# Zinc Complexes as Anticancer Agents

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The search for anticancer metal-based drugs alternative to platinum derivatives could not exclude zinc derivatives due to the importance of this metal for the correct functioning of the human body. Zinc, the second most abundant trace element in the human body, is one of the most important micro-elements essential for human physiology. Its ubiquity in thousands of proteins and enzymes is related to its chemical features, in particular, its lack of redox activity and its ability to support different coordination geometries and to promote fast ligands exchange. Analogously to other trace elements, the impairment of its homeostasis can lead to various diseases and in some cases can be also related to cancer development. However, zinc complexes generally exert lower toxicity in comparison to other metal-based drugs and many zinc derivatives have been proposed as antitumor agents. Among them zinc complexes comprising N-donor ligands have been surveyed and analyzed.

Zinc(II) | Zinc(II) complexes | N-donor ligands | metal-based drugs | medicinal chemistry | antitumor agents

## 1. Introduction

Zinc is among the few transition metals, namely Mn, Fe, Co, Cu, Zn and Mo, which, together with the first and second series metals Na, K, Mg and Ca, are essential for human physiology. In the human body, zinc, after iron, is the second most abundant trace element. About 3 g of zinc, mostly localized in testicles, muscles, liver, and brain, are present in an average adult provided by a daily intake of 8–11 mg.[1] At the physiological concentration, zinc is crucial for increasing cell survival and protecting tissues against damages. Zinc concentration (about 0.6 mM) is regulated by specific homeostasis and, similarly to the other micro-elements, either a deficiency or an overload can lead to toxic effects to the organism.[2][3][4][5] Zinc deficiency can be related to inadequate zinc intake due to nutritional or absorption problems, ageing (several data showed that 35–45% of adults over 60 have a Zn intake below the required estimated average), Zn losses from the body or deregulation of zinc homeostasis. Zinc deficiency can depress immune function as Zn plays a crucial role in the immune system through cellular proliferation and RNA and DNA synthesis and is necessary for T-lymphocyte development. It also can determine other effects including growth retardation, impotence, and hypogonadism. Many symptoms due to Zn deficiency are not specific and can be related to other health conditions so that the diagnosis is not always straightforward. Zinc excess, however, is less frequent and most often occurs via excess supplementation. Most toxic effects due to a chronic high Zn intake (e.g., myeloneuropathy) are mainly related to the inhibition of copper absorption, and hence are secondary to a zinc-induced copper deficiency.[6]

The vital importance of zinc can be easily understood considering that this metal is present in more than 3000 human proteins including nucleic acid binding proteins; is involved in the catalytic activity of thousands of enzymes; plays a role in DNA synthesis, protein synthesis and immune functions.[7][8] The binding of $Zn^{2+}$ with catalytic and/or structural sites of a large number of proteins is a key-factor in determining their conformations.[2] All in all, zinc is essential for virtually all cellular functions and also for the growth and development of all forms of life, not only human.[9] The majority of Zn in the human body (95%) is intracellular and the lack of specialized zinc storage systems makes a suitable daily intake necessary for maintaining a steady concentration in the organism. In biological systems the concentration of free $Zn^{2+}$ ions is extremely low (pM-nM), i.e., it is not a relevant pool for trafficking, transport and cellular actions of zinc, so that these processes occur by a direct exchange of the metal from donor to acceptor Zn ligands.[10] Specific Zn transporters (ZIP and ZnT proteins) regulate Zn homeostasis and control its efflux via plasma membranes when the concentration of intracellular Zn is too high or when it must be transferred to other organs. But, whereas zinc coordination and its role in proteins and enzymes have been clarified and extensively reviewed, further studies are still necessary to completely explain the mechanisms of the exchange processes between intra- and extra-cellular space.[11]

The importance of zinc in biological systems is definitively related to its unique chemical features: $Zn^{2+}$ is redox inactive, is a strong Lewis acid, has a $d^{10}$ configuration, is diamagnetic, can support a variable coordination geometry and is prone to a fast exchange of ligands. Its electron affinity resembles that of copper or nickel, but the lack of redox activity of divalent zinc ion, differently from copper or iron, eliminates any chances of free radical reactions and makes it crucial for the body's antioxidant protection system.

