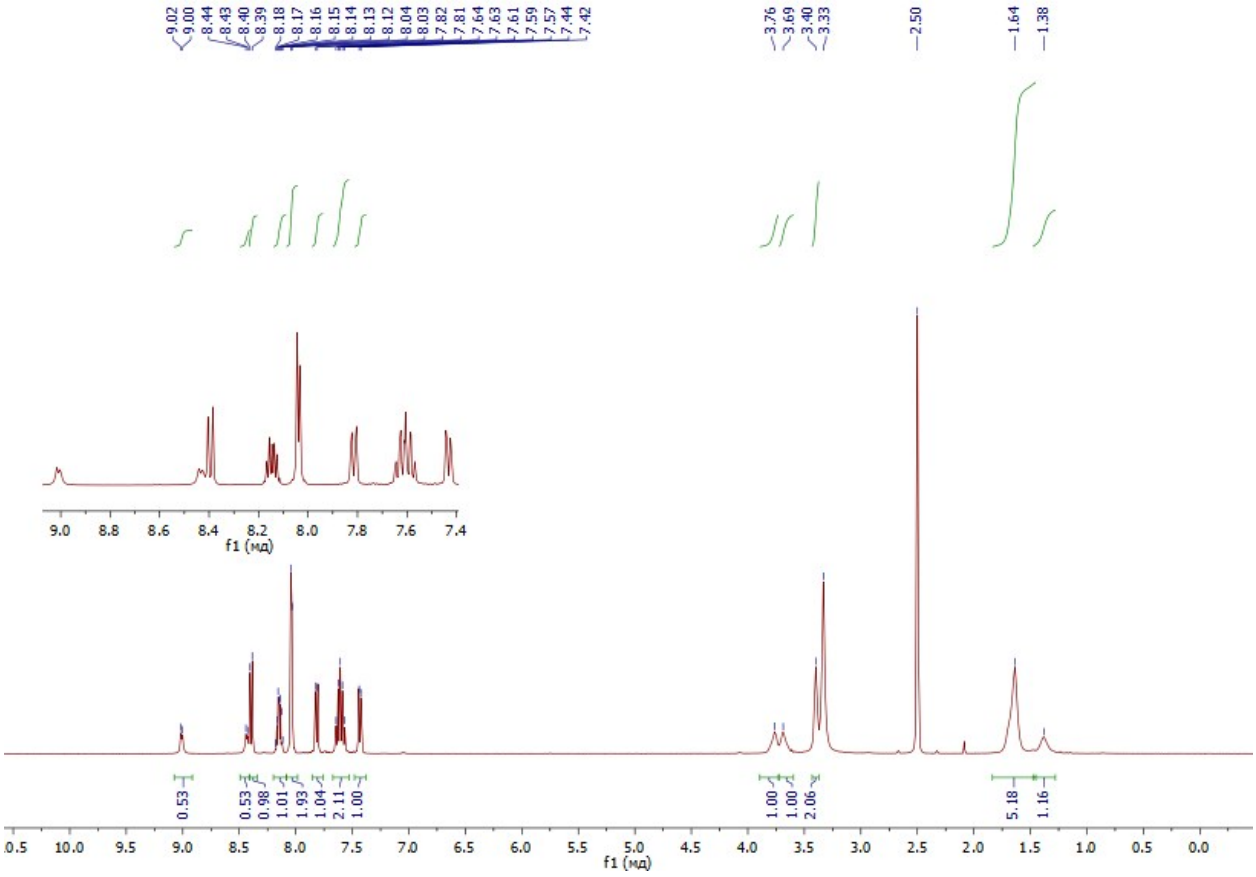


Figure S14. ^{1}H NMR spectrum of **4** in dmso-d_6.

