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Review Article

Anti-pathogenic Activity of Cu(II) Complexes Incorporating Schiff Bases: A Short Review

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Abstract: Metals contribute important roles in biological system. It is recognized that metals are highly linked in cellular and subcellular functions. With the application of novel and experienced tools to study biological and biochemical systems the true role of inorganic salts in biological systems can be studied. Schiff base metal complexes show a broad range of biological activity. The activity of Schiff base ligand is usually increased by complexation with the metal ion. The copper complexes of Schiff bases have striking properties such as antibacterial, antifungal, antiviral, anti-inflammatory, anti-tumor and cytotoxic activities, plant development controller, enzymatic activity and applications in pharmaceutical fields. The divalent cations $Zn^{2+,}$ Ca^{2+} and Mg^{2+} prevent cytotoxicity and in vivo antagonize Cd- induced carcinogenesis. Lack of body iron is common in cancer patients and it is associated with complications in surgery and in animal experiments. The transport of iron and other metal ions by the blood plasma is achieved through the formation of protein complexes. Copper is placed as a vital metalloelement and is primarily connected with copper-dependent cellular enzymes. Metals are also used as inorganic drugs for many diseases. In this review our main focused on research undertaken for biological activity study of Cu(II) metal complexes containing Schiff bases over the past few decades.

Keywords: Schiff Bases, Biological Activity, Copper Complexes, Antibacterial, Antifungal, Antiviral, Anti-inflammatory, Anti-tumor and Cytotoxic Activity

1. Introduction

Schiff bases containing imine or azomethine (-RC=N-) are condensation products of primary amines and carbonyl compounds. They were first brought to light by a Nobel Prize winner German chemist, Hugo Schiff in 1864. The versatility and flexibility of Schiff base compounds having, acyl, aryl and heteroaryl Schiff bases have additional donor sites >C=O, >C=N-, and so on. It has made the Schiff base to function as excellent complexing agents that form multifarious complexes with several transition and inner transition metals and has strengthened the attention of many researchers [1]. Schiff-bases may function as mono-, di-, tri-, or tetradentate ligands depending on the number of coordinating atoms present in the molecule and can construct usually five or six membered chelate rings upon reaction with a metal ion [2]. They are well known for their biological applications as antibacterial, antifungal, anticancer, antiviral, antiparasitic, and antitumor agents [3-5]. The complexes of copper (II) ion containing Schiff bases possess remarkable properties as catalysts in various biological systems, polymers, dyes, antimicrobial activities, antifungal activities, antiviral activities, anti-inflammable activities, antiradical activities, plant growth regulator, enzymatic activity, insecticides, antitumor and cytotoxic activities. They also possess wide applications in analytical chemistry, agrochemical and pharmaceutical fields [6]. Copper(II) complexes exhibit distorted octahedral and tetrahedral symmetries due to d^9

configuration (Jahn Teller effect). The distortion is usually seen as axial elongation consistent with the lability and geometric flexibility of the complex. For that reason, typical Cu(II) complexes have square planar or square pyramidal geometries with weakly attached ligands in the axial position (s), but some copper(II) complexes possess trigonal bipyramidal geometry. The significant role of copper and the acceptance of its complexes as important bioactive compounds *in vitro* and *in vivo* actuated an ever-increasing interest in these agents as potential drugs for therapeutic finding in various diseases [7]. Different biological activity of Cu(II) containing Schiff base metal complexes have been mentioned in the later descriptions.

2. Biological Activity of Schiff Base Metal Complexes

2.1. Antibacterial Activity

Antibiotics are substances which, even at low concentrations, resist the growth and regeneration of bacteria and fungi. Now a days the treatment of infectious diseases would be incomprehensible without antibiotics [8]. *N. Raman et al.* have synthesized three transition metal complexes $[CuL_2Cl_2]$, $[NiL_2Cl_2]$, and $[ZnL_2Cl_2]$, where L = Schiff base derived from isatin (1*H*-indole-2,3-dione) and tyramine(4-(2-aminoethyl) phenol). The in-vitro antibacterial activity of the ligand and its complexes were tested against the bacteria *Klebsiella pneumoniae, Staphylococcus aureus, Bacillus subtilis, Escherichia coli,* and *Salmonella typhi* by use of the paper disc method using nutrient agar as the medium. The copper complex has greater antibacterial activity (16–27 mm) against the tested microorganisms than the nickel and zinc complexes, for which the zones of inhibition were in the range of 11–24 mm. The binding model of the Schiff base complexes in the enzyme active site of Staphylococcus aureus sortase-A were also demonstrated by the authors [9]. Four new Schiff base metal complexes of Ni(II), Cu(II), Co(II) and Cd(II) ions where the Schiff base (SB) *(figure-1)* was derived from salicylaldehyde and 2-aminopyridine were synthesized by Md. Motahar Hossain *et al.*

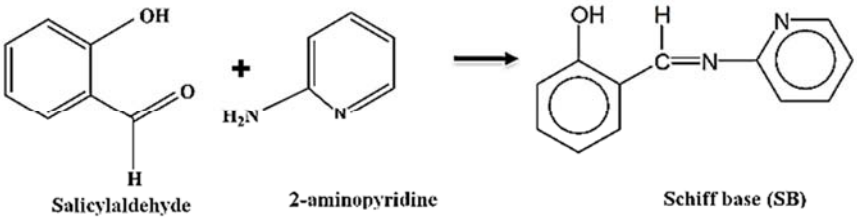


Figure 1. *Reaction for the formation of Schiff base.*

The complexes were screened for their antimicrobial activity against various types of bacteria, Gram-positive *Bacillus cereus*, *Streptococcus agalactiae,* and Gram-negative *Escherichia coli, Shigella dysenteriae.* Among the various complexes only Cu(II) complex exhibited strong activity toward human pathogenic Gram-positive and Gram-negative bacteria whereas the Ni(II), Co(II) and Cd(II) complexes showed week to moderate antimicrobial activity compared with standard Kanamycin and Ampicillin [10]. *Jasmin Ara Shampa et al.* have synthesized Schiff base ligand and its Cu(II) complexes by the condensation reaction of isatin with amino acids (cysteine/glycine/leucine/alanine). The Schiff base Cu(II) complexes were screened for their antibacterial activity against *Bacillus subtilis, Staphylococcus aureus, Escherichia coli, Proteus vulgaris.* All the synthesized complexes showed strong antibacterial activity compared with Streptomycin [11]. *Zahid H. Chohan et al.* have synthesized Schiff base metal complexes of the type $[M(L)_2]Cl_2$, where M= Co(II), Cu(II), Ni(II) or Zn(II) and L= Schiff base, obtained by condensation of 2-amino-l,3,4-thiadiazole with 5-substituted salicylaldehydes. The synthesized Schiff base and the metal complexes were screened for antibacterial activity against several bacterial strains such as *Escherichia coli, Staphylococcus aureus,* and *Pseudomonas aeruginosa.* Activity of the Schiff base compounds became more pronounced when coordinated to the metal ions [12]. Two new metal complexes *(figure-2)* of general formula $M(Ha\alpha ft)_2$ [M = Ni(II) and Cu(II)] of asymmetrical Schiff base ligand (HL = Haαft) derived from amoxicillin and α formylthiophene were synthesized by *N. K. Chaudhary and P. Mishra*. The antibacterial sensitivity study suggests promising activities of Haαft (Ligand) and $M(Ha\alpha ft)_2$ complexes against four clinical pathogenic bacteria, namely, *E. coli*, *P. vulgaris*, *P. aeruginosa*, and *S. aureus*, though being less active than the standard drug amikacin [13].

