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Review

Copper Complexes: Propitious Tool for Cancer Treatment

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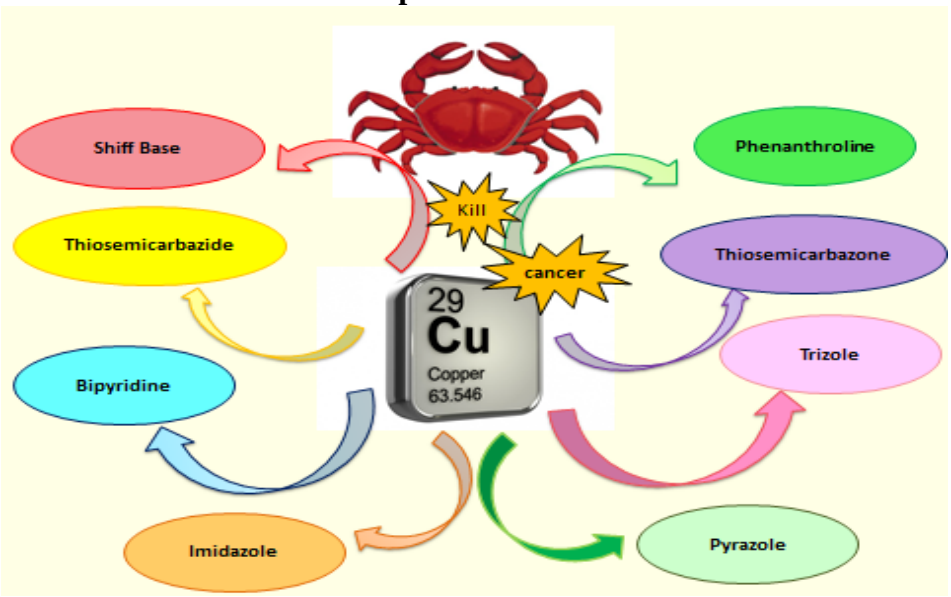
ABSTRACT

Platinum complexes have turned out as the cornerstones of modern cancer chemotherapy. The perceptible disadvantages of existing chemotherapeutics have led to the build out of novel anticancer agents with alternative modes of action. The antitumor properties of different metal complexes have been evaluated. Among these copper has been found to be involved in biological systems driving a vital array of chemical reactions. It accumulates in tumors due to selective permeability of the cancer cell membranes. In this review, we highlight recent advances in the development of copper complexes as anticancer drug candidates.

GraphicalAbstract



Keywords: Copper, Thiosemicarbazides, Schiff Base, Chemotherapeutics.

INTRODUCTION

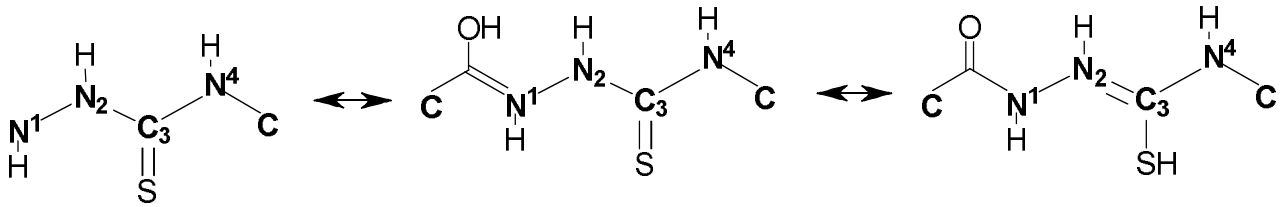
Cancer is an imperative area of interest in the life sciences as it has been a prime assassin disease throughout human history. It is not one disease, but a bulky group of diseases characterized by uncontrolled growth and spread of abnormal cells. The discovery of anticancer properties of cisplatin marked a turning point in the medicinal inorganic chemistry. Currently, cisplatin is commonly used to treat numerous cancers, particularly malignant solid tumors like testicular cancer, ovarian cancer, esophageal cancer, bladder cancer, head and neck cancer, and small-cell lung carcinomas [1]. However, the development of resistance to chemotherapy leads to the failure of cisplatin treatment, leading to the search of new effective metallodrugs.

Coordination and organometallic compounds of transition metals have shown great potential for use as therapeutic agents due to their wide structural diversity and binding modes [2, 3].The alchemy of metal complexes offers enormous opportunities for the design and development of compounds with excellent bioactivities due to the assortment of available metals and the ability to tune the reactivity and structure of the metal complexes by their ligand sphere [4, 5]. The biological activities of the metal complexes are widely influenced by the nature of metal ions, its oxidation state, the type and nature of bound ligands and isomers [6-8]. Hence, the understanding of the factors affecting the biological activity of metal complexes should enable the design of metal complexes with specific medicinal properties and also to overcome the disadvantages of available medicines. For example, cisplatin, a platinum (II) diamine complex used in 70% of cancer treatment has some drawbacks like toxic side-effects and lack of activity (drug resistance) against several types of cancer which are problems need to be overcome [9]. So, the search for anticancer activity amongst complexes of other metals has received much interest. Copper is widely distributed in the biological system and its complexes are known to have a broad spectrum of biological action. It has been demonstrated that Cu accumulates in tumors due to selective permeability of the cancer cell membranes. Therefore, a number of copper complexes have been screened for anticancer activity and some of them were found active both *in vivo* and *in vitro* [10]. Copper-based complexes have been investigated on the assumption that endogenous metals may be less toxic for normal cells with respect to cancer cells. The altered metabolism of cancer cells and deferential response between normal and tumor cells to copper are the basis for development of copper complexes endowed with antineoplastic characteristics.

Copper Complexes: Copper forms a rich variety of coordination complexes with oxidation states Cu(II) and Cu(I), and very few examples of copper(III) compounds are reported [11].The coordination chemistry of copper is dominated by Cu(II) derivatives with little but important examples of Cu(I) compounds. Since copper(I/II) complexes are (i) redox active, (ii) frequently labile, and (iii) a typical in their preference for distorted coordination geometries, they are much less structurally predictable than other first-row transition metal complexes.

This review describes advances in the synthesis, design, and development of copper complexes as anticancer agents in the last few years. Only distinct copper complexes have been included in this review.

Thiosemicarbazides: Complexes of thiosemicarbazide and 1,4-substituted thiosemicarbazide are of general interest as models for bioinorganic processes [12-13]. Acylthiosemicarbazide contains O, S, and N as potential donor atoms and is liable to form complexes by loss of hydrazinic proton via enolization/thioenolisation via formation of several tautomeric forms **(1)**. A recent investigation focused on the design of a glycosylsaccharide derivative (D-glucopyranose)-4-phenylthiosemicarbazide (HL^{13}). Introduction of a thiosemicarbazide anchoring group provided a well-defined binding environment as well as increased the stability of the resulting metal complexes.



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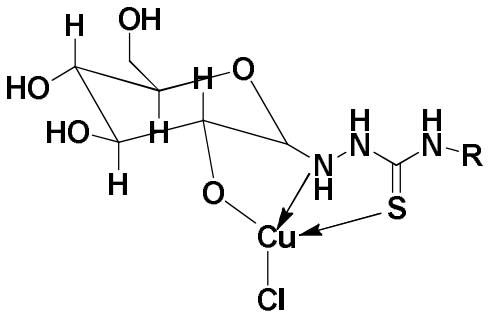
There is a potential benefit of utilizing this approach relied on the availability of a pendant carbohydrate moiety able to interact with carbohydrate transport and metabolic pathways in the body. The copper complex **(2)** inhibited EAC in Swiss albino mice [14].



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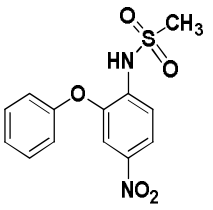
Schiff Base Complexes: Padhye *et al.* [12] have modified the structure of nimesulide **(3),** a well-known cyclooxygenase-2 (COX-2) inhibitor [13, 14] with pharmacophores capable of targeting vascular endothelial growth factor (VEGF) [15,16] and anti-apoptotic proteins like Bcl-2 and Bcl-XL, besides targeting the COX enzymes [17-20]. Copper conjugates of Schiff base derivatives of nimesulide **(4)**, were synthesized, structurally characterized and evaluated for their COX selectivity indices and cytotoxicities on pancreatic tumor BxPC-3 (COX-2 positive) and MiaPaCa (COX-2 negative) cell lines. Copper conjugates exhibited distorted square planar geometries, as revealed by the single crystal X-ray structure determination of **(5),** and showed significantly higher growth inhibition in both cell lines(IC_{50} values 3–26 μM for COX-2 positive and 5–9 μM for COX-2 negative cell line) than nimesulide (35 μM for COX-2 positive and >100 μM for COX-2 negative cell line). It has been reported that the mechanistic pathway responsible for the biological activity involved the inhibition of VEGF and COX-2, as well as the down regulation of antiapoptotic Bcl-2 and Bcl-XL proteins.

