American Journal of Chemistry 2021, 11(3): 43-48
DOI: 10.5923/j.chemistry.20211103.01

Synthesis, Structure Analysis and Antibacterial Activity of Zn(II) and Co(III) Complexes

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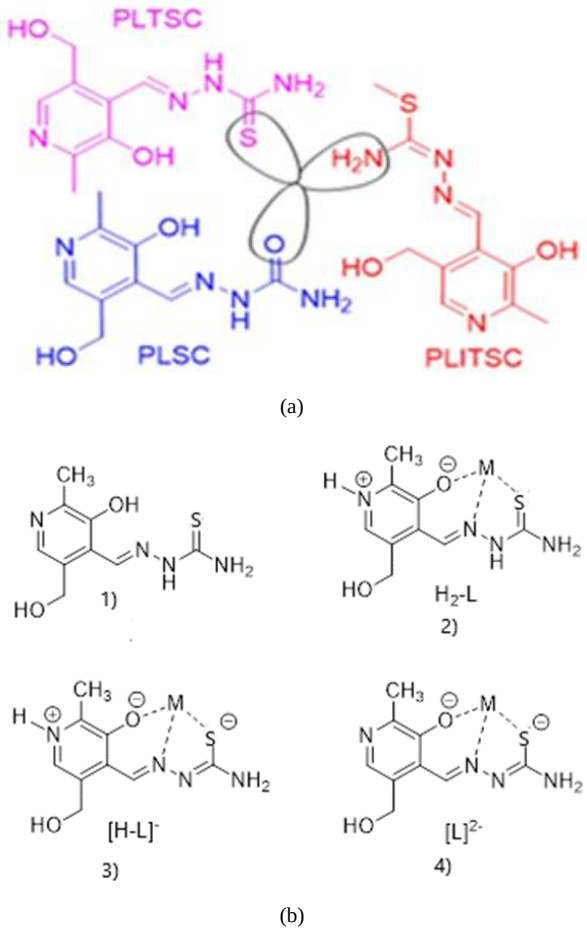
Abstract This paper presents the synthesis, structure and biological activity of two new complexes Zn (II) and Co (III) with the pyridoxal-thiosemicarbazone as ligand. Complexes are with molecular formula [Zn (PLTSC) $(H_2O)_2$]$SO_4 \cdot H_2O$ and [Co (PLTSC-H)$_2$] $Cl \cdot H_2O$. The synthesized complexes were structurally characterized and biological activity was performed on several microorganisms. The zinc complex has the structure of a distorted square pyramid, while the bis-ligand cobalt complex is a regular octahedron.

Keywords Pyridoxal-thiosemicarbazone, Zn (II) and Co (III) complexes, Structure, Synthesis and biological activity

1. Introduction

Complexes with the ligand pyridoxal thiosemicarbazone (PLTSC) have been investigated so far and many papers [1,2] on the subject are known, including one book [3]. Pyridoxal- thiosemicarbazone (PLTSC) belongs to the family of ligand pyridoxal and carbazone derivatives, where, in addition to Pyridoxal- thiosemicarbazone (PLTSC) exist Pyridoxal-semi carbazone (PLSC) and Pyridoxal- S-methyl iso-thiosemicarbazone (PLITSC) (Scheme 1) are also known.

All three ligands are tridentate. First place of coordination is oxygen from phenol hydroxyl, the second is Nitrogen from hydrazine group. Can be seen in Scheme 1 (a), for these three types of ligands differs is only third place of coordination with the central metal. Actually, for PLTSC it is a sulphur, for PLSC it is oxygen, while in ligand PLITSC in coordination is the NH group in the third place of coordination. Can be concluded that with manipulate its ligand backbone, lateral functionalities, and metal core to realize purpose specific ligands (Scheme 1 (b)). An added advantage of such ligands is that they can coordinate to the metallic core via different mode (Scheme 1 (b) (1-4)). For instance, it has been demonstrated that in complexes based on Pyridoxal semi-carbazones (PLSC) [3-11] and Pyridoxal S methyl iso-thiosemicarbazone (PLITSC) [12-18], metal can coordinate to the ligand via three different modes namely neutral (H2L), monoanionic (HL-) and dianionic (L2-) forms.



