Journal of Molecular Structure 1120 (2016) 50–61

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Synthesis, thermal analyses, characterization and biological evaluation of new enrofloxacin vanadium(V) solvates(L) (L = An, DMF, Py, Et_3N and o-Tol)

Wael A. Zordok [a, b, *], Sadeek A. Sadeek [a]

[a] Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt
[b] Department of Chemistry, University College of Quanfudha, Umm Al -Qura University, Saudi Arabia

ARTICLE INFO

Article history:
Received 23 January 2016
Received in revised form
3 April 2016
Accepted 3 May 2016
Available online 9 May 2016

Keywords:
Enrofloxacin
^{1}HNMR
IR
TGA
V(V)
DFT and antibacterial activity

ABSTRACT

Five metal complexes of antibacterial agent enrofloxacin with vanadium(V) in the presence of aniline, pyridine, orthotolidine and triethylamine as nitrogen donor molecules and dimethylformamide as oxygen donor molecule have been prepared and characterized with physicochemical and diverse spectroscopic techniques (IR, UV–Vis. and ^{1}H NMR spectroscopes) as well as thermal analysis. The deprotonated enrofloxacin complexes of V(V) were isolated as solids with the general formulas; $[VO(Enr)_2DMF]Cl\cdot 5H_2O$, $[VO(Enr)_2An]Cl\cdot 2H_2O$, $[VO(Enr)_2o\text{-}Tol]Cl\cdot H_2O$, $[VO(Enr)_2Py]Cl\cdot 4H_2O$ and $[VO(Enr)_2Et_3N]Cl\cdot 6H_2O$. The prepared complexes are formed with a metal to ligand ratios as 1:2:1 for all complexes. The lowest energy model structure of each complex has been proposed by using the density functional theory (DFT) at the B3LYP/CEP-31G level of theory. The energy barrier for the pyridine complex greater than others complexes while, Et_3N complex has lower value. The ligand and their metal complexes were also evaluated for their antibacterial activity against three Gram (+ve) and three Gram (−ve) microorganisms.

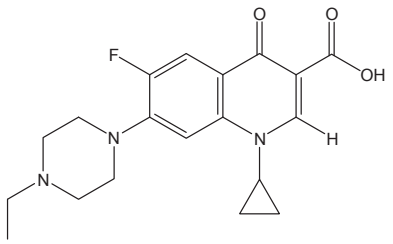
1. Introduction

Enrofloxacin (HEnr = 1-cyclopropyl-7-(4-ethyl-piperazin-1- yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid) (Scheme 1) is one of second-generation antimicrobial with a broad spectrum of activity against a wide range of Gram-negative and Gram-positive bacteria, including those resistant to β-lactam antibiotics and sulfonamides [1,2].

Enrofloxacin is the first fluoroquinolone developed for veterinary application and is potentially available for the treatment of some urinary tract, respiratory tract and skin infectious diseases in pets and livestock [3–6]. It is also used for the treatment of complicated urinary tract infections, pyelonephritis, sexually transmitted diseases, skin prostatitis and tissue infections, urethral and cervical gonococci infections [7–9]. Its mechanism of action is not thoroughly understood, but it is suspected to act by inhibiting bacterial DNA gyrase (a type-II topoisomerase), thereby preventing DNA supercoiling and synthesis. In September 2005, the FDA withdrew approval of enrofloxacin for use in water to treat flocks of poultry, as this practice was noted to promote the evolution of fluoroquinolone resistant strains of the bacterium Campylobacter, a human pathogen. Thus, an alternative is necessary. In that way, it was shown that metallo-antibiotics are very stable at physiological pH and they seem to be a good approach for the development of drugs with similar activity against bacteria but with the possibility of lowering their level of resistance [10]. The coordination chemistry of fluoroquinolones drugs with metal ions of biological and pharmaceutical importance is of considerable interest. There have been several reports about the synthesis and crystal structure of metal complexes [11–14]. In view of the interest and importance of fluoroquinolones compounds the work reported herein is focused on synthesis and characterization of new enrofloxacin vanadium(V) complexes. These complexes were characterized by elemental, thermal analyses, spectral, and conductivity studies.The lowest energy model structure of each complex has been proposed by using the density functional theory (DFT) at the B3LYP/CEP-31G level of theory. The work was extended to study the antibacterial activity of the ligand and its metal complexes against three Gram (+ve) and three Gram (−ve) microorganisms.

* Corresponding author. Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt
E-mail address: Wazordok@yahoo.com (W.A. Zordok).

http://dx.doi.org/10.1016/j.molstruc.2016.05.011
0022-2860/



Scheme 1. Structure of enrofloxacin (ENR) (1-cyclopropyl-7-(4-ethyl-piperazin-1- yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid).

2. Materials and methods

2.1. Chemicals

All chemicals used for the preparation of the complexes were of analytical reagent grade commercially available from different sources and used without further purification. Enrofloxacin was obtained from EIPICO, $VOCl_3$ (99.9%) was purchased from Aldrich Chemical Co. NaOH, $AgNO_3$, NaCl and all solvents were purchased from Fluka Chemical Co.

