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ANTIMICROBIAL EFFECT OF OLIGOMERIC COPPER(II) DERIVATIVES OF BIS(PYRIMIDIN-2-YLTHIO)- AND BIS(4,6-DIMETHYLPYRIMIDIN-2-YLTHIO)ALKANES

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ABSTRACT: A novel series of copper(II) derivatives of bis(pyrimidin-2-ylthio)- and bis(4,6-dimethylpyrimidin-2-ylthio)alkane of general formula $[Cu_xCl_y(L)_z]_n$ {x = 1, y = 2, z = 1, L = *ptm* (**1**), *pte* (**2**), *dptm* (**4**), *dpte* (**5**), *dpth* (**6**); x = 2, y = 4, z = 3, L = *pth* (**3**)} were tested for antimicrobial activity. These complexes were characterized by elemental analysis, infrared spectroscopy (IR) and gel permeation chromatography (GPC). Complex-**4**, **5** and **6** have the metal at the center of a square planar geometry, and in complex-**1**, **2** and **3** the metal is at the center of a square pyramidal geometry. The structure of complex-**4**, determined by X-ray diffraction analysis, shows this compound as an oligomer with one-dimensional chain in zigzag conformation. The high average molecular weight (Mw) of these copper(II) complexes confirms their oligomeric character. Although the free ligands were inactive against the microorganisms tested, the copper(II) derivatives showed good antifungal and antibacterial inhibition against *C. albicans*, *C. tropicalis*, *S. aureus* and *E. coli*, more effective than *Nystatin* and *Norfloxacin*.

KEYWORDS: Antimicrobial activity; Bis(pyrimidin-2-ylthio)alkanes; Oligomeric copper(II) complexes; Bactericide; Fungicide.

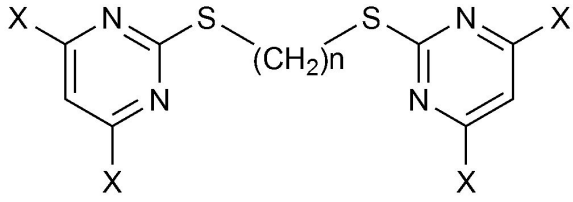
1. INTRODUCTION

Copper is an essential element to plants and humans. This metal is located in the active sites of proteins and enzymes which are crucial to the metabolism of living organisms executing several important functions such as electron transfer and reduction of oxygen (Silva and Williams, 1993; Lewis *et al.*, 2001; Donnelly *et al.*, 2008; Rocchi *et al.*, 2012). The use of copper-based compounds as fungicides for plant disease control are known since

19th century with the discovery of the antifungal properties of copper(II) sulfate. Afterwards new copper(II)-based fungicides were developed such as cufraneb and cuprobam which can be currently purchased from the market. However, because of the appearance of resistant population of microorganisms to commercial drugs, such as *S. aureus* and *E. coli* to vancomycin (Chakraborty *et al.*, 2012), there is a continued need for novel fungicides and bactericides to control fungal plant and human diseases. Copper(II) compounds are good candidates owing to their unquestionable antifungal (Recio Despaigne *et al.*, 2012) and antibacterial activity (Yuan *et al.*, 2015). Nevertheless, the preparation of desired coordination compounds sometimes is not an easy task considering that the molar composition between reactants may not lead to the expected chemical product. The literature provide examples on that where several transition metal derivatives of bis(pyridin-2-ylthio)alkanes were isolated in 1:1, 1:2 and 1:6 (M:L) molar ratio starting from equimolar reactants (Xie *et al.*, 2005).

The bis(pyrimidin-2-ylthio)alkanes are polydentate ligands with several possibilities of bonding to metallic centers through monodentate and chelating coordination modes. These ligand types are expected to show antimicrobial activity against fungi, Gram-positive and Gram-negative bacteria similarly to other compounds containing the elements sulfur and nitrogen in their chemical composition such as thiazoles, 1,3,4-thiadiazines and 1,3,4-thiadiazoles (Abdel-Aziem, 2015). In addition, only a few studies regarding to the coordination chemistry of pyrimidinthioalkanes and corresponding compounds are reported (Kinoshita *et al.*, 2003; Xie e Bu, 2003; Xie *et al.*, 2005; Samanamu *et al.*, 2008; Xie *et al.*, 2004).

To continue with our research program regarding the coordination chemistry and biological activity of metal-based complexes, a series of copper(II) derivatives of bis(4,6-dimethylpyrimidin-2-ylthio)alkanes and bis(pyrimidin-2-ylthio)alkanes were prepared as showed in Figure 1. Herein we report the characterization of these copper(II) complexes and their bioactive effect on phytopathogens (*A. flavus*, *F. graminearum*, *A. solani* and *B. sorokiniana*), pathogenic fungi (*C. albicans*, *C. tropicalis*), Gram-negative (*E. coli*) and Gram-positive (*S. aureus*) bacteria as well. Several molar ratio reactions were also carried out to evaluate the stoichiometry influence on the preparation of these coordination copper(II) complexes.



X = H (n = 1, *ptm*; n = 2, *pte;* n = 6, *pth*)
X = CH_3 (n = 1, *dptm*; n = 2, *dpte*; n = 6, *dpth*)

Figure 1 – Structural representation of the pyrimidin-2-ylthio derivatives.

