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Research Article

Comparison of the antibacterial activity of Metal Complexes Derived from 2,6 -Diaminopyridine with the corresponding metal salts

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Abstract

The presence of the pyridine nucleus, as a hydrocarbon linker, creates a specific molecular structure, which leads to interaction with proteins in the microorganisms and subsequently increases selectivity and antimicrobial activity. In addition, Because of solubility of pyridine in water, it has been highly considered in the structure of pharmaceutical compounds. Therefore, in the present study, we tried to prepare organometallic schiff base 2,6 -Diaminopyridine and transition metal complexes by reacting 2,6 –diaminopyridine with Hg (II), C(II), N(II), chlorides. All prepared compounds have been characterized by using IR, UV-Vis and 1H-NMR, and 13C-NMR. The antimicrobial activities of the ligands and their metal complexes have been studied by using different bacterial species [staphylococcus aureus PTCC 1112, Bacillus cereus PTCC 1015, Pseudomonas aeruginosa ATCC 27853 and Escherichia coli ATCC 25922] by Agar Dilution and Well Agar Diffusion methods. The results showed that all the synthesized compounds against the tested bacteria have moderate to good antibacterial activity.

Key Words: complexes; antimicrobial; antibacterial; diaminopyridine

Introduction

Schiff bases are so important group of medicinal compounds that have an azomethine group (C=N) in their structure. pyridine used as ligand for coordination complexes or as an organic solvent so it has received much attention in the pharmaceutical chemistry industry. [1]. Pyridine is in the structure of many natural compounds, such as coenzymes, alkaloids, vitamins and many drugs and pesticides [2,3]. The presence of substitutions such as amines in the vicinity of pyridine leads to an increase in antimicrobial activity and improve the medicinal nature of the synthetic compounds [4–8]. Due to pyridine ability to coordinate with different metal ions, stable forming of complexes with attractive structure, and significant geometry, they have been introduced as good candidates in various applications like: medicine, pharmaceutical fields, catalysis, material science ant etc. [9-11]. In this reserch, we have described a *synthesis* of metal complexes based on 2,6 -Diaminopyridine and evaluate their in vitro antibacterial activities.

Experimental

Preparation of complexes

The chloro complexes of cobalt, nickel and mercury with 2,6-diaminopyridine were prepared by a previously reported method [12]. The metal derivatives were dried and after solubilization and filtration were prepared for antibacterial studies.

Qualitative method of determining the antibacterial activity of synthetic compounds

In this part, metal complexes solution of 2,6-diaminopyridine and metal salts were prepared with a concentration of 1 mg/ml in dimethyl sulfoxide solvent. The prepared solution was analyzed for the qualitative study of antimicrobial activity using Agar well diffusion method [13-15]. In this study, Dimethyl sulfoxide was used as a negative control and Ciprofloxacin was used as a positive control.

Quantitative method of determining the antibacterial activity of synthetic derivatives

In the continuation of the study, the Agar diffusion method was used to determine the minimum inhibitory concentration of the studied compounds [16-18]. In this method, 6-8 concentrations of all compounds were prepared and their antimicrobial activity was compared with the Ciprofloxacin as reference drug.

Result and Discussion:

Metal complexes of 2,6 -Diaminopyridine were first purified by recrystallization using appropriate solvents then their structure was identified by using IR, and ^{1}H-NMR and ^{13}C-NMR. The picture of the synthetic compounds is presented in the figure 1.

Figure 1: The picture of the 2,3 –diaminopyridine with Hg (II), Co (II), Ni (II), chlorides.

Antimicrobial activity:

Qualitative method of determining the antibacterial activity of synthetic compounds were determined by Agar well diffusion method. Antibacterial tests were performed against *Staphylococcus aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa* and *Escherichia coli*.

The antibacterial activity of compounds was tested at a concentration of 1000 mg/ml in Dimethylsulfoxide. The inhibition zone of synthesized compounds against tested bacteria were measured after 24 h of incubation at 37°and then were compared with Ciprofloxacin as reference drug (Table 1). In general, all synthesized compounds exhibited good inhibitory activity against tested pathogenic bacteria.

Compounds Code	***Staphylococcus aureus PTCC 1112***	***Bacillus cereus PTCC 1015***	***Escherichia coli ATCC 25922***	***Pseudomonas aeruginosa ATCC 27853***
$Co_2(C_5H_7N_3)_4$	*9±0.4*	*9±0.6*	*10±0.6*	*8±0.6*
$CoCl_2$	*14±0.7*	*8±0.5*	*11±0.5*	*9±0.18*
$Ni(C_5H_7N_3)CI_2$	*10±0.8*	*8±0.2*	*9±0.20*	*9±0.56*
$Ni\ CI_2$	*13±0.2*	*8±0.2*	*10±0.6*	*9± 1/15*
$Hg\ (C_5H_7N_3)CI_2$	*22±0.3*	*23±0.23*	*25± 1/52*	*15± 1/15*
HgCl2	*26±0.6*	*8±0.2*	*28± 1/15*	*10±0.2*
Ciprofloxacin	*40±0.4*	*35±0.6*	*44±0.6*	*35±0.3*

NA:No Activity

Table1: In vitro antibacterial activity of metal complexes of 2,6 -Diaminopyridine by Agar well diffusion method (1mg/ml).

