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SYNTHESIS AND BIOCIDAL ACTIVITY OF Co (II) AND Zn (II) COMPLEXES OF SULFA DRUG SCHIFF BASES

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Keywords:

4-benzoyl-3-methyl-1-phenyl-2-pyrazoline-5-one, sulfamethoxazole, sulfamerazine, anti bacterial activity

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ABSTRACT: The novel Co (II) and Zn (II) complexes have been synthesized by reaction of $CoCl_2$/$ZnCl_2$ with Schiff bases of benzoyl derivative of 3-methyl-1-phenyl-2-pyrazoline-5-one and sulfa drugs in 1:2 ratio. 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. Complexes of Schiff base ligand sulfamerazine and bmphp (L_2) were also found to be more active.

INTRODUCTION: Schiff bases containing azomethine (imine) group (–RC=N–) are usually prepared by the condensation of a primary amine with an active carbonyl compound [1, 2]. 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 [3, 4].

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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[5-7].

They were used as catalyst, in medicine like antibiotics and anti-inflammatory agents and in the industry as anticorrosion agents[8-13]. 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[14-17].

MATERIALS AND METHODS:

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). $CoCl_2$. $6H_2O$ 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 (**Figure1**). A solution was obtained by gentle heating and stirring. Calcium hydroxide (4gm) was added and when the solution became light yellow then 6mL benzoyl chloride was added drop wise in 2-3 minutes. The reaction was observed to be exothermic and reaction mixture became paste like. The mixture was allowed to cool and was refluxed with stirring for an hour. During this period the bright yellow complex formed, immediately turned yellowish brown. The complex was decomposed by pouring the reaction mixture in 250mL of 2N chilled dilute HCl. A yellowish brown solid of benzoyl derivative (bmphp) (**Figure 2**) settled. This was collected on the sintered glass crucible, washed with distilled water and then dried in *vacuo*[18].

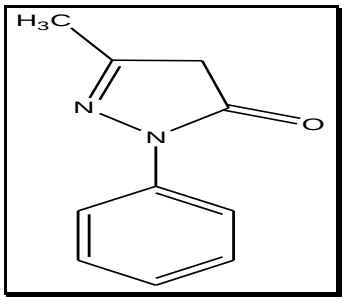

FIGURE 1: STRUCTURE OF 3-METHYL-1-PHENYL-2-PYRAZOLINE-5-ONE

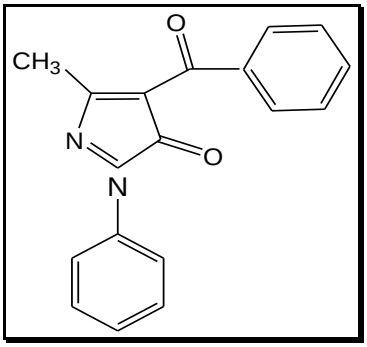

FIGURE 2: STRUCTURE OF 4-BENZOYL-3-METHYL-1-PHENYL-2-PYRAZOLINE-5-ONE

Synthesis of schiff bases of bmphp and sulfa drugs

To 15mL of ethanolic solution of bmphp (1.39 gm) was added a solution of sulfamethoxazole L_1 (1.26 gm)/ sulfamerazine L_2 (1.32 gm) in ethanol. The resulting solution was refluxed with stirring for 4-5 hours and then filtered to remove insoluble sulfa drug, if any. The filtrate so obtained was concentrated on a water bath and left overnight at room temperature when colored crystals of schiff base separated out from the solution. The crystals were washed with ethanol and dried in the oven[19].

