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Synthesis and structure of new 2-aryl-substituted pyrrolidines containing phosphine oxide group

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Experimental Section

General

NMR experiments were recorded on a Bruker AVANCE-600 spectrometer at 303 K equipped by 5 mm broadband probe head working at 600.1 MHz in ^{1}H and 150.9 MHz in ^{13}C experiments. The ^{31}P NMR spectra were obtained on a Bruker MSL-400 NMR-Fourier spectrometer. Chemical shifts were measured relative to residual protons (^{1}H) or solvent signal (^{13}C). The pulse programs of the COSY, NOESY, HSQC and HMBC experiments were taken from Bruker software library. NMR-experiments were carried out in solutions (30 mmol·l^{-1}) at 303 K. The IR spectra of the compounds as emulsions in Nujol were recorded on a Vector 22 FTIR Spectrometer (Bruker) in the 4000–400 cm^{-1} range at a resolution of 1 cm^{-1}. MALDI mass spectra were run on an Ultra Flex III TOF/TOF mass spectrometer (Bruker Daltonic, Bremen, Germany) operated in the linear mode. Elemental microanalyses data were obtained on a CHN-3 analyzer and they were within ±0.4% of the theoretical values for C and H. The uncorrected melting points were measured on a Boetius hot-stage apparatus. All solvents were dried according to standard protocols.

Synthesis

*General procedure for the synthesis of [(pyrrolidin-1-yl)methyl]phosphine oxides **3a-c**.*
To the appropriate resorcinol **2a-c** (1.27 mmol) dissolved in dry benzene (7 ml), *P*-(4,4-diethoxybutylaminomethyl)-*P,P*-di-*p*-tolylphosphine oxide **1** (0.4 g, 1.28 mmol) and trifluoroacetic acid (0.2 ml, 2.5 mmol) were added. The mixture was stirred for 24 h at room temperature. The benzene layer was decanted, the oily residue was dried in vacuum, washed with diethyl ether, filtered off, and dried in vacuum to give the desired product.

2-(2,4-Dihydroxyphenyl)-1-(di-*p*-tolylphosphorylmethyl)pyrrolidin-1-ium trifluoroacetate 3b. Yield: 0.36 g (67%), m.p. 130 – 132ºC. IR (KBr, ν/cm^{-1}):1177, 1220 (P=O), 1602 (C=C$_{arom}$), 1677 (C=O), 2588 – 2710 (NH^{+}), 3057, 3395 (OH). ^{31}P NMR (242.9 MHz), δ: 24.9. ^{1}H NMR (600.1 MHz, acetone-d_6) δ: 2.14 – 2.31 (m, 4H, CH$_2$), 2.40 (s, 3H, CH$_3$), 2,41 (s, 3H, CH$_3$), 3.29 – 3.32 (m, 1H, NCH$_2$), 3.85 – 3.88 (m, 1H, NCH$_2$), 4.00 (dd, 1H, CH$_2$P, $^{2}J_{PH}$ 5.6 Гц, $^{2}J_{HH}$ 15.2 Гц), 4.09 – 4.13 (m, 1H, CH$_2$P, $^{2}J_{HH}$ 15.1 Hz, $^{2}J_{PH}$ 7.13 Hz), 4.68 (t, 1H, CH, $^{2}J_{HH}$ 8.5 Hz), 6.36 (d, 1H, ArH, $^{3}J_{HH}$ 8.3 Hz), 6.69 (s, 1H, ArH), 7.10 (d, 1H, ArH, $^{3}J_{HH}$ 8.3 Hz), 7.34 – 7.35 (m, 2H, ArH),7.37 – 7.38 (m, 2H, ArH), 7.62 (dd, 2H, ArH, $^{3}J_{HH}$ 11.9 Hz, $^{3}J_{HP}$ 10.9 Hz), 7.72 (dd, 2H, ArH, $^{3}J_{HH}$ 11.9 Hz, $^{3}J_{HP}$ 7.2 Hz). ^{13}C NMR (150.9 MHz, acetone-d_6) δ: 21.12 (s, C-16), 22.79 (s, C-8), 50.91 (d, C-11, $^{1}J_{PC}$ 72.2 Hz), 55.61 (s, C-10), 71.59 (d, C-7, $^{3}J_{PC}$ 7.5 Hz), 104.03 (C-5), 107.77 (C-6), 110.92 (C-1), 114.35 (q, CF$_3$, $^{1}J_{CF}$ 292.7 Hz), 127.29 (d, C-12, $^{1}J_{PC}$ 121.3Hz), 128.09 (d, C-12', $^{1}J_{PC}$ 121.1 Hz), 130.11 (d, C-14, $^{1}J_{PC}$ 12.4 Hz), 130.19 (d, C-14', $^{1}J_{PC}$ 12.2 Hz), 131.00 (s, C-3), 131.30, 131.37 (s, C-13), 143.85 (s, C-15), 158.02 (s, C-2),

