Synthesis, Characterization and DNA Binding Investigations of a New Binuclear Ag(I) Complex and Evaluation of Its Anticancer Property

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Aim: A new Ag(I) complex (A3) was synthesized and evaluated for its anticancer activity against human cancer cell lines.

Materials and Methods: The complex A3 was characterized by 1H, 13C, and 31P nuclear magnetic resonance (NMR), infrared (IR) spectra, elemental analysis, and X-ray crystallography. The interaction of the complex with CT-DNA was studied by electronic absorption spectra, fluorescence spectroscopy, and cyclic voltammetry; cell viability (%) was assessed by absorbance measurement of the samples.

Results: The interaction mode of the complex A3 with DNA is electrostatic, and this complex shows good potential in anticancer properties against HCT 116 (human colorectal cancer cells) and MDA-MB-231 (MD Anderson-metastatic breast) cell lines with 0.5 micromolar concentrations.

Conclusion: The Ag(I) complex could interact with DNA noncovalently and has anticancer properties.

Keywords: binuclear Ag(I) complex, X-ray crystallography, DNA, electrostatic binding, anticancer

Introduction
Cancer is a challenging disease and global deaths owing to it are increasing.1 Important methods for the treatment of cancer patients include surgery, chemical medication, radiotherapy, biological immunization, and chemotherapy. In chemotherapy, 5-fluorouracil (5-Fu) is the main anticancer drug, possessing an inhibitory capability against many cancers, particularly for gastrointestinal tumors.2,3 However, critical side effects have been observed associated with the clinical use of 5-Fu.4 In addition, 5-Fu possesses a short half-life and is swiftly removed after operation. Many studies have been carried out to combat these problems and increase the antitumor activity of 5-Fu; some procedures include modulations of 5-FU in combination with other compounds and advanced delivery systems.2,5,6 Choi et al indicated that chloroquine can augment the antitumor effect of 5-FU by cell cycle blockage in human colon cancer cells.7 More research is needed to find new types of anticancer drugs. Metal complexes display good potential in cancer therapy due to their unique features, for example, various coordination routes, reactivity, and redox ability against organic materials. Therefore, based on these characteristics, it is possible to design metal complexes with the ability to interact...
with target biomolecules, and, as a result, to modify the cellular cycle.\textsuperscript{8} In some cases, metal complexes show better antitumor properties than the ligands. The complexes may act via their impact on electron transport, inhibition of DNA replication by the metal ion center, perturbation in the proteins and enzyme actions as well as redox balance in cells, reactive oxygen species (ROS) production and alteration of the cell membrane.\textsuperscript{9,10}

Cisplatin is a compound that is currently used in cancer treatment. Despite some favorable results, the function of cisplatin is restricted to only some types of tumor, and its usage leads to toxicity and resistance in clinical application. Hence, it is essential to develop new types of anticancer compounds. Many researchers have focused on coinage metals (Au, Cu, and Ag) because the complexes of these metals exhibit a wide range of anticancer activity with less toxicity to non-cancerous cells.\textsuperscript{11} Among coinage metals, silver is of special importance since it is compatible with biological systems, and silver complexes display low toxicity to human cells, are selective against cancer cells, and act as antimicrobial agents.\textsuperscript{8,12} A few active anticancer complexes of Ag(I) such as carboxylate, phosphate, and bipyridine complexes have been reported.\textsuperscript{12–14}

The presence of the ligands in the silver complexes leads to the improvement of the silver function.\textsuperscript{15} Moreover, the high number of Ag(I) center ions in a complex can improve the biological activity of silver complexes,\textsuperscript{16} and the cytotoxic effect of binuclear silver(I) complexes is significantly more in cancer cells in comparison with the normal cells.\textsuperscript{14} Haque et al showed that silver ions have a fundamental importance in the destruction of tumor cells.\textsuperscript{3,12}

Anticancer agents mostly act through the DNA molecule.\textsuperscript{15} Molecules may interact with DNA by changing or preventing its operation, disordering gene sequences and introde in transcription.\textsuperscript{17}

