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A Review on Biological Applications of Schiff Base Metal Complexes

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Abstract

Schiff bases are versatile ligands that are generated by combining primary amines with carbonyl groups. Because of their broad range of biological activities, these compounds are extremely significant in the medical and pharmaceutical fields. The majority of them have biological properties such as antibacterial, antifungal, and antitumor properties. Transition metal complexes with biological activity derived from Schiff base ligands have been extensively studied. The biological activities of Schiff bases and their complexes are summarized in this study.

Keywords: Schiff bases; ligands; biological activity; transition metal complexes; pharmaceutical applications

1. Introduction

Schiff base are ligands formed by the condensation between a carbonyl compound and a primary amine. Structurally, a Schiff base (also known as imine or azomethine) (Fig. 1) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (C,O) has been replaced by an imine or azomethine group[1].

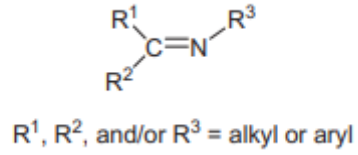

Fig. 1 General structure of Schiff base (taken from reference [1])

The synthesis of Schiff base ligands and their metal complexes has become increasingly relevant in basic and applied science in recent years [2–3]. Because of their direct synthesis and ease of variation, the vital position

of Schiff bases is one of the most intriguing fields of Co-ordination chemistry [4–6]. The majority of Schiff bases can be conveniently made using basic synthetic procedures involving an amine and a carbonyl compound. Many Schiff bases can act as ligands in coordinate chemistry [2,7,8]. In coordination chemistry, Schiff base ligands provide a great forum for the creation of a variety of ligand systems with controllable binding to metal ions. Schiff base metal complexes are one of the most studied groups of compounds and are crucial in coordination chemistry. The broad groups of Schiff base complexes have primarily been studied for biological and pharmaceutical applications, with many of them proving to be successful and commercially available [9–11]. Metal complexes derived from Schiff bases have found uses in a variety of fields, including their ability to reversibly bind oxygen, catalytic activity in the hydrogenation of olefins, photochromic properties, and the ability to complex with certain toxic metals.

In this review, we present examples of compounds from this class that have been documented in the literature to have antibacterial, antifungal, and antitumor activities.

2. Biological activities of Schiff base complexes

Many biologically essential Schiff bases with antimicrobial, antibacterial, antifungal, anti-inflammatory, anti-convulsant, antitumor, and anti-HIV activities have been published in the literature [12–15]. Pharmaceutical compounds with metal ion(s) in their structural backbone now play an important role in medicine [16,17]. Co, Cu, Zn, Ni, Mn, Fe, V, and Cr are found in trace quantities in living organisms and play an important role [18].

Cancer is without a doubt one of the world's most serious health problems, with millions of people dying from it each year. Cisplatin is a promising and well-known metal-based drug for cancer treatment in this regard [19]. The toxicity of cisplatin and its second-generation analogs, on the other hand, has necessitated the development of new drugs with limited side effects and maximum curative potential [20]. Because of their biochemical, pharmacological, antitumor activity, and exceptional chelating capacity, Schiff base ligands and complexes have gained a lot of attention in medicinal chemistry [21-24]. It's worth noting that, as compared to Schiff base complexes, literature reports indicate that Schiff base ligands have little or no cytotoxic activity [25, 26].

2.1 Antimicrobial activity

The Schiff base ligand obtained from 5-amino-4H1,2,4-triazole-3-thiol and 3-hydroxy-4-methoxy benzaldehyde and its complex with Cu (II), Co (II), Mn (II), Zn (II) and Ni (II) were synthesised. Ligand and its metal complexes have been characterized using different spectral studies. The Schiff base ligand and their complexes were analysed for their in vitro antibacterial activity against nine food pathogens- Gram-negative bacteria Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Pseudomonas fluorescens, Pseudomonas aeruginosa & Salmonella enteritidis and the Gram-positive bacteria Staphylococcus aureus, Bacillus cereus & Micrococcus luteus. Their potential activity was qualitatively and quantitatively assessed by the presence/absence for zone of inhibition and MIC values. The metal complexes showed higher antibacterial property than the corresponding ligands. Among the complexes, Zn complex is more potent antimicrobials[27].

The condensation reactions of dialdehyde cellulose (DAC), developed by oxidation of periodate, with L-lysine gave a Schiff base which was tested for antibacterial activity against four bacteria (S. aureus and B. subtilis, E. coli and S. typhimurium. The MIC assay results indicated that the DAC-Lys Schiff base improved antibacterial activity against these bacteria's compared with DAC[28].

The bidentate Schiff base ligands were synthesized from the condensation of 2,5-dimethylaniline (HL1) or 3,5- dimethylaniline (HL2) with 4-acetyl-3-methyl-1-phenyl-5-pyrazolone and from the condensation of Prop-2-en-1-amine (allylamine) (HL3) with 4- acetyl-3-methyl-1-phenyl-5-pyrazolone. The Schiff base ligands were then subjected to complexation with copper. HL1 and HL2 successfully complexed with copper but all attempts to complex the third ligand with copper failed. The ligands and complexes were characterized by general spectroscopic techniques including 1HNMR, IR, UV-Vis spectroscopy as well as elemental analysis. Anti-bacterial activity of these ligands and complexes were tested against four bacteria, namely Escherichia coli (G-), Pseudomonas aeruginosa (G-), Staphylococcus aureus (G+) and Bacillus subtilis (G+). The results clearly indicated that ligands have better anti-bacterial activity than the corresponding copper complex. This may be due to the bulkiness of the group that may hinder penetration of the complexes through the bacterial membrane and hence, the smaller and more penetrable ligands exhibited enhanced antibacterial activity [29].