Scheme 1. (a) General chemical structure for pyridoxal semi-carbazone (PLSC), thiocarbazone (PLTSC) and pyridoxal S-methyl-iso thiosemicarbazone PLITSC; (b) 1) PLTSC(Pyridoxal-thiosemicarbazone) ligand without coordination, 2) neutral (H_2-L), 3) mono-anionic ([H-L]$^-$) and 4) di-anionic ([L]$^{2-}$) modes of coordinations

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Received: Jun. 30, 2021; Accepted: Jul. 17, 2021; Published: Jul. 31, 2021
Published online at http://journal.sapub.org/chemistry

However, special attention in our case should be paid to the Zink and Cobalt complexes with PLTSC (Pyridoxal-thiosemicarbazone) [19-21]. The focus will be on the structure of the zinc and cobalt complex (formula [Zn (PLTSC) $(H_2O)_2$]$SO_4 \cdot H_2O$ and [Co (PLTSC-H)$_2$] $Cl \cdot H_2O$), of course, but the biological activity of the mentioned complexes will also be emphasized. Based on the experience so far, it is to be expected that these complexes will show biological activity, especially since there are many works that show that [22]. That study [22] reported the synthesis and crystal structures of Cu (II) complexes with pyridoxal -thiosemicarbazones(H2L2 = pyridoxal-N4-phenyl-3-thiose micarbazone. The single-crystal X-ray study reveals, the Schiff base coordinated tridentately through the ONS-donor atoms, resulting in distorted square planar coordination geometries with the copper atoms.

Three complexes with pyridoxal thiosemicarbazone, [Cu (HL2) Cl] ·dmf, [Cu (HL2) Br] $\cdot H_2O \cdot$dmf and [Cu(H2L3) Br] $Br \cdot H_2O$, were also characterized by spectroscopic and physical–chemical analyses. The cytotoxicity of the complexes toward two kinds of cancerous cells (Ehrlich and S-180 cells) was evaluated by an MTT assay. The complex [Cu(H2L3) Br] Br·H2O was selected to study both the cellular and molecular mechanisms underlying its promising cytotoxicity. The Hoechst 33342/PI dual-staining assay showed the typical apoptotic morphology of cancer cells, and the RT-qPCR analysis revealed that the expressions of Bax, Casp3, Casp8, Casp9 and TP53 were markedly increased in both the Ehrlich and S-180 cells exposed to 10 μM for 3 h. According to our results, this complex induces cell death through apoptosis, showing potential as a future drug against cancer. In our case, the complexes (Zn and Co) not were examined in terms of anticancer activity, but antibacterial activity, which only confirmed that pyridoxal-thiosemicarbazone-based complexes with different transition metals as central, has a comprehensive application as biologically active substances.

2. Experimental Part

Commercial pyridoxal hydrochloride (PL·HCI, "Aldrich") and thiosemicarbazone (TSC, "Merck") were used for ligand synthesis.

2.1. Synthesis of Ligand PLTSC·H_2O

Solution 0.60g (3mmo1) PL·HCI was mixed with warm solution 0.27 g (3 mmol) TSC 8 cm3 H_2O and it was poured into 2 cm3 H_2O. The obtained yellow solution was stirred and left at room temperature for 10 hours. Deposited yellow acerate crystals were filtered off and washed two times with H_2O. Yield: 0.60 g (69%).

2.2. Synthesis of [Zn (PLTSC) $(H_2O)_2$]$SO_4 \cdot H_2O$ Complex

0.10 g (0.45 mmol) of the ligand PLTSC was dissolved in 15 cm3 of warm H_2O and this solution was added 0.17 g (0.7 mmol) $ZnSO_4$. The obtained yellow solution was left at room temperature around 3 days. Large yellow-orange crystals (monocrystals can also be found there) were filtered off and washed with H_2O. Yield: 0.12 g (58%).

