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Pharmacological Importance of Some Transition Metal Complexes of Schiff Bases Derived From Substituted Anilines: A Review

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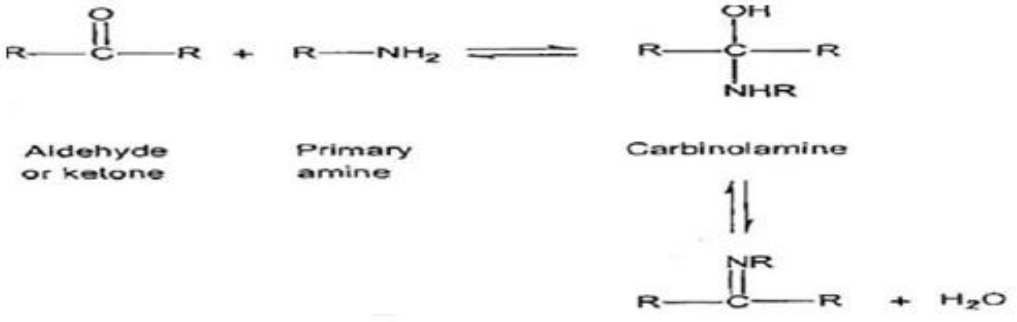
Abstract: *Schiff bases are condensation products of primary amines with carbonyl compounds. They are an important class of ligands that coordinate via azomethine nitrogen to metal ions and have been studied extensively. Transition metals ions are the trace elements present in the biological system. Schiff bases and their transition metal complexes are widely used for industrial purposes and they also exhibit a broad range of pharmacological activities including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, antifertility, herbicidal and antipyretic and many more. Present review deals with the pharmacological importance of some of the transition metal complexes of Schiff bases derived from substituted anilines.*

Keywords: Metal complexes, Schiff base, Transition metals, azomethine coordination chemistry, antifungal, antibacterial

I. INTRODUCTION

Schiff bases are condensation products of primary amines and carbonyl compounds and they were discovered by a German chemist, Hugo Schiff bases [1].Structurally, Schiff base (also known as imine or azomethine) is an analogue of a ketone or aldehyde in which the carbonyl group (C=O) has been replaced by an imine or azomethine group [2].Schiff base ligands form highly stable complexes with transition metal ions [3]. These play important role by serving as chelating ligands in the transition metal coordination chemistry. Various transition metals complexes of Schiff bases derived from anilines and substituted aniline have been widely studied due to their antimicrobial, anticancer, analgesic, anti-inflammatory, antifertility and herbicidal applications [4-6]. This review summarizes the rapeutical importance of transition metal complexes of Schiff bases derived from anilines and substituted anilines.



II. SUBSTITUTED ANILINES

Anilines are a vital synthetic core of pharmaceuticals, agrochemicals, natural products and building blocks. Its most prominent materials used for the production of many industrial fields. Metal-catalyzed C-H functionalization has emerged as a powerful tool to derivatize biologically relevant molecules. To this end, the derivation of anilines via

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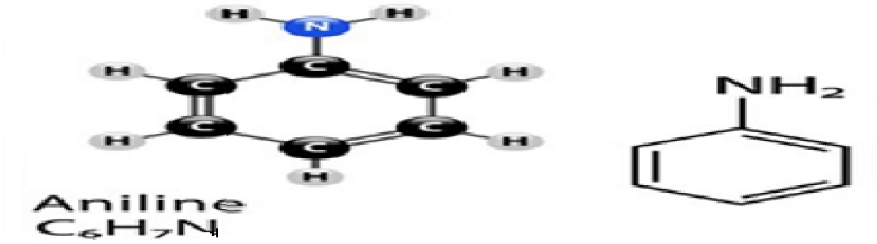
catalytic C-H functionalization has been the subject of important new synthetic methodology. These structures contain substitution patterns at the ortho, meta and para positions. For these reasons, regio selective C-H functionalization of aniline derivatives could provide a key [7].



Aniline and its derivatives are not only important in their coordinating ability but are found to exhibit broad spectrum of biological activity. They show wide range of biological activities like analgesic, malaricidal, bactericidal, fungicidal, herbicidal, and insecticidal activities. It was also observed that this activity was enhanced by complexing with certain transition metal elements [8].

III. Transition Metals

Transition elements or transition metals are elements that have partially filled d orbitals. Some important transition metals are iron, cobalt, nickel, copper, zinc etc. Transition metals have play｛ l an important role in the development of new metal-based drugs. Transition metals exhibit different oxidation states and can interact with number of negatively charged molecules. This activity of transition metals has started the development of metal-based drugs with promising pharmacological application and may offer unique therapeutic opportunities. Research has shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases like carcinomas, lymphomas, infection control, anti-inflammatory, diabetes, and neurological disorders [9].

