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Bispidine-based bis-azoles as a new family of supramolecular receptors: the theoretical approach

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Experimental

All solvents, including deuterated solvents ($CDCl_3$), and other chemicals were purchased from commercial sources. 1,5-Dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one[S1] and 1-benzyl-5-(chloromethyl)-1H-tetrazole[S2] were prepared according to literature. ^1H, ^{13}C NMR spectra were recorded at 25 °C using Bruker Avance 400 spectrometer with the operating frequency of 400 and 100 MHz respectively. Chemical shifts are reported in ppm relative to residual solvent signals. Mass-spectra were recorded on Bruker Solarix XR 15 Tesla.

The crystallographic data for the structures **2** and **4** described in this paper have been deposited at the Cambridge Crystallographic Data Centre (CCDC) as supplementary publication number CCDC 1969853-1969854.

All quantum chemistry computations were performed in the Gaussian09 program[S3] using the density functional theory (PBE0)[S4] and the 6-311+G(d,f) basis set. The choice of the PBE0 functional was based on the recent paper in which errors of various DFT functionals in reproduction of an exact electron density and energy are discussed.[S5] The geometry of 3 and 4 was optimized using the very tight optimization criteria and emirical dispersion corrections on the total energy[S6] with the Becke-Johnson damping (D3).[S7]

Topological analysis of the ρ(r) function, calculations of the v(rbcp) and integration over interatomic zero-flux surfaces were performed using the AIMAll program.[S8] All expected critical points were found and the whole set of critical points in each system satisfies the Poincaré-Hopf rule.

Synthesis

3,7-bis((1-benzyl-1H-tetrazol-5-yl)methyl)-1,5-dimethyl-3,7-diaza-bicyclo[3.3.1]nonan-9-one (2): 1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**1**) (261 mg, 1.6 mmol) was dissolved in dry acetonitrile (8 ml) and 1-benzyl-5-(chloromethyl)-1H-tetrazole (649 mg, 3.2 mmol) and DIPEA (0.554 ml, 3.2 mmol) were added. The reaction mixture was refluxed for 18 h under inert atmosphere. The solvent was evaporated and the residue was dissolved in DCM (30 ml) and washed with water (2*15 ml). The organic layer was separated, dried over sodium sulfate and evaporated to dryness. White foam. Yield 0.740 g (93%). M.p. 166.3-167.8 °C. X-ray-quality crystals were obtained by slow diffusion of petroleum ether into the solution of product in chloroform.
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 0.92 (s, 6H, CH_3), 2.33 (d, ^{2}J = 11.0 Hz, 4H, CH_2 axial), 2.93 (d, ^{2}J = 11.1 Hz, 4H, CH_2 eq), 3.63 (s, 4H, NCH_2-tetrazole), 5.65 (s, 4H, Ph$\underline{CH_2}$), 7.15-7.16 (m, 4H, m-Ph), 7.34-7.36 (m, 6H, o-, p-Ph).
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 19.78 (CH3), 46.20 (C1, C5), 49.16 (N$\underline{CH_2}$-tetrazole), 51.19 (Ph$\underline{CH_2}$), 65.14 (C2, C4, C6, C8), 127.52 (o-CH), 129.00 (p-CH), 129.20 (m-CH), 133.15 (ipso-CH), 151.23 (C-tetrazole), 212.78 (CO).
HRMS (ESI), m/z: 513.28312 $[M+H]^+$ (Calc. for $C_{27}H_{32}N_{10}O$, m/z 513.28333).