A series of mixed ligand Cu (II) complexes were synthesised of general formula [Cu (L1)(L2)]ClO_4 in which L1 is an NN′O type unsymmetrical tridentate Schiff base ligand and L2 is an N-donor heterocyclic ligand, i.e. 2,2′-bipyridine in complex (2), 4,4′-dit-butyl-2,2′-bipyridine in (3) and 1,10-phenanthroline in (4).The Schiff base ligand is the mono-condensed form of the reaction between ethylenediamine with salicylaldehyde. The anti-bacterial property was studied against two gram positive and two-gram negative human pathogenic bacteria, i.e. Staphylococcus aureus (Gram-positive), Bacillus subtilis (Gram-positive), Salmonella typhi (Gram-negative), and Escherichia coli (Gram-negative). All the complexes had anti-bacterial potential. The presence of bidentate N-donor heterocyclic co-ligands reduces the chance of the dissociation of the co ligand which may result in unwanted bacterial inhibition due to the toxicity of pyridine itself. The most powerful antibacterial agent was complex (4) with phen co-ligand, which may be attributed to its higher lipophilic character than complex (1) and (2). The lower activity of complex (3) is due to the bulkiness of t-butyl group which hinders the penetration of cell membrane[30].

The Schiff base derived from 2-aminofluorene and 2-pyridinecarboxaldehyde and its complex with silver and copper were synthesised. The antibacterial activity studies in Gram-positive bacteria (MSSA, MRSA, and E. faecalis) and E. coli showed that the silver complex showed an enhanced activity than the corresponding ligand. The complexation with copper did not produce any considerable change in antibacterial activity[31].

A series of chitosan Schiff base Ruthenium (II) complexes were synthesised by the reaction between chitosan and aldehydes like 4-hydroxy-3-methoxy benzaldehyde, 2-hydroxy benzaldehyde, and 2- hydroxy-3-methoxy benzaldehyde. These formed complexes were characterised by Elemental analysis, Thermo-gravimetric analysis (TGA) and FT-IR spectroscopy. The antibacterial activity of both the ligand and the complexes were studied against Gram positive and Gram-negative bacteria such as B. subtilis, S. aureus, E. coli, K. pneumoniae and P. aeruginosa using nutrient agar medium by disc diffusion method with an incubation period of 18 hat 37 ◦ C. T The results indicated that co-ordination to the ruthenium improved the anti-bacterial activity. It can be concluded that the antibacterial activities are increased upon chelation[32].

A new cellulose-based Schiff base ligand was synthesized by selectively oxidising the cellulose fibre to introduce aldehydic group followed by the reaction with amino acid Glycine. the synthesised ligand complexed with copper (II) ion to give cellulose-based Schiff base copper (II) complex. Antibacterial activity was studied on the Gram-negative E. coli and the Gram-positive S. aureus. The fluorescence study revealed that the was a tremendous decrease in the red fluorescence signals of bacterial sample in contact with complex than the free ligand indicating that the antibacterial activity increased upon complexing with the copper. The

schematic diagram of the anti-bacterial mechanism of the complex taking E. coli as example is shown in Fig. 2. The anti-bacterial activity of both the ligand and the complex may be due to the enhancement of membrane permeability by combining with the lipophilic outer membrane resulting in the entry of the ligand and the complex to damage its DNA and kill the bacteria[33].

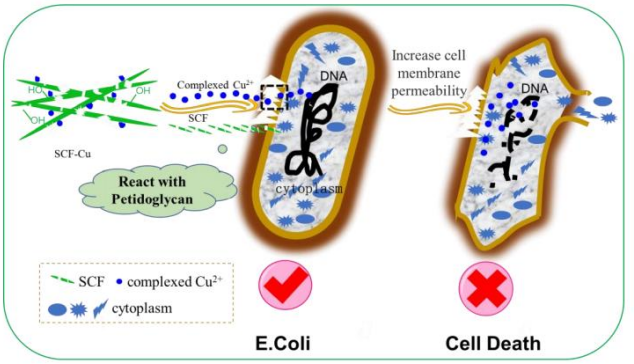

Fig. 2 The schematic diagram of the bactericidal mechanism for cellulose-based Schiff base-Cu (II) complex against *E. coli* (taken from reference[33])

A novel Schiff-base ligand (L) from reaction of 2-formylpyridine with 2- ((4-(2-aminobenzyl)-1,4-diazepan-1-yl)methyl benzenamine and its copper complex were synthesised and characterised. A striking point is that during complexation the ligand has changed from a N6 donor ligand to a N5 donor ligand. The biological property namely anti-bacterial activity with bacteria's *Serratia marcesens* , *Staphylococcus, Escherichia coli* and *Bacillus cereus* were studied[34,35]. The antibacterial assessment results showed that the complex had better antibacterial potential than the free ligand.[36]

A series of new water-soluble transition metal (Co (II), Ni (II), Cu (II), and Zn (II)) complexes with N, N, O donor ligand obtained from glycylglycine and 4-nitrobenzaldehyde were synthesized and characterized. The antibacterial activity of both the complex and ligand were studied with *E. coli, B. subtilis, P.aereuguioa*, S. aureus and the results show that the complex have better activity. The antimicrobial test reveals that the Copper complex shows superior activity against gram-negative bacteria such as *E-coli* compared to some previous works[37-39]

Novel Schiff base ligands were synthesised from a series of hydrazones and its metal chelates namely Copper (II). Nickel (II) and Cobalt (III) were synthesised and characterised and were screened for antibacterial activity against the bacterial species *E. coli, K. pneumonia* (Gram-negative) and *S. aureus, B. subtilis* (Gram-positive). The results revealed that the complexes had better antibacterial activity than the free ligands which can be explained on the basis of Tweedy's chelation theory[40]. The lipophilic character of the complexes is enhanced by the reduction in the polarity. This may result in the formation of hydrogen bonding between coordinated anion and azomethine group with active centers. This might aid the metal to get attached to specific sites retarding its growth[41-42].

