Applied Chemical Engineering (2023) Volume 6 Issue 1
doi:10.24294/ace.v6i1.1943

REVIEW ARTICLE

Chemistry in biosystem—A contemporary review of Schiff bases and their metal complexes as antioxidants and anti-fungal agents

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ABSTRACT

Schiff bases are a class of organic compounds which have good chelating properties. Due to this, they can form complexes with metal ions of the transition series. Schiff bases and their derivatives are bioactive and hence find widespread uses in various fields of inorganic, organic and medicinal chemistry. These are synthesised by condensation reactions and have been studied extensively as they can exhibit biological properties like anti-oxidant, anti-fungal, anti-cancer, anti-bacterial and anti-microbial, apart from finding uses in the field of material science. With the advent of nanotechnology and its increasing importance, the introduction of nanoparticles of Schiff bases can increase the effectiveness of their various biological properties. In the present article, we aim at providing an exhaustive review of the behaviour of metal complexes of Schiff bases and their various derivatives as anti-oxidant and anti-fungal agents. The most pertinent and contemporary literature has been chosen for this review article.

Keywords: Schiff Bases; Transition Metal Ions; Chelation; Bioactive; Chitosan

ARTICLE INFO

Received: 28 January 2023
Accepted: 10 May 2023
Available online: 27 June 2023

1. Introduction

Schiff bases belong to a category of compounds which contain the bioactive azomethine (>C=N-) group, and have the capability of behaving as potential pharmacological agents[1]. They have the general formulas $R_1R_2C=NR_3$[2] and $R_1CH=NR_2$[3]. Schiff bases can be formed by the condensation of a carbonyl compound with a primary amine or an aromatic aldehyde with an aromatic amine[4,5]. Schiff bases and their derivatives are of much significance in medicinal chemistry as anti-inflammatory[6], anti-cancer[7], anti-depressant[8], analgesic[9], anti-HIV[10], anti-fungal[11], anti-microbial[12] agents and as antioxidants, because of their high solubility in lipids. Many Schiff base complexes are now being used as nanoparticles to overcome the resistance towards anti-bacterial drugs. Apart from this, they are used to create discrete supramolecular metallo ligand units[13,14]. They are used as pigments, bio-lubricants and catalysts in a variety of reactions involving transition metal ions[15,16] and help in stabilising polymers[17]. A number of biochemical processes are catalysed by Schiff base ligands complexed with d block metal ions[18]. Apart from serving as intermediates in organic reactions[19], Schiff bases also play an important role in electrochemistry as corrosion inhibitors, by form-

ing a corrosion preventing film on the surface of the metal with the help of the electron rich imine. Schiff bases can form good complexes with transition metal ions, because they are good π electron acceptors[20]. Chitosan is a polysaccharide present in fungi and other marine organisms. Chitosan based Schiff bases are used in treating water to make it fit for industrial and domestic consumption[21]. Apart from this, chitosan and their derivatives show AF (anti-fungal), AO (antioxidant), anti-tumor and anti-bacterial activities[22]. Many methods of preparation of Schiff bases have been described in literature as they are easily synthesised and are inexpensive[23]. Some polymeric Schiff bases containing indol have been synthesised by condensation methods and have many biological applications[24]. Free Schiff bases have lesser AF and AO activities as compared to metal complexed Schiff bases[25,26]. The present review aims to highlight the recent studies on Schiff base—metal ion complexes as anti-fungal agents and antioxidants, which can be useful in developing new techniques for the effective use of Schiff base complexes.

2. Antioxidant and anti-fungal activity

2.1 Inulin derivatives of Schiff bases

Chen *et al*.[27] synthesised some inulin derivatives of Schiff bases and analysed their AF behaviour in some plant pathogenic fungi. The authors reported the increase in the bioactivity of the Schiff base inulin derivatives in comparison to free inulin. The synthesised derivatives exhibited a strong AO activity against DPPH (1,1-diphenyl-2-picrylhydrazyl) free radicals (since free radicals cause oxidative stress and trigger a number of diseases). Also, a broad AF spectrum against the plant pathogenic fungi—*B. cinerea*, *F. oxysporum* and *P. asparagi* was observed.

Wei *et al*.[28] reported that inulin, obtained from crops, is a biodegradable polysaccharide and has good physiological functions. It is used as an alternative to fat in foods. It is non-toxic and biodegradable and is thus used as an alternative to fat in foods and also in the pharmaceutical industry. However, inulin has lower bioactivity and for its improvement, it needs to be chemically modified. The synthesis of inulin derivative improves the biological properties of inulin. Hence, the authors synthesised three Schiff bases of 6-amino-6-deoxy-3,4-acetyl inulin having pyridine rings (**Figure 1**).

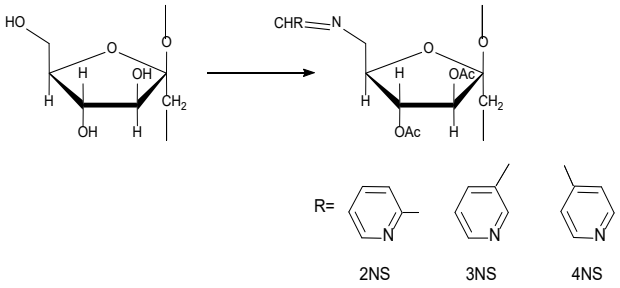


Figure 1. Schiff base derivatives of inulin.

AF activities were studied by in vitro studies against pathogenic fungi. Inulin showed no AF activity against the pathogenic fungi whereas the Schiff base derivative of inulin showed considerable AF activity. The AF studies carried out on three kinds of plant pathogens—*B. cinerea*, *F. oxysporum* and *P. asparagi*, showed that the amino group in the synthesised compound could cause AF activity by the interaction of amino group with anionic component of cell membranes and destroy the cell membranes of fungi, thus preventing the growth of fungi. All the prepared complexes were reported to show excellent AF activity as compared to free inulin.

