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Synthesis and spectroscopic studies of levofloxacin uni-dentate complexes of Ru(II), Pt(IV) and Ir(III): Third generation of quinolone antibiotic drug complexes

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ABSTRACT

The monobasic unidentate levofloxacin (LEV; (S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-7H-pyrido[1,2,3-de]-1,4—benzoxazine-6-carboxylic acid) complexes of Ru(III), Pt(IV) and Ir(III) were prepared and well discussed using elemental analyses (CHN), molar conductance, infrared, electronic, effective magnetic moment, ^{1}H-NMR, X-ray powder diffraction, scanning electron microscopy, transmittance electron microscopy and thermogravimetric (TG/DTG) analyses. The IR and electronic spectra of LEV complexes with their assignments were discussed in details which were confirmed that LEV is binding to the metal ions as a neutral unidentate ligand through the nitrogen atom of 4-methylpiperazin-1-yl moiety. The molar ratio of Ru(III) and Ir(III) chelates is 1:3 (Metal: LEV), while Pt(IV) complex has a 1:2 M ratio. The general formulas of LEV complexes have been designed as $[M(L)_n(Cl)_x]\cdot yH_2O$ ((**1**) M = Ru^{3+}, L: LEV, $n = 3, x = 3, y = 8$; (**2**) M = Pt^{4+}, L: LEV, $n = 2$, $x = 4, y = 4$ and (**3**) M = Ir^{3+}, L: LEV, $n = 3, x = 3, y = 6$. The X-ray powder diffraction was used as technique to estimate the particle size of LEV complexes. Thermogravimetric analysis (TG-DTG) was utilized to identify the presence of coordinated, uncoordinated water molecules, mass losses and residual products.

1. Introduction

The levofloxacin drug (LEV; Fig. 1) was considering as a one of the 3rd generation of quinolone drug families that has been a broad spectrum antibiotic drug against bacteria which responsible for respiratory, urinary tract, gastrointestinal, and abdominal infections [1,2]. The LEV drug has been effective against G(+) rather than G(−) bacteria [3,4]. The metal ions play an important role in the branch of medicinal chemistry upon the chelation towards various antibiotic drugs that led to change the antimicrobial potent activities. Metallo-antibiotics binding with proteins, DNA, lipids and RNA helping to recruit new and specific targets [5–8]. The quinolones acts as antibacterial agents by inhibition of both DNA-gyrase (topoisomerase) and DNA topoisomerase enzymes [9,10]. Quinolones interacted with the enzyme-DNA complex, forming a drug-enzyme-DNA complex which blocks progression and the replication process [11–14]. Quinolones were formed metal chelates due to their capacity to binding with metal ions. The quinolones act as bidentate ligand, unidentate ligand and bridging ligand [13–15]. The quinolones were coordinated in a bidentate manner, through one of the oxygen atoms of deprotonated carboxylic group and the ring carbonyl oxygen atom. Rarely, quinolones were acted as bidentate ligand coordinated via two carboxyl oxygen atoms or through both piperazinic nitrogen atoms [13,14]. Quinolones were also formed complexes as unidentate ligand coordinated to the metal ion through the terminal piperazinyl nitrogen [15].

The quinolone molecules possess two main sites of metal chelate formation [16–24]. The first of these, represented by the carbonyl and carboxyl groups in neighboring positions, this was the most common coordination mode in the quinolone chelates. Quinolones have been interacted with some divalent cations like (Mg^{2+}, Ca^{2+}, Cu^{2+}, Zn^{2+}, Fe^{2+}, Co^{2+}), that forming chelates with different molar ratios of 1:1 or 1:2 (metal: ligand) or with trivalent cations ($A1^{3+}$, Fe^{3+}), forming chelates with 1:1, 1:2 or 1:3 (metal: ligand stoichiometry). A higher stoichiometry (1:4) was found in complexes with Bi^{3+} [16–18]. The general structures of the quinolones chelates with divalent cations have been 1:2 (metal: ligand) molar ratio. The number of coordinated quinolone ligands depends on the pH media as well as type of solvents. Thus, in the more acidic region, a 1:1 complex was favored, whereas 1:2 complexes were the main species at higher pH values [16]. In literature survey, there were numerous studies regarding the complexation between quinolone drugs and metal ions [19–30].

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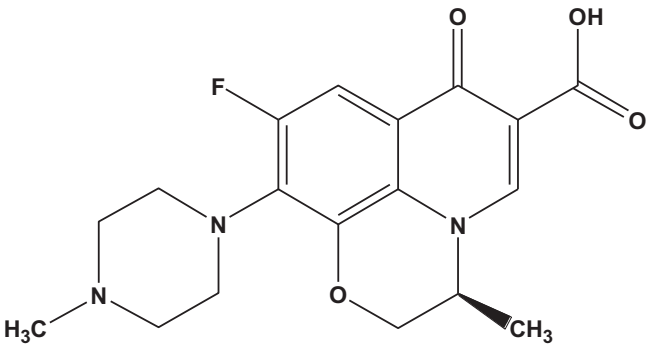

Fig. 1. Structure of levofloxacin antibiotic drug (LEV).

Literature survey has been included the chelation behaviors of levofloxacin (LEV) which can be summarized as follows:

M^{n+}:LEV ratio	1:1	$[PdCl_2(L)]$, $[AuCl_2(levo)]Cl$ $[M(levo)_2(H_2O)_2]\cdot nH_2O$(M=Mn, Co, Ni, Cu, Zn(II))	[31–36]
	1:2	$[Zn(levo)_2(H_2O)_2]$, $[Pt(levo)_2]$	
	1:3	–	

It's much less common for the coordination to happen by way of the piperazine nitrogen atoms. The literature contains only few papers about the coordination between metal ions and fluoroquinolone through the nitrogen atoms of the piperazine ring [15,20,25].

