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Biological activity of transition metal complexes incorporating Schiff bases: A review

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Abstract
Schiff bases and their complexes are versatile compounds synthesized from the condensation of an amino compound with carbonyl compounds and widely used for industrial purposes and also exhibit a broad range of biological activities including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties. Many Schiff base complexes show excellent catalytic activity in various reactions and in the presence of moisture. Over the past few years, there have been many reports on their applications in homogeneous and heterogeneous catalysis. The high thermal and moisture stabilities of many Schiff base complexes were useful attributes for their application as catalysts in reactions involving at high temperatures. The activity is usually increased by complexation therefore to understand the properties of both ligands and metal can lead to the synthesis of highly active compounds. The influence of certain metals on the biological activity of these compounds and their intrinsic chemical interest as multidentate ligands has prompted a considerable increase in the study of their coordination behavior. Development of a new chemotherapeutic Schiff bases and their metal complexes is now attracting the attention of medicinal chemists. This review compiles examples of the most promising applied Schiff bases and their complexes in different areas.

Keywords: Complex, Schiff base, bio-inorganic chemistry, catalysis, antimicrobial, dyes, polymers

1. Introduction
Schiff bases are formed when any primary amine reacts with an aldehyde or a ketone under specific conditions. Structurally, a Schiff base (also known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (CO) has been replaced by an imine or azomethine group (Fig. 1).

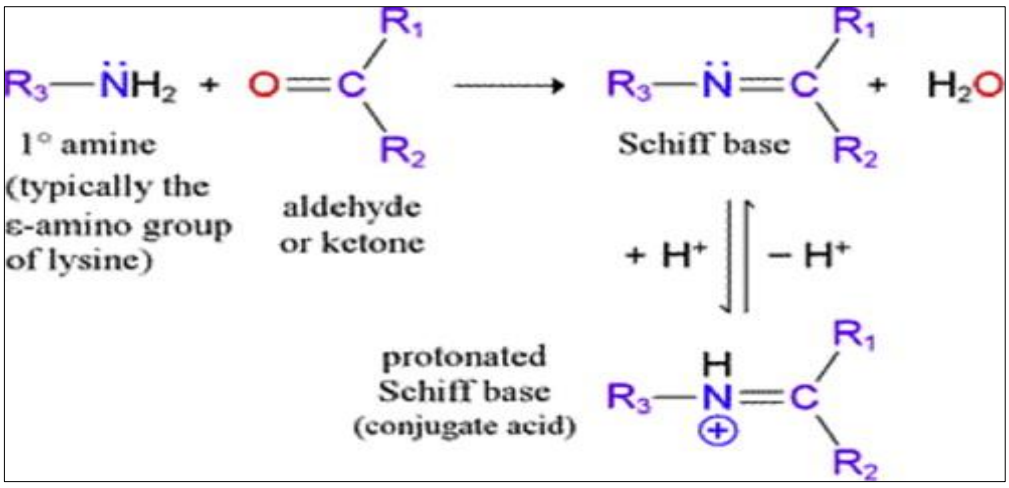

Fig 1: General scheme for formation of Schiff bases.

Schiff base ligands are easily synthesized and form complexes with almost all metal ions. Over the past few years, there have been many reports on their applications in biology including antibacterial, antifungal, anticancer, antioxidant, anti-inflammatory, antimalarial, antiviral activity. Hence the need for a review article highlighting the uses of Schiff base ligands and their complexes in biological system. The development in the field of bio-inorganic chemistry has increased the interest in Schiff base complexes, since it has been recognized that many of these complexes may serve as models for biologically important species. Thus, we report them in the following:

2. Anti-bacterial activity of Schiff base complexes

Metal complexes of Schiff base derived from 2-thiophene carboxaldehyde and 2-aminobenzoic acid (HL) and Fe(III) or Co(II) or Ni(II) or UO_2(II) showed a good antibacterial activity against *Escherichia coli*, *Pseudomonas aeruginosa* and *Staphylococcus* pyogenes. Fe(III), Cu(II), Zn(II) and UO_2(II) complexes caused inhibition for *E. coli*. The importance of this lies in the fact that these complexes could be applied fairly in the treatment of some common diseases caused by *E. coli*. However, Fe(III), Co(II), Cu(II), Zn(II) and UO_2(II) complexes were specialized in inhibiting Gram-positive bacterial strains (*Staphylococcus pyogenes* and *P. aeruginosa*). The importance of this unique property of the investigated Schiff base complexes lies in the fact that, it could be applied safely in the treatment of infections caused by any of these particular strains.

Four Platinum (II) Schiff bases complexes containing of salicylaldehyde and 2-furaldehyde with o- and p-phenylenediamine were reported as antibacterial against *E. coli*, *Bacillus* subtilis, *P. aeruginosa*, *Staphylococcus aureus*. The activity data show that the Platinum (II) complexes are more potent antimicrobials than the parent Schiff base ligands against one or more microorganisms.