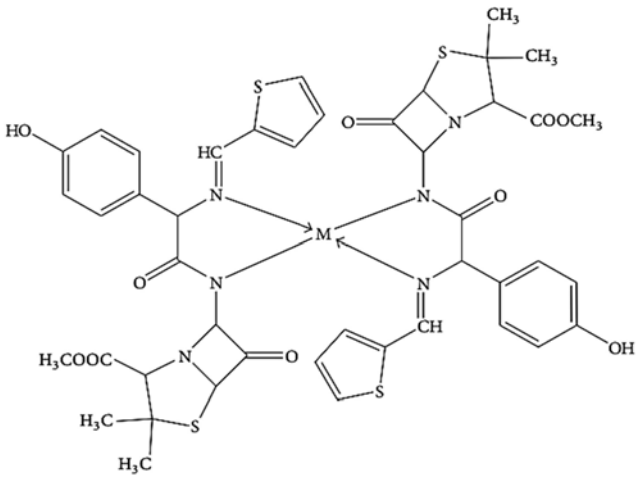


Figure 2. *Structure of metal complex (M = Ni & Cu).*

Schiff base metal complexes of type $ML_2.H_2O$ (M=Mn, Fe, Co, Ni and Cu), where the Schiff base derived from the condensation of 4-Acyl-1-phenyl-3-methyl-2-pyrazolin-5-ones with 2-amino-4(4'-methylphenyl)-thiazole were synthesized by *K. S. Pandya et al.* The compounds were tested *in vitro* for the Antibacterial activity against Gram-negative *Escherichia coli* (responsible for diarrhea), Gram-positive *Bacillus subtillis* (general contaminant) and *Staphylococcus aureus* (causative agent for wound infection). Most of the compounds were moderate active against both Gram-negative and Gram-positive bacteria [14]. A series of new polymeric complexes of Mn(II), Co(II), Ni(II), Cu(II), and Zn(II) with a Schiff base ligand derived from condensation of 2,4-dihydroxy acetophenone and p-phenylene were prepared by *S. N. Kotkar and H. D. Juneja*. The synthesized Schiff base and its corresponding mixed ligand metal complexes were screened against *E. coli, S. aureus, B. subtilis,* and *P. aeruginosa* [15]. Ethylenediamine (en), putrescine (pu), diethylenetriamine (dien), dipropylenetriamine (dpta), spermidine (spmd) & their Cu(II) complexes as well as the Schiff bases with 2-furaldehyde (dienOO), 2-thiophenecarboxaldehyde (dienSS) and pyrrole-2-carboxaldehyde (dienNN) of dien and that of dpta with 2- thiophenecarboxaldehyde (dptaSS), were prepared by *C.A. Bolos et al*. They were tested against *Bacillus substilis, Bacillus cereus, Staphylococcus aureus, Escherichia coli, Proteus vulgaris* and *Xanthomonas campestris* as antibacterial reagents, the highest activity being exhibited by $Cu(dptaSS)(NO_3)_2$ complex, which acts as antibiotic [16]. *Zahid H. Chohan and Samina Kausar* have synthesized tridentate NNO, NNS and NNN Schiff base complexes of the type $[M(L)_2]X_2$, where [M= Co(II), Cu(II), Ni(II) or Zn(II), L= N-(2-furanylmethylene)-2-aminothiazole (L^1), N-(2-thiophenylmethylene)-2-aminothiazole (L^2), N-(2-pyrrolylmethylene)-2-aminothiazole (L^3) and X= CI. The synthesized Schiff bases and their complexes were screened against bacterial species *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Klebsiella pneumoniae* to evaluate their antibacterial properties. All the Schiff bases were found to be biologically active and their metal complexes showed more significant antibacterial activities against one or more bacterial species in comparison to the un-complexed Schiff bases [17]. *K. Sathish Kumar et al.* have synthesized binary complexes of Cu(II), Ni(II), and Zn(II) ions by reacting metal salts with a Schiff base, 2-((E)-(5-methylisoxazol-3-ylimino)methyl)-4-methoxyphenol (MIIMMP) in an alcoholic medium. The ligand and its metal complexes were screened against bacteria and fungi. The bacterial organisms used are *Staphylococcus aureus* and *Escherichia coli*. The variation in the activity of different complexes against different organisms was measured and compared with the standard antibiotic Ciprofloxacin. The Cu complex observed relatively higher activity than the others. The tentative structure of metal complexes also shown in *(figure-3)* [18].

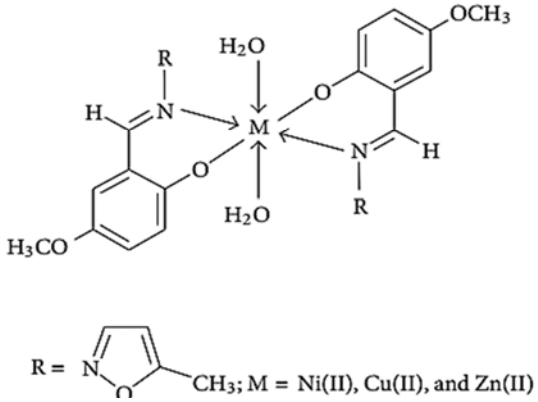


Figure 3. *Tentative structure of M(II) complexes.*

The Schiff base *(figure-4)* [*bis*-(2-aminobenzaldehyde) malonyl dihydrazone] and metal complexes *(figure-5)* with Cu(II), Ni(II), Zn(II) and oxovanadium(IV) were synthesized by *R. Rajavel et al.*

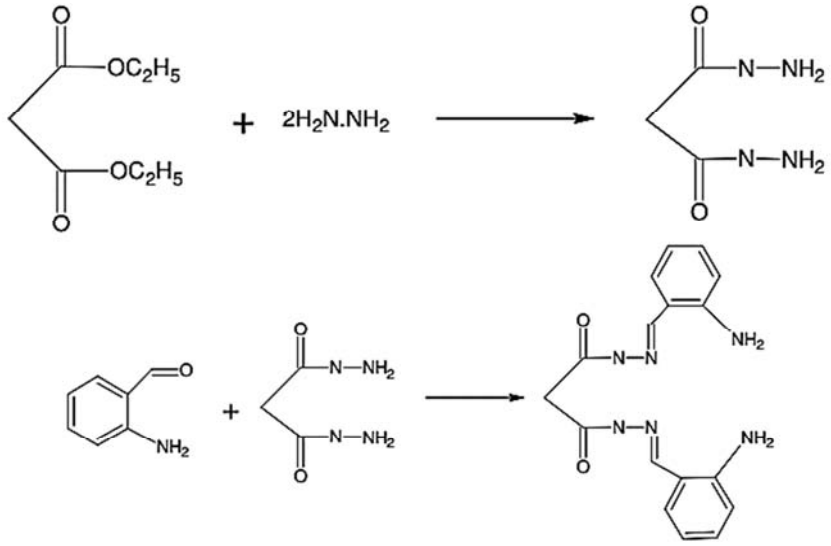


Figure 4. *Synthesis of bis-(2-aminobenzaldehyde) malonyl dihydrazone.*

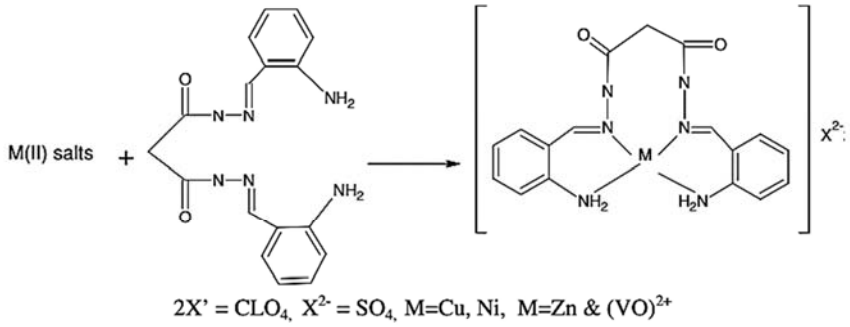


Figure 5. *Synthesis of metal complexes.*

The free ligand and its metal complexes were tested against the bacterial species *Staphylococcus aureus*, *Bacillus subtilis, Pseudomonas aeruginosa*, and *Escherichia coli*. Their antibacterial activity was evaluated by Chloramphenicol as a standard antibacterial agent or reference and the result was compared with the free ligand and its metal complexes [19]. Some transition metal [Co(II), Cu(II), Ni(II) and Zn(II)] complexes of substituted pyridine Schiff-bases were synthesized by *Zahid H. Chohan et al.* The Schiff bases and their complexes have been screened for antibacterial activity against the species such as *Escherichia coli, Staphylococcus aureus,* and *Pseudomonas aeruginosa* [20]. *A. K. Mapari et al.* have synthesized mixed ligand complexes of Co(II), Ni(II), Cu(II) and Zn(II) with Schiff bases *N*-(2-hydroxy-1-naphthylidene)-4-methylaniline (L^1H) and *N*-(2-hydroxybenzylidene)-2,3-dimethylaniline (L^2H). They were screened against *E. coli, S. aureus, B. subtilis* and *S. typhi* to assess their potential as antimicrobial agent [21]. Schiff base metal complexes of Cu(II), VO(IV), Mn(II), Co(II), Ni(II) and Zn(II) ion where the Schiff base derived from 2-(aminomethyl) benzimidazole and thiophene-2-carbaxaldehyde (1-(1*H*-benzimidazol-2-yl)-*N*-[(*E*)-Thiophenylmethylidene] methanamine-BNTM) were synthesized by *C. Gyanakumari et al.* Antibacterial activity of the ligand and its metal complexes were studied against two Gram-negative bacteria; *Escherichia coli, Pseudomonas aeruginosa* and two Gram-positive bacteria; *Bacillus subtilis*, *Staphylococcus aureus*. It has been found that all the complexes were antimicrobially active and showed higher activity than ligand [22]. Biologically active tridentate amino acid (Alanine, Glycine & Tyrosine) derived Schiff bases and their Co(II), Cu(II) & Ni(II) complexes have been synthesized by *Zahid. H. Chohan et al.* They were screened for their antibacterial activity against *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Proteus vulgarus* and *Pseudomonas aeruginosa* [23]. *Md. Motahar Hossain et al.* have synthesized Schiff base transition metal complexes of Ni(II), Cu(II), Co(II), Cd(II), Zn(II) and Cr(III) where the Schiff base (SB) derived from p-hydroxy benzaldehyde and 4-aminobenzoic acid. The reaction scheme *(Figure-6)* of the preparation of Schiff base and the probable structure of the complexes *(figure-7,8,9)* are given below.