2. MATERIALS AND METHODS

2.1. Chemical Characterization

A Perkin Elmer Spectrum 1000 grating spectrometer was used to obtain the infrared spectra in Nujol between CsI windows, scanning from 4000 to 200 cm^{-1}. The microanalysis were obtained from a Perkin Elmer 2004 CHNS/O equipment. The molecular mass of the complexes were determined by gel permeation chromatography (GPC) through a GPC803D-GPC802D, 2 x 300 x 8 mm column in dimethylformamide (DMF). Single crystal X-ray data were collected at room temperature by the Oxford GEMINI A – Ultra diffractometer with MoKα (λ = 0.71073 Å). Data reduction and cell refinement were done by CrysAlis RED, (Oxford diffraction Ltd – Version 1.171.32.38 program) (Crysalisred, 2008). The structures were resolved and refined by SHELXL-97 (Sheldrick, 1997). Multiscan absorption corrections were applied according to the method previously reported in the literature (Blessing, 1995). The non-hydrogen atoms were correlated with anisotropic displacement parameters. A rigid model with C–H distances of 0.93 Å for aromatic and 0.96 Å for methylene groups defines all hydrogen atoms. The displacement parameters of H atoms were at 1.2 Ueq of their corresponding carbon atoms. The structures were drawn by ORTEP-3 for Windows and Mercury computing programs (Farrugia, 1997; Macrae *et al.*, 2006).

2.2. Phytopathogen Bioassay

The bioassay on the phytopathogens (*Aspergilus flavus*, *Fusarium graminearum*, *Alternaria solani*, *Bipolaris sorokiniana*) was conducted by the use of filter paper transfer technique as described in the literature (Dhingra e Sinclair, 1995). The conidia of the fungi were produced on freshly prepared standard potato-dextrose agar (PDA) containing 100 μg mL^{-1} of streptomycin sulphate to inhibit bacterial growth. The conidial suspension of each species was prepared by washing off the conidia from the agar surface, and the concentration of that in the wash water was adjusted to 10^4 mL^{-1}. An aliquot of PDA (10 mL) was poured into sterile 9 cm plastic culture plates. The synthesized copper(II) complexes were dissolved in methanol at the concentration of 500 μg mL^{-1}, and an aliquot of 10 μL was imbibed into sterile filter paper discs of 10 mm diameter. The discs absorbed with methanol only were used as control. After evaporation of the methanol under a laminar flow hood, 10 μL of the desired conidial suspension was placed at the center of the discs, which were transferred to the PDA culture plates and incubated at 25 °C. The presence or absence of fungal growth was examined after 48 h. In case of no growth, the incubation period was extended to 7 days. The experiment was finished in triplicate and repeated.

2.3. Pathogenic Fungi and Bacteria Bioassay

The bioassay on the pathogenic fungi and bacteria was conducted using specific culture medium for each microorganism. The *Candida albicans* (ATCC 10231) and *Candida tropicalis* (Squibb 750) were grown in aerobic conditions in Sabouraud dextrose broth (peptone 1.0 %, extract of pathogenic fungi 0.5 %, dextrose 2.0 %) or Sabouraud dextrose agar (peptone 1.0 %, extract of pathogenic fungi 0.5 %, dextrose 2.0 %, agar 1.5 %) at 37 °C and stored at 4 °C. Strains of *Escherichia coli* (ATCC 11229) and *Staphylococcus aureus*

(ATCC 25923) were grown in Nutrient broth (peptone 1.0 %, extract of meat 0.5%, NaCl 0.5%, pH 6.0) or Nutrient agar (peptone 1,0 %, extract of meat 0.5%, NaCl 0.5%, agar 1.5 %, pH 6.0) at 37 ºC and stored at 4 ºC.

2.4. Minimum Inhibitory Concentration (MIC)

The minimum inhibitory concentration (MIC) was determined by the broth dilution assays, according to the National Committee for Clinical Laboratory Standards protocol (NCCLS, 2003; 2002). The experiment consists of sterile tubes containing each 980 μL of culture medium, a suspension of the microorganism in sterile water (10 μL) and the substance test under investigation dissolved in DMSO (10 μL). The control is composed of 10 μL of sterile water (Tube 1, positive control), 10 μL of the solvent (Tube 2) and 20 μL of water (Tube 3, negative control). The tubes, sealed with sterile cotton, were incubated at 37 °C for a period of 24 h. The MIC was determined using standard solutions of the substance test in the range of 230 to 2550 μmol L^{-1}.