2.2 Imidazole based Schiff bases

Slassi *et al*.[29] studied the AO and AF activities of imidazole and azo-based Schiff base ligands. Imidazoles are heterocylic molecules which are the core of biological systems. Having potent biological activity, they are important in the field of medicinal chemistry. Four different Schiff base ligands were chosen for this study. At first, azo-salicylaldehyde (1a-c) was synthesised by reacting ortho-hydroxybenzaldehyde with alkyl-anilines. The product obtained was further condensed with N-(3-aminopropyl) imidazole to form the Schiff base ligands (L1–L4) (**Figure 2**).

The AF activity was studied on three fungal species (*Candida albicans*, *Aspergillus fumigatus*, and *Scedosporium apiospermum*) which affected humans. It was observed that the Schiff base ligands (L2, L3, L4) showed weaker AF activities due to the absence of azole group. L1 showed the best AF activity. Azole Schiff bases are able to overcome fungal infections and therefore are useful as

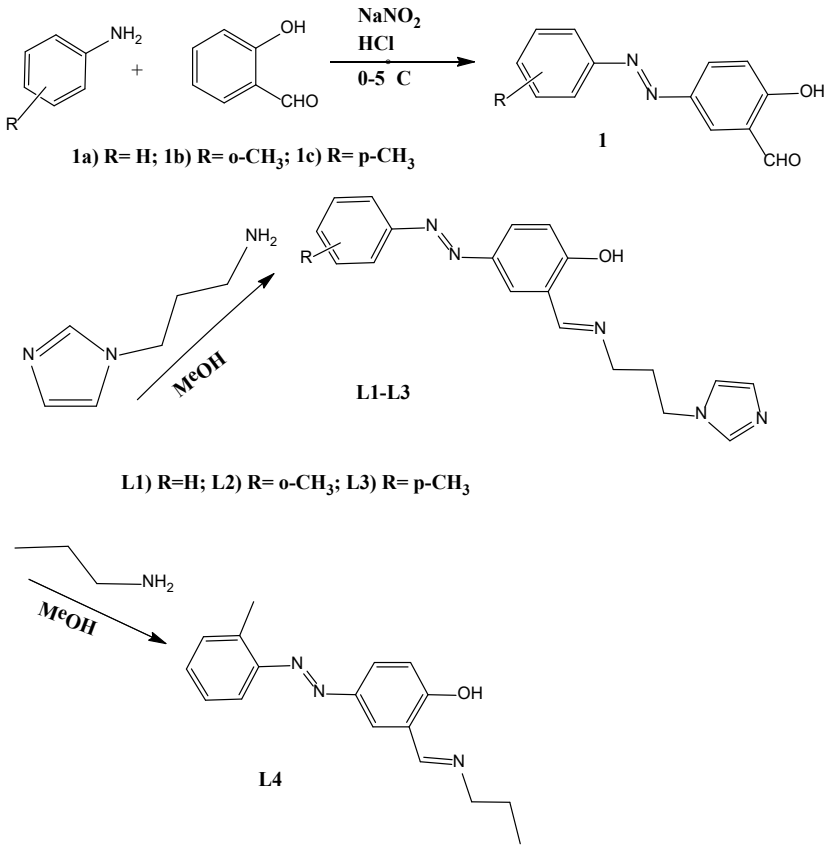


Figure 2. Schiff base ligands (L1–L4) from azo-salicylaldehyde.

therapeutic agents. AO activity depends upon the scavenging or capturing the free radicals which are the cause of many diseases. A study of DPPH radical scavenging activity (RSA) of the derivatives of Schiff bases was performed and evaluation was done by UV-Vis spectroscopic technique. The comparison was done with RSA of ascorbic acid as the reference. The IC50 values for L1, L2, L3, L4 and ascorbic acid were reported as (95.98), (94.48), (96.01), (116.39) and (25.88), respectively. All the synthesised derivatives were found to show AO activity, but lesser than that of ascorbic acid. This was due to the hydroxyl group (active scavenger of free radicals, involving the transfer of hydrogen atom of the hydroxyl group from the AO to the free radicals). The ligands L1–L3 have lower values of IC_{50} as compared to L4, showing their better activity as antioxidants as compared to L4 (which does not have an imidazole ring). Hence, the authors deduced that the imidazole ring present in the synthesised ligand contributed to the bio-activity of Schiff base derivatives.

2.3 Chitosan based Schiff bases

Some chitosan derivative bearing Schiff bases were reacted with a quaternary ammonium salt through the intermediate 6-O-chloroacetyl-2-N,N,N-trimethyl quaternary ammonium salt chitosan and studied by Wei *et al*.[30]. The authors synthesised such complexes and then studied their AF and AO activity. AF activity against various fungi like *F. oxysporum*, *B. cinera* and *F. oxysporum* was determined by mycelium growth rate test method. 6-[4-(2,3-dihydroxyl-benzimide) pyridine] acetyl-2-N,N,N-trimethyl chitosan chloride (2,3HBPATC) was one of the derivatives which was tested. It showed greater RSA against DPPH and superoxide free radical species. It was further deduced by the observations that due to halogen, hydroxyl and phenolic groups in chitosan, the AF as well as AO activities of chitosan increased.

Mi *et al*.[31] synthesised a number of chitosan derivatives by ion exchange reactions between glyoxylate bearing Schiff base and the quaternary ammonium salt of chitosan (TMCI-N,N,N-trimethyl chitosan iodide and HACC-hydroxypropyl trimethyl ammonium chloride chitosan) to study the AO and AF activity. A reaction between glyoxylic acid and heterocyclic compounds comprising of amino groups was carried out to synthesise glyoxylate, and further substituted it with iodide or chloride ions. The AF and AO activity of TMCI and HACC was

reported to increase by the presence of glyoxylate bearing Schiff base. Cytotoxicity of the prepared samples was found to be low.

Wei *et al.*[32] synthesised chitosan derivatives of halogenated aromatic amines through Schiff bases. It was observed by the authors that the derivative showed increased AF activity as compared to chitosan when tested on the fungi—*B. cinerea* and *F. oxysporum* by hyphal measurements. Increased AF activity was shown by Schiff bases of chitosan having halogenated benzene because of the greater degree of substitution on the Schiff bases due to the electron withdrawing nature of halogens.