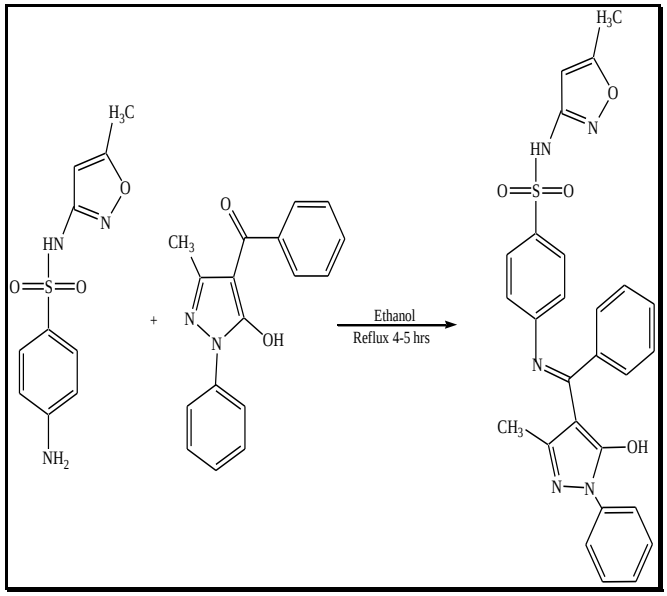

FIGURE 3: SCHIFF BASE LIGAND OF SULFAMETHOXAZOLE AND BMPHP (L_1)

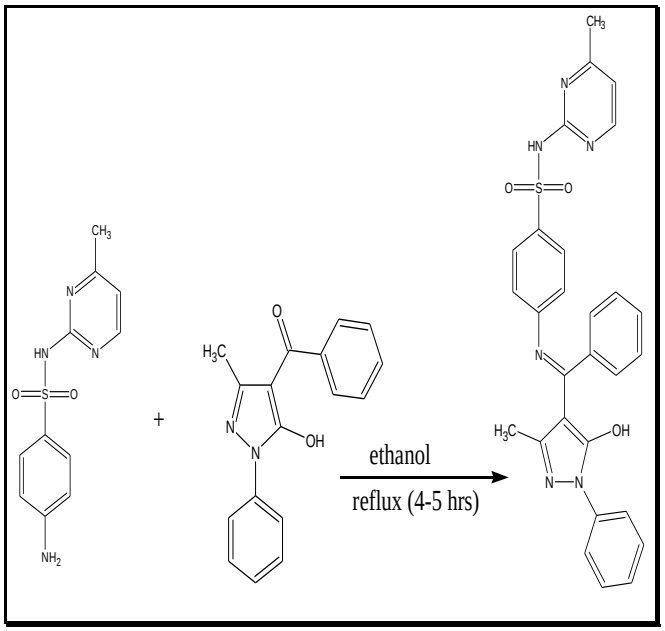

FIGURE 4: SCHIFF BASE LIGAND OF SULFAMERAZINE AND BMPHP (L_2)

Synthesis of Metal Complexes of Schiff Base Ligands

The metal complexes were isolated, by reaction of aqueous solution of (0.001M) $CoCl_2$ (0.238 gm)/ $ZnCl_2$ (0.136 gm) and acetone solution (0.002M) of schiff base ligand L_1 (**Figure 3**) / L_2 (**Figure 4**) in 1:2 ratio. The reaction mixture was stirred for 3-4

hours and the resulting colored crystals were washed with distilled water, crystallized from ethanol and dried in *vacuo*

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).

The test samples were prepared by immersing 0.5 cm sterile paper disc in drug solution for 48 hours. The solutions were dried by air in order to remove acetone. The test medium is nutrient agar on which 200µL of bacterial inoculate 24 hours old was spread with the help of a sterile spreader. The discs were then placed on the surface of nutrient agar medium containing bacterial cultures. After incubation for 24 hours at 37^0C, antibacterial activities of the drugs were estimated by measuring the diameter of inhibition zones, which had been reduced, by the diameter of disc.

RESULT AND DISCUSSION:

IR Analysis

The Schiff base ligands of the present investigation may exist in *keto* and *enol* form (**Figure 5**). The IR spectra of all the Schiff bases show a broad band centered at 3540-3580 cm^{-1} indicating the involvement of 5-OH group of the pyrazolone moiety (*enol* form) in the intra molecular hydrogen bonding with the lone pair of the azomethine nitrogen[20]. This concludes that these Schiff base ligands exist in the *enol* form in the solid state. The broad band due to phenolic (-OH) in all the ligands is absent in the complexes under study indicating the coordination of the phenolic oxygen after deprotonation to the metal center [21].

