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Emergence of copper complexes in the ongoing battle against cancer

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Abstract

Copper has been described as the 'workhorse mineral'. It is ubiquitously involved in biological systems driving a vital array of chemical reactions that strengthen human health and development. Cu accumulates in tumors due to selective permeability of the cancer cell membranes. Because of this, a number of copper complexes have been screened for anticancer activity and some of them were found active both *in vivo* and *in vitro*. This review discusses the role of copper metal in biological processes in cells as they pertain to malignancy and highlight the application of the copper and its complexes with thiosemicarbazonein the design and development of metallodrugs for the treatment of cancer.

Keywords: Copper, metallodrugs , anticancer activity.

1. Introduction

Cancer is undoubtedly one of the main health concerns facing our society and one of the primary targets regarding medicinal chemistry. It is the second leading cause of death in economically developed countries and the third leading cause of death in developing countries. Discovery for new types of anticancer drugs is continuing and the mechanism of interaction of such drugs with DNA is under exploration. Cisplatin (cis-diamminedichloroplatinum(II)) is a widely used chemotherapeutic agent for the treatment of testicular cancer and it is used in combination regimens for a variety of other tumors, including ovarian, cervical, bladder, lung and those of the head and neck. Despite the success of cisplatin, problems regarding intrinsic or acquired resistance and side effects have encouraged the development of new platinum [1].Even though platinum-based complexes had been in primary focus of research on chemotherapy agents, the interests in this field have shifted to non-platinum-based agents, in order to find different metal complexes with less side effects and similar, or better, cytotoxicity. The choice of metal ion is the most important factor in the design of metal-based chemotherapeutic agent.

Varieties of metal complexes have been used as drugs and are well known to increase their activity or when administered as metal complexes show higher activity towards specific targets [2]. Copper is a bio-essential and bio-relevant element [3].Cu(II) is an essential element in human normal metabolism because of its functions as cofactor of several metalloenzymes. Copper is widely distributed in the biological system and copper 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. Because of this, a number of copper complexes have been screened for anticancer activity and some of them were found active both in vivo and in vitro [4]. Furthermore, copper(II)-based complexes appear to be very promising candidates for anticancer therapy; an idea supported by a considerable number of research articles describing the synthesis and cytotoxic activities of numerous copper(II) complexes [5].

In this field, copper complexes showed encouraging perspectives [6-10]. Copper-based complexes have been investigated on the assumption that endogenous

metals may be less toxic for normal cells with respect to cancer cells. However, copper can also be toxic due to its redox activity and affinity for binding sites that should be occupied by other metals. 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.

2. Copper Chemistry

Humans first used copper about 10000 years ago. A copper pendant discovered in Northern Iraq is thought to date back to around 8700 BC, and for nearly 5000 years copper was the only metal known to man. During the Roman Empire, copper was principally mined on the island of Cyprus, hence the origin of the name of the metal as Cyprium, "metal of Cyprus", later shortened to Cuprum, from which the chemical symbol Cu.

Copper is the 29th chemical element of the Periodic Table and belongs to the first row of Group 11 metals with electronic configuration $3d^{10}4s^{1}$. Thus, the Cu(I) ion has a completed $3d^{10}$shelland the Cu(II) ion, losing two electrons, has a partially filled d-block $3d^{9}$ configuration behaving as a common transition metal.

Copper is an essential trace nutrient to all high plants and animals. In mammals, it is found primarily in the bloodstream, as a co-factor in various enzymes, and in copper-based pigments. Out of a total of 80-120 mg in a healthy human adult of 70 kg there are 8 mg in liver, 15 mg in heart, spleen, kidneys, brain and blood. However, in sufficiently high amounts, copper can be poisonous and even fatal to organisms. In the form of bivalent ion, copper is very poisonous to lower organisms. For example, bacteria and other decay microorganisms die in water in a copper vessel, and copper com-pounds in general prevent growth of algae [11]. Analogously in humans, it can become toxic for cells at elevated concentrations [12]. Copper was found to bind DNA with high affinity than any other divalent cation, thus promoting DNA oxidation [13]. The binding of copper ions to specific sites can modify the conformational structures of proteins, polynucleotides or DNA and biomembranes [14]. This binding is dependent on copper size, charge electron affinity and geometry of the formed adduct. It is known that copper ions as Cu^{+}/Cu^{2+} in blue copper proteins act by changing the redox potential and facilitating electron transfer phenomena. A high degree of selectivity is reached in molecular recognition through transition metal ions, which can perform a change of valence in redox reactions [15].

