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A Glance on Bio-Significant Metallo-Organic Complexes of Copper(II).

Tummalapalli Kiran, Vuppalapati Giri Prasanth and Madhvesh Pathak*

Department of Chemistry, School of Advanced Sciences, VIT University, Vellore 632014, Tamilnadu, India

ABSTRACT

Metallo-organic complexes of copper(II) have established their recognition in bioinorganic chemistry due to the several in vitro & in vivo activities and reflected their worth in medicinal field during the studies and in treatment of considerable number of serious ailments. In many bio-systems, plenty information is available to exhibit their biochemical properties and route of function in numerous biological schemes, blended with novel prospects furnished by the blooming technologies of clinical field, is paving an exciting consequence for the expansion of an unusual group of vastly active medicine with curtailed side effects that could enhance considerably the present medical exploration. We are making herewith a sincere endeavour to document all the literature concerned in an appropriate chronology.

Keywords: Copper(II) complexes, Metallo-organic complex, DNA binding, DNA cleavage, Antimicrobial, Anticancer

Corresponding author

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INTRODUCTION

Metal based complexes have recorded their existence in several biological systems as well as in medicinal field from the evolution of life. Some of those as Haemoglobin (transportation of oxygen in red blood cells), chlorophyll (photosynthesis in green plants) and a few natural metalloenzymes (Vitamin B_{12}) have already established their significance prominently in bio chemistry. These type of complexes are composed by the association of organic moiety and metal ions. The first metal conjugates were synthesized by Sophus Jorgensen in Denmark in the middle of 1870. In 1893, Alfred Werner discovered a series of cobalt complexes as potential therapeutic agents, and bagged laurels in the form of Noble Prize in 1913. Further, a lot of inventions occurred in the field of coordination chemistry and some of those metal complexes were used as a therapeutic agents significantly for diseases, e.g. Syphilis was cured by using Salvarsan [1, 2]. The bio-activity of the metal complexes obviously depends on the nature of functional groups of the ligand, metal atoms as well as on their oxidation states. Researchers and chemists received much attention and interest in bioinorganic chemistry of metal complexes after the discovery of cisplatin on various types of malignancy. Though it is remarkably efficient for treating a variety of malignancy but these platinum complexes exhibited considerable drawbacks in cancer therapy as neurotoxicity, nephrotoxicity and emetogenesis, finally are not orally bioavailable [3]. These limitations endorsed researchers to improve alternative approaches based on various metals along with substantial biological activity on pointed targets. Among the first row of transition metals as divalent ions, copper(II) is reflecting notable properties due to Ligand Field Stabilization Energy (LFSE) favouring various plausible geometries due to Jahn-Teller distortions of d^9electronic configuration [4]. These features provoked concerned chemists to develop copper(II) complexes as alternatives of platinum based drugs. In this chapter, we are making our sincere efforts by providing a systematic and detailed elevation history of copper(II) derivatives along with their biological prominence by throwing light on shortcomings of platinum based drugs wherever it requires.

A brief chemical history of copper and its Metallo-organic derivatives

A red-orange pendant had been identified as copper in Northern Iraq 3700 years ago before Mahabharata period (5000 BC) and it is believed that it was the single metal known by humans for approximately 5000 years after its discovery. Cu as a symbol of copper appeared from the name of its origin – Island of Cyprus, where it was getting mined at the time of Roman Empire.

According to the atomic number (29) and unusual electronic configuration $3d^{10}4s^1$of copper, it is occupying place in the first transition series of periodic table, where copper(I) gives rise 3d shell completed while copper(II) ion exhibits $3d^9$ pattern, resulting in the production of numerous valuable products.

For the survival and thrival of living organisms, copper as a third most significant element after iron and zinc, has been established as an extremely necessary nutrient in trace. In entire living organism, key role played by copper (1-3 mg intake per day) has been well documented in detoxification of oxygen radicals, electron transfer and oxidase & oxygenase activities. However, excess accumulation of copper could be deleterious and lethal to homo-sapiens. Cupric ions are popularly known as venom for microorganisms and algae [5]. Of course, at enhanced concentration it is toxic to humans too [6]. For promoting DNA oxidation, copper(II) ions have been found to exhibit better binding with DNA as compared to any other relevant existing bivalent metal ion [7]. It has been closely observed that stereo structures of DNA, proteins and bio membranes could be influenced by attaching copper ions to the particular sites of these entities [8] where binding mode is absolutely affected by the size and electron affinity of metal ion as well as on the structure of the final product.

Preliminary anticancer agents-derivatives of platinum

Peyrone synthesized *Cis*-platin {*cis*-[Pt $(NH_3)_2Cl_2$]} in 1844 [9] but its biological activities were discovered much later by Rosenberg *et al*. in 1956 [10]. It was observed a partial inhibition in the growth of *Escherichia coli* followed by an inhibition of binary cell division of bacteria cell with negligible effect on cell growth that directed towards a keen and extensive interest in the concerned field of research. It was confirmed that small amount of platinum from the electrodes had reacted with NH_4Cl to produce various platinum amine halide complexes. Indeed, the interesting fact that, the complexes *cis*-[Pt $(NH_3)_2Cl_2$] and its corresponding tetrachloro complex cis-[Pt $(NH_3)_2Cl_4$] were capable to induce filamentous growth crystal

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structure in the absence of an electric field [11]. Rosenberg and co-workers [12, 13] screened the cisplatin on leukaemia L1210 and sarcoma 180 bearing mice for the evaluation of its biological activity later in 1971, which pushed this complex for study in phase I clinical trials. As a result of these, *cis*-platin was approved for the treatment of testicular and ovarian cancer [14]. Nowadays, *cis*-platin is one of the most widely used antitumor drug for testicular, ovarian, bladder, cervical, head, neck, small-cell and non-small cell lung cancers [12, 14]. Despite good clinical success of *cis*-platin, it lacks selectivity of tumour tissue leading to some severe side effects like renal impairment, neurotoxicity and cytotoxicity (loss of balance/hearing). Moreover, long term or high-dose therapy of *cis*-platin may cause severe anaemia. In reviewing the status of platinum complexes as anti-cancer drugs, various aspects such as discovery cis-platin, second and third generation platinum analogues, comparison of complexes chemotherapies, mechanism of action, therapeutic status and future perspective of platinum anticancer drugs were evaluated.