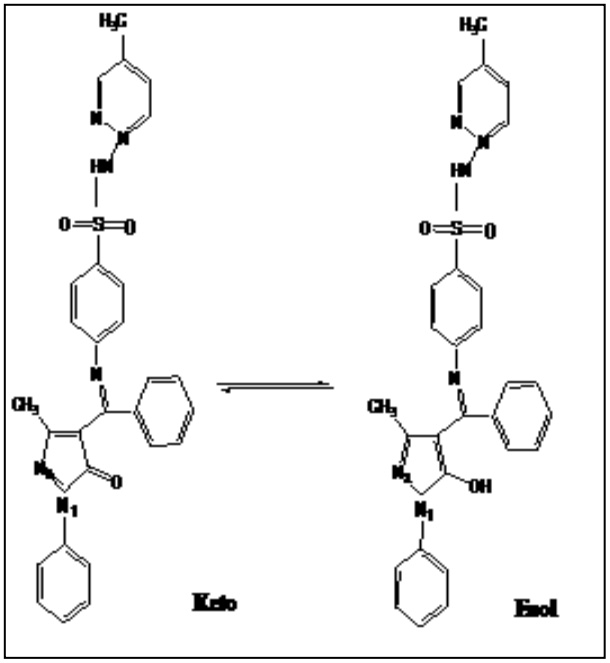

FIGURE 5: *KETO- ENOL* FORM OF SCHIFF BASE LIGAND OF SULFAMERAZINE AND BMPHP (L_2)

The ligands L_1 and L_2 contain five potential donor sites: (i) the enolic oxygen, (ii) the cyclic nitrogen N_1, (iii) cyclic nitrogen N_2, (iv)sulfonamide (SO_2NH) oxygen or nitrogen, (v) azomethine nitrogen.

The ligands show a sharp and strong band due to υ(C=N) of azomethine group at 1598-1600cm^{-1}. The observed low energy shift of this band in the complex suggests the coordination of azomethine nitrogen[22] in all the complexes.

The υ(C=H) (cyclic) arising pyrazolone skeleton and sulpha drug skeleton in the ligand appear at ~1590 (merged with azomethine nitrogen) and at 1620-1630 cm^{-1} respectively, do not show any change in their position in the IR spectra of complexes. The υ($C=N_2$) appears to be merged with υ(C=N) azomethine group. These observations indicate the non-participation of the respective cyclic nitrogen in the coordination. The coordination of ring nitrogen[23] N_1 is unlikely due to sterric demand of the bulky phenyl group attached with it.

The IR spectra of the two ligands exhibit two strong bands at 1325-1360 cm^{-1} and 1105-1145 cm^1, which are attributed respectively, to asymmetric and symmetric stretching vibration of SO_2 group. The bands are observed at the same

position in the complexes (**Figure 6 and 7**) indicating its non- coordination to the metal center.