Metal complexes of a novel Schiff base derived from condensation of sulphametrole and varelaldehyde were screened against bacterial species (*E. coli* and *S. aureus*). The newly prepared Schiff base and its metal complexes showed a higher effect on *E. coli* (Gram-negative bacteria) and *S. aureus* (Gram-positive bacteria) It is known that the membrane of Gram-negative bacteria is surrounded by an outer membrane containing lipopolysaccharides. The synthesized Schiff base and its metal complexes seem to be able to combine with the lipophilic layer in order to enhance the membrane permeability of the Gram-negative bacteria. The lipid membrane surrounding the cell favours the passage of only lipid soluble materials; thus the lipophilicity is an important factor that controls the antimicrobial activity. Also the increase in lipophilicity enhances the penetration of Schiff base and its metal complexes into the lipid membranes and thus restricts further growth of the organism). The Schiff base and its metal complexes are more toxic on *S. aureus* than on *E. coli*, probably due to the sulphonic OH, OCH_3, S and CH_3CH_2CH groups, which might interact with the double membrane). This activity is related to the nature and structure of the complexes (Fig. 2).

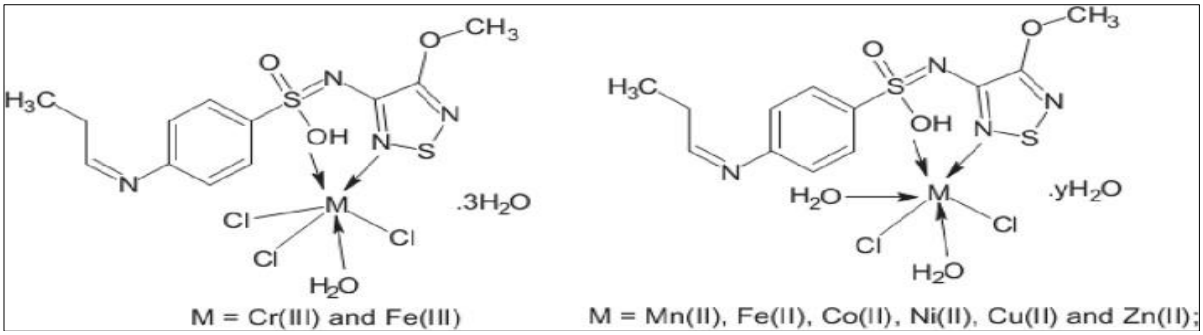

Fig 2: The proposed structural formulae of metal complexes.

2-Aminomethylthiophenyl-4-bromosalicylaldehyde Schiff base and its metal complexes have been screened for their antimicrobial activities using the disc diffusion method against bacteria, the results of antimicrobial activity show that the metal complexes exhibit antimicrobial properties and they show enhanced inhibitory activity compared to the parent ligand under experimental conditions. The antibacterial activity has been explained on the basis of chelation theory. Also, the results indicated that tested complexes were more active against Gram-positive than Gram-negative bacteria. It may be concluded that antibacterial activity of the compounds is related to cell wall structure of the bacteria. It is possible because the cell wall is essential to the survival of many bacteria and some antibiotics are able to kill bacteria by inhibiting a step in the synthesis of peptidoglycan (Fig. 3).

