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Biological Utility of Schiff's Bases with Special Reference to Mixed Ligand Complexes: A Review

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Abstract: *Nowadays, the research field dealing with coordination chemistry including Schiff bases as ligands has expanded enormously. The biological importance of Schiff base complexes has shown antimicrobial, anticancer, antidiabetic, antioxidant and antimalarial activities. This review article highlights the most important research related to the mixed ligand complexes of the Schiff's bases and Schiff base ligands and heterocyclic nitrogen base for the past some years where these Schiff's bases has been used as chelating agents and gives the stability to the complexes with transition metal ions where these were synthesized and evaluated for biological utilities.*

Keywords: Schiff bases.

I. INTRODUCTION

Researchers have published reviews about complex metals and their contributions to biological activities; it was made clear that a number of antibiotics contain a metal-binding site. Sometimes, transition metal ions are tightly bound forming stable coordination connections, which have an important structural function and/or are responsible for effective antibiotic action. There are a number of antibiotics that require metal ions to function properly and complexes often show better physicochemical properties and are much more effective than parents drugs. Therefore, bioinorganic chemistry provides a powerful weapon for overcoming numerous challenges encountered in antibiotic chemistry. The fast growing field of bioinorganic chemistry is centered on coordination compounds in living systems. The understanding of structure of coordination compounds of transition metals has captured much interest. They do reveal prominent role in the chemistry of almost all elements. [1] Numerous mixed ligands transition metal complexes have been investigated by various techniques and their biological activities and exhibit many neurophysiological and neuro pharmacological effects like antimicrobial, antiviral, anticonvulsant, anticancer, anti-mycobacterial, antimalarial, cysticidal, herbicidal and anti-inflammatory activity were extensively studied [2-6]

Introduction to mixed ligand complexes

Traditional metal complexes are normally those which involve one metal attached to one type of ligand only. But in recent years a new trend has been developed to study mixed complexes where two metals or two types of ligands are normally involved in one metal complex. Such complexes can show variation in properties and thus keep the researchers always interested.

Mixed complexes involving more than one metal atom in a complex are called as mixed metal complexes. Metal-metal interaction if present in mixed metal type of complexes can give rise to variations in magnetic properties of complexes. Synthesis of complexes involving more than one type of ligands attached to the same metal is also possible. Such complexes are called as mixed ligand complexes. Both mixed metal or mixed ligand complexes are important as there are chances of altering the properties of basic metal complex due to involvement of more than one metal or ligand.

Hugo Schiff in 1864 introduced the world with a new type of ligands, known as 'Schiff bases' using condensation reaction of primary amines with carbonyl compounds [7]. Since then many researchers have worked in this area and the field dealing with Schiff base coordination chemistry has expanded enormously. The common structural feature of these compounds is the azomethine group with a general formula **RHC=NR$_1$**, where R and R$_1$ are alkyl, aryl or heterocyclic groups which may be variously substituted. These compounds are also known as anils, imines or

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azomethines. Several studies revealed that the presence of a lone pair of electrons in a sp^2 hybridized orbital of nitrogen atom of the azomethine group is of considerable chemical and biological importance [8-12]

Mixed ligand complexes of Schiff's Bases

A research paper on synthesis of mixed ligand complexes of transition metal ions Co(II), Ni(II), Cu(II) and Zn(II) using Schiff base, obtained by condensation of thiophene-2-carboxaldehyde with o-phenylenediamine, and 1,10-phenanthroline ligands was reported by SJ Raja et al [13]. All the synthesized compounds were characterized using various techniques such as elemental analysis, molar conductance, magnetic susceptibility measurements, IR, electronic, ^{1}H-NMR and mass spectra. All the synthesized mixed ligand complexes were tested for their catalytic activity in the reaction of oxidation of alcohols by H_2O_2 as oxidant and were proposed to show good activity. The complexes were also tested for antibacterial activity against bacterial pathogens *B. subtilis, S. aureus, E. coli* and *P. mirabilis* and for their DPPH radical scavenging activity (antioxidant studies).

Mixed ligand complexes of transition metal ions Mn(II), Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) using Schiff base ligand, obtained using microwave irradiation of trimethoprim and 2-benzoyl benzoic acid, and 8-hydroxyquinoline were synthesized by RK Al-Shemary et al [14]. All the compounds including the free ligands and their complexes were structurally characterized using techniques such as melting point determination, elemental analysis, AAS, FTIR, UV-Visible, ^{1}H and ^{13}C-NMR, mass spectroscopy, molar conductance and magnetic moment measurements. The obtained results indicated that all the complexes were of octahedral geometry. All the ligands and mixed ligand complexes were tested for their antibacterial activity against *S. aureus, E. coli, E. cloacae* and *B. subtilis*. Based on the results obtained all the complexes were proposed to have an octahedral geometry.