Raouf *et al.*[33] studied Schiff base compounds of Chitosan-4-aminoacetophenone (A) and Chitosan-4-bromoacetophenone (B) (**Figure 3)**.

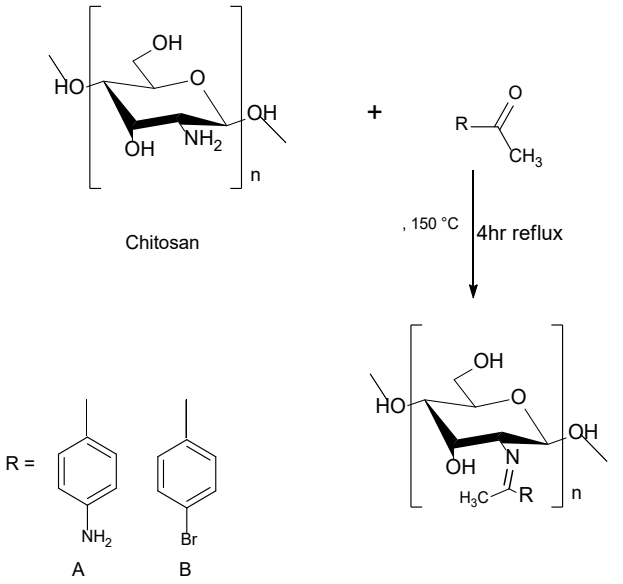


Figure 3. Chitosan-Schiff base derivatives.

Chitosan, obtained from deacetylation and alkaline treatment of chitin (a biopolymer in sea shells, cell walls of yeast and fungi) finds its use as AM, AF, AO and AT agents. Its commercial uses are in the textile industry and cosmetic industry. The AO behaviour of the above compounds was reported using DPPH and FRAP (Ferric Reducing Antioxidant Power) method and the AF activity was tested using *Candida albicans*. Both the AO and AF activities of the compound were found to be good in (A) and (B) compounds, but the compound (A) was found to have a greater biological activity because of its electron donating nature.

A new Schiff base based on methyl acrylate-functionalised chitosan containing p-nitro benzaldehyde units (aminated chitosan) (AmCs-*p*NBA) (**Figure 4**) was synthesised and studied in vitro for its AF, AO activity by Kenawy *et al.*[34]. The synthesised chitosan derivative showed good AF and AO activities. This derivative was also reported to show proliferation of cell without hemolysis.

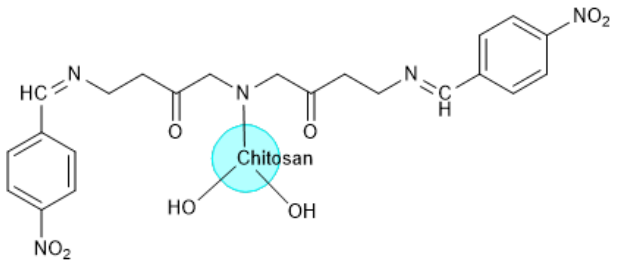


Figure 4. AmCs-pNBA.

2.4 Isatin hydrazone based Schiff bases

Singh *et al.*[35] synthesised five isatin hydrazone Schiff bases by reacting isatin hydrazone with aldehydic groups (**Figure 5a–e**). For studying their AF properties, the authors chose fungal strains like *C. glabrata*, and *C. parapsilosis*. All the synthesised complexes of Schiff bases were reported to show AF activity. The AO action of synthesised Schiff base derivative was found to be greater than the reference ascorbic acid. By these observations, the authors were able to conclude that isatin hydrazone acetylenic Schiff base derivatives could behave as biomaterials having AF and AO properties. Their organometallic compounds using silicon as the metal ion were also synthesised and they were also found to show good AF and AO activities.

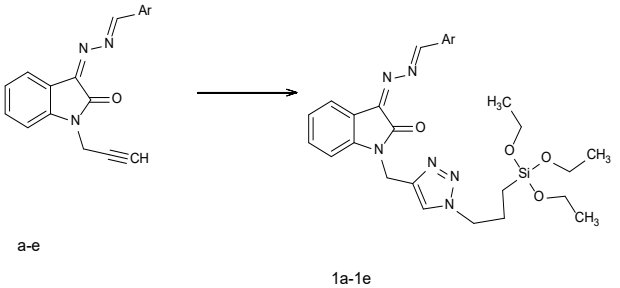
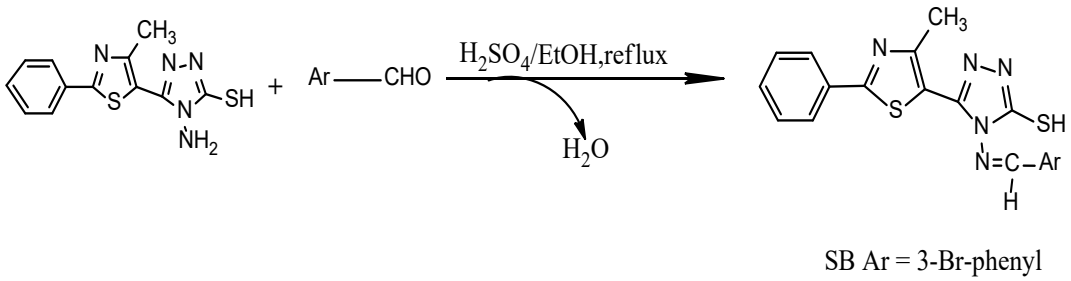


Figure 5. Isatin-hydrazone Schiff bases.

Login *et al.*[36] synthesised and reported a new thiazolyl-triazole Schiff base and studied it for its AO and AF activities. The Schiff base synthesised by the authors using pre-described methods was 4-(3-bromobenzylideneamino)-5-(4-methyl-2-phenylthiazol-5-yl)-4H-1,2,4-triazol-3-thiol, by condensing 4-amino-5-(4-methyl-2-phenyl-thiazol-5-yl)-



SB Ar = 3-Br-phenyl

Figure 6. Synthesis of Schiff base.

