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Review Article

Antimicrobial Activity of Mn Complexes Incorporating Schiff Bases: A Short Review

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Abstract: Antibiotic resistance has been growing at an anxious rate and as a result the activity of antibiotics against Gram-negative and Gram-positive bacteria has dropped dramatically day by day. Metal ions play many critical functions in humans. Deficiency of some metal ions can lead to disease like pernicious anemia, growth retardation, heart disease in infants etc. In this sense there is a strong need to synthesis new substances that not only have good spectrum of activity, but having new mechanisms of action. Inorganic compounds particularly Mn metal complexes have played an important role in the development of new metal based drugs. Over the past few years, there have been many reports on their applications in homogeneous and heterogeneous catalysis. The activity is usually increased by complexation therefore to understand the properties of both ligands and metal can lead to the synthesis of highly active compounds. The influence of certain metals on the biological activity of these compounds and their intrinsic chemical interest as multidentate ligands has prompted a considerable increase in the study of their coordination behavior. Development of a new chemotherapeutic Schiff bases and their metal complexes is now attracting the attention of medicinal chemists. In this review we have focused on research of Mn complexes incorporation of Schiff bases carry out over the past few decades which has sought to possess preclinical pharmacological screenings like anti-bacterial, anti-fungal, anti-tuberculosis, anti-inflammatory, anti-cancer, DNA- interaction and anti-tumor action of synthetic metal complexes.

Keywords: Schiff Bases, Mn Complexes, Metal Based Drugs, Antibacterial, Anti-Inflammatory

1. Introduction

Interest in the study of Schiff base hydrazones has been growing because of their antimicrobial, anti-tuberculosis, and anti-tumour activity [1-12]. Schiff bases play an important role in inorganic chemistry, as they easily form stable complexes with most transition metal ions. The development of the field of bioinorganic chemistry has increased the interest in Schiff base complexes, since it has been recognized that many of these complexes may serve as models for biologically important species [1-5]. Coordination compounds derived from aroyl hydrazones have been reported to act as enzyme inhibitors and are useful due to their pharmacological applications [6-12]. Schiff bases are a class of compounds having azomethine linkage (C=N) and they are widely used in the field of coordination chemistry due to their ability to form stable complexes [13]. Manganese Schiff base complexes have subsequently been found to play an important role in many biological processes such as trans amination, decarboxylation, condensation and -elimination

and racemization [14] gave complexes of various metals with Schiff bases derived from thiazoles and their carbohydrazones having antimicrobial activity. Seleem reported stability constants and thermodynamic parameters of some complexes with Schiff base hydrozones containing pyrimidine moiety [15]. They are among the most expedient and versatile ligands which are easily synthesized in a one-step classical condensation reaction through common aldehydes with amines or ketones usually in quantitative yields. Schiff base ligands of heterocyclic compounds and their transition metal complexes are of great interest as simple structural models of biological system due to the presence of hetero atoms such nitrogen, oxygen and sulphur groups [13]. Schiff bases have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like anti-inflammatory [16-20], analgesic [21-23], antimicrobial [24, 25], anticonvulsant [26], antitubercular [27], anticancer [28, 29], antioxidant [30], antihelmintic [31], and so forth. The wide ranges of applications of these compounds have continued to attract interest among inorganic chemists. Many of them are also thermally stable and have synthetic flexibility. Some of these compounds are found to be useful both as clinical diagnostic agents and in chemotherapeutic application. In view of the properties mentioned above, a large number of Schiff bases have been synthesized and extensively studied the literature [32]. The design and synthesis of organic–inorganic hybrid complexes based on strong coordinate bonds and multiple weak non-covalent forces has become a rapidly growing field of research [32]. Microbes encounter a variety of metal ions in the environment and interact with them, which is sometimes beneficial or detrimental depending on the chemical/physical nature and oxidation state of the metal ion. The microbes have the ability to bind to metal ions present in the external environment at the cell surface and to transport them into the cell for various intracellular functions [33]. In this review we explored the overview application of antimicrobial activities of Mn complexes incorporating Schiff bases.