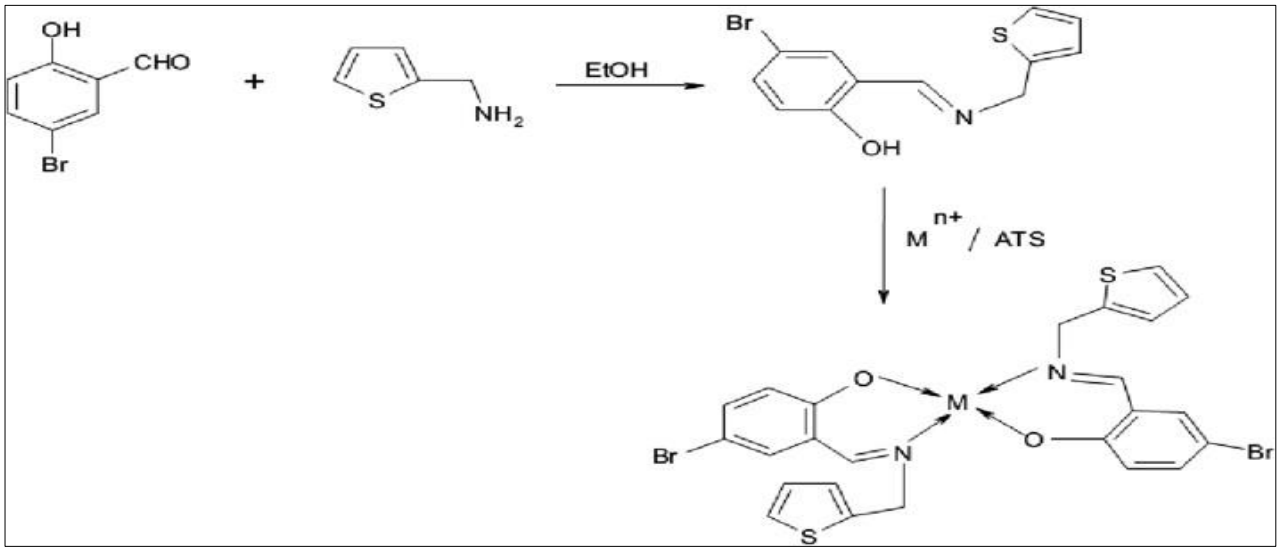

Fig 3: Suggested structure of Schiff base ligand and its metal(II) complexes where M = Cu(II), Ni(II) and Zn (II).

Schiff base complexes of Co(II), Ni(II), Cu(II) and Zn(II) incorporating indole-3-carboxaldehyde and m-aminobenzoic acid were screened by disc diffusion method. The activity order of the synthesized compounds is as follows: Cu(II) > Co(II) > Ni(II) > Zn(II) > Ligand. The higher activity of the metal complexes may be owing to the effect of metal ions on the normal cell membrane. Metal chelates bear polar and nonpolar properties together; this makes them suitable for permeation to the cells and tissues. In addition, chelation may enhance or suppress the biochemical potential of bioactive organic species.

A series of new Iron(II) Schiff base amino acid complexes derived from the condensation of amino acid and sodium 2-hydroxybenzaldehyde-5-sulfonate have been synthesized. The complexes were characterized by elemental, electronic, IR spectral analyses and conductance measurements. The stability and solubility of the prepared complexes were determined. The antibacterial activity of the prepared complexes has been tested against *Bacillus cereus*, *P. aeruginosa* and *Micrococcus bacteria*.

Also a series of new iron(II) complexes based on Schiff bases amino acids ligands have been designed and synthesized from condensation of 5-bromosalicylaldehyde (bs) and α-amino acids (l-alanine (ala), l-phenylalanine (phala), l-aspartic acid (aspa), l-histidine (his) and l-arginine (arg)). The structure of the investigated iron(II) complexes was elucidated using elemental analyses, infrared, ultraviolet–visible, thermogravimetric analysis, as well as conductivity and magnetic susceptibility measurements. The structure of the complexes was validated using quantum mechanics calculations based on accurate DFT methods. Geometry optimization of the Fe-Schiff base amino acid complexes showed that all complexes had octahedral coordination. Moreover, the prepared compounds are screened for their *in vitro* antibacterial activity against three types of bacteria, *E. coli*, *P. aeruginosa* and *B. cereus* using disk diffusion method. The results of these studies indicated that the metal complexes exhibit a stronger antibacterial and antifungal efficiency than their corresponding Schiff base amino acid ligands. Further more, the DNA interaction of these complexes with was tested at pH = 7.2, by using electronic absorption spectra and viscosity measurements. The experimental results indicated that the investigated complexes could bind to DNA via intercalative mode and showed a different DNA binding according to the sequence: bsari > bshi > bsali > bsasi > bsphali (Fig. 4).

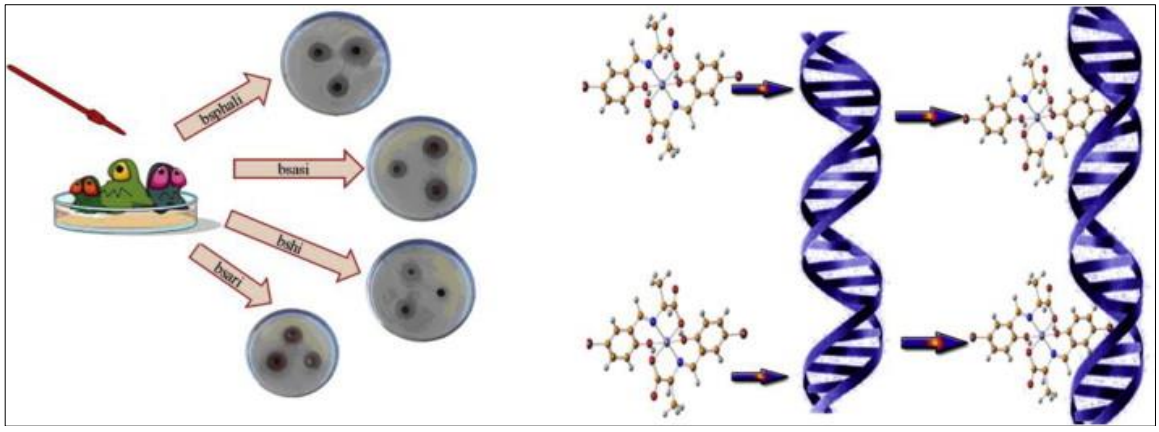

Fig 4: Schematic diagram for antibacterial activity and DNA interaction of the investigated complexes.

