Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 122 (2014) 598–608

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Coordination modes of bidentate lornoxicam drug with some transition metal ions. Synthesis, characterization and in vitro antimicrobial and antibreastic cancer activity studies

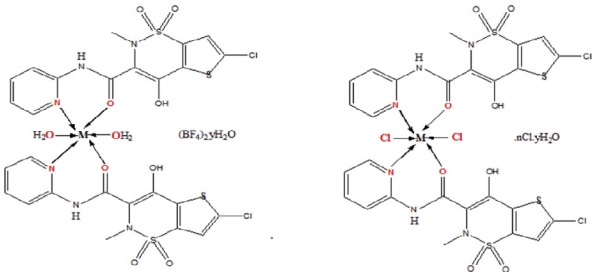
Walaa H. Mahmoud, Gehad G. Mohamed *, Maher M.I. El-Dessouky

Chemistry Department, Faculty of Science, Cairo University, Giza 12613, Egypt

HIGHLIGHTS

- Mononuclear complexes of lornoxicam drug with transition metal ions were prepared.
- The bonding and stereochemistry were deduced from elemental and spectroscopic data.
- The activation kinetic parameters are calculated using DTG curves.
- The metal complexes showed antimicrobial inhibition capacity comparable to LOR ligand.
- The Cr(III), Fe(II) and Cu(II) complexes have high anticancer activity against MCF7.

GRAPHICAL ABSTRACT



M = Co(II), Cu(II) and Zn(II) complexes M = Cr(III), Mn(II), Fe(III) and Ni(II) complexes

ARTICLE INFO

Article history:
Received 19 August 2013
Received in revised form 19 October 2013
Accepted 10 November 2013
Available online 21 November 2013

Keywords:
Lornoxicam
Metal complexes
Spectroscopy
TG–DTG
Antimicrobial activity
Antitumor agents

ABSTRACT

The NSAID lornoxicam (LOR) drug was used for complex formation reactions with different metal salts like Cr(III), Mn(II), Fe(III) and Ni(II) chlorides and Fe(II), Co(II), Cu(II) and Zn(II) borates. Mononuclear complexes of these metals are obtained that coordinated to NO sites of LOR ligand molecule. The nature of bonding and the stereochemistry of the complexes have been deduced from elemental analyses, IR, UV–Vis, ^{1}H NMR, mass, electronic spectra, magnetic susceptibility and ESR spectral studies, conductivity measurements, thermogravimetric analyses (TG–DTG) and further confirmed by X-ray powder diffraction. The activation thermodynamic parameters are calculated using Coats–Redfern and Horowitz–Metzger methods. The data show that the complexes have composition of ML_2 type except for Fe(II) where the type is $[ML_3]$. The electronic absorption spectral data of the complexes suggest an octahedral geometry around the central metal ion for all the complexes. The antimicrobial data reveals that LOR ligand in solution show inhibition capacity less or sometimes more than the corresponding complexes against all the species under study. In order to establish their future potential in biomedical applications, anticancer evaluation studies against standard breast cancer cell lines (MCF7) was performed using different concentrations. The obtained results indicate high inhibition activity for Cr(III), Fe(II) and Cu(II) complexes against breast cancer cell line (MCF7) and recommends them for testing as antitumor agents.

Introduction

Medical inorganic chemistry is becoming an emerging area of research due to the demand for new biologically active compounds. Various investigations have proved that binding of a drug to a metallo element enhances its activity and in some cases, the complex possesses even more healing properties than the parent drug [1]. Oxicam ligands are wide spread among coordination compounds and are important components of biological transition metal complexes [2]. The oxicam group of nonsteroidal anti-inflammatory drugs (NSAIDs) has emerged as highly effective class

* Corresponding author. Tel.: +20 235676896.
E-mail address: ggenidy@hotmail.com (G.G. Mohamed).