2. Antimicrobial Activity of Schiff Base Manganese Complexes

The antimicrobial activity of the Schiff base ligand and their metal complexes at low concentrations were evaluated against Gram positive and Gram negative bacteria as well as fungal species [34]. Antimicrobial activity of Schiff base metal complexes of Mn(II) derived from 2-amino pyridine have been synthesized by Rehab K Al-Shemary and et al. The in-vitro antimicrobial activity of the scrutinised ligand and its metal complexes was tested against the bacteria Escherichia coli and Staphylococcus usurious by disc diffusion method using nutrient agar as a medium. The stock solution was prepared by dissolving the compounds in DMSO. In a typical procedure, a well was made on agar medium inoculated with the microorganism. The well was filled with the test solution using a micropipette and the plate was incubated 24 h for bacteria at 37°C and 72 h for fungi at 30°C. After incubation, the diameter of the clear zone of inhibition surrounding the sample is taken as a measure of the inhibitory power of the sample against the particular test organism. This may be due to that the chelation considerably reduces the polarity of the metal ion mainly because of partial sharing of its positive charge with the donor groups and possible electron delocalization over the whole created ring such, chelation could also enhance the lipophilic character of the central metal atom, which subsequently favors its permeation through the lipid layer of the cell membrane [35]. Schiff base metal complexes of Mn derived from Ofloxacin have been synthesized by Rabia Arshad and et al. All metal complexes except Ni complex showed enhanced antimicrobial activity while the Mn complex being more active. Similarly against *E. coli*, metal complexes showed somewhat comparable or enhanced activity than the parent drug except Ni complex which has just lower activity than the drug. The order of antibacterial activity is as follows; Metal Complexes of ligands > Ligands > Parent Drug. Ofloxacin is an antibacterial drug so it does not show any activity against fungi. In case of antifungal activities, we know that some other quinolones show very low activities against any fungi. Besides very poor antifungal records of quinolones, we managed to measure the antifungal properties of our prepared complexes in order to know any effect on certain fungi. The prepared complexes were used on two fungal strains *i.e.* A. flavus and A. niger. Activities of ligands are not better enough to be declared as good antifungal agents. Metal complexes of these ligands also exhibited very slight increase in antifungal activities [36].

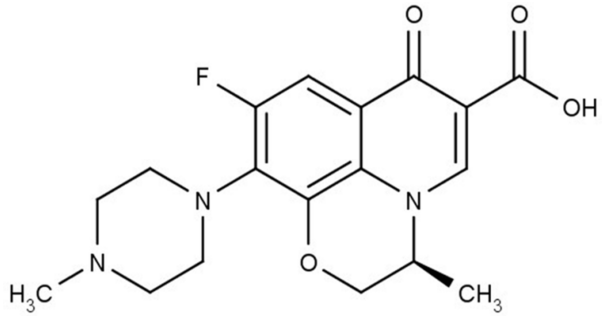


Figure 1. *Structural formula of Ofloxacin.*

G. kumar and *et all* were synthesized some M(III) complexes of Cr, Mn and Fe (figure 3)with a Schiff base derived from2-amino-4-ethyl-5-hydroxybenzaldehyde and thiocarbohydrazide(figure 2). The antibacterial and antifungal activities of the newly synthesized compounds were evaluated by the agar well diffusion method. The Mn(III)complex exhibited moderate activity against P. aeruginosa and B. megaterium, was highly effective against K. fragilis, C. albicans and T. reesei, but showed no activity against E. coli, S. aureus and R. rubra.