160.02 (q, C=O, $^{2}J_{CF}$ 34.8 Hz), 160.47 (s, C-4). ^{31}P NMR (242.9 MHz), δ: 24.9. MS (MALDI), m/z: 422 [*M*+H]$^{+}$. Found (%): C, 60.60; H, 5.60; F, 10.54; N, 2.58; P, 5.76. Calc. for $C_{25}H_{28}NO_3P$*CF_3COOH (%): C, 60.56; H, 5.46; F, 10.64; N, 2.62; P, 5.78.

1-(Di-*p*-tolylphosphorylmethyl)-2-(2,3,4-trihydroxyphenyl)pyrrolidin-1-ium trifluoro-acetate 3c. Yield 0.4 g (73%), m.p. 126 – 127ºC. IR (KBr, ν/cm^{-1}): 1198 (P=O), 1602 (C=C), 1676 (C=O), 2754 (NH^{+}), 3150, 3391 (OH). ^{1}H NMR (400.1 MHz, acetone-*d*$_6$) δ: 2.1 – 2.23 (m, 4H, CH_2), 2.38 (s, 3H, CH_3), 2,39 (s, 3H, CH_3), 3.28 – 3.35 (m, 1H, NCH_2), 3.86 – 3.92 (m, 1H, NCH_2), 3.96 (dd, 1H, CH_2P, $^{2}J_{HH}$ 15.3 Hz, $^{2}J_{PH}$ 5.8 Hz), 4.08 (dd, 1H, CH_2P, $^{2}J_{HH}$ 15.3 Hz, $^{2}J_{PH}$ 7.1 Hz), 4.67 – 4.71 (m, 1H, $CHCH_2$), 6.36 (d, 1H, ArH, $^{3}J_{HH}$ 8.4 Hz), 6.96 (d, 1H, ArH, $^{3}J_{HH}$ 8.4 Hz), 7.30 – 7.33 (m, 2H, ArH), 7.35 – 7.38 (m, 2H, ArH), 7.53 – 7.58 (m, 2H, ArH), 7.66 – 7.71 (m, 2H, ArH). ^{13}C NMR (150.9 MHz, acetone-*d*$_6$) δ: 20.68 (s, C-16), 22.33 (s, C-8), 29.26 (s, C-9), 50.15 (s, C-11, $^{1}J_{PC}$ 72.2 Hz), 55.54 (s, C-10), 71.11 (d, C-1, $^{3}J_{PC}$ 6.9 Hz), 107.31 (s, C-5), 111.07 (s, C-1), 115.42 (q, CF_3, $^{1}J_{CF}$ 293.1 Hz), 119.17 (s, C-6), 126.12 (d, C-12, $^{1}J_{PC}$ 105.6 Hz), 126.82 d (12'-C, $^{1}J_{PC}$ 105.6 Hz), 129.71, 129.82 (d, C-14, $^{3}J_{PC}$ 12.5 Hz), 130.68, 130.78 (d, C-13, $^{2}J_{PC}$ 18.3 Hz), 133.33 (s, C-3), 132.77 (s, C-15), 143.65 (s, C-2), 146.20 (s, C-4), 160.01 (q, C=O, $^{2}J_{CF}$ = 34.5 Hz). ^{31}P NMR (242.9 MHz) δ: 25.2. MS (MALDI), m/z: 438 [*M*+H]$^{+}$. Found (%): C, 58.48; H, 5.34; F, 10.25; N, 2.51; P, 5.64. Calc. for $C_{25}H_{28}NO_4P$*CF_3COOH (%): C, 58.80; H, 5.30; F, 10.33; N, 2.54; P 5.62.

