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Review Article

Antitumor and antioxidant activity of some metal complex compounds

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Abstract

In the last few years, interest in platinum drugs has increased. Successful treatment depends to a large extent on complex therapy and early diagnosis, which determines the great importance of knowledge of risk groups, clinical symptoms, and targeted use of diagnostic methods with biomarkers, biopsy and diagnostic imaging for early detection of the malignant process. Today, the mono-target strategy is being replaced by a poly-target therapy strategy, which achieves greater clinical efficacy in tumors with defined biomarkers. Key developments include elucidation of the mechanisms of tumor resistance to these drugs, the introduction of some new platinum- based agents and clinical combination studies using platinum drugs with resistance modulators or new drug-targeted drugs. Improved delivery of platinum drugs to tumors has been studied in early clinical trials using liposomal or copolymer-based products. Other investigated as anticancer agents are ruthenium and iron complexes. Ln(III) complexes have been shown to exert antioxidant activity.

Keywords

Platinum and non-platinum metal-based organic complexes, lanthanides, ligands, with potential anticancer activity, antioxidant activity

I. Metal complexes stability

Metals and their related ions are an integral part of living organisms. Biogenic metals play a crucial role in the diverse processes of life, e.g., gas transport, enzymatic catalytic reactions, chemical signalling, etc (Roat-Malone 2007).

Responsible for the antineoplastic properties of drugs containing some metal complexes is thought to be the metal ion (Kostova 2005; Fricker 2006), and many of these ions have attractive coordination chemistry (Bünzli 2005). For example, the high coordination number of lanthanide complexes and their substitution lability are the major factors in the coordination of biomolecules.

The "hard" and "soft" metal ion concentration (HSAI), also known as Pearson's acid-base concept, is widely used in chemistry to explain the stability of compounds, reaction mechanisms and pathways. In general, "hard" metal ions have a small atomic radius, a high effective nuclear

charge, and a low polarizability, whereas "soft" ions have the opposite characteristics (Pearson 1963, 2005; Ho 2002). Calculations of the interaction of the metal ions Mg(II), Ca(II), Li(I), and Na(I) with thymine (5-methyluracil) have been performed (Sagarik and Rode 1983). The results show that there are two suitable sites for electrophilic attack, O(2) and O(4), with relative binding energies in the following order Mg(II)>Ca(II)>Li(I)>Na(I). Although for metal ions the metal-oxygen bond length is the same 36 at O(2) and O(4), the bond energy at metal-O(4) is greater than that at metal-O(2). The influence of methylated isomers of uracil on their noncovalent interactions with alkali metals has been studied. Both theoretical and experimental studies have been carried out by mass spectral fragmentation. Five different forms of methylated uracil, xMeU = 1-methyluracil, 3-methyluracil, 6-methyluracil, 1,3-dimethyluracil, and 5,6-dimethyluracil, were used (Yang and Rodgers 2005). Comparison of lithium complexes of adenine, uracils, and thymine revealed that the most stable structure for adenine was obtained upon bidentate coupling of Li/L^+ to the N7 atom of the imidazole ring and the NH2 group of the pyrimidine ring. For uracil and thymine, the most stable Li/Li^+ bond is at the O4 atom (Krasnokutski et al. 2010). Complexes of neutral uracil and thymine with coordination at O(4) have also been reported (Goodgame and Johns 1977). Complexes of the general formula (MX2Ln).xH2O have been obtained, where X = Cl^-, Br^-, ClO^-, NO^-; L = uracil or thymine; n = 1, 2; x = 0, 1, 2, 3, 4; M = Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II). All complexes are insoluble in nonpolar solvents and decompose in polar solvents. Many of the complexes are hygroscopic and their degree of hydration varies (Sarkar and Ghosh 1983).

Mixed ligand complexes in which uracil is the primary ligand and adenine is the secondary ligand are also described. It is concluded that the 1:1 metal-uracil and 1:1:1 metal-uracyladenine bonding is mediated by the N(3) atom, with uracil in its dihydroxy form. The greater stability of the 1:1:1 complex compared to 1:1 is presumably caused by the interactions between uracil and adenine. A most probable structure is also presented. The synthesis and characterization of mixed complexes of uracil and glycine with Cu(II), Ni(II), Co(II) and Zn(II) are reported. The results show that glycine is bidentate in each case, while uracil appears as a bidentate 40 ligand at the Cu(II) complex, binding via one carbonyl oxygen and one nitrogen atom, and is monodentate in the other cases, binding only via the nitrogen atom (Gupta and Srivastava 1985).