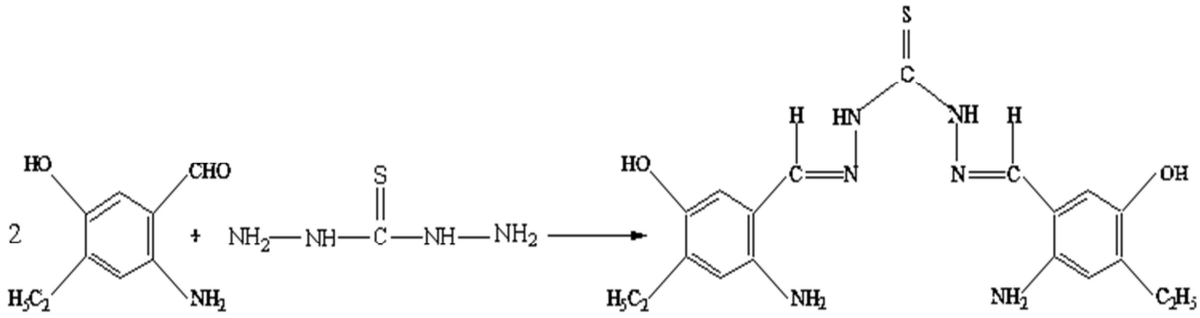


Figure 2. *Synthesis of the Schiff base ligand.*

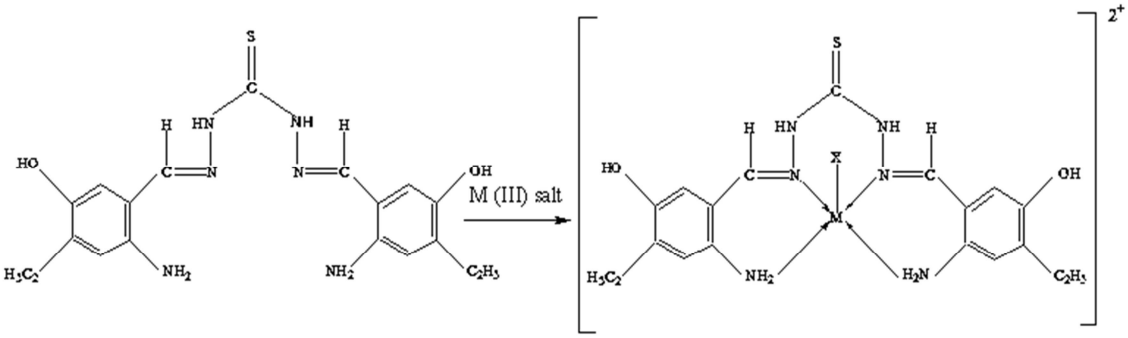


Figure 3. *Synthesis of the M(III) Schiff base complexes.*

Sangita Sharma and et al were investigated Antimicrobial Activity of Some Transition Metal Complexes (Mn, Co, Zn, Ni) derived from L-Proline and Kojic Acid. The antimicrobial effect of metal complexes at $2x10^{-3}$ M concentration on the growth of bacteria(Escherichia coli and Bacillus subtilis), yeast (Sacharomycescerevisiae) and fungi (Aspergillusniger) was investigated in liquid media. The highest activity was reported with Ni(II) complexes with 92.65%, 88.09%, 85.77% and 45.1% growth inhibition for S. cerevisiae, E. coli, B. subtilis and A. niger respectively. The second highest antimicrobial activity was exerted by cobalt complex with 80.39%, 71.38%, 70.51% and 52.62% growth inhibitory effect respectively for *B. subtilis, S. cerevisiae, E. coli, and A. niger*. The Ni(II) complexes exerted the highest activity amongst all test organisms under study except for A. Niger which was best with Zn(II) complexes. The least activity has been reported for the Mn(II) complexes. This may be due to fact that manganese is an essential trace nutrient in living cell life and a wide group of enzymes have manganese as cofactor [37] Schiff base, (E)-N'-(-1-(1-ethyl-4-hydroxy-2-oxo-1, 2-dihydroquinolin-3-yl) ethylidene)nicotinohydrazide and its Cu(II), Ni(II), Co(III), Mn(II)and Fe(III) complexes have been prepared by Trimbak K Chondhekar et al (figure 4). The ligand and its metal complexes have been screened in vitro for their antibacterial and antifungal activities by agar- cup method using DMSO as a solvent and poison- plate method using potato dextrose agar medium in DMSO respectively. All the metal complexes do not show any activity against Gram – ve bacteria, E. coli and S. typhi, except Mn(II) complex which show highest activity against E. coli comparable to the standard, penicillium. On the other hand, the ligand show considerable activity against Gram +ve bacteria, S. aureus and remains inactive against *B. subtilis*. The most active is the Ni(II) complex which shows better inhibitory action against both gram positive bacterial species. Mn(II) and Cu(II) complexes also inhibit the growth. However Co(III) and Fe(III) complexes do not have significant effect against both the species. All these active metal complexes exhibited a more inhibitory effect compared to the ligand. This is because the chelation reduces the polarity of the metal ion because of partial sharing of its positive charge with the donor groups which results in to the increase of lipophilic nature of the complexes which in turn favors its permeation to the lipid layer of the membrane. Moreover, other factors, like stability constants, molar conductivity, solubility and magnetic moments also affect the antimicrobial activity of the complexes [38].

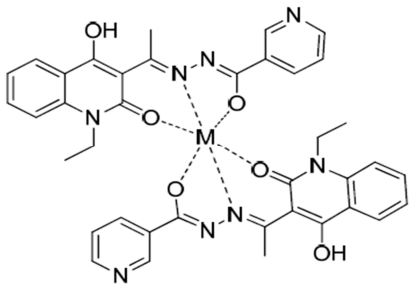


Figure 4. *Proposed structure for the complexes.*

Novel Schiff base and its 3d transition metal complexes of Mn(II), Fe(III) and V(IV) has been designed and synthesized form 4-aminoantipyrine and Ethyl 4- methyl – oxo-6-phenylhexahyro pyrimidine-5-carboxylate by Mohanambal D. and Arul Antony S. In vitro antibacterial

(E.coli, Staphylococcusaureus, *Bacillus spp*, Salmonella spp.) and invitro antifungal (Candida, Aspergillusniger,) tested by Mueller Hinton Agar solid media (MHA) and Sabouraud's dextrose 9SDA) media. Agar diffusion assay was carried out to evaluate the antimicrobial activity of ligand and its metal complexes synthesized. The plates were incubated at 37°C for 24hr, during which activity was evidenced by the presence of azone of inhibition surrounding the well and antibacterial and antifungal activity was expressed as the mean diameter of inhibition zones (mm) produced by the synthesized compounds [39]. Aishatu Salihu Mohammed and et all were investigated Antifungal Activity of Manganese (II) Complex with Schiff Base Derived from Acetylacetone and Leucine. The antifungal activities of the prepared compounds were studied using Candida albican and Sacchro mycescerevisia *et al*. The manganese (II) complex showed strong activity on the fungal isolates at medium and high concentrations. All organisms were found to be resistant to the Schiff base at all concentrations. The diameter of inhibition zone for each treatment ranged from 7 mm to 38 mm [40]. Complexes of Mn(II) and Fe(III) with trimethoprim Schiff base ligands, HL^1 (figure 5) and HL^2 (figure 6) derived from salicyldehyde and benzaldehyde were synthesized and investigated by Naomi P. Ndahi and et all. The results obtained on antimicrobial studies, the ligand (HL^1) and its complexes did not show much effect against the bacterial isolates as well as the fungus *Candida albicans* tested as compared with the standard trimethoprimdrug at all concentrations with the exception of Fe(HL^1) Cl]Cl which indicated susceptibility with zone of 2 2 inhibition of 30.00 mm (30 µg/ml), 24.70 mm (20 µg/ml) and 20.30 mm (10 µg/ml) against Corynae bacterium species compared to 23.30 mm (30 µg/ml), 18.7 mm (20 µg/ml) and15.00 mm (10 µg/ml) shown by the parent drug trimethoprim. In contrast, HL^2 complexes showed greater activity against Streptococcus pyogenes, Corynaebacterium species and Shigelladysentriaat all concentrations compared to the trimethoprim standard. $Mn(HL_2)Cl_2$ complex (Figure 8) showed low to moderate activity against all the tested organisms.[Fe(HL_2) Cl]Cl did not show any visible inhibition against Bacillus subtilis. Antimicrobial resistance against some promising antibiotics drugs such as trimethoprim and others was commonly observed in many countries worldwide during in vivo analysis of pathogens [41].