One of the main mechanisms proposed to explain copper-induced cellular toxicity comes from the propensity of free copper ions to participate in the formation of ROS. Cupric and cuprous copper ions can participate in oxidation and reduction reactions. In the presence of superoxide ($*O_2^-$) or reducing agents such as ascorbic acid or glutathione (GSH), Cu(II) can be reduced to Cu(I), which is capable of catalyzing the formation of hydroxyl radicals ($OH^{\bullet}$) from hydrogen peroxide (H_2O_2) *via* the Haber-Weiss reaction [16]:

$$Cu(II) + O_2^{-\bullet} \rightarrow Cu(I) + O_2$$
$$Cu(I) + H_2O_2 \rightarrow Cu(II) + OH^{\bullet} + OH^{-}$$
$$---$$
$$O_2^{-\bullet} + H_2O_2 \rightarrow O_2 + OH^{\bullet} + OH^{-}$$

The highly reactive hydroxyl radical is able to interact with any biological molecule by abstracting the hydrogen from an amino bearing carbon to form a carbon centered protein radical and from an unsaturated fatty acid to form a lipid radical. This results in oxidative damage of cells [17]. In particular, it has been demonstrated that copper is capable of inducing DNA strand breaks and oxidation of bases by producing ROS. GSH was shown to inhibit free radical formation by copper ions in the presence of hydrogen peroxide, ascorbate and DNA. The protective effect of GSH was attributed to its ability to stabilize Cu(I), preventing redoxcyc lingand the generation of free radicals.

According to the below equation copper(II) also forms thioxyl radicals, RS•:

$$RSH + Cu(II) \rightarrow RS^{\bullet} + Cu(I) + H^{+}$$

and copper-cysteine and copper-methionine ions, which may produce metallothioneines and disulfides, RSSR, that can be damaging [18]. Anyway, when considering copper as a metal participating in Fenton chemistry, it has to be reminded that intracellular free copper is limited to less than one free copper ion per cell, thus suggesting a significant over capacity for chelation of copper in the cell [19].

3. Copper Homeostasis

As already mentioned, excess accumulation of copper as well as its deficiency can be deleterious to human health; therefore, copper homeostasis is tightly regulated [20]. A conserved group of proteins that contain unique cysteine, methionine or histidine-rich domains referred to as metal binding sequences maintain the concentration of free Cu in cells at $< 10^{-18}$M [26]. Figure 1presents a summary of the known Cu homeostasis pathways in mammalian cells. Dietary copper is absorbed from the stomach and small intestine and then enters the blood circulation through mainly the action of ATP7A protein (Menkes protein). Most of the copper in normal human serum is bound to ceruloplasmin, an enzyme containing six copper atoms both in Cu(II) and Cu(I) state. Copper in this form is not exchangeable. The exchangeable form of

copper is bound to albumin and amino acids [21]. Copper-histidine complex was identified as the main copper-amino acid complex in human serum. It was also shown that human albumin forms a ternary complex with copper-histidine [22, 23].

During the uptake process, Cu(II) is reduced to Cu(I) by a hypothetical membrane bound metalloreductase and is absorbed by the cell through the transmembrane transporters. The main copper influx transporter in human cells is the 190 amino acid Cu transporter 1 (hCtr1). hCtr1 resides predominatly in the plasma membrane and is expressed in highest levels in the liver, kidney and heart, followed by the intestine, with the lowest level in the brain and muscle. It has been suggested that hCtr1 binds copper *via* the methionine and histidine–rich amino terminal domain and trans-ports it across cell membrane through pores [24]. Competition experiments have also demonstrated that hCtr1 is a monovalent metal transporter [25].

