ANTIBACTERIAL EVALUATION OF SALEN-METAL COMPLEXES

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ABSTRACT : Two salen type Schiff bases were synthesized and characterized by using physical methods. Then their metal complexes were formed. The metals selected for the preparation of complexes were nickel, zinc, copper, cadmium, manganese and cobalt. Hence, in total 12 metal complexes were synthesized and screened for antibacterial activity against some clinically important bacteria, such as *Aspargillusniger, Pseudomonas aeruginosa, Proteus vulgaris, Staphylococcus aureus, Escherichia coli* and *Salmonella typhi*. The *in-vitro* antibacterial activity was determined by the agar cup technique using Dimethyl formamide as solvent. The Schiff bases showed considerably greater activity than their metal complexes; the metal complexes showed differential effects on the bacterial strains investigated and the solvent used, suggesting that the antibacterial activity is dependent on the molecular structure of the compound and the bacterial strain under consideration.

KEYWORDS : Salens, Schiff base complexes, antibacterial activity

INTRODUCTION:

Man is closely influenced by the activities of microorganisms. Microorganisms are a part of our lives in more ways than most of us understand. They have shaped our present environment and their activities will greatly influence our future. Microorganisms should not be considered separate from human beings, but profound beneficial influence as a part of our life. They are employed in the manufacture of dairy products, certain foods, min processing of certain medicines and therapeutic agents, in manufacture of certain chemicals and in numerous other ways.

To overcome the alarming problem of microbial resistance to antibiotics, the discovery of novel active compounds against new targets is a matter of urgency. Many of the crude drugs, which are sources of medicinal preparations, still originate from wild-growing material. However, plant-based drugs have shortened the life span of the source of material. There is a continuous search for more potent and cheaper raw materials to feed the industry. Compounds, which on dissolution do not give ions of which they are made but instead give complex ions are called co-ordination compounds. Co-ordination compounds exhibit different characteristic properties which depend on the metal ion to which they are bound, the nature of the metal as well as the type of ligand, *etc*. These metal complexes have found extensive applications in various fields of human interest.

The metallo-elements, which are present in trace and ultra-trace quantities, play vital roles at the molecular level in a living system. In a healthy body of an adult, the trace and ultra-trace elements weigh less than 10 grams in total but life depends upon these elements for more than these figures.[1] The transition metal ions are responsible for the proper functioning of different enzymes. If their concentration exceeds a certain level, then their toxic effects are evident. Drugs play a vital role as bioligands in the biological systems. Nitrogen containing bases, such as derivatives of pyridine, pyrimidine, purin and pyrrole, amines such as histamines, carbohydrates such as pentose, glucose and different vitamins such as ascorbic acid are well recognized bioligands. With increasing knowledge of the properties of functional groups, as well as the nature of donor atoms and the central metal ion, ligands with more selective chelating groups, *i.e.*, imines or azomethines which are more commonly known as Schiff bases, are used for complex formation studies. Schiff bases have been studied extensively because of their high potential chemical permutation. Magnetic susceptibility, absorption spectra, elemental analysis, molecular weight determination, conductivity, thermal analysis of many Schiff bases and their complexes have been reported.[2-9] Several workers also studied their biological properties, such as antibacterial, antifungal, *etc*., activities.[10-13] It is reported that the rapidly developing field of bioinorganic chemistry is centered on the presence of coordination compounds in living systems.[14]

Complexes of nickel, zinc, copper, cadmium, manganese and cobalt with two Salen type Schiff bases 3a & 3b have been synthesized.[15] Application of 3a in spectrophotometric determination of Nickel and Palladium have been studied.[16-17] In the present work, antibacterial activity of salen bases and their complexes towards some clinically important bacteria was evaluated.

MATERIALS AND METHODS :

Antibacterial activity was determined by the Agar-cup method. The investigated microorganisms were such as *Aspargillusniger, Pseudomonas aeruginosa*, *Proteus vulgaris*, *Staphylococcus aureus, Escherichia coli* and *Salmonella typhi*.. The compounds were dissolved in DMF to obtain a final concentration 1mg/0.1 ml. Aloop full of the given test strain was inoculated in 25 ml of N-broth (nutrient broth) and Sabouraud's broth incubated for 24 h in an incubator at 37 °C to activate the microorganism strain. 28–30 ml of the nutrient agar media was added into a 90 mm diameter Petri-plate. Inoculation was done by the Pour-plate technique. 0.4 ml of the activated strain was inoculated into the media when it reached a temperature of 40–45 °C. The complete procedure of the plate preparation was done in a laminar

airflow to maintain strict sterile and aseptic condition. The medium was allowed to solidify. After solidification of the media, a well was made in the plates with the help of a cup-borer (0.85 cm), which was then filled with one of the test sample solutions. Controls were run (for each bacterial strain and each solvent), where pure solvent was inoculated into the well. The plates were incubated for 24 h at 37 °C. The inhibition zone formed by these compounds against the test bacterial strain determined the antibacterial activities of the synthetic compounds. The mean value obtained for three individual replicates was used to calculate the zone of growth inhibition of each sample.

RESULTS AND DISCUSSION :

The in vitro biological screening results are given in Tables 7.1. The six metal complexes along with ligands and intermediate compounds and their respective controls produced different inhibition zones against the tested bacterial strains.

The antibacterial activity of complexes of GBS-3a and GBS-3b in DMF against Gram negative bacteria *Proteus vulgaris*is shown in Fig. 7.1. The Schiff bases GBS-3a and GBS-3b showed considerably greater antibacterial activity than their metal complexes. Of the Schiff bases, GBS-3b showed greater activity than GBS-3a. In DMF, the Zn complex of GBS-3a showed the best activity against *Proteus vulgaris* followed by the cobalt and cadmium complexes while cadmium cobalt and copper complexes of GBS-3b possessed excellent activity. Thus, it appears that the metal ion in the complex influences the antibacterial activity.

