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Research paper

Copper complexes based on chiral Schiff-base ligands: DNA/BSA binding ability, DNA cleavage activity, cytotoxicity and mechanism of apoptosis

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ABSTRACT

Four copper(II) complexes with chiral Schiff-base ligands, [Cu(***R*-L**^{1})$_2$]·EtOAc (**1**) and [Cu(***S*-L**^{1})$_2$]·EtOAc (**2**), [Cu(***R*-L**^{2})$_2$]·EtOAc (**3**) and [Cu(***S*-L**^{2})$_2$]·EtOAc (**4**), (***R/S*-HL**^{1} = (*R/S*)-(1-naththyl)-salicylaldimine, ***R/S*-HL**^{2} = (*R/S*)-(1-naththyl)-3-methoxysalicylaldimine, EtOAc = ethyl acetate) were synthesized to serve as artificial nucleases and anticancer drugs. All complexes and ***R/S*-HL**^{1} ligands were structurally characterized by X-ray crystallography. The interaction of these complexes with CT-DNA was researched *via* several spectroscopy methods, which indicates that complexes bind to CT-DNA by moderate intercalation binding mode. Moreover, DNA cleavage experiments revealed that the complexes exhibited remarkable DNA cleavage activities in the presence of H_2O_2 *via* the generation of hydroxyl radical. Particularly, complex **4** also could nick DNA with the production of $^1O_2$. And all complexes exhibited excellent cytotoxicity to MDA-MB-231, A549 and Hela human cancer cells in micromole magnitude. Furthermore, complex **4** exhibited comparable cytotoxic effect to cisplatin against the proliferation of MDA-MB-231 and A549 cancer cells, as well as showed better anticancer ability to the three cancer cells than the other complexes. The results of cell cycle analysis indicated that complexes **3**–**4** could induce G_2/M phase cell cycle arrest. Furthermore, MDA-MB-231 cells treated with **3** and **4** were subjected to apoptosis and death by generation of ROS and the activation of caspase-3. Interestingly, the chiral complexes **3** and **4** may induce cell apoptosis through extrinsic and mitochondrial intrinsic pathway, respectively.

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1. Introduction

Cisplatin, acting as a DNA targeting drug, has been successfully used as an effective anticancer drug in the clinical treatment of various types of human cancers [1–4]. Though cisplatin was first synthesized by an Italian in 19th century, its anticancer ability was first reported in the 1960s [5,6]. Hence, the widespread application of cisplatin for anticancer drug contributes coordination chemistry of metal-based drugs to the frontline of the fight against cancer [7,8]. However, many side-effects such as nephrotoxicity, neurotoxicity, inherited or acquired resistance phenomena limited its comprehensive application in the therapy of cancers [8,9]. These problems had prompted chemists to research more optimal strategies based on different metals and ligands, with the wide range of coordination numbers and geometries, available redox states, thermodynamic and kinetic characteristics, and intrinsic properties of the metal ions. In this field, copper complexes were definitely considered as alternative metal-based anticancer drugs.

As copper is an essential element for most aerobic organisms, an assumption that this endogenous metal may be less toxic for normal cells than cancer cells is raised. It is reported that the metabolism and cell response to copper between normal and tumor cells are generally different, which ground the basis of copper complexes endowed with antineoplastic characteristics [3]. Scientists found that the concentration of copper in numerous *ex-vivo* cancerous tissues (e.g., breast, prostate, lung, and brain) was exceeded than that of in normal tissues [10–13]. Actually, control of

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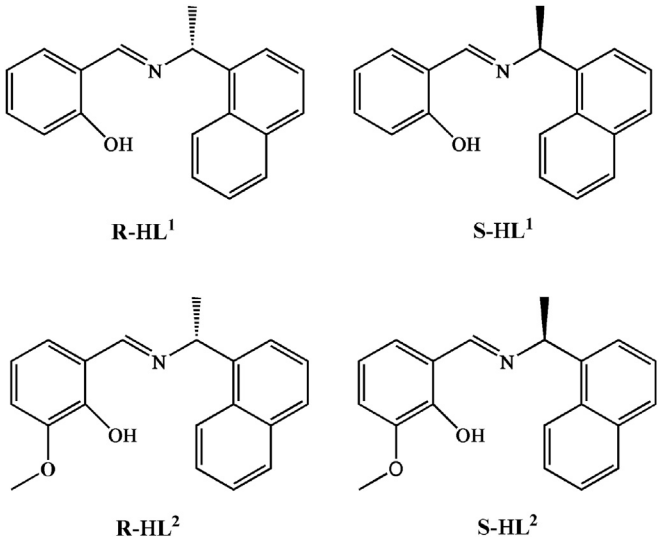
tumor growth, and metastasis could be attained by chelating the excess of copper with several small molecules. At present, many researches are focusing on the synthesis, DNA cleavage activity and anticancer mechanism of copper-based complexes. For example, some 2-oxo-quinoline-3-carbaldehyde Schiff-base ligands and their copper(II) complexes were found to interact with CT-DNA through intercalation [14]; A novel copper(II) complex bearing zoledronic acid derivative with effective antitumor activity and low hepatotoxicity was designed and evaluated [15]. And the cytotoxic studies of several N,N-disubstituted semicarbazone derivatives and their corresponding copper(II) complexes indicated their broad-spectrum anticancer ability against several human cancer cell lines [16]. Likewise, H. Liang group synthesized four binuclear copper(II) complexes derived from Schiff base thiosemicarbazones to evaluate their anticancer properties and anticancer mechanism [17].