A mononuclear complex of Cu (II) **(6)**, with the Schiff base ligand (Z)-2-hydroxy-N'-(2-oxoindolin-3-ylidene) benzohydrazide, has been prepared by Zhong *et al*. [21]. This complex has been characterized by X-ray crystallography as a distorted octahedral species. The cytotoxicity assays, carried out in four kinds of human cancer cell lines (SPCA-1, Tb, MGC, and K562), indicated that this complex was substantially more active than related compounds previously reported [22, 23].For the enhanced antitumor activity, Zhong *et al*. claimed the generation of cytotoxic Cu(I) species through intracellular enzymatic reduction [24]. Sarkar *et al.* [25,26] have shown that the central ketonic function of 3-benzoyl-α-methyl benzene acetic acid (ketoprofen) could be easily appended with pharmacophores such as TSCs bearing amino groups to yield Schiff base type compounds. Reaction of these ligands with transition metals, in particular with copper, yielded potent anticancer agents against breast cancer cells. Recently, Sarkar *et al.* have synthesized and biologically characterized a ketoprofen derivative named **(7)**, as a selective COX-2 inhibitor [27]. The Complex **(7)** exhibited a potent antiproliferative and proapoptotic activity in COX-2

positive cells. However, further escalation of dose than the one needed for inhibition of COX-2 activity indicated that other non COX-2 dependent pathways might also be involved.

A similar speculation had been proposed in previous studies reporting the ability of non-steroidal anti-inflammatory drugs (NSAIDs) to inhibit the growth of a colorectal cancer cell line that lacked COX-1 and COX-2 enzymatic expression. The results showing a decrease in the COX-2 mRNA and protein subsequent to treatment with **(7)** suggested that it inhibited NF kappa B activation leading to the inhibition of COX-2 expression and its activity, there by inducing apoptotic cell death.

Adsule *et al.* [28] have reported the synthesis of some 1:1 Schiff base copper complexes of quinoline-2-carboxaldehyde ligands **(8, 9).** The quinoline and related copper-quinoline derivatives were tested for their cytotoxic and apoptosis induction effects in prostate cancer cell lines PC-3 and LNCaP. The results showed that these compounds induced apoptosis without causing an oxidative stress. Moreover, the introduction of thiocarbonyl side chains enhanced the antitumor potency. Actually, **(8)** was the most potent analog which inhibited proteasome activity with a IC_{50} value of one order of magnitude lower than those of clioquinol and pyrrolidine DTC.



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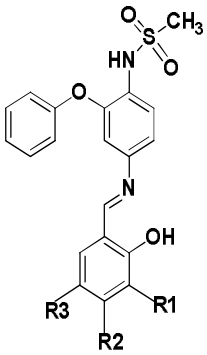

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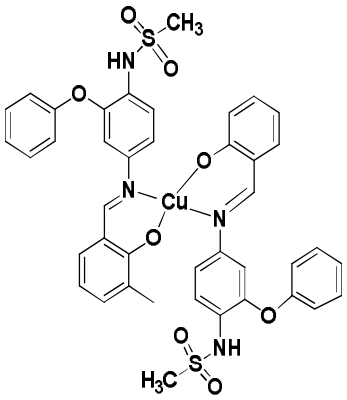
a. R_1=H, R_2=H, R_3=H
b. R_1=H, R_2=OMe, R_3=H
c. R_1=OH, R_2=H, R_3=H
d. R_1=Bu^t, R_2=H, R_3=Bu^t



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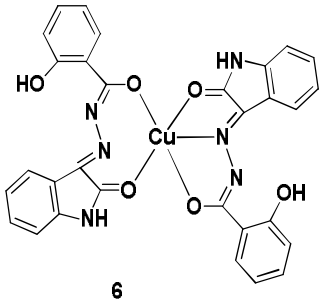

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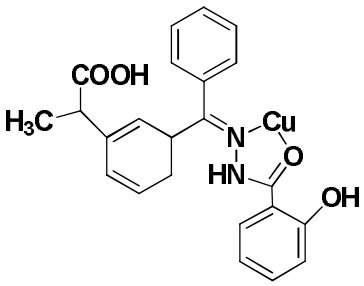

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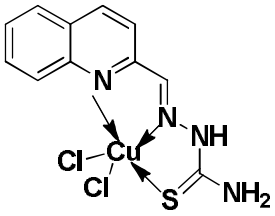

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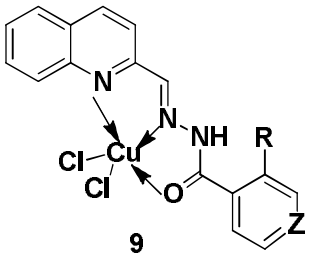
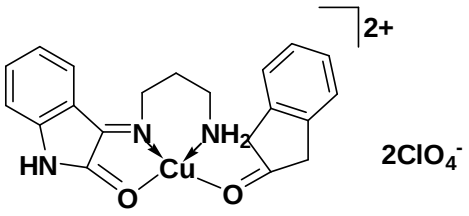


9

a. R=H, Z=CH
b. R=H, Z=N
c. R=OH, Z=CH

Some isatin-Schiff base copper(II) complexes have been recently prepared and spectroscopically characterized by Cerchiaro *et al*. [29]. These complexes exhibited keto-enol equilibria and a relatively high stability. Studies concerning the cytotoxic properties of this class of oxindoliminecopper(II) complexes revealed that some of them activated the apoptotic program in human promonocytic U937 and neuroblastoma SH-SY5Y cells [29].Very recent studies characterized the pro-apoptotic activity of the two most interesting isatin-Shiffbase copper complexes **(10)** and **(35),** obtained from isatin and 1,3-diaminopropane and 2-(2-aminoethyl) pyridine, respectively. It was found that they induced apoptosis via the mitochondrial pathway through both p-53 dependent and independent mechanisms and the extent of apoptosis correlated well with intracellular copper uptake. Therefore, it was suggested that these copper complexes were able to vehicle copper into the cell, thus producing ROS. On the other hand, considering the chemical structure of the isatin-Shiff base, **(10)** and **(11)** might behave as delocalized lipophilic cations, thus specifically targeting mitochondria [30].



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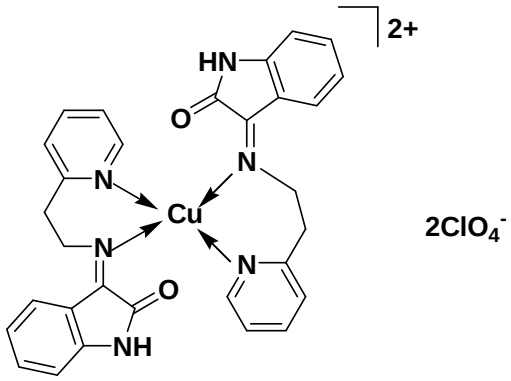

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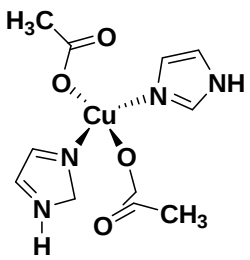
Imidazole, Benzimidazole, Pyrazole and Triazole Complexes: The strong antitumor activity shown by the [trans-bis (acetato) bis (imidazole)] copper (II) complex **(12)** against the B16 murine melanoma cell line [31] stimulated the synthesis of imidazole substituted copper complexes. The crystal structure of **(13)**, with the 1-methyl-4,5-diphenylimidazole, indicated that two trans-oriented imidazoles and two acetate ligands were coordinated to the Cu(II) ion forming a distorted octahedral environment. The effects of the bis-phenyl imidazole complex on the induction of cell division delays, as well as of Sister Chromatid Exchanges (SCEs) and on the suppression of Mitotic Indices (MIs) were examined [32].At concentrations between $0.77^{x}10^{-7}$ and $1.54^{x}10^{-6}$ M, this compound significantly induced SCEs and MI and reduced proliferation rate indexes (PRIs) in cultured human lymphocytes, indicating a high cytostatic and cytotoxic action of this copper complex. Moreover, an unwinding effect on the plasmid pKS DNA was clearly observed after incubation with low concentrations of **(13)**. In particular, concentrations above 0.5mM

caused scissions on both closed supercoiled and open relaxed forms of DNA, and probably drug insertion occurred not randomly, but with some preference to guanosines, as detected by endonuclease inhibition experiments. An interstrand cross-linking of DNA bases were also observed in ds DNA calf thymus and plasmid DNA treated with complex **(13).**



