

REVIEW: A RECENT REVIEW IN APPLICATIONS OF HETEROCYCLIC COMPOUNDS AS ANTIMICROBIAL AGENT

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ABSTRACT

A wide development in the field of multidrug resistance in antimicrobial activity which enhance the search for development of new medicinal drugs with high potential. Schiff base heterocyclic metal complex with imine moiety, act as important antimicrobial agents due to their versatile properties such as chelation, adaptability of fine structure for a specific biological action, and chemotherapeutic drugs. Schiff base compounds derived from various heterocyclic platforms have been competently reviewed.

Keywords: Ligand, Antimicrobial, Antifungal, Anticancer, Metal complex.

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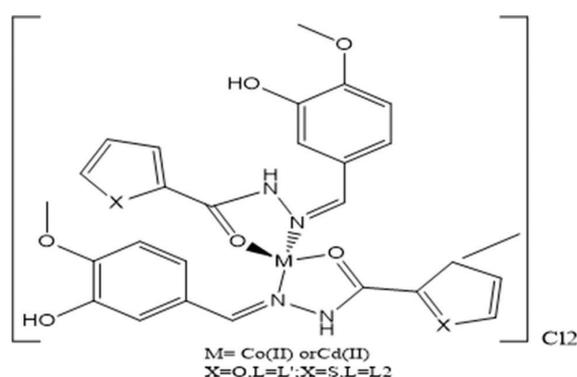
INTRODUCTION

Schiff base metal complex, the name you heard about more than 5 decades were considered as a splendid topic in the field of research. The use of Schiff base metal complex and their progress in medical research as a fine powder of drug occupied an optimistic role in the field of pharmaceutical research. In this review article, we are discussing the on-going aspects of biological activities of metal complex such as anticancer, antifungal, antimalarial, antibacterial, antiproliferative, anti-inflammatory, and antipyretic. Apart from the biological activities of the metal complex it also shows excellent catalytic activity due to the thermal and moisture stabilities. Heterocyclic compounds possess impressive biological activity due to the strong aromaticity of the ring containing heteroatoms such as O, S, and N. Antimicrobial resistance metamorphoses a global concern in the field of advanced multidrug research. Heterocyclic compounds used in the implementation of metal complexes as drugs to serve as remarkable medicine in the drug discovery. The pharmacological properties of heterocyclic compounds have promoted to a different level in the field of Schiff base metal complex.

The data collected from the various journals were indexed by Scopus, Pubmed, Google scholar, etc., during the past 10 years. There are more numbers of journals, but we considered that pertinent studies which have a sporting idea of the research. This review is summarized to know about the existing aspect of microbial activities of the Schiff base metal complex [1-15].

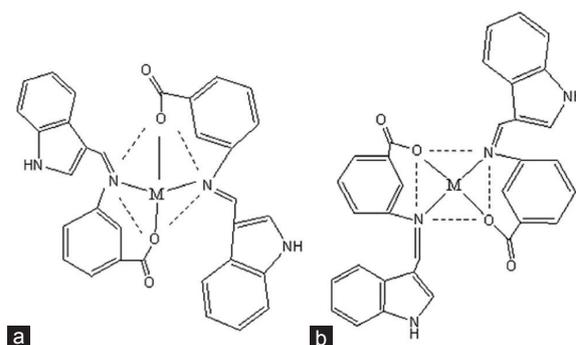
APPLICATIONS OF HETEROCYCLIC COMPOUNDS AS ANTIMICROBIAL AGENT

Heterocyclic Schiff base ligands were derived by the condensation of 3-hydroxy-methoxy benzaldehyde (iso vanillin) with furan-2-carboxylic acid hydrazide and thiophene-2-carboxylic acid hydrazide. Metal complexes such as Co (II) and Cd (II) prepared with corresponding ligands. Spectroscopic methods such as Fourier transform infrared (FTIR), UV-Vis, ¹H and ¹³C, and magnetic measurements proved that the metal complex geometry is tetrahedral. Gram-positive bacteria and Gram-negative bacteria against metal complex and ligands proved ligands have high microbial activity [16].



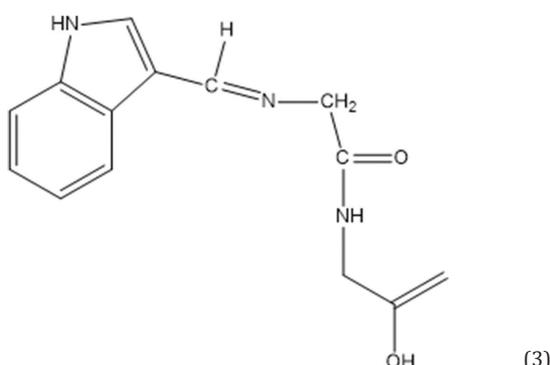
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Indole-3-carboxaldehyde and m-aminobenzoic acid produce new Schiff base ligands, and their metal complexes were derived from 3rd transition elements. They were characterized by many spectroscopic studies which are useful to prove their geometry of the molecule. The geometry reveals that Co (II) and Ni (II) are tetrahedral and Cu (II) is square planar. Disc diffusion method is taken to screen the metal complexes and their ligand with antibacterial and antifungal species. The gel-electro pores method is followed. For the nuclear activity of the ligand was assayed on CT DNA. Proposed structure of Schiff base metal complexes (a) tetrahedral geometry for Co(II), Ni(II), and Zn(II) complexes and (b) square planar geometry for Cu(II) complex [17].