2.5. Bis(pyrimidin-2-ylthio)- and Bis(4,6-dimethylpyrimidin-2-ylthio)alkane

The bis(pyrimidin-2-ylthio)methane (*ptm*), ethane (*pte*), hexane (*pth*), bis(4,6-dimethylpyrimidin-2-ylthio)methane (*dptm*), ethane (*dpte*) and hexane (*dpth*) were prepared and characterized according to the method previously described in the literature (De Castro *et al.*, 2002; Berlini *et al.*, 2009). Typical infrared bands (cm^{-1}) recorded in Nujol / CsI related to ν(C=N + C=C) are: 1563, 1547 (*ptm*), 1563, 1546 (*pte*), 1563, 1549 (*pth*), 1579, 1532 (*dptm*), 1580, 1531 (*dpte*), 1578, 1529 (*dpth*). Similarly for ν(C–S), out-of-plane C–H and ring bending: 770, 753, 730, 666, 629 (*ptm*), 770, 749, 731, 694, 629 (*pte*), 771, 758, 739, 719, 630 (*pth*), 764, 736, 592, 564, 545 (*dptm*), 764, 727, 592, 563, 547 (*dpte*), 766, 722, 595, 564, 544 (*dpth*).

2.6. Preparation of Copper(II) Complexes

Several reactions were carried out to prepare the copper(II)-bis(pyrimidin-2-ylthio)alkanes and -bis(4,6-dimethylpyrimidin-2-ylthio)alkanes complexes. The influence of the stoichiometry on the chemical composition of the final reaction products was investigated considering the molar ratios of 1:1 and 2:1 (M:L) in methods A, B and C, and 1:2 in method D.

Method A: In a rounded bottom flask of 50 mL, 1.0 mmol of copper(II) chloride dihydrate was dissolved in ethanol (20 mL), then 0.5 or 1.0 mmol of solid bis(pyrimidin-2-ylthio)alkane was added into that. The mixture stirred for 45 minutes at room temperature leading to the formation of green precipitates. The solids were filtered off in air washed with ethanol and stored in desiccators.

$[CuCl_2(ptm)]_n.0.5\ H_2O$ (**1**). Colour: green. Yield of 0.334 g (47 %). Mp (°C): 178 d. Elemental analysis required for $C_9H_8N_4S_2Cl_2Cu$ (½H_2O): C, 28.53; H, 2.37; N, 14.79; found: C, 28.53; H, 2.02; N, 14.71; Mol Weight (Mw): 3.46 x 10^4; IR (Nujol / CsI): 3372 ν(H_2O),

1575, 1543 ν(C=N + C=C), 275 ν(Cu–N), 317, 376 ν(Cu–Cl). ν(C–S), out-of-plane C–H and ring bending: 770, 752, 730, 666, 649, 630.

$[CuCl_2(pte)]_n.H_2O$ (**2**). Colour: green. Yield of 0.266 g (59 %). Mp (°C): 186 d. Elemental analysis required for $C_{10}H_{12}N_4OS_2Cl_2Cu$: C, 29.82; H, 3.00; N, 13.91; found: C, 29.18; H, 2.23; N, 13.14; Mol Weight (Mw): 3.54 x 10^4; IR (Nujol / CsI): 3380 ν(H_2O), 1567, 1555 ν(C=N + C=C), 264 ν(Cu–N), 329, 382 ν(Cu–Cl). ν(C–S), out-of-plane C–H and ring bending: 763, 755, 736, 722, 700, 653.

$[Cu_2Cl_4(pth)_3].H_2O$ (**3**). Colour: green. Yield of 0.288 g (41 %). Mp (°C): 135 d. Elemental analysis required for $C_{42}H_{56}N_{12}OS_6Cl_4Cu_2$: C, 41.82; H, 4.68; N, 13.93; found: C, 41.28; H, 4.74; N, 13.68; Mol Weight (Mw): 7.93 x 10^2; IR (Nujol / CsI): 3387 ν(H_2O), 1578, 1562, 1548 ν(C=N + C=C), 253 ν(Cu–N), 318, 360 ν(Cu–Cl). ν(C–S), out-of-plane C–H and ring bending: 774, 761, 722, 651, 631.

Method B: The bis(4,6-dimethylpyrimidin-2-ylthio)alkane (0.5 or 1.0 mmol) was dissolved in dichloromethane (15 mL), then it was immediately added into the copper(II) chloride dehydrate (1.0 mmol) solution. The mixture was stirred for 50 minutes at room temperature, and the colored precipitates filtered off in air washed with ethanol and kept in desiccators.

$[CuCl_2(dptm)]_n$ (**4**). Color: purple. Yield of 0.329 g (70 %). Mp (°C): 167 d. Elemental analysis required for $C_{13}H_{16}N_4S_2Cl_2Cu$: C, 36.58; H, 3.78; N, 13.12; found: C, 37.03; H, 3.60; N, 13.21; Mol Weight (Mw): 2.9 x 10^4; IR (Nujol / CsI): 1588, 1528 ν(C=N + C=C), 247 ν(Cu–N), 341 ν(Cu–Cl). ν(C–S), out-of-plane C–H and ring bending: 722, 593, 579, 564.