A series of benimidazole Schiff base ligands with Zinc (II), Copper (II), Nickel (II) and Palladium (II) were synthesised and characterised and were tested for anti-bacterial activity against Escherichia coli,

Enterobacter aerogenes and Micrococcus luteus. It was found that the metal complexes are more potent than the free ligands against the bacteria. Complexation enhances lipophilicity of the ligands which in turn increase the penetration of the chelate through the membrane favouring the interaction with DNA. Comparing the DNA binding and biological results obtained we can conclude that there is no correlation between the two. For instance, the uncoordinated ligand (1) exhibits the best DNA binding but this is not reflected in its antibiotic activity. The Cu (II) chelate shows promising antibacterial activity, though not related to its poor DNA binding. Some studies reveal that the antibacterial properties of Cu (II) complexes could be due the rupturing of bacterial membrane. However, Zn (II) and Ni (II) complexes exhibit a good correlation between the DNA binding and the MIC values[43].

Schiff base ligand formed by the reaction between anthracene 9 carbaldehyde and 3,4 diaminopyridine and its complex with rare earth metals like Er, Pr and Yb were synthesised and characterised. The antibacterial studies with performed against against Bacillus subtilis, Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa. The Pr complex showed better results than that of Yb and Er. The enhanced antibacterial activity may be attributed to the increase in lipophilicity upon complexation[44].

The biological properties such as antibacterial as well as their affinity to bind to Salmon melt (SM) DNA of complexes of ruthenium, rhodium and iridium containing 9-fluorenone derivative ligands were studied. These complexes showed good anti-bacterial property against both gram positive and gram-negative bacteria. The main reason for the potency is attributed to chelation property of ligands. As the derivatives of fluorenone being fluorescent, DNA binding studies showed that certain complexes exhibited good affinity to SM-DNA[45].

Macroacyclic Schiff base complexes were synthesised by condensation of metal ions (Cobalt (II), Copper (II), Manganese (II) and Nickel (II)) with ligands prepared from reaction of 2-formylpyridine and 2-hydroxy-3- methoxybenzaldehyde with 2-((4-(2-aminobenzyl)-1,4-diazepan1-yl)methyl) benzenamine respectively. The antibacterial activities were tested by disc diffusion methods. The assessment of antibacterial properties of the samples showed the acceptable concentration-dependent inhibition effect against bacteria like Serratia marcesens, S. aureus, E. coli. The inhibitory ability of some of the complexes were found to be good when we compare the antibacterial activity of the complex with reference antibiotics[46].

Four macrocyclic Schiff-base complexes of Mn (II) and Zn (II) were prepared by cycloaddition of 2,6-pyridinedicarbaldehyde or 2,6-diacetylpyridine with the diamine synthesised by condensation of 2-nitrobenzylchloride and piperazine. The synthesised complexes were characterised by using physical techniques. All the products were investigated for antibacterial properties. The results show that certain complexes were found to exhibit more activity against B. thuringiensis, S. saprophyticus and Pectobacterium SP than Tobramycin and Tetracycline as standards[47].

A Schiff base derived from cephalothin and sulfadiazine and its transition metal complex have been prepared. The imido nitrogen (-SO_2-N) and carboxylate moieties are responsible for metal coordination. Complexation reduces the solubility of the Schiff base antibiotic and its metal complexes in water and typical organic solvents. The cephalothin Schiff base, copper (II), and zinc (II) complexes were found to have higher bactericidal activity against bacteria strains than the uncomplexed cephalothin and sulfadiazine, indicating that they are effective bactericides. The complexes of manganese (II), cobalt (II), and nickel (II) were found to be less toxic than the two referenced drugs as well as the Schiff base ligand. Apart from membrane permeability, the antibacterial activity of cephalothin Schiff base and its metal complexes is primarily

determined by the metal ion and microorganism type. Schiff base ligands and their metal (II) complexes were tested for antibacterial activity against *S. aureus,* a Gram-positive bacterium, and *E. coli*, a Gram-negative bacterium, and compared with Cephalothin and sulfadiazine used as standards. The ligand is slightly more toxic to Gram-positive bacteria than Gram-negative bacteria, which may be due to the different cell wall structure of the tested microorganisms, while the reference compounds cephalothin and sulfadiazine have nearly identical activity against both strains tested. The results revealed that the Schiff base ligand and its metal complexes behave differently against the same bacteria than standard antibiotics. The Schiff base ligand, copper (II), and zinc (II) complexes were found to have higher activity against the bacteria strains studied under the test conditions than the two established drugs, indicating that they have good activity as antibacterial agents. Manganese (II), cobalt (II), and nickel (II) complexes have less toxic antibacterial activity than the two reference drugs and Schiff base ligand. Chelation, according to Tweedy's theory [40], increases the lipophilic character of the central metal atom, allowing it to pass through the lipid layers of the cell membrane and block metal binding sites on microorganism enzymes. In this case, antibacterial activity in vitro revealed that copper (II) and zinc (II) complexes have higher antimicrobial activity than the ligand. In comparison to the manganese (II), cobalt (II), and nickel (II) complexes, the ligand displayed a high level of biological activity against the tested strains. As a result, antimicrobial activity is affected by factors other than membrane permeability. Cell wall synthesizing enzymes (penicillin binding proteins, PBPs), which are found as membrane bound and cytoplasmic enzymes that catalyse crosslinking reactions, are the targets of β–lactam antibiotics. Antibiotics that bind covalently to the catalytic site of PBPs interfere with cell wall synthesis. PBPs are found in almost all bacteria, but their number, molecular weight, affinity for β–lactam antibiotics, and enzymatic function (e.g., transpeptidase, carboxypeptidase, or endopeptidase) differ from species to species[48]. The findings make sense when you realize that the enzyme's primary function is to keep catalytic groups or substrate in their proper positions, and it's conceivable that Schiff base metal complexes may alter the stereochemistry required in solvolytic reactions on an enzyme surface. The findings suggest that the behavior of the compounds is most likely linked to their conformational adaptability, which is influenced by the size and nature of the metal complexes as well as the geometrical constraints imposed by intramolecular H bonds. Thus, the bactericidal activity of cephalothin Schiff base and cephalothin Schiff base metal complexes may represent a different mechanistic mechanism by which they react with the PBP active sites to form a stable PBP inhibitor adduct than cephalothin antibacterial activity. The number, structure, and kinetic properties of PBPs decide the degree of resistance to β–lactam complexes[49].