The main binding types in DNA complexes are covalent and non-covalent. The mechanism of action of many anticancer drugs is by covalently binding to DNA. Covalent binding is observed at several binding sites including the nitrogen centers of the bases, and the phosphates. The antitumor activity of the covalent binding leads to blockage of DNA, irreversibly and completely. The non-covalent interactions with DNA consist of electrostatic bindings with the negatively charged phosphate, intercalation between adjoining base pairs, and groove interaction.\textsuperscript{18} Non-covalent interaction has advantages including reversibility and less cytotoxicity. This type of interaction can unwind and break the DNA double helix.\textsuperscript{19} Metal ions may play the role of a counter ion as a result of interaction with DNA noncovalently.\textsuperscript{20} Also, the groove binding of some octahedral complexes with DNA with base pairs has been reported.\textsuperscript{18,21–23}

Silver compounds can interact with DNA via metalization of DNA. This is important in the development of biotechnological areas and also the ligands of the complexes can intercalate between bases of DNA. DNA may be metalized by the coordination of silver to bases of DNA\textsuperscript{15} or with the aid of electrostatic binding.\textsuperscript{24,25}

This report describes the synthesis and characterization of a new binuclear Ag complex, $[\text{PPh}_3\text{Ag}(\text{L}_1)]$$[\text{PPh}_3\text{Ag (L}_1\text{)}]$ (A\textsubscript{3}), where PPh\textsubscript{3}=tri phenylphosphine, L\textsubscript{1}=5-fluorour acil-1-yl acetic acid, and its interaction with calf thymus DNA (CT-DNA). Also, we investigated the anticancer activity of the complex A\textsubscript{3} toward human cancer cell lines.

Materials and Methods

Apparatus and Reagents

The ligand was prepared according to the method mentioned in this report, and all other chemicals and solvents were purchased from Aldrich Chemical Company or other commercial vendors. \textsuperscript{1}H, \textsuperscript{13}C, and \textsuperscript{31}P nuclear magnetic resonance (NMR) spectra were recorded on an AVANCE III AV 500 spectrometer using tetramethylsilane (TMS) as an internal standard and DMSO-d\textsubscript{6} as the solvent at room temperature. IR spectra were recorded on a Nicolet IS10 spectrophotometer. Elemental analysis was carried on a EURO EA 3000 Elemental Analyzer. UV–vis absorption spectra were provided by a UV-6100 double beam spectrophotometer. Fluorescence measurements were made on an F-2700 FL spectrophotometer at room temperature. The electrochemical experiments were performed with a CHI 1030b electrochemical workstation (Shanghai Chenhua Co.). The absorbance (A) of wells in biological investigations was measured using a multiplate reader on a Multiskan Mk3, Thermo Scientific, Waltham, USA, at 450 nm. All cell lines were purchased commercially from the Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences (Shanghai, China).

X-Ray Crystallography

The specifications of the single crystal of the A\textsubscript{3} class, orientation matrix, and cell dimensions were determined by the founded methods and Lorentz polarization and absorption corrections were performed. Empiric absorption
corrections were provided by the SADABs program. Most of the non-hydrogen atoms were determined according to direct procedures, and the rest were located by subsequent Fourier synthesis. All non-hydrogen atoms were refined anisotropically, and all hydrogen atoms were maintained changeless and took in the final stage of full-matrix least squares refinement based on F² by the SHELXS-97, SHELXL-97 and SHELXTL programs.

**Syntheses**

*Synthesis of 5 FUAA Ligand 5-Fluorouracil-1-yl Acetic Acid (L1)*

First, 31.2 g (240 mmol) 5-fluorouracil was added to 160 mL of aqueous solution of 51.2 g (92 mmol) potassium hydroxide and heated up to 40°C; then, 50 g (360 mmol) 80 mL bromoacetic acid solution was slowly added in the mixture for 120 min. Under this temperature mixing reaction was stirred overnight, cooled to room temperature, adjusted pH to 5.5 by concentrated hydrochloric acid and put in the refrigerator frozen for 2 h. After removing precipitate, sediment filtered off and a solution of strong hydrochloric acid was added to it to bring the pH value to 2 then it was put in the refrigerator frozen for 6 h. After filtering sediment and washing in cold water three times, the compound was dried (Figure 1).26 Yield: 89%. M. p: 241ºC, Anal. Calc. for C\(\text{fl}\)− for 1 h) was diluted to 0.5, (0.052 g, 0.3 mmol) under ultrasonic until a stable cyclic as μ Zheng et al with or without NIR irradiation was measured in cell lines of HCT 116 (human colorectal cancer cells) and MDA-MB-231 (MD Anderson-metastatic breast) using the cell counting kit-8 (CCK-8) assay. Cancer cells were seeded in 96-well plate with a cell density of 10,000 cells/well and incubated in a humidified 37°C incubator with an atmosphere of 5% CO₂/95% air. After 24 h, A₃ with or without NIR irradiation (808 nm laser, 0.2 W/cm² for 1 h) was diluted to 0.5, the suspension was sealed and heated to 70°C for 20 h. After cooling to room temperature, the solution was filtered off. After slow evaporation of the colorless and transparent solution, colorless crystals were obtained.