Synthesis of mixed ligand complexes of transition metal ions Co(II), Ni(II), Cu(II), Zn(II) and Cd(II) using Schiff base and phenyl dithiocarbamate as ligands was reported by OE Oyeneyin et al [15]. All the synthesized mixed ligand complexes were characterized for their structure determination using common analytical techniques such as solubility, colour, melting point determination, elemental analysis and FTIR, UV-visible spectra. All the compounds including the free ligands and mixed ligand complexes were tested for their antimicrobial activities against *E. coli, P. vulgaris, S. pneumonia, P. aeruginosa, V. cholera, K. typhii, S. flexneri, S. aureus, B. subtilis, S. umonia, C. albicans, A. flavus, A. fumigetus, R. stolon, M. mucedo, M. amaricana.*

A series of mixed ligand complexes of Co(II) using Schiff base obtained by condensing 4-aminophenol with salicylaldehyde, vanillin, 2-chorobenzaldehyde and benzaldehyde and 8-hydroxyquinoline ligands was synthesized by S Mirza et al [16]. All the synthesized mixed ligand complexes are characterized for their structure determination using gravimetric analysis, CHNS, conductivity measurement and IR, NMR spectroscopy.

Synthesis of two new mixed ligand complexes of transition metals Cu(II) and Ni(II) using Schiff base, obtained by condensation reaction of isoniazid and p-anisaldehyde, as primary ligand and 2,2'-bipyridine as secondary ligands was reported by Md. Maqusul Haque et al [17]. All the compounds used in present investigation including the free ligands and synthesized mixed ligand complexes were structurally characterized using molar conductance, magnetic susceptibility measurement, IR and UV-Visible spectroscopy. The obtained results indicated that all the synthesized mixed ligand complexes were of square planar geometry. All the compounds including the free ligands and mixed ligand complexes were screened for their antibacterial activity against *E. coli* and *B. cereus*.

IN Witwit et al [18] have reported a series of mixed ligand complexes of Mn(II), Co(II), Ni(II), Cu(II) and Hg(II) using E-5-((4-nitrophenyldiazanyl)quinoline-8-ol (L_1) as primary and imidazole (L_2) as secondary ligands. The primary ligand L1 was obtained by diazotization reaction of 4-nitroaniline with 8-hydroxyquinoline. The obtained results indicated that the complexes exhibited various geometries such as octahedral, square planar and tetrahedral. All the synthesized compounds were characterized using elemental analysis, IR, electronic, mass spectra, molar conductance and magnetic susceptibility measurements. All the synthesized compounds were tested for antibacterial activities against *S. aureus, E. faecalis, P. mirabilis, E. coli, P. aeruginosa, K. pneumonia.*

Mohapatra et al [19] have reported a novel series of mixed ligand complexes of Co(II), Ni(II), Cu(II) and Zn(II) using 2-(α-methyl salicylidene hydrazine) benzimidazole as primary and 2,2'-bipyridine as secondary ligands. All the synthesized compounds were structurally investigated using elemental analysis, FT-IR, electronic, ^{1}H-NMR spectra and thermal analysis methods. All the synthesized compounds were tested for their in vitro antibacterial activity against *B.*

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subtilis, E. coli, S. typhi using agar well diffusion method and the obtained results were compared with standard drug ciprofloxacin.

LK Abdul Karem and TH Al-Noor [20] have reported synthesis of mixed ligand complexes of Cr(III), Fe(III), Co(II), Ni(II), Cu(II), Cd(II) and Hg(II) using Schiff base ligand, obtained from amoxicillin drug and 4-Chlorobenzophenone, and Nicotinamide. All the synthesized compounds were structurally investigated using CHN analysis, FTIR, UV-Visible, ^{1}H & ^{13}C NMR spectra, molar conductance, magnetic susceptibility measurements, thermal analysis and atomic absorption methods. The obtained results indicated that all the synthesized mixed ligand complexes exhibited octahedral geometries. All the compounds were also tested for their antibacterial activities against *P. aeruginosa, E. coli, S. aureus* and *B. subtilis*.

MA Oladipo et al [21] have reported synthesis of Ni(II) mixed ligand complexes using tridentate Schiff base ligands L_1: N-salicylidene-o-aminophenol, L_2: N-(5-methoxysalicylidene-o-aminophenol, L_3: N-(2-hydroxy-1-naphthalidene)-o-aminophenol and ammonia. All the synthesized compounds including Schiff bases and mixed ligand complexes were characterized by elemental analysis, IR, electronic, ^{1}H & ^{13}C NMR spectra. The obtained results indicated that all the Ni(II) mixed ligand complexes exhibited square planar geometry. All the compounds were tested for their antibacterial activities against *S. agalactiae, S. aureus, E. coli, K. pneumonia, P. mirabilis, P. aeruginosa, S. typhimurium* using agar well diffusion method and the obtained results were compared with standard gentamycin. The compounds were also tested for their total antioxidant capacities using phosphomolybdenum assay and ascorbic acid was used as standard.