From the reaction of the ligand sapH2 (salicylidene-2-aminophenol) with $Ni(OAc)_2.4H_2O$, three new Ni(II) complexes have been synthesized, in the presence of relevant amine: imidazole (1), 1-methylimidazole (2), and morpholine (3).. The antibacterial properties were studied against Gram-negative bacteria (*E. faecalis*; ATCC 29212 and E. coli; TCC 25922) and Gram-positive bacteria (*Bacillus subtilis*; ATCC 6633 and Staphylococcus aureus. The positive control used was DMSO. In comparison to the control, nickel salts, and ancillary ligands, the complexes display higher activity against bacteria, according to the results. The MIC and MBC values for Schiff base ligand and its complexes were compared, and the complexes were found to have higher antimicrobial activity than the free Schiff base ligand. On the basis of Overtone's principle[50] and Tweedy's chelation theory[40], such a more readily occurring behavior of the complexes can be explained. *S. aureus* stands out of all bacteria was the most susceptible to nickel (II) complexes. In terms of antibacterial activity, complex 1 outperforms complex 2 and 3 due to structural, mechanical, and volume considerations. The findings were compared to Kanamycin as a reference standard in our research. These findings are consistent with previous studies[51–53] of biological activities of nickel Schiff base complexes (II)[54].

With a Schiff base, 3-(2-hydroxy-5-chlorophenylimino)-1,3-diphenylpropen-1-one, three new

transition metal complexes have been synthesized. Schiff base is fully deprotonated and coordinated to metal as tridentate ligand through phenolic and enolic oxygens, as well as imine nitrogen, in all complexes. Antibacterial activity was tested in vitro against Gram-positive (Enterococcus faecalis ATCC 29212 and Staphylococcus aureus ATCC 6538) and Gram-negative (Escherichia coli ATCC 35218 and Pseudomonas aeruginosa ATCC 27853) bacteria strains and compared to standard drugs. When the biological activity of the Schiff base, complexes, and standard drugs is compared, it's clear that the parent ligand has a lot of activity against Gram-positive bacteria. The action of Schiff bases may be due to the chelating properties of the azomethine group, which is used in metal transport across bacterial membranes or in attaching to a particular site of bacterial cells from which it may interfere with their growth[55,56]. This activity may also be due to the presence of OH groups within the Schiff base, which can aid antibacterial activity by hydrogen bonding with enzyme active sites[57]. Both the ligand and its complexes were clearly more toxic to Gram-positive bacteria strains than Gram-negative bacteria strains. The disparity in cell wall structures is the explanation for this. Lipopolysaccharides form an outer lipid membrane and lead to Gram-negative cells' complex antigenic specificity[58]. The results show that all complexes have greater inhibitory effects against E than the parent ligand. *S.* This increased antibacterial activity may be attributed to electron delocalization around the entire chelate ring when it is complexed. Chelation increases lipophilicity and improves permeation across the cell membrane's lipid layer (chelation theory)[59–62]. It's interesting that complexes, especially 1, were found to inhibit P. aeruginosa while standard drugs had no effect on it. According to the above results, the Schiff base is fully deprotonated and tridentately coordinated to the metal ion through imine nitrogen and phenolic and enolic oxygens in all complexes, and there is no hydrated and coordinated water in the structure. One oxygen from a ligand belonging to a neighbouring complex is thought to complete the coordination sphere of the complex. As a result, a dimer is formed when two adjacent metal ions are joined together by two oxygen atoms from adjacent Schiff bases. Similar dimeric structures have previously been reported for Schiff base complexes, and similar Schiff bases have also been reported to act as bridges through phenolic oxygen[63,64]. A dimeric structure for synthesized complexes with a distorted square planar geometry around metal ions was proposed based on these findings. All complexes were found to have strong antibacterial activity against Grampositive bacteria and have the potential to be used as drugs[65].

Three new chitosan Schiff base derivatives were synthesized with a Heterocyclic Pyrazole moiety as a substituent. Three heteroaryl pyrazole derivatives were prepared and reacted with chitosan to form Schiff bases: 1-phenyl-3-(thiophene-2-yl)-1H-pyrazole-4-carbaldehyde, 1-phenyl-3-(furan-2-yl)-1H-pyrazole-4-carbaldehyde, and 1-phenyl-3-(pyridine-3-yl)-1H-pyrazole-4-carbalde The biological activity of the Schiff bases was tested against gram-negative bacteria (*Escherichia coli* and *Klebsiella pneumoniae*), gram-positive bacteria (*Staphylococcus aureus* and *Streptococcus mutans*), and fungi (*Asperagillus fumigatus* and *Candida albican*). The results revealed that the bactericidal property is based on the Schiff base moiety type. According to the study, all derivatives have nearly the same effect on both E. coli and K. pneumonia and are comparable to Chitosan. The cell structure of E. coli and S. aureus can be destroyed by chitosan[66] causing enzymes and nucleotides to leak from various parts of the cell. Gram negative bacteria have a thinner cell wall than gram positive bacteria, making them more vulnerable than Grampositive bacteria. As compared to Chitosan-Schiff bases with pyrazole rings bearing furanyl or thiophenyl moieties, those with pyrazole rings bearing pyridyl moieties displayed higher antibacterial activity (Fig.3). Antimicrobial activity is influenced by a number of factors, including hydrophobic/hydrophilic character, interactions between localized functional groups on Chitosan's surface and bacterial cells, degree of modification of Chitosan, and dispersion of modified Chitosan in the culture medium. The charge of the cell surfaces is another important factor in the microbial balance and antimicrobial resistance. The antimicrobial activity of chitosan Schiff base with pyrazole derivative bearing pyridyl moiety was higher[67].