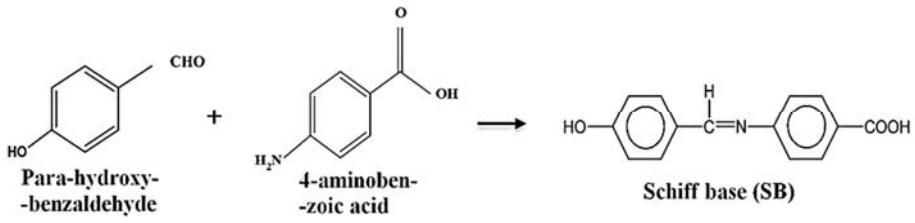


Figure 6. *Reaction scheme for the preparation of Schiff base (SB).*

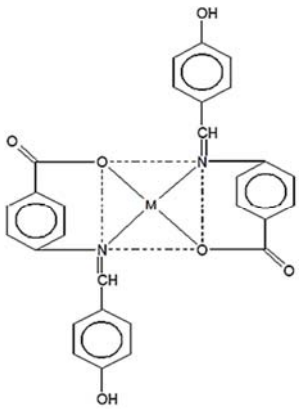


Figure 7. *Probable structure of the complexes. Here, M = Ni(II) and Co(II).*

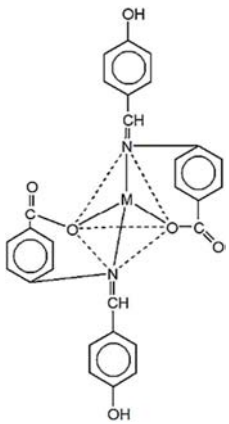


Figure 8. *Probable structure of the complexes. Here, M= Cu(II), Cd(II) and Zn(II).*

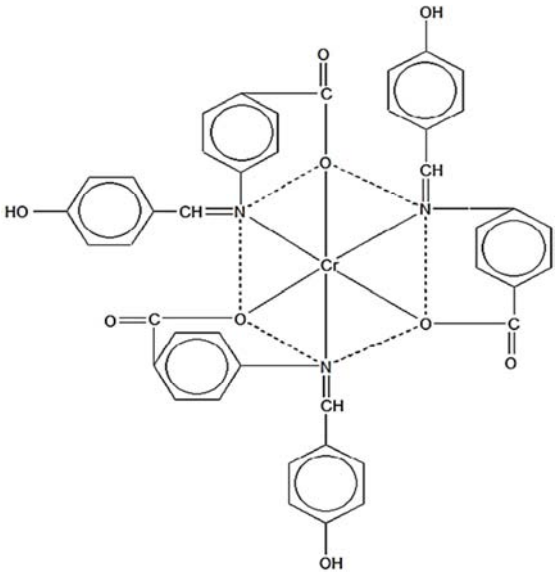


Figure 9. *Probable structure of Cr(III) complex.*

All the complexes and ligand were screened for their antibacterial activity against four pathogenic (two Gram-positive *Bacillus cereus* & *Streptococcus agalactiae* and two Gram-negative *Escherichia coli* & *Shigella dysenteriae*) bacteria. Cu(II) complex showed higher activity against *Escherichia coli* and *Streptococcus agalactiae* [24]. A new tridentate ONO donor Schiff base ligand derived from the condensation of 3-amino-2-methylquinazoline-4-one with 2-hydroxy-1-naphthaldehyde and its Cu(II), Ni(II), Co(II), Mn(II), Zn(II), and Cd(II) complexes were synthesized by *Kuruba Siddappa et al.* The ligand and its metal complexes evaluated for their antibacterial activity against *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* [25]. Synthetic route for the preparation of ligand *(figure-10)* and the Proposed structure of the complexes *(figure-11)* are given below.

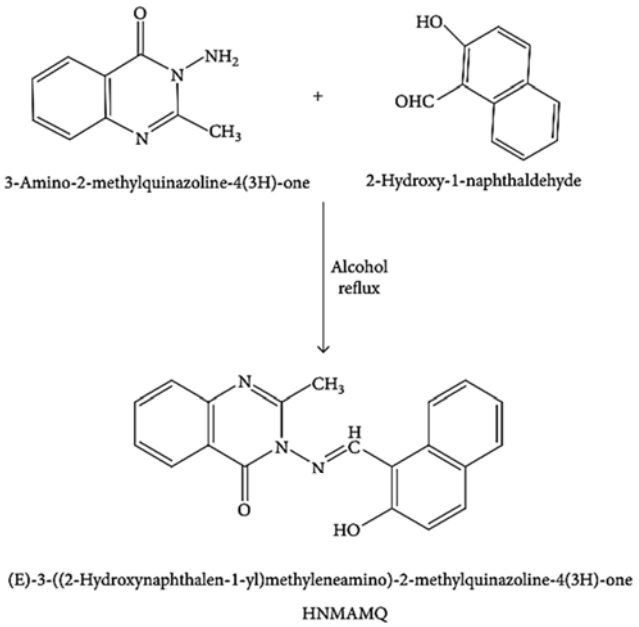
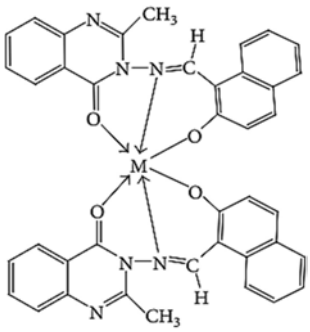


Figure 10. *Synthetic route for the preparation of ligand HNMAMQ.*



M = Cu(II), Ni(II), Co(II), and Mn(II)

Figure 11. *Proposed structures of Cu(II), Ni(II), Co(II), and Mn(II) complexes.*

Schiff base metal complexes of type $ML_2.(H_2O)_2$, (M= Mn, Fe, Co, Ni, and Cu) where the Schiff bases derived from some heterocyclic β-diketones with 4-phenyl-2-aminothiazole were synthesized by *A. S. Thakar et al.* All the compounds were tested for their antibacterial activity against *Escherichia coli, Bacillus subtilis* and *S. aureus* and the metal complexes showed moderate antibacterial activity [26]. *Ikechukwu P. Ejidike and Peter A. Ajibade* have synthesized Co(II), Ni(II), Cu(II), and Zn(II) complexes of (4*E*)-4-[(2-{(*E*)-[1-(2,4-dihydroxyphenyl)ethylidene]amino}ethyl)imino]pentan-2-one. The ligand and its metal complexes were tested against 6 bacteria strains consisting of three Gram-positive bacteria, namely, *Staphylococcus aureus*, *Streptococcus faecalis*, and *Bacillus cereus*, and three Gram-negative bacteria, namely, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Shigella flexneri*. In their antimicrobial studies Ciprofloxacin and Amoxicillin were used as the standard antibacterial agents [27]. New $[ML_2(H_2O)_2]$ complexes, where M = Co(II), Ni(II), Cu(II), and Zn(II) while L corresponds to the Schiff base ligand, which prepared by condensation of cefotaxime with salicylaldehyde were synthesized by *Aurora Reiss et al.* All the synthesized complexes and Schiff base were tested for *in vitro* antibacterial activity against some pathogenic bacterial strains, namely, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Bacillus subtilis,* and *Staphylococcus aureus* [28]. Biologically active nickel(II), copper(II) and zinc(II) chelates with thiazole derived nitro- and chloro-salicylaldehyde Schiff-bases having the same metal ion but different anions were synthesized by *Zahid H. Chohan.* In order to evaluate the antibacterial properties, these ligands and their synthesized metal chelates were screened against bacterial species *Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus* [29]. *Shahul Hameed Sukkur Saleem et al.* have synthesized a pyrimidine based Schiff base ligand (HL) and its four complexes of type $[MLOAc]\cdot nH_2O$ where M= Cu(II), Zn(II), Co(II) and Ni(II). Antimicrobial activities of HL and the complexes were screened against the four different bacteria *Staphylococcus aureus*, *Staphylococcus pneumonia*, *Salmonella enterica typhi* and *Haemophilus influenzae.* Sparfloxacin was used as the standard antibacterial agent [30]. Schiff base ligand, (1-((2-hydroxynaphthalen-1-yl)methyleneamino)-2-thioxo-4-

p-tolyl-1,2-dihydropyrimidin-5-yl)(p-tolyl)methanone (Hnafmmp) and its Ni(II), Pd(II), Pt(II), Cu(II), Co(II) complexes were prepared by *Halime Güzin Aslan et al.* The Ligand and its complexes were evaluated for their in vitro antibacterial activity. All the compounds displayed activity against *M. luteus*, *P. mirabilis*, *P. aeruginosa*, and *C. renale*. On the other hand, none of the compounds displayed activity against *E. aerogenes* and *S. epidermidis* bacteria. *E. aerogenes* and *S. epidermitis* are pathogenic bacterium. The Cu, Ni, Pt complexes and Hnafmmp generally seemed to be more active against Gram-positive bacteria. But, the Co and Pd complexes displayed poor activity against all Gram-positive and Gram-negative bacteria [31]. Two pyridine carboxaldehyde-derived Schiff bases and their copper, nickel and manganese complexes have been synthesized by *Selma Bal et al.* The ligands and complexes were screened for their antimicrobial activity against microorganisms *B. megaterium, K. pneumoniae, E. coli, P. aeruginosa, S. aureus, B. subtilis* and *E. aerogenes* [32]. Novel bioactive complexes of Co(II), Cu(II), Ni(II) and Zn(II) metal ions with Schiff base ligand derived from histidine and 1,3-indandione were synthesized by *V. Violet Dhayabaran et al.* The complexes were screened for their antibacterial activity against the selected bacterial strains of *Escherichia coli, Salmonella typhi, Salmonella sp., Bacillus subtilis* and *Vibrio cholerae.* Ciprofloxacin was chosen as standard for antibacterial activity [33]. *Ayla Balaban Gündüzalp and Hande Fecriye Özbay* have synthesized Schiff base; N, N'-bis-(2-hydroxy-1-naphthaldimine)-1,3-diaminopropanol (napdapOH) which reacts with metal chlorides to form dinuclear complexes of the type $[M_2L_2] \cdot nCl_2$ where M = Ni, Cu, Fe and $n = 0, 1$. The ligand and complexes were tested for their antibacterial activities against *Escherichia coli, Bacillus subtilis, Bacillus megaterium, Salmonella enteritidis and Staphylococcus aureus.* Schiff base has the highest activity against *Bacillus megaterium.* All of the complexes have a remarkable decrease in antibacterial activities than Schiff base [34]. *Narendra Kumar Chaudhary and Parashuram Mishra* have synthesized a series of three new metal(II) complexes of Schiff base from the novel ligand derived from Streptomycin and Amoxicillin in stoichiometric ratio. Antibacterial sensitivity of the ligand and its metal complexes were studied against four bacterial pathogens viz. *E. coli, B. subtilis, S. aureus* and *K. pneumonia* [35]. The Schiff bases, formed by condensation of 2-thiophenecarboxaldehyde with 2-aminothiophenol (LH) and propane-1,2-diamine (L_1), and their complexes of Ni(II), Cu(II), Zn(II) and Cd(II) have been synthesized by *Mohammad Nasir Uddin et al.* The Schiff bases and their metal complexes have been screened for their in vitro antibacterial activity against four human pathogenic bacteria such as Gram positive- *Bacillus cereus* and Gram negative- *Salmonella typhi*, *pseudomonas aeruginosa*, *Escherichia coli*. Ligands showed moderately whereas some of metal chelates showed highly antibacterial activity against them [36]. Macrocyclic complexes of Cu(II), Ni(II), Co(II) and Zn(II) of a tetradentate Schiff base ligand derived from 3-benzalideneacetoacetanilide and N-(2-aminoethyl)-1,3-propanediamine were synthesized by *N. Raman et al.* The investigated compounds were screened for their antibacterial activity against the bacteria *E. coli*, *S. aureus*, *S. typhi*, and *K. pneumoniae* [37]. Complexes of Co(II), Ni(II) and Cu(II) with the Schiff base derived from ceftazidime and salicylaldehyde were synthesized by *Aurora Reiss et al.* The *in vitro* biological screening effects of the investigated compounds were tested against some selected Gram-negative and Gram-positive bacterial strains, viz. *Escherichia coli, Klebsiella pneumoniae, Bacillus subtilis* and *Staphylococcus aureus* [38]. A tetradentate Schiff base *(figure-12)* derived from the reaction of malonyl hydrazide with dehydroacetic acid in ethanol under refluxing condition and its complexes *(figure-13)* of Cu(II), Ni(II), Co(II), Mn(II), Zn(II) metal ion were synthesized by *R. P. Saini et al.*