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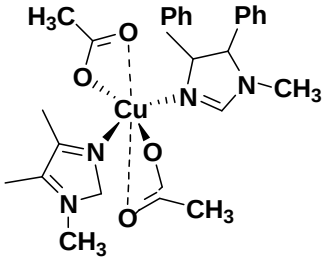
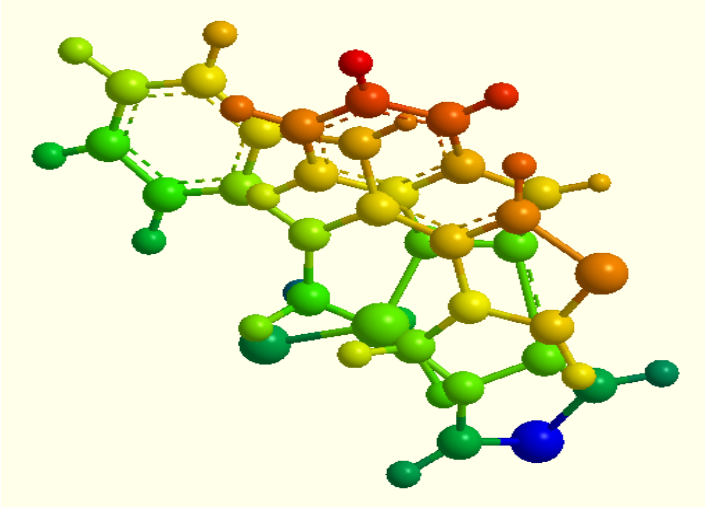


13

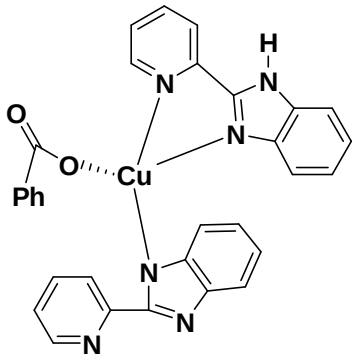
Benzimidazole and many of its derivatives are known to exhibit a variety of biological actions, including antibacterial, antiviral, anticancer and antifungal activity [33]. 2-(4-Thiazolyl)-benzimidazole, orthiabendazole (HTBZ), with structural features common to phenanthroline and benzimidazole is non-toxic to humans and used as a fungicide in agriculture. Reactions of HTBZ with copper(II)acetate, chloride, nitrate and butanedioate yielded $[Cu(HTBZ)_2(H_2O)_2]$, $[Cu(HTBZ)_2Cl]Cl.H_2O.EtOH$ **(14)**, $[Cu(HTBZ)_2(NO_3)_2]$ and $[Cu(HTBZ)_2(CO_2\text{-}C_2H_4\text{-}CO_2)]$, respectively. The molecular structure of **(14)** comprised a five-coordinate copper centre with the metal bound to two chelating HTBZ and one chloride ion. The geometry of this complex was best described as trigonalbipyramid [34]. Testing HTBZ, **(15)** and $[Cu\ (HTBZ)_2(NO_3)_2]$ against the human squamous carcinoma tongue cell line (CAL-27) and the malignant melanoma skin cell line (SK-MEL-31), revealed that the chemotherapeutic potential of HTBZ was significantly enhanced upon metal coordination.



14

In an effort to further develop this class of potential anticancer agents, Devereux *et al.* [35] studied the synthesis and chemotherapeutic potential of a series of novel copper(II) carboxylate complexes derived from HTBZ and 2-(2-pyridyl)benzimidazole(PYBZ). Because of the contemporary presence of the benzimidazole moiety and of the carboxylic group, the ligand potential could be enhanced by the chance to act both as acid and base [36] suggesting that HTBZ and PYBZ could be either neutral or anionic chelators or that they might simply act as counter cations [34,37]. As for HTBZ complexes, the syntheses of mono-,

bis- and tris-chelate compounds of PYBZ have been reported [38-42] but, so far, the only authenticated structure included mono-chelate derivatives of copper(I) [43]. Complex **(15)** and the corresponding free ligand (PYBZ) were assessed for their cancer chemotherapeutic potential against the hepatocellular carcinoma (Hep-G2) and kidney adenocarcinoma (A-498) cell lines. The bis-chelate derivatives [Cu $(HTBZ)_2(BZA)](BZA).0.5(HTBZ).H_2O$ (BZA = benzoic acid) and **(15)** elicited a significant cytotoxic response. Replacing HTBZ and PYBZ with phenanthroline (phen) to give $[Cu(BZA)_2(phen)(H_2O)]$ did not significantly increase the anticancer activity. This study [35] supported the hypothesis that the nitrogen donor ligands enabled copper complexes to interact with biomolecules, such as DNA.



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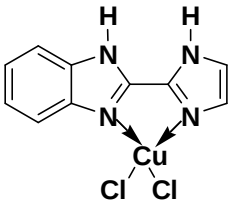
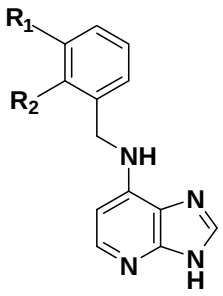


16

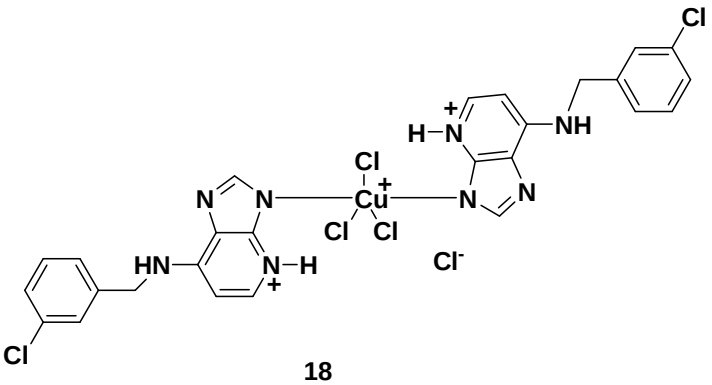
An additional series of Cu(II) coordination compounds with benzimidazole-derived bidentate chelating ligands has been prepared and characterized by Saczewski *et al.* [44]. Complex **(16)** showed a very potent Cu,Zn-SOD activity *in vitro* with a IC_{50} value of 0.09 μM, comparable to those described in the literature for the best low molecular weight Cu,Zn-SOD mimics, including imidazolate-bridged Cu(II)–Zn(II) heterodinuclear complexes[45-48]. *In vitro* cytotoxicity studies, with seven different human tumor cell lines, showed a moderate cell growth inhibitory activity, being the A-427 lung the most sensitive cancer cell line (IC_{50} values of 4.76– 10.12 μM).

The synthesis, characterization and anti-proliferative activity of mononuclear or binuclear copper(II) complexes with 6-(2-chloro-benzylamino)purine **(17a)** and 6-(3-chlorobenzylamino)purine **(17b)** have been reported by Travnycek *et al.* [49]. The X-ray single-crystal structural analysis of **(18)** showed that the metal is penta-coordinated, the Cu (II) ion adopting distorted trigonalbipyramid geometry with the protonated HL_2 ligands coordinated in *trans*- apical positions, and the three chloride ions situated on the equatorial plane. Binuclear complexes were characterized as well, and through comparison with crystallographic parameters observed for similar complexes [50] their structures were proposed as $[Cu_2(\mu\text{-}Cl)_2(\mu\text{-}$**17a**$)_2(H_2O)_2]$ and $[Cu_2(\mu\text{-}Cl)_2(\mu\text{-}$**17a**$)_2($**17a**$)Cl_2]$. Biological activity testing against mouse melanoma B16-*FO*, human malignant melanoma G361, human osteogenic sarcoma HOS and human breast adenocarcinoma MCF7 cell lines were performed for the three complexes and compared with those exhibited by uncoordinated (**17a**) and (**17b**). The cytotoxic activity of the ligands strongly increased after formation of the Cu(II) complexes, which in turn showed potent activities against B16-F0 cells (IC_{50} from 8.2 to 19 μM). G361, HOS and MCF7 cell lines were less sensitive, with IC_{50} values ranging from 20 to 88 μM. For the G361 and HOS cell lines, the mononuclear complex was found to be several times less potent than the binuclear Cu (II) species.