The antibacterial activity against the gram-negative bacterium *Pseudomonas aeruginosa*is shown in Fig. 7.2. Here, the Schiff bases showed comparatively weaker activity than their Zinc and copper metal complexes. Both GBS-3a and GBS-3b showed very similar antibacterial activity in DMF. The Zn complexes of GBS-3a & GBS-3b showed the greater antibacterial activity, followed by the Cu and Cd respectively while all the other metal complexes showed negligible activity. These results again suggest that the antibacterial activity is affected by the ligand & metal used for investigation of the antibacterial activity.

The antibacterial activity against the gram-negative bacterium *Escherichia coli*is shown in Fig. 7.3. Here also the Schiff base complexes of Zn showed better antibacterial activity than their respective ligands. GBS-3b in DMF showed greater antibacterial activity than GBS-3a. Amongst the metal complexes, the best antibacterial activity was shown by the Zinc and cadmium complexes.

The antibacterial activity against the gram-negative bacterium *Salmonella typhi*is shown in Fig. 7.4. Here, the Schiff bases showed comparatively weaker activity than their metal complexes. The Zn complexes of GBS-3a & GBS-3b showed the greater antibacterial activity, followed by the Cd, Mn, Co and Cu complexes of GBS 3b while all the other metal complexes showed negligible activity. These results again suggest that the antibacterial activity is affected by the ligand & metal used for investigation of the antibacterial activity. Here, the precursors of Schiff bases i.e. GBS 1 & GBS 2 are exhibiting considerable antibacterial activity.

The antibacterial activity against the gram-positive bacterium *Staphylococcus aureus* is shown in Fig. 7.5. Here also the Schiff base complexes of Zn showed better antibacterial activity than their respective ligands. Complexes of GBS-3b are found to be more active than GBS-3a in DMF.

The susceptibility zones for the compounds against fungal species *Aspargillusniger*were measured in mm and are shown in fig. 7.6. In contrast to the earlier observations, the ligands showed better antifungal activities than complexes. Among different complexes, Zn complexes showed better antifungal activities followed by Ni(II) Mn (II) and Cu(II) complexes.

CONCLUSION :

The results of the preliminary study on antimicrobial activity against the bacterial strains indicate that most of the compounds are less to highly active. These observations show that the majority of the compounds are more active than their respective Schiff bases. In some cases, Schiff bases and their complexes have similar activity against bacteria and fungi. Amongst the six metals used for complexation, Zn & Cd showed the best antibacterial activity followed by Cu, Co &Mn in DMF. However, these microorganisms show general resistance to some of the Ni(II) complexes. The cursory view of the data indicates the following trend in the antimicrobial activity of the tested complexes. Zn(II) > Cd(II) > Cu(II) Co(II) >Mn(II) > Ni(II). This once again confirms our earlier conclusion that antibacterial activity is dependent on the molecular structure of the compound.

It is generally observed that metal chelates have higher antibacterial activity than the free ligand. This is because of an increase in cell permeability. Chelation may enhance or suppress the biochemical potential of bioactive organic species. The higher activity of the metal complexes may be owing to the effect of metal ions on the normal cell membrane. Metal chelates bear polar and nonpolar properties together; this makes them suitable for permeation to the cells and tissues. Changing hydrophilicity and lipophilicity probably leads to bring down the solubility and permeability barriers of cell, which in turn enhances the bioavailability of chemotherapeutics on one hand and potentiality at another[18].

The lipid membrane which surrounds the cell favours the passage of only lipid soluble materials and it is known that liposolubility is an important factor controlling antimicrobial activity. The studies show enhancement of the activity of the ligands on complexation and hence on chelation, which reduces considerably the polarity of the metal ions in the complexes[19]. This is mainly due to the partial sharing of its positive charge with the donor group and possible π-electron delocalization over the whole chelate ring system through pπ or dπ-dπ interactions of the orbitals of the ligands and metal ions, which in turn increases the hydrophobic character of the chelate and thus enables its permeation through the lipid layer (cell membrane) of microorganisms.[20]

Such screening of various organic compounds and identifying the active agents is essential because the successful prediction of a lead molecule and the drug-like properties at the onset of drug design will pay off later in drug development.

Table 7.1: Antibacterial and Antifungal Activity Data (Agar cup method)

Sample Concentration of (1mg/ml)	Inhibition Zone in mm					
	Aspargillusniger	*Proteus vulgaris*	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Escherichia coli*	*Salmonella typhi*
GBS-1	23	8	10	6	11	11
GBS-2	21	12	10	9	16	13
GBS-3a	29	16	13	10	11	8
GBS3a-Ni	24	8	12	12	11	11
GBS3a-Zn	26	20	19	21	23	18
GBS3a-Cu	24	11	18	13	11	11
GBS3a-Cd	23	13	13	11	16	10
GBS3a-Mn	25	11	9	12	11	8
GBS3a-Co	24	16	14	7	14	12
GBS-3b	27	19	16	12	14	10
GBS3b-Ni	25	8	16	16	16	12
GBS3b-Zn	26	12	22	26	22	20
GBS3b-Cu	22	15	18	18	10	14
GBS3b-Cd	19	17	20	16	22	18
GBS3b-Mn	22	14	10	15	12	19
GBS3b-Co	15	15	10	19	12	15
Solvent Control	10	8	1	6	11	8

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