Chapter 1

Introduction

1 Introduction

1.1 The element

Copper metal has been known and used tremendously since prehistoric times. The word copper and its symbol Cu is formulated from cuprum. This metal is among the 25 richest elements in the earth's crust. It has performed an important role in industrial, technological and cultural developments in ancient times. Hence, along with iron and gold, copper was one of the first metals used extensively. One of the most extensive and well-established uses of copper is for commercial purposes. The metal and its alloys have been used in a variety of applications because they show several useful qualities including malleability, ductility, strength, corrosion resistance and high thermal and electrical conductivity.

Copper is an essential trace element. It exhibits essential biochemical action either as the nutritional element or a constituent of various exogenously administered compounds in humans. It associates with ceruloplasmin, albumin and other proteins. The participation of copper in human disease has been discussed from a biomedical [1] and a biomedical view [2] concentrating on the molecular physiology of copper transport [3]. Recent interest in copper complexes is developed from their potential application as antimicrobial, antiviral, anti-inflammatory, antitumor agents and enzyme inhibitors.

Copper shows wide coordination chemistry. Its main oxidation state is ranging from 0 to 4 but +1 and +2 oxidation states are most common. Very few copper(III) complexes have been reported. The majority of copper(III) complexes d^8 complexes have square planar geometry and are diamagnetic. Similarly, copper(0) complexes and copper(IV) oxidation states are very rare. The coordination number and geometry around the copper metal center vary with the oxidation state. The common geometries of Cu^1 d^{10} ion are two coordinates linear, three coordinates trigonal planar and four coordinates tetrahedral. The metal Cu(II) d^9 particle is mostly found in an exceedingly tetragonal shape coordination setting [4, 5]. Although, four-coordinate tetrahedral and square planar complexes are according [6].

1.2 Copper in Biology

Copper is a crucial trace element, but excessive quantities are toxic to humans [7]. About 2-5 mg of copper is absorbed per day from the diet. Copper deficiency can

develop if there is insufficient nutritional copper and show low blood cell counts and osteopenia (low bone density). Though, copper deficiency is rarely seen in developed countries. Sometimes severe copper deficiency noticed like those examined in genetic disorder, Menkes disease [8]. This disease mainly happens in boys since it is X-linked and generally apparent at birth. Such babies are born premature and have unusual appearances and have brain damage that causes mental retardation. For the treatment of such disease metal-based drugs are useful. One of such useful drugs is copper-histidine complexes which may be prescribed. For this drug, clinical trials are underway. Also, chronic toxicity is seen in some individuals. The excessive accumulation of copper damages the liver and then the nervous system and other organs. The dominant, relatively rare disorder is called Wilson's disease [8]. This disease is generally identified in infants too young adults with liver and neurological problems. Wilson's disease is curable with anti-copper agents including zinc acetate (Galzin^{Tm}) which blocks copper absorption and has the lowest rate of side effects or D-penicillamine (Cuprimine, depen) or trientine (suprine) to chelate and remove the excess copper. Tetra thiomolybdate is also being considered to cure this disease and at present is in the phase of the final clinical trial. The roles of copper in other diseases have also been investigated. For Alzheimer's disease cases, it is observed that amylase protein interacts with copper to produce increased oxidant damage and little amount of copper causes the precipitation of the amyloid β-protein on copper and its complexes.

Alzheimer's [8] disease is a neurological condition in which the death of brain cells causes memory loss and a person may experience difficulty with reasoning, complex tasks and judgment. The drug Nomenda (Memantine) and N-methyl D-aspartate antagonist is prescribed to Alzheimer patients. It is believed to work by regulating glutamate which is an important brain chemical. When produced in excess amount, glutamate may lead to brain cell death. The lowering of copper levels causes to produce antiangiogenesis (retardation of blood vessel growth) and proliferation and hence, is being probed for its potential anticancer effect. Thus, copper lowering agent tetrathiomolybdate is recently involved in several clinical trials for a variety of cancers.

1.3 Biological importance of Schiff base copper complexes

The evolution in the field of bio-inorganic chemistry has aroused interest in Schiff base copper complexes, as long as it has been admitted that many copper(II) Schiff base complexes may serve as models for biologically important species. Schiff bases are

formed when primary amine reacts with aldehydes or ketone under specific conditions. Therefore, Schiff base is an analog of aldehydes or ketone in which the carbonyl group has been replaced by an imine or azomethine group (Fig. 1). These Schiff base compounds are easily synthesized and form complexes with almost all metal ions. There are several reports on their applications in biology together with medicine, antifungal, anticancer, inhibitor, an anti-inflammatory drug, an antimalarial drug, antiviral activity and conjointly as catalysts in many reactions. Some major importance of Schiff base copper(II) complexes are given as:

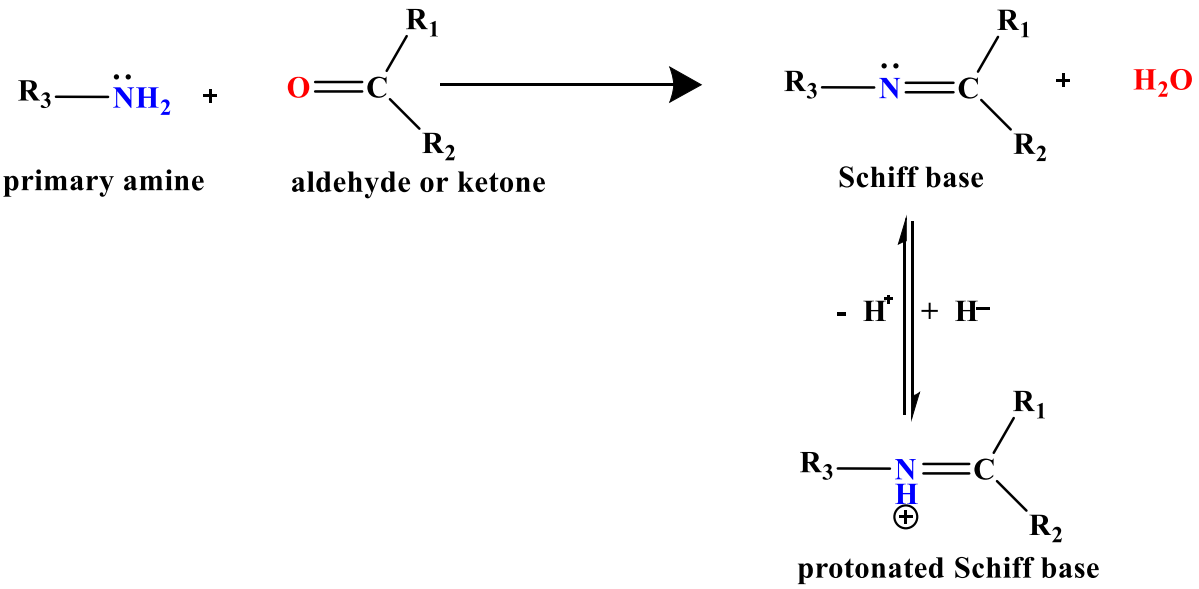


Fig. 1. The general strategy for the synthesis of Schiff base.

1.3.1 Antibacterial activity

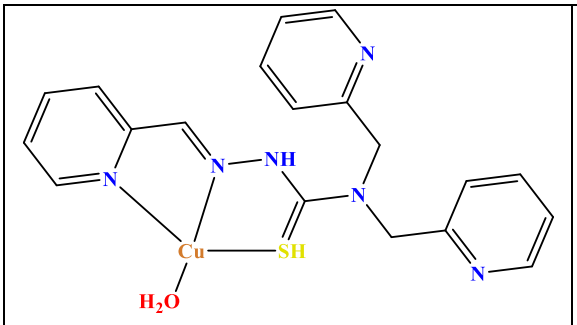
Many copper(II) Schiff base complexes have been synthesized and characterized using various physicochemical techniques. These complexes have been screened for their antimicrobial activities using the diffusion disc method against bacteria. The obtained results of antibacterial activity of these complexes show increased inhibitory activity compared to their parent ligands under experimental conditions. The antibacterial activity is explained based on chelation theory. The higher antibacterial activity of metal complexes may be due to the effect of metal ions on the normal cell membrane. Metal complexes bear polar and nonpolar properties and these features make them suitable for permeation to the cells and tissues. The antibacterial activity of copper(II) Schiff base complexes has been reported in the literature [9, 10].

