Inorganica Chimica Acta 406 (2013) 230–240

Contents lists available at SciVerse ScienceDirect

Inorganica Chimica Acta

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

Metal complexes of moxifloxacin–imidazole mixed ligands: Characterization and biological studies

Amina A. Soayed [a,b,*], Heba M. Refaat [a], Doaa A. Noor El-Din [c]

[a] Faculty of Science, Alexandria University, Chemistry Department, P.O. Box 426, Ibrahimia, Alexandria 21321, Egypt
[b] University of Dammam, Chemistry Department, Saudi Arabia
[c] Stability Laboratory, Medizen Pharmaceutical Industries, Alexandria, Egypt

ARTICLE INFO

Article history:
Received 11 December 2012
Received in revised form 23 April 2013
Accepted 24 April 2013
Available online 9 May 2013

Keywords:
Moxifloxacin
Imidazole
Mixed ligands
Characterization
Biological activity

ABSTRACT

Solid complexes $[M(MOX)(HIm)Cl_x]\cdot nH_2O$, [M = Mn(II), Co(II), Ni(II), Cu(II), Zn(II), Cr(III)] and $[Ag(MOX)(HIm)\cdot 2.5H_2O]$; MOX = moxifloxacin, HIm = imidazole were prepared and characterized using elemental analyses, IR spectroscopy, conductance measurements, UV–Vis spectra, ESR of the copper complex, magnetic moments measurements, ^1H and ^{13}C NMR for the nickel (II) complex and thermal analyses. The results indicate that moxifloxacin reacts as a bidentate ligand and is bound to the metal ions through the pyridone oxygen and one carboxylic oxygen, except for the silver (I) complex where the metal ion is chelated to the hydro pyridinium nitrogen. The activation energies, ΔE^*; entropies ΔS^*; enthalpies ΔH^* and order of reactions have been derived from differential thermogravimetric (DTA) curves, using Horowitz–Metzeger method. The mixed ligands complexes were evaluated for their antibacterial activity against two bacterial species, namely *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*). Antifungal screening was studied against two species (*Aspergillus flavus* and *Condida albicans*). The complexes under investigation were found to possess better antibacterial agents than uncomplexed Moxifloxacin and have antifungal activity as well.

1. Introduction

Recently, research areas in the development of new metal-based complexes with biologically relevant molecules and the role of these metal complexes in detecting disease and sensing biologically occurring metal ions with specially designed ligands has attracted enormous interest [1]. Complexes of some metal ions were not only used in treating cancer, Wilson's and Alzheimer's diseases, but were also used for controlling the growth of pathogens and parasites that are harmful to humans [1]. There is more need for designing novel therapeutic and diagnostic agents that target specific properties, show reduced side effects, improve selectivity and are able to treat a wide range of human diseases. Coordination compounds combine the features of metals which have a wide range of coordination numbers, geometries, variable oxidation states, and ability to bind a variety of organic ligands or mixed ligands in an attempt to get the optimal stability and the biological in vitro activity. where the action of many drugs depends on the coordination with metal ions or the inhibition on the formation of metallo-enzyme [2,3].

The imidazole ring is a constituent of several important natural products, including purine, histamine, histidine and nucleic acid and is also found in almost all copper (II) and zinc(II) enzymes. Being a polar and ionizable aromatic compound, it improves pharmacokinetic characteristics and thus is used as a remedy [4,5]. The high therapeutic properties of the imidazole related drugs have encouraged medicinal chemists to synthesize a large number of novel chemotherapeutic agents remedying various dispositions in clinical medicines [6]. Complexes of imidazole with transition metal ions are of interest because of their close relationship with biological systems involving histidine residues [7].