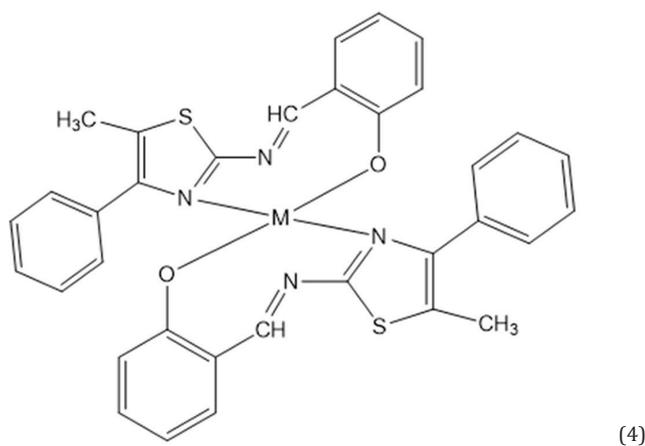


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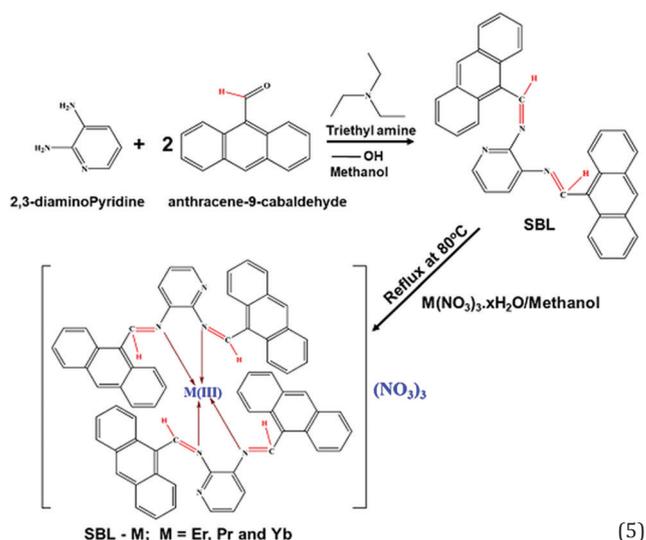
Pyrrole ring fused heterocyclic ligands were derived from indole-3-carboxyaldehyde and glycylglycine (glygly). They were characterized by electronic spectra, nuclear magnetic resonance (NMR) studies, and magnetic measurements. The metal complexes are 1:1 electrolytes proved by the conductance measurement. Coordination of the metal complexes is through azomethine nitrogen, peptide nitrogen, and carboxylate oxygen atoms. The studies about the magnetic measurements revealed that the weak ferromagnetic behaviors of Co (II) and Cu (II) show paramagnetic behavior. Metal complexes coordination through water molecule can be identified by IR and thermal studies. Thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) analysis show the process of decomposition steps. The metal complex crystalline structures were derived from the X-ray diffraction (XRD) studies. The ligand and its complexes were screened by the antimicrobial activity of Kirby-Bayer disc diffusion [18].



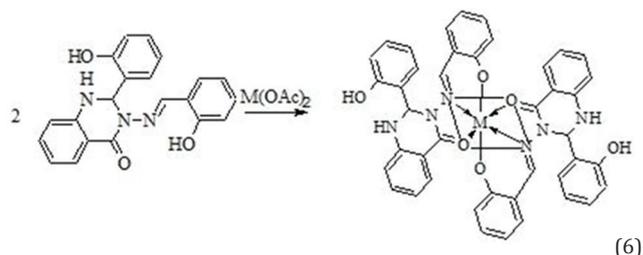
A new substituted heterocyclic moiety of Schiff base ligands was prepared by the condensation of salicylaldehyde with 2-amino-4-phenyl-5-methylthiazole and their metal complexes using the transition metal such as Co(II), Cu(II), Ni(II), and Zn(II). All the spectroscopic studies such as FTIR, NMR, and conductance were studied for the ligands and the metal complexes. Their compounds were screened against the anticancer activity of human tumor cell MCF-7 cell, liver cancer Hep G2, lung carcinoma A549, and colorectal cancer HCT116 in comparison with the activity of doxorubicin as a reference drug and the metal complex of Zn(II) complex showed potent inhibition [19].



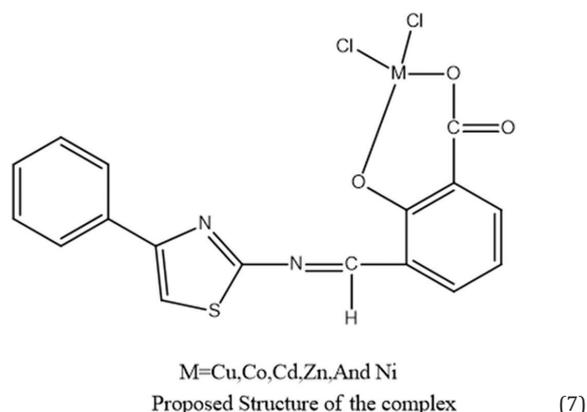
The newly formed lanthanide Schiff base complex is prepared by the condensation of 2,6-diaminopyridine and anthracene-9-carbaldehyde and they complex with lanthanide ions such as Praseodymium (Pr), Erbium (Er), and Ytterbium (Yb). FTIR data show the coordination through two azomethine-nitrogen and the ligand act as a bidentate ligand. The metal complexes were screened against human breast cancer MCF-7 and cervical anticancer cell line which shows high resistance [20].



Alkaloid-containing heterocyclic Schiff base ligand 2-((E)-(2-hydroxyphenyl)-3-((E)-(2-hydroxyphenyl)methylidene)amino)-2,3-dihydroquinazolin-4(1H)-one (H-HHAQ) was synthesized. The ligands with metal ions form the complexes which are studied for urease inhibitory activity. The metal ions such as Cu(II), Co(II), and Ni(II) showed better activities for the enzyme except for Zn which is inactive against the enzyme. In addition to that Cu(II) complex has greater inhibitory action [21].

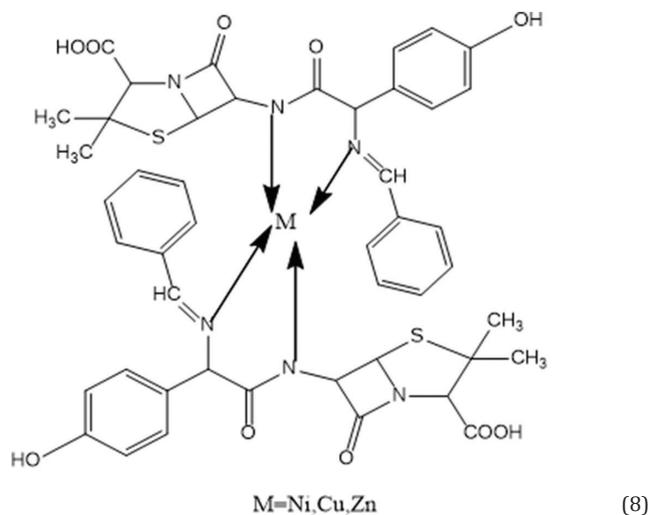


The *in vitro* cytotoxicity and DNA cleavage of Schiff based ligand 3-((4-phenylthiazol-2-ylidene)methyl)-2-hydroxybenzoic acid were synthesized and react with transition metal complexes such as Cu(II), Co(II), Ni(II), Cd(II), and Zn(II). For these complexes, elemental analysis, TG/DTA, FTIR, H-NMR, and UV-vis studies were characterized, and the data give an idea about the geometry and coordination through bidentate O-O donor. Moreover, Cu(II), Co(II), and Zn(II) show an enhanced DNA cleavage activity [22].

