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Oxidation step in the preparation of benzocamalexin: the crystallographic evidence

Yordan Stremski, Anife Ahmedova, Anna Dołęga, Stela Statkova-Abeghe and Desislava Kirkova

Contents

Complete experimental procedures – synthesis and spectroscopic characterization

General information: All reagents and solvents were obtained from commercial suppliers (Sigma-Aldrich or Merck) and were used without further purification. Melting points were taken on Boetius hot stage apparatus and are not corrected. NMR spectra were measured on Bruker Avance AV600 (600/150 MHz $^{1}H/^{13}C$) spectrometer at BAS-IOCCP—Sofia and chemical shifts (δ, ppm) are downfield from TMS. High resolution mass spectral measurements were performed on a Thermo Scientific Q Exactive hybrid quadrupole-orbitrap mass spectrometer. IR spectra were measured on VERTEX 70 FT-IR spectrometer (Bruker Optics, Germany). TLC was done on aluminium-backed Silica gel 60 sheets.

Synthesis and characterization

[2-(1H-indol-3-yl)benzo[d]thiazol-3(2H)-yl](phenyl)methanone **1**:

To benzothiazole (1 mmol) dissolved in dry 1,2-dichloroethane (7 mL) were added sequentially benzoyl chloride (1 mmol) and indole (1 mmol). Triethylamine (1 mmol) dissolved in 1,2-dichloroethane (2 mL) was added slowly (for 30 minutes) as hydrochloric acceptor. The reaction mixture was stirred for 2 h at room temperature. After completion of the reaction (monitored by TLC), CH_2Cl_2 (30 mL) was added, and the mixture was treated successively with HCl (10%, 30 mL), Na_2CO_3 (3% aq., 30 mL) and water (2x30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The product **1** was purified by column chromatography on neutral alumina using as eluents mixture of petroleum/diethyl ether (1:1); white solid; Yield: 60%; mp = 190–193 ^{o}C;

^{1}H-NMR (600 MHz, 20 ^{o}C, $CDCl_3$, δ ppm, *J* Hz): 7.02 – 7.50 (m, 14H) 7.34 (s, 1H), 8.28 (br s, 1H);

^{13}C-NMR (150 MHz, 20 ^{o}C, $CDCl_3$, δ ppm): 64.1, 111.6, 116.7, 119.3, 120.0, 120.2, 122.6, 122.7, 123.4, 124.1, 124.9, 125.7, 127.1, 127.6, 128.5, 128.9, 131.0, 132.4, 135.3, 136.7, 138.2, 165.1;

IR (KBr, cm^{-1}): 3378, 3303, 1659, 1627, 1574, 1547, 1463, 1377, 748;

HRMS m/z (ESI): calcd for $C_{22}H_{16}N_2NaOS^+$ $[M+Na]^+$ 379.0876, found 379.0872;

Benzocamalexin, 2-(1H-indol-3-yl)benzo[d]thiazole **2**:

Purified product **1** (0.3 mmol) was dissolved in MeCN (5 mL), 1.5 eq *o*-chloranil (3,4,5,6-tetrachloro-1,2-benzoquinone, 0.45 mmol) was added, and the reaction mixture was stirred at 25 ^{o}C for 2 h (monitored by TLC). The solvent was removed in vacuo, CH_2Cl_2 (30 mL) was added, and the mixture was treated with water (30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The crude residue was chromatographically purified on neutral

Al_2O_3 with eluents mixture of petroleum/diethyl ether (3:1, with increasing polarity to 2:1); Benzocamalexin **2** was recrystallized with diethyl ether to give colourless crystals in 96% yield; mp = 171–172 ^oC;

^{1}H-NMR (600 MHz, 20 ^oC, DMSO-d_6, δ ppm, *J* Hz): 7.27 (m, 2H), 7.36 (m, 1H), 7.48 (m, 1H), 7.53 (m, 1H), 7.97 (d, *J* = 8.2, 1H), 8.05 (d, *J* = 8.2, 1H), 8.28 (s, 1H), 8.39 (m, 1H), 11.97 (s, 1H);

^{13}C-NMR (150 MHz, 20 ^oC, DMSO-d_6, δ ppm): 110.9, 112.8, 121.2, 121.6, 122.1, 122.2, 123.2, 124.7, 125.0, 126.6, 129.4, 133.5, 137.3, 154.2, 163.4;

IR (KBr, cm^{-1}): 3218, 2963, 1594, 1552, 1443, 1246, 749;

HRMS m/z (ESI): calcd for $C_{15}H_{11}N_2S^+$ $[M+H]^+$ 251.0637, found 251.0634, calcd for $C_{15}H_9N_2S^-$ $[M-H]^-$ 249.0492, found 249.0499;

