COPPER(II) AND ZINC(II) COMPLEXES BASED ON ANTIMICROBIAL DRUG SARAFLOXACIN: SYNTHESIS, STRUCTURE AND BIOLOGICAL EVALUATION

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ABSTRACT

Two novel sarafloxacin complexes, [CuII(detam)(srx)](ClO4)2·1.5H2O (1) and [ZnII(pydam)(srx)2](ClO4)2 (2) (Hsrx = sarafloxacin, srx = deprotonated sarafloxacin, detam = N,N-diethyl ethylenediamine, pydam = 1,2-propylene diamine) have been synthesized and characterized by elemental analysis, infrared spectra and single crystal analysis. In both complexes sarafloxacin acts as deprotonated bidentate ligand coordinated to Cu(II) and Zn(II) ions through the pyridone oxygen and a carboxylate oxygen. The antimicrobial activity of the complexes 1,2 against four bacterial species were tested and the results indicated that they exhibit enhanced or similar activity to the free sarafloxacin. Both complexes 1 and 2 exhibit good binding propensity to human or bovine serum albumin protein (HSA or BSA) with relatively high binding constant values. UV studies and cyclic voltammograms of the interaction of sarafloxacin and its complexes with calf-thymus DNA (CT DNA) show that complex 2 exhibits the higher binding constant to CT DNA and the results indicated that sarafloxacin and complexes 1, 2 interact with DNA mainly via intercalation and electrostatic binding. The agarose gel electrophoresis assay reveals complex 1 also shows better cleavage ability.

Keywords: Quinolone; Sarafloxacin; Zn(II) complex; Cu(II) complex; biological evaluation.

1. INTRODUCTION

Sarafloxacin (Hsrx) (Scheme 1) is the first third-generation fluoroquinolone drug approved by the FDA for food animals in the August 18, 1995. It presents a broad spectrum of activity against Gram-positive, Gram-negative bacteria and mycoplasma [1–4]. The mechanisms of it either inhibit the supercoiling of DNA catalyzed by the DNA gyrase, or interact with the
DNA molecule via a metal complex intermediate \[5\]. Sarafloxacin complexes’ biological properties have never been involved and mononuclear complexes were never acquired before \[6,7\].

![Scheme 1. Sarafloxacin](image)

The importance of copper as a bio-metal is mainly focused on its biological role in proteins and its potential synergetic activity with drugs \[8\]. Numerous copper (II) complexes with diverse drugs have shown different biological activities such as antitumor \[9\], antibacterial \[10,11\], antifungal \[12\], urease inhibitors \[13\] and xanthine oxidase inhibitors \[14\]. Zinc is the second most prominent trace metal in the human body. The importance of zinc as a bio-metal is mainly due to its biological role in various biological systems and numerous cell processes. Furthermore zinc is a major regulatory ion in the metabolism of cells \[15\]. Diverse zinc complexes’ biological activities have been reported, such as antibacterial \[16\], anti-diabetic \[17\], anti-inflammatory \[18\], and antiproliferative–antitumor \[19\], besides, it can also be used for the treatment of Alzheimer disease \[20\].

Serum albumin is the most abundant protein in plasma and involved in the transport of metal ions and metal complexes. Binding to proteins may lead to loss or enhancement of the biological properties of the original drug or provide paths for drug transportation. Therefore it is important to study the interaction of sarafloxacin and its complexes with the serum albumin. \[21\]. In this study, we investigate the affinity for bovine and human serum albumin proteins involved in the transport of metal ions and metal-drug complexes through the blood stream. The study of the interaction of quinolones and their complexes with DNA is of great importance since their activity as antibacterial drugs is mainly focused on the inhibition of DNA replication by targeting essential type II bacterial topoisomerases such as DNA gyrase and topoisomerase IV \[22\]. As reported, DNA can provide three distinctive binding sites for quinolones and their metal complexes, namely, groove binding, electrostatic binding to
phosphate group and intercalation \cite{23-26}. In this paper we study the interaction of the complexes with calf-thymus DNA (CT DNA).

The interactions of copper(II) and zinc(II) with sarafloxacin have never been studied. In many cases, mixed-ligand copper(II) and zinc(II) complexes with drugs, especially quinolone ligands, and N-donor ligands have shown better activity than free drug \cite{9}. In this context, we report the synthesis, characterization and biological properties of sarafloxacin and its copper(II) and zinc(II) complexes \([\text{Cu(detam)}(\text{srx})]\text{(ClO}_4\text{)}_2\cdot1.5\text{H}_2\text{O} (1)\) and \([\text{Zn(pydam)}(\text{srx})_2]\text{(ClO}_4\text{)}_2 (2)\). The study of the biological properties of the complexes has been focused on (i) the affinity for bovine and human serum albumin proteins, involved in the transport of metal ions and metal-drug complexes through the blood stream, investigated by fluorescence spectroscopy, (ii) the binding properties of the complexes with DNA analyzed by UV spectroscopy, cyclic voltammetry and agarose gel electrophoresis in order to study the existence of a potential intercalation of the complexes to DNA. (iii) the antibacterial activity of the complexes by the minimum inhibitory concentration (MIC) against four microorganisms.

2. MATERIALS AND METHODS

Materials – instrumentation – physical measurements

In procedures of synthesis the following chemicals were used: \(\text{Cu(ClO}_4\text{)}_2\cdot6\text{H}_2\text{O}, \text{Zn(ClO}_4\text{)}_2\cdot6\text{H}_2\text{O}, \text{serafloxacin, N, N-diethyl ethylenediamine and 1, 2-propylene diamine were purchased from Aladdin Chemistry Co. Ltd (Shanghai). Calf-thymus DNA (CT DNA), Plasmid DNA (pUMT), ethidium bromide (EB), bovine serum albumin protein (BSA) and human serum albumin protein (HSA) were purchased from Sigma and Trisodium citrate, NaCl and all solvents were purchased from Tian Jin Zhiyuan Chemical Reagent Co. Ltd (Tianjin). All reagents were commercially available and used as received without further purification unless noted specifically.