In the literature survey, there was only one example of a Ru(III) complex towards LEV drug [37], with formula $[Ru(levofx)_2Cl_3(DMSO)]DMSO(H_2O)_8$ that LEV ligand was coordinated to Ru(III) as a neutral unidentate ligand through the $N^4{}_{(piperazyl)}$—CH_3 atom. This paper aims to study the interactions between different metal ions (e.g. Ru(III), Pt(IV) and Ir(III)) and levofloxacin drug in the neutralization manner. These complexes were characterized using spectroscopic, and thermal analyses. The complexation behavior of LEV complexes with Ru(III), Pt(IV) and Ir(III) have not been reported yet, to the best of our knowledge.

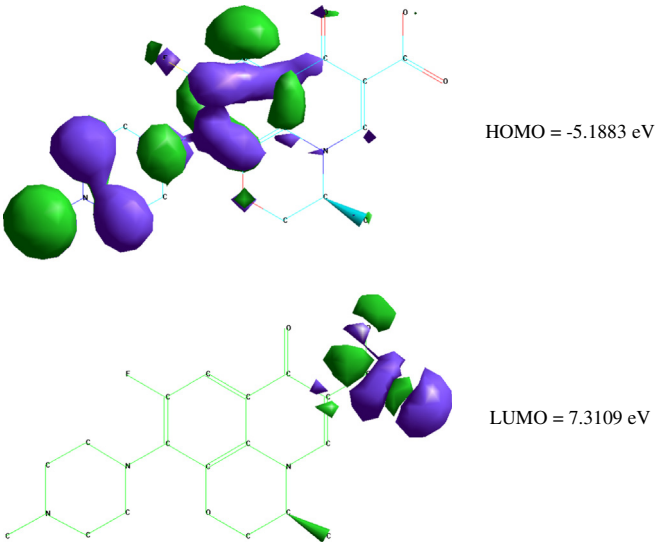

Fig. 2. HOMO and LUMO structure of LEV free drug.

Table 1
The quantum chemical parameters of LEV drug chelate.

Parameters	LEV
Total energy (a.u)	−153
Binding energy (a.u)	−3.78
Heat formation (a.u)	2.07
Electronic energy (a.u)	−1105
Dipole moment/debye	13.32
E_{HOMO} (eV)	−5.188
E_{LUMO} (eV)	7.311
ΔE (eV)	12.50
χ (eV)	−1.06
η (eV)	6.25
σ (eV)	0.16
P_i (eV)	1.06
S (eV)	0.08
ω (eV)	0.09
ΔN_{max} (eV)	−0.169

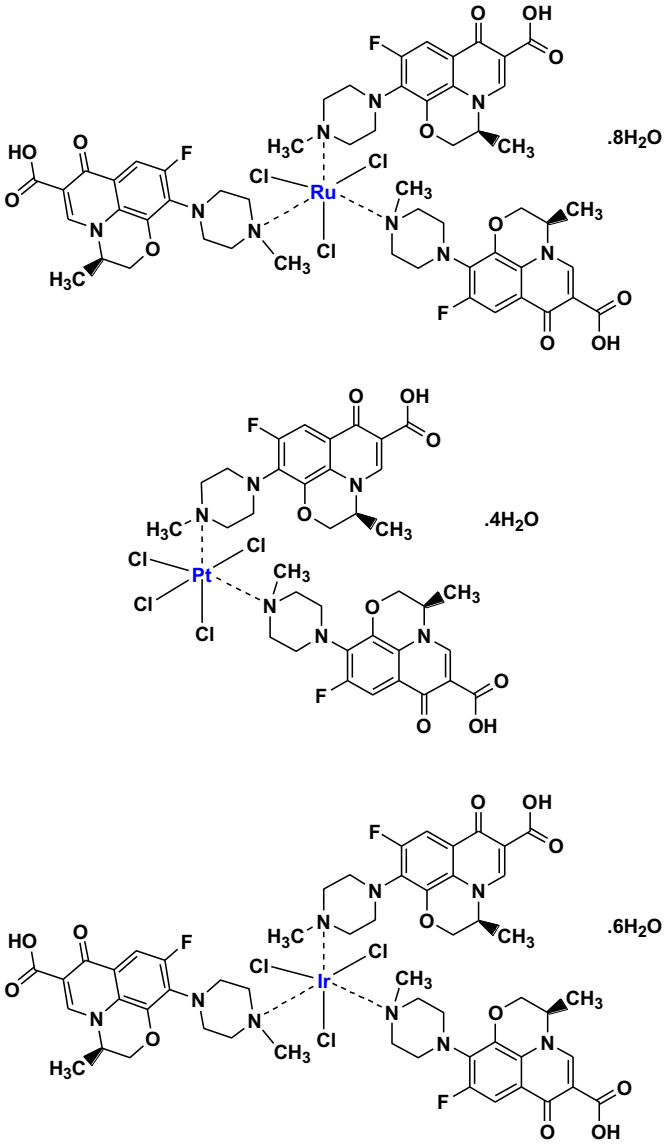

Fig. 3. Speculated structures of Ru(III), Pt(IV) and Ir(III) LEV complexes **1**–**3**.