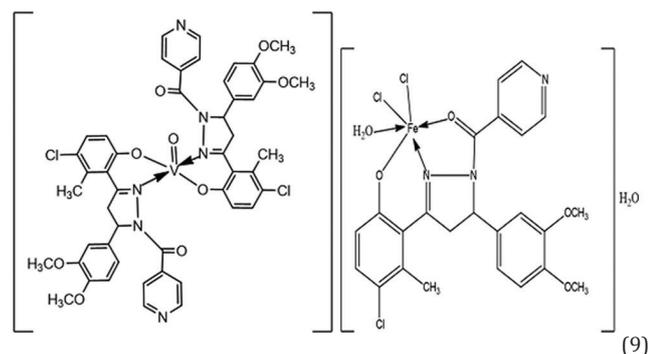


Benzene fused ring system has been used in the condensation of Schiff base complexes which gives new complexes with Amoxicillin trihydrate and nicotin aldehyde. Their metal complexes were characterized under spectrochemical techniques such as UV-Vis, scanning electron

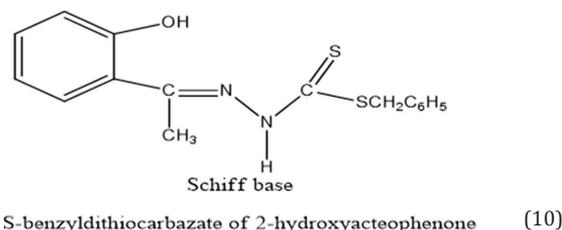
microscopy (SEM), electron paramagnetic resonance (EPR), FTIR, Mass spectroscopy, melting point, and conductivity measurements. The powder XRD pattern reveals the crystal structure of Cu (II) complex as a triclinic crystal system. Further tetrahedral geometry was recommended for EPR studies. Using two different concentrations the *in vitro* antibacterial studies were tested, and the data showed that their bacterial activity was high with the parent drug [23].



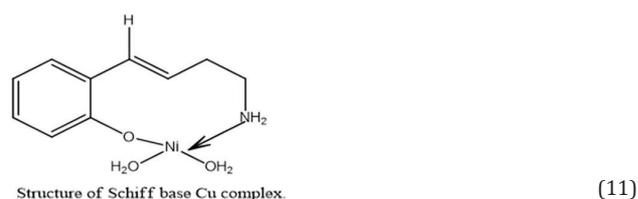
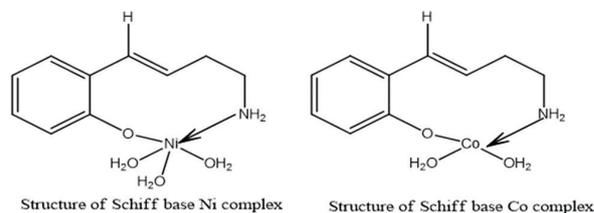
Recently reported article about the newly synthesized heterocyclic Schiff based compounds which are prepared from chalcone-3-chloro-6-hydroxy-2-methyl phenyl-3-(3,4 dimethoxy phenyl) prop-2-en-1-one with isonicotinohydrazide in the ethanolic medium. The characterization of these compounds and their results are obtained using the techniques such as UV, Mass, FTIR, and molar conductance IR studies suggest that toward Fe(III) ligand act as a monobasic tridentate ONO donor and ON donor against VO (IV). Some more studies regarding thermal stability and decomposition of the complex are also obtained [24].



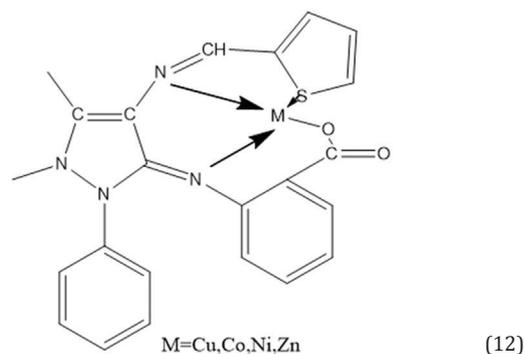
Coordination of the metal complexes plays a good role in the field of medical research. A series of tridentate Schiff base ligands are derived from the condensation of 2-hydroxyacetophenone with S-benzylthio carbamate have been synthesized and characterized by magnetic measurements, IR, Electronic Spectra, and molar conductance, etc. The geometry of the molecule is also correlated with the biological activity. The complexes are screened and found to have high potential microbial character [25].



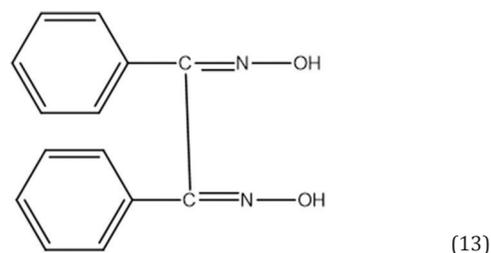
The antibacterial activity of new Schiff base ligands and their metal complexes were studied by the combination of ethylenediamine and salicylaldehyde. Using different concentration, the antibacterial activity was tested for different types of bacteria such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumonia*, *Bacillus cereus*, and *Salmonella typhi*, and *Staphylococcus aureus*. Comparing the metal complexes such as Cu, Co, and Ni, Cu showed 9.5, 9.0, and 8.0 mm zone of inhibition against *E. coli*, *S. typhi*, and *S. aureus*, and Co showed the zone of inhibition against *E. coli*, *B. cereus*, *K. pneumonia*, and *S. aureus*, in the range of 17, 19, and 22.5. Hence, these types of complexes provide useful antibiotic drugs in the research field of medicine [26].



