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A review on biological activities of Schiff base ligand and their metal complexes

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Abstract : Schiff bases and their metal complexes are wide range of biological applications and are synthesized from the condensation reaction of amino compounds with carbonyl compounds. Schiff base and their metal complexes have a wide variety of applications in food and dye industry, agrochemical, polymer, catalysis, analytical chemistry, antifertility, anti-inflammatory activity, antiradical activity, and biological system as enzymatic agents. Several have reviewed them of their antimicrobial, antibacterial, antifungal, antitumor, and cytotoxic activities. This review summarized the most promising biological activities of Schiff bases and their metal complexes.
Keywords : Schiff bases, metal complexes, biological activity.

Introduction:

Schiff base in a broad sense have the general formula $R_1R_2C=NR_3$, where R is an organic side chain. In this definition, Schiff base is synonymous with azomethine. Thus, the general formula RCH=NR [1]. Schiff base can be synthesized from an aromatic amine and a carbonyl compound by nucleophilic addition forming a hemiaminal, followed by a dehydration to generate an imine. Imines that contain an aryl group bounded to the nitrogen or to the carbon atom are called Schiff base(Fig.1)[2].Schiff base are capable of forming coordination bond with many metal ions through both azomethine group and phenyl group.Schiff base are capable of forming coordination bond with many metal ions through both azomethine group and phenyl group(Fig.2). Many Schiff bases were prepared by condensation reaction of certain aromatic amines a with aromatic aldehydes derivatives.

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$$Ar\text{-}NH_2 + Ar\text{-}CHO \longrightarrow Ar\text{-}N{=}CH\text{-}Ar$$

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Figure 1. General Scheme for synthesis of Schiff Base

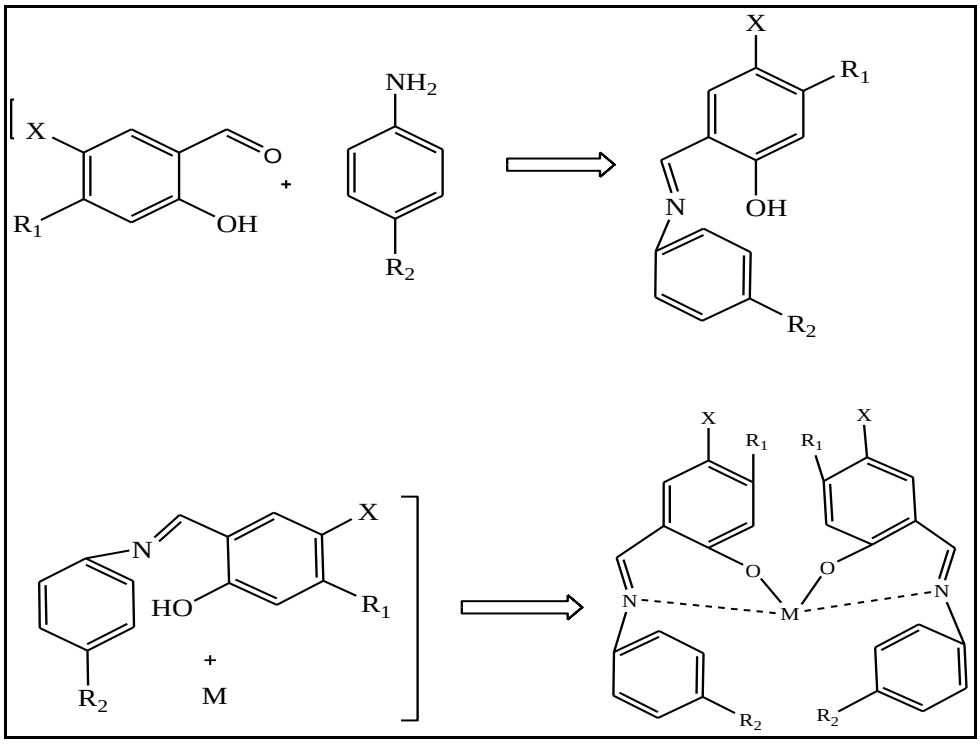

Figure 2. General Scheme for synthesis of Schiff Base Metal Complex

The Schiff base are more effective as chelating agents and form five or six member chelates, such variation in Schiff base are responsible to great flexibility in the structure of their metal complexes[3]. Particularly, the Schiff base complexes are widely useful in various biological systems, catalysis, polymers, dyes as well as enzymatic agents. Amongst various oxygen-nitrogen donor ligands, β-diketones, simple as well as substituted ones, bear special status amongst organic compounds because of their excellence co-ordination capability towards metal ions and increased biological activity.

