Anais da Academia Brasileira de Ciências (2019) 91(4): e20181077
(Annals of the Brazilian Academy of Sciences)
Printed version ISSN 0001-3765 / Online version ISSN 1678-2690
http://dx.doi.org/10.1590/0001-376520181077
www.scielo.br/aabc | www.fb.com/aabcjournal

Synthesis, characterization and antimicrobial activity of Cr (III), Co (II) and Ni (II) complexes with 2-thiazoline-2-tiol derivative ligands against bacteria and yeasts of clinical importance

KARINA M.S. HERRERA[1], LORENA S. FERREIRA[2], ALYSSON V. BRAGA[1], JULIANO P. SOUZA[1], JÉSSICA T. ANDRADE[1], ADRIANA C. SOARES[3], LUIS F. SOARES[2], RAFAEL C.R. CHAGAS[2] and JAQUELINE M.S. FERREIRA[1]

[1]Laboratório de Microbiologia Médica, Universidade Federal de São João Del-Rei/UFSJ, Campus Centro Oeste Dona Lindu, Av. Sebastião Gonçalves Coelho, Chanadour, 400, 35501-296 Divinópolis, MG, Brazil
[2]Laboratório de Compostos Bioativos e Catalíticos, Universidade Federal de São João Del-Rei/UFSJ, Campus Centro Oeste Dona Lindu, Av. Sebastião Gonçalves Coelho, Chanadour, 400, 35501-296 Divinópolis, MG, Brazil
[3]Laboratório de Farmacologia da Dor e Inflamação, Universidade Federal de São João Del-Rei/UFSJ, Campus Centro Oeste Dona Lindu, Av. Sebastião Gonçalves Coelho, Chanadour, 400, 35501-296 Divinópolis, MG, Brazil

Manuscript received on October 15, 2018; accepted for publication on February 28, 2019

How to cite: HERRERA KMS, FERREIRA LS, BRAGA AV, SOUZA JP, ANDRADE JT, SOARES AC, SOARES LF, CHAGAS RCR AND FERREIRA JMS. 2019. Synthesis, characterization and antimicrobial activity of Cr (III), Co (II) and Ni (II) complexes with 2-thiazoline-2-tiol derivative ligands against bacteria and yeasts of clinical importance. An Acad Bras Cienc 91: e20181077. DOI 10.1590/0001-3765201920181077.

Abstract: Four novel Cr (III), Co (II) and Ni (II) complexes with 2-thiazoline-2-tiol derivative ligands were synthesized and characterized using elemental, physiochemical, and spectroscopy analytical methods. The results showed the formation of ligands coordinated by sulfur atoms of the C = S bond to the L1 ligand and by the sulfur atom of the C-S bond and/or nitrogen of the intra C-ring bond of the L2 ligand. The activity of the complexes against Gram-negative, Gram-positive bacteria and yeasts of clinical importance was evaluated by broth microdilution method. The best result was obtained to L2-Ni compound against *E. cloacae* (Minimal Inhibitory Concentration (MIC) = 62.5 μg/mL). Additionally, the compounds showed anti-*Candida* activity (MIC values ranging from 250 to 500 μg/mL), except the L1-Cr that was not active against any tested microorganism.

Key words: 1,2-bis (2-thiazolin-2-isulfanyl) ethane, antimicrobial activity, hidrotris (2-mercaptothiazolyl) borate, complexes.

INTRODUCTION

There is a considerable concern related to the development of new classes of antimicrobial agents due to the increasing resistance to the drugs in current clinical use (Ling et al. 2015, Scorciapino et al. 2017). In this regard, synthetic compounds are an attractive alternative whereas they present some advantages over natural compounds, such as better yields in obtaining the products and easiness of carrying out structural modifications aiming to control and potentialize their biological properties (Moellering Jr 2011).

The complexes are considered a promising source of research for new antimicrobial agents since metal ions have a high capacity of interaction with biological molecules (Alaghaz et al. 2013). In

Correspondence to: Karina Marjorie Silva Herrera
E-mail: kmsherrera@gmail.com
ORCid: https://orcid.org/0000-0002-1259-9087

addition, the association of a ligand with different metal ions allow the generation of a variety of compounds with distinct structural complexity, contributing to obtain molecules with diverse properties (Godoi-Neto et al. 2008) such as anti-inflammatory (Shawish et al. 2014), anti-cancer (Jungwirth et al. 2011), and antimicrobial (Gwaram et al. 2012, Muneera and Joseph 2016).

Five- or six-membered heterocyclic compounds containing electron donating nitrogen and sulfur atoms, such as thiazolines, are of great relevance in coordination chemistry studies and in biological systems because they have a versatile chelating capacity (Wang et al. 2012). The thiazolinic derivatives have been investigated in studies due to their wide pharmacological activity, being used in the search of new drugs (Bernalte-Garcia et al. 2006, Patel et al. 2014). 2-thiazoline-2-thiol derivatives are known as antithyroid, competitive inhibitors for acetylcholinesterase, and radioprotective compounds (Rabie et al. 2011). In this work, a series of four novel complexes with 2-tiazoline-2-tiol derivative ligands has been synthesized, and their potential as antimicrobial agents was examined against microorganisms of clinical importance, including Gram-negative and Gram-positive bacteria and yeasts.

