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Journal of Inorganic Biochemistry 101 (2007) 1140–1152
Journal of Inorganic Biochemistry
www.elsevier.com/locate/jinorgbio

Unusual coordinating behavior by three non-steroidal anti-inflammatory drugs from the oxicam family towards copper(II). Synthesis, X-ray structure for copper(II)–isoxicam, –meloxicam and –cinnoxicam-derivative complexes, and cytotoxic activity for a copper(II)–piroxicam complex

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Received 5 January 2007; received in revised form 27 April 2007; accepted 30 April 2007
Available online 10 May 2007

Abstract

Cytotoxic tests recently performed at National Cancer Institute, NCI (USA), on $[Cu(HPIR)_2(DMF)_2]$, **1**, (H_2PIR = piroxicam, 4-hydroxy-2-methyl-*N*-pyridin-2-yl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide) a widely used non-steroidal anti-inflammatory drug, NSAID [see R. Cini, G. Giorgi, A. Cinquantini, C. Rossi, M. Sabat, Inorg. Chem. 29 (1990) 5197–5200, for synthesis and structural characterization, DMF = dimethylformamide] (NSC #624662) by using a panel of ca. 50 human cancer cells, showed growth inhibition factor GI_{50} values as low as 20 μM against several cancer lines, with an average value 54.4 μM. The activity of **1** is larger against ovarian cancer cells, non-small lung cancer cells, melanoma cancer cells, and central nervous system cancer cells. The widely used anticancer drug carboplatin (*cis*-diammine(1,1-cyclobutanedicarboxylato)platinum(II)) (NSC #241240) has average GI_{50} value of 102 μM. The reactions of copper(II)–acetate with other NSAIDs from the oxicam family were tested and crystalline complexes were obtained and characterized. Isoxicam (H_2ISO = 4-hydroxy-2-methyl-*N*-(5-methylisoxazol-3-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide) produced $[Cu(HISO)_2] \cdot 0.5DMF$, $\mathbf{2} \cdot 0.5DMF$ (DMF = dimethylfomamide). The coordination arrangement is square-planar and the $HISO^-$ anions behave as ambi-dentate chelators via O(amide),N(isoxazole) and O(enolate),O(amide) donors. Meloxicam (H_2MEL = 4-hydroxy-2-methyl-*N*-(5-methyl-1,3-thiazol-2-yl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide) produced $[Cu(HMEL)_2(DMF)] \cdot 0.25H_2O$, $\mathbf{3} \cdot 0.25H_2O$. The coordination arrangement is square-pyramidal, the equatorial donors being O(amide),N(thiazole) from two $HMEL^-$ anions and the apical donor being O(DMF). Unexpectedly, cinnoxicam (HCIN = 2-methyl-1,1-dioxido-3-[(pyridin-2-ylamino)carbonyl]-2*H*-1,2-benzothiazin-4-yl-(3-phenylacrylate)) produced $[Cu(MBT)_2(PPA)_2]$ (MBT = 3-(methoxycarbonyl)-2-methyl-2*H*-1,2-benzothiazin-4-olate 1,1-dioxide, PPA = 3-phenyl-*N*-pyridin-2-ylacrylamide).

Keywords: Cu complexes; X-ray structures; Cytotoxic activity; Non-steroidal anti-inflammatory drugs; Oxicam

1. Introduction

The importance of copper(II) complexes with non-steroidal anti-inflammatory drugs (NSAIDs) as ligands has been stressed in several articles and in review papers in the last 15 years [1–19].

Experimental evidences collected during decades of research work by several teams all over the world proved that the coordination of copper(II) ion by NSAIDs improves the pharmaceutical activity of the drugs themselves and reduce their undesired toxicity effects in human