3.1 Pharmacological Activities

Following are some Pharmacological activities shown by transitional transition metal complexes of Schiff bases derived from anilines and substituted aniline.

3.2 Anti-Fungal Activity

Sridhar. G and co-workers synthesized and characterized transition metal (II) ion Cu(II), Ni(II), Co(II), Cr(III) metal complexes with Schiff bases derived from 2,6-dimethyl-5-heptenaldehyde and 4-fluoro aniline. The antifungal activity studies indicated that cobalt (II) complex exhibited activity better than standard drug amphotericin against *Penicilliumchrysogenum* [10].

Justin Dhanraj*et al.* have been prepared complexes of Cu (II) with Schiff bases derived from 3-nitrobenzylidene-4-amino antipyrine and aniline or p-nitroaniline or p-methoxy aniline showed antifungal activity. A comparative study of the MIC values for the ligands and their complexes indicates that the complexes exhibit higher antifungal activity. *In vitro* biological screening effects of the investigated compounds were tested against fungal species *Aspergillusniger, Rhizopusstolonifer, Aspergillusflavus, Rhizoctoniabataicola,* and *Candida albicans* by the well-diffusionmethod [11].

S. B. Salve *et al.* synthesized Schiff base 5-chloro-2-hydroxy-4-methyl-acetophenone with aniline and its derivatives each separately viz aniline, 4-aminophenol, 2-aminothiophenol, 4-amino-thiophenol 4-chloro nitro aniline, amino-benzonitrile and 4-amino-benzonitrl and reacted efficiently to produced a series of Ketimine in high yield and purity. They were characterized by analytical and spectral technique. After confirming their desired molecular studies, these ketimines were studied for their antifungal activity using *A. alternata* and *F. oxysporum* [12].

3.3 Anti-Bacterial Activity

Raman N. *et al*. synthesised Cu (II) complex with the Schiff base derived from salicylidene-4-aminoantipyrine and $PhNH_2$/substituted anilines. Compound show antimicrobial activity against the bacteria *Staphylococcus aureus,*

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Klebsiellapneumoniae, Salmonella typhi, Pseudomonas aeruginosa and Bacillus subtilis are also reported. Moreover, they have higher activity than the control (ampicillin) except for *Klebsiellapneumoniae*and *Pseudomonas aeruginosa*[13].

A.O. Soboba *et al*. synthesized copper (II) complexes of some Schiff base ligands derived from 2-hydroxy-3-methoxybenzaldehyde(o-vanillin)/2-hydroxybenzaldehyde (salicylaldehyde) and ortho-substituted anilines. Copper metal complexes with Schiff base ligands were screened for their *in vitro* antibacterial and antifungal activity against *Escherichia coli, Staphylococcus aureus Subsp., Bacillus subtilis subsp., aureus ATCC spizizenii ATCC and Candida albicans ATCC ss*. The compounds were not as active as penicillin, but showed significant antifungal activity against the tested organisms. The o-vanillin-based ligands exhibited higher activity than the salicylaldehyde-based compounds which were virtually non-active against the tested organisms [14].

Sahar Shayganet *al*. reported theantimicrobial activity of Co(II) complexes of synthesized bidentate Schiff bases ligands by the condensation of Pharmacological aldehyde with ortho substituted aniline derivatives in the presence of N-Propyl benzoguanamine as a catalyst. The ligands and their metal complexes were screened by broth dilution and using disc diffusion methods against *Escherichia coli, Pseudomonas aeruginosa, Serratiamarcescens (gram negative bacteria), Staphylococcus aureus and Bacillus Subtilis (gram positive bacteria)*. The result showed higher antimicrobial activity of transition metal complex compare to the parent ligands [15].

3.4 Anti- Inflammatory Activity

Y.Pradeep Kumar*et al.* have been synthesized Schiff bases metal complexes (2-((3-chlorophenylamino)methyl)Phenol) with Cu (II) ions. Synthesized compounds were screened for their *in vitro* anti- inflammatory activity by Anti enaturation Assay method using diclofenac sodium as standard compound at specific concentration 100 µg/ml, among the synthesized compounds L_2Cu was shown good anti-inflammatory activity when compared to standard, remaining compounds shown moderate anti-inflammatory activity[16].