Also, five novel Cu(II) complexes derived from the condensation between 5-bromosalicylaldehyde (bs) and α-amino acids (l-alanine, l-phenylalanine, l-aspartic acid, l-histidine and l-arginine) were synthesized and characterized by their elemental analyses, thermogravimetric analysis, IR, mass and electronic spectra, conductance and magnetic measurements. Moreover, the stoichiometry and the stability constants of the prepared complexes have been determined spectrophotometrically using continuous variation and molar ratio methods. The obtained results indicated that the Schiff bases of the amino acids: l-alanine, l-phenylalanine, l-histidine and l-arginine behave as tridentate ligands. The ligands are coordinating with the Cu(II) via azomethine nitrogen, deprotonated carboxylate oxygen and phenolic oxygen. While in the case of L-aspartic, the ligand acts as tetradentate due to the coordination of the second carboxylate group. Based on the studies of magnetic moments and electronic spectra, a square planar geometry has been proposed for all Cu(II) complexes except bromosalicylaldehydine aspartate complex which has a distorted tetrahedral structure. The representative Schiff bases and their Cu(II) complexes were tested *in vitro* for their antibacterial activity against two Gram-Positive bacteria (*Micrococcus luteus* and *B. cereus*) and one Gram-negative bacteria (*P. aeruginosa*). All the complexes showed activity against the organisms more than the free Schiff base ligands and the activity increases with the increase in concentration of test solution containing the new complexes. The activity data show that the metal complexes have a promising biological activity comparable with the parent Schiff base ligand against bacterial species.

3. Anti-fungal activity of Schiff base complexes

Metal complexes Cu(II), Co(II), Ni(II) and Mn(II) are synthesized with Schiff bases derived from o-phthalaldehyde and amino acids viz., glycine l-alanine, l-phenylalanine, then tested against three fungi. It is clear that Cu(II) and Ni(II) complexes exhibit inhibition towards all the studied microorganisms. However, Co(II) and Mn(II) complexes exhibit less inhibition and VO(II) complexes have no activity towards the microorganisms.

The metal complexes of Cu(II), Ni(II) and Co(II) with Schiff bases of 3-(2-hydroxy-3-ethoxybenzylideneamino)-5-methyl isoxazole and 3-(2-hydroxy-5-nitroben-zylidene amino)-5-methyl isoxazole which were obtained by the condensation of 3-amino-5-methyl isoxazole with substituted salicylaldehydes were screened against *Aspergillus niger* and *Rhizoctonia solani*. The ligands presented here and their transition metal complexes gave better results against the growth of fungi. It is found that the activity increases upon coordination. The

increased activity of the metal chelates can be explained on the basis of chelation theory. The orbital of each metal ion is made so as to overlap with the ligand orbital. Increased activity enhances the lipophilicity of complexes due to delocalization of pi-electrons in the chelate ring. In some cases increased lipophilicity leads to breakdown of the permeability barrier of the cell. The results of anti-fungal screening, indicate that Cu(II) complexes show more activity than the other complexes. These results may be due to higher stability constant of the Cu(II) complexes than the other complexes.

A Schiff base ligand derived from 1,4-dicarbonyl-phenyl-dihydrazide and chromene-2,3-dione (2:2) formed complexes with Cr(III), Mn(III), and Fe(III) metal salt in methanolic medium, then tested for their antimicrobial activities to assess their inhibiting potential. The antifungal experimental results of the compounds were compared with the standard antifungal drug (Miconazole) at the same concentration. All the metal complexes exhibited greater antifungal activity against *Aspergillus* sp. However, they show slightly lesser activity against *Rhizoctonia* sp. than standard drug Miconazole. The Cr(III) and Fe(III) complexes are more effective against *Penicillium* sp. than the standard drug. From the data it has been also observed that the activity depends upon the type of metal ion and varies in the following order of the metal ion: Cr > Fe > Mn.

The Gd(III), Dy(III) and Sm(III) complexes of Schiff base derived from acetoacetanilide and 1,3-diaminopropane, $[MX_3(LH_2)]$, where $X = Cl^-$, NO_3^-, NCS^-, have been synthesized in alcohol and characterized by elemental analysis, electrical conductance in non-aqueous solvents, spectral as well as magnetic susceptibility measurements. In these complexes, ligand LH_2 acts as a tetradentate ligand coordinating through the two azomethine nitrogen atoms and the two enolizable carbonyl group of acetoacetanilide moiety. The antifungal activity of the ligands LH_2 and some of their complexes were evaluated by agar diffusion method against the fungi *Candida albicans* and *Fusarium oxysporum* using Fluconazole as standard (Fig. 5).