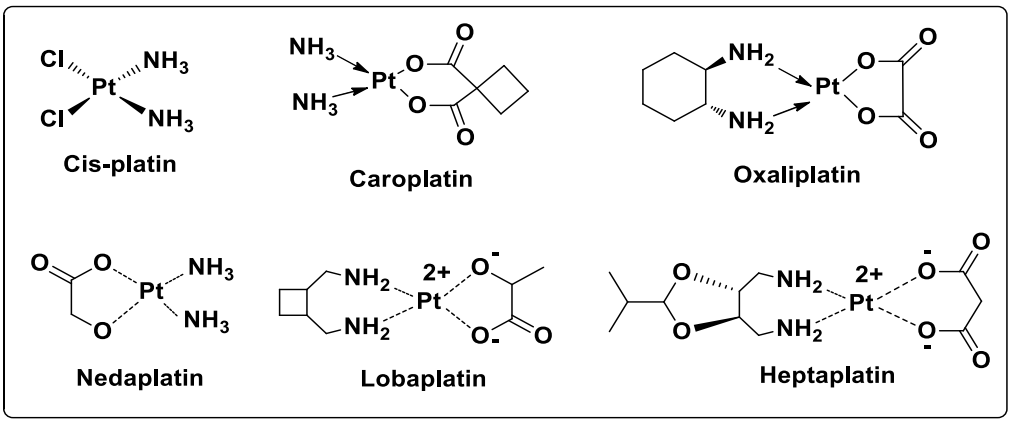

Figure 1: Some of the anticancer derivatives of platinum analogues

On the other hand, this sort of medication has strong potential to eradicate other diseases through gene therapy because of its same drawback as several side effects e.g. emetogenesis, neurotoxicity and nephrotoxicity [15]. Nevertheless, these drawbacks have stimulated to switch in search of other active bioinorganic molecules for antitumor activity with pharmacological properties. Recently, many debates have emphasized that molecularly target metal based drugs which have the ability to bind and inhibit a single molecular target with high specificity and selectivity with cytotoxic as well as broad-spectrum agents. The key fact in the metal based drugs is that the metal can coordinate with the ligands in the three dimensional configuration, which allows and helps the molecule to recognize and interact with specific targeted sites. Consequently, the metal complexes easily undergo redox reactions and ligand exchange that helps them to participate in biological redox reactions. Now a days, there are remarkable investigations in this area much focused on biologically active metal complexes by vital ions, such as copper(II) complexes [16]. These metal complexes are essential as they escapes from its normal metabolic pathway which were found to be toxic to the organisms and hence act as effective cytotoxic agents [17]. In view of short comings of platinum derivatives, bioactive complexes of copper(II) emerged as an auxiliary remedy for cancer therapy.

Bio-active derivatives of copper(II)

In view of above-described need of relevant remedy for cytotoxicity as an improved substitute of cis-platin, metallo-organic complexes of copper(II) have exhibited its potential worth as copper having some special features in biological system of living organisms with less toxic effect to the normal cells instead of cancer cells [18]. Tremendous research have been carried out on copper based metal complexes with different type of organic ligands till date. The anticancer activity of metal complexes mainly depending upon the nature of ligand system (bidentate, tridentate), functional groups involved in ligand moiety and planarity of ligands. Planarity of the metal complex system plays an important role in their activity because planar molecules exhibit better binding interactions with DNA and protein molecules. A few important relevant copper(II) derivatives are going to be described in the forthcoming paragraphs.

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Cassiopeias

Several copper(II) based antitumor complexes have been synthesized and explored for their anticancer activity *in vitro* and *in vivo* for past few decades [19]. Among those, Cassiopeias are showing significant activity and these were reported as alternatives for cancer treatment. Cassiopeias are coordination complexes which bound with organic ligands like β-diketones, ancillary ligands and amino acids with general molecular formula: $[Cu(N\text{-}N)(O\text{-}N)]NO_3$ and $[Cu(N\text{-}N)(O\text{-}O)]NO_3$. These complexes have chelating nature which could be used for the formation of cis-configuration around the central metal ion while forming a stable metal complex where they experienced different levels of hydrophobicity [20]. Cassiopeias have been tested for cytotoxic and cytostatic effect of various types of tumour cell lines *in vivo* and implanted tumours in mice [21-25]. The anti-tumour activity of Cassiopeias mechanism takes place through reactive oxygen species (ROS) mechanism and these are the good representatives as antineoplastic drugs [26].

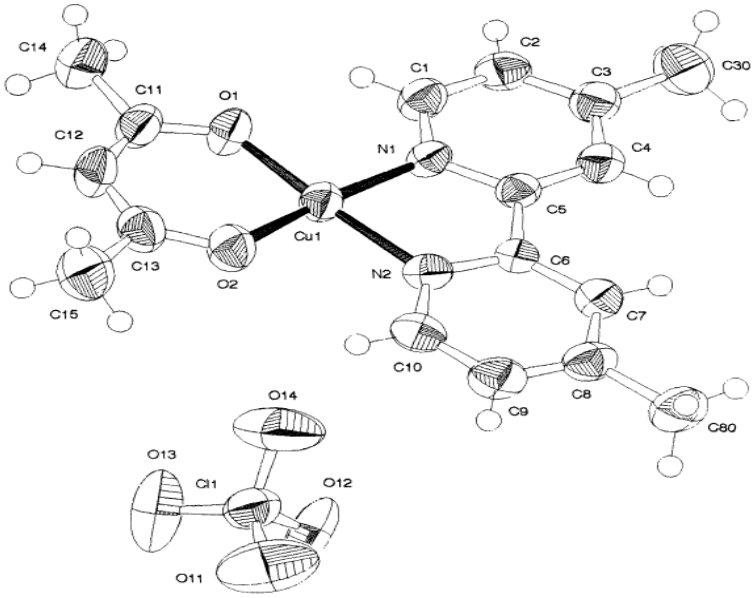

Figure 2: Structure of Cassiopeia III-I (4, 4-dimethyl, 2,2-bipyridine) (acetylacetonate) copper (II) perchlorate

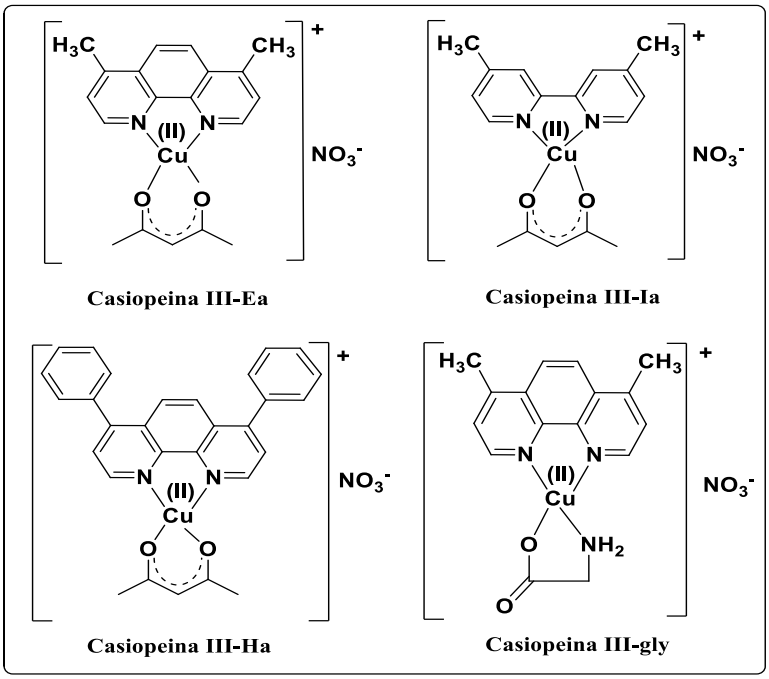

Figure 3: Cassiopeias derivatives of copper(II)

