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Review Article

A REVIEW ON BIOLOGICAL APPLICATIONS OF ONO, ONN, ONNO TYPE SCHIFF BASE LIGANDS AND THEIR METAL COMPLEXES

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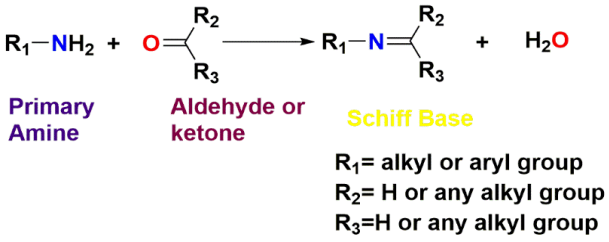
ABSTRACT

Schiff base ligands are generally prepared by the condensation reaction of an aldehyde or ketone with primary amines. These compounds are also called imine or azomethines. These ligands can contain both hard and soft electron donor and some rigid and flexible parts in their structure. These legends' having high tendency to coordinate with transition metals to form large number of stable complexes. Transition metal complexes derived from Schiff base ligands with their biological activities have been widely studied. This review summarizes the importance of ONO, ONN, ONNO Schiff base and their metal complexes in biological fields. Methods of preparations of tridentate and tetradentate Schiff base ligands are also described briefly.

Keywords: Schiff base, imines, antibacterial, antifungal, antitumor, metal complexes

1. INTRODUCTION

Schiff bases are yellow nitrogenous analogs of carbonyl compounds (aldehydes or ketones) which were synthesized by condensation of >C=O group with primary amines. They were first proposed by Hugo Schiff [1] in 1864. So, these are named after him. The other common names of these types of compounds containing azomethine group are imine compounds, azomethines, anils, aldimines and ketimines depending upon types of precursors [2].The general scheme for the preparation of Schiff base molecules is given in Scheme 1.



Scheme 1: General schematic view for synthesis of Schiff bases

Schiff bases containing aryl substituents can be synthesized easily and are more stable because of effective conjugation, while those containing alkyl substituents are relatively less stable. So, by variation of the aryl or alkyl groups, several reaction conditions in different solvents were already reported in literature [3, 4]. Generally, methanol and ethanol are used as solvents for the preparation of Schiff bases.

Furthermore, number of symmetric and asymmetric Schiff bases, viz. Salen, Salophen, Hydrazone etc. were known. Salen and salophen can form symmetric or asymmetric ligands but hydrazone forms asymmetric Schiff base.

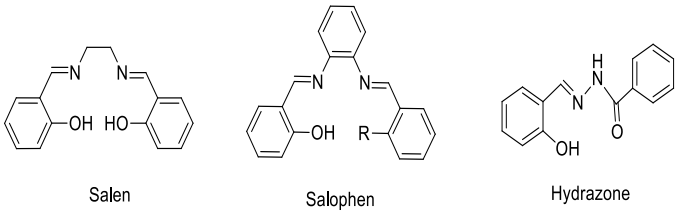


Fig. 1: General structure of Salen, Salophen and Hydrazone

Preparation of Salen type molecules/ligands can be performed by combination of two equivalents of salicylaldehyde and suitable diamine. These ligands contain four coordinating sites whereas two axial sites open to ancillary ligands. Originally, the term Salen was used to describe the tetradentate Schiff base obtained from salicylaldehyde and ethylenediamines, but now this term is used to describe the class of ONNO tetradentate Schiff base ligands [5]. Salen type Schiff base ligands are insoluble in aqueous solution and decompose easily in acidic solution.

Salophen are a popular class of compounds which are synthesized by condensation of a salicyldehyde and diamine. The schiff bases are tetradentate with N_2O_2 atoms belonging to the ligand lying in the same plane. The metal is well positioned in the plane, with imine nitrogen and phenolic oxygen participating to metal binding through coordinate and covalent bond respectively. The possibility to functionalize both salicyldehyde and diamine together with the ease of methods of prepration makes this excellent option for the prepration of huge number of compounds [6-8]. When the diamine is trans-1, 2-diamino cyclohexane, resultant salophen were found to be chiral in nature.

