CHAPTER II

LITERATURE REVIEW AND SCOPE OF THE PRESENT STUDY

2.1 Literature Review

Recently published literature reports relevant to our present study are discussed in this chapter.

2.1.1 Review of Phenanthrenequinone based Schiff bases

9,10-Phenanthrenequinone is an aromatic tricyclic diketone. It can form “diimine” Schiff base and stable chelates with metal ions. 9,10-Phenanthrenequinone has been found to exhibit photoreactivity and DNA binding/cleavage ability. The Schiff base complexes derived from 9,10-Phenanthrenequinone show good fluorescence properties. Recently many researchers are working on 9,10-Phenanthrenequinone and its Schiff base complexes.

R. Sellappan[1] et al. have synthesized new macrocyclic Schiff base ligand by the condensation reaction between 9,10-phenanthrenequinone and o-phenylenediamine derivatives in 1:1 molar ratio and complexed with vanadylsulphate. The synthesized macrocyclic ligands and the isolated Schiff base complexes have been characterized by elemental analysis, molar conductivity, IR, electronic spectroscopy and cyclic voltammetric studies. The ligands and the oxovanadium(IV) complexes have been screened for the evaluation of antibacterial activities. The complexes exhibited higher activities compare to that exhibited by the standard.
T. R. Arun and N. Raman\textsuperscript{[2]} have synthesized phenanthrenequinone based Schiff base complexes incorporating methionine amino acid. DNA binding ability of these complexes has been explored using diverse techniques viz. UV-Vis. absorption, fluorescence spectroscopy, viscometry and cyclic voltammetry.

These studies prove that CT-DNA binding of the complexes follows the intercalation mode. In addition, the biocidal action of the complexes has been investigated against few pathogenic bacteria and fungi by disc diffusion method. Importantly, the amylase inhibition activity of Cu(II) complex has been explored. The amylase inhibition property has been found to be increased upon increasing the complex concentration.

Appraisal of DNA obligatory, DNA cleavage and in vitro anti-biogram efficiency of 9,10-phenanthrenequinone based metal complexes have been reviewed by N. Raman\textsuperscript{[3]} \textit{et al.}

The complexes exhibit admirable DNA binding and chemical nuclease activity. They have efficient antimicrobial effect against various pathogens.

Phenanthrenequinone thiosemicarbazones and their metal complexes have been studied by Zahra Afrasiabi\textsuperscript{[4]} \textit{et al}. The complexes were tested against triple negative
breast cancer cells and found to be effective. Complexation of ligands with redox active copper ions exhibit comparable cytotoxicity.

Jian Zhang\(^5\) and his coworkers have synthesized a phenanthrenequinone macrocyclic trimer and used as a heterogeneous catalyst for oxidative dehydrogenation of ethylbenzene. This model molecule under comparable kinetic conditions is up to 47 times more active than extended solid catalysts including nanocarbons, metal phosphates, and oxides, confirming the hypothesis that diketone-like groups can serve as active sites.

Naser Samadi\(^6\) and et al. have synthesized phenanthrenequinone thiosemicarbazone Schiff bases and have determined the stability constants for complexation reaction. In the present work spectrophotometric titration of several cationic metal ions with new synthetic ligand were studied in order to calculate the formation constants.

Tetradentate dimeric Schiff bases having the -ONNO- donor was synthesized by B. N. Ghose\(^7\) from 9,10-phenanthrenequinone and ethanolamine and reacted with diorganosilicon dichlorides to give monomeric, hexacoordinated chelate complexes.

Zeglis\(^8\) et al. have synthesized Rh(bpy)\(_2\)(phi)\(^{3+}\)(phi=9,10-phenanthrenequinone) and analysed the DNA photocleavage reaction of mismatch-selective Rh complexes by MALDI-TOF mass spectrometry as well as gel electrophoresis analysis of radioactively tagged oligonucleotide.
Saman Damavandi\cite{9} have synthesized a range of substituted imidazoles in excellent yields from one-pot reaction of aromatic aldehydes, 9,10-phenanthrenequinone, and ammonium acetate. The remarkable features of this new procedure are introducing a new one-pot method for synthesis of 2-aryl-1H-phenanthro[9,10-d]imidazoles, high conversion, short reaction time, and simple experimental and workup procedure. Applicability of the method for the various compounds, high efficiency of the catalyst system, short reaction times, and high yields of the products prove the merit of this research.

LIU Qiaoru\cite{10} et al. have synthesized Schiff base Metal Complex from 9,10-phenanthrenequinone and S-methyl Dithiocarbazate.

Panneerselvam Anitha\cite{11} et al. A new series of octahedral ruthenium(II) complexes supported by tridentate ligands derived from phenanthrenequinone and derivatives of thiosemicarbazide/semicarbazide and other co-ligands have been synthesized and characterized. Antioxidative activity proved that the complexes have...
significant radical scavenging activity against free radicals. Cytotoxic activities showed that the ruthenium(II) complexes exhibited more effective cytotoxic activity against selected cancer cells.

Lidong Li\textsuperscript{[12]} et al. have synthesized Schiff bases from phenanthrenequinone and 2,6-dialkylaniline (alkyl = Me, iPr), catalyzed by formic acid, in refluxing methanol which gave rise exclusively to 10-(2,6-dialkyl-phenylimino)-10H-phenanthren-9-one compounds (alkyl = Me (1), iPr (2)). In refluxing toluene, and when diisopropylaniline is employed, the heterocyclic compound 7-isopropyl-3,3-dimethyl-10'H-spiro(indoline-2,9'-phenanthren)-10'-one (3) was unexpectedly prepared as the major reaction product, in the presence of catalytic amounts of various Brønsted acids.
2.1.2 Review of Curcumin based Schiff bases

Curcumin is a diketone with aromatic phenolic groups. It is naturally available in Turmeric. It is a very good antiseptic and shows high bioactivity. The Schiff base complexes derived from curcumin can also exhibit high bioefficacy, and recently some reports are being published with curcumin Schiff base complexes.

Ping Deng\cite{13} et al. have studied the structure of a Schiff base containing phenylalanine derived from curcumin by computational simulations using density functional theory (DFT) and time-dependent density functional theory.

