BIOLOGICAL ACTIVITIES OF SCHIFF BASE AND ITS COMPLEXES: A REVIEW

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ABSTRACT
Schiff bases are versatile ligands which are synthesized from the condensation of primary amines with carbonyl groups. These compounds are very important in medicinal and pharmaceutical fields because of their wide spectrum of biological activities. Most of them show biological activities such as antibacterial, antifungal as well as antitumor activity. Transition metal complexes derived from the Schiff base ligands with biological activity have been widely studied. This review summarizes the synthesis and biological activities of Schiff bases and its complexes.

Keywords: Schiff bases, Metal complexes, antimicrobial activity, antitumor activity, nonlinear optical properties.

INTRODUCTION
Compounds containing an azomethine group (-CH=N-) known as Schiff bases are formed by the condensation of a primary amine with a carbonyl compound. Schiff bases of aliphatic aldehydes are relatively unstable and are readily polymerizable while those of aromatic aldehydes, having an effective conjugation system, are more stable. Schiff bases have number of applications viz., preparative use, identification, detection and determination of aldehydes or ketones, purification of carbonyl or amino compounds, or protection of these groups during complex or sensitive reactions. They also form basic units in certain dyes.

Schiff bases are generally bi- or tri-dentate ligands capable of forming very stable complexes with transition metals. Some are used as liquid crystals. In organic synthesis, Schiff base reactions are useful in making carbon-nitrogen bonds.

Schiff bases appear to be an important intermediate in a number of enzymatic reactions involving interaction of an enzyme with an amino or a carbonyl group of the substrate. One of the most important types of catalytic mechanism is the biochemical process which involves the condensation of a primary amine in an enzyme usually that of a lysine residue, with a carbonyl group of the substrate to form an imine, or Schiff base.

Scheme-1
Stereochemical investigation carried out with the aid of molecular model showed that Schiff base formed between methylglyoxal and the amino group of the lysine side chains of proteins can bent back in such a way towards the N atom of peptide groups that a charge transfer can occur between these groups and oxygen atoms of the Schiff bases. In this respect pyridoxal Schiff bases derived from pyridoxal and amino acids have been prepared and studied from the biological point of view. Transition metal complexes of such ligands are important enzyme models. The rapid development of these ligands resulted in an enhance research activity in the field of coordination chemistry leading to very interesting conclusions.

This review concentrates on the synthesis and biological activity of Schiff bases and its complexes. Ugars et al\textsuperscript{1} have reported the synthesis, complexation, antifungal and antibacterial activity studies of a new macro cyclic Schiff base (Scheme 1).

Preparation, physical characterization and antibacterial activity of Ni (II) Sciffbase complex was reported by Morad et al\textsuperscript{2} (Scheme 2).

Elzahany et al\textsuperscript{3} have synthesized some transition metal complexes with Schiff bases derived from 2-formylindole, salicylaldehyde and N-amino Rhodanine. The Schiff base ligands were characterized by elemental analysis, IR, Mass, \textsuperscript{1}H NMR and electronic spectra. The free ligands and their metal complexes were also screened for antimicrobial activities against Bacillus cerens, Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Candida albicans. The results indicated that the ligands do not have any activity, where as their complexes showed more activity against the same organisms under identical experimental conditions.

Synthesis and pharmacological studies of novel schiff bases of 4-Hydroxy 6-carboxyhydrazino benzofuran was reported by Gopal Krishna Rao et al\textsuperscript{4}.
4-Chloro-2-oxo-2H-chromene-3-carbaldehyde was made to react with different anilines in rectified spirit to yield a series of Schiff bases of the type 4-chloro-3-(substituted-phenylimino)methyl)-2H-chromen-2-one. These compounds were characterized on the basis of their spectral (IR, $^1$H NMR) data and evaluated for antimicrobial activity in vitro against fungi, gram positive and gram negative bacteria.

