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# Cobalt(II) and copper(II) covalently and non-covalently dichlorido-bridged complexes of an unsymmetrical tripodal pyrazolylpyridyl amine ligand: structures, magnetism and cytotoxicity

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### ABSTRACT

The reaction of a methanolic solution containing  $M^{II}Cl_2$  (M = Co or Cu) with bis(3,5-dimethyl-1H-pyrazol-1-yl-1-ethyl)(2-pyridylmethyl)amine (bedmpzp) in the presence of NH<sub>4</sub>PF<sub>6</sub> afforded the dinuclear doubly bridged-dichlorido complex [Co<sub>2</sub>(bedmpzp)<sub>2</sub>( $\mu$ -Cl)<sub>2</sub>](PF<sub>6</sub>)<sub>2</sub> (1) and the mononuclear [Cu(bedmpzp)Cl]PF<sub>6</sub> (2) one. The complexes were structurally and magnetically characterized. The weak ferromagnetic exchange and the axial type of magnetic anisotropy found in 1 is associated with slow relaxation of magnetization as revealed by AC susceptibility measurements. This finding puts 1 into a class of polynuclear single-molecule magnets based on 3*d* metals. X-ray structure of **2** revealed mononuclear nature of the complex, forming supramolecular dimers in the solid state. The non-covalent interactions of the Cu····Cl type present in its crystal structure induced a weak antiferromagnetic exchange. The results of magnetic analysis were also supported by DFT and CASSCF/NEVPT2 calculations. The *in vitro* cytotoxicity of the complexes against MCF7 and HeLa human cancer cell lines were also tested. The best cytotoxicity was achieved for complex **2** on HeLa, with IC<sub>50</sub> = 2.5(0.9)  $\mu$ M.

### 1. Introduction

The chemistry of tripodal tetradentate amines containing four *N*-donor atoms is very rich due to the possibility synthetizing ligands with either aliphatic- or aromatic-based *N*-donor arms as well as due to the feasibility of combining different arm groups resulting in unsymmetrical tripod ligands [1]. Restricting our discussion to unsymmetrical tripod ligands comprising pyridyl and pyrazolyl groups, we have found that only three such ligands were utilized in the transition metal coordination chemistry according to Cambridge Crystallographic Database up to now [2]. Namely, (3,5-dimethyl-1H-pyrazol-1-yl)-*N*,*N*-bis(pyridin-2-ylmethyl)methanamine (pzpy<sub>2</sub>), (3,5-dimethyl-1H-pyrazol-1-yl)-*N*-((3,5-dimethyl-1H-pyrazol-1-yl)methyl)-*N*-(pyridine-2-ylmethyl)methanamine (pz<sub>2</sub>py), bis(1-pyrazolylmethyl)(2-pyridylmethyl)amine (bppa) – Scheme



Scheme 1. Unsymmetrical tripod ligands comprising pyridyl and pyrazolyl groups.

Most widely used ligands are  $pz_2py$  and  $pzp_2$  for which mononuclear penta-coordinate  $[Co(pz_2py)Cl]BF_4\cdot\frac{1}{2}CH_3OH$  [3],  $[Co(pz_2py)(CH_3COO)]PF_6$  [4], and hexa-coordinate  $[Fe(pz_2py)Cl_2]$  [5], and  $[Fe(pzp_2)(NCS)_2]$  [6] complexes were prepared, and their cytotoxic activities [3], catalytical properties [5] were investigated, or pressure-driven thermal SCO behavior was observed [6]. Moreover, terminal  $pz_2py$  ligand was introduced in the preparation of cyanato-bridged  $[{Ni(pz_2py)(\mu-NCO)}_2](PF_6)_2$ ,  $[{Cu(pz_2py)(\mu-NCO)}_2](PF_6)_2$  [7], or azido-bridged  $[{Ni(pz_2py)(\mu-N_3)}_2](CIO_4)_2\cdot 2EtOH$ ,  $[{Cu(pz_2py)(\mu-N_3)}_2](CIO_4)_2$  [8]. Dinuclear complexes and magnetic exchange within these compounds were studied. Interestingly, removing the bulky methyl substituents from pyrazolyl groups resulted in the bppa ligand (Scheme 1) for which bridging mode was observed in polymeric Cu(I) compound  $[Cu_2(\mu-bppa)(\mu-I)_2]_n$  [9].

Herein, we report the synthesis of a novel unsymmetrical tripodal ligand bis(3,5dimethyl-1H-pyrazol-1-yl-1-ethyl)(2-pyridylmethyl)amine (bedmpzp) shown in Scheme 1, in which two pyrazolyl groups are attached to tertiary nitrogen atom by longer ethyl groups. The first two structurally characterized covalently and non-covalently doubly bridged dichlorido  $[Co_2(bedmpzp)_2(\mu-Cl)_2](PF_6)_2$  (1) and  $[Cu(bedmpzp)Cl]PF_6$  (2) complexes, respectively, were synthesized. Their static and dynamic magnetic properties and *in vitro* cytotoxicity were studied. Furthermore, the DFT and CASSCF calculations were used to rationalize their magnetic behavior.

### 2. Experimental

#### 2.1. Materials and physical measurements

Bis(2-chloroethyl)amine hydrochloride, 3,5-dimethylpyrazole and (2chloromethyl)pyridine hydrochloride were purchased from Aldrich Chem. Company. All other chemicals were commercially available and used without further purification. Infrared spectra of compounds were recorded on a JASCO FTIR-480 plus spectrometer as KBr pellets. Electronic spectra were recorded using an Agilent 8453 HP diode array and Perkin-Elmer Lambda35 UV-Vis spectrophotometers. <sup>1</sup>H and <sup>13</sup>C NMR spectra were obtained at room temperature on a Varian 400 NMR spectrometer operating at 400 MHz (<sup>1</sup>H) and 100 MHz (<sup>13</sup>C). <sup>1</sup>H and <sup>13</sup>C NMR chemical shifts ( $\delta$ ) are reported in ppm and were referenced internally to residual solvent resonances (DMSO-d<sub>6</sub>:  $\delta_{\rm H} = 2.49$ ,  $\delta_{\rm C} = 39.4$  ppm). ESI-MS spectrum of bis(3,5-dimethyl-1Hpyrazol-1-yl-1-ethyl)(2-pyridylmethyl)amine (bedmpzp) was measured on an LC-MS Varian Saturn 2200 spectrometer. The conductivity measurements were performed using a Mettler