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\end{center}

According to the theoretical calculations of three tautomers, enolic tautomer (A), enamine tautomer (B) and ketonic tautomer (C), of the schiff base molecular, the geometry, relative stability, charge density population and UV-Vis characteristics of every tautomer are investigated.

Imran Ali\cite{14} and his co-workers have synthesized Schiff bases from Pyrazolealdehydes and curcumin. These compounds were purified, characterized and the Hemolysis assays, cell line activities, DNA bindings and docking studies were carried out. It has been observed that DNA-compound adducts were stabilized by three governing forces (Van der Wall's, H-bonding and electrostatic attractions). It has also been observed that compounds preferred to enter the minor groove and major grooves of DNA. The anticancer activities of the reported compounds might be due to their interactions with DNA.
Few curcumin based metallointercalators having the amino acid (cysteine) have been synthesized and characterized by IR, UV–vis, NMR, EPR and magnetic susceptibility measurements by T.Chandrasekar, N. Pravin and N.Raman.\textsuperscript{[15]}

The electronic absorption spectral data of the complexes suggest a square planar geometry around the central metal ion. The interaction of the complexes with DNA is explored using absorption spectra, cyclic voltammetric, viscosity measurements and gel electrophoresis technique. The data reveal that the complexes are strong intercalators and potential nucleases as compared to curcumin based free ligand. The antimicrobial activities of the ligand and its complexes are also explored and it is found that the complexes exhibit better activity against bacteria and fungi than the ligand.

DNA interaction studies of a novel Cu(II) complex as an intercalator containing curcumin and bathophenanthroline ligands has been reported by Nahid Shahabadi and coworkers.\textsuperscript{[16]}
The complex displays significant binding properties to the CT-DNA. In fluorimetric studies, the binding mode of the complex with CT-DNA was investigated using methylene blue as a fluorescence probe. The cleavage of plasmid DNA by the complex was also studied. We found that the copper(II) complex can cleave puC18 DNA. Furthermore, mentioned complex induces detectable changes in the CD spectrum of CT-DNA, a decrease in absorption spectrum, and an increase in its viscosity. All of the experimental results showed that the Cu(II) complex bound to DNA by an intercalative mode of binding.

Serena Riela\cite{17} and coworkers have studied co-loaded curcumin/triazole-halloysite systems and evaluation of their potential anticancer activity.

Positively charged halloysite nanotubes functionalized with triazolium salts (f-HNT) were employed as a carrier for curcumin molecules delivery. Their interaction with curcumin was evaluated by means dynamic light scattering (DLS) and UV-vis spectroscopy in comparison with pristine unmodified HNT (p-HNT). The curcumin load into HNT was estimated by thermogravimetric analysis (TGA) measurements, while the morphology was investigated by scanning electron microscopy (SEM) techniques. Release of curcumin from f-HNT, at three different pH values, by means of UV-vis spectroscopy was also studied.

Synthesis, spectra and DNA interactions of certain mononuclear transition metal(II) complexes of macrocyclic tetraaza diacetyl curcumin ligand, has been reported by J.Rajesh\cite{18} et al. The electrochemical responses of these metal complexes both in presence and absence of DNA have also been demonstrated. The spectral and electrochemical response of these complexes designate that the square-planar Cu(II),
Ni(II) and Co(II) complexes interact much better than the axially coordinated octahedral Mn(II) complex.

S. Sundarananthavalli\textsuperscript{[19]} \textit{et al.} have synthesized new Schiff bases of Curcumin by condensing it with o-phenylenediamine. The structural features of the synthesized compounds have been determined from their elemental analysis, melting point, IR, UV-Vis, 1H-NMR and mass spectral data. The investigated compounds were utilized to test the various biological activities like analgesic, anti-inflammatory, anti-ulcer and wound healing effects on albino rats.

A. Kulandaisamy and M. Thomas\textsuperscript{[20]} have synthesized neutral complexes of Cu(II), Ni(II), Co(II), VO(II) and Zn(II) from the new Schiff base derived from curcumin and 4-aminoantipyrine. The structural features of the complexes have been determined from their microanalytical, magnetic susceptibility, molar conductance, IR, UV-Vis, 1H-NMR, mass and ESR spectral data. The antimicrobial activity of the ligand and its complexes against the bacteria Staphylococcus aureus, Bacillus subtilis, Klebsiella pneumoniae, Salmonella typhi, Pseudomonas aeruginosa and Shigellaflexneri are also reported.

Ajit P. Zambre\textsuperscript{[21]} \textit{et al.} have synthesized novel curcumin analogs using Knoevenagel condensation to convert enolic diketones of curcumin intonon-enolizable ones and Schiff bases were prepared using a bioactive thiosemicarbazide pharmacophore.
Copper(II) conjugates of all synthesized ligands were prepared and structurally characterized as well as evaluated for their potential of inhibiting TNF induced NF-κB activation and proliferation in human leukemic KBM-5 cells. Compounds were further examined on other tumor cell lines such as Jurkat, H1299, and MM1, respectively.

Sabari Dutta\textsuperscript{[22]} and his coworkers have synthesized new Schiff bases of Curcumin by condensing it semicarbazone and thiosemicarbazone. Antioxidant properties of Curcumin derivatives and their copper conjugates are examined. The copper conjugates of the Schiff base derivatives of curcumin yield highly potent SOD mimics. The observed correlation between the SOD activity and the redox potential of the Cu\textsuperscript{+}/Cu\textsuperscript{2+} emphasizes the roles played by the electronic as well as stereochemical factors in the biological activities of these curcuminoids.

J. Joseph\textsuperscript{[23]} \textit{et al.} have described the synthesis and structural characterization of highly conjugated curcumin analogs (acetoacetanilide) Knoevenagel condensates, their Schiff bases, and corresponding copper conjugates. Copper complexes have higher anti-
mycobacterial activity than ligands due to the presence of highly conjugated curcumin analog system containing two azomethine groups and redox properties of metal.