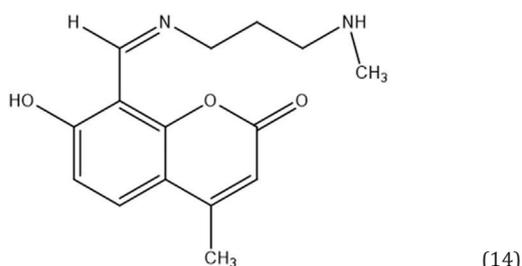
New Schiff base ligand has been prepared using 4-AminoAntipyrine and Thioephene-2-carbaldehyde, and their metal complexes are prepared using the metals Cu(II), Ni(II), and Zn for which the spectroscopic studies were characterized and results give an idea about the structure of the metal complexes. The biological activity of the compound also tested with the ligands and their metal complexes [27].



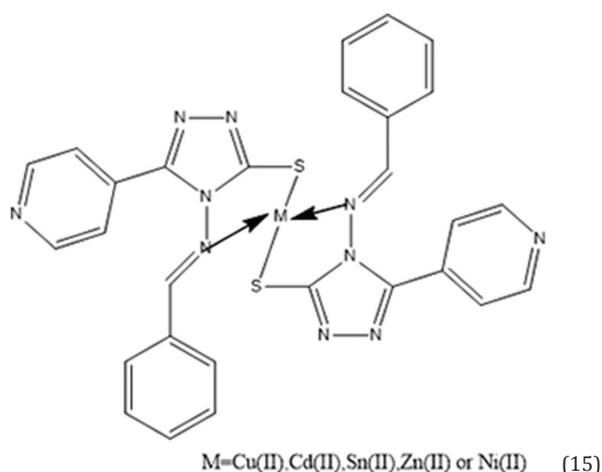
Heterocyclic compounds containing sulfur and Nitrogen of 2-aminothiazole and 8-hydroxyquinoline are mixed with Benzoinoxime to form the primary and secondary ligands. These ligands react with metal such as Co (II) and Zn (II). The metal complexes are formed in the ratio 1:2:2 with oxime as a primary ligand. The Co (II) metal complexes show distorted the octahedral geometry of mixed ligands and complexes of oxime form a square planar geometry. The mixed ligand of Zn (II) complexes shows distorted octahedral geometry and with oximes shows square planar geometry. The complexes are screened for the antimicrobial activity [28].



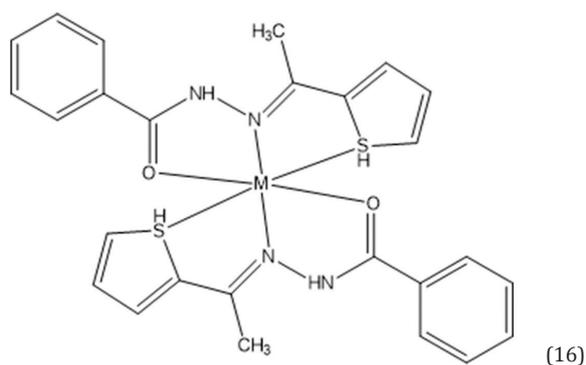
New synthesis of Zn(II) complexes using novel heterocyclic compounds have been derived from the ligands 8-[(Z)-{[3-(N-methylamino)propyl]imino}methyl]-7-hydroxy-4-methyl-2H-chromen-2-one, 2-[(E)-{[4-(1H-1,2,4-triazol-1-ylmethyl)phenyl]imino}methyl]phenol, and (4S)-4-{4-[(E)-(2-hydroxybenzylidene)amino]benzyl}-1,3-oxazolidin-2-one. Zn(II) complexes were studied by many spectroscopic techniques proposed for the structure to be Octahedral. The *in vitro* antimicrobial activity was a screened against Gram-negative bacteria and Gram-positive bacteria and fungi such as *Candida albicans* and *niger* which showed the enhanced biological activity of Zn(II) complexes [29].



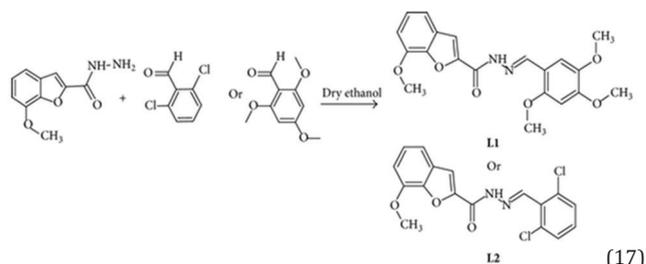
1,2,4 Triazole Schiff base ligands are prepared, and their metal complexes such as Cu(II), Cd(II), Sn(II), Zn(II), and Ni(II) are synthesized. Physicochemical techniques have been studied for these compounds which reveal that the azomethine nitrogen and S atom of thiol group are responsible for coordination through metal complexes. Cu(II) complexes form the proposed square planar structure, and tetrahedral structure has been proposed to other metal complexes [30].



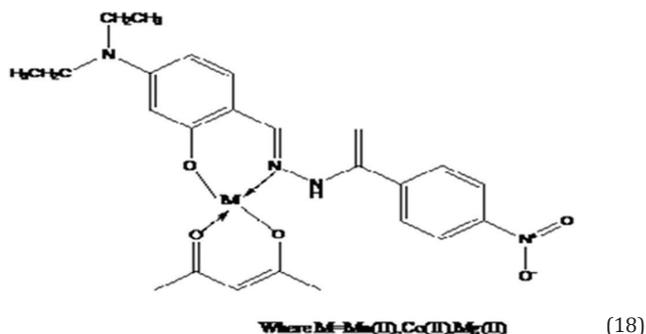
New ligand containing trifunctional SNO donor system and metal II complexes were prepared using 2-acetyl thiophene benzoyl hydrazone ligand. These complexes are characteristics by various studies such as molar conductance, thermogravimetric, and magnetic moment distorted Octahedral complexes are produced in which the ligand act as SNO tridentate [31].



