



A REVIEW ON THERAPEUTIC APPLICATION OF COPPER COMPLEXES

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Abstract

Bioinorganic compounds, such as copper compounds, are cancer chemotherapeutics used alone or in combination with other drugs. One small group of copper complexes exerts an effective inhibitory action on topoisomerases, which participate in the regulation of DNA topology. Copper complexes inhibitors of topoisomerases and work by different molecular mechanisms, analyzed herein.

Keywords: Copper Complexes, Crystal structure, DNA-interaction, Cytotoxicity.

1. Introduction

Chemotherapy is a systemic treatment proposed to patients suffering from cancer. It is often a complementary approach to surgery or radiotherapy. The discovery of platinum's inhibitory effect on tumor cell growth was a milestone for anticancer drug application in medicine [1-2]. Cisplatin and related platinum-based antitumor drugs could be the most successful example of metal antitumor drugs. However, serious side effects including toxicities on the kidney, heart, ear, and liver, decrease in immunity, hemorrhage, and gastrointestinal disorders limit the use of platinum derivatives. So, many other transition-metal complexes as well as small-molecule-based antitumor agents have been developed, and some of them are under clinical trial [3-4]. Among the essential heavy metal ions in the human body, Cu^{2+} is third in abundance and it plays very important roles in several biological processes. DNA is the hereditary material in humans and almost all other organisms. Although simple in structure, DNA can code for all the complex necessities of life [5]. Thus, many antitumor drugs are designed to target DNA because the interaction between drugs and DNA can cause DNA damage and show toxic and antitumoral effects [6]. Copper plays central roles in various cellular processes being an essential micronutrient and an important cofactor for several metalloenzymes involved in mitochondrial metabolism

(cytochrome c oxidase), or cellular radical detoxification against reactive oxygen species (ROS) (superoxide dismutase). Copper is essential for angiogenesis, proliferation, and migration of endothelial cells. Elevated copper favors tumor growth and metastasis. It is detected in several brain, breast, colon, prostate, and lung tumors and serves as an indicator of the course of the disease [7-8].

Scheme 1:

Neutral and cationic copper bis(thiosemicarbazone) complexes bearing methyl, phenyl, and hydrogen, on the diketo-backbone of the ligand have been synthesized. All of them were characterized by spectroscopic methods and in three cases by X-ray crystallography. In vitro cytotoxicity studies revealed that they are cytotoxic unlike the corresponding zinc complexes. Copper complexes Cu(GTSC) and Cu(GTSClCl) derived from glyoxal-bis(4-methyl-4-phenyl-3-thiosemicarbazone) (GTSC₂) are the most cytotoxic complexes against various human cancer cell lines, with a potency similar to that of the anticancer drug adriamycin and up to 1000 fold higher than that of the corresponding zinc complex. Tritiated thymidine incorporation assay revealed that Cu(GTSC) and Cu(GTSClCl) inhibit DNA synthesis substantially. Cell cycle analyses showed that Cu(GTSC) and Cu(GTSClCl) induce apoptosis in HCT116 cells. The Cu(GTSClCl) complex caused distinct DNA cleavage and Topo II α inhibition unlike that for Cu(GTSC). In vivo administration of Cu(GTSC) significantly inhibits tumor growth in HCT116 xenografts in nude mice [9].

Scheme 2:

Three new tridentate copper(II) complexes [Cu(dthp)Cl₂] (1) (dthp = 2,6-di(thiazol-2-yl)pyridine), [Cu(dmtp)Cl₂] (2) (dmtp = 2,6-di(5-methyl-4H-1,2,4-triazol-3-yl)pyridine) and [Cu(dtp)Cl₂] (3) (dtp = 2,6-di(4H-1,2,4-triazol-3-yl)pyridine) have been synthesized and characterized. Crystal structure of complex 1 shows that the complex existed as distorted square pyramid with five co-ordination sites occupied by the tridentate ligand and the two chlorine anions. Ethidium bromide displacement assay, viscosity measurements, circular dichroism studies and cyclic voltammetric experiments suggested that these complexes bound to DNA via an intercalative mode. Three Cu(II) complexes were found to efficiently cleave DNA in the presence of sodium ascorbate, and singlet oxygen (¹O₂) and hydrogen peroxide were proved to contribute to the DNA cleavage process. They exhibited anticancer activity against HeLa, Hep-G2 and BEL-7402 cell lines. Nuclear chromatin cleavage has also been observed with AO/EB staining assay and the alkaline single-cell gel electrophoresis (comet assay). The results demonstrated that three Cu(II) complexes cause DNA damage that can induce the apoptosis of BEL-7402 cells [10].

