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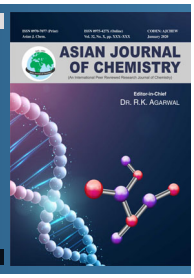

Antimicrobial Activity of Copper(II) and Cobalt(II) Complexes of Citral-Valine Derived Schiff Base

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In present work, the screening of antimicrobial activities of copper(II) and cobalt(II) complexes with Schiff base ligand derived from the condensation of citral with valine (amino acid) was carried out on agar plates are reported. The antibacterial activity of Schiff base and its copper(II) and cobalt(II) complexes were evaluated against two bacterial strains *Staphylococcus aureus* (Gram-positive), *Escherichia coli* (Gram-negative) and fungus *Candida albicans*. The results revealed that the Schiff base ligand exhibited the poor antimicrobial activity against *Escherichia coli* and *Candida albicans* except for *Staphylococcus aureus*. Generally, Gram-negative bacteria shows rigid outer membrane, well enough to defend against the drug but Schiff base (citral with valine derived) impregnated cobalt(II) complex seem to be more active against *Escherichia coli* organisms in comparison to copper(II) complex, which exhibits higher activity than uncomplexed ligand. The antimicrobial results revealed that cobalt(II) and copper(II) complexes have a considerable antibacterial activity than antifungal activity and suggest their potential application as antibacterial agents.

Keywords: Schiff base ligand, Citral, Valine, Antimicrobial activity, Copper(II), Cobalt(II) complexes.

INTRODUCTION

Schiff bases are an important class of multidentate organic ligand which possess (-C=N-) as the functional donor site, O, and S as additional binding sites [1,2]. The transition metal complexes of amino acid based Schiff base have acknowledged considerable interest because of their excellent coordination nature owing to their flexible behaviour to act as a multidentate ligand. Schiff base ligands in combination with the positively charged transition, metal centers yield the complexes of well-defined geometries and exhibit diverse pharmacological properties, specially the antibacterial, antifungal, antitumor activities [3,4]. In general, the transition metal complexes have been of great significance owing to their effective biological activities [5-7]. Several studies have been carried out on the inhibitory activity of transition metal complexes against infectious microbes, considerably depends on metal chelation by an organic ligand. Chelation nature tremendously enhances the antimicrobial activity of ligand, which has been well explained by Tweedy's chelation theory [8-11].

Citral is less explored in the field of coordination chemistry. It is a natural origin aliphatic monoterpene aldehyde, naturally gifted with strong lemon odor and used in fragrance industries, flavour in foods [12-19]. Nowadays the development of resistance to different antimicrobial agents by various microbes, for instance, bacteria, fungi, *etc*. considered as a great public concern, challenge to the medical field and hence, requiring attention to look for new and novel antimicrobial agents. In the present study, the aim is to investigate the antimicrobial activity of citral with valine (amino acid) derived Schiff base organic ligand and its copper(II) and cobalt(II) complexes against, *Staphylococcus aureus* (Gram-positive), *Escherichia coli* (Gram-negative) and fungus *Candida albicans* using the disc diffusion method.

EXPERIMENTAL

All the chemicals and solvents used were of analytical reagent grade. Citral and valine in extra pure form were purchased from Spectrochem, Mumbai, India, are used without further purification. Ethanol and distilled water were used as a solvent for the synthesis. The metal salts copper(II) and cobalt(II) nitrates (Merck) were used for the synthesis of metal complexes.

Synthesis of Schiff base ligand: A mixture of citral (0.5 mol, 10 mL) and an aqueous solution of L-valine (0.5 mol, 10 mL) was heated under reflux for 5-6 h at 60-65 ºC. The comp-

letion of the reaction was monitored by TLC. The solution was concentrated till its volume attains one-fourth of its initial volume. Then the concentrated mixture was allowed to stand for overnight and the brownish red precipitate was obtained. The obtained precipitate of brownish red was filtered and repeatedly washed with diethyl ether and dried. Yield 79 %; m.p. 232-238 °C; Anal. calcd. (found) (%): C, 71.67 (71.62); H, 10.2 (9.98); N, 5.57 (5.60).

Synthesis of metal(II) complexes: Metal(II) complexes were prepared by the addition of a 0.5 mol (20 mL) of copper(II) nitrate or cobalt(II) nitrate into a hot magnetically stirred ethanolic solution of Schiff base ligand (0.5 mol) at 60-65 ºC. The mixture was continuously stirred for 30 min, the colour of the solution mixture changes to translucent. To a solution, 0.5 mol KOH solution was added to maintain the pH of medium. The resulting mixture was further refluxed for 1 h. A light green copper(II) complex or dirty brown cobalt(II) coloured complexes were filtered off and washed repeatedly with ethanol followed by diethyl ether and dried.

Copper(II) complex (1): Yield 60 %; m.p. > 300 °C; Anal. calcd. (found) (%): C, 38.09 (38.05); H, 5.75 (5.79); N, 8.88 (8.91).

Cobalt(II) complex (2): Yield 66 %; m.p. > 300 °C; Anal. calcd. (found) (%): C, 38.47 (38.42); H, 5.81 (5.86); N, 8.99 (9.01).

