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Synthesis, spectroscopic, thermal, biological, morphological and molecular docking studies of the different quinolone drugs and their cobalt(II) complexes

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ABSTRACT

New six cobalt(II) complexes **1**–**6** with four generation of quinolone drugs (nalidixic acid (Nal), oxolonic acid (Oxo), pipemidic acid (Pip), lomefloxacin (Lom), pefloxacin mesylate (Pef) and levofloxacin (Lev)) have been synthesized in methanol medium, and the general formula was designed as $[Co(L)_2(Cl)_2(H_2O)_2]\cdot 4H_2O$ (L = Nal (**1**), Oxo (**2**), Pip (**3**), Lom (**4**), Pef (**5**), and Lev (**6**)). The Co(III) complexes were identified using micro–analytical, FT–IR spectroscopy, conductance data, effective magnetic moments, electronic UV–vis spectra, and thermal analyses. The six quinolone drug chelates acts as uni–dentate via nitrogen atom of pyridone/piperazyl moiety. Electronic spectroscopic tools are in agreement with an octahedral geometrical structure. Thermal degradation analyses TG–DTG in nitrogen gas environmental are discussed the number and location of water molecules. The thermal decomposition process is completely in 3–4 steps, that the first step is responsible to loss of four uncoordinated water molecules. The stabilities of Co(II) complex **1**–**6** were studied dependent on activations of energy E*, entropy ΔS*, enthalpy ΔH* and Gibbs free energy ΔG* that have been estimated using Coats–Redfern and Horowitz–Metzeger non–isothermal methods. Molecular docking was used to predict the binding between some quinolone drugs with the receptor of breast cancer mutant *3hb5*-oxidoreductase. The structural view of the synthesized cobalt(II)-quinolone nanoparticles has been documented with the help of transmission electron microscope (TEM). The synthesized metal chelates have been screened in vitro antibacterial activity against bacteria, gram-positive (*Staphylococcus aureus*) and gram-negative (*Escherichia coli*) and two strains of fungus (*Aspergillus flavus* and *Candida albicans*). The cobalt(II) chelates were shown to possess more antibacterial activity than the free chelates.

1. Introduction

The fluoroquinolones drugs are an essential kind of antibacterial, and widely used in clinical application [1,2]. In 1986, fluoroquinolones were introduced and they were modified from the class of antibiotics known as quinolones in early 1960. Quinolones consist of bicyclic ring structure and different functional groups are substituted at position N–1 carboxyl group is substituted at 3 positions, a keto group at 4 positions, fluorine atom at 6 positions and piperazinyl group or a methyl piperazinyl group at C–7 position. Presences of different functional group at N–1 or at C–7 positions influence both microbiological and pharmacokinetic properties [3]. Although, the new generation of quinolones achieved significant improvements in terms of potency, spectrum, and pharmacokinetics, but these agents faced a growing incidence of resistance especially to Gram-positive bacteria (e.g., *Staphylococcus aureus*, Streptococcus pneumonia, and Enterococci) [4,5]. Historically, since the discovery of norfloxacin and ciprofloxacin in the early 1980s, most of the attentions have been focused on the basic group at the C-7 position of quinolones which greatly influences their spectrum, potency, and safety [6]. Structure–activity relationship studies of quinolones have indicated that the 5– or 6–membered cyclic amines such as pyrrolidine or piperazine have been proven to be the optimal substituents for chemical modification. Piperazine substituent at the C–7 position of quinolone core structure has resulted in a large number of marketed antibacterial agents including norfloxacin, ciprofloxacin, enoxacin, pefloxacin, ofloxacin, levofloxacin, fleroxacin, lomefloxacin, sparfloxacin, and gatifloxacin [5,7]. Quinolones form metal complexes due to their capacity to bind metal ions. In their metal complexes, the quinolones can act as bidentate ligand, as unidentate ligand and as bridging ligand. Frequently, the quinolones are coordinated in a bidentate manner, through

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one of the oxygen atoms of deprotonated carboxylic group and the ring carbonyl oxygen atom (Fig. 1a). Rarely, quinolones can act as bidentate ligand coordinated via two carboxyl oxygen atoms (Fig. 1b) or through both piperazinic nitrogen atoms (Fig. 1c). Quinolones can also form complexes as unidentate ligand coordinated to the metal ion through by terminal piperazinyl nitrogen (Fig. 1d) [8].