X-ray diffraction data

The X-ray diffraction data for the crystal of **4** were collected on Bruker Apex Smart CCD diffractometer with graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by direct methods using the SHELXS program [S1]. Non-hydrogen atoms were first refined in the isotropic approximation and then anisotropic using the SHELXL-14 program [S2]. Hydrogen atoms were placed in the calculated positions and refined in the riding model. All calculations were performed using the WinGX [S3] and APEX2 [S4] programs. The figures were made using the OLEX2 [S5] program. CCDC 1585981 contains 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.

Crystallographic data for **4**: crystals of $C_{55}H_{66}N_2O_7P_2$ (M = 929.03) are triclinic, space group P-1, at 296 K: a = 10.338(4), b = 15.622(6) and c = 16.489(6) Å, α = 80.468(5), β = 80.247(5), γ = 79.930(5)°, V = 2558.6(16) Å^3, Z = 2, dcalc = 1.206 g cm^{-3}, μ(Mo) = 0.138 mm^{-1}, F(000) = 992. 18889 reflections were measured and 8963 independent reflections (Rint = 0.1477) were used in a further refinement. The refinement converged to wR2 = 0.1960 and GOF = 0.803 for all independent reflections [R_1 = 0.0660 was calculated against F for 2698 observed reflections with I > 2σ(I)].

Table S1. H-bond in crystal of compound **4**.

H-bond	D - H	H...A	D...A	D - H...A
O2B-H2B...N1B	0.82	2.10	2.795(6)	142
O4A-H4A...O1A	0.82	1.83	2.644(6)	174
O4B-H4B...O1B	0.82	1.83	2.644(6)	175
O6A-H6A...N1A	0.82	1.97	2.706(6)	148
C6B-H6B...O6A	0.93	2.51	3.431(7)	171
C24A-H24A...O6A	0.93	2.60	3.483(7)	159
C26A-H26B...O4A	0.96	2.30	2.761(8)	109
C26B-H26D...O2B	0.96	2.40	2.832(7)	107

Table S2. C-H…π interactions in crystal of compound **4**.

Interaction	H..Cg	H-Perp	Gamma	X-H..Cg	X..Cg	X-H,Pi
C16A-H16A...Cg6	2.99	2.89	15.32	151	3.864(7)	46
C21A-H21A...Cg7	2.99	-2.89	14.96	129	3.654(7)	47
C21B-H21B…Cg3	2.93	-2.92	4.22	141	3.702(7)	55

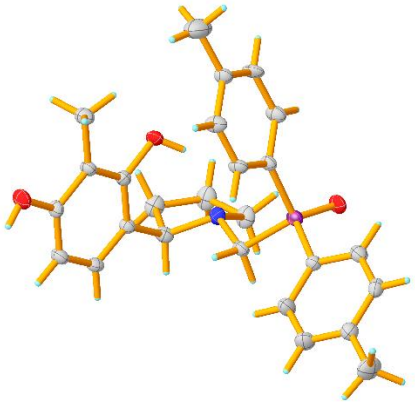


Figure S1. Molecular structure of compound **4** in crystal.

