International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Impact Factor (2012): 3.358

Biological Applications of Schiff base and its Metal Complexes-A Review

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Abstract: ***Schiff Bases play an important role in Inorganic chemistry due to formation of very stable complexes with various transition and inner-Transition Metals. It has been extensively studied over past decades as Schiff bases provide potential sites for bio-chemically active compounds. This review is to summarize various Biological activities of Schiff Bases complexes as it has been recognized widely and Complexes may serve as biologically important species. Most of them show Biological activities such as antifungal, antibacterial, antimicrobial, and enzymatic activities.***

Keywords: Antibacterial, Antifungal, Antimicrobial Biological activities, enzymatic activities, Schiff Bases.

1. Introduction

Schiff Bases have been known since 1864 when Hugo Schiff reported the condensation of primary amines with carbonyls compounds [1]. Schiff Bases of aliphatic aldehyde are unstable in nature and readily get polymerized where as Schiff Bases with aromatic aldehyde are more stable due to conjugation system. Schiff Bases derived from amino acids are an important class of ligands that coordinate to metal ion by azomethine nitrogen. Ligands with heterocyclic molecules containing heteroatoms such as N, O, S and in azomethine derivatives, C=N linkage is essential for biological activities. The presence of lone pair of electron in sp2 hybridized orbital of nitrogen atom of the azomethine is of considerable chemical and biological importance. Schiff Bases are good chelating agents; generally bi- or tri- dentate ligands are more capable of forming very stable complexes with transition metals. Therefore Schiff bases metal complexes were widely investigated for their antifungal, antibacterial, antimicrobial, diuretic and antitumor, Antifertility and enzymatic activities [2]-[6].

2. Antibacterial Activities

Methicillin resistance *staphylococcus aureus* causes many problems as it has become resistance to almost currently available antibiotics. Two Antibiotics, vancomycin and Teicoplanin does not show resistance to *s.aureus*. But recently studies and data from many countries show that VISA (Vancomycin-intermediate *s.aureus*) and VRSA (Vancomycin-resistance *s.aureus*) increasing in many countries, as susceptibility toward Vancomycin has been decrease.

Two Schiff base ligand derived from condensation of 1-naphtylamin and 2-Hydroxynapthalene-1-carbaldehyde (HL) and 1, 2-bis-(p-aminophenoxy) ethane with 2-hydroxynaphthalene-1-carbalddehyde (H_2L') used over the growth of Gram-positive bacteria (*staphylococcus aureus*) and Gram- Negative bacteria *(pseudomonas aeruginosa*) added in the base media at different concentration to observe the bacterial growth. Effect of ligand H2L' and its complexes with the metals Co, Zn, Cu and Ni on Gram-positive (*Staphylococcus aureus*) and Gram-negative (*pseudomonas aeruginosa*) show decrease in the colony when the concentration of Schiff base complex was 4.8 µg/100 ml and same effect was noticed with ligand HL and its complex with Ni and Cu on Gram-positive (*Staphylococcus aureus*) and Gram-negative (*pseudomonas aeruginosa*) when the concentration was 4.8 µg/100 ml. It was found that Schiff Base complexes with this ligand mainly with Cu metal show more inhibiting effect on *Escherichia coli, pseudomonas acurtuginan, Aspergillus niger, aspergillus ferreus, Barilium sp and Penisilium rubrum.*

The Schiff base derived from 2-furancarboxaldehyde and 2-aminobenzoic acid and its metal complexes with Cu (II), Ni (II), Co (II), and Fe (III) has biological activities against *bacteria staphylococcus pyogenes, E.coli* and *pseudomonas aeruginosa* [7]-[8], taking streptomycin as a standard, using Mueller- Hinton agar as a medium with 2% glucose. The diameter of inhibition was visualized after 24 hr at 37^{o}c and found to be effective against them.

Macro cyclic Hydrozone Schiff Bases synthesized by condensation of 1, 6- bis (2-formylphenyl) hexane and Glutaraldehyde with dihydrazide of isophthalic acid and dihydrazide of terephthalic acid were tested for their microbial activities against four species of bacteria *Bacillus subtilis, staphylococcus aureus* (Gram-negative), *Salmonella typhi and E. coli (*Gram-positive) using different concentration (50, 100 and 200 µg/ml) by dissolving in DMSO individually. The diameter of inhibition zone (mm) was measured at the end of the incubation period that is 24 hr and 37^o c for bacteria. Ciprofloxacin used as reference material for bacteria. In another method, Schiff Bases derived from indoline-2, 3-dione and 2-aminobenzoic acid and its complex with Tin metal also show some antibacterial activity against Gram-positive bacteria *staphyloco-ccus aureus.* This activity might be due to presence of phenyl and hydroxyl group. The result was compared with standard drug called imipinem and it is found to be more active then the Schiff base complex with Tin metal [9] - [10].

Schiff base derived by condensation of 3-hydroxy-4-methoxybenzaldehyde with furan-2- carboxylic acid hydrazide and thiophene-2-carboxylic acid hydrazide gave L_1 and L_2 with Co (II) and Cd (II) metals. The free Schiff Base ligands and their metal complexes were tested against