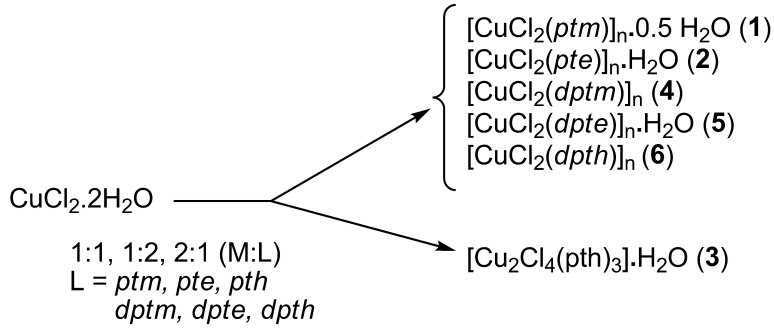
$[CuCl_2(dpte)]_n.H_2O$ (**5**). Color: grey. Yield of 0.242 g (90 %). Mp (°C): 158 d. Elemental analysis required for $C_{14}H_{20}N_4S_2OCl_2Cu$: C, 36.64; H, 4.39; N, 12.21; found: C, 36.90; H, 3.83; N, 12.00; Mol Weight (Mw): 3.1 x 10^4; IR (Nujol / CsI): 1591, 1532 ν(C=N + C=C), 249 ν(Cu–N), 324 ν(Cu–Cl). ν(C–S), out-of-plane C–H and ring bending: 759, 731, 586, 562, 575.

$[CuCl_2(dpth)]_n$ (**6**). Color: purple. Yield of 0.250 g (89 %). Mp (°C): 154-156. Elemental analysis required for $C_{18}H_{26}N_4S_2Cl_2Cu$: C, 43.50; H, 5.27; N, 11.27; found: C, 44.20; H, 5.34; N, 11.21; Mol Weight (Mw): 2.3 x 10^4; IR (Nujol / CsI): 1588, 1537 ν(C=N + C=C), 254 ν(Cu–N), 335 ν(Cu–Cl). ν(C–S), out-of-plane C–H and ring bending: 760, 724, 591, 577, 565.

Method C: Copper(II) chloride dihydrate (1.0 mmol) was dissolved in ethanol (20 mL), then 0.5 or 1.0 mmol of the appropriate ligand (*ptm*, *pte*, *pth*, *dptm*, *dpte*, *dpth*), dissolved in ethanol (15 mL), was added dropwise into the solution of the metal. The mixture stirred for approximately 45 minutes at room temperature. The precipitates were filtered off in air washed with ethanol and kept in desiccators.

Method D: To a rounded bottom flask of 100 mL, copper(II) chloride dihydrate (1.0 mmol) was dissolved in ethanol (20 mL). Then 2.0 mmol of the appropriate pyrimidin-2-ylthioalkanes (*ptm*, *pte*, *pth*, *dptm*, *dpte*, *dpth*), dissolved in ethanol (25 mL), was added at once into the solution of copper(II) choride. The mixture stirred for 1 h at room temperature

and the precipitates filtered off in air washed with ethanol or acetonitrile and kept in desiccators. The route for the preparation of the copper(II) compounds is summarized in Scheme 1.



Scheme 1 – Synthetic route of copper(II)-bis(pyrimidin-2-ylthio)alkanes and copper(II)-bis(4,6-dimethylpyrimidin-2-ylthio)alkanes

2.6.1. Supplementary material

X-ray crystallographic data was deposited with the Cambridge Crystallographic Data Centre (CCDC), and can be obtained free of charge on request at www.ccdc.cam.ac.uk/conts/retrieving.html or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1233 336033; e-mail: deposit@ccdc.cam.ac.uk, quote CCDC 781130 for complex-**4**.

3. RESULTS AND DISCUSSION

The reaction of bis(pyrimidin-2-ylthio)alkanes and bis(4,6-dimethylpyrimidin-2-ylthio)alkanes with copper(II) chloride led to the formation of oligomers that showed antimicrobial activity in several concentrations. The synthesis of inorganic polymers is not an easy task, although some polymeric compounds of copper(II) analogues are reported (Goher *et al.*, 1997; Kinoshita *et al.*, 2003). Among the copper(II) complexes prepared in this work, the structure of complex-**1** has been previously determined by single crystal X-ray diffraction analysis which shows this compound as an oligomer of two-dimensional arrangement (Samanamu *et al.*, 2008). This chemical aspect arouse our interest to synthesize inorganic polymers. In this context, four slightly different synthetic methods (A, B, C and D) were applied to accomplish this objective.

3.1. Gel Permeation Chromatography (GPC)

To confirm the polymerization reaction, the GPC technique was used to gain information on the average molecular mass of the copper(II) derivatives (Hossain *et al.*, 2011; Pauline *et al.*, 2011; Szuromi *et al.*, 2011). The complexes **1**, **2**, **4**, **5** and **6** showed high molecular mass corroborating with the oligomeric crystal structure of complex-**4** as well as that of complex-**1** (Samanamu *et al.*, 2008). Complex-**3**, synthesized by method A, C and D, showed average molar mass consistent with the formation of dimers, trimers or tetramers.

These synthetic approaches (A, B, C and D) had two common empirical aspects: (i) the reactions were carried out at room temperature and (ii) they all started with the metal precursor previously dissolved in ethanol. The differences between them, beyond the stoichiometry, were the physical state of the ligands. In the case of A, a solid amount of the ligand was added into the solution of copper(II) chloride, which dissolved slowly in course; in C, the ligand was dissolved in ethanol and afterwards added dropwise into the prior solution of the metal. In method A and C, both the experiments were set down to a kinetic control. In method B and D, after dissolving the ligand in the appropriate solvent, the mixture was poured at once into the copper(II) solution.