Upon entering the cytoplasm, copper may be complexed to a variety of ligands to prevent the interaction of free copper with cellular membranes, proteins, or DNA that can lead to oxidative damage. However, it is thought that the majority of cytoplasmatic copper is complexed to GSH as Cu(I) [26].The Cu(I)-GS complex can then donate copper to various intracellular proteins such as metallothionein (MT), a family of proteins important for metal detoxification [27]. Another important class of molecules that are vital for copper delivery is copper chaperones. This is a group of cytosolic peptides that includes ATOX1 (HAH1),that delivers Cu to the P-type ATPase ATP7A and ATP7B at the *trans*-Golgi net-work, COX17 that delivers Cu to cytochrome-c oxidase in mitochondria and CCS1 which loads Cu onto cytoplasmic SOD [28]. To avoid copper excess, mammals cells have two structurally similar P-type ATPases, ATP7A and ATP7B, that mediate the cellular efflux of Cu. Defects in the function of ATP7A produce Menkesdisease, while defects in ATP7B cause Wilson disease. ATP7A is expressed in the intestinal epithelium [29] as well as most other tissues except liver [30]. ATP7B is expressed in liver and kidney and to a lesser extent in brain of normal individuals [31]. Both proteins function as monomers and have 8 membrane spanning domains and 6 repeats of GMTCXXCIE motif that has very high affinity to copper [19]. Binding of copper to ATP7A and ATP7B triggers highly regulated subcellular relocalization that involves movement from their basal position in the trans-Golgi network to other vescicular compartments, and in the case of ATP7A, to the plasma membrane [19].

Recent studies have demonstrated that copper transporters including hCtr1, ATP7A and ATP7B, are involved in the import, subcellular distribution and export of cisplatin-related drugs. This means that Cu transporters can regulate the sensitivity of human cancer cells to platinum drugs. These observations are undoubtedly appealing, because conventional thinking of the inorganic physiologic chemistry of cisplatin and copper is quite different. Up to now, the mechanisms by which these transporters shuffle platinum-based antitumor agents are largely unknown. The Cu transporters are excellent at discriminating between closely related metal ions, and even between Cu(I) and Cu(II). Thus, their promiscuity with respect to the Pt drug suggests that alterations in platinum drug cellular pharmacology associated with a modified expression of the copper transporters are mediated by secondary effects of Cu on other metabolic pathways, such as MT and GSH levels [19].

