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Metal complexes of the fourth generation quinolone antimicrobial drug gatifloxacin: Synthesis, structure and biological evaluation

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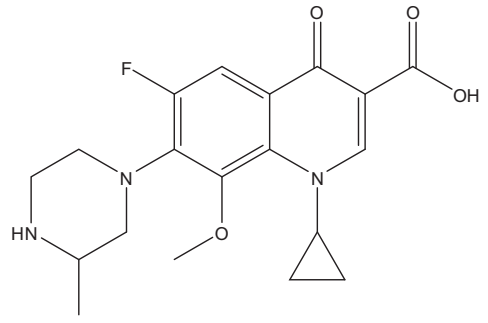
ABSTRACT

Three metal complexes of the fourth generation quinolone antimicrobial agent gatifloxacin (GFLX) with Y(III), Zr(IV) and U(VI) have been prepared and characterized with physicochemical and spectroscopic techniques. In these complexes, gatifloxacin acts as a bidentate deprotonated ligand bound to the metal through the ketone oxygen and a carboxylato oxygen. The complexes are six-coordinated with distorted octahedral geometry. The kinetic parameters for gatifloxacin and the three prepared complexes have been evaluated from TGA curves by using Coats–Redfern (CR) and Horowitz–Metzeger (HM) methods. The calculated bond length and force constant, F(U=O), for the UO_2 bond in uranyl complex are 1.7522 Å and 639.46 N m^{-1}.

The antimicrobial activity of the complexes has been tested against microorganisms, three bacterial species, such as *Staphylococcus aureus* (*S.* aureus), *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) and two fungi species, *penicillium* (*P. rotatum*) and *trichoderma* (*T.* sp.), showing that they exhibit higher activity than free ligand.

1. Introduction

Bristol-Myers Squibb and Allergon produced Gatifloxacin (Formula I) under the brand names Tequin and Zymor. Gatifloxacin sold under these names is an antibiotic of the fourth generation fluoroquinolone family, that like other members of that family inhibits the bacterial enzymes DNA gyrase and topoisomeraseIV. In many countries, gatifloxacin is also available as tablets and in various aqueous solutions for intravenous therapy.



Formula I: 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

The fluoroquinolones constitute an important class of synthetic antimicrobial agents. Recent studies indicate an important role of metal ions on the mechanism of action of these drugs. The dissociation and coordination behavior of fluoroquinolone antibiotics have been studied and published [1]. Metal complex is known to enhance the biological activities of quinolone antibiotics due perhaps to resulting higher liposolubilities leading to greater intracellular accumulations [2–5].

Number of studies regarding the interaction between various quinolones with the metallic cations has been reported in the literature [6–17]. These studies have been primarily directed towards the identification of function groups directly linked to the metal and to establish the structure formed by these coordination complexes. Infrared spectroscopic and solid state paramagnetic resonance spectroscopy studies of metallic complexes derived from these compounds suggest that they are formed by interaction through ring carbonyl and carboxylate oxygen atoms [2,6–18]. In basic media the quinolones bearing a piperazinyl ring in position 7 could also form complexes where terminal nitrogen is involved in the coordination to the metal [19–24].

As a continuation of our work on metal interactions with fluoroquinolone derivatives [10,11] we describe the synthesis of gatifloxacin with Y(III), Zr(IV) and U(VI) complexes, with the objective of better understanding the structures formed by these compounds. For the characterization of the complexes formed, the following techniques were employed: ^{1}H NMR, UV spectroscopies, Elemental analysis, Infrared, conductance measurements and thermal analysis.

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2. Materials and methods

Metal salts and solvents were purchased from Merck Germany. Gatifloxacin was obtained from Sigma, these materials used without further purification.

The infrared spectra of the three solid complexes, gatifloxacin and the final products of the thermogravimetric analysis were recorded from KBr discs using FTIR 460 plus, ^{1}H NMR spectra were recorded on Varian Mercury VX-300 NMR Spectrometer using DMSO-d_6 as solvent. C, H, N and halogen elemental analysis were carried out on a Perkin Elmer CHN 2400. The percentage of Y(III), Zr(IV) and U(VI) metal ions were determined gravimetrically by transforming the solid products into oxide, and also determined by using atomic absorption method. A spectrometer model PYE-UNICAM SP 1900 fitted with the corresponding lamp was used for this purposed. Electronic solid reflection spectra of gatifloxacin and the isolated solid complexes were obtained in the region of 800–200 nm using UV-3101PC Shimadzu with a 1 cm quartz cell. Thermogravimetric (TG) and differential (DTG) thermogravimetric analysis were carried out under N_2-atmosphere using detectors model TGA-50H Shimadzu. The rate of heating of the sample was kept at 10 °C/min. Molar conductivities in DMSO at 1.0×10^{-3} M were measured on CONSORT K410.