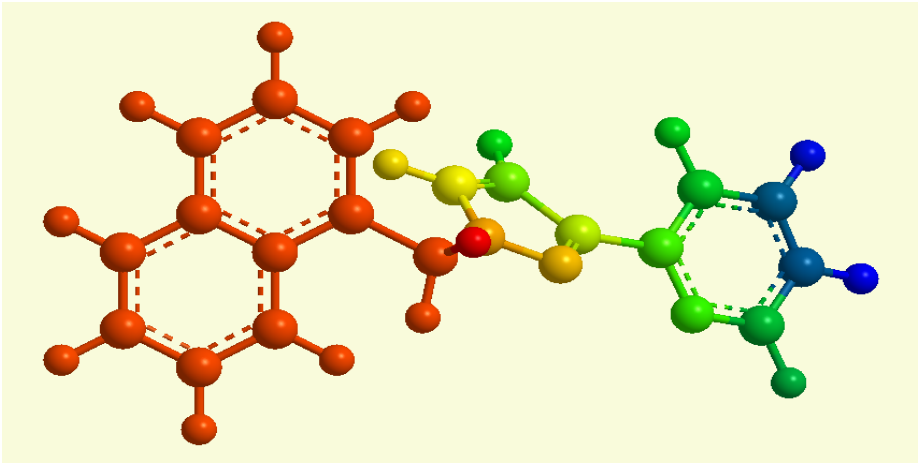
17

a. R_1=Cl, R_2=H
b. R_1=H, R_2=Cl



18

Recently, a series of ligands based on bidentate pyrazolylpyridine or tridentate pyrazolyl-bipyridine frameworks, and the corresponding metal complexes have been synthesized [51,52]. In particular, Yang *et al*. [53] reported the synthesis and characterization of the 2-[1-(naphthalen-1-ylmethyl)-1H-pyrazol-3-yl] pyridine ligand **(19)** and its octahedral [M (**19**)$_3$][ClO_4]$_2$ complexes (M = Cu(II), Zn(II)). The Cu complex was found to possess a higher affinity toward DNA and a superior cytotoxicity against human leukemia HL-60, human gastric cancer BGC-823 and human mammary gland cancer MDA5 cell lines compared to those shown by the isostructural Zn(II) complex and uncoordinated **(19)**. Also the related complex [Cu (**19**)$_2$(NO_3)][NO_3][54] was evaluated against six different cancer cell lines (HL-60 cells, PC-3M-1E8 human prostate tumor cells, BGC-832 cells, MDA cells, Bel-7402 human hepatoma cells and Hela human cervix cancer cells) showing considerable inhibitory rate and cytotoxic specificity. Compound **(19)** and the corresponding metal complexes had an extended aromatic p-system (like those shown by typical bidentate chelating ligands bipy and phen) and they bound to DNA by intercalation mode showing a marked DNA-cleavage activity.



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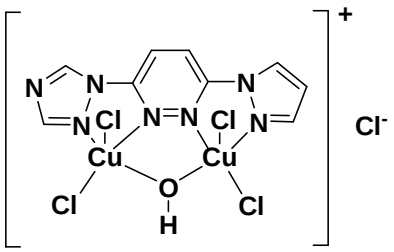
More recently, Padhye *et* al. [55] have described the synthesis of the bis (3,6-pyrazol-1-yl) pyridazine ligand and of the related Cu(II) complex **(20)**. The superoxide radical scavenging activity of this cationic dimeric species revealed that this compound was among the best SOD mimics (IC_{50} value of 3.90×10^{-7} M) whose antioxidant potential was nicely reflected in its antiproliferative and apoptosis inducing effects against estrogen independent breast BT-20 and androgen independent prostate PC-3 cancer cells. The

lowest IC_{50} values observed were 1.73 μM and 1.42 μM for BT-20 and PC-3 cells, respectively.



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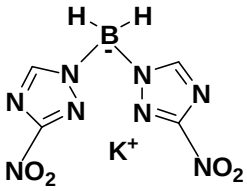
A series of Cu(I) mixed-complexes containing dihydridobis (3-nitro-1,2,4-triazolyl)borate **(21)** [63] sodium bis(1,2,4-triazol-1-yl)acetate **(22)** or sodium bis(3,5-dimethyl-pyrazol-1-yl)acetate **(23)** ligands [57],and phosphine coligands were tested for their cytotoxic properties against a panel of several human tumor cell lines.



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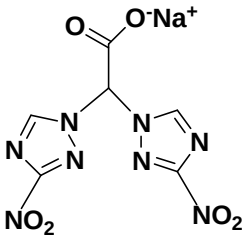

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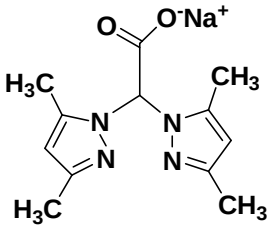
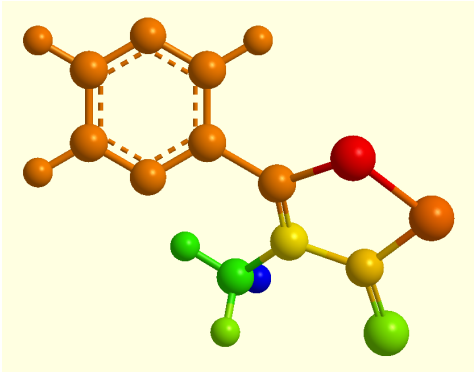


23

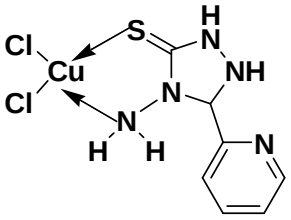
Copper complexes bearing a thioxo group, such as disulfiram, showed strong toxicity against cancer cell lines or cancer xenografts [28, 58]. The rich redox chemistry of the thione group [59] can confer interesting biological properties, as demonstrated by the chemopreventive agent **(26)** [60] which were reported to induce protective biological mechanisms against radical generation.



24

Dallavalle *et al*. [61] demonstrated that the 4-amino-5-(pyri-din-2-yl)-2H-1,2,4-triazole-3(4H)-thione copper(II) complex **(25)** exhibited in HT1080 human fibro sarcoma cells a cytotoxic activity comparable to that exhibited by cisplatin. Interestingly, normal human fibroblasts (HF) were not sensitive to the cytotoxic effects of **(25)**. These effects were further investigated, leading to the conclusion that **(25)** caused a variant of programmed cell death (PCD) clearly distinct from apoptosis [62]. Indeed, the morphological hallmark of the death process induced by **(25)** was found to consist of a massive cytoplasmic vacuolization. No

evidence of nuclear fragmentation neither of caspase-3 activation, biochemical features of apoptosis [63,64] were observed. These results suggested that **(25)** drove sensitive cells toward a nonapoptotic PCD because it blocked caspase-3-dependent apoptotic pathways. Similar cellular effects have been recently described in human ovarian adenocarcinoma cells treated with some Cu(I) phosphine complexes (vide infra) [65].



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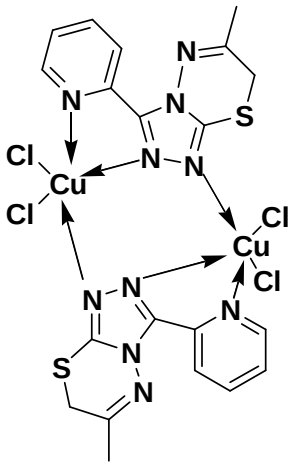

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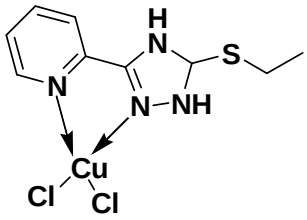


27

To gain insight into the SARs of thioxo-1,2,4-triazole copper(II) complexes, Tardito *el al.* [66] modified the thioamido function of the ligand 4-amino-5-(pyridin-2-yl)-2H-1,2,4-triazole-3(4H)-thione. The resulting Cu (II) thioether complexes **(26)** and **(27)** were less potent than **(25)** showing, in HT1080 cells, IC_{50} values of 100, 68 and 12 μM, respectively. The complexes **(26)** and **(27)** also triggered the same peculiar type of cell death observed in **(25)** treated cells, hallmarked by an extensive cytoplasmic vacuolization in the absence of apoptotic or oncotic features. HT1080 fibrosarcoma cells and HeLa cells exhibited a marked sensitivity to **(25)**, while normal human fibroblasts and SW872 liposarcoma cells were substantially insensitive to the complex. The sensitivity to **(25)** appeared to be correlated with the ability of the complex to facilitate copper accumulation in the cells, which, in turn, might be related to the enhanced stability of **(25)** conferred by the thioamido coordination. In HT1080 cells treated with **(25)**, copper uptake was paralleled by an evident perturbation of the cell oxidative status, as indicated by a 5-fold increase of the oxidized form of GSH, pointing to an interaction of the metal with cell thiols.