Antibacterial susceptibility testing by disc diffusion method: The antibacterial susceptibility testing was performed by disc diffusion method (Kirby-Bauer method), using sterile filter paper discs saturated with solutions of testing compounds. Initially, the culture agar medium (Muller-Hinton) was distributed on each petri-plates. After the solidification of medium, the plates were incubated at 27 ºC for approximately 30 min until the excess moisture was evaporated. The agar culture media were inoculated with a standardized broth culture of respective bacterial strains (*S. aureus* and *E. coli*) using a sterile cotton swab. Immediately thereafter, the plates were put to dry in an incubator at 35 ºC for 10 min. After inoculation, the discs impregnated with corresponding testing compounds were placed over the surface of inoculated culture media and the distance between each disc must be in 20-24 mm. Next, they were incubated for about 24 h at 32 ± 2 ºC. After 24 h, the plates were examined and the diameter of zones of inhibition was accurately measured. Antibacterial drug, streptomycin was used as a standard. An additional control disc without any sample but impregnated with an equivalent amount of solvent was also used.

Antifungal susceptibility testing by disc diffusion method: The testing compounds were impregnated on the sterilized discs placed on the surface of agar plates already inoculated with fungus *Candida albicans*. The plates were incubated at 37 ºC and examined after 72 h for the zone of inhibition, if any, around the disc. The diameter of zone of inhibition was measured with the help of a scale. Antifungal drug, fluconazole was used as a standard. An additional control disc without any sample but impregnated with an equivalent amount of solvent was also used.

RESULTS AND DISCUSSION

Schiff base ligand was afforded from citral with valine *via* condensation process. The obtained Schiff base ligand is well soluble in all organic solvents, but its metal(II) complexes are soluble in organic solvents only in ethanol, DMSO and DMF. The colour of Schiff base and its copper(II) and cobalt(II) complexes are brownish red, light green and dirty brown respectively.

Antimicrobial activity: The antimicrobial susceptibility effect of Schiff base and its metal complexes were tested against two bacteria, namely, *Staphylococcus aureus* (Gram-positive), *Escherichia coli* (Gram-negative) and fungus *Candida albicans* using disc diffusion method. The compounds were tested at the concentration of 10 mg mL^{-1} in ethanol and compared with known standard antibacterial drug streptomycin and antifungal drug fluconazole, respectively (Table-1).

TABLE-1
ANTIMICROBIAL ACTIVITY OF SCHIFF BASE LIGAND (L) AND ITS COPPER(II) AND COBALT(II) METAL COMPLEXES

Compounds	Zone of inhibition against microorganism (mm)		
	Escherichia coli (Gram-negative)	*Staphylococcus aureus* (Gram-positive)	*Candida albicans*
Schiff base	5	10	2
Complex **1**	12	14	4
Complex **2**	18	18	5
Standard	20	22	10

The antimicrobial studies clearly suggest that the complexes exhibited the enhancement in antibacterial effect than antifungal effect furthermore demonstrated that metal complexes exhibited superior inhibition activity than the parent ligand [20-22]. The ligand possesses very low activity against *E. coli* and inactive against *C. albicans*, but displayed some inhibition activity against *S. aureus*. The reason could be suggested that the functional donor sites of ligand may interfere with cell wall constituents of an organism which may lead to a collapse in the cell wall synthesis. Cobalt(II) complex exhibited hyper inhibition activity against both *S. aureus* (Gram positive) and *E. coli* (Gram-negative) bacteria strains with inhibition halos 18 mm considerably equal to standard, but moderate fungal activity (5 mm). On the other hand, copper(II) complex exhibited slight effect against *C. albicans* and moderate to good activity against *S. aureus* and *E. coli* with 12 mm and 14 mm inhibition halos, respectively. The variation in the activity of both complexes against tested organisms depends on either the impermeability of cells of microbes or difference in ribosomes of microbial cells [23,24].

Generally, the higher biological activity of metal(II) complexes than that of ligand (L) can be explained on the basis of Overtone′s concept and Tweedy′s chelation theory [25-28]. On chelation, metal ion polarity is reduced to a greater extent due to the overlapping of ligand orbital and partial sharing of positive charge of the metal ion with donor groups. Further, delocalization of π-electrons is increased over the whole chelate sphere and enhances the lipophilicity of complex. Based on the above theory, citral with valine derived Schiff base when incorporated with cobalt(II) complex demonstrated the enhancement in the lipophilic quantity of complex, which may helps the complex to overcome the lipid layer of cell membrane, subsequently favours the compound to diffuse through the cell mem-

brane and collapse the entire system of organism in contrast to copper(II) complex [29,30]. Generally, Gram-negative bacteria possess rigid outer membrane which strongly defence against antibiotics. In the present study, noteworthy inhibtion activity was performed against the Gram negative bacteria *Escherichia coli* by the complexes. The bioactivity of ligand and its complexes is found to be in the following order: Co(II) > Cu(II) > L.

Conclusion

In this report, copper(II) and cobalt(II) complexes having Schiff base ligand obtained by the condensation of citral with valine has been presented. The synthesized Schiff base and its metal(II) complexes were screened for their antibacterial activity against *Staphylococcus aureus* (Gram-positive), *Escherichia coli* (gram-negative) bacteria and antifungal activity against *Candida albicans* using disc diffusion method. Tabulated results revealed that Schiff base ligand exhibited a poor antibacterial activity against *Escherichia coli* and *Candida albicans* and good against *Staphylococcus aureus*. The metal(II) complexes show enhanced activity notably cobalt(II) complex show higher antimicrobial activity when compared to copper(II) complex and uncoordinated ligand.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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