Yi Yi and coworkers have reported the synthesis and color-tunable fluorescence properties of Schiff base Zinc (II) complexes which are used as electroluminescent materials. These authors have reported that the
Schiff base Zinc (II) complexes synthesized by them have good thermo stability, solubility and film forming capability and can be used as organic electroluminescent materials. These new complexes may afford the feasibility to realize full-color display with materials based on similar molecular structures.

\[
\begin{align*}
\text{PhCHO} + \text{H_N-R} &\rightarrow \text{PhCHOH} \quad \text{Zinc (II) complex}\nonumber
\end{align*}
\]

Scheme- 5

Vijey Aanandhi et al.\(^7\) have reported the synthesis of a series of 1-(5-substituted-2-oxoindolin-3-ylidene)-4-(substituted-pyridin-2-yl)thiosemicarbazide derivatives. These compounds were screened for in vitro antibacterial and antifungal activity against \textit{B.subtilis}, \textit{S. aureus}, \textit{E.coli}, \textit{P. aeruginosa}, \textit{C. albicans}, and \textit{A. niger}. All the compounds were reported to exhibit moderate to good antibacterial and antifungal activity.

\[
\begin{align*}
\text{R} &+ \text{NH}_2\text{NH}_2 \rightarrow \text{R-NHCSNH}_2 \quad \text{Schiff reaction}\nonumber
\end{align*}
\]

Scheme- 6

Karaoglan et al.\(^8\) have reported the synthesis and characterization of a new Schiff base and its metal complexes. The Schiff base ligand were characterized by FT-IR, \(^1\)H-NMR, UV-Visible, Mass spectra, elemental analysis and fluorescence spectrophotometry. Protonation constants of the ligand and overall
formation constants of the complexes have also been calculated from potentiometric data using a computer program.

![Scheme- 7](image)

Farias and Bastos²⁹ have studied the electrochemical behavior of copper (II) complexes of the Schiff’s base (3) N, N’-ethylene bis(salicylidimine) in aqueous phosphate (pH 7) by polarographic and voltammetric techniques at a mercury electrode. It is a symmetrical molecule and exhibits chiral properties.

![Structure](image)

Khalil et al.¹⁰ were the first group to announce the possibility of using a Schiff base as an acid-base indicator. This surprising phenomenon can be considered as an interest due to the fact that Schiff bases are usually unstable in solutions and definitely undergo hydrolysis. It was found that such a specific observation depends merely upon the chemical structure and type of the substitute of amine that reacts with aldehyde to give the Schiff base. The latter reagent 4{(4-dimethylamino-benzylidine)-amino}-benzene sulfonamide was synthesized from the condensation of sulfanilamide with p-dimethylaminobenzaldehyde. The reagent solution shows a reproducible change in its color due to the addition of acid and base. A UV-Visible spectroscopic characterization and acid-base equilibrium study of the reagent for its possible use as an indicator were investigated. The results show that the reagent is amphoteric which possesses four ionization constants $K_{a1}$, $K_{a2}$, $K_{b1}$ and $K_{b2}$ of weak dibasic and diacidic properties. It was concluded that the benzyl sulfonamide group plays a key role in the stability of the reagent towards hydrolysis and also for indicator characteristics through breaking the conjugation.

Jamil and coworkers¹¹ have reported the synthesis, characterization and antimicrobial activities of novel organotin Schiff base compounds. (5)

![Structure](image)

Metal complexes of Schiff bases derived from 2-furancarboxaldehyde and o-phenylenediamine and 2-thiopheneacarboxaldehyde and 2-aminothiophenol was reported by Gehad Geindy et al.¹² These authors have reported the ligand dissociation as well as the metal-ligand stability constants for these complexes.
The synthesized ligands, in comparison to their metal complexes were also screened for their antibacterial activity against bacterial species, *Escherichia coli, Pseudomonas aeruginosa and Staphylococcus Pyogones as well as fungi (Candida)*. The activity data reveal that the metal complexes are found to be more potent antibacterial than the parent Schiff base ligand against one or more bacterial species.