Padhye\textsuperscript{[24]} \textit{et al.} have designed and synthesized new difluoro Knoevenagel condensates of curcumin and Schiff bases along with their copper (II) complexes and evaluated their biological activities with respect to the inhibitory effects on purified rabbit 26S proteasome, and growth inhibition and induction of apoptosis in colon and pancreatic cancer cell lines. The studies indicate that the potency of fluoro analog of curcumin on the inhibition of the proteasome and cell growth and the induction of cell death was better than the parental curcumin, which is likely to be in part due to the metabolic stability afforded by the fluoro substituents.

![Chemical structure](image)

Tridib K. Goswami\textsuperscript{[25]} \textit{et al.} have prepared and characterized Copper(II) complexes [Cu(Fc-aa)(cur)] of curcumin (Hcur) and N-ferrocenylmethyl-L-amino acids viz., ferrocenylmethyl-L-tyrosine (Fc-TyrH), ferrocenylmethyl-L-tryptophan (Fc-TrpH) and ferrocenylmethyl-L-methionine (Fc-MetH).
The DNA photocleavage activity, photocytotoxicity and cellular localization in HeLa and MCF-7 cancer cells of these complexes were studied. The complexes showed visible light-induced plasmid DNA cleavage activity. Interestingly, the complexes that are nontoxic in dark to the cancer cells showed significant photo enhanced cytotoxicity when irradiated with 400-700 nm visible light.

Y. M. Song\textsuperscript{[26]} \textit{et al.} using Ce, La, Nd (III) nitrate and a curcumin aniline Schiff base and a curcumin bis (4-methyl aniline) Schiff base as raw materials, have synthesized six complexes. Through the molar conductance, IR, TG-DTA and element analysis methods, the structures of complexes were characterized. Moreover, the properties of UV-Visible spectra and photochromic properties of the complex, and the solvate chromic performance in organic solvents were explored.
2.1.3 Review of Amino acid based Schiff bases

Amino acids are biologically highly significant. A large number of papers have been published in the amino acid derived Schiff base complexes. Owing to this special nature of amino acids, still many researchers continue to work in this area. The Schiff base derived from amino acids form chelates with large number of metal ions, which have shown variety of applications.

Nasser Mohammed Hosny et al. have reported “Synthesis, spectral characterization and DNA binding of Schiff-base metalcomplexes derived from 2-amino-3-hydroxyprobanoic acid and acetylacetone.”

The Schiff-base ligand acts as bi-negative tridentate. The optical band gap measurements indicated the semi-conducting nature of these complexes. Molecular docking predicted the binding between the ligand and the receptor of prostate cancer mutant H874Y. Cu(II) complex efectively binds to CT-DNA.

Li-Jun Li et al. have synthesized a series of platinum(II) complexes with reduced amino acid esters Schiff-bases as ligands as potential anticancer agents, and characterized them by NMR, IR spectroscopy, elemental analysis and molar conductivity.
These compounds were tested for their stability and DNA interaction with salmon sperm DNA by ultraviolet spectrum. The cytotoxicities of these complexes were validated against HL-60, BGC-823, Hela, and HepG2 cell lines by the MTT test. The complexes 5e and 5f exhibited better cytotoxic activity than cisplatin against HepG2 and BGC-823 cell lines, respectively.

Zong-Ze Li[29] and coworkers have reported “Two 2D grid-based Co(II) amino acid Schiff base complexes with left- and right-handed helical chains: Structures and magnetism.” Two layered Co(II) amino acid Schiff base complexes, \([\text{Co}(\text{napala})(\text{tbpe})_{0.5}]_n\) (1) and \([\text{Co}(\text{napgly})(\text{tbpe})_{0.5}]_n\) (2) \([\text{H}_2\text{napala} = N-(2\text{-hydroxy-1-naphthylmethylidene})-\text{D/L-alanine, } \text{H}_2\text{napgly} = N-(2\text{-hydroxy-1-naphthylmethylidene})-\text{glycine and } \text{tbpe} = \text{trans-1,2-bis(4-pyridyl)ethylene}], have been synthesized by solvothermal methods and characterized using single-crystal X-ray diffraction. The complexes show high thermal stability.

Intercalation of \(\text{Ga}^3^+\)-salicylidene-amino acid Schiff base complexes into layered double hydroxides: Synthesis, characterization, acid resistant property, in vitro release kinetics and antimicrobial activity has been reported by Mingzhao Wang[30] et al.
Ga$^{3+}$ salicylidene amino acid Schiff base complexes are intercalated into Mg/Al-LDH. Monolayer, bilayer and trilayer models of guest molecules in hybrids are proposed. Protection of LDH increases Ga$^{3+}$ complexes acid resistance in wide pH range of 7-1. The hybrids release guests following first-order kinetics via ion exchange. The hybrids keep the antibacterial activity of guests against *P. Aeruginosa*.

New Fe(II) Schiff base amino acid complexes derived from the condensation of o-hydroxynaphthaldehyde with L-alanine, L-phenylalanine, L-aspartic acid, L-histidine and L-arginine were synthesized and characterized by Laila H. Abdel-Rahman$^{[31]}$ *et al.* The investigated Schiff bases exhibited tridentate coordination mode with the general formulae [Fe(HL)$_2$.nH$_2$O for all amino acids except L-histidine. But in case of L-histidine, the ligand acts as tetradebate ([FeL(H$_2$O)$_2$.2H$_2$O), where HL = mono anion and L = dianion of the ligand. The structure of the prepared complexes is suggested to be octahedral. The interaction between CT-DNA and the investigated complexes were followed by spectrophotometry and viscosity measurements. It was found that, the prepared complexes bind to DNA via classical intercalative mode and showed a different DNA cleavage activity with the sequence: nhi > nari > nali > nasi > nphali.

Synthesis, X-ray structure and ascorbic oxidation properties of ternary a-amino acid Schiff base-bipy Cu(II) complexes as functional models for ascorbic oxidase has been reported by Zeinab Moradi-Shoeili$^{[32]}$ *et al.*

Crystal structures of the complexes displayed a distorted square-pyramidal geometry around Cu(II). The complexes are one-electron paramagnetic and show one d-d transition and one LMCT bands near 664 and 378 nm in aqueous methanol, respectively. The electrochemical studies in DMF medium exhibit an irreversible Cu(II)/Cu(I) redox couple in the potential range of -0.3 to 0.5 V and one additional irreversible anodic wave associated with oxidation of ligands about 0.8 V. These complexes are also catalytically
active in oxidation of ascorbic acid in presence of dioxygen, models the ascorbate oxidation property of the Cu(II) sites in ascorbate oxidase.