Also hydrazone important class of organic compound having structure R_1R_2C =NNH_2 which are related to aldehyde and ketones by replacement of oxygen with NNH_2 functional group. These are generally formed by condensation of substituted hydrazides and carbonyl compounds. Hydrazones are the compounds having azomethine characterized by the presence of triatomic grouping >C= N-N<. The presence of two interlinked (-N- N-) nitrogen atoms in hydrazones distinguishes it other members of this class like oxime, imine etc. Depending upon the requirement of polydentate ligand, the group functionalties may be increased by substitution and condensation. The hydrazones are generally named after the carbonyl compounds from which they are prepared. Hydrazone moiety acts as intermediate and play an important role in hetrocyclic chemistry [9, 10].

Preparation of Schiff bases having potential ligating ability has drawn a lot of attention because of their use as analytical reagents, metal sensors in complexometric titration and in biochemical research [11]. The imine group –N=CH- facilitates the mechanism of transamination and racemization reaction in biological systems [12]. Therefore, they show numerous biological activities such as antifungal and antibacterial properties [13-15], antifertility, enzymatic and insecticidal activities [16, 17]. For example, Isatin Schiff base ligand shows antiviral activity, which is very useful in the treatment of HIV [18]. Some Schiff bases show high antitumor activity, biocidal and cytotoxic activities [19, 20].

1.1. Schiff Base systems

The nature of >C=N- bond strongly depends on the structure of amine moiety, which controls the efficiency of conjugation and also incorporates structural elements which enable to modulate the steric crowding around coordination sphere. Schiff base systems with various coordination sites can be synthesized containing different set of donor atoms i.e. ONO, ONN ONNO etc. Some examples are shown in **Fig 2**.

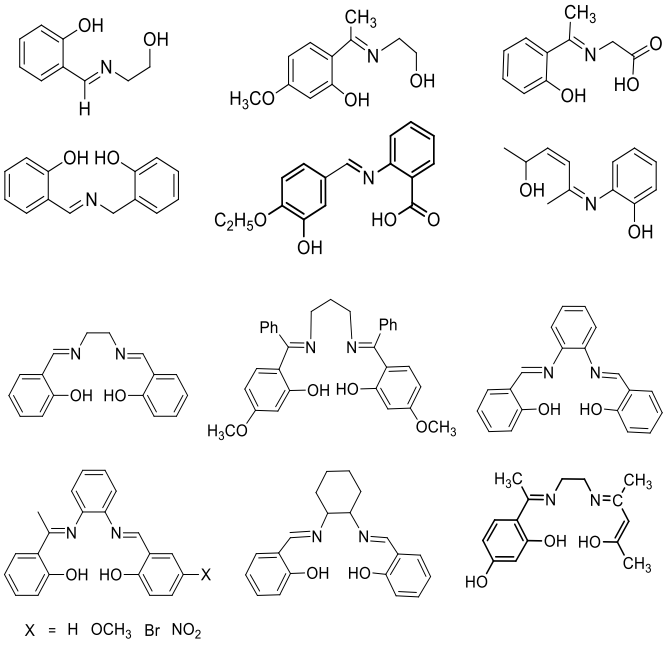


Fig. 2: Structures of some common ligands with ONNO, ONO, ONN systems

Tridentate and tetradentate Schiff bases having ONO and ONNO donor systems are well known to coordinate with various metal ions. They have attracted a great deal of interest in recent years because of their rich coordination chemistry [21-26]. Schiff base ligands mainly coordinate to a metal generally through the imine nitrogen and other groups usually oxygen or sulphur. Tetradentate ligands have four donor sites, which makes them ideal for the equatorial coordination of transition metal leaving the two axial sites open for auxiliary ligands.