Yield: 85.23%. M. p: 171.1ºC-173.7ºC. ¹H NMR, ¹³C NMR, and ³¹P NMR are given in Supporting Information, Figure 1S–3S.

**DNA Binding and Anti-Cancer Activity Experiments**

The binding of A₃ with CT-DNA was investigated by electronic absorption spectra, fluorescence spectroscopy, and cyclic voltammetry studies. Biological activity tests of complex A₃ as a drug, with a molecular size of 14.46×20.05Å³ as measured using Diamond Software, have been performed in the solution and on a molecular scale. The size of complex A₃ is suitable for delivery and penetration as a drug in the body.27 To determine the anticancer activity of the complex, the cell viability (%) was investigated by absorbance measurement of the samples.

**Preparation of DNA-Modified Electrode**

For preparation of the electrode-modified DNA, gold disk electrodes were glossed by the alumina powder (1.0, 0.5, and 0.05 μm). Then, the Au electrode was refined and left in fresh piranha solution (30% H₂O₂ and 70% H₂SO₄) to remove adsorbed impurities, then it was placed in an ultrasound bath for 5 min.

In order to prepare a neat Au electrode, the surface of the electrode was activated electrochemically through sweeping from −0.3 to +1.5 V in 0.1 M H₂SO₄ until a stable cyclic voltammogram was created. After washing with water, the Au electrode was modified by pouring a droplet of 10 μL of 1.0 μg μL⁻¹ CT-DNA solution onto its surface, then drying in the air overnight. Then, the DNA-modified electrode (named CT-DNA/Au all over) was immersed in water for about 4 h to eliminate any unadsorbed CT-DNA.

**The Preparation of the Samples for Cytotoxic Measurements**

The cell viability of A₃ was measured in cell lines of HCT 116 (human colorectal cancer cells) and MDA-MB-231 (MD Anderson-metastatic breast) using the cell counting kit-8 (CCK-8) assay. Cancer cells were seeded in 96-well plate with a cell density of 10,000 cells/well and incubated in a humidified 37°C incubator with an atmosphere of 5% CO₂/95% air. After 24 h, A₃ with or without NIR irradiation (808 nm laser, 0.2 W/cm² for 1 h) was diluted to 0.5,
1, 2, 4, and 6 μM, respectively, and added into the plate. For comparison, free 5-Fu with the same concentrations was also added into the plate. 24 h post-treatment, the medium in each well was refreshed with the culture medium (200 μL with 10 μL CCK-8 reagent). After 2 h, the absorbance (A) of each well was measured at 450 nm.

**Results**

**Structural Studies**

The complex [(PPh₃)₂Ag(L1)][(PPh₃)₂Ag(L1)] (A₃) was formed by reaction of AgBF₄ with CH₂CN solution of PPh₃, Et₃N and 5-FUAA. Slow evaporation of the resulting solution led to the formation of colorless and transparent crystals. After preparation of A₃ it was characterized by Fourier-transform infrared spectroscopy (FT-IR) spectroscopy, ¹H NMR, ¹³C NMR, ³¹P NMR, and X-ray crystallography. The structural data and description of the diffraction experiment are listed in Table 1 and a schematic representation of the complex is given in Figure 2. The structural details are discussed in the Discussion section.

**Electronic Absorption Spectra Studies**

UV-vis absorption spectroscopy is one of the prevalent methods for studying the interactions between DNA and complexes. Absorption titration experiments were carried out at a constant concentration of complex A₃ (10 μM) with changing concentrations of (0–0.045 mg mL⁻¹) from CT-DNA in buffer containing KH₂PO₄/NaOH (at pH = 6.2, 7.2, and 8.2). Absorption spectra were measured at each increase in the CT-DNA solution (Figure 3).