S. Theodore David and M. Sivasankaran Nair\cite{33} have synthesized and characterized Schiff base complexes of Thiophene-2-carboxaldehyde and L-histidine with Co(II), Ni(II), Cu(II) and Zn(II). The results show that the Schiff base ligand is bound to the metal ions in a tridentate manner involving thiophene sulphur, azomethine nitrogen and carboxylato oxygen atoms, while the fourth position in the coordination sphere is occupied by the chloride ion. The geometrical structures of Co(II),Ni(II) and Zn(II) complexes are found to be tetrahedral whereas Cu(II) complexes are square planar. The antimicrobial results show that the metal complexes were found to be more active than the ligand. The complexes showed increased nuclease activity in the presence of an oxidant when compared to the ligand.

I. Sakiyan\cite{34} and his coworkers have studied the in vitro antibacterial and antifungal activities of five different amino acid Schiff bases derived from the reaction of 2-hydroxy-1-naphthaldehyde with glycine, L-alanine L-phenylalanine, L-histidine, L-tryptophane and the manganese(III) complexes of these bases.

Series of Pb(II) complexes of the type Pb(L) have been synthesized with fluorinated Schiff bases derived from 3-methyl-4-fluoroacetophenone and amino acids (viz phenylalanine, alanine, tryptophan, valine, isoleucine, and glycine) by Singh\cite{35}.

Alghool\cite{36} et al. have prepared Metal complexes of La(III), Ce(IV), and Th(IV), with the amino Schiff base ligand, [ N-(2-hydroxybenzyl)- l-methionine acid](HL), in the presence of triethylamine as a deprotonating agent.

Zahid H. Chohan\cite{37} et al. have synthesized a new series of Schiff bases and their cobalt(II), copper(II), nickel(II) and zinc(II) metal complexes by condensation of salicylaldehyde with glycine, alanine, phenylalanine, methionine and cysteine.
New water-soluble zinc(II) Schiff-base complexes derived from amino acids (glycine, L-phenylalanine, and L-valine) and salicylaldehyde-5-sulfonates (sodium salicylaldehyde-5-sulfonate and sodium 3-methoxy-salicylaldehyde-5-sulfonate) have been synthesized by Davar M. Boghaei and Mehrnaz Gharagozlou.[38]

YOU Jun[39] et al. have described a new solvent-free method for the synthesis of L-amino acids Schiff bases by the reactions of L-alanine (L-ala), L-serine (L-ser), L-valine (L-val), L-leucine (L-leu), L-isoleucine (L-Ile), L-phenylglycine (L-phg), L-phenylalanine (L-phe) with salicylaldehyde or 2-hydroxy-1-naphthaldehyde, respectively, in the present of KOH at room temperature.

S. Merajuddin Ahmed[40] et al. have synthesized Schiff bases from the amino acids, alanine (Ala) and phenyl alanine (Phe) and the Schiff bases (Ala-Sal), (Phe-Sal) were complexed with iron [III] metal. The catalytic performance of prepared complexes were investigated by using various reaction conditions, such as temperature, pressure, amount of catalyst, time, oxidant to substrate ratio in order to find out the optimum conditions for the oxidation reaction of cyclohexane.
Reddy\textsuperscript{[41]} and his coworkers have studied the DNA cleavage activity of tridentate Schiff-base ligands derived from the condensation of salicylaldehyde with glycine, L-alanine and L-phenylalanine.

A series of new ternary zinc(II) complexes $[\text{Zn}(L(1-10))(\text{phen})]$, where phen is 1,10-phenanthroline and $\text{H}(2)L(1-10)$=tridentate Schiff base ligands derived from the condensation of amino acids (glycine, L-phenylalanine, L-valine, L-alanine, and L-leucine) and salicylaldehyde-5-sulfonates (sodium salicylaldehyde-5-sulfonate and sodium 3-methoxy-salicylaldehyde-5-sulfonate), have been synthesized by D.M. Boghaei, M. Gharagozlou.\textsuperscript{[42]}

M. Ali Shaker\textsuperscript{[43]} et al. have synthesized a series of new Iron(II) Schiff base amino acid complexes by the condensation of L-phenylalanine and sodium 2-hydroxybenzaldehyde-5-sulfonate. 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, Pseudomonas aeruginosa and Micrococcus bacteria. The effect of HCl on investigated complexes studied spectrophotometrically.

Two new Schiff base compounds derived from the condensation reaction of L-glycine and L-tryptophan with 4-methylbenzaldehyde have been synthesized by M. Zahraa Salim.\textsuperscript{[44]} Their effects on the activity of total (ACP), prostatic (PAP) and non
prostatic (NPA) acid phosphatase enzymes were studied. The Schiff base derived from L-glycine (A) demonstrated inhibition effect on the ACP and NPA activities and activation effect on PAP activity. The Schiff base derived from L-tryptophan (B) demonstrated semi fixed inhibition effects on the ACP and NPA activities at high concentrations.

Yan Zhang\textsuperscript{[45]} et al. have studied the interaction of the Schiff base with herring sperm DNA was studied by UV–Vis absorption, fluorescence and viscosity methods in a physiological pH environment (pH 7.40), where the Schiff base was derived from vanillin and L-tryptophan. Thermodynamic parameters suggest that the interaction between K[HL] and DNA is driven mainly by enthalpy.

K. L. P. Sheeja Lovely and M. Christudhas\textsuperscript{[46]} have synthesized Schiff base complexes of Co(II), Ni(II), Cu(II) and Zn(II) derived from 3-pyridine carboxaldehyde and L-tryptophan. They have been synthesized and investigated by different physicochemical techniques. The low conductance values indicate that all the complexes are non-electrolytes. The synthesized compounds were tested for antimicrobial activity
against the bacteria Klebsiella pneumonia, Pseudomonas aeroginosa, E.Coli, Staphylococcus aureus, Proteus and Aspergillus niger.