A series of biologically active pyrazine-derived Schiff base ligands have been synthesized by the condensation reaction of 2-aminopyrazine with salicylaldehyde and acetamidobenzylaldehyde. Then their Co(II), Ni(II) & Zn (II) complexes have been prepared. The biological evaluation of the simple uncomplexed ligand in comparison to their complexes have been determined against bacterial strains namely *Escherichia coli, Staphylococcus aureous and Pseudomonas aerugiosa*.

SARI and coworkers have reported the synthesis and antibacterial activities of some new amino acid-Schiff bases.
Mixed ligand transition metal complexes of Cu$^{+2}$, Ni$^{+2}$ and Co$^{+2}$ ions with Schiff base ligands derived from the condensation of o-hydroxy benzaldehyde with amino phenols and nitrogen donor amine bases was reported by Saidul Islam et al.$^{15}$ The authors have also studied the antibacterial and antifungal activities of the compounds (Scheme 8).

Daniel Thangadurai and Son-Ki Ihm$^{16}$ have reported the synthesis, characterization, catalytic and antibacterial studies of chiral Schiff base Ruthenium (III) complexes. These authors have tentatively proposed an octahedral structure for all the new complexes. The catalytic and antibacterial activities of these compounds have also been reported.
Baluja et al.\textsuperscript{17} have studied the biological activities of the following Schiff base (Scheme 9) and metal complexes.

Metal complexes ML\textsubscript{2}Cl\textsubscript{2} where M is Fe (II), Co (II), Ni(II), Cu(II), Zn(II) or Cd(II) and L is the Schiff base formed by the condensation of 2-thiophenecarboxaldehyde with 2-aminopyridine, N-(2-thienylmethylidene)-2-aminopyridine (TNAPY) have been reported by Spinu et al.\textsuperscript{18}

Thilagavathi and coworkers\textsuperscript{19} have reported the synthesis of 3-[4-[benzylideneamino]benzenesulfonyl]-phenyl]-2-phenylquinazolin-4(3H)-one (Scheme 10).
Synthesis, characterization and electrochemical behaviour of Cu(II), Co(II), Ni(II) and Zn(II) complexes derived from acetylacetone and p-anisidine was reported by Raman and coworkers\textsuperscript{20}. These authors have observed that the complexes synthesized by them show fairly good antimicrobial activity.

New Schiff base of the type, 2-[4-methyl-2-oxo-2\textit{H}-chromen-7-yl]oxy]-N\textsubscript{1}-(substituted methylene)acetohydrazides were synthesized\textsuperscript{21} by the condensation of aryl/hetero aromatic aldehydes with 2-[(4-methyl-2-oxo-2\textit{H}-chromen-7-yl)oxy]acetohydrazides under conventional and microwave conditions and characterized through IR, \textsuperscript{1}H NMR and mass spectral data. The synthesized compounds have been screened for antimicrobial activity.

\begin{center}
\textbf{Scheme-11}
\end{center}

Kulkarni \textit{et al}\textsuperscript{22} have synthesized Schiff base of the type \textbf{16} and studied the electrochemical properties of their complexes.
Raman et al.\textsuperscript{23} have reported the synthesis of the following Schiff base ligand (17). These authors have also studied the DNA cleavage and antimicrobial activity of the Schiff base transition metal complexes.

Racanska and coworkers\textsuperscript{24} have studied the antidiabetic activity of some Copper (II) Schiff base complexes (18) on Alloxan-induced diabetic mice.
Chittilappilly and Yusuff have reported the synthesis, characterization and biological properties of ruthenium (III) Schiff base complexes derived from 3-hydroxy quinoxaline-2-carboxaldehyde and salicylaldehyde.