1.3.2 Antifungal activity

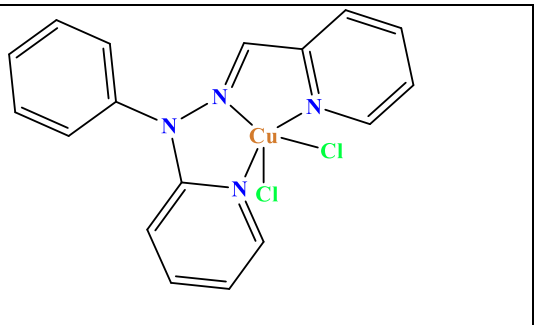
Many copper(II) Schiff base complexes were synthesized and characterized [11, 12]. These complexes were screened against *Aspergillus niger* and *Rhizoctonia solani*. The used ligands and complexes showed better results against the growth of fungi. It is observed that the antifungal activity increases upon coordination. The increased antifungal activity can be explained based on chelation theory [12]. Increased activity enhances the lipophilicity of the complexes due to the delocalization of π-electrons in the chelate rings [13]. Even, in few cases increased lipophilicity causes the breakdown of the permeability barrier of the cell [14]. The obtained results of antifungal activity of copper(II) Schiff base complexes showed better activity than the other metal complexes. Such observations may be due to the higher stability constants of copper(II) complexes than the other complexes.

1.3.3 Anticancer activity

Cancer is a class of disease in which a group of cells shows uncontrolled growth, invasion, or even some times metastasis. This disease creates a serious public health problem throughout the world. Cancer is the second leading cause of human death after cardiovascular diseases [15]. The treatment of cancer primarily includes surgery and chemotherapy, but the curative effects of the existing chemotherapeutic drugs are not good enough owing to their several side effects. The development of more effective drugs for treating cancer patients has been a main focus over the past few years. In recent years, several Schiff base copper(II) complexes are associated with anticancer properties [16-20]. The development of novel copper(II) complexes with anticancer activity is an encouraging and relevant area of medical chemistry [21]. Fig. 2 shows a few copper(II) Schiff base complexes that were recently tested in *in vitro* experiments [22-24].



(1)



(2)

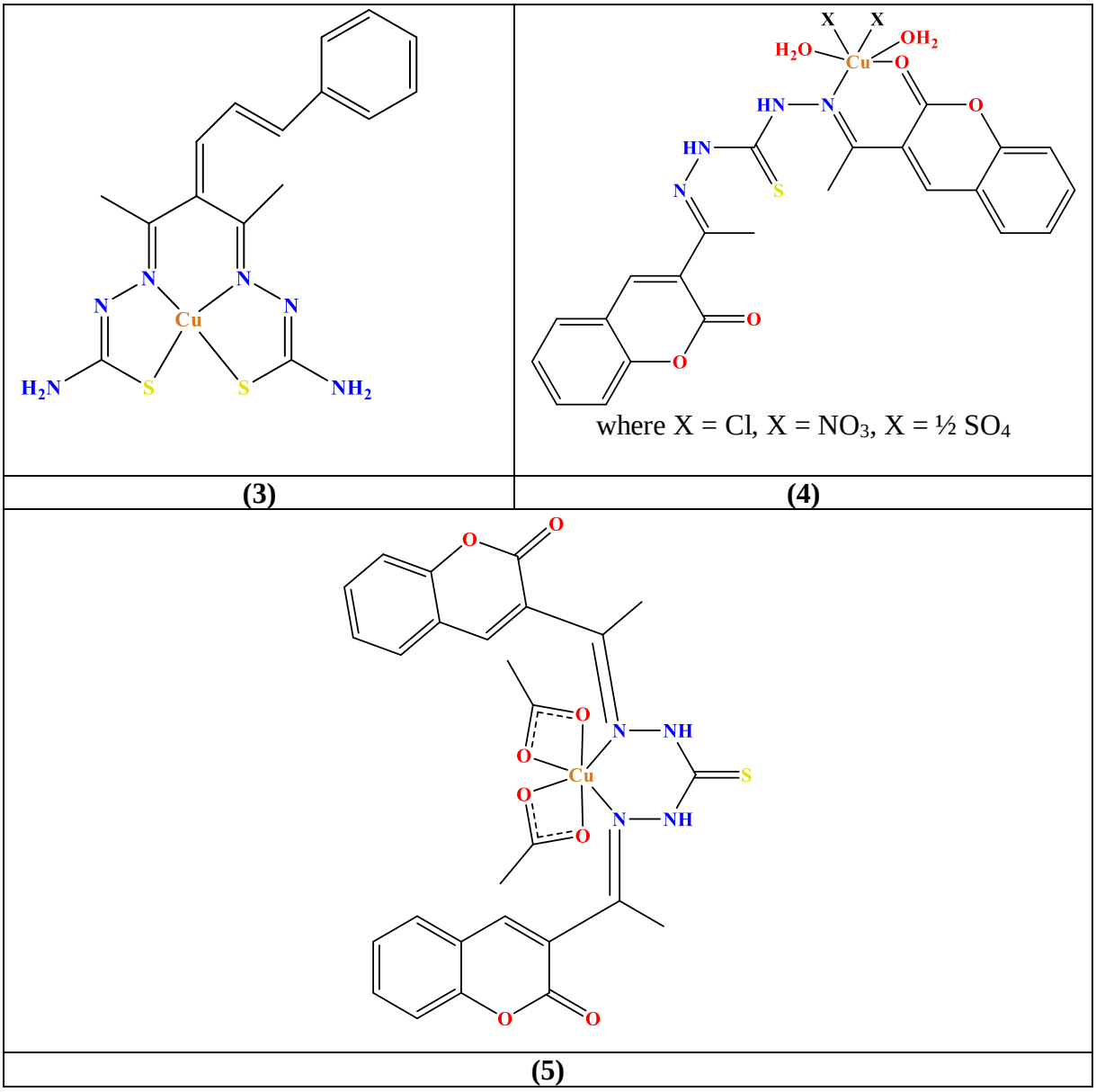


Fig. 2. Copper(II) Schiff base complexes (**1-5**) recently tested in *in vitro* experiments.

1.3.4 Antioxidant activity

Many copper(II) Schiff base complexes which having a high capacity in scavenging free radicals related to the various disorder and diseases are associated with oxidative damage, caused by reactive oxygen species (ROS). Synthetic oxidants are widely used because they are effective and cheaper than natural oxidants. Recently, several Schiff base metal complexes have been explored as an effective treatment of ROS, acting as potent antioxidants. Antioxidant superoxide dismutase (SOD) is an endogenous and defense enzyme-containing Cu-Zn at the active sites of SOD. A large number of copper(II) low

molecular weight complexes have been synthesized and showed substantial antioxidant properties [25-29]. However, these low molecular weight complexes showed lower activity and selectivity than the corresponding natural metalloenzymes. Recently, few copper(II) Schiff base complexes have been synthesized and their antioxidant properties collected [30-35]. The structure of a few copper(II) Schiff base complexes is shown in Fig. 3.