DNA stock solution was prepared by dilution of CT DNA to buffer (containing 15 mM trisodium citrate and 150 mM NaCl at pH 7.0) followed by exhaustive stirring for three days, and kept at 4 °C for no longer than a week. The stock solution of CT DNA gave a ratio of UV absorbance at 260 and 280 nm (\(A_{260}/A_{280}\)) of 1.8–1.9, indicating that the DNA was sufficiently free of protein contamination \cite{27}. The DNA concentration was determined by the UV absorbance at 260 nm after 1:20 dilution using \(\varepsilon = 6600 \text{ M}^{-1}\text{cm}^{-1}\) \cite{28}.
Infrared (IR) spectra (400–4000 cm\(^{-1}\)) were recorded on a Nicolet FT-IR 5700 spectrometer with samples prepared as KBr disk, Elemental analyses for C, H and N were performed on a Perkin-Elmer 240C analyzer and UV–visible (UV-vis) spectra were recorded in the range 2×10\(^{-5}\)–5×10\(^{-3}\)M on a Hitachi U-3310 spectrophotometer. Fluorescence spectra were recorded on a Hitachi F-4500 fluorescence spectrophotometer.

Cyclic voltammetry studies were performed on an electrochemical analyzer CHI600C. Cyclic voltammetry experiments were carried out in a 30 mL three-electrode cell. The working electrode was platinum disk, a separate Pt single-sheet electrode was used as the counter electrode and a Hg/Hg\(_2\)Cl\(_2\) electrode saturated with KCl was used as the reference electrode. The cyclic voltammograms of the complexes were recorded in 0.4 mM 1/2 DMSO/buffer solutions at \(\nu = 100 \text{ mVs}^{-1}\) where the buffer solution were the supporting electrolytes. Oxygen was removed by purging the solutions with pure argon which had been previously saturated with solvent vapors. All electrochemical measurements were performed at 25.0 ± 0.2 °C.

**Synthesis of the complexes**

\([\text{Cu}(\text{detam})(\text{Hsrx})](\text{ClO}_4)_2 \cdot 1.5\text{H}_2\text{O} \ (1)\] Sarafloxacin (0.1 mmol, 38.5 mg) was dissolved in methanol (8 mL) and acetonitrile (2 mL), and a few drops of NH\(_3\)·H\(_2\)O was added. After 5 min of stirring, the solution was adjusted to pH 9. Cu(ClO\(_4\))·6H\(_2\)O (0.1 mmol, 37.1 mg) and N,N-diethyl ethylenediamine (0.1 mmol, 11.6 mg) were added slowly and orderly. After stirring for 3h, the solution was left for slow evaporation. Blue crystals of \(1\), suitable for X-ray structure determination, were collected after one week. Yield: 49.0 mg, 62%. Calcd for C\(_{26}\)H\(_{35}\)Cl\(_2\)F\(_2\)N\(_5\)O\(_{12.5}\)Cu (%): C, 39.53; H 4.47; N 8.86; Anal. Found: C 39.48; H, 4.39; N 8.92. Main IR (KBr, cm\(^{-1}\)) peaks: \(\nu(\text{O-H})_w, 3302\text{m}, \nu(\text{C = O})_\text{ket}, 1620\text{m}, \nu(\text{as}(\text{CO}_2)): 1581, 1501, \nu(\text{sym}(\text{CO}_2)): 1385\text{m}, \Delta=\nu(\text{asym}(\text{CO}_2) - \nu(\text{sym}(\text{CO}_2)) = 196, 116 \text{ cm}^{-1}\). The complex is soluble in dmso and dmf and is nonelectrolyte.

\([\text{Zn}(\text{pydam})(\text{Hsrx})_2](\text{ClO}_4)_2 \ (2)\] A mixture of Zn(ClO\(_4\))·6H\(_2\)O (0.2 mmol, 74.5 mg), sarafloxacin (0.2 mmol, 77.1 mg), 1,2-propylene diamine (0.2 mmol, 14.8 mg) were dissolved in methanol (20 mL), acetonitrile (2 mL) and NH\(_3\)·H\(_2\)O (1 mL). After stirring for 3h, the solution was left for slow evaporation. Light yellow crystals of \(2\) suitable for X-ray structure determination, were collected after one week. Yield: 71.8 mg, 65%. Calcd for C\(_{43}\)H\(_{39}\)Cl\(_2\)F\(_4\)N\(_8\)O\(_{14}\)Zn (%): C, 46.78; H, 3.56; N, 10.15; Anal. Found: C, 46.71; H, 3.50; N, 10.23. Main IR (KBr, cm\(^{-1}\)) peaks: \(\nu(\text{O-H})_w, 3354\text{m}, \nu(\text{C = O})_\text{ket}, 1620\text{m}, \nu(\text{as}(\text{CO}_2)): 1581, 1501, \nu(\text{sym}(\text{CO}_2)): 1385\text{m}, \Delta=\nu(\text{asym}(\text{CO}_2) - \nu(\text{sym}(\text{CO}_2)) = 196, 116 \text{ cm}^{-1}\). The complex is soluble in dmso and dmf and is nonelectrolyte.
1506, \( v_{\text{sym}}(\text{CO}_2) \): 1379 m, \( \Delta = v_{\text{asym}}(\text{CO}_2) - v_{\text{sym}}(\text{CO}_2) = 196, 127 \text{ cm}^{-1} \). The complex is soluble in dmso and dmf and is nonelectrolyte.