Scheme 3:

A series of copper(II) complexes with tripodal polypyridylamine ligands (derived from the parent ligand tris(2-pyridylmethyl)amine, tmpa) has been synthesized. Crystallographic characterization was possible for all complexes obtained. The copper(II) chloride complexes were investigated for their in vitro anticancer potential

using human tumor cell lines containing examples of cervical, colon, ovarian cancers and melanoma. Some compounds showed a similar activity compared to that of cisplatin, however no systematic behavior could be observed [11].

Scheme 4:

In this study, three new organic ligands *N'*-(benzylidene)-6-chloropyrazine-2-carbohydrazonamide (L1), 6-chloro-*N'*-(4-nitrobenzylidene)picolinohydrazonamide(L2), and *N'*-(benzylidene)-4-chloropicolinohydrazonamide (L3) and three copper coordination compounds (Cu(L1)Cl₂, Cu(L2)Cl₂ and Cu(L3)Cl₂) based on them were synthesized. All obtained compounds were characterized using appropriate analytical techniques: elemental analysis (EA), thermogravimetric analysis (TG–DTG), Fourier transform infrared spectroscopy (FTIR) and flame-atomic absorption spectrometry (F-AAS). These methods of physicochemical analyses helped to assume that the complexation in three cases proceeds in a bidentate manner. The X-ray investigation confirmed the synthesis pathway and molecular structures for L1 and L3 ligands. The antimicrobial activity of the obtained compounds was then comprehensively investigated, where Cu(L3)Cl₂ showed the strongest antibacterial properties against all tested bacteria (*Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*). LN229 human glioma cells and BJ human normal fibroblasts cells were treated with tested compounds and their cytotoxicity was evaluated with MTT test. The effect of complexing on antitumor activity has been investigated. The ligand L1 and its complex showed similar activity against normal cells while complexation increases toxicity against cancer cells in concentrations of 50 and 100 μM. For the one pair of ligand/complex compounds the apoptosis detection, cell cycle analysis and gene expression analysis (qRT-PCR) were performed. Cu(L1)Cl₂ showed the stronger toxic effect in comparison with L1 due to the population of early apoptotic cells which revealed metabolic activity in MTT assay [12].

Scheme 5:

Certain metal complexes can have a great antitumor activity, as the use of cisplatin in therapy has been demonstrating for the past fifty years. Copper complexes, in particular, have attracted much attention as an example of anticancer compounds based on an endogenous metal. In this paper we present the synthesis and the activity of a series of copper(II) complexes with variously substituted salicylaldehyde thiosemicarbazone ligands. The *in vitro* activity of both ligands and copper complexes was assessed on a panel of cell lines (HCT-15, LoVo and LoVo oxaliplatin resistant colon carcinoma, A375 melanoma, BxPC3 and PSN1 pancreatic adenocarcinoma, BCPAP thyroid carcinoma, 2008 ovarian carcinoma, HEK293 non-transformed embryonic kidney), highlighting remarkable activity of the metal complexes, in some cases in the low nanomolar range. The copper(II) complexes were also screened, with good results, against 3D spheroids of colon (HCT-15) and pancreatic (PSN1) cancer cells. Detailed investigations on the mechanism of action of the copper(II) complexes are also reported: they are able to potently inhibit Protein Disulfide Isomerase, a copper-binding protein, that is recently emerging as a new therapeutic target for cancer treatment. Good preliminary results obtained in C57BL

mice indicate that this series of metal-based compounds could be a very promising weapon in the fight against cancer [13].