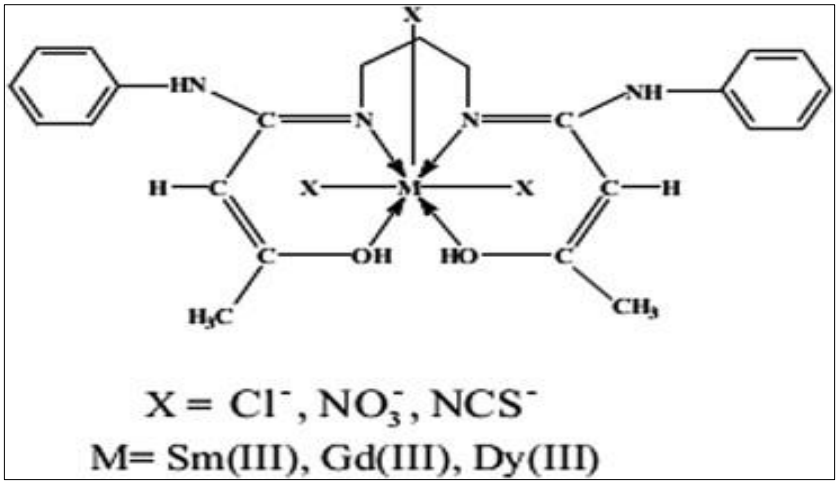

Fig 5: Proposed structure for the complexes.

4. Anti-cancer activity of Schiff base complexes

Cancer or malignant neoplasm is a class of diseases in which a group of cells display uncontrolled growth, invasion and even sometimes metastasis. It continues as a serious public health problem throughout the world as the most feared diagnosis. It is the second leading cause of human death after cardiovascular diseases in developing as well as in developed countries. Currently, the treatment for cancer primarily includes surgery and chemotherapy, but the curative effects of the existing chemotherapeutic drugs are not good enough and they have plentiful side effects. The development of more effective drugs for treating patients with cancer has been a main attempt over the past 50 years. In recent years, various Schiff bases derivatives have been found to be associated with anticancer properties.

Five ternary complexes of the rare earth ions with o-phenanthroline and Schiff base salicylaldehyde l-phenylalanine were tested as anti-cancer. Methyl thiazolyl tetrazolium colorimetry and flow cytometry were used to test the anticancer effect of the complexes with K562 tumour cell. The research showed that the complexes could inhibit K562 tumour cell's growth, generation, and induce apoptosis. The inhibition ratio was accelerated by increasing the dosage, and it had significant positive correlation with the medication dosage. The anticancer activities testing showed that all these complexes exhibited excellent anticancer ability against K562 tumour cell.

Three transition metal coordination complexes $Cu(C_{18}H_{16}N_3O_2)_2{\cdot}2CH_3OH$ (1), $Zn(C_{18}H_{16}N_3O_2)_2{\cdot}2CH_3CH_2OH$ (2) and $Cd(C_{18}H_{16}N_3O_2)_2{\cdot}2CH_3OH$ (3), derived from the same ligand of 2-acetylpyridine and l-tryptophan ($C_{18}H_{16}N_3O_2$) are prepared, then the anticancer activities of these three complexes on MDA-MB-231 breast cancer cells were also investigated. The results indicate that all of the three complexes can inhibit the cellular proliferation. Furthermore, $Cd(C_{18}H_{16}N_3O_2)_2{\cdot}2CH_3OH$ (3) has the highest anti-proliferative activity among the three complexes. In addition, complex (3) can inhibit proteasomal chymotrypsin like activity and also can induce apoptosis on human breast cancer MDA-MB-231 cells. Complex (3) has potential to be used as a proteasome inhibitor and anticancer agent. A series of water-soluble platinum(II) complexes of reduced amino acid Schiff bases as potential anticancer agents and characterized them by ^1H NMR, EA, MS, IR, and molar conductivity. These compounds were tested for their DNA interaction with salmon sperm DNA, and their *in vitro* anticancer activities have been validated against HL-60, KB, BGC-823, and Bel-7402 cell lines by the MTT assay. The cytotoxicity of one complex (5g) is better than that of cisplatin against BGC-823 and HL-60 cell lines, and show close cytotoxic effect against Bel-7402 cell line (Fig. 6).