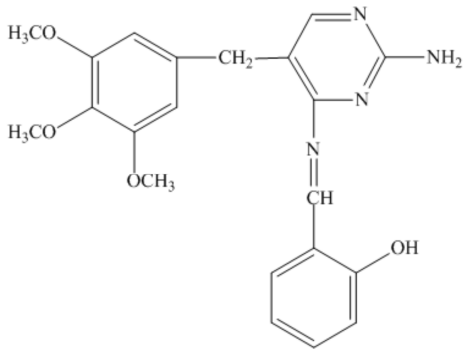


Figure 5. *Proposed structure of HL^1.*

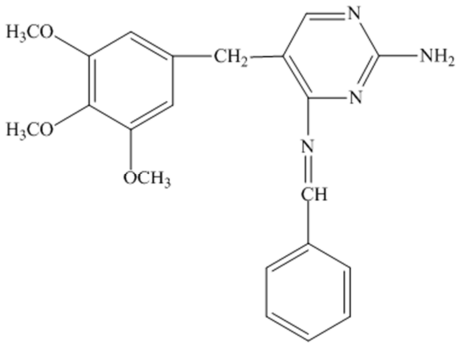


Figure 6. *Proposed structure of HL^2.*

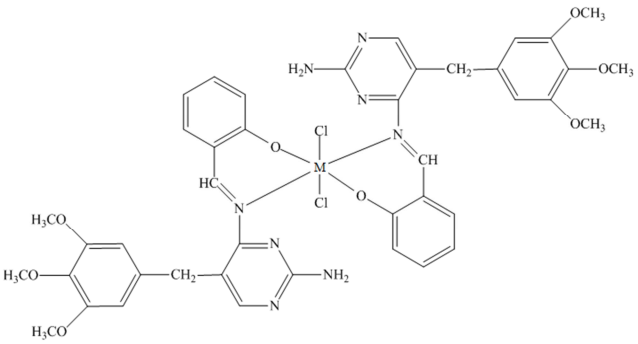


Figure 7. *Proposed structure of [Mn (HL^1)$_2Cl_2$].*

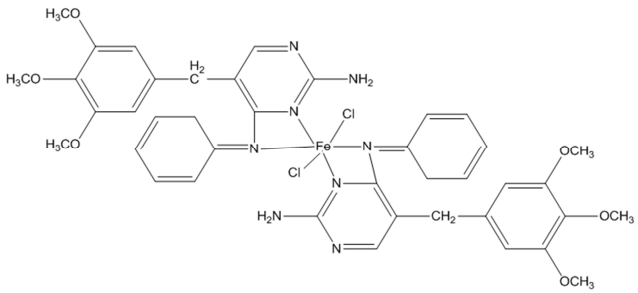


Figure 8. *Proposed structure of [Mn(HL^2)$_2Cl_2$]Cl.*

Mohammad Muzammil Y. Kuddushi and et al were Synthesis And Characterization of Schiff Base Aniline With 5-Bromo -2- Hydroxyl Benzaldehyde and Their Metal Complexes. The ligands and the metal complexes show very good antimicrobial properties against The gram-positive bacteria-B. megaterium and gram-negative-Escherichia coli [42]. Manganese(III) complexes derived from the bis_Schiff bases N, N' bis (5 fluorosalicylidene)-1, 2 diaminoethane (H2La) and 3, 4-bis(2-hydroxybenzylideneamino)pyridine (H2Lb), respectively, have been prepared and characterized by Q. R. Liu, L. W. Xue and G. Q. Zhao. Qualitative determination of antimicrobial activity was done using the disk diffusion method [24, 25]. In general complex I shows greater antibacterial and antifungal activities against Staphylococcus aureus, Escherichia coli, and Candida albicans compared to complex II and it is obvious that H_2L^a has also greater antibacterial and antifungal activities against Staphylococcus aureus, Escherichia coli, and Candida albicans compared to H_2L^b [43]. Carbazoles containing two