Investigated crystal is the solvate with the ratio of compound **4** and acetone 2:1. There are two molecules of pyrrolidine and one molecule of acetone in independent part of a unit cell. The bond lengths, valence and torsion angles in molecules of compound 1 in a crystal are within the standard values for each type of chemical bond [S6] (Figure S1). The crystal structure of compound 4 consists of chains formed by classical O-H…O=P hydrogen bonds. Chains are connected with each other by C-H…O and CH...π interactions (Figure S2, Tables S1 and S2).

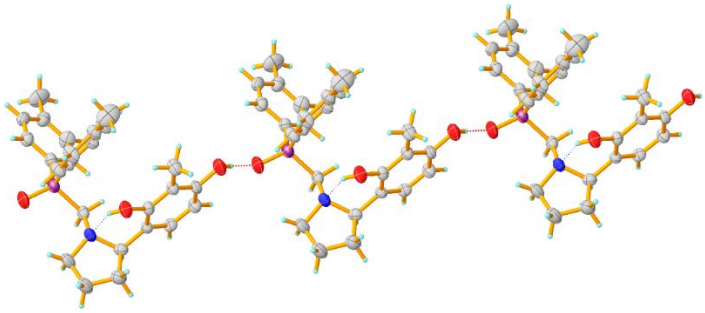
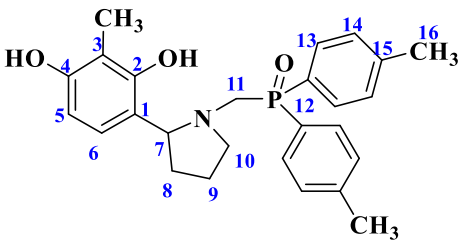


Figure S2. H-bonds in crystal of compound **4**.



