IJARSCT
ISSN (Online) 2581-9429
International Journal of Advanced Research in Science, Communication and Technology (IJARSCT)
Volume 3, Issue 2, February 2023
Impact Factor: 7.301

Synthesis and Biocidal Activity of Co (II) and Zn (II) Complexes of Sulfa Drug Schiff Bases

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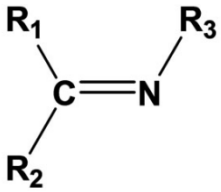
Abstract: *Schiff bases are the most widely used organic compounds. They have been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties. The synthesized complexes were screened/tested for their antimicrobial activity against pathogenic bacterial strains i.e. E. coli, Staphylococcus aureus strain I, Staphylococcus aureus strain II, Staphylococcus aureus strain III, Vibrio cholera, Gram positive Cocci, Gram positive Bacillus, Gram negative Bacillus, Bacillus subtilis and Salmonella typhimurium. It was found that metal complexes have more antimicrobial activity than their parent Schiff bases. A series of new Schiff base compounds derived from substituted 3-aminopyrazoles and dialdehydes were synthesized and characterized by ^{1}H, ^{13}C nuclear magnetic resonance, Fourier-transform infrared, ultraviolet-visible, gas chromatography-mass spectrometry and high-resolution mass spectrometry. Furthermore, the Schiff complexes were a tetrahedral in complexes Ni(II), Zn(II), Cd(II), and Hg(II), octahedral Pt(II), and square planer complex Pd(II). Additionally, density functional theory (DFT) was applied for calculations of both spectroscopic properties and electronic structure of prepared Schiff bases.*

Keywords: Schiff Bases; Metal Complexes; Antibacterial; Biological Activities, Cytotoxic Activity, sulfamethoxazole, sulfamerazine

I. INTRODUCTION

Schiff bases are studied widely due to their synthetic flexibility, selectivity and sensitivity towards the central metal atom; structural similarities with natural biological compounds and also due to presence of azomethine group(-N=CH-) which imports in elucidating the mechanism of transformation and racemization reaction biologically [1,2]. Schiff bases having chelation with oxygen, nitrogen etc. donors and their complexes have been used as drugs and reported to possess a wide variety of biological activities against bacteria, fungi, and certain type of tumors and also, they have many biochemical, clinical and pharmacological properties [3]. Imine or azomethine groups are present in various natural, naturally derived and nonnatural compounds (Figure 1). The imine group present in such compounds has been shown to be critical to their biological activities [4].



R_1, R_2 and / or R_3=alkyl or aryl

Figure 1: General Structure of a Schiff base.

Schiff bases containing azomethine (imine) group (–RC=N–) are usually prepared by the condensation of a primary amine with an active carbonyl compound [5]. The formation of variety of metal complexes with such ligands, indicate the spectacular progress in coordination and bioinorganic chemistry. Schiff base complexes of transition metals containing ligand with N, O donors exhibit interesting biological activity. It has now been observed that some of these drugs show increased biological activity when administered in the form of metal complexes.

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Metal complexes containing the sulphonamide group has found importance because of their applications as biological, biochemical, analytical, antimicrobial, anticancer, antibacterial, antifungal and antitumor activity.[6-8]
They were used as catalyst, in medicine like antibiotics and anti-inflammatory agents and in the industry as anticorrosion agents. Thus, the aim of this study is to observe the impact of chelation on the therapeutic value of the organic compounds/ drugs as biocidal or static agent by creating impact on morphological or physiological cycles.

II. RESEARCH METHODOLOGY

The chemicals 3- methyl-1-phenyl-2-pyrazolin-5-one and sulfamerazine was purchased from Lancaster. Sulfamethoxazole was obtained from Sigma. Benzoyl chloride was obtained from Chemical Drug House (CDH). $CoCl_2$. 6H2O and $ZnCl_2$ were obtained from Merck. All the chemicals were of AR grade.
Preparation of benzoyl derivative of 3-methyl-1-phenyl-2-pyrazoline-5-one
To 50 mL of DMF, 8.5gm of 3-methl-1-phenyl-2-pyrazoline-5-one (mphp) was added (Figure 2).

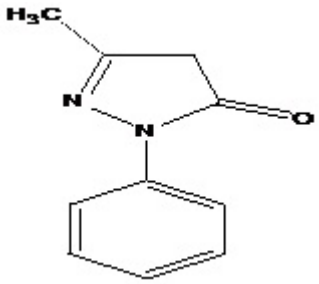

Figure 2: Structure of 3-Methyl-1-Phenyl-2-Pyrazoline-5-One

Biological Studies

In vitro antimicrobial susceptibility tests were performed using a panel of pathogenic and non-pathogenic microorganisms' isolates. The bacterial cultures were maintained on nutrient agar slant medium (0.5% NaCl, 0.5% peptone, 0.3% beef extract and 1.5% agar) kept at 4°C and sub cultured every six months. The bacteria were grown in Nutrient broth and incubated at 35ºC for 24 hours before the assay. The test drug sample solutions were prepared at concentration of 10 mg/mL in acetone. Determination of antibacterial activity by disc diffusion technique was based on the method described by National Committee for Clinical Laboratory Standards (NCCLS) (2001).