**X-ray structure determination**

Single-crystal X-ray diffraction data were collected at 293K on a Bruker D8 VENTURE PHOTON diffractometer with graphite-monochromated Mo-K radiation (\( \lambda = 0.71073 \text{ Å} \)) using Genenic multi scan technique. Structures were solved by direct methods \(^{[29]}\) and refined on \( F^2 \) by full-matrix least-squares with the Bruker’s SHELXS-97 program \(^{[30]}\). All nonhydrogen atoms were refined anisotropically, and all hydrogen atoms attached to C and N atoms were readily located in a difference Fourier map and were placed at calculated positions and treated using appropriate riding models.

**Albumin binding experiments**

The protein binding study was performed by tryptophan fluorescence quenching experiments using BSA (3 \( \mu M \)) or HSA (3 \( \mu M \)) in buffer (containing 15 mM trisodium citrate and 150 mM NaCl at pH 7.0). The quenching of the emission intensity of tryptophan residues of BSA at 343 nm or HSA at 351 nm was monitored using the sarafloxacin or complexes 1, 2 as quenchers with increasing concentration (up to \( 2.2 \times 10^{-5} \text{ M} \)) \(^{[31]}\). Fluorescence spectra were recorded in the range 300–500 nm at an excitation wavelength of 296 nm. The fluorescence spectra of sarafloxacin and complexes 1, 2 in buffer solutions were recorded under the same experimental conditions and a maximum emission appeared at 440 nm for the sarafloxacin and 420nm for complexes 1, 2.

**DNA binding studies**

The interaction of sarafloxacin and complexes 1, 2 with CT DNA has been studied with UV spectroscopy in order to investigate the possible binding modes to CT DNA and to calculate the binding constants to CT DNA (\( K_b \)). The binding constants (\( K_b \)) of the complexes with CT DNA have been calculated using UV spectra of the complexes recorded at a constant concentration in the absence or presence of CT DNA solution for diverse \( r \) values in the range 0.1–4.0. The synthesized complexes and ligand were dissolved in DMSO to make 2.0 mM stock solutions for DNA binding studies. The \( 6\times10^{-4} \text{ M} \) CT-DNA stock solution was stored at 4°C for no more than 4 days before use. The final working solutions of the complexes for DNA binding studies are diluted in the buffer and the containing DMSO is limited in 1%. In UV spectra, the working solutions of sarafloxacin and complex 1 are 20 \( \mu M \), and complex 2 is 10 \( \mu M \). The CT-DNA stock solution was added 10 \( \mu L \) per scan and gradually increased up
to a sufficient concentration to achieve saturation for analysis. After each addition, the solution was allowed to incubate for 10 min before the absorption spectra were recorded.

The interaction of sarafloxacin and complexes 1, 2 with CT DNA has also been investigated by monitoring the changes observed in the cyclic voltammogram of a 0.40 mM 1:2 DMSO: buffer solution of complex upon addition of CT DNA at diverse r values. The buffer was also used as the supporting electrolyte and the cyclic voltammograms were recorded at ν = 100 mV·s⁻¹.

Plasmid DNA (pUMT) cleavage activity of sarafloxacin, complexes 1 and 2 was monitored by agarose gel electrophoresis. In a typical experiment, the DMSO solution of sarafloxacin, Zn(ClO₄)₂·6H₂O, Cu(ClO₄)₂·6H₂O and complexes 1, 2 were diluted to 100 and 200 µM in buffer (containing 15 mM trisodium citrate and 150 mM NaCl at pH 7.0). The 30 µL mixture sample contains super coiled pUMT DNA (300µg/mL) in 27µL buffer (containing 15 mM trisodium citrate and 150 mM NaCl at pH 7.0) and 3µL DMSO solution of sarafloxacin, Zn²⁺, Cu²⁺ and complexes. The samples were incubated at 37°C for 24 h and then loaded on a 1% agarose gel containing 0.5g/mL ethidium bromide after quenching the reaction by adding 5 µL loading buffer (40% sucrose, 0.2% bromophenol blue). Electrophoresis was carried out at 50 V in 1X TAE buffer (0.04 M Tris-Acetate, pH 8, 0.001 M EDTA). Bands were visualized by UV light and photographed followed by the estimation of the intensity of the DNA bands using AlphaInnotech 2200-5.

**Antimicrobial activity studies**

Two different cultivation media were used for antimicrobial activity test: (1) Luria–Bertani broth (LB) medium, containing 1% tryptone, 0.5% NaCl and 0.5% yeast extract and (2) minimal medium salts broth (MMS), containing 1.5% glucose, 0.5% NH₄Cl, 0.5% K₂HPO₄, 0.1% NaCl, 0.01% MgSO₄·7H₂O and 0.1% yeast extract. The pH of the media was adjusted to 7.0.

The antibacterial efficiency of the compounds (Hsrx and complexes 1,2) were estimated by their ability to inhibit the growth of microorganisms in the cultivation medium. The tests were performed according to minimum inhibitory concentration (MIC) in mg·mL⁻¹ with four bacteria species: *Escherichia coli* (*E. coli*), *Pseudomonas putida* (*P. putida*), *Bacillus subtilis* (*B. subtilis*) and *Staphylococcus aureus* (*S. aureus*). Bacterial growth was performed in LB, while the screening for antibacterial activity was performed by the MIC method [³²], using the method of progressive double dilution in MMS contained the concentrations of 100, 50, 20,
10, 5, 2.5, 1.25, 1 μg·mL−1 of the complexes in DMSO were tested and the MICs were determined. Two milliliters of MMS were inoculated with 20mL of a preculture of each bacterial strain, which was grown in LB overnight at the optimal growth temperature of each species to assure the sufficient bacterial growth. In a similar second culture, 20 μL of the bacteria as well as the tested compound at the desired concentration were added. A third sample was supplemented with the same concentration of the compounds tested and was used as cultures of reference to check the effect of each compound on MMS. All samples were measured in duplicate. The stock solutions of the compounds (10 mg·mL−1) were prepared by previously dissolving in DMSO. Then two fold serial dilutions were carried out in MMS to introduce the compounds at a final concentration ranging from 10 to 0.1mg·mL−1 to the cultures. The bacterial growth was monitored by measuring the turbidity of the culture after 24 h in order to check if bacteria grow at the concentration of compound tested. The lowest concentration that inhibited bacterial growth was determined as the MIC value. All the equipment and culture media were sterile.