Bacillus (Gram-Positive) and *E.coli* (Gram-Negative) to check their potential as an antibacterial agent by disc diffusion method. It was found that the ligand has higher antibacterial activity than its metal complexes. The lower antibacterial activity of metal complexes is may be due to strong interaction between the imine moieties and the metal ions. This type of interaction reduces the activity of imine moieties toward inhibition of bacterial activities where as the ligand has higher antibacterial activity than its metal complexes [11]-[12]. The lanthanide complexes of the newly reported Schiff base were tested for antibacterial activity against bacteria *E.Coli* and *B.Subtilis* in which both ligand and metal complexes are active against the two bacteria namely *E.Coli* and *B.Subtilis*. All metal complexes namely $[LaL_2(NO_3)_3]$,$[NdL_2(NO_3)_3]$, $[SmL_2(NO_3)_3]$, $[GdL_2(NO_3)_3]$, $[TbL_2(NO_3)_3]$, $[DyL_2(NO_3)_3]$, $[CeL_2(NO_3)_3]$,$[PrL_2(NO_3)_3]$, and $[ErL_2(NO_3)_3]$ are all highly active against the two bacteria. Metal complexes of praseodymium and erbium show high antibacterial activity where as lanthanum and samarium moderately active towards bacteria *E.coli.* whereas *B.subtilis* was found to be highly active against cerium, praseodymium and erbium complexes and moderately active with lanthanum complex. The ligand was active towards both *E.coli* and *B.subtilius* [13]-16].

Another Schiff Base, Potassium 2-N(4-N,Ndimethylaminobenzylidene)-4-trithiocarbonate1,3,4-thiadiazole a dark orange colored ligand and its complex with metals Co(II),Cu(II) and Ni(II) show anti -bacterial activities. The results show that Schiff base ligand Potassium 2-N (4-N, N dimethylaminobenzylidene)-4-trithiocarbonate1, 3, 4-thiadiazole does not show any antibacterial activity towards Gram-positive (*Staphylococcus aureus*) and Gram-negative (*pseudomonas aeruginosa*). But the Cu (II) complex show slight effect with both bacteria used. Co (II) complex show moderate activity against Gram-positive (*Staphylococcus aureus*) while against Gram-negative (*pseudomonas aeruginosa*) result show no activity. Moreover Ni (II) complex exhibited maximum activity towards both Gram-positive (*Staphylococcus aureus*) and Gram-Negative (*pseudomonas aeruginosa*). Ampicillin used as a reference drug [17]. More activity of metal complexes than those of ligands can be explained on the basis of Overtone's concept and chelation theory. On the basis of these theory, it may be understand that it enhance the penetration of metal complexes into the lipid membranes blocking of the metal binding sites in the enzyme of micro-organism [18].

3. Antifungal Activities

Study shows that some of the Schiff Base is very effective in prevention of fungal infection. As fungal infection not only limited to superficial tissues but in some cases it is become life threatening [19]-[21].

Production of most of the cruciferous crops like cauliflower, cabbage, mustard, radish etc is effective by Fungi like *Alterneria brassicae* and *Alterneria brassicicola*[22]. Schiff Base N-(salicylidene)-2-hydroxyaniline inhibited the growth of both fungi by 67-68% at the concentration of 500 ppm [23]. Chitison-derived Schiff Base inhibited the growth of *Botrytis cinerea* fungi by 26-33% at concentration of 1000 ppm and inhibited the growth of *colletotrichum lagenarium* fungi by 35-38% at same concentration i.e 1000 ppm [24].

Antifungal activities of 2-amino-benzthiazole and 4-amino-salicylic acid Schiff Bases against *Asperigillus niger* and *Chalara Corda* evaluated by using Sabarod's agar (agar disc-diffusion method), pouring about 50 µL Schiff base dissolved in DMSO(25 mg/ml), incubated at 27^0c for 3-7 days. From the result obtained after antifungal activity, it is found that benzthiazole Schiff base are more effective against all tested Fungi than the salicylic Schiff base. The greater activity of these compounds is probably due to the presence of benzthiazole moiety [25]-[29].

Ruthenium (II) triphenylposphine complex containing bidentate Schiff Base derived from condensing salicyladehyde with aniline o,m, and p-toluidine show antifungal action against fungi *Aspergillus flavus*. Fungi *Aspergillus* flavus cultured on sabouraud and maltose agar medium incubated at 30^oc for 72 hr and then using metal complex in DMSO in control manner inhibited the growth of fungi about 68% [30].

Various other Schiff bases of 4(2-aminophenyl) morpholine like 4(2-(Benzylideneimino) phenyl) morpholines, 4(2-(3-nitrobenzylidine imino phenyl) morpholine, *4*(2-(2-chloro Benzylidene imino) phenyl) morpholines and 4(2-(phenyl propylideneimino) phenyl) morpholines compounds [31] evaluated for their *in vitro* antifungal activity against *Aspergillus Niger* and *Candida albicans* using the agar dilution method with sabouraud's dextrose agar. Suspension of these micro-organism (10^5cfu/ml) incubated with diluted Schiff base compounds prepared of concentration of 10 µg/ml for 48-72 hrs at 26^oc and minimum inhibitory concentration (MIC) were determined. Zone of inhibition was found maximum for 4(2-(phenyl propylideneimino) phenyl) morpholines against *Aspergillus Niger* and 4(2-(Benzylideneimino) phenyl) morpholines show maximum inhibition zone toward *Candida albicans.* Ketoconazole (10µg/ml) used as reference [32]-[37].

4. Enzymatic Activities

Schiff base linkage with pyridoxal 5' phosphate (PLP) a derivative of pyridoxine commonly known as vitamin B_6 abolished the enzyme activities of Proteins. PLP binds to number of specific enzymes and play a critical role in helping these enzymes to catalyze their reaction. Most enzymes that interact with PLP catalyze reactions involved in the metabolism of amino acids. In many PLP dependent enzymatic reactions, PLP forms a Schiff base link with Lysine residue on the enzyme. Another Schiff Base complex of 2-pyridine carboxyaldehyde and its derivative show high super oxide dismutase activities [38]. Ternary complex of Cu (II) containing NSO donar Schiff base showed DNA Cleavage activities.

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