4H-1,2,4-triazole-3-thiol and 3-bromobenzaldehyde (**Figure 6**).

The AF activity against *Candida albicans* was tested in vitro by diffusion method for which the reference chosen was fluconazole. The AF activity of the Schiff base was greater than the reference. This was because the azomethine group of the Schiff base, complexed with the metal ion present in the active site of the metalloenzyme. The AO activity was studied using DPPH, where the Schiff base was taken in DMSO, DPPH was taken in methanol and the standard sample. These were assessed by measuring MDA (lipid peroxidation level) and COX2 (marker for inflammation) levels in vitro. The MDA and COX2 levels decreased after treatment with Schiff base, showing its AO activity in vitro. It was observed by the authors that low IC_{50} value was shown by the Schiff base derivative, implying high AO activity. When the Schiff base was low in concentration then it was found to decrease lipid peroxidation. This was because of the fact that it was able to form good complexes with the metal ion in the metalloenzyme which caused the scavenging of the free radicals. Also, morphological changes were seen in the cells which was in accordance with the AO activity of the Schiff base.

2.5 Heteroatomic dyes and Schiff base compounds

AF and AO activities of thiazolidinone and tetrazole compounds obtained from acriflavine and Schiff bases as intermediate compounds, have been studied by Rasheed *et al.*[37]. Acriflavine is a heteroatomic dye having AF and AO effects. Schiff bases which have been used as intermediates were prepared by the reacting acriflavine with a variety of aldehydes. The thiazolidinone compounds were prepared by reacting the Schiff bases with thioacetic acid whereas the tetrazole compounds were prepared using the Schiff bases and sodium azide. Their AF activity was tested against fungi like *C. albicans* and it was established that the synthesised compounds behaved as better AF agents in comparison to the standard Nystatin drug. The AO activity was measured by DPPH method, using gallic acid as standard. The data showed good AO activity of the synthesised complex.

Schiff base ligands were synthesised by refluxing 2-hydroxy-1-naphthaldehyde with L-histidine and sulfamethazine(**Figure 7**). Further, the complexes of the ligands with Sn(II) were made by taking equimolar solutions of HNLH (2-hydroxy-1-naphthaldehyde + L-histidine) and HNSM (2-hydroxy-1-naphthaldehyde + sulphamethazine) with $SnCl_2$ and refluxing them (**Figure 8**). This synthesis and studies for AO and AF activities were carried out by Neelofar *et al.*[38].

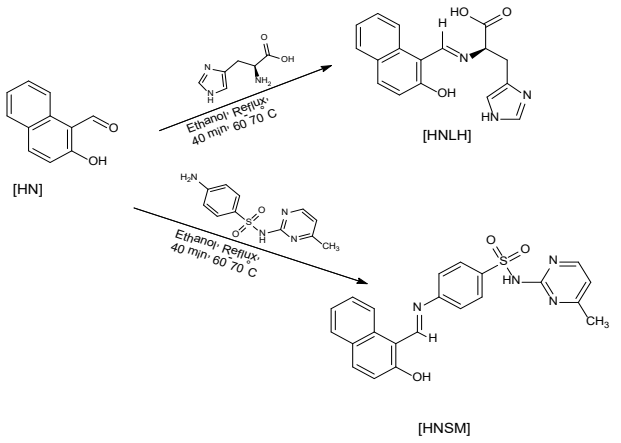


Figure 7. Preparation of HNLH and HNSM.

The fungal strains chosen for AF activity were *A. niger* and *A. flavus*. The tin (Sn) complex of HNSM was found to show AF activity against the fungal strains. The AO activity was studied by the RSA of DPPH. However, when the compound was added to it, the purple colour of fresh DPPH solution was found to discharge and the solution became colourless. Thus, the quenching of DPPH radicals

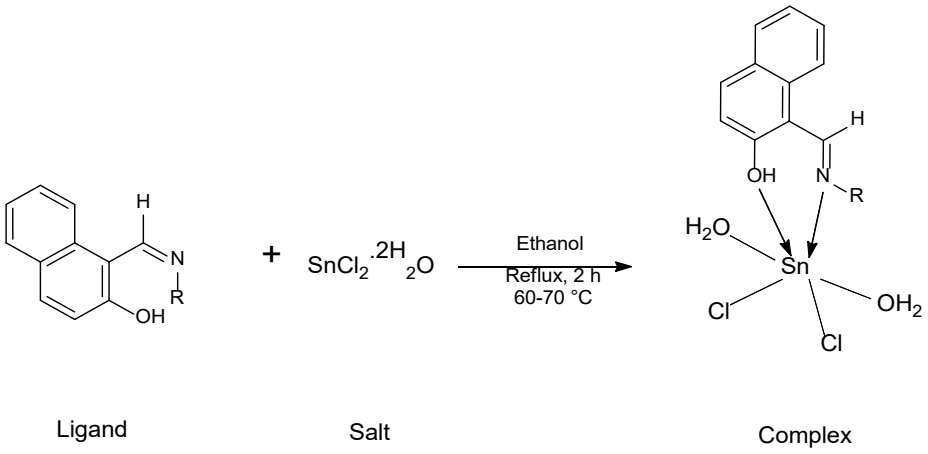


Figure 8. Synthesis of metal ion-Schiff base complex.

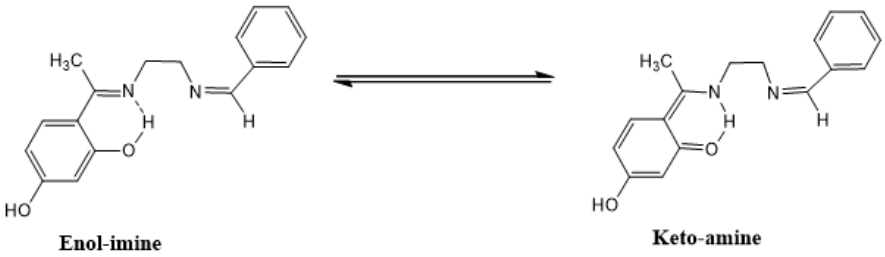


Figure 9. Structure of BEB.

by the synthesised Schiff base complex, indicated a good AO activity of the complex.