1,5-dimethyl-3,7-di(prop-2-yn-1-yl)-3,7-diazabicyclo[3.3.1]nonan-9-one (3): 1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonan-9-one (**1**) (1.008 g, 6 mmol) was dissolved in dry acetonitrile (11 ml) and propargyl bromide (0.91 ml, 12.0 mmol) and DIPEA (2.092 ml, 12.0 mmol) were added. The reaction mixture was refluxed for 6 h under inert atmosphere. The solvent was evaporated and the residue was dissolved in DCM (30 ml) and washed with water (2*15 ml). The organic layer was separated, dried over sodium sulfate and evaporated to dryness. The product was purified by flash chromatography on silica (PE:EA 1:1). Beige solid. Yield 1.037 g (71%).
^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 1.04 (s, 6H, CH_3), 2.25 (t, ^{4}J = 2.3 Hz, 2H, C$\underline{CH}$), 2.61 (d, ^{2}J = 10.9 Hz, 4H, CH_2 axial), 3.09 (d, ^{2}J = 11.0 Hz, 4H, CH_2 eq), 3.40 (d, ^{4}J = 2.3 Hz, 4H, $CCCH_2$).
^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 19.87 (CH_3), 45.74 (C1, C5), 46.31 (N$\underline{CH2}$CC), 64.29 (C2, C4, C6, C8), 73.61 (C$\underline{CH}$), 78.16 ($CH_2\underline{C}$C), 214.58 (C9).

3,7-bis((1-benzyl-1H-1,2,3-triazol-4-yl)methyl)-1,5-dimethyl-3,7-diaza-bicyclo[3.3.1]nonan-9-one (3): compound **3** (244 mg, 1.0 mmol) and benzyl azide (266 mg, 2.0 mmol) were dissolved in tert-butanol (10 ml) and aqueous solutions of

sodium ascorbate (53 mg, 0.2 mmol, 2.5 ml) and copper sulfate pentahydrate (25 mg, 0.1 mmol, 2.5 ml) were added sequentially. The solution was stirred for 36 h under inert atmosphere. The solution was evaporated to dryness. The residue was dissolved in DCM (30 ml) and washed with water (10*8 ml). The organic layer was separated, dried over sodium sulfate and evaporated to dryness. White foam. Yield 406 mg (80%). X-ray-quality crystals were obtained by slow diffusion of petroleum ether into solution of product in DCM. M.p. 155.5-156.9 °C.

^{1}H-NMR (400 MHz, $CDCl_3$, ppm): 0.89 (s, 6H, CH_3), 2.37 (d, ^{2}J = 10.9 Hz, 4H, CH_2 axial), 2.98 (d, ^{2}J = 10.9 Hz, 4H, CH_2 eq), 3.63 (s, 4H, NCH_2-triazole), 5.52 (s, 4H, Ph$\underline{CH_2}$), 7.24-7.27 (m, 4H, m-Ph), 7.33-7.38 (m, 6H, o-, p-Ph), 7.47 (s, 2H, CH-triazole).

^{13}C-NMR (100 MHz, $CDCl_3$, ppm): 19.70 (CH_3), 46.51 (C1, C5), 49.16 (NCH_2-triazole), 53.98 (Ph$\underline{CH_2}$), 65.09, (C2, C4, C6, C8), 122.67 (CH-triazole), 127.88 (o-CH), 128.60 (p-CH), 128.99 (m-CH), 134.87 (ipso-CH), 145.34 (C-tetrazole), 215.20 (CO).

HRMS (ESI), m/z: 511.29294 $[M+H]^+$ (Calc. for $C_{29}H_{35}N_8O$, m/z 511.29283).