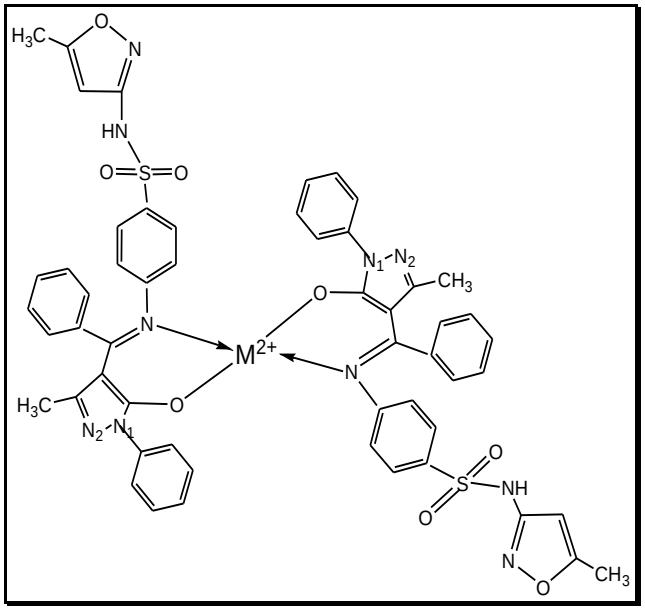

FIGURE 6: COMPLEX OF Zn^{2+} AND Co^{2+} WITH SCHIFF BASE LIGAND L_1

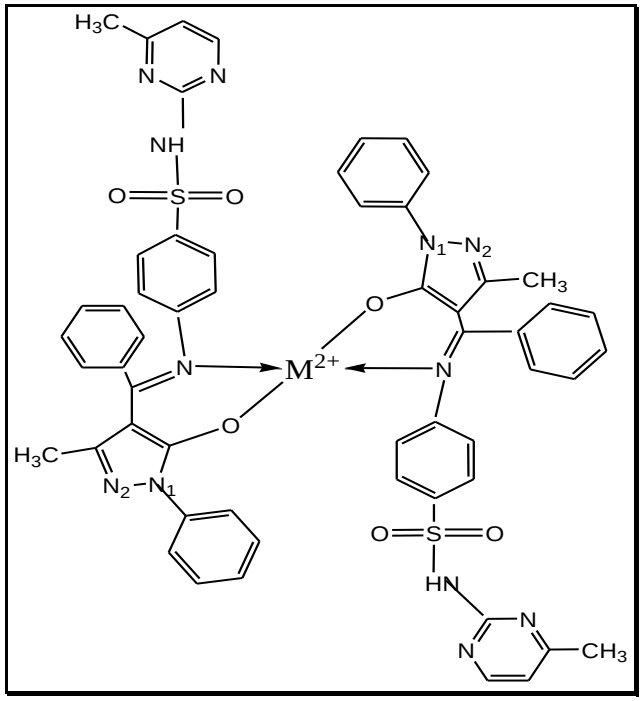

FIGURE 7: COMPLEX OF Zn^{2+} AND Co^{2+} WITH SCHIFF BASE LIGAND L_2

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[24].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.

TABLE 1: ANTIBACTERIAL ACTIVITIES OF L_1 AND ITS COMPLEXES

S. No.	Bacterium	Zone Of Inhibition (in cms)		
		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.	*Gram negative 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 L_1 (**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.

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 *Salmonella typhimurium.*

TABLE 2: ANTIBACTERIAL ACTIVITIES OF L_2 AND ITS COMPLEXES

S. No.	Bacterium	Zone Of Inhibition (in cms)		
		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.	*Gram negative Bacillus*	0	1	1.5
9.	*Bacillus subtilis*	0	1.0	1.8
10.	*Salmonella typhimurium*	0	2.5	2.5

A comparative study of the two ligands was done, L_1 was found to be more effective and of broad range than L_2.