Ejidike[39] in his article has reported the synthesis and AO and AF activity studies carried out on the synthesised Cu^{2+} ion complex of 4-[(1E)-N-{2-[(Z)-Benzylidene-amino]ethyl}ethanimidoyl] benzene-1,3-diol Schiff base (BEB) (**Figure 9**).

The AO property of the square planar complex so formed was studied and it was found that the complex showed AO potential against DPPH. For studying the AF activity, *C. albicans* and *C. neoformans* were chosen. The ability of the Cu complex of (BEB) prepared in DMF as the solvent to behave as scavenger for DPPH and ABTS (2,2'-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid) was studied. It was observed and reported in the article that $[Cu(BEB)NO_3]$ showed high scavenging ability. It was observed that with gallic acid as the reference, nitrate, thiocyanate, acetate, bromide and chloride complexes of Cu-BEB and BEB showed good AO activity. Free Radical Scavenging (RSA) was studied by ABTS method which was moderate in activity. The AF activities of the synthesised complex on *Candida albicans* were higher in comparison to the standard Amphotericin B. It was explained that the complex was able to penetrate the lipid membranes, due to the delocalisation of electrons. As a result, the solubility of the complex increased in the lipids resulting in disruption of cell wall synthesis, causing cell death. However, Cu present in the Schiff base complex blocked the active sites of the cell, restricting the growth of the fungi.

Indole based compounds of Schiff base were synthesised and their AF activity was studied by Wang *et al*.[40]. In their article, they have reported the synthesis of Schiff base thioether derivatives of 1,3,4-thiadiazole. The AF activity of the Indole derivatives was studied against *F. graminearum* and *F. oxysporum fungi*. Indole is a heterocyclic compound which contains nitrogen. Introducing Schiff bases into 1,3,4-thiodiazoles exhibits various biological activities. The novel compounds synthesised by the authors showed AF activities against plant fungi. The AF activity was found to increase in the presence of an electron withdrawing group on the benzene ring in the synthesised complex, due to decrease in the delocalisation on the benzene ring. As a result, the target molecules became accessible to the synthesised complex. Hence the authors reported that the indole derivatives of Schiff base containing 1,3,4-thiadiazole with a nitro group showed good AF activity because of the electron withdrawing nature of the nitro group.

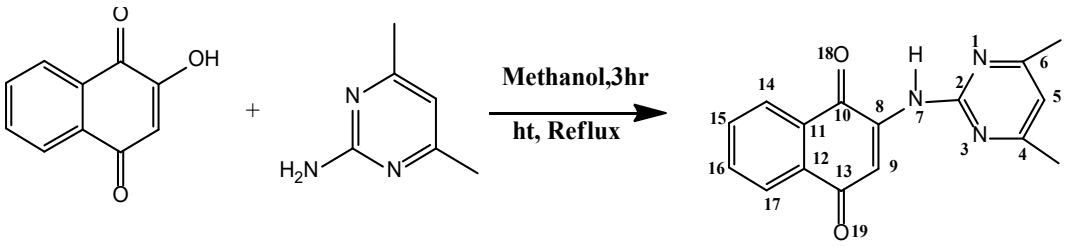


Figure 10. Synthesis of HL Schiff base.

Biological studies were carried out on synthetic metal ion complexes of pyrimidyl Schiff base ligand with 2,2'-bipyridine unit, by Festus *et al*.[41]. For the studies, some divalent transition metal ions were used to form complexes with the Schiff base derivatives. Pyrimidyl Schiff base ligands which were synthesised were: 2-(4,6-dimethypyrimidin-2-ylamino) naphthalene-1,4-dione (HL) and 2,2'-bipyridine (**Figure 10**).

AO behaviour study was done by DPPH method. For AF screening, potato dextrose agar (PDA) media was chosen. AF studies were carried out on *A. niger* and *A. flevus* on agar surface and the synthesised compound was inoculated into it, wherein diflucan drug was used as the reference. The authors observed good inhibition of growth of the fungi. The action of Schiff base ligands against the fungi was greater than the divalent metal complexes. AO activities were seen by DPPH assay method, where blank DPPH in DMSO was tested for absorbance and then the synthesised compound was mixed with DPPH and absorbance was recorded. It was observed that the compounds synthesised had considerable radical scavenging abilities, which increased upon complexation with metal ions.

Gur'eva *et al*.[42] synthesised chiral Cu(II) complexes from terpene derivatives of ethylene diamine and studied their AO and AF activities. AF activities were studied against *C. albicans*, *S. salmonicolor* and *P. notatum* and the comparison was done with amphotericin. These fungi tend to show resistance to a number of drugs over a period of time, hence the need for search of new AF drugs. In their work, the authors prepared Cu chelates by using terpene derivatives of ethylene diamine L1–L4 (**Figure 11**) as ligands for the preparation of Cu chelates. After the synthesis, studies on biological activity showed high AF activity of ligands L1–L4. When compared with free ligands, Cu chelated ligands were found to have greater AF activity. The AO activity of the Cu complexes was determined in vitro by studying the ability for lipid peroxidation in a substrate containing lipids of laboratory mice brain. It was observed that the Cu complex ligand was more reactive than the free ligand. The AO behaviour of the drug slightly increased as the concentration of the drug increased. Hemolysis of erythrocytes was used to assess the toxicity of the compounds (1–4, L1, L2). All the compounds were found to have low hemolytic activity. Regarding AO activity, in ligand complex pairs (L1-1 and L2-2), highest inhibitory action was seen in complexes 1 and 2 (**Figure 12**).

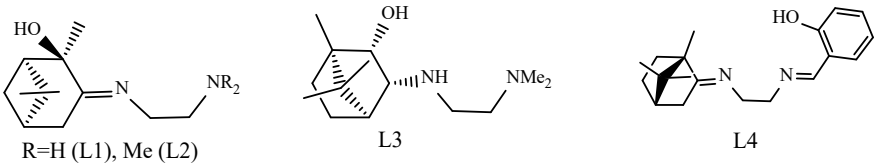


Figure 11. Ligands L1–L4.

