Medicinal chemistry
ISSN: 2161-0444

Tabti et al., Med Chem (Los Angeles) 2017, 7:5
DOI: 10.4172/2161-0444.1000445

Review Article OMICS International

Progress in Copper Complexes as Anticancer Agents

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Abstract

The clinical success of cisplatin has stimulated the quest for novel anticancer metallodrugs during the last two decades. A major emphasis has been put on copper due to its selective cytotoxicity toward malignant cells. This selectivity stems from the hypoxic environment of cancer cells that promotes the reduction of Cu(II) to Cu(I), leading a pro-apoptotic oxidative stress. At the current time, two copper complexes have reached clinical assay, which paves the road to the first copper-based anticancer therapeutics.

Keywords: Cancer; Copper; Cu-complexes; Metallodrugs; Oxidative stress; Elesclomol

Introduction

The advent of targeted therapies, i.e., small molecules or antibodies that interfere with signaling proteins involved in the etiology of cancer, revolutionized the treatment of tumors with an addiction to specific oncogenes (e.g., ALK in lung cancer, Bcr-Abl in chronic myeloid leukemia, KIT in GIST, EGFR in lung cancer, HER2 in breast cancer or MET in liver tumors). However, for many cancers, the progression-free survival of patients treated with targeted therapy is less than one year, which justify for a regain of interest in cytotoxic agents including metallodrugs [1]. Indeed, the prevalent success of cisplatin in the treatment of various types of cancers has placed organometallic compounds on the forefront in the development of anticancer drugs. In this quest, copper derivatives hold promising opportunities due to opportunities provided by the hypoxic environment that is a hallmark of cancer cells coupled with the ability of copper complexes to catalyze the formation of Reactive Oxygen and Nitrogen species (ROS and RNS) [2].

Role of Copper in Physiology and in Cancer Physiology

Tumors display a lack of blood vessels that results in a low oxygen level, which promotes invasion, metastasis and a metabolic shift to an anaerobic process known as the 'Warburg effect' [3]. Gratefully, tumor hypoxia can be exploited to develop prodrugs that become activated in the reducing environment of cancer cells. In this regard, copper is very appealing because it can exist under two different oxidation states in cells. The anoxic character of cancer cells promotes the reduction of Cu(II) to Cu(I), which is not possible in normal cells and thus provides a therapeutic opportunity to target tumors [2]. Cu(I) can catalyze the formation of ROS and RNS, to induce a pro-apoptotic oxidative stress. In addition, the redox state of copper modulates its affinity to ligands: copper(I) is a softer Lewis acid than copper(II) and displays a high affinity toward sulfur ligands, whereas copper(II) preferentially coordinates to nitrogen and oxygen donors in proteins and DNA [4].

Not only copper salts are much less toxic than platinum derivatives, but they are necessary to the organism. Indeed, the physiological concentration of copper in the body is highly regulated by several mechanisms that involve ceruloplasmin and albumin in the liver to regulate blood levels and also copper transporter proteins (CTR1 and Cu ATP7A/B) at the cellular level [4]. Due to its ability to oscillates between oxidized and reduced states in biological medium, copper acts as a co-factor for enzymes involved in energy metabolism (cyt. C oxidase), destruction of ROS (superoxide dismutase 1), melanin synthesis (tyrosinase), dopamine synthesis (dopamine-β-hydroxylase), cross-linking of collagen and elastin (lysyl oxidase). However, an excess of copper may be toxic also to non-cancer cells due to the generation of ROS and NOS, which explains why copper homeostasis is highly regulated (Table 1) [5-31]. Importantly, many types of tumors accumulate abnormally high concentrations of copper, and the concentration of copper in serum is almost doubled in breast cancer patients [32-36]. These observations may be explained by the involvement of copper in tumor growth and survival through several mechanisms. First, copper is essential to angiogenesis, which is necessary for tumor growth and metastasis. More precisely, copper sulfate induces the expression of HIF-1α, the G-protein estrogen receptor (GPER) and VEGF in breast and hepatic cancer cells through the activation of the EGFR/ERK/c-fos pathway [37]. Second, copper inhibits the apoptosis of cancer cells by binding to the XIAP protein to promote its anti-apoptotic activity [38,39]. Third, copper interacts with MEK1 to promote the phosphorylation of ERK and oncogenesis [40,41]. Fourth, coper activates the pro-survival phosphoinositide 3'-kinase (PI3K)/Akt pathway [42,43].