^{1}H-NMR, ^{13}C-NMR, IR and MS data for compound 1

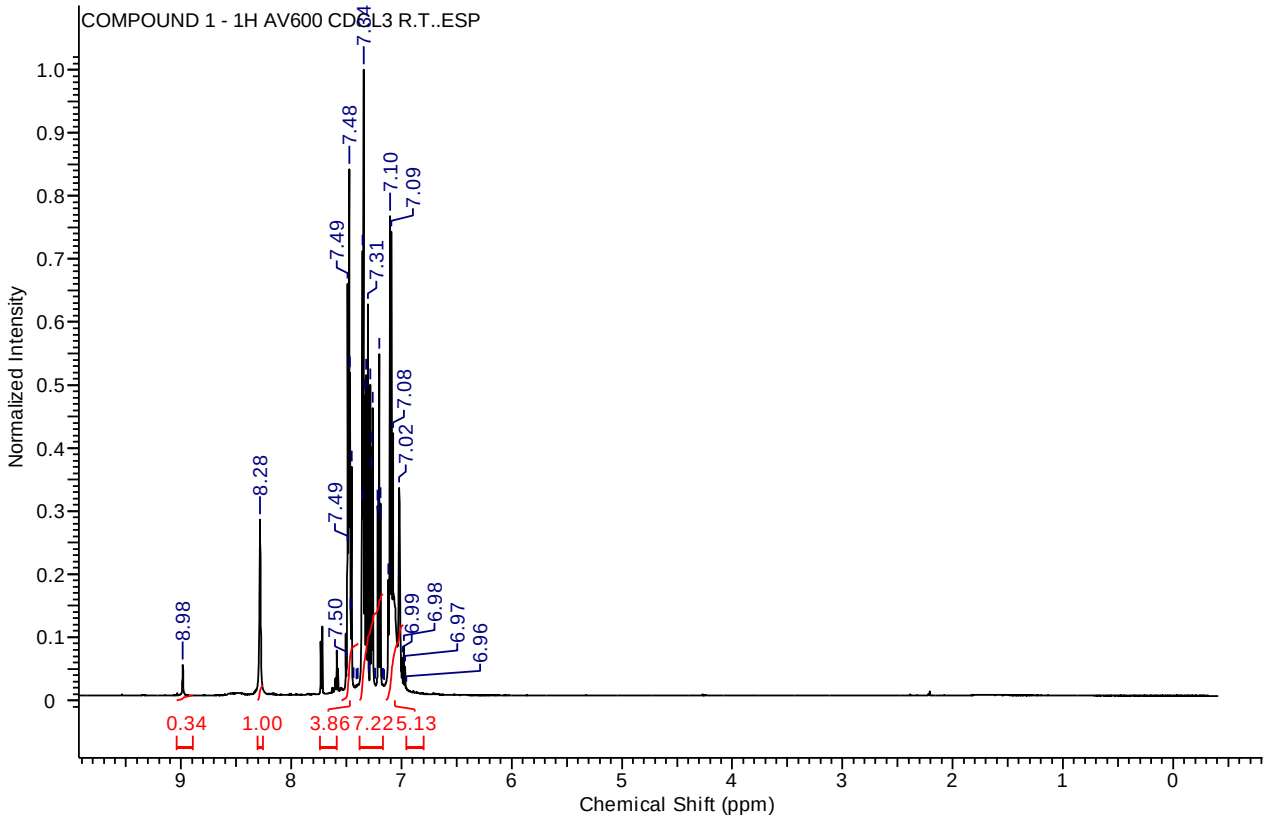

Figure S1. ^{1}H-NMR spectrum ($CDCl_3$, RT, 600 MHz) of compound **1**.