NMR spectra

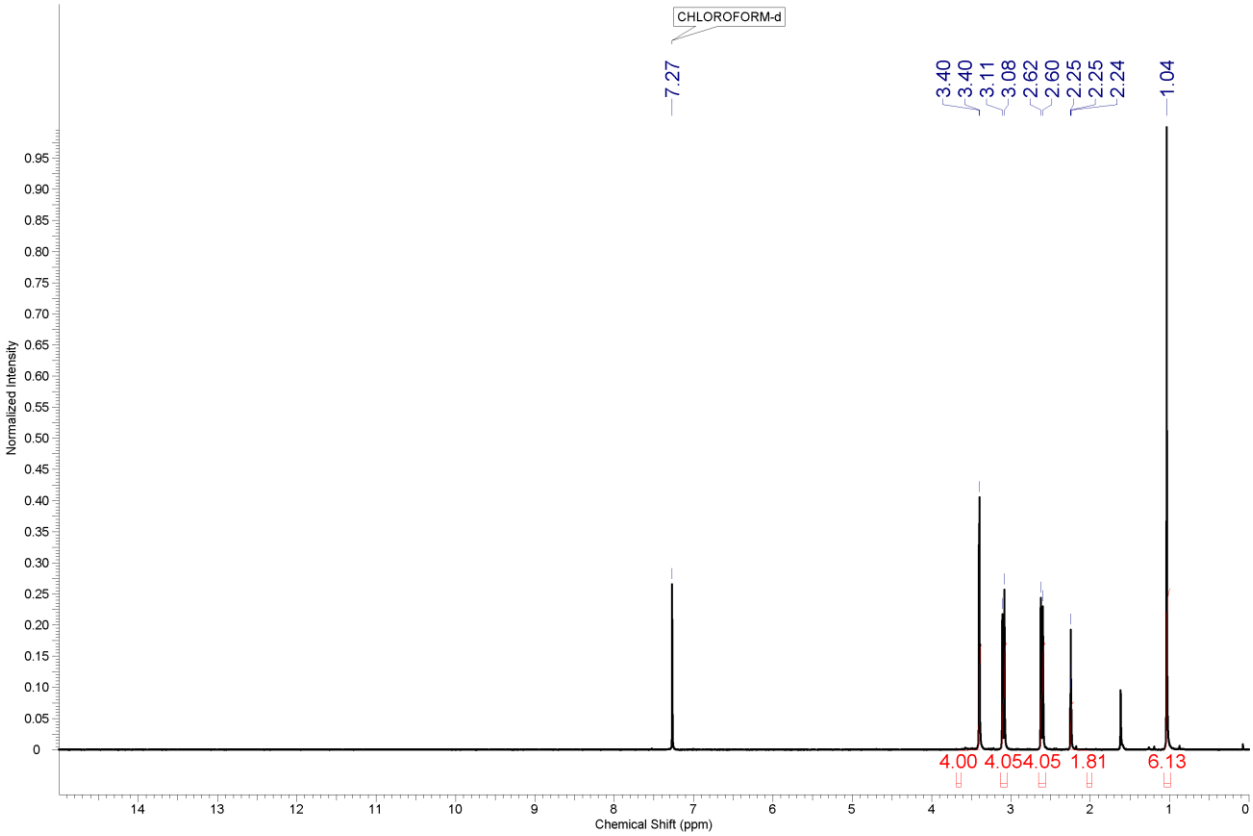

Figure S1. ^{1}H NMR spectrum of **2**.