Phenanthroline and Bipyridine Complexes: The metal chelator 1, 10-phenanthroline (phen) and copper salts form stable bis-phen complexes which showed nuclease activity in the presence of reducing agents and molecular oxygen. The biological activity of such cuprous complexes was investigated by Sigman *et al.* since the seventies [67] and reviewed in the nineties [68]. The bis-phen complex $[Cu(phen)_2]^+$ **(28)** was described as an agent able to oxidatively degrade DNA and RNA by attacking the sugar groups [68]. In addition, it has been shown to exhibit interesting clinical activities including antitumoral, antimycobacterial, antifungal and antimicrobial properties [69,70]. The DNA cleavage activity of $[Cu(phen)_2]$, which was significantly more reactive than the mono-phen complexes [71-84], was supposed to occur according to the following mechanisms[85]:

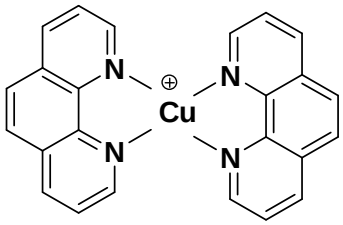
a) $[Cu(phen)_2]^{2+}$ is reduced in solution to $[Cu(phen)_2]^+$

b) $[Cu(phen)_2]^+$ binds DNA non-coordinatively

c) $[Cu(phen)_2]^+$ is oxidized to $[Cu(phen)_2]^{2+}$ by H_2O_2 produced in situ;

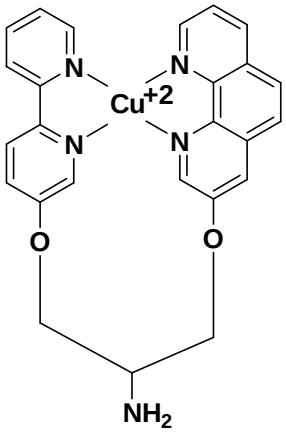
d) upon oxidation, the metal ion gains one ligand leading to Cu-"oxo" and/or Cu-"hydroxyl" species, the exact nature of which is still unknown;

e) an oxidative attack mediated by these copper compounds leads to DNA cleavage mainly at C-1', C-4', or C-5' of the 2-deoxyribose units [80,81,86].



28

Zhou *et al.* have reported that [Cu $(phen)_2$] induced G1-phase specific apoptosis in liver carcinoma Bel-7402 cell line [87]. More recently, Cai *et al.* [88] demonstrated that the apoptosis pathway in Bel-7402 cells treated with [$Cu(phen)_2$] might be initiated by the excessive copper in cells transported by the lipophilic phen ligand. Moreover, the catalysis of the redox-active copper with intracellular reductants induced an increase of ROS production and a decrease of the GSH/GSSG ratio. Furthermore, the same complex exhibited a potent cytotoxicity against human leukaemic HL60 cells and human stomachal SGC-7901 cells, with growth inhibition up to 90% [89]. On the other hand, the use of Cu-phen complexes presents some restrictions: **a)** their formation is rather unfavorable under physiological conditions because of the very small association constant of the second phen; **b)** $[Cu(phen)_2]^{2+}$ shows a minor DNA sequence selectivity, although it is not nucleotide specific. In an effort to overcome these limits, Pitie *et al.* [90] used a serinol bridge (abbreviated as Clip) to link two phen ligands on positions 2, resulting in [Cu(2-Clip-phen)]$^{2+}$ **(29)** and 3, resulting in [Cu(3-Clip-phen)]$^{2+}$ **(30)** [91]. These chemical modifications led to several advantages: **a)** the link ensured that the two phen ligands coordinated to Cu; **b)** [Cu(2-Clip-phen)]$^{2+}$ and [Cu(3-Clip-phen)]$^{2+}$ complexes turned out to cleave DNA macromolecules 2 and 60 times more efficiently than $[Cu(phen)_2]^{2+}$, respectively, using a mechanism similar to that shown by the bis phen complex [90,92,93]. The reason for this increase in DNA-cleavage activity was not completely clear, but it was supposed to arise from structural characteristics [94] rather than from electronic properties.The presence of the serinol bridge has allowed the functionalization of copper phen compounds with sequence specific anticancer drugs, rendering the compound highly sequence selective and possibly even providing it with anticancer properties. In this respect, examples included a conjugate of 3-Clip-phen with a distamycin analog [95-97] or a cisplatin derivative [98]. The combined interest in (i) improving the DNA cleavage specificity of **(30)** type complexes together with their ability to perform double-strand breaks (DSB) and (ii) circumventing drug resistance owing to the use of cisplatin [99-103] inspired the design of bi-functional molecules (**31a**) and **(31b)** [98]. It has been proposed that the amino group of [Cu (3-Clip-Phen)] **(30)** could be protonated, favoring its interaction with the polyanionic structure of DNA [91]. Thus, it could interact *via* hydrogen bonding with the oxygen atom of the phosphate, thereby pointing toward the minor groove [104,105]. The *in vitro* cytotoxic activities of **(31a)** and **(31b)** have been determined for several human cancer cell lines and a significant antiproliferative activity of **(30)**, **(31a)** and **(31b)** has been measured on the L1210 murine leukemia cell line [106]. Results showed that, in most cases, **(31a)** was more efficient than **(31b)** [98,107]. These noticeable activities confirmed the high potential of [Cu(3-Clip-Phen)] as an antitumor agent and strengthened the potential of strategy to prepare hybrid [Cu(3-Clip-Phen)/ *cis*-Pt] derivatives.



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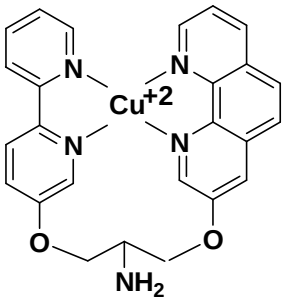

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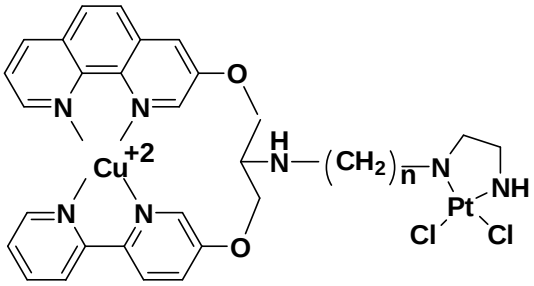
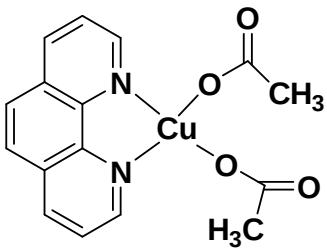


31

a. n=6
b. n=10

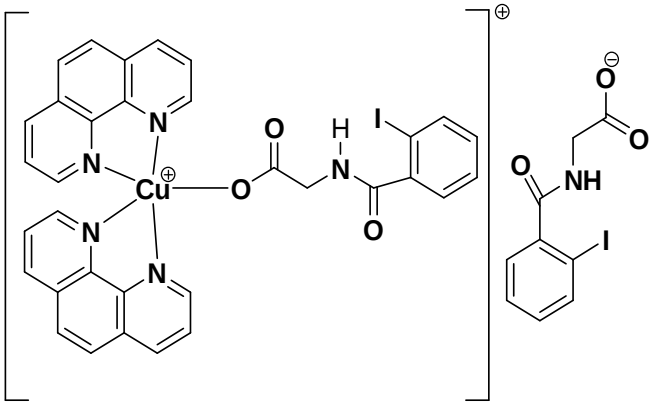
The chemotherapeutic potential of $[Cu(phen)_2(mal)]\cdot 2H_2O$($malH_2$=malonic acid) was determined by Egan *et al*. [108] using two human cell lines (A-498 kidney carcinoma and Hep-G2 hepa- to cellular carcinoma). Phen and the copper-phen complex induced a concentration-dependent cytotoxic effect; in particular, the metal complex demonstrated the greatest cytotoxic response, between 3 and 18 times greater than that observed with cisplatin. The $[Cu\ (phen)_2(mal)]\cdot 2H_2O$ complex inhibited DNA synthesis which did not appear to be mediated through intercalation. Also, the potential cancer chemotherapeutic application of this compound was seen to be enhanced by results obtained from Ames tests [109], which showed that this agent and its phase I metabolite were mutagenic. In an effort to throw some light on the SARs of this class of copper complexes, Devereux *et al*. [110] have studied systems in which only two nitrogen atoms (either as chelates or monodentate ligands) were bound to the copper centre. In particular, a series of Cu(II) carboxylate complexes, some containing one chelating, phen or bipy, have been prepared and characterized. All of the complexes were poor catalase mimics in the presence of imidazole and totally inactive in its absence. Conversely, all the complexes exhibited excellent SOD mimetic activity. The phen derivatives $[Cu(CH_3COO)_2(phen)]$ **(32)** and [Cu(sal)(phen)] (salH = salicylic acid) displayed potent *in vitro* cytotoxicity against human hepatic Hep-G, renal A-498 and lung A-549 cancer cell lines, approximately seven times higher than that shown by cisplatin. They were relatively soluble and they had cytotoxicities comparable with those of the copper (II) bis-phen complexes [108]. The lack of correlation between the SOD and cytotoxic activities supports the notion that mechanisms other than SOD mimicking may also be responsible for the anticancer properties of these complexes.