Literature survey included the chelation behaviors of some quinolones drugs (nalidixic acid (Nal), oxolonic acid (Oxo), pipemidic acid (Pip), lomefloxacin (Lom), pefloxacin mesylate (Pef), and levofloxacin (Lev) that can be summarized as follows:

Quinolone drug	Molar ratio	Formula	Reference
Nalidixic acid	1:1	$[Ca(Ndx)(Cl)(NH_3)(H_2O)_2]$	[9–12]
		$[Mg(Ndx)(Cl)(NH_3)(H_2O)_2]\cdot 20H_2O$	
		$[Zn(Ndx)(SO_4)(NH_4)(H_2O)]\cdot 3H_2O$	
		$[Fe(Ndx)(NO_3)_2(NH_3)_2]\cdot 2H_2O$	
		$[VO(Ndx)(SO_4)(NH_4)]\cdot 2H_2O$	
		$[Ca(nix)(Cl)(H_2O)_3]\cdot H_2O$	
		$[Fe(nix)(Cl)_2(H_2O)_2]\cdot 3H_2O$	
		$[Pd(nix)(Cl)(H_2O)]$, $[Au(nix)(Cl)_2]$	
	1:2	[Ag(Nal)2]	
	1:3	$[Fe(Nal)_3]$	
Oxolonic acid	1:1	–	[13–18]
	1:2	$[Cu(oxo)_2(H_2O)]$, $[Ni(oxo)_2(H_2O)_2]$	
		$[Zn(oxo)_2(H_2O)_2]$, $[VO(oxo)_2(H_2O)]$	
		$[Mn(oxo)_2(H_2O)_2]$, $[Co(oxo)_2(H_2O)_2]$	
		$[Ni(oxo)_2(H_2O)_2]$, $[Zn(oxo)_2(H_2O)_2]$	
		$[Cd(oxo)_2(H_2O)_2]$, $[MoO_2(oxo)_2]$,	
		$[UO_2(oxo)_2]$	
	1:3	$[Fe(oxo)_3]$	
Pipemidic acid	1:1	$[Fe\ (PPA)(HO)_2(H_2O)]$	[19–21]
	1:2	$[VO(PPA)_2(H_2O)]$, $[Mn(PPA)_2(H_2O)_2]$	
		$[Co(PPA)_2(H_2O)_2]$, $[Ni(PPA)_2(H_2O)_2]$	
		$[Zn(PPA)_2(H_2O)_2]$, $[MoO_2(PPA)_2]$	
		$[Cd(PPA)_2(H_2O)_2]$, $[UO_2(PPA)_2]$,	
		$[Cu(PPA)_2(H_2O)]$	
	1:3	$[Fe(PPA)_3]$	
Lomefloxacin	1:1	$[Cr(LFX)(H_2O)_4]Cl_3$, $[Mn(LFX)(H_2O)_4]Cl_2$	[22–24]
		$[Fe(LFX)(H_2O)_4]Cl_3\cdot H_2O$, $[Co(LFX)(H_2O)_4]Cl_2$	
		$[Ni(LFX)(H_2O)_4]Cl_2\cdot H_2O$,	
		$[Cu(LFX)(H_2O)_4]Cl_2\cdot 2H_2O$	
		$[Zn(LFX)(H_2O)_4]Cl_2$, $[Th(LFX)(H_2O)_4]Cl_4$	
		$[UO_2(LFX)(H_2O)_2](NO_3)_2$	
	1:2	$[Y(LFX)_2Cl_2]Cl\cdot 12H_2O$,	
		$[ZrO(LFX)_2Cl]Cl\cdot 15H_2O$	
	1:3	$[Bi(LFX)_3(H_2O)_2]$, $[UO_2(LFX)_3](NO_3)_2\cdot 4H_2O$	
Pefloxacin	1:1	–	[22,25]
	1:2	$[Zn(Pf)_2(H_2O)]\cdot 2H_2O$, $[Pt(Pf)_2]$	
	1:3	$[Bi(Pf)_3(H_2O)_2]$	
Levofloxacin	1:1	$[PdCl_2(L)]$, $[AuCl_2(levo)]Cl$	[26–31]
	1:2	$[M(levo)_2(H_2O)_2]\cdot nH_2O$(M = Mn, Co,	
		Ni, Cu, Zn(II))	
		$[Zn(levo)_2(H_2O)_2]$, $[Pt(levo)_2]$	
	1:3	–	

This paper was discussed the influence of complexation between some kinds of quinolone drugs with cobalt(II) chloride hydrated in methanol solvent with 1:2 ratio. These complexes have been prepared and discussed using micro–analytical, FT–IR, conductance, magnetic, UV–vis, and thermo-gravimetric analyses. Molecular docking theoretical program for the breast cancer mutant *3hb5*-oxidoreductase and biological assessment against two kinds of bacteria and two types of fungi were employed.

2. Experimental

2.1. Chemical materials

Nalidixic acid (Nal), oxolonic acid (Oxo), pipemidic acid (Pip), lomefloxacin (Lom), pefloxacin mesylate (Pef), and levofloxacin (Lev) were purchased from Aldrich–Sigma. Cobalt(II) chloride hexahydrate and reagents (methanol and dimethylsulfoxide) were purchased from Aldrich chemical company, these chemicals and solvents were used without further purification.