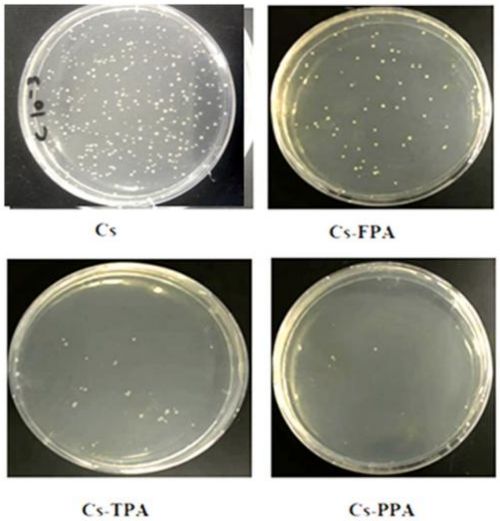

Fig.3 Representative images of viable S.aureus grown on different samples(Chitosan- Cs, 1-Phenyl-3-(thiophene-2-yl)-1H-pyrazole-4-carbaldehyde, TPA, 1- phenyl-3-(furan-2-yl)-1H-pyrazole-4-carbaldehyde, FPA, and 1- phenyl-3-(pyridine-3-yl)-1H-pyrazole-4-carbaldehyde, PPA) after 24 h of culture(taken from reference [70])

Mechanism for bactericidal action of chitosan Schiff base

Previous studies[68] has proposed three mechanisms to explain chitosan interaction with different microorganisms, which vary depending on cell wall structure and metabolic process. The first mechanism may be due to the electrostatic interaction between the anionic residue of bacteria (-COO^- or PO_4^{3-}) groups and the cationic NH_3^+ groups of chitosan, which disrupts the cell membrane's normal functions. The penetration of chitosan into the nuclei of microorganisms inhibits mRNA and protein synthesis, according to the second proposed mechanism. The chelating ability of chitosan to metal ions like Ca^{2+}, Mg^{2+}, and Zn^{2+}, which are essential constituents for bacterial growth and metabolic pathways, is the third mechanism. The difference in the obtained data between the prepared Schiff bases may be due to the change in hydrophilic/hydrophobic balance, surface charge, and solubility, according to the results. The imine group's -electrons in Schiff bases, as well as conjugated systems arising from heterocyclic moieties (Thiophene, Furan, and Pyridine) with pyrazole and phenyl rings, increase the imine group's electron density, disrupting the microbial cell's respiration process. Finally, bacterial growth is prevented by inhibiting protein synthesis[69]. Gram-negative bacterial pathogens were more vulnerable to Schiff bases than Gram-positive bacterial pathogens, which was most likely due to bacteria's thick cell walls[70].

From salicylalidene-4-imino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one and 2-aminothiazole, new mono cationic Cu (II), Co (II), Ni (II), VO(II), and Zn (II) Schiff base complexes have been synthesized. Elemental analysis, UV–Vis., FTIR, 1H-NMR, 13C-NMR, EPR, Fluorescence emission, Powder XRD, FESEM, and FAB-Mass spectral measurements were used to investigate the prominent structural features of synthesized compounds. The well diffusion approach was used to evaluate the in-vitro antimicrobial activities of the investigated compounds against bacterial and fungal strains. Metal chelates have lower MIC values than free ligands

against microorganism growth. This is attributed to the reduction in size of metal chelates upon complexing with the ligands. FESEM and powder XRD data back up these observations. The [CuL]Cl and [VOL]Cl were found to be slightly more potent than the other investigated Schiff base transition metal complexes based on MIC values. According to a comparison of the Schiff base and its complexes, metal complexes have greater antimicrobial activity than the Schiff base. This is due to the fact that when a metal chelate is coordinated with a ligand, the size of the metal chelate shrinks, increasing the lipophilicity of the complex. Powder XRD data and FESEM images(Fig.4) of the Schiff base and complexes supports this up[71]. When compared to the size of Schiff base, FESEM images show grain size contraction up to nano level in metal chelates, which is further supported by XRD data[72]. The compounds' mode of action is to form a hydrogen bond with the active center of cell constituents through the azomethine atom, causing interference with normal cell growth[73].

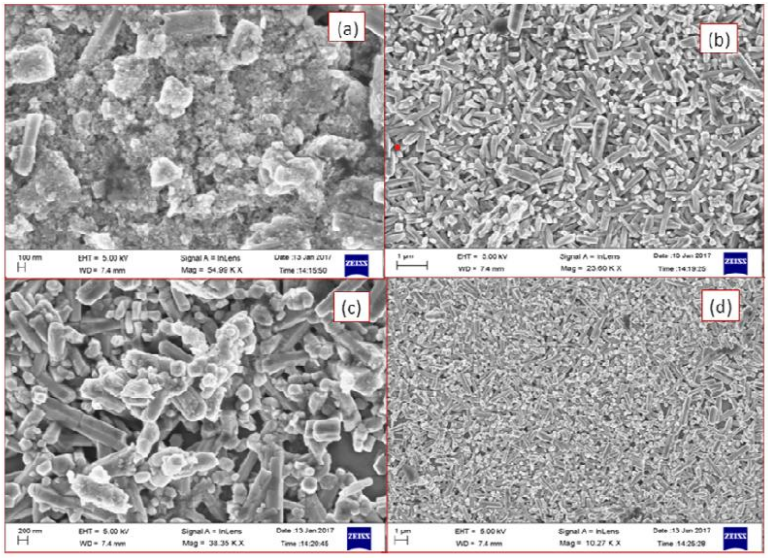

Fig. 4 FESEM (100 nm, 200 nm & 1µm) images for Schiff base (a), [NiL]Cl (b), [CuL]Cl (c) & [ZnL]Cl (d) complexes (taken from reference[70])