32

A series of copper-based drugs registered with the name of Casiopeinas (CAS) has been developed by Ruiz-Azuara *et al*. [111,112]. These compounds are mixed chelate copper (II) complexes with a general condensed formula $[Cu\ (N–N)(A–A)][NO_3]$, where N–N represents neutral diimmine donors, either phen

or bipy, A–A stands for uninegative N–O or O–O donors, either aminoacidates or acetylacetonate [113-124]. CAS were designed as a chemotherapeutic alternative for cancer treatments and, according to some preliminary experiments, some of them have indeed shown antineoplastic activity both *in vitro* and *in vivo* [113,116] and were able to induce apoptosis in murine cancer cell lines, such as L1210 and CH1 [114]. Experiments in rats employing one of the most promising derivatives **(32)**, showed a strong inhibition of cell proliferation against C6 glioma cells. It was observed that the drug promoted an increment in ROS which in turn caused subsequent damage to mitochondria followed by apoptosis elicited through both, caspase-dependent and caspase-independent pathways [124]. However, besides mitochondria, other potential cellular targets have been identified. Actually, COMET assay in peripheral blood lymphocytes and HeLa cells suggested a potential DNA damage that seemed related to the nature of the substituents on the chelate structure. The mechanism of action could be consistent with the promotion of the Fenton and Haber–Weiss like reactions [125,126] due to reduction of the coordinated copper(II) to copper(I), with subsequent generation of ROS, which might react with different macromolecules causing a general cellular oxidative damage [120,127]. Escriba *et al.* [128] have described the synthesis, structural characterization and biological activity of a ternary copper (II) coordination complex with phen and an amino acid conjugated with the ortho-iodohippurate **(33)**. This ternary complex generated the copper(I) species $[Cu(phen)_2]^+$ in aqueous solution without the addition of any external reductant, possibly by an intramolecular redox process in the presence of oxygen; the ESI-HRMS spectra confirmed the presence of the ternary species, but after 24h, $[Cu(phen)_2]^+$ was the main product. The complex was able of cleaving pBR322 plasmidic DNA confirming the nuclease effect. Moreover, tested on A549 human non-small lung adenocarcinoma cells, it induced a marked growth inhibition and apoptosis at nanomolar concentration. The molecular mechanisms underlying this inhibitory effect was studied by flow cytometry analyses that revealed that **(33)** induced a marked decrease in the number of cells in phases G1, S and G2/M and an increase in the number of apoptotic cells. The induction of apoptosis was confirmed by microscopic analyses of treated cells and by determination of poly ADP-ribose polymerase (PARP) fragmentation through immunoblotting. Moreover, treatment with the same concentrations of **(33)** did not affect adipocyte survival attesting a useful selectivity against cancer cells.



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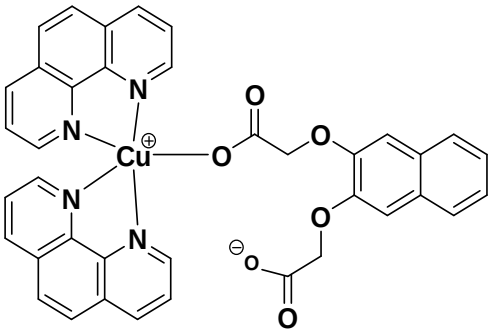
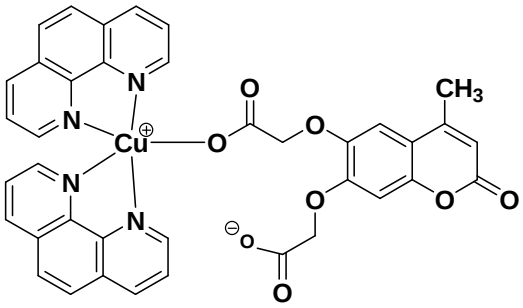


34

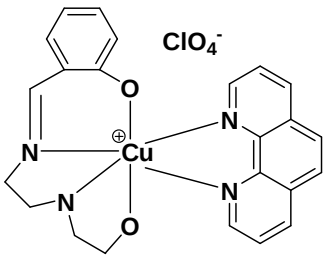
Egan *et al.* have investigated the potential *in vitro* anti-proliferative properties of the ligands coumarin-dioxy-acetic acid (cdoaH2) [129] and 4-methylcoumarin-6,7-dioxyacyeic acid (4-MecdoaH_2)[130]and their phen-copper complexes $[Cu(cdoa)(phen)_2]$ **(34)** [130] and $[Cu(4\text{-}Mecdoa)(phen)_2]$ **(35)** [129]. The results indicated that copper complexes, rather than the ligands, could alter the proliferation of both human neoplastic renal (A-498) and hepatic (Hep-G2) cells, while hepatic non-neoplastic cells (Chang) appeared to be less sensitive. However, this effect was not mirrored in non-neoplastic renal (HK-2) cells, a profile shared with cisplatin. The complexes were shown to decrease cellular DNA synthesis, but did not

intercalate with it. Based on IC_{50} values, **(34)** and **(35)** were shown to be almost 6 and 12 times more potent as antitumor agents than cisplatin, respectively. Moreover, there was no evidence that P-glycoprotein (P-gp)-mediated multi-drug resistance (MDR) was likely to play a role in decreasing the anti-proliferative activity of the complexes. Cytological stains, analysis of genomic DNA, and biochemical assays (caspase-3 and -9 and PARP proteins), suggested that cell death could switch between apoptosis and necrosis. Additionally, flow cytometric analysis showed that the complexes functioned through an alteration in cell cycle progression.



35

Another series of mixed ligand $[Cu(tdp)(N\text{-}N)]^{+}$ complexes, where Htdp is the tetradentate ligand 2-[(2-(2-hydroxyethylamino)-ethylimino)methyl] and N-N is bipy, phen, 3,4,7,8-tetramethyl-1,10-phen (tmp) and dipyrido-[3,2-d:2',3'-f]-quinoxaline (dpq), have been isolated and characterized by Palaniandavar *et al.* [131]. The representative complex [Cu (tdp)(phen)][ClO_4] **(36)** has been structurally characterized showing a distorted octahedral geometry around copper(II). Coordinated dpq and phen were found to be involved in strong partial intercalation into the DNA base pairs in the minor groove. Instead, the tmp-complex was involved in strong hydrophobic interaction with DNA through the four methyl groups on phen ring, which was relevant to its ability to confer the B to A conformational change on DNA. All the complexes cleaved super-coiled DNA in the presence of ascorbic acid as reducing agent with the phen- and dpq-complexes exhibiting cleavage efficiencies higher than those of the other complexes. It is noteworthy that the [Cu (tdp)(tmp)][ClO_4] complex **(37)**, despite its lower DNA binding and cleavage activity, exhibited the highest anticancer activity against the human cervical epidermoid carcinoma ME180 cell line. Its potency was also greater than those of cisplatin and mitomycin C, which are currently in clinical use for treating cervical cancer. All the complexes brought about condensation and breakage of chromatin into clumps typical of apoptosis and also caused necrotic cell death.