MATERIALS AND METHODS

SYNTHESIS OF COMPOUNDS

Synthesis of ligands

For the synthesis of ligand sodium hydrotris(2-mercaptothiazolyl) borate (NaL1)-($Na[C_9H_{13}N_3S_6B]$) (L1) (Figure 1), it was used the methodology described by Soares et al. (2004) with adaptations. The reaction was carried out in the stoichiometric ratio of 3.5:1 between 2-thiazolin-2-thiol ($C_3H_5NS_2$) (1.1000 g, 9.23 mmol) and sodium borohydride ($NaBH_4$) (0.1000 g, 64 mmol). The white and air-stable solid obtained was washed three times with dichloromethane for purification and elimination of 2-thiazolin-2-thiol excess, separated by simple filtration, and allowed to evaporate at room temperature.

The synthesis of 1.2-bis(2-thiazoline-2-isulfanyl)ethane (L2) was performed according to Wang et al. (2012) with modifications. An alcoholic solution (1:1) of 2-thiazoline-2-thiol (4.4 mmol) and potassium hydroxide (4.4 mmol) was stirred until fully clarified. Subsequently, 1.2-dibromoethane (2.1 mmols) were added and the new solution was kept under stirring for another 72 hours. After the reaction time, the resulting white residue was decanted and purified by successive washes with ethanol. Finally, the solvent was removed by simple filtration and the solid was allowed to dry at room temperature.

Ligand sodium hydrotris(2-mercaptothiazolyl) borate (L1) - $Na[C_9H_{13}N_3S_6B]$: yield 87%; mp:140-142 °C; ESI-MS (-): 365.9 m/z; IR-FT/cm^{-1} 1089-1010(C=S), 2459(B-H), 1481(B-N), 2943-2856(C-H); uv-vis (nm) 284 (n-π*) NMR^1H(ppm): 4.17 (t, 7.8 Hz, 6H), 3.18 (t, 7.8 Hz, 6H);^{13}C: 195.2 (C=S), 59.74 (C1-N), 30.56 (C2-S).

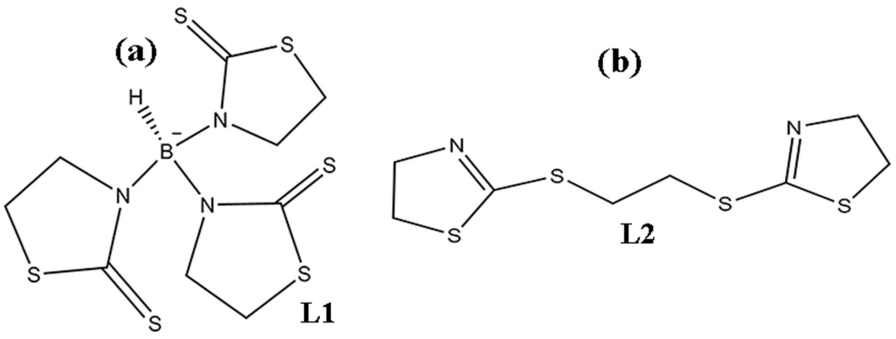

Figure 1 - Chemical structure of ligands. **(a)** L1 and **(b)** L2.

Ligand 1,2-bis (2-thiazoline-2-isulfanyl) ethane (L2) - $C_8H_{12}N_2S_4$:Yield 40%; m.p 128-130 °C; ESI-MS (+) 265.1 m/z; IR-FT(cm^{-1}) 1570(C=N), 2959-2847(C-H); uv-vis (nm): 266 (n-π*). NMR ^{1}H (ppm): 4.13 (t, 7.9 Hz, 4H), 3.43 (t, 7.9 Hz). 13C: 63.95 (C1=N), 35.14 (C2-S), 33.51 (S-C3-S).

*Synthesis of complexes (**1-2**) with L1*

The nickel (II) and chromium (III) complexes were prepared following a general method. Methanol solutions (10 mL) of the metal precursors ($NiCl_2{\cdot}6H_2O$ and $Cr(NO_3)_3{\cdot}6H_2O$) with L1 ligand in the ratio of 1:1 were refluxed for 3h. Then, the brown precipitate formed in the synthesis of the nickel (II) complex (**1**) was washed with water and methanol and dried in desiccator at room temperature. The solution of chromium (III) complex (**2**) was evaporated at room temperature and the resulting product was washed with water and acetone followed by desiccator drying at room temperature.