Scheme 6:

The chemical properties of copper allow it to take part in many biological functions such as electron transfer, catalysis, and structural shaping. The ability to cycle between +1 and +2 oxidation state is one of the features that has been exploited by organisms throughout the evolutionary process. Since copper is potentially toxic to cells also a finely controlled mechanism for copper handling has evolved. On the other side, many copper complexes were synthesized and tested for their anticancer activity in vitro and in vivo. Their ability to kill cancer cells is mainly related to the induction of an oxidative stress, but recently it emerged their ability to inhibit the proteasome, a protein complex whose proteolytic activity is needed by several cellular process [14].

Scheme 7:

It has generally been described that the toxic effects of copper complexes leads to cell death either by necrosis or through the activation of the apoptotic process. Evidences are rising about the ability of some copper compounds to induce alternative non-apoptotic form of programmed cell death. Since copper is indispensable for the formation of new blood vessels, angiogenesis, a different antitumor approach based on the administration of copper sequestering agents has been attempted and its effectiveness is currently under evaluation by clinical trials. The proven essentiality of copper for angiogenesis, together with the marked sensitivity shown by several cancer cell lines to the copper toxicity, open a new perspective in the anticancer strategy: exploiting the tumor need of copper to accumulate toxic amount of the metal inside its cells [15].

Scheme 8:

In the present paper, we synthesized and characterized four N-donor polypyridyl copper(II) complexes (C1-C4); $[\text{Cu}(\text{mono-CN-PIP})_2]^{2+}$ (C1), $[\text{Cu}(\text{tri-OMe-PIP})_2]^{2+}$ (C2), $[\text{Cu}(\text{di-CF}_3\text{-PIP})_2]^{2+}$ (C3) and $[\text{Cu}(\text{DPPZ})_2]^{2+}$ (C4). The (Calf-Thymus) CT-DNA binding studies depicted that the complexes could interact with DNA via intercalative mode. All the complexes, particularly C3 and C4 attenuated the proliferation as well as migration of various cancer cells, indicating their anti-cancer and anti-metastatic activity. Additionally, chick embryo angiogenesis (CEA) assay exhibited the inhibition of vascular sprouting in presence of C3 and C4, suggesting their potential in inhibiting the blood vessel growth. Mechanistic studies revealed that the complexes induced the excessive production of cellular reactive oxygen species (ROS) leading to apoptosis through up regulation of p53 and downregulation of Bcl-xL, which might be the plausible mechanisms underlying their anti-cancer properties. To understand the feasibility of practical application of anti-cancer copper complexes C3 and C4, in vivo sub-chronic toxicity study (4 weeks) was performed in C57BL6 mice and the results exhibited almost non-toxic effects induced by these complexes in terms of haematology and serum biochemical analyses,

suggesting their biocompatible nature. The current study provides the basis for future advancement of other novel biocompatible metal complexes that could be employed for the therapy of different cancers [16].

Scheme 9:

We report 15 new Cu(II) complexes with tridentate NNO β -acylenamino ligands derived from 2-picolylamine and bearing up to three alkyl, alkoxy, alkoxy-carbonyl, or (pseudo)halide substituents. The structures of nine complexes were elucidated by single crystal X-ray diffraction analysis. Complexes with an unsubstituted pyridine ring crystallised with a square pyramidal coordination sphere, whereas substitution of the pyridine ring led to a square planar coordination sphere around the metal centre. The solution structures and properties of the complexes were characterised by UV-Vis spectroscopy and cyclic voltammetry. They were also tested for their cytotoxic effect on four human cancer cell lines. Two complexes were identified that were highly active with single-digit IC₅₀ values, exceeding those of cisplatin by far. A tentative structure–activity relationship was proposed as well as topoisomerase I inhibition as a possible mode of action, while any significant interference with DNA and the level of reactive oxygen species could be excluded [17].

