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Research Article

Antibacterial Activity of 2,6 –Diaminopyridine Metal Complexes and Corresponding Metal Salts against some Pathogenic Bacteria

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Abstract

Due to the new life-threatening COVID-19 pandemic caused by the SARS-CoV-2 virus, discovery, synthesis and introduction new antiviral and antimicrobial compounds is one of the research priorities in the last decade. Due to therapeutic properties of pyridine such as antimicrobial, antiviral, antitumor, analgesic, anticonvulsant, anti-inflammatory, antioxidant, anti-Alzheimer and anti-wound or anti-diabetic, it is known as a unique nucleus among heterocycles and improves therapeutic properties. 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 Cu (II), Fe (II). 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: metal complexes; antimicrobial; antibacterial, 2,6 –diaminopyridine

Introduction

Traditional organic compounds exert their antimicrobial effect by exerting their effect on biochemical processes such as translation, replication and transcription. But due to repeated microbial resistances from various microorganisms, the need to synthesize and introduce compounds with antibacterial activity is urgent need. One way to overcome this problem is the simultaneous use of several strategies that can affect several biochemical mechanisms and lead to the destruction of microorganisms. Recent studies show that metal ions with processes such as membrane destruction and oxidative stress can lead to the destruction of bacteria [3-5]. Pyridine is an aromatic ring that is obtained by replacing a CH group with a nitrogen. Often, pyridine is used as an organic solvent or ligand for the preparation of organic and inorganic compounds or complexes. Pyridine is abundantly found in vitamins, alkaloids, pesticides, coenzymes and medicinal compounds [6-9]. This heterocycle either individually or in combination with other heterocycles or metals, has shown very unique antibacterial and antifungal activity [10-13]. In addition to the mentioned cases, the presence of groups such as amino, hydroxy, methoxy, sulfamide and hydrazide, leads to increase in the biological and medicinal activity of pyridine and its use in a wide range of medicinal compounds [14-16].

In the present research, we have tried to synthesize metal complexes derived from 2,6 -Diaminopyridine by using all the mentioned strategies, that the simultaneous use of three main groups of amine, pyridine and metal ions can use their medicinal mechanisms to overcome defense processes of bacteria and eliminate them.

Experimental

Preparation of complexes

The complexes of Copper and Iron with 2,6-diaminopyridine were prepared by a previously reported method [17]. 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

The Qualitative antimicrobial activity of the synthesized compounds was assessed against *staphylococcus aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa* and *Escherichia coli* by the agar well diffusion method. In this step all the used pathogenic bacteria were inoculated on nutrient agar medium plates and seeded with 0.1 mL of 10^{5} –10^{6} cells/ml bacterial suspension. 1mg of each sample was dissolved in 1 mL of DMSO and 100

µl of prepared solutions in concentration of 1mg/ml were poured in wells in inoculated plate and then kept at 37 °C overnight. Ciprofloxacin was used as reference drug. The clear zone inhibition created by aminopyridine metal derivatives around each well expressed in millimeter (mm). The experiment was carried out three times and their mean were recorded.

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 [18]. Diaminopyridine metal complexes and corresponding metal salts were serially diluted from 1000 to 7.8125 µg/mL and Ciprofloxacin were made into five concentration series based on the Clinical and Laboratory Standards Institute. DMSO was used as the negative control, while Ciprofloxacin was used as the positive control. The minimum inhibitory concentration (MIC) was determined by observing the lowest concentration with no bacterial growth.

Result and Discussion

Cu (II) and Fe (II) complexes with 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 Cu (II) and Fe (II) complexes with 2,6 -Diaminopyridine

Antimicrobial activity:

Qualitative antibacterial activity of Cu (II) and Fe (II) complexes with 2,6–Diaminopyridine 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 Cu (II) and Fe (II) complexes were tested at a concentration of 1000 mg/ml in Dimethylsulfoxide. The inhibition zone formed around each well by synthesized compounds against tested bacteria were measured in millimeters after 24 h of incubation at 37°and then were compared with Ciprofloxacin as broad-spectrum antibiotic and reference drug (Table 1). In general, Cu (II) and Fe (II) complexes exhibited good inhibitory activity against tested pathogenic bacteria.

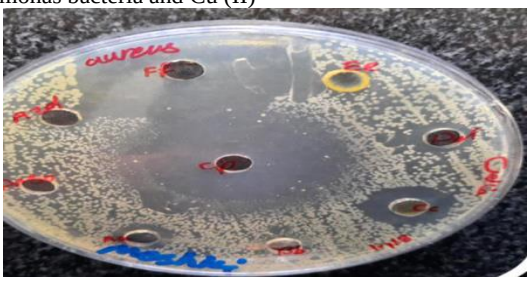
Compounds Code	***Staphylococcus aureus PTCC 1112***	***Bacillus cereus PTCC 1015***	***Escherichia coli ATCC 25922***	***Pseudomonas aeruginosa ATCC 27853***
Fe ($C_5H_7N_3$) SO_4	*11±0.4*	*9±0.6*	*10±0.6*	*12±0.6*
$FeSO_4$	*7±0.7*	*4±0.5*	*8±0.5*	*10±0.18*
Cu ($C_5H_7N_3$) CI_2	*9±0.8*	*11±0.2*	*13±0.20*	*12±0.56*
$CuCI_2$	*8±0.2*	*4±0.2*	*11±0.6*	*9± 1/15*
Ciprofloxacin	*40±0.4*	*35±0.6*	*44±0.6*	*35±0.3*

Table 1: In vitro antibacterial activity of Cu (II) and Fe (II) complexes with 2,6 -Diaminopyridine by Agar well diffusion method (1mg/ml).