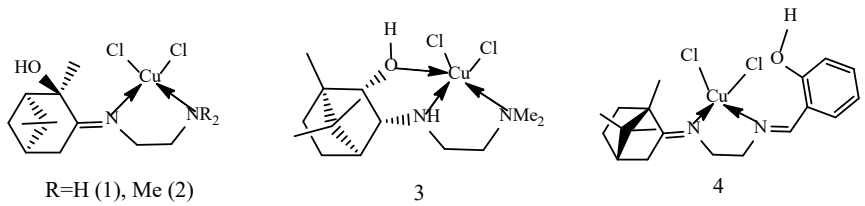


Figure 12. Copper complexes of the synthesised ligands.

Schiff base was obtained from benzidine with 1,3-diphenyl-1,3-propanedione and its AO and AF activities were studied by Horozić *et al*.[43] (**Figure 13**).

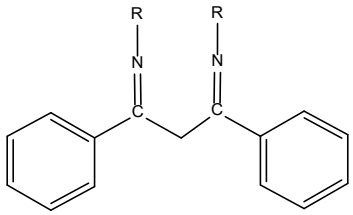


Figure 13. Schiff base.

The AO activity was studied in vitro using DPPH method. Similarly, the AF activity was studied on *Candida albicans*. The AO activity results showed that the IC_{50} value for the Schiff base was higher than the reference Vitamin C. According to FRAP analysis, the reduction potential value (FRAP) of Schiff base was lower than that of Vitamin C. By this observation, the authors deduced that Schiff base behaved as a good antioxidant. The results of AF activity (by the agar diffusion method) of the Schiff base showed more effective action against *C. albicans*, implying a good AF behaviour of the synthesised Schiff base.

New chitosan heterocyclic derivatives of Schiff base were synthesised and analysed for their AO and AF activity by Hamed *et al*.[44]. 1-phenyl-3-(thiophene-2-yl)-1H-pyrazole-4-carbaldehyde, 1-phenyl-3-(furan-2-yl)-1H-pyrazole-4-carbaldehyde, 1-phenyl-3-(pyridine-3-yl)-1H-pyrazole-4-carbaldehyde were prepared. A reaction was carried out with chitosan to form new Schiff bases (**Figure 14**). They were further analysed for their AF activities against *Asperagillus fumigatus* and *Candida albicans*. Depending upon the type of moiety present in the Schiff base, AF activities were found to vary, due to solubility and charge factors. The conjugated Schiff bases formed as a result of combination of thiophene, furan and pyridine with phenyl and pyrazole groups interfered with fungal growth by increase in the electron density of the imine group. Also, the compounds were reported to be devoid of cytotoxicity.

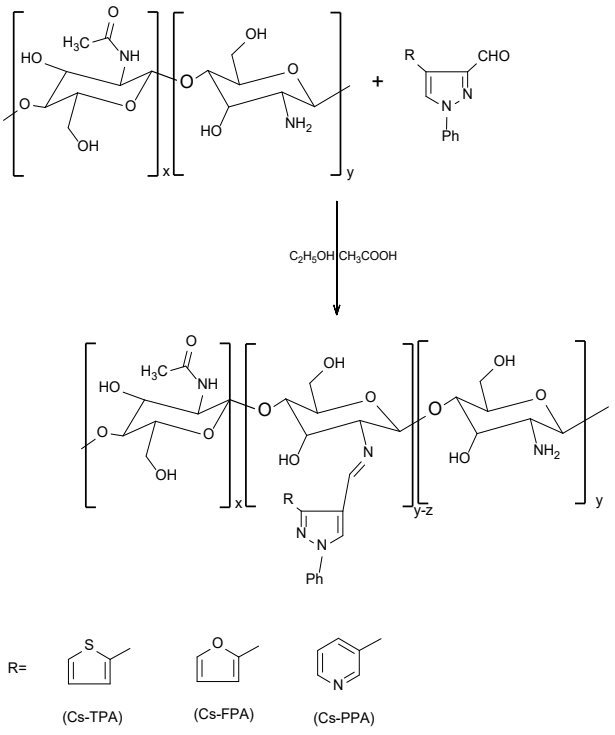


Figure 14. Chitosan-Schiff bases.

Cu(II)-Schiff base interactions have been reported by Horozić *et al*.[45] wherein the Schiff base was obtained by 2,2-dihydroxy indane 1,3-dione (Ninhydrin) and tryptophan (**Figure 15**), an amino acid needed for protein synthesis in the body, which upon metabolism gets converted to serotonin, melatonin and nicotinamide. The AO activity was determined by DPPH and FRAP methods. AF activity was also determined by diffusion technique. The AO activity in vitro showed IC_{50} values of Cu^{2+} ion complex to be higher than the reference Vitamin C showing the higher AO power of the metal ion complex. Similarly, the FRAP (Ferric Reducing Antioxidant Power) of Cu^{2+} metal ion complex was lesser than Vitamin C value, again showing the AO activity of the synthesised complex. Significant AF activity was found against *Candida albicans*.

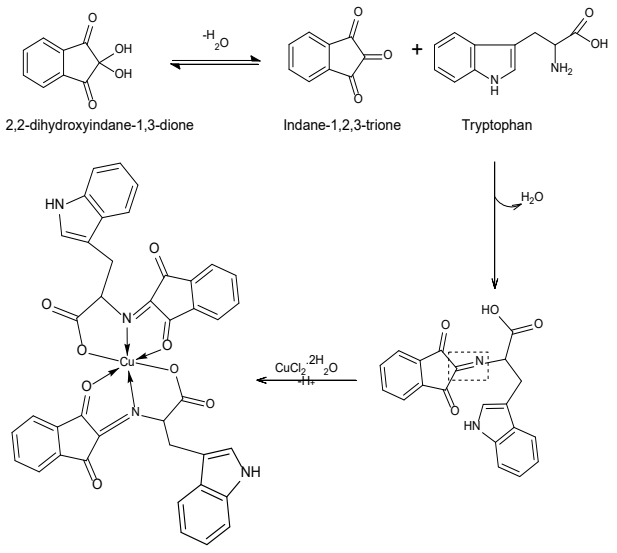


Figure 15. Synthesis of the Schiff base.