2.1. Synthesis of gatifloxacin metal complexes

The yellowish white solid complex $[Y(GFLX)_2(H_2O)Cl]Cl_2{\cdot}11H_2O$ was prepared by adding 0.5 mmol (0.0977 g) of Yttrium chloride (YCl_3) in 10 ml bidistilled water drop wisely to a stirred suspended solution of 1 mmol (0.37516 g) of GFLX in 50 ml ethanol. The reaction mixture was stirred for 48 h at 30 °C in a water bath. The yellowish white precipitate was filtered off and dried in vacuum over $CaCl_2$. The orange and faint yellow solid complexes of $[ZrO(GFLX)_2H_2O]Cl_2{\cdot}14H_2O$ and $[UO_2(GFLX)_3](NO_3)_2{\cdot}6H_2O$ were prepared in a similar manner described above by using methanol and acetone as a solvents instead of ethanol and using $ZrOCl_2{\cdot}8H_2O$ and $UO_2(NO_3)_2{\cdot}6H_2O$ in 1:2 and 1:3 M ratio. Unfortunately we were not able to obtained appropriate monocrystals to perform X-ray diffraction analysis. Qualitative black ring test for ionic nitrate using freshly prepared $FeSO_4$ solution and concentrated sulfuric acid, a black ring of $FeSO_4{\cdot}NO$ is formed led to the presence of nitrate as counter ions in the uranyl/GFLX complex and for the other complexes the qualitative reactions revealed the presence of chloride as counter ions. The three complexes were characterized by their elemental analysis, infrared, electronic, ^{1}H NMR and thermal analysis.

2.2. Antibacterial and antifungal activity

Antibacterial activity of the ligand and its metal complexes was investigated by a previously reported modified method of Beecher and Wong [25], against different bacterial species, such as *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) and antifungal screening was studied against two species, *penicillium* (*P. rotatum*) and *trichoderma* (*T.* sp.). 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) and for antifungal (3% Sucrose, 0.3% $NaNO_3$, 0.1% K_2HPO_4, 0.05% KCl, 0.001% $FeSO_4$, 2% 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 cork-borer. 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 and for seven days at 30 °C for fungi. The activity was determined by measuring the diameter of the inhibition zone (in mm). Growth inhibition was calculated with reference to the positive control, i.e., gatifloxacin.

3. Results and discussion

Gatifloxacin of Y(III), Zr(IV) and U(VI) were synthesized as solids of a color characteristics of the metal ion. The molar ratio for all complexes synthesized is M:GFLX = 1:2 for Y(III) and Zr(IV) and 1:3 for U(VI). The prepared complexes are hydrates with various degrees of hydration. The structures of the complexes suggested from the elemental analysis agree well with their proposed formula (Table 1). The found values of elemental analysis agree well with the calculated percentage of C, H, N and halogen data are in a well agreement with each other and prove the molecular formulas of the prepared complexes. The physical characteristics of these complexes are given in Table 1. The molar conductance values of the complexes were found to be in the range from 133.12 to 332.8 S cm^2 mol^{-1} at 25 °C.

3.1. Infrared absorption studies

The infrared spectra of anhydrous gatifloxacin and its complexes are listed in Table 2, Fig. 1. The IR spectra of the complexes are compared with those of the free ligand in order to determine the coordination sites that may involved in chelation. All gatifloxacin metal complexes exhibit a broad band between 3444 and 3373 cm^{-1}, which corresponds to the vibration ν(O—H) as well as to N—H vibration of the piperazinyl moity [2,17,26–28]. The N—H vibration of the piperazinyl appears in the region of 2591–2343 cm^{-1}, it indicates that the carboxylic group is deprotonated and the molecules exists in zwitterionic form with two of the hydrogen atoms attached to N-3 forming donor hydrogen bonds with water molecules [29]. The valence vibration of the carboxylic stretch ν(C=O) and the pyridone stretch ν(C=O) for free gatifloxacin were found at 1724 and 1635 cm^{-1} [30]. These bands disappears in the complexes which indicative of the involvement

Table 1
Elemental analysis and physicochemical parameters data of gatifloxacin and its metal complexes.

Complexes M.Wt. (M.F.)	Yield%	mp (°C)	Color	Content (calculated) found					Λ (S cm^2 mol^{-1})
				% C	% H	% N	%M	%Cl	
GFLX 375.16 ($C_{19}H_{22}N_3O_4F$)	–	158	White	(60.79) 60.75	(5.91) 5.91	(11.19) 11.17	–	–	−8.32
$[Y(GFLX)_2(H_2O)Cl]Cl_2{\cdot}11H_2O$ 1161.4 ($C_{38}H_{68}N_6O_{20}F_2Cl_3Y$)	85.20	>360	Yellowish white	(39.26) 39.16	(5.86) 5.80	(7.23) 7.23	(7.66) 7.65	(9.17) 9.11	267.28
$[ZrO(GFLX)_2H_2O]Cl_2{\cdot}14H_2O$ 1198.22 ($C_{38}H_{74}N_6O_{24}F_2Cl_2Zr$)	52.48	300	Orange	(38.06) 38.00	(6.18) 6.18	(7.01) 7.00	(7.61) 7.61	(5.93) 5.92	332.8
$[UO_2(GFLX)_3](NO_3)_2{\cdot}6H_2O$ 1627 ($C_{57}H_{78}N_{11}O_{26}F_3U$)	64.66	260	Faint yellow	(42.04) 41.98	(4.79) 4.70	(9.47) 9.46	(14.63) 14.62	 –	133.12