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New metal based drug as a therapeutic agent: Spectral, electrochemical, DNA-binding, surface morphology and photoluminescence properties

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HIGHLIGHTS

- We synthesized a new drug metal complex.
- The interaction of complex with DNA has been investigated.
- The electrochemical properties of complex have been investigated.

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ABSTRACT

Cu(II) complexes of non-steroidal anti-inflammatory drug (NSAID) Meloxicam (H_2MLX) was synthesized and characterized via spectroscopic and analytical techniques. The thermal behavior of the complex was also analyzed. The photoluminescence properties of the compounds were analyzed under different conditions. The electrochemical properties of both ligand and complex have been analyzed by Cyclic Voltammetry (CV) using glassy carbon electrode. The biological activities of the compounds were evaluated through examining their capacity to bind to fish sperm double strand DNA (FSdsDNA) with absorption spectroscopy and differential pulse voltammetry (DPV). Absorption studies of the interaction of the H_2MLX and its Cu(II) complex with FSdsDNA have indicated that these compounds could bind to FSdsDNA, and the binding constants were calculated. The morphology of the FSdsDNA, H_2MLX, and Cu(II) complex were analyzed thanks to using scanning electron microscopy (SEM). In the DPV technique, pencil graphite electrode was used as a working electrode. The decrease in the intensity of the guanine oxidation signals was used as an indicator for the interaction mechanism.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) were used to treat a wide variety of disorders such as inflammation, pain and fever. The anti-inflammatory effect of NSAIDs result from their interaction with enzyme cyclooxygenase (COX) while their other biological effects are COX-independent, including their effects on tight junctions [1], neutrophil adhesion and transmigration [2], and cell apoptosis and proliferation [3,4]. Although NSAID-COX interactions are well-characterized, molecular mechanisms for their COX-independent activities are still not clear. In addition to its anti-inflammatory effects, NSAIDs are also used to treat various illnesses and diseases such as different types of cancers (colon, gastric, esophageal, pulmonary, prostate, ovarian and breast), cardiovascular diseases (myocardial infarction, thrombosis and stroke), diabetes (insulin-resistant and related metabolic syndrome), and peripheral and central nervous system diseases (Alzheimer and Parkinson's) [5]. Oxicams is a type of non-steroidal anti-inflammatory drugs (NSAIDs) which bind closely to plasma proteins. Most oxicams are unselective inhibitors of the cyclo-oxygenase (COX) enzymes. Meloxicam stands out as an exception, (H_2MLX) 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide, (Fig. 1) with a slight (10:1) preference for COX-2, which, however, is only clinically relevant at lower doses [6].

The curative properties of copper [7] led to the development of numerous organic Cu(II) complexes as potential therapeutic agents for cancer, diabetes, cardiovascular, skin, inflammatory, and Alzheimer and Parkinson diseases [8,9]. Copper is also an essential trace element in living systems and it plays an important role in many biological processes as a critical component of enzymes and proteins [10]. Metal based antitumor drugs play an important role in chemotherapy [11]. Following the discovery of anti-cancer

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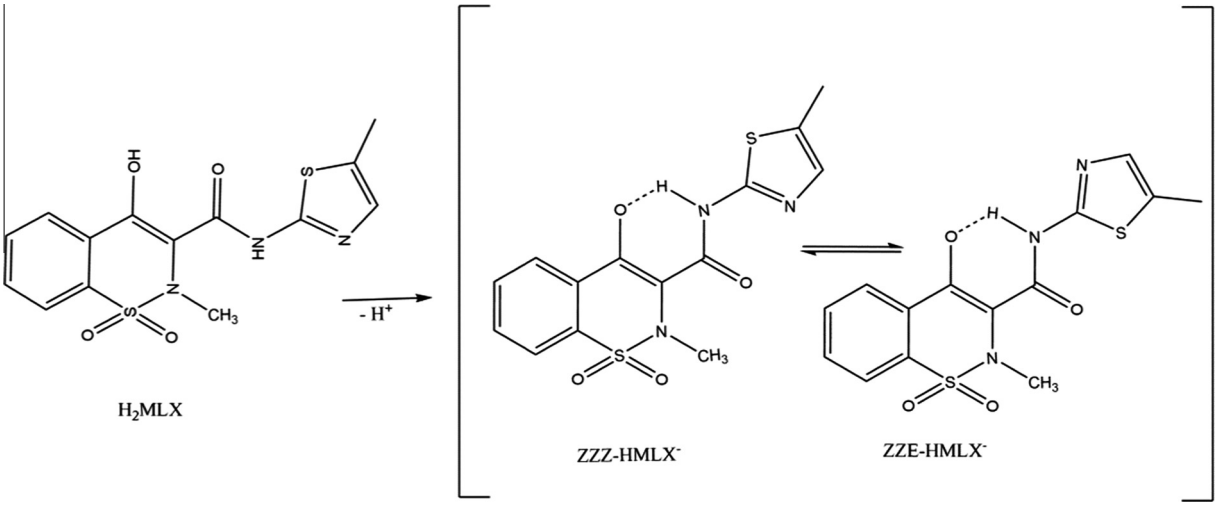