III. RESULT AND DISCUSSION

3.1 IR Spectrum

The preliminary allocations of the major IR bands of DMPTHP and its M(II) complexes show the following characteristics:

1. New band of ν (C=N) stretching vibration at 1615 cm^{-1} with disappearance of the ν (>C=O) confirming the condensation reaction and formation of the DMPTHP compound.
2. Presence of -NH-C=S linkage support thione ↔ thiol tautomerism of thiosemicarbazone compounds [9], but ν (S-H) absorption band at 2500–2600 cm^{-1} was absent with an appearance of ν (C=S) band at 798 cm^{-1} indicating the presence of the DMPTHP compound in the solid state as a thione form
3. For the DMPTHP thiosemicarbazone compound, vibrational bands with the wave numbers of 3012 cm^{-1} (ν_{C-H} and Ar-H), 1615 cm^{-1} ($\nu_{C=N}$), 1548 cm^{-1} ($\nu_{C=C}$), and 1082 cm^{-1} (ν_{N-N}) were detected.

3.2 Antibacterial Activity

Antibacterial activity of the ligands and its complexes were carried out against a set of pathogenic and non-pathogenic bacteria by the disc diffusion method.The tabulated values (**Table 1 and 2**) exhibit that the antibacterial activity of the ligands is markedly low as compared to the standard reference drug. The antibacterial activity of the synthesized complexes was found to be higher than the respective ligands.

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Table 1: Antibacterial Activities of L_1 and Its Complexes

S. No.	Bacterium	Zone Of Inhibition (incms)		
		L_1	Co (II) L_1 (C_1)	Zn (II) L_1 (C_2)
1.	*E. coli*	0	1.9	1.6
2.	*Staphylococcus aureus*strain I	1.5	2.5	3.5
3.	*Staphylococcus aureus* strain II	0.0	1.2	1.3
4.	*Staphylococcus aureus* strain III	0	2.5	0.1
5.	*Vibrio cholera*	1.6	2.5	1.5
6.	*Gram positive Cocci*	1.6	1.9	1.5
7.	*Gram positive Bacillus*	0	2.5	3.5
8.	*Gramnegative Bacillus*	0	0.9	0
9.	*Bacillus subtilis*	0.4	0.8	1
10.	*Salmonella typhimurium*	1.8	1.5	0.6

The complexes of L1 (Table 1) have enhanced activity compared to the ligand. Complex of cobalt was found to be a broad range compound and it inhibited the growth of all the tested organisms. Zinc complex was also found be very potent, inhibiting the growth of nearly all organisms.

Table 2: Antibacterial Activities of L2 And Its Complexes

		Zone Of Inhibition (in cms)		
S. No.	Bacterium	L_2	Co (II)L_2 (C_3)	Zn (II)L_2 (C_4)
1.	*E. coli*	1.2	0.0	1.3
2.	*Staphylococcus aureus*strain I	0.6	0	1.7
3.	*Staphylococcus aureus* strain II	0	0.5	0
4.	*Staphylococcus aureus* strain III	0	1.3	0.5
5.	*Vibrio cholera*	0	2	1.2
6.	*Gram positive Cocci*	0.4	1.3	1.5
7.	*Gram positive Bacillus*	0	1.0	1.5
8.	*Gramnegative Bacillus*	0	1	1.5
9.	*Bacillus subtilis*	0	1.0	1.8
10.	*Salmonella typhimurium*	0	2.5	2.5

Complexes of L_2 (**Table 2**) were also found to be more active compared to the ligand. Cobalt complexes were found to be active on a broad range of bacteria and were very toxic on *Salmonella typhimurium*, the causative agent of acute human Salmonella gastroenteritis. Zinc complexes were also found be very potent, inhibiting growth of nearly all organisms. The activity was found to be much pronounced on *Salmonellatyphimurium.*

3.3 Bioactivity and Physicochemical Properties of Synthesized Compounds

Dipolar moment can provide a description of the substances hydrophobicity/hydrophilicity. Studies of SAR have shown that complex dipole moment is inversely related to their bioactivity versus the tested bacterial strains. As the dipole moment decreases, polarity increases through lipophilicity that enhances its permeation more effectively through the microorganism's lipid layer [10], thus more violently destroying them. As tabulated in Table 3, (Cd (DMPTHP) Cl) has a lower dipole moment ($\mu = 2.63$). It therefore has greater biological activity and lipophilic nature than the other compounds.

Table 3: The calculated quantum chemical parameters of the DMPTHP ligand and M(II)-DMPTHP complexes.

Compound	E_H	E_L	ΔE	IE	EA	x	η	S	ΔN_{max}	ω	ω^-	ω^+
DMPTHP	−8.50	−2.19	6.31	8.50	2.19	5.35	3.16	0.32	−2.69	4.53	7.59	2.25
Zn-L	−4.61	−2.17	2.44	4.61	2.17	3.39	1.22	0.82	−3.78	4.71	6.56	3.17
Cd-L	−4.75	−1.98	2.77	4.75	1.98	3.37	1.39	0.72	−3.43	4.09	5.94	2.58

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Therefore, this sequence of synthesized compounds(Cd(DMPTHP)Cl) > (Zn(DMPTHP)) > DMPTHP represents the order of lipophilicity, which in turn facilitates cytoplasmic membrane penetration and disables the essential enzymes of the microorganisms tested for respiration processes. Lower values of the dipole moment thus help increasing the antibacterial activity.

(Cd(DMPTHP)Cl) complex with the lowest energy values of HOMO ($E_H = -3.47$) and the highest energy values of LUMO ($E_L = -1.98$) among the synthesized compounds showed high activity vs. the investigated bacterial strains. This corresponds to the values provided in the literature [11].

IV. CONCLUSION

In this report, the synthesis of a Schiff base ligand obtained from the reaction ofsulfamethoxazole L_1/ sulfamerazine $L_2$with bmphp has been described. Co (II) and Zn (II) complexes have been synthesized using the Schiff base ligand and characterized by IR spectral data.Based on the IR data the azomethine-N and pyrazoline- O has been found to be the coordination sites. These metal complexes have been found to have higher antimicrobial activity than the corresponding ligands.

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