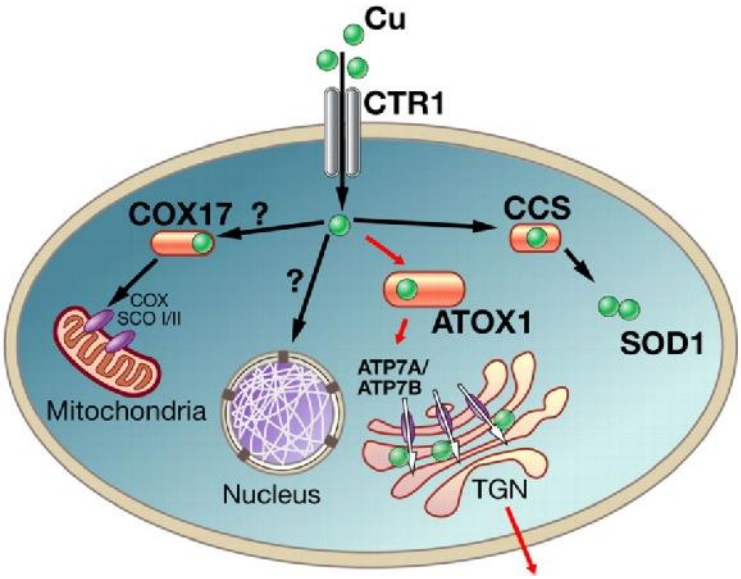


Fig.1 Homeostatic regulation of copper in the body

4. Copper, Angiogenesis And Proteasome Pathway

The involvement of copper in angiogenesis has been known for a couple of decades [32, 33]. Folkman [34, 35] pioneered the concept that tumor growth requires angiogenesis and this requirement might be an Achilles heel for cancer because in adults there is little requirement for angiogenesis. The concept of anti-angiogenic therapy for cancer has taken off in the last decade[35].Researches aimed at understanding the role of copper in promoting angiogenesis demonstrated that this metal interacts with several proangiogenic factors. Despite the functional significance of these interactions remains often unclear, it has been suggested that the role of copper in angiogenesis is preferable to several mechanisms: i) copper may act through binding of angiogenic growth factors and increasing their affinity for endothelial cells, as with angiogenin, ii) copper may control the secretion of angiogenic cytokines, as demonstrated with FGF1 and IL-1 and iii) copper may induce expression of angiogenicgrowth factors such as VEGF [36]. Thus, therapy aimed at depleting copper may be a successful anticancer strategy which may target multiple angiogenic growth factors. Several anti-copper drugs used in Wilson disease [37] have been evaluated for use in cancer. It has been shown that three copper chelators, such as *D*-penicillamine, trientine, and tetrathiomolybdate (TM) [38], which quickly and effectively deplete copper stores, have antiangiogenic effects in murine cancer models [39,40]. In particular, promising results *in vitro*, in preclinical animal models and in an early (phase I) clinical trial have led to ongoing phase II evaluation of TM in patients with advanced cancers [36].

Recently, it has been demonstrated that mixtures of dithiocarbamates (DTCs) or clioquinol with Cu(II) salts spontaneously bind with tumor cellular copper forming a proteasome inhibitor and an apoptosis inducer. The anti-angiogenesis effects, as well as the potential use of proteasome inhibitors in cancer therapies, have been extensively reviewed [41,42]. It has been found that, like other established proteasome inhibitors, copper-binding compounds were only effective in inducing ubiquinated protein accumulation and apoptosis in tumor, but not in non-trasformed cells. Therefore, it can be hypothesized that such a strategy could result in highly effective and selective cancer killing that avoids toxicity.

It is important to note that not all copper-binding compounds have proteasome-inhibitory and apoptosis inducing capability. For example, TM and ethylenediaminetetraacetic acid are potent copper chelators but have no proteasome-inhibitory activity when combined with copper [43]. However, the ability of some copper-binding compounds to inhibit the proteasome and induce apoptosis by themselves in copper-enriched cancer cells is promising for their development as anticancer compounds in a non toxic chemotherapeutic strategy [44].

5. 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 [45].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) atypical in their preference for distorted coordination geometries, they are much less structurally predictable than other first-row transition metal complexes.

Due to the closed-shell d^{10}electronic configuration, Cu(I) complexes are usually colorless solids and strongly prefer ligands having soft donor atoms such as P and aromatic amines. Although two coordinated linear and three-coordinated trigonal arrangements are known, Cu(I) complexes are mostly four-coordinated species adopting a tetrahedral geometry.

The d^9 electronic configuration typical of Cu(II) derivatives promotes, instead, d-d transitions resulting in intense colored species. In these complexes the coordination number varies from four to six, including four-coordinate square planar (sp), five-coordinate trigonal bipyramidal (tbp) and six-coordinate octahedral (oc) geometries. The variety of accessible arrays allows for a great assortment in the choice of the ligands (from mono to hexadentate chelates) and of the donor atoms (N, O, S, and halides) [46].

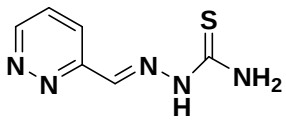
The redox potential of the physiologically accessible Cu(I)/Cu(II) couple varies dramatically depending upon the ligand environment due to the donor set, geometry, substituent electronic and steric effects, and chelation [47]. For example, in the one-electron oxidation of Cu(I) complexes toward dioxygen, a wide range of reduction potentials (from -1.5to+1.3Vvsstandard hydrogen electrode) [47] is known for copper complexes. In addition, such an electron transfer always involves important modifications of the stereochemistry of the pertinent oxidized/reduced complexes. This feature together with the possibility to release coordinating groups ongoing, for example, from octahedral Cu(II) to tetrahedral Cu(I) species, are chemical factors that illustrate the complexity of the Cu(I)/Cu(II) system in physiological media [48,49].

This review describes advances in the synthesis, design, and development of copper complexes as anticancer agents in the last 4 years. Interest in this field has rapidly grown in recent years, as illustrated by the increasing number of publications reported

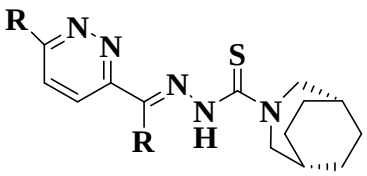
since 2000. This summary covers the period 2008−2012 and follows our previous efforts in the samearea. Onlydiscrete copper complexes have been included in this review. Other preparations referred to as 'mixtures of copper compounds' comprising copper(II) salts mixed with ligands without a clear structural identification of the resulting copper complex have not been considered.