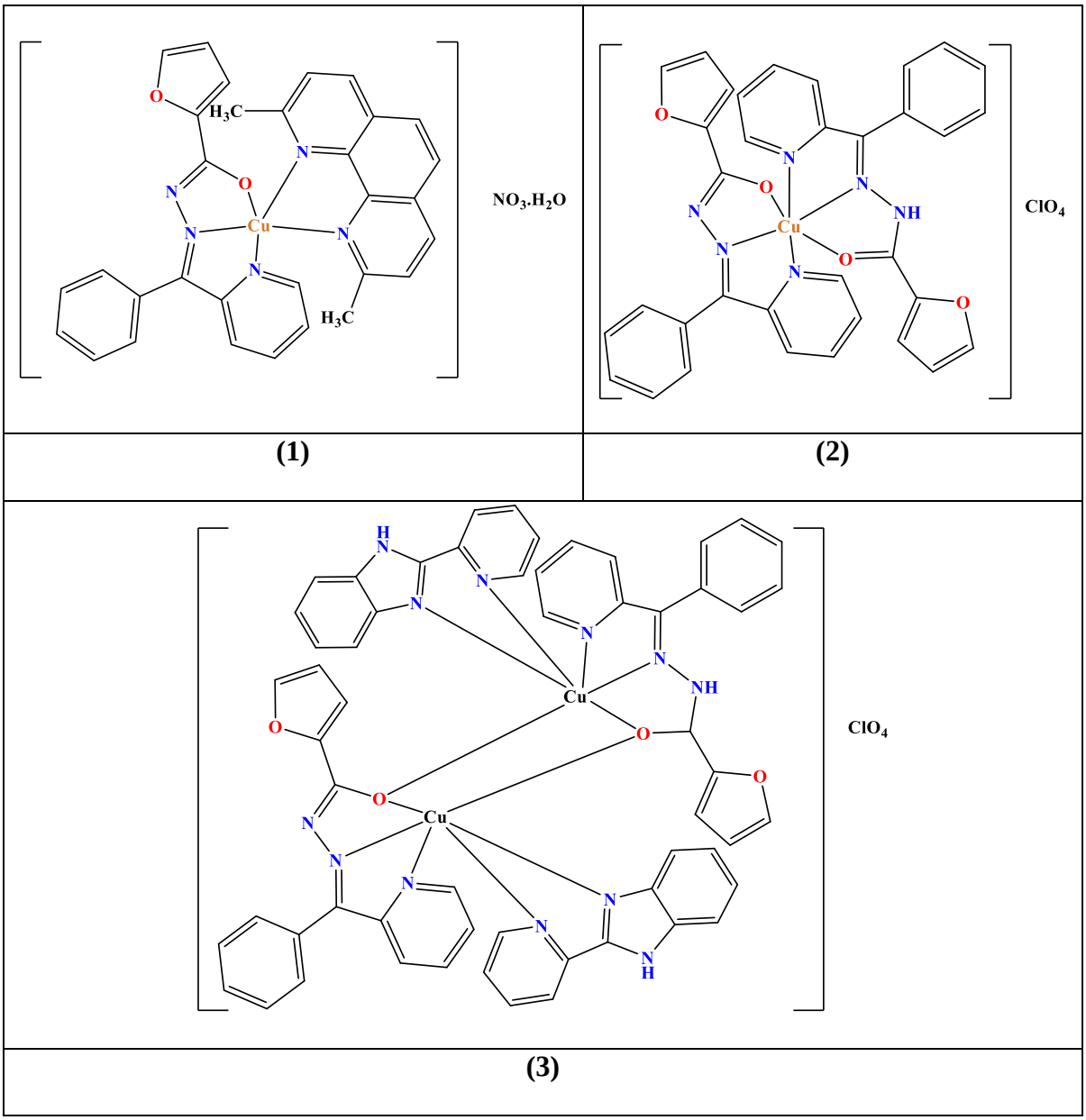


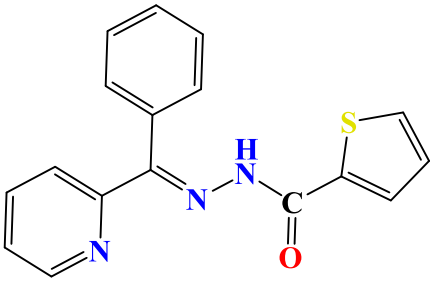
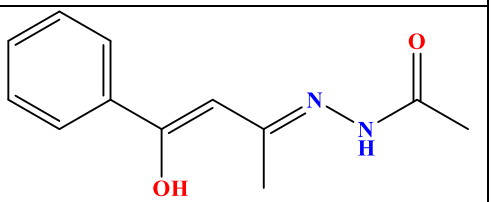
Fig. 3. Schiff base complexes **1-3**.

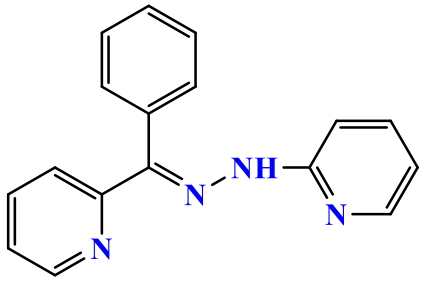
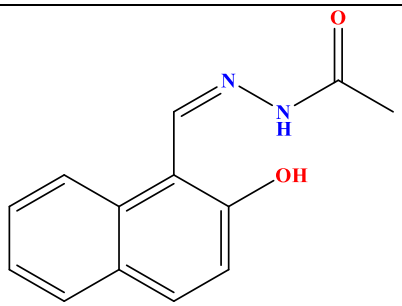
1.4 Copper(II) complexes with Schiff bases

Transition metal complexes show diversity in structures depending on the metal ion used, its coordination number and the binding sites of ligands. Schiff bases with electronegative nitrogen and oxygen, atoms show good coordination with various metal ions to yield air-stable metal complexes [36, 37]. Schiff bases are the organic compounds having azomethine linkage (>C=N) and have been applied in different fields such as efficient degradation of a wide range of unwanted human cells [38], food flavoring [39], production of gold nanoparticles with C_{60} for solar cells [40] and antibacterial, antioxidant and anti-inflammatory materials [41]. Transition metal complexes with Schiff bases have been explored extensively over the last few decades [42-48]. The azomethine, nitrogen and amide oxygen are available donor sites present in the Schiff bases. Further, the number of chelation sites can be increased by the suitable substitution on the aldehyde and primary amine or in the hydrazone framework. Consequently, these organic compounds can coordinate to transition metal ions, forming the complexes with flexible stereochemistry, chemical applications and with enhanced bioactivity. These compounds attribute more than two chelation sites.

In the present thesis work various Schiff bases have been synthesized by taking aldehydes and primary amines. The details of these synthesized Schiff bases areas;

Table 1 Schiff base used during in this work.

S.No.	Name of Schiff base	Structure
1	(E)-N'-(phenyl(pyridin-2-yl)methylene)thiophene-2-carbohydrazide	
2	N'-[(2E,3Z)-4-hydroxy-4-phenylbut-3-en-2-ylidene]acetohydrazide	

3	(E)-2-(phenyl(2-(pyridin-2-yl)hydrazono) methyl)pyridine	
4	(Z)-N'-((2-hydroxynaphthalen-1-yl)methylene) acetohydrazide	

Copper ions remain as centres of the active site of various metalloproteinase and play an essential role in the biological process like electron transfer, oxidation and oxygen transport [49]. In copper proteins, the copper ions are coordinated by donor atoms of amino acid residues. Many model complexes have been designed to mimic the active sites of binuclear copper metalloproteinase [50]. Copper complexes with biologically relevant donors are increasingly studied as model compounds for copper metalloproteins active sites [51-54]. The biological activity of such metalloproteins is due to the presence of a particular coordination environment of the metal active sites [55]. For example, copper-zinc superoxidase dismutase (Cu-Zn SOD) contains an imidazolate bridged copper(II)-zinc(II) heterodinuclear metal center in the active site of metalloproteins [56-62].