01) Antimicrobial activity

Antibacterial activity:

Schiff base copper complex derived from imidazole-2-carboxaldehyde with L-phenylalanine exhibited a higher antibacterial activity than the Co (II), Ni (II), Zn(II) metal complexes [4]. Comparative studies of Schiff base derived from 2-aminophenol and furan 2-carbaldehyde and its metal complexes show moderate to better antibacterial activity due to the chelation of metal ion with the ligand enhanced lipophilicity due to delocalization of pi electron over the whole chelate ring. This increased lipophilicity enhances the penetration of complexes into the lipid membranes and blocks the metal binding site in enzymes of microorganism [5]. The complex of 2-(salicylimino)-3-hydroxypyridine exhibited moderate antibacterial activity against *E. Coli, S. Typhi, S. Aureus* [6]. Schiff base derived from 4-aminoantipyrine,3-hydroxy-4-nitrobenzaldehyde and o-phenylenediamine and its metal complexes where tested against the bacteria *S.typhi, S. Aureus, E. Coli and B. subtilis* by the well diffusion method indicate that most of the complexes have higher antibacterial activity than free ligand. These increases in activity of the metal complexes are due to the chelation [7].The Schiff base ligand derived from o-Acetoacetylphenol and 2-hydroxy benzohydrazied and its metal complexes tested against organism *S.typhi, S. Aureus, E. Coli and B. subtilis*by using standardized disc-agar diffusion method. Antibiotic chloramphenicol was used as reference in case of gram positive bacteria while cephalothin in case of gram negative bacteria. The observation showed that ligand is highly active against *S.typhi, S. Aureus* whereas low active against other microorganism however activity of metal complexes toward microorganism is very high [8]. The Schiff base of 1,2-diaminopropane with substituted salicyaldehyde 2-hydroxy-6-isopropyl-3-methyl benzaldehyde and its metal complexes tested against *S. Aureus, E. Coli and B. subtilis* bacteria were compared with standard drug Ciprofloxacin and Ampicillin. The observation showed better antibacterial activity as

compared to the standard drug Ampicillin and lower activity than Ciprofloxacin [9]. The antibacterial activity of the ligand derived from 4-Acetyl-5,6-diphenyl-3(2H)-pyridazinone and ethylenediamine and its metal complexes was investigated against *S. aureus* and *B. subtilis* as Grampositive bacteria, *E.coli* and *S. typhimurium* as Gram enegative bacteria, yeast: *Candida albicans.* The ligand is only active towards Bacillus subtilis and the complexation process enhanced this activity of complexes. The some complexes showed a lower antimicrobial activity against Salmonella typhimurium, few complexes showed intermediate to higher activity against Escherichia coli, some complexes showed lower to intermediate activity towards Candida albicans, all complexes are biologically active with higher activity for most of them [10].The antibacterial activity study indicated that the metal complexe of 2-benzo[*d*]thiazol-6 ylimino)methyl)benzene-1,4-diol are more active compared to free ligand[11].The Schiff base ligand was synthesized from leucine and salicyldehyde and its metal complexes have higher values of antibacterial activities thanSchiff base ligands[15]. The bacterial screening results revealed that the Schiff base ligands namely 1-ferrocenyl-3- (2-furyl) propenonediamino (thio) urea and its metal complexes were shown to have significant activity against all bacterial strains. In addition, the results showed that all Schiff base complexes containing ferrocene groups have higher inhibitory activity [21].

Antifungal Activity:

