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New copper(II) thiohydantoin complexes: Synthesis, characterization, and assessment of their interaction with bovine serum albumin and DNA

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ABSTRACT

New copper(II) complexes of 2-alkylthio-5-arylmethylene-4H-imidazolin-4-ones: (5Z)-2-(methylsulfanyl)-3-(prop-2-en-1-yl)-5-(pyridin-2-ylmethylidene)-3,5-dihydro-4H-imidazol-4-one) (**1a**), (5Z,5′Z)-2,2′-(ethan-1,2-diyldisulfanyldiyl)bis(5-(2-pyridilmethylen)-3-allyl-3,5-dihydo-4H-imidazole-4-one) (**2a**) and (5Z,5′Z)-3,3′-hexan-1,6-diylbis[5-(2-pyridilmethylen)-2-methylthiotetrahydro-4H-imidazole-4-one)] (**3a**) were synthesized as possible anticancer drugs. Their structures were characterized by ^{1}H NMR spectroscopy, elemental analysis, and X-ray crystallography. The composition of the complexes were found for **1a** (Cu:L = **1**:**1**), **2a** (Cu:L = **2**:**1**), and **3a** (Cu:L = **2**:**1**). The chelation constants were found by competitive complexation with ethylenediamine tetraacetate: **1a** $(6.7 \pm 0.6) \times 10^{15}\ M^{-1}$, **2a** $= (4.9 \pm 0.4) \times 10^{19}\ M^{-2}$, and **3a** $(5.7 \pm 0.5) \times 10^{19}\ M^{-2}$. Supramolecular binding with calf thymus DNA by competitive ethidium bromide quenching was made for complex **2a** as the most promising anticancer model, the Stern–Volmer constants were found to be $K_{SV} = (8.0 \pm 0.4) \times 10^{6}\ M^{-1}$, $K_q = (6.5 \pm 0.4) \times 10^{5}\ M^{-1}$. The binding of the complex **2a** to BSA was made by the Scatchard method, the value of the constant is $K_b = (1.9 \pm 0.2) \times 10^{6}\ M^{-1}$.

1. Introduction

A wide variety of biological functions of transition metals determines the main criteria for the development of potential metallodrugs. They should be more efficacious, less toxic, target specific, and able to bind to DNA [1,2]. First, anticancer activity of different types of tumor cells has been investigated for various Pt-based compounds [3,4]. Along with extremely high selectivity to cancer cells, numerous Pt complexes demonstrated high toxicity, which consequently has led to further extensive search for other transition metal-based compounds as potential anticancer drugs [5–7].

Copper complexes proved their effectiveness in the treatment of various neurodegenerative diseases as well as malignant tumors, such as brain, mammary gland, large intestine cancers, and other pathologies [8–12]. It was also demonstrated that inorganic copper complexes can be effective in cancer therapy owing to their cytotoxic action on tumor cells [13]. Being an essential endogenous element, copper, in comparison with nonessential elements like platinum, is almost nontoxic to normal but active in cancer cells [14,15]. Recently, it has been shown that a novel class of copper-based chemotherapeutic agents, Casiopeinas® (II-gly (CSII) or casiopeina III-i-a (CSIII)), increases the cancer-cell death by apoptosis [16,17]. Casiopeinas® are attractive for preclinical and clinical studies on various lines of cancer cells, and several representatives are going through clinical trials [18–23]. It was stressed [24] that the molecular mechanisms underlying the cardiotoxicity and anticancer activity of these agents are not completely understood. Previously, it was assumed that Casiopeinas® can bind DNA through interactions with adenine and thymine and can also block oxidative phosphorylation [25]. It was also shown [22] that these copper complexes interact with DNA through different binding modes; the mode and intensity of the interaction are influenced by both ligands coordinated to copper.

Abbreviations: CT-DNA, calf thymus DNA; DMEM, Dulbecco's Modified Eagle Medium; DMSO, dimethylsulfoxide; EB, ethidium bromide; EDTA, ethylenediamine tetraacetate; FBS, fetal bovine serum; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

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Copper complexes could be used clinically as imaging agents in positron-emission tomography (PET) and magnetic resonance imaging [26,27]. Radionuclides of copper offer a varying range of half-lives and positron energies in the development of new radiopharmaceuticals, which combine PET imaging and targeted radiotherapy capabilities [28]. The increasing interest to PET nowadays is based on successful imaging capabilities used for the identification and characterization of relevant disease biomarkers at cellular and sub-cellular levels and a targeting moiety highly specific for the target [29].

Recently, we have shown that complex compounds of organic ligands containing a thiohydantoin (2-thioxo-imidazolidin-4-one) cycle could be attractive towards this aim [30–32]. Thiohydantoin complexes with transition metals (Co, Ni, and Cu) have shown their antibacterial, anticancer, and antiviral activity [33–35]. Using various lines of cancer cells, such as MDA-MB-231, HepG2, PC3 that represent human breast adenocarcinoma, human hepatocellular carcinoma, and human prostate adenocarcinoma, studies of activity and anticancer activity demonstrated the ability of these compounds to block the activity of the telomerase, the enzyme present in 95% of cancer cells [2,36]. The most promising results were shown for copper complexes. Currently, delivery applications of thiohydantoin complexes as potential drugs into human body and to the target cells are also under intensive study [37–39].