Nickel (II) complex L1-Ni (**1**): yield 32%; m.p 75d; molar conductivity (DMF): 23.65$\Omega^{-1}cm^2$ mol^{-1}; IR-FT (cm^{-1}) : 1043.987 (C=S), 1523 (B-N; . uv-vis (nm): 280 (π-π*), 402 (n-π*). CHN: calculate - 22.59 (C), 3.16 (H), 7.88 (N) and experimental 22.68 (C), 2.97 (H), 7.49 (N). RMN ^{1}H (ppm): 3.86 (t, 7.8 Hz), 3.49 (t, 7.8 Hz, 6H). ^{13}C: 51.19 (C1=N), 33.37 (C2-S).

Chromium (III) complex L1-Cr (**2**): yield 65%; m.p: 115° C; molar conductivity (DMF) 68.3$\Omega^{-1}cm^2$ mol^{-1}; IR-FT (cm^{-1}): 1051.999 (C=S), 1517 (B-N); uv-vis (nm): 280 (π-π*), enlargement (n-π*). CHN: calculate 26.37 (C), 3.76 (H), 10.76 (N) and experimental: 28.04 (C), 3.81 (H), 11.30 (N).

*Synthesis of complexes (**3-4**) with L2*

The cobalt (II) and nickel (II) complexes were prepared following a general method. Methanol solutions (20 mL) of the metal precursors ($CoCl_2{\cdot}6H_2O$ and $NiCl_2{\cdot}6H_2O$) with L2 ligand in the ratio of 1:2 (ligand:metal) were prepared. For the cobalt (II) complex (**3**), the reaction was stirred and refluxed for 2 and 3h, respectively. After the reaction time, the resulting blue precipitate was decanted and purified with methanol. For the nickel (II) complex (**4**) the reaction mixture was refluxed for 3h and the solution was dried at ambient temperature. The obtained green solid was purified with methanol.

Cobalt (II) complex (L2-Co) (**3**): yield 44%; m.p255^d; molar conductivity (DMF) 39.37$\Omega^{-1}cm^2$ mol^{-1}; IR-FT (cm^{-1}) 1514 (C=N); uv-vis (nm) 274 (n-π*), 612.682 (M-L); CHN: calculate 18.33 (C), 2.31 (H), 5.34 (N) and experimental 18.20 (C), 2.61 (H), 5.64 (N).

Nickel (II) complex (L2-Ni) (**4**): yield 33%; m.p 110^d. molar conductivity (DMF) 29.15$\Omega^{-1}cm^2$ mol^{-1}; IR-FT (cm^{-1}) 1570 (C=N), 2956 (C-H); uv-vis (nm) 266 (n-π*); CHN: calculate 18.35 (C), 2.31 (H), 5.35 (N) and experimental 17.98 (C), 2.35 (H), 5.51 (N). NMR^{1}H (ppm) 4.12 (t, H-C1), overlapping water signs (H-C2).

Experimental

All reagents and solvents were purchased from commercial sources and used without further purification. The ligands and complexes were synthetized and characterized by the following physico-chemical and spectroscopic techniques: mass spectrometry, melting point, molar conductivity, elemental analysis, infrared and UV-visible.

ANTIMICROBIAL ASSAYS

The microorganisms used in this study were obtained from the American Type Culture Collection (ATCC). Antimicrobial activity was determined against six Gram-negative bacteria: *Acinetobacter baumannii* 19606, *Enterobacter*

cloacae 23355, *Escherichia coli* 25922, *Klebsiella pneumoniae* 4352, *Pseudomonas aeruginosa* 25619, and *Proteus mirabilis* 15290; three Gram-positive bacteria: *Streptococcus agalactiae* 13813, *Staphylococcus aureus* 29213, and *Staphylococcus saprophyticus* 15305; and three yeasts of the *Candida* genus: *Candida albicans* 14053, *Candida glabrata* 2001, and *Candida krusei* 34135.

Antimicrobial assays were evaluated by determining the minimal inhibitory concentration (MIC) using the broth microdilution assay as described by Clinical and Laboratory Standards Institute (CLSI) in documents M07-A9 (CLSI 2012) for bacteria and M27-A3 (CLSI 2008), with minor modifications (Allochio Filho et al. 2016), for yeasts. The mediums used for the antibacterial and antifungal assays were Mueller Hinton broth (Kasvi, Italy) and Sabouraud Dextrose broth (Kasvi, Italy), respectively, both in pH 7.3 ± 0.1 at 25° C. The minimal bactericidal concentration (MBC) and minimal fungicidal concentration (MFC) were determined according to Lyu et al. (2016) and Allochio Filho et al. (2016), respectively. The MBC and MFC were defined as the lowest compound concentration that reduces the viability of the initial microorganism inoculum by ≥99.9%. The ligands and complexes were solubilized in DMSO (2% in water) and tested at concentrations ranging from 3.90 to 500 μg/mL. Streptomycin (Sigma-Aldrich, USA) and ketoconazole (Pharma Nostra, Brazil) were used as positive control for bacteria and yeasts, respectively. The assays were performed in triplicate and repeated three times in independent experiments.