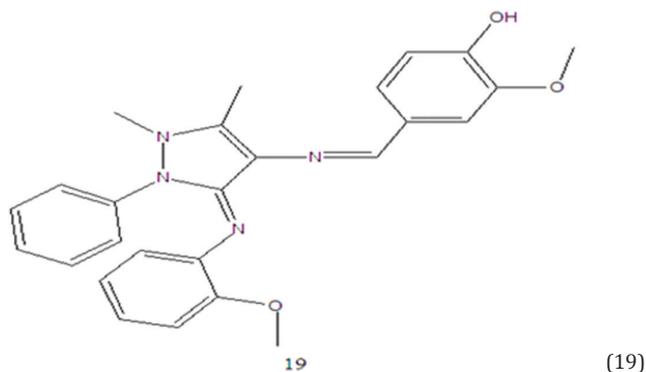
Substituted Benzofuran derivatives have been synthesized, and their metal complex was characterized by elemental analysis, magnetic moments, and conductance measurements. The elemental analysis confirms the formula ML (CL) n where L= E-1-Methoxy-N1-(2, 4, 5- trimethoxy benzylidene)benzofuran -2-carbohydrazone (L1) or (E)-N1-(2,6 dichlorobenzylidene)-7-methoxy benzofuran-2-carbohydrazone L2 of the complex. The complexes were screened for their antibacterial activity. Among the metal complexes Co, Cu, and Ni show high activity against all microbes [32].



The acetylacetonate Schiff base ligand was obtained from the condensation of 4-(diethyl amino)-2-hydroxy benzaldehyde and 4 nitro benzo hydrazide or 4 methoxy-benzohydrazide. The metal complexes were prepared with Co (II), Mn(II), and Mg(II) metals. FTIR reveals the Schiff base as bidentate chelating ligands through nitrogen of azomethine and phenolic oxygen atoms. The *in vitro* antimicrobial screening was done against *S. aureus* and *Enterococcus facials* which showed the high potential activity of metal complex [33].

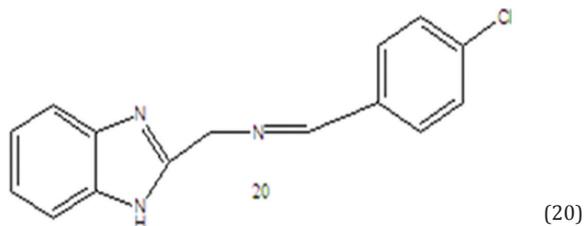


Metal complexes derived from 4-aminoantipyrine, vanillin, and O-anisidine were prepared and synthesized. The spectroscopic techniques such as FTIR, NMR, and ¹H and ¹³C NMR are analyzed and obtained the following data. Antimicrobial screening test was performed within the metal complexes. The minimum inhibitory concentration values of metal complex exhibit greater antimicrobial activity than free ligand [34].



Transition metal complex derived from 2-aminomethylbenzimidazole and 4-chlorobenzaldehyde (1-(1H-benzimidazol)-2H-N-(4- chlorobenzylidene methamine) was synthesized. The spectroscopic methods such as ¹H and ¹³C NMR, electron spin resonance (ESR), FTIR, UV-Vis spectra were analyzed

for all these metal complexes which proposed an octahedral geometry to all metal complexes. The *in vitro* screening of antimicrobial activity was studied against two Gram-negative and Gram-positive bacteria. All the metal complexes are highly active than the ligand [35].



The synthesis of new benzaldehyde thiosemicarbazone-BTSC and 3,4-dimethoxy benzaldazine-DMBA and their metal complex was prepared and screened for antibacterial activity with the five human pathogenic bacteria strains such as *S. aureus*, *Bacillus subtilis*, *K. pneumonia*, *E. coli*, and *Proteus vulgaris*. The concentration ranging between 0.01 and 10 µg/ml has a very good antibacterial activity of the metal complex [36].

New metal chelates of the type M (NQO)₂ were synthesized from metals such as Hg, Cd, Zn, and Pb where NQO-1,2 Naphthoquinone dioxime. The metal chelates were synthesized and characterized by FTIR, electronic Spectra, ¹H and ¹³C NMR, DSC, and Electron Microscopy with EDAX. Square Planar structure was proposed for these metal chelates, and it is thermally stable up to 350°C. The antimicrobial activity was screened with Gram-positive and Gram-negative bacteria and fungi with cisplatin as chemotherapeutic agent [37].

Walaah, Mohamed and *et al.* synthesized a new series of metal complexes derived from lornoxicam and 1, 10 phenanthroline and characterized by spectroscopic tools such as mass spectra, IR, UV-visible, ¹H and ¹³C NMR, and ESR. Electrolytic nature was confirmed by the molar conductance. IR studies reveal the coordination of metal ions in a neutral bidentate manner. ESR spectra and electronic spectra assigned octahedral geometry of the ternary complexes. These complexes are screened for their antimicrobial, anticancer activity against cancer cell line. The result revealed complexes have more potent than the parent ligand [38].

Transition metal complexes of Ni (II), Zn (II), Cd (II), and Hg(II) have synthesized from dihydropyrimidine derivative of vanillin and 4-AminoAntipyrine. The complexes are characterized by UV-Vis, ¹H, and ¹³C NMR, which proposed the complexes have ML₂ type. The tetrahedral geometry was suggested by UV-Vis and susceptibility data expects Nickel which shows a square planar complex. The *in vitro* antimicrobial studies were carried on these ligand and metal complexes. The metal complexes show more activity than the ligand [39].

Two metal complexes were synthesized from 2,6 bis (2-Aminophenoxymethyl)pyridine and 2,2'-bipyridine 6,6'-dicarboxyaldehyde in the presence of Hg(II) and Cu(II) perchlorate salts. Both compounds showed cytotoxicity on 2 cell line as a dose-dependent manner. Among the complexes, the one with Hg(II) according to apoptotic morphology and DNA fragmentation exhibits promising potential as an anticancer compounds [40].

Unsymmetrical Schiff base ligands derived from Salicylaldehyde/5-methylsalicylaldehyde and ethylene diamine or diaminomaleonitrile. They were characterized by elemental analysis and spectroscopic methods. ESR spectra showed that Cu (II) complexes show four lines which are a characteristic of square planar geometry. The antimicrobial activity was tested against bacteria such as *S. aureus*, *Bacillus subtilis*, *K. Pneumonia*, and also antifungal activities. The metal complexes generally show more potent than the ligand [41].

Schiff base ligands were derived from imidazole-2-carbaldehyde and glycine-glycine. The ligands react with metals such as Co (II), Cu (II),

and Ni (II). Molar conductance indicates the 1:1 electrolytic nature and IR data showed that the ligand is tetradentate with imidazole nitrogen and carboxylate oxygen donor group. The SEM image shows the surface morphology of the complex. Antibacterial and antifungal studies were carried out using bacterial and fungal species which shows high for metal complex [42].