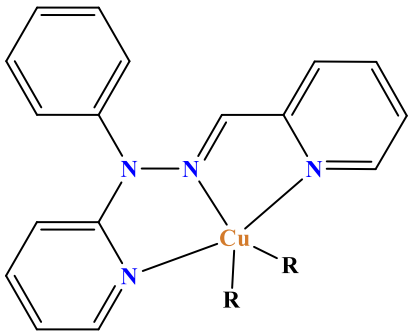
All mammalian life consumes oxygen as the ultimate oxidant supporting cellular respiration, but a considerable portion of molecular oxygen is metabolized through its one-electron reduction product, superoxide anion ($O_2^{\cdot-}$). This free radical anion ($O_2^{\cdot-}$) is a mediator of reperfusion diseases, such as those following acute myocardial stroke, shown to be associated with development and continuation of the inflammatory process, involved in diseases such as arthritis and cause neurological disorders such as Parkinson's diseases. The Cu-Zn SOD catalyzes a very rapid two-step dismutation of $O_2^{\cdot-}$ to O_2 and H_2O_2 through an alternate reduction and oxidation of an active site copper ion [52, 53]. The design and application of synthetic low molecular weight complexes transition metal complexes as SOD mimetics have gained considerable attention during the last 20 years. Several copper(II)

complexes have been synthesized and characterized as models of the enzyme including Schiff base ligands [63, 64] and imidazole bridged complexes [65-69].

1.5 Work done on copper Schiff base complexes: A brief review

The exploration of the structural and magnetic properties of copper(II) complexes of various Schiff base ligands has been an attractive area of research in the field of coordination chemistry for a long time [70-76]. Tridentate Schiff base ligands are flexible due to the reduction of the Schiff base and help to overcome the ligand instability. Several copper(II) complexes of reduced Schiff base ligands fashioned by the equimolar quantitative relation of salicylaldehyde and amino acids were investigated to serve as models for the intermediate species in biological racemization and transamination reactions [77-78]. Vittal et. al. [79] have also synthesized binuclear copper(II) complexes by using such reduced Schiff base ligands [80-81]. They have also designed flexible Schiff base ligands formed by the reaction of salicylaldehyde and L-glutamic or L-histidine and their copper(II) complexes [82, 83]. Recently the same research group has also synthesized copper(II) complexes with H_2Sams and H_2Saes and the reduced Schiff base ligands formed by the reaction of salicylaldehyde and aminothiosulphonic acid or aminoethane sulphonic acid [84]. The molecular structure of these complexes was obtained by using single-crystal X-ray analysis. Further, these complexes are tested for catecholase activity and activity information is compared with those of binucleate copper(II) complexes of comparable ligands obtained with treat analogs of the corresponding sulphonic acids. Research has also intended to focus on copper(II) complexes with salicyledine glycine Schiff base [85, 86], with imidazole, pyrazole and related derivatives. The pyridine ternary adduct [87] was also isolated using this Schiff base with copper(II) and the redox behavior of these adducts was also measured [88].

A series of copper(II) complexes containing tridentate Schiff base ligand L (L= 2-{(2-phenyl-2-(pyridyl-2-1)hydrazono}methyl pyridine has been synthesized and characterized [89, 90] (Fig. 4.).



R = Cl / ImH / 2,2'-bipy / N_3 / SCN / OAC / CN/H_2O / ClO_4

Fig. 4. Structures of copper(II) complexes with ligand L.

These complexes were checked for their anticancer activities. Such complexes showed varying degrees of antiproliferative properties which were consistent with those of similar copper(II) complexes already reported [91].

Copper(II) complexes with NNO donor tridentate ligands have been synthesized and characterized employing several physicochemical techniques [92]. These complexes can catalytically cleave DNA. The uncoordinated ligand 4-methyl-2-N-(2-pyridylmethyl) aminophenol (H_2L) was reported to cleave DNA oxidatively and catalytically without any added reluctant and to exhibit high to moderate antitumor properties [93]. Upon coordination with copper(II) undergoes oxidative dehydrogenation and associative deprotonation to give anion ligand (L^{2-}) and forms square planar complexes (Fig. 5). This square planar complex showed a high anticancer activity similar to those of cisplatin in cisplatin-sensitive sublines (IC_{50} = 3.4µM) and lower in cisplatin-resistant cells (IC_{50} = 8.3µM) [94].

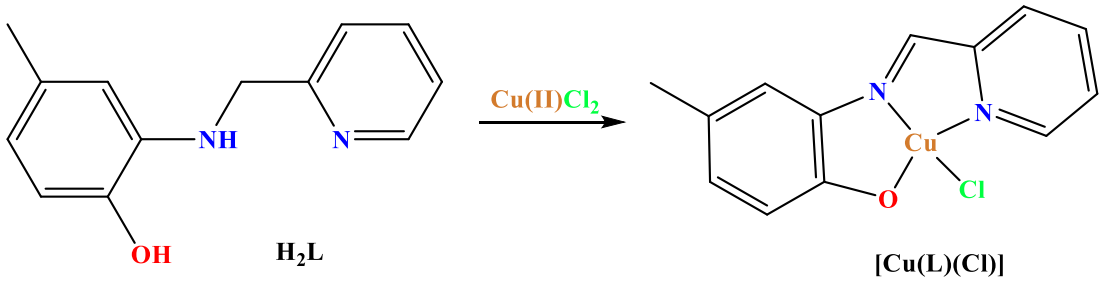


Fig. 5. H_2L Schiff base ligand and it's complex [Cu(L)(Cl)].

The copper(II) complex with H_2L (= N-2-pyridinylmethylidene-2-hydroxy-5-chlorophenylamine) when reacted with copper acetate, yielded a square pyramidal complex with apical water (Fig. 6). This showed the efficient oxidative cleavage of supercoiled DNA

due to reactive oxygen species production (ROS). This complex induced an S-phase cell cycle arrest and triggered the intrinsic mitochondrial apoptotic pathway [95].

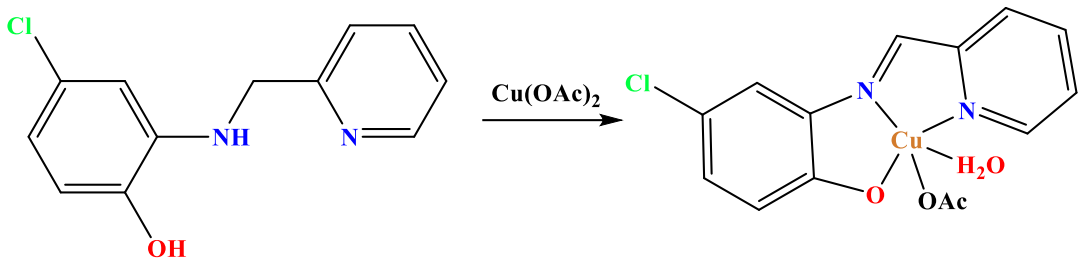


Fig. 6. H_2L Schiff base and is complex.

Tridentate pyrazole containing Schiff bases (HL) [97, 97] were used to prepare mononuclear copper(II) complexes in an aqueous solution (Fig. 7) [98]. In solid-state binuclear complexes $[Cu_2(\mu\text{-}Cl)_2(L)_2]$ with best described monomeric unit [Cu(L)Cl] was isolated. The *in-vitro* evaluation of [Cu(L)Cl] types of mononuclear complexes shows moderate anticancer properties against a panel of human cancer cell lines. It is observed that the introduction of halogens in the phenolic ring of ligands enhanced the cytotoxicity of the complexes.