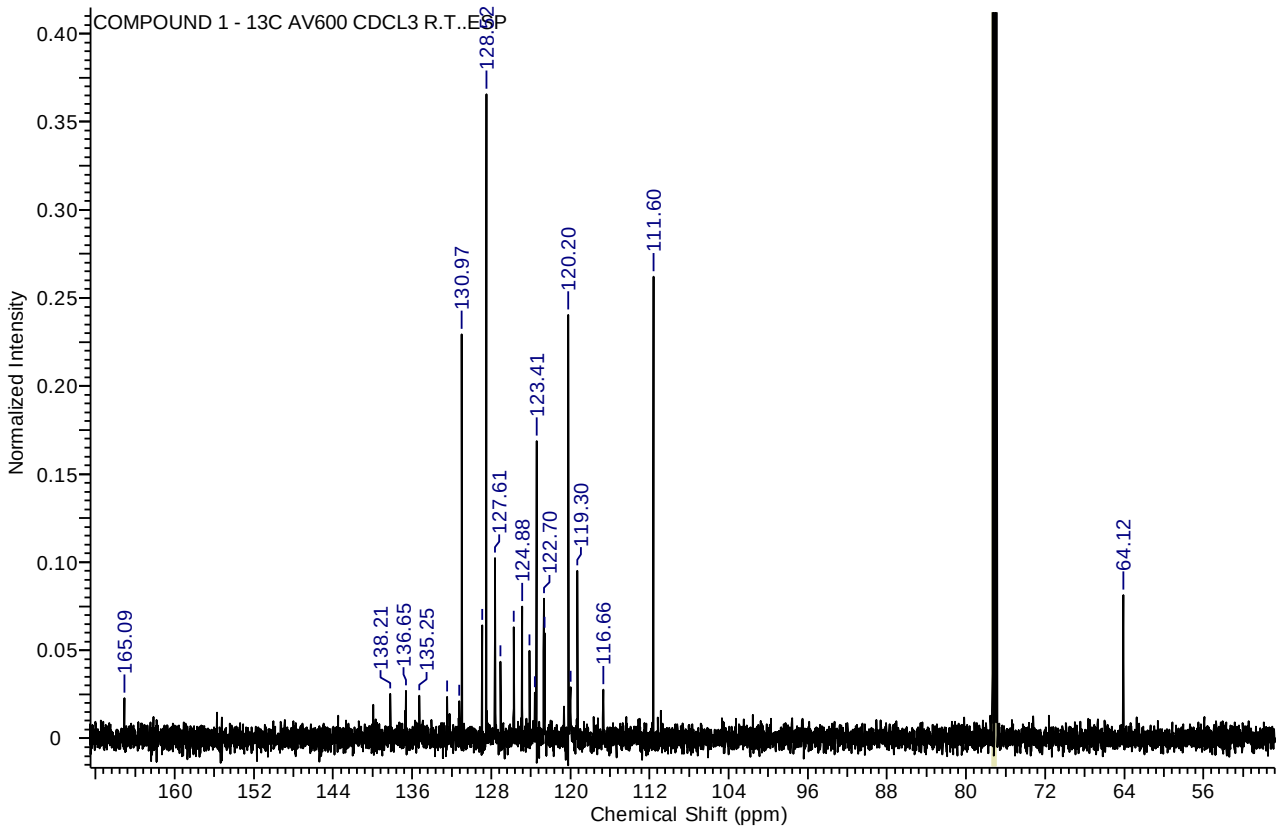

Figure S2. ^{13}C-NMR spectrum ($CDCl_3$, RT, 150 MHz) of compound **1**.

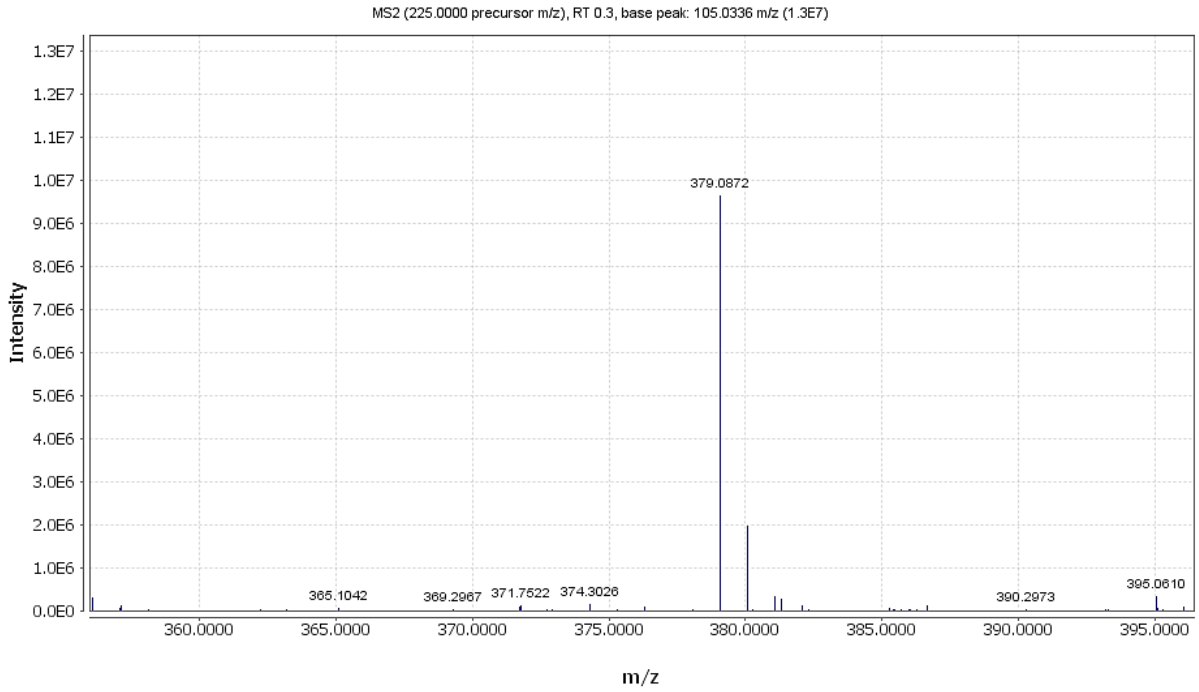

Figure S3. HRMS-ESI (positive mode) of compound **1**.