Toledo Seven Easy conductivity meter and the cell constant was determined by the aid of 1413  $\mu$ S/cm conductivity standard. The molar conductivity of the complexes were determined from  $\Lambda_{\rm M} = (1.0 \times 10^3 \text{ K})/\text{M}$ , where  $\kappa$  = cell constant and M is the molar concentration of the complex. Magnetic measurements were performed with SQUID MPMS magnetometer for **1** (*T* = 1.9–300 K at *B* = 0.1 T; *B* = 0–5 T at *T* = 2 and 5 K) and with PPMS Dynacool VSM magnetometer for **2** (*T* = 1.9–300 K at *B* = 1 T; *B* = 0–9 T at *T* = 2 and 5 K). The magnetic data were corrected for sample holder signal and for diamagnetic susceptibility. Elemental analyses were carried out by the Atlantic Microlaboratory, Norcross, Georgia U.S.A.

#### 2.2. Syntheses

#### 2.2.1. Bis(3,5-dimethyl-1H-pyrazol-1-yl-1-ethyl)(2-pyridylmethyl)amine (bedmpzp)

A mixture of bis(3,5-dimethyl-1H-pyrazol-1-yl-1-ethyl)amine [10] (1.31 g, 5 mmol), 2-(chloromethyl)pyridine hydrochloride (0.82 g, 5 mmol) and anhydrous  $K_2CO_3$  (1.73 g, 12.5 mmol) was suspended in dry CH<sub>3</sub>CN. The resulting mixture was stirred and refluxed gently under N<sub>2</sub> gas for 3 days, during which color turns yellowish-brown. This was cooled in ice, filtered off KCl and unreacted  $K_2CO_3$  and solvent was removed by rotary evaporator under reduced pressure. The resulting residue was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 25 mL) and 10% NaOH followed by washing with  $H_2O$  (3 x 25 mL), and addition of anhydrous MgSO<sub>4</sub>. The solution was then filtered and charged on a column containing silica gel. The desired product was collected upon elution with 5% MeOH/CH<sub>2</sub>Cl<sub>2</sub> (by volume). The collected organic layer was further treated with anhydrous MgSO<sub>4</sub>, filtration and evaporating solvent resulted in the formation of the compound as a pure orange-yellow liquid (yield: 1.20 g, 68%). Characterization of bedmpzp: IR (KBr disc, cm<sup>-1</sup>): 3054 (vw) (C-H, aromatic); 2949 (m), 2924 (m), 2932(vw) (C-H, aliphatic); 1664 (m), 1591 (s), 1570 (m), 1552 (vs), 1461 (vs), 1435 (vs), 1387 (s) (pyridyl and pyrazolyl groups). ESI-MS (MeOH): m/z = 353.245 (Calcd for  $[M+H]^+ = 353.49$ ). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 400 MHz,  $\delta$  in ppm):  $\delta$  = 2.01, 2.04, 2.11, 2.13 (s, each corresponds to 3H, CH<sub>3</sub>); 2.90, 3.93 (t, each corresponds to 2H, NCH<sub>2</sub>CH<sub>2</sub>-pz); 3.75 (s, 2H, CH<sub>2</sub>-py); 5.75 (s, 2H, H-pz); 7.12, 7.22, 7.39, 7.65 (py-protons). <sup>13</sup>C NMR: (DMSO-d<sub>6</sub>, 100 MHz)  $\delta$  = 10.46, 13.30 (CH<sub>3</sub>-pz); 46.09, 53.69, 59.69 (CH<sub>2</sub>-pz and CH<sub>2</sub>-py carbons); 104.36, 104.60, 122.46, 122.60 (pz-carbons); 136.4, 138.7, 145.7, 147.6, 148.6 (py-carbons).

#### 2.2.2. $[Co_2(bedmpzp)_2(\mu-Cl)_2](PF_6)_2(1)$

To the bedmpzp ligand (0.088 g, 0.25 mmol) dissolved in MeOH (20 mL),  $CoCl_2 \cdot 6H_2O$  (0.060 g, 0.25 mmol) was added and the reaction mixture was heated for 10 min, followed the

addition of NH<sub>4</sub>PF<sub>6</sub> (0.065 g, 0.40 mmol). The resulting solution was filtered through celite and then allowed to stand at room temperature. After two days, the dark magenta crystals which were separated were collected by filtration, washed with propan-2-ol, ether and dried in air (overall yield: 0.120 g, 81%): Characterization: Anal. Calcd for  $(C_{20}H_{28}ClCoF_6N_6P)_2$  (MM = 1183.668 g/mol): C, 40.59; H, 4.77; N, 14.20%. Found: C, 40.63; H, 4.89; N, 14.08%. Selected IR bands (cm<sup>-1</sup>): 2969 (vw), 2932(vw) (C-H, aliphatic); 1606 (m), 1555 (m) 1463 (m), 1445)1392 (m) (pyridyl and pyrazolyl groups); 842 (vs) v(P-F) (PF<sub>6</sub><sup>-</sup>). UV-VIS in CH<sub>3</sub>CN:  $\lambda_{max}$  in nm ( $\varepsilon_{max}$ /Co atom, M<sup>-1</sup>cm<sup>-1</sup>): 479 (74, sh), 536 (87), 560 (74, sh), 617 (80), 799 (15, b).  $\Lambda_M$  (CH<sub>3</sub>CN) = 283  $\Omega^{-1}$ cm<sup>2</sup>mol<sup>-1</sup>.