Two new Schiff base ligand containing cyclobutane and thiazole rings-(1-methyl-1-mesitylcyclobutane-3yl)-2-(2,4-dihydroxybenzylidenehydrazino)thiazole and 4-(1-methyl-1-mesitylcyclobutane-3-yl)-2-(2-hydroxy-3-methoxybenzylidenehydrazino)thiazole and their mononuclear complexes with Co(II), Cu(II), Ni(II) and Zn(II) in EtOH was reported by Cukorovali and co workers.

Scheme-12
Hearn and Cynamon\textsuperscript{27} have reported the synthesis and antitubercular activity of Schiff base of the following type (20).

\begin{center}
\begin{tabular}{c}
\includegraphics[width=0.3\textwidth]{image1.png}
\end{tabular}
\end{center}

Nair and coworkers\textsuperscript{28} have studied the synthesis and antibacterial activity of some Schiff base complexes. The Schiff bases showed greater activity than their metal complexes.

\begin{center}
\begin{tabular}{c}
\includegraphics[width=0.5\textwidth]{image2.png}
\end{tabular}
\end{center}

Van den Ancker \textit{et al}\textsuperscript{29} have reported the synthesis of the following bis-imine Schiff bases. These authors have claimed that bis-imine Schiff bases are obtained in high yield (>95\%) when aliphatic diamine/aldehyde condensation reactions are carried out under solvent-free conditions or in polypropylene glycol (PPG) as a recyclable reaction medium with negligible waste. (Scheme 13)

\begin{center}
\begin{tabular}{c}
\includegraphics[width=0.8\textwidth]{image3.png}
\end{tabular}
\end{center}

Two potentially heptadentate tripodal Schiff-base ligands: tris(3-(salicylidene(imino)propyl)amine and tris (3-(4\'-hydroxysalicylideneimino)-propyl)amine have been prepared\textsuperscript{30} and characterized by various spectroscopic methods such as IR, FAB-MS and NMR.
Dong-Hoon Won and coworkers\textsuperscript{31} have studied the synthesis and crystal structure of the following Schiff base macro cycles bearing thiophene (23).

Shabani \textit{et al.}\textsuperscript{32} have reported the synthesis, characterization and anti-tumor activity of Iron (III) Schiff base complexes (Scheme 14). Iran Sheikhshoaie and Samira Samira\textsuperscript{33} have reported the synthesis, characterization and nonlinear optical properties of the following four Schiff bases (24-27).
Gao and Zheng\textsuperscript{34} have reported the synthesis of optically active Schiff base ligand derived from condensation of 2-hydroxyacetophenone and
1,2-diaminocyclohexane.

Synthesis of Schiff bases of naptha[1,2-d]thiazol-2-amine and metal complexes of 2-(2\(^1\)-hydroxy)benzylideneaminonaphthathiazole as potential antimicrobial agent was reported by Faizul and co-workers\(^ {35} \).

Ibrahim and Sharif\(^ {36} \) have studied the synthesis, characterization of some Schiff bases (28-33) which can be used as fluorometric analytical reagents.
Gudasi et al.\textsuperscript{37} have reported the synthesis, characterization and biological studies of dioxouranium(II) and thorium(IV) complexes of Schiff base derived from 2-amino pyridine and acetophenones.

More et al.\textsuperscript{38} have reported the synthesis of the following Schiff base (34). These authors have studied the proton ligand stability constant of the Schiff bases and the formation constants of their transition metal complexes.
Bag et al.\textsuperscript{39} have synthesized a series of Schiff bases of benzidene and examined the mercuration reaction (Scheme18).

Two new Schiff bases (35 and 36) and eight transition metal complexes derived from 2, 3-diminopyridine (DAPY) and ortho-\textit{vanillin} have been synthesized\textsuperscript{40} and characterized by elemental analysis, magnetic susceptibility measurements, IR and NMR spectra. The Schiff bases and most of the metal complexes display antibacterial activity.
Rajendran and Karvembu\textsuperscript{41} have reported the synthesis of Schiff bases derived from 3-amino-2H-pyrano[2,3-\(b\)]quinolin-2-ones. The synthesized Schiff base compounds were screened against the fungal strains, such as \textit{Aspergillus niger} and \textit{Fusarium sp.}

\[
\begin{array}{c}
\text{Scheme-19}
\end{array}
\]