Based on the experimental procedures and the stoichiometry of the final reaction products (see Scheme 1), it is reasonable to postulate that despite the methodology used to prepare these complexes, the synthetic route follows a thermodynamic control. The only exception, complex-**3**, is probably related to an entropic factor in connection to the alkane configuration in between the sulfur atoms from the *pth* ligand.

3.2. Infrared Spectroscopy

The infrared spectra of the ligands showed vibrational bands in the range of 1580 to 1529 cm^{-1} related to the ν(C=N + C=C) stretching mode and 770 to 544 cm^{-1} associated with the ν(C–S) and the pyrimidyl ring deformation-stretching mode (Nakamoto, 1997; Jaskova *et al.*, 2007). The infrared shift observed in the range of 1591 to 1528 cm^{-1} and 774 to 564 cm^{-1} on the spectra of the copper(II) compounds are consistent with the stretching vibrations of the ligands upon coordination.

At the low frequency, the bis(pyrimidin-2-ylthio)alkane derivatives (**1**, **2**, **3**) showed two infrared bands in the region of 350 cm^{-1} related to terminal and bridging vibrations of ν(Cu–Cl). The Δν(Cu–Cl) is within 51 cm^{-1}. Usually chlorine atoms in cis position are within a maximum range of 30 cm^{-1}. The similarity of the infrared spectral feature between these copper(II) compounds suggests that they probably have the same stereochemistry as that shown by the crystal structure of complex-**1**, especially concerning the chlorine atoms (Samanamu *et al.*, 2008). The bis(4,6-dimethylpyrimidin-2-ylthio)alkane derivatives (**4**, **5**, **6**) showed one infrared band in the region of 330 cm^{-1} related to ν(Cu–Cl). This unique band supports the chlorine atoms in trans position (Palicova *et al.*, 2000; Jaskova *et al.*, 2007; Meenongwa *et al.*, 2011). The infrared spectral feature of these three compounds also suggests the same stereochemistry as that shown by the crystal structure of complex-**4**.

The stretching vibration of the metal-nitrogen bond, N-sp^2 hybridization, are usually observed in the range of 265 to 219 cm^{-1} (Nakamoto, 1997). Owing to the overlapping bands below 260 cm^{-1}, an absorption of ν(Cu–N) was assigned with uncertainty in the region of 257 cm^{-1}. Nevertheless, the crystal structure of complex-**4** has confirmed the formation of copper(II)-nitrogen bond.

3.3. Crystallography Data

Suitable crystals for structural determination of complex-**4** were collected from methanol when the container was placed as far apart as possible of any surrounding

disturbance during three days (Kinoshita *et al.*, 2003). The crystal structure of the complex-**4** is shown in Figure 2 and Tables 1 and 2 list the crystallographic data and geometric parameters. The copper(II) atom in complex-**4** is 4-coordinate at the center of a square planar geometry with the chloride and nitrogen atoms in *trans* position. The bis(4,6-dimethylpyrimidin-2-ylthio)methane is acting in a bridging bidentate mode bonded between Cu(II) sites.

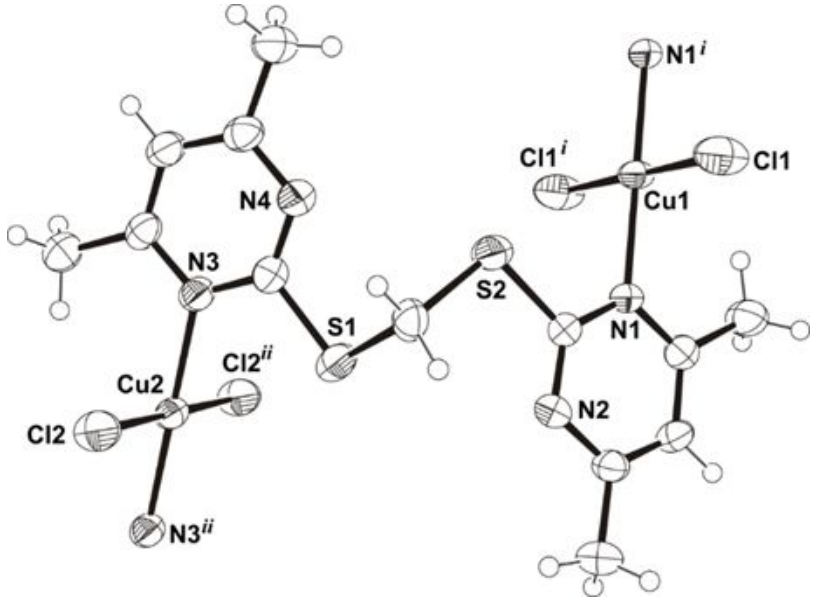


Figure 2 – Crystal structure of complex-**4**, symmetry code (i) 1- x, 1- y, - z; (ii) 1-x, 1-y, -z.