2.3. Synthesis of [Co (PLTSC-H)$_2$] $Cl \cdot H_2O$ Complex

Mixture of 0.20 g (0.7 mmol) PLTSC·3H2O and 0.22 g (1 mmol) $CoCl_2$ $6H_2O$ was perfused with 30 cm3 H_2O. It was heated until complete dissolution of reactants and purple solution was left at room temperature for 24 hours. The obtained crystals were filtered off and dried in vacuum. Yield: 0.24 g (88%).

2.4. X-ray Crystallography

A single crystal of 0.12 x 0.09 x 0.17 dimension was examined. The temperature was 296 K on a computing data collection For the X-ray measurements, single crystal of the complex was mounted on a glass fibber and examined at 296 K on a Bruker D8 Venture APEX diffractometer equipped with Photon 100 CCD area detector using graphite-monochromate Mo-Kα radiation [λ = 0.71073 Å]. In general, in the difference map the hydrogen atoms were 109 visible. Hydrogen atoms bound to carbon were initially positioned geometrically while the hydrogen atoms for the coordinated water molecules were located in the difference map. All hydrogen positions and isotropic displacement parameters were then refined in a separate cycle. Hydrogen positions were checked for feasibility by examination of the hydrogen-bonding network. Crystallographic data in the Cambridge Crystallographic Data Centre (CCDC, 12 Union Road, Cambridge CB2 IEZ, UK; e-mail: depos-it@ccdc.cam.ac.uk) were deposit, CCDC deposition number are 2092612 2092620. Crystal data collection and structure refinement are given in Table 1.

Table 1. Crystal data and structure refinement details of the complexes of Zn and Co

Empirical formula	C9 H18 N4 O9 S2 Zn	C18 H26 Cl Co N8 O6 S2
Formula weight	455.76	608.97
Temperature	123 K	123 K
Wavelength	1.54184	1.54184
Crystal System	Triclinic	Triclinic
Space group	P -1	P -1
Unit cell dimensions	a=8.6798(3) b=10.1416(3) c=10.7975(4) alpha=64.253(3) beta=72.011(3) gamma=87.010(2)	a=7.51020(13) b=12.6408(3) c=12.9868(2) alpha=91.8457(16) beta=104.0580(16) gamma=93.4508(16)
Volume	810.52(5)	1192.41(4)
Z	2	2

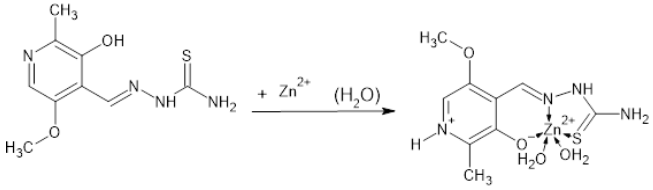
2.5. Bioassays

In order to obtain the quantitative data for the reported compounds, the micro dilution technique was used (NCCLS, 2000) [23]. The following bacteria were tested: Escherichia

coli (ATCC 10526), Pseudomonas aeruginosa (ATCC 27853), Staphylococcus aureus (ATCC 11632), and Bacillus cereus (ATCC 10876). Cultures of the test bacteria were growing overnight in Müller-Hinton agar at 37℃ and then transferred to sterile saline. The bacterial suspension was adjusted with sterile saline to a concentration of approximately 1.0 × 107 cells/ml. The 1 ml of bacterial suspension was homogenized with 9 ml of melted (45℃) Müeller-Hinton agar. Minimum inhibitory concentrations (MICs) determination was performed by a serial dilution technique, using 96-well microtiter plates. The inoculate applied contained approximately 1.0×10^5 cells in a final volume of 100 µl/well. The compounds tested were dissolved in H_2O (compounds [Zn (PLTSC) $(H_2O)_2]SO_4$. H_2O and [Co (PLTSC-H)$_2$] Cl H_2O.; conc. 5 × 10-3/10 ml H_2O) and added to the broth medium with bacterial inoculate in a volume of 100 µl/well. The covered plates were incubated under aerobic conditions at 37℃ for 24 h. The lowest concentrations without visible growth (at the binocular microscope) were defined as concentrations which completely inhibited bacterial growth (MICs). DMSO was used as a negative control, while chloramphenicol was used as a positive control. Dilutions of the inoculate were also cultured on solid MH to verify the absence of contamination and to check their validity. All tests were performed in triplicate.