3. RESULTS AND DISCUSSION

Chemistry

Characterization of the complexes

A comparison of the IR spectra of the complexes with that of the free ligand revealed important features relating to the metal-ligand interactions. The bands at 1707(s) cm−1 and 1276(s) cm−1 attributed to the stretching vibrations ν(C=O)carboxylic and ν(C–O)carboxylic, respectively, of the carboxylic moiety (–COOH) of sarafloxacin, shifted to 1575–1581 cm−1 and 1379–1385 cm−1 assigned as antisymmetric, νasym(C=O), and symmetric, νsym(C=O), stretching vibrations of the carboxylato group, respectively. The difference Δν [=νasym(C=O) – νsym(C=O)], a useful characteristic tool for determining the coordination mode of the carboxylate ligands, reaches a value of 196 cm−1 indicates a monodentate coordination mode. The vibration ν(C=O)ketone is slightly shifted from 1626 cm−1 to 1610–1630 cm−1 upon bonding. The all changes of the IR spectrum suggest that sarafloxacin ligand is coordinated to the metal atoms via the pyridone oxygen and a carboxylate oxygen[31].

Description of the crystal structures of the complexes

Crystal structure of [Cu(detam)(srx)](ClO4)2·1.5H2O. 1

The crystal structure of the compound, as shown in Fig. 1, consists of [Cu(detam)(srx)]2+, two perchlorate anions acting as counterions and one and a half of H2O solvent molecules. In
complex 1, sarafloxacin is in zwitter-ionic form and behaves as a bidentate ligand being coordinated to copper atom via the pyridone oxygen and a carboxylate oxygen. The crystallographic data for complex 1 are showed in Table 1 and selected bond distances and angles are listed in Table 2.

The copper atom is four-coordinate and is surrounded by a sarafloxacin and a N,N-diethyl ethylenediamine showing a distorted square planar geometry. The distance between O8 and Cu1 is 2.808(2), which is longer than [Cu1-O1=1.940(6)] [Cu1-O2=1.893(7)][Cu1-N4=1.963(9)][Cu1-N5=2.034(10)], so the interaction between O8 and Cu1 is weaker.

The bond distance of C=O$_{\text{ketone}}$ is 1.291(9) Å and C–O$_{\text{carboxylic}}$ is 1.278(11) Å, while the bond distance of C=O$_{\text{ketone}}$ and C–O$_{\text{carboxylic}}$ are 1.258(6) Å and 1.230(7) Å in sarafloxacin. The distances between oxygen atom and carbon atom in the complex are longer than sarafloxacin, but the distances between carboxylic oxygen and carbon atom changed more. The angles of the complex [O2-C1-O3=122.4(8)°][O3-C1-C2=117.8(8)°][O2-C1-C2=119.8(8)°] are similar to the sarafloxacin [O2-C10-O3=125.2(5)°][O2-C10-C2=117.9(5)°][O3-C10-C2=116.8(5)°]. The O2-Cu1-O1 angle observed is 93.1(3)° which is similar to reported value of other quinolone complexes. The Cu and N bond and the Cu and O bond distances are similar to reported values of other amine complexes.[33]

![Fig. 1. Molecule structure of complex [Cu(detam)(srx)(ClO$_4$)$_2$].1.5H$_2$O](image)
Table 1 Crystallographic data for complexes 1 and 2

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Table 2 Selected bond distances and angles for complex 1

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Crystal structure of [Zn(pydam)(srx)_2](ClO_4)_2. 2

The crystal structure of the compound consists of two sarafloxacin, two perchlorate anions and a 1,2-propylene diamine. In the complex 2, sarafloxacins behave as bidentate ligand coordinated to zinc atom via the pyridone oxygen and a carboxylate oxygen. A diagram of complex 2 is showed in Fig 2, the crystallographic data for 2 are showed in Table 1 and selected bond distances and angles are listed in Table 3.
The zinc atom is six-coordinate and is surrounded by two sarafloxacin ligands and a 1,2-propylene diamine showing a distorted octahedron with the six vertices occupied by two nitrogen atoms of pydam and four oxygen atoms from the two sarafloxacin ligands.

The bond distance of C=O\textsubscript{ketone} are 1.257(9) and 1.251(9) Å and C–O\textsubscript{carboxylic} are 1.254(11) and 1.260(9) Å, while the bond distance of C=O\textsubscript{ketone} and C–O\textsubscript{carboxylic} are 1.258(6) Å and 1.230(7) Å in sarafloxacin. The distance between carboxylato oxygen atom and carbon atom in the complex is longer than sarafloxacin. The angles of the complex [O2-C1-O3=123.0(7)°] [O3-C1-C2=118.3(7)°] [O2-C1-C2=118.7(7)°] [O5-C21-O6=124.8(7)°][O6-C21-C22=116.77°][O5-C21-C22=118.6(7)°] are similar to the sarafloxacin [O2-C10-O3=125.2(5)°][O2-C10-C2=117.9(5)°] [O3-C10-C2=116.8(5)°]. The O2-Zn1-O1 angle observed is 83.53(19)°, O4-Zn1-O5 angle observed is 87.0(2)° is similar to reported value of other quinolone complexes. The Zn and N bond and the Zn and O bond distances are similar to reported values of other amine complexes \cite{34}.