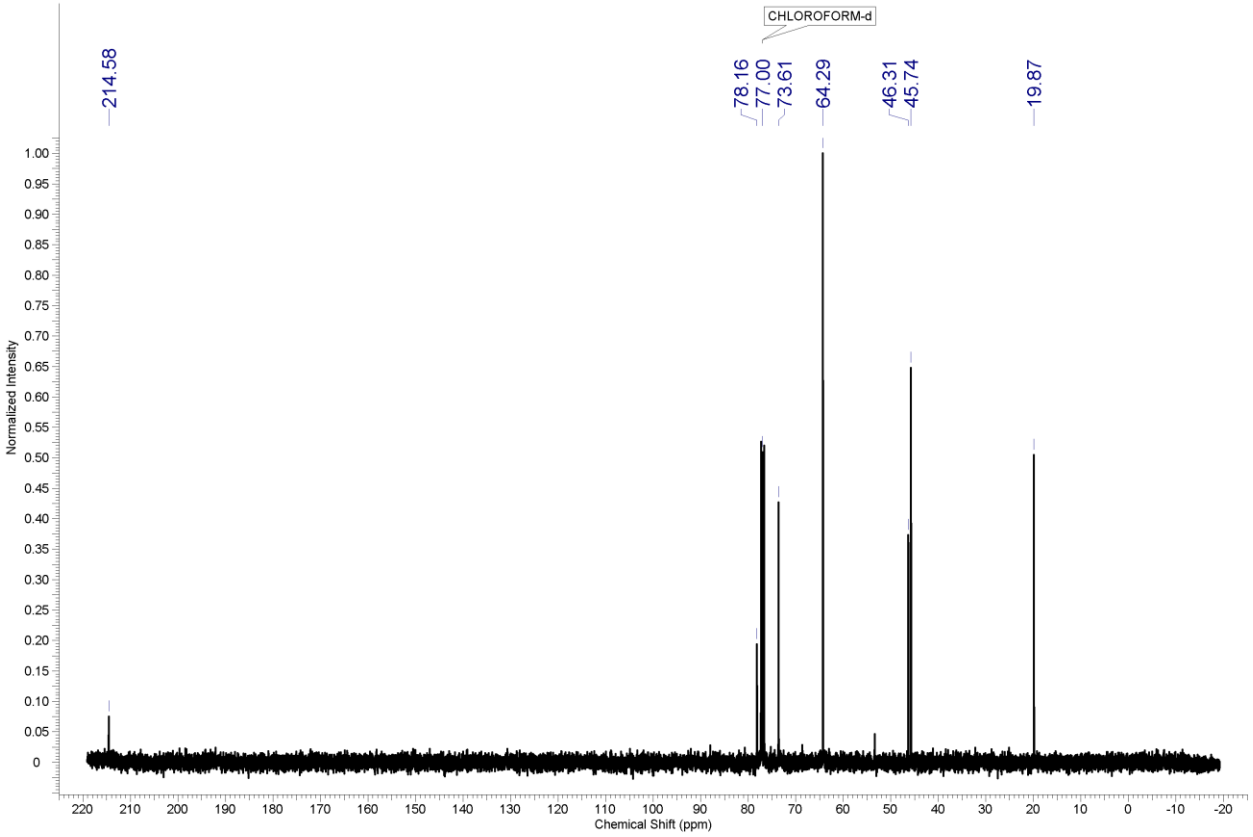

Figure S2. ^{13}C NMR spectrum of **2**.