In addition, congeners containing C-8 fluorine display high activity against bacterial topoisomerases, eukaryotic topoisomerases and are toxic to cultured mammalian cells and in vivo tumor models [6–9]. Moxifloxacin hydrochloride is a fourth-generation, synthetic, broad spectrum antibacterial agent. It is marketed worldwide under the brand names Avelox, Avalox, and Avelon for oral treatment and in an ophthalmic solution (eye drops) under the brand name Vigamox for the treatment of conjunctivitis. Evidence demonstrated that some fluoroquinolones, besides acting as large-spectrum antibiotics, also present anticancer [10] and anti-HIV activity [11] and some of them, are able to modulate lipopolysaccharide induced pro-inflammatory cytokine production [12]. Recently, anticancer potency have been shown for Ruthenium η-p-Cymene complexes containing antibacterial quinolones such

* Corresponding author at: Faculty of Science, Alexandria University, Chemistry Department, P.O. Box 426-Ibrahimia, Alexandria 21321, Egypt. Fax: +203 39 11 794.
E-mail addresses: amsoayed@yahoo.com, aminasoayed@yahoo.com (A.A. Soayed).

0020-1693/$ - see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.ica.2013.04.040

as nalidixic acid and cinoxacin [13]. Metal complexes of fluoroquinolines are also known to play important roles in biological activities. The in vitro antibacterial and antifungal activities of the metal complexes against gram positive and gram negative bacteria and fungal species indicate their having appreciable antimicrobial activity [14–21].

Studies of copper complexes of mixed ligands (including quinolone) such as the antibacterial drugs oxolinic acid, enrofloxacin, flumequine and gatifloxacin in the presence of nitrogen donor heterocyclic ligands have shown that the quinolone ligands act as deprotonated bidentate ligands and are coordinated to the metal ion through the pyridone and one carboxylate oxygen atoms. X-ray crystallography has determined the crystal structure of complexes which was found to have distorted square pyramidal environment around the Cu(II) ion [22–25].

Due to the increase demand for novel biologically active complexes in technology and medicine, we attempted the syntheses of metal(II) ions complexes of moxifloxacin–imidazole mixed ligands, with the objective of understanding the structures and geometries of these complexes and to study their biological effect. For the characterization of the complexes, the following techniques were employed: IR spectroscopy, ^{1}H NMR and ^{13}C NMR for the Ni(II) complex, molar conductance, elemental analyses, ESR for the Cu(II) complex and thermal decomposition studies. Effects on gram positive and gram negative bacteria, as well as the effect on *Aspergillus flavus* and *Condida albicans* fungi has also been studied.

2. Experimental

2.1. Materials and preparation of complexes

2.1.1. Chemicals used

Moxifloxacin, imidazole, $CoCl_2$, $NiCl_2$, $CuCl_2$, $MnCl_2$, $ZnCl_2$, $CrCl_3$ and $AgNO_3$ and all solvents were purchased from Sigma–Aldrich Chemical Co. All the chemicals and solvents were analytical reagent grades and were used as purchased without further purification.

2.1.2. Synthesis of moxifloxacin–imidazole metal complexes

All the complexes were prepared in a similar manner. The complexes were prepared by the addition of a 2 mmol of methanolic solution of $MX{\cdot}nH_2O$ (M = Co, Cu, Ni, Zn, Mn, Ag and Cr, X = Cl or NO_3; n = 0, 2, 4 or 6) to 0.875 g (2 mmol) of moxifloxacin (MOX) dissolved in (2 mmol) of NaOH solution, after which, 0.136 g (2 mmol) of imidazole (Him) in 20 mL of methanol in 1:1 ratio was added. The reaction mixture was stirred at 60 °C for 2 h. The solution was left for slow evaporation, the precipitates formed were filtered off, washed with distilled water several times and dried over calcium chloride in a descicator. Unfortunately we were not able to prepare single crystals of the complexes. It is well known that low solubility of quinolones and their complexes presents a great difficulty in preparing single crystals.

The complexes were characterized by elemental analyses, Table 1, infrared, electronic absorption spectra, ESR for the Cu(II) complex, ^{1}H NMR and ^{13}C NMR spectra for the Ni(II) complex and thermal analyses. All the complexes under investigation are non-electrolytes.

2.2. Physicochemical studies

Elemental analyses (C, H and N) were performed with a model 240 Perkin Elmer elemental analyzer. The metal ion content was determined using atomic absorption spectrophotometer 850-Fisher Jarrell-Ash computer controlled. Infrared spectra were recorded on a Perkin-Elmer FT-IR type 1650 spectrophotometer in wavenumber region 4000–200 cm^{-1}. The spectra were recorded as KBr pellets. The NMR spectra were measured with a Jeol Eclipse 400 spectrometer at 400 MHz for ^{1}H and 100 MHz for ^{13}C and measured in ppm downfield from tetramethylsilane (TMS) using DMSO-d^6 (Merck) as a solvent.

