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Review Article

APPLICATION OF METAL COMPLEXES OF SCHIFF BASES AS AN ANTIMICROBIAL DRUG: A REVIEW OF RECENT WORKS

KUMBLE DIVYA*, GEETHA M. PINTO, ASHA F PINTO

Department of Post Graduate Studies and Research in Chemistry, *St. Agnes* College, Mangaluru 575002, Karnataka, India
Email: kumbledivya71088@gmail.com

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ABSTRACT

Schiff bases are versatile ligands which are synthesized from the condensation of primary amines with carbonyl groups. Synthesis of Schiff base transition metal complexes by using Schiff base as ligands appears to be fascinating in view of the possibility of obtaining coordination compounds of unusual structure and stability. These transition metal complexes have received exceptional consideration because of their active part in metalloenzymes and as biomimetic model compounds due to their closeness to natural proteins and enzymes. These compounds are very important in pharmaceutical fields because of their wide spectrum of biological activities. Most of them show biological activities including antibacterial, antifungal, antidiabetic, antitumor, antiproliferative, anticancer, herbicidal, and anti-inflammatory activities. The biological activity of the transition metal complexes derived from the Schiff base ligands has been widely studied. This review summarizes the importance, Scope and antimicrobial activities of Schiff base metal complexes.

Keywords: Schiff bases, Metal complexes, Microorganism and antimicrobial activity

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INTRODUCTION

Synthesis of metal complexes attained increasing interest owing to their versatile coordination behaviour and in the understanding of molecular processes [1, 2]. Metal complexes are of significant attention in terms of its structural and coordination chemistry. They display diverse chemical, optical and magnetic properties by tailoring with different ligands. In specific, the study of metal complexes of Schiff base (SB) ligands appears to be fascinating in terms of unusual structure and stability. SB complexes are considered to be among the most important stereochemical models in transition metal coordination chemistry due to their preparative accessibility and structural variety [3, 4]. Structurally, a SB (also known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (>C = O) is replaced by an imine or azomethine group, (Aromatic aldehydes especially with an effective conjugation system) [5]. Transition metal complexes which usually contain nitrogen, sulphur or oxygen as ligand atoms have become increasingly important because these SB can bind with different metal centres involving various coordination sites and allow successful synthesis of metal complexes [6]. The high affinity for the chelation of the SB towards the transition metal ions is utilized in preparing their solid complexes [7]. The interaction of these donor ligands and metal ions gives complexes of different geometries and literature survey reveals that these complexes are biologically active compounds. Thus, in recent years SB and their metal complexes have attained much attraction because of their extensive biological activities [8, 9].

These complexes have also received exceptional consideration because of their active part in metalloenzymes and as biomimetic model compounds due to their closeness to natural proteins and enzymes [10]. The research field dealing with metal complexes is very broad and includes a number of interdisciplinary areas such as bioinorganic chemistry, catalysis, photochemistry and magneto chemistry [11]. The advances in inorganic chemistry provide better opportunities to use metal complexes as therapeutic agents. Research has shown significant progress in utilization of SB transition metal complexes as drugs to treat several human diseases. The use of SB transition metal complexes as therapeutic compounds has become more and more pronounced. Synthetic SB metal complexes are an emerging class of compounds with varying chemistry, different molecular topologies and sets of donor atoms. It is a known fact that N atom plays a key role in the coordination of metals as the active site of numerous metallobiomolecules [12-14]. These complexes offer a great diversity in their action; as antibacterial [15-18], antifungal [19-22], anticancer [23-25] and anti-inflammatory agents [26-29]. Due to the demand of new metal-based antibacterial compounds, metallorganic chemistry is becoming an emerging area of research [30].

Important characteristics that can be correlated with good antimicrobial activities are the lipophilicity and penetration of complexes through the lipid membrane. Microorganisms have existed on the earth for more than 3.8 billion years and exhibit the greatest genetic and metabolic diversity. For the maintenance and sustainability of the ecosystem these microorganisms have an important role and thus they are considered as an essential component of the biosphere [31]. Currently, antimicrobial resistance among bacteria, viruses, parasites, and other disease-causing organisms is a serious threat to infectious disease management [32]. The actions of antimicrobial agents are studied by understanding its mechanism of resistance. Antimicrobial agents show a minimal effect or no effect on host function when it's acted upon vital microbial functions. Different antimicrobial agents act in different ways. The mechanism of action of antimicrobial agents can be categorised on the basis of the structure of bacteria or the function that is affected by the agents and these include the following:

_ Inhibition of the cell wall synthesis.

_ Inhibition of ribosome function.

_ Inhibition of nucleic acid synthesis.

_ Inhibition of folate metabolism.

_ Inhibition of cell membrane function.