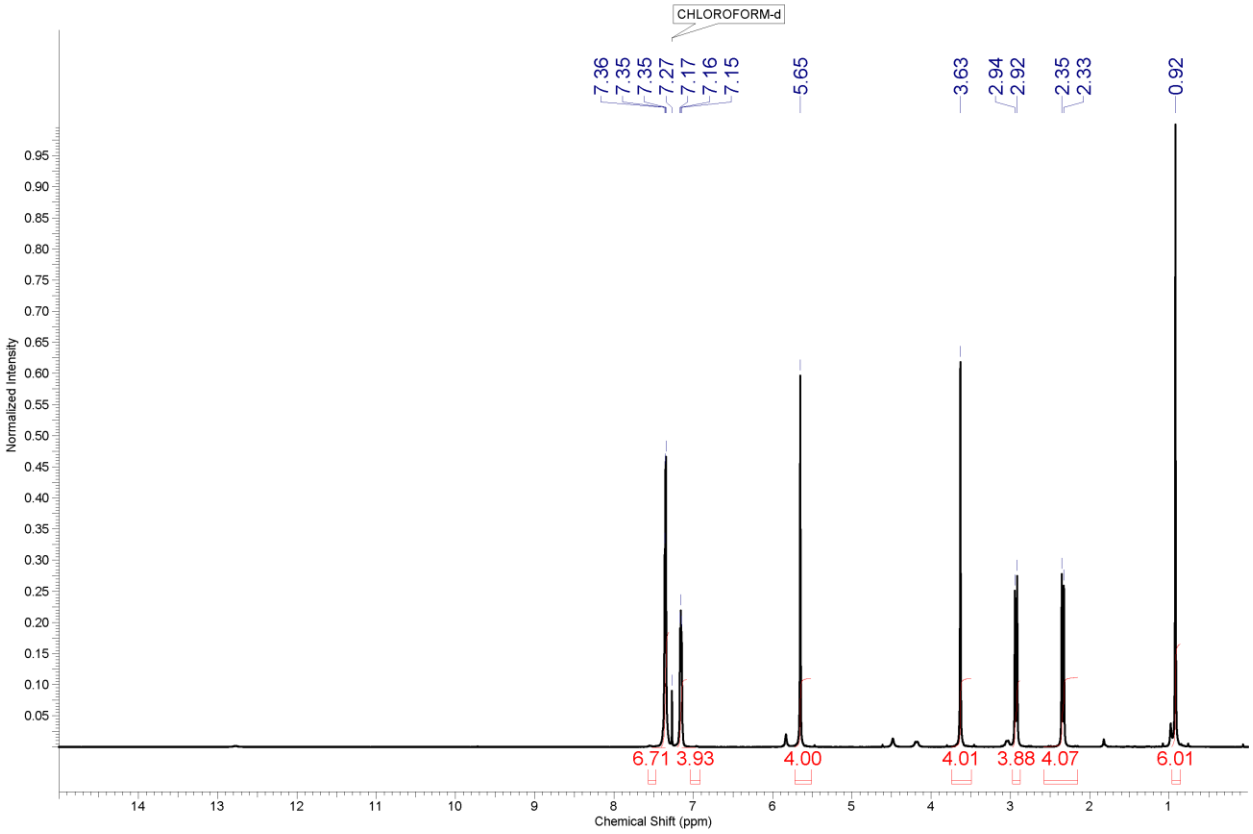

Figure S3. ^{1}H NMR spectrum of **3**.