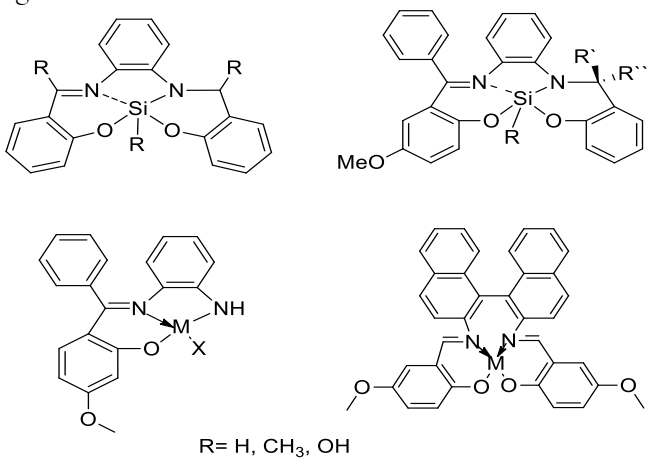


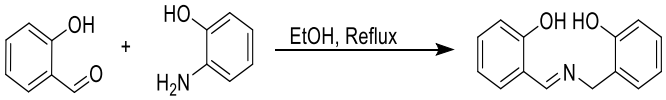
Fig. 3: Structures of metal complexes with ONNO and ONN systems

2. BIOLOGICAL APPLICATIONS

The escalation in the morality rate accompanying with infectious disease is related to bacteria which have manifold resistance to antibiotics. The development of some new antibacterial drugs with more effective mechanism of action is an urgent medical need [27]. Schiff base have been identified as promising antibacterial agents. The mechanism behind the antibacterial properties shown by Schiff base moieties includes various structural features. On chelation there is partial sharing of positive charge of metal ion with the donor groups, hence the polarity of metal ion and possibly the delocalization of π electrons within the whole chelate ring [28, 29]. All these factors enhance lipophilic nature of the central metal ion and thus enhance the hydrophobic character and liposolubility of the compound, leads to penetration through lipid layer of the bacterial membrane. It increases the entrance and antibacterial activity of the testing compound, Thus biological activities of Schiff base metal complexes is influenced by following factors (i)The nature of donor atoms (ii) The type and nature of metal ions (iii) The total charge on the complex ion and The geometrical structure of the complex.

2.1. Biological Activities of ONO and ONN type Schiff base ligands and their metal complexes

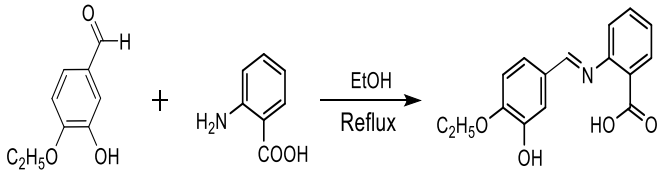
Tridentate Schiff base ligand and its metal complexes have been reported in literature [30], synthesized from 2- aminophenol and salicylaldehyde have been tested for their antimicrobial properties.



Scheme 2: Synthesis of ONO donor type of salicylaldehyde

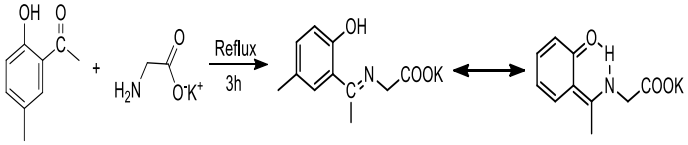
The antimicrobial properties of Schiff base ligand and their metal complexes were screened against bacterial strains *S. aureus* (gram positive), *E. Coli* (gram negative) and fungal strains *C. Albicans*, *A. flavus* by modified Kirby-Bauer disc diffusion method. In a brief procedure 100 µL of the test fungi/bacteria were grown in 10 mL of fresh media until their account reaches up to 105 cells/ mL and 108 cells/mL for fungi and bacteria, respectively. The fungal strain *C. Albicans* and *A. flavus* were incubated for 23 hrs at 37°C and bacterial strains *E. Coli* and *S. aureus* were incubated for 23 hrs at 37°C, respectively. Standard antifungal (*Amphofericin B*) and antibacterial drug (*Tetracyline*) were used as reference to check the potency of the tested compounds under similar conditions. Finally, by measuring the diameter of the inhibition zone its activity was determined, the results were calculated as a means of triplicates.