![Image](image.png)

**Fig. 2.** Molecule structure of complex [Zn(pydam)(srx)\textsubscript{2}](ClO\textsubscript{4})\textsubscript{2}, 2. Anions are omitted for clarity.

**Table 3 Selected bond distances and angles for complex 2**

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<th>Angle</th>
<th>(°)</th>
</tr>
</thead>
</table>
Stability of Complexes 1, 2 in aqueous solution

Complexes 1 and 2 are soluble at $3 \times 10^{-5}$ M and $2 \times 10^{-5}$, respectively. Concentration level in the buffer at 25°C contains 1% DMSO. The kinetic stability of two complexes was evaluated by UV-vis absorption under this condition. The kinetic UV-vis spectras of complexes 1 is showed in Fig 3 (2 in Fig. S1). Over the time course, the characteristic absorption of each complex showed hypochromicity but no bathochromic shift. The hypochromicity can be attributed to the gradual formation of aggregates of the complexes in solution, which will decrease their effective concentration for UV−vis absorption $^{[35]}$.

![Complex 1 Absorbance](image)

Fig. 3. Time-dependent stability studies on complex 1 in buffer solution (150 mM NaCl and 15 mM trisodium citrate at pH 7.0) monitored by UV-vis absorption spectra.

Interaction of the complexes with serum albumin

The serum albumin is the most abundant protein in plasma and involved in the transport of metal ions and metal complexes. BSA is the most extensively studied serum albumin, due to its structural homology with HSA. BSA has two tryptophans, Trp-134 and Trp-212, while HSA has only one tryptophan located at position 214 $^{[36]}$. When excited at 295 nm, the
solution of BSA and HSA will exhibit an intense fluorescence emission band with a peak at 343 nm and 351 nm due to the tryptophan residues, respectively \[24\]. The binding constant (K) between a compound and BSA/HSA should be optimum and less than the observed highest protein-ligands binding affinity (\(K_{avidin-ligands} \approx 10^{15} \text{M}^{-1}\)). If K is too high, the compound will not get released from the SA to the target cells \[37\]. The interaction of sarafloxacin, complexes 1 and 2 with serum albumins has been studied with tryptophan emission-quenching experiments. The changes and quenching occurred in the fluorescence emission spectra of tryptophan in BSA or HSA upon addition of sarafloxacin, complex 1 or 2 are primarily due to change in protein conformation, subunit association, substrate binding or denaturation \[36\].

**Binding of the complexes to BSA**

Addition of Hsrx, 1 or 2 to BSA leads to a decrease of the fluorescence signal at 343 nm with the simultaneous appearance of an isoemissive point at ~380 nm for the sarafloxacin complexes. The quenching provoked by the compounds is up to 59% of the initial fluorescence intensity for Hsrx, 56.3% for 1 and 59.3% for 2 (Fig. 4A), as calculated after the correction of the initial fluorescence spectra and may due to possible changes in protein secondary structure leading to changes in tryptophan environment of BSA, and thus indicating the binding of each compound to BSA \[36\].

The Stern–Volmer and Scatchard equations and graphs may be used in order to study the interaction of a quencher with SAs. According to Stern–Volmer quenching equation \[38\]: 

\[
\frac{I}{I_0} = 1 + k_q \tau_o [Q] = 1 + K_{sv} [Q],
\]

the dynamic quenching constant \((K_{sv}, \text{M}^{-1})\) may be obtained by the slope of the diagram \(I/I_0 \) vs \([Q]\) (Fig. S3) \((I_0 = \text{the initial tryptophan fluorescence intensity of SA}; I = \text{the tryptophan fluorescence intensity of SA after the addition of the quencher (sarafloxacin or 1, 2)}; k_q = \text{the quenching rate constants of SA}; K_{sv} = \text{the dynamic quenching constant}; \tau_o = \text{the average lifetime of SA without the quencher (} \tau_o \text{ of tryptophan in SA at} \sim 10^{-8} \text{ s}); [Q] = \text{the concentration of the quencher}) and the approximate quenching constant \(k_q \) \((\text{M}^{-1} \text{s}^{-1})\) may be calculated with the use of equation: 

\[
K_{sv} = k_q \tau_o.
\]

The calculated \(K_{sv}\) and \(k_q\) values (Table 4) for the interaction of the free sarafloxacin and 1, 2 with BSA indicate good BSA binding propensity of the complexes with 2 exhibiting the stronger quenching ability \((k_q=4.92(\pm0.30)\times10^{12}\text{M}^{-1}\text{s}^{-1})\). The \(k_q\) values (>10^{12}\text{M}^{-1}\text{s}^{-1}) are higher than diverse kinds of quenchers for biopolymers fluorescence \((2.0\times10^{10}\text{M}^{-1}\text{s}^{-1})\) indicating the existence of static quenching mechanism \[39\].
From the Scatchard equation: \[ \frac{\Delta I/I_0}{[Q]} = nK - K \frac{\Delta I}{I_0} \]
the association binding constant \(K\) (M\(^{-1}\)) may be calculated from the slope in plots \( \frac{\Delta I/I_0}{[Q]} \) versus \( \frac{\Delta I}{I_0} \) (Fig. S4) while the number of binding sites per albumin \(n\) is given by the ratio of y intercept to the slope \(^{26}\). It is obvious (Table 4) that the coordination of sarafloxacin to Cu(II) or Zn(II) in the co-existence of a N-donor ligand results in an increased \(K\) or \(n\) value, with complex 1 exhibit the higher \(K\) and complex 2 show the higher \(n\) values.