The $Zn^{2+}$ $d^{10}$ configuration, and the consequent absence of d-d transition, could be seen as a limit for the spectroscopic characterization of Zn derivatives, together with their diamagnetism and white colour, but on the other hand, the absence of ligand field stabilization can guarantee highly flexible coordination geometry determined only by the charge and steric hindrance of the ligands.[12][13] In biological systems zinc can be tetra-, penta-, or hexacoordinated to N, O or S donor atoms comprised in histidine, glutamate/aspartate, and cysteine residues, or to water molecules with a tetrahedral, pyramidal, or octahedral coordination geometry. In proteins, the most frequent geometry is tetrahedral, with few examples of distorted trigonal bipyramidal. In proteins, also multiple zinc clusters, comprising from two to four metal ions, can be found in the metal intrasphere binding geometry.

In addition to its physiological role, zinc can have beneficial therapeutic and preventive effects on infectious diseases and, compared to other metal-based drugs, Zn(II) complexes generally exert lower toxicity and have fewer side effects. An example of a worldwide commercial Zn-derivative is pyrithione zinc, first described in 1930 and used as a topical antimicrobial to treat fungal or bacterial infections of skin and hair. In the years different classes of zinc coordination complexes have shown a good potential in different applications, among which as radioprotective agents,[14] tumor photosensitizer,[15] antidiabetic,[16][17][18] anticonvulsant,[19] anti-inflammatory,[20] antimicrobial,[21][22][23][24][25][26] antioxidant,[27][28] antiproliferative/antitumor,[29][30][31] anti-Alzheimer's disease[32] and in several neglected diseases.[33]

On the other hand, deregulation of zinc homeostasis can determine cell apoptosis and hence trigger cancer progress.[34] The relationship between zinc deficiency and cancer has been recognized in human, animal, and cell culture studies[35][36] and zinc-containing metalloenzymes have been identified as alternative targets for metal-based anticancer agents.[37] Zinc deficiency causes oxidative DNA damage,[38][39] and chromosome breaks have been reported in zinc-deficient diet-fed animals [40] In addition, zinc is useful in reducing cardio and hepatotoxicity caused by some anticancer drugs.[41]

The relationship between Zn deficiency and prostate cancer has been deeply analysed,[42] as well as the effect that Zn imbalance can have on the genesis and development of different forms of leukaemia.[43]

Examples of the detrimental effects of both excess or depletion of Zn in tumoral pathologies have been faced with opposite approaches: on one hand, a chelation therapy approach based on depletion of excess cellular Zn by the use of suitable chelating ligands,[44][45] on the other hand, the use of ionophore systems such as clioquinol.[46]

Another approach consists in using zinc complexes as metal-based antitumor drugs. This approach is very promising due to the fact that (1) having a specific homeostasis zinc metal ion could be better managed by human physiology and cause fewer side effects in comparison to non-essential metal-based compounds;[47][48] (2) zinc is significantly non-toxic even at higher doses than other metals (Fe, Cu, Hg, etc.), with obvious advantages for bio-compatibility;[47][48][49][50][51] (3) Zn(II) complexes probably have targets and mechanisms of action different from the classical platinum-based drugs;[52][53][54][55] (4) zinc is one of the most studied metals in the coordination of photosensitive systems for Photo Dynamic Therapy (PDT),[56][57][58] and (5) due to their ability to assist Lewis activation, nucleophile formation and rapid ligand exchange, zinc compounds can be employed as catalysts of hydrolytic reactions, such as hydrolysis and DNA cleavage, thus making anti-tumor activity possible.[59][60] Recent studies have confirmed the above assumptions showing that Zn(II) derivatives could be potential anticancer agents with low toxicity in vivo, low side effects and probably different cellular targets and modes of action when compared with classical metal-based drugs.[53][55][61][62][63][64][65][66]

## 2. Nitrogen Ligands in Zn Complexes

As reported in the Introduction, Zn(II) has a very versatile chemistry. It can adopt a range of coordination numbers giving rise to different geometry, even though especially in solution octahedral stereochemistries dominate. Zinc can coordinate various donor atoms, especially the first-row donor atoms oxygen or nitrogen rather than second-row sulphur or phosphorus, according to its hard acid nature. Accordingly, N-donor ligands are almost the most representative category. Homoleptic and mixed-ligand complexes have been reported and, due to the variety of accessible arrangements, a great assortment of frameworks (from mono- to hexadentate chelates) have been employed.