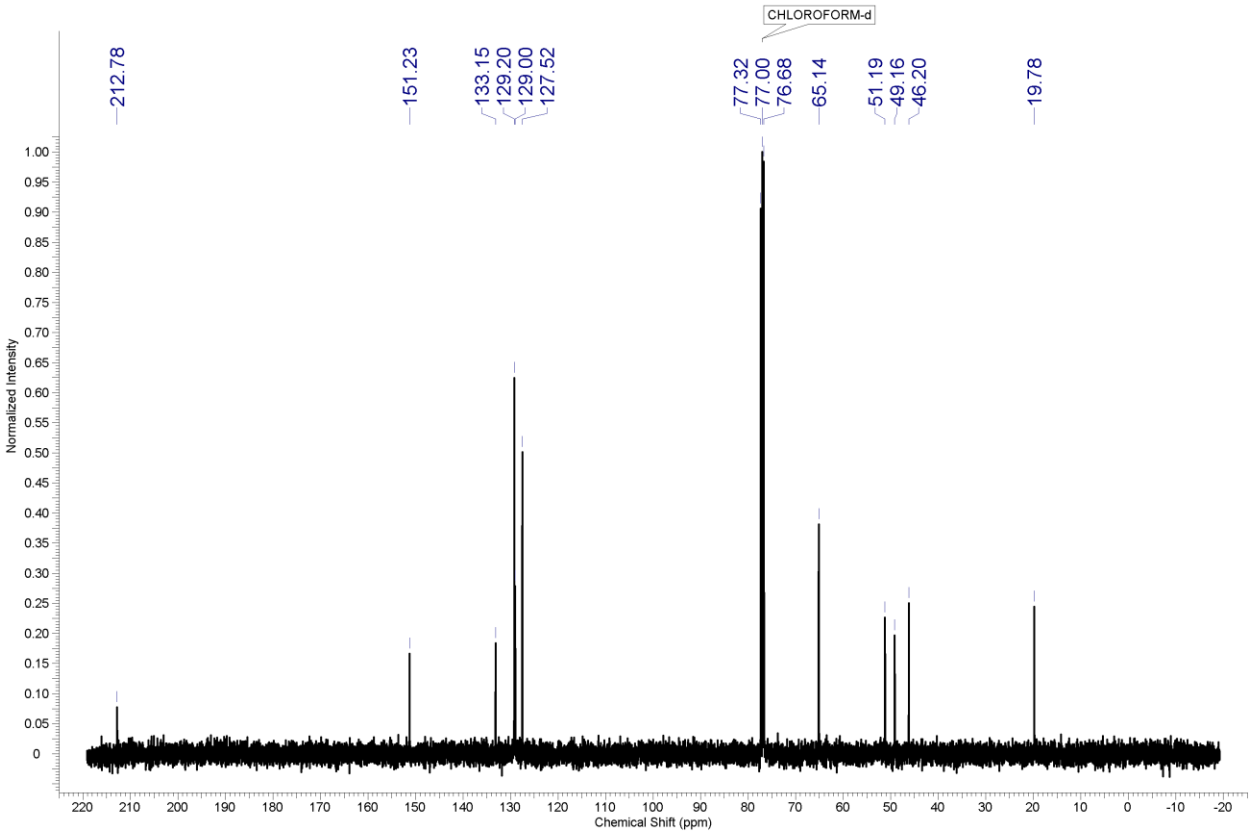

Figure S4. ^{13}C NMR spectrum of **3**.

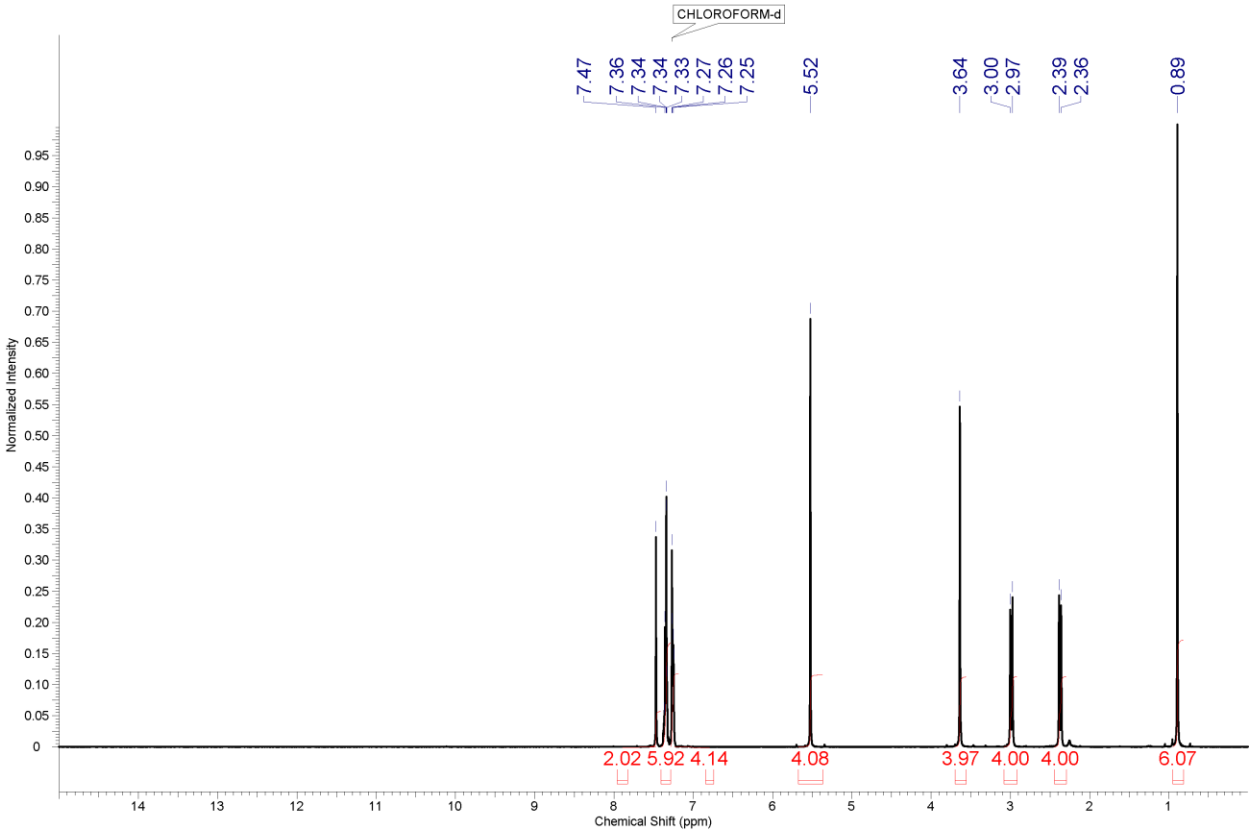

Figure S5. ^{1}H NMR spectrum of **4**.