**Binding of the complexes to HSA:** Addition of sarafloxacin or complexes 1 and 2 to HSA leads to a decrease of the fluorescence signal at 351 nm with the simultaneous appearance of aniso emissive point at 384 nm (Fig. S2). The quenching provoked by Hsrx or complexes 1 and 2 to the HSA fluorescence is rather moderate (up to 65% of the initial fluorescence intensity for Hsrx, 57% for 1, 57% for 2) (Fig. 5B) indicating that the binding of Hsrx or each complex to HSA quenches the intrinsic fluorescence of the single tryptophan in HSA \(^{40}\).

The calculated values of \(K_{sv}\) and \(k_q\) as obtained by the slope of the Stern–Volmer diagram (Fig. S5), Hsrx and 1,2 are given in Table 4 and indicate their good HSA binding propensity and complex 2 exhibits the stronger protein-binding ability (\(k_q= 4.65(\pm0.21)\times10^{12}\)M\(^{-1}\)s\(^{-1}\)). The \(k_q\) ( > \(10^{12}\)M\(^{-1}\)s\(^{-1}\)) are higher than diverse kinds of quenchers for biopolymers fluorescence (\(2.0 \times 10^{10}\)M\(^{-1}\)s\(^{-1}\)) suggesting a static quenching mechanism \(^{25}\). From the Scatchard graph (Fig. S6), the association binding constant of each compound has been calculated (Table 4) with complex 2 exhibiting the higher \(K\) value. Both complexes exhibit higher \(K\) and lower \(n\) values than free sarafloxacin.

Comparing the affinity of complexes for BSA and HSA (\(K\) values), it is obvious (Tables 4) that 1 shows higher affinity for BSA than HSA, while 2 exhibits a higher binding constant for HSA than for BSA. In conclusion, the association binding constants \(K\) of all complexes for both albumins exhibit values in the range \(2.29\times10^4\)–\(1.96\times10^5\)M\(^{-1}\) (Table 4) and are lower than that of the avidin-ligands binding affinity (\(K_{avidin-ligands}\approx10^{15}\)M\(^{-1}\)). The existing data for the sarafloxacin and complexes 1,2 showed that they can bind on the albumin and have simultaneously the potential to get released from the albumins upon arrival at the target cells. Therefore, the interaction of compounds with albumins may provide useful information concerning any potential application.
Fig. 4. Plot of % relative fluorescence intensity at (A) at $\lambda_{em}=342$ nm (%) vs $r$ ($r = [\text{compound}]/[\text{BSA}]$) and (B) $\lambda_{em} = 351$ nm (%) vs $r$ ($r = [\text{compound}]/[\text{HSA}]$), for the sarafloxacin and complexes 1, 2 in buffer solution (150 mM NaCl and 15 mM trisodium citrate at pH 7.0).

Table 4 The BSA and HSA binding constants and parameters ($K_{sv}$, $k_q$, $K$, $n$) derived for the Hsrx and complexes 1 and 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>$K_{sv}$(M$^{-1}$)</th>
<th>$k_q$(M$^{-1}$s$^{-1}$)</th>
<th>$K$(M$^{-1}$)</th>
<th>$n$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hsrx</td>
<td>$2.87(\pm0.12) \times 10^4$</td>
<td>$2.87(\pm0.12) \times 10^{12}$</td>
<td>$7.52(\pm0.31) \times 10^4$</td>
<td>0.63</td>
</tr>
<tr>
<td>1</td>
<td>$3.05(\pm0.19) \times 10^4$</td>
<td>$3.05(\pm0.19) \times 10^{12}$</td>
<td>$1.96(\pm0.11) \times 10^5$</td>
<td>0.51</td>
</tr>
<tr>
<td>2</td>
<td>$4.92(\pm0.30) \times 10^4$</td>
<td>$4.92(\pm0.30) \times 10^{12}$</td>
<td>$8.62(\pm0.71) \times 10^4$</td>
<td>0.78</td>
</tr>
<tr>
<td>HSA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hsrx</td>
<td>$2.43(\pm0.05) \times 10^4$</td>
<td>$2.43(\pm0.05) \times 10^{12}$</td>
<td>$1.13(\pm0.05) \times 10^4$</td>
<td>1.74</td>
</tr>
<tr>
<td>1</td>
<td>$3.49(\pm0.03) \times 10^4$</td>
<td>$3.49(\pm0.03) \times 10^{12}$</td>
<td>$2.29(\pm0.05) \times 10^4$</td>
<td>1.29</td>
</tr>
<tr>
<td>2</td>
<td>$4.65(\pm0.21) \times 10^4$</td>
<td>$4.65(\pm0.21) \times 10^{12}$</td>
<td>$1.22(\pm0.03) \times 10^5$</td>
<td>0.64</td>
</tr>
</tbody>
</table>
Interaction of the complexes with CT DNA
Despite the presence of other biological targets in tumor cells, including RNA, enzyme, and protein, it is generally accepted that DNA is the primary target for many metal-based anticancer drugs such as cisplatin. Here we only consider DNA as the main target in the cell and leave the possible interaction of the Hsrx-metal complexes with other targets, such as RNA, enzyme, and protein for future studies.

Transition metal complexes are known to bind to DNA via both covalent and/or non-covalent interactions. In the case of covalent binding, a labile ligand of the complexes can be replaced by a nitrogen base of DNA such as guanine N7, while the non-covalent DNA interactions include intercalative, electrostatic and groove (surface) binding of metal complexes outside of DNA helix, along major or minor groove.