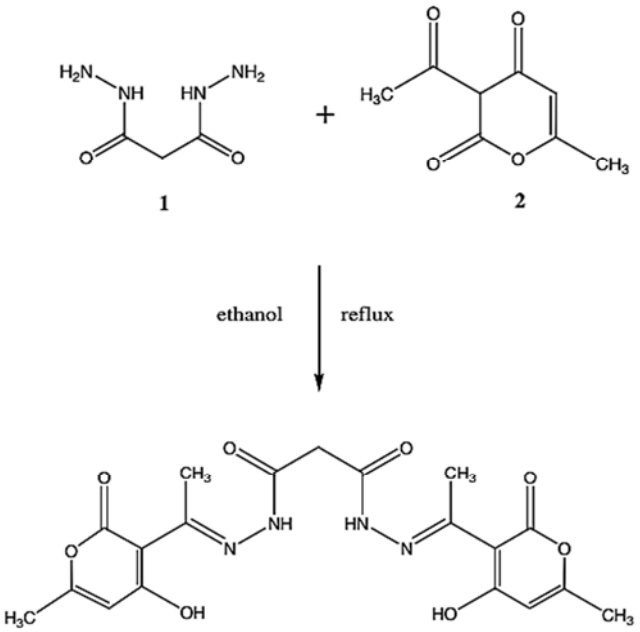
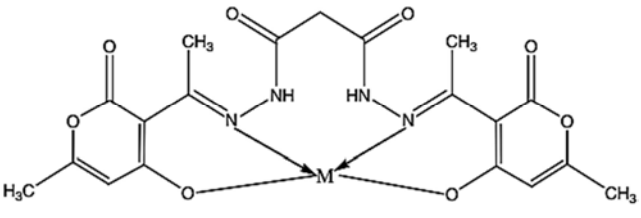


Figure 12. *Synthesis of a Schiff base.*

N, N'-bis(1-(4-hydroxy-6-methyl-2-oxo-2H-pyran-3-yl)ethylidene)malonohydrazide



$M = Cu^{2+}, Ni^{2+}, Co^{2+}, Mn^{2+}$, and Zn^{2+}.

Figure 13. *Proposed structure of synthesized metal complexes.*

The antibacterial activity of synthesized Schiff base and its metal complexes have been studied by the agar well diffusion method using dimethylformamide (DMF) as a solvent against various bacterial pathogenic strains such as *Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae,* and *Enterococcus* [39].

2.2. Antifungal Activity

Antifungal agents are active against fungi, they used to prevent fungal growth. The complexes of the type ML_2 [where M = Cu(II), Co(II), and Ni(II)], L= 1-phenyl-1-ene-3-(2-hydroxyphenyl)-prop-2-ene with 3-substituted-5-mercapto-4-amino-1,2,4-triazoles were synthesized by *S.D. Angadi et al.* The synthesized ligands and its complexes were screened for their antifungal activity against *A. niger* and *A. flavous.* The standard drug chlotrimazole was also tested for their antifungal activity. The antifungal activity results exposed that the ligands and its complexes have exhibited weak to good activity against *A. niger* and *A. flavous*. The ligand and its Cu(II) and Co(II) complexes showed weak activity when compared to the standard drug chlotrimazole [40]. *C. Anitha et al.* have synthesized a series of metal(II) complexes ML [where M= VO(II), Co(II), Ni(II), Cu(II), and Zn(II)] from azo Schiff base ligand (N'E)-N'-(5-((4-chlorophenyl)diazenyl)-2-hydroxybenzyliden e)-2 hydroxybenzohydrazide. The synthetic rout of Schiff base *(figure-14)* and proposed structure of its Cu complex *(figure-15)* are given below.

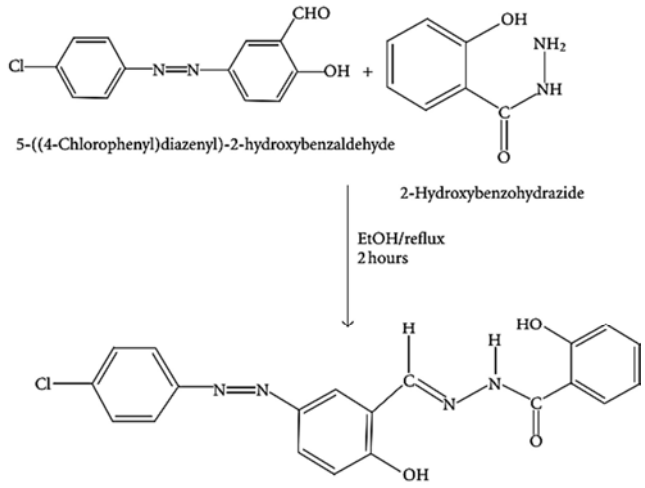


Figure 14. *Synthesis of ligand (CDHBHZ).*

(*N'E*)-*N'*-(5-((4-Chlorophenyl) diazenyl)-2-hydroxybenzylidene)-2-Hydroxybenzohydrazide [CDHBHZ]

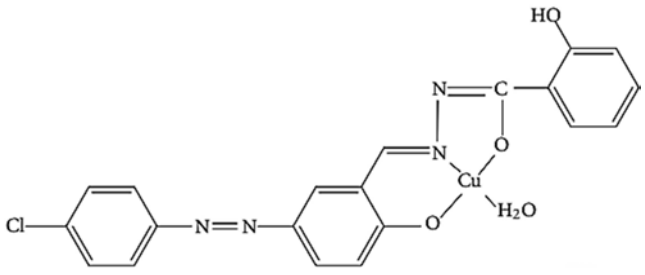


Figure 15. *Proposed structure of Cu(II) complexes.*

The biological activities of synthesized azo Schiff base and their metal complexes have been studied for their antifungal activities against *Aspergillus niger, Candida albicans,* and *Rhizoctonia bataticola.* Also, standard antifungal drug nystatin was used for comparison [41]. *M. M. Haque et al.* have synthesized Copper(II) complexes containing two Schiff base ligands derived from 2-hydroxybenzaldehyde with 2-aminophenol and 3-aminophenol. The Schiff bases and complexes were tested for their antifungal activity against *Aspergillus niger, Tinea pedis* and *Coniothyrium sp*. [42]. *B.P. Yadav et al.* have synthesized a series of Schiff base macrocyclic complexes *(figure-16)* of the type $[HLMX_2]$ where M = Cu(II), Ni(II), Co(II) and X = Cl, OAc and L= The Schiff base, derived from the condensation of acetylacetone and thiocarbohydrazide (2:2) in the presence of divalent metal salt in methanolic medium.

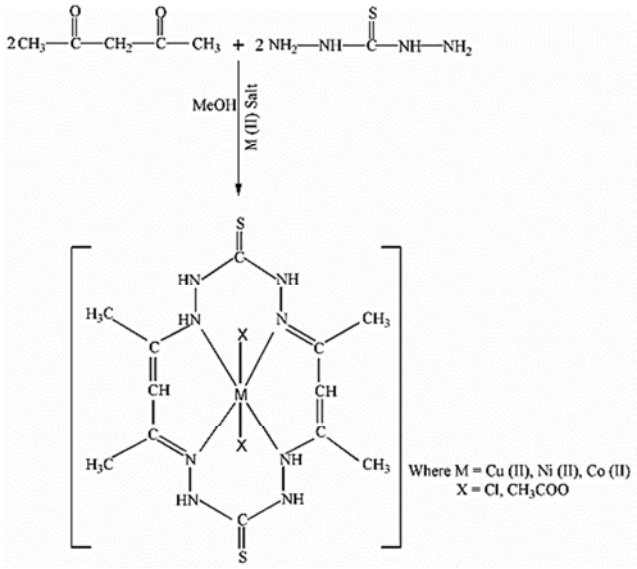


Figure 16. *Scheme for synthesis of novel macrocyclic metal complexes.*

The free ligand, its metal complexes, fungicide fluconazole and the control DMSO (dimethylsulfoxide) were screened for their antifungal activity against various fungi *viz*. *Rizoctonia* sp*., Aspergillus* sp. *and penicillium* sp. [43]. *H.B. Singh et al.* have synthesized the monofunctional bidentate Schiff base ligand (*o*-vanillin) *p*-chloroaniline and its four new complexes of Cr(III), Co(II), Ni(II) and Cu(II) transition metal ion by classical thermal and microwave-irradiated techniques. Antifungal activities of the ligand and its complexes were evaluated against two pathogenic fungi, *Aspergillus nigre* and *Fusarium oxysporum* [44]. A pyrimidine based Schiff base ligand (HL) *(figure-17)* and its four complexes *(figure-18)* of type $[MLOAc]\cdot nH_2O$ where M= Cu(II), Zn(II), Co(II) and Ni(II) were synthesized by *Shahul Hameed Sukkur Saleem et al.*