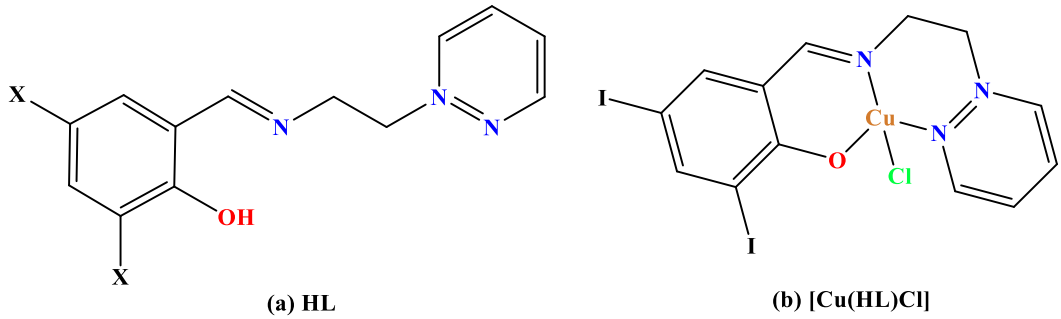


Fig. 7. Structures of (a) HL and (b) complex [Cu(L)Cl].

Such complexes showed similar behavior which is already observed in related tridentate NNO ligands containing phenolic and pyridyl rings and were used to prepare Ga(III) and Cu(II) complexes acting as inhibitors [99-101]. Complexes formed by HL have shown similar cytotoxicity against cisplatin-sensitive A2780 and cisplatin-resistant A2780R cell lines [96].

The coordination chemistry of hydrazones is connected with their wide application as inorganic drugs, photo thermochromic compounds and precursors as organic synthesis [102-105]. The presence of the carbonyl oxygen atom promotes the formation of chelate ring

[106]. Acyl hydrazones and their complexes possess increased biological and pharmaceutical activities [107-112]. Copper(II) salicylaldehyde benzoyl hydrazone and 2-pyridine carboxyaldehyde-2-pyridyl hydrazone binary complexes have been reported [113, 114] and also showed good antiproliferative properties [115]. The copper(II) hydrazone mononuclear complexes (Fig. 8) of HL (HL= N'- phenyl(pyridine-2-yl) methylidene)benzo hydrazide) yielded a 1:2 metal-ligand stoichiometry [116]. This complex interacted with CT-DNA and caused almost complete conversation from supercoiled to the nicked circular form. This complex showed moderate antiproliferative activity.

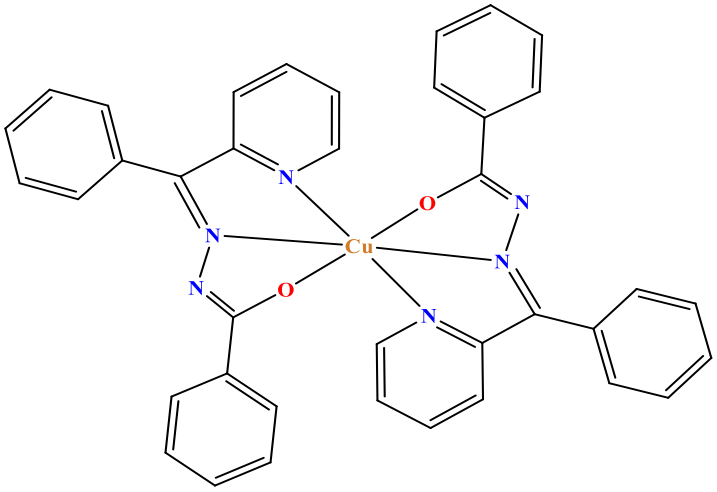
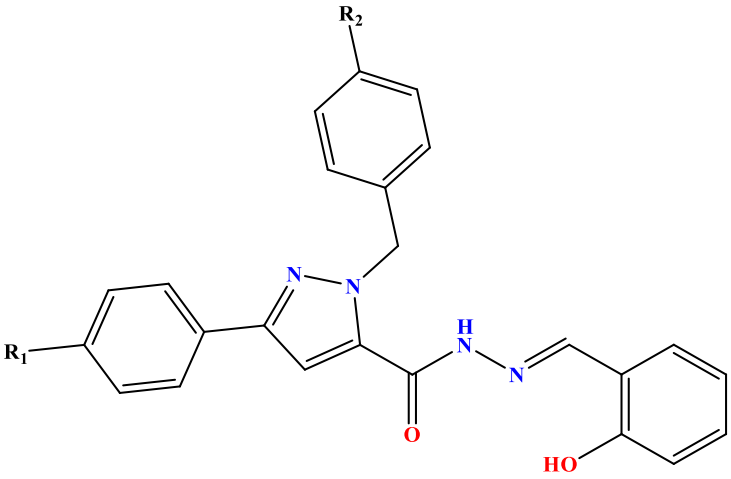


Fig. 8. Structure of binary $[Cu(L)_2]$ complex.

A new binary complex [Cu(Phimp)Cl] (Phimp = phenyl-(pyridine-2-yl) hydrazono]methyl]phenol] was synthesized [117]. It also showed DNA cleavage and antiproliferative properties against MCF cells [118]. Several Schiff hydrazones (H_2L) have been designed and synthesized (Fig. 9). These hydrazones reacted with copper salt and yielded binary $[Cu(L)_2]$ complex. These complexes were able of inhibiting the growth of A549 lung carcinoma cells [119, 120].



R_1 = H; R_2 = Cl; X = N
R_1 = Cl; R_2 = Cl; X = N
R_1 = OCH_3; R_2 = Cl; X = N
R_1 = H; R_2 = H; X = C
R_1 = H; R_2 = tBu; X = C
R_1 = Cl; R_2 = H; X = C
R_1 = Cl; R_2 = tBu; X = C
R_1 = OCH_3; R_2 = tBu; X = C
R_1 = OCH_3; R_2 = tBu; X = C

Fig. 9. Structure of salicylaldehyde pyrazole hydrazone (H_2L) ligand.

Among these one copper(II)-HL (1:2) complex with R_2 = tBu showed an advantage in selectivity and efficiency and prompted apoptosis in H322 cells [121].

Copper(II) complexes with Schiff base (HL) (HL = 2-oxo-quinoline-3-carbaldehyde) were synthesized and characterized by Liu. et al. [122] (Fig. 10). These complexes were found to interact with CT-DNA through interaction. These complexes showed higher effectiveness compared to the corresponding ligands due to the extended planar structure. Complexes were found to be the most promising candidate against HL-60 cells [122].