new Schiff bases (Z,Z)-N,N'-bis[(9-ethyl-9H-carbazole-3-yl)methylene]propane-1, 3-diamine (L1) and (Z,Z)-N,N'-bis[(9-ethyl-9H-carbazole-3-yl)methylene]-2, 2-dimethylpropane-1, 3-diamine (L2) and their Co(II) and Mn(II) complexes were synthesized and their antimicrobial properties investigated by Selma Bal and Sedat Salih Bal. The synthesized Mn and Co compounds were effective for almost all of the microorganisms; in particular, for the microorganisms K. pneumoniae, E. aerogenes, S. faecalis, and S. aureus. The title ligands brought about bigger inhibition zones. Generally, they were most effective, both antimicrobial and antifungal. Among the fungi, they gave the biggest inhibition zones for C. Utilis with 27mm and 25mm zones, respectively. Among the coordination compounds, the higher values, that are both antimicrobial and antifungal, were recorded for the manganese (II) complex compounds [44]. M (III) complexes of Cr, Mn and Fe with a Schiff base derived from 2-amino-4-ethyl-5-hydroxybenzaldehyde and thiocarbohydrazide were synthesized and characterized by G. Kumar and et all. The Cr (III) complex showed high antibacterial and antifungal activity against B. megaterium, K. fragilis, R. rubraand C. albicans, moderate activity against E. coli, S. aureus and P. aeruginosa, but no activity against T. reesei. The Mn(III)complex exhibited moderate activity against P. aeruginosa and B. megaterium and highly effective against K. fragilis, C. albicans and T. reesei, but showed no activity against E. coli, S. aureus and R. rubra. The Fe (III) complex exhibited moderate activity against S. aureus, P. aeruginosa, B. megaterium and T. reesei, had a higher effect against K. fragilis and C. albicans, but no activity against E. coliand R. rubra microorganisms [45]. A new series of transition metal complexes of Cu (II), Ni (II), Co (II), Mn (II), Zn (II), VO (IV), Hg (II) and Cd (II) have been synthesized from the Schiff base (L) derived from 4-aminoantipyrine, 3-hydroxy-4-nitrobenzaldehyde and o-phenylenediamine by N Raman and et al. The in vitro biological screening effects of the investigated compounds were tested against the bacteria: Salmonellatyphi, Staphylococcus aureus, Escherichiacoli, and Bacillus subtilis. The antifungal activities of the compounds were evaluated by the well-diffusion method against the fungi viz., Aspergillusniger, Aspergillus flavus and Rhizoctonia bataicola [46]. Metal complexes of Mn(II), Cu(II) and Ni(II) with Schiff base ligand (HL) derived from condensation of propionaldehyde with ethylenediamine were synthesized and investigated their antimicrobial activity by Wakil IM and et al. The antimicrobial activity of the Schiff base ligand and their metal complexes [Mn(II), Cu(II) and Ni(II) complexes] at concentrations of 10, 20 and 30 µg/ml were evaluated against Gram positive (Staphylococcus aureus, Streptococcus pyogenes) and Gram negative(Escherichia coli, Salmonella typhi)bacteria as well as fungal specie – Candida albicans. The Schiff base ligand (HL1) did not show efficacy against all the microorganisms tested. But, on complexation with Mn(L1-L1)X2 showed increased activity ($P<0.001$) against all the organisms that were previously resistant to the parent ligand. Albicans which was resistant to the Mn(II) complex. At concentration of 30 µg/ml, it was observed that all the test organisms were susceptible on Cu(L1- L1)X2 complex. $Ni(L^1\text{-}L^1)X_2$ was found to be resistant to E. coli while S. typhi, S. aureus, S. pyogenes and C. Albicans were found to be susceptible to Ni(II) complex. Enhanced activity ($P<0.001$) was observed for Cu(II) complex on comparison with Mn(II) and Ni(II) [47].

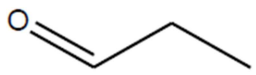


Figure 9. *Propionaldehyde.*

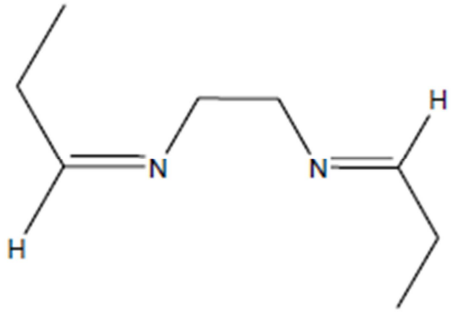


Figure 10. *Proposed structure of Schiff base (HL).*

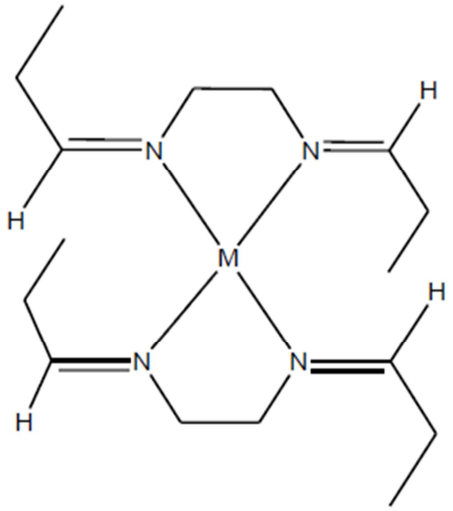
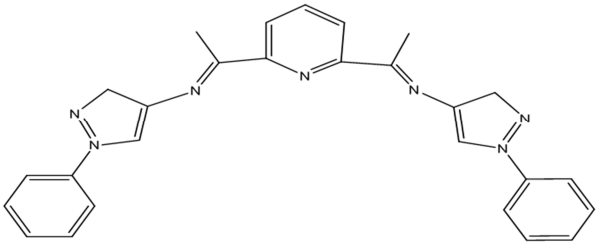