The fluorescence properties of tryptophan and tryptophan-retinal Schiff base are investigated in a reverse micellar matrix of sodium bis (2-ethylhexyl)sulphosuccinate), a membrane mimetic system by A.K. Singh and R.V. Aruna.\textsuperscript{[47]}

New dibutyltin (IV) complexes of Schiff base derived from 5-chloroindoline-2,3-dione, indoline-2,3-dione with amino acids (tryptophan, alanine and valine) were synthesized by Har Lal Singh and Jangbhadur Singh.\textsuperscript{[48]}

S. Çakir and E. Biçer\textsuperscript{[49]} have synthesized a novel Schiff-base by the reaction of saccharin with tryptophan and characterized by elemental analysis as well as UV-Vis, FT-IR, 1H NMR spectroscopic data. The voltammetric behavior of Schiff-base was also studied on the hanging mercury drop electrode (HMDE) by using Square-Wave Voltammetry (SWV) and Cyclic Voltammetry (CV) techniques.
M. H. Salunke\textsuperscript{[50]} and his coworkers have synthesized Schiff base from 4-methoxy benzaldehyde and L-tryptophan.

Nan Zhang\textsuperscript{[51]} et al. have reported the Syntheses, crystal structures and anticancer activities of three novel transition metal complexes with Schiff base derived from 2-acetylpyridine and L-tryptophan.

A new ternary Schiff base transition metal complexes of general formula [ML1L2] were prepared by template synthesis where, L1 is a Schiff base ligand derived from L-tryptophan and 2' hydroxyacetophenone by D.Badma Priya and S. Santha Lakshmi.\textsuperscript{[52]}

Kaku Dutta\textsuperscript{[53]} et al. have synthesized Schiff base from benzil and L-tryptophan and studied its fluorescent behavior.

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Isabel Correia\textsuperscript{[54]} et al. have prepared Schiff bases of salicylaldehyde and pyridoxal (and o-vaniline) with L-tyrosine (Tyr) and D,L-o-tyrosine (o-Tyr), as well as the oxidovanadium(IV) complexes. The compounds have been characterized in the solid state and in solution.

Z. H. Chohan\textsuperscript{[55]} and his coworkers have synthesized and characterized biologically active tridentate amino acid (Alanine, Glycine & Tyrosine) derived Schiff-bases and their Co(II), Cu(II) & Ni(II) complexes on the basis of their conductance and magnetic measurements, elemental analysis and $^{13}$C-NMR, $^1$H-NMR, IR and electronic spectral data. These Schiff-bases and their complexes have been evaluated for their
antibacterial activity against bacterial species such as Staphylococcus aureus, Escherichia coli, Klebsiella pneumonae, Proteus vulgarus and Pseudomonas aeruginosa and this activity data show the metal complexes to be more antibacterial than the Schiff-bases against one or more bacterial species.

G. Indira Devi\cite{56} et al. have synthesized and characterized Cobalt(II), nickel(II), and copper(II) complexes of the Schiff base anthracene -9-carboxaldehyde - tyrosine on the basis of elemental analysis, magnetic moment, molar conductance, UV-visible and IR spectra. Cobalt (II), nickel (II), and copper (II) complexes were subjected to thermal analysis to determine their thermal stability and decomposition pattern.

Shi Wei-Liang and Chen De-Yu\cite{57} have synthesized a new Schiff base derived from tyrosine and salicylaldehyde and its copper(II) complex and characterized by elemental analyses, molar conductances, thermal analyses, infrared spectra, electronic spectra and EPR spectra.

Ara Nunez-Montenegro\cite{58} et al. have synthesized three Schiff bases derived from 2,4-dihydroxybenzaldehyde or 2,4-dihydroxyacetophenone and esters of tyrosine and histidine and the crystal and molecular structures were determined by single crystal X-ray diffraction.

Anjali Karande\cite{59} et al. have synthesized Copper(II) complexes of ferrocene(Fe)-conjugated reduced Schiff base of L-tyrosine.
BIAN Lin and his coworkers have synthesized a new Schiff base oxovanadium(IV) complex, derived from 2-hydroxy-1-naphthaldehyde and L-Tyrosine and characterized by elemental analyses, IR spectra.

WANG Ming-Zhao and his coworkers have synthesized one novel complex of (99m)Te-salicylidene-tyrosine Schiff base and its biodistribution was investigated.

Elisabete Oliveira et al. have synthesized two new tyrosine Schiff-base ligands bearing an indole or a thianaphthene moiety and characterized by elemental analysis, $^1$H NMR, IR spectroscopy (KBr discs), MALDI-TOF-MS spectrometry, UV–Vis and fluorescence emission spectroscopy. The sensing ability towards Ca$^{2+}$, Zn$^{2+}$, Cd$^{2+}$, Cu$^{2+}$, Ni$^{2+}$, Hg$^{2+}$ and Al$^{3+}$ metal ions was explored in absolute ethanol.

Patrizia Siega et al. have reported the synthesis of a new series of inorganic and organometallic cobalt Schiff base complexes containing the tetradentate ligand derived from the condensation of two equivalents of protected 3-acetyl-l-tyrosine with one equivalent of ethylenediamine.

2.1.4 Review of BSA binding studies of Schiff base metal complexes

Fei Wang et al. have synthesized five diorganotin(IV) complexes of benzoylformic acid 3-hydroxy-2-naphthoyl hydrazone. The complexes were structurally characterized by X-ray crystallography, elemental, IR and NMR ($^1$H and $^{13}$C ) spectroscopy. Structural analysis reveals that the ligand presents as tridentate ligand with ONO donors and coordinates to the tin center in an enolic form.
Furthermore, the protein fluorescence quenching studies reveal that there are strong binding interactions between compounds and bovine serum albumins (BSA).

The mononuclear nickel(II) complexes of ligands bappz [1,4-bis(3-aminomethyl)piperazine] and its Schiff bases $L^1$ with 5-methyl salicylaldehyde; and $L^2$ with 5-bromosalicylaldehyde have been synthesized and characterized by Arumugam Jayamani$^{[65]}$ and coworkers.