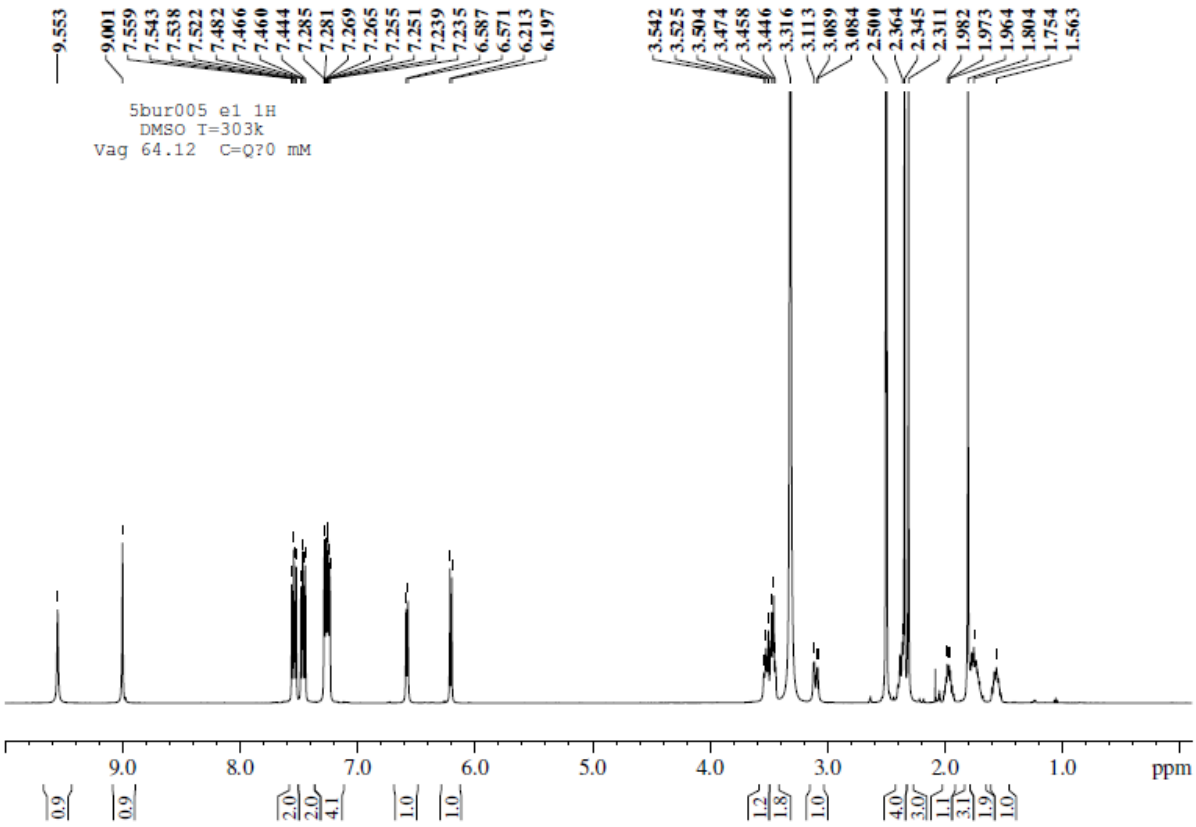


Figure S3. [1]H NMR Spectrum of compound **4** (DMSO-d_6).

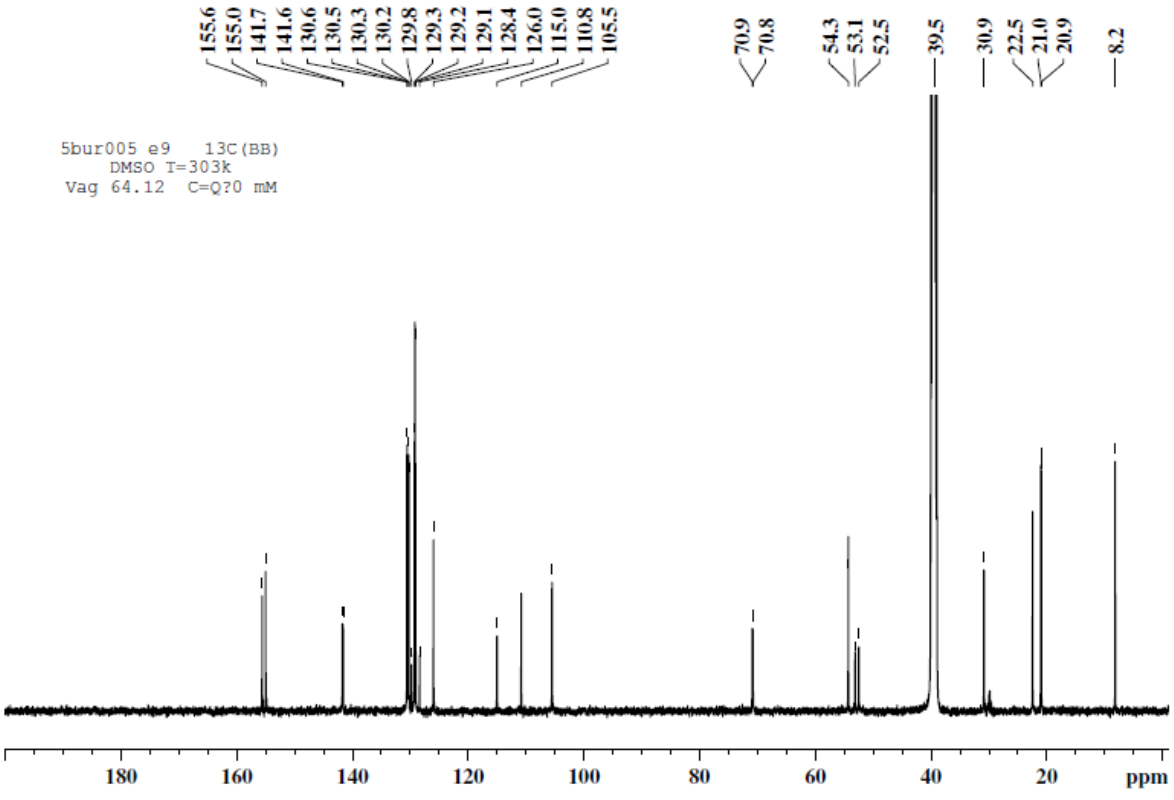


Figure S4. [13] C spectrum of compound **4** (DMSO-d_6)