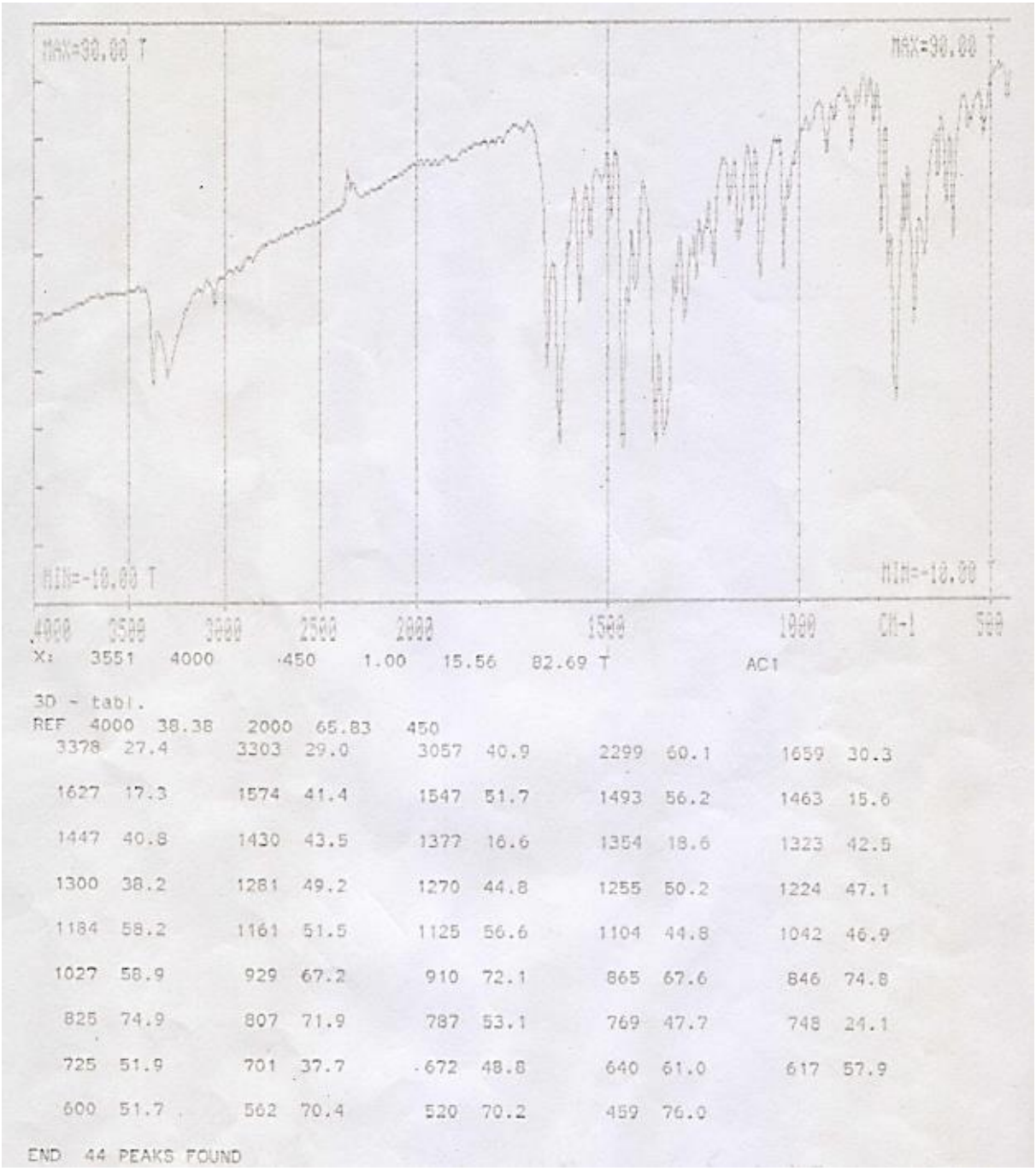

Figure S4. IR spectrum (KBr) with list of vibration frequencies (cm^{-1}) of compound **1**.