Scheme 10:

Two water-soluble ternary copper(II) complexes of [Cu(L)Cl](ClO₄) (1) and [Cu(L)Br₂] (2) (L = (2-((quinolin-8-ylimino)methyl)pyridine)) were prepared and characterized by various physico-chemical techniques. Both 1 and 2 were structurally characterized by X-ray crystallography. The crystal structures show the presence of a distorted square-pyramidal CuN₃Cl₂ (1) or CuN₃Br₂ (2) geometry in which Schiff-base L acts as a neutral tridentate ligand. Both complexes present intermolecular π – π stacking interactions between quinoline and pyridine rings. The interaction of two complexes with CT-DNA (calf thymus-DNA) and BSA (bovine serum albumin) was studied by means of various spectroscopy methods, which revealed that 1 and 2 could interact with CT-DNA through intercalation mode, and could quench the intrinsic fluorescence of BSA in a static quenching process. Furthermore, the competition experiment using Hoechst 33258 indicated that two complexes may bind to CT-DNA by a minor groove. DNA cleavage experiments indicate that the complexes exhibit efficient DNA cleavage activities without any external agents, and hydroxyl radical (HO) and singlet oxygen (¹O₂) may serve as the major cleavage active species. Notably, the in vitro cytotoxicity of the complexes on three human tumor cells lines (HeLa, MCF-7, and A549) demonstrates that two compounds have broad-spectrum antitumor activity with quite low IC₅₀ ranges of 0.43–1.85 μ M. Based on the cell cycle experiments, 1 and 2 could delay or inhibit cell cycle progression through the S phase [18].

Scheme 11:

A copper complex $[\text{Cu}(\text{HPBM})(\text{L-Phe})(\text{H}_2\text{O})]\cdot\text{ClO}_4$ (1) (HPBM = 5-methyl-2-(2'-pyridyl)benzimidazole, L-Phe = L-phenylalanine anion) was synthesized and characterized by elemental analysis, IR, ESI-MS, HR-ESI-MS, ESR spectroscopy, and by X-ray single-crystal analysis. The binding constant of the complex with calf thymus DNA (CT-DNA) was determined as $7.38 (\pm 0.57) \times 10^4 \text{ M}^{-1}$. Further studies indicated that the complex interacts with CT-DNA through minor groove binding. The in vitro cytotoxic activities of both the free proligand and the complex against Eca-109, HeLa and A549 cancer cells and normal LO2 cells were evaluated by the MTT method. The IC₅₀ values range from 5.7 ± 0.1 to $8.3 \pm 0.6 \mu\text{M}$. Free HPBM displays no cytotoxic activity against the selected cancer cells, with IC₅₀ values more than 100 μM . Double staining analysis showed that the complex can induce apoptosis in Eca-109 cells. Comet assays demonstrated that the complex can damage DNA and cause apoptosis. The complex also induces an increase in intracellular reactive oxygen species and a reduction in mitochondrial membrane potential. The complex can also increase the intracellular Ca²⁺ level and induce release of cytochrome c. The cell cycle arrest was investigated by flow cytometry. The results demonstrate that the complex induces apoptosis in Eca-109 cells through DNA-binding and ROS-mediated mitochondrial dysfunctional pathways [19].

Scheme 12:

A series of eight bis(thiosemicarbazone) ligands and 16 of their respective copper(II) and zinc(II) complexes containing a combination of hydrogen, methyl, pyridyl, phenyl, and/or ethyl substituents at the diimine position of the ligand backbone were synthesized and characterized. The objective of this study was to identify the structure-activity relationships within a series of analogues with different substituents at the diimine position of the backbone and at the terminal N atom. The Cu(II) complexes Cu(GTSM2), Cu(GTSCM), Cu(PyTSM2), Cu(EMTSM2) and Cu(PGTSM2) demonstrated a distorted square planar geometry, while the Zn(II) complexes Zn(ATSM2)(DMSO), Zn(PyTSM2)(DMSO), and Zn(PGTSM2)(H₂O) formed a distorted square pyramidal geometry. Cyclic voltammetry showed that the Cu(II) complexes display quasi-reversible electrochemistry. Of the agents, Cu(II) glyoxal bis(4,4-dimethyl-3-thiosemicarbazone) [Cu(GTSM2)] and Cu(II) diacetyl bis(4,4-dimethyl-3-thiosemicarbazone) [Cu(ATSM2)] demonstrated the greatest antiproliferative activity against tumor cells. Substitutions at the diimine position and at the terminal N atom with hydrophobic moieties markedly decreased their antiproliferative activity [20].