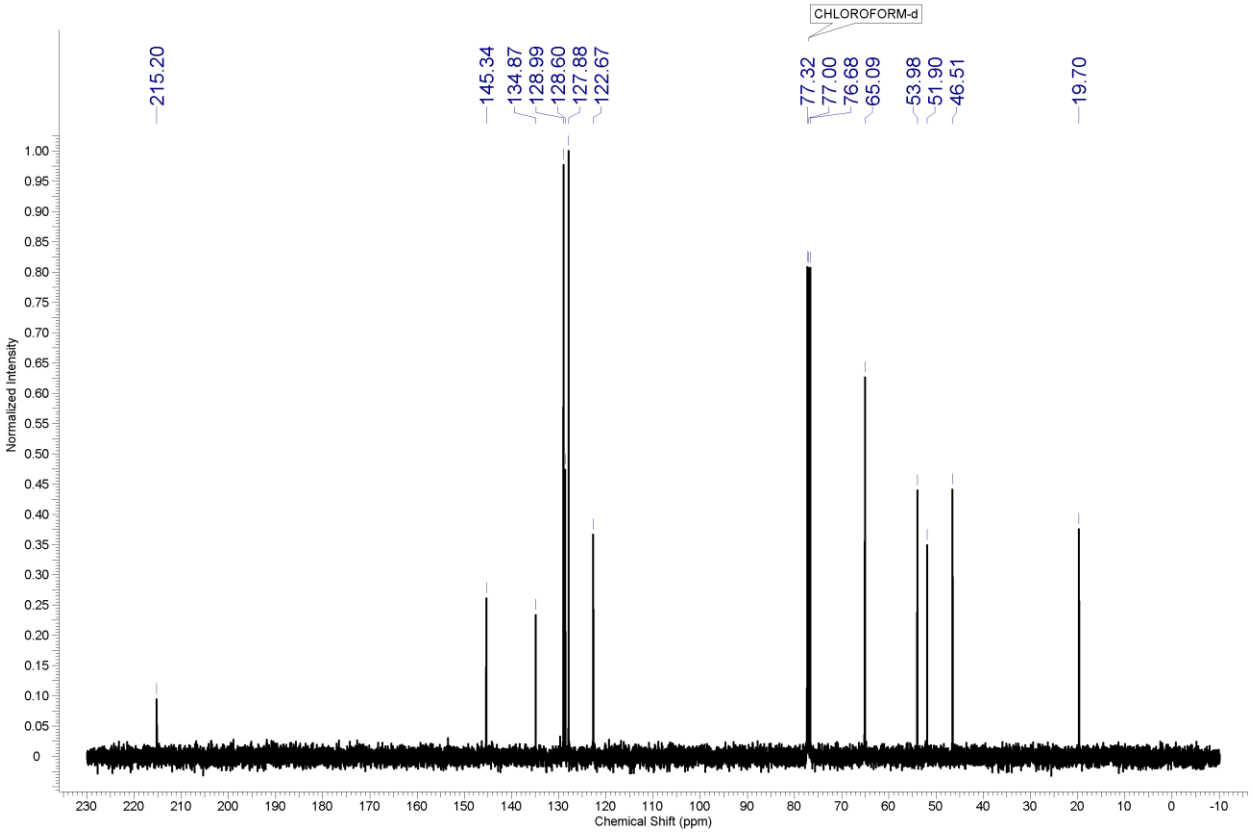

Figure S6. ^{13}C NMR spectrum of **4**.