Similarly other Schiff base ligand derived from 3-ethoxy salicylaldehyde and 2-amino benzoic acid have been reported by Mounika et al [31]. The antibacterial and antifungal activities of schiff base ligand and its metal complexes were explored by disc diffusion method. It was found that, metal complexes of this tridentate ligand (Co(II), Ni(II), Zn(II) and Cu(II)) showed better antibacterial property as compared to Schiff base ligand.



Scheme 3: Synthesis of 3- ethoxysalicyldehyde amino benzoic acid

Schiff base molecules of amino acids like glycine as their potassium salts with 2-hydroxy- 5- methyl acetophenone and their complexes with divalent iron, nickel, zinc and manganese ions were prepared by V.B. Baiwai et al [32].

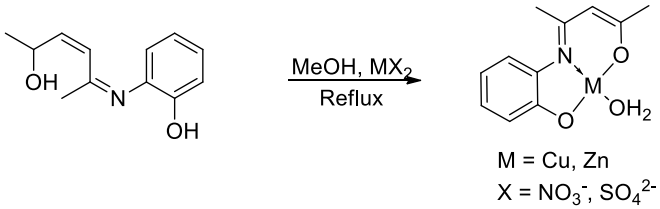


Scheme 4: Synthesis of amino acids Shiff base ligand

The antibacterial action of reported ligand and their metal complexes against various gram-positive and gram-negative bacterial strains were studied *in-vitro* using Single Disc method. Streptomycin was taken as standard antibiotic and DMSO as negative control. It was found that ligand and the metal complexes exhibited good antibacterial activity against bacterial strains except *Shigella flexneri*, *Bacillus coagulans* and *Proteus vulgaris*. the metal complexes showed better activity as compared to ligand against the same organism under similar experimental conditions [33], however antibacterial activity of ligand and metal complexes was found to be lower than standard antibiotic.

Additionally, Zn(II), Cu(II) tetrahedral complexes and Mn(II), Co(II), Fe(III) complexes of Schiff base of 2-

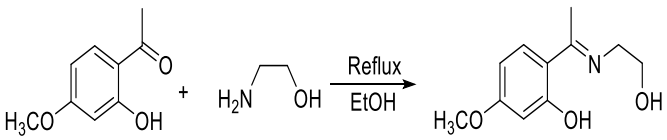
aminophenol and acetylacetone have been reported by K. Francisk et al [34].



Scheme 5: Synthesis of Schiff base metal complex possessing antibacterial properties

In-vitro antibacterial and antifungal activities were carried out against bacterial strains: *P. aeruginosa, S. typhi, S. aureus, E. coli* and fungal strains *Albicans ATCC P37037*, *albican ATCC 37039, C. albicans ATCC 12C* and *neoforinans*. The Schiff base ligand itself showed moderate antibacterial activity against bacteria *P. aeruginosa*, *S. aureus, E. coli* and fungi *C. albicans ATCC12C*. It was found that Cu(II) complex exhibited highest activity, but the Mn(II), Co(II) and Zn(II) complexes exhibited moderate activity on most of the bacterial and fungal strain. Their antioxidant activities were also scrutinized in comparison with garlic acid. Thus, CuL, ligand, and ZnL exhibited greater free radical scavenging activity. The IC_{50} value for CuL, Ligand and ZnL was found to be 0.21, 0.37 and 0.45 mg/mL, respectively. Results showed that IC_{50} value for garlic acid was 0.26 mg/mL which means CuL complex was more active toward antioxidant activity.

Furthermore, A new paeonol Schiff base ligand and its Cu(II) complexes has been synthesized by D. D. Qin et al [35] and explored their cytotoxic activity against human cell lines carcinomas Hep-2(Larynx).



Scheme 6: Synthesis of paeonol type Schiff base

It was found that when the incubation time varies from 24 to 72 hrs, the inhibitory rate of the reported complex even reaches near to 95%, but in case of free Schiff base ligand it was found near to 20%. So, Cu in complex play a very important role in the entire process through stimulating the directed migration of endothelical cells in angiogenesis as tumor cells are angiogenesis dependent [36].