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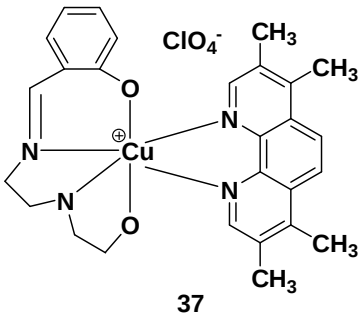
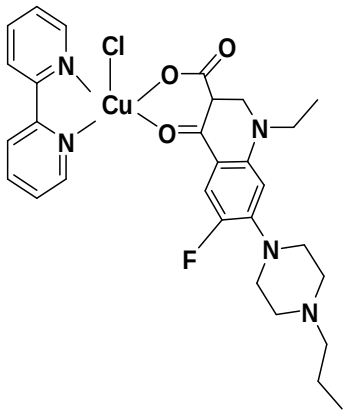


37

Miscellaneous Complexes: The sequestering agent 1,2-propylenediamine-N,N,N,N-tetra-acetic acid (PDTA) has been proposed as a good example of a polycarboxylic ligand forming active metal complexes against several human tumour cells [132-135]. It is well known that Cu(II) complexes with chelating ligands play an important role as models of the associative complexes involved in the substitution reactions at the copper site of SOD enzymes; indeed, strongly donor ligands as PDTA should favour the

formation of six-coordinate copper complexes [136]. Based on these arguments, an octahedral monomeric compound $[Cu(PDTA\text{-}H_2)(H_2O)_2]\cdot H_2O$ was synthetized by Kamah *et al.* [137]. Potentiometric and electronic measurements identified the ligand as tetradentate, two nitrogen and two oxygen atoms being bonded to the Cu (II) in planar positions. The anticancer properties of this complex have been evaluated against ovarian tumour TG cell line and solid tumour Sarcoma 180 [137]. The results attested a significant *in vitro* antitumor activity (ID_{50} = 2.29 μM at 48h) and an important *in vivo* antitumor activity with complete regression of the tumor at a dose of 12.5 mg kg^{-1} body weight. Quinolones, a commonly used term for the quinolonecarboxylic acids or 4-quinolones, are a group of synthetic antibacterial agents containing the 4-oxo-1,4-dihydroquinoline skeleton. The interaction of diverse metal ions with quinolones has been thoroughly studied [138]. Biological properties of quinolones have been monitored with regards to their interaction with DNA [139,140], cytotoxicity [141-143] and potential antitumor activity [144,145]. Hpr-norfloxacin is the N-propyl protected form of norfloxacin and is a typical quinolone that can act as a bidentate ligand through the pyridine oxygen and one carboxylate oxygen atom [138]. The interaction of Cu (II) with Hpr-norfloxacin in the presence of bipy to give complex **(38)** has been studied in an attempt to examine the mode of binding and possible synergistic effects [146]. Complex **(38)** showed a concentration dependent antiproliferative effect as well as a time and concentration dependent necrotic effect on both human HL-60 promyelocytic leukemia and chronic myelogenous leukemia K562 cells.



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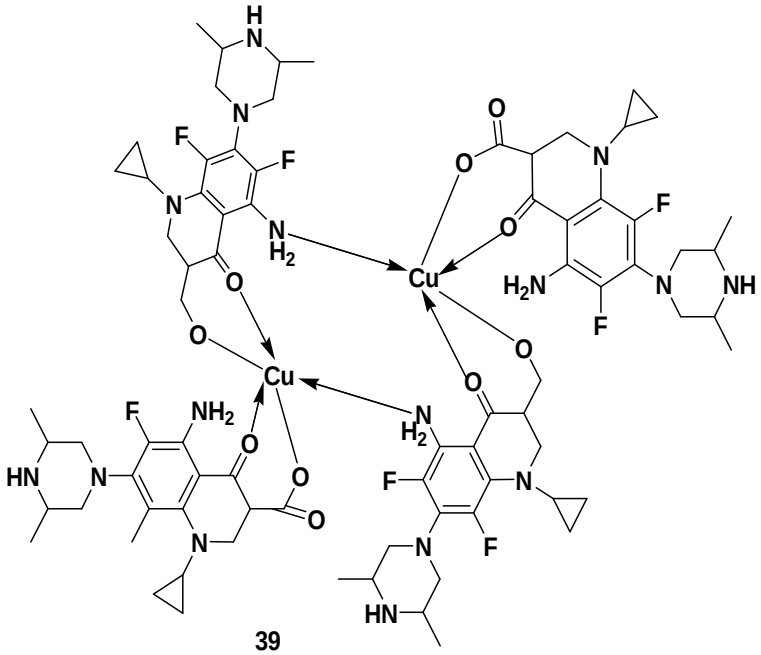
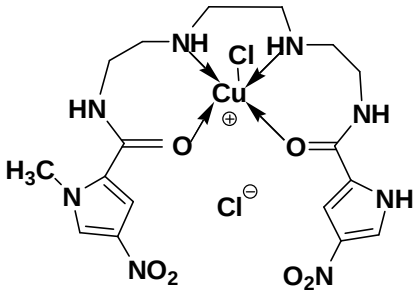


39

Sparfloxacin is the first aminodifluoroquinolone currently available in Japan and United States for clinical use as antibacterial agent [147]. Padhye *et al.* [148] described the synthesis, characterization and antiproliferative activity against hormone independent BT20 breast cancer cell line of the sparfloxacin mixed-ligand copper complexes, with appended ancillary ligands such as bipy, phen and 4,5-diazafluoren-9-one. Amongst the compounds examined, the dimeric copper compound **(39)** was the most potent derivative. This suggested that the facile Cu^{2+}/Cu^{+} redox couple might act as redox trigger for activating apoptotic processes [148].

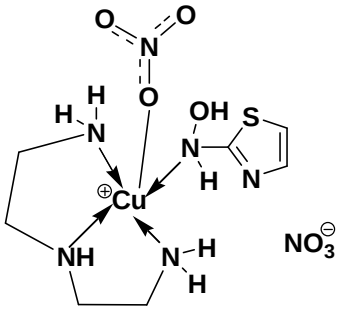
Polyamine complexes with pyrole and others arms substituents have been synthesized and characterized by Yang *et al.* [149]. The structure of **(40)** with the N1,N8-bis(1-methyl-4-nitropyrrole-2-carbonyl) tri ethylenetetramine ligand was investigated with theoretical DFT calculations, and the DNA-binding of the

Cu(II) complex and its effects on tumor cell viability were examined. The results showed that the mode of binding of the complex to DNA was the classical intercalation; moreover, **(40)** efficiently cleaved plasmid pBR322 DNA suggesting that it worked as a new kind of chemical nuclease. At 1 μM concentration, **(40)** induced a 34% reduction of human QBC-939 biliary tract carcinoma cell viability. Diethylentetramine (dien), a biologically occurring substance, represents an excellent complexating reagent, capable of coordinating to a number of transition metal ions, including Cu (II).



40

Bolos *et al.* [150] have synthetized some mixed-ligand copper complexes with dien and thiazole or imidazole derivatives that showed antiproliferative activity against a panel of human cancer cells. In particular, the complex **(41)**, with the 2-amino-5-methylthiazole ligand, was cytotoxic against human cervical HeLa, breast T47D, colon HT-29 cancer cells (IC_{50} values ranging from 41 to 131 μM), whereas normal fibroblasts were not affected. The absence of apoptotic pattern and a strong inhibition of cell cycle progression as well as of DNA synthesis were detected in tumor treated cells. The authors suggested that G2/M cell cycle arrest could be related to p34cdc2 inhibition by tyrosine phosphorylation and/or to induction of cyclin-dependent kinase inhibitor $p21^{WAF1}$.



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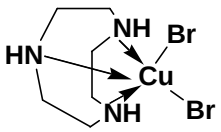
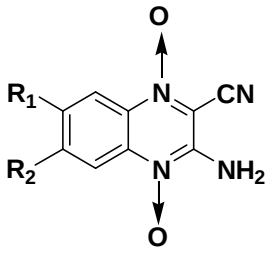


42

Edvetz *et al*. [151] have reported that the copper(II) complex **(42)** with the 1,4,7-triazacyclononane ligand, possessed an anticancer activity against the human ovarian NuTu-19 cancer cell line comparable with that shown by cisplatin. 4-Nitropyridine N-oxide and its methyl derivatives represent an important group of compounds due to their potential biological applications as radiosensitizers, cytotoxins, antifungal, antibacterial, anti-inflammatory and tranquilizing substances [152]. It was found that the degree of electron flow between the para positioned electron withdrawing (NO_2) and electrodonating (NO) groups is strongly dependent upon the nature of ring substituents [153]. For example, the introduction of one or more methyl groups may modify hydrophobicity with consequences for molecule transport through the cellular membrane [152]. The N-oxide group is known to be a binding site to metal centers, including copper. *In vitro* studies on the antiproliferative activity of copper complexes containing various methyl substituted 4-nitropyridine N-oxides showed a significant sensitivity of human MCF-7 breast cancer cells depending upon the number and position of the methyl groups. Several heterocyclic N-oxides and related compounds