2.2. Synthesis

An ethanolic suspended solution (20 ml) of Enrofloxacin (1.0 mmol, 0.359 g) and NaOH (1 mmol, 0.04 g) was added to an ethanolic solution of $VOCl_3$ (0.5 mmol, 0.095 ml) and the reaction mixture was stirred at room temperature for 1 h and then adding 1 ml dimethylformamide (0.5 mmol, d = 0.949) after that the reaction mixture was stirred for 3 days at room temperature. The solution was left for slow evaporation, after that a greenish yellow $[VO(Enr)_2DMF]Cl\cdot 5H_2O$ product was deposited. The solid obtained was filtered under vacuum, washed with ethanol and dried over anhydrous $CaCl_2$. The pale green, dark green, brown and yellowish green solid complexes $[VO(Enr)_2An]Cl\cdot 2H_2O$, $[VO(Enr)_2o\text{-}Tol]Cl\cdot H_2O$, $[VO(Enr)_2Py]Cl\cdot 4H_2O$ and $[VO(Enr)_2Et_3N]Cl\cdot 6H_2O$ were prepared in a similar manner described above by using ethanol as a solvent and aniline, o-toluidine, pyridine and triethylamine, respectively. Single crystal suitable for X-ray crystallographic measurements was not obtained. The complexes were characterized by their elemental analysis, infrared, electronic, ^{1}HNMR, thermal analyses as well as density functional theory (DFT) at the B3LYP/CEP-31Glevel of theory.

2.2.1. $[VO(Enr)_2DMF]Cl\cdot 5H_2O$

Bis [1-cyclopropyl-7-(4-ethyl-piperazin-1- yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylato] N,N-dimethylformamideoxo vanadium chloride pentahydrate.

2.2.2. $[VO(Enr)_2An]Cl\cdot 2H_2O$

Bis [1-cyclopropyl-7-(4-ethyl-piperazin-1- yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylato] phenylamineoxo vanadium chloride dihydrate.

2.2.3. $[VO(Enr)_2o\text{-}Tol]Cl\cdot H_2O$

Bis [1-cyclopropyl-7-(4-ethyl-piperazin-1-yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylato] 4-(4-amino-3-methylphenyl)-2-methylaniline oxo vanadium chloride monohydrate.

2.2.4. $[VO(Enr)_2Py]Cl\cdot 4H_2O$

Bis [1-cyclopropyl-7-(4-ethyl-piperazin-1- yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylato] pyridine oxo vanadium chloride tetrahydrate.

2.2.5. $[VO(Enr)_2Et_3N]Cl\cdot 6H_2O$

Bis [1-cyclopropyl-7-(4-ethyl-piperazin-1- yl)-6-fluoro-4-oxo-1,4-dihydro-quinoline-3-carboxylato] N,N-Diethylethanamineoxo vanadium chloride hexahydrate.

2.3. Instruments

Elemental C, H and N analysis was carried out on a Perkin Elmer CHN 2400. The percentage of the V(V) was determined gravimetrically by transforming the solid products into oxide and also determined by using atomic absorption method. Spectrometer model PYE-UNICAM SP 1900 fitted with the corresponding lamp was used for this purpose. IR spectra were recorded on FTIR 460 PLUS (KBr discs) in the range from 4000 to 400 cm^{-1}, ^{1}HNMR spectra were recorded on Varian Mercury VX-300NMR Spectrometer using DMSO-d_6 as solvent. TGA-DTG measurements were carried out under N_2 atmosphere within the temperature range from room temperature to 800° C using TGA-50H Shimadzu. Electronic spectra were obtained using UV-3101PCShimadzu. The solid reflection spectra were recorded with KBr pellets. Molar conductivities of the solution of the ligand and metal complexes in DMSO at 1×10^{-3} M were measured on CONSORT K410. All measurements were carried out at ambient temperature with freshly prepared solution.

2.4. Antimicrobial investigation

Antibacterial activity of the ligands and its metal complexes was investigated by a previously reported modified method of Beecher and Wong [15], against different bacterial species, such as three Gram-negative, *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*) and *Klebsiella pneumonia* (*K. pneumoniae*) and three Gram-positive, *Staphylococcus aureus* (*S. aureus*), *Staphylococcus epidermidis* (S. epidermidis) and *Bacillus pumilus* (B. pumilus) microorganisms in the regional center for mycology and biotechnology, Al-Azhar University. The nutrient agar medium for antibacterial was (0.5% Peptone, 0.1% Beef extract, 0.2% Yeast extract, 0.5% NaCl and 1.5% Agar-Agar) was prepared and then cooled to 47 °C and seeded with tested microorganisms. After solidification 5 mm diameter holes were punched by a sterile corkborer. The investigated compounds, i.e., ligand and their complexes, were introduced in Petri-dishes (only 0.1 ml) after dissolving in DMSO at 1.0×10^{-3} M. These culture plates were then incubated at 37 °C for 20 h for bacteria. The activity was determined by measuring the diameter of the inhibition zone (in mm). The plates were kept for incubation at 37° C for 24 h and then the plates were examined for the formation of zone of inhibition.

3. Results and discussion

The mononuclear vanadium(V) complexes with enrofloxacin in the presence of oxygen and nitrogen donor molecules such as dimethylformamide, aniline, pyridine, orthotolidine and triethylamine have been prepared in high yield and characterized with physicochemical and diverse spectroscopic techniques (IR, UV–Vis. and ^{1}H NMR spectroscopes) as well as thermal analysis. The deprotonated enrofloxacin complexes of V(V) were isolated as solids with the general formulas; $[VO(Enr)_2DMF]Cl\cdot 5H_2O$, $[VO(Enr)_2An]Cl\cdot 2H_2O$, $[VO(Enr)_2o\text{-}Tol]Cl\cdot H_2O$, $[VO(Enr)_2Py]Cl\cdot 4H_2O$ and $[VO(Enr)_2Et_3N]Cl\cdot 6H_2O$. The prepared complexes are formed with a metal to ligand ratios as 1:2:1 for all complexes. The found values of elemental analysis agree well with the calculated percentage of C, H and N and prove the suggested molecular