There are many other Schiff base complexes possesses considerable cytotoxic activities [37-39]. Cytotoxic activities of ligands fig. (4a-c) and their Cu(II) metal complexes were tested against the following human cancer cells lines; breast cancer MCf-7cells, A2780 human ovarian carcinoma cells, prostate cancer PC-3 cells and respective cis-platin resistant cell line(A2780 cis R).The ligand and their metal complexes exhibits similar cytotoxicity againstA2780 and A 2780 cis R cell lines.

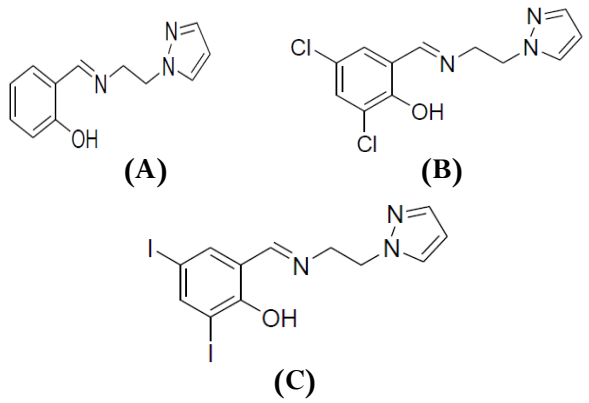
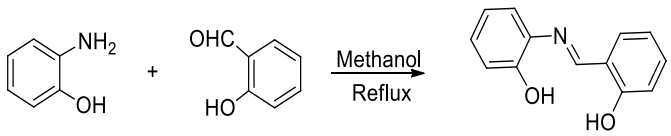


Fig. 4: Schiff base ligands 4(a-c) possessing cytotoxic properties.

Recently there was a considerable increase in life threatening incidence of fungal infections [40]. So development of some effective antifungal agents has become the necessity, hence Schiff base and their metal complexes are considered to be promising antifungal medicines [41]. Saidul et al [42] synthesized Schiff base ligands derived from the condensation of o-hydroxybenzaldehyde with amino phenol and form metal complexes with Co(II),Ni(II) and Cu(II) ions. These complexes show significant antifungal activities.



Scheme 7: Synthesis of Schiff base ligand possessing antifungal activity

A series of mixed ligand Copper (ll) complexes of amino acid Schiff base [CuL(X) (L= N-(2'-hydroxy acetophenone) glycinate, X= nicotinamide (nic), benzimidazole (benz) and 5, 8-hydroxyquinoline (8-hq) have been prepared by H.A.R Pramanik et al [43].

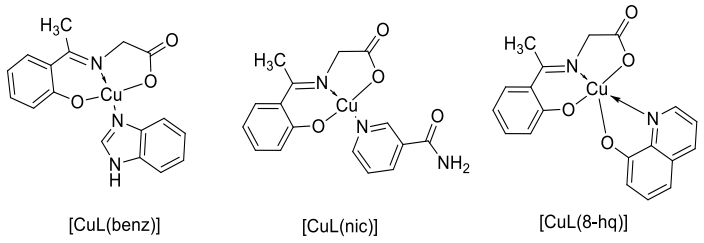


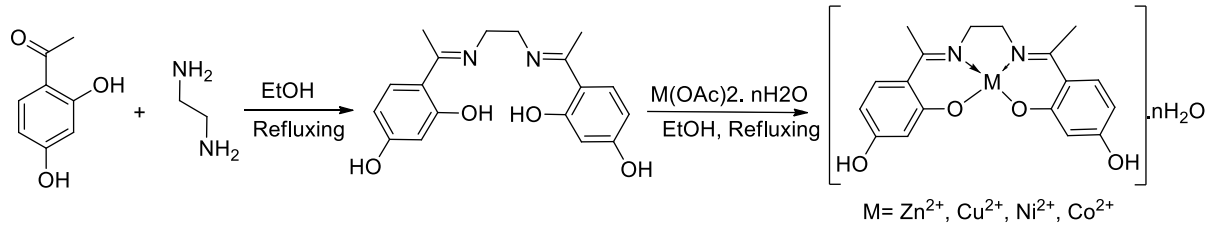
Fig. 5: Cu(II) Mixed Schiff base complexes