Tudor Rosu \textit{et al} \textsuperscript{42} have reported the synthesis of Cu (II) complexes derived from Schiff base ligands obtained by the condensation of 2-hydroxybenzaldehyde or terephthalic aldehyde with 4-aminoantipyrine.

\[
\begin{array}{c}
\text{37}
\end{array}
\]
Aliasghar jarrahpour et al. have reported the synthesis of twelve new bis-Schiff bases of istatin, benzylisatin and 5-fluoroisatin by the condensation with primary aromatic amines.

The UV visible spectra of some Schiff bases derived from 2-aminopyridine and 2-aminopyrazine have been investigated in acetonitrile and toluene. The compounds were in tautomeric equilibrium in polar and non-polar solvents. This was suggested by Asiri et al. 

Scheme-20
Sivakumar *et al* \(^{45}\) have reported the proton dissociation constant of the ligand and the stability of the complexes of Co(II), Ni(II), Zn(II), Cd(II), Hg(II) and Pb(II) ions with 2-phenyl-3-(2'-hydroxy-5'-benzylidine)-quinazoline-4-(3H)-one. The proton-ligand and metal-ligand stability constants of the complexes have been determined pH metrically by the Calvin Bjerrum titration technique.

Yi-Jun Wei *et al* \(^{46}\) synthesized a pair of iso structural azido or thiocyanato bridged centre of symmetric dinuclear copper(II) complexes derived from the Schiff base ligand, 4-nitro-2-[(2-diethylaminoethylimino)methyl]phenol. These compounds are characterized by elemental analysis, IR spectra and single X-ray diffraction. The antimicrobial activities of the complexes have been tested.

Natarajan Raman *et al* \(^{47}\) have reported the synthesis of a novel 14-membered macrocyclic Schiff base derived from 3-cinnamalideneacetanalide and \(o\)-phenylenediamine which acts as a tetradentate and strongly conjugated ligand to form a cationic solid complex with Cu(II)/Ni(II)/Co(II) and /Zn(II). The ligand and the complexes were characterized by the usual spectral and analytical techniques. The antimicrobial tests were also recorded and gave good results in the presence of metal ions in the ligand system.
An investigation dealing with the impact of Schiff base derived from anthranilic acid and acetoacetanilide and its copper complex on instar larvae of Spodoptera litura was done by Raman et al.  

Twenty Schiff bases of 2-amino-5-1,3,4-oxadiazoles have been synthesized with different aromatic aldehydes. The antibacterial properties of the compounds were investigated against *proteus mirabilis* and *basilus subtilis*.

A series of 4-substituted-emoni-methyltetrazolo[1,5-a]quinoline with appropriate aromatic amine by refluxing in dioxane. They have been evaluated for their anti-inflammatory and antimicrobial activities.

Mukesh Kumar Biyala et al. have studied the synthesis of mono basic bidentate Schiff base complexes of palladium (II) and platinum (II) from 1H-indol-2,3-dione thiosemicarbazone. These complexes were characterized on the basis of elemental analysis, molecular weight determination, 1H NMR and UV spectral studies. Antimicrobial effects of both the ligands and their complexes on different species of pathogenic fungi and bacteria have been recorded and these are found to possess significant fungicidal and bactericidal properties.
Synthesis, crystal structures and antimicrobial activities of two thiocyanato-bridged dinuclear copper (II) complexes derived from 2,4-dibromo-6-[(2-diethylaminoethylimino)methyl]phenol and 4-nitro-2-[(2-thylaminoethylimino) methyl]phenol was proposed by Zhe Hong. These complexes have been characterized by physico-chemical and spectroscopic methods. These are found to be antimicrobial.