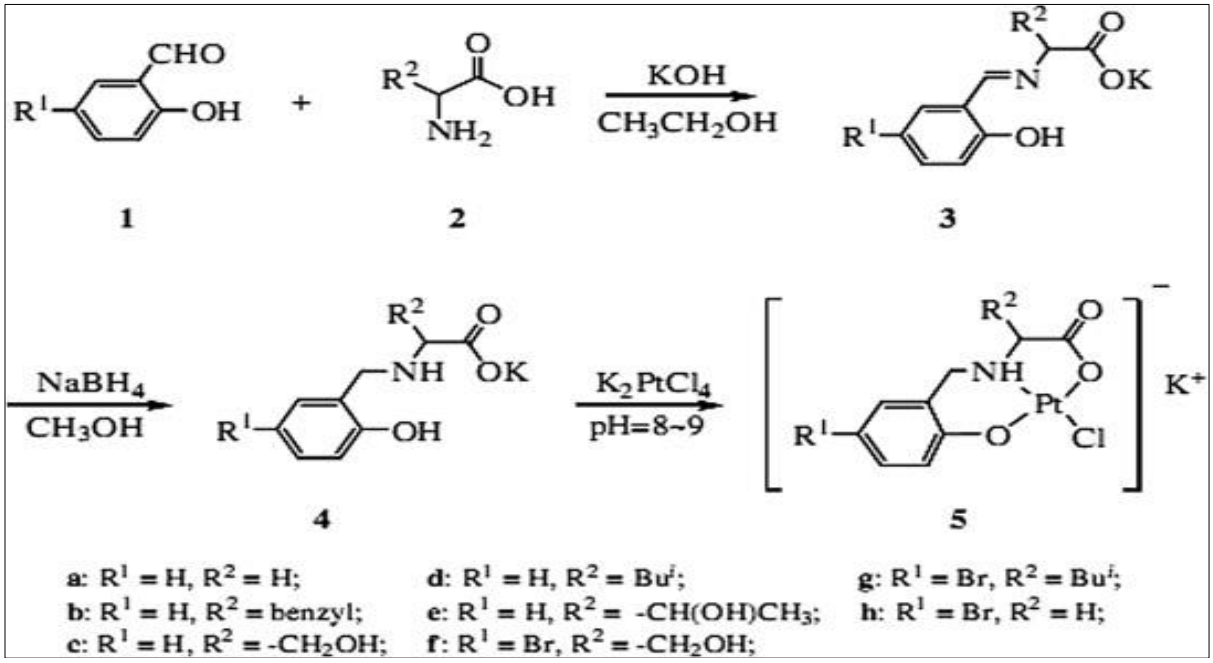

Fig 6: Pt(II) complexes of reduced amino acid Schiff bases.

Antiproliferative effect of a copper (II) complex on HT-29 colon cancer cells has been examined. The $Cu(BrHAP)_2$ Schiff base compound demonstrated a potent antiproliferative effect in HT-29 cells, with an IC_{50} value of 2.87 μg/ml after 72 h of treatment. HT-29 cells treated with Cu (II) complexes underwent apoptosis death, as exhibited by a progressive elevation in the proportion of the G1 cell population. At a concentration of 6.25 μg/ml, the $Cu(BrHAP)_2$ compound caused significant elevation in ROS production following perturbation of mitochondrial membrane potential and cytochrome *c* release, as assessed by the measurement of fluorescence intensity in stained cells. Furthermore, the activation of caspases 3/7 and 9 was part of the Cu (II) complex-induced apoptosis, which confirmed the involvement of mitochondrial-mediated apoptosis. Meanwhile, there was no significant activation of caspase-8. Taken together, these results imply that the $Cu(BrHAP)_2$ compound is a potential candidate for further *in vivo* and clinical colon cancer studies to develop novel chemotherapeutic agents derived from metal-based agents.

5. Antioxidant activity of Schiff bases

The search for metal-derived antioxidants has received much attention and effort in order to identify the compounds having high capacity in scavenging free radicals related to various disorders and diseases associated with oxidative damage, caused by reactive oxygen species (ROS). Presently, synthetic antioxidants are widely used because they are effective and cheaper than natural antioxidants. Currently a number of Schiff-base metal complexes have been investigated as effective scavengers of ROS, acting as antioxidants.

Five kinds of Schiff bases of chitosan and carboxymethyl chitosan (CMCTS) prepared and the antioxidant activity was studied using an established system, such as superoxide and hydroxyl radical scavenging. Obvious differences between the Schiff bases of chitosan and CMCTS were observed, which might be related to contents of the active hydroxyl and amino groups in the molecular chains. The scavenging effect increases with increases the concentration of the Schiff bases.

Glutamic acid–salicylaldehyde Schiff-base metal complexes are bound into bovine serum albumin (BSA), which afforded BSA binding Schiff-base metal complexes (BSA-SalGluM, M = Cu, Co, Ni, Zn). It showed that the protein structures of BSA kept after coordinating amino acid Schiff-bases metal complexes. The effect of the antioxidant activity was investigated. The results indicate that the antioxidant capacity of BSA increased more than 10 times after binding Schiff-base metal complexes.