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Curcumin complexes

Curcumin is a polyphenolic compound which is obtained from rhizome of Curcuma longa L and it is called with general name turmeric. It acts as an antimetastatic, antiangiogenic and antiproliferative agent which limits tumour growth and inhibits carcinogenesis [27]. Due to its broad spectrum of biological activity and chelation properties, several curcumin based metal complexes have been synthesized and tested for varied biological studies. Among a series of cobalt(II), vanadyl(V=O), nickel(II) and copper(II) curcumin complexes, cupric curcumin derivatives have displayed significant antitumor activity towards cancer cell lines [28].

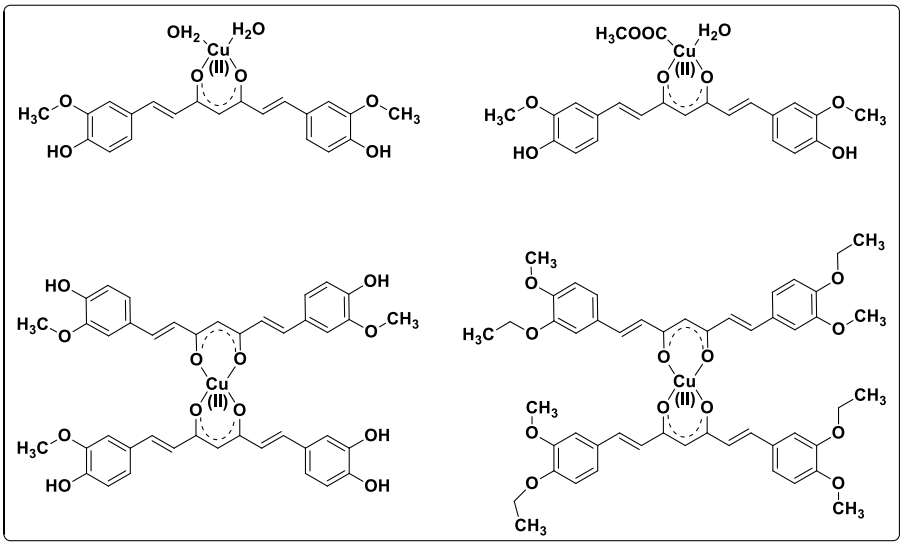

Figure 4: Copper(II)-curcumin derivatives

Thiosemicarbazone complexes

Thiosemicarbazones (TSCs) are a class of organic molecules with wide range of biological applications e.g. anticancer activities of these derivatives were reported firstly in the year of 1960 [29, 30]. These ligands are existing in tautomeric forms which could be helpful in the formation of utility complexes. Thiosemicarbazones have shown promising activity towards inhibitory action on the DNA enzyme ribonucleotide diphosphate reductase and hormone-responsive cancers [31]. Because of its versatile bio-applications, a large number of copper complexes have been synthesized and studied for antitumor activity against different type of cell lines. A few of the TSCs such as Triapine and Marboran are in the clinical trials [32].

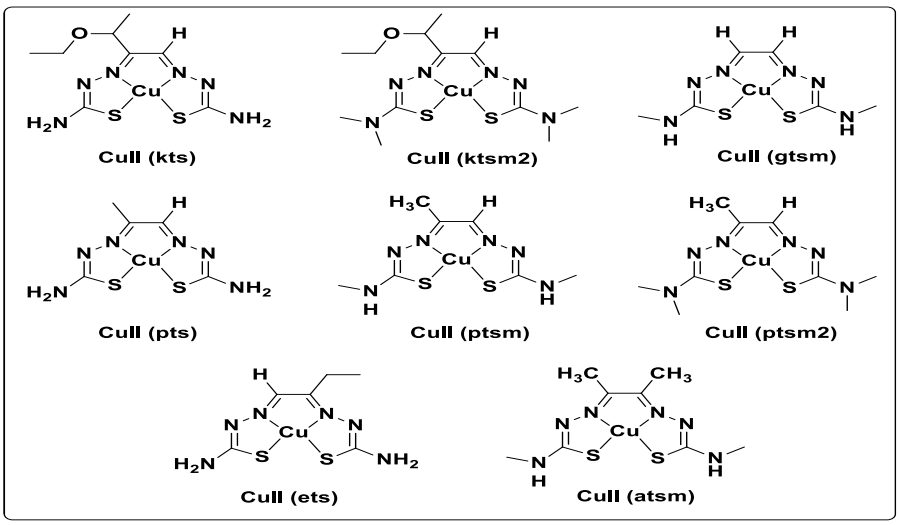

Figure 5: Copper(II) complexes of bis (thiosemicarbazones)

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In addition to the above elaborated only three types of anticancer agents of copper(II) derivatives, there are plenty reports available on it, therefore, we have made our sincere efforts to tabulate herewith the progress in the field of bioinorganic chemistry in 21st century contributed by the complexes of copper(II) in a chronology as below:

Table 1: Recent bio-active copper(II) derivatives at a glance

Year	Ligands Used	Applications	Reference
2001	Pyridyl-2-carboxamidrazone	Anticancer	Gokhale *et al*., 2001 [33]
2002	2,6-bis(benzimidazo-2-yl) pyridine	Protease mimetic	Shrivastava *et al*., 2002 [34]
2003	Acetyl acetone, glycine and phenanthroline bases	Anticancer	Marin-Hernandez *et al*., 2003 [35]
2003	2-Clip-Phen and 3-Clip-Phen ligands	DNA nuclease activity	Pitie *et al*., 2003 [36]
2004	L-threonine and 1,10 phenanthroline	DNA binding, cleavage studies and cytotoxicity studies (HL-60, SGC-7901, BEL-7402 and A-549 cell lines)	Zhang *et al*., 2004 [37]
2005	Ciproflaxin, Enoxacin	Antibacterial	Jimenez-Garrido *et al*., 2005 [38]
2006	4-methyl-2-N-(2-pyridylmethyl)aminophenol (Hpyrimol) ligand	DNA cleavage studies and cytotoxicity (L1210 and A2780 cell lines)	Maheswari *et al*., 2006 [39]
2006	Quinoline-2 Carboxaldehyde hydrazine derivatives	Antiproliferative and proapoptotic activity (PC-3 and LNCaP cells)	Adsule *et al*., 2006 [40]
2007	3-benzoyl-a methyl benzene acetic acid	Cytotoxicity (MIAPaCa and BxPC-3 cells)	Ahmed *et al*., 2007 [41]
2006	L-lysine (L-lys), L-methionine(L-met), tridentate NSO-donor Schiff's bases and phenanthroline bases	Photonuclease activity	Chakravarty *et al*., 2006 [42]
2007	2-[(2-(2-hydroxyethylamino)ethylimino)methyl] phenol (Htdp) and phenanthroline bases	DNA and protein binding studies, DNA cleavage activity and cytotoxicity (ME180 cell line)	Rajendiran *et al*., 2007 [43]
2007	bisphenanthroline-coumarin-6,7-dioxacetic acid ($cdoaH_2$) and 1,10 phenanthroline	DNA binding, DNA cleavage studies and cytotoxicity studies (Hep-G2, A-498, Chang and HK-2 cell lines)	Thati *et al*., 2007 [44]
2007	*o*-iodohippuric acid (I-hipH) and 1,10 phenanthroline	Cytotoxicity (A549 cell line)	Barcelo-Oliver *et al*., 2007 [45]
2007	Salicylic acid ($SalH_2$), benzoic acid (BZAH); benzimidazole (BZDH) and 5,6-dimethylbenzimidazole (5,6-DMBZDH)	superoxide dismutase and cytotoxicity (Hep-G, A-498 and A-549)	Devereux *et al*., 2007 [46]
2007	Bis[(2-oxindol-3-ylimino)-2-(2-aminoethyl)pyridine-N,N′] and bis-[(2-oxindol-3-yl-imino)-1,3-diaminopropane-N,N′,O,O′] ligands	Pro-apoptotic Activity	Filomeni *et al*., 2007 [47]
2007	Nimesulide ligands	Cyclooxygenase-2 (COX-2) inhibitor and cytotoxicity (BxPC-3 and MiaPaCa cell lines)	Ambike *et al*., 2007 [48]
2007	(Z)-2-hydroxy-N prime -(2-oxoindolin-3-ylidene) benzohydrazide	Cytotoxicity (SPCA-1, Tb, MGC, and K562 cell lines)	Zhong *et al*., 2007 [49]
2009	2,4-diiodo-6-(pyridine-2-yl methylamino)methyl phenolate	Proteasome inhibitor and apoptosis inducer	Hindo *et al*., 2009 [50]
2009	Bis[(2-oxindol-3-ylimino)-2(2-aminoethyl)pyridine-N,N′] ligand	mitochondrial oxidative damage and AMP-activated protein kinase-dependent apoptosis	Filomeni *et al*., 2009 [51]
2009	Acetyl acetone, glycine and phenanthroline bases	Antiproliferative activity and QSAR study	Bravo-Gomez *et al*., 2009 [52]
2009	Maltol and phenanthroline Bases	DNA binding, cleavage and cytotoxicity (HeLa cell line)	Barve *et al*., 2009 [53]
2009	Ethyl 2-[bis(2-pyridylmethyl)amino]propionate (ETDPA)ligand and 1,10 phenanthroline	DNA binding studies and cytotoxicity (HepG2, HeLa, A549 and Eca-109 cell lines)	Chen *et al*., 2009 [54]
2010	N-allyl di(picolyl)amine(Aldpa) and phenanthroline bases	DNA binding studies and cytotoxicity (Mcf-7, Eca-109, A549 and HeLa cell lines)	Chen *et al*., 2010 [55]
2010	(4′-phenyl)-2,2′:6′,2″-terpyridine (ph-tpy) and phenanthroline bases	DNA binding interactions, Photoactivated nucleolytic activity and cytotoxicity (HeLa	Roy *et al*., 2010 [56]

