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Review Article

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ANTIMICROBIAL POTENTIAL OF SCHIFF BASE METAL COMPLEXES: AN OVERVIEW

[1]Rajkumar G. Momle, [2]Suresh G. Vedpathak and [3]*Gopal K. Kakade

[1]Late Shankarrao Gutte ACS College Dharmapuri, 431 515 Maharashtra, India.
[2]Department of Chemistry, S. M. Dnyandeo Mohekar College, Kallam, 413 507 (MH), India.
[3]Department of Chemistry, MSP Mandal's ASC College, Kille-Dharur, 431 124 (MH), India.

Corresponding Author: Dr. Gopal K. Kakade

Department of Chemistry, MSP Mandal's ASC College, Kille-Dharur, 431 124 (MH), India.

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ABSTRACT

The implication of metal chelation is carried in many important biological processes, where the coordination occurs between different metal ions and a broad range of ligands. Coordination compounds have been considered as characteristic compounds for bio-coordination compounds which controls the process of metabolism. Schiff bases play a vital in the development of chemistry of coordination compounds. As the transition metal complexes contribute a diverse and rich field of research, these complexes received much attention because of their applications in biology, medicine and industry. Schiff bases and its transition metal complexes possess numerous biological properties like antimicrobial, anti-inflammatory, anticancer, analgesic, anticonvulsant, antiviral, anticonvulsant, anthelmintic, anti-HIV, antioxidant, and CNS depressant activities. The present review provides a brief overview on the recent developments on antimicrobial potential of Schiff base transition metal complexes reported in the last few decades.

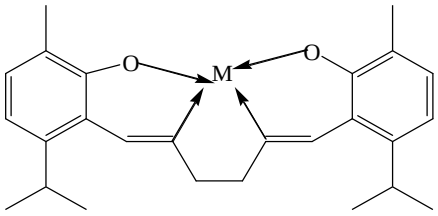
KEYWORDS: Antibacterial, Antifungal, Antimicrobial, Metal Complexes, Schiff base.

INTRODUCTION

Schiff bases, named after Hugo Schiff (1864), are the condensation compounds of primary amine and carbonyl compound.[1] In a modern era, the term Schiff base denotes all compounds, possessing azo methine group >C = N-, which is intermediate between >C=C< and >C=O group. Due to the presence of a lone pair of electrons on the nitrogen atom and the electron donating character of double bond, compounds containing >C=N- group have basic in nature, in which azo methine group can act as a n accepter. Generally, Schiff's bases show hard character and are effective, as coordinating ligands if they bear functional group, usually -OH or -COOH sufficiently near the site of condensation. They are capable of forming five or six membered chelate ring during the complexation with a metal ion in which, the >C = N-, and >C = C< can be located in internal positions in chains or rings. Schiff bases and its transition metal complexes possess numerous biological properties like antimicrobial, anti-inflammatory, anticancer, analgesic, anticonvulsant, antiviral, anticonvulsant, anti-HIV, anthelmintic, antioxidant, CNS depressant activities etc.

Antimicrobial activities of Schiff base transition metal complexes

Tadavi S. K. et al[2] have reported the synthesis of a novel salen type Schiff base ligand and its Mn(II), Co(II) and Ni(II) complexes **1**. All the compounds were evaluated for antimicrobial, antioxidant and pBR 322 DNA cleavage in the presence of H_2O_2. *Kirubavathy S. J. et al*[3] synthesized a novel pyrimidine bearing Schiff bases **2** and their Cu(II), Co(II) and Ni(II) complexes. The metal complexes were screened for their cytotoxic potency against human breast cancer cell line MCF-7 and also evaluated for antimicrobial activities.



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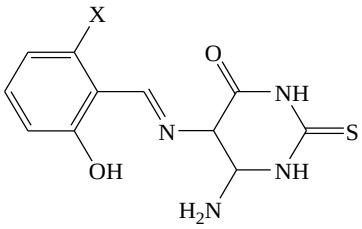
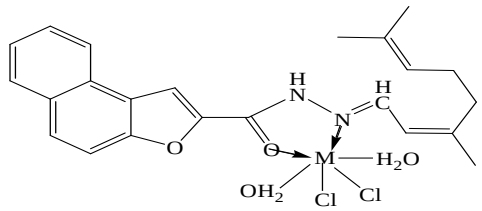


2

A series of Co(II), Ni(II), Cu(II), Cd(II), Zn(II) and Hg(II) complexes **3** of Schiff base, derived from condensation of citral and naphthofuran-2-carbohydrazide, were synthesized by *M.B. Halli et al*.[4] The Schiff bases and metal complexes were screened for their antioxidant, antibacterial and antifungal activities and found to be increased after complexation. *Sharaby C. M. et al*[5] have reported the synthesis of metal complexes and mixed ligand complexes of new sulfonamide Schiff base ligands **4** and screened for their microbial and anticancer activities. The metal complexes shows enhanced microbial and anticancer activities than Schiff base ligands and the mixed ligand complexes are more effective than the metal complexes.