3. Results and Discussion

3.1. Zink Complex [Zn (PLTSC) $(H_2O)_2]SO_4 \cdot H_2O$



Scheme 2. Synthesis of Zn complex compound

The molecular structure for new complex of Zn is [Zn (PLTSC) $(H_2O)_2]SO_4 \cdot H_2O$ shown in Figure 1. It crystallizes in P -1 space group with one discrete neutral unit [Zn (PLTSC) $(H_2O)_2$] and one SO_4 anion and H_2O molecule in out sphere. The environment around the central zinc atom can be best described as a distorted square-planar pyramid geometry. Scheme 2 shows the synthetic routes to the Zn (II) complex. The reactions of ZnSO4 with warm H_2O solution of PLSC $2H_2O$, produced the title complex compound of Zn in the reaction of Zn salt with ligand the molar ratio was 1:1. 1992. Italian researchers managed to synthesize a complex formed in the reaction of $ZnCl_2$ and PLTSC [19]. Reaction of zinc chloride or acetate with ligand, pyridoxal thiosemicarbazone (PLTSC), in that paper [19], lead to the formation of novel complexes which have been characterized by spectroscopic methods and X-ray analysis. That Zn complex is with formula [Zn (HL)Cl] $2H_2O$. The ligand PLTSC is in monoanionic form coordinated, the central metal Zn with two chlorine atoms in coordination also, so, the geometry is the square-pyramid.

In our case Zn complex with PLTSC have same geometry, square-planar pyramid. The central metal Zn is in coordination with ONS PLTSC ligand, and two molecule H_2O (Figure 1) in coordination. Certainly, the coordination number of the zinc complex is 5, and as already mentioned, the geometry corresponds to a distorted square pyramid (Figure 2) The zinc atom is not in the plane of the base pyramid, he is slightly raised above (Figure 2). The basis of pyramid is created by 3 atoms donors from ligand (O1, S1 and N1), and one oxygen O2 from coordinated water. This is actually the base of the pyramid, while at the top is an oxygen atom O4 from another water molecule.

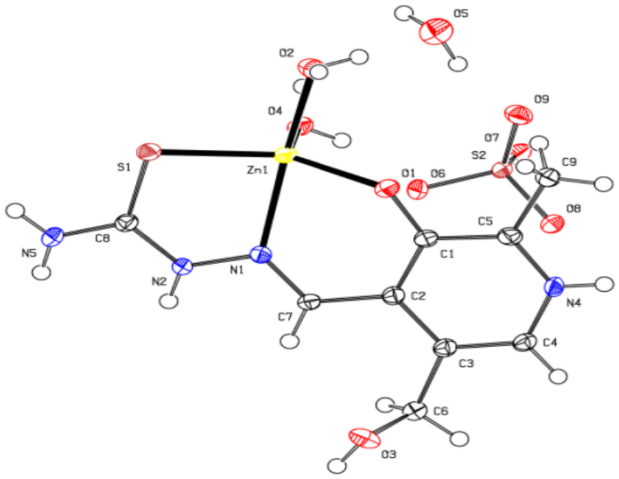


Figure 1. The crystal structure for Zn complex

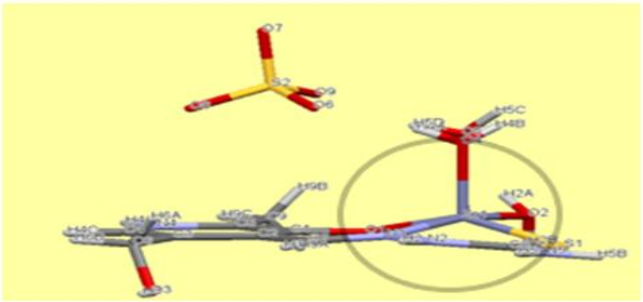


Figure 2. A distorted square pyramid of Zn complex

The PLTSC ligand is coordinated in a neutral form, which is clearly seen from the crystal structure, namely hydrogen is present on pyridine N4 and hydrazine N2 nitrogen [3].