Resistance can be described in two ways:

a) intrinsic or natural resistance whereby microorganisms naturally do not possess target sites for the drugs and therefore the drug does not affect them or they naturally have low permeability to those agents because of the differences in the chemical nature of the drug and the microbial membrane structures especially for those that require entry into the microbial cell in order to effect their action or

b) Acquired resistance whereby a naturally susceptible microorganism acquires ways of not being affected by the drug.

Overall, the activities of all the complexes obtained were found to be moderate even though higher concentrations were applied. In order to survive, microorganisms were increasingly becoming more resistant against the arsenal antimicrobial agents to which they were being targeted [33-34].

Test methods in detecting antimicrobial resistance

Selection of the appropriate method will depend on the intended degree of accuracy, convenience, urgency, availability of resources, availability of technical expertise and cost. Many antimicrobial susceptibility testing methods can be followed but each has their own advantages and disadvantages.

Different methods are available to estimate the antimicrobial activity of metal complexes, for example, automated methods Mechanism-specific tests such as beta-lactamase detection test and chromogenic cephalosporin test. Genotypic methods such as PCR and DNA hybridization methods. The two most commonly used methods in laboratories are the agar disk diffusion method and the broth microdilution method [35].

This review's aim is to at have an insight on the application of transition metal complexes of SB as an antimicrobial agent. Literature survey reveals that metal complexes have a wide range of application as an antimicrobial drug. In the present paper, the summary of the reported work on antimicrobial activity of SB metal complexes are briefly discussed.

Three novel heteroaromatic hydrazone derivatives of 5-methyl-2-furfural hydrazone glyoxime, 3-acetylpyridine hydrazone glyoxime and 4-acetylpyridine hydrazone glyoxime and their Ni(II), Cu(II) and Co(II) complexes were prepared. Microbial activity of complexes was evaluated using the disc diffusion method against different species of bacteria and yeasts. Complexes were tested against stains of Bacteria like (*B. thuringiensis*, *B. cereus* ATCC 11778, *Streptococcus pneumoniae* ATCC 49617), *B. cereus* ATCC 11778, *B. thuringiensis*, *S. pneumoniae* ATCC 49617 and yeasts like *S. cerevisiae* ATCC 9763 and *C. tropicalis C. utilis* and against the yeasts (*Saccharomyces cerevisiae* ATCC 9763, *Candida utilis* and *Candida tropicalis*) [15].

Co(II), Ni(II), Zn(II) and Cu(II) complexes of (3*E*)-3-[(2-{(*E*)-[1-(2,4-dihydroxyphenyl)ethylidene]amino}ethyl)imino]-1-phenylbutan-1-one (DEPH2) derived from ethylenediamine, 2′,4′-dihydroxy-acetophenone and 1-phenylbutane-1,3-dione have been synthesized and screened to establish their potential as antibacterial agents, The ligand and their metal complexes were screened for antibacterial activity against Gram (+) and Gram (−) bacteria by the agar well diffusion method. In general, metal(II) complexes have been shown to be more effective than the free ligands and the same was observed in this study, *i.e.*, that the complexes are more active than the parent SB ligand. The Cu(II) complex was found to show bactericidal activity against *B. cereus*, *S. aureus* and *S. flexineri* and bacteriostatic activity against *S. faecalis*, *P. aeruginosa*, and *E. Coli* [16].

Novel Co(II) complexes of SB 2-amino-4-nitrophenol-N-salicylidene with some amino acids were synthesised. The SB and mixed ligand complexes were preliminary scanned against various strains of microbes to study their biological effect. It's evident from the obtained result that microbial activity of metal complexes was found to be higher than the free ligand [17].

A new heterocyclic SB ligand bis(2-(pyridin-2-ylimino)phenyl)-4,4'-(diazene-1,2-diyl)dibenzoate (BPPD, L) and its metal complexes with divalent transition metal ions viz., Co(II), Ni(II), Cu(II) and Zn(II) have been synthesized and screened for the antibacterial activities towards bacteria *Staphylococcus aureus* (gram positive) and Escherichia coli (gram-negative), and antifungal activities towards fungi *Aspergillus niger and Candida albicans*. The results showed that the complexes have higher antimicrobial activities than the ligand. The order of antimicrobial activities was Cu(II) L>Zn(II) L>Ni(II)L>Co(II)L>L [18].

A new SB containing 2-[(2-chloro-4-methylbenzylidene) amino] pyridin-4-ol with some transition metal ions with general formula of the complexes [M(L2)nH2O] [where M= Mn(II), Co(II), Ni(II) Cu(II), Zn(II), Pt(II) and L= 2-[(2-chloro-4-methylbenzylidene) amino] pyridin-4-ol] were synthesized and tested against some bacteria. It was showed that Pt (II) complexes are more active towards all bacteria. Bacteria like *E coli, S flexenari, P aeruginosa* and *S typhi* and two Gram-positive bacteria like *B subtilis* and *S aureus* strains were tested using agar gel diffusion method [36].