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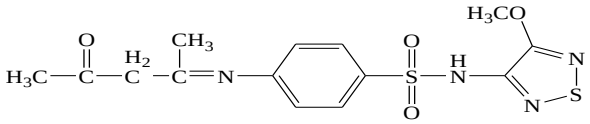
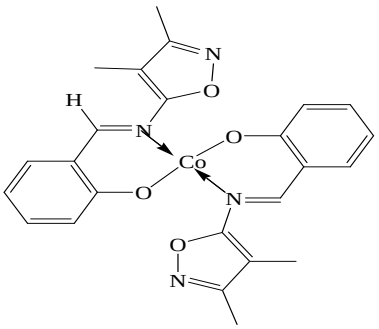


4

Two new series of binary metal complexes (Cu(II), Ni(II) & Co(II)) of (3,4-dimethylisoxazol-5-ylimino)methyl)benzene-1,3-diol and 2-((3,4-dimethylisoxazol-5-ylimino)methyl)-5- methoxyphenol **5** were synthesized by *Ganji N. et al*.[6] The antimicrobial activities of the Schiff bases and their metal complexes were evaluated and the data indicates that the complexes are more compelling than their Schiff base ligands. *Mahmoud W. H. et al*[7] have reported the synthesis of transition metal complexes **6** of Cr(III), Mn(II), Fe(III), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) with (Z)-4-(1-((2-carboxycyclohexa-2,4-dien-1-yl)imino)-ethyl)[bis(h5 -cyclopenta-1,3-dien-1-yl)]iron mixed with 1,10-phenanthroline. The mixed ligand complexes were evaluated for anticancer, antibacterial and antifungal activities.



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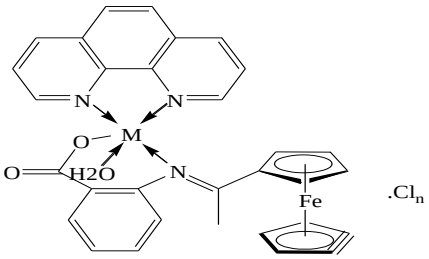
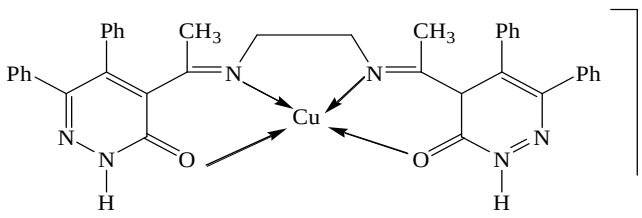


6

A new Schiff base ligand was synthesized by the reaction of 4-acetyl-5,6-diphenyl-3(2H)-pyridazinone with ethylenediamine by *Shebl M. el al*.[8] A series of binary copper(II) Schiff base complexes have been synthesized by using various copper (II) salts, whereas ternary complexes **7** were synthesized by using auxiliary ligands. The synthesized complexes were screened for the antimicrobial activity against Gram positive and Gram negative bacteria, yeast and fungus. The antitumor activity of the Schiff base and some of its Cu(II) complexes was investigated against HepG-2 cell line.

Two novel Schiff base ligands containing 1,2,4-triazole moiety have been synthesized and Co(II), Ni(II), Cu(II) and Zn(II) metal complexes **8** were prepared by *Tyagi P. et al*.[9] The synthesized ligands and their complexes were screened for the anticancer activity against human breast cancer cell line (MCF-7) and human hepatocellular liver carcinoma cell line (Hep-G2). The comparative data indicates that the metal complexes show increased cytotoxicity in proliferation to cell lines as compared to free ligand.



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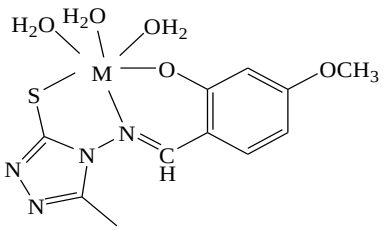
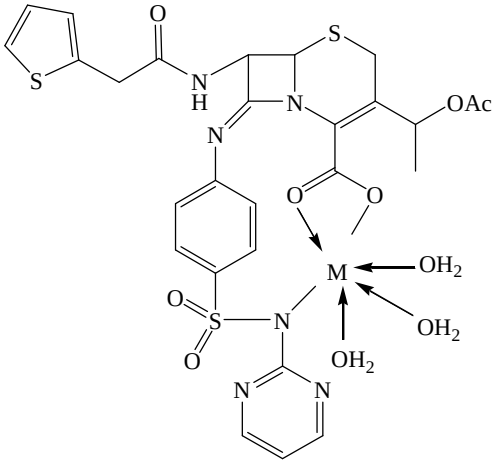


8

Cephalothin and sulfadiazine derived Schiff bases and its transition metal complexes **9** have been prepared by *Anacona J. R. et al*.[10] Cu(II) and Zn(II) complexes of cephalothin Schiff base were found to have privileged bactericidal activity than the cephalothin and the sulfadiazine Schiff bases. The antibacterial activity of cephalothin Schiff base and their metal complexes depends largely on the metal ion and the kind of microorganism. *Nagesh G. Y. et al*[11] reported the synthesis of Cu(II), Co(II), Ni(II), Zn(II) and Cd(II) complexes **10** of the novel Schiff base ligand 2-((2-hydroxynaphthalen-1-yl)methylene)-N-(4-phenylthiazol-2-yl)hydrazinecarboxamide (L), obtained by the condensation of N-(4-phenylthiazol-2-yl)hydrazinecarboxamide with 2-hydroxy-1-naphthaldehyde, and the synthesized ligand and its metal complexes were evaluated for their antimicrobial activity and DNA cleavage activity. Furthermore, *in vitro* cytotoxicity and antioxidant activity of the synthesized ligand and its complexes were determined. Where the data shows that the ligand exhibited better in vitro-antioxidant activity than its metal complexes.