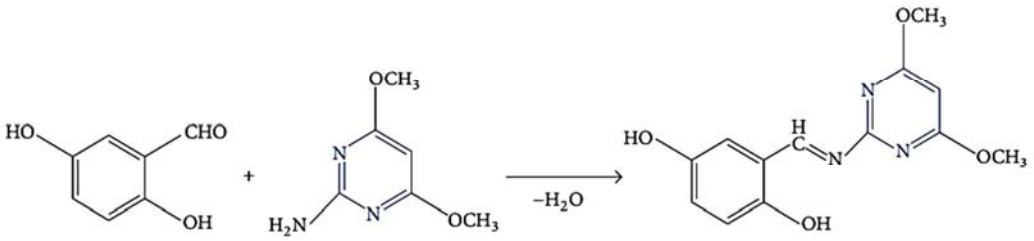


Figure 17. *Synthetic route of ligand (HL).*

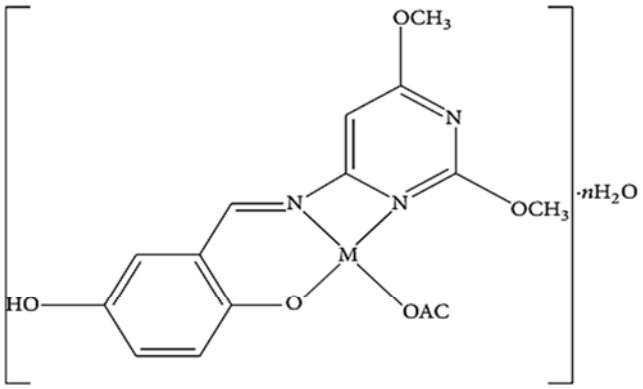


Figure 18. *Proposed structure of complexes.*

The antifungal activities of ligand (HL) and complexes were screened against two different fungi, *Aspergillus flavus (A. flavus)* and *Aspergillus niger (A. niger)* strains & ketoconazole was used as standard drug [30]. The condensation product of 4-acetyl-3-methyl-1-phenylpyrazol-5-ones (mainly exists as the 3-methyl-1-phenyl-4-acetylpyrazolin-5-ol tautomer) with 1,2-diaminobenzene, and 2-aminophenol resulted in ONN-and ONO-type tridentate ligands & their transition metal complexes of VO(II), Cu(II), Fe(III), and Co(II) were synthesized by *Ramasamy Jayarajan et al.* The complexes tested for antifungal activity against *C. albicans, Rhizopus sp., and A. niger* compared to the ligands and showed enhanced antifungal activity [45]. *Praveen S. Mane et al.* have synthesized the solid complexes of Cu(II), Ni(II), Co(II), Mn(II) and Fe(III) with Schiff base ligands derived from heterocyclic compounds 3-acetyl-6-methyl-(2*H*)-pyran-2,4(3*H*)-dione (Dehydroacetic acid) and *o*-chloroaniline. The ligand and the corresponding metal complexes were studied against *Aspergillus niger* to evaluate their antifungal activity [46]. Two new series of copper(II) and nickel(II) complexes with two new Schiff base ligands 2-((2,4-dimethylphenylimino)methyl)-6-methoxy-4-nitrophe nol and 2-((3,4-difluorophenylimino) methyl)-6-methoxy-4-nitrophenol were synthesized by *K. R. Joshi et al.* The Schiff base ligands and their metal complexes were tested for antifungal activity against fungus *Candida albicans, Aspergillus niger,* and *Aspergillus clavatus.* Nystatin and Griseofulvin were also used as standard drugs [47]. A series of cobalt, nickel, copper, and zinc complexes of bidentate Schiff bases derived from the condensation reaction of 4-amino-5-mercapto-3 methyl/ethyl-1,2,4-triazole with 2,4-dichlorobenzaldehyde were synthesized by *Kiran Singh et al.* The synthesized Schiff bases and their metal complexes were screened for antifungal activities against *Aspergillus niger and A. flavus*. The metal complexes exhibited significantly enhanced antifungal activity than their simple Schiff bases [48]. *R. B. Sumathi and M. B. Halli* were synthesized A new Schiff by the condensation of naphthofuran-2-carbohydrazide and diacetylmonoxime. The Schiff base transition metal complexes of Co(II), Ni(II), Cu(II), Cd(II), and Hg(II) ion were also prepared. Antifungal activity of the Schiff base and its complexes were tested against *Aspergillus niger*, *Aspergillus flavus*, *Cladosporium oxysporum* and *Candida albicans* fungi, here also Fluconazole was used as the standard drug [49]. The Schiff base ligand (E)-2-(3-(2-imino-1-methylimidazolidin-4-ylidene)-1-methyl guanidino) acetic acid (L) and its Cr(III), Co(II), Ni(II), and Cu(II) complexes were synthesized by *Ahmed A. Al-Amiery.* Antifungal screening effects of the ligand and complexes were evaluated against *Aspergillus niger* and *Candida albicans* [50]. Metal complexes of the type $[NiL_2Cl_2].H_2O$ and ML_2Cl_2 [M = Co(II), Cu(II), Cd(II), Zn(II), and Hg(II)] where L = Schiff base, derived from condensation of naphthofuran-2-carbohydrazide and 2-chloro-3-formylquinoline were synthesized by *M. B. Halli & R. B. Sumath.* All the compounds were tested for their antifungal activity against *A. flavus, A. niger, C. oxysporum,* and *C. albicans* [51]. *A. P. Mishra et al.* have synthesized the coordination complexes of VO(II), Co(II), Ni(II) and Cu(II) with the Schiff bases derived from 3-bromobenzaldehyde/3-chlorobenzaldehyde with 2-aminophenol. The biological screening effects of the investigated compounds were tested against fungi *Aspergillus niger, Trichoderma polysporum* and *Candida albicans* by serial dilution method [52]. *Natarajan Raman et al.* have synthesized Neutral tetradentate chelate complexes of Cu(II), Ni(II), Co(II), Mn(II), Zn(II) and VO(II) in EtOH using Schiff bases derived from acetoacetanilido-4-aminoantipyrine and 2-aminophenol/2 aminothiophenol. The antifungal activity of the investigated compounds was tested against fungi *Aspergillus niger* and *Rhizoctonia bataicola*. Most of the metal chelates have higher antifungal activity than the free ligands [53]. A novel tetradentate N_2O_2 type Schiff base, derived from 1-phenyl-2,3-dimethyl-4-aminopyrazol-5-one(4-aminoantipy rine) and 3-salicylidene-acetylacetone, and its stable

complexes with transition metal ions such as Cu(II), Ni(II), Co(II) and Zn(II) were synthesized by *Natarajan Raman et al.* The antifungal activities of the investigated compounds were tested against fungi like *Aspergillus niger* and *Rhizoctonia bataicola* [54]. A series of metal complexes of the type ML_2H_2O [M = Co(II), Ni(II), and Cu(II)] where L= Schiff bases *(figure-19)* derived from 1,8-diaminonaphthalene and 8-formyl-7-hydroxy-4-methylcoumarin/8-acetyl-7-hydroxy-4 -methylcoumarin were synthesized by *Sangamesh A. Patil et al.* Structure of metal complexes are shown in *(figure-20)*.