New metal complexes of the ligand 2-[1H-Pyrrol-2-ylimino methyl]-5-phenyl-1, 3,4-oxadiazol (HL) with the metal ions Co(II), Ni(II) and Cu(II), were prepared in an alcoholic medium. The SB were condensed by using [Pyrrolcarboxaldehyde] with [2-amino-5-(phenyl-1, 3, 4-oxadiazole] in an alcoholic medium. As the SB prepared was a tridentate ligand, it was used for forming complexes with Co^{+2}, Ni^{+2}, Cu^{+2} and Zn^{+2} ions of type M (HL). All the synthesised SB and their metal complexes were tested for their antimicrobial activity. The antimicrobial activity of these compounds was determined by the agar diffusion method. *Staphylococcus aureus, Escherishia coli, Pseudononasaeroginosa* and *Cndidaalbicans* bacteria were used to show the biological activities of the ligand and its complexes [37].

The condensation reaction of malonoyldihydrazide and 2-aminobenzaldehyde carried out for the synthesis of SB. 3D-transition metals like Cu(II), Ni(II), Zn(II) and oxovanadium (IV) were complexed with the newly synthesised SB ligand. Antibacterial activity of metal complexes was examined against species like *Staphylococcus Aureus*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, and *Escherichia coli*. It was observed that the metal complexes were biologically active than free ligand [38].

Metal-ligand complex of Co(II), Ni(II), Cu(II) and Mn(II) and SB derived from a pyridine-2 aldehyde, furfur aldehyde or thiophene-2 carboxy aldehyde with vinyl aniline were prepared and tested for antibacterial activity. The paper disc diffusion method was used for the determination of antibacterial activity against bacterial strains like-*Escherichia coli*, *Staphylococcus aureus*, *Klebsiella* and *Psuedomonas* and *Candida albicans* or *Candida kruse*. Antibacterial activity of ligand was enhanced while complexing with the metal atom [39].

New SB namely *{*1-[(5-bromo-2-hydroxy-benzylidene)-amino]-4-phenyl-2-thioxo-1,2-dihyro-pyrimidin-5-yl*}*-phenyl-methanone, was synthesized from N-amino pyrimidine-2-thione and 5-bromsalicylaldehyde. Synthesized SB was used as a ligand for the preparation of metal complexes from acetate salts of Cu(II), Ni(II), Co(II), Pd(II), and $PtCl_2$ in methanol. The SB and the Cu(II) and Co(II) complexes showed good biological antibacterial activity against four gram-positive (*S. aureus* ATCC 6538, *S. aureus* ATCC 25923, *B. cereus* ATCC 7064, and *M. luteus* ATCC 9345) and one gram-negative (*E. coli* ATCC 4230) bacteria, *Ampicillin trihydrate* was used as the reference antibacterial agent. It was reported in their studies that the antibacterial activities of all of the complexes were greater than those of the free SB ligand [40].

Tetradentate SB ligands derived from the Knoevenagel condensation of β-ketoanilides and furfural with *o*-phenylenediamine and diethyl malonate and their Cu(II) complexes showed antibacterial activity against *Escherichia coli, Salmonella typhi, Staphylococcus aureus, Klebsiella pneumoniae* and *Pseudomonas aeruginosa.* And also the revived in their result that bidentate complexes of Co(II), Cu(II) and Cd(II) with benzofuran-2-carbohydrazide and benzaldehyde [BPMC] or 3,4-dimethoxybenzaldehyde [BDMePMC] showed biological activities but Cu(II) complex of [BPMC] and [BDMeOPMC] are more active against *S. aureus* as compared to Co(II) and Cd(II) complexes.

The bidentate ligand of 2-[(2-[1-(hydroxyphenyl) ethyl] aminophenyl) ethanimidoyl] phenol derived from o-phenylenediamine are effective against *Bacillus cereus*, *Staphylococcus aureus* and *E. Coli*. Antibacterial activity of the Clomiphene citrate copper complex has been determined against *E. coli, Staphylococcus aureus* and *Xanthomonas vesicatoria* by. The mixed ligand complexes of Cu (II) with SBs N-(2-hydroxy-1-naphthylidene)-4-chloroaniline (L1) and N-(2-hydroxybenzylidene)-2,3-dimethylaniline (L2) reported to show some antibacterial activity to certain extent against *E. coli*, *S. aureus*, *B. subtilis*, and *S. typhi.,* but their complexes exhibit comparatively greater amount of activity against these bacteria [41].