II. Platinum complexes

Platinum compounds such as Cisplatin, Oxaliplatin, (Fig. 1), and Carboplatin (Fig. 2), well-known metal-based antitumor chemotherapy drugs, have serious side effects (Gao et al. 2017a, 2017b).

This has led to an increased demand for metal complexes with low toxicity and improved therapeutic characteristics

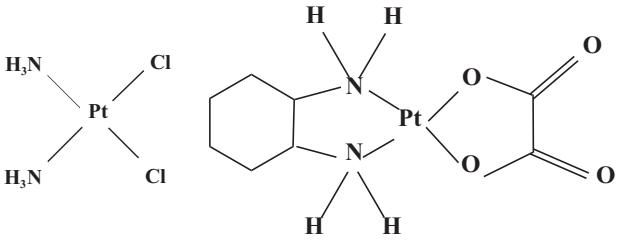

Figure 1. Chemical structures of cisplatin and oxaliplatin.

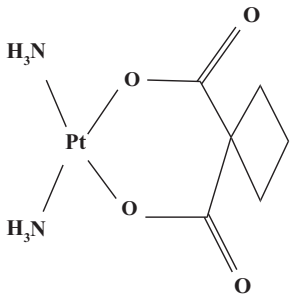

Figure 2. Chemical structures of carboplatin.

as antineoplastic agents (Gaber et al. 2017; Kumaravel et al. 2018; Y.-X. Liu et al. 2018; Martínez et al. 2018; Qi et al. 2018; Tang et al. 2018; Weng et al. 2018; Yi et al. 2018).

The discovery of the mechanism of action and the main structure-activity dependencies of platinum complexes and the observed serious side effects of Cisplatin, Oxaliplatin, and Carboplatin (Gao et al. 2017a, 2017b), create opportunities for rational synthesis of new Cisplatin analogues as potential antitumor drugs with reduced resistance, low toxicity and/or a wider spectrum of antitumor activity, and improved therapeutic characteristics as antineoplastic agents (Gaber et al. 2017; Kumaravel et al. 2018; Y.-X. Liu et al. 2018; Martínez et al. 2018; Qi et al. 2018; Tang et al. 2018; Weng et al. 2018; Yi et al. 2018).

In Table 1 are presented some Pt II complexes with anticancer and antioxidant activity.

Table 1. Pt II complexes with anticancer and antioxidant activity.

Ligand
1) (4-{2-[(2-hydroxy-benzylidene)-amino]-ethyl}-benzene-1,2-diol) [278] (Kareem et al. 2021)
2) (1*H*-1,2,4-triazole-3-ylimino)methyl]naphthalene-2-ol [285] (Gaber et al. 2015)
3) 1-(benzo[*d*]thiazol-2-yl)-3-phenylthiourea (Jambi 2017)
4) macroacyclic ligands [287] (Keypour et al. 2020)

In the field of targeted synthesis of antitumor complexes has been working hard for 40 years. Initial research focused on obtaining complexes with a structure similar to Cisplatin, and later on the search for new "non-classical" antitumor complexes. Approaches to the synthesis of such compounds include: development of new structures based on knowledge of the biochemical mechanism of action of Cisplatin. For overcoming the drug resistance and reduction of toxicity of Cisplatin derivatives is the application of nanocarriers (polymers and liposomes), which provide

improved targeted delivery, increased intracellular penetration, selective accumulation in tumor tissue, and enhanced therapeutic efficacy. An important approach for overcoming the drug resistance and for reduction of toxicity is the combination therapy of liposomal encapsulated Cisplatin and Oxaliplatin with other anticancer agents, which provide improved targeted delivery, improved intracellular penetration, selective accumulation in tumor tissue, and enhanced therapeutic efficacy.

One of the strategies to reduce the overall toxicity and resistance is the use of "prodrugs" that can be activated locally by internal stimuli - physiological changes in the environment (pH, redox potential); by enzyme-catalyzed chemical transformation or by external stimuli such as light.

III. Non-platinum metal complexes

Various strategies for the synthesis of antitumor agents have been developed, such as selection of a suitable ligand system, ensuring effective accumulation in the antitumor tissue (Da Silva and Williams 2001). Replacement of platinum with other metals of the platinum group – ruthenium and palladium or metals with similar properties, such as gold (Halliwell 2006; Momekov et al. 2013). Changing the degree of oxidation of the metal ion with for the purpose of kinetic and thermodynamic control over the binding of the metal complex to DNA bases. Different investigated metal organic complexes have been reported to be promising agents for biomedical applications (Loginova et al. 2019) in medicine and pharmacy (Habala and Valentová 2020). The possibilities of medicinal applications in the therapy of coordination complexes are increased (Mohammed and Tripathi 2020). Due to the specific mechanisms of action (Boros et al. 2020) and different pharmacological activities (Selvaganapathy and Raman 2016), metallopharmaceuticals provide new trend for scientific research (Chylewska et al. 2017), and for perspectives in the discovery and development (Anthony et al. 2020) of drug design Singh et al. 1991).