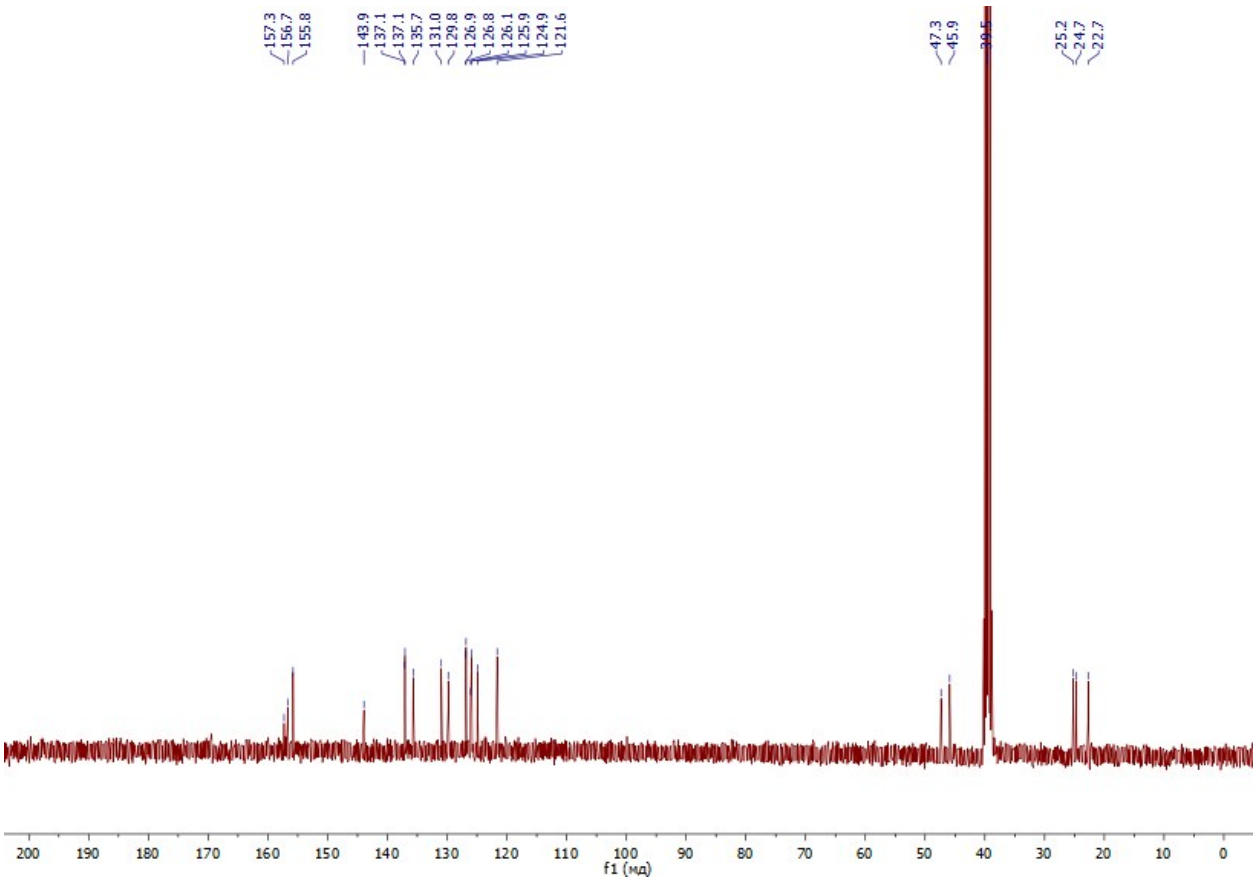


Figure S15. ^{13}C NMR spectrum of **4** in dmso-d_6.

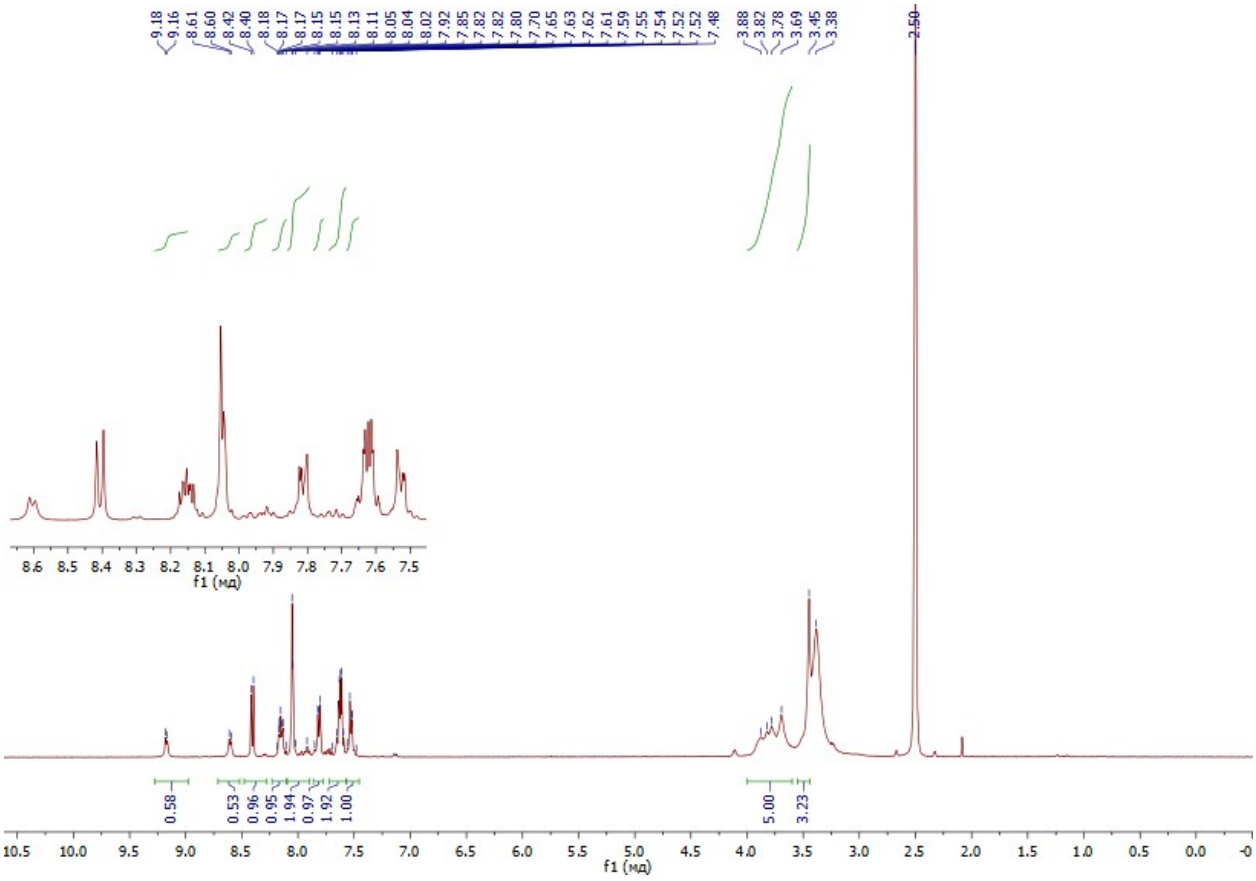


Figure S16. ^{1}H NMR spectrum of **5** in dmso-d_6.