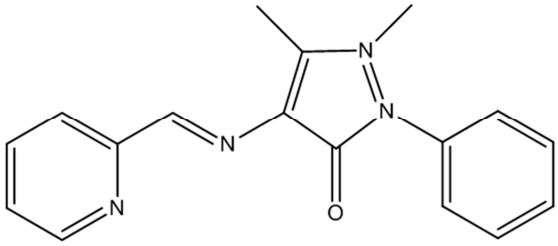
Figure 11. *Proposed structure of the metal complexes.*

Two new Schiff base ligands (L1, L2) have been prepared from the reaction of 2, 6 diacetylpyridine and 2-pyridinecarboxyaldehyde with 4-amino-2, 3-dimethyl-1-phenyl-3-pyrozolin-5-on, and their Co(II), Cu(II), Ni(II), Mn(II), and Cr(III) metal complexes have also been prepared by E. Ispir and et al. The antibacterial and antifungal activities of the new compounds against eight bacteria, namely, *Escherichia coli, Staphylococcus aureus*, *Klebsiellapneumoniae, Mycobacteriums megmatis, Pseudomonas aeruginosa, Enterococcus* cloacae, *Bacillus megaterium,* and *Micrococcusluteus*, and five fungi, namely, Kluyveromyces fragilis, Rhodotorularubra, Candida albicans, Saccharomycescerevisiae, and Trichodermareesei. Cefodizime, Cefuroxime, Cephalothin, Oxacillin and Nystatin are taken as the standard reference antibiotics for antibacterial and antifungal activities. The antibacterial and antifungal

activities of standard antibiotics gave 45 and 8 mm inhibition zones for fungi and bacteria respectively [49].

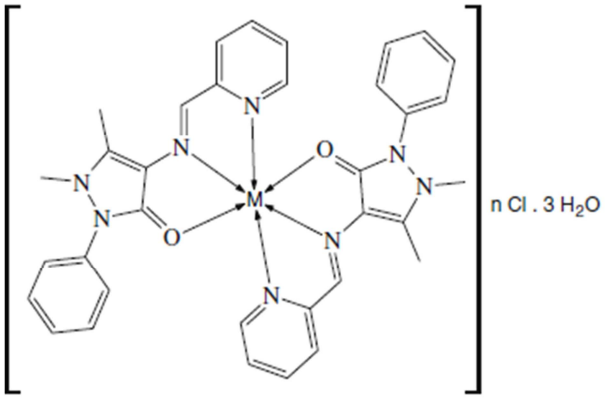


L^{I}(I)



L^{II}(II)

Figure. 12. *The proposed structure of the new Schiff base ligands.*



M= Co(II), Cr(III), Cu(II), Mn(II), Ni(II)

Figure 13. *The proposed structures of the L1 (a) and L2 (b) complexes.*

Metal complexes of Mn(II), Fe(II), Co(II) and Cd(II) ions (Figure 15) with Schiff base ligand 4-{(pyridin-2-ylimino)methyl}phenol (figure 14) derived from condensation of 2-amino pyridine with 4-hydroxybenzaldehyde was prepared and investigated their antimicrobial properties by M. S. Hossain and et al. The free Schiff base ligand and their metal complexes were screened for their antibacterial activity against the strains the *Escherichia coli, Pseudomonas aereuguinosa, Acetobacteraceti.* The susceptibility zones were the clear zones around the discs killing the bacteria. All the Schiff base and metal complexes individually exhibited varying degrees of inhibitory effects on the growth of tested bacterial species. Most of the metal complexes showed more antibacterial activity than Schiff base ligand [50].