**Fluorescence Studies**

A simple method to check the interaction characteristics between the complex and DNA is fluorescence spectroscopy. Ethidium bromide, 3,8-diamino-5-ethyl-6-phenyl phenanthridium bromide (EtBr), is widely used to study small molecule–DNA interactions because of its high fluorescence when binding to DNA.²⁸ Emission spectra were carried out with EtBr (0.05 mM) connected to CT-DNA (0.12 mg mL⁻¹) in the absence and presence of A₃ in buffer KH₂PO₄/NaOH (pH = 7.2) with a range of concentrations of 0–0.1 mM (Figure 4).

<table>
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<th>Table 1 Data Collection and Refinement Parameters for A₃</th>
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<td>Largest diff. peak and hole</td>
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Electrochemical Characterization

Cyclic Voltammetry

Voltammetric measurements were performed in a prevalent three-electrode cell contains a bare gold or CT-DNA/Au as the working electrode, a saturated calomel electrode (SCE), and a platinum wire auxiliary electrode. The CV experiments were performed using a 5 mM solution of K₃[Fe(CN)₆]/K₄[Fe(CN)₆] (1:1) in 0.05 M KH₂PO₄/NaOH buffer at pH 7.2 with 0.1 M KCl at room temperature (25ºC). All solutions were deaerated with pure nitrogen, and the electrochemical experiments were carried out at a scan rate of 0.1 V s⁻¹.

A typical cyclic voltammogram of the bare Au electrode (curve a) and CT-DNA/Au (curve b) in 5.0 mM Fe(CN)₆³⁻/⁴⁻ solution at a scanning rate of 0.1 V s⁻¹ is observed in Figure 5. As seen from Figure 5, two redox peaks were obtained in both cases. In addition, the peak current at CT-DNA/Au was lower than that in the bare Au electrode. This is because DNA acts as an electron and mass transfer blocker layer, which prevents the motion of Fe(CN)₆³⁻/⁴⁻ toward the electrode surface. The results also demonstrate the good modification of the DNA on the surface of Au electrode. The CV of the DNA-modified Au electrode remained stable after 20 scans in the KH₂PO₄/NaOH buffer solution, representing electrochemical stability of the DNA films.

The electrochemical behaviors of Fe(CN)₆³⁻/⁴⁻ at CT-DNA/Au were further investigated by a change in scan rate in KH₂PO₄/NaOH buffer solution (pH 7.14) containing 5 mM Fe(CN)₆³⁻/⁴⁻. From Figure 6, it can be seen that the anodic peak currents increased with increasing the scan rate, and there is a good linear relation between peak current and scan rate in the range of 0.01–0.13 V s⁻¹. These results show that the electrochemical kinetic process is a typical surface adsorption-regulated electrochemical process.

Since complex A₃ is a non-electroactive organic small molecule, Fe(CN)₆³⁻/⁴⁻ was employed as a redox probe to study the interactions of non-electroactive of the complex with CT-DNA. Cyclic voltammogram changes of Fe(CN)₆³⁻/⁴⁻ at different concentrations of A₃ at CT-DNA/Au are observed in Figure 7.

As observed in Figure 7, both the reduction and oxidation peak currents gradually decrease with increasing concentrations from 0.26 mM to 2.50 mM of A₃ (some concentrations have been omitted in the Figures). This process can be ascribed to the fact that DNA films cause the redox activation of Fe(CN)₆³⁻/⁴⁻ to be harder at the Au electrode because of the physical blockage and possible electrostatic repulsion. After adding the prodrugs to the solution, they interact with DNA, resulting in the formation of a denser DNA film; therefore, the migration of Fe(CN)₆³⁻/⁴⁻ ions via the film becomes harder and the redox peak current of Fe(CN)₆³⁻/⁴⁻ is decreased.