Ranka et al [22] have reported synthesis of mixed ligand complex of Ni(II) using Schiff base ligands 3-(2-phenylhydrazinyl)indol-2-one (L_1) and p-bromo-3-(2-phenylhydrazinyl)indol-2-one (L_2) obtained by condensation of phenylhydrazine with isatin and 5-bromoisatin. All the synthesized compounds were characterized using physicochemical analysis, elemental analysis, molecular weight determination, molar conductance measurements, FTIR, electronic and mass spectra. The obtained results indicated that the Ni(II) complex exhibited slightly distorted octahedral geometry. All the synthesized compounds were also tested for their antimicrobial activities against *S. aureus, P. aeruginosa* and *C. albicans*.

EM Atiyah et al [23] have reported synthesis of mixed ligand complexes of Mn(II), Co(II), Cu(II), Zn(II), Cd(II) and Hg(II) using Schiff base 4,4'-((naphthalene-1-ylimino)methylene) dibenzene-1,3-diol and 8-ydroxyquinoline ligands. The Schiff base ligand used in present investigation was obtained by reacting 2,2,4,4-tetrahydroxybenzophenone and 1-naphthylamine. All the synthesized compounds were structurally analyzed using elemental analysis, chloride content determination, molar conductance, magnetic susceptibility measurements, FTIR, electronic, ^{1}H & ^{13}C NMR spectroscopy and thermal methods. All the compounds were tested for their antibacterial activities against *E. coli* and *S. aureus* by agar well diffusion technique.

Azam et al [24] have reported synthesis of mixed ligand complexes of Uranyl(IV), Th(IV) and Zr(IV) ions using Schiff base S-methyl-2-4(4-methoxybenzylidine)dithiocarbazate and quinoline ligands. The synthesized mixed ligand complexes were structurally investigated using various techniques such as elemental analyses, ^{1}H-NMR, IR, UV-Visible spectra and molar conductance measurements. The obtained results indicated that all the complexes exhibited octahedral geometry. All the compounds were tested for their antibacterial activity against *S. dysenteriae, B. subtilis, A. tumefaciens, E. coli* and obtained results were compared with standard Kanamycin. Also all the compounds were tested for their toxicity study. Molecular docking study using CLC drug discovery Workbench software was conducted for all the synthesized mixed ligand complexes.

Tofiq et al [25] have reported synthesis of mixed ligand complexes of Cu(II), Co(II), Ni(II), Pt(II), Pd(II) and Zn(II) using Schiff base ligand, obtained under solvent free conditions by reacting 2,6-diaminopyridine with cinnamaldehyde using formic acid as catalyst, and 2,2'-bipyridine. All the synthesized compounds were structurally investigated using elemental analysis, molar conductivity, magnetic susceptibility, FTIR, ^{1}H NMR, UV-Visible, mass spectra and thermal methods. The obtained results indicated that Cu(II), Co(II), Pt(II) and Pd(II) complexes exhibited square planar geometry, Ni(II) complex exhibited octahedral geometry while Zn(II) complex exhibited octahedral geometry. All the compounds including the newly prepared Schiff base and mixed ligand complexes were tested for their antibacterial activities against *E. coli, S. aureus* using agar well diffusion method and the obtained results were compared with gentamycin.

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NS Yahaya and MS Mukhtar [26] have reported synthesis of Schiff base using mixed ligands of 3-aminophenol and benzaldehyde and mixed ligand complexes of divalent transition metal ions. All the synthesized compounds were characterized using various analytical techniques such as melting point determination, solubility, FTIR, UV-Visible spectra and molar conductance measurements. The obtained results indicated octahedral and tetrahedral geometries for the complexes. All the synthesized compounds were tested for their antibacterial activity against *E. coli, S. typhi, S. aureus, S. pyrpgens* using disc diffusion method and the obtained results were compared with those of standard drug Ceftriaxone.

Md Kudrat-E-Zahan et al [27] have reported synthesis of a series of transition metal complexes of Cu(II), Ni(II) and Zn(II) using Schiff base Thiophene-2-Carbaylidene-isonicotinohydrazone, obtained by condensing isoniazid with thiophene-2-carbaldehyde, and 1,10-phenanthroline. All the synthesized compounds were structurally investigated using melting point/decomposition temperature determination, elemental analysis, IR, electronic spectra, molar conductance and magnetic susceptibility measurements. The obtained results indicated that Cu(II) and Ni(II) complexes exhibited square planar geometry while Zn(II) complex was of tetrahedral geometry. All the compounds were investigated for their antibacterial activity against *E. coli, Pseudomonas sp.* and the obtained results were compared with Kanamycin. Also all the compounds were tested for their antioxidant activity using DPPH radical assay.

II. CONCLUSION

The chemists and pharmaceutical researchers are always in search of new drugs which can prove better than the earlier drugs available for the society in different aspects such as cost factor, availability and use. The variations or alterations in the biological activities expected may lead to new antifungal, antibacterial or antimalarial drugs which may prove helpful for the society. From above cited work on the mixed ligand complexes of Schiff's bases and other secondary ligands it is found that they were synthesized and evaluated for the biological utilities.

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