Anticancer Copper Complexes

Except for the complexes that are based on the anticancer natural product Paullone (Figure 1) [44], a majority of the cytotoxic Cu complexes were originally designed for their chemical and physical properties [1]. As a consequence, many of them do not exhibit drug-like properties and significant anticancer effects *in vivo*.

The synthesis, design, and development of copper complexes as anticancer agents have been presented in several reviews over the last decade [45-52]. We focus therein on the *in vivo* anticancer activity of this type of drugs and include recent advances, which were not covered

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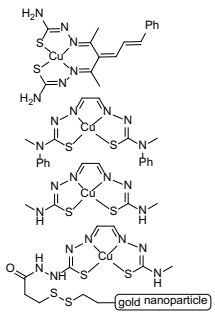
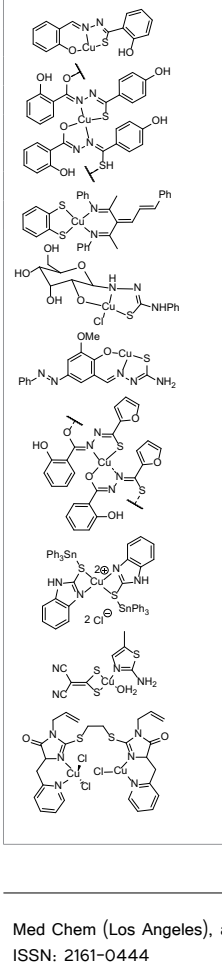
Received May 02, 2017; **Accepted** May 09, 2017; **Published** May 15, 2017

Citation: Tabti R, Tounsi N, Gaiddon C, Bentouhami E, Désaubry L (2017) Progress in Copper Complexes as Anticancer Agents. Med Chem (Los Angeles) 7: 875-879. doi: 10.4172/2161-0444.1000445

Compound	Type of rodents/type of tumor/anticancer effect (dose)	Reference
	Adult Swiss female albino mice/ EAC cells/ increase in life span of 86% (100 $mg.kg^{-1}.d^{-1}$ p.o. for 9 days).	[5]
	Nude mice/ HCT116 cells/ inhibition of tumor growth: of 95 % (5 $mg.kg^{-1}$. d^{-1} i.p. for 7 days).	[6]
	Male transgenic adenocarcinoma of the mouse prostate (TRAMP) model/ significant reduction (~70%) in the weight of their genitourinary tracts (2.5 $mg.kg^{-1}.d^{-1}$).	[7]
	Female nude mice / HeLa cells/ reduction in tumor volume of 3.8-fold (7.5 $mg.kg^{-1}.d^{-1}$ i.p 7 days).	[8]
	Albinos swiss mice/ EAC cells/ increase in life span of 61% (50 $mg.kg^{-1}.d^{-1}$ i.p. for 5 days).	[9]
	Albinos swiss mice/ EAC cells/ increase in life span of 42% (50 $mg.kg^{-1}.d^{-1}$ i.p. for 5 days).	[9]
	Male BALB/c nude mice/ Human acute monocytic sarcoma/ 69% inhibition of tumor growth (6 $mg.kg^{-1}.d^{-1}$ every other day for 6 weeks; benchmarking: 37 % for 0.5 $mg.kg^{-1}.d^{-1}$ of cisplatin).	[10]
	Male C57BL-6 mice/ B16-F10 melanoma/ 87 % inhibition of tumor growth (45 $mg.kg^{-1}.d^{-1}$ every other day for 3 weeks; benchmarking: 80 % for 0.5 $mg.kg^{-1}.d^{-1}$ of cisplatin).	[11]
	Female athymic nude mice/ HL-60/ optimal (% T/C)[d]: 42%/ (3 $mg.kg^{-1}.d^{-1}$. i.p. for 5 days) (MTD=15 $mg.kg^{-1}$ i.v and 10 $mg.kg^{-1}$ i.p.).	[12]
	Female BALB/c mice/ A549 cells/ reduction of tumour growth > 50% (0.78 µmol Cu kg^{-1} every 2 days for 26 days).	[13]
	Female nude mice/ COLO 357 cells/ significant reduction of tumour growth and NF-κB activity (25 $mg.kg^{-1}$ i.v. once every 2 days for 10 days).	
	BALB/c mice/ DL (106) cells/ increase of lifespan of 267% (10 $mg.kg^{-1}$ i.p.) (benchmarking: 150 % for cisplatin).	[14]
	C_3H/J female mice/ breast-tumor/ increase of lifespan of 125 % ($mg.kg^{-1}$ i.p., 1 injection).	[15]
	Adult Swiss female albino mice/ EAC cells/ increase in life span of 120% (100 $mg.kg^{-1}.d^{-1}$ p.o. for 9 days).	[16]
	Swiss albino mice/ Ehrlich ascites carcinoma/ increase in life span of 52% (50 $mg.kg^{-1}$ i.p., 6 injections).	[17]
	BDFI mice/ P388S/ increase in life span of 56 % (200 $mg.kg^{-1}$ i.p., 3 injections).	[18]
	Dba mice/ Dalton's Lymphoma/ increase in tumor-free survivors: 65 % (25 $mg.kg^{-1}$ i.p., 1 injection).	[19]
	Wistar rats/ C6 glioblastoma/ significant antiproliferative activity, minimal toxicity (4 $mg.kg^{-1}.d^{-1}$ i.p. for 2 weeks).	[20]
	BDF1mice/ P388 leukemia/ increase in lifetime of 64% (10 $mg.kg^{-1}$.i.p, 1 injection; LD_{50} = 40 $mg.kg^{-1}$, LD_{10}=10 $mg.kg^{-1}$).	[21]
	Female C57BL/6 mice / breast adenocarcinoma 755/ inhibition of tumor growth: 73 % (24 $mg.kg^{-1}.d^{-1}$ i.p. for 5 days).	[22]