#### 2.2.3. $[Cu(bedmpzp)Cl]PF_6$ (2)

This complex was synthesized using a procedure similar to that described for complex **1**, but CuCl<sub>2</sub>·2H<sub>2</sub>O was used instead of the corresponding CoCl<sub>2</sub>·6H<sub>2</sub>O. Crystallization of the precipitate from CH<sub>3</sub>CN and further re-crystallization from MeOH afforded bluish-green single crystals (overall yield: 67%): Characterization: Anal. Calcd for C<sub>20</sub>H<sub>28</sub>ClCuF<sub>6</sub>N<sub>6</sub>P (MM = 596.45 g/mol): C, 40.28; H, 4.73; N, 14.09%. Found: C, 40.29; H, 4.68; N, 14.13.99%. Selected IR bands (cm<sup>-1</sup>): 2932 (vw) (C-H, aliphatic); 1611 (m), 1577 (m); 841 (vs) v(P-F) (PF<sub>6</sub><sup>-</sup>). UV-VIS in CH<sub>3</sub>CN:  $\lambda_{max}$  in nm ( $\varepsilon_{max}$  M<sup>-1</sup>cm<sup>-1</sup>): 370 (s, sh), 674 (260, b).  $\Lambda_{M}$  (CH<sub>3</sub>CN) = 139  $\Omega^{-1}$ cm<sup>2</sup>mol<sup>-1</sup>.

### 2.3. X-Ray crystal structure analysis

The X-ray single-crystal data of the two compounds were collected on a Bruker-AXS SMART APEX II CCD diffractometer at 100(2) K. The crystallographic data, conditions retained for the intensity data collection and some features of the structure refinements are listed in Table S1. The intensities were collected with Mo-K $\alpha$  radiation ( $\lambda$ = 0.71073 Å). Data processing, Lorentz-polarization and absorption corrections were performed using SAINT, APEX and the SADABS computer programs [11]. The structures were solved by direct methods and refined by full-matrix least-squares methods on  $F^2$ , using the SHELXTL program package [12]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located from difference Fourier maps, assigned with isotropic displacement factors and included in the final refinement cycles by use of geometrical constraints. Molecular plots were performed with the Mercury program [13].

#### 2.4. Theoretical calculations

All *ab initio* calculations were performed with ORCA 3.0.3 computational package [14] on the molecular fragments derived from X-ray structures of **1** and **2**. Polarized triple-zeta basis set def2-TZVP(-f) were used for all atoms except carbon and hydrogen atoms for which de2-SVP basis set was utilized [15]. The DFT calculations were based on B3LYP functional [16] and utilized the RI approximation with the decontracted auxiliary def2-TZV/J or def2-SVP/J Coulomb fitting basis set and the chain-of-spheres (RIJCOSX) approximation to exact exchange [17]. Increased integration grids (Grid5 and GridX5in ORCA convention) and tight SCF convergence criteria were also used. The isotropic exchange J values were calculated by Ruiz's formula [18] and also by the more general Yamaguchi's formula [19].

The calculations of zero-field splitting (ZFS) and *g* tensors were based on state average complete active space self-consistent field (SA-CASSCF) [20] wave functions complemented by N-electron valence second order perturbation theory (NEVPT2) [21]. The active space of the CASSCF calculations comprised of seven electrons in five metal-based *d*-orbitals (CAS(7,5)). The state averaged approach was used, in which all ten quartet states and forty doublets states were equally weighted. The calculations utilized the RI approximation with the decontracted auxiliary def2-TZV/C and def2-SVP/C Coulomb fitting basis sets and the chain-of-spheres (RIJCOSX) approximation to exact exchange. Increased integration grids (Grid5 in ORCA convention) and tight SCF convergence criteria were used. The ZFS parameters, based on dominant spin–orbit coupling contributions from excited states, were calculated through quasi-degenerate perturbation theory (QDPT) [22] in which an approximation to the Breit-Pauli form of the spin-orbit coupling operator (SOMF approximation) [23] and the effective Hamiltonian theory were utilized [24].

### 2.5. The analysis of the magnetic data

The experimental magnetic data were fitted with program POLYMAGNET [25], in which both temperature and field dependent magnetization data were treated simultaneously using this error functional

$$F = w_1 \sum_{i=1}^{N_1} \left| \frac{\mu_{\text{eff},i}^{\text{calc.}} - \mu_{\text{eff},i}^{\text{obs.}}}{\mu_{\text{eff},i}^{\text{obs.}}} \right| / N_1 + (1 - w_2) \sum_{i=1}^{N_2} \left| \frac{\mu_{\text{eff},i}^{\text{calc.}} - \mu_{\text{eff},i}^{\text{obs.}}}{\mu_{\text{eff},i}^{\text{obs.}}} \right| / N_2$$

where the calculated and observed effective magnetic moments are used. The  $N_1$  and  $N_2$  are numbers of temperature, and field dependent experimental magnetic data, respectively. The weights were set to  $w_1 = 0.65$  and  $w_2 = 0.35$ .

The standard deviations of the fitted parameters were calculated as  $\sigma_i = (P_{ii}^{-1} \cdot S/(N-k))^{-1/2}$ , where  $P_{ij} = \Sigma(\delta \mu_{\text{eff},n}^{calc} / \delta a_i \cdot \delta \mu_{\text{eff},n}^{calc} / \delta a_j)$  and  $S = \Sigma(\mu_{\text{eff},n}^{calc} - \mu_{\text{eff},n}^{obs.})^2$  with n = 1 to N.  $a_i$  and  $a_j$  are fitted parameters, N is number of experimental points (sum of temperature and field dependent data),  $\mu_{\text{eff},n}^{calc}$  and  $\mu_{\text{eff},n}^{obs.}$  are the calculated and observed effective magnetic moments for given temperature and magnetic field. The  $\sigma_i$  was then multiplied by Student's  $t_{95\%}$  to provide confidence limits with 95% probabilities listed in text.

#### 2.6. Cytotoxicity

*In vitro* cytotoxicity of complexes (1) and (2), and cisplatin as a standard, was studied by the MTT assay (MTT = 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) on human breast adenocarcinoma (MCF7; ECACC No. 86012803) and human cervix epithelioid carcinoma (HeLa; ECACC No. 93021013) cell lines. The human cancer cell lines were purchased from European Collection of Cell Cultures (ECACC). The cells were cultivated according to the manufacturer's manuals and maintained in an atmosphere containing 5% CO<sub>2</sub> in a humidified incubator at 37 °C. The experimental procedure was performed according to the literature [26]. All the experiments were conducted in triplicate. The results are expressed as IC<sub>50</sub> values with their standard deviations (SD). The significance of the differences between the compared groups of results was assessed by the ANOVA analysis, with p < 0.05 considered to be significant (QC Expert 3.2, Statistical software, TriloByte Ltd.) [27].