The antioxidant capacities of ferrocenyl Schiff bases including o-(1-ferrocenylethylideneamino)phenol (OFP), m-(1-ferrocenylethylideneamino)phenol (MFP), and p-(1-ferrocenylethylideneamino)phenol (PFP) were evaluated in 2,2′-azobis(2-amidinopropane hydrochloride) (AAPH), Cu^{2+}/glutathione (GSH), and hydroxyl radical (OH^-) induced oxidation of DNA, and in trapping 2,2′-diphenyl-1-picrylhydrazyl (DPPH) and 2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonate)cationic radical ($ABTS^{\bullet+}$), respectively. OFP, MFP and PFP possessed similar activities to trap DPPH and $ABTS^{\bullet+}$. All the ferrocenyl Schiff bases employed herein behaved as prooxidants in Cu^{2+}/GSH^- and $^{\bullet}OH^-$ induced oxidation of DNA except that OFP exhibited weak antioxidant activity in $^{\bullet}OH^-$ induced oxidation of DNA. PFP, OFP and MFP can terminate about 15.2, 11.3, and 9.4 radical-chain-propagations in AAPH-induced oxidation of DNA. Especially, the introduction of ferrocenyl group to Schiff base increased the antioxidant effectiveness more remarkably than benzene-related Schiff bases.

The developing of more efficient, less toxic, target specific metal drugs and evaluate their anticancer properties in terms of oxidation state and co-ligand sphere, a sequence of Ru(II), Ru(III) complexes bearing 4-hydroxy-pyridine-2,6-dicarboxylic acid and PPh3/AsPh3 were synthesized and structurally characterized. Biological studies such as DNA binding, antioxidant assays and cytotoxic activity were carried out and their anticancer activities were evaluated. Interactions of the complexes with calf thymus DNA revealed that the triphenylphosphine complexes could bind more strongly than the triphenylarsine complexes. The free radical scavenging ability, assessed by a series of *in vitro* antioxidant assays involving $DPPH^{\bullet}$ radical, hydroxyl radical, nitric oxide radical, superoxide anion radical, hydrogen peroxide and metal chelating assay, showed that the Ru(III) complexes

possess excellent radical scavenging properties compared to those of Ru(II). Cytotoxicity studies using three cancer lines viz. HeLa, HepG2, HEp-2 and a normal cell line NIH/3T3 showed that Ru(II) complexes exhibited substantial cytotoxic specificity towards cancer cells.

6. Anti-inflammatory activity of Schiff bases

Schiff base of functionalised 5-nitroisoquinolines was synthesized and the *in vitro* activity of these compounds against an ACC Niger chloroquine resistant *P. falciparum* strain investigated. The schiff base *N*-[(1*E*)-(5-nitro-1-naphthyl)methylene]-1-[2 (trifluoromethyl)phenyl]methanamine was the most effective antimalarial agent among the synthesized 5-nitroisoquinoline derivatives. The concentration of this Schiff base necessary to inhibit *P. falciparum* growth by 50% (IC_{50}) was 0.7 µg/mL.

A new series of complexes of the type [Cu (dien) (2a-2tzn) Y_2] and [Cu (dienXXY_2) (2a-5mt)] and of the type [Cu (dptaS) Cl_2] and [Cu (dptaS) Br_2] (dptaS ¼ 1, 3-propanediamine) or Schiff mono-base of dipropylenetriamine with 2-thiophene-carboxaldehyde, has been tested for anti-inflammatory and antioxidant activity. The tested compounds inhibit the carrageenin-induced rat paw oedema (52.0–82.6%) and present important scavenging activity. Compound 6 is the most potent (82.6%) in the *in vivo* experiment. Lipophilicity-as RM values – has been determined. The results support that in general, adducts of the type [Cu (dienXXY_2) (2a-5mt)] exhibit increased activity compared to the starting material of type [Cu (dienXXY_2)]. An attempt to correlate the biological results with their structural characteristics and physicochemical parameters has been made.

A series of novel 3-(4-(benzylideneamino) phenylimino) 4-fluoroindolin-2-one derivatives were synthesized and characterized by spectral (I.R, ^{1}H NMR, mass). The title compounds (N_1–N_{10}) were evaluated for analgesic, anti-inflammatory, and ulcerogenic index activities. Results displayed that compound N_3 exhibited significant analgesic activity. Among the title compounds studied, N_2, N_3, and N_8 exhibited significant anti-inflammatory activity comparable to reference standard diclofenac sodium. Interestingly, the test compounds showed only mild ulcerogenic side effect when compared to aspirin.

Schiff base derived from 4-aminoantipyrine (4-amino-1,5-dimethyl-2-phenylpyrazole-3-one) and benzaldehyde derivative was tested for its anti-inflammatory. The results showed promising anti-inflammatory activity which could be beneficial for use in the treatment of inflammatory diseases. The results of this study may lead to the development of a new therapeutic agent useful in fighting diseases caused by oxidative stress and inflammation.