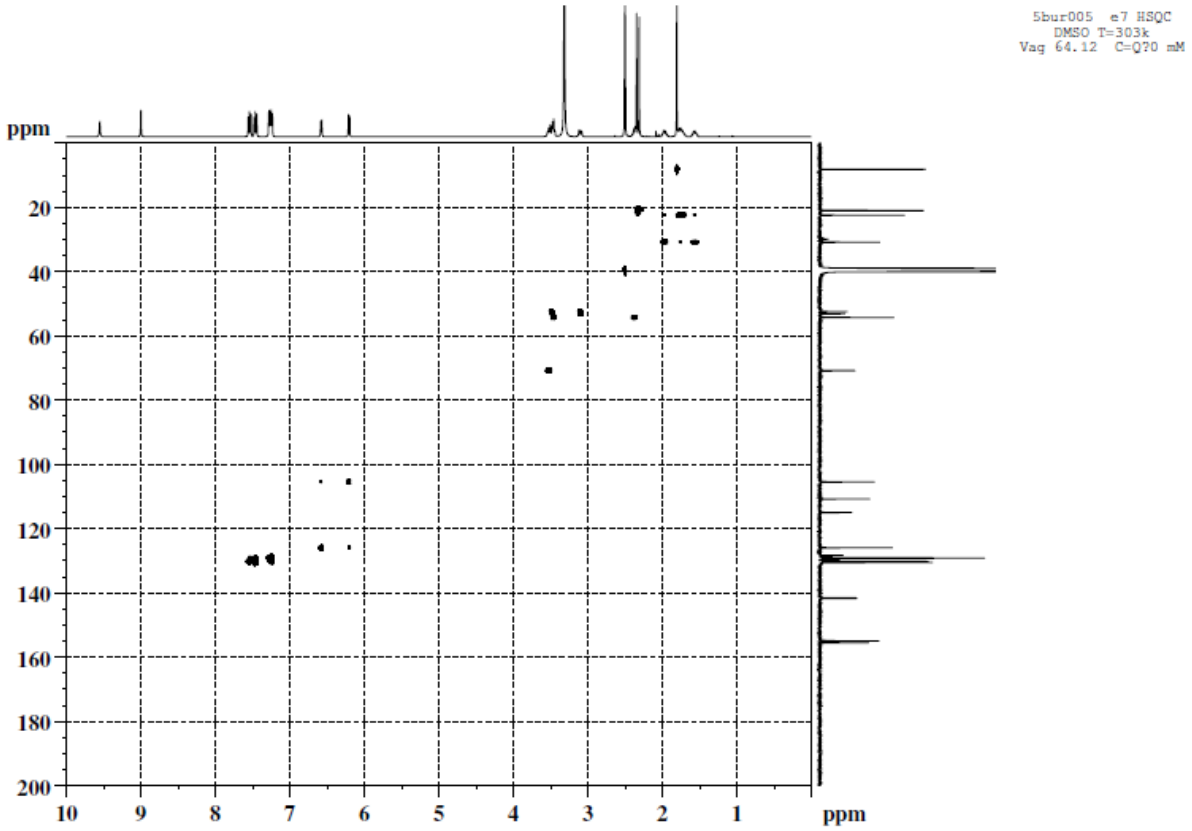


Figure S5. HSQC-spectrum of compound **4**.