The copper(II)-nitrogen and copper(II)-chlorine bond distances in complex-**4** resembles that found in complex-**1** as well as in copper(II) derivatives of bis(4-pyridin-2-ylthio)methane (Amoedo-Portela *et al.*, 2005; Carballo *et al.*, 2007; Samanamu *et al.*, 2008). The known crystal structure of complex-**1** has two-dimensional chain with the copper(II) ion at the center of a square pyramidal geometry. Contrasting with that, the copper(II)-nitrogen bonds in complex-**4** has one-dimensional chain (1D) in zigzag conformation, having a torsion angle of 52.3° and the Cu···Cu distance of 8.471(1) Å.

The bis(4,6-dimethylpyrimidin-2-ylthio)methane is a flexible ligand and can display four different conformational arrangements, G+G+, GA, AA and G+G^{-}, depending on the dihedral angles around the C–S bonds. (Page *et al.*, 2000). The crystal packing of complex-**4** shows that the angle between the pyrimidyl rings is 52.68(8), and the dihedral angles around the C–S bonds are -79.8(3)° and -83.1(3)°. Consequently the bis(4,6-dimethylpyrimidin-2-ylthio)methane is in G+G+ form upon coordination (Carballo *et al.*, 2009; Carballo *et al.*, 2008). In addition, there is no π-stacking interactions in the crystal packing of complex-**4** but the CH···Cl hydrogen bonds link the 1D chain, forming a 2D arrangement as shown in Figure 3.

Table 1 – Crystal data and refinement parameters of complex-**4**.

Formula	$C_9H_8Cl_2CuN_4S_2$
Formula weight (g. mol^{-1})	370.08
Crystal system	Monoclinic
Space group	$P2_1/n$
a (Å)	10.611(2)
b (Å)	11.702(2)
c (Å)	11.935(2)
β (°)	113.84(3)
Volume (Å3)	1355.4(5)
Z	4
dcalc. ($g.cm^{-3}$)	1.817
Radiation	λ = 0.71073 Å (KαMo)
θ limits (°)	3.32 - 29.52
Reflections collected/independent	11191 / 3446
Reflections observed [Fobs > 4σ (Fobs)]	2821
Parameters	163
R indices for [Fobs > 4σ (Fobs)]	R1=0.028, wR2=0.078
R indices for all data	R1=0.036, wR2=0.078, S = 1.04

Table 2 – Selected bond distances and bond angles of complex-**4**.

Bond lengths (Å)		Bond angle (^{0})	
Cu1-Cl1	2.241(1)	Cl1-Cu1-N1	89.14(9)
Cu2-Cl2	2.224(1)	Cl1-Cu1-N1i	90.86(9)
Cu1-N1	2.024(3)	Cl2-Cu2-N3	89.24(9)
Cu2-N3	2.029(3)	Cl2-Cu2-N3ii	90.76(9)
		C1-S2-C13	101.0(2)
		C7-S1-C13	100.6(2)
		S1-C13-S2	115.5(3)
Hydrogen bond interactions			
D H A	D-H / Å	H···A / Å	D···A/ Å	D-H···A / °
C3-H3···Cl1iii	0.930	2.872	3.623(2)	138.7
C11-11B···Cl2iv	0.960	2.864	3.653(2)	140.2