### 3. Results and discussion

### 3.1. Synthesis and spectroscopic characterization of the complexes

The tripod tetraamine ligand bis(3,5-dimethyl-1H-pyrazol-1-yl-1-ethyl)(2pyridylmethyl)amine (bedmpzp) was obtained in 68% in a pure state following the reactions outlined in Scheme 2 (see Experimental section for more details).



**Scheme 2.** The reaction pathway to tripod ligand bis(3,5-dimethyl-1H-pyrazol-1-yl-1-ethyl)(2-pyridylmethyl)amine (bedmpzp).

Reaction of bedmpzp in a methanolic solution containing  $CoCl_2$  or  $CuCl_2$  in a 1:1 molar ratio, followed by the addition of NH<sub>4</sub>PF<sub>6</sub> afforded the dinuclear  $[Co_2(bedmpzp)_2(\mu-Cl)_2](PF_6)_2$  (1) and mononuclear  $[Cu(bedmpzp)Cl]PF_6$  (2), complexes in reasonable yields. The isolated complexes were characterized by elemental microanalyses, molar conductivity, IR and UV-VIS spectroscopy, and single crystal X-ray crystallography. The molar conductivity measurements in CH<sub>3</sub>CN as 283  $\Omega^{-1}$ cm<sup>2</sup>mol<sup>-1</sup> is consistent with the 1:2 electrolytic nature of complex (1), whereas a value of 139  $\Omega^{-1}$ cm<sup>2</sup>mol<sup>-1</sup> for the Cu(II) complex (2) is typical for 1:1 electrolytic behavior. The IR spectra of the complexes display a very strong band at 841 cm<sup>-1</sup> which is assigned to stretching vibration of v(P-F) of the hexafluorophosphate counter ions.

The UV-visible spectra of the two complexes were recorded in CH<sub>3</sub>CN and in the solid state for compound **1**. The Co(II) complex (**1**) exhibits absorption bands at 477, 529, 570 with shoulder at 610, broad weaker band at 720 nm and another band above 1100 nm in the solid state (Fig. S1). The measurement in CH<sub>3</sub>CN revealed three absorption bands at 799, 617 and 536 nm with shoulders around 479 and 560 nm. Such richness of the absorption bands attributable to *d-d* transitions is the result of lowering the symmetry of the chromophore (O<sub>h</sub>  $\rightarrow$  C<sub>2v</sub>), thus three electronic transitions  ${}^{4}T_{2}(F) \leftarrow {}^{4}T_{1}(F)$ ,  ${}^{4}T_{1}(F) \leftarrow {}^{4}T_{1}(F)$  and  ${}^{4}A_{2}(P) \leftarrow {}^{4}T_{1}(F)$  spin allowed in the octahedral symmetry are split into six transitions in the idealized C<sub>2v</sub> symmetry of *cis*-[CoN<sub>4</sub>Cl<sub>2</sub>] chromophore of **1**. The corresponding Cu(II) complex (**2**) displayed a broad single absorption maximum at 674 nm with no indication of absorption maximum beyond  $\lambda > 800$  nm. This

spectral feature is consistent with a distorted square pyramidal geometry (SP) around the central Cu(II)atom. The strong intense absorption shoulder observed around 370 nm is most probably attributed to CT ( $L \rightarrow M$ ) transition. The geometrical assignments in acetonitrile solution were in full agreements with those obtained from X-ray structural determinations (see next section).

3.2. Description of X-ray structures of  $[Co_2(bedmpzmpy)_2(\mu-Cl)_2](PF_6)_2$  (1) and  $[Cu(bedmpzmpy)Cl]PF_6$  (2)

Single crystal structure determination revealed that Co(II) compound (1) forms dinuclear  $[Co_2(bedmpzp)_2(\mu-Cl)_2]^{2+}$  complex cations, whereas Cu(II) compound (2) forms mononuclear  $[Cu(bedmpzp)Cl]^+$  units and both compounds co-crystallize with PF<sub>6</sub><sup>-</sup> counter anions. Perspective views together with the atom numbering scheme are presented in Figures 1 and 2, respectively, while the selected interatomic parameters are given in Table 1. Each Co(II) center of the dinuclear complex cation is octahedrally coordinated by four *N*-donor atoms of the bedmpzp ligand [Co(1)-N from 2.0807(14) to 2.2446(14) Å] and two bridging chlorido ligands [Co(1)-Cl(1) = 2.4036(5) and Co(1)-Cl(1') = 2.7503(5) Å]. The centrosymmetric dinuclear cations show a Co(1)…Co(1') intra-dimer distance of 4.0061(6) Å, whereas the shortest interdimer Co…Co separation is 8.6540(10) Å. The Co(1)-Cl(1)-Co(1') and Cl(1)-Co(1)-Cl(1') bond angles are 101.82(2), and 78.18(2)°, respectively.



Fig. 1. Perspective view of the dinuclear unit  $[Co_2(bedmpzp)_2(\mu-Cl)_2]^{2+}$  of (1) with the atom numbering scheme.

2.1065(14)	Co(1)-N(5)	2.2087(15)
2.2446(14)	Co(1)-Cl(1)	2.4036(5)
2.0807(14)	Co(1)-Cl(1')	2.7503(5)
166.28(6)	N(2)-Co(1)-Cl(1)	165.37(4)
171.70(4)	Cl(1)-Co(1)-Cl(1')	78.18(2)
101.82(2)		
2.005(4)	Cu(1)-N(3)	1.991(4)
2.147(4)	Cu(1)-N(5)	2.291(4)
2.2868(12)		
166.17(15)	N(2)-Cu(1)-Cl(1)	161.64(11)
103.27(10)		
	$\begin{array}{c} 2.1065(14) \\ 2.2446(14) \\ 2.0807(14) \\ 166.28(6) \\ 171.70(4) \\ 101.82(2) \\ \\ \\ 2.005(4) \\ 2.147(4) \\ 2.2868(12) \\ 166.17(15) \\ 103.27(10) \\ \end{array}$	2.1065(14)       Co(1)-N(5)         2.2446(14)       Co(1)-Cl(1)         2.0807(14)       Co(1)-Cl(1')         166.28(6)       N(2)-Co(1)-Cl(1)         171.70(4)       Cl(1)-Co(1)-Cl(1')         101.82(2)

Table 1. Selected bond lengths (Å) and angles (°) for compounds 1 and 2.