RESULTS AND DISCUSSION

The characterization methods that have been performed allowed to propose the compound structures, although it was not possible to obtain useful crystals to elucidate the exact molecular structure by x-ray crystallography.

Through mass spectrometry analysis with electron spray type interface, peaks with m/z 365.9 (M) in the negative mode (L1) and 265.1 (M+H) in the positive mode (L2) confirmed the expected mass in accordance with the molecular mass. The ligands IR spectrum showed the following patterns of bands absorption: (**1**) for the L1 ligand: 1089-1010 cm^{-1} (νC=S), 2459 cm^{-1} (νB-H), 1481 cm^{-1} (νB-N); (**2**) for the L2 ligand**:** 1570 cm^{-1} (νC=N) e 2956-2847 cm^{-1} (νC-H). The UV spectrum obtained in DMF with wavelength ranging from 200 to 800 nm showed absorption bands corresponding to the patterns the expected for transitions molecules: (**1**) L1 in the range of 284 and 340 nm (transition π-π* and n-π*); (**2**) L2 with a single band in the region of 266 nm (transition π-π*). The proposed chemical structures of L1 and L2 ligands are showed in Figure 1.

The coordination and formation indicative of the complexes were evidenced from the characterizations. With regard to the electrolytic nature of the compounds, it was observed that complexes **1**, **3**, and **4** are non-electrolytic, since the conductivity values obtained were below the range of 65-90 $\Omega^{-1}cm^2mol^{-1}$ (Geary 1971). The complex **2**, however, presented values within the range of 65-90 $\Omega^{-1}cm^2mol^{-1}$, indicating the presence of electrolytes in the stoichiometric ratio of 1:1 between cations and anions (Geary 1971).

We have also performed elemental analysis to gain information about the compounds structures. For compound **2**, characterization showed the formation of a 2:1 (ligand:metal) coordination complex, although the reaction was carried out in a 1:1 ratio. In addition, methanol molecules have been identified, but judged to be outside the coordination sphere. For the compounds L2-Co and L2-Ni (**3** and **4**), there is the presence of two molecules of the metal centers ($CoCl_2$ and $NiCl_2$ respectively) coordinated to the ligand molecule.

The IR spectrum of the L1-Ni and L1-Cr compounds compared to the ligand showed a shift

to lower wavelength values of the assigned band at C=S binding, indicating it as a coordination site, since the binding is weakened by coordination (Romanholi 2005). For compound L2-Co, the IR spectrum showed a displacement in the 1570 cm^{-1} region attributed to the stretching of the C=N bond, indicating the N atom as the metal bonding site due to the donation of electrons to the metals. On the other hand, the displacement at the C=N band position was not observed for compound **4**, suggesting that the coordination site is guided by the sulfur atom of the C-S bond, which was not identified in the spectrum as a result of its instability (Silverstein and Webster 1998).

UV-visible spectra of the ligand and complexes were also evaluated since bands displacements and/or enlargement are evidences of coordination (Farias 2009, Konstantinovic et al. 2003).

For the compound L1-Ni (**1**), a band at 272 nm (ε = 7650 $L.mol^{-1}.cm^{-1}$) was observed and attributed to the n-π* transition, confirming the coordination via the sulfur atom of the C= S bond inferred by the IV since this band was present in the ligand at 282 nm (ε = 8370 $L.mol^{-1}.cm^{-1}$). Any other bands could not be seen in the spectrum probably due a low molar extinction coefficient of d-d bands in this complex. Therefore, we could not get information about its geometry. For the L1-Cr (**2**) compound, an enlargement and a bathochromic displacement to 298 nm (ε = 7730 $L.mol^{-1}.cm^{-1}$) for the n-π* transition was evidenced, also indicating coordination (Farias 2009, Konstantinovic et al. 2003). The spectrum also presented a two weaker bands with maximum in 434 nm (ε= 160 $L.mol^{-1}cm^{-1}$) and 592 nm (ε= 160 $L.mol^{-1}cm^{-1}$), attributed to *d-d* transition in a distorted octahedral field (Chandra and Pipil 2014).

For the compound L2-Co, the n-π* bands present in ligand at 266 nm (ε= 12580 $L.mol^{-1}cm^{-1}$) has suffered a bathochromic shift to 274 nm (ε= 11700 $L.mol^{-1}cm^{-1}$), confirming the coordination. Two bands at 608 nm (ε= 910 $L.mol^{-1}cm^{-1}$) and 682 nm (ε= 1390 $L.mol^{-1}cm^{-1}$), attributed to *d-d* transitions in a tetrahedral field, were evidenced in the spectrum (Konstantinovic et al. 2003). In the L2-Ni compound (**4**), the n-π* at 266 nm (ε= 9210 $L.mol^{-1}cm^{-1}$) was not dislocated when compared with the ligand. This result indicates coordination by the sulfur atom, which affects sigma bonds that occur in a very energetic ultraviolet region, being outside the traditional limits of UV-vis and, therefore, it was not observed. A shoulder at 324 nm (ε= 750 $L.mol^{-1}cm^{-1}$) is present in the spectrum and was attributed to *d-d* transitions. The proposed structures for the four complexes synthesized with the ligands L1 and L2 are shown in Figure 2.