New ONO donor Schiff base ligand derived from the condensation of 5-Methyl, 3-Phenyl -1H-Indole-2-Carbohydrazide with 2-hydroxy-1-naphthaldehyde. The spectral analysis of the metal complex was characterized by UV-vis spectra, ESR, Thermal analysis, power XRD, and conduct metric, and magnetic susceptibility measurements. Co (II), Cu (II), and Ni (II) complexes have octahedral geometry and 1:2 stoichiometric ratio of the type M (L)₂. The antimicrobial activity was screened for metal complexes and found that it possesses high potential activity [43].

A series of novel Schiff base derivatives with different substituent were screened for antibacterial activity against *S. aureus*. Synthesized compounds showed a significant antibacterial activity [44].

Synthesis and biological activity of transition metal complexes containing a tetradentate N₂O₂ donor type Schiff base derived from the condensation of 4-aminoantipyrine (1-phenyl-2,3-dimethyl-4-aminopyrazol-5-one) with benzyl which forms stable complexes with transition metal ions such as Cu(II), Ni(II), Co(II), Mn(II), Zn(II), and VO(IV) were reported [45]. Screening results indicated that the complexes show higher antimicrobial activity than the free ligand. Such increased activity of the metal chelates can be explained on the basis of Overton's concept [46] and the Tweedy's chelation theory [47].

The synthesized and screened for their antimicrobial Schiff base and its 3d transition metal complexes (7) of Mn(II), Fe(III), and VO (IV) derived from Ethyl 4-methyl-2-oxo-6-phenylhexahydro pyrimidine-5- carboxylate and 4-aminoantipyrine suggesting the possible use of the complexes as antibiotics [48].

The complexes of different Schiff bases (5- methyl 2-hydroxy acetophenone morpholine-Nthiohydrozone, 5-chloro2hydroxy acetophenonemorpholine-N-thiohydrozone and 5-methyl 2-hydroxy acetophenone antipyrine) with Mn (III) and Mn (II) have been synthesized [49].

Five new novel metal complex derivatives of 2N-salicylidene-5-(*p*-nitro phenyl)-1,3,4-thiadiazole, HL with the metal ions Vo(II), Co(II), Rh(III), Pd(II), and Au(III) have been successfully prepared in an alcoholic medium. The complexes obtained are characterized quantitatively and qualitatively using micro elemental analysis, FTIR spectroscopy, UV-Vis spectroscopy, mass spectroscopy, ¹H and ¹³C NMR, magnetic susceptibility, and conductivity measurements. From the spectral study, all the complexes obtained as the monomeric structure and the metals center moieties are four-coordinated with square planar geometry except VO (II) and Co complexes which existed as a square pyramidal and tetrahedral geometry, respectively. The preliminary *in vitro* antibacterial screening activity revealed that complexes showed moderate activity against tested bacterial strains and slightly higher compared to the ligand, HL [50]. Coordination of biomolecules to the metal ions significantly alters the effectiveness of the biomolecules. In view of the antimicrobial activity, a series of nickel, copper, and zinc complexes of tridentate Schiff base derived from the condensation reaction of S-benzylthiocarbamate with 2-hydroxyacetophenone have been synthesized and found to be potential antimicrobial agents. An attempt is also made to correlate the biological activities with the geometry of the complexes. The complexes have been characterized by molar conductance, magnetic susceptibility, IR, and electronic spectroscopic techniques [27]. Novel Schiff base ligand derived from 2-hydroxybenzophenone with S-benzylthiocarbamate and its metal complexes with Ni (II), Cu (II), Zn (II), and Cd (II) have been synthesized and evaluated for their antibacterial activities by disc diffusion method

and antifungal activities by PDA medium. The complexes have been characterized by conductance, magnetic, IR, and electronic spectroscopic techniques [51]. Transition metals such as Cr, Mn, and Fe with a Schiff base derived from 2-amino-4-ethyl-5-hydroxybenzaldehyde and thiocarbohydrazide were synthesized and characterized by several techniques, including elemental analysis (C, H, and N), molar conductance measurements, magnetic measurements, and electronic, mass, and IR spectral studies. Based on these studies, a five-coordinated square pyramidal geometry for all the complexes was proposed. The Schiff base ligand and the complexes were also tested for their antimicrobial activity (against the bacteria *E. coli*, *S. aureus*, *P. aeruginosa*, and *Bacillus megaterium*, and the fungi *Kluyveromyces fragilis*, *Rhodotorula rubra*, *C. albicans*, and *Trichoderma reesei*) to assess their inhibiting potential. An attempt was also made to correlate the antimicrobial activity with the geometry of the complexes. All complexes were found to be less active against the pathogens *E. coli*, *S. aureus*, and *P. aeruginosa*. The Cr(III) complex showed the best antimicrobial activity, but the ligand alone was found to be active against the fungus *T. reesei* [52]. A new series of Copper(II), Nickel(II) Cobalt(II), and Zinc(II) complexes with two newly synthesized Schiff base ligands N-[(E)-(5-Methylfuran-2-yl)methylidene]-ethane-1,2-diamine (MFMEDA) and N-p-hydroxybenzalidine-2-aminopyridine (HBAPy) have been prepared. The Schiff bases FMFEDA and HBAPy ligands were synthesized by the condensation of 5-methyl furfural with ethylene-1,2-diamine and p-hydroxybenzaldehyde with 2-aminopyridine, respectively. The ligands and their metal complexes have been characterized by FT-IR, Mass, ¹H NMR, UV-vis., elemental analysis, and Thermal gravimetric analysis. The Schiff base and their metal complexes were tested for antimicrobial activity against Gram-positive bacteria *S. aureus* and Gram-negative bacteria *E. coli*, *S. typhi* murium and fungus *Aspergillus nidulense*, *C. albicans*, and *Saccharomyces cerevisiae* using Broth Dilution Method [53]. Shambuling Karabasannavar and et al. synthesized that new five metal complexes with a Schiff-base ligand, 3-((4-phenylthiazol-2-ylimino) methyl)-2-hydroxybenzoic acid were synthesized with metal ions such as Cu(II), Co(II), Ni(II), Cd(II), and Zn(II). The reaction likely proceeds through condensation of 2-amino-4-phenyl thiazole with 3-aldehydosalicylic acid and characterized by elemental analysis and various spectral studies such as FT-IR, ¹H NMR, ESI mass, and TGA/TDA, and molar conductance studies. The spectral results revealed bidentate O-O donor and forms the complexes having square planar geometry. The antibacterial and antifungal activity of the ligand and its metal complexes was found based on the determination of minimum inhibitory concentrations [54]. Schiff base metal complexes were prepared from 3,3'-diaminodipropylamine with different benzaldehyde derivatives. The structures of these compounds were confirmed through different spectroscopic methods such as ¹H-NMR, ¹³C-NMR, and mass spectrometry. The prepared compounds were evaluated *in vitro* for their antimicrobial activity against a number of pathogenic Gram-positive and Gram-negative bacteria and *Candida* by the two-fold serial dilution method. These compounds showed bacteriostatic rather than bactericidal activities against Gram-positive and Gram-negative bacteria. In addition, compound 3c exhibited significant anticandida activity with an MIC of 24 µg/ml and is, therefore, considered as a promising and potential antifungal agent; further modification can be done on the structure of the compound for a better drug candidate in the future [55]. This work was performed to synthesize various Schiff base metal complexes using cobalt, nickel, and copper followed by their antibacterial activity. Schiff bases were synthesized by the combination of Ethylene-diam in and salicyldehyde. Metal complexes of these Schiff bases were prepared from nitrate and chloride salts of Ni, Co, and Cu in an alcoholic medium. The chemical structures of Schiff base metal complexes were established by IR spectroscopy. The antimicrobial activities of these complexes were checked against *P. aeruginosa*, *E. coli*, *K. pneumonia*, *B. cereus*, *S. Typhi*, and *S. aureus*. Disc diffusion method was used to assess their inhibiting potential. The copper based Schiff complex displayed 9.5, 9.0, and 8.0mm zone of inhibitions against *E. coli*, *S. typhi*, and *S. aureus* at the concentration level of 16.6µg/100µL. The results of the antibacterial activity of the copper complexes at the concentration of 33.2µg/100µL