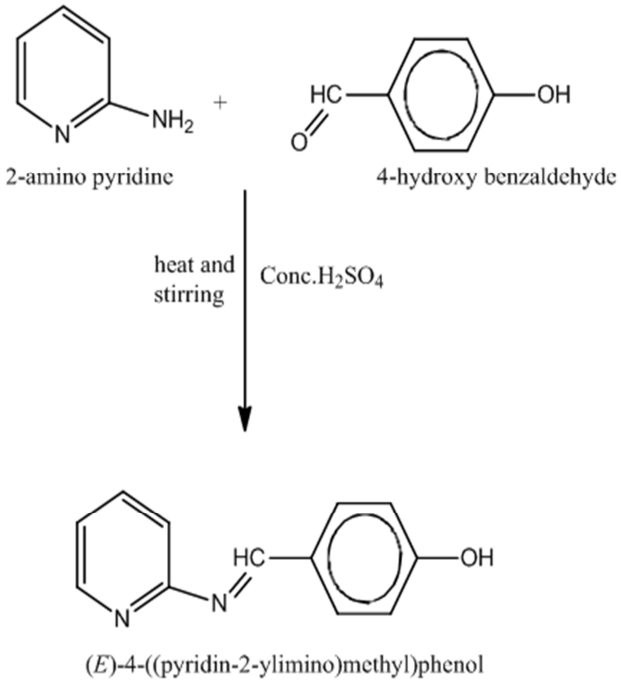


Figure 14. *Structure of Schiff base L= [$C_{12}H_{10}N_2O$].*

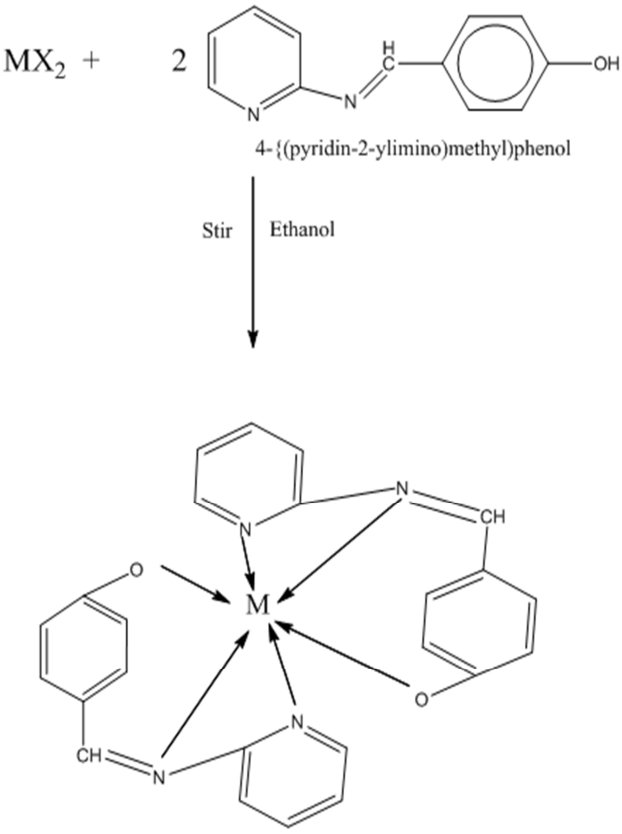


Figure 15. *Structure of metal complexes.*

The new Schiff base ligand Salicylaldehyde-4-Chlorobenzoylhydrazone (HL) (figure 16) and its Mn(II), Co(II) and Ni(II) metal complexes (figure 17) were synthesized and characterized by A. H Manik shete et al. The anticancer activity of the ligand (HL) and its Mn(II) complexes was determined by sulforhodamine -B colorimetric

assay. Mn(II) complex shows moderate activity for breast (MCF7) cell line with IC50 value of 11.1 µM and resistant to the colon (HT29) cell line with IC50 value of 84.9 µM. Mn(ii) complexes showed significant anticancer activity. Ligand and its Mn(II), complexes were active against MCF7 than HT29 cell line [51].