Turan and Buldrun[46] in their article described

the preparation and AO activity of certain Schiff base metal complexes with certain divalent transition metal ions like Mn^{2+}, Fe^{2+} and Zn^{2+}. They prepared ethyl-2-(2-hydroxy-3-methoxy benzylidene amino)-6-methyl-4,5,6-tetrahydrobenzo-6-thiphene-3-carboxylate (L) and its metal ion complexes. The AO behaviour of the complex was measured by DPPH, ABTS (2,2'-azino-bis-3-ethylbenzthiazoline-6-sulphonic acid), FRAP and CUPRAC (Cupric Reducing Antioxidant Capacity) methods. DPPH RSA required different concentrations of the prepared sample and ascorbic acid as the standard antioxidant. ABTS method required the production of $ABTS^{*+}$ radical cation by reacting ABTS with H_2O_2 and $K_2S_2O_8$. Then this was added to a solution of the sample and also standard antioxidants. FRAP method required the reduction of Fe^{3+} to Fe^{2+} (for which $K_3[Fe(CN)_6]$ was added). By CUPRAC, wherein Cu^{2+} reducing powers of the complex were determined, it was noted that Schiff base complexes of the ligand had low $ABTS^{*+}$ RSA, in contrast to the original ligand which had no $ABTS^{*+}$ RSA. DPPH RSA showed that the Ruthenium(II) ion complex (**Figure 16**) had the greatest ability to act upon DPPH and scavenge it. By the FRAP method, the order observed for the antioxidant behaviour of the complex and the standard antioxidants was reported to be after ascorbic acid which was taken as the reference. Ru(II) complex again showed highest AO power, followed by Zn(II), Fe(II) and then Mn(II) complex. CUPRAC method showed the antioxidant power of Ru(II) complex to be high, almost similar to the reference antioxidant.

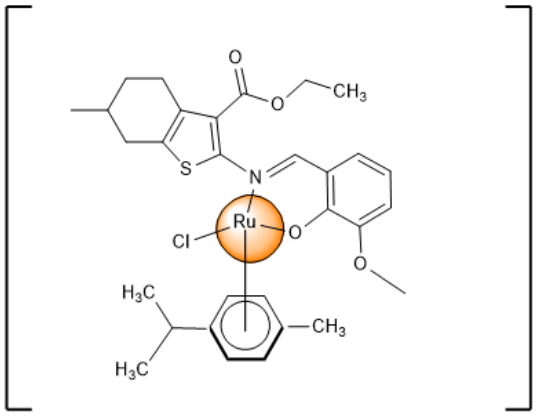


Figure 16. Ruthenium complex of the Schiff base.

Elsayed *et al*.[47] reported the AO behaviour of V(IV), Mo(IV, VI) and Ru(II) complexes of pyridoxal-Schiff base complexes, where Schiff base was derived from pyridoxal S-benzyldithiocarbazate or p-toluidine. DPPH was used to test the AO activity of the complexes which were synthesised. The authors observed that DPPH radical scavenging activity is high for Oxovanadium(IV) complexes (**Figure 17**) since they were found to have low IC_{50} values. This is comparable to ascorbic acid, used as the reference antioxidant.

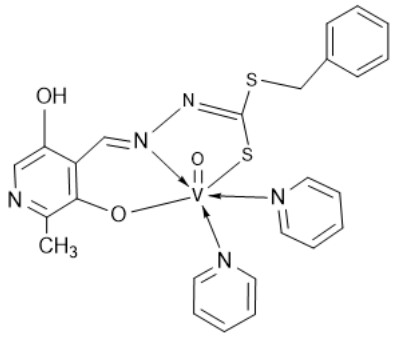


Figure 17. Vanadium pyridoxal Schiff base complex.

Aziz and Seda[48] reported the synthesis and AO activity study of complexes of divalent d-block metal ions obtained from a tetradentate Schiff base having a thiophene unit. Complexes of such metal ions were synthesised with a Schiff base ligand obtained by the reaction between 2-aminophenol and 2,5-thiophene-dicarboxylaldehyde. All prepared complexes exhibited good AO activity.

Tridentate N4-Schiff base obtained from reaction between 2-hydrazinopyridine and pyridine-2-carbaldehyde along with Nd(II) and Sm(II) lanthanide ions (**Figure 18**), was studied for its AO activity by Gueye *et al*.[49]. DPPH in methanol was added to the solution of the complex. It was observed that RSA of lanthanide ions increased as their concentration increased whereas the free ligand had low RSA. Also, the free ligand had lower IC_{50} values than complexes of the ligand with Nd(III) and Sm(III), implying that the metal ion complex with Lanthanide(III) was a better reducing agent and thus a better antioxidant.

Complexes of transition metal ions with 2,4-dihydroxybenzaldehyde-benzoyl hydrazone Schiff base were synthesised and analysed for their AO activity by Aboafia *et al*.[50]. The complexes of vanadium, zinc, molybdenum, ruthenium and palladium ions with the Schiff base derived from 2,4-dihydroxybenzaldehyde and benzoylhydrazone (**Figure 19**) were studied by the authors for their AO activity against DPPH and the authors observed