As shown in Figure 8, both the peak currents of the cyclic voltammograms decreased with increasing the concentrations of drugs and reached a saturation value according to Langmuir adsorption behavior.
Biological Activity

In order to perform a quantitative comparison of the binding strength of A₃ with CT-DNA, the binding constant (K) was calculated according to the Langmuir formula in Equation (A.1).²⁹ Based on the procedure of Qu et al³⁰ it is considered that DNA and DRUG only create a single complex DNA.DRUG<sub>m</sub>, DNA + mDRUG ⇔ DNA × DRUG<sub>m</sub>  (A)

Using Equations 1S-8S in Supporting Information, Equation (A.1) is obtained:

\[
\frac{1}{\Delta I_p} = \frac{1}{\Delta I_{p,\text{max}}} + \frac{1}{\Delta I_{p,\text{max}} \cdot K \cdot [\text{DRUG}]} \quad (A.1)
\]

where \(\Delta I_p = I_{p0} - I_p\), \(I_p\) and \(I_{p0}\) show the oxidation peak current of Fe(CN)<sub>6</sub><sup>3-/4-</sup> in the presence and absence of the drugs, respectively; \(\Delta I_{p,\text{max}}\) is the maximum difference of the oxidation peak current; and [DRUG] shows the concentration of the drug. Therefore, the binding constant (K) is \(3.13 \times 10^3\) L mol⁻¹.

Anti-Cancer Activity

Anticancer potential of A₃ on both HCT 116 (human colorectal cancer cells) and MDA-MB-231 cancer cell lines was evaluated by cell counting kit-8 (CCK-8) assay. The results were reported as percentage inhibition of cell proliferation (±SD). The relative cell viability was calculated by the following equation:

\[
\text{Cell viability (\%)} = \left( \frac{A_{\text{treatment}} - A_{\text{blank}}}{A_{\text{control}} - A_{\text{blank}}} \right) \times 100\%
\]

\(A_{\text{blank}}\) indicates the absorbance of the well without adding CCK-8 reagent and \(A_{\text{control}}\) indicates the absorbance of the...
Figure 4 Emission spectra of EtBr (0.05 mM) connected to CT-DNA (0.12 mg mL\(^{-1}\)) in the absence and presence of A\(_3\) (0.00, 0.02, 0.04, 0.06, 0.08, 0.10 mM) in KH\(_2\)PO\(_4\)/NaOH buffer (pH = 7.2). Inset: Stern–Volmer quenching curve. The \(K_{SV}\) value is \(2.789 \times 10^3\) M\(^{-1}\).

Figure 5 Cyclic voltammograms of Fe(CN)\(_6^{3-}/4-\) in pH 7.2 KH\(_2\)PO\(_4\)/NaOH buffer solution at a bare Au electrode (a), CT-DNA/Au (b). The scan rate is 0.1 V s\(^{-1}\) and the concentrations of Fe(CN)\(_6^{3-}/4-\) and KCl are 5 mM.
Figure 6 The relationship between anodic peak current and the scanning rate (0.01–0.13 V s⁻¹) for CT-DNA/Au.

Figure 7 Cyclic voltammograms of Fe(CN)₆³⁻/⁴⁻ in KH₂PO₄/NaOH buffer solution (pH 7.2) containing different concentrations of drugs. The scan rate is 0.1 V s⁻¹ and the concentrations of Fe(CN)₆³⁻/⁴⁻ and KCl are 5 mM.
well with the addition of saline buffer instead of any drugs. The compounds $A_3$+NIR and $A_3$ in counteranions (0.5–6µM) were found to be well active (Figures 9 and 10). At the various concentrations, significant differences in the activity of compounds 5-$A_3$+NIR and $A_3$ were observed. Increasing the concentrations led to an enhancement of compounds' activities.

**Discussion**

**Structural Characterization**

Characteristic absorption bands of the ligands PPh$_3$ and L1 are observed in the FT-IR spectra for complex [(PPh$_3$)$_3$Ag(L1)],[(PPh$_3$)$_2$Ag(L1)] ($A_3$) with the some extent shift except of absorption band of OH (3414 cm$^{-1}$) that is related

![Figure 8](image_url)

**Figure 8** Adsorption isotherm of drug $A_3$ on CT-DNA/Au. The solid line corresponds to the Langmuir model. Inset: The relationship between 1/[DRUG] and 1/Δ$A$.