6.Thiosemicarbazone Complexes

Thiosemicarbazones (TSCs) are a class of compounds of medicinal interest whose anticancer activity has been reported as early as 1960s [50,51]and their development is still in progress [52-56].Some of them, such as Marboran TM or Triapine TM, are in the clinical practice [57].TSCs have been intensively studied due to their inhibitory action on the DNA enzyme ribonucleotide diphosphate reductase and their selectivity towards hormone-responsive cancers [58].For many years it has been known that a large number of bisthiosemicarbazones (bTSCs) and series of their copper complexes showed promising antitumor activities [59-61]. A critical property of many of these copper complexes is the poor water solubility and the relatively high in vivo toxicity [62,63].Many attempts have been made in the last decades to improve the hydrophilicity and reduce the toxic effects by modifying the TSCs frameworks of the copper complexes [64]. For example, the water solubility increased by a factor of about 100 when the 2-pyridine moiety of classical TSCs was replaced by the 1,2-diazine function **(1)** [65]; moreover, the diazinyl-derived TSCs turned out to be less cytotoxic, as compared to the pyridylcongeners (by a factor of 50) [66]. It has been shown that the replacement of the terminal primary or secondary amino function by a tertiary amino group resulted in a marked enhancement of cytotoxic activity [66].

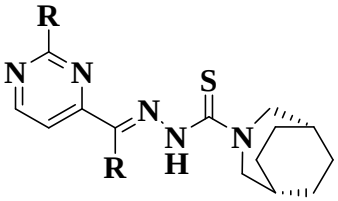


(1)



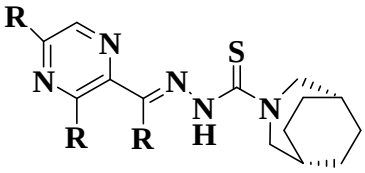
(2)

a. R=CH_3, R'=H
b. R=CH_3, R'=CH_3
c. R=CH_2CH_3, R'=H



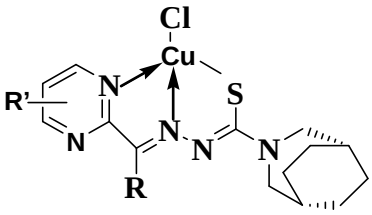
(3)

a. R=CH3, R'=H
b. R=CH3, R'=CH3



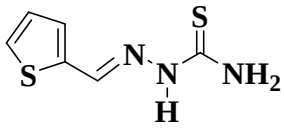
(4)

a. R=CH3, R'=H, R''=H
b. R=CH3, R'=CH3, R''=H
c. R=CH3, R'=H, R''=CH_3

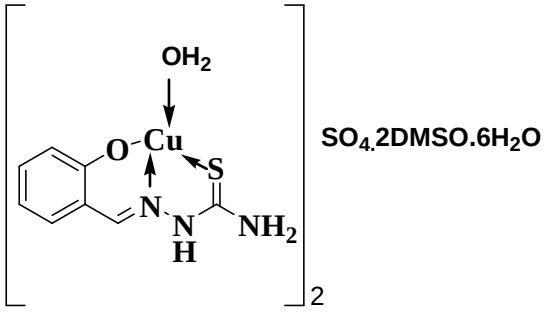


(5)

These findings led to the design of acyldiazinyl TSCs bearing an N4-azabicyclo [3.2.2]nonane group and their copper complexes**(2-5)** [67]. These compounds inhibited the proliferation of a series of tumor cell lines at nanomolar range, being more potent than free TSCs. In particular, the TSCs ligands 2-4 exhibited potent cytotoxic activities against human acute lymphoblastic leukemia CCRF-CEM cells (IC_{50} = 0.05-0.77 μM) and colon adenocarcinoma HT-29 cells(IC_{50}= 0.011-2.22 μM), whereas related copper(II) complexes **(5)** showed a significant improvement in cytotoxic activity against HT-29 cells by a factor of 3 (IC_{50} = 0.004-1.51 μM). As an example of TSCs with non-pyridine heterocyclic rings, thiophene-2-carbaldehyde TSC **(6)** exhibited a lower cytotoxicity against melanoma B16F10 and Friend erythroleukemia cells thanthe corresponding Cu(II) complexes [68,69].



