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# Structural consequences of the introduction of 2,2′-bipyrimidine as auxiliary ligand in triazolopyrimidine-based transition metal complexes. *In vitro* antiparasitic activity

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ABSTRACT

Five new metal complexes containing 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives and the chelating-bridging ligand 2,2′-bipyrimidine have been synthesized and structurally characterized for Cu(II), Zn(II) and Cd(II) ions. Three different 1,2,4-triazolo[1,5-*a*]pyrimidine ligands have been used: the unsubstituted (tp), 5,7-dimethylated (dmtp) and 7-amine substituted (7atp) derivatives. In all metal complexes, triazolopyrimidines coordinate monodentately via N3, while the versatile binding behaviour of 2,2′-bipyrimidine ligand (bpym) leads to mononuclear units $[Cd(tp)(bpym)_2(H_2O)](ClO_4)_2$ (**2**) and $[Cu(dmtp)_2(bpym)(H_2O)_2](ClO_4)_2{\cdot}H_2O$ (**3**), dinuclear species $[Cu_2(tp)_2(bpym)_2(\mu\text{-}bpym)(ClO_4)_2](ClO_4)_2$ (**1**) and $[Zn_2(7atp)_4(\mu\text{-}bpym)(H_2O)_4](ClO_4)_4{\cdot}2(7atp)$ (**5**) and the helicoidal chain-like complex $\{[Cd(dmtp)\text{-}(H_2O)\text{-}(\mu\text{-}bpym)_2Cd(dmtp)_2](ClO_4)_4{\cdot}dmtp{\cdot}H_2O\}_n$ (**4**). Different supramolecular motifs are originated in the crystal structures of compounds **2**, **3** and **5** by hydrogen bonds formation and π–π interactions, being the latter especially relevant. A weak antiferromagnetic coupling occurs across bpym-bridge for copper(II) dimer **1** ($J = -7.2\ cm^{-1}$). In order to evaluate the chemotherapeutic potential of the non-cadmium complexes (**1**, **3** and **5**), they have been tested *in vitro* against *Leishmania infantum*, *Leishmania braziliensis* and *Trypanosoma cruzi*, which cause leishmaniasis and Chagas disease, respectively.

## 1. Introduction

The condensation of a 1,2,4-triazole ring with a pyrimidine ring leads to the formation of bicyclic heterocycles called 1,2,4-triazolo[1,5-*a*]pyrimidines. These heterocycles have proved to be versatile ligands as they have several nitrogen atoms with accessible lone pairs to bind to Lewis acids like metal ions (see Scheme 1). Moreover, their versatility can be increased by the ring-substitution with functional groups containing donor atoms like nitrogen, sulfur or oxygen, leading to a wider range of coordination modes and structural topologies in their metal complexes. Previous studies reveal that the most frequent binding mode of these heterocycles is monodentate through its N3 position, followed by bidentate through N3 and N4 atoms [1].

The increasing interest aroused recently around these type of ligands does not lie only in their great capacity to act as suitable building blocks for the synthesis of novel metal–organic multidimensional systems [1,2] but also in their biomimetic character, since they resemble the natural occurring puric nucleobases adenine and guanine. The only difference between 1,2,4-triazolo[1,5-*a*]pyrimidine and purine heterocycles is the presence of a nitrogen atom in a bridgehead position and the disappearance of the proton of the five-membered ring. Metal complexes with 1,2,4-triazolo[1,5-*a*]pyrimidines have been the subject of chemical and biological studies due to their interesting pharmacology including antipyretic, analgesic, antiinflammatory, antitumoral and antiparasite properties [3,4].

One of our main research aims is to combine the use of triazolopyrimidine derivatives with another polydentate ligands, which can act either as chelate ligands or as spacers, in order to obtain novel multidimensional metal–organic systems showing interesting biological, magnetic, luminescent, adsorption or catalytic properties [1–4]. In this work, we have chosen the chelating-bridging ligand 2,2′-bipyrimidine (bpym) due to its great capability to form multidimensional metal complexes, the nuclearity of which might depend mainly on its coordination mode. Moreover, its presence may also influence the coordination behaviour of triazolopyrimidine derivatives [2], and vice versa, and confers interesting magnetic properties to the resulting compounds.