1386-1425/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.saa.2013.11.069

of drugs against various arthritic conditions and post-operative inflammation. Recently several other functions of these groups of drugs have been identified which included chemoprevention, chemosuppression, UV-sensitization, UV-protection, etc. These drugs are also found to be very good anti-oxidants. Most oxicams are congeneric compounds generated by the concept of isosteric substitution in drug design [3]. Oxicam family, piroxicam, tenoxicam, meloxicam, lornoxicam and isoxicam, are widely used in inflammatory and painful diseases of rheumatic and non-rheumatic origin. They are potent inhibitors of cyclo-oxygenase in vitro and in vivo, thereby decreasing the synthesis of prostaglandins, prostacyclin, and thromboxane products [3,4].

New studies from the last years revealed that in addition to arthritis and pain, cancer and neurodegenerative diseases like Alzheimer's disease could potentially be treated with COX-2 inhibitors [4]. The direct interaction of NSAIDs and their metal complexes with DNA is of interest since their anticancer activity may be explained [5].

Lornoxicam (LOR) is a non-steroidal anti-inflammatory drug (Fig. 1) of the oxicam class with analgesic, anti-inflammatory and antipyretic properties. It is available in oral and parenteral formulations. It is used for inflammatory disease of the joints, osteoarthritis, pain following surgery and pain in the lower back and hip which travels down the back of the thigh into the leg (sciatica). LOR differs from other oxicam compounds in its potent inhibition of prostaglandin biosynthesis, a property that explains the particularly pronounced efficacy of the drug [6].

The goal in this research was to explore the probability to extend the pharmacological profile of lornoxicam (LOR) drug, in order to disk over new properties such as antimicrobial and anti-cancer activity and to prepare new complexes of LOR with essential metal ions, which probably would exhibit different biological behaviour compared to the parent drug [4]. The structures of the metal complexes were characterized by elemental analyses, IR, ^{1}H NMR, ESR, UV–Vis, XRD, conductivity, mass spectra and magnetic susceptibility measurements at room temperature, thermal analyses as well as some results of bioactivity tests are also included.

Experimental

Materials and reagents

All chemicals used were of the analytical reagent grade (AR), and of highest purity available. The chemicals used included lornoxicam drug (supplied from National Organization for Drug Control and Research), $CrCl_3{\cdot}6H_2O$ and $MnCl_2{\cdot}2H_2O$ (Sigma), $NiCl_2{\cdot}6H_2O$ (BDH), $FeCl_3{\cdot}6H_2O$ (Prolabo), $Fe(BF_4)_2{\cdot}6H_2O$ and $Co(BF_4)_2{\cdot}6H_2O$ (Aldrich), $Cu(BF_4)_2{\cdot}6H_2O$ (Merck) and $Zn(BF_4)_2$ (Strem Chemicals). Organic solvents were spectroscopic pure from BDH included ethanol, diethyl ether and dimethyl formamide. Hydrogen peroxide, sodium chloride, sodium carbonate and sodium hydroxide (A.R.) were used.

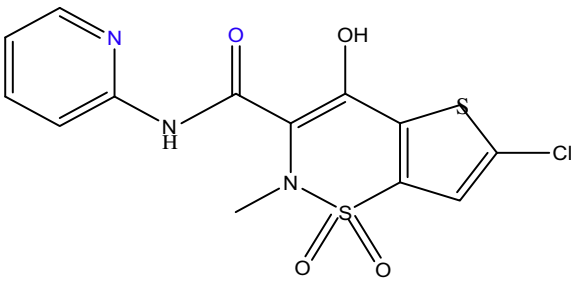


Fig. 1. The structure of lornoxicam drug.

Human tumor cell line (Brest cell) was obtained frozen in liquid nitrogen (−180 °C) from the American Type Culture Collection and was maintained in the National Cancer Institute, Cairo, Egypt, by serial sub-culturing.