The surveyed complexes were organized on the basis of the ligand nature according to the following classification:

1. Quinoline and Diimine Systems and 2,2'-Bipyridine and 1,10-Phenanthroline Systems (24 Zn Complexes)

2. Terpyridine and Pyridine-Based Systems (23 Zn complexes)
3. Imidazoles and Analogous Imidazole-Based Systems (36 Zn complexes)
4. Schiff Base Systems (9 Zn complexes)

Planar aromatic quinoline, 2,2′-bipyridine and 1,10-phenanthroline ligands have often been the ligands of choice for medicinal chemists, due to their DNA intercalation properties and often to their intrinsic toxicity, which could enhance the metal effect. On the other hand, it's known that several diimines have low specificity for tumor cell lines and can be genotoxic.[67] Terpyridine metal complexes are able to intercalate into DNA showing inhibitory effects on tumor cells and possess photoluminescence properties.[68][69][70][71] Imidazolyl derivatives are among the most utilized N-donor ligands due to their excellent coordination ability,[72][73] different hapticity and possibility to be derivatized or conjugated to active moieties. Within this class, benzoimidazolyl derivatives are the most representative (22 out of 36 Zn complexes), mainly thanks to the accessibility of phenyl ring substitution, which in turn allows SAR determination for different families of Zn complexes. Schiff bases are generally one of the most representative classes of ligands, mainly due to their easy way of synthesis. N-donor Schiff bases have been surveyed on the basis of their different hapticity, whereas some examples of *N*,*O*-coordination are reported in the miscellanea (10 Zn complexes).

An important application of Zn derivatives in medicinal chemistry is Photo Dynamic Therapy. Zinc complexes with photo-activable N-donor ligands, such as porphyrins and phthalocyanines, used in PDT, have been extensively reviewed in the last years [56,57] and are not treated in this survey. Zinc-phthalocyanine complexes generally show low toxicity, high chemical and photochemical stability [56]. Anyway, low dark cytotoxicity is generally a prerequisite for photosensitizers in biological applications, even though chemotoxicity is sometimes associated to some Zn derivatives. The phototoxicity of the reported complexes is generally very high ($IC_{50}$ values in micro-nanomolar range) and cannot be compared to the toxicity showed by the other families of zinc complexes surveyed in this paper, as the mechanism of action is not relied upon a biological involvement of the metal.

Considering the antiproliferative activity of the reviewed complexes, we found out that 43 out of 102 derivatives exhibited an antitumoral activity with $IC_{50}$ values ≤10 micromolar against one or more cancer cell lines, reaching in some cases the nanomolar range. In addition to the complexes showing micromolar or sub-micromolar anticancer activity, 10 compounds exhibited a noticeable antitumor activity with $IC_{50}$ values of 10–20 μM, whereas the remaining ones showed a moderate/low activity. Considering that antiproliferative activity in vitro is not predictive of an activity in vivo, it would be important to have more data of in vivo experiments with the most promising candidates to effectively evaluate the potential of Zn-based anticancer agents, as only few examples of in vivo studies have been reported. Looking critically at these data, without making any considerations on action mechanisms and proposed targets, some general considerations can be made trying to find a correlation between structure and activity. As far as the chemical structure is concerned, among the different geometries which Zn can adopt, hexa- and penta-coordination are by far the most common situations for active compounds, differently from zinc proteins where tetrahedral coordination, frequently slightly distorted, is the preferred geometry. The hapticity of the ligands is not decisive for the activity of the final complex, whereas the frequent presence of water molecules in the coordination sphere can allow an easy exchange with biological substrates. The use of active ligands does not always determine an increase of cytotoxicity upon coordination. From studies carried on with analogous complexes

of different bivalent metal (such as Ni(II), Cu(II), Co(II), Fe(II), Mn(II)), it very often came out that zinc derivatives were less active, suggesting a minor effect of the metal compared to other metals. It seems that, excluding the use of hypotoxic Zn as a carrier of photoactive species for PDT or of active ligands, the antitumor efficacy of Zn-coordination complexes is not so appealing in comparison to other metal-based derivatives. The concentration of Zn in cells is probably so (relatively) high, that small variations do not induce an antiproliferative action of the metal unless specific mechanisms are involved. Probably an interesting application could be the use the low active, but at the same time low toxic zinc derivatives in combination with other chemotherapeutic agents to reduce their side effects.

Anyway this analysis has to be extended to all the classes of zinc coordination complexes, not only those with N-donor ligands, to confirm the above general considerations.

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