		cell line)	
2010	benzene-1,2-dithiolate ligand (bdt) and para substituted aniline Schiff's base derivatives of 3-(3-phenyl-allylidene)-pentane-2,4-dione	DNA interaction studies, Anti-tuberculosis activity and cytotoxicity (EAC, HeLa, Hep2, HepG2 and MCF-7 cell lines)	Raman *et al*., 2010 [57]
2010	Ferrocenyl terpyridine (Fc-tpy) and phenanthroline bases	DNA binding studies, photoactivated DNA cleavage studies	Maity *et al*., 2010 [58]
2010	PhimpH ligand	DNA binding and nuclease activity	Ghosh *et al*., 2010 [59]
2010	Derivatives of (2-oxo-quinoline -3-carbaldehyde-benzoyl hydrazone ligands	DNA binding studies and cytotoxicity (HeLa and HL-60 cell lines)	Liu *et al*., 2010 [60]
2010	1,7-Di-9-anthracene-1,6-heptadiene-3,5-dione (9Accm) and 1,10 phenanthroline ligand	DNA binding interactions and cytotoxicity (A498, EVSA-T, H226, IGROV, M19, MCF-7,WIDR cell lines)	Aliaga-Alcalde *et al*., 2010 [61]
2010	3,5-di-tert-butyl-2-hydroxybenzyl)(2-pyridylmethyl)imine, 2-hydroxybenzyl)(2-pyridylmethyl) imine and phenanthroline ligands	DNA binding studies and Photonuclease activity	de Souza *et al*., 2010 [62]
2011	N-2-pyridiylmethylidene-2-hydroxy-5-chloro-phenylamine (5-Cl-pap) ligand	DNA interaction studies and cytotoxicity (HeLa cell line)	Qiao *et al*., 2011 [63]
2011	Pentane-2,4-dione or glycine and Ancillary ligands	Cytotoxicity (HeLa and lymphocytes) Genotoxicity	Serment-Guerrero *et al*., 2011 [64]
2011	*S*-methyl dithiocarbazate and *S*-benzyl dithiocarbazate based Isatin Schiff's base	Cytotoxicity (MCF-7 cell line)	Manan *et al*., 2011 [65]
2011	Imidazole terpyridine (itpy), pyridine terpyridine (ptpy) and dimethyl phenanthroline (dmp)	DNA binding and cleavage studies and Cytotoxicity (A549 cell line)	Rajalakshmi *et al*., 2011 [66]
2011	2-((2-phenyl2-(pyridin-2-l)hydrazono)methyl)pyridine (Pyimpy) ligand	DNA binding, cleavage studies and cytotoxicity (MCF-7, PC-3 and HEK-293 cell lines)	Ghosh *et al*., 2011 [67]
2011	N'-(phenyl(pyridine-2-yl)methylidene)benzohydrazide	DNA and protein binding studies, DNA cleavage studies and cytotoxicity (HeLa and NIH 3T3 cell lines)	Krishnamoorthy *et al*., 2011 [68]
2011	Salicylidene-2-aminothiophenol and phenanthroline bases	DNA binding, photocleavage studies and cytotoxicity (HeLa cell line)	Lahiri *et al*., 2011 [69]
2011	Bis(2-picolyl)amine ligand	DNA cleavage studies and cytotoxicity (Caco-2 cell line)	Ibrahim *et al*., 2011 [70]
2011	Acetyl acetone and 2-(Naphthalen-1-yl)-1H-imidazo[4,5-f][1,10]phenanthroline(nip)	DNA, protein binding, DNA cleavage and cytotoxicity studies (MCF-7, HeLa, HL-60 and MCF-12A cell lines)	Bhat *et al*., 2011 [71]
2011	N-benzyl di(pyridylmethyl)amine (phdpa) and 1,10 phenanthroline	DNA binding studies and cytotoxicity (HeLa cell line)	Chen *et* al., 2011 [72]
2011	4'-(9-anthryl)-2,2':6',2''-terpyridine ligand	DNA cleavage studies and cytotoxicity (HeLa, SiHa, CaSki, MCF-7, HepG2 and H1299 cell lines)	Kumar *et* al., 2011 [73]
2011	Glyoxal-bis(thiosemi carbazone) (H_2gts), 2-keto-3-ethoxybutyraldehyde-bis(thiosemicarbazone) (H_2kts), 2-keto-3-ethoxybutyr aldehyde-bis(4-methyl thiosemicarbazone) (H_2ktsm)	Cytotoxicity studies	Paterson *et* al., 2011 [74]
2012	2-oxo-1,2-dihydrouinoline-3-carbaldehy hydrazone	DNA and protein interaction studies, antioxidant activity, and cytotoxicity (HeLa, HEp-2,HepG2 and NIH 3T3)	Raja *et al*., 2012 [75]
2012	Methoxybenzyl terpyridine (meotpy), benzimidazolyl terpyridine (bitpy) and dimethyl phenanthroline(dmp)	DNA binding and cleavage studies, cell cycle study and cytotoxicity (MCF-7 and VERO cell lines)	Rajalakshmi *et al*., 2012 [76]
2012	4-Hydroxy-N'-[(1E)-1-(4 -methylphenyl)ethylidene]benzohydrazide and 4 ethyl [4-({(2E)-2-[1-(4-methylphenyl)ethylidene]hydrazinyl}carbonyl) -phenoxy]acetate	DNA binding and cleavage studies	Gokce *et* al., 2012 [77]
2012	1,7-bis(3-methoxyl-4-acetoxyl)phenyl-1,6-heptadiene-3,5-diketone	Cytotoxicity studies (HeLa, MCF-7 and A549 cell lines)	Zhou *et al*., 2012 [78]
2012	(E)-2, 4-Di-tert-butyl-6-((phenyl(pyridin-2-yl)hydrazono)methyl)	Nuclease activity and cytotoxicity (MCF-7 cell line)	Ghosh *et al*., 2012 [79]

	phenol (^{t}BuPhimpH) ligand		
2012	2-oxo-1,2-dihydroquinoline-3-carbaldehyde(4′-methylbenzoyl) hydrazone ligand	DNA, protein (BSA) binding studies, antioxidant activity and cytotoxicity(HeLa, Hep-2 cell lines)	Raja *et al*., 2012 [80]
2012	N-((1H-imidazole-2-yl)methyl) -2(pyridine-2-yl) ethanamine, N-((1-methyl-1H-imidazole-2-yl)methyl)-2-(pyridine-2-yl)ethanamine, 2-(pyridine-2-yl)-N-((pyridine-2-yl) methyl) ethanamine ligand	DNA binding, nuclease activity and cytotoxicity (MCF7, HCT116 and A549 cell lines)	Kumar *et al*., 2012 [81]
2012	N,N-Bis(benzimidazol-2ylmethyl)amine(BBA) and phenanthroline bases	DNA binding, nuclease activity, Protease active-ityand cytotoxicity (SiHa cell line)	Loganathan *et al*., 2012 [82]
2012	Salicylic acid ($salH_2$), 3,5-diisopropyl salicylic acid ($dipsH_2$), 3-methoxysalicylicacid (3-$MeOsalH_2$), benzimidazole (BZDH), 2 methanolbenz-imidazole (2-MeOHBZDH) and 1,10-phenanthroline	DNA binding, cleavage activity and cytotoxicity studies (MCF-7, DU145, HT29 and SK-OV-3 cell lines)	O'Connor *et al*., 2012 [83]
2012	Indole-3-acetic acid (IAA), indole-3-propionic acid (IPA) and 1,10-phenanthroline	proteasome activity and cytotoxicity (MDA-MB-231 and MCF-10A cell lines)	Zhang *et al*., 2012 [84]
2012	2,2′:6′,2″-terpyridine and dipyrido[3,2-*a*:2′,3′-*c*]phenazine (dppz)	DNA binding studies and cytotoxicity (MCF-7 cell line)	Abdi *et al*., 2012 [85]
2013	Acetyl acetone or 3-chloro acetyl acetone and 2-(4-pyridine)oxazo[4,5-*f*]1,10-phenanthroline (4-PDOP)	DNA interactions, DNA unwinding assay, chemical nuclease activity and cytotoxicity (HepG2)	Li *et al*., 2013 [86]
2013	Ferrocenylmethyltyrosine (Fc-TyrH), Ferrocenylmethyl- phenylalanine (Fc-pheH), Ph-TyrH, Ph-PheH and phenanthroline bases	DNA binding and cleavage studies, cyto-toxicity study (HeLa and MCF-7 cell line)	Goswami *et al*., 2013 [87]
2013	4-hydroxy-N′-[(1Z)-1-(naph- thalen-2-yl)ethylidene]benzohydrazide and (Z)-ethyl 2-(4-(2-(1-(naphthalene-2-yl) ethylidene)hydrazinecarbonyl)-phenoxy)acetate	DNA binding and Nuclease activity	Gokce *et al*., 2013 [88]
2013	2-acetylpyridine benzoyl Hydrazone and 2-acetylpyridine thiophene-2-carboxylicacid hydrazine	DNA , Protein binding, DNA cleavage studies and cytotoxicity studies (HeLa, PANC-1, EAC, DLA and NIH3 cell lines)	Alagesan *et al*., 2013 [89]
2014	Imidazole terpyridine (itpy)	DNA interactions, protein binding studies and cytotoxicity (A549 cell line)	Manikandamathavan *et al*., 2014 [90]
2014	N-phenyl -N′-(aryl/alkyl)-N″-thiophenecarbonyl Guanidine	DNAand protein inter-action studies and cytotoxicity (MCF7 and A549 cell lines)	Jeyalakshmi *et al*., 2014 [91]
2014	Amino acids and 1,10 phenanthroline	Cytotoxicity studies (MDA-MB-231, MCF10A, Hela, SKOV3,A549,PC9, Hone1, HK1, C666-1, MCF7, T47D, Nalmawa, HL60, SW480, SW48 and HCT118 cancer cell lines)	Ng *et al*., 2014 [92]