Solutions

A fresh stock solution of 1×10^{-3} M of LOR (0.372 g/L) was prepared in the appropriate volume of absolute ethanol and DMF by a ratio (1:5 v/v ethanol:DMF). Dimethylsulphoxide (DMSO) (Sigma Chemical Co., St. Louis, Mo, and USA): It was used in cryopreservation of cells. RPMI-1640 medium (Sigma Chemical Co., St. Louis, Mo, and USA) was used. The medium was used for culturing and maintenance of the human tumor cell line. The medium was supplied in a powder form. It was prepared as follows: 10.4 g medium was weighed, mixed with 2 g sodium bicarbonate, completed to 1 L with distilled water and shaked carefully till complete dissolution. The medium was then sterilized by filtration in a Millipore bacterial filter (0.22 μm). The prepared medium was kept in a refrigerator (4 °C) and checked at regular intervals for contamination. Before use, the medium was warmed at 37 °C in a water bath and supplemented with penicillin/streptomycin and FBS.

Sodium bicarbonate (Sigma Chemical Co., St. Louis, Mo, USA) was used for the preparation of RPMI-1640 medium. 0.05% Isotonic Trypan blue solution (Sigma Chemical Co., St. Louis, Mo, USA) was prepared in normal saline and was used for viability counting. 10% Fetal Bovine Serum (FBS) (heat inactivated at 56 °C for 30 min), 100 units/ml Penicillin and 2 mg/ml Streptomycin were supplied from Sigma Chemical Co., St. Louis, Mo, USA and were used for the supplementation of RPMI-1640 medium prior to use. 0.025% (w/v) Trypsin (Sigma Chemical Co., St. Louis, Mo, USA) was used for the harvesting of cells. 1% (v/v) Acetic acid (Sigma Chemical Co., St. Louis, Mo, USA) was used for dissolving the unbound SRB dye. 0.4% Sulphorhodamine-B (SRB) (Sigma Chemical Co., St. Louis, Mo, USA) dissolved in 1% acetic acid was used as a protein dye. A stock solution of trichloroacetic acid (TCA, 50%, Sigma Chemical Co., St. Louis, Mo, USA) was prepared and stored. 50 μl of the stock was added to 200 μl RPMI-1640 medium/well to yield a final concentration of 10% used for protein precipitation. 100% Isopropanol and 70% ethanol were used. Tris base 10 mM (pH 10.5) was used for SRB dye solubilization. 121.1 g of tris base was dissolved in 1000 ml of distilled water and pH was adjusted by HCl acid (2 M).

Measurements

Microanalyses of carbon, hydrogen and nitrogen were carried out at the Microanalytical Center, Cairo University, Egypt, using CHNS-932 (LECO) Vario Elemental Analyzer. Analyses of the metals followed the dissolution of the solid complexes in concentrated HNO_3, neutralizing the diluted aqueous solutions with ammonia and titrating the metal solutions with EDTA. FT-IR spectra were recorded on a Perkin-Elmer 1650 spectrometer (4000–400 cm^{-1}) in KBr pellets. Electronic spectra were recorded at room temperature on a Shimadzu 3101pc spectrophotometer as solutions in ethanol. ^{1}H NMR spectra, as a solution in DMSO-d_6, were recorded on a 300 MHz Varian-Oxford Mercury at room temperature using TMS as an internal standard. Electron spin resonance spectra were also recorded on JES-FE2XG ESR spectrophotometer at Microanalytical Center, Tanta University.

Mass spectra were recorded by the EI technique at 70 eV using MS-5988 GS-MS Hewlett–Packard instrument at the Microanalytical Center, National Center for Research, Egypt. The molar magnetic susceptibility was measured on powdered samples using the Faraday method. The diamagnetic corrections were made by Pascal's constant and $Hg[Co(SCN)_4]$ was used as a calibrant. Molar conductivities of 10^{-3} M solutions of the solid complexes in DMF