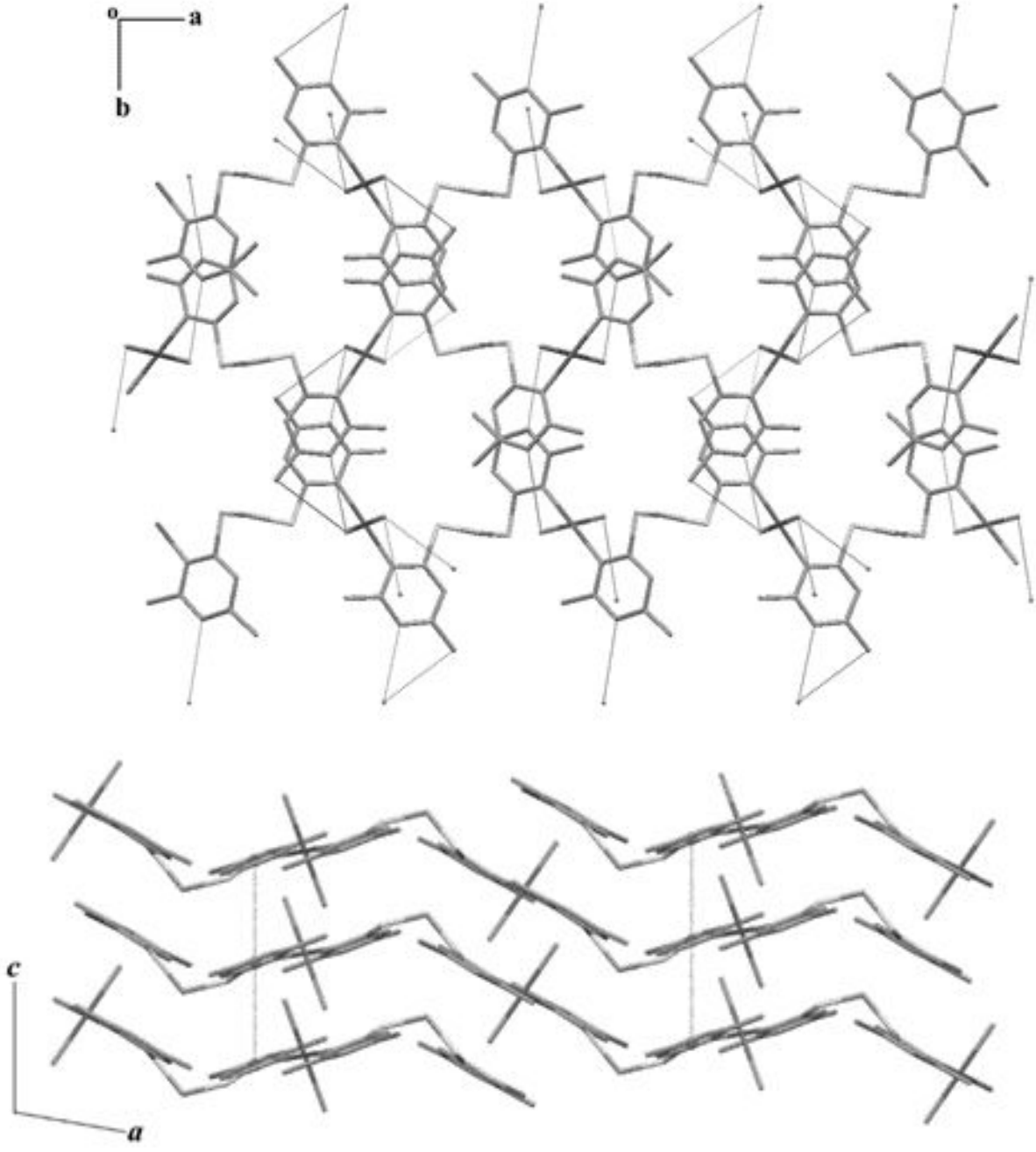


Figure 3 – Two-dimensional crystal array of complex

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3.4. Antimicrobial Activity

The antimicrobial effect of copper(II)-based compounds is unquestionable. Several of the known active compounds show a diversity of geometric arrangements, coordinating sites and coordination modes. In general, the MICs are in the range of 1.0 to 60.0 μg mL^{-1} or 30 to 300 μmol L^{-1} (Shoja *et al.*, 1998; Palicova *et al.*, 2000; Patel *et al.*, 2006; Patel *et al.*, 2004; Segla *et al.*, 2004; Rodriguez-Arguelles *et al.*, 2005). The bioassay of complex-**1**, **4**, **5** and **6** was on phytopathogens, and complex-**1**, **2** and **3** on pathogenic fungi and bacteria. The phytopathogen species for the bioassay of complex-**1** were *A. flavus*, *F. graminearum*, *A. solani* and *B. sorokiniana* and for the complexes **4-6**, *A. flavus* and *B. sorokiniana* only. All bis(pyrimidin-2-ylthio)alkanes (*ptm*, *pte*, *pth*) and bis(4,6-dimethylpyrimidin-2-ylthio)alkanes (*dptm*, *dpte*, *dpth*) were inactive on the microorganisms tested.

3.4.1. Phytopathogens

The copper(II) complexes were not active to all the fungi tested. Complex-**1** was inhibitory to *A. solani* only at 1000 and 500 μg mL^{-1}. The compounds **4-6** did not inhibit the growth of *A. flavus*, but the complex-**4** inhibited *B. soro*kiniana at 1000 and 500 μg mL^{-1}.

Although the mechanism of action is uncertain, it seems that complex-**1** and **4** are selective towards the phytopathogens tested. This selective effect may be related to the two-dimensional and one-dimensional oligomeric character of these complexes as well as to a synergistic effect between the metal and the ligands involved (*ptm* and *dptm*). Although these two ligands have in common a CH_2 moiety between the sulfur atoms, the two-methyl substituent groups at the pyrimidyl fragment of *dptm* reinforce the difference among them, concerning the strength of the synergistic effect.

3.4.2. Pathogenic fungi and bacteria

The bioassay data in Graph. 1 compare the fungicide and bactericide bioassay of complex-**1**, **2** and **3** with the commercial drugs *Nystatin* and *Norfloxacin*. The MIC of $CuCl_2.2H_2O$ was 1953 μmol L^{-1} and for *Nystatin* as well as *Norfloxacin* 31.2 and 75.0 μmol L^{-1}, respectively. The pathogenic fungi bioassay revealed the best MIC value on *C. albicans* (4.7 μmol L^{-1}) for complex-**3** and on *C. tropicalis* (6.3 μmol L^{-1}) for complex-**1**; complex-**2** showed comparable activity to *Nystatin*. Although all **1-3** copper(II) compounds showed significant bactericidal effect, complex-**3** had the best result on *E. coli* and *S. aureus* (9.5 μmol L^{-1}) when in comparison to complex-**1** (25.5 μmol L^{-1}), complex-**2** (24.9 μmol L^{-1}) and *Norfloxacin* as showed in Figure 4.