The single crystal X-ray study showed that the complex 1 crystallized in the orthorhombic Pbca space group with distorted square planar geometry. The ligands and their nickel(II) complexes presented good binding propensity to bovine serum albumin protein (BSA).

Synthesis and structure elucidation of a copper(II) Schiff-base complex: In vitro DNA binding, pBR322 plasmid cleavage and HSA binding studies has been reported by Sartaj Tabassum$^{[66]}$ et al.
The spectroscopic and analytical and single crystal X-ray diffraction studies revealed that the complex exist in a distorted octahedral environment. The HSA binding results showed that ligand and complex I has ability to quench the fluorescence emission intensity of Trp 214 residue available in the subdomain IIA of HSA.

Noor-ul H Khan\textsuperscript{[67]} et al. have studied the interaction of new chiral V(V) Schiff base complexes with calf thymus (CT) DNA and bovine serum albumin (BSA) protein.

M. K. Prashanth\textsuperscript{[68]} et al. have synthesized some Some New Benzamides by N-acylation of Schiff base with different substituted acid chlorides in the presence of triethylamine and its interaction with bovine serum albumin (BSA) was investigated using fluorescence and ultraviolet spectroscopic techniques at 298K under imitated physiological conditions.

Some new water-soluble Schiff-base complexes Na\textsubscript{2}[M(5-SO\textsubscript{3}-2,3-salpyr)(H\textsubscript{2}O)\textsubscript{n}] \cdot 2H\textsubscript{2}O (5-SO\textsubscript{3}-2,3-salpyr\textsuperscript{N,N'}-bis(5-sulphosalicylidien)-2,3-diaminopyridine and M(Zn, Cu, Ni) were synthesized and the mechanism of binding of Na\textsubscript{2}[M(5-SO\textsubscript{3}-2,3-salpyr)(H\textsubscript{2}O)\textsubscript{n}] \cdot 2H\textsubscript{2}O with bovine serum albumin (BSA) was investigated by fluorescence spectroscopy by Mozaffar Asadi\textsuperscript{[69]} and his coworkers.

Velusamy Gomathi Sankareswari\textsuperscript{[70]} et al. have studied the potential of the salphen ligands and oxovanadium(IV)–salphen complexes as drugs by their binding with bovine serum albumin (BSA). The quenching of the fluorescence of BSA and appearance of enhanced luminescence of the salphen ligand/vanadium(IV) complex at the increased [quencher] show efficient FRET from the protein to the quencher and the distance of energy transfer estimated using Forster's theory is in the range of 1.4–3.5 nm. Molecular docking studies (DFT) utilizing oxovanadium(IV)–salphen derivatives show strong binding with BSA and give insight into the binding modes, interaction pattern and stability.
of synthesized complexes in the target site. The cytotoxicity study shows the ability of these VO(IV) complexes to inhibit the growth of AGS gastric cell lines.

Aurkie Ray\textsuperscript{[71]} \textit{et al.} have spectroscopically monitored that a mononuclear nickel(II)-Schiff base complex \textit{\{NiL·CH(3)OH=NSC\}} exhibits greater binding affinity for bovine serum albumin (BSA) than that of its human counterpart (HSA). Nickel(II)-Schiff base interacts differently with two serum albumins. A rare type of superficial binding of the complex at domain IIB of HSA.. Docking studies predict certain mobility of the complex. Spectroscopic and docking results are well correlated. Binding selectively enhances protein stability in the presence of chaotrope.

Ping Mei\textsuperscript{[72]} \textit{et al.} have reported the binding interaction of a Schiff base compound containing a 1,2,4-triazole ring \textit{[4-(4-chlorobenzyl-ideneamino)-5-methyl-1,2,4-triazole-3-thiol, CTT]} with bovine serum albumin (BSA) by spectroscopy methods including fluorescence and circular dichroism spectrum under simulative physiological conditions. Fluorescence investigation revealed that the fluorescence quenching of BSA was induced by the formation of a relative stable CTT-BSA complex.

Mehrnaz Gharagozlou and Davar M Boghaei\textsuperscript{[73]} investigated the interaction of water-soluble amino acid Schiff base complexes, \textit{[Zn(L1,2)(phen)]} where phen is 1,10-phenanthroline and H2L1,2 is amino acid Schiff base ligands, with bovine serum albumin
(BSA) under the physiological conditions in phosphate buffer solution adjusted to pH 7.0 using fluorescence spectroscopy in combination with circular dichroism (CD) spectroscopy.

Xiao-Chun Yin[74] and coworkers have prepared insoluble salphen \([\text{N,N-}(\text{phenylene})\text{salicylidene}]\) Schiff-base metal complexes (HO-salphen-M, \(M = \text{Co}, \text{Mn}, \text{Cu}\)) and studied their binding with bovine serum albumin (BSA).

The interaction between a Cu(II) complex of taurine Schiff base and CT-DNA and BSA were studied by Lianzhi Li[75] et al.

Hua Ying Niu[76] et al. investigated the binding of three amantadine Schiff bases (ASBs) to BSA by fluorescence spectroscopy, UV-Vis spectroscopy and circular dichroism (CD).

A divanadium(V) complex, \([\text{V}_2\text{O}_3(\text{o-van-val})_2]\) (\(\text{o-van-val}=\text{Schiff base derived from o-vanillin and L-valine}\)), has been synthesized and structurally characterized by Qiong Guo[77] et al. The interaction of the complex with bovine serum albumin (BSA) has been studied by UV-Vis absorption, fluorescence and CD spectra. Results indicated that the complex can markedly quench the intrinsic fluorescence of BSA via a static quenching process, and cause its conformational change.

Some novel chalcones consisting unsaturated carbonyl group and C=N bond were synthesized i.e. 1-(4-(benzylideneamino)phenyl)-3-phenylprop-2-en-1-ones and studied
the influence of their presence on bovine serum albumin by Shweta Garg and Neera Raghav.\textsuperscript{[78]}

Jayaraman Jayabharathi\textsuperscript{[79]} and coworkers have studied the interaction between a trifluoromethyl substituted imidazole derivative 2-(4-(trifluoromethyl)phenyl)-1-phenyl-1H-imidazo[4,5-f] [1,10] phenanthroline (tfmppip) and bovine serum albumin (BSA) was investigated by solution spectral studies.

