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Novel zinc complexes of a non-steroidal anti-inflammatory drug, niflumic acid: Structural characterization, human-DNA and albumin binding properties

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Abstract

Three novel Zn(II) complexes of NSAID niflumic acid (H*nif*) were prepared and studied, namely; $[Zn(MeOH)_4(nif)_2]$ (**1**), $[Zn(cyclam)(nif)_2]$ (**2**) and $[Zn(nif)_2(tmen)]$ (**3**), where *nif* is deprotonated niflumic acid, *cyclam* is 1,4,8,11-Tetraazacyclotetradecane and *tmen* is N,N,N',N'-Tetramethylethylenediamine. The complexes have been characterized by infrared spectroscopy, elemental and thermal analysis and single-crystal X-ray structure analysis. All three complexes contain two deprotonated niflumato anions monodentately coordinated *via* carboxylato groups. Furthermore, fluorescence binding studies of the prepared compounds with human genomic DNA-EB (ethidium bromide) were carried out, which suggest that all complexes are able to bind to DNA *via* intercalation. Moreover, from the obtained results it followed that complexes **2** and **3** bind to DNA from the tissue with aortic aneurysm (aDNA) and control (cDNA) with a different strength. Additionally, complexes **1**-**3** exhibit good binding affinity to human serum albumin with high binding constant.

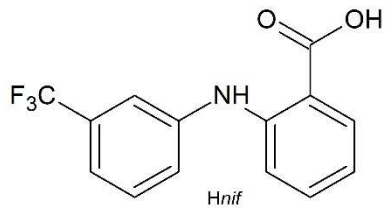
Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used in human and veterinary medicine for the treatment of fever and pain, since they are very efficient and available without a medical prescription. Niflumic acid is a potent non-steroidal anti-inflammatory drug (NSAID) with similar nature as fenamates – derivates of 2-(phenylamino)benzoic acid. Fenamates possess analgesic, anti-inflammatory, and anti-pyretic activity. They are used to relieve painful conditions such as osteoarthritis, rheumatoid arthritis and gout. Although NSAIDs are very widely used, they are well known for causing gastrointestinal ulceration and bleeding [1-4].

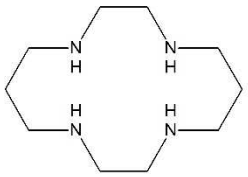
Niflumic acid is believed to act through inhibition of the cyclooxygenase, inhibiting both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), (also known as prostaglandin H2 synthetase-1 and synthetase-2) isoenzymes. Cyclooxygenase catalyzes the synthesis of prostaglandins and thromboxane from arachidonic acid. Prostaglandins act (among other functions) as messenger molecules in the process of inflammation. Inhibition of the COXs with NSAIDs reduces inflammation, pain, and fever [5, 6]. Recently, novel studies revealed, that in addition to arthritis and pain, also cancer and neurodegenerative diseases like Alzheimer's disease could potentially be treated with COX-2 inhibitors [7, 8]. NSAIDs have also presented a synergistic effect on the activity of certain antitumor drugs leading to cancer cell death via apopthosis [9, 10].

Interaction of metal ions with fenamates has been the subject of recent studies covering the characterization of the complexes, their tentative biological (antimicrobial, anticancer, antioxidant) activity and the interaction of these complexes with biomolecules such as nucleic acids and serum albumin proteins, to examine their mode of binding and possible biological relevance [11-15]. In addition, recent reports showed that transition metal complexes of these drugs were found to be more potent NSAIDs than the parent drugs [16]. In the light of this information we were interested in the biological activity of new niflumic acid complexes, since, the complexes of drugs can increase pharmaceutical or biological activity [16-18]. Among the different niflumato metal complexes, zinc(II) analogues are scarce. A literature survey revealed that the crystal structure of three dinuclear [18, 19], one mononuclear [20] and one polymeric [21] copper(II) complexes, one mononuclear manganese(II) [12], one cobalt(II) [22] and one silver (I) complex [23] of niflumic acid were characterized, but none zinc complex.

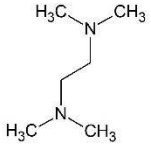
Therefore, within our broader study of metal complexes of NSAIDs, in the present paper, we report synthesis, structural, spectral and thermal characterization, as well as an interaction of human genomic DNA and serum albumin protein with three novel zinc(II) niflumate complexes, namely; $[Zn(MeOH)_4(nif)_2]$ (**1**), $[Zn(cyclam)(nif)_2]$ (**2**) and $[Zn(nif)_2(tmen)]$ (**3**), where *nif* is deprotonated niflumic acid, *cyclam* is 1,4,8,11-Tetraazacyclotetradecane and *tmen* is N,N,N',N'-Tetramethylethylenediamine. The formulaes of the respective organic ligands used in our study are shown in Scheme 1.



H*nif*



cyclam



tmen