Study of the DNA-interaction with UV spectroscopy
The changes observed in the UV spectra upon titration may give evidence of the existing interaction mode, since a hypochromism due to $\pi \rightarrow \pi^*$ stacking interactions may appear in the case of the intercalative binding mode $^{[41]}$. 

The UV absorption spectra of complex 1,2 in the absence and presence of CT-DNA are shown in Fig.6 (Hsrx in Fig. S7). In the absence of DNA, complexes 1, 2 and free sarafloxacin all showed characteristic absorption peaks at ~274 and 325 nm, which is ascribed to the $\pi \rightarrow \pi^*$ electronic transition of the conjugated system of sarafloxacin. The absorbance at 274 nm for sarafloxacin and complexes 1, 2 was analyzed upon addition of CT-DNA. When the ratio of [DNA]/[Hsrx] was increased from 0.1:1 to 1:1, a moderate hypochromicity of 9.6% was observed, suggesting the characteristic intercalation of sarafloxacin to DNA with a moderate degree of binding. Under similar condition, evident hypochromicity for complexes 1, 2 ([DNA]/[1]=0.1:1 to 2:1, 4.3% for 1; [DNA]/[2]=0.2:1 to 4:1, 4.8% for 2). For further quantitative comparison, the intrinsic binding constant $K_b$ was also calculated.

The binding constant $K_b$ is obtained by the ratio of slope to the y intercept in plots [DNA]/($\varepsilon_A - \varepsilon_f$) versus [DNA], according to the equation $^{[41]}$: $\frac{[\text{DNA}]}{(\varepsilon_A - \varepsilon_f)} = \frac{[\text{DNA}]}{(\varepsilon_b - \varepsilon_f)} + \frac{1}{K_b(\varepsilon_b - \varepsilon_f)}$, where [DNA] is the concentration of DNA in base pairs, $\varepsilon_A=A_{\text{obsd}}/[\text{compound}]$, $\varepsilon_f$ = the extinction coefficient for the free compound and $\varepsilon_b$= the extinction coefficient for the compound in the fully bound form.
The $K_b$ values for Hsrx and 1, 2 are $5.70 \times 10^5$, $3.97 \times 10^5$ and $1.37 \times 10^6$ M$^{-1}$, respectively (Table 5) suggesting that complexes 2 has stronger intercalative binding ability to DNA than sarafloxacin and classical intercalator EB ($K_b$ = $1.23$ (± $0.07$) $\times 10^5$ M$^{-1}$) [43].

![Fig. 5. UV spectra of (A) [Cu(detam)(srx)](ClO$_4$)$_2$·1.5H$_2$O, 1, (B) [Zn(pydam)(srx)$_2$](ClO$_4$)$_2$, 2 in the absence (---) and presence (—) of CT-DNA with increasing [DNA]/[Hsrx] ratios range from 0.1:1 to 2:1; 2 in the absence (---) and presence (—) of CT-DNA with increasing [DNA]/[Hsrx] ratios range from 0.2:1 to 4:1. The arrows show the changes upon increasing amounts of CT DNA. Inset: plot of $[\text{DNA}]_A/([\text{DNA]}_A - [\text{f}]_A)$ vs [DNA].](image)

Table 5 The DNA binding constants ($K_b$) of sarafloxacin and complexes 1,2.

<table>
<thead>
<tr>
<th>Compound</th>
<th>hypochromicity (%)</th>
<th>$K_b$ (M$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsrx</td>
<td>9.6</td>
<td>$5.70 \times 10^5$</td>
</tr>
<tr>
<td><a href="ClO$_4$">Cu(detam)(srx)</a>$_2$·1.5H$_2$O, 1</td>
<td>4.3</td>
<td>$3.97 \times 10^5$</td>
</tr>
<tr>
<td><a href="ClO$_4$">Zn(pydam)(srx)$_2$</a>$_2$, 2</td>
<td>4.8</td>
<td>$1.37 \times 10^6$</td>
</tr>
</tbody>
</table>
Study of the DNA binding with cyclic voltammetry

The quasi-reversible redox couple Cu(II)/Cu(I) and Zn(II)/Zn(I) for 1 and 2, respectively, in 1/2 DMSO/buffer solution has been studied upon addition of CT DNA (Fig. S8) and the corresponding potentials as well as their shifts are given in Table 6. No new redox peaks appeared after the addition of CT DNA to each complex, but the current intensity of all the peaks decreased significantly, suggesting the existence of an interaction between each complex and CT DNA. The decrease in current intensity can be explained in terms of an equilibrium mixture of free and DNA-bound complex to the electrode surface [44].

For increasing amounts of CT DNA, the cathodic ($E_{pc}$) of all complexes exhibit a negative shift ($\Delta E_{pc}=(-101) - (-98)$ mV), while the anodic ($E_{pa}$) potentials show a positive shift (Table 6) suggesting that the complexes can bind to DNA by both intercalation and electrostatic interaction [45]. The external binding of the complexes with CT DNA through electrostatic interaction can be explained.

Table 6: Cathodic and anodic potentials (in mV) for the redox couple Cu(II)/Cu(I) and Zn(II)/Zn(I) in 1/2 DMSO/buffer solution of the complexes (0.4 mM) in the absence and presence of CT DNA.

<table>
<thead>
<tr>
<th>Complex</th>
<th>$E_{pc(a)}$</th>
<th>$E_{pc(b)}$</th>
<th>$\Delta E_{pc}$</th>
<th>$E_{pa(a)}$</th>
<th>$E_{pa(b)}$</th>
<th>$\Delta E_{pc}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><a href="ClO$_4$">Cu(detam)(srx)</a>$_2$·1.5H$_2$O, 1</td>
<td>-411</td>
<td>-512</td>
<td>-101</td>
<td>+23</td>
<td>+264</td>
<td>+241</td>
</tr>
<tr>
<td><a href="ClO$_4$">Zn(pydam)(srx)$_2$</a>$_2$, 2</td>
<td>-535</td>
<td>-437</td>
<td>-98</td>
<td>+43</td>
<td>+285</td>
<td>+242</td>
</tr>
</tbody>
</table>

$E_{pc(a)}$ in DMSO/buffer solution in the absence of CT DNA ($E_{pc(a)}$).