A series of Schiff base derivatives of 4-aminophenazone (4APZ-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazol-3-one) with different aldehydes were synthesized. The synthetic compounds were screened for their anti-inflammatory, analgesic and antipyretic activities. Carrageen an-induced paw oedema (CIPO) and histamine induced paw oedema (HIPO) methods were used to determine the anti-inflammatory activity of commercial sample of 4APZ and its synthesized Schiff bases in mice. The anti-inflammatory activity was in the order of 4APZAB > 4APZBB > 4APZCB > 4APZVn and all the test compounds exhibited considerable dose dependent inhibition of the paw oedema. The effect of the compounds on membrane stabilization was also determined which showed that compounds 4APZ (120 and 240 mg/kg doses), 4APZAB (160 mg/kg) and 4APZVn (600 mg/kg) produced highly significant inhibition (P<0.001) of hypotonicity-induced haemolysis. Further, it was also observed that 4APZ (120 and 240 mg/kg doses), 4APZBB (500 mg/kg) and APZCB (150, 300 and 600 mg/kg dose) produced highly significant inhibition (P<0.001) of albumin denaturation; a consistent dose dependent anti-inflammatory effect of test compounds as compared to the standard drug. Analgesic activity of the compounds was investigated by formalin-induced paw licking (FIPL) and acetic acid-induced writhing (AIW) methods in mice. It was observed that 4APZ (240 mg/kg), 4APZAB (160 mg/kg), 4APZBB (500 mg/kg), 4APZCB (600 mg/kg) and 4APZVn (600 mg/kg) showed analgesic effect with highly significant (P<0.001) reduction of paw licking and writhing activity in the treated mice. The order of analgesic effect of the compounds was 4APZAB > 4APZBB > 4APZVn > 4APZCB. Moreover, phenobarbitone-induced sleeping time (PIST) in mice was also studied but only 600 mg/kg of 4APZVn significantly increased the duration of induced sleep which also suggested its sedative property. Brewer's yeast was used to induce fever in rabbits and analyzed the compounds for their antipyretic activity. Different doses of 4APZ for different time durations (240 mg/kg-after 1 h, 120 and 240 mg/kg doses-after 2 h) produced highly significant (P<0.001) inhibition of hyperpyrexia. Other compounds showed good antipyretic activity after 2, 3 and 4 h.

7. Antiviral activity of Schiff bases

Although there are many therapeutic options for viral infections, currently available antiviral agents are not yet fully effective, probably due to the high rate of virus mutation. They may also present any of a number of side effects. Salicylaldehyde Schiff bases of 1-amino-3-hydroxy-guanidine tosylate are a good platform for the design of new antiviral agents (Sriram *et al*., 2006) [37]. In fact, from a set of different 1-amino-3-hydroxyguanidine tosylate-derived Schiff bases, 2-(3-allyl-2-hydroxybenzylidene)-N-hydroxyhydrazinecarboxi-midamide derivative was shown to be very effective against mouse hepatitis virus (MHV), inhibiting its growth by 50% when employed at concentrations as low as 3.2 µM).

A new series of 3-(benzylideneamino)-2-phenylquinazoline-4(3H)-ones were prepared through Schiff base formation of 3-amino-2-phenyl quinazoline-4(3)H-one with various substituted carbonyl compounds. Their chemical structures were elucidated by spectral studies. Cytotoxicity and antiviral activity were evaluated against herpes simplex virus-1 (KOS), herpes simplex virus-2 (G), vaccinia virus, vesicular stomatitis virus, herpes simplex virus-1 TK-KOS ACVr, para influenza-3 virus, reovirus-1, Sindbis virus, Coxsackie virus B4, Punta Toro virus, feline corona virus (FIPV), feline herpes virus, respiratory syncytial virus, influenza A H1N1 subtype, influenza A H3N2 subtype, and influenza B virus. Compound 2a showed better antiviral activity against the entire tested virus.

8. Conclusion

Schiff bases are considered as a very important class of organic compounds because of their ability to form complexes with transition metal ions and of their pharmacological properties. Transition metal complexes containing Schiff bases have been of much interest over the last years, largely because of its various applications in biological processes and potential applications in designing new therapeutic agents. But still there is need to explore the biological properties of

these already synthesized transition metal complexes and to synthesize new complexes with more properties
IR infrared
Bs bromosalicylaldehyde
Ala alanine
Phala phenylalanine
Aspa aspartic acid
His histidine
Arg arginine
NMR nuclear magnetic resonance
MS mass spectroscopy
ROS reactive oxygen species
CMCTS carboxymethyl chitosan
BSA bovine serum albumin
OFP o-(1-ferrocenylethylideneamino)phenol
MFPm-(1-ferrocenylethylideneamino)phenol
PFP p-(1-ferrocenylethylideneamino)phenol
AAPH 2,2′-azobis(2-amidinopropane hydrochloride)
GSH glutathione
DPPH 2,2′-diphenyl-1-picrylhydrazyl
ABTS 3-ethylbenzothia-zoline-6-sulfonate
CIPO carrageenan-induced paw oedema
HIPO histamine induced paw oedema
FIPL formalin-induced paw licking
AIW acetic acid-induced writhing
PIST phenobarbitone-induced sleeping time
MHV mouse hepatitis virus
FIPV feline corona virus
Salen salicylaldehyde ethylenediamine

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