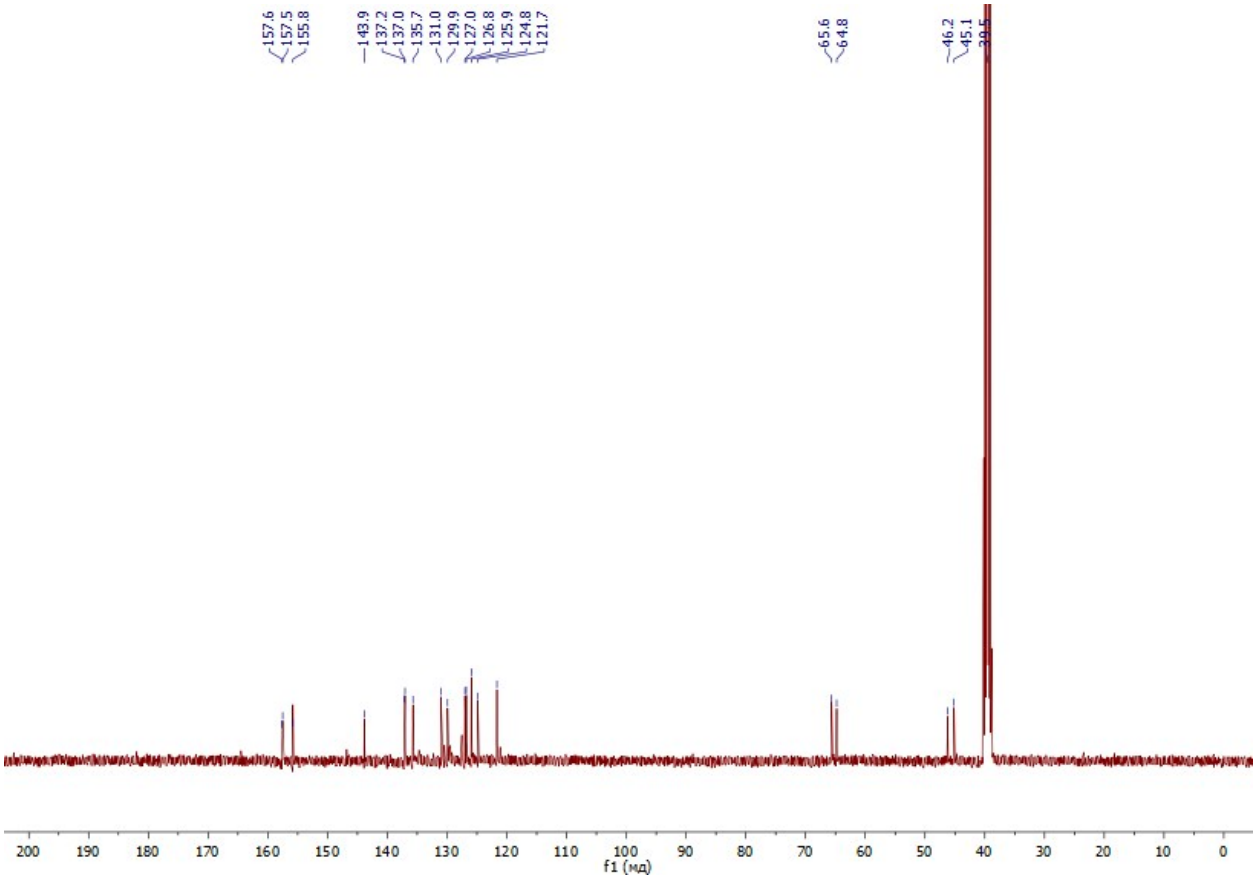


Figure S17. ^{13}C NMR spectrum of **5** in dmso-d_6.

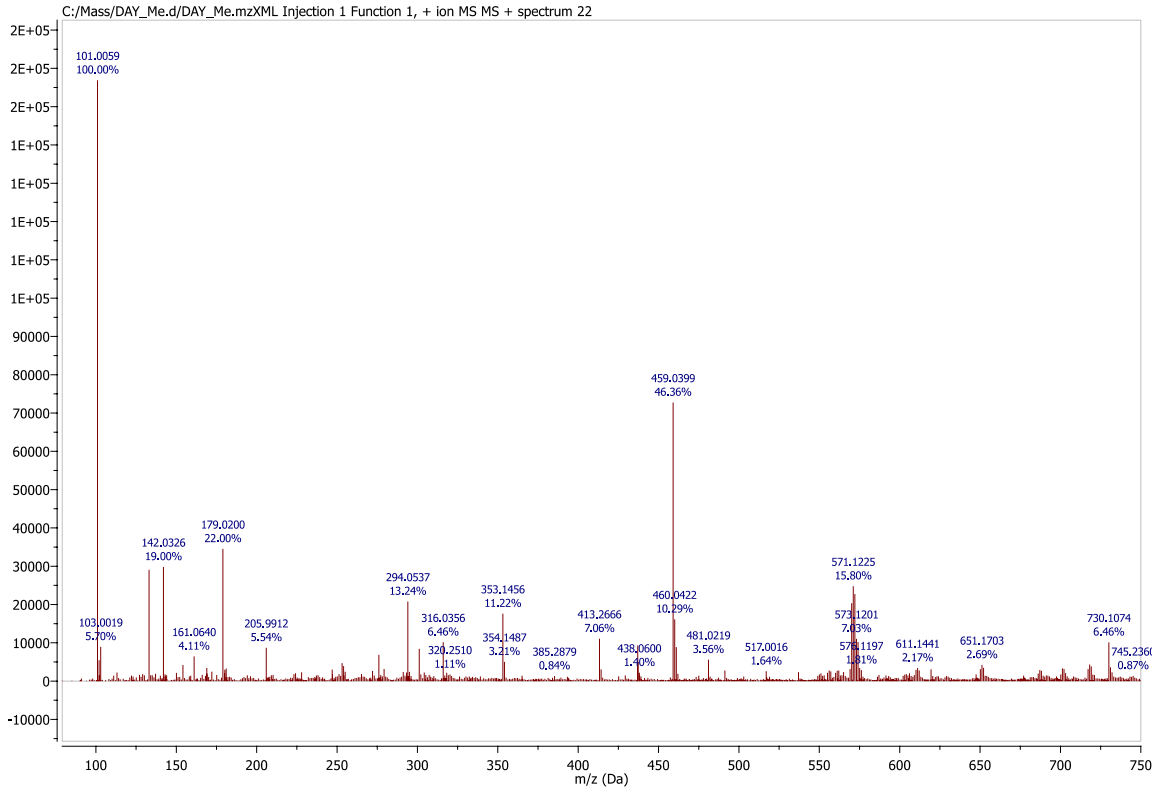


Figure S18. HRESI-MS$^+$ spectrum of **1**.