To characterize biologically active chelates is to understand their behavior in human body as well as to assess the targeted drug delivery to the infected cell. The mechanism of interaction with DNA as well as the knowledge of the nature of the drug interaction with human serum albumin (HSA) as the main transport protein in the body, makes it possible to predict the pharmacokinetics of a potential drug [40–42]. Also, in the case of strong binding, it becomes possible to create conjugates of the drug with HSA for the selective delivery of the therapeutic agent into the tumor tissue. Due to the similarity of the structures of HSA and bovine serum albumin (BSA), studies are usually carried out with the latter due to its availability [43–45]. Therefore, the stability of the complexes under physiological conditions and their ability to bind to DNA molecules and various proteins are key criteria in the evaluation of their biological effect.

Previously [2], we have reported the synthesis and investigations of a number of ligands and their mixed-valence Cu(I,II) complexes containing 2-alkylthio-5-arylmethylene-4H-imidazolin-4-ones. Based on the previously synthesized library of 2-alkylthio-5-arylmethylene-4H-imidazolones and the research conducted to date [33,46–49], we have selected three most promising, different ligand types of 2-alkylthio-5-arylmethylene-4H-imidazolin-4-ones for further synthesis of model copper complexes. Along with the small size of the organic molecule, principal differences in the structures of model complexes are the presence of one or two coordination centers in the complex, as well as the nature of the substituents in the imidazolone ring. Different nature of substituents in the ligands is crucial for cytotoxicity of corresponding complexes.

In this paper, we carry out a comparison study of the physicochemical parameters of the copper coordination compounds of this type to determine the long-term agents for further study of its binding to BSA and DNA.

2. Results and discussion

2.1. Synthesis of the complexes

Initial 5-pyridinemethylene thiohydantoins were synthesized by the Knoevenagel condensation reaction [50]. All the complexes were produced by the interaction of the corresponding ligand with copper chloride (see Experimental Procedures). From the ligand **1** instead of the expected copper complex with a composition of L:$CuCl_2$ = 1:1, we have isolated the coordination compound **1a** with an unexpected structure proved by X-ray crystallography [46]. According to X-ray data, we obtained a binuclear copper cluster of the ligand, in which there was no substitute at the sulfur atom. Each copper atom is linked to the sulfur atom and two nitrogen atoms of the pyridine and imidazole cycles. Two copper atoms are also linked by the bridging chlorine atom. They have equivalent metal coordination geometries and are located in a tetrahedral environment (disregarding the neighboring Cu atom) bound by one bridging chlorine atom. The Cu–Cu distance is 2.5620(10) Å. This distance is similar to those found for the Cu_I–Cu_{IV} center in N_2OR (2.6 Å) [13,51]. Thus, complex **1a** may be considered as a conventional structural analogue of the active site of N_2O-reductase. The identical coordination sphere geometry of both copper atoms in complex **1a** suggests that it exists in a delocalized mixed-valence form with a [$Cu^{+1.5}Cu^{+1.5}$] oxidation state (see [52] and references therein). EPR spectra recorded at room temperature for the polycrystalline powder of compound **1a** show features typical for such mixed-valence copper complexes [52]: they contain an isotropic signal centered at g = 2.1258, and no hyperfine splitting is observed at 300 K, but it observed at 77 K in frozen DMF (Supp. Information, Fig. S1). The proposed scheme of the ligand cleavage in the formation of this complex with the participation of solvent molecules (methanol) is shown below (Fig. 1). As a Lewis acid, copper chloride increases the nucleophilicity of the sulfur-containing fragment and facilitates the course of the reaction as SN_2-substitution at the carbon atom of the methyl group. Copper complexes **2a** and **3a** were prepared by existing procedures. The structures were determined by elemental analysis and X-ray crystallography and were discussed in detail previously [2,53,54]. EPR spectra of both complexes **2a**, **3a** for polycrystalline samples at 300 K show a typical signal of Cu^{+2} at $g \approx 3.27$ (Supp. Information, Fig. S2). Molar conductance values of all the complexes in DMSO–water solvents at 10^{-4} M at 298 K are very low (see experimental) indicating their non-electrolytic nature [55].

The experiments at this stage showed that the synthesized copper complexes are relatively lowly soluble in water; therefore, we changed the system environment and, based on previous investigations [56,57], added small amounts of DMSO to facilitate the solubility. In addition, such a system is simple for preparation and suitable for the introduction into human body.

2.2. Absorption parameters and the estimation of stability constants

Ligand spectra were evaluated using spectrophotometry in DMSO (Supp. Info., Fig. S3). The results show the similarity of the chromophores

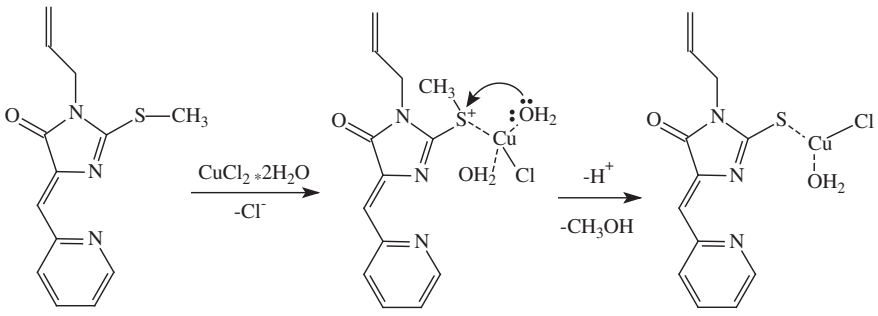

Fig. 1. Proposed formation mechanism of copper complex **1a**.

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