2.2 Anticancer Activity

The anticancer activity of the tetradenate N2OS type Schiff base and its Cu(II), Co(II), Ni(II), VO(II) and Zn(II) were investigated using the MTT assay process, which revealed that chelates have a higher percent of inhibition against breast cancer cell line culture growth than Schiff base. Metal complexes have higher biological activity than the Schiff base, according to the findings of in vitro biological screening studies. The effect of metal ions on the normal cell membrane is responsible for the higher activities of metal complexes. Furthermore, chelation increases the biochemical capacity of bioactive Schiff bases by altering their hydrophilicity and lipophilicity, lowering cell permeability barriers and controlling the rate at which molecules enter the cell wall. This type of effect enhances the penetration of metal complexes into lipid membranes and prevents metal binding sites in microorganism enzymes from being blocked. Furthermore, it disrupts the cell's respiration mechanism and, as a result, prevents the synthesis of proteins, limiting the organism's ability to expand further. Furthermore, the compounds' mode of action could involve the formation of a hydrogen bond with the active center of cell constituents through the azomethine group, resulting in

interference with normal cell processes[70,74].

The possible tridentate O, N, N0 donor sets of HL and HL' have been used to synthesize two copper (II) complexes, namely $[Cu(HL)(pdc)]_2$ (1) and $[Cu(L')_2]_2$ (2), where HL = 2-([2-(piper azin-yl)ethylimino]methyl)phenol, pdc = py-2,5-dicarboxylate, and Complex 1 has a centro-symmetric dimer, according to X-ray single crystal analysis. It crystallizes with a network of H-bonds formed by a number of lattice water molecules, as well as the protonated piperazinium fragment, resulting in a 3D supramolecular architecture. Complex 2 also crystallizes as a dinuclear $[Cu(L')_2]2$, formed by mutual bridging phenol oxygen atoms, while an ESI mass spectrometry analysis shows that the complex exists in solution as a mononuclear $[Cu(L')_2]$ (2). Using electronic absorption and fluorescence spectroscopic techniques, the interaction of complexes 1 and 2 with calf thymus DNA (CT-DNA) and bovine serum albumin (BSA) was investigated. The electronic absorption spectroscopic technique was used to investigate the interactions of complexes 1 and 2 with CT-DNA. It's worth noting that when CT-DNA is added, the absorbances of 1 and 2 steadily decrease while the absorption wavelength remains constant. Intercalative binding is shown by the hypochromism[75]. Electrostatic interactions between compounds and DNA bases are primarily responsible for hypochromicity[76]. BSA-compound interaction fluorimetric analysis was investigated. BSA fluorescence strength quenches after gradual addition of complex solution, according to studies. The key causes of BSA fluorescence quenching are complex formation with metal species, denaturation, and conformational changes in serum albumins[77]. For complexes 1 and 2 interacting with BSA[78], the Stern–Volmer constant values (Ksv) have been determined. The Ksv value shows that the compounds have a strong capacity to quench serum albumin. The electronic absorption spectra of BSA are affected by the addition of the complexes, suggesting a static interaction between BSA and the compounds, as revealed by UV–Vis spectroscopic activity of BSA after gradual addition of the complexes. In both experiments, the results suggest that complex 1 has a higher binding affinity than complex 2. Complex 1 has moderate growth suppressing activity against MCF7 cells, according to the anticancer activity of the complexes against human breast (MCF7) cancer cell lines. It inhibits MCF7 cell growth in a dose-dependent manner, with an IC_{50} of 24 6.24IM. Complex 2 on the other hand has only a minor impact on the development of the breast cancer cell line MCF7[79].

The reaction of halogenated salicylaldehydes with 3-Amino-1,2-propanediol (R or S) in water as a green solvent at room temperature yielded eight enantiomerically pure halogenated Schiff base compounds. Elemental analyses, NMR (^1H and ^{13}C), circular dichroism (CD), and FT-IR spectroscopy were used to classify all of the compounds. Fluorescence quenching and UV–vis spectroscopy was used to study the FS-DNA binding of these compounds. The results showed that the ligands bind to DNA in the following order: (R-ClBr) > (R-Cl2) > (R-Br2) > (R-I2) and (S-ClBr) > (S-Cl2) > (S-Br2) > (S-I2), suggesting that halogen has an effect on binding constant. Furthermore, the DNA-binding constants of the S- and R-enantiomers vary from one another. Molecular docking verified that the ligands can form halogen bonds with DNA. The bond distances and angles were also calculated using this method. The strength of halogen bonds influences the binding affinity of ligands to DNA, according to the data collected. It's worth noting that introducing bulky groups like halogens into organic molecules will enhance binding affinity, membrane permeability, and thus oral absorption. Since bulky groups occupy the entire active site of molecular targets, including the deeper pockets[80]. The MTT assay was used to investigate the potential anticancer activity of ligands on MCF-7 and HeLa cancer cell lines. The anticancer activity and FS-DNA interaction were found to be strongly influenced by the stereoisomers of Schiff base compounds, with R-enantiomers having significantly higher activity than S-enantiomers. According to the results of MTT assays, microscopic monitoring of cell morphology revealed different levels of cytotoxicity depending on the cell line and chirality of Schiff base compounds. The major variations in cell morphology between the cells exposed to various compounds could be clearly seen. In the treated cells, cell shrinkage and

rounding, which are key signs of cell death, were clearly visible. The slightly lower cell density after 48 hours of treatment compared to control cells may be due to the compounds inhibiting cell growth or causing cell death. MCF-7 cells showed significantly fewer of the aforementioned changes than HeLa cells, confirming the findings of MTT assays. Overall, the findings suggest that these Schiff base compounds, especially R enantiomers, have a lot of potential as anticancer agents[81].