Chih-Hua Tseng and co-workers synthesized and reported 4-chloro-1H-pyrazolo[4,3-c]quinolin-3-amine (1) was reacted with substituted anilines to give 3-amino-4-(substituted phenylamino)-1H-pyrazolo[4,3-c]-quinoline derivatives. Important structure features were analyzed by quantitative structure activity. relationship (QSAR) analysis to give better insights into the structure determinants for predicting the inhibitory effects on the accumulation of nitric oxide for RAW 264.7 cells in response to LPS [17].

Parashar, R.K and co-workers have been synthesized Schiff bases derived from salicylaldehyde and 2-substituted aniline and their metal chelates with Cu(II) ions were synthesized and screened for the anti-inflammatory and antiulcer activity. The compound salicylideneanthranilic acid (SAA) was found to possess the anti-inflammatory and antiulcer activity. The copper complexes showed an increased antiuler activity [18].

3.5 Anti-Cancer Activity

Mohamed Abdel and co-workers synthesized a series of 5-(substituted phenyl)-3-[(substituted phenylamino)methyl]-3H-[1,3,4]oxadiazole-2-thione derivatives. Synthesized compound characterized by various spectral technique and the synthesized compounds displayed weak to moderate cytotoxic activity against the three tested cell lines their*in vitro* cytotoxicity were done against a panel of three cancer cell lines, namely, hepatocarcinoma HepG2, breast adenocarcinoma MCF-7, and leukaemia HL-60 cells, using the widely accepted MTT assay. Compounds showed a good inhibitory effect on cellular tubulin of hepatocellular carcinoma. Compound exhibit tubulin inhibitor in HepG2 cells, with 81.1 % inhibition of the original control tubulin [19].

Laila H. and co-workers synthesized new nano sized Cu(II) complexes of imine ligand derived from the condensation of 2-amino-3-hydroxypyridine and 3-methoxysalicylaldehyde have been prepared and investigated using various chemical techniques. Cu(II) complex which is tetrahedral geometry. Nano-sized particles of the investigated complexes were prepared by sonochemistry method. Its complexes and their metal oxides have been checked *in vitro* against a number of bacteria and fungi in order to assay their antimicrobial activities. The results showed that the investigated complexes could bind to DNA via an intercalative mode. The cytotoxicity of the Schiff base complexes on human

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colon carcinoma cells, (HCT-116 cell line) and Breast carcinoma cells, (MCF-7 cell line) showed potent cytotoxicity effect against growth of carcinoma cells compared to the clinically used Vinblastine standard [20].

Hejchman E, *et al*. have been prepared the copper (II) complexes with coumarin-derived Schiff base ligands. Two series of Schiff bases were prepared by condensation of 8-formyl-7-hydroxy-4-methylcoumarin and 8-acetyl-7-hydroxy-4-methylcoumarin with p - substituted anilines derivatives. These compounds were used as ligands in the synthesis of copper (II) complexes and the obtained are mostly novel molecules and their antibacterial, antifungal and anticancer activities make the compounds attractive for further derivatization and screening as novel therapeutic agents having dose-dependent antiproliferative activity on HeLa cancer cell line [21].

3.6 Anti-Malarial Activities

Jean Baptiste Niyibizi and co-workers prepared Sarcosine-aniline hybrid has been synthesized using sar-cosine and 3-chloro-4-(4-chlorophenoxy) aniline pharmacophores, and the product formation was monitored and confirmed by thin layer chromatography. Sarcosine-aniline hybrid drug is a promising anti plasmodialprodrug as it showed activity for *in vitro* and in vivo studies with an IC50of 44.80 ±4.70 ng/ml and an ED50of 6.49 mg/kg, which are within acceptable ranges of drugs used to treat severe malaria. It should be the use of covalent bio therapy in drug development. The use of covalent biotherapy in drug resistance mitigation is recommended. (P. falciparum ATCase) [22].

Rupanjali Sharma and co-workers has been synthesised Schiff base, N-(pyridine-4-yl-methylene) quinuclidine-3-amine from 4-pyridine carboxaldehyde and 3-aminoquinuclidine. Synthesised compound exhibited *in vitro* antimalarial activity against chloroquine-sensitive Plasmodium falciparum strain. Although higher dose of synthesized compound was required for antimalarial activity (EC50 = 13.125 g/ml) in comparison to chloroquine (EC50 5.144 g/ml), the correlation coefficient confirmed good fit of the data [23].

IV. Conclusion

Schiff bases metal complexes of substituted aniline considered as a very important class of organic compounds because of their ability to form complexes with substituted aniline and of their pharmacological properties being used as drugs against various diseases. Metals complexes of Schiff bases have been shown to be more efficient antimicrobial, antibacterial, antifungal, antiviral, anti-inflammatory, antimalarial, and antioxidants agents.

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