	Male BALB/c/nude mice/ HepG2 cells/ tumor inhibition rate: 66% (4 mg. kg^{-1} i.p. for 3 weeks).	[23]
	Male nude mice/ HCT-15 cells/ inhibition of tumor growth (6 $mg.kg^{-1}$ i.p. one dose each 4 days, 6 doses	[24]
	Wister Albino rats/mammary carcinoma/ inhibition of tumor growth (4.3 $mg.kg^{-1}$ i.p. 5 injections).	[25]
	Norwegian rat/ breast tumor/ reduction of tumor growth superior to that of cisplatin.	[26]
	DBA/2 mice / P388 leukemia/ increase in life span of 26% (19 $mg.kg^{-1}$ i.p., 1 single injection) (LD_{50}=48 $mg.kg^{-1}$).	[27]
	DBA/2J male mice/L1210 leukemia cells/ increase in life span of 23% (10 $mg.kg^{-1}$, 2 i.p. injections).	[28]
	C_3H/He mice/Sarcoma-180/ increase in life span of 12% (25.0 $mg.kg^{-1}$, 1 i.p. injection).	[29]
	Mice/P388 Leukemia/ increase in life span of 100% (2 $\mu mol.kg^{-1}$).	[30]
	C57BL mice/ LLC cell / inhibition of tumor growth: 78% / (25 $mg{\cdot}kg^{-1}.d^{-1}$ i.p. for 1 week).	[31]

Table 1: Copper complexes that display antitumor effects in mouse models of cancers.

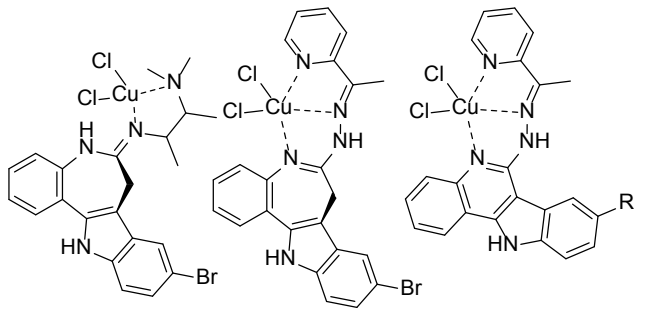


Figure 1: Representative examples of cytotoxic paullone analogues conjugated to Cu(II) [44].