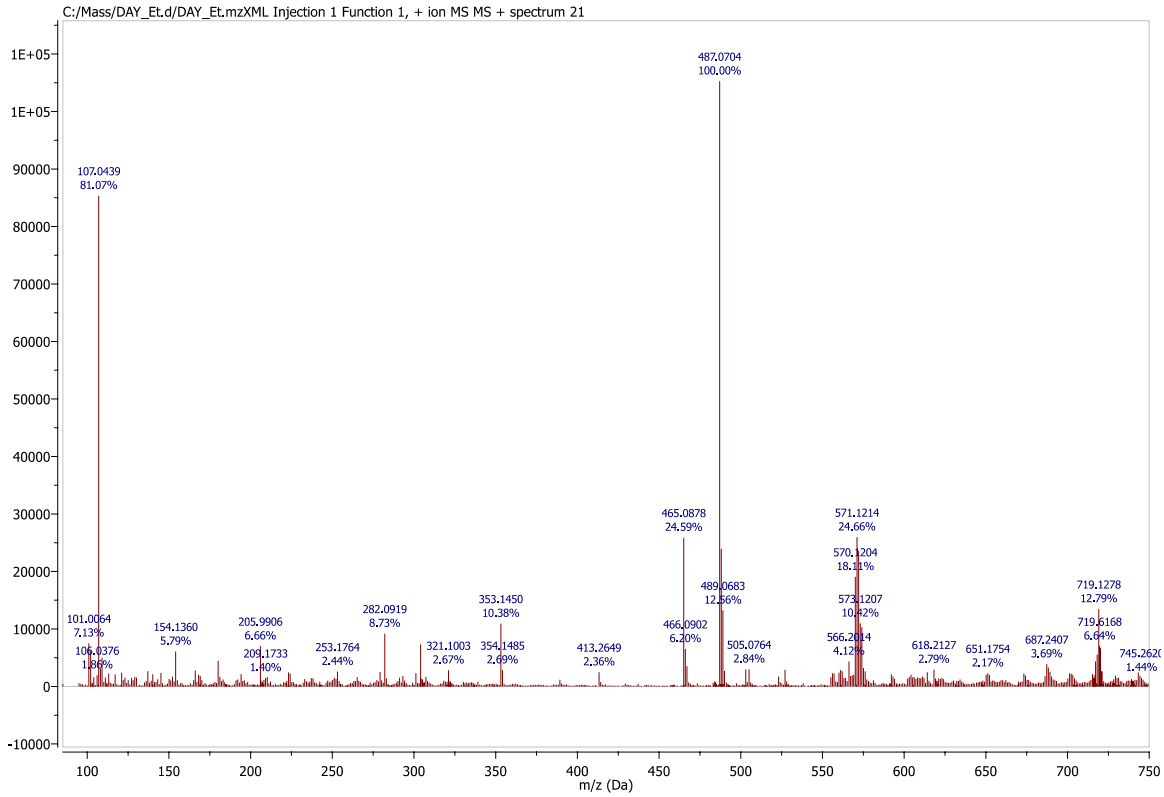


Figure S19. HRESI-MS$^+$ spectrum of **2**.