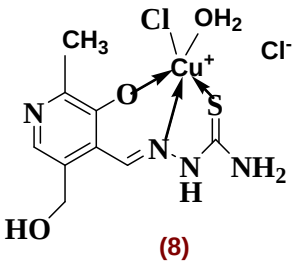
(6)



(7)

All this notwithstanding, TSCs bearing an aromatic heterocyclic moiety seem to be endowed with an implemented biological activity [70-78].Ferrari *et al*. reported a series of TSCs derivatives by changing the 2-pyridine group with salicylaldehyde [79], pyridoxal [70-76]and 5-formyluracil [80-82].The salicylaldehyde TSC(H_2salt), exhibited specificity for copper(II) leading to the dimeric metal complex [Cu(Hsalt)(H_2O)]$2SO_4$.2DMSO.$6H_2O$] **(7).** This complex has been tested in vitro on human leukaemic U937 cells, focusing the experiments on the activity with respect to cell proliferation inhibition and apoptosis induction. The results indicated that**(7)** inhibited about 40% of cell proliferation at 0.3 and 0.5 µg/ml, but DNA fragmentation and apoptosis were not observe at these concentrations. This unusual biological behavior could be connected with the square planar copper coordination geometry shown by **(7).** 2 Instead, the monomeric copper complex **(8)** of the pyridoxal TSC ligand **(9a)** [70] and the complexes **(10),(11)** and **(12)** of the 5-formyluracil-TSC ligand **(13),** all adopting five coordinated structures, caused DNA fragmentation leading to apoptosis.

Continuing their research on the biological properties of pyridoxal TSC **(9a)** derivatives, Ferrari et al.[83] have synthesized copper(II) complexes with nitroprusside as a counter ion because of its use in medical practice, thanks to the role of the nitric oxide released [84-86], as well as because of its inductive role in apoptosis [85-86]. From the biological view point, the two complex [Cu(**9a**)][$Fe(CN)_5(NO)$].$2H_2O$ and [Cu**(9a**)]$_2$[Fe(CN)NO)].$6H_2O$ with 4+1 coordination geometry were found to inhibit leukaemic cell proliferation of both CEM and U937 cell lines and in inducing apoptosis. The study of the effects on the cell cycle revealed an increase of cells in G2/M phase [83].



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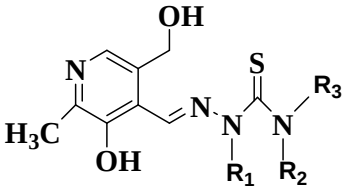
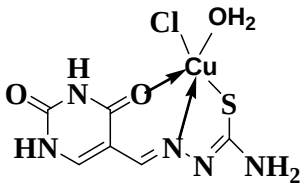


(9)

a. R_1=H, R_2=H, R_3=H
b. R_1=H, R_2=Me, R_3=Me
c. R_1=Me, R_2=H, R_3=Me
d. R_1=H, R_2=H, R_3=E



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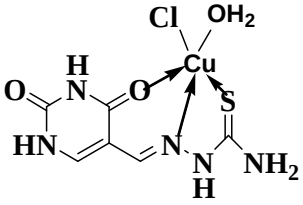

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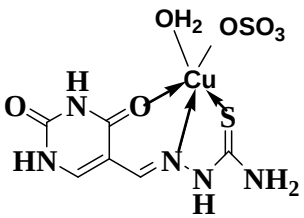

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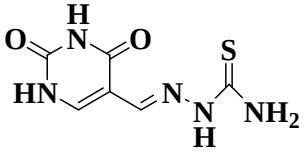
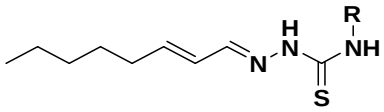


(13)