Metal complexes of silver (Ag), arsenic (As - metaloid), gold (Au), boron (B - metaloid), bismuth (Bi), cobalt (Co), chromium (Cr), copper (Cu), iron (Fe), magnesium (Mg), manganese (Mn), molybdenum (Mo), nickel (Ni), antimony (Sb - metaloid), zinc (Zn), cerium (Ce), europium (Eu), gallium (Ga), gadolinium (Gd), iridium (Ir), lanthanum (La), neodymium (Nd), osmium (Os), palladium (Pd), rhenium (Re), rhodium (Rh), ruthenium (Ru), samarium (Sm), selenium (Se - metaloid), titanium (Ti), vanadium (V), and tungsten (W), are potential therapeutic agents for medical applications(Turel 2015), due to possess potential antiproliferative activity (Bruijnincx and Sadler 2008; P. Zhang and Sadler 2017).

Some complexes of metals have been approved as drugs with potential effects on some cancer. Orally active Auranofin was approved from FDA in 1985 as an antirheumatic drug, which inhibits cathepsins. Combinations with Auranofin have been investigated towards different types of cancer: non-small cell lung, small cell lung and ovarian cancer, and over chronic lymphocytic leukemia (Bruijnincx and Sadler 2008).

In the US in 2003 was approved the proteasome inhibitor Bortezomib for treating a multiple myeloma(Selvaganapathy and Raman 2016)

The more common used ligands are derivatives of pyridine (Marcon et al. 2002; Auzias et al. 2008; Ali et al. 2013; J. Chen et al. 2015; Poynton et al. 2017; Mital and Ziora 2018), pyrazine (Tan et al. 2014), imidazole (Medvetz et al. 2008), benzimidazole (S. Liu et al. 2013; Song et al. 2014), oxadiazole (Maftei et al. 2015), 1,10-phenanthroline (Luís et al. 2014), quinoline (H. R. Zhang et al. 2016), thiazole (Tan et al. 2014), and thiosemicarbazone (Stanojkovic et al. 2010; Manikandan et al. 2014). Very often in structures of organic complexes of Ag(I) (Maftei et al. 2015), Au(I) (Maftei et al. 2015; Mora et al. 2019), Ni(II) (Ray et al. 2009), and Ir(I) (F. Chen et al. 2018) are included N-heterocyclic carbenes, with substituents as 1,2,4-oxadiazole (Maftei et al. 2015; Mora et al. 2019), imidazole (Medvetz et al. 2008), and Caffeine (Bertrand et al. 2014).

The important trend in cancer treatment is the investigation of new non-platinum metal complexes, which possess similar antiproliferative effect, but at lower concentrations than Cisplatin, or higher anticancer effect and best selectivity than Cisplatin. In the investigations for the development of non-platinum compounds with a promising therapeutic potential in current therapy in cancer, Ru complexes are among the most investigated, and advanced organic agents.

1. Ruthenium complexes

Ru complexes are among the most investigated, and advanced organic agents, and are a promising candidate for the increased efficiency of anticancer activity, and for excellent selectivity over healthy cells/tissues.

The superior anticancer activity of Ru complexes than Cisplatin are a result of their increased selectivity toward cancer cells. In 2008 in phase I/II study NAMI-A in combination with Gemcitabine was applied in patients with non-small cell lung cancer.

It has been demonstrated that NAMI-A exhibit selective activity against lung metastases of solid metastasizing tumors with mild toxicity over Cisplatin as a result from its reduced reactivity against DNA in intact cells.

The Ru(II) complexes, which have been entered in clinical trials are NAMI-A with imidazole and dimethylsulfoxide ligands, trans-tetrachlorobis-(1H-indazole)ruthenate (III)] (KP 1019) and KP1339.

It has been reported that NAMI-A possesses antimetastatic activities in secondary tumors, and KP1019 is active against primary tumors. Ru complexes show similar or better efficacy compared to platinum agents.

2. Ferrocene complexes

The antiproliferative potential show Ferrocene-podophyllotoxin (Beaupérin et al. 2017). The compound [3-ferrocenyl-6-methoxybenzo[*b*]thiophen-2-yl][4-(piperazin-1-yl)

methyl-phenyl] methanone is even more potent than the reference compound Cisplatin (Ferreira et al. 2009).