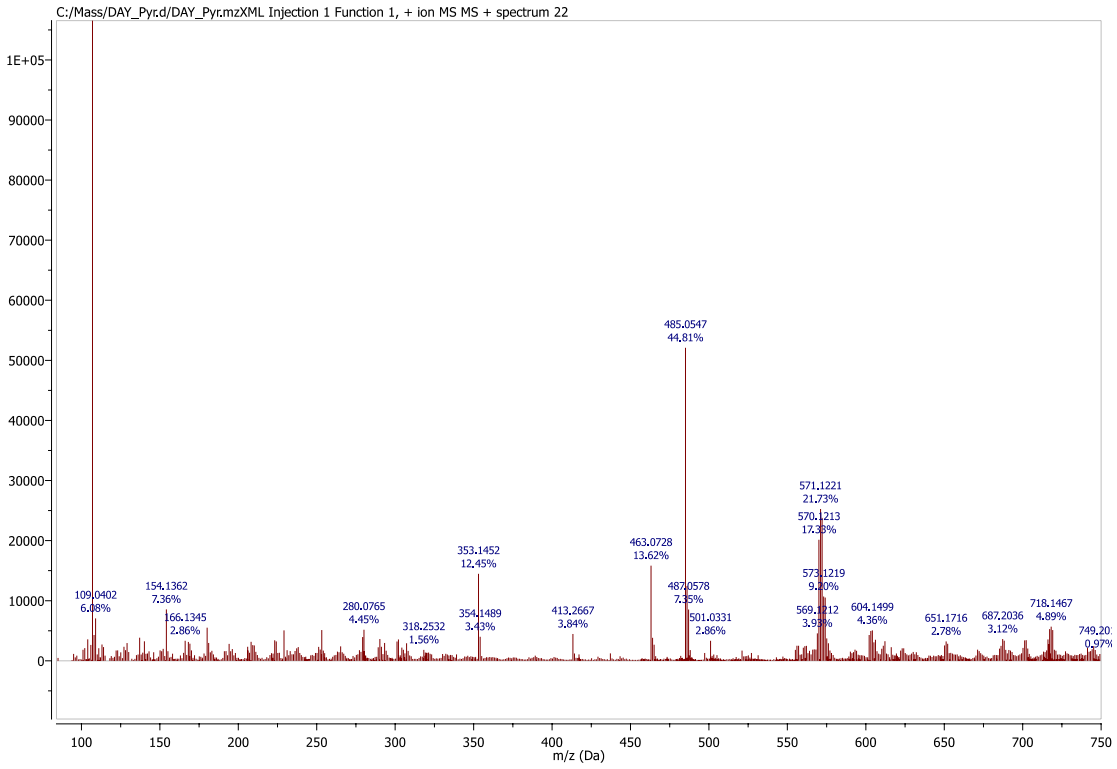


Figure S20. HRESI-MS$^+$ spectrum of **3**.

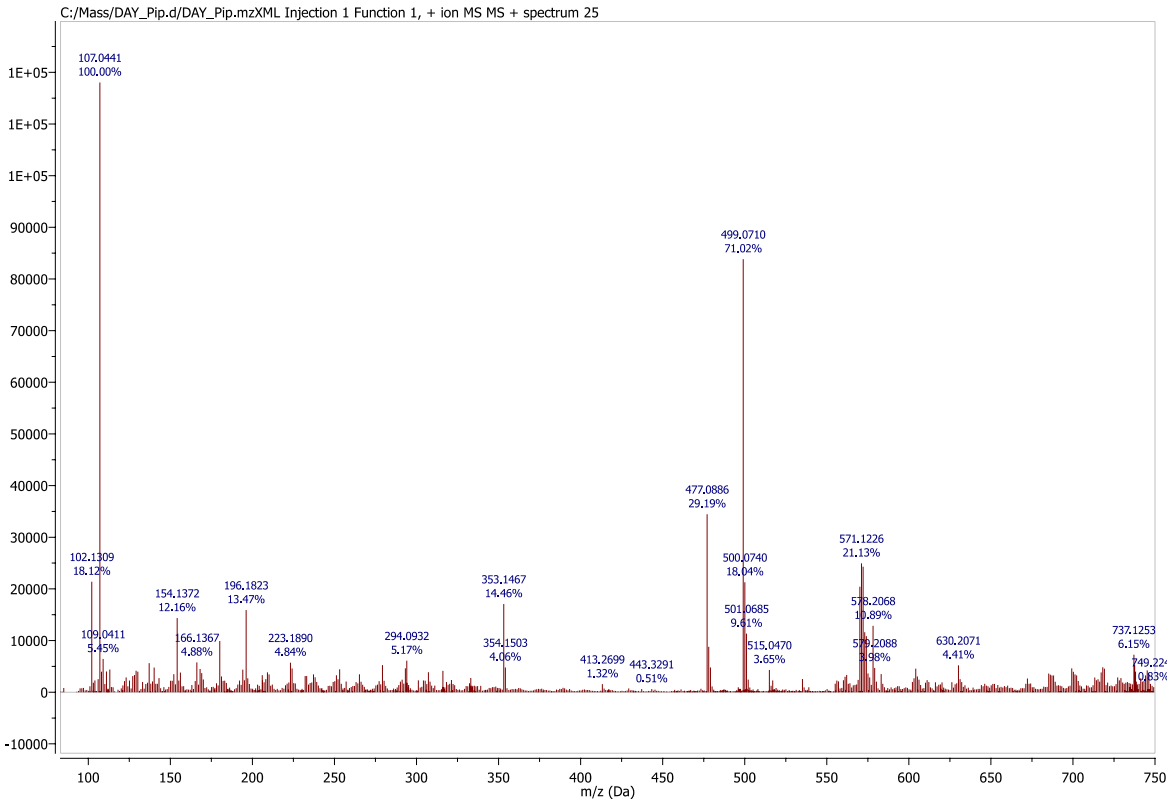


Figure S21. HRESI-MS$^+$ spectrum of **4**.