^{1}H-NMR, ^{13}C-NMR, IR and MS data for benzocamalexin **2**

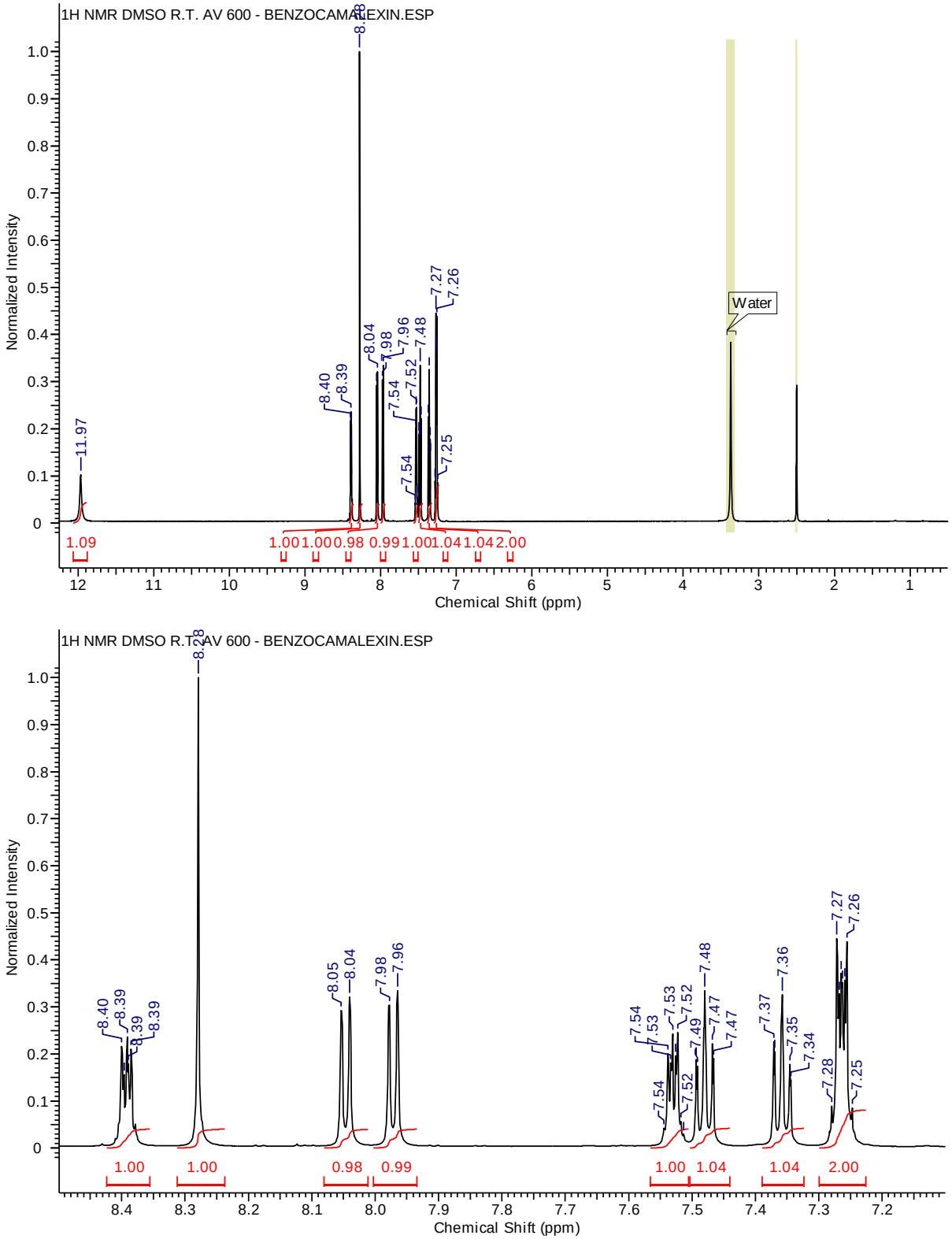

Figure S5. ^{1}H-NMR spectrum (DMSO-d_6, RT, 600 MHz) of compound **2** – top: full-range spectrum; bottom: spectrum with peak integrations.