The result are expressed as mean ±sem

The results show that all synthetic compounds against tested bacteria have antibacterial activity, and among these compounds, the antibacterial power of two compounds $Ni(C_5H_7N_3)\ CI_2$ and $Hg\ (C_5H_7N_3)\ CI_2$ is higher than other compounds (Figure 1 and 2). The interesting point is that the antibacterial power of metal salts is more than metal complexes (Table 1).

Figure 2: Inhibition zone of metal complexes of 2,6 -Diaminopyridine against *Pseudomonas aeruginosa and Escherichia coli* in 1mg/ml concentration.

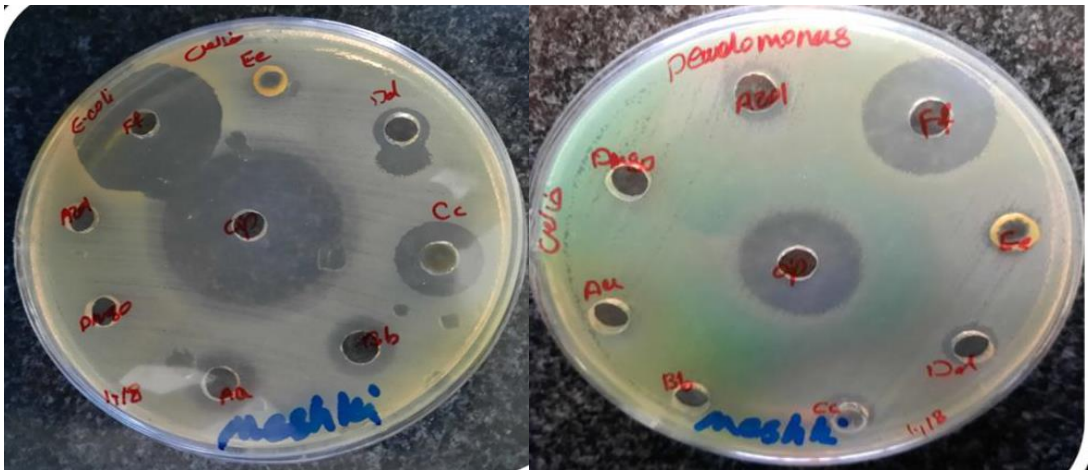

Figure 3: Inhibition zone of metal salts against *Pseudomonas aeruginosa and Escherichia coli* in 1mg/ml concentration.

Compounds Code	*Staphylococcus aureus PTCC 1112*	*Bacillus cereus PTCC 1015*	*Escherichia coli ATCC 25922*	*Pseudomonas aeruginosa ATCC 27853*
$Co_2(C_5H_7N_3)_4$	*1000*	*250*	*500*	*500*
$CoCl_2$	*500*	*250*	*250*	*250*
$Ni(C_5H_7N_3)CI_2$	*250*	*500*	*1000*	*500*
$Ni\ CI_2$	*125*	*250*	*500*	*250*
$Hg\ (C_5H_7N_3)CI_2$	*500*	*250*	*500*	*500*
HgCl2	*250*	*125*	*250*	*250*
Ciprofloxacin	*0/07*	15	15	*1/5*

Table 2: Minimum inhibitory concentrations (µg/ mL) of metal complexes of 2,6 -Diaminopyridine against tested bacteria

The results shows that the antibacterial power of compounds containing mercury has the highest antibacterial power. And compounds containing nickel also have good antibacterial activity. But in all cases, the antibacterial power of the tested compounds was lower than the reference drug ciprofloxacin (Table 2).

Results And Discussion

One of the strategies to deal with antimicrobial resistance is the use of metal complexe in the combination of antibiotics. In fact, these metal complexes can exert their antimicrobial activity by different mechanisms including ligand exchange reactions, the production of ROS, the release of bioactive molecules or interacting with nucleic acids and prevent microbial resistance [16]. Studies shows that due to the diversity of the resistance mechanism of metal complexes against microbial resistance, the possibility of drug resistance by microorganisms is greatly reduced, so that in the next few generations, there will be no noticeable resistance of these microbes [17]. But still, there are limitations in the use of metal complexes as antibacterial agents that cannot be ignored. For example, the studies that has been done by organic compounds against microorganisms, is in a wide range, but the studies conducted on metal complexes as the basic structure in drugs are few.

On the other hand, due to the many similarities between bacterial cells and human cells, as metals can affect bacterial cells and destroy them, they can lead to toxicity in human cells. So, in order to decrease the toxicity of metal complexes, we try to use them in the structure of other organic compounds as part of the antibacterial agents to reduce their toxicity. In the current study, the antibacterial power of compounds containing nickel and mercury was higher than other compounds and in all tested bacteria, the antibacterial power of metal salts against gram positive and gram-negative bacteria is more than diaminopyridine metal complex, and this fact shows that as the presence of diethylamine substitution causes to reducing the antibacterial activity the toxic nature of these metals can be reduced in the presence of this substitution in the body.

Conclusion:

We have synthesized the Schiff base ligands from 2,6 -diaminopyridine. All the synthesized Schiff bases compounds are screened for *in vitro* antibacterial activities and compared with the Ciprofloxacin. All of the investigated compounds show moderate to good antibacterial activity.

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