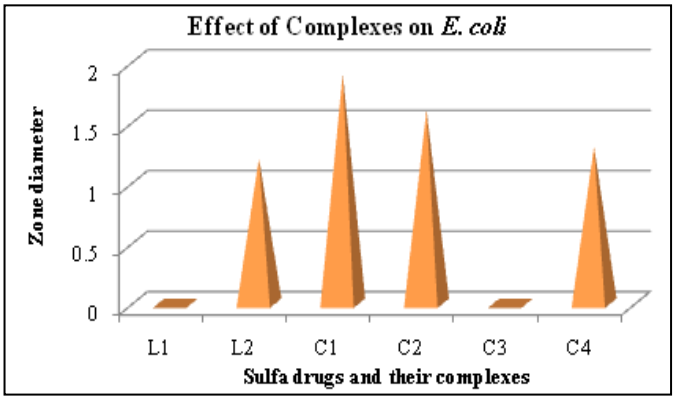

FIGURE 8: EFFECT OF COMPLEXES ON *E.COLI*

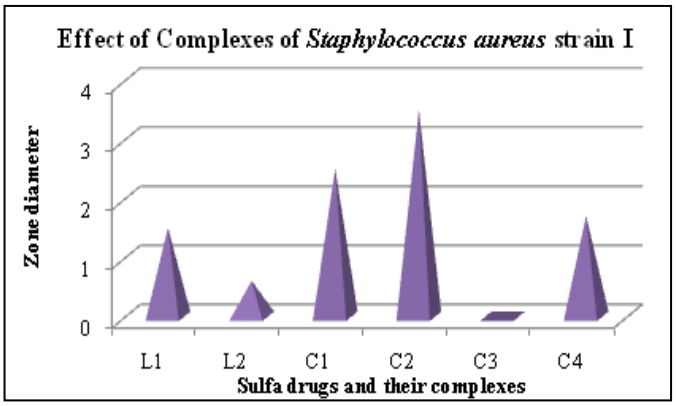

FIGURE 9: EFFECT OF COMPLEXES ON *STAPHYLOCOCCUS AUREUS* STRAIN I

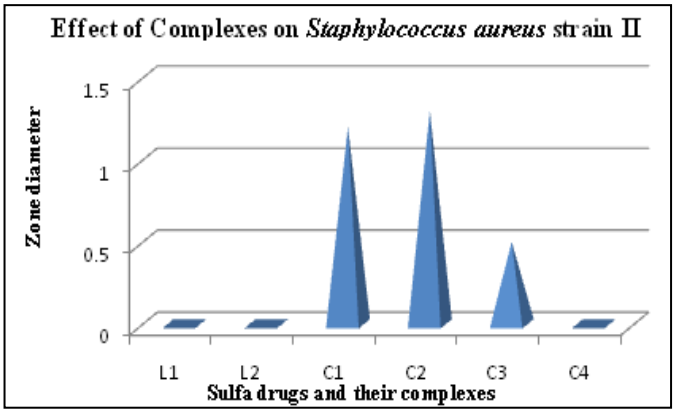

FIGURE 10: EFFECT OF COMPLEXES ON *STAPHYLOCOCCUS AUREUS* STRAIN II

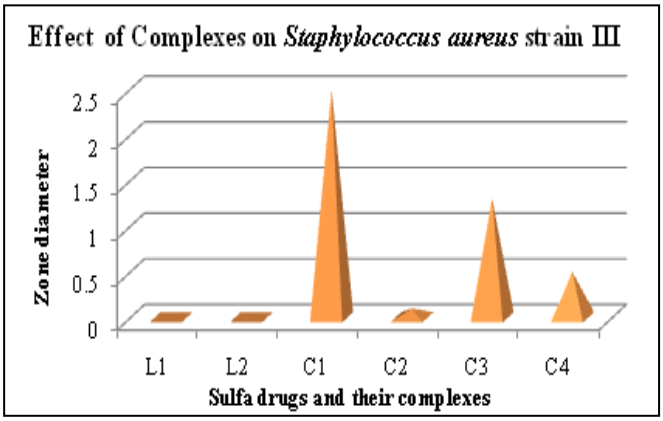

FIGURE 11: EFFECT OF COMPLEXES ON *STAPHYLOCOCCUS AUREUS* STRAIN III

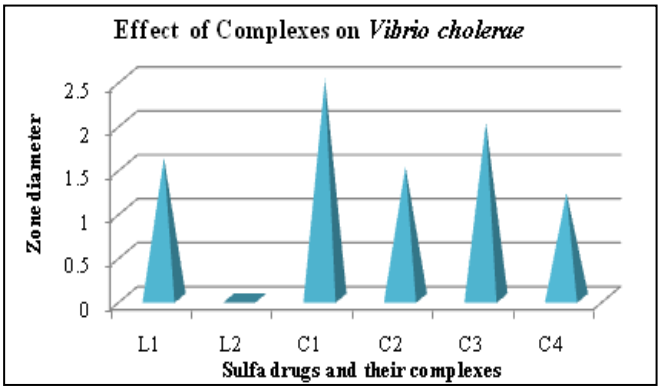

FIGURE 12: EFFECT OF COMPLEXES ON *VIBRIO CHOLERAE*

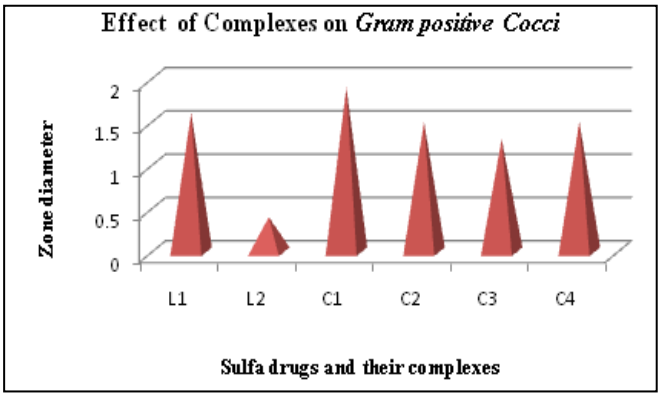

FIGURE 13: EFFECT OF COMPLEXES ON *GRAM POSITIVE COCCI*