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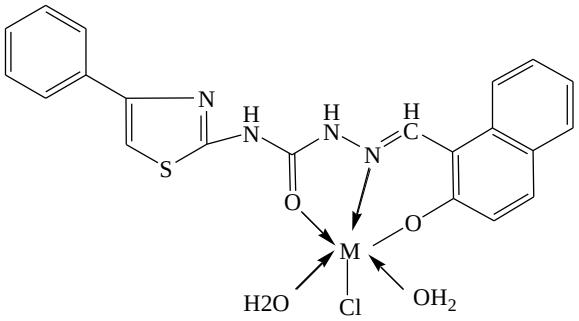
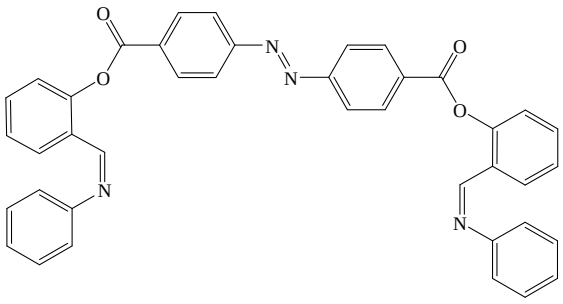


10

Kumar H. et al[12] reported a new heterocyclic Schiff base ligand bis(2-(pyridin-2-ylimino)phenyl)-4,4'-(diazene-1,2- diyl)dibenzoate and its Co(II), Ni(II), Cu(II) and Zn(II) metal complexes **11**. The ligand and its complexes were screened for the antibacterial and antifungal activities. The results revealed that the complexes have superior antimicrobial activities than the ligand and the order of activities was Cu(II)L > Zn(II)L > Ni(II)L > Co(II)L > L. Furthermore, *Kumar H. et al*[13] reported the synthesis of heterocyclic ligand **12**, bis(2-(5-chloropyridin-2-ylimino)phenyl)-4,4'- (diazene-1,2-diyl)dibenzoate and its metal chelates with Co(II), Ni(II), Cu(II) and Zn(II) and were screened for their antipestal activities.



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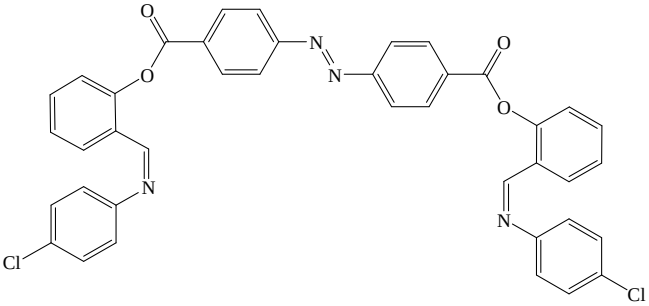
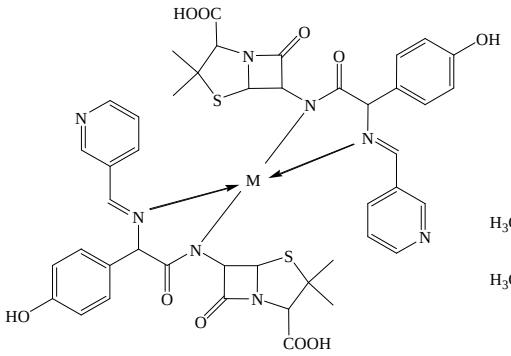


12

A novel synthesis of Schiff base ligand of amoxicillin and their metal complexes **13** of Co(II), Ni(II), Cu(II), and Zn(II) were investigated by *Chaudhary N.K. et al*.[14] The in vitro screening of metal complexes ware carried against four bacterial pathogens, *E. coli*, *P. vulgaris*, *K. pneumoniae*, and *S. aureus*, and showed superior activity compared to parent drug and control drug. *Al-adilee K.J. et al*[15] reported the synthesis of 2- ((*E*) – (1*H*- benzo [d] imidazol-2-yl)diazenyl)-5-(*E*-4-(dimethyl amino) benzyliden amino) phenol from condensation of 2-[(- 2-benzimidazolyl) azo] -5- amino phenol with N,N-dimethyl benzaldehyde. The resultant azo-schiff base ligand was reacted with transition metal ions such us Co(II),Ni(II), Cu(II), Zn(II), Pd(II) and Pt(IV) forming six chelates complexes **14**. The microbial activities of ligand and its complexes were tested in vitro against *Escherichia coli*, *staphylococcus* as antibacterial and *candida albicans*, *Aspergillus Niger* as antifungal. Where, the results showed that the metal complexes have promising activities than the free ligand.



