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Synthesis, crystal structure and spectroscopy of bioactive Cd(II) polymeric complex of the non-steroidal anti-inflammatory drug diclofenac sodium: Antiproliferative and biological activity

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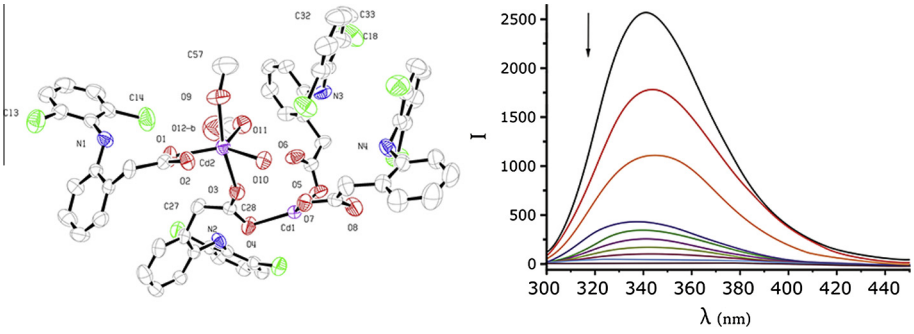
HIGHLIGHTS

- The crystal structure of complex cadmium(II) with diclofenac sodium has been determined.
- The complex shows antioxidant and antibacterial activity.
- The complex can bind to human or bovine serum albumin proteins.
- The complex has been evaluated for antiproliferative activity.

GRAPHICAL ABSTRACT



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ABSTRACT

The interaction of Cd(II) with the non-steroidal anti-inflammatory drug diclofenac sodium (Dic) leads to the formation of the complex $[Cd_2(L)_4 1.5(MeOH) 2(H_2O)]_n$(L = Dic), **1**, which has been isolated and structurally characterized by X-ray crystallography. Diclofenac sodium and its metal complex **1** have also been evaluated for antiproliferative activity in vitro against the cells of three human cancer cell lines, MCF-7 (breast cancer cell line), T24 (bladder cancer cell line), A-549 (non-small cell lung carcinoma), and a mouse fibroblast L-929 cell line. The results of cytotoxic activity in vitro expressed as IC_{50} values indicated the diclofenac sodium and cadmium chloride are non active or less active than the metal complex of diclofenac (**1**). Complex **1** was also found to be a more potent cytotoxic agent against T-24 and MCF-7 cancer cell lines than the prevalent benchmark metallodrug, cisplatin, under the same experimental conditions. The superoxide dismutase activity was measured by Fridovich test which showed that complex **1** shows a low value in comparison with Cu complexes. The binding properties of this complex to biomolecules, bovine or human serum albumin, are presented and evaluated. Antibacterial and growth inhibitory activity is also higher than that of the parent ligand compound.

Abbreviations: Dic, diclofenac sodium; NSAID, non-steroidal anti-inflammatory drug; PG, prostaglandins; Cox, cyclooxygenase; Cd, cadmium; IC_{50}, half maximal inhibitory concentration; SOD, superoxide dismutase; BSA, bovine serum albumin; HAS, human serum albumin; FT-IR, Fourier transform infrared spectroscopy; calc, calculated; DMSO, dimethyl sulfoxide; MIC, Minimal Inhibitory Concentration; DMF, dimethylformamide; asym, antisymmetric; sym, symmetric; ORTEP, Oak Ridge Thermal Ellipsoid Plot; NBT, nitro blue tetrazolium; SA, serum albumin; Trp, tryptophan; SV, Stern–Volmer; eqn, equation; Sm, streptomycin; CCDC, Cambridge Crystallographic Data Centre; IUT, Isfahan University of Technology.

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Introduction

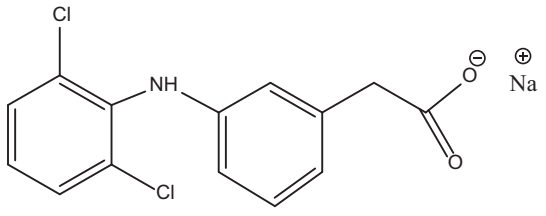
It is well-known that most anti-inflammatory drugs are carboxylic acids in which the carboxylate group is presented for metal–ligand interaction [1]. Diclofenac sodium [2-[(2,6-dichlorophenyl)amino]-phenyllacetate is a effective non-steroidal anti-inflammatory drug (NSAID), therapeutically used in inflammatory and painful diseases of rheumatic and non-rheumatic origin. The anti-inflammatory activity of diclofenac and most of its other pharmacological effects are thought to be related to the inhibition of the conversion of arachidonic acid to prostaglandins, which are the mediators of the inflammatory process [2,3]. The mode of action of the NSAIDs is attributed primarily to the inhibition of prostaglandins (PG) synthesis, and more specifically inhibition of the cyclooxygenase enzyme system, Cox, Cox-1 and Cox-2. Inhibition of the Cox-2 system results in anti-inflammatory action, while inhibition of the Cox-1 enzyme system results in anti-inflammatory action as well as gastric irritation [4]. Diclofenac is a potent reversible inhibitor of the secondary phase of induced platelet aggregation. Like other NSAIDs, diclofenac is highly (>95%) protein bound [1].