Hambley and co-workers [87] described that the stability of Cu-TSCs species was increased when the external surface of the complex molecule was hydrophobic. On this subject, the alpha-ketoglutaric acid TSC is an aliphatic ligand with many potential donor atoms and with a variety of possible conformations which determine a versatile chelating behavior. Seven N-substitute alpha-ketoglutaric thiosemicarbazides **(14),** possessing either aliphatic or aromatic groups were synthesized and used for preparing copper complexes [88]. DNA binding constants were determined and studies of thermal denaturation profiles and nuclease activity were also performed tests in vitro on human leukemia U937 cell line were carried out concerning with cell growth inhibition, cell cycle effects, and apoptosis induction. Among all the substituents introduced on the aminicnitrogen, the ethyl derivatives led to the highest biological activity.

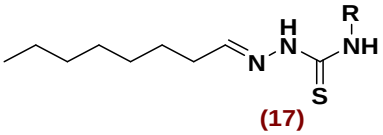
A group of methylpyruvate TSCs **(15)** was obtained by reacting methyl pyruvate with thiosemicarbazidesderivatized on the aminicnitrogen with both alkyl and aryl groups [89]. Tests on cell proliferation against human leukemic U937 cell line, showed that the copper complex [Cu(**15b**)Cl].HO was the most powerful agent, even if it was not able to induce apoptosis.

Another series of TSCs **(16-19),** derived from natural aldehydes, containing both N and S metal binding sites and an alkyl or terpenic group was designed in order to identify additional SARs [90]. The aromatic moiety of classic TSCs was replaced by analkyl group of eight carbon backbone. Both ligands and the corresponding Cu(II) complexes (16, R=H) and (18, R=Ph) showed are mark able inhibition ability towards human leukemia U937 cell line and were capable of trigger in cell apoptosis.



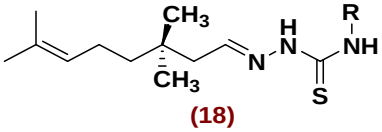
(16)

R=H, Ph



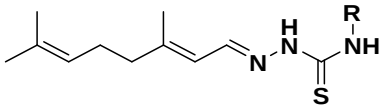
(17)

R=H, Ph

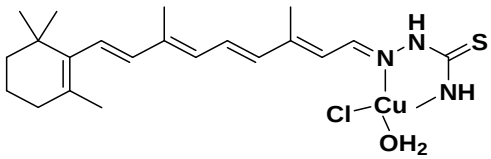


(18)

R=Ph, MePh, Me, Et



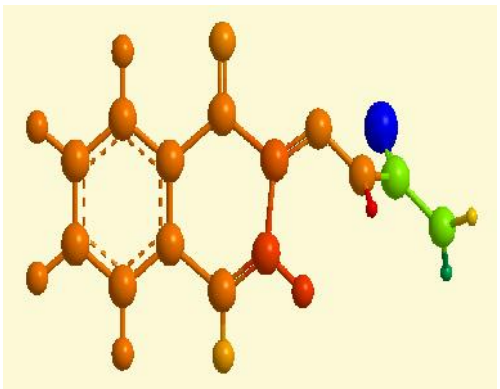
(19)



(20)

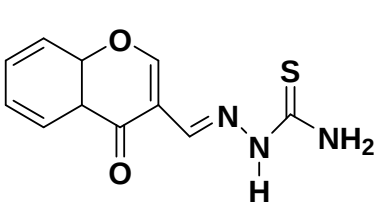
These studies showed that the presence of an unsaturated bond inposition2 with respect to theimineon hydrocarbon chain as well as the absence of as ubstituent on the terminal amino group of TSCs enhanced the cytotoxic activity.

The ligand 9-cis-retinal-TSC and its square planar Cu(II) complex **(20)** have been recently synthesized and characterized by Bis-ceglie *et al.* [91]. The DNA binding constants and spectroscopic data showed an external binding mode for the ligand and its copper complex. They possess a good lipophilic degree useful for an efficient cellular uptake. The metal complex inhibited human leukaemic U937 cell proliferation at micromolar concentration by activating an apoptotic cell death mechanism. Afrasiabi*et al.* reported the synthesis and structural characterization of copper conjugates of 1,2-naphthaquinone TSC **(21a)** and significant antitumour properties against MCF7 breast cancer cell line.