showed 18.5, 10.5, and 10mm zone of inhibitions against *E. coli*, *S. typhi*, and *S. aureus*. The nickel base complex showed no activity against the tested organisms at both concentrations. The cobalt based Schiff complex showed 17, 19, 22.5, and 26.5 zones of inhibition against *E. coli*, *B. cereus*, *K. pneumonia*, and *S. aureus*, respectively, at 16.6 µg/100 µL while at 33.2 µg/100 µL this complex displayed 23.5, 30.5, 26.5, and 28.5mm zone of inhibition against *E. coli*, *B. cereus*, *K. pneumonia*, and *S. aureus*. These new derivatives may provide a wide choices and flexibility for the development of new, safe, and highly active antibiotics [28]. A new Schiff base has been derived from 1,2-diacetyl benzene and 4,5-dimethyl -O-Phenylenediamine and their complexes with Cu(II), Co(II), and Ni(II) have been synthesized and evaluated for their antibacterial activities by disc diffusion method. The complexes have been characterized by conductance, magnetic, IR, and electronic spectroscopic techniques [56]. Transition metal complexes with Schiff bases derived from 2-formylindole, salicylaldehyde, and N-amino Rhodanine. The Schiff base ligands were characterized by elemental analysis, IR, Mass, ¹H NMR, and electronic spectra. The free ligands and their metal complexes were also screened for antimicrobial activities against *Bacillus cereus*, *E. coli*, *P. aeruginosa*, *S. aureus*, and *C. albicans*. The results indicated that the ligands do not have any activity, where as their complexes showed more activity against the same organisms under identical experimental conditions [57]. Nickel II metal complex of Schiff base derived from benzoin and o-amino benzoic acid has been prepared and characterized by IR spectral analysis, conductance measurement, UV-visible spectral studies, and elemental analysis. The melting point of the Schiff base determined is 120°C. The decomposition temperature of the nickel (II) complex is 155°C, while the molar conductance value is 10.7 ohm⁻¹ cm²mol⁻¹. Antimicrobial screening of the compounds was carried out *in vitro* against *E. coli*, *S. typhi* (Gram-negative), and *S. aureus*, and *Streptococcus* spp. (Gram-positive). The bioassay reveals a considerable activity of the Schiff base complex against the bacterial isolates [58]. The synthesis of a series of some novel Schiff base complexes of Cu(II), Ni(II), Co(II), Mn(II), and Zn(II) with a tetradentate Schiff base has been achieved by the reaction of malonyl hydrazide with dehydroacetic acid in ethanol under refluxing condition. All the synthesized metal complexes and ligand were characterized on the basis of elemental analysis, UV-Visible, ¹H and ¹³C NMR, IR spectroscopy, and mass spectrometry. The IR spectral data suggest that azomethine N and enolic O atom are involved in coordination with metal ions, and the ligand behaves as a tetradentate ligand with ONNO donor atoms. The mass spectrum of the complexes reveals the formation of metal ligand bonding in stoichiometric ratio 1:1 (M: L). The UV-Visible data suggest the square planar geometry for the synthesized complexes. All compounds were screened for their antibacterial activity against Gram-positive and Gram-negative bacteria using ampicillin as a standard drug. It has been found that metal complexes show enhanced activity as compared to ligand, and some modification in ligand structure may lead to better antibacterial agents in future [59]. Ni(II) and Cu(II) metal complexes of simple unsymmetrical Schiff base ligands derived from salicylaldehyde/5-methylsalicylaldehyde and ethylenediamine or diaminomaleonitrile (DMN) were synthesized. The ligands and their complexes were characterized by elemental analysis, ¹H NMR, FT IR, and mass spectrometry. The electronic spectra of the complexes show d-d transitions in the region at 450–600 nm. Electrochemical studies of the complexes reveal that all mononuclear complexes show a one-electron quasi-reversible reduction wave in the cathodic region. ESR spectra of the mononuclear copper(II) complexes show four lines, characteristic of square-planar geometry, with nuclear hyperfine spin 3/2. The *in vitro* antimicrobial activity of the investigated compounds was tested against human pathogenic bacteria such as *S. aureus*, *Bacillus subtilis*, *K. pneumonia*, *P. aeruginosa*, and *E. coli*. The antifungal activity was tested against *C. albicans*. In general, the metal complexes have higher antimicrobial activity than the free ligands [42]. Metal complexes of (E)-N-(4-(thiophen-2-ylmethyleneamino) phenylsulfonyl) acetamide (S. TH) Schiff bases derived from sulfacetamide (N-[4-(amino-phenyl) sulfonyl] acetamide) and 2-thiophenecarboxaldehyde were synthesized and characterized. Spectroscopic studies suggested that most of the