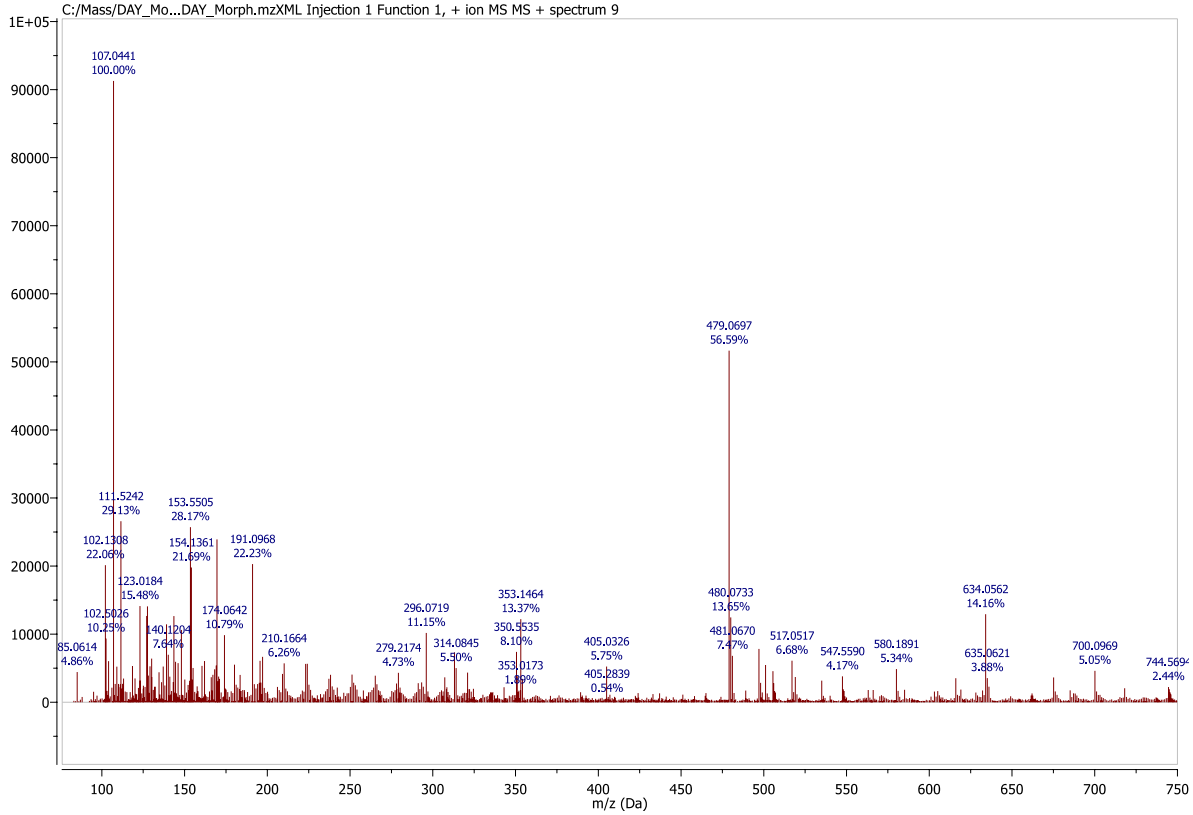


Figure S22. HRESI-MS$^+$ spectrum of **5**.

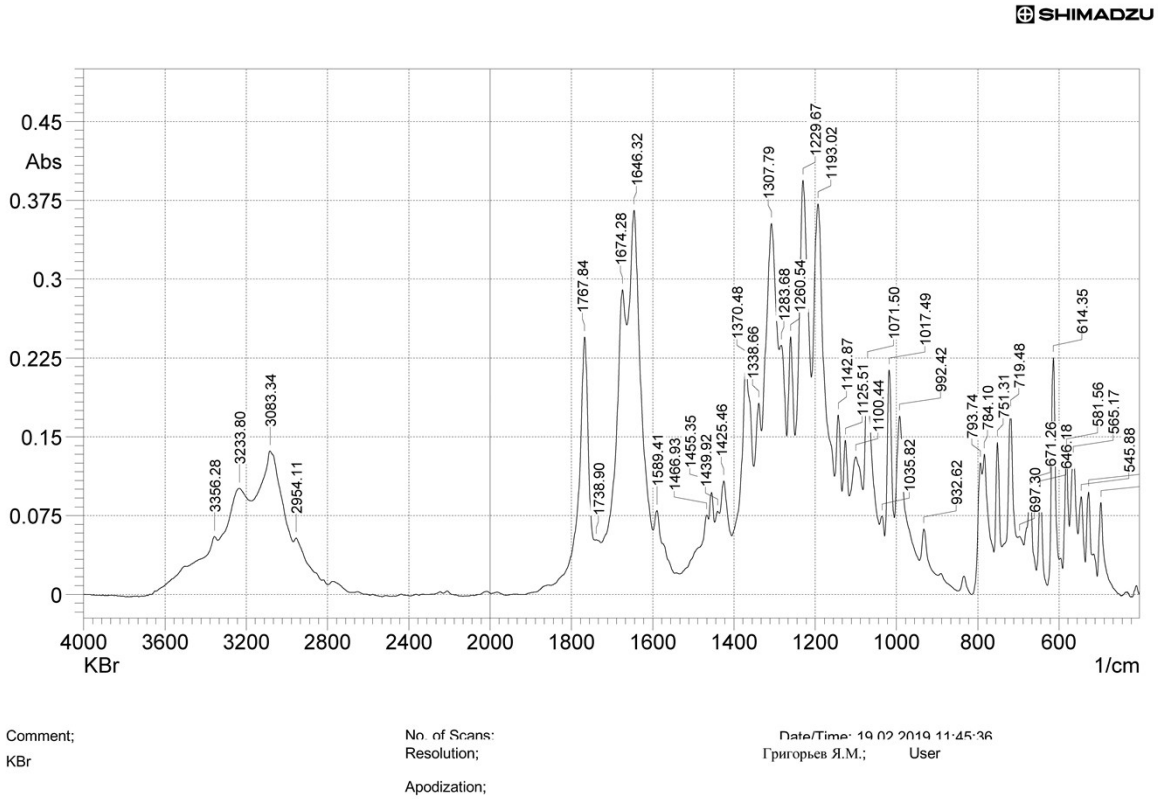


Figure S23. IR spectrum of **1**.