These complexes showed antibacterial activities, and were tested against selected gram-positive and gram-negative stains. These complexes showed antimicrobial response against *P. aeruginosa* and *S. aureus.*

Schiff base derived from 4-hydroxy salicyldehyde and amine shows high anticancer activity [44]. Cis-platin an anticancer agent is considered to be most important contribution to the use of metals in medical field. In this genomic DNA is the major cellular target for platinum drug, its intrastrand cross links and formation of DNA kinks [45] contribute to its major antitumor activity. Considerable effots are going on to further find more DNA targeting drugs. The interaction of metal complexes with DNA results complex, called chemical nuclease. In chemical nuclease cleavage of DNA is by oxidatively degrading the deoxyribose moiety on the other hand, natural nuclease cleavage of phosphate diester backbone DNA is by hydrolysis. Chemical nuclease have certain advantages as due to small size they can approach more effectively to stearically hindered regions of DNA as compared to natural nuclease.

2.2. Biological Activities of ONNO type Schiff base ligands and their metal complexes

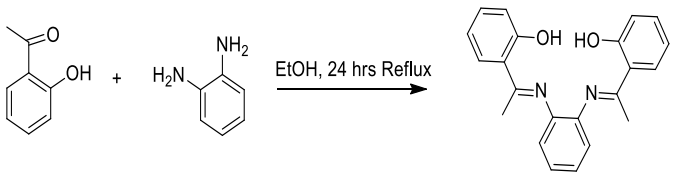
In addition to tridentate ONO, ONN Schiff base ligands, well know examples of tetradentate ONNO Schiff base ligands have been reported in literature, possessing numerous biological activities against microbes. A Schiff base has been derived from1-2 ethanediamine and 4-acetylresorcinol has been reported in literature [46].



Scheme 8: Schematic procedure of synthesis of tetradentate Schiff base ligands and its metal complexes

Furthermore, its metal complexes have been reported, which were tested by Agar diffusion method [47] for five bacterial strains against gram positive bacteria: *B. cerus*, *S. faecalis*, *S. aureus* and *E. Coli*, *P. aeruginosa* and gram-negative bacteria. Amoxicillin and ciprofloxacin were used as reference to check the potency of compounds under similar conditions. Results showed that metal complexes exhibited high antibacterial activity as compared to free ligand, but smaller than the standard antibiotics.

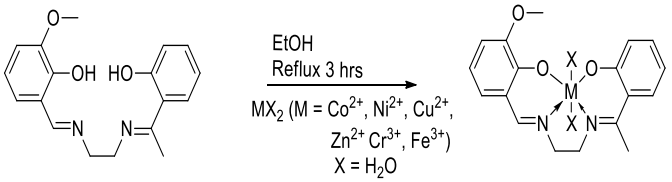
Some tetradentate ligand with N_2O_2 donor sites and its complexes with Co (II) and Cu (II) metal ions were synthesized by A. M. Hamil et al [48]. Further these were tested for their antibacterial activity against three bacterial strain *E. Coli*, *B. cereus* and *S. aureus.*



Scheme 9: Synthesis of Schiff base of N_2O_2 donor sites by condensation of 2-hydroxy acetophenone and benzene-1, 2-diamine

It was observed that Schiff base metal complexes show greater antibacterial potency against bacteria strain as compared to Schiff base ligand.

An unsymmetrical Schiff base and its metal complexes (viz. Co(II), Ni(II), Cu(II), Zn(II), Cr(III) and Fe(III) have been reported by Subin Kumar et al [49], which were synthesized by condensation of o-vanilline, o-hydroxyacetophenone and 1,2-ethylenediamine.