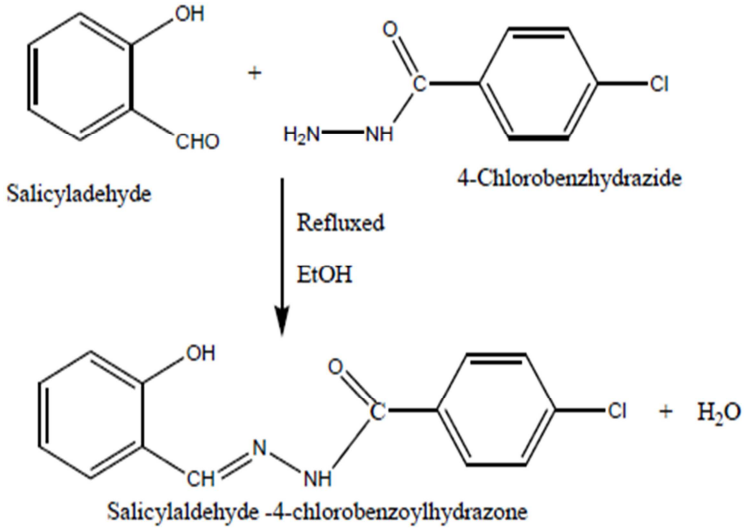


Figure 16. *Synthesis of Schiff base.*

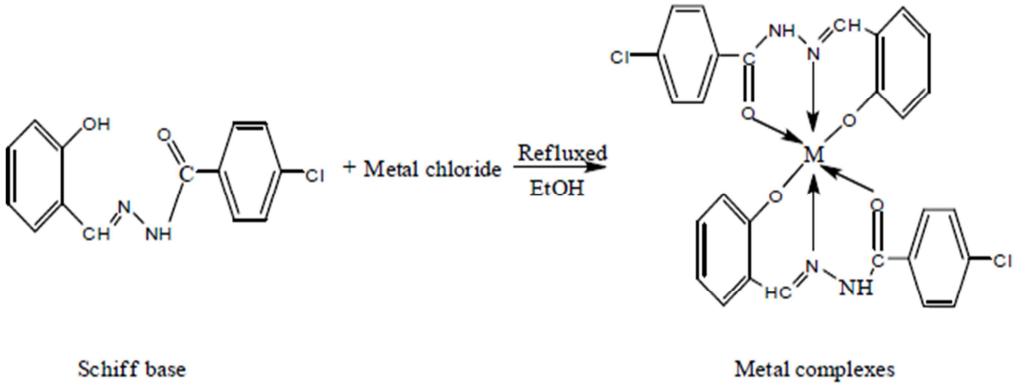


Figure 17. *Synthesis of metal complexes.*

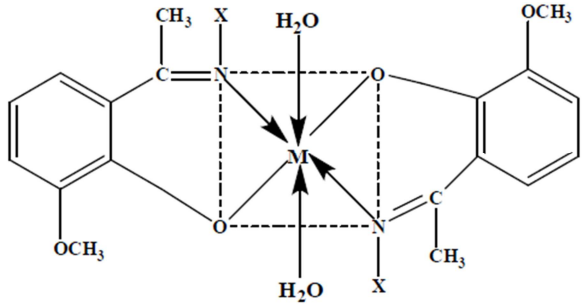


Figure 18. *SOVPTH metal complexes (M=Mn^{2+}).*

Metal complexes of a novel Schiff base derived from condensation of p-toluichydrazide and o-Vanillin are reported and characterized by S. Kondaiah and *et al.* The biological activity of the Schiff base ligand and their metal complexes and streptomycin (as a standard compound) were tested against bacteria because bacteria can achieve resistance to antibiotics through biochemical and morphological modifications. The organisms used in the present investigations included *Staphylococcus aureus* and *Bacillus subtillis* (as gram positive bacteria) and *Pseudomonas aereuguinosa and Escherichia coli* (as gram negative bacteria). The data obtained reflect that the Schiff base ligand shows moderate activity in comparison with *Staphylococcus aureus, Bacillus subtillis* and less active in comparison with *Pseudomonas aereuguinosa, Escherichia coli* [52].

A series of manganese(II) and copper(II) complexes with reduced Schiff bases derived from o-phenylenediamine has been prepared and characterized by S. Belaid et al. Mn(II) complexes (figure 20) present a good activity against most of the dermatophytes tested and fungi of the genus Scedosporium, especially for $[MnL1(H_2O)_2]$ which possesses the more simple structure. In addition, their activity against Scedosporium species, i.e., *S. apiospermum* which ranks the second among the filamentous fungi colonizing the airways of patients with cystic fibrosis and *S. prolificans* which causes severe disseminated infections in leukemic patients. [53].

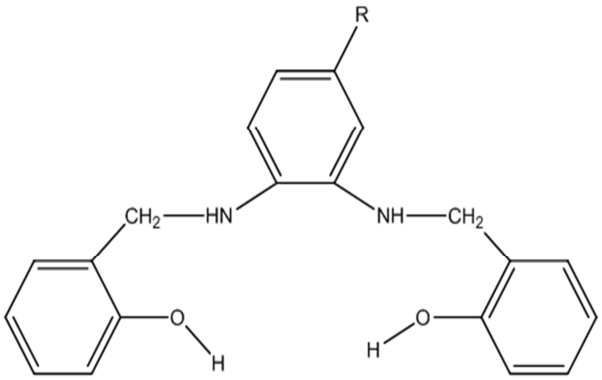


Figure 19. *Formula of the ligands: R=H: H2L[1], R=CH3: H2L[2], R=Cl: H2L[3].*

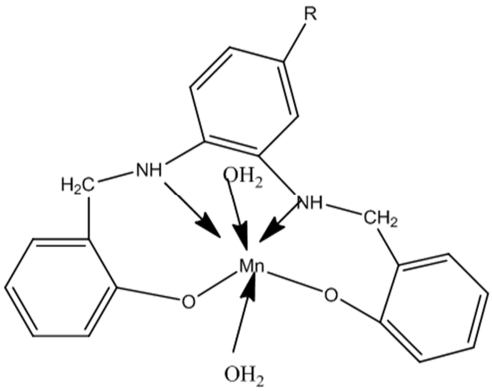


Figure 20. *Structural scheme of the complexes (b) $[MnL^1(H_2O)_2]$, $[MnL^3(H_2O)_2]$.*

Manganese (II) complexes of bishydrazones were prepared and investigated their antimicrobial activities by P. Mittal and V. Uma. The results of antibacterial and antifungal activity show that these compounds exhibit greater antibacterial and antifungal activity against the *E. Coli, Klebsiella, Enterococci, S. Aureus Candida Albicans* and *Candida Krusei* [54].

3. Conclusions

In this work, the antimicrobial activity of Mn complexes has been reviewed. With the improvement in the field of medicinal chemistry, the role of transition metal complexes especially Mn complexes as therapeutic compounds is becoming increasingly significant. Recent advances in medicinal chemistry have made possible formation of number of transition metal complexes with organic ligand of interest, which can be used as therapeutic agent. Significant progress in the synthesis of platinum based anti-cancer drugs like cisplatin has been made. These drugs have proven to be highly effective chemotherapeutic agents for treating various types of cancers. The use of transition metal complexes as therapeutic compounds has become more and more pronounced. These complexes offer a great diversity in their action; they do not only have anti-cancer properties but have also been used as anti-inflammatory, anti-infective and anti-diabetic compounds. Development of Mn complexes as drugs is not an easy task; considerable effort is required to get a compound of interest. Besides all these limitations and side effects, Mn complexes would be widely used as antimicrobial agents and make a large contribution to medicinal therapeutics.

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