Rong Min Wang\textsuperscript{[80]} et al. have reported that 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).

J. Gao\textsuperscript{[81]} et al. synthesized three o-Vanillin Schiff Bases (o-VSB: o-Vanillin-D-Phenylalanine (o-VDP), o-Vanillin-L-Tyrosine (o-VLT) and o-Vanillin-L-Levodopa (o-VLL)) with alanine constituent by direct reflux method in ethanol solution, and then were used to study the interaction to bovine serum albumin (BSA) molecules by fluorescence spectroscopy.

Paramasivam Krishnamoorthy\textsuperscript{[82]} et al. synthesized tridentate chelating hydrazone Schiff bases from salicylaldehyde and benzhydrazide studied their interaction with calf thymus DNA (CT DNA) and bovine serum albumin (BSA).

The interactions between N,N’-di(2-hydroxy-3-methoxy-phenyl-1-methylene)-o-phenyldiamine-mone Zn(II), Nd(III) nitrate (2LZnNd) and bovine serum albumin (BSA) was investigated by various spectroscopic techniques under physiological conditions by Qi Xiao\textsuperscript{[83]} and coworkers.

Ting-Ting Xing\textsuperscript{[84]} et al. have studied the reactivity of a new tetracopper(II) complex bridged by oxamido and carboxylate, [Cu\textsubscript{4}(bhyox)\textsubscript{2}(phen)\textsubscript{2}(H\textsubscript{2}O)\textsubscript{2}](pic)\textsubscript{2}, where
H$_3$bhyox, phen and Hpic denote $N$-benzoate-$N'$-[2-(2-hydroxyethylamino)ethyl]oxamide, 1,10-phenanthroline, and 2,4,6-trinitrophenol, towards protein bovine serum albumin (BSA) and suggests that the tetracopper(II) complex binds to protein BSA.

Li Yan$^{[85]}$ et al. investigated the interaction between 4,5-dimethyl-3-cyano-2-furanamine salicylaldehyde Schiff base and Bovine Serum Albumin by fluorescence spectrometry and ultraviolet spectroscopy at different temperatures.

Yanling Xiang and Fangying Wu$^{[86]}$ synthesized a new Schiff-base compound, $N'$-(2-hydroxynaphthalenemethylene)-4-(2-hydroxynaphthalenemethylenamine)benzoylhydrazine and the interaction between zinc complex and bovine serum albumin (BSA) was investigated by fluorescence and absorption spectroscopies.

Tridib K. Goswami$^{[87]}$ et al. have studied the UV light induced oxidative cleavage of bovine serum albumin using Ferrocene-appended ternary copper(II) complexes of phenanthroline bases having CuN$_3$OS coordination with an axial Cu–S bond derived from L-methionine reduced Schiff base.

The interaction of lanthanum(III) 2-oxo-propionic acid salicyloyl hydrazone complex ($\text{La}^{3+}\text{L}_2$) with bovine serum albumin (BSA) was studied under physiological conditions by Ye-Zhong Zhang$^{[88]}$ et al.

Maria Lucia Pires dos Santos$^{[89]}$ et al. prepared di-Schiff base complexes, [$N,N'$-bis(2-pyridyl)methylene-1,2-diaminoethane]-$\text{La}^{3+}\text{L}_2$ and [$N,N'$-bis(2-acetylpyrazyl)methylene-1,3-diaminopropane]-$\text{La}^{3+}\text{L}_2$ and their relative thermodynamic stabilities were estimated by circular dichroism (CD), using bovine albumin as the competitive ligand.
H. Yamini Shrivastava and Balachandran Unni Nair\cite{90} have found that transdiaqua \( [N,N'-\text{propylenebis(salicylideneimino)}\text{chromium(III)}] \text{perchlorate} \) ([Cr(salprn)(H_2O)_2]ClO_4) complex in the presence of sodium azide and upon photoexcitation can bring about non-selective cleavage of bovine serum albumin (BSA).

Satish S. Bhat\cite{91} et al. have synthesized two mononuclear fluorophore-labeled copper(II) complexes \([\text{Cu(nip)(acac)}]\) and \([\text{Cu(nip)}_2]^{2+}\), where fluorophore is 2-(naphthalene-1-yl)-1H-imidazo[4,5-f][1,10]phenanthroline (nip) and acac is acetylacetone. The protein binding ability has been monitored by quenching of tryptophan emission in the presence of complexes using bovine serum albumin (BSA) as model protein.
2.2 Scope of the present investigation

Now, basic research is providing an increasingly detailed description of how living systems work at the molecular level, and of the biomolecular pathways involved in many diseases. Knowledge of such pathways now guides the development of new drugs, “targeted molecules” that work by binding to a specific protein and thus blocking its activity.

In order to serve as a drug, a compound must bind the targeted protein. It must also be sufficiently non-toxic and chemically and physically stable, and it must reach the targeted protein upon being administered by mouth (most convenient), or by some other route (e.g., intravenous). Finding or designing a compound that meets all these requirements is an ongoing challenge to scientists trying to develop new medications.

Proteins play a fundamental role in sustaining life and are closely related to the origin, evolution and metabolism of life. Serum albumins, as the major soluble protein constituents of the circulatory system, have many physiological functions. They play a dominant role in transport and disposition of various drugs in blood. It is responsible for the maintenance of blood $P^H$ and the contribution of colloid osmotic blood pressure.

The serum albumin is a versatile protein, principally characterized by its remarkable ability of binding a wide range of insoluble endogenous and exogenous compounds. Since the serum albumin was considered to be non-antigenic and biodegradable, and was readily available, the albumin has been used as a bio-material, such as drug delivery and novel hydrophilic carriers. Recently, the macromolecules conjugation has been proved to be an effective method to improve their bioactivity. The most outstanding property of albumins is their ability to bind reversibly a large variety of ligands. So, investigation on the interaction between serum albumins and small drug
molecules is very important for understanding the mystery of life and the interaction mechanisms of drugs.