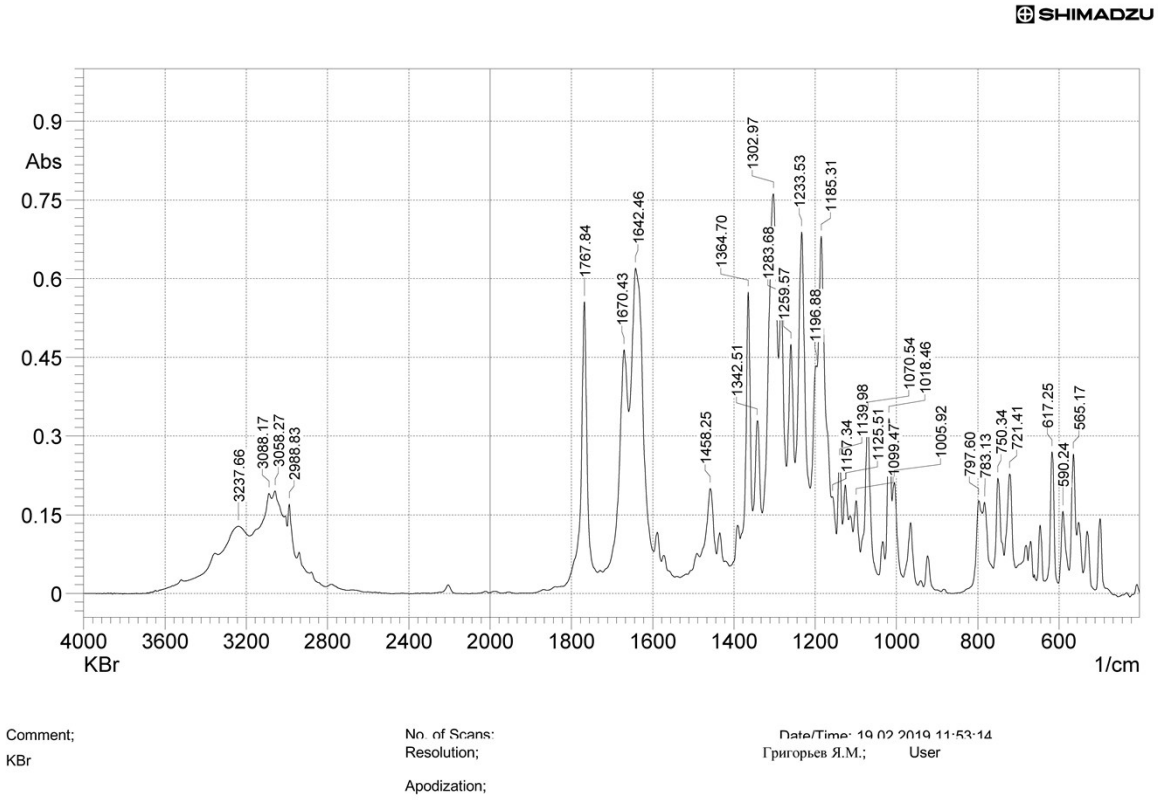


Figure S24. IR spectrum of **2**.

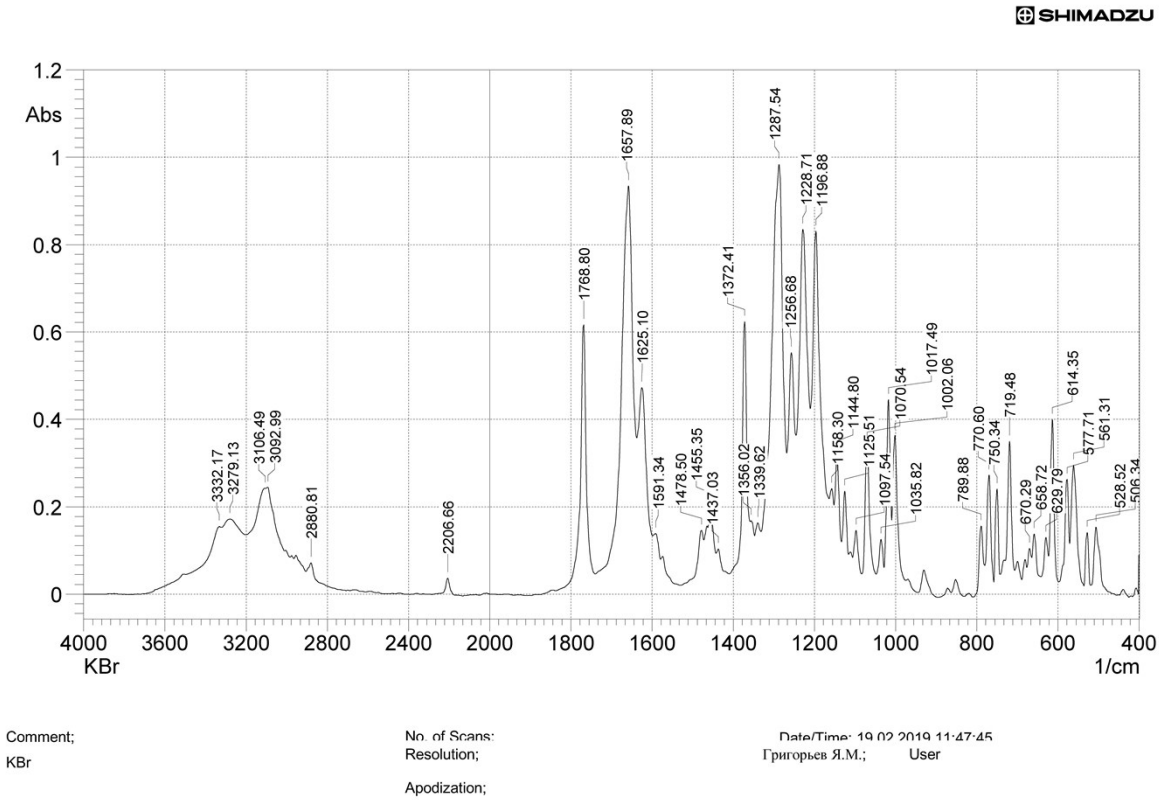


Figure S25. IR spectrum of **3**.