For the nickel (II) and Cr (III) complex (**1** and **2**), the geometries proposed are quadratic plane and octahedral, respectively. The octahedral configuration is typical of metal complexes in the stoichiometric ratio of 2:1 between the scorpionate ligand and the metal center (Çetin and Ziegler 2006). In relation to the square planar geometry indicated for the nickel (II) complex, it refers to the obtainment of useful NMR spectra, which characterizes it as diamagnetic and excludes the tetrahedral geometry that would classify the complex as paramagnetic.

For the complexes of Co (II) and Ni (II) (**3** and **4**) the it was proposed a tetrahedral geometry based on the characterization results, mainly because the non-appearance of useful NMR spectrum. Several studies, such as that developed by Li et al. (2013), showed that complexes synthesized with thiother ligands presented this configuration.

ANTIMICROBIAL ACTIVITY

The free ligands did not exhibit antimicrobial activity at any of the concentrations tested. In contrast, the values of MIC and MBC or MFC of the novel complexes are show in Table I. The antibacterial activity was observed for the complexes with L2 ligand. The more intense activity

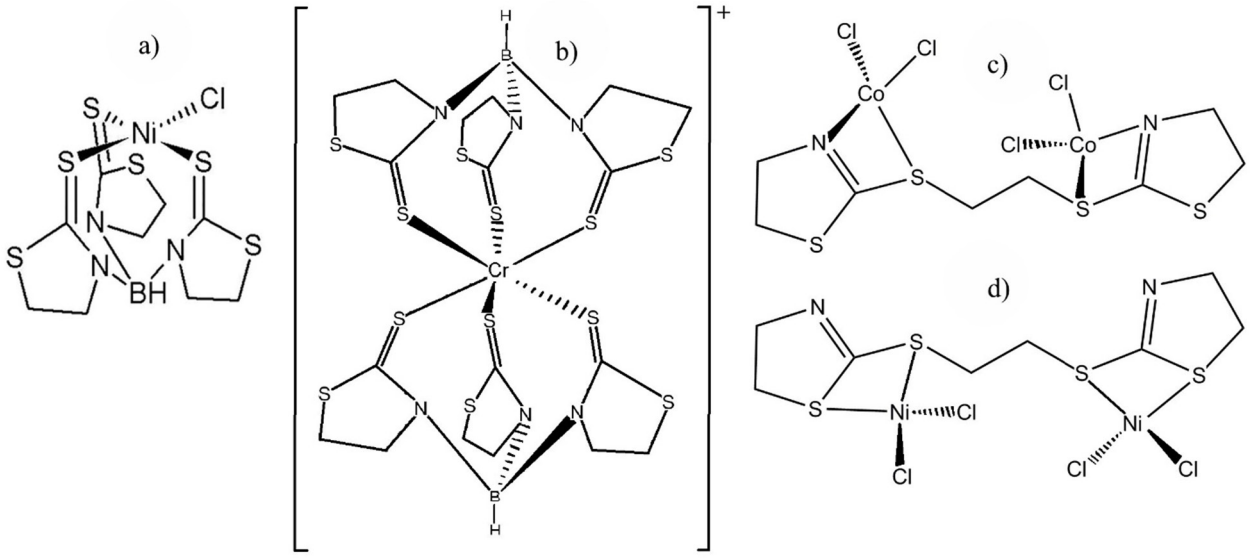

Figure 2 - Structures proposed for complexes 1 and 2 (**a** and **b**) formed from the hidrotris(2-mercaptothiazolyl) borate ligand and complexes 3 and 4 (**c** and **d**) formed from 1,2-bis(2-thiazoline-2-isulfanyl)ethane.

was observed for the compound L2-Ni against *E. cloacae* (MIC = 62.5 µg/mL), indicating a more promising result than that described by Arslan et al. (2009), where nickel (II) complexes with derived thiourea ligands exhibited antibacterial activity against the same microorganism with MIC values in the range of 200 to 400 µg/mL. The L2-Ni compound was not active against the other bacteria evaluated in this work, differently of benzoxazole and thioether derivative ligands complexed with nickel (II), which showed action (25 to 200 µg/mL and 6.25 to 50µg/mL, respectively) against *E. coli*, *P. aeruginosa*, and *S. aureus* (Bouchoucha et al. 2014, Zhang et al. 2011).

Additionally, the L2-Co was active against *K. pneumoniae* and *S. saprophyticus* (MIC = 250 µg/mL). However, the literature indicated that more promising results were obtained with a complex of cobalt (II) hydrazone ligand for *S. aureus* (0.7 µg/mL) (Pahontu et al. 2017). On the other hand, complexes of cobalt (II) with derived thiazoline/thiosemicarbazone ligands were not active against any of the Gram-negative and Gram-positive bacteria evaluated by Viñuelas-Zahinos et al. (2011).