The in-vitro antibacterial and antifungal activities of five different amino acid Schiff bases derived from the reaction of 2-hydroxy-1-napthaldehyde with glycine, L-alanine, L-phenylalanine, L-histidine, L-tryptophane and the manganese(III) complexes of these bases were investigated by Iffet Sakiyan et al. The in-vitro activities against some Gram positive and Gram negative bacteria and fungi were determined.

M. Tofazzal H Tarafder et al. have reported the synthesis of complexes of a tridentate schiff base from the condensation of S-benzyldithiocarbazate with salicylaldehyde. These complexes have been characterized by elemental analysis and spectral analysis. Square planar structures are proposed for the Ni(II) and Cu(II) complexes. These authors have also studied the antimicrobial tests which indicate that Schiff base and five of the metal complexes of Cu(II), Ni(II), U(IV), Zr(II) and Sb(II) are strongly active against bacteria. The Schiff base exists in tautomeric form as follows:

Azam Faizul et al. have studied a series of 2-benzylideneaminonaphthothiazoles and they are synthesized incorporating the liophilic naphthalene ring to render them more capable of penetrating various bio membranes. The results obtained indicate that the Schiff bases having substitution with
halogens, hydroxyl group and nitro group at phenyl ring showed good antibacterial activity while methoxy group at different positions in the aromatic ring has minimal role in the inhibitory activity.

\[
\begin{align*}
\text{NH}_2 & \quad \text{NH}_2 \\
\text{KSCN/HCl} & \quad 1. \text{BrCH}_2\text{COOH} \\
& \quad 2. \text{NH}_2\text{OH}
\end{align*}
\]

Scheme-26

Esin Ispir et al\textsuperscript{56} have reported the synthesis of Schiff base ligands containing -SiOH or -SiOCH\textsubscript{3} groups, 4-{[3-trimethoxysilanepropyl]iminomethyl} benzene-1,3-diol (1) and 4-{[3-triethoxysilanepropyl]iminomethyl} benzene-1,3-diol(5) from 2,4-dihydroxybenzaldehyde and 3-aminopropyltrimethoxysilane and 3-aminopropyltriethoxysilane.

\[
\begin{align*}
\text{HO} & \quad \text{HO} \\
\text{HO} & \quad \text{HO}
\end{align*}
\]

H. L. Singh\textsuperscript{57} proposed a reaction of bis(triorganotin)oxide with Schiff bases derived by condensation of heterocyclic ketones, 2-acetylfuran and 2-acetyltiophene with various sulfa drugs. The structures of the complexes have been established by spectral studies. Molar conductance measurements were carried out for the Schiff bases. The results of antimicrobial effects of some representative complexes on different species of pathogenic fungi and bacteria have also been recorded.
N. Raman et al \(^{58}\) have reported the synthesis of Schiff bases of 4-aminoantipyrine neutral complexes of Cu (II) from salicylidine-4-aminoantipyrine and PhNH\(_2\) / substituted anilines. These authors confirmed their structure using IR, UV-visible, \(^1\)HNMR and \(^{13}\)C-NMR spectra.

Mixed ligand complexes of the type [M(SB)\(_2\) acphen], where M=Mn(II), Co(II), Ni(II), Cu(II) and Cd(II), HSP=3,5-tribromosalicylidineanilin and acphen= bis(acetophenone)ethylenediamine have been prepared and characterized on the basis of elemental analysis, magnetic measurements, thermogravimetry, infrared and electronic absorption spectroscopy. All the mixed ligand complexes exhibit an octahedral geometry. The mixed ligand complexes show antimicrobial activities against bacteria, yeast and fungi. This study was done by Patel et al \(^{59}\).

CONCLUSION

The chemistry of Schiff bases is a field that is being noticed. Schiff base ligands are considered privileged ligands because they are easily prepared by a simple one pot condensation of an aldehyde and primary amines. These compounds and their metal complexes had a variety of applications including clinical, analytical, industrial they also play important roles in catalysts.

In this review, the biological activities of Schiff base and its complexes have been summarized from 2000-2010.
REFERENCES

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