The zinc central atom is surrounded by phenolic hydroxyl O1, sulfur S1 and with hydrazine nitrogen N1, which are belongs to the PLTSC ligand, the other coordination sites around zinc are occupied by two molecules of water (O2 and O4). The bonds with the central metal atom in the planar plane of the base of the pyramid are very identical. The longest bond is with sulfur (Zn1 S1 2.3201(6)), and the shortest with phenolic hydroxyl oxygen (Zn1 O1 1.9429(15))

(Table 2). The top of the pyramid is covered by an oxygen O4 atom of one coordinated water. The largest angle around the zinc atom is formed by O2 Zn1 N1 167.01 (7), while the smallest angle is formed by O1 Zn1 N1 83.19 (6) (Table 3).

Table 2. Bond lengths [Å] of the Zn and Co complexes

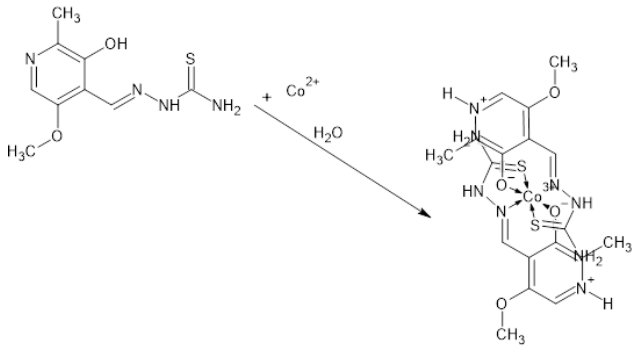
Zn complex		Co complex	
Zn1-O4	2.0184(15)	Co1-S2	2.2126(9)
Zn1-O1	1.9429(15)	Co1-S4	2.2201(8)
Zn1-O2	2.0658(16)	Co1-N1	1.909(3)
Zn1-N1	2.1932(17)	Co1-N2	1.911(3)
Zn1-S1	2.3201(6)	Co1-O3	1.967(2)
		Co1-O1	1.950(2)

Table 3. Angles [°] of the Zn and Co complexes

Zn complex		Co complex	
O4 Zn1 S1	104.31(5)	S2 Co1 S4	92.91(3)
O4 Zn1 O2	96.29(7)	N1 Co1 S2	94.50(8)
O4 Zn1 N1	96.18(6)	N1 Co1 S4	85.76(8)
O1 Zn1 S1	147.37(5)	N1 Co1 N2	179.50(11)
O1 Zn1 O4	106.27(7)	N1 Co1 O3	91.04(10)
O1 Zn1 O2	89.81(7)	N1 Co1 O1	86.86(10)
O1 Zn1 N1	83.19(6)	N2 Co1 S2	85.77(8)
O2 Zn1 S1	97.96(5)	N2 Co1 S4	94.65(8)
O2 Zn1 N1	167.01(7)	N2 Co1 O1	92.86(11)
N1 Zn1 S1	82.47(5)	O3 Co1 S2	89.12(7)
		O3 Co1 S4	176.34(7)
		O1 Co1 S2	177.46(7)
		O1 Co1 S4	89.34(7)
		O1 Co1 O3	88.70(9)

3.2. Cobalt Complex [Co (PLTSC-H)$_2$] Cl·H$_2$O

As for the second complex, cobalt with PLTSC, the papers on that topic have been described so far [20,21]. Cobalt (III) Pyridoxal Thiosemicarbazone Complexes with Nitroprusside [20] is interesting from the aspect of pronounced biological activity, proving to be a good antileukemic agent.