Zahra Saedi et al. reported on the synthesis, characterization, and anticancer properties of four cadmium (II) complexes of a new asymmetrical bidentate Schiff base ligand (abbreviated as L) with a $CdLX_2$ (X= Cl^-, Br^-, I^-, and SCN^-) general formula. Elemental study, molar conductance, UV-Vis, FT-IR, ^1H NMR, and ^{13}C NMR spectra were used to characterize the ligand and its complexes. On cancer cell lines HT29 and A549, the anticancer function of ligands and complexes was investigated in vitro. Some of the cadmium complexes were found to be more active than the ligand in HT29 and A549 cancer cells. Regardless, as seen in the photomicrograph (Fig. 5), the morphology of the cells changed dramatically after treatment with ligand and complexes. The treated cells took on a circular form, which indicates cellular shrinkage, vacuolated cytoplasm, and small nuclei, all of which are hallmarks of apoptosis. IC50 values of ligand and complexes are less than normal, and A549 values are less than HT29, based on obtained data for both cases of used cell lines. IC50 values are the concentration of sample that triggers the death of 50% of the cells. The results clearly show that the cytotoxicity of CdLBr2 is higher or comparable to other observed systems in both HT29 and A549 cells. As a result, these findings suggest that ligand and its complexes treatment significantly reduces the viability of HT29 and A549 cancer cell lines in a dose- and time-dependent manner. According to the results, in case of bromide complexation resulted in an increase in anticancer activity, while iodide and thiocyanate complexation resulted in a decrease in anticancer activity compared to the free ligand[82].

2-((2-mercaptophenyl)imino)-1,2-diphenylethan-1-ol(H2L) Schiff base ligand from benzoin and 2-aminothiophenol was prepared. The complexes of Co (II), Cd (II), La (III), and Gd (III) were prepared in bulk size, with the La (III) complex being prepared in nano size. Elemental analysis, ^{1}HNMR, IR, Mass spectroscopy, UV-VIS spectra, thermal analysis, conductivity measurements, and magnetic moments were used to characterize the Schiff base and its complexes. The complexes are octahedral and non-electrolytic in nature, according to the selected studies, and the azomethine nitrogen has not participated in complexation. On Vero, Caco-2, and MCF-7 cells, the cytotoxicity effect of Cd (II) complex using the MTT method showed a strong nontoxic activity and higher cell viability than the free ligand. According to the cytotoxicity results, the Cd (II) complex could be used as an anticancer agent in Vero, Caco-2, and MCF-7 cells. We discovered new active and selective anticancer drugs by studying their pharmacological activity[83].

New Schiff base ligands (HL1 and HL2) derived from morpholine, as well as their Cu (II) complexes $[Cu(L_1)_2]$ (1) and $[Cu(L_2)_2]$ (2), have been synthesized and characterized using ^{1}H NMR, IR, UV-Vis, EPR, and cyclic voltammetric analyses. The structure of newly synthesized Schiff base ligands HL1 and HL2 has been confirmed by single crystal X-ray crystallography studies. The MTT colorimetric assay was used to investigate the anticancer activities of the synthesized Schiff base ligands (HL1 and HL2) and their Cu (II) complexes 1 and 2 on human breast cancer cell lines (MCF-7) in vitro

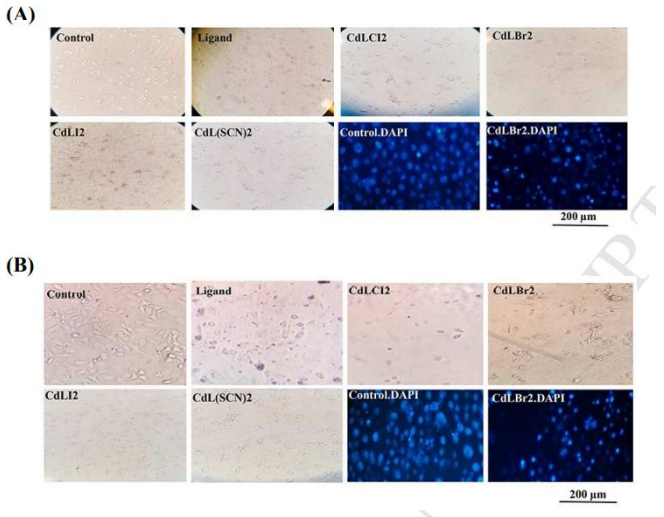

Fig. 5 Inverted microscopic observation and DAPI staining for a survey of cytotoxicity of ligands and their complexes with the IC50 concentration in HT29 (A) and A549 (B) cells lines after 24 h. (taken from reference[82])

The anticancer behavior of the ligand complex is influenced by its structure. Thus, after combining with metal ions, the attachment of hydrophobic groups in ligands rigid shows a better anticancer potential, since it can require a strong hydrophobic interaction with cancerous cells DNA and kill via an apoptosis mechanism. Due to the existence of two t-butyl groups in complex 2, which may provide more hydrophobicity to complex 2 and allow for a stronger interaction with cancerous cells DNA, complex 2 exhibited more cytoxicity on MCF-7 cancer cells than complex 1. Furthermore, metal ion complexation improves anticancer activity, as shown by the lower IC50 values of the Cu (II) complexes 1 and 2 relative to the uncoordinated ligands HL1 and HL2. This may be due to an increase in ligand moiety conjugation upon complexation. The Schiff base ligands (HL1 and HL2) and their Cu (II) complexes 1 and 2 induced characteristic morphological changes in MCF-7 cells, which were evaluated using fluorescent microscopic analysis with acridine orange/ethidium bromide (AO/EB). Complex 2 induces cell death through both apoptosis and more effectively than complex 1 and Schiff base ligands (HL1 and HL2). AO/EB staining was used to observe morphological changes of late apoptosis indication (cancer cells with green-to-brown fluorescing nuclei with condensed or scattered chromatin) after treatment of MCF-7 cancer cells with IC50 concentrations of compounds (Fig. 6). Furthermore, all of the morphological changes observed for the Schiff base ligands (HL1 and HL2) and their Cu (II) complexes 1 and 2 show that the cells are committed to death in such a way that apoptotic cells increase in number in a time-dependent manner, and the ability of the compounds to cause apoptotic cell death follows the order complex 2 > complex 1 > HL2 > HL3 > HL1[84].