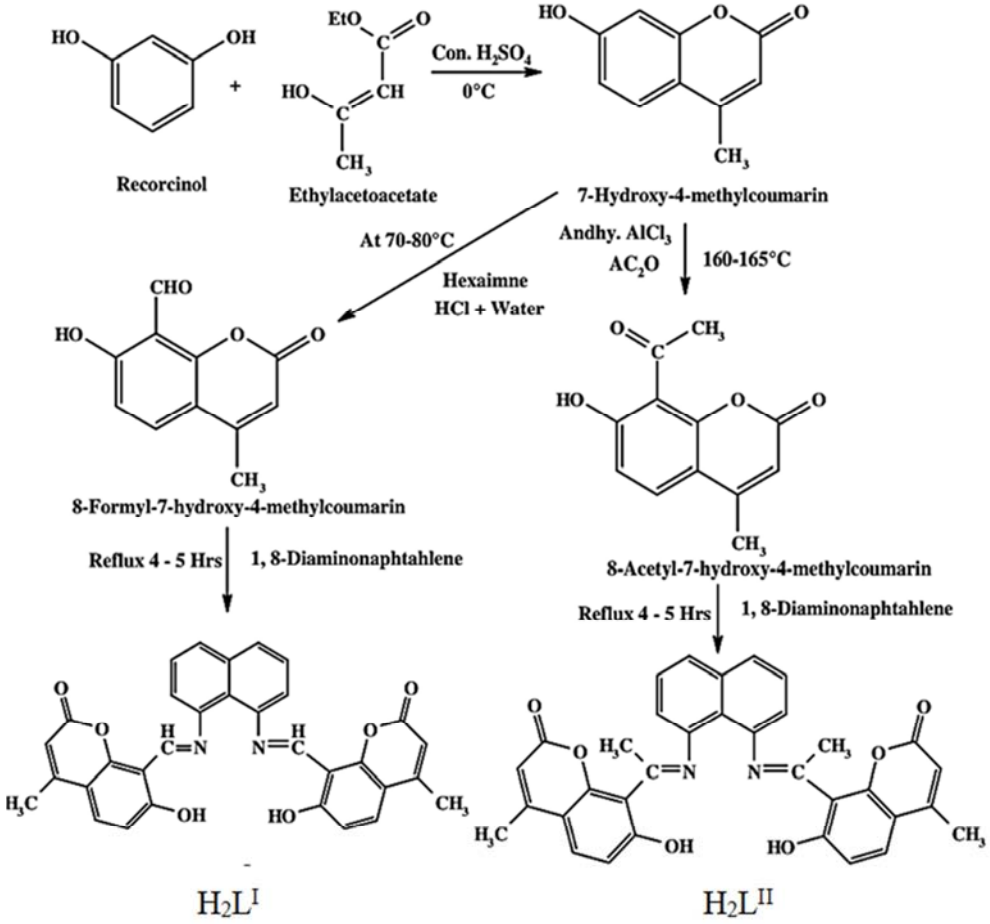


Figure 19. *Synthesis of Schiff bases H_2L^I and H_2L^{II}.*

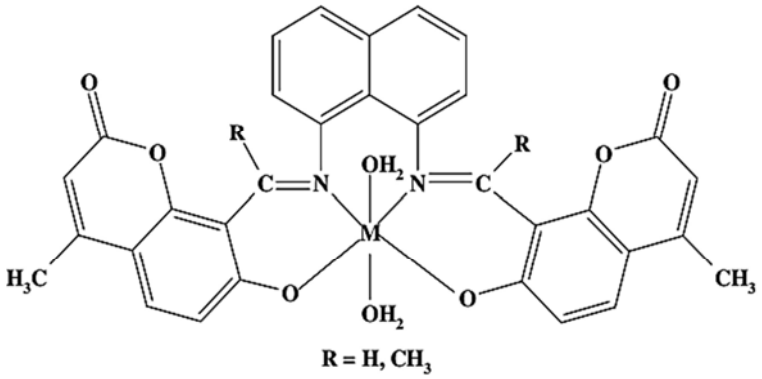


Figure 20. *Structure of metal complexes, M = Co(II), Ni(II) and Cu(II).*

The Schiff bases and their complexes have been screened for their antifungal activities against *Aspergillus niger, Aspergillus flavus,* and *Cladosporium.* The results of the studies show the metal complexes to be more effective antifungal as compared with the uncomplexed coumarins [55]. A Schiff base ligand(L) derived from 4-aminoantipyrine, 3-hydroxy-4-nitrobenzaldehyde and o-phenylenediamine and its metal complexes of Cu(II), Ni(II), Co(II), Mn(II), Zn(II), VO(IV), Hg(II) & Cd(II) were synthesized by *N Raman et al.* The antifungal activities of the compounds were evaluated by the well-diffusion method against the fungi viz., *Aspergillus niger, Aspergillus flavus* and *Rhizoctonia bataicola.* Among

all the metal complexes, Cu complex exhibited relatively higher antifungal activity than the others [56]. *N. Raman and A. Selvan* have synthesized two novel Schiff bases, 4,4'-methylenedianilidene-bis(3-methoxy-4-hydroxy-benzaldehyde) (L) and 4,4'-methylenedianilidene-bis(3,4-dimethoxybenzaldehyde) (L), by condensing 4,4'-methylenedianiline (MDA) with vanillin and 3,4-dimethoxybenzaldehyde (DMB) respectively in ethanolic medium. Metal complexes of the above Schiff bases were prepared from salts of Cu(II), Zn(II), Co(II) and VO(IV). The Schiff bases and their metal complexes were evaluated for their antifungal activities against different species of pathogenic fungi such as *Aspergillus niger, Aspergillus flavus, Rhizopus stolonifer, Candida albicans* and *Rhizoctonia bataicola*. Also, their results were compared with the standard drug Nystatin [57].

2.3. DNA Interaction Studies

Five new Cu(II) complexes derived from the condensation between 5-bromosalicylaldehyde (bs) and α-amino acids (L-alanine, L-phenylalanine, L-aspartic acid, L-histidine and L-arginine) were synthesized and characterized by *Ahmed M. Abu-Dief and Lobna A. E. Nassr* [58]. The Schiff bases and their Cu(II) complexes were tested in vitro for their antibacterial activity against two Gram-positive bacteria (*Micrococcus luteus* and *Bacillus cereus*) and one Gram-negative bacteria (*Pseudomonas aeruginosa*). All the complexes showed activity against the organisms more than the free Schiff base ligands and the activity increases with the increase in concentration of test solution containing the new complexes. The interaction of the prepared Schiff base amino acid Cu(II) complexes with calf thymus DNA has been investigated by absorption spectra, viscosity and gel electrophoresis measurement and the mode of CT-DNA binding to the complexes were shown moderate to strong binding property as well. *Mohan N. Patel et al.* [59] were synthesized Cu(II) complexes containing N, O donor ligand and ciprofloxacin. The complexes were screened for their antimicrobial activity against Gram(+Ve), i.e. *Staphylococcus aureus*, *Bacillus subtilis*, and Gram(−Ve), i.e. *Serratia marcescens*, *Pseudomonas aeruginosa* and *Escherichia coli*, microorganisms in terms of minimum inhibitory concentration and colony-forming unit. The interaction of the prepared Cu(II) complexes has been investigated with Herring Sperm DNA. Copper(II), zinc(II) and nickel(II) complexes containing novel Schiff-base ligand, hesperetin-2- hydroxy benzoyl hydrazone have been synthesized by *Yong Li and et al*. [60]. DNA binding properties of the ligand and its metal complexes have been investigated by electronic absorption spectroscopy, fluorescence spectra, ethidium bromide displacement experiments, iodide quenching experiments, salt effect and viscosity measurements. Results reveled that all the compounds bind to DNA via an intercalation binding mode. Cu(II), Ni(II), and Zn(II) complexes containing two new Schiff base-hydrazones bearing furan ring, (Z)-4-butoxy-N-(furan-2-ylmethylene)benzohydrazide(IV) and (Z)-N-(furan-2-ylmethylene)-4-(hexyloxy)-benzohydrazide have been synthesized by *Cansu Gokce and et al.* [61]. The DNA-binding and DNA-cleavage activities of both arylhydrazone ligands and their transition metal complexes were examined using UV-VIS titration and agarose gel electrophoresis in the presence of an oxidative agent (H_2O_2). The results indicate that the copper complexes bind significantly to calf thymus DNA and effectively cleave pBR322 DNA whereas the nickel and zinc complexes interact slightly with DNA. Copper(II) and Zinc(II) complexes containing Schiff base, 2-methoxy-6((E)-(phenylimino) methyl phenol ligand were synthesized and characterized by *Parirokh Lavaee et al.* [62]. The Cu(II) complexes showed prominet DNA binding activity. *M.P. Kesavan et al.* [63] were prepared Cu(II) complexes and tested CT-DNA binding activity. *S. B. Moosun et al.* were synthesized four Cu(II) complexes containing Schiff base ligand derived from a disulfide N,N'-(1,10-dithio-bis(phenylene))-bis(salicylideneimine). The interactions of the Schiff base Cu(II) complexes with DNA were investigated by UV– visible and fluorescence spectroscopies and agarose gel electrophoresis. The binding constants were in the order 10^{-3}–10^{-5} M suggesting moderate binding affinity of the complexes toward CT-DNA [64]. *Qinghua Zhou and Pin Yang* were synthesized Cu(II) complex containing lignad [N,N,N',N'-tetrakis [(2-benzimidazolyl)methyl]-1,3-diaminopropane). The interaction of the complex with DNA has been investigated using equilibrium dialysis, UV spectra, fluorescent spectra, and gel electrophoresis. The results show that the Cu(II) complex can electrostatically bind to the phosphate group of DNA backbone, and partially intercalate into the double helix of DNA because of the bulky structure of the complex and the planarity of the benzimidazole rings [65].

3. Conclusion

Schiff bases and their metal complexes are one of the most important chemical classes of compounds having a common integral feature of a variety structural diversity and of active medicinal agents. This review reflects the contribution of Schiff bases to the design and development of novel lead having potential biological activities. The present paper is an attempt to review of important biological activity reported for Schiff bases and their metal complexes over the past few decades. In this review we have explored the various synthesis routes of Schiff bases and their Cu(II) metal complexes also antibacterial, antifungal and DNA interaction activity studies.

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Conflict of Interest

The authors have no conflict of interest to publish the article.

References

[1] B. Lakshmi, K. N. Shivananda, G. A. Prakash, K. R. K. Rama and K. N. Mahendra, "Synthesis of Co(II), Ni(II) and Cu(II) Complexes from Schiff base Ligand and Reactivity Studies with Thermosetting Epoxy Resin", Bull. Korean Chem. Soc., 2011, 32 (5): 1613 1619.

[2] A. Alim, M. Kudrat-E-Zahan, M. M. Haque, M. T. H. Tarafder, "Synthesis and Characterization of Some Metal Complexes of Cu(II), Ni(II), Zn(II), Cd(II), Sn(II), Co(II), Sb(III) and Fe(III) Containing Bidentate Schiff Base of Smdtc", Science Journal of Chemistry., 2014; 3 (3): 35-39.

[3] L. Cheng, J. Tang, H. Luo, X. Jin, F. Dai, J. Yang, Y. Qian, X. Li, and B. Zhou, "Antioxidant and antiproliferative activities of hydroxyl-substituted Schiff bases", Bioorg. Med. Chem. Lett., 2010; 20: 2417-2420.