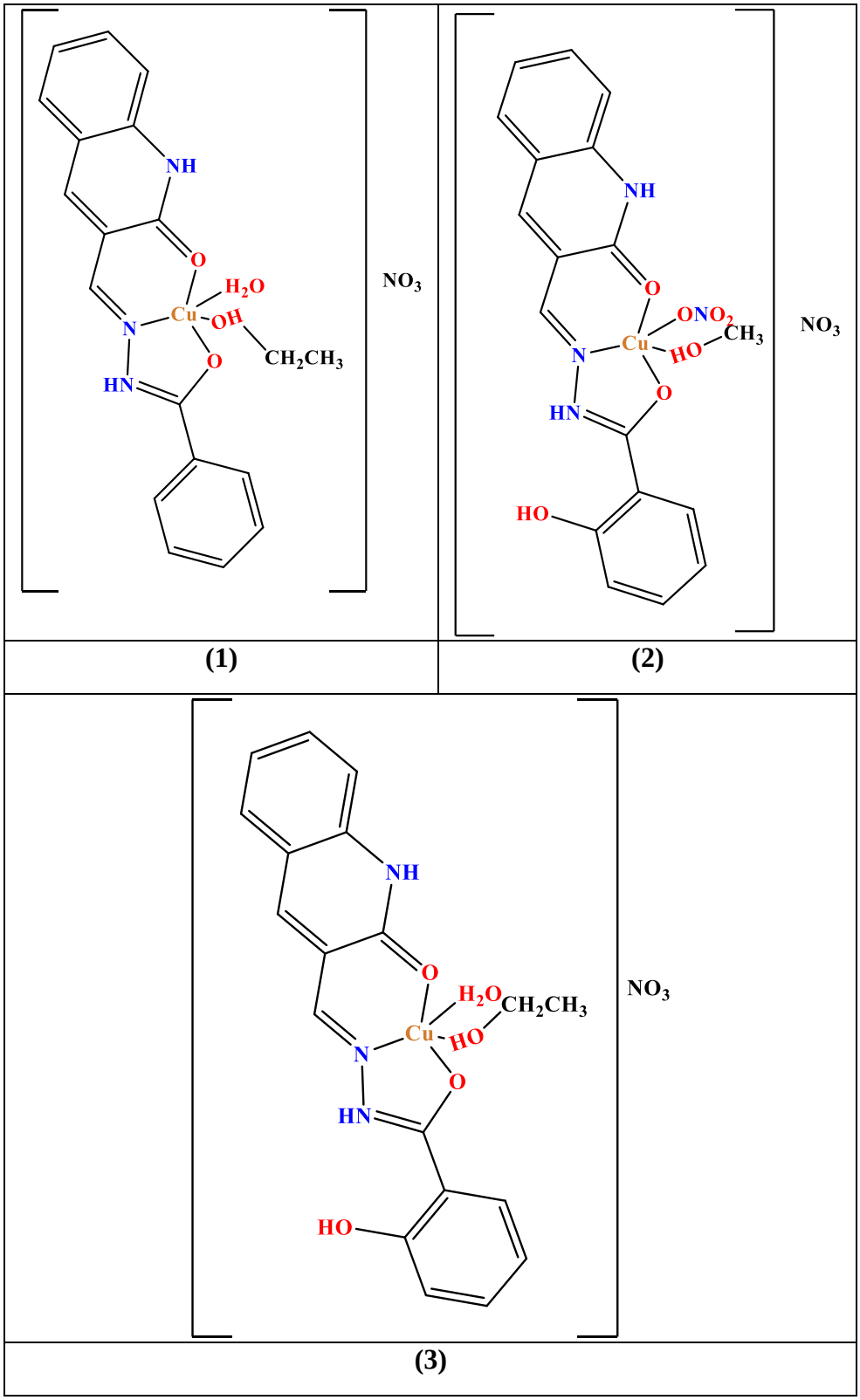
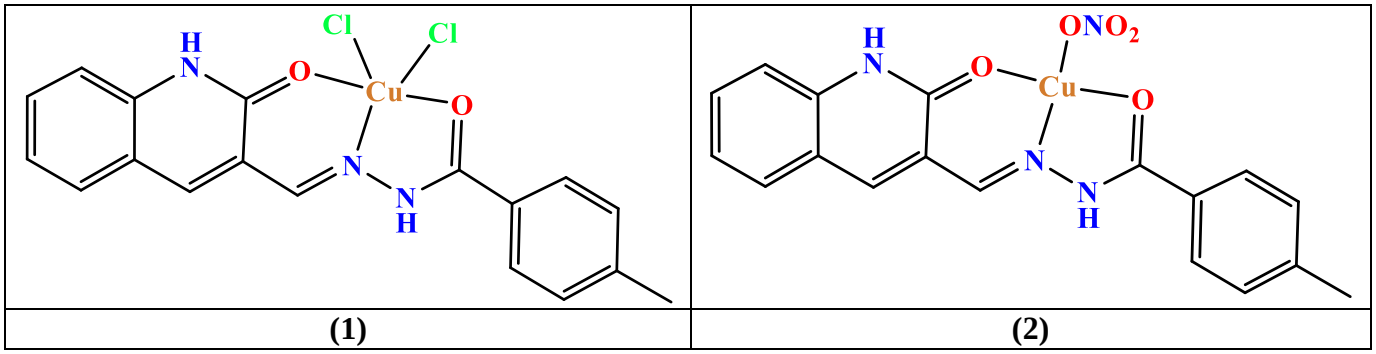


Fig. 10. Structures of copper(II)-HL complexes.

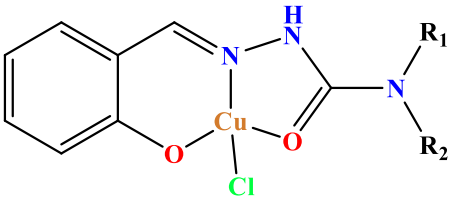
Raja et al. [123] reported two copper(II) complexes with Schiff base (HL) (HL = 4-methyl-N-((2-oxo-1,2-dihydroquinolin-3-yl)-methylene)benzohydrazide) (Fig. 11). The planar nitrate complex showed an important role in determining both superior DNA binding and enhanced cytotoxic potency in Hella cells. These complexes also showed significant radical scavenging activity against free radicals [123].



(1) **(2)**

Fig. 11. Structures of copper(II) complexes with HL.

Copper(II) complexes with semi-carbazone ligands (Fig. 12) have shown significant biological properties [124-126]. The copper(II) complexes exhibited higher *in vitro* activities compared to those shown by uncomplexed ligands. These complexes induced aptosis cell death in most 4 cells.

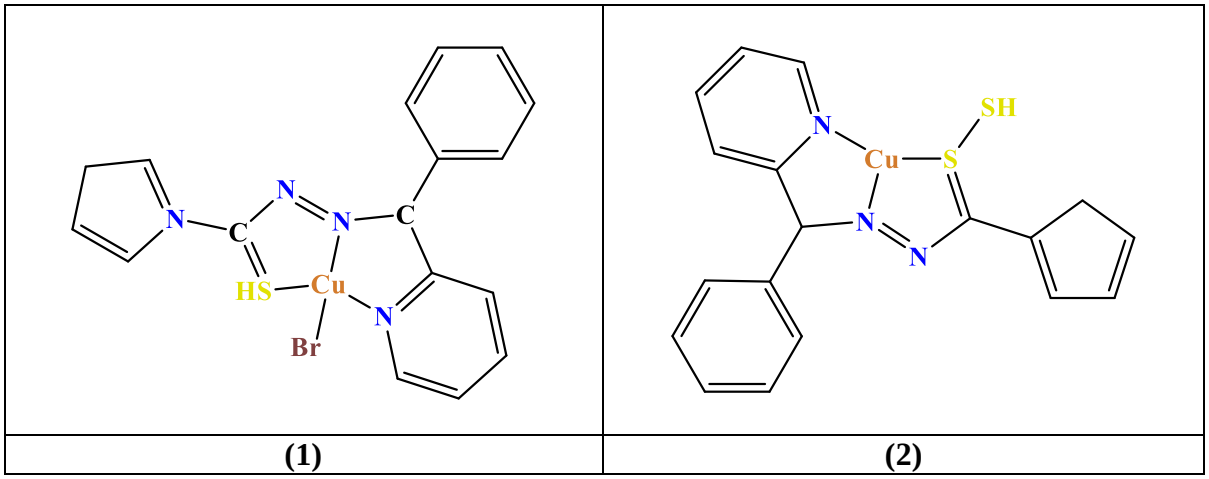


R_1, R_2 = Bn
R_1, R_2 = Ph
R_1, R_2 = n-Bu
R_1, R_2 = n-xed
R_1 = n

Fig. 12. Structures of copper(II) complexes.