Regarding to antifungal activity, the screening showed anti-*Candida* activity for all compounds (MIC values ranging from 250 to 500 µg/mL), except to the L1-Cr compound that was not active against any microorganism tested. According to Bouchoucha et al. (2014) and Pahontu et al. (2017), complexes of nickel (II) benzoxazole ligands and nickel (II) or cobalt (II) hydrazone ligands, respectively, were actives against *C. albicans* at 100 to 200 µg/mL. Furthermore, Arslan et al. (2009) reports the antifungal activity of nickel (II) thiourea complexes ranging from 25 to 100 µg/mL against *C. albicans*, *C. krusei* and *C. glabrata*.

The complexes evaluated in this study were able to act in Gram-positive and Gram-negative bacteria and yeasts. Interestingly, the most promising MIC value was obtained in *E. cloacae*. Usually, Gram-negative bacteria are more resistant to antimicrobials than Gram-positive, since they have a much simpler cell wall composed primarily of peptidoglycan and teichoic acid (Denny et al. 2005). Besides that, Gram-negative bacteria have an additional barrier: the outer membrane, which can avoid the entry of compounds into the cell (Thangamani et al. 2015).

TABLE I
Antibacterial and antifungal activities showed by complexes and positive controls.

	Compounds									
	L1-Cr		L1-Ni		L2-Co		L2-Ni		Positive controls	
	MIC	MBC/ MFC	MIC	MBC/ MFC	MIC	MBC/ MFC	MIC	MBC/ MFC	MIC	MBC/ MFC
Gram-negative bacteria										
A. baumannii 19606	>500	-	>500	-	>500	-	>500	-	250	>500
E. cloacae 23355	>500	-	>500	-	>500	-	**62.5**	>500	3.90	31.25
E. coli 25922	>500	-	>500	-	>500	-	>500	-	15.6	15.62
K. pneumoniae 4352	>500	-	>500	-	**250**	>500	>500	-	7.81	>500
P. aeruginosa 25619	>500	-	>500	-	>500	-	>500	-	3.90	>500
P. mirabilis 15290	>500	-	>500	-	>500	-	>500	-	15.62	250
Gram-positive bacteria										
S. agalactiae 13813	>500	-	>500	-	>500	-	>500	-	3.90	125
S. aureus 29213	>500	-	>500	-	>500	-	>500	-	7.81	31.25
S. saprophyticus 15305	>500	-	>500	-	**250**	>500	>500	-	3.90	500
Yeasts										
C. albicans 14053	>500	-	**250**	>500	**500**	>500	**250**	>500	62.5	>500
C. glabrata 2001	>500	-	**250**	>500	**250**	>500	>500	-	125	>500
C. krusei 34135	>500	-	**250**	**500**	**250**	**500**	**500**	>500	7.81	15.6

The microorganisms were obtained from American Type Culture Collection. MIC: Minimal inhibitory concentration. MBC: Minimal bactericidal concentration. MFC: Minimal fungicidal concentration. Positive controls: streptomycin for bacteria, and ketoconazole for yeasts.
Values in μg/mL. (-) Not tested.

The complexes evaluated in this work appear to have certain specificity for yeasts. This result may be due to the differences between the cell structures of bacteria and yeasts. While the cell walls of fungi contain chitin, the cell walls of bacteria contain murein (Eweis et al. 2006). In addition, the fungal cell membrane is composed of the ergosterol, which the main role is to maintain the integrity of fungal cells (Andrade et al. 2018), while the bacterial cells lack this sterol in their membrane.

According to our results, the *Candida* strains evaluated in this work were particularly sensitive to the complexes. These results are considerably relevant since these yeasts have a significant medical importance, show several virulence factors as thermotolerance, dimorphism with production of filamentous structures (allowing tissue invasion), enzymatic production, and the ability to form biofilms (Ramos et al. 2016). Moreover, the complexes L1-Ni and L2-Co present fungicidal activity against *C. krusei*, strengthening the evidences that these compounds have to be evaluated in more details in terms of antifungal activity because being able to kill the pathogens

is a relevant criterion for the selection of antibiotic candidates for clinical use (Wong et al. 2014). Even though they exhibited antifungal action in concentrations higher than those already described in the literature, they constitute an important source of research for anti-*Candida* prototypes.

In view of the clinical importance of the microorganisms studied and of the difficulty of finding effective antimicrobials, mainly against Gram-negative bacteria and yeasts, the results obtained in this work encourage the accomplishment of directed structural modifications in the compounds aiming to potentialize their antimicrobial activity.

ACKNOWLEDGMENTS

The authors are grateful to Conselho Nacional de Desenvolvimento Científico Tecnológico (CNPq), Fundação de Amparo à Pesquisa do Estado de Minas Gerais (FAPEMIG) and Universidade Federal de São João Del-Rei (UFSJ) for financial support.