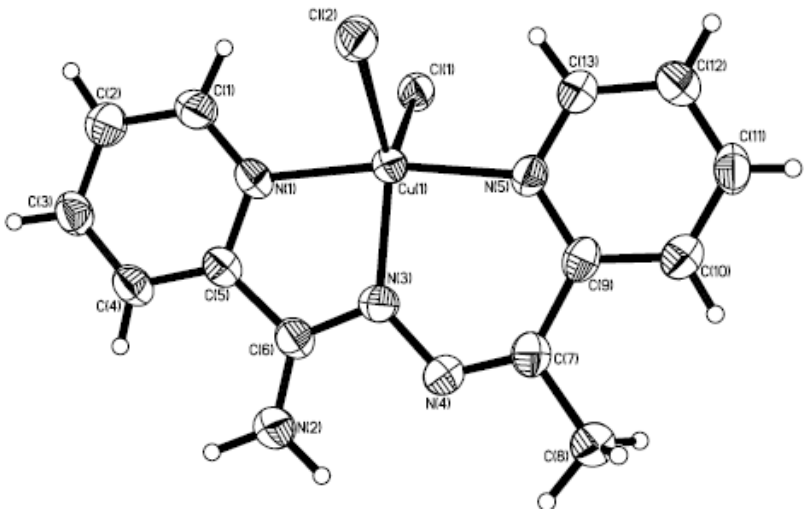

Figure 6: Molecular structure (50% thermal ellipsoids) of Cu(II) complex [$CuCl_2(C_{13}H_{13}N_5)$] with anticancer activity

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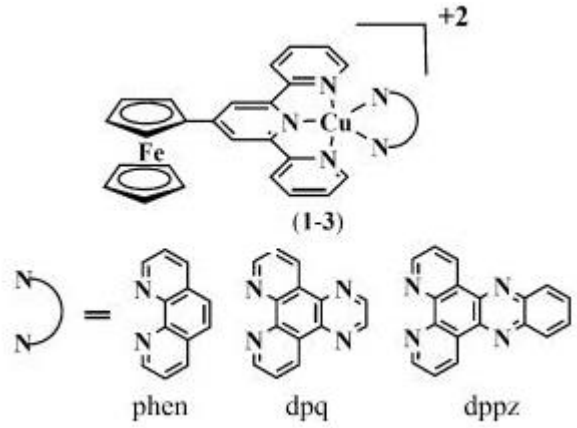


Figure 7: Ferrocene-appended terpyridine copper(II) complexes bearing phenanthroline bases with photoactivated DNA cleavage and anticancer activity

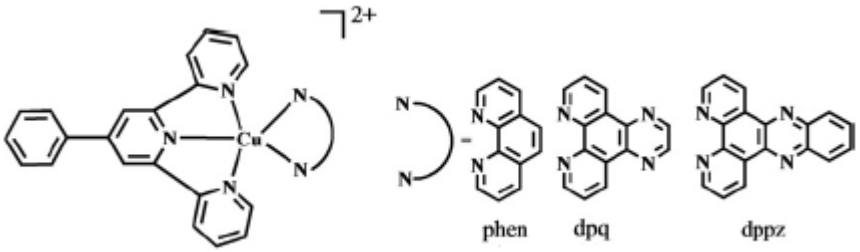
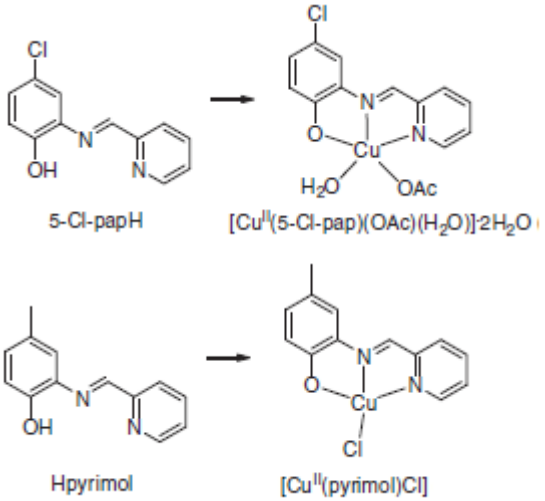
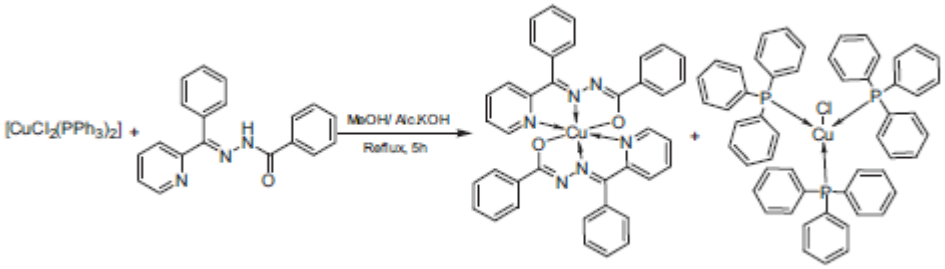


Figure 8: Terpyridine copper(II) complexes having phenanthroline bases with DNA photocleavage and anticancer activity



Scheme 1: Molecular structures of Schiff base ligands and their copper(II) complexes



Scheme 2: Synthesis of Cu(II) hydrazone complexes

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Interaction of copper(II) derivatives with DNA

Eminent discovery for the structure of Deoxyribonucleic acid (DNA) consisting two complementary polymeric strands twisted with each other and emerged as a right handed double helical appearance made Watson and Crick noble laurate in 1962. These strands of DNA are composed of purine and pyrimidine (A=T, G≡C) nucleobases with hydrogen bonding between two separate polymeric strands. It contains deoxyribose and phosphate groups as sugar-phosphate backbone.