Scheme 13:

Aiming at obtaining new copper complexes with good cytotoxicity against cancer cells, triphenylphosphine (TPP) was introduced to obtain insight into the influence of the co-ligands. In this paper, two copper complexes, $\text{Cu}(2\text{-pbmq})(\text{CH}_3\text{OH})\text{Br}_2$ (1) and $[\text{Cu}(2\text{-pbmq})(\text{TPP})\text{Br}]_2$ (2) were designed, synthesized, and characterized by X-ray crystallography, 2-((2-(pyrazin-2-yl)-1H-benzo[d]imidazol-1-yl)methyl)quinolone (2-pbmq), to investigate the influence of the TPP group on the anticancer activity of the metal complex. Although the presence of the TPP group diminished the intensity of the interaction properties of the complex with DNA, the in vitro anticancer activity and cellular uptake of the TPP-containing complex were markedly superior to those of its TPP-lacking counterpart. Detailed studies on the more potently cytotoxic complex 2 revealed that it accumulated in nucleus, arrested the cell cycle at the G₀-G₁ phase, causing mitochondrial dysfunction, involving the potential simultaneous mitochondrial membrane collapse, cellular ATP level depletion, and Ca²⁺ leakage, eventually inducing cell apoptosis. In summary, the introduction of a TPP group enhances the biological activity and cytotoxicity of the complex [21].

Scheme 14:

$[\text{CuI}(2,9\text{-dimethyl-}1,10\text{-phenanthroline})\text{P}(\text{p-OCH}_3\text{-Ph})_2\text{CH}_2\text{SarcosineGlycine}]$ (1-MPSG), highly stable in physiological media phosphino copper(I) complex—is proposed herein as a viable alternative to anticancer platinum-based drugs. It is noteworthy that, 1-MPSG significantly and selectively reduced cell viability in a 3D spheroidal model of human lung adenocarcinoma (A549), in comparison with non-cancerous HaCaT cells. Confocal microscopy and an ICP-MS analysis showed that 1-MPSG effectively accumulates inside A549 cells with colocalization in mitochondria and nuclei. A precise cytometric analysis revealed a predominance of apoptosis over the other types of cell death. In the case of HaCaT cells, the overall cytotoxicity was significantly lower, indicating the selective activity of 1-MPSG towards cancer cells. Apoptosis also manifested itself in a decrease in mitochondrial membrane potential along with the activation of caspases-3/9. Moreover, the caspase inhibitor (Z-VAD-FMK) pretreatment led to decreased level of apoptosis (more pronouncedly in A549 cells than in non-cancerous HaCaT cells) and further validated the caspases dependence in 1-MPSG-induced apoptosis. Furthermore, the 1-MPSG complex presumably induces the changes in the cell cycle leading to G₂/M phase arrest in a dose-dependent manner. It was also observed that the 1-MPSG mediated intracellular ROS alterations in A549 and HaCaT cells. These results, proved by fluorescence spectroscopy, and flow cytometry, suggest that investigated Cu(I) compound may trigger apoptosis also through ROS generation [22].