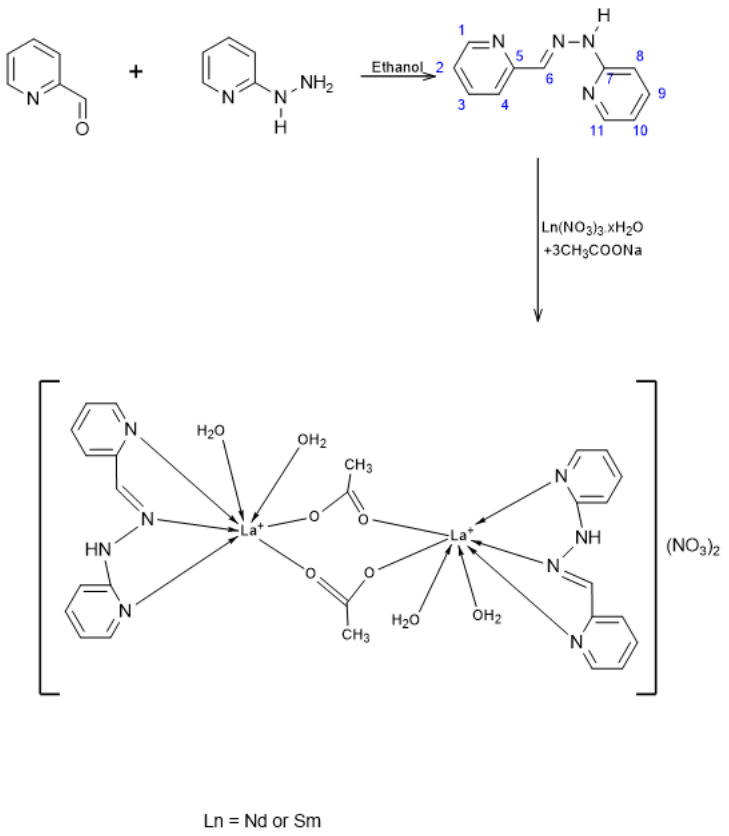


Figure 18. Schiff base of Lanthanide ions.

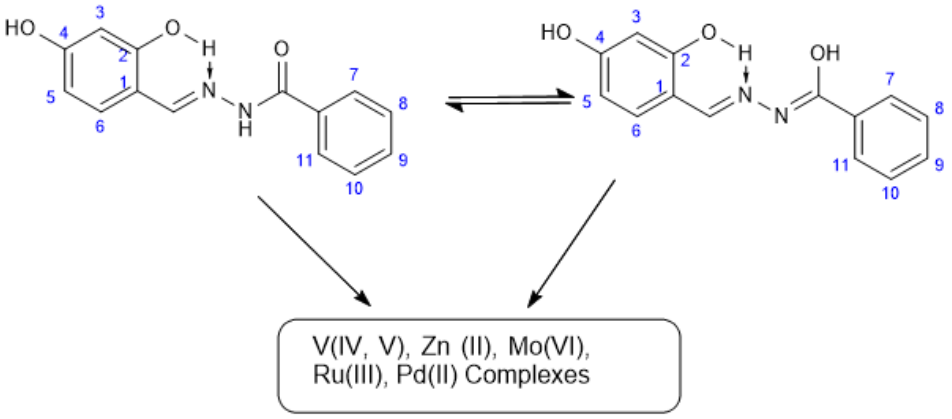


Figure 19. Metal complexes of Schiff base.

that the highest radical scavenging activity was depicted by Oxovanadium(IV) complex, comparable to standard antioxidant ascorbic acid.

2.6 Schiff bases synthesised by sphere modifications

Öğütçü *et al.*[51] synthesised nanospheres of Schiff bases from amino methyl polystyrene (APS) and o-methoxy benzaldehyde and their halogen derivatives and further bound them with Pt(II) or Pt(IV) (**Figure 20**). The complexes were studied for their anti-microbial activity against *C. albicans* in potato Dextrose Agar media. The authors observed that the order of AF activity in the halogen derivatives of the synthesised polymers with nanospheres (Amino methyl polystyrene+ halogen derivatives of the Schiff base) followed the order F < Cl < Br and [APS-Schiff base-Pt]$^{4+}$ was particularly active against *C. albicans*. As explained by chelation, Pt derivatives with the nanospheres were found to be more effective as AF agents than the ligand itself.

In a similar manner, Bozkir *et al.*[52] studied Schiff bases formed by the condensation of amino methyl polystyrene and p-substituted salicylalde-

hydes as their Ni(II) and Cr(III) complexes. The modified polymers were found to be particularly effective as AF agents against *C. albicans.*

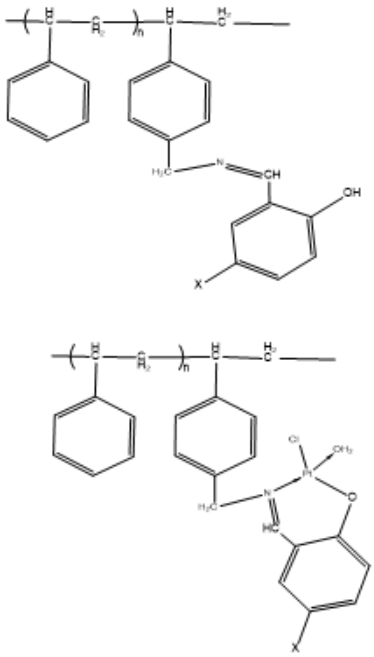


Figure 20. Schiff base synthesised by sphere modification.

3. Conclusion

Metal ion complexes of Schiff bases and their derivatives have gained importance over the years because they are easily synthesised and are cost effective. They have numerous applications in biomedical and material science. More and more bacteria and fungi are becoming resistant to many-a-drugs. Hence this poses the need for the searching for newer, inexpensive alternatives. The present review provides an all-inclusive summary of the synthesis and biological activities of various kinds of transition metal ion complexes of Schiff bases and their derivatives. Since the complexes are between metal ions and carbon of Schiff base ligands so they can be put in the category of organometallic compounds. Newer synthesised Schiff base metal complexes with chitosan and their derivatives and also those synthesised by sphere modifications have been tested for AF and AO activities. The increased AF and AO activities of the lanthanides and certain other transition metal complexes of Schiff bases have been reported in various articles and summarised in the present review. The study of AO activity in terms of lower IC_{50} value has been reported. Thus, as a result of analysis of most recent articles, it has been deduced that metal ion–Schiff base complexes behave as better antioxidants and anti-fungal agents when compared to free Schiff base and hence can serve as potential drugs.

Conflict of interest

The authors declare no conflict of interest.

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