2.2. Synthesis of cobalt(II) quinolones complexes

A warm methanolic solution (0.2 mmol, 20 mL) of nalidixic acid (46 mg), oxolonic acid (52.3 mg), pipemidic acid (60.7 mg), lomefloxacin (59 mg), pefloxacin mesylate (93.1 mg), and levofloxacin (42.5 mg) was added to an methanolic solution (20 mL) of $CoCl_2\cdot 6H_2O$ (0.1 mmol, 23.9 mg) and the reaction mixtures were refluxed for 3 h. The solutions were filtered and left for slow evaporation. After a three days a red-pink microcrystalline products were deposited, collected with filtration, washed with methanol and dried.

2.2.1. $[Co(Nal)_2(Cl)_2(H_2O)_2]\cdot 4H_2O$ (**1**) complex

Yield: 74%. Anal. calc. for complex (**1**) ($C_{24}H_{39}Cl_2CoN_4O_{12}$) (MW = 705.43): C, 40.86; H, 5.57; N, 7.94. Found: C, 40.65; H, 5.34; N, 7.86%. The complex is soluble in DMSO and DMF and is a non-electrolyte.

2.2.2. $[Co(Oxo)_2(Cl)_2(H_2O)_2]\cdot 4H_2O$ (**2**) complex

Yield: 80%. Anal. calc. for complex (**2**) ($C_{26}H_{34}Cl_2CoN_2O_{16}$) (MW = 760.39): C, 41.07; H, 4.51; N, 3.68. Found: C, 41.00; H, 4.50; N, 3.55%. The complex is soluble in DMSO and DMF and is a non-electrolyte.

2.2.3. $[Co(Pip)_2(Cl)_2(H_2O)_2]\cdot 4H_2O$ (**3**) complex

Yield: 67%. Anal. calc. for complex (**3**) ($C_{28}H_{46}Cl_2CoN_{10}O_{12}$) (MW = 844.56): C, 39.82; H, 5.49; N, 16.58. Found: C, 39.54; H, 5.42; N, 16.47%. The complex is soluble in DMSO and DMF and is a non-electrolyte.

2.2.4. $[Co(Lom)_2(Cl)_2(H_2O)_2]\cdot 4H_2O$ (**4**) complex

Yield: 74%. Anal. calc. for complex (**4**) ($C_{34}H_{50}Cl_2CoF_4N_6O_{12}$) (MW = 940.63): C, 43.41; H, 5.36; N, 8.93. Found: C, 43.21; H, 5.17; N, 8.85%. The complex is soluble in DMSO and DMF and is a non-electrolyte.

2.2.5. $[Co(Pef)_2(Cl)_2(H_2O)_2]\cdot 4H_2O$ (**5**) complex

Yield: 71%. Anal. calc. for complex (**5**) ($C_{36}H_{60}Cl_2CoF_2N_6O_{18}S_2$) (MW = 1096.86): C, 39.42; H, 5.51; N, 7.66. Found: C, 39.32; H, 5.42; N, 7.54%. The complex is soluble in DMSO and DMF and is a non-electrolyte.

2.2.6. $[Co(Lev)_2(Cl)_2(H_2O)_2]\cdot 4H_2O$ (**6**) complex

Yield: 68%. Anal. calc. for complex (**6**) ($C_{36}H_{52}Cl_2CoF_2N_6O_{14}$) (MW = 960.67): C, 45.01; H, 5.46; N, 8.75. Found: C, 44.95; H, 5.37; N, 8.67%. The complex is soluble in DMSO and DMF and is a non-electrolyte.

2.3. Instrumentations and analytical measurements

The micro–analytical analyses of %C, %H and %N percentages were calculated using a Perkin Elmer CHN 2400 (USA). The molar conductivities of Co(II) quinolone complexes with 10^{-3} mol/cm^3 concentration in DMSO solvent were measured by Jenway 4010 conductivity meter. The UV–vis absorption spectra were recorded in DMSO solvent within 800–200 nm range using a UV2 Unicam UV/Vis Spectrophotometer fitted with a quartz cell of 1.0 cm path length. The infrared spectra with KBr discs were recorded on Bruker FT-IR Spectrophotometer (4000–400 cm^{-1}). Magnetic moments were calculated using the Magnetic Susceptibility Balance, Sherwood Scientific, Cambridge Science Park, Cambridge, England, at Temp 25 °C. The thermal studies TG/DTG–50H were carried out on a Shimadzu thermo-gravimetric analyzer under nitrogen till 800 °C. The transmission electron microscopy images (TEM) were performed using JEOL 100s microscopy.