[4] M. S. Hossain, S. Sarker, A. S. M. Elias Shaheed, M. M. Hossain, A. Alim-Al-Bari, M. R. Karim, C. M. Zakaria, M. Kudrat-E-Zahan, "Thermal and Spectral Characterization of Cr(III), Co(II) and Cd(II) Metal Complexes Containing Bis-Imine Novel Schiff Base Ligand Towards Potential Biological Application", Chemical and Biomolecular Engineering, 2017; 2 (1): 41-50.

[5] G. T. Rahman, M. Kudrat-E-Zahan, M. M. Haque, M. M. Alam, M. A. Farooque, "Structural Analysis of Newly Synthesized NO Donor Schiff Base Complexes of Cu(II), Ni(II), Co(II) and Fe(III) Metal Ions by Conventional Method", Science Journal of Chemistry, 2015; 3 (6): 91-94.

[6] S. V. Rathod, S. S. Giri and S. D. Maind, "Synthesis, Spectral Characterization and Antimicrobial Studies of Copper(II) Complex Containing Mixed Ligands Nitrogen-Oxygen Donor Schiff Base (4-Bromo-(2-carboxyphenyl)-pyridine-2-yl ethylene amine) and 2,2' bipyridine", world journal of pharmaceutical research, 2016; 5 (3): 702-707.

[7] R. Katwal, H. Kaur and B. K. Kapur, "Applications of Copper-Schiff's Base Complexes: A Review", Sci. Revs. Chem. Commun., 2013; 3 (1): 1-15.

[8] M. S. Hossain, C. M. Zakaria, M. Kudrat-E-Zahan, "Metal Complexes as Potential Antimicrobial Agent: A Review", American Journal of Heterocyclic Chemistry, 2018; 4 (1): 1-21.

[9] N. Raman, S. Sobha, L. Mitu, "Synthesis, structure elucidation, DNA interaction, biological evaluation, and molecular docking of an isatin-derived tyramine bidentate Schiff base and its metal complexes", Monatsh Chem., 2012; 143: 1019–1030.

[10] M. M. Hossain, M. A. Bashar, M. N. Khan, P. K. Roy, M. A. Mannan, M. S. Ali, M. A. Farooque, "Physical and Spectral Characterization of Ni(II), Cu(II), Co(II) and Cd(II) Complexes with Schiff Base of Salicylaldehyde and 2- Aminopyridine Towards Potential Microbial Application", American Journal of Applied Chemistry, 2018; 6 (4): 147-155.

[11] J. A. Shampa, M. R. Islam, M. S. Hossain, G. T. Rahman, C. M. Zakaria, M. Kudrat-E-Zahan, "Physiochemical & Antibacterial Activity Investigation on Noble Schiff Base Cu(II) Complex", American Journal of Heterocyclic Chemistry, 2017; 3 (4): 37-41.

[12] Z. H. Chohan, M. F. Jaffery and C. T. Supuran, "Antibacterial Co(II), Cu(II), Ni(II) and Zn(II) Complexes of Thiadiazoles Schiff Bases", Metal Based Drugs, 2001; 8 (2): 95-101.

[13] N. K. Chaudhary and P. Mishra, "Spectral Investigation and In Vitro Antibacterial Evaluation of Ni(II) and Cu(II) Complexes of Schiff Base Derived from Amoxicillin and α-Formylthiophene (αft)", Journal of Chemistry, 2015; 12 pages.

[14] K. S. Panday, A. S. Thakar, K. K. Singh, K. T. Joshi, and A. M. Pancholi, "Synthesis, Characterization and Antibacterial Activity of Schiff Bases and their Metal Complexes Derived from 4-Acyl-1-phenyl-3-methyl-2-pyrazolin-5-ones and 2-Amino-4(4' methylphenyl) thiazole", E-Journal of Chemistry, 2010; 7 (4): 1396-1406.

[15] S. N. Kotkar and H. D. Juneja, "Synthesis, Characterization, and Antimicrobial Studies of N, O Donor Schiff Base Polymeric Complexes", Journal of Chemistry, 2013; 5 pages.

[16] C. A. Bolos, G. S. Nikolov, L. Ekateriniadou, A. Kortsaris and D. A. Kyriakidis, "Structure-Activity Relationships for Some Diamine, Triamine and Schiff Base Derivatives and their Copper (II) Complexes", Metal-Based Drugs, 1998; 5 (6): 323-332.

[17] Z. H. Chohan and S. Kausar, "Synthesis, Characterization and Biological Properties of Tridentate NNO, NNS and NNN Donor Thiazole Derived Furanyl, Thiophenyl", Metal-Based Drugs, 2000; 7 (1): 17-22.

[18] K. S. Kumar, V. K. Chityala, N. J. P. Subhashini, Y. Prashanthi and Shivaraj, "Synthesis, Characterization, and Biological and Cytotoxic Studies of Copper(II), Nickel(II), and Zinc(II) Binary Complexes of 3-Amino-5-methyl Isoxazole Schiff Base", ISRN Inorganic Chemistry, 2013; 7 pages.

[19] R. Rajavel, M. Senthil, Vadivu and C. Anitha, "Synthesis, Physical Characterization and Biological Activity of Some Schiff Base Complexes", E-Journal of Chemistry, 2008; 5 (3): 620-626.

[20] Z. H. Chohan, A. Munawar and C. T. Supuran, "Transition Metal ion Complexes of Schiff-Bases. Synthesis, Characterization and Antibacterial Properties", Metal Based Drugs, 2001; 8 (3): 137-143.

[21] A. K. Mapari, M. S. Hate and K. V. Mangaonkar, "Synthesis, Characterization and Antimicrobial Activity of Mixed Schiff Base Ligand Complexes of Co(II), Ni(II), Cu(II) and Zn(II)", E-Journal of Chemistry, 2011; 8 (3): 1258-1263.

[22] P. Jogi, K. Mounika, M. Padmaja, M. Lakshmi and C. Gyanakumari, "Synthesis, Characterization and Antibacterial Studies of Some Transition Metal Complexes of a Schiff Base Derived from 2-(Aminomethyl)-benzimidazole and Thiophene-2-carbaxaldehyde", E-Journal of Chemistry, 2011; 8 (4): 1662-1669.

[23] Z. H. Chohan, M. Praveen and A. Ghaffar, "Structural and Biological Behaviour of Co(II), Cu(II) and Ni(II) Metal Complexes of Some Amino Acid Derived Schiff-Base Ligands", Metal Based Drugs, 1997; 4 (5): 267-272.

[24] M. M. Hossain, M. A. Bashar, M. N. Khan, P. K. Roy, M. S. Ali, M. A. Farooque, "Preparation, Physical Characterization and Antibacterial Activity of Ni(II), Cu(II), Co(II), Cd(II), Zn(II) and Cr(III) Schiff Base Complex Compounds", Science Journal of Chemistry, 2018; 6 (2): 17-23.

[25] K. Siddappa, S. B. Mane and D. Manikprabhu, "Spectral Characterization and 3D Molecular Modeling Studies of Metal Complexes Involving the O, N-Donor Environment of Quinazoline-4(3H)-one Schiff Base and Their Biological Studies", The Scientific World Journal, 2014; 13 pages.

[26] A. S. Thakar, K. S. Pandya, K. T. Joshi & A. M. Pancholi, "Synthesis, Characterization and Antibacterial Activity of Novel Schiff Bases Derived from 4-Phenyl-2-aminothiazole and their Mn(II), Fe(II), Co(II), Ni(II) and Cu(II) Metal complexes", E-Journal of Chemistry, 2011; 8 (4): 1556-1565.

[27] I. P. Ejidike and P. A. Ajibade, "Synthesis, Characterization, Antioxidant, and Antibacterial Studies of Some Metal(II) Complexes of Tetradentate Schiff Base Ligand: (4E)-4-[(2-{(E)-[1-(2,4-Dihydroxyphenyl)ethylidene]amino}ethyl)imino]pentan-2-one", Bioinorganic Chemistry and Applications, 2015; 9 pages.

[28] A. Reiss, M. C. Chifiriuc, E. Amzoiu and C. I. Spînu, "Transition Metal(II) Complexes with Cefotaxime-Derived Schiff Base: Synthesis, Characterization, and Antimicrobial Studies", Bioinorganic Chemistry and Applications, 2014; 17 pages.

[29] Z. H. Chohan, "Biologically Active Transition Metal Chelates of Ni(II), Cu(II) and Zn(II) with 2-Aminothiazole-Derived Schiff-Base Ligands Their Synthesis, Characterization and The Role of Anions (NO_3^-, SO_4^{2-}, $C_2O_4^{2-}$ and CH_3CO^{2-}) on Their Antibacterial Properties", Metal-Based Drugs, 1999; 6 (3): 187-192.

[30] S. H. S. Saleem, M. Sankarganesh, P. R. A. Jose, K. Sakthikumar, L. Mitu and J. D. Raja, "Investigation of Antimicrobial, Antioxidant, and DNA Binding Studies of Bioactive Cu(II), Zn(II), Co(II), and Ni(II) Complexes of Pyrimidine Derivative Schiff Base Ligand", Journal of Chemistry, 2017; 8 pages.

[31] H. G. Aslan, S. Akkoç, Z. Kökbudak, L. Aydın, "Synthesis, characterization, and antimicrobial and catalytic activity of a new Schiff base and its metal(II) complexes", J. Iran Chem. Soc., 2017; 14: 2263–2273.

[32] S. Bal, B. Orhan, J. D. Connolly, M. Dıgrak and S. Koytepe, "Synthesis and characterization of some Schiff bases, their metal complexes and thermal, antimicrobial and catalytic features", J Therm Anal Calorim, 2015; 9 pages.

[33] V. V. Dhayabaran, T. D. Prakash, R. Renganathan, E. Friehs and D. W. Bahnemann, "Novel Bioactive Co(II), Cu(II), Ni(II) and Zn(II) Complexes with Schiff Base Ligand Derived from Histidine and 1,3-Indandione: Synthesis, Structural Elucidation, Biological Investigation and Docking Analysis", J Fluoresc, 2016; 16 pages.