Table 1
CHN Microanalyses of MOX and its metal complexes.

Complex	%C	%H	%N	%Cl	%M
	Calc. found	Calc. found	Calc. found	Calc. found	Calc. found
$Co(MOX)(HIm)Cl{\cdot}H_2O$	49.88	5.02	12.12	6.15	10.16
	50.62	5.19	11.89	6.43	10.40
$Ni(MOX)(HIm)Cl{\cdot}H_2O$	49.81	5.01	12.10	6.14	10.18
	50.11	4.80	12.06	6.65	10.34
$[Cu(MOX)(HIm)Cl{\cdot}H_2O]_2{\cdot}2H_2O$	47.92	5.15	11.65	5.91	10.17
	47.67	4.99	12.11	6.39	9.80
$Zn(MOX)(HIm)Cl{\cdot}2H_2O$	47.76	5.14	11.61	5.88	10.84
	48.30	5.55	11.94	5.63	10.20
$Cr(MOX)(HIm)Cl_2{\cdot}H_2O$	47.13	4.75	11.45	11.62	8.51
	47.51	5.21	11.01	11.22	8.63
$Ag(MOX)(HIm){\cdot}2.5H_2O$	46.37	5.15	11.27	–	17.39
	46.10	5.44	10.80		16.90
$Mn(MOX)(HIm)Cl{\cdot}2H_2O$	48.44	5.51	11.80	5.97	9.25
	48.02	5.80	12.10	6.00	8.99

The thermal analyses: thermogravimetric analyses, (TGA), Differential thermogravimetry, (DTG) and Differential thermal analyses, (DTA) were carried out in a dynamic nitrogen atmosphere (20 mL min^{-1}), with a heating rate of 10 °C min^{-1} and were recorded in the temperature range from 25 up to 800 °C using a LINSELS STA PT 1000 thermal analyzer. Platinum crucibles were used; sample weights were 10.0–25.0 mg. All the samples were placed in an desiccator over sulphuric acid immediately after heating. Electronic absorption spectra were carried out using an automated spectrophotometer UV–Vis Perkin-Elmer Model Lambda 20, and ranged from 200 to 1200 nm. Molar magnetic susceptibilities, corrected for diamagnetism using Pascal's constants, were determined at room temperature (298°K) using Gouy's method and Hg $[Co(SCN)_4]$ as a calibrant (χ_g = 16.44 × 10^{-6} cgs units at 20 °C). Molar conductance of 10^{-3} M solutions in DMF was measured at room temperature on a Hanna 8033 conductivity meter. ESR measurements were performed at 298°K using a Varian E-12 spectrometer and DPPH as an external standard. All measurements were carried out at ambient temperature with freshly prepared solutions.

2.3. Antimicrobial and antifungal investigation

Antimicrobial activities of MOX ligand and the mixed ligands metal complexes were conducted using a modified Kirby–Bauer disc diffusion method [26]. 100 μL of the test bacteria or fungi were grown in 10 mL of fresh media until they reached a count of approximately 108 cells/mL for bacteria or 105 cells/mL for fungi [27]. 100 μL of the microbial suspension was spread into agar plates in which they were maintained. Plates were incubated with filamentous fungi as *A. flavus* at 25 °C for 48 h; Gram (+) bacteria as *Staphylococcus aureus*, Gram (−) bacteria as *Escherica coli* were incubated at 35–37 °C for 24–48 h and yeast as *C. albicans* incubated at 30 °C for 24–48 h and then the diameters of the inhibition zones were measured in millimeters [26].

3. Results and discussion

3.1. Microanalyses and molar conductivity studies

Microanalyses suggest the formation of $[M(MOX)(Him)Cl_x{\cdot}nH_2O)]$, where MOX = moxifloxacin, HIm = imidazole, M = Co(II), Ni(II),