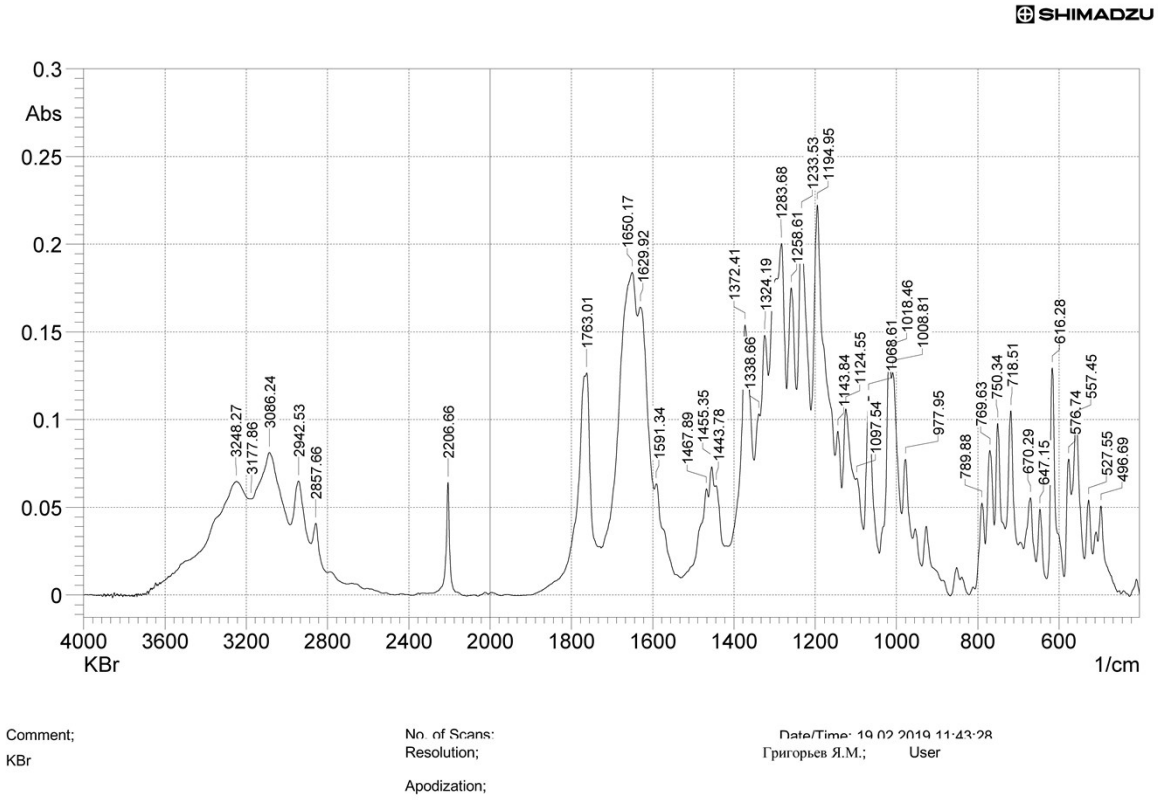


Figure S26. IR spectrum of **4**.

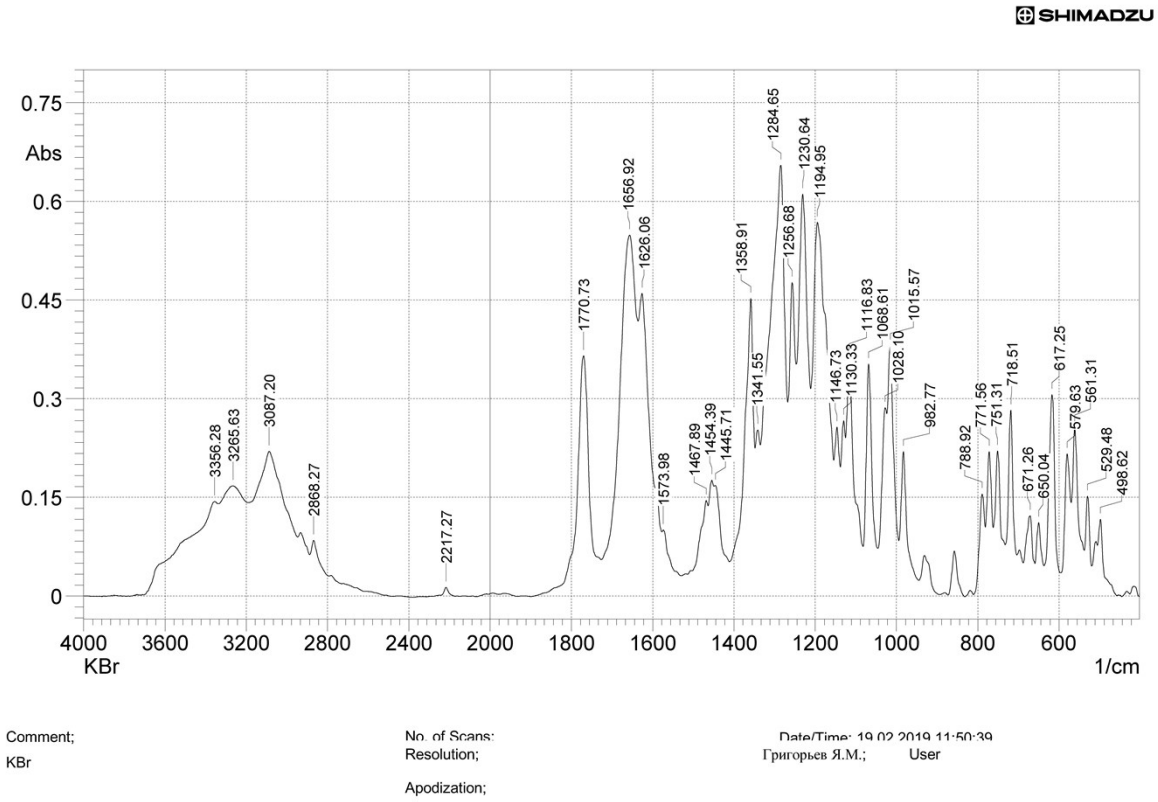


Figure S27. IR spectrum of **5**.

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