The resultant MICs for the antimicrobial effect of complexes **1-3** demonstrate that they are powerfully active, similarly to other copper(II) compounds (Patel and Patel, 2009; Despaigne *et al.*, 2012; Recio Despaigne *et al.*, 2012; Patel and Patidar, 2014; Mehta *et al.*, 2015). In addition, the MIC of these complexes in μg mL^{-1} (1.86 to 10.06) embraces several drugs such as Gentamincin and Pleuromutilin derivatives which have shown inhibition against *S. aureus* and *E. coli* within the range of 0.5 to 64 μg mL^{-1} (Islambulchilar *et al.*, 2011; Shang *et al.*, 2014).

Therefore, the selectivity of these copper(II) complexes towards the phytopathogens and the pathogenic microorganisms tested let to postulate that a synergistic effect in association with the oligomeric character of these complexes was crucial to accomplish good antimicrobial activity.

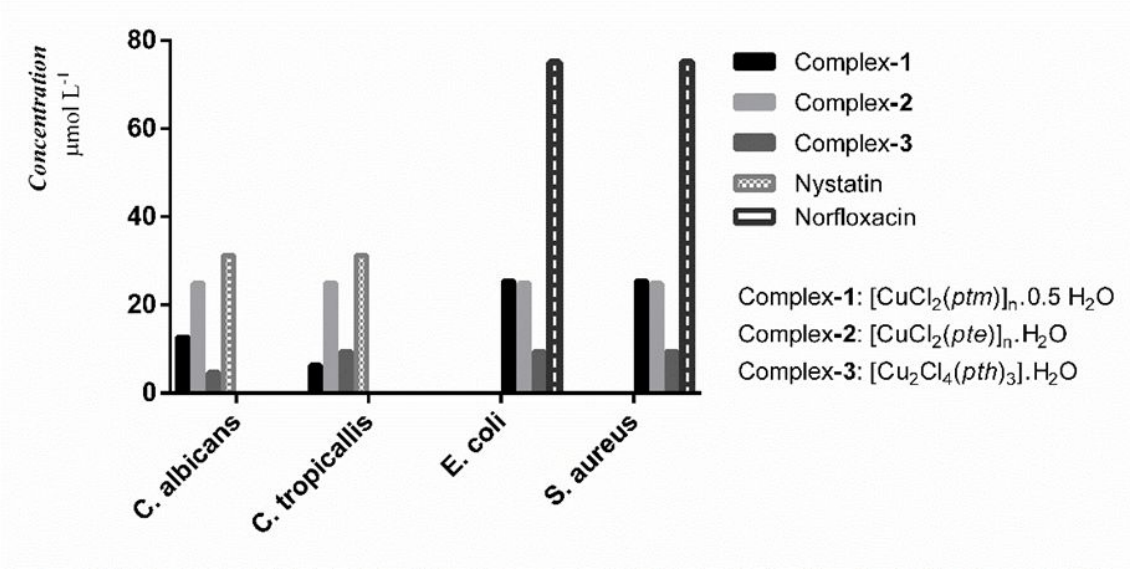

Figure 4 – MIC for the pathogenic fungi and Bacteria.

4. CONCLUSION

The copper(II) complexes showed significant antimicrobial activity in comparison to the free ligands, the commercial drugs *Nystatin* and *Norfloxacin* as well as copper(II) chloride. The formation of a copper(II)-nitrogen bond activate the ligands, establishing upon coordination a synergistic effect that is enhanced by the oligomeric character of these copper(II) complexes. These chemical properties appears to be essential to accomplish selective antimicrobial effect on the microorganisms tested.

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EFEITO ANTIMICROBIANO DE OLIGOMEROS DE COBRE(II) DERIVADOS DO BIS(PIRIMIDIN-2-ILTIO)- E BIS(4,6-DIMETILPIRIMIDIN-2-ILTIO)ALCANOS

RESUMO: Uma nova série de compostos de cobre(II) derivados do bis(pirimidin-2-iltio)- e bis(4,6-dimetilpirimidin-2-iltio)alcanos de formula geral $[Cu_xCl_y(L)_z]_n${x = 1, y = 2, z = 1, L = *ptm* (**1**), *pte* (**2**), *dptm* (**4**), *dpte* (**5**), *dpth* (**6**); x = 2, y = 4, z = 3, L = *pth* (**3**) foram preparados e sua atividade antimicrobiana avaliada. Os complexos foram caracterizados por analise elementar, espectroscopia no infravermelho (IV) e cromatografia por exclusão molecular (GPC). Os complexos **4**, **5** e **6** têm o metal no centro de uma geometria quadrática plana e, nos complexos **1**, **2** e **3**, o metal encontra-se no centro de uma geometria piramidal quadrada. A estrutura do complexo-**4**, determinada por difração de raios-x, mostra o caráter oligomérico deste composto de cadeia unidimensional em conformação zigue-zague. A massa molecular (M_W) destes compostos confirmam o seu caráter oligomérico. Apesar dos ligantes livres serem inativos contra os microrganismos testados, os complexos de cobre(II) mostraram uma boa atividade antifúngica e antibacteriana contra *C. albicans*, *C. tropicalis*, *S.aureus* e *E. coli*, mais eficiente que Nystatina e Norfloxacina.

PALAVRAS-CHAVE: Atividade Antimicrobiana; Bis(pirimidin-2-iltio)alcanos; complexos oligoméricos de cobre(II); Bactericida; Fungicida.