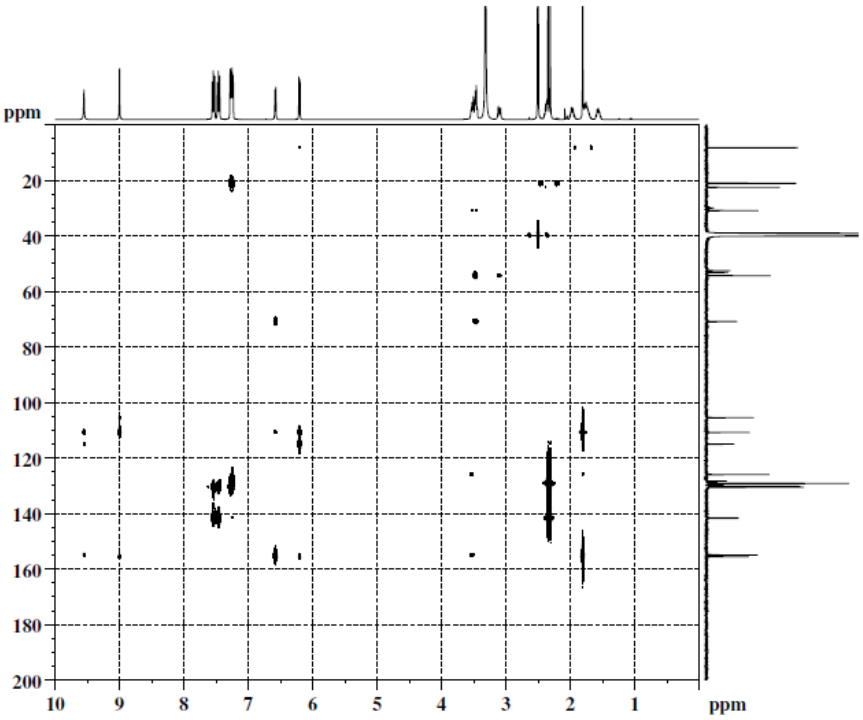


Figure S6. HMBS spectrum of compound **4**

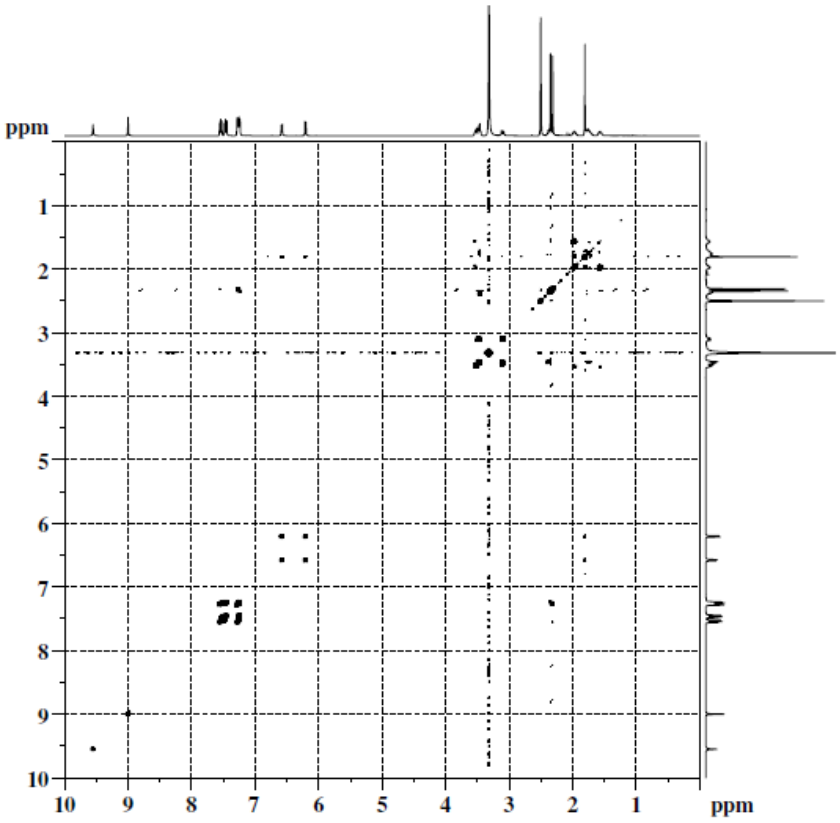


Figure S7. COSY spectrum of compound **4**.

References

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