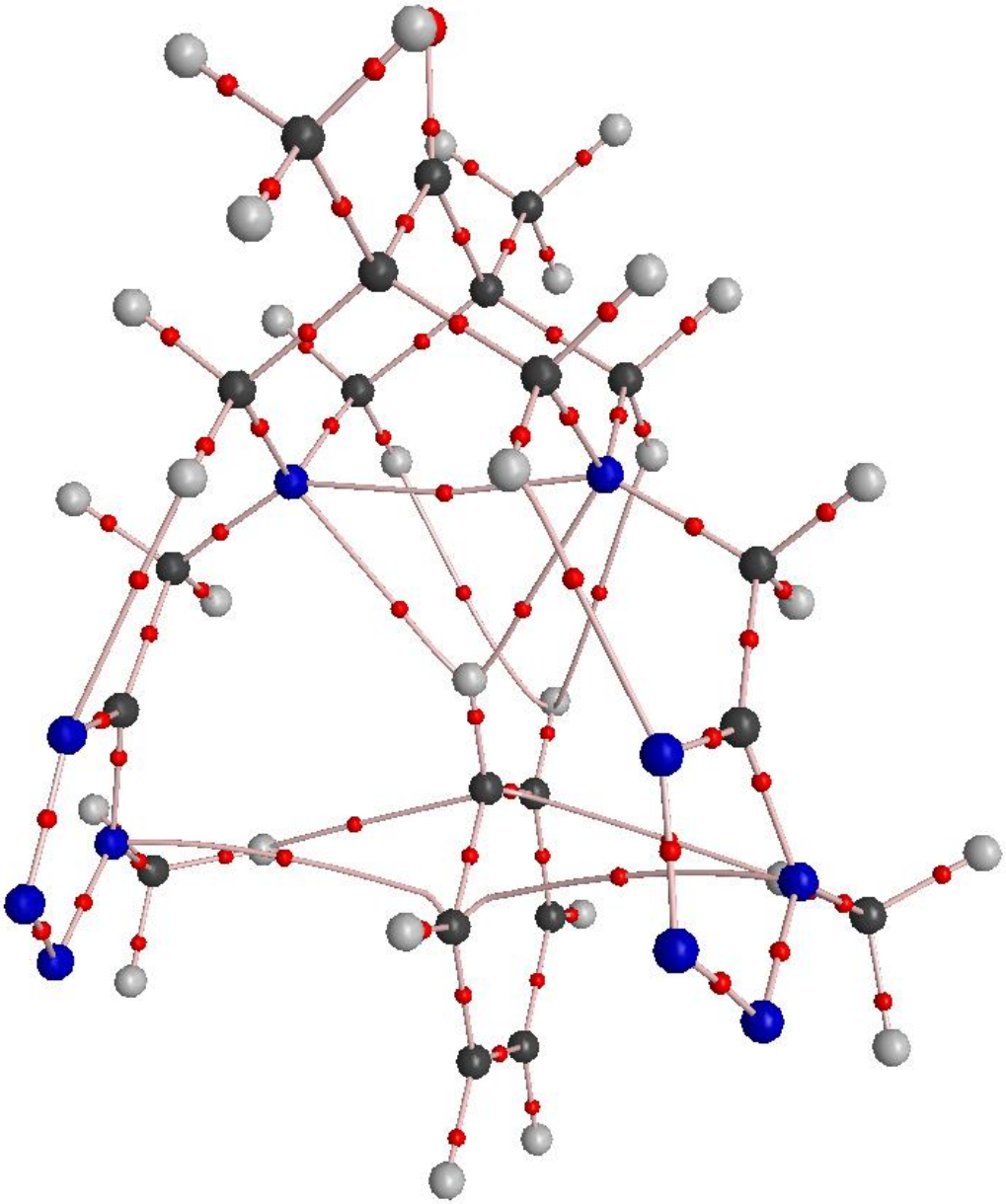

Figure S7. The molecular graph illustrating the formation of supramolecular complex of «tweezer» with benzene according to PBE1PBE/def-2-TZVP calculations. The CP (3,-1) are shown by small red spheres, The CP (3,+1) and (3,+3) are omitted for clarity.

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