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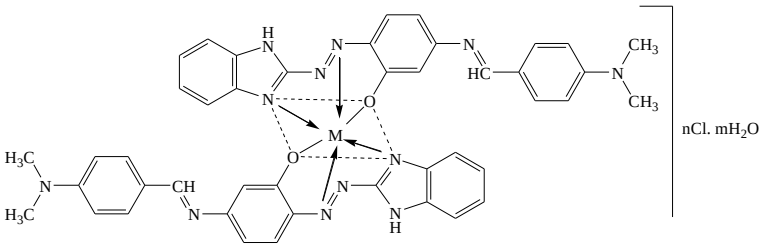
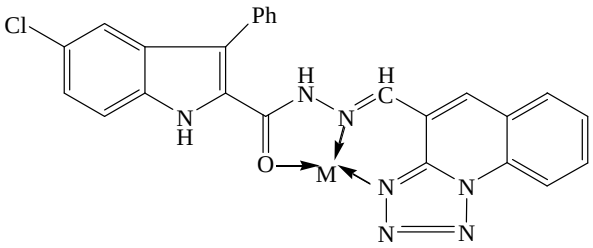


14

The coordination complexes **15** of Cu(II), Co(II), Fe(III), Ni(II), Zn(II) and Cd(II) of 5-chloro-3-phenyl-N'-(tetrazolo[1,5-a]quinolin-4-ylmethylene)-1H-indole-2-carbohydrazide have reported by *Mruthyunjayaswamy B.H.M. et al.*[16] The ligand was synthesized by the reaction between 5-chloro-3-phenyl-1H-indole-2-carboxyhydrazide and tetrazolo[1,5- a]quinoline-4-carbaldehyde. The antibacterial screening of ligand and its metal complexes against *Klebsiella* and *Pseudomonous aeruginosa* and antifungal activity against *Aspergillus niger* and *Aspergillus flavus* was carried in minimum inhibitory concentration (MIC). The data results showed that the synthesized ligand and their complexes have exhibited promising antimicrobial, antioxidant and DNA cleavage activities. *Pelosi G. et al*[17] have evaluated two thiosemicarbazone metal complexes **16** as potential antiviral agents. Particularly, copper complex (3) presents the better results. Moreover, the discovery of new potential anti-HIV drugs has taken into account the screening of the complexes against other retroviruses which frequently coinfect HIV-1 positive patients and interfere with AIDS progression.



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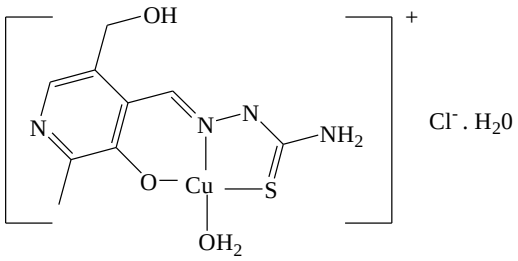
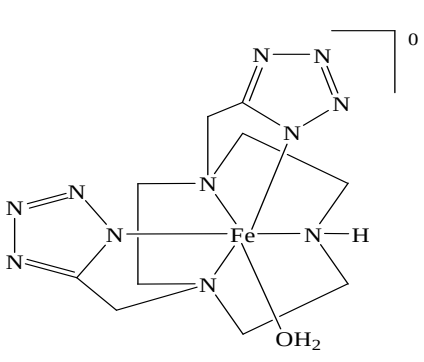


16

The notion of biocompatibility of binary and macrocyclic ferrous complexes **17** at the chosen doses whether displaying an open or closed coordination shell has reported by *Touti F. et al*.[18] The results also demonstrated the principal two objections to the use of iron-based MRI agents in oxidation state II. The synthetic route and the *in vivo* imaging constitute an important step toward to discover an iron(II)-based contrast agent that passes from the low-spin (off) to the high-spin (on) state leading the encounter of a specific target enzyme in the live animal. Six transition metal compounds of Schiff bases were evaluated for the inhibitory activity on jack bean urease by *Chen W. et al*.[19] In particular, the copper (II) complex **18** exhibited potent activity to inhibit jack bean urease (IC_{50} ¼ 0.52 and 0.46 mM) than those of the nickel(II), cobalt(II) and zinc(II) compounds.



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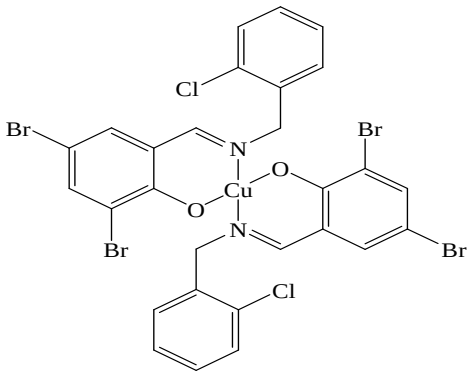
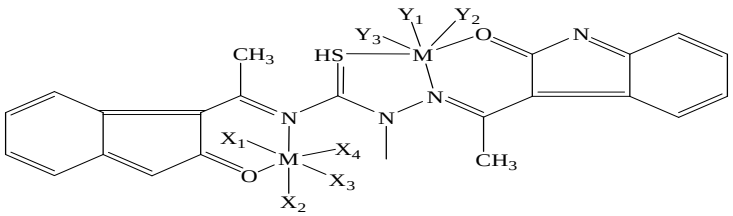


18

Indol-carbothioamide based Ni (II) and Co(II) complexes **19** have been synthesized by *Kumar G. et al*[20] and screened for their promising antibacterial and antifungal activities. *Campbell N.H. et al*[21] have presented the X-ray crystal structures of nickel(II) and copper(II) salphen metal complexes **20** bound to a quadruplex DNA and showed that these salphen−metal complexes bind to human telomeric quadruplexes by endstacking, with the metal in each case almost in line with the potassium ion channel. The complexes show significant antiproliferative activity for the compounds in a panel of cancer cell lines. Furthermore, it shows telomerase inhibitory activity in the telomerase TRAP-LIG assay.