Scheme 10: Synthesis of unsymmetrical Schiff base ligand and its metal complexes

The synthesized metal complexes were evaluated for their antitumor and antifungal activities.The antitumor activities were studied on *Ehrliches Ascites Carcinoma* cells (EAC) induced ascites and *Lymphoma Ascites* cells (DLA) induced solids tumour models. The cytotoxic action of Cu complex was monitored at different concentration in mice, it was found that copper complex monitored at different concentration in mice, inhibited the solid tumour development and increased the mean survival rate and life period of Ascites tumour enduring mice having dependence on concentration. Amongst all these complexes, Cu (II) complex showed a high IC_{50} value. Antifungal activity of Schiff base and its metal complexes were tested on of *A. Flavus, C. Albicans* and *C. Tropicalis*. It was found that metal complexes have better antifungal activity than the ligand itself.

Furthermore, same Schiff base ligand and their metal complexes were tested for their antibacterial activity against *P. Aeruginosa, E. Coli, S. Aureus* and *B. Cereus*. It was found that Schiff base ligand has more potent for gram positive than gram negative bacterias. For Schiff base metal complexes, the activity was found in the order viz. Cu complex > Ni complex > Fe complex > Co complex > Cr complex. Metal complexes were found to be more potent than parent Schiff base ligand due to chelation of metal ion, which increase the antibacterial activity of the metal complexes.

Many other tetradentate Schiff base ligands and their metal complexes have been reported M.A. Neelakantan et al [50], synthesized by template synthesis of o-phthaldehyde and different amino acids. The biological activity of synthesized complexes has been tested against eight bacterial and three fungal species.

Eleven microbial species were used to test the antimicrobial activity of the Schiff base metal complexes viz. 1) *E. coli*; 2) *Proteus species*; 3) *Pseudomonas aeruginosa*; 4) *Staphylococcus aureus*; 5) *Klebsiella species*; 6) *Streptococcus*; 7) *Pastruella species*; 8) *Enterobacter*; 9) *Aspergillus*; 10) *Candida species* and 11) *Mucor species*. The antimicrobial activity of the extract was determined by using Modified disc diffusion method [51].

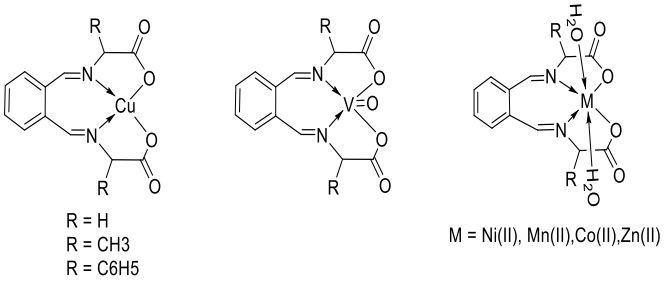
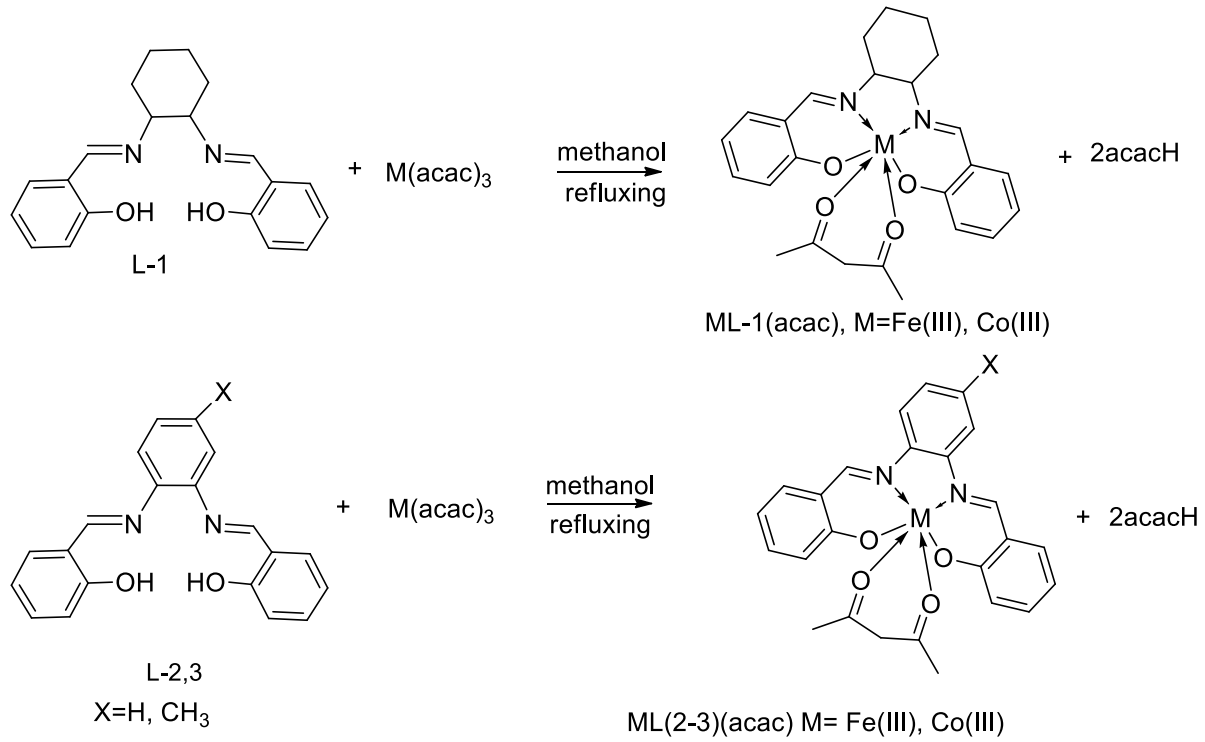