Since DNA is the basis for the storage, transmission and expression of genetic information, therefore, any damage or reaction occurring with it will have remarkable consequences. Thus, DNA molecule appears as primary target for the treatment of several types of anticancer and antiviral agents. The binding of small molecule *i.e.* metal complex to DNA at specific site is significant and the bio-activities of complexes mainly depend upon the size and complexity. Generally, metal complexes interact with double helix of DNA *via* three binding modes as follows:

- Electrostatic mode of binding (External binding)
- Groove binding
- Intercalative binding (Intercalation)

Electrostatic binding

Positively charged metallic ions of the complexes interact with negatively charged phosphate sugar back bone of the DNA *via* electrostatic interaction and it is called as external binding too. This type of interaction is observed in ruthenium based metal complexes e.g. $[Ru(bpy)_3]^{2+}$ and Mg^{2+} cation typically interact through this mode of binding.

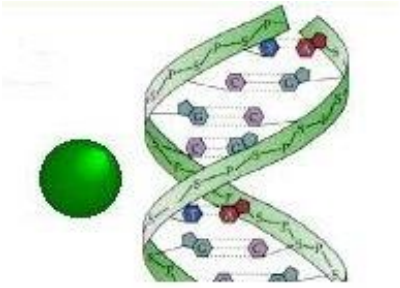

Figure 9: Representation of electrostatic binding

Groove binding

The metallo-organic derivatives or small molecules interact with DNA groove *via* van der Walls forces. Hydrophobic and hydrogen bonding are the important components for the groove binding and these bondings establish stable interaction between metal complex and DNA. Netropsin (antibiotic) is the example for groove binding and its methyl functional group prevent the intercalation mode of binding.

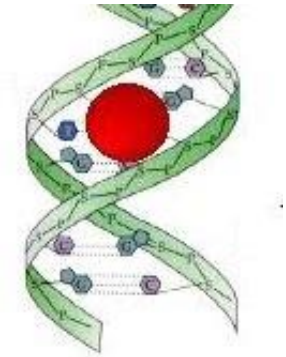

Figure 10: Representation of groove binding

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Intercalative binding

The intercalation mode of binding occurs due to insertion of planar fused aromatic systems between the stacked DNA base pairs. This type of binding is getting stabilized by the π-electrons cloud of the intercalator (molecule) and closely situated nucleobases of DNA furnishing binding mechanism from their major groove or minor groove. Intercalative mode of binding usually favoured by the extended aromaticity of ligands and planarity of the molecule. DPPZ ligand is having extended aromaticity compared to other ancillary ligands, the intercalation is generally prevented through clashing of ancillary ligand with phosphodiester backbone. That is why partial intercalation was observed in $[Ru(phen)_3]^{2+}$ complexes. The complexes of platinum associated with ancillary ligands have encouraging cytotoxic effect due to intercalative mode of binding. Some of the intercalative ligands employed to produce copper(II) complexes for intercalative mode of binding have been displayed in the Fig. 12.

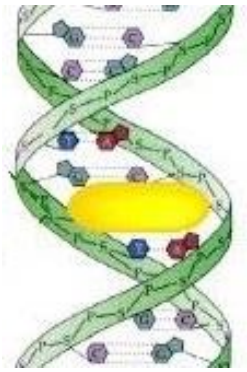

Figure 11: Representation of intercalative binding

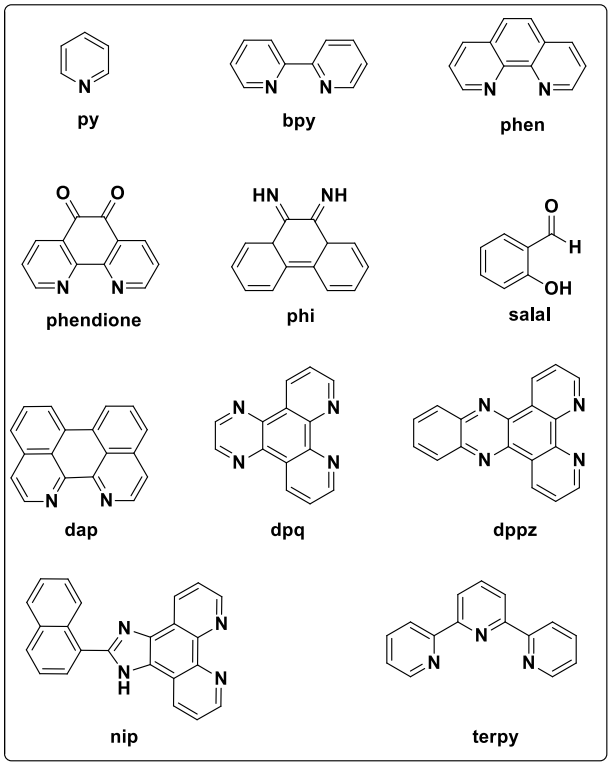

Figure 12: Some examples of intercalative ligands; pyridine (**py**), bipyridyl (**bpy**), 1,10 phenanthroline (**phen**), 1,10-Phenanthroline-5,6-dione (**phendione**), phenanthrene-9,10-diimine(**phi**), Salicylaldehyde (**salal**), 1,12–diazaperylene (**dap**), dipyridoquinoxaline (**dpq**), dipyridophenazine (**dppz**), 2-(naphthalen-1-yl)-1H-imidazo[4,5-f][1,10]phenanthr- oline (**nip**), terpyridine (**terpy**)

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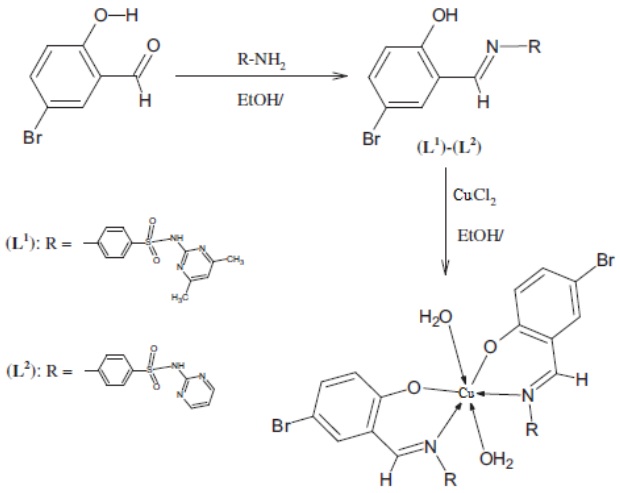
DNA nuclease (cleavage) activity

According to the biochemistry of cell, DNA is the primary target molecule for the treatment of various malignancy and antiviral therapies. Metallo drugs bound with DNA, either inhibit the biosynthesis of nucleic acids or dislocate the hormonal stimulation of cell growth [93]. Transition metal complexes are used as chemical nucleases due to its stability and redox properties. The transition metal complexes which contain multidentate (bi, tri and tetra) ligands bound with DNA may interfere the transcription and replication process and this property of metal complexes could be exploited as metallo drugs for various types of cancerous cell lines. Prominently DNA cleavage could be achieved by two ways such as oxidative (targeting base pairs or sugar units) pathway or hydrolytic (hydrolysis of phosphoester bonds) pathway. Copper complexes may be employed for both oxidative and hydrolytic pathways, but, cleavage pathway depends on the nature of ligand moiety [94]. The first copper complex bis(phen)copper(I) used as chemical nuclease in the presence of hydrogen peroxide and thiol [95]. In case of oxidative cleavage co-regents (oxidative reagents) used to initiate the cleavage mechanism *via* radical formation. Generally, hydrolytic mechanism was initiated by the metal ions (Lewis acids).