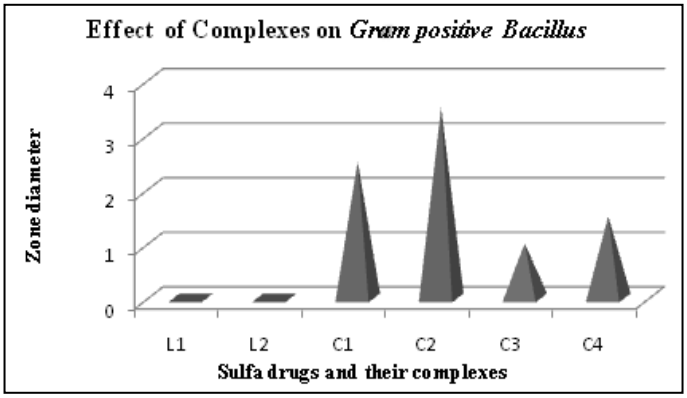

FIGURE 14: EFFECT OF COMPLEXES ON *GRAM POSITIVE BACILLUS*

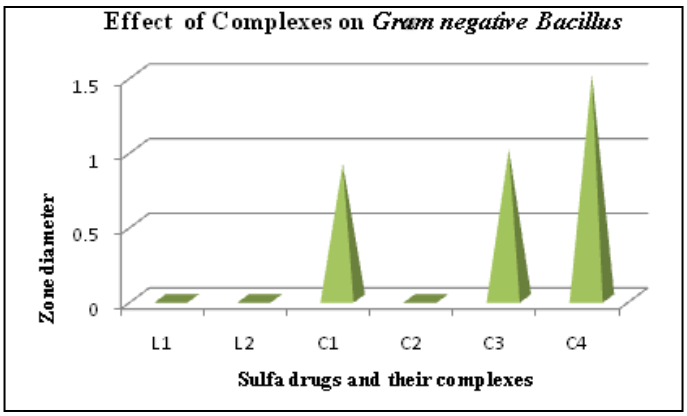

FIGURE 15: EFFECT OF COMPLEXES ON *GRAM POSITIVE BACILLUS*

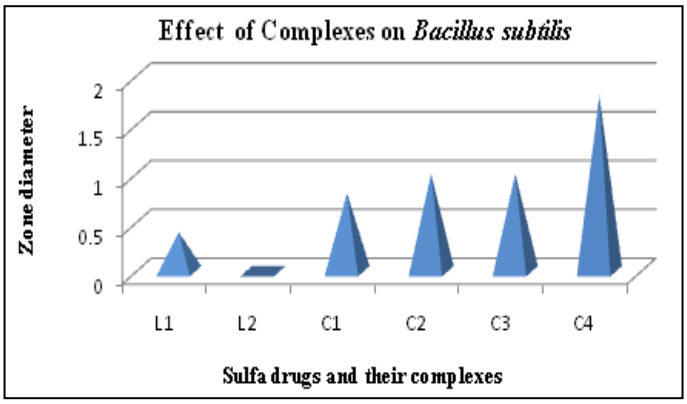

FIGURE 16: EFFECT OF COMPLEXES ON *BACILLUS SUBTILIS*

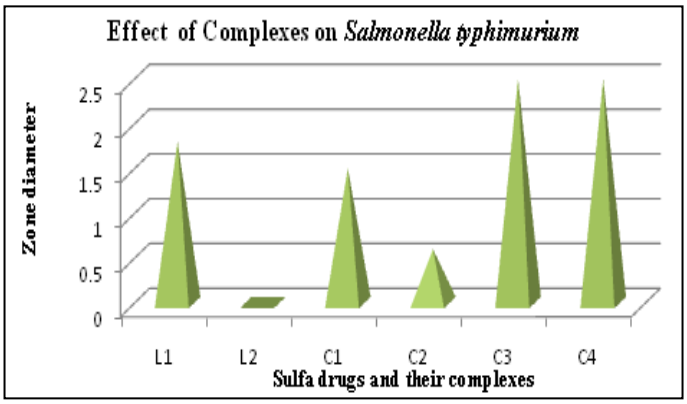

FIGURE 17: EFFECT OF COMPLEXES ON *SALMONELLE TYPHIMURIUM*

CONCLUSION: In this report, the synthesis of a Schiff base ligand obtained from the reaction of sulfamethoxazole 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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