New SB ligand were synthesised from benzofuran-2-carbohydrazide and 4-methyl-thiobenzaldehyde. Prepared SB was used as a selective ligand for the complexation of metals like Cu(II), Co(II), Ni(II), Zn(II), Cd(II), Hg(II). This complex was tested against the bacteria namely *E. coli,* and *S. aureus* using agar diffusion method*.* Studies revealed that Cu(II) and Hg(II) complexes showed good activity against bacteria *E. coli* and *S. aureus* while Ni(II),Co(II) and Cd(II) complexes show moderate activity against both bacteria *E. coli* and *S. Aureus* [42].

Transition metals like Co(II), Ni(II), Zn(II) and Cu(II) were used for the preparation of biologically active metal complexes. SB namely (3*E*)-3-[(2-{(*E*)-[1-(2,4-dihydroxyphenyl)ethylidene]amino} ethyl) imino]-1-phenylbutan-1-one (DEPH2) derived from ethylene-diamine, 2′,4′-dihydroxyacetophenone and 1-phenylbutane-1,3-dione have been used as a active ligand. The ligand and their metal complexes were screened for antibacterial activity against Gram (+) and Gram (−) bacteria. Three Gram-positive *viz*. *Staphylococcus aureus* (ATCC 25923), *Streptococcus faecalis* (ATCC 29212), *Bacillus cereus* (ATCC 10702), and three Gram-negative bacteria *viz*. *Pseudomonas aeruginosa* (ATCC 19582), *Escherichia coli.* (ATCC 25922) and *Shigella flexineri* (KZN) using agar diffusion method. The standards used were Ciprofloxacin and amoxicillin [43].

Nano-sized SB complexes of Mn(II), Co(II), Ni(II), Zn(II) and Cu(II) were synthesized and it was screened against gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*). Results indicates that all the SB complexes individually exhibited varying degrees of inhibitory effect on the growth of the tested bacterial species and the SB complexes were more pronounced when coordinated with the metal ions. The biological activity of the complexes follow the order: Antibacterial effect: Co(II)> Zn(II)>Cu(II)>Ni(II)>Mn(II) and Antifungal effect: Cu(II)> Co(II)>Zn=Mn=Ni [44].

New titanium (IV) complexes were synthesized by reacting $TiCl_4$ with different SB ligand like tetracycline hydrochloride, Streptomycin, Cefixime and ampicillin in fixed molar ratio (1:2). These complexes were examined for their biological activity against pathogenic bacterial strains i.e. *Bacillus cereus* MTCC 6728, *Micrococcus luteus* MTCC 1809, *Staphylococcus aureus* MTCC 3160, *Staphylococcusepidermidis* MTCC 3086, *Aeromonas hydrophila* MTCC 1739, *Aclaligenes faecalis* MTCC 126, *Shigella sonnei* MTCC 2957, *Klebsiella pneumoniae* MTCC 3384, *Pseudomonas aeruginosa* MTCC 1035, and *Salmonella typhimurium* MTCC 1253. They reported that metal complexes have more biological activity than their parent SB Preliminary *in vitro* antibacterial study indicated that all the complexes obtained showed a moderate activity against the tested bacterial strains and a slightly higher activity compared to the ligand [45].

New SB was prepared from piperonal and diamine compounds (ethane-1,2-diamine, propane-1,3-diamine, butane-1,4-diamine). These ligands were Complexed with Co(II) chloride. The ligands and metal complexes were screened for their antimicrobial activities against gram-positive bacteria and gram negative bacteria. It was found that they were biologically active. All ligand showed high activity compared to the complexes due to the chalation hold the azomethine groups in complexes by coordination bonds with metal ion leading low inhibition in biological activity [46].

Metal complexes of Fe(II), Co(II), Ni(II), Cu(II) and Zn(II) were synthesized by complexation of SB derived from the condensation of 2-thiophenecarboxaldehyde with 2-aminipyridine and 2-thienylmethylidine. Obtained complexes were examined for their antibacterial activity on *E. coli, Staphylococcus aureus* and *Pseudomonas aeruginosa* using the paper disk diffusion method. Metal chelates showed very good antibacterial activity than free SB. *E. coli* was inhibited to a greater degree by the Co(II) and Fe(II) complexes. From the result, it's clear that the complexes formed by Co(II) and Fe(II) can used for the treatment of some common diseases caused by *E. Coli* [47].

CONCLUSION

Development of SB transition metal complexes as drugs is not an easy task; considerable effort is required to get a compound of interest. Beside all these limitations and side effects, transition metal complexes are still the most widely used chemotherapeutic agents and make a large contribution to medicinal therapeutics.

CONFLICT OF INTERESTS

Declare none

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