The Schiff base of 1,2-diaminopropane with substituted salicyaldehyde 2-hydroxy-6-isopropyl-3-methyl benzaldehyde and its metal complexes of Mn (II) and Ni(II) showed very poor antifungal activity as compared to the standard drug Miconazole and Fluconazole whereas metal complex of Co(II) possesses equal antifungal activity against the *C. neoformans*as compared to the standard drug Miconazole[4].The antifungal activity of the ligand derived from 4-Acetyl-5,6-diphenyl-3(2H)-pyridazinone and ethylenediamine and its metal complexes was investigated against Aspergillus fumigatus showed lower to intermediate activity[10].The antifungal activity study indicated that the metal complexe of 2-benzo[*d*]thiazol-6 ylimino)methyl)benzene-1,4-diol are more active compared to free ligand[11]. The Schiff base ligand was synthesized from leucine and salicyldehyde and its metal complexes have higher values of antifungal activities than schiff base ligands ligands[15]. The fungicidal screening show that Schiff base ligand prepared from p-nitrobenzaldehyde and 2 (aminomethyl)benzimidazoledihydrochloride and its metal complexes with l-histidine as a coligand were highly active than the free ligand against phytopathogenic fungi. The increase in biological activity of the metal chelates may be due to the effect of the metal ion on the normal cell process[19]. Antifungal activity of the Schiff base ligands were synthesized by the reaction of Salicylaldehyde with semi-aromatic diamines and its metal complexes was checked against five fungal strains including Mucor species, Aspergillus niger, Aspergillus fumigates, Aspergillus flavus, and Fusarium solani. The test compounds showed varying degree of inhibition on the growth of the fungal strains[20].The Schiff base 1-ferrocenyl-3- (2-furyl) propenonediamino (thio) urea and its complexes exhibited varying degrees of inhibitory effect on the growth of selected microorganisms. The antifungal activity of the compounds was tested against *C. albicans* and *A.flavus*. From the comparison of the activity of complexes with these Schiff base, it seemed that all complexes have better values of antifungal activities than their bare Schiff base ligand under the same experimental conditions with the highest antifungal activity observed for Cd(II) complex[21].

Cytotoxic activity:

Schiff base ligand derived from o-Acetoacetylphenol and 2-hydroxy benzohydrazied and its metal complexes Ni(II), Cu(II) tested. Cell toxicity was monitor on HePG2 cell. From observation, complexes showed lower anti-cancer activity against human cancer cell line liver carcinoma. The order of activity is as Cu(II) complex > Ni(II) complex > H_3L ligand[8].The potential anti proliferate impact of Schiff base ligand 2-(phenyl((2-piperazin-1-yl)ethyl) imino) methyl) phenol with flexible piperazinyl moiety on cancer cell line show no cytotoxic effect while the complex show considerable cytotoxic effect toward cancer cell line[9]. The antitumor activity of the Schiff base ligand derived from 4-Acetyl-5,6-diphenyl-3(2H)-pyridazinone and ethylenediamine and its complexes was determined in vitro against human cancer cell line liver Carcinoma (HEP-G2). The ligand showed activity towards HEP-G2 and complexes are more active than the free ligand. The higher activity of the complexes than the ligand may be due to the increased conjugation in the ligand skeleton as a result of complex-formation [10].The Schiff base ligand derived from 2-hydroxy 1-naphthaldehyde and 2-methoxyethylamine and their metal complexes showed cytotoxic activity against MKN-45 cancer cell line. The treatment of cells with compounds showed changes in their morphology in form of chromatin condensation and nuclear fragmentation [11]. The ONO-tridentate Schiff base derivative of

galactochloralose and its dinuclearCu(II) complex may be considered as a new metal-based anticancer drug as alternative to *cis*platin[18]. The in vitro cytotoxicity of the Schiff base ligand prepared from p-nitrobenzaldehyde and 2 (aminomethyl)benzimidazoledihydrochloride and its metal complexes with l-histidine as a coligand on human cell lines HeLa, HepG2 and MCF-7 along with NHDF was determined by MTT based assay. The observation showed that metal complexes can exhibit greater activities than the free ligand. The IC_{50} values suggest that the Cu(II) complex shows superior activity compared to the other metal complexes and the ligand. All the metal complexes achieved some activity than the ligand signifying the presence of a metal ion in the complex[19]. The antitumor activity of the Schiff base ligands were synthesized by the reaction of salicylaldehyde with semi-aromatic diamines and its metal complexes was checked by Potato disc antitumor assay since mechanisms for tumor induction are reported to be similar in plants and animals. The results showed their antitumor effects through binding to DNA thereby changing the replication of DNA and inhibiting the growth of the tumor cell [20].

The cytotoxic ability of Schiff base 1-ferrocenyl-3- (2-furyl) propenonediamino (thio) urea and its complexes were valuated against mouse leukemia cells (P-388) and lung cancer (A-549) cell lines. In addition, an endothelial cell line, EA.hy926 was also used as a model for normal cells. The in vitro screening of the anticancer activity detected that the investigated compounds have a significant cytotoxicity against P-388 and A-549 cell lines. Moreover, the results revealed that Cu (II), Cd(II) and Ni(II)have more anticancer activity than their corresponding Schiff base ligands. It was observed that Cu (II)was more potent against mouse leukemia cells (P-388), but both Cd(II) and Ni(II)have more cytotoxic activity against lung cancer (A-549) cell lines [21].