Fig. 1. ZZZ and ZZE conformations of $HMLX^{-}$.

effect of cis-platin, other organometallic materials came into prominence. Among non-Pt compounds, copper complexes are potentially favorable as anticancer agents. Besides bare drugs anticancer effects, Cu(II)–NSAID complexes display remarkable anticancer effects. Oxicam family drugs such as meloxicam exist in an anionic form in physiological pH, which makes their approach to the poly-anionic backbone prohibitory [12]. However, this problem has was eliminated in the Cu(II) complex form of the drugs.

Several MLX metal complexes were synthesized and characterized [13–18,12,19]. For example, Snatkar et al. synthesized Cu(II), Co(II), Ni(II), and Zn(II) complexes of meloxicam [13,14]. Meloxicam exist in a solvent in a deprotonated form. In this form, the enolic oxygen is not involved in coordination. Instead, it is linked to the N–H function via a strong intramolecular hydrogen bond created by the ZZZ–$Hmel^{-}$ and ZZE–$Hmel^{-}$ conformations and deprotonated meloxicam is coordinated to the metal ion through the amide oxygen and the nitrogen atom from the thiazolyl ring [20]. The structure of the complex is shown in Fig. 2. In addition, they obtained single crystal of $[(HMLX)_2Cu]$ complex and determined the structure of complex by X-ray crystallography analysis. Meloxicam molecules coordinates to the Cu(II) ion. However, solvents affect the coordination properties of Cu(II) ion in these complexes. In this study, no solvent or water molecule in the structure of the complex exists.

Sanatkar et.al studied The DNA interaction of MLX–Cu(II) complex with circular dichroism (CD), fluorescence, and UV–Vis spectroscopy. No study on the electrochemical behavior and interaction of meloxicam and its metal complexes are available in the literature. In this study, electrochemical behavior and interaction of MLX and its Cu(II) complex with fish sperm double stranded DNA (FSdsDNA) by Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) techniques are analyzed. The decrease in intensity of the guanine oxidation signals was used as an indicator for the interaction mechanism. The binding properties of the complexes with FSdsDNA were analyzed with UV–Vis. titration, too. In addition, the morphology of the FSdsDNA, MLX, metal ion, and metal complex were analyzed via scanning electron microscope (SEM).

Experimental

Materials and reagents

Meloxicam (H_2MLX) was kindly provided by Deva Drug. Comp. (Istanbul, TURKEY) while solvents and chemicals of analytical grade were purchased from the market. $CuCl_2{\cdot}2H_2O$, NaCl, and tris–HCl were purchased from Merck. Fish Sperm DNA (FSdsDNA) was purchased from Sigma. DNA stock solution was prepared by dilution of FSdsDNA to buffer solution (containing 150 mM NaCl and 15 mM tris–HCl at pH 7.0) followed by exhaustive stirring at 4 °C for three days [21], and kept at 4 °C for than a week. The stock solution of FSdsDNA gave a ratio UV absorbance of 260 and 280 nm

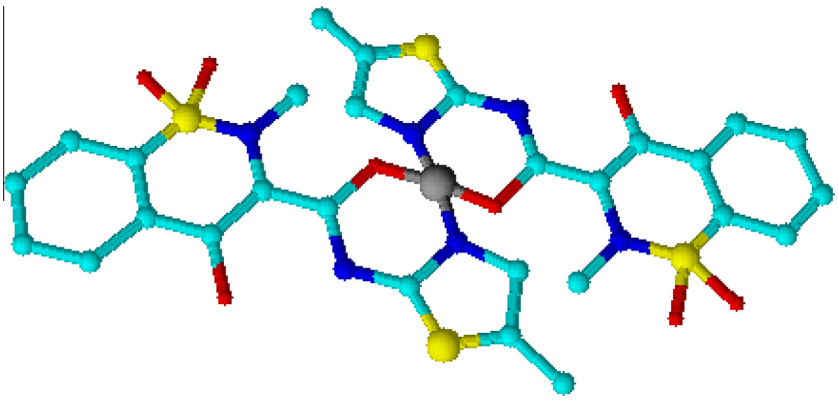

Fig. 2. Proposed structure of $[(HMLX)_2Cu]$.