complexes were coordinated in a regular octahedral arrangement where S.Th ligand and the central metal atom were coordinated through two N amino azomethine groups (-HC=N-) and two sulfur atoms of S thiophene rings in 2L:1M molar ratio. Complexes have shown a promising activity on screening for the antibacterial characteristics, and antifungal (*Aspergillus fumigates* and *C. albicans*) [60]. A new Schiff base derivative ligand (LI) has been produced by condensed isatin and 2,3-diaminobutane (2:1) molar ratio. The (LI) ligand has been separated and distinguished by ¹H, ¹³C-NMR, (CHN) elemental analysis, UV-visible, mass spectroscopy, and FTIR methods. The metal ions, cobalt(II), nickel(II), and copper(II) complexes were synthesized with the ligand. The complexes were typified by, UV-Visible, FTIR, atomic absorption, molar conductance, magnetic susceptibility, and elemental analysis (CHN) techniques. Octahedral geometry are suggested for the metal complexes based on the results of physicochemical and spectral techniques. The TLC for (LI) ligand and complexes demonstrated single spot for each, signifying their compounds purity. All these compounds were determined aligned with two classes of human pathogenic; bacteria Gram-positive and Gram-negative [61]. The synthesis and characterization of novel transition 3d metal complexes of copper (II), nickel (II), cobalt (II), and chromium (III) involving the Schiff base of melonol were explored to examine their biological activity. Characterization of the complexes was carried out using matrix-assisted laser desorption/ionization-time-of-flight, gas chromatography-mass spectrometry, TGA, UV-Visible, and IR spectrophotometry. The antimicrobial studies were conducted against six bacterial strains and six fungi. The minimum inhibition concentration observed was compared against the standard antibiotic gentamycin and the antifungal drug amphotericin. The activity studies indicated that cobalt (II) complex exhibited activity better than standard drug amphotericin against *Penicillium chrysogenum*. Molecular docking study confirms the protein binding and supports the experimental finding. Binuclear cobalt (II) and chromium (III) bridging complexes of Schiff base ligand were obtained [62]. Metal complexes of Mn(II), Fe(II), Co(II), and Cd(II) ions with Schiff base ligand 4- ((pyridin-2-ylimino)methyl)phenol derived from condensation of 2-amino pyridine with 4- hydroxybenzaldehyde were prepared. The ligand and complexes were isolated from the reaction in the solid form and characterized by conductivity, magnetic moment, TLC, IR, UV-Visible, thermal analysis, and some physical measurements. During complexation reaction with transition metal ions Schiff base act as a deprotonated tridentate ligand and IR spectra showed that N and O atoms are coordinated to the central metal atom. The observed values confirmed that the complexes have octahedral geometry. The Schiff base and its metal complexes have been found to have moderate to strong antibacterial activity [63]. The transition metals with the Schiff bases, formed by condensation of 2-Hydroxy-1- naphthaldehyde/Salicylaldehyde and p-Anisidine with Neutral bidentate ligand 4-Hydroxybenzaldehyde/3-Ethoxy-4-hydroxybenzaldehyde (Ethylevanilline) and o-Phenylenediamine have been synthesized and characterized. All prepared compounds were also evaluated for their antibacterial and antifungal activities by the agar well diffusion method. The antibacterial activity was tested against the bacteria *B. subtilis* (Gram-positive), *E. coli* (Gram-negative). The antifungal activity was tested against *A. niger*. The standard Streptomycin has been evaluated with the results obtained for antibacterial and antifungal activities [64]. Schiff base ligand derived from 2-amino 4,6 dihydroxypyrimidine and P- chlorobenzaldehyde has been reported and the ligand was treated with Cu, Ni, and Co to obtained the following metal complexes. The ligand and its complexes were screened for their antifungal and antibacterial activity against *A. niger*, *P. chrysogenum*, *Fusarium moneliforme* and *Aspergillus flavus* and *E. coli*, *S. typhi*, *S. aureus*, and *B. subtilis*. The result indicated that the complexes exhibited good antifungal and antibacterial activities [65]. The synthesized ligands, along with its metal complexes were screened for their *in vitro* antibacterial activity against four bacterial pathogens (*E. coli*, *B. subtilis*, *S. aureus*, and *Proteus vulgareous*). A novel Schiff base metal complexes were synthesized and well characterized by elemental analyses and spectral studies. Physical and analytical data suggest that the Schiff base acts as tridentate ligand toward metal ions through

azomethine-N, deprotonated-O of 2-aminophenol, and O-atom of furan moiety. The results of these studies revealed that the free ligand and its metal complexes showed significant antibacterial potency [66]. All the newly synthesized compounds were screened for their antimicrobial activity. For antibacterial activity, we used *S. aureus* microbial type culture collection (MTCC 96) and *Streptococcus pyogenes* (MTCC 443) as Gram-positive, *E. coli* (MTCC 442) and *P. aeruginosa* (MTCC 441) as Gram-negative strains using ampicillin, chloramphenicol, and ciprofloxacin as a standard antibacterial drug. Antifungal activity was screened for three different fungal species *C. albicans* (MTCC 227), *A. niger* (MTCC 282), and *Aspergillus clavatus* (MTCC 1323). Griseofulvin and nystatin used as a standard antifungal drug. Majority of the compounds exhibited good antibacterial, antifungal, and antituberculosis activity [67].

CONCLUSION

Schiff base explored versatile antimicrobial activity in the research field. Moreover, metal on complex formation, their *in vitro* antimicrobial activity has increased more when compared to ligands. This review will create new ideas in the field of medicine which helps the scientist to produce more new drugs which are specific in action. In spite of various syntheses in the drug analysis there is still a need to explore new drugs which are useful for future generation.

AUTHOR'S CONTRIBUTIONS

Corresponding author has reviewed all the research article about antimicrobial activity of Schiff base metal complexes.

CONFLICTS OF INTEREST

Authors declare that they have no conflicts of interest.

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