In the present work, we have used three different triazolopyrimidine ligands: 1,2,4-triazolo[1,5-*a*]pyrimidine (tp) 5,7-dimethyl-1,2,

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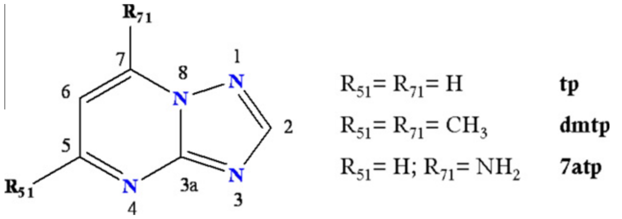

**Scheme 1.** Triazolopyrimidine derivatives used as ligands in this work, displaying the IUPAC ring-numbering system.

4-triazolo[1,5-*a*]pyrimidine (dmtp) and 7-amine-1,2,4-triazolo[1,5-*a*]pyrimidine (7atp) (see Scheme 1), and we report the results obtained from combining them with bpym ligand to form new transition metal complexes with the divalent ions Cu(II), Zn(II) and Cd(II).

As a result, the following five new metal compounds have been isolated from reaction with perchlorate salts in water: $[Cu_2(tp)_2(bpym)_2(\mu\text{-bpym})(ClO_4)_2](ClO_4)_2$ (**1**), $[Cd(tp)(bpym)_2(H_2O)](ClO_4)_2$ (**2**), $[Cu(dmtp)_2(bpym)(H_2O)_2]$ $(ClO_4)_2{\cdot}H_2O$ (**3**), $\{[Cd(dmtp)(H_2O)$-$(\mu\text{-bpym})_2Cd(dmtp)_2](ClO_4)_4{\cdot}dmtp{\cdot}H_2O\}_n$ (**4**) and $[Zn_2(7atp)_4(\mu\text{-bpym})(H_2O)_4](ClO_4)_4{\cdot}2(7atp)$ (**5**). The five compounds show different nuclearity, ranging from mononuclear units **2** and **3** to dimers **1** and **5** and the helicoidal chain-like compound **4**. The structures of these compounds show clearly the critical role of bpym in determining the topologies as it increase complexes nuclearity when acting as bridging ligand. On the other hand, triazolopyrimidine derivatives interact with metal ions only through their N3 atom, its more usual coordination mode [1].

Apart from a structural analysis of these five new compounds, this article also includes their spectroscopic characterization (IR and UV–Vis on solid samples) together with a study of the Cu(II) dimer **1** magnetic behaviour and EPR spectra for both copper complexes, as well as the results for *in vitro* antiparasitic activity of the non-cadmium complexes **1**, **3** and **5**.

## 2. Experimental

### 2.1. General

All analytical reagents were purchased from commercial sources and used without further purification. Caution! Perchlorate salts are potentially explosive and only should be handled in small quantities.

### 2.2. Preparation of $[Cu_2(tp)_2(bpym)_2(\mu\text{-bpym})(ClO_4)_2](ClO_4)_2$ (1) and $[Cd(tp)(bpym)_2(H_2O)](ClO_4)_2$ (2)

Over a 15 mL-aqueous solution containing 0.4 mmol of the respective metal perchlorate ($Cu(ClO_4)_2{\cdot}6H_2O$, 0.148 g; $Cd(ClO_4)_2{\cdot}H_2O$, 0.0124 g) and 0.8 mmol of tp ligand (0.096 g), an ethanolic solution of 2,2′-bipyrimidine (0.8 mmol, 0.126 g for **1**; 0.4 mmol, 0.065 g for **2**, 10 mL) was added. The resulting clear solution was refluxed for 1 h. After 1–2 weeks standing at room temperature, crystals of compounds **1** and **2** suitable for X-ray studies were isolated by filtration.

Compound **1**: Yield ~70%. *Anal.* Calc. for $C_{34}H_{26}Cl_4Cu_2N_{20}O_{16}$: C, 32.94; H, 2.11; N, 22.60. Found: C, 33.03; H, 2.12; N, 22.53. Main IR bands ($cm^{-1}$): 1624s ($\nu_{tp}$), 1544s ($\nu_{pym1}$), 1514s ($\nu_{pym2}$), 1582vs ($\nu_{pym}$ bpym), 1089vs ($\nu_{ClO4}$), 3095m ($\nu_{C-H}$).

Compound **2**: Yield ~60%. *Anal.* Calc. for $C_{21}H_{18}CdCl_2N_{12}O_9$: C, 32.94; H, 2.37; N, 21.95. Found: C, 33.01; H, 2.48; N, 22.02. Main IR bands ($cm^{-1}$): 1625s ($\nu_{tp}$), 1544s ($\nu_{pym1}$), 1524s ($\nu_{pym2}$), 1575vs ($\nu_{pym}$ bpym), 1088vs ($\nu_{ClO4}$), 3102m ($\nu_{C-H}$), 3425m ($\nu_{O-H}$).