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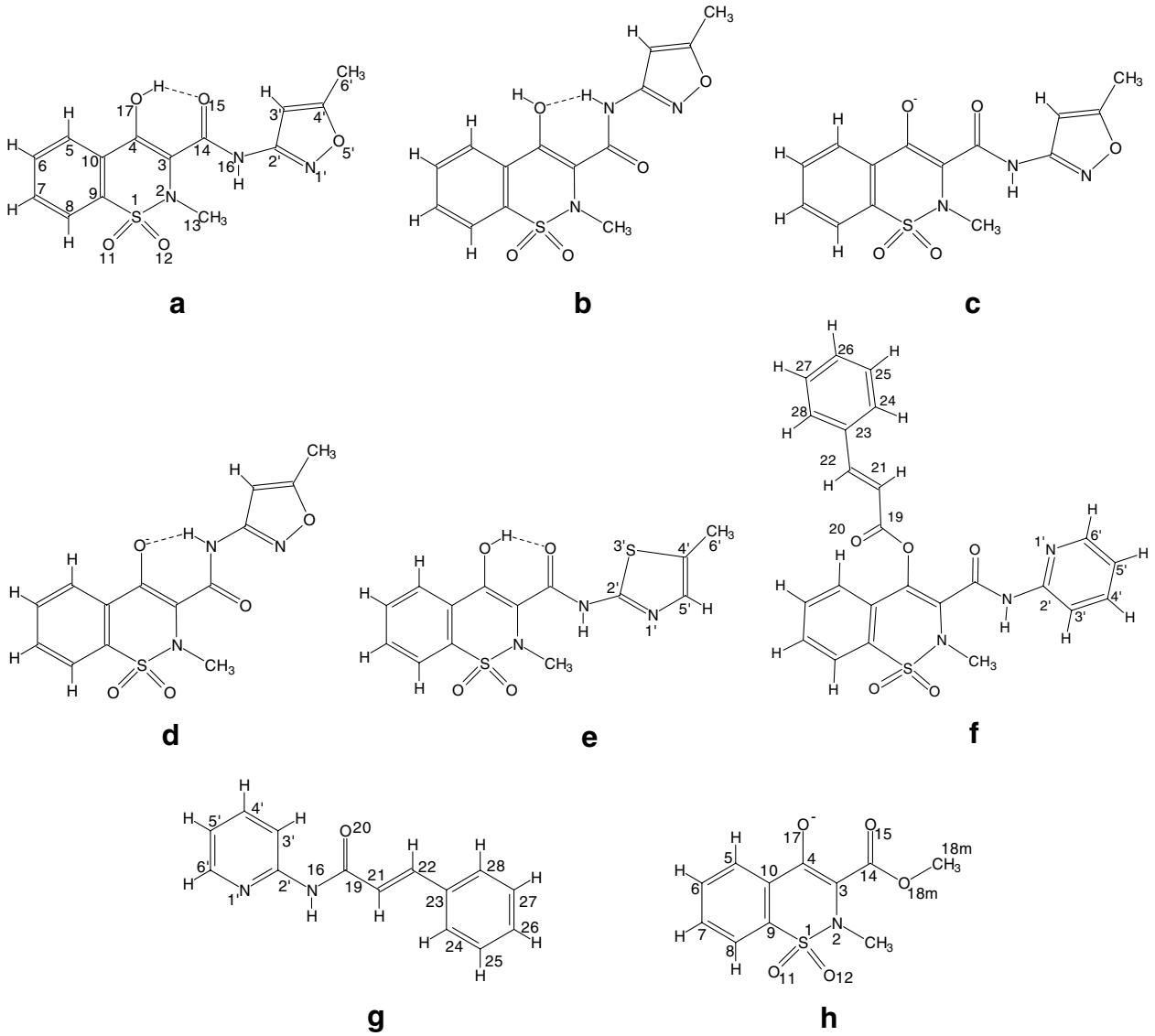
doi:10.1016/j.jinorgbio.2007.04.015

and veterinary medicine. A successful Cu–NSAID complexes as a pharmaceutical compound is $[Cu_2(INDO)_4(DMF)_2]$ (HINDO = Indomethacin, a well known NSAID, DMF = dimethylformamide) that a few years ago was approved in Australasia countries as remedy against inflammation and arthritis in domestic animals such as dogs, horses and camels [1–7]. Its usage is presumably going to quickly expand to several other countries. The major quality of the metal-based drug when compared to free HINDO is a much decreased toxicity in the gastrointestinal tract (it is well known that HINDO is lethal for many animals after a few low-dose administrations). Other copper complexes of NSAIDs have shown promising improvements of the pharmaceutical properties and reduction of side effects when compared to free ligands [4].

Beside that, the effects against other types of pathologies shown by certain copper complexes, like copper–thiosemicarbazones has been ascertained in *in vitro* studies and against tumors implanted on animals [20–22]. Furthermore, certain NSAIDs have been claimed as able in decreasing the onset of tumors in patients to whom the drugs have been administered for prolong period of time [23,24].

Among NSAIDs those from the ''oxicam'' family have been extensively used all over the world in a variety of inflammatory and rheumatic diseases in humans [8]. Schematic structures for selected drugs, and for the ligands MBT (3-(methoxycarbonyl)-2-methyl-2*H*-1,2-benzothiazin-4-olate 1,1-dioxide) and PPA (3-phenyl-*N*-pyridin-2-ylacrylamide) obtained in this work from the reaction of HCIN with copper(II)–acetate, are represented in Scheme 1. They are versatile ligands for copper(II) ions and several other metal ions, as confirmed by the structures of the many metal complexes that have been isolated and



Scheme 1. (a) Representation of schematic structures of H_2ISO, in its *EZE* conformation around the C3–C14, C14–N16 and N16–C2′ linkages. The numbering of the atoms used in the manuscript is also reported. (b) H_2ISO, *ZZZ*; (c) $HISO^-$ anion, *EZE*; (d) $HISO^-$, *ZZZ*; (e) H_2MEL, *EZE*; (f) HCIN, *EZZ*; (g) PPA; and (h) MBT.