3. Lanthanides complexes

3.1. Medical applications of lanthanides

Lanthanides have some well-established medical applications - as MRI contrast agents, bactericides, and wound treatment. Their potential antiviral, antineoplastic and anti-inflammatory properties are being extensively investigated. The role of lanthanum-containing complexes as diagnostic tools in medicine and biology as well as their potential therapeutic applications has also been discussed in scientific literature. Gadolinium (III) ion with its available seven unpaired electrons is one of the most preferred for NMR medical application. Two other ions, Sysprosium (III) and Holmium (III), have much larger magnetic moments than Gadolinium, but the symmetric S-state of Gadolinium results in a slower and more favorable NMR electron relaxation rate that is more suitable for the excitation of water molecules, as noted by Roat-Malone (Roat-Malone 2007). There is significant interest in radiolabeled biomolecules as target-specific radiopharmaceuticals in the diagnosis and treatment of cancer. DOTA (1,4,7,10-tetraazacyclododecanetetraacetic acid) and its analogues are used as bifunctional chelators to produce a variety of radiolabeled biomolecules.

3.2. Oxidative stress

Free radicals contain unpaired electrons, making them highly reactive and non-selective in their chemical interactions. Thus, they damage various biomolecules (intracellular, extracellular and membrane). This leads to toxin formation, tissue damage and development of pathological processes. For this reason, elevated levels of some substances harmful to the body lead to toxic effects, can alter the redox state of cells, cause DNA damage leading to cell death (apoptosis/necrosis). The formation of free radicals as a result of normal physiological processes in living organisms is compensated by a number of antioxidant defense mechanisms. A disturbed balance between radical formation and elimination, in which free radical accumulation predominates, is defined as oxidative stress. Free radicals react with all biomolecules, including antioxidants. This can lead to depletion of antioxidant enzyme activity, release of metal ions from ion-binding proteins, and depletion of radical scavengers. All these factors lead to the inability of antioxidant defenses to control oxidative stress. It can also be compromised by any disturbances of metal ion homeostasis (Halliwell 2007).

3.3. Antioxidant and antineoplastic activity of lanthanides

The potential antioxidant and antineoplastic activity of lanthanides are being extensively investigated. Lanthanide based coordination complexes as anticancer agents are classified based on different ligands such as acridine, benzothiazole, coumarin, 5-fluorouracil, phenanthroline, plumbagin, porphyrins, quercetin, quinolone, schiff bases, transferrin, and miscellaneous ligands (Chundawat et al. 2021).

Lanthanides cannot be administered as simple salts or metal ions in clinical practice because of their toxic effect. In studies on mice treated with several different lanthanide chlorides, significant oxidative damage to the lungs was observed due to a simultaneous weakening of antioxidant defense mechanisms and an increase in reactive parts (RP) production. Long-term exposure to LaCl3 in mice is known to result in significant impairment of memory and spatial orientation. Intracellular Ca^{2+} in hippocampal cells was increased, whereas Ca^{2+}-dependent ATPase activity was suppressed. There was a dose-dependent increase in malondialdehyde (MDA) and attenuation of SOD, CAT and GPx in the cerebral cortex and hippocampus (Zheng et al. 2000).

The described property of some elements to induce oxidative stress makes their simple salts and coordination complexes significant targets in the development of antitumor drugs. Of particular interest are complexes of these metals with organic ligands that exhibit antioxidant properties. Lanthanides can be administered as a stable complex. The basic idea of this approach is the transport of the metal ions to the target tissue, with their release from the complex taking place in the tumor. There, the metal ion can stimulate the formation of free radicals, destroying the tumor by apoptosis. Ligands play an important role in coordinating the properties of the respective complexes (Krinochkin et al. 2015) and they are particularly important for biological, biochemical, and medical applications (Bünzli and Eliseeva 2013).

Various Ln(III) complexes have been described in the literature to have significant biological activities, e.g. DNA binding and antioxidant activity (B. dui Wang et al. 2007; Q. Wang et al. 2009; Xu et al. 2009), and the exhibited cytotoxic activity of lanthanide complexes is usually attributed to lanthanide-DNA interactions, inhibition of calcium transport in mitochondria (Reed and Bygrave 1974), and apoptosis of the endoplasmic reticulum (Kwong et al. 2013). Inhibition of thioredoxin reductase and targeting of the glutathione-independent lipoate reduction pathway by gadolinium (III) texaphrin (MGd, Xcytrin) is the other important mechanism by which cancer cell replication is subsequently inhibited in DNA, restored, and oxidative stress induced (Citta et al. 2012). Tumorigenesis, for example, could be induced by iron overload and iron-mediated oxidative stress. Lanthanides competitively inhibit iron uptake, inhibit iron-mediated formation by interacting with hydroperoxides, participate in magnetic interactions with free radicals, thus affecting signal transduction. For this reason, lanthanide compounds are being investigated for antitumor activity and could potentially affect a wide range of iron-dependent pathologies (Cho et al. 2013).