AUTHOR CONTRIBUTIONS

ACS, LFS, RCRC and JMSF conceived, designed and coordination research. KMSH, LSF, AVB, JPS and JTA conducted the laboratory experiments. All authors discussed the results and contributed to the final manuscript.

REFERENCES

ALAGHAZ ANMA, BAYOUMI HA, AMMAR YA AND ALDHLMANI SA. 2013. Synthesis, characterization, and antipathogenic studies of some transition metal complexes with N,O-chelating Schiff's base ligand incorporating azo and sulfonamide moieties. J Mol Struct 1035: 383-399.

ALLOCHIO FILHO JF ET AL. 2016. Synthesis, *in vitro* antifungal activity andmolecular modeling studies of new mannich bases derived from lawsone. J Braz Chem Soc 27: 2127-2140.

ANDRADE JT, SANTOS FRS, LIMA WG, SOUSA CDF, OLIVEIRA LSFM, RIBEIRO RIMA, GOMES AJPS, ARAÚJO MGF, VILLAR JAFP AND FERREIRA JM. 2018. Design, synthesis, biological activity and structure-activity relationship studies of chalcone derivatives as potential anti-*Candida* agents. J Antibiot 1: 1-11.

ARSLAN H, DURAN N, BOREKCI G, KORAY OZER C AND AKBAY C. 2009. Antimicrobial activity of some thiourea derivatives and their nickel and copper complexes. Molecules 14(1): 519-527.

BERNALTE-GARCIA A, LOZANO-VILA AM, LUNA-GILES F AND PEDRERO-MARÍN R. 2006. Structural characterization of a thiazoline-pyrazole ligand and its complexes with cobalt (II) and copper (II). Polyhedron 25: 1399-1407.

BOUCHOUCHA A, TERBOUCHE A, BOUROUINA A AND DJEBBAR S. 2014. New complexes of manganese (II), nickel (II) and copper (II) with derived benzoxazole ligands: Synthesis, characterization, DFT, antimicrobial activity, acute and subacute toxicity. Inorg Chim Acta 418: 187-197.

CLSI - CLINICAL AND LABORATORY STANDARDS INSTITUTE. 2008. Reference method for broth dilution antifungal susceptibility testing of yeasts, 3rd ed., Approved standard M27-A3, Wayne (PA).

CLSI - CLINICAL AND LABORATORY STANDARDS INSTITUTE. 2012. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 9th ed., Approved standard M07-A9, Wayne (PA).

ÇETIN A AND ZIEGLER GJ. 2006. Coordinative flexibility in hydrotris(methimazolyl)borate divalent metal compounds. Dalton Trans 60(8): 1006-1008.

CHANDRA S AND PIPIL P. 2014. Chromium (III) complexes: Synthesis, spectral characterization and microbiolstudies. J Chem Pharm Res 6(6): 44-54.

DENNY BJ, NOVOTNY L, WEST PWJ, BLESOVA M AND ZAMOCKA J. 2005. Antimicrobial activity of a series of 1-alkyl-2-(4-pyridyl)pyridinium bromides against Gram-positive and Gram-negative bacteria. Med Princ Pract 14: 377-381.

EWEIS M, ELKHOLY SS AND ELSABEE MZ. 2006. Antifungal efficacy of chitosan and its thiourea derivatives upon the growth of some sugar-beet pathogens. Int J Biol Macromol 38: 1-8.

FARIAS RF. 2009. Química de coordenação: fundamentos e atualidades. Campinas, SP: Editora Átomo.

GEARY WJ. 1971. The use of conductivity measurements in organic solvents for the characterization of coordination compounds. Coord Chem Rev 7: 81-122.

GODOI NETTO AV, FREM RCG AND MAURO AE. 2008. A química supramolecular de compostos pirazólicos. Quím Nova 31(5): 1208-1217.

GWARAM NS, ALI HM, KHALEDI H, ABDULLA MA, HADI AH, LIN TK, CHING CL AND OOI CL. 2012. Antibacterial evaluation of some Schiff bases derived from 2-acetylpyridine and their metal complexes. Molecules 17: 5952-5971.

JUNGWIRTH U, KOWOL CR, KEPPLER BK, HARTINGER CG, BERGER W AND HEFFETER P. 2011. Anticancer activity of metal complexes: Involvement of redox processes. Antioxid Redox Signal 15(4): 1085-1127.

KONSTANTINOVIC SS, RODOVANOVIC BC, CAKIC Z AND VASIC V. 2003. Synthesis and characterization of Co(II), Ni(II), Cu (II) and Zn (II) complexes with 3-solicylidenehydrazono-2- indolinone. J Serb Chem Soc 68(8-9): 641-647.

LI Y, ZHANG JA, WANG YB, PAN M AND SU CY. 2013. Crystal structures, DFT calculations and biological activities of three mercury complexes from a pentadentate thioether ligand. Inorg Chem Commun 34: 4-7.