Symmetry code: ('): -x,-y,2-z.

The CuN<sub>4</sub>Cl chromophore of the monomeric [Cu(bedmpzp)Cl]<sup>+</sup> complex cation of (2) with a distorted SP geometry ( $\tau = 0.076$ ) [28] is achieved by the four *N*-donor atoms of the bedmpzp ligand and one terminal chlorido ligand. The basal sites are occupied by Cl(1) [Cu(1)-Cl(1) = 2.2826(12) Å], N(1), N(2) and N(3) donor atoms [Cu(1)-N from 1.991(4) to 2.147(4) Å], whereas the apical site is occupied by N(5) donor atom [Cu(1)-N(5) = 2.291(4) Å]. The Cu(1) center deviates by 0.056(4) Å from its basal N<sub>3</sub>Cl plane. The shortest Cu···Cu separation is 4.6307(10) Å, and the Cu(1)···Cl(1) [2-x,1-y,-z] separation is 3.5712(14) Å, thus forming supramolecular dimer is observed (Fig. 2).



**Fig. 2.** Perspective view of the supramolecular dimer  $[{Cu(bedmpzp)Cl}]^{2+}$  of **2** with the atom numbering scheme. The non-covalent Cu···Cl interactions are shown with magenta dashed lines.

### 3.3. Theoretical calculations

The DFT broken-symmetry (BS) approach with the B3LYP functional and def2-TZVP(-f) basis set was employed to estimate the isotropic exchange coupling J between paramagnetic metal(II) atoms in the two compounds. The computational software ORCA 3.0 was used and we followed the same procedure as described in details in ref. 29 to calculate J-values for the dinuclear spin Hamiltonian defined as

$$\hat{H} = -J(\vec{S}_A \cdot \vec{S}_B)$$

(1)

by both Ruiz's ( $J^{\text{Ruiz}}$ ) and Yamaguchi's ( $J^{\text{Yam}}$ ) formulas. The results of DFT calculations are summarized in Table 2. The spin densities for broken-symmetry spin states (BS) states are visualized in Fig. 3 and the corresponding orbitals of BS spin states with the highest overlap ( $S_{\alpha\beta}$ ) are shown in Fig. S2 (Supplementary Material). The DFT calculations predict weak antiferromagnetic coupling for both compounds with spin delocalization to be more pronounced in the copper(II) compound (**2**).

**Table 2** The DFT-calculated net Mulliken spin densities ( $\rho$ ), expected values  $\langle S^2 \rangle$ , overlap  $S_{\alpha\beta}$  between the corresponding orbitals and isotropic exchange parameters (*J*) from high-spin (HS) and broken symmetry spin (BS) states of the dinuclear molecular fragments based on X-ray structural structures of (1) and (2).

		(1)	(2)
	$\rho^{\rm HS}({\rm M1})/\rho^{\rm HS}({\rm M2})$	2.71/2.71	0.59/0.59
	$\rho^{\rm BS}({\rm M1})/\rho^{\rm BS}({\rm M2})$	-2.71/2.71	-0.59/0.59
	$\langle S^2_{HS} \rangle$	12.01	2.01
	$\langle S^2_{BS} \rangle$	3.01	1.01
	$S_{lphaeta}$	0.04654	0.01215
1		0.03524	
		0.00180	
	ε <sub>BS</sub> -ε <sub>HS</sub> /cm <sup>-1</sup>	-27.306	-2.213
	$J^{\text{Ruiz}}/\text{cm}^{-1}$	-4.56	-2.21
	$J^{\text{Yam}}/\text{cm}^{-1}$	-6.07	-4.43
	$J^{\rm mag}/{\rm cm}^{-1}$	+2.82	-4.45
	$<(M-Cl-M)/^{\circ}$	101.82	102.32
	$d(M-M)/10^{-10} m$	4.006	4.631



**Fig. 3**. The calculated isodensity surfaces of the broken symmetry spin states using B3LYP/def2-TZVP(-f) for  $[Co_2(bedmpzp)_2(\mu-Cl)_2](PF_6)_2$  (1) (*left*) and  $\{[Cu(bedmpzp)Cl]PF_6\}_2$  of (2) (*right*). The positive and negative spin densities are represented by blue and red surfaces, respectively, with the cutoff values of 0.005 e boh<sup>-3</sup>. Hydrogen atoms are omitted for clarity.

We also calculated ZFS D and g tensors for the Co(II) atom in (1) with ORCA using state average complete active space self-consistent field (SA-CASSCF) wave functions complemented by N-electron valence second order perturbation theory (NEVPT2) with the active space defined as CAS (7,5). The calculations were done for the dinuclear fragment  $[CoZn(bedmpzmpy)_2(\mu-$ Cl)<sub>2</sub>l<sup>2+</sup>, in which one cobalt atom in 1 was replaced by zinc. The resulting values of ZFS parameters were as follows: D = -111.9 cm<sup>-1</sup> and E/D = 0.270, where individual contributions to ZFS parameters from excited states are listed in Table S2 (Supplementary Material). In addition, g-tensor values were found as:  $g_1 = 1.839$ ,  $g_2 = 2.244$ ,  $g_3 = 3.150$  resulting in  $g_{iso} = 2.411$ . However, these parameters must be treated with caution because according to these calculations, there are low-lying excited states, which means that ground spin state is not well separated and spin Hamiltonian formula may not hold (Table S3). As can be seen in Fig. 4 both the g- and Dtensors coincide. Therefore, from the mutual relationship we can conclude that  $g_x = g_2$ ,  $g_y = g_1$ , and  $g_z = g_3$ . The DZ axis can be identified with N-Co-N bonds within the chromophore, where the N atoms belong to the pyrazole and pyridine rings, while other D-tensor axes do not coincide with the donor-acceptor bonds tightly. Moreover, CASSCF/NEVPT2 calculations of ligand field terms were used to interpret *d*-*d* transitions for **1** at 409, 441, 511, 582, 1028, 1205 nm (Fig. S1) which is an agreement with the experimental solid state electronic spectrum.