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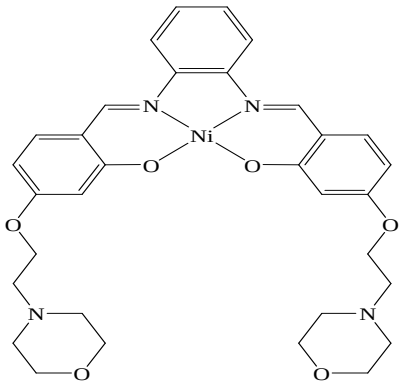
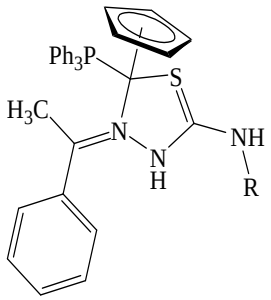


20

Four new cyclopentadienylruthenium(II)-acetophenone-4(N)-substituted thiosemi-carbazone complexes were synthesised and the binding ability of complexes to calf-thymus DNA (CT DNA) **21** and Bovine Serum Albumin (BSA) has been explored by *Devagi G. et al*.[22] The *in vitro* free radical scavenging activity was performed by DPPH radical method where the complexes (1-4) exhibited highest scavenging activity than the standard vitamin C (IC_{50} ¼ 5.65 ± 0.12). Besides, the complexes have been screened for antibacterial activity against four pathogenic bacteria such as *S. paratyphi*, *S. aureus*, *E. coli* and *B. subtilis*. *Zafarian H. et al*[23] reported the synthesis of two bis-hydrazone, by reacting 5,50 -methylene-bis-salicylaldehyde with benzhydrazide and furan-2-carbohydrazide, and new organotin(IV) complexes **22**. The ligands and their binuclear complexes have been evaluated for *in vitro* antibacterial activity against *B. subtilis* and *S. aureus* (Gram-positive bacteria) and *E. coli* and *P. aeruginosa* (Gram-negative bacteria). Besides, they have been investigated for the chromosomal and plasmid DNA cleavage activity. The complexes notably inhibited bacterial growth, despites none of compounds showed DNA cleavage activity.



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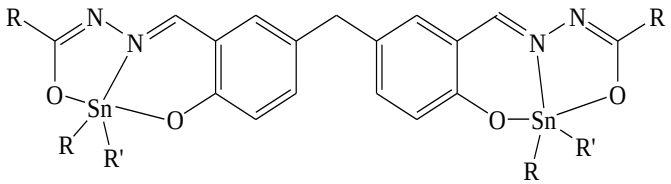
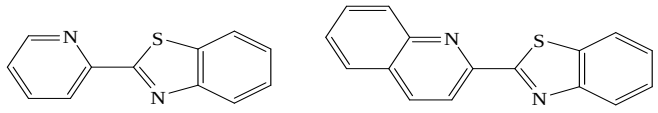


22

The synthesis and bactericidal effect of the two Ag(I) complexes derived from 2-(pyridyl)benzothiazole (pbt) and 2-(quinolyl)benzothiazole (qbt) **23** have reported by *Smith J.S. et al*.[24] Both complexes exhibited significant antibacterial activity against Gram-positive and Gram-negative bacteria, where the bactericidal effect is accompanied by the enrichment in fluorescence due to silver to target the bacteria. *Gulab H. et al*[25] synthesized a new Ca-complex **24**, by the reaction of calcium chloride, sodium 2-mercaptobenzothiazole and 1, 10-phenanthroline, and screened against different bacterial strains i.e. *S. aureus*, *E. coli*, *A. baumanni*, *P. stuartii* and *P. aeruginosa*. The complex exhibited potent anti-bacterial activity against *P. aeruginosa* with an inhibition zone of 25 mm and *A. baumanni* with a zone of inhibition of 16 mm comparable to the Levofloxacin standard with inhibition zone of 25 mm.



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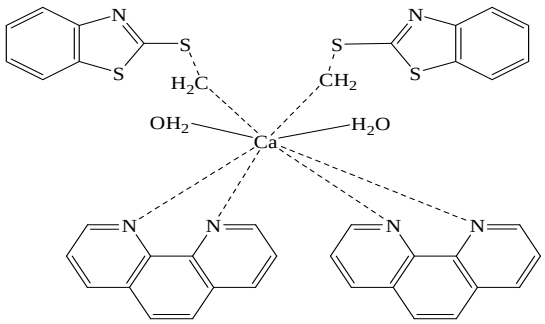
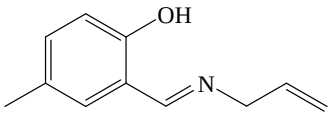


24

A new Schiff base ligand **29** and four new Schiff base complexes have been synthesized and structures of the complexes were elucidated by the single crystal X-ray technique.[26] Piri Z. and co-workers[27] have synthesized 2-acetylpyridine-4*N*-p-chlorophenylthiosemicarbazone ligand, by the condensation of 2- acetylpyridine and p-chlorophenylthiosemicarbazide, and the corresponding Cu (II) complex **25**. The *in vitro* antibacterial activities of pClT, ligand and complex were studied against different bacteria strains where the data results revealed that the involvement of pyridine cycle in the ligand backbone improves the bactericidal effect of thiosemicarbazone ligand in comparison with its thiosemicarbazide precursor (pClT). Additionally, the complex showed higher antibacterial activity than the free ligand.