Thiosemicarbazones are tridentate sulfur donor ligands for transition metal ions in the last few decades and showed a variety of biological activity [127-131]. Using these ligands Kurup et al. [132-136] synthesized and characterized several copper(II) complexes with

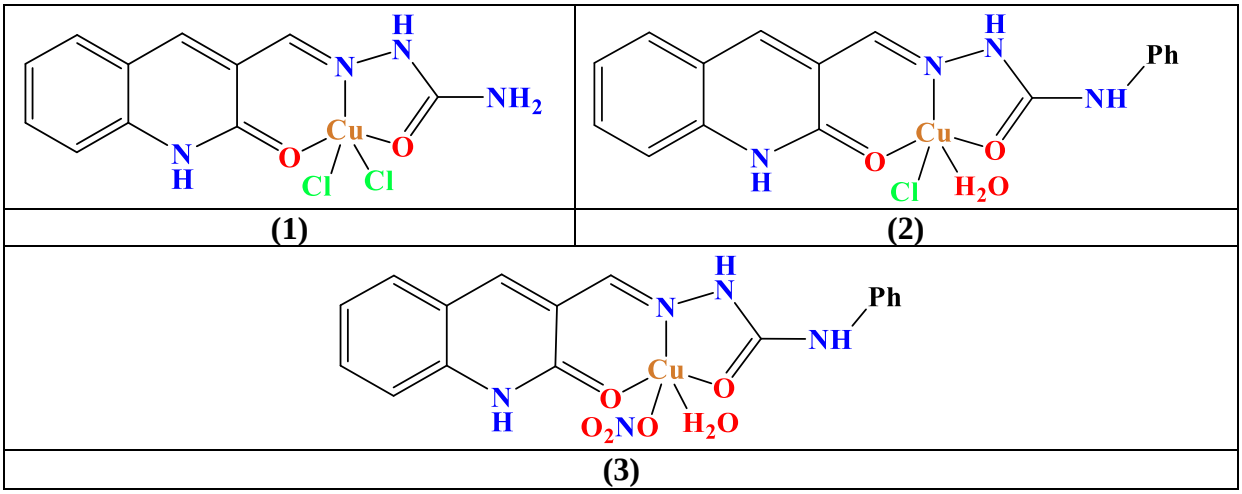
thiosemicarbazones and also measured some biological activities. Some representative of these complexes may have the structures are shown in Fig. 13.



(1) (2)

Fig. 13. Structures of some copper(II)-HL complexes (HL = 2-benzoylpyridine N(H), N(4)-butane-1,4-diyl)thiosemicarbazone.

Raja et al. [137], synthesized and characterized three new copper(II) complexes with semi-carbazones (Fig. 14). The biological activities of these complexes have also been explored. N(4)-Phenyl substitution in the semicarbazone moiety and change of counter anions (Cl^- to NO_3^-) in copper(II) precursors affected the nature and molecular structure of the complexes along with a change in pharmacological properties. The square pyramidal complex (c) was found to be the strongest CT-DNA intercalative binder and most effective in BSA binding due to hydrophobic and electrostatic interaction.



(1) (2)

(3)

Fig. 14. Structures of semi carbazone complexes Cu: L (L = 2-oxo-1,2-dihydroquinoline-3-carbaldehyde semi carbazone).

Zhang et al. [138] synthesized taurine Schiff base copper(II) complexes with 1,10-phen as co-ligand [Cu(HL)(1,10-phen)] Fig.15(1). These complexes inhibited the cellular proteasomal chymotrypsin-like activity and induced ptosis in the dose and time-dependent manners in human breast cancer and leukemia cells. Similarly, copper(II) 4glutamine-o-vanillin shown proteosome-inhibitory and apoptosis-inducing activities [139] in Jurkat T and MDA-MB-231 cells but not in normal cells (Fig. 15(2)).

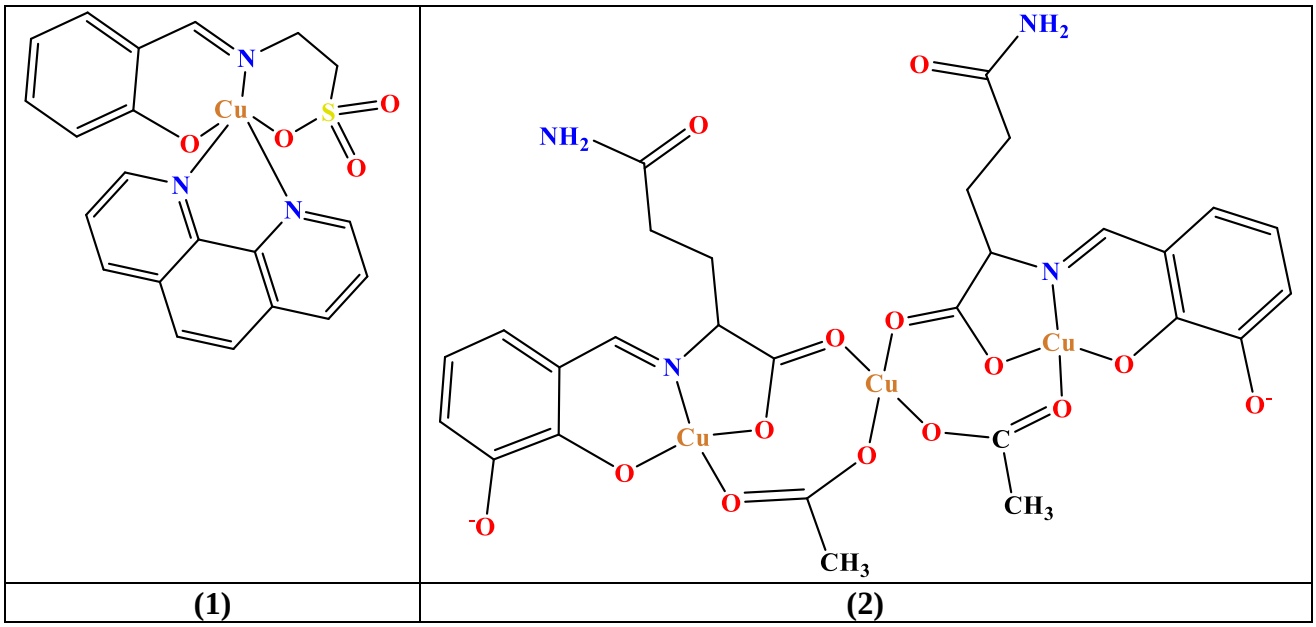


Fig. 15. Structures of copper-Schiff base (NOO) systems.

Copper(II) complexes with Schiff base (NOS) donor atoms polypyridyl (1:1:1) synthesized and characterized (Fig. 16). These copper(II) complexes have the ability to photocleave the duplex DNA in red light and are considered as potent agents in photodynamic therapy (PDT) of cancer [140-143]. These ternary complexes with salicylidene-2-aminothiophenol and polypyridyl as co-ligand exhibited anaerobic DNA cleavage activity in red light, while DNA photo-cleavage proceeded by via a hydroxyl radical pathway [144]. Molecular Docking calculations have also been performed to explore DNA binding.