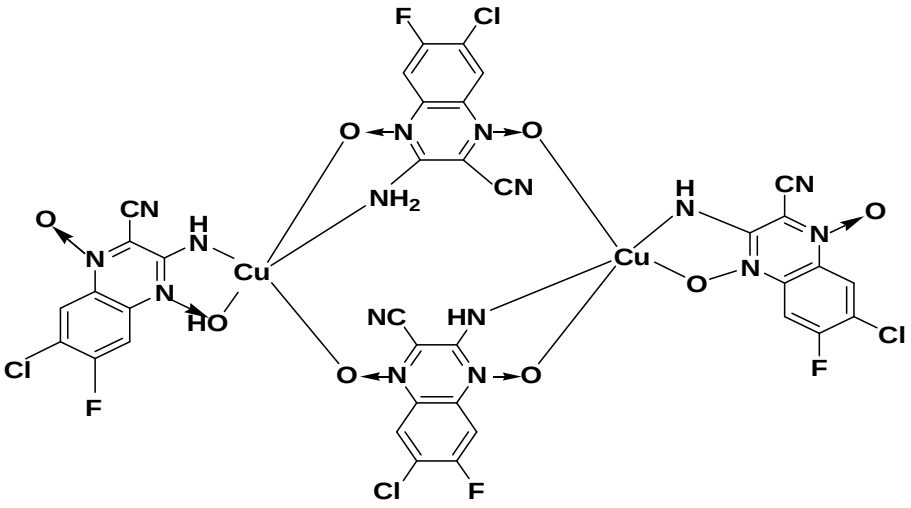
such as quinoxaline N-dioxide derivatives can be reduced in hypoxic conditions forming cytotoxic species having DNA as the main biological target [154-156]. Recently, Torre *el al.* [157-159] have developed some copper(II) complexes as selective hypoxic cytotoxins trying to improve the bioavailability and the pharmacological and toxicological properties of the 3-aminoquinoxaline-2-carbonitrile N1,N4-dioxide (AQCD) derivatives, **(43a)** and **(43b)**, which have proved to act as bioreductive compounds [157-159]. In these first series, the cytotoxicity in hypoxia of copper (II) complexes was similar or slightly better than that of the free ligands whereas, under well-oxygenated conditions, the complexes were almost non cytotoxic [159,160]. Subsequently, a new series of Cu (II) complexes with other AQCD derivatives were synthesized and characterized by different spectroscopic methods [161].



43

a. R_1=Cl, R_2=Cl
b. R_1=Br, R_2=Br
c. R_1=F, R_2=Cl
d. R_1=H, R_2=H
e. R_1=Cl, R_2=OMe

The hypoxic selective cytotoxicity towards V79 cells and the SOD like activity of the complexes were determined and related to physicochemical properties. In particular, the copper (II) complex with **(43c)** showed cytotoxic selectivity in hypoxia being the most lipophilic compound of the series. On the contrary, the complex [Cu–(**43d**)] was cytotoxic but not selective and [Cu–(**43e**)] was not cytotoxic towards V79 cells neither in oxia nor in hypoxia, probably due to its insolubility or its low lipophilicity. In addition, the potency for the hypoxic selective complex **(44)** and the previously reported complexes [Cu–(**43a**)] and [Cu–(**43b**)] [157-159] could be correlated with the sum of Hammett σm constants, showing that compound with better hypoxic potency have higher σ values due to the halogen substituents in aromatic rings.



44

Hydroxamic acids (HAs) are important bioligands [162] involved in numerous biological processes including metal-ion trans-port and inhibition of metalloenzymes [163,164]. Several HAs compounds, including benzo-hydroxamic acid HBHA and substituted-HBHA analogues [165], and phthal-hydroxamic acid HPHA have been synthesized and tested for their antitumour properties, most of them showing significant cytotoxic activity. Furthermore, complexes of the type $[Cu(BHA)_2]$ were isolated and evaluated not only for their efficacy in tumour cell growth inhibition and enhancement of longevity in tumour-bearing mice, but also as correctors of the perturbed biological parameters produced by the action of oxygen free radicals [166]. Treatment of Ehrlich ascetic carcinoma bearing mice with $[Cu(BHA)_2]$ (25 mg/kg, ip dose/day, 4 days) resulted in a significant cancer growth inhibition (65%) and increase of tumour-bearing mice life span (150%). Additionally, the early perturbed haematological parameters were totally restored by the host [167].

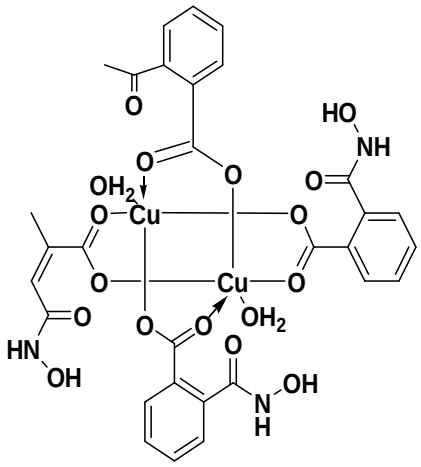
Wang *et al.* [168] have reported the self-assembly synthesis of the waterwheel-like dimetal HPHA complex **(45)** appended with four free hydroxamic acid groups. Waterwheel-like dimetal copper and zinc complexes were evaluated for their *in vitro* cytotoxic activity against SMMC-7721 and HO-8910 cancer cells. The relative cytotoxicities of copper and zinc compounds were similar and more predominant than those shown by HPHA (IC_{50}: Cu(II) > Zn(II) >> HPHA or $Cu(CH_3COO)_2{\cdot}2H_2O$). Copper complex was 40 and 11-fold more potent than HPHA toward SMMC-7721 and HO-8910 cells, respectively. It was proposed that these Cu compounds might induce cell death through necrosis pathways.

Choudhuri *et al.* [169] have described the effect of oxalyl bis(N-phenyl) hydroxamic acid and the metal chelate copper[N-(2-hydroxy-acetophenone) glycinate] **(46)** [170] on multidrug-resistant P-gp-expressing CEM/ADR5000 T-cell acute lymphoblastic leukemia cells. Compound **(46)** was found to overcome doxorubicin resistance by depleting GSH, by inhibiting GST through formation of (**46**)-GSH conjugates. Complex **(46)** also modulated P-gp-mediated drug resistance. Copper (II) complexes with NSAIDs belonging to the oxicam group, vizpiroxicam and meloxicam, have been described [171]. Piroxicam and meloxicam exhibited anticancer properties in various cancer cell lines and in animal models [172-176].

In a recent work by Cini *et al.* [177], the *in vitro* cytotoxic activity of copper (II) piroxicam **(47)** was tested against a panel of about 50 human tumor cell lines. The highest activity was relevant to small lung, non-small lung, central nervous system, melanoma, ovarian and renal cell lines. The growth inhibition values for many of these cells were significantly smaller (ca. 20 μM) than those found for carboplatin that was selected as reference drug [177]. Results from studies on oxygen radical scavenger activity by the octahedral **(47)** complex [178-180] showed that it was a better scavenger than copper (II) ion and free piroxicam [181].

CONCLUSIONS

The field of inorganic medicinal chemistry has boomed in recent years following the hallmark discovery of the anticancer activity of DNA-targeting cisplatin and later its analogs carboplatin and oxaliplatin. Nowadays, these platinum-based drugs are routinely used in cancer therapy regimens. However, analogous to many other chemotherapeutics, their therapeutic efficacy is limited by the development of drug resistance and severe adverse effects. This has provided great incentive for investigations of metal complexes with higher selectivity and enriched efficacy, thus creating a new paradigm in the field of anticancer drug discovery. Copper complexes containing aromatic heterocycles such as pyrazoles, triazoles and imidazoles, Schiff base ligands, phenanthroline and bipyridine complexes have been summarized in this review. In future the wide-ranging applications of copper complexes possibly will provide a target oriented information to the chemist to develop variable copper complexes with effectual antiproliferative activity.



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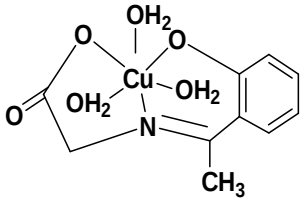

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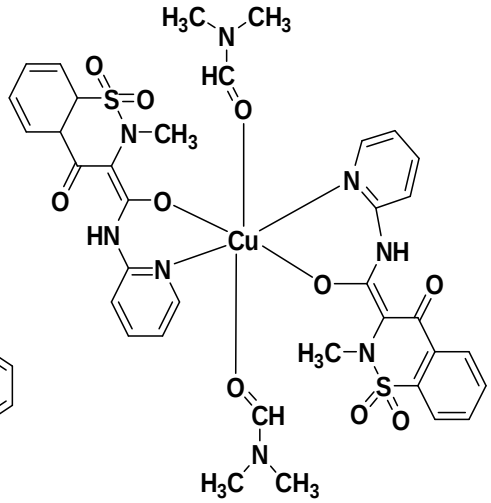

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