DNA cleavage activity:

Schiff base derived from 4-aminoantipyrine, 3-hydroxy-4-nitrobenzaldehyde and o-phenylenediamine and its metal complexes showed interaction with CT-DNA was investigated by gel electrophoresis. From the observation Cu (II), Ni(II) and Co(II) complexes cleavage DNA as compared to control DNA and other complexes in presence of H_2O_2[7]. The chemical nuclease activity of Schiff base of 1,2-diaminopropane with substituted salicyaldehyde 2-hydroxy-6-isopropyl-3-methyl benzaldehyde and its cobalt metal complex showed pBR 322 DNA cleavage in presence of H_2O_2 [9].The DNA binding ability studies of metal complexe of 2-benzo[*d*]thiazol-6-ylimino) methyl) benzene-1,4-diol showed that metal complexes effectively cleaved supercoiled pBR322 DNA as compared to the Schiff base ligand in the presence of H_2O_2as well as UV light[11]. The Curcumin derived Schiff base and their metal complexes displayed moderate to good cytotoxicity on different cancer cell lines during their *in-vitro* anticancer evaluation [17]. The DNA cleaving ability of the synthesized metal (II) complexes from Schiff base ligand of p-nitrobenzaldehyde and 2-(aminomethyl)benzimidazoledihydrochloride with l-histidine as a coligand was assessed. Studies showed the cleaving abilities of the complexes from supercoiled form to nicked circular and linear forms [19]. The dinitrometal complexes and Schiff base ligands derived from salicylaldehyde with semi-aromatic diamines were found DNA protecting in nature in concentration dependent manner while the complexes caused a significant damage to the plasmid DNA at all the tested concentrations. The ability of test compounds to unwind or condense the Plasmid pBR322 DNA is checked by observing the increase or loss of percentage of supercoiled form of DNA [20].

Antioxidant Activity:

The Schiff base of 1,2-diaminopropane with substituted salicyaldehyde 2-hydroxy-6-isopropyl-3-methyl benzaldehyde possesses better antioxidant property as compared to ascorbic acid as standard and its metal complexes exhibited higher scavenging activity than Schiff base ligand [9]. The antioxidant activity of Curcumin derived Schiff base and their metal complexes shows that Cu(II) and Zn(II) complexes have more antioxidant activity[17].The ability of the Schiff base ligands derived from Salicylaldehyde with semi-aromatic diamines to act as free radical scavengers or hydrogen donors was measured by DPPH free radical scavenging assay. The results reveal that the antioxidant activity of all the compounds was concentration dependent and generally increased with increase in their concentration. The dinitro compounds and diamine precursors showed moderate percentage scavenging values in DPPH free radical [20].

Anthelminthic activity:

The anthelminthic activity was performed using Pheretimaposthuma. The order of anthelminthic activity of Curcumin derived Schiff base and its complexes confirms that the copper and zinc complex was comparatively more effective [17].

02) Catalytic activity:

Reduced tridentate Schiff base ligands synthesized from 2(2-aminoethyl)pyridine with 5-bromosalicylaldehyde and 3,5-dibromosalicylaldehyde and their Mn(III) and Mn(II) complexes are promising catalysts for epoxidation reaction using H_2O_2as oxidant. These complexes catalyzed the efficient epoxidation of cyclohexene and 1-hexene[12]. Complexes of Schiff base derived from hydroxybenzaldehyde are used for the oxidation of cyclohexane in presence of H2O2. The Fe(II)complex is most efficient as compared to the Co(II) and Ru(III) complexes[13]. The catalytic potential and antioxidant activity of Curcumin derived Schiff base and their metal complexes shows that Co(II) complex is more potent for catalytic power and Cu(II) and Zn(II) complexes have comparatively more antioxidant activity [17].

Concluding remarks:

Schiff bases and its metal complexes have been widely explored for Pharmaceuticals applications.However, the biological activities of this class of Schiff base metal complexes need further investigation. The researchon this subject is incipient, a number of literature disclosingthe effects of the Schiff bases on the pathogens of clinical interesthave been increase recently. Schiff base compounds havebeen shown to be promising leads for the synthesis of more efficientantimicrobial and antifungal agents.

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