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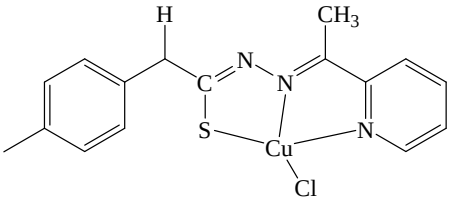
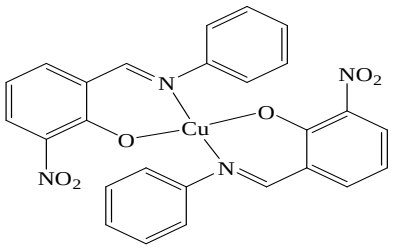


26

A new 3-nitrosalicylaldehyde based Schiff base copper (II) complex **27** was synthesized and the structure was characterized by single-crystal X-ray diffraction and HRMS.[28] The complex displayed the strongest binding ability and high selectivity for hydrogen sulfide among other anions in organic-aqueous solutions at neutral pH. The results also showed that the copper(II) complex exhibited efficient and broad antibacterial activity. *Galini M. et al*[29] reported the four transition-metal complexes **28** of tridentate Schiff base ligand with 2-((*E*)-(2-methoxyphenylimino) methyl)-4-bromophenol and screened for their *in vitro* antibacterial activity against *B. subtilis*, *S. aureus*, *E. cloacae* and *E. coli* and was found higher than the free ligand. The antioxidant activity of the complexes was found to be superior in comparison with ascorbic acid.



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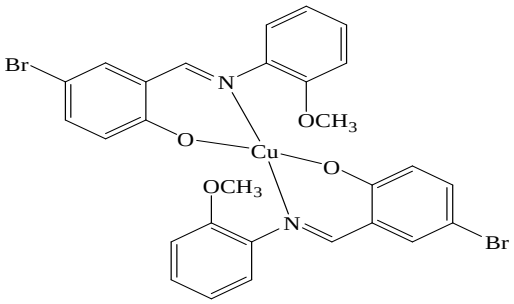
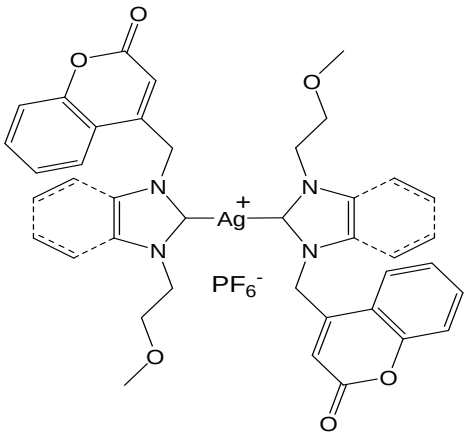


28

Achar G. et al[30] have explored the impact of different coumarin substituted *N*-heterocyclic carbene ligand backbones and their corresponding Ag (I) complexes **26** on the biological applications. A series silver(I) complexes structurally related ether-functionalized imidazolium and benzimidazolium hexafluorophosphate salts bearing 6-methylcoumarin, 6-chlorocoumarin and 5,6-benzannulated coumarin substituents have been reported and evaluated for their the preliminary antibacterial effect against *S. aureus*, *B. subtilis*, *E. coli* and *S. typhi*. Furthermore, Schiff base complexes **30** were tested for their *in vitro* antimicrobial activity against *S. aureus* and *E. coli*. *Reddy N.B.G. et al*[31] have reported the synthesis of novel ligand, *N*-[(4-ethylphenyl)methylidene]-4-hydroxy benzohydrazide and its Co(II), Ni(II), Cu(II) and Cd(II) complexes and

evaluated for their DNA binding studies which revealed that the complexes bind to CT-DNA via intercalation/electrostatic interaction. The results showed remarkable DNA cleavage activity in the presence of H_2O_2 and *in vitro* antibacterial activity against bacterial pathogens.



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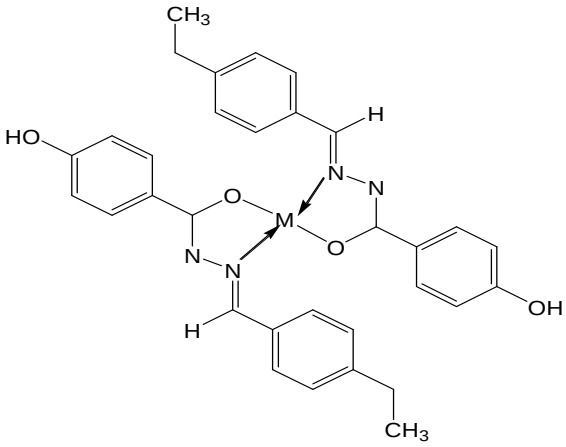
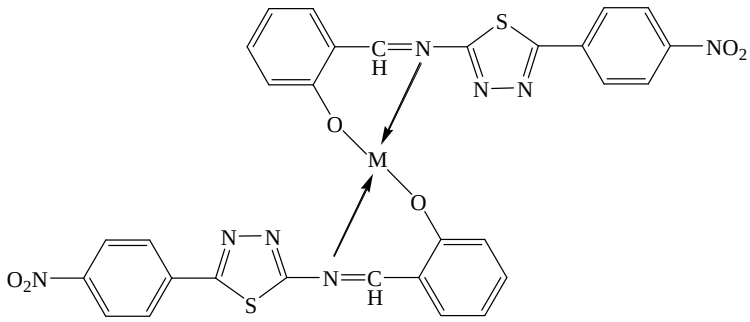