![Figure 9](image_url)

**Figure 9** Cell viability of $A_3$+NIR, $A_3$ and 5-Fu in HCT 116 cell line. Significant differences are indicated as ***$p<0.001$, **$p<0.01$, *$p<0.05$, n=3.
to the carboxylic functional group due to coordination bonding of it as an O-donor moiety in A. Single X-ray crystal analysis shows that there are two Ag(I) ions with different coordination environments consisting of AgOP$_3$ and AgO$_2$P$_2$. Ag1 is coordinated by one O atom of carboxylate: Ag1-O1: 2.3787(64) Å and three P atoms of PPh$_3$ molecules: Ag1-P1: 2.5316(22) Å, Ag1-P2: 2.5817(15) Å, Ag1-P3: 2.5855(15) Å. The coordination sphere of Ag2 includes two O atom belonging to a carboxylate group: Ag2-O5: 2.4990(55) Å, Ag2-O6: 2.4507(69) Å and two P atoms of PPh$_3$ molecules, Ag1-P4: 2.4209(21) Å, Ag1-P5: 2.4550(17) Å; therefore, four coordinated and binuclear complexes are formed in which the Ag−Ag distance of the two silver atoms Ag1 and Ag2 is 8.5318(13) Å. The structure of A$_3$ crystallizes in the triclinic space group P with lattice constants a = 13.806(3) Å, b = 14.652(3), c = 27.796(5), Z = 2 (Figure 2).

### The Interaction of the Complex with the DNA Molecule

The binding mode between DNA and complexes can be determined by absorption spectroscopy based on the shifts and absorption strength. According to Figure 3 the absorption spectra of the complex incubated with increasing concentrations of CT-DNA. The absorption bands of A$_3$ undergo hyperchromism in molar absorptivity, which is ascribed to the electrostatic interaction between the metal ions of the complex and phosphate group of DNA.$^{31}$ The higher $K_\theta$ value for b in comparison to a (or c) indicates that neutral environments provide more favorable conditions for this interaction.

In the other investigation, the study of complex binding to DNA was carried out using the fluorescence feature of EtBr. As given in Figure 4, with an increase in the concentration of the complex, the intensity of the emission band in the EtBr-DNA system decreased as indicated by the replacement of the EtBr with the complex at DNA binding sites. The fluorescence quenching efficiency is evaluated by the Stern–Volmer constant ($K_{SV}$) based on the classical Stern–Volmer equation: $F_0/F = 1 + K_{SV}[Q]$, in which $F_0$ and $F$ are related to the fluorescence intensities of EtBr-DNA in the absence and presence of the complex, respectively, and [Q] is the concentration of the complex. $K_{SV}$ is a linear Stern–Volmer quenching constant achieved from the linear regression of $F_0/F$ with [Q].

Voltammetric measurements display good electrochemical stability of the DNA on the Au electrode and the correlation between the peak currents of the cyclic voltammograms and concentrations of drugs shows a Langmuir adsorption behavior.

### Anti-Cancer Activity

According to the literature, silver complexes exhibit anticancer activity by various mechanisms.$^{3,16}$ Herein silver(I) ions interfere with the function of cancer cells by interacting with the phosphate group of DNA molecules.

The cell viability of A$_3$ with or without NIR irradiation was evaluated in both HCT 116 (human colorectal cancer cells) and MDA-MB-231 (MD Anderson-metastatic breast) cell lines by cell counting kit-8 (CCK-8) assay. According to Table 2 and the IC$_{50}$S (half-maximal inhibitory concentrations), the comparison of the anticancer activities of compounds is as follows: A$_3$+NIR$>$A$_3$$>$5-Fu.
The results demonstrate a significant influence of the silver complex on the anticancer activity.

Conclusion

In summary, a new Ag(I) complex, \((\text{PPh}_3)_2\text{Ag(L1)}\), \((\text{PPh}_3)_2\text{Ag(L1)}\) (\(A_3\)), \(L_1=5\)-fluorouracil-1-yl acetic acid, was prepared and the crystal structure of it was studied by single crystal X-ray analysis. The binding of the complex to CT-DNA was studied by electronic absorption spectra, fluorescence emission, and cyclic voltammetry, and the results suggested an electrostatic interaction with DNA. The prepared binuclear complex, because it includes ion metal centers (Ag\(^{+}\)) and ligand \(L_1\) (5-fluorouracil-1-yl acetic acid) with a molecular size of 14.46×20.05 Å\(^2\), can be regarded as a new agent for evaluation of anticancer properties. The results of the biological study indicated that complex \(A_3\) possesses a good potential in antiproliferative activity against human cancer cell lines, with the 0.5 micromolar concentrations.

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Disclosure

The authors report no conflicts of interest in this work.

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