**Fig. 4**. Molecular fragment of  $[CoZn(bedmpzp)_2(\mu-Cl)_2]^{2+}$  overlaid with *g*-tensor and *D*-tensor axes derived from CASSCF/NEVPT2 calculations.

#### 3.4. Magnetic properties of complexes

The experimental magnetic data of complexes **1** and **2** are depicted in Figures 5, and 6, respectively. The room temperature values of the effective magnetic moment,  $\mu_{eff}$  are equal to 6.8  $\mu_B$  for **1** and 1.9  $\mu_B$  for **2**. These values are higher than spin only values (5.58  $\mu_B$  and 1.73  $\mu_B$  for **1** and **2**, respectively, where the first value corresponds to two non-interacting spins  $S_i = 3/2$  and g = 2.0, while the second one is for one spin S = 1/2 and g = 2.0) due to the significant contribution of angular momentum of excited states to the ground spin states [30]. In the case of cobalt(II) complex (**1**), there is shallow maximum around 260 K and then the  $\mu_{eff}$  drops reaching a minimum value of 6.3  $\mu_B$  at T = 21 K, afterwards it starts to rise to a maximal value of 6.8  $\mu_B$  at T = 2.3 K. This behavior is typical for octahedral Co(II) complexs with non-zero orbital angular momentum in the ground state [30] and the very low temperature data are affected by weak ferromagnetic isotropic exchange (*J*). On contrast, the copper(II) complex (**2**) shows almost constant  $\mu_{eff}$  down to  $\approx 20$  K and then decreases to a value of 0.81  $\mu_B$  at T = 1.9 K which is also accompanied by a maximum on the mean susceptibility located at T = 3.6 K ( $M_{mol}$  vs. *T* curve, see inset in Fig. 6). This feature is a fingerprint for antiferromagnetically coupled homospin dimer.



**Fig. 5** Magnetic data for (1). *Left*: the temperature dependence of the effective magnetic moment and molar magnetization measured at B = 0.1 T. *Right*: the reduced magnetization data measured at T = 2 and 5 K. Open circles: experimental data and red solid lines: calculated data using the equation 4, with J = +2.8(2) cm<sup>-1</sup>,  $\lambda = -136(4)$  cm<sup>-1</sup>,  $\alpha = 1.27(1)$ ,  $\Delta = -383(18)$  cm<sup>-1</sup>.



**Fig. 6** Magnetic data for (2). *Left*: the temperature dependence of the effective magnetic moment and molar magnetization measured at B = 1 T. *Right*: the reduced magnetization data measured at T = 2 and 5 K. Open circles: experimental data and red solid lines: calculated data using the equation 2, with J = -4.45(7) cm<sup>-1</sup>, g = 2.12(1),  $\chi_{TIP} = 4.8(7)$  x10<sup>-9</sup> m<sup>3</sup>mol<sup>-1</sup>. Data are scaled per one Cu(II) ion.

In order to quantitatively analyze the experimental magnetic data of Cu(II) compound (2), the following spin Hamiltonian for dinuclear system was postulated

$$\hat{H} = -J(\vec{S}_A \cdot \vec{S}_B) + \mu_B Bg\left(\hat{S}_{z,A} + \hat{S}_{z,B}\right)$$
<sup>(2)</sup>

where the isotropic exchange parameter *J* determines the energy gap between the singlet (*S* = 0) and triplet states (*S* = 1), resulting from the coupling of two local spins  $S_A = S_B = 1/2$ . The, simple formula for the molar magnetization exists (*x* =  $\mu_B g B$ ) [30]

$$M_{\rm mol} = \mu_{\rm B}gN_{\rm A} \Big[ \exp((J+x)/kT) - \exp((J-x)/kT) \Big] / \Big[ 1 + \exp((J+x)/kT) + \exp(J/kT) + \exp((J-x)/kT) \Big]$$
(3)

which was subsequently used to fit both temperature and field dependent data of (2). The best fit parameters were found as  $J = -4.45(7) \text{ cm}^{-1}$ , g = 2.12(1),  $\chi_{\text{TIP}} = 4.8(7) \times 10^{-9} \text{ m}^3 \text{mol}^{-1}$ , where  $\chi_{\text{TIP}}$  is the temperature-independent paramagnetism (Fig. 6). The fitted *J*-value ( $J = -4.45(7) \text{ cm}^{-1}$ ) is in good agreement with value derived from a simple formula for dinuclear homospin species,  $J/kT_{\text{max}} = 1.599$  [30], which yields  $J = -4.0 \text{ cm}^{-1}$ . Also, the fitted *J*-value is close to  $J^{\text{Yam}} = -4.43 \text{ cm}^{-1}$  derived from DFT calculations (Table 2).

It is well known that the six-coordinated octahedral Co(II) complexes may have more complex magnetic behavior due to the contribution of the orbital angular momentum (*L*) as also suggested by CASSCF/NEVPT2 calculations. Concisely, the lowest-lying atomic term <sup>4</sup>F is split in octahedral ligand field symmetry to three crystal-field terms <sup>4</sup>T<sub>1</sub>, <sup>4</sup>T<sub>2</sub> and <sup>4</sup>A<sub>2</sub>, from which only the first term is thermally populated and has non-zero orbital angular momentum. On lowering the symmetry, the <sup>4</sup>T<sub>1</sub> term is further split into lower crystal field terms separated by  $\Delta$  [31]. Due to the heteroleptic distorted octahedral coordination sphere of Co(II) in **1**, such energy splitting is expected and accordingly the following Hamiltonian was used to describe the magnetic properties of **1**:

$$\hat{H} = -J \left( \mathbf{S}_{1} \cdot \mathbf{S}_{2} \right) - \alpha \lambda \left( \mathbf{S}_{1} \cdot \mathbf{L}_{1} + \mathbf{S}_{2} \cdot \mathbf{L}_{2} \right) + \Delta \left( L_{z,1}^{2} - L_{1} (L_{1} + 1) / 3 + L_{z,2}^{2} - L_{2} (L_{2} + 1) / 3 \right) + \mu_{B} \mathbf{B} \left( g_{e} \mathbf{S}_{1} + g_{e} \mathbf{S}_{2} - \alpha \mathbf{L}_{1} - \alpha \mathbf{L}_{2} \right)$$

$$(4)$$

where  $\alpha$  is orbital reduction factor,  $\lambda$  is spin-orbit coupling and  $g_e = 2.0023$ . The Hamiltonian is applied to  $|M_{L,1}, M_{S,1}\rangle|M_{L,2}, M_{S,2}\rangle$  functions with  $M_{L,k} = 0$ ,  $\pm 1$  and  $M_{S,k} = \pm 1/2$ ,  $\pm 3/2$ . The angular orbital momentum *L* is considered as fictitious angular momentum, L = 1, with the effective Lande *g*-factor,  $g_L = -\alpha$ , due to T<sub>1</sub>-P isomorphism [32]. Then, there are 144 magnetic levels, which are calculated and used in partition function *Z* to calculate molar magnetization as

$$M_a = N_A kT \frac{d\ln Z}{dB_a}$$
(5)

for given direction of magnetic field  $\mathbf{B}_a = B \cdot (\sin\theta \cos\varphi, \sin\theta \sin\varphi, \cos\theta)$ . Finally, the integral (orientational) average of molar magnetization is calculated by Eq. 6 in order to properly simulate experimental powder magnetization data.

 $M_{mol} = 1/4\pi \int_0^{2\pi} \int_0^{\pi} M_a \sin\theta d\theta d\varphi$  (6) The orbital reduction factor comprises of two parameters,  $\alpha = A\kappa$ ; where A varies from 1 to 3/2 and results from admixture of the excited terms reflecting the ligand field strength, and  $\kappa$ describes the lowering orbital contribution due to covalency of the metal-ligand bond and it usually holds  $0.70 < \kappa < 1$ . Moreover, the spin-orbit coupling parameter  $\lambda$  can also be reduced compared to its free-ion value  $\lambda_0 = -180$  cm<sup>-1</sup> as a result of the covalent character of the donoracceptor bond. By employing this advanced model, we obtained the following parameters: J =+2.8(2) cm<sup>-1</sup>,  $\lambda = -136(4)$  cm<sup>-1</sup>,  $\alpha = 1.27(1)$ ,  $\Delta = -383(18)$  cm<sup>-1</sup>, again by simultaneously fitting both temperature and field dependent data (Fig. 5). The negative value of  $\Delta$  means that there is an easy axis type of magnetic anisotropy in contrast to the positive  $\Delta$  found in another ferromagnetically coupled Co(II) complex with easy plane anisotropy [33]. The easy axis type of magnetic anisotropy is clearly demonstrated and visualized in 3D plot of molar magnetization in Fig. S2.

It is evident from analysis of the experimental magnetic data of 1 that there is a weak ferromagnetic exchange between Co(II) ions. This contradicts DFT calculations predicting antiferromagnetic exchange, which may be surprising, because we used this method several times for complexes with related ligands and always good agreements were found between the calculated and fitted *J*-parameters [29]. However, in this peculiar case, we can speculate that this discrepancy is caused by unquenched orbital momentum in the ground state and therefore the broken-symmetry procedure is not suitable to treat this system.

Unfortunately, there are not many information available about hexa-coordinated di-( $\mu$ -Cl) Co(II) complexes as manifested in Table 3. Magnetic exchange seems to be weak and either ferro- or anti-ferromagnetic, and its proper determination was often hampered either by large ZFS or magnetic ordering. Therefore, more data are needed in order to properly correlate the magneto-structural properties in this class of Co(II) complexes.

**Table 3.** Magneto-structural data for hexa-coordinate  $\mu$ -dichlorido-bridged Co(II) compounds.<sup>*a*</sup>

Complex	Chromophore	d(Co-Cl)	< (Co-Cl-Co)	d(Co-Co)	J	Ref.
_	_	(Å)	(°)	(Å)	$(cm^{-1})$	
$[Co_2(L^1)_2Cl_2][CoCl_4]$	CoN <sub>4</sub> Cl <sub>2</sub>	2.480	94.97	3.657	<i>J</i>   << 1 <sup>b</sup>	29
		2.481	95.24			
$[Co(4,4)-bpy)Cl_2]_n$	CoN <sub>2</sub> Cl <sub>4</sub>	2.487	93.11	3.611	$J > 0^{b,c}$	30
${(Me_3NH)[CoCl_3(H_2O)_2]}_n$	CoO <sub>2</sub> Cl <sub>4</sub>	2.456	95.52	3.637	+5.4 <sup>c</sup>	31
		2.503	93.14			
1	CoN <sub>4</sub> Cl <sub>2</sub>	2.404	101.82	4.006	+2.8(2)	This work
		2.750				

<sup>*a*</sup> Ligand abbreviations:  $L^1 = 1,1'-[(5-methyl-1,3-phenylene)bis(methyleneoxy)]bis[3-methyl-$ *N* $-[(2-pyridinyl-<math>\kappa N$ )methylene]-2-butanamine- $\kappa N$ ]

<sup>b</sup> Experimental magnetic data were not quantitatively analyzed.

<sup>c</sup> Magnetic ordering at low temperatures.