30

Yousif E. et al[32] have reported five new metal complexes **31** of 2*N*-salicylidene-5-(*p*-nitro phenyl)-1,3,4-thiadiazole with the metal ions Vo(II), Co(II), Rh(III), Pd(II) and Au(III) and evaluated for their preliminary *in vitro* antibacterial screening which revealed that the complexes showed notable activity against bacterial strains and slightly higher compared to free ligand. *Balan K. et al*[33] have investigated the antioxidant, antibacterial and enzyme inhibition effects of Schiff base Zn(II) complex **32**. The percentage scavenging activity shows that Zn(II) complex had a potential antioxidant activity. The antibacterial activity of the complex was evaluated against *S. aureus* and *S. Typhi*. The complex displayed strong inhibition toward a-amylase and a-glucosidase with an IC_{50} value of 0.18 and 0.23 mg, respectively. The initial evaluation of a complex showed that it can be used as an antioxidant, antibacterial and antidiabetic agents.



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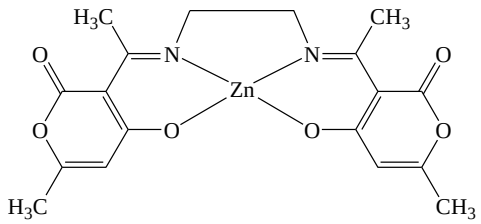
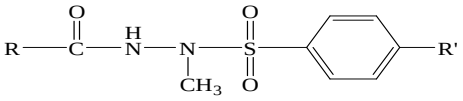


32

The derivatives of acylhydrazine such as; 5-substituted-2-mercapto-1,3,4-oxadiazoles their corresponding S-esters, amides and benzenediazasulfonamides **33** have been reported for their significant *in vitro* antibacterial and antifungal activities.[34] *Kumar A.* and *Kumar D.*[35] have synthesized new metal viz. Mg(II), Fe(II), Co(II), Ni(II), Zn(II) and Cd(II) complexes **34** from 2-(1'/2'-hydroxynaphthyl)benzoxazoles and evaluated for their significant antifungal activity.



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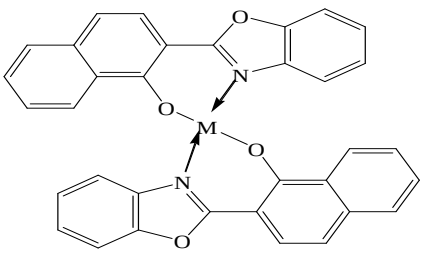
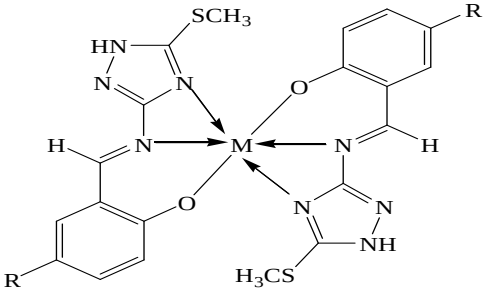


34

Four bioactive triazole derived Schiff base ligands and their Co (II), Ni (II),Cu (II) and Zn (II) complexes **35** have been reported for their potent antibacterial and antifungal activity.[36] The condensation product of 1,8-diaminonaphthalene and glyoxal in the presence of trivalent metal salts in methanolic medium results a new series of complexes **36** of the type $[M(C_{24}H_{16}N_4)X]X_2$.[37]

These complexes were found to show remarkable *in vitro* antimicrobial activities against some bacterial strains, viz. *B. subtilis*, *B. stearothermophilus* (gram-positive bacteria) *E. coli*, and *P. putida* (gram-negative bacteria), and some fungal strains, viz. *A. flavus* and *A. niger*.



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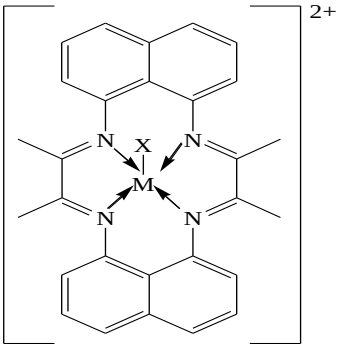
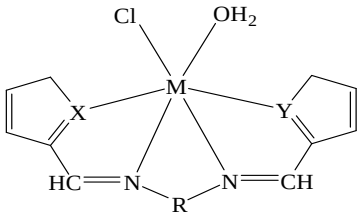


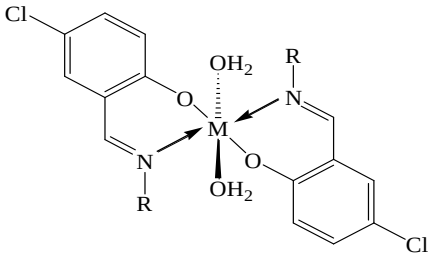
36

Asymmetric salicyl-, furanyl-, thienyl- and pyrrolyl-derived Schiff-bases and their copper(II) and zinc(II) metal complexes **37** were found to exhibit significant antibacterial activity against *B. cereus*, *C. diphtheriae*, *E. coli*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, *S. typhi*, *S.dysenteriae* and *S. aureus* strains and *in-vitro* antifungal activity *against T. schoenleinii*, *C. glabrata*, *P. boydii*, *C. albicans*, *A. niger*, *M. canis* and *T. mentagrophytes*.[38] In this view, Cobalt(II), copper(II), nickel(II) and zinc(II) metal complexes with Schiff base sulfonamides have been synthesized and screened for their *in vitro* antibacterial, antifungal, and cytotoxic properties. Cobalt(II), copper(II), nickel(II) and zinc(II) metal complexes **38** with Schiff base sulfonamides have been synthesized and screened for their *in vitro* antibacterial, antifungal, and cytotoxic properties.[39]