Metal complexes with active drugs as ligands are a research area of increasing interest for inorganic and medicinal chemistry and have attracted much attention as an approach to new drug development in the past decade [5,6]. The information collected from preparative, structural and reactivity studies have high importance for several fields which span the range from bioscience to material science. The combination of two or more different active parts into the same compound may generate a multi-therapeutic agent which can expand its potency by the synergic action of the metal residue once the coordination compound has dissociated inside the target tissue [7–10].

In the literature, the crystal structures of three copper(II) [11–13], a cadmium(II) [14], a tin(IV) [15], three nickel(II) [16] complexes with diclofenac ligands have been found. Also, cetirizine dihydrochloride interaction with some diclofenac complexes, forming a ternary compound in the case of the divalent metal clusters (Ca{(dic)$_2$·2H$_2$O}, Mg{(dic)$_2$·2H$_2$O}, Zn{(dic)$_2$·2H$_2$O}) and a quaternary one with the trivalent iron cluster (Fe{dic}$_3$·3H$_2$O), have been investigated [17]. In addition, the anti-infammatory activity and drug-metalloelement interactions of complexes of Cu(II), Co(II), Ni(II), Mn(II), Fe(II), Fe(III), and Pd(II) with diclofenac have been studied [18].

Cadmium compounds have been found to be environmental pollutants. The toxicity of metals such as cadmium in biological systems may result from blocking an essential functional group in biomolecules and inhibiting or enhancing their enzymatic activities or from displacing the essential metal ion in biomolecules. Indeed cadmium appears to compete with zinc at the active sites of enzymes; isolation in the kidney and liver of a cadmium-containing metalloprotein, metallothionein, suggested that proteins are involved in the detoxification processes [19].

We have prepared a novel complex of diclofenac sodium (Dic), Scheme 1, with Cd(II), [Cd$_2$(L)$_4$1.5(MeOH)2(H$_2$O)]$_n$(L = Dic), **1**, in order to obtain information on structure–activity relationships for biopolymer systems involving metal atoms. The cytotoxic activity of diclofenac sodium and its metal complex have been evaluated for antiproliferative activity in vitro against the cells of three human cancer cell lines: MCF-7 (human breast cancer cell line), T24 (bladder cancer cell line), A-549 (non-small cell lung carcinoma) and a mouse L-929 (a fibroblast-like cell line cloned from strain L). Also, the superoxide dismutase activity was measured and IC_{50} values were determined by Fridovich test [20]. Herein, the goal is to extend the pharmacological profile of diclofenac sodium, in order to discover new properties such as anti-cancer activity and SOD activity, to prepare a new bioactive polymer of diclofenac containing the metal ion cadmium, which would be likely to exhibit different biological and pharmaceutical behavior when compared to the "parent drug", diclofenac sodium. In this report the affinity of **1** for bovine (BSA) and human serum albumin (HSA) proteins involved in the transport of metal ions and metal complexes with drugs through the blood stream, was determined using fluorescence spectroscopy and antibacterial assays are also reported.



Scheme 1. Diclofenac sodium.

Experimental

Materials

All chemicals and solvents were purchased from Merck or Sigma–Aldrich and were used without any further purification. Diclofenac sodium was obtained from the Raha Pharmaceutical Company.

Physical measurements

Fourier transform infrared spectra were recorded on a FT-IR JASCO 680-PLUS spectrometer in the 4000–400 cm^{-1} region using KBr pellets. Elemental analyses were performed by using a Leco, CHNS-932 elemental analyzer. Fluorescence spectra were obtained using a Perkine-Elmer LS55 fluorescence spectrofluorometer. UV–visible (UV–Vis) spectra were recorded as Nujol mulls and in solution at concentrations in the range 10^{-5}–10^{-3} M on a JASCO 7580 UV–Vis-NIR double-beam spectrophotometer using a quartz cell with a path length of 10 mm.

Synthesis of [Cd$_2$(L)$_4$1.5(MeOH)2(H$_2$O)]$_n$(L= Dic),1

An aqueous solution (20 mL) containing diclofenac sodium (1 mmol, 318 mg) was added drop wise to a methanolic solution (10 mL) of CdCl$_2$ (0.5 mmol, 92 mg). The reaction mixture was stirred for 4 h, filtered and left for slow evaporation. Colorless crystals of **1** (75%) suitable for X-ray structure determination were deposited after a few days.

Elemental analysis results were in good agreement with the C13.53 H11.76 Cd0.47 Cl1.88 N0.94 O2.71 stoichiometry for **1**. Found (calc.%): C, 46.50 (46.37); N, 3.77 (3.75); H, 3.12 (3.35). IR data on KBr (ν, cm^{-1}) pellets: $\nu_{asym}(CO_2)$, 1540 (vs), 1610(m), 1580(s); $\nu_{sym}(CO_2)$, 1400 (vs); 1420 (s), 1320(m).

Crystal structure determination

Relevant data about the collections and structure solutions are summarized in Table 1. Crystals of **1** for X-ray crystallography were grown by slow evaporation from solution. An Oxford Diffraction Xcalibur system was used to collect X-ray diffraction data. The crystal structures were solved by direct methods (Shelxs2014) and refined by full matrix least squares using Shelxs2014 within the Oscail package [21,22]. Non-hydrogen atoms were refined anisotropically. The O10–H10A distance was restrained to 0.89 Å.