Antimicrobial activity of copper(II) complexes

Metals and their derivatives have been used as antimicrobial agents in the field of pharmaceutics for past thousands of years. Copper and silver vessels were used for food preservation and water disinfection during the period of Persian dynasty. Silver ions have a broad spectrum of applications in medical sciences e.g. silver bandages were used for the treatment of burns and silver foils were used for surgical wounds to prevent against infections. Zinc is the one of the important ingredient in the preparation of antiseptic ointments and lotions. Numerous antibiotics have been explored against microorganisms during last three decades. Metallo-organic complexes derived from transition metals incorporated with nitrogen, oxygen and sulphur containing ligands have been established for wide range of biological applications such as antimicrobial and anticancer studies. Among those, copper(II) derivatives have found to be one of the most significant biomaterial as it is a micronutrient for anti-microbes while excess of copper is toxic to microorganisms, which influences the bacterial metabolism, in turn affects the bacteria. Different types of Schiff's bases were shown predominantly active for both antibacterial and antifungal strains [96].

Antibacterial studies



Scheme 3: Preparation of sulphonamide derived Schiff bases and their copper complexes

Tetradentate Schiff's bases of furfural, β-ketoanilides with diethylmalonate, *o*-phenylenediamine ligands and its metal complexes were subjected for anti-bacterial studies against gram positive (*Staphylococcus aureus*) and gram negative bacteria (Salmonella typhi, Klebsiella pneumoniae, Pseudomonas aeruginosa and Escherichia coli) by disc diffusion method and complexes have shown greater activity than its corresponding ligands [97, 98]. The hetero atoms (O, N, S) containing bidentate Schiff's bases coordinated with metal ions *via* azomethane groups and showed remarkable antibacterial activity against *Bacillus megaterium, Enterococcus cloacae,*

Escherichia coli, Klebsiella pneumoniae, Micrococcus leteus, Mycobacterium Smegmatis, Pseudomonas aeruginosa and Staphylococcus aureus than its free ligands [99, 100]. Various types of aroyl hydrazide ligands have been prepared and their complexes with few transition metal ions (V, Co, Ni, Cu and Zn) were subjected for their anti-bacterial studies. Among all the metal aroyl hydrazone complexes, copper(II) metal ion containing complexes have shown prominent activity. The antimicrobial activity of metal complexes could be arranged in the order as Cu(II) > Co(II) > Ni(II) > Zn(II) > V(II) > aryl hydrazone ligands [101]. Sulphonamide Schiff's base derivatives of copper(II) complexes have pronounced antibacterial activity [102].

Fluoroquinolones such as ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin are the world class antibiotics and they are potent against gram negative bacteria, which could be utilized for the treatment of numerous bacterial infections, including bacterial bronchitis, pneumonia, sinusitis urinary tract infections, joint and bone infections. These antibiotics are less effective against gram positive bacteria. In order to increase their biological activity, the fluoroquinolones were treated with copper(II) metal ions and investigated for its antimicrobial studies. The obtained results suggested that the complexes have exhibited better activity than their free ligands [103, 104].

Scheme 4: Mixed ligand Cu(II) complexes of ciprofloxacin and N, O donor Schiff bases

Anti-fungal studies

Fungi are eukaryotic organism and biochemically resembles with the human host. Fungi were recognized before the identification of bacterial organisms. The basic reasons for fungal infections are advanced age, lack of care after surgery and poor immunity etc. During Second World War time for the treatment of fungal infections various weak acids and phenolic dyes have been used and the first orally bioavailable antibiotic (griseofulvin) has also been used. Later, lot of organic molecules (Imidazole's, triazole's…etc.) have been synthesized and tested for their antifungal studies and they have revealed good activity against selective fungal strains. In order to overcome the severe fungal infections, the development of more potent drugs gets the thirst area of research. Some of the Schiff's bases are known as potent antifungal agents but, metal complexes of Schiff's bases are showing better activity compared with their respective ligands and corresponding metal ions.

In 2006, Gudasi *et al* have synthesized amino acid based Schiff's base i.e. N-(2-hydroxy-1-naphthylidene) phenyl glycine (Hhnpg) ligand and further prepared various metal chloride complexes [105] and subjected for antifungal investigations. All the metal complexes have confirmed their vital activity compared with the ligand Hhnpg. Clomiphene citrate copper complexes were subjected for antifungal studies against *Aspergillus niger and Aspergillus flavus* while using batemann poisoned food technique for this investigation and results obtained were quiet encouraging [106]. Sulphonamide moiety containing copper complexes have displayed predominant activity against few fungal strains [102]. Metal complexes incorporated with heteroleptic as well as ligands containing N, O donor atoms exhibited splendid activity towards fungal strains [107]. The fungal activity depends prominently on electron withdrawing groups as well as its positioning aromatic ring [108].

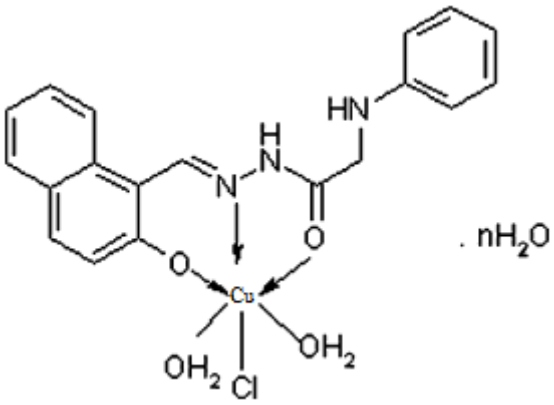


Figure 13: N-(2-hydroxy-1-naphthalidene) phenyl glycine supported cu(II) complex with antifungal activity

CONCLUSION

The above said account of literature review on copper(II) has enlighted the existing quantum of emerged research but at the same time directed towards more interesting exploration in the field concerned. In view of further investigations on synthetic, structural as well as on bio-applications, copper(II) complexes incorporated with nitrogen, oxygen and/or sulphur donor atoms could be of more importance. Therefore, a systematic investigation of the title metal with a variety of ligands should be carried out to explore and establish many more bio-application and clinical utilities.

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