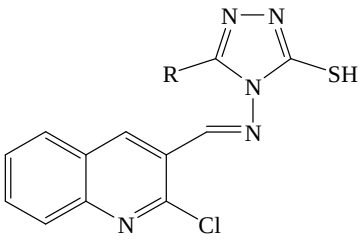
R = Ph; $-(CH_2)_2-$
X = O; S
Y =N

37



38

3- Substituted-4-amino-5-mercapto-1,2,4-triazole derived a new series of Co (II), Ni (II) and Cu (II) metal complexes **39** have been synthesized and screened for their potent *in vitro* antibacterial (*S. aureus*, *E. coli* and *P. aeruginosa*) and antifungal activities (*A. niger*, *P. chrysogenum* and *C. albicans*) by Minimum Inhibition Concentration(MIC) Method.[40] *Celen S. et al*[41] have reported two Schiff base complexes **40**, $[Cu(HL)_2]$, and $[Ni(HL)_2]$, $[H_2L$ =2–((E)–(2–hydroxyethylimino)methyl)–1–naptaphenol] for their antibacterial and antifungal activities.



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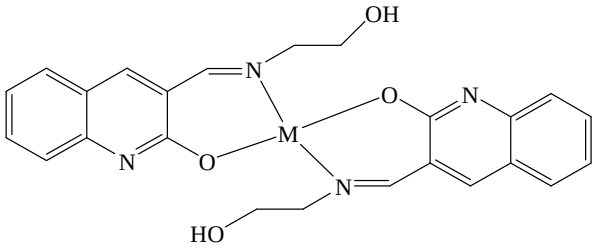

40

Aryl alkylthiosulfinates showing aromatic rings with varying electronic demand have shown good stability as potential allicin mimics and one of them (*p*-OMe) has been characterised as its inclusion compound in the cyclodextrin.[42] Metal complexes of first transition series with Tridentate ligands containing ONO, ONS or ONN as donor atoms have been synthesized and screened for their in vitro antibacterial and antifungal activities.[43] Three bioactive thiourea (carboxamide) derivatives,[44] N-dipropylcarbamothioyl)-thiophene-2-carboxamide, N-(dipropylcarbamothioyl)-5-methylthiophene-2-carboxamide and 5-bromo-N-(dipropylcarbamothioyl)furan-2-carboxamide and subjected to *in vitro* antibacterial and antifungal activity against six bacterial pathogens where bio activity data showed the metal(II) complexes to be more potent than the parent ligands.

The new carboxamides; N,N-bis(thiophene-2-carboxamido)-1,3-diaminopropanol and N,N-bis(furan-2carboxamido)-1,3-diaminopropanol, were synthesized and, screened against *E. coli*, exhibited good to moderate antibacterial effects when compared with sulfamethoxazole and sulfisoxazole antibiotics.[45] A polymeric Cd(II) complex, a trinuclear Ni(II) complex, and a mononuclear Ni(II) complex of ligand 5-methyl-4-phenyl-1,2,4-triazole-3-thione were synthesized and evaluated for antibacterial activity where a trinuclear Ni(II) complex showed potent activity as compared to the ligand and mononuclear Ni(II) complex.[46]

A novel homologous series of alkyl sulfonic acid hydrazides complexes were synthesized as Silver(I) Methanesulfonic acide hydrazide, ethanesulfonic acide hydrazide, propanesulfonic acide hydrazide and butanesulfonic acide hydrazide and the anticancer activities on MCF-7 human breast cancer cell line were investigated by comparing IC_{50} values. The antibacterial activities of complexes were studied against bacterial pathogens and the inhibition activities of Ag(I) complexes on carbonic anhydrase II enzyme (hCA II) by comparing IC_{50} and Ki values.[47]

Three new mononuclear square planar Ni(II) complexes[48] containing pincer type tridentate Schiff base ligands and Two new Schiff bases complexes[49] of 2-((E)-(4-bromo-2-chlorophenylimino)methyl)-4-bromophenol and 1-((E)-(4-bromo-2-chlorophenylimino) methyl)naphthalene-2-ol were investigated separately for their antibacterial activities. Whereas salicylaldehyde derived 2,4-diiodo-6-((2-phenylaminoethylimino)methyl) phenol Schiff base transition metal complexes of Cu(II), Ni(II), Co(II), Mn(II) and Zn(II) have synthesized, characterized and evaluated for their binding efficiency and mode of these complexes with biological macromolecules viz., herring sperm DNA (HS- DNA) and bovine serum albumin (BSA).[50] Furthermore, the ligand and all metal(II) complexes were evaluated for their antibacterial activities.

Chohan Z.H. et al[51] have reported the synthesis, characterization and antimicrobial activities of i) Schiff-base complexes of isatins incorporating thiazole, thiadiazole, benzothiazole and *p*-toluene sulfonyl hydrazide moieties, ii) Isonicotinoylhydrazide Schiff's base complexes, iii) triazine-derived mono- and di-substituted (symmetrical and unsymmetrical) Schiff-base complexes, iv) sulfonamides Schiff's base, v) coumarin-derived compounds.

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