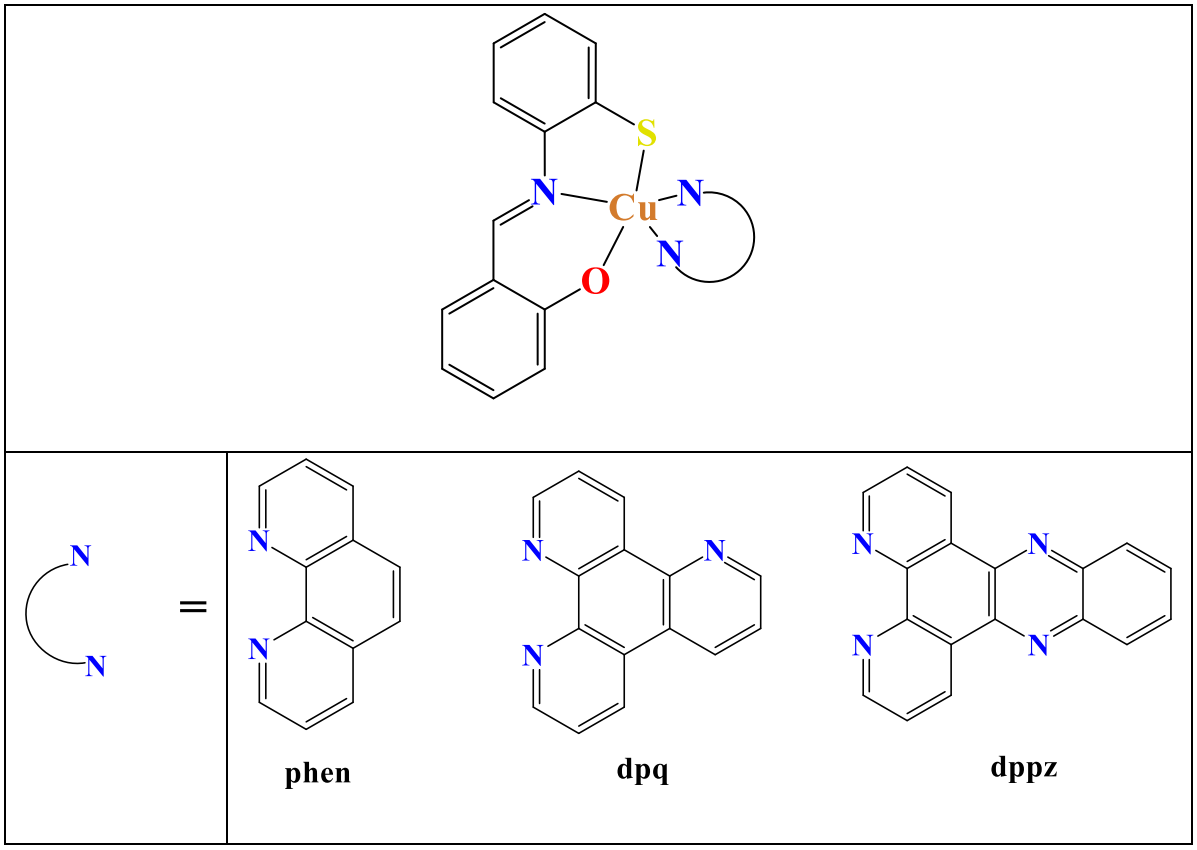


Fig. 16. Structures of ternary complexes with ONS donor Schiff base and polypyridine as co-ligands.

Few copper(II) complexes were synthesized by the Schiff base which was obtained by condensation of 2-[N-α-picolyl-amino]benzophenone with different amino acids (Fig. 17) [145]. From the results of cytotoxicity assay indicated that the substituents of the aromatic rings strongly influenced the biological activity. It is found that all complexes were more cytotoxic than 5-fluorouracil drug (reference) and circumvented drug-resistance mechanism [145].

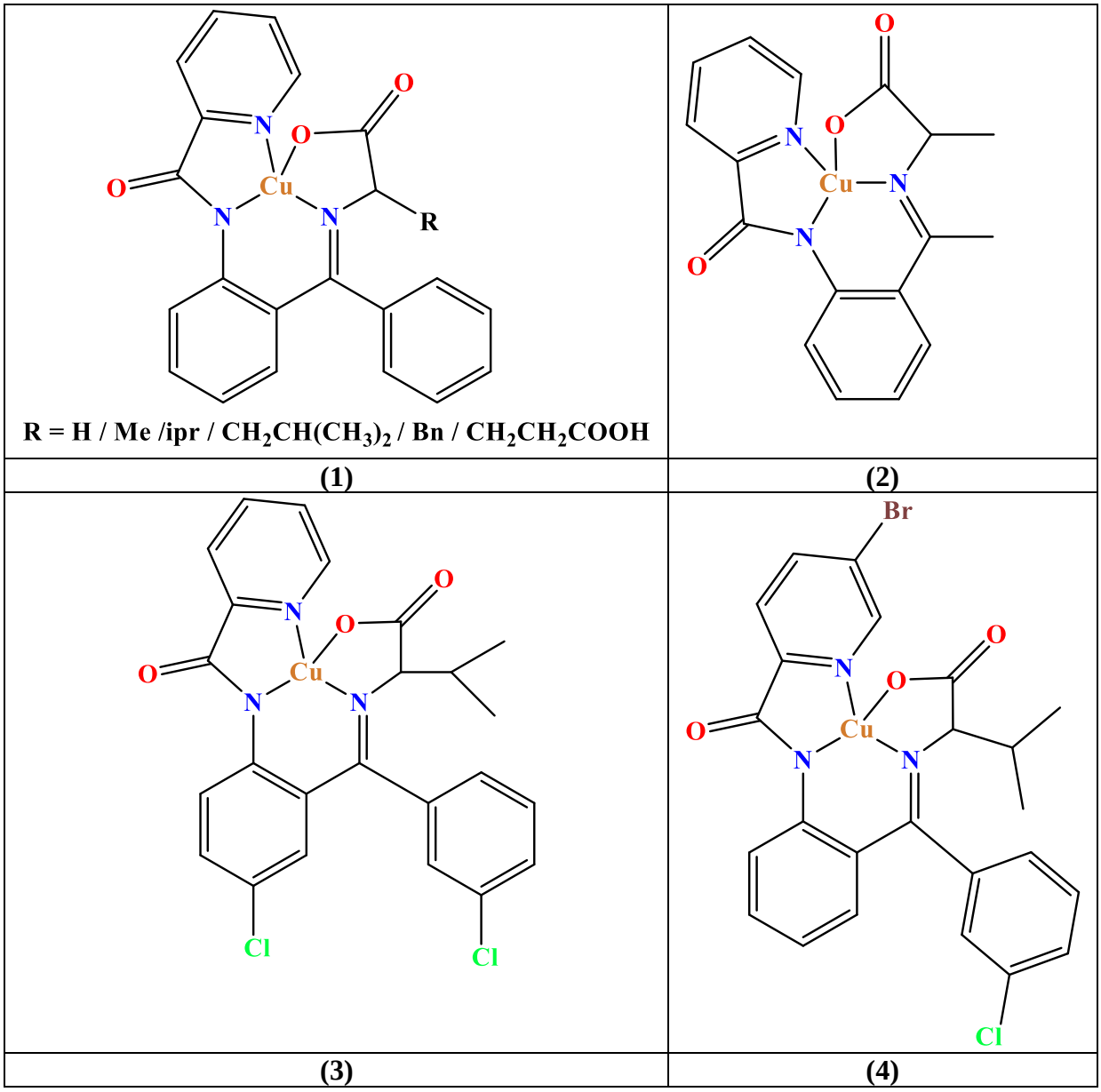


Fig. 17. Structures of complexes (**1-4**).

1.6 Aims and objective of work

The aim of this thesis work has been the synthesis and characterization of new Schiff base ligand and copper(II) complexes. It is immense to synthesize and characterize new small molecular weight copper(II) complexes that mimic the enzyme activity and that assist to explain the structural and electronic features. These features can be varied by changing the ligand and the presence of substituents. The above objective has been obtained with the synthesis, characterization and use of new mono and bi-nuclear copper(II) complexes with active redox centers. The modulation of ligand structure has a great influence on the

physicochemical properties of the complexes. Emphasis is given by collecting quantum chemical parameters and SOD activity data of all synthesized complexes. Nowadays quantum chemical method has become a common and useful tool for the prediction of the structure and properties of complexes. During the tenure of this work, various copper(II) complexes have been synthesized. These complexes were characterized using micro-analysis, molecular mass analysis, spectral (UV-Vis, IR and epr) and electrochemical techniques. Finally, molecular structures of these complexes were obtained from single-crystal X-ray analysis. Quantum chemical calculations (DFT) were also performed to verify the experimental bond parameters. Biological activity (SOD) and anticancer of these complexes have also been explored.

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