### 2.3. Preparation of $[Cu(dmtp)_2(bpym)(H_2O)_2](ClO_4)_2{\cdot}H_2O$ (3) and $\{[Cd(dmtp)(H_2O)(\mu\text{-bpym})_2Cd(dmtp)_2](ClO_4)_4{\cdot}dmtp{\cdot}H_2O\}_n$ (4)

Over a 15 mL-aqueous solution containing 0.4 mmol of the respective metal perchlorate ($Cu(ClO_4)_2{\cdot}6H_2O$, 0.148 g; $Cd(ClO_4)_2{\cdot}H_2O$, 0.0124 g) and 0.8 mmol of dmtp ligand (0.118 g), an ethanolic solution of 2,2′-bipyrimidine (0.4 mmol, 0.065 g, 10 mL) was added. The resulting clear solution was refluxed for 1 h. After 1–2 weeks standing at room temperature, deep-blue prismatic crystals of **3** and colourless prismatic crystals of **4** were collected. Single-crystals for both compounds were studied by X-ray diffraction.

Compound **3**: Yield ~40%. *Anal.* Calc. for $C_{22}H_{28}Cl_2CuN_{12}O_{11}$: C, 34.27; H, 3.66; N, 21.80. Found: C, 33.73; H, 3.59; N, 21.92. Main IR bands ($cm^{-1}$): 1634vs ($\nu_{tp}$), 1558s ($\nu_{pym}$), 1581vs ($\nu_{pym}$ bpym), 1089vs ($\nu_{ClO4}$), 3087m ($\nu_{C-H}$), 3458s, 3579s ($\nu_{O-H}$).

Compound **4**: Yield ~65%. *Anal.* Calc. for $C_{44}H_{48}Cd_2Cl_4N_{24}O_{18}$: C, 33.71; H, 3.09; N, 21.44. Found: C, 33.67; H, 3.14; N, 21.26. Main IR bands ($cm^{-1}$): 1629s ($\nu_{tp}$), 1556s ($\nu_{pym}$), 1577s ($\nu_{pym}$ bpym), 1090vs ($\nu_{ClO4}$), 3084m, 3111m ($\nu_{C-H}$), 3426s ($\nu_{O-H}$).

### 2.4. Preparation of $[Zn_2(7atp)_4(\mu\text{-bpym})(H_2O)_4](ClO_4)_4{\cdot}2(7atp)$ (5)

In 20 mL of ethanolic-aqueous mixture (1:2), 0.15 mmol of $Zn(ClO_4)_2{\cdot}6H_2O$ (0.056 g), 0.3 mmol of 7atp ligand (0.040 g) and 0.15 mmol of 2,2′-bipyrimidine ligand (0.024 g) are dissolved. The clear mixture is stirred at 80 °C for 30 min. and then kept standing at room temperature. After 5 days, yellow prismatic crystals of **5** were isolated and studied by single-crystal X-ray diffraction. Yield ~15%. *Anal.* Calc. for $C_{38}H_{44}Cl_4N_{34}O_{20}Zn_2$: C, 29.08; H, 2.92; N, 30.34. Found: C, 28.83; H, 2.82; N, 29.70. Main IR bands ($cm^{-1}$): 1671vs ($\nu_{tp}$), 1582vs ($\nu_{pym}$), 1601s, 1416m ($\nu_{pym}$ bpym), 1085vs ($\nu_{ClO4}$), 3333s, 3416s ($\nu_{O-H}$).

### 2.5. Physical measurements

Microanalysis of C, H and N were performed in a Fisons Instruments EA-1008 analyser. Reflectance diffuse spectra were made on a VARIAN model CARY-5E spectrophotometer. All this equipment is sited at the Centro de Instrumentación Científica of the University of Granada. IR spectra were recorded on a ThermoNicolet IR 200 spectrometer using KBr pellets.

Q-band EPR spectra were registered on a Bruker EMX system equipped with an ER-510-QT resonator and a ER-4112-HV liquid helium cryostat. The magnetic field was calibrated by a NMR probe and the frequency inside the cavity was determined with a Hewlett-Packard 5352B microwave frequency counter. The spin Hamiltonian parameters were estimated by comparison of the experimental spectra with those obtained by a computer simulation program (WINEPR Simfonia® v1.25 of Bruker) working at the second order of the perturbation theory. The parameters were then optimized by the trial-and-error method looking for the best-fit results.

Magnetization and variable temperature (1.9–300 K) magnetic susceptibility measurements on polycrystalline sample of compound **1** were carried out on a Quantum Design SQUID MPMS XL-5 device operating at 10 *T*. The experimental susceptibilities were corrected for the diamagnetism of the constituent atoms by using Pascal's tables.

### 2.6. Single-crystal structure determination

Suitable crystal of compounds **1**–**5** were mounted on glass fibre and used for data collection at room temperature (293 K) in a Bruker SMART APEX CCD system with Mo Kα radiation ($\lambda$ = 0.7107 Å). The data were processed with APEX2 [5] and corrected for absorption using SADABS [6]. The structures were solved by direct methods using SIR97 [7], revealing positions of all non-hydrogen atoms.