The mononuclear and dinuclear Ni (II) and Co (II) complexes of a Schiff base ligand, 6,6' -dimethoxy-2,2' -[o-phenylenebis(nitrilomethylidyne)]diphenolato (LA), were synthesized. Elemental analysis, molar conductivity, IR, NMR, UV–Vis spectroscopy, TGA, and magnetic susceptibility were used to deduce the structure. The Ni (II) centre has a square planar geometry, with the ligand acting as a tetradentate ONNO chelate, according to single crystal X-ray diffraction of the Ni (LA) complex. The relative cytotoxicity of LA and its complexes against HCT116 is of Ni_2(LA) > Ni (LA) > LA > Co_2(LA) > Co (LA).

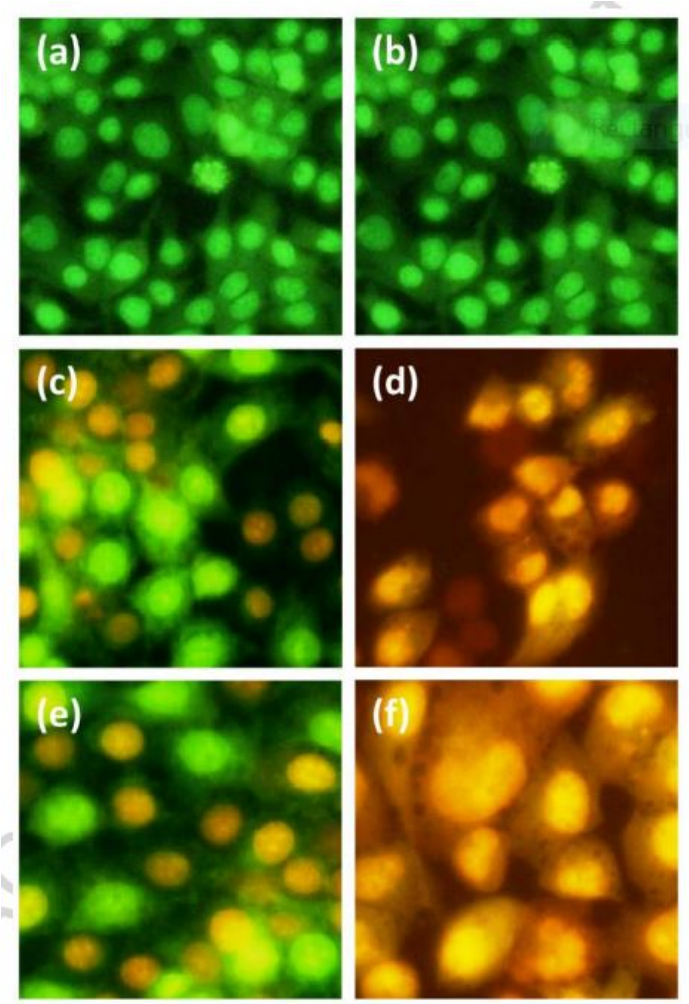

Fig. 6 Fluorescent images of (a-b) controlled MCF-7 cancer cells, (c) treated with Schiff base ligands HL1 and (d) HL2 and their (e) Cu (II) complexes 1 and (f) 2 (taken from reference[84])

The ligand, LA, had an IC50 of 29.40 5.90 mM, indicating that even without the presence of any metal, the ligand can interact with and alter the DNA in HCT116, thereby slowing its development. The Ni_2(LA) complex, on the other hand, was the most effective anticancer agent. It's worth noting that, unlike nickel (II) complexes, both cobalt (II) complexes have lower anticancer properties than their parent ligand. Although nickel (II) complexes outperformed their cobalt (II) counterparts in terms of anticancer activity, both dinuclear complexes outperformed their mononuclear counterparts. This study indicates that the anticancer potency of these compounds is metal-dependent to some degree[85].

The bivalent Cu (II) (1), Ni (II) (2), and Co (II) (3) metal complexes of a novel Schiff base (L) derived from 6-aminobenzothiazole and 4-methoxy salicylaldehyde were synthesized and thoroughly characterized using various analytical and spectral techniques. For all complexes, a square planar geometry is assigned based on the data. UV–Vis absorption, fluorescence, and viscosity measurements were used to investigate the DNA

interaction of complexes with CT-DNA. The complexes bind to CT-DNA in an intercalative mode, according to these studies. MTT assay was used to investigate the cytotoxicity of L and its complexes 1, 2, and 3 in cancer cells such as HeLa (cervical cancer cell), A549 (adenocarcinomic human alveolar basal epithelial cells), and MCF-7 (breast cancer cells). In comparison to the other metal complexes and the ligand, the IC50 values indicate that complex 1 has more activity. Furthermore, these compounds are found to be more effective against HeLa cells than MCF-7 and A-549 cells. The order of toxicity of the compounds found was cisplatin > 1 > 2 > 3 > L. This significant increase in cytotoxicity of compounds as compared to ligand suggests that the coordination power of the metal center in complexes has a significant impact on cytotoxicity. This may be because the charge of metal ions in complexes decreases, favoring increased permeability of complexes through the cell membrane's lipid layer[86].

3. Conclusion

Because of their ability to form complexes with transition metal ions and their pharmacological properties, Schiff bases are a very important class of organic compounds. Transition metal complexes containing Schiff bases have piqued researchers' interest in recent years, owing to their numerous biological applications and possible applications in the development of new therapeutic agents. Researchers have been interested in obtaining the most suggestive and definitive access in the field of various Schiff bases of medicinal significance for decades because of this bioactive core. The contribution of Schiff bases to the design and production of novel lead with potential biological activities is highlighted in this review paper. However, there is still a need to investigate the biological properties of these transition metal complexes that have already been synthesized, as well as to create new complexes with additional properties.

Declaration of Conflicting Interests

The authors declare no potential conflicts of interest with respect to the research, authorship and publication of this article.

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