[34] A. B. Gündüzalp and H. F. Özbay, "The Synthesis, Characterization and Antibacterial Activities of Dinuclear Ni(II), Cu(II) and Fe(III) Schiff Base Complexes", Russian Journal of Inorganic Chemistry, 2012; 57 (2): 257–260.

[35] N. K. Chaudhary and P. Mishra, "In Vitro Antimicrobial Screening of Metal Complexes of Schiff Base derived from Streptomycin and Amoxicillin: Synthesis, Characterization and Molecular Modelling", American Journal of Applied Chemistry, 2014; 2 (1): 19-26.

[36] M. N. Uddin, D. A. Chowdhury, M. M. Rony, M. E. Halim, "Metal Complexes of Schiff Bases Derived from 2-Thiophenecarboxaldehyde and Mono/Diamine as the Antibacterial Agents", Modern Chemistry, 2014; 2 (2): 6-13.

[37] N. Raman, S. J. Raja, J. Joseph, and A. Sakthivel, "Designing, Structural Elucidation, Comparison of DNA Cleavage, and Antibacterial Activity of Metal(II) Complexes Containing Tetradentate Schiff Base", Russian Journal of Coordination Chemistry, 2008; 34 (11): 842–848.

[38] A. Reiss, M. C. Chifiriuc, E. Amzoiu, N. Cioatera, I. Dabuleanu and P. Rotaru, "New metal(II) complexes with ceftazidime Schiff base", J Therm Anal Calorim, 2018; 131: 2073–2085.

[39] R. P. Saini, V. Kumar, A. K. Gupta and G. K. Gupta, "Synthesis, characterization, and antibacterial activity of a novel heterocyclic Schiff's base and its metal complexes of first transition series", Med. Chem. Res., 2014; 23: 690–698.

[40] V. Reddy, N. Patil and S. D. Angadi, "Synthesis, Characterization and Antimicrobial Activity of Cu(II), Co(II) and Ni(II) Complexes with O, N, and S Donor Ligands", E-Journal of Chemistry, 2008; 5 (3); 577-583.

[41] C. Anitha, S. Sumathi, P. Tharmaraj and C. D. Sheela, "Synthesis, Characterization, and Biological Activity of Some Transition Metal Complexes Derived from Novel Hydrazone Azo Schiff Base Ligand", International Journal of Inorganic Chemistry, 2011; 8 pages.

[42] M. M. Haque, M. Kudrat-E-Zahan, L. A. Banu, M. Shariful Islam, and M. Saidul Islam, "Synthesis and Characterization with Antineoplastic, Biochemical, Cytotoxic, and Antimicrobial Studies of Schiff Base Cu(II) Ion Complexes", Bioinorganic Chemistry and Applications, 2015; 7 pages.

[43] G. Kumar, A. Kumar, N. Shishodia, Y. P. Garg and B. P. Yadav, "Synthesis, Spectral Characterization and Antimicrobial Evaluation of Schiff Base Cu(II), Ni(II) and Co(II) Novel Macrocyclic Complexes", E-Journal of Chemistry, 2011; 8 (4): 1872-1880.

[44] K. Rathore, R. K. R. Singh and H. B. Singh, "Structural, Spectroscopic and Biological Aspects of O, N- Donor Schiff Base Ligand and its Cr(III), Co(II), Ni(II) and Cu(II) Complexes Synthesized through Green Chemical Approach", E-Journal of Chemistry, 2010; 7 (S1): S566-S572.

[45] R. Jayarajan, G. Vasuki, and P. S. Rao, "Synthesis and Antimicrobial Studies of Tridentate Schiff Base Ligands with Pyrazolone Moiety and Their Metal Complexes", Organic Chemistry International, 2010; 7 pages.

[46] P. S. Mane, S. M. Salunke and B. S. More, "Synthesis and Structural Studies of Transition Metal Complexes with Bidentate Schiff Base Derived from 3-Acetyl-6-methyl-(2H)-pyran-2,4(3H)-dione", E-Journal of Chemistry, 2011; 8 (S1): S245-S252.

[47] K. R. Joshi, A. J. Rojivadiya, and J. H. Pandya, "Synthesis and Spectroscopic and Antimicrobial Studies of Schiff Base Metal Complexes Derived from 2-Hydroxy-3-methoxy-5-nitrobenzaldehyde", International Journal of Inorganic Chemistry, 2014; 8 pages.

[48] K. Singh, Y. Kumar, P. Puri, C. Sharma, and K. R. Aneja, "Metal-Based Biologically Active Compounds: Synthesis, Spectral, and Antimicrobial Studies of Cobalt, Nickel, Copper, and Zinc Complexes of Triazole-Derived Schiff Bases", Bioinorganic Chemistry and Applications, 2011; 10 pages.

[49] R. B. Sumathi and M. B. Halli, "Metal(II) Complexes Derived from Naphthofuran-2-carbohydrazide and Diacetylmonoxime Schiff Base: Synthesis, Spectroscopic, Electrochemical, and Biological Investigation", Bioinorganic Chemistry and Applications, 2014; 11 pages.

[50] A. A. Al-Amiery, "Synthesis and antioxidant, antimicrobial evaluation, DFT studies of novel metal complexes derivate from Schiff base", Res Chem Intermed, 2012; 38: 745–759.

[51] M. B. Halli and R. B. Sumathi, "Antimicrobial, DNA cleavage, and antioxidant properties of new series of metal(II) complexes derived from naphthofuran-2-carbohydrazide Schiff base: synthesis and physico-chemical studies", Med Chem Res., 2014; 23: 2093–2105.

[52] A. P. Mishra, R. K. Mishra, and M. D. Pandey, "Synthetic, Spectral, Structural and Antimicrobial Studies of Some Schiff Bases 3-d Metal Complexes", Russian Journal of Inorganic Chemistry, 2011; 56 (11): 1757–1764.

[53] N. Raman, A. Kulandaisamy and C. Thangaraja, "Redox and antimicrobial studies of transition metal(II) tetradentate Schiff base complexes", Transition Metal Chemistry, 2003; 28: 29–36.

[54] N. Raman, C. Thangaraja, S. Johnsonraja, "Synthesis, spectral characterization, redox and antimicrobial activity of Schiff base transition metal(II) complexes derived from 4-amino antipyrine and 3-salicylidene acetyl acetone", Central European Journal of Chemistry, 2005; 3 (3): 537–555.

[55] S. A. Patil, S. N. Unki, P. S. Badami, "In vitro antibacterial, antifungal, and DNA cleavage studies of coumarin Schiff bases and their metal complexes: synthesis and spectral characterization", Med Chem Res, 2012; 21: 4017–4027.

[56] N. Raman, J. D. Raja and A. Sakthivel, "Synthesis, spectral characterization of Schiff base transition metal complexes: DNA cleavage and antimicrobial activity studies", J. Chem. Sci., 2007; 119 (4): 303–310.

[57] N. Raman and A. Selvan, "Synthesis, Spectroscopic, Electrochemical, DNA Binding and Photocleavage Studies on Coordination Compounds of Bis(4-aminophenyl) methane Based Novel Schiff Bases", Russian Journal of Inorganic Chemistry, 2011; 56 (5): 759–770.

[58] A. M. Abu‐Dief, L. A. E. Nassr, "Tailoring, physicochemical characterization, antibacterial and DNA binding mode studies of Cu(II) Schiff bases amino acid bioactive agents incorporating 5‐bromo‐2‐hydroxybenzaldehyde", Springer, J Iran Chem Soc., 2015; 12: 943–955.

[59] M. N. Patel, C. R. Patel & H. N. Joshi, "Metal-Based Biologically Active Compounds: Synthesis, Characterization, DNA Interaction, Antibacterial, Cytotoxic and SOD Mimic Activities", Appl Biochem Biotechnol, 2013; 169 :1329–1345.

[60] Y. Li, Z. Y. Yang, M. F. Wang, "Synthesis, Characterization, DNA Binding Properties, Fluorescence Studies and Antioxidant Activity of Transition Metal Complexes with Hesperetin-2-hydroxy Benzoyl Hydrazone", J Fluoresc, 2010; 20: 891–905.

[61] C. Gokce, R. Gup, "Synthesis and characterisation of Cu(II), Ni(II), and Zn(II) complexes of furfural derived from aroyl hydrazones bearing aliphatic groups and their interactions with DNA", Chemical Papers, 2013; 67 (10): 1293–1303.

[62] P. Lavaee, H. E. Hosseini, M. R. Housaindokht, J. T. Mague, A. A. Esmaeili1 & K. Abnous, "Synthesis, Characterization and Fluorescence Properties of Zn(II) and Cu(II) Complexes: DNA Binding Study of Zn(II) Complex", J Fluoresc, DOI 10.1007/s10895-015-1719-6.

[63] M. P. Kesavan, G. G. V. Kumar, J. D. Raja, K. Anitha, S. Karthikeyan, J. Rajesh, "DNA interaction, antimicrobial, antioxidant and anticancer studies on Cu(II) complexes of Luotonin A", Journal of Photochemistry & Photobiology, B: Biology, 2017; 167: 20–28.

[64] S. B. Moosun, S. J. Laulloo, E. C. Hosten, T. I. A. Gerber, M. G. Bhowon, "Antioxidant and DNA binding studies of Cu(II) complexes of N,N0-(1,10-dithio-bis(phenylene))-bis(salicylideneimine): synthesis and characterization", Transition Met Chem, 2015; 40: 445–458.

[65] Q. Zhou and P. Yang, "Crystal structure and DNA-binding studies of a new Cu(II) complex involving benzimidazole", Inorganica Chimica Acta, 2006, 359 (4):1200-1206.