LING LL ET AL. 2015. A new antibiotic kills pathogens without detectable resistance. Nature 517(7535): 455-459.

LYU Y, YANG Y, LYU X, DONG N AND SHAN A. 2016. Antimicrobial activity, improved cell selectivity and mode of action of short PMAP-36-derived peptides against bacteria and *Candida*. Sci Rep 6: 1-12.

MOELLERING-JR RC. 2011. Discovering new antimicrobial agents. Int J Antimicrob Agents 37: 2-9.

MUNEERA MS AND JOSEPH J. 2016. Design, synthesis, structural elucidation, pharmacological evaluation of metal complexes with pyrazoline derivatives. J Photo Chem Photobiol 163: 57-68.

PAHONTU E, ILIES DC, SHOVA S, OPREAN C, PAUNESCU V, OLARU OT, RADULESCU FS, GULEA A, ROSU T AND DRAGANESCU D. 2017. Synthesis, characterization, antimicrobial and antiproliferative activity evaluation of Cu(II), Co(II), Zn(II), Ni(II) and Pt(II) complexes with isoniazid-derived compound. Molecules 22: 650-666.

PATEL MN, PATEL CR, JOSHI HN AND THAKOR KP. 2014. DNA interaction and cytotoxic activities of square planar platinum(II) complexes with N, S-donor ligands. Spectrochim Acta Part A Mol Biomol Spectrosc 127: 261-267.

RABIE UM, ABOU-EL-WAFA MHM AND WASSAR H. 2011. *In vitro* simulation of the chemical scenario of the action of an anti-thyroid drug: Charge transfer interaction of thiazolidine-2-thione with iodine. Spectrochimica Acta Part A 78: 512-517.

RAMOS MAS, TOLEDO LG, CALIXTO GM, BONIFÁCIO BV, FREITAS AMG, SANTOS LC, ALMEIDA MT, CHORILLI M AND BAUAB TM. 2016. Syngonanthusnitens Bong. (Rhul.)-loaded nanostructured system for vulvovaginal candidiasis treatment. Int J Mol Sci 17: 1-19.

ROMANHOLI LKS. 2005. Estudos das propriedades dos complexos de ácido hialurônico com os íons metálicos Cu2+, Zn2+, Gd+3. Dissertação (Mestrado em Engenharia e Ciências dos Materiais). Universidade Federal do Paraná, Curitiba. (Unpublished).

SCORCIAPINO MA, SERRA I, MANZO G AND RINALDI AC. 2017. Antimicrobial dendrimeric peptides: Structure, activity and new therapeutic applications. Int J Mol Sci 18: 542-554.

SHAWISH HBET AL. 2014. Nickel(II) complex of polyhydroxybenzaldehyde N4- thiosemicarbazone exhibits anti-inflammatory activity by inhibiting NF-kB transactivation. PLoS ONE 9(6): e100933.

SILVERSTEIN RM AND WEBSTER FX. 1998. Identificação Espectrométrica de Compostos Orgânicos, 6ª ed., Rio de Janeiro: Livros Técnicos e Científicos Editora, 460.

SOARES LF, MENEZES DO, SILVA RM, DORIGUETTO AC, ELLENA J, MASCARENHAS YP AND CASTELLANO EE. 2004. Syntheses, characterization and x-ray structure of potassium hydrotris(2-mercaptothiazolyl)borate, KMt, and potassium hydrotris(methimazole)borate, KTm. J Braz Chem Soc 15(5): 695-700.

THANGAMANI S, MOHAMMAD H, ABUSHAHBA MFN, HAMED MI, SOBREIRA TJP, HEDRICK VE, PAUL LN AND SELEEM MN. 2015. Exploring simvastatin, an antihyperlipidemic drug, as a potential topical antibacterial agent. Sci Rep 5: 16407-16419.

VIÑUELAS-ZAHÍNOS E, LUNA-GILES F, TORRES-GARCÍA P AND FERNÁNDEZ-CALDERÓN MC. 2011. Co(III), Ni(II), Zn(II) and Cd(II) complexes with 2-acetyl-2-thiazolinethiosemicarbazone: Synthesis, characterization, X-ray structures and antibacterial activity. Eur J Med Chem 46: 150-159.

WANG W, ZHAO B, XU C AND WU W. 2012. Synthesis and antitumor activity of the thiazoline and thiazine multi thioether. Int J Org Chem 2: 117-120.

WONG SSW, KAO RY, YUEN KY, WANG Y, YANG D, SAMARANAYAKE LP AND SENEVIRATNE CJ. 2014. *In vitro* and *in vivo* activity of a novel antifungal small molecule against *Candida* infections. PLoS ONE 9: 1-17.

ZHANG JA, PAN M, JIANG JJ, SHE ZG, FAN ZJ AND SU CY. Syntheses, crystal structures and antimicrobial activities of thioether ligands containing quinoline and pyridine terminal groups and their transition metal complexes. Inorg Chim Acta 374: 269-277.