It has been shown that La (III) complex containing 2,2′-bipyridine ligand exert *in vitro* cytotoxicity towards MCF-7 (breast cancer) and A-549 cell lines (Aramesh-Boroujeni et al. 2021). The complexes of La(III)) with usnic acid (2,6-diacetyl-7,9-dihydroxy-8,9-dimethyl-1,3(2*H*,9b*H*)-dibenzofurandione were more

toxix against tumor cells MCF-7 (breast cancer) than in normal breast tissue cells (MCF-10A), demonstrating selectivity. (Nunes et al. 2020).

3.4. Lantanium(III) complexes

3.4.1. Dinuclear lanthanium(III) complexes

It has been reported that dinuclear lanthanide complex with ligand N'-(2-hydroxybenzylidene) nicotinohydrazide exhibits specific cytotoxicity to A549 cancer cells and less toxicity than Cisplatin for normal human cells HUVEC (Song et al. 2020). A binuclear La(III) complex $\{[La_2(HA)_4(H_2O)_4(C_2H_5OH)_2Cl_2]Cl_4$ (**C1**)} with 2-aminobenzoic acid exerts cytotoxicity against human breast (MDA-MB-231), prostate (PC-3) and bladder (T-24) cancer cells (Zidan et al. 2022).

3.4.2. Dimeric lanthanum(III) complexes

It has been described that dimeric lanthanum(III) complex with 1,10-phenanthroline shows in vitro cytotoxicity against A-549 cell (Niroomand et al. 2023).

3.4.3. Lanthanum mixed ligand complexes

It has been investigated that primary schiff base of lanthanum (III) benzimidazole complex with ligand 2-(1H-benzimidazol-2-ylmethyliminomethyl) phenol in vitro exerts cytotoxicity on the HCT116 cell line superior to that observed with the HEPG2 cell line (El-Sayed and Alhakimi 2022).

3.4.4. La-based metal organic frameworks

It has been described that a La-based metal organic frameworks can be used for anticancer delivery of 3,4-dihydroxycinnamic acid shows citotoxicity against the human breast cancer cell line MDA-MB-468 (Safinejad et al. 2022).

3.4.5. Nano-structure La (III) complexes

Lanthanide nanoparticles (Nanoceria) are not only small molecules but also exhibit *in vitro* cytotoxicity to various human cancer cells, such as pancreatic, hepatocellular, and squamous-cell carcinoma (Momekov et al. 2013; Wason and Zhao 2013). This cytotoxicity may result from induction of oxidative stress, activation of mitogen-activated protein kinase, and mimics of superoxide dismutase, glutathione peroxidase, and catalase activity (Cheng et al. 2013; Wason and Zhao 2013). It has been demonstrated that nano structure metal complexes of La (III) with two different nitrogen donor tridentate ligands: N-(2-Aminoethyl)-1,3-propanediamine and 1-(2-Aminoethyl)piperazine possess antitumor activitiy. (Hassan and Mohamed 2020).

Conclusion

A future trend is the widespread use of platinum-containing regimens with a new generation of molecularly targeted therapies in combination with carboplatin and paclitaxel in patients with lung cancer. The introduction of different leaving groups and / or carrier ligands leads to significant changes both in the antitumor activity and spectrum of action and in the toxicological profile of platinum analogues.

This expands the possibilities for search and development of new platinum complexes as antitumor drugs in; development of platinum complexes with high oral bioavailability; increasing the crossing of the blood-brain barrier and developing platinum-directed platinum cytostatic.

Lanthanide nanoparticles exert *in vitro* cytotoxicity against pancreatic, hepatocellular, and squamous-cell carcinoma.

Other trend is the synthesis of mixed liligand complexes with Cu(II), Ni(II), Co(II) and Zn(II).

The synthesis and study of complex compounds has a targeted nature related to the discovery of the diverse potential biological possibilities, a logical consequence of the diverse properties of the starting ligand and complexing agents with a view to a future rational approach in the selection of metals and biologically active ligands.

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