**Dynamic magnetic properties of (1).** The observed axial magnetic anisotropy and weak ferromagnetic exchange motivated us to measure the AC susceptibility for (1). At zero static magnetic field, there was no out-of-phase susceptibility signal, which also confirms that there is no long-range ferromagnetic ordering. However, the field dependent measurement performed at T = 1.9 K revealed non-zero imaginary susceptibility (Fig. S3). Therefore, the AC susceptibilities were measured at non-zero static field,  $B_{dc} = 0.5$  T at low temperatures. The susceptibility data, depicted in Fig. 7 showed a pattern that is characteristic for slow relaxation of the magnetization and similar to that observed in single-molecule magnets (SMM) [34]. Unfortunately, the curves did not show the clear maxima for out-of-phase susceptibility up to the lowest available temperature. This trend prohibits us from getting detailed analysis (relaxation times and spin reversal barrier). So far, there are many reports of the mononuclear Co(II) SMM compounds [35,36,37], and there is also a large group of polynuclear Co(II) SMMs [38], but to the best of our knowledge, only one paper on dinuclear Co(II) complexes showing slow relaxation of magnetization was reported up to now [39]. The borderline between mononuclear and dinuclear Co(II) SMM is found in penta-coordinate Co(II) complex [40], where a weak ferromagnetic exchange coupling was mediated through  $\pi$ - $\pi$  stacking interactions. Therefore, herein presented dinuclear Co(II) complex (1) seems to be rare example of dinuclear Co(II) complex exhibiting slow relaxation of the magnetization.



Fig. 7. In-phase  $\chi_{real}$  and out-of-phase  $\chi_{imag}$  molar susceptibilities for 1 measured at the applied external field  $B_{dc} = 0.5$  T and various frequencies showed in legend. Lines serve as guides for the eyes.

### 3.5. Cytotoxic activity

A number of pyrazole-containing metal complexes were demonstrated to be effective against some cancer cells [41], therefore we made an effort to explore the biological potential of complexes **1** and **2**. The compounds were evaluated by means of the MTT assay for their *in vitro* cytotoxicity against human breast adenocarcinoma (MCF7) and human cervix epithelioid carcinoma (HeLa) cell lines. The results showed that the cobalt(II) complex **1** is inactive up to the tested concentration of 50  $\mu$ M. On the other hand, complex **2** exceeded the cytotoxicity of the reference drug cisplatin significantly in the case of HeLa [IC<sub>50</sub> = 2.5(0.9)  $\mu$ M as compared to IC<sub>50</sub> of 25.4(7.3)  $\mu$ M for cisplatin], while the complex was found to be less cytotoxic against MCF7 [IC<sub>50</sub> = 20.1(0.1)  $\mu$ M] as compared to cisplatin [IC<sub>50</sub> = 11.9(2.5)  $\mu$ M]. Thus, the copper(II) complex **2** has been revealed to be a promising compound for further and deeper biological study.

#### 4. Conclusions

The  $[Co_2(bedmpzp)_2(\mu-Cl)_2](PF_6)_2$  (1) and  $[Cu(bedmpzp)Cl]PF_6$  (2) complexes, where bis(3,5dimethyl-1H-pyrazol-1-yl-1-ethyl)(2-pyridylmethyl)amine (bedmpzp) is a tripod tetradenate *N*donor ligand, were synthesized and structurally characterized. It is worth mentioning that increased flexibility of the pyrazolyl groups in bedmpzp in comparison with pz<sub>2</sub>py resulted in change of coordination number and nuclearity in Co(II) complexes with similar composition, which is apparent from comparison of molecular structures of  $[Co(pz_2py)Cl]BF_4 \cdot 1/2CH_3OH$  [3], and compound (1). Magnetic data of (1) revealed a weak ferromagnetic exchange (J = +2.8(2)cm<sup>-1</sup>) and the axial type of magnetic anisotropy. Moreover, the AC susceptibility measurements

disclosed slow relaxation of magnetization in non-zero static magnetic field, thus setting (1) into a class of field-induced single-molecule magnets. The X-ray structural analysis of (2) confirmed the formation of supramolecular dimers of {[Cu(bedmpzp)Cl]PF<sub>6</sub>}<sub>2</sub> connected through noncovalent contacts of the Cu···Cl type with the separation distance of 3.5712(14) Å. This arrangement is then associated with the observation of a weak antiferromagnetic exchange (J = -4.45(7) cm<sup>-1</sup>), which was also supported by DFT calculations. Finally, the screening of *in vitro* cytotoxicity revealed that complex **2** is a promising compound for forthcoming biological study owing to its significant cytotoxicity on the HeLa cell line, with IC<sub>50</sub> = 2.5(0.9) µM. To conclude, the herein prepared unsymmetrical tripod ligand bedmpzp seems to be perspective for the synthesis of magnetically and biologically interesting coordination compounds, thus investigation of the small alternations of anionic ligands aiming at improving the physical properties is underway.

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### **Appendix A and Supplementary Material**

CCDC-1452109 and -1452110 contain the crystallographic data in CIF format for 1 and 2, respectively. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www. ccdc.cam.ac.uk/data request/cif. The crystallographic data for 1 and 2 are Table S1. Individual contributions in to D-tensor for molecular fragment  $[CoZn(bedmpzmpy)_2(\mu-Cl)_2]^{2+}$  of 1 calculated by CASSCF/NEVPT2 and its energy levels of ligand field multiplets in zero magnetic field derived from CASSCF/NEVPT2 calculations are summarized in Tables S2 and S3, respectively. Figure S1 shows comparison of UV-VIS spectra for 1, Figure S2 shows selected magnetic orbitals for 1 and 2, Figures S3-S4 are showing the magnetic properties of the complexes. Supplementary data associated with this article can be 

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### **Graphical Abstract (Synopsis)**

The dinuclear doubly bridged-dichlorido complex  $[Co_2(bedmpzp)_2(\mu-Cl)_2](PF_6)_2$  (1) and the mononuclear  $[Cu(bedmpzp)Cl]PF_6$  (2) were structurally and magnetically characterized. Complex 1 revealed weak ferromagnetic exchange with slow relaxation of magnetization, whereas 2 showed weak antiferromagnetic exchange. The *in vitro* cytotoxicity of the complexes against MCF7 and HeLa human cancer cell lines were also tested.

## **Highlights**

- Dinuclear Co(II) and mononuclear Cu(II) complexes were prepared using a tripodal ligand •
- Bis(3,5-dimethyl-1H-pyrazol-1-yl-methyl)(2-pyridylmethyl)amine was utilized as the ligand
- Co(II) complex revealed weak ferromagnetic exchange, axial anisotropy and slow relaxation of • magnetization
- The in vivo cytotoxicity against MCF7 and HeLa human cancer cell lines were also examined.