Among these copper-based anticancer drugs, complexes based on Schiff-base ligands with planar aromatic group showed favorable DNA intercalative abilities and potential antiproliferative abilities. Schiff-base ligands generally coordinate with metal ion *via* the lone pair of the nitrogen atom from the −C═N−R moiety and additional functional groups, leading to stabilization of many metals in various oxidation states [18]. And the planar aromatic ring of ligands may cause strong $\pi-\pi^*$ stacking interaction between aromatic chromophore and the base pairs of DNA [19]. For instance, four amino acid Schiff-base copper(II) complexes were synthesized and considered as potent proteasome inhibitors and apoptosis inducers of human cancer cells [20]. In our previous work, two water-soluble copper(II) complexes derived from Schiff-base ligand (2-((quinolin-8- ylimino)methyl)pyridine) were reported to act as moderate DNA intercalating agents and potential anticancer drugs [21].

With the in-depth research of metal-based drugs, the lipophilicity of metal complexes gains extensive attention because excellent lipophilicity allows the complexes to rapidly cross the membrane, resulting in better cell uptake [22]. S. Tardito and coworkers illuminated the mechanism of action of different copper binding agents with various lipophilic ligands [23]. It had been recently noted that the cyclometalation of metal complexes could efficiently increase the lipophilicity of metal complexes and significantly improve their cellular uptake, eventually enhancing the anticancer abilities of complexes [24]. Otherwise, researchers found that the cell membrane is a natural phospholipid chiral molecule showing very high preference to L-enantiomer [25,26]. Thus, chirality could influence the pharmacological activities of complexes remarkably. According to this theory, Liang et al. synthesized three water-soluble ruthenium(II) complexes with chiral 4-(2,3-dihydroxypropyl)-formamideoxoaporphine (FOA), in which complex cis-[$RuCl_2$(S-(−)-FOA)$(DMSO)_2$] showed better cell uptake and anticancer activity than the other enantiomer or racemate [27]. Therefore, the synthesis of metal complexes considering chirality and lipophilicity of may be a new tendency for meta-based anticancer drugs.

In this study, we had designed and synthesized two couples of chiral ligands: (*R*/*S*)-(1-naththyl)-salicylaldimine (***R/S*-HL^1**) and (*R*/*S*)-(1-naththyl)-3-methoxysalicylaldimine (***R/S*-HL^2**) (Scheme 1), and their corresponding copper(II) complexes **1**–**4**. In addition, the lipophilic modified methoxy group of **HL^2** may enhance the hydrophobicity of complexes **3**–**4** [28,29]. All complexes were structurally characterized by X-ray crystallography and exhibit excellent DNA binding and cleavage activities. Also, the cytotoxicity and preliminary apoptotic mechanism studies of complexes **3**–**4** had been tested and analyzed in this work.



Scheme 1. Chemical formation of ligands.

2. Result and discussion

2.1. Synthesis and characterization

Ligands ***R/S*-HL^1** was prepared by the typical aldimine condensation reaction, while the solid of ***R/S*-HL^2** ligand was failed to obtain for their high-solubility in methanol. Thus these copper complexes were synthesized by different methods. Complexes **1**–**2** were synthesized *via* adding copper(II) acetate into 15 mL methanol solution of ***R*-HL^1** or ***S*-HL^1**. However, complexes **3**–**4** were obtained by in-situ synthesized reaction. And the resulting black precipitates were filtrated and dried in vacuum, then resolved in ethyl acetate and filtered, slow evaporating at room temperature for several days to get the single crystals of corresponding complexes. The results of ESI-MS analysis ($[Cu(\mathbf{L})_2 + H]^+$) indicated these copper complexes keep stable in DMF solution. The CD spectra of the two enantiomeric couples in DMF solution were measured at room temperature from 500 to 300 nm. The two chiral enantiomers emitted the equal intense peak with the opposite orientation (Fig. 1), respectively, which demonstrated the existence of two chiral enantiomers. At last, the absolute configurations of the two enantiomeric couples were confirmed by single X-ray diffraction.

2.2. X-ray crystal structure of complexes *1*–*4*

Single crystals of the four mononuclear copper complexes suitable for X-ray diffraction (Fig. 2) were obtained by slow evaporation of the compounds in ethyl acetate solution at room temperature. All complexes crystallized in the monoclinic space group P2(1) (Table 1) and selected bond angles and distances were noted in Table 2. The copper ions were tetra-coordinated by two ligand molecules which acted as mono-anionic bidentate N, O-donor *via* phenolic hydroxyl oxygen and Schiff-base nitrogen. Also the bond lengths of Cu−N and Cu−O were naturally 1.958−1.963 Å and 1.885−1.895 Å for complexes **1**–**4**. The angles of N1−Cu−N2 were 157.47°, 157.37°, 156.9° and 155.47°, respectively, indicating the square planar geometry of copper ions with small deviations. Besides, the dihedral angle of plane [N1−Cu−O1] and [N2−Cu−O2] ([N2−Cu−O3] for **3**–**4**) were 33.971° (**1**), 34.037°(**2**), 34.144° (**3**) and 34.456° (**4**), respectively, which strongly testified the distorted square planar geometry of copper centers. The naphthalene ring

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