$E_{pc(b)}$ in DMSO/buffer solution in the presence of CT DNA ($E_{pc(b)}$) ([DNA]=0.1 mM).

$\Delta E_{pc}=E_{pc(b)}-E_{pc(a)}$.

**Agarose gel electrophoresis assay**

Transition metal complex mediated DNA cleavage is the center of interest. When plasmid DNA was subjected to electrophoresis after interaction, upon illumination of gel (Fig. 6) the fastest migration was observed for super coiled (SC) Form I, whereas the slowest moving was open circular (OC) Form II and the intermediate moving is the linear (LC) Form III generated on cleavage of open circular. Here complex 1 shows the maximum cleavage ability compare to all compounds. The different DNA-cleavage efficiency of the complexes, metal salt and drug is due to the difference in binding affinity of the complexes to DNA and the functionality present on ligand.
Fig. 6. Photogenic view of cleavage of pUMT DNA (300 µg/mL) with compounds using 1% agarose gel containing 0.5 µg/mL ethidium bromide. All reactions were incubated in buffer (containing 15 mM trisodium citrate and 150 mM NaCl at pH 7.0) in a final volume of 30µL, for 24 h, at 37°C. Lane 1, DNA control; Lane 2, DMSO; Lane 3, Cu(ClO$_4$)$_2$·6H$_2$O (100 µM); Lane 4, Cu(ClO$_4$)$_2$·6H$_2$O (200 µM); Lane 5, Zn(ClO$_4$)$_2$·6H$_2$O (100 µM); Lane 6, Zn(ClO$_4$)$_2$·6H$_2$O (200 µM); Lane 7, Hsrx (100 µM); Lane 8, Hsrx (200 µM); Lane 9, complex 1 (100 µM); Lane 10, complex 1 (200 µM); Lane 11, complex 2 (100 µM); Lane 12, complex 2 (200 µM).

Antibacterial activity

The efficiencies of Hsrx and complexes 1, 2 have been tested against two Gram(-), Escherichia coli (E. coli) and Pseudomonas putida (P. putida) and two Gram(+), Bacillus subtilis (B. subtilis), Staphylococcus aureus (S. aureus). The results are presented in Table 7.

It has been found that complex 1 exhibits higher activity to that of Hsrx against B. subtilis (MIC = 1.112 µg·mL$^{-1}$) and P. putida (MIC = 0.798 µg·mL$^{-1}$) and lower activity against S. aureus and E. coli. While complex 2 has higher activity to that of Hsrx against B. subtilis (MIC = 1.062 µg·mL$^{-1}$) and lower activity against others. As can be seen from the results, the antimicrobial inhibition (MIC = 0.511–1.316µg·mL$^{-1}$) of complexes 1, 2 is inspirin.

Table 7 Minimal inhibitory concentrations (MICs, µg·mL$^{-1}$)

<table>
<thead>
<tr>
<th>Complex</th>
<th>Gram(+)</th>
<th>Gram(-)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B. subtilis</td>
<td>S. aureus</td>
</tr>
<tr>
<td>1</td>
<td>1.112</td>
<td>0.511</td>
</tr>
<tr>
<td>2</td>
<td>1.062</td>
<td>0.516</td>
</tr>
<tr>
<td>Hsrx</td>
<td>1.228</td>
<td>0.453</td>
</tr>
</tbody>
</table>

4. CONCLUSION

The synthesis and characterization of the copper(II) and zinc(II) complexes with the third-generation quinolone antibacterial agent sarafloxacin and a nitrogen-donor heterocyclic ligand N,N-diethyl ethylenediamine or 1,2-propylene diamine have been achieved. The
Crystal structures of the complexes [Cu(detam)(srx)](ClO₄)₂·1.5H₂O (1) and [Zn(pydam)(srx)₂](ClO₄)₂ (2) have been determined by X-ray crystallography. In these complexes, sarafloxacin is bound to copper(II) and zinc(II) via the pyridone oxygen and a carboxylate oxygen. The complexes exhibit higher binding affinity (K values) for both albumins than free sarafloxacin. 1 and 2 exhibit the highest K values for BSA and HSA, respectively, among the compounds examined. The association binding constants K of all complexes for both albumins present lower values than that of the avidin-ligands binding affinity revealing their ability to bind on the albumins and the potential to get released at the target cells. Complexes 1,2 can bind to DNA via intercalation and electrostatic binding. The complex 2 exhibit much higher binding constants to CT DNA than free sarafloxacin with complex 2 having the highest calculated Kₘ value (=1.37 × 10⁶) among the compounds examined. Additionally, agarose gel electrophoresis assay have revealed 1 shows better cleavage ability compare to all synthesized compound. Despite DNA is not the only target in tumor cells, for many metal-based anticancer drugs DNA is the primary target such as cisplatin. In the paper, we only think that DNA is the most important target in the cell and leave possible interaction of Hsrx-metal complexes with other targets for future studies. The antimicrobial activity of the complexes 1,2 were tested against four bacterial species showing that they exhibit significant activity (MIC = 0.511–1.316μg·mL⁻¹) and some of them are higher than the corresponding free quinolone antibacterial drugs.

In conclusion, the two new complexes present promising biological features. Further experiments in relation to other potential biological activity of the complexes such as antitumor are under consideration.

ACKNOWLEDGMENTS

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REFERENCES