Particular attention has recently been paid to the synthesis and study of the diimino tetradeutate Schiff bases and their complexes. This is due to their uses as biological models in understanding the structure of biomolecules and biological processes. In recent years, there is a growing interest in investigating the interaction between BSA and Schiff base metal complexes.

Binding of Schiff base metal complexes with the most abundant carrier protein (serum albumins) have also been a subject of interest as such drug-protein binding greatly influences absorption, drug transport, storage, and metabolism and excretion properties of typical drugs in vertebrates. To gain further insights about how Schiff base metal complexes can be administered intravenously by primary target molecules like serum albumins, the biochemical behavior of these complexes have been studied using spectroscopic tools.

The literature survey clearly indicates that studies on the Schiff base complexes derived from 9,10-Phenanthrenequinone, as well as Curcumin are limited.

Knowing the immense significance and huge variety of application interests of Schiff base complexes, we are also motivated to synthesize some novel and new class of amino acid based tetradeutate Schiff bases and their Mn(III) and Fe(III) complexes. The synthesized ligands and their complexes have been characterized by various analytical spectroscopic investigations \textit{viz.}, FT-IR, Elemental analysis, NMR, Mass, Absorption and Cyclic voltammetric techniques. The interaction of the metal complexes with BSA was investigated through absorption and emission techniques.
The scope of the present study is as follows.

➢ To Synthesize the Schiff bases;
   1. 9,10-Phenanthrenequinone-L-Phenylalanine (PQ-Phe)
   2. 9,10-Phenanthrenequinone-L-Tryptophan (PQ-Trp)
   3. 9,10-Phenanthrenequinone-L-Tyrosine (PQ-Tyr)
   4. Curcumin-L-Phenylalanine (Cur-Phe)
   5. Curcumin-L-Tryptophan (Cur-Trp)
   6. Curcumin-L-Tyrosine (Cur-Tyr)

➢ To Synthesize the Schiff base Complexes;
   1. Manganese(III)-9,10-Phenanthrenequinone-L-Phenylalanine (Mn(III)-PQ-Phe)
   2. Iron(III)-9,10-Phenanthrenequinone-L-Phenylalanine (Fe(III)-PQ-Phe)
   3. Manganese(III)-9,10-Phenanthrenequinone-L-Tryptophan (Mn(III)-PQ-Trp)
   4. Iron(III)-9,10-Phenanthrenequinone-L-Tryptophan (Fe(III)-PQ-Trp)
   5. Manganese(III)-9,10-Phenanthrenequinone-L-Tyrosine (Mn(III)-PQ-Tyr)
   6. Iron(III)-9,10-Phenanthrenequinone-L-Tyrosine (Fe(III)-PQ-Tyr)
   7. Manganese(III)-Curcumin-L-Phenylalanine (Mn(III)-Cur-Phe)
   8. Iron(III)-Curcumin-L-Phenylalanine (Fe(III)-Cur-Phe)
   9. Manganese(III)-Curcumin-L-Tryptophan (Mn(III)-Cur-Trp)
   10. Iron(III)-Curcumin-L-Tryptophan (Fe(III)-Cur-Trp)
   11. Manganese(III)-Curcumin-L-Tyrosine (Mn(III)-Cur-Tyr)
   12. Iron(III)-Curcumin-L-Tyrosine (Fe(III)-Cur-Tyr)
To Characterize these ligands and complexes by:

1. Elemental analysis
2. Molar Conductance studies
3. Magnetic Moment Measurement
4. Mass Spectrometry
5. UV-Vis Spectroscopy
6. $^{13}$C NMR Spectroscopy
7. EPR Spectroscopy

To study the electrochemical behavior of the synthesized complexes.

To study the thermal behavior of the synthesized complexes.

To Study the Protein Binding of the synthesized complexes with Bovine Serum Albumin (BSA) by:

1. Fluorescence Spectroscopy and
2. UV-Vis Spectroscopy.
The present task involves the synthesis of amino acid based tetridentate ligands and their mononuclear complexes as follows.

A. The Schiff base ligand **PQ-Phe** (9,10-Phenantraquinone)-L-Phenylalanine) and its mononuclear Mn(III) and Fe(III) complexes are synthesized. (Fig 2.2a)

![Schematic representation for synthesis of PQ-Phe and its complexes](image)

Fig 2.2a Schematic representation for synthesis of PQ-Phe and its complexes
B. The Schiff base ligand **PQ-Trp** (9,10-Phenanthraquinone-L-Tryptophan) and its mononuclear Mn(III) and Fe(III) complexes are synthesized. (Fig 2.2b)

![Diagram showing the synthesis of PQ-Trp and its complexes](image)

**Fig 2.2b** Schematic representation for synthesis of PQ-Trp and its complexes
C. The Schiff base ligand **PQ-Tyr** (9,10-Phenanthraquinone-L-Tyrosine) and its mononuclear Mn(III) and Fe(III) complexes are synthesized. (Fig 2.2c)

**Fig 2.2c** Schematic representation for synthesis of PQ-Tyr and its complexes
D. The Schiff base ligand **Cur-Phe** (N,N’-bis(diferuloylmethane)-L-phenylalanine) and its mononuclear Mn(III) and Fe(III) complexes are synthesized. (Fig 2.2d)

**Fig 2.2d Schematic representation for synthesis of Cur-Phe and its complexes**
E. The Schiff base ligand **Cur-Trp** (Curcumin-L-Tryptophan) and its mononuclear Mn(III) and Fe(III) complexes are synthesized. (Fig 2.2e)

![Chemical structures](image)

**Fig 2.2e** Schematic representation for synthesis of Cur-Trp and its complexes
F. The Schiff base ligand Cur-Tyr (Curcumin-L-Tyrosine) and its mononuclear Mn(III) and Fe(III) complexes are synthesized. (Fig 2.2f)

![Diagram of the synthesis of Cur-Tyr and its complexes]

**Fig 2.2f** Schematic representation for synthesis of Cur-Tyr and its complexes
References