Scheme 3. Synthesis of Co complex compound

From the structural aspect, pyridoxal N (4)-substituted thiosemicarbazone cobalt (III) complex [20] is much more important for us. The structure of Cobalt in the work of Indian authors [20] is absolutely identical to our structure of cobalt, the only difference is in the existence of C_6H_6 molecule on the terminal nitrogen from the thiocarbazone chain. Actually, the investigation of effect of substitution (CH or C H) on terminal N (4)-nitrogen of thiosemicarbazone exhibited its influence on the potential binding and cleavage ability with DNA, BSA binding, free radical scavenging and cytotoxicity.

Our cobalt (III) complex, perhaps thanks to a similar structure as the complex from the research of Indian authors [20], is also very biologically active, more precisely its antibacterial effect on several known bacteria has been investigated in this paper.

The our [Co (PLTSC-H)$_2$] Cl·H$_2$O complex was obtained from the simple salt $CoCl_2$, while the starting salt for the complex pyridoxal N (4)-substituted thiosemicarbazone cobalt (III) [20] was [$CoCl_2$ (PPh_3)$_2$].

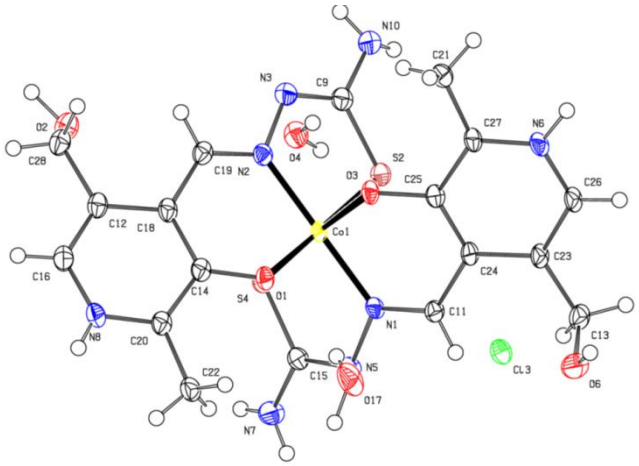


Figure 3. Crystal Structure of Co complex

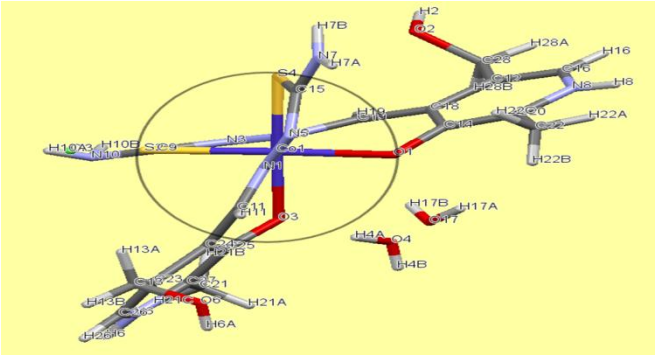


Figure 4. Octahedral structure of Co complex

The title cobalt complex is a bis-ligand complex, with the octahedral structure (Figure 3). The synthesis process is given in Scheme 3, an aqueous solution of cobalt (II) chloride salt is used which, in reaction with the PLTSC ligand in a ratio of 1: 2, gives purple crystals, stable in air.

In this complex, both ligands are coordinated in monoanionic form, as indicated by the crystal structure with deprotonated hydrazine hydrogen in the N3 and N5 positions,

respectively. The octahedral environment around the central Cobalt atom was realized through two ONS donor sets of two ligands. The longest bond of the Cobalt atom is with sulfur (Co1 S4 2.2201 (8)), while the shortest is with hydrazine nitrogen (Co1 N1 1.909 (3)) (Table 2). The largest angle covers N1-Co1-N2 179.50 (11), while the smallest corresponds to the N2-Co1-S2 85.77 (8) (Table 3). The angles around the cobalt are almost at right angles with minor deviations, so it can be said that there is a one regular octahedral (Figure 4).

3.3. Biological Activity

In the Table 4 is given the summary of the antimicrobial activities of the ligand (PLTSC) and complexes (Zn and Co). As can see, the complex Co shows the greatest antibacterial activity in comparison to the other tested substances. The fact that complex Co showed activity towards both Gram negative (Escherichia coli, Pseudomonas aeruginosa) and Gram positive (Staphylococcus aureus, Bacillus cereus) bacteria. According that fact, can be concluded that the antibacterial mechanism of complex Co is not dependent on the structural features of the bacterial cell wall, what give high performance to Co complex like antibacterial compound.