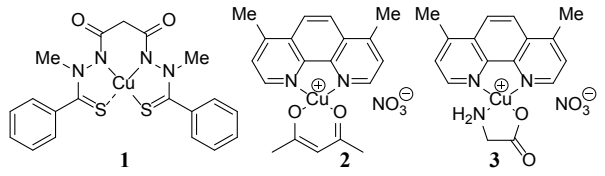


Figure 2: Cu(II) Elesclomol (**1**), Casiopeínas IIIia and II-Gly (**2** et **3**).

by previous review. By focusing on *in vivo* data, we aim at providing a critical overview of the most promising anticancer copper complexes.

On the opposite of classical anticancer drugs that display a high selectivity for their molecular target, copper complexes affect DNA and a myriad of proteins to induce a general toxicity that is lethal to cancer cells. Due to its ability to participate in redox reactions, copper is able to produce large amounts of ROS through a Fenton-like reaction to damage DNA and proteins [50].

Over the last two decades, copper complexes have consolidated their place in medicinal chemistry, which is manifested by an increased number of compounds that showed their efficacy in animal models of cancers (Table 1). Two of these drugs have been examined in clinical trial (Figure 2). The first one, elesclomol, synthesized as complex with Cu(II), has entered a phase I clinical trial to treat acute myeloid leukemia where it displayed a very favorable safety profile, but unfortunately no clinical results at the maximal evaluated dose of 400 mg/m^2 [53]. This drug has also been examined in a phase II trial against ovarian, fallopian, and peritoneal cancers [54]. Importantly, it was demonstrated to exert its anticancer activity as a complex with Cu(I), indicating that elesclomol is in fact a prodrug [55,56]. Regarding its mechanism of action, it seems to be similar to other cytotoxic copper chelating compounds based on a NCI COMPARE analysis [56]. Elesclomol binds to Cu(II) in the serum, which get reduced to Cu(I) once inside cancer cells, where it induces DNA double strand breaks and catalyzes the formation of ROS in a larger amount that in non-cancer cells, explaining why this drug is more cytotoxic to malignant cells than to normal ones [57,58].

Another drug, Casiopeína IIIia has also entered a phase I clinical trial against acute myeloid leukemia [59]. This agent induces DNA fragmentation and base oxidation, indicating that its mode of action involves reactive oxygen species (ROS) generation after copper reduction. Recently, Hernández-Lemus and coll. used transcriptomic approaches and pathway analysis tools to demonstrate that a novel analogue that is ready to start clinical phase I, Casiopeína II-Gly, enhances the metabolism of metal ions and block the migration and proliferation of HeLa cells [45]. A similar approach was recently used to identify metabolic signaling pathways deregulated by a novel ruthenium organometallic compound with interesting anticancer properties [60]. These works illustrate well how advanced techniques in metalloproteomics and system biology are expected to enlighten the mechanism of action of metallodrugs in a close future [61].

Conclusion

Preclinical and clinical studies have gathered encouraging evidences to endorse the therapeutic potential of copper complexes. The main benefit of copper complexes lies on their ability to be selectively reduced as Cu(I) complexes in malignant cells to induce cell death. The goal is now to move from compounds that were originally designed for their catalytic or physical properties to more drug-like compounds that display improved *in vivo* pharmacological properties. One of the challenges to develop this class of drugs is to deal with the complexity of their mechanism of action that does not involved a single molecular target. Thanks to the development of new technologies to explore the effects on every signaling pathway, this limitation is under implementation and we expect that more drug candidates will be soon examined in clinical trials.

Acknowledgements

This work was supported by the "Association pour la Recherche sur le Cancer" (ARC) and "Campus France" for a Tassili fellowship to RT.

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Citation: Tabti R, Tounsi N, Gaiddon C, Bentouhami E, Désaubry L (2017) Progress in Copper Complexes as Anticancer Agents. Med Chem (Los Angeles) 7: 875-879. doi: 10.4172/2161-0444.1000445