Fig. 6: Structures of Schiff base metal complexes

It has been suggested that Schiff base ligand with N and O donor system might have inhibited the enzyme production, since enzyme require free hydroxyl group for their activity, seems susceptible to deactivation by the ions of complex. The complex makes possible their diffusion through the lipid layer of spore mechanism to the point of action, ultimately killing them by hydroxyl group of the certain cell enzymes. The effectiveness of different biocidal agents against different depends upon the impermeability of the cell. On the dilution polarity of the central metal atom reduces because of sharing of positive charge with the ligand. Results shows that Cu(II) and Ni(II) complexes exhibited inhibition against all the studied microorganism but Co(II) and Mn(II) complexes exhibits less inhibition.

Similarly N.K. Choudhary and co-worker [52] synthesized Cu^{2+} and Ni^{2+} complexes of Schiff base ligands derived from the condensation of 2-aminophenol with furan-2-carbaldehyde.The synthesized Schiff base ligands and their metal complexes were tested for their invitro antibacterial activity against bacterial pathogens *E. coli*, *Bacillus subtilis*, *Staophlococcus* and *P.vulgareous*. Both Schiff base ligand and their metal complexes show significant antibacterial activity. M.B. Fugu et al, [53] synthesized metal complexes of Cu^{2+}, Ni^{2+} ,Co^{2+} and Mn^{2+} with Schiff base ligands derived from condensation of vaniline with 2-aminophenol.Thesecomplexes were tested against bacteria *E. coli*, *klebsiella pneumonia*, *salmonella typhe*, *Staophlococcus Aureus*, *corynebacteriam* species by disc diffusion method and found significant activity against these microorganisms.

Harun A. R. Pramanik and others [54] have synthesized and characterized mixed Schiff base ligand and their metal complex with Co(III) and Fe(III).



Scheme 11: synthesis of mixed metal complexes possessing antioxidant activities

Their antioxidant activities of Schiff base ligand and their metal complexes were investigated by using the 2, 2, -diphenyl -1-picrylhyrazyl (DPDH) scavenging method. It has been observed that metal complexes show better oxidant activities as compared to free Schiff baseligand, may be due to presence of phenolic -OH gp.Studies revealed that Co(III) complexes are more potent antioxidant than that of Fe(III) complex.

3. CONCLUSION

Schiff bases are capable of forming large number of stable complexes with different transition metals in various oxidation states. The most important advantage of preparation of Schiff's base and their metal complexes is different types of activities like antibacterial, antifungal, antioxiant and anticancer etc. Advances in this field will further require analyses of the structure activity relationships of the schiff bases as well as the mechanism of action of these compounds against different types of pathogens.

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