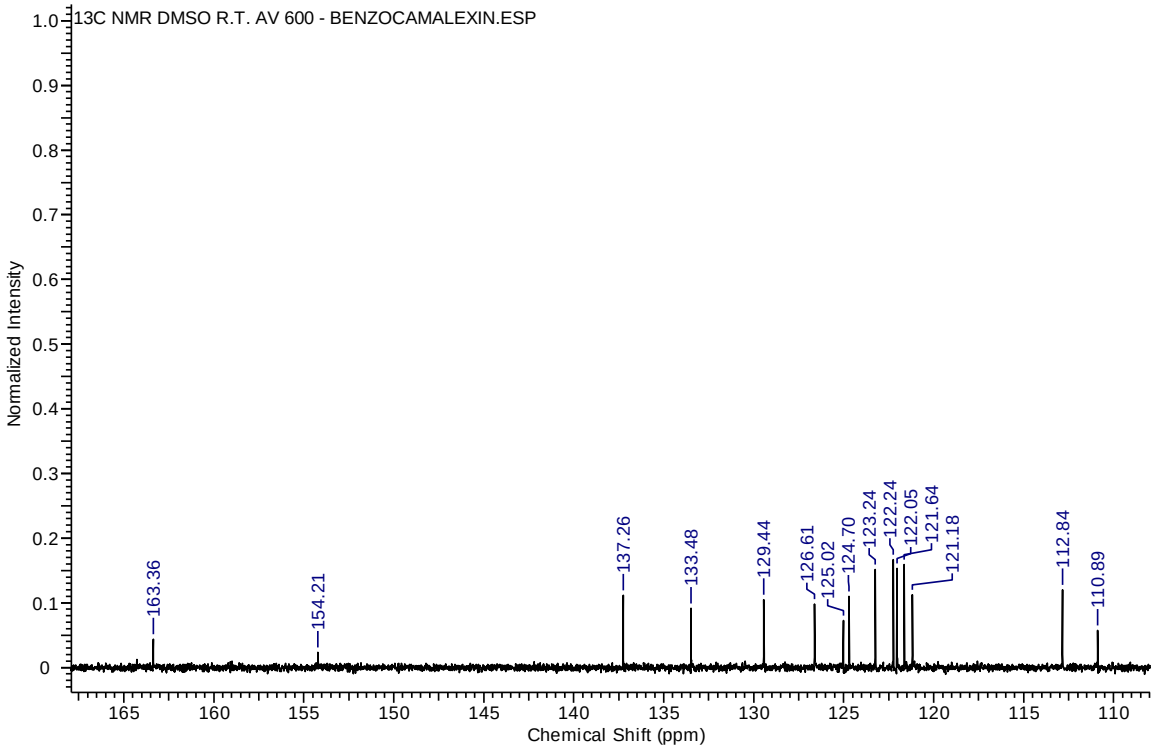

Figure S6. ^{13}C-NMR spectrum (DMSO-d_6, RT, 150 MHz) of compound **2**.

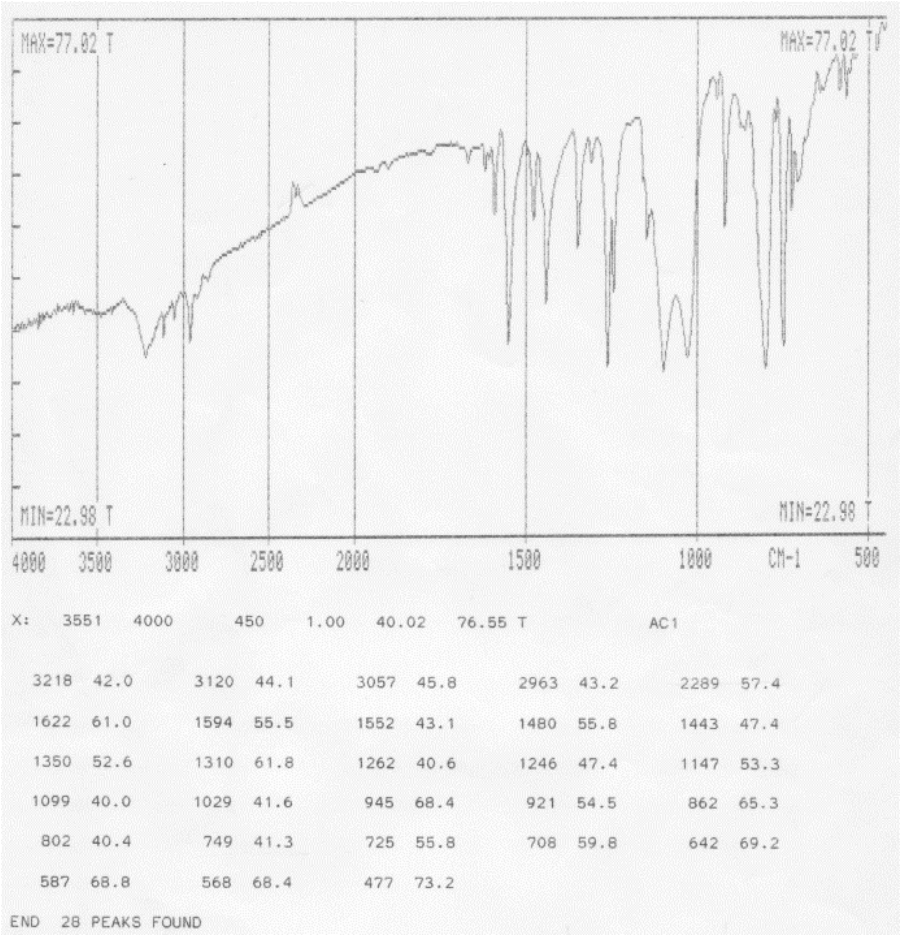

Figure S7. IR spectrum (KBr) with list of vibration frequencies (cm^{-1}) of compound **2**.