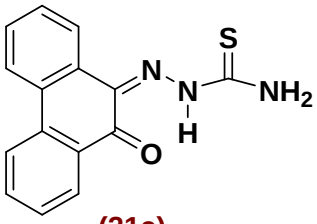


(21a)

This cytotoxic action has been attributed to its topoisomerase II inhibitory activity.3-Formylchromone TSC **(21b)**, the minimal biologically active structural motif of soy isoflavone (genistein), and its square planar copper(II) complexes have been reported by Sarkar*et al.*. They were stabilized in both $Cu^{2+/}Cu^{+}$ redox states and formed stronger charge interactions in the kinase domain than genistein, leading to better stabilization in the active pocket. In vitro evaluation of copper complexes against hormone-independent and metastatic breast (BT20), prostate (PC-3), K-ras mutant (COLO 357) and K-ras wild-type (BxPC-3) pancreatic cancer cells revealed that [Cu(**21b**)Cl_2] complex exhibited PKB (Akt protein) inhibitory activity and caused NF kappa B inactivation in COLO 357 cells.



(21 b)

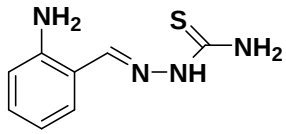


(21c)

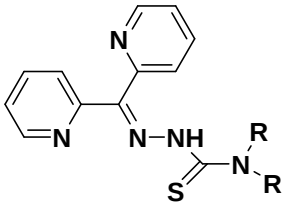
The TSC derivative of 9,10-phenanthrenequinone **(21c)** and its copper complex were synthesized by Padhye*et al*. [92]. The complex exhibited maximum antiproliferative activity against the human breast T47D cancer cell line, probably due to inhibition of steroid binding to the cognitive receptor or by preventing dimerization of the estrogen receptor.

Currently, the most promising therapeutic compounds among all investigated TSCs are triapine (3-aminopyridine-2carboxaldehyde TSC, 3-AP) **(22)** and di-2-pyridylketone-4,4-dimethyl-3-TSC (Dp44mT) (**23)**showed potent antitumor activity [93-94] and marked and selective activity against tumor engrafts in mice.

Related studies exploring the biological activity and redox properties of copper complexes of ApT and DpT analogues have shown that these compounds, particularly monovalent $[Cu(TSC)]^{+}$ species, were potent cytotoxic agents.

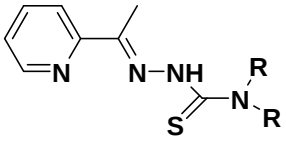


(22)



(23)

R=H, Me



(24)

R=H, Me

Further, the Cu(I)/Cu(II) redox cycling of these complexes, like their Fe(II/III) analogs, played a significant role in their biological activity. This work and others strongly supported the hypothesis that the copper complexes rather than any dissociated ligands or cellular metabolites were responsible for the biological effects *in vitro* and *in vivo*.

Interestingly, the study of the Cu(II) coordination chemistry of these compounds revealed that both 1:1 and 1:2 Cu/ligand complexes could be isolated and that the 1:2 complexes dissociated to give significant amounts of the 1:1 species. The higher biological activity of the 1:1 complexes suggested that they may be the active species in cells, while the 1:2 complexes could be precursors to the 1:1 complex formed by partial dissociation. Moreover, the copper complexes of HDp44mT ligand containing an electron-withdrawing substituent exhibited higher Cu(II/I) redox potentials and higher antiproliferative activity than the Cu complexes of HAp44mT **(24).**

Conclusion

The research on copper complexes as antitumour agents has boosted dramatically in the last few years as surveyed in this review. Platinum based complexes had been in focus of research in the treatment of cancer but the interest in this field have shifted to non-platinum based drugs in order to find different complexes with less side effects and better cytotoxicity. Among transition metal complexes copper complexes were found to have high activity. Up to now, a pronounced variety of copper complexes have been tested as cytotoxic agents and found to be endowed with an antitumour activity in several in vitro tests (on cultured cancer cell lines) and a few in vivo experiments.

Thiosemicarbazones (TSCs) and series of their copper complexes exhibiting promising antitumor activities 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 capricious copper complexes with efficacious antiproliferative activity.

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