That complex Co showed antibacterial activity towards Pseudomonas aeruginosa (MIC) 0.06 mg ml-1) bacteria, which has been re-ported to show the least amount of susceptiveness towards antibiotic chloramphenicol (MIC 0.05 mg) [24]. Also, Co complex showed activity against Staphylococcus aureus (MIC 0.125 mg ml-1). Gram negative (Escherichia coli, Pseudomonas aeruginosa) and Gram positive (Staphylococcus aureus, Bacillus cereus) are typical soil and water bacteria which are widely distributed among fresh foods, especially vegetables, meats, poultry, and seafood products [24]. Staphylococcus aureus one of the common Gram-positive bacteria causing food poisoning. The conclusion can be that the cobalt complex can potentially be used as a one potential preservative, based on the properties shown above. On the other hand, a zinc complex that has established values (>1) for the tested microorganisms cannot be reliably said to be an effective antibacterial agent as a cobalt complex. Perhaps future testing in relation to other strains of bacteria on this complex, can give a more complete picture of whether this complex can be included in the promising compounds with biological activity.

Table 4. Minimum Inhibitory Concentrations of the Compounds Tested (mg ml-1)

Organism	Ligand PLTSC	Complex Zn	Complex Co	Chloramphenicol
P. aeruginosa	> 0.20	>1	0.060	0.050
E. coli	> 0.20	>1	0.060	0.005
S. aureus	> 0.20	>1	0.125	0.005
B. cereus	> 0.20	>1	0.060	0.010

4. Conclusions

Two new complexes of Zinc and Cobalt were synthesized with the ligand Pyridoxal thiosemicarbazone (PLTSC), with formulas [Zn (PLTSC) $(H_2O)_2]SO_4 \cdot H_2O$ and [Co $(PLTSC\text{-}H)_2]$ $Cl \cdot H_2O$. X-ray structural analysis showed that in the case of the zinc complex it is a monoligand complex, with coordination number 5, (ONS ligand PLTSC and 2 molecules of water in coordination with Zn (II) central metal), square pyramidal geometry. The cobalt complex is a bis-ligand complex (two ONS ligands PLTSC in coordination with Co (III) central metal, octahedral geometry. The syntheses for both complexes were performed in aqueous solution, with the corresponding Zn and Co salts ($ZnSO_4$ and $CoCl_2$), during which the oxidation of Co^{2+} to Co^{3+} occurred during the coordination reaction, while the oxidation number of zinc remained unchanged (+2) as in the initial salt $ZnSO_4$.

The complexes were biologically tested where they proved to be promising antibacterial agents. The cobalt complex has been shown to be more active than the zinc complex or the ligand itself. Surprisingly, its activity is enforceable regardless of whether it is gram-positive or negative bacteria, so it can be expected that its good therapeutic performance may find practical application in some of the further research.

Actually, Gram-negative bacteria are surrounded by a thin peptidoglycan cell wall, which itself is surrounded by an outer membrane containing lipopolysaccharide. Gram-positive bacteria lack an outer membrane but are surrounded by layers of peptidoglycan many times thicker than is found in the Gram-negatives [25].

Based on this, it is little unexpected that our results show the best activity in the case of Gram-positive Staphylococcus aureus. In the case of Gram-positive Bacillus cereus, such an effect would also be absent, since these are positive bacteria in both cases. In any case, without a doubt, the tests should be expanded and cover as many different types of bacteria as possible, but also other types of tests should be done, anticancer, for example.

ACKNOWLEDGEMENTS

Author Amna Saud Altamimi, a Master student at University Hail, along with her mentors, would like to thank University Hail for its support and opportunities to use the university's laboratory services. Also, she expresses great gratitude for the analyzes done at the University of Monash, Victoria, Australia, especially to Dr. Dragoslav Vidovic and his research group of PhD students, who helped a lot in creating this research work.

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