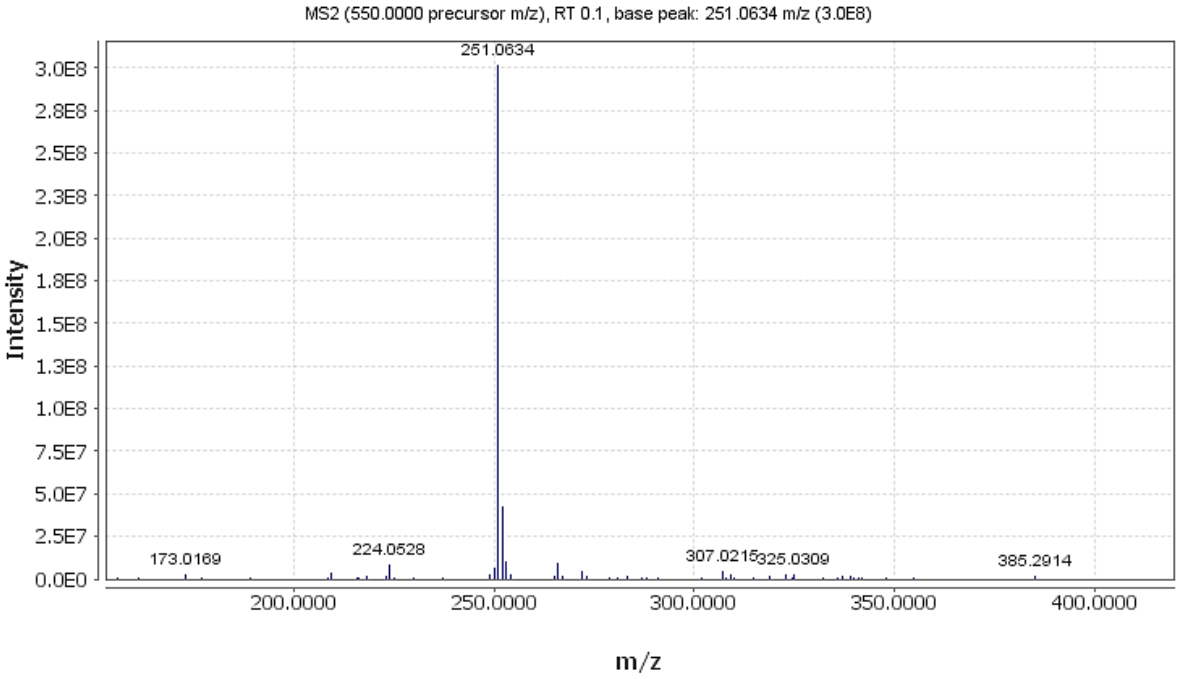

Figure S8. HRMS-ESI (positive mode) of compound **2**.

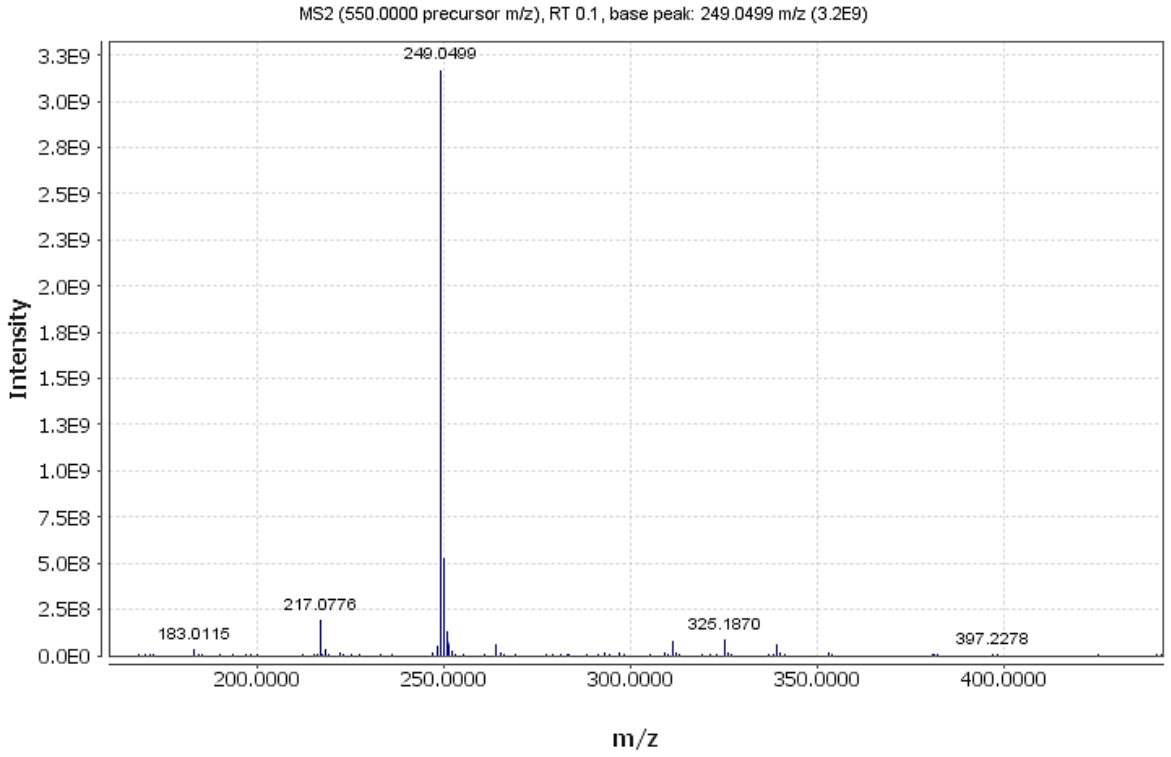

Figure S9. HRMS-ESI (negative mode) of compound **2**.