Scheme 15:

Based on the anticancer pharmacophore of anthrahydrazone and quinoline, a new quinolylanthrahydrazone ligand, 9-AQH (anthracene-9-quinolylylhydrazone), was synthesized to further afford four metal complexes, $[\text{CoII}(9\text{-AQH})(\text{NO}_3)_2(\text{H}_2\text{O})]$ (1), $[\text{NiII}(9\text{-AQH})_2(\text{H}_2\text{O})_2] \cdot 2\text{NO}_3$ (2), $[\text{CuI}(9\text{-AQH})_2] \cdot \text{NO}_3$ (3), $[\text{ZnII}(9\text{-AQH})_2(\text{NO}_3)] \cdot \text{NO}_3$ (4), determined by X-ray single crystal diffraction analysis. The reaction of $\text{Cu}(\text{NO}_3)_2$ with 9-AQH formed the stable and repeatable copper(I) complex 3. In vitro screening demonstrated only 3 showed significant and broad-spectrum anticancer activity, indicating that Cu(I) played a key role in exerting the anticancer activity. In solution, Cu(I) was not naturally oxidized to Cu(II) suggested by $^1\text{H-NMR}$ (Nuclear Magnetic Resonance) and EPR (Electron Paramagnetic Resonance) analysis. The presence of 3 could also catalyze the H_2O_2 system to give hydroxyl free radicals, suggested by further EPR and electrophoresis assay. At the cellular level, although no obvious Cu(II) signals were detected and the total ROS (Reactive Oxygen Species) scavenging in the tumor cells treated with 3, the potential redox property between Cu(I)/Cu(II), as a key role, should not be denied for the significant anticancer activity of 3, considering the much complicated circumstance and other reductive substances in cells. The anticancer mechanism of 3 on the most sensitive MGC-803 cells pointed to significant cell apoptosis through mitochondrial pathway, rather than cell cycle arrest. While the autophagy observed in tumor cells treated by 3 suggested its complicated anticancer mechanism, and whether there was an intrinsic correlation still needed to be further investigated [23].

Scheme 16:

Cells require tight regulation of the intracellular redox balance and consequently of reactive oxygen species for proper redox signaling and maintenance of metal (e.g., of iron and copper) homeostasis. In several diseases, including cancer, this balance is disturbed. Therefore, anticancer drugs targeting the redox systems, for example, glutathione and thioredoxin, have entered focus of interest. Anticancer metal complexes (platinum, gold, arsenic, ruthenium, rhodium, copper, vanadium, cobalt, manganese, gadolinium, and molybdenum) have been shown to strongly interact with or even disturb cellular redox homeostasis. In this context, especially the hypothesis of “activation by reduction” as well as the “hard and soft acids and bases” theory with respect to coordination of metal ions to cellular ligands represent important concepts to understand the molecular modes of action of anticancer metal drugs. The aim of this review is to highlight specific interactions of metal-based anticancer drugs with the cellular redox homeostasis and to explain this behavior by considering chemical properties of the respective anticancer metal complexes currently either in (pre)clinical development or in daily clinical routine in oncology [24].

Scheme 17:

The purpose of this study was to identify new metal-based anticancer drugs; to this end, we synthesized two new copper(II) complexes, namely $[\text{Cu}(\text{ncba})_4(\text{phen})]$ (1) and $[\text{Cu}(\text{ncba})_4(\text{bpy})]$ (2), comprised 4-chloro-3-nitrobenzoic acid as the main ligand. The single-crystal XRD approach was employed to determine the copper(II)

complex structures. Binding between these complexes and calf thymus DNA (CT-DNA) and human serum albumin (HSA) was explored by electronic absorption, fluorescence spectroscopy, and viscometry. Both complexes intercalatively bound CT-DNA and statically and spontaneously quenched DNA/HSA fluorescence. A CCK-8 assay revealed that complex 1 and complex 2 had substantial antiproliferative influences against human cancer cell lines. Moreover, complex 1 had greater antitumor efficacy than the positive control cisplatin. Flow cytometry assessment of the cell cycle demonstrated that these complexes arrested the HepG2 cell cycle and caused the accumulation of G0/G1-phase cells. The mechanism of cell death was elucidated by flow cytometry-based apoptosis assays. Western blotting revealed that both copper(II) complexes induced apoptosis by regulating the expression of the Bcl-2(Bcl-2, B cell lymphoma 2) protein family [25].

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