NA: No Activity

The results are expressed as mean ± sem

The results show that both of the Cu (II) and Fe (II) complex against tested bacteria have antibacterial activity. Fe (II) complexe of 2,6 -Diaminopyridine had the most antibacterial activity against Pseudomonas bacteria and Cu (II) complexe of 2,6 -Diaminopyridine showed the most antibacterial activity against Escherichia coli (Figure 1 and 2). The interesting point is that the antibacterial power of metal complexes is more than metal salts (Table 1).



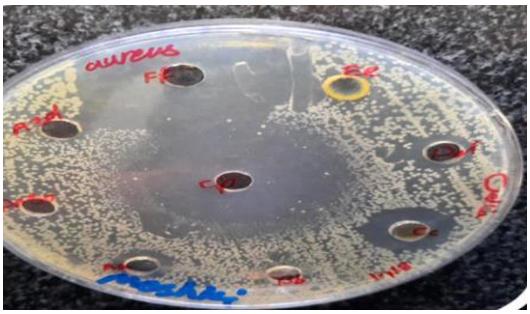


Figure 1: Inhibition zone of metal complexes of 2,6 -Diaminopyridine against *Pseudomonas aeruginosa and Staphylococcus aureus* in 1mg/ml concentration.

Compounds Code	*Staphylococcus aureus PTCC 1112*	*Bacillus cereus PTCC 1015*	*Escherichia coli ATCC 25922*	*Pseudomonas aeruginosa ATCC 27853*
Fe ($C_5H_7N_3$) SO_4	*500*	*500*	*1000*	*1000*
$FeSO_4$	*1000*	*1000*	*1000*	*1000*
Cu ($C_5H_7N_3$) CI_2	*1000*	*500*	*1000*	*500*
$CuCI_2$	*1000*	*500*	*1000*	*500*
Ciprofloxacin	*0/07*	15	15	*1/5*

The results shows that the antibacterial power of Fe ($C_5H_7N_3$) SO_4 is more effective against Gram-positive bacteria than Gram-negative bacteria while Cu ($C_5H_7N_3$)CI_2 had the highest antibacterial activity against *Bacillus cereus* and *Pseudomonas aeruginosa.*

Discussion:

Due to the unique biological activity of Schiff base metal complexes, they will play an important role in the future of pharmaceutical industry. In our previous studies, we explored the antibacterial activity of Schiff base complexes of 2,6 -Diaminopyridine ligand, as well as different metal ions such as Hg (II), Co (II) and Ni (II). In the present work, we designed new derivatives of diaminopyridine based on two metals, iron and copper, and investigated their antibacterial activity against a number of pathogenic bacteria. The antibacterial activity of of the Cu (II) and Fe (II) complexes was evaluated by measuring the inhibitory (MIC) and bactericide (MBC) properties against *Staphylococcus aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa* and *Escherichia coli*. From the results summarized in Table 1, we can conclude that the metal salts used as controls in this study do not have significant antibacterial activity, but when diaminopyridine substitutes were added to them, the compounds show significant antibacterial activity, which can be attributed to the increase in lipophilicity of metal salts that are in binding to diaminopyridine substitution. The previous studies by Sylvia and her colleagues also confirm this point [19]. The antibacterial effect of Cu (II) complexe of diaminopyridine show good activity against both S. aureus (Gram-positive) and *Pseudomonas aeruginosa*

(Gram-negative) bacteria while Cu (II) complexe of diaminopyridine show antibacterial activity against *Escherichia coli* and *Pseudomonas aeruginosa.*

In general, both metal complexes had significant antibacterial activity, but the highest antibacterial activity was related to the copper metal complex against *Escherichia coli* with 13 mm IZ. The type of metal ion is crucial for the antimicrobial activity. The Cu (II) and Fe (II) complexes of 2,6 -Diaminopyridine exhibited similar activity in *Pseudomonas aeruginosa*, but the Cu (II)complex was slightly more active against E. coli. The difference in the antibacterial power can be attributed to the difference in the penetration and entry of metal complexes into the bacterial cell wall, which is also due to the difference in the cell membrane of bacteria that is completely subject to structural complexity of cell membrane in various bacteria.

Conclusion:

Our findings suggest that Cu (II) and Fe (II) complexes of 2,6 -Diaminopyridine is a good candidate for developing and investigating new iron (II) and Cu (II) based inorganic materials for medicinal and biological application.

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