Crystallographic data

Table S1. Selected experimental bond lengths of benzocamalexin **2** and perchloro-1,2-phenylene dibenzoate **3**, for the atoms numbering see Figs. 1 and 3 (main text), respectively.

Benzocamalexin **2**		compound **3**	
bond	**length (Å)**	**bond**	**length (Å)**
S1 – C2	1.729(10)	Cl1 – C9	1.716(2)
S1 – C1	1.751(10)	Cl2 – C10	1.721(2)
N1 – C3	1.410(11)	O2 – C8	1.383(2)
N1 – C1	1.324(13)	C8 – C13	1.382(3)
N2 – C9	1.370(12)	O2 – C7	1.384(3)
N2 – C10	1.389(13)	O1 – C7	1.198(3)
C1 – C8	1.435(13)	C7 – C1	1.480(3)

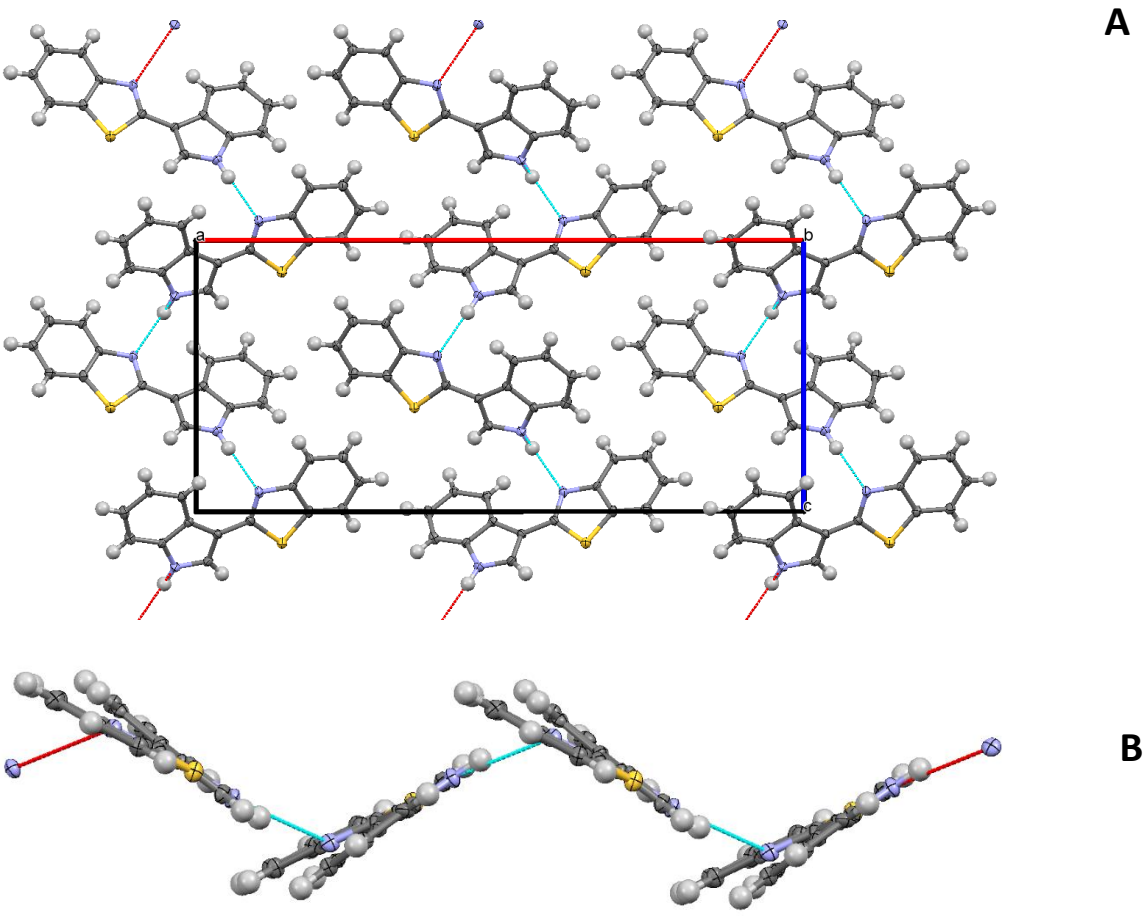

Figure S10. Intermolecular hydrogen bonding network of benzocamalexin (**2**): A) packing view along b-axis; B) side view of the zig-zag chain.