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Original article

Synthesis and antitubercular activity of palladium and platinum complexes with fluoroquinolones

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ABSTRACT

The fluoroquinolones are an important family of synthetic antimicrobial agents being clinically used over the past thirty years. In addition, some fluoroquinolones have been used in the development of anti-cancer drugs, and others have demonstrated anti-HIV activity. Furthermore, there has been some additional work investigating the effect of metal ions on biological activity.

Aiming to obtain novel palladium(II) and platinum(II) complexes that exhibit biological activity, we have synthesized complexes using fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, and gatifloxacin) as ligands. The compounds were characterized using IR and NMR spectroscopy, thermogravimetric and elemental analyses.

The complexes show activity against *Mycobacterium tuberculosis* strain $H_{37}Rv$. The minimal inhibitory concentration (MIC) of the complexes was determined.

1. Introduction

The fluoroquinolones constitute an important class of synthetic antimicrobial agents which have been subjects of intensive study [1]. Norfloxacin, which was patented in 1978, can be cited as the first fluoroquinolone to present potent antibacterial activity [1,2]. Numerous other fluoroquinolones have been synthesized and evaluated, most notably ciprofloxacin, ofloxacin, levofloxacin, sparfloxacin and gatifloxacin (Fig. 1). These possess a broad spectrum of activity against various pathogenic microorganisms, which are resistant to aminoglycosides, penicillins, cephalosporins, tetracyclines and other antibiotics. This class of compounds, when compared to existing bactericidal drugs, shows improved pharmacokinetic properties and a broad spectrum of activity against parasites, bacteria, and mycobacteria, including resistant strains [3,4].

Metal coordination to biologically active molecules can be used as a strategy to enhance their activity and overcome resistance. For instance, metal complexes of thiosemicarbazones can be more active than the free ligand, or they can be employed as a vehicle for activation of the ligand as the cytotoxic agent [5–7]. Pd(II) [8] and Pt(II) [9] complexes with antibiotics of the tetracycline family are more potent against *Escherichia coli* HB101/pBR322, a bacterial strain resistant to tetracycline. Quinolones are particularly interesting to apply this strategy to due to their ability to coordinate metal ions. Thus, numerous studies regarding the interaction between quinolones with metallic cations have been reported in the literature [10–13]. Some of these metal complexes have been tested successfully for antibacterial activity [14–19]. The effect of the metallic ion on the antibacterial activity of norfloxacin has been previously reported. Fe(III) and Zn(II) complexes were obtained and they showed increased activity over norfloxacin against Gram negative *E. coli* and *Bacillus dysenteriae* [20].

Jain et al. [21] have reported a Co(II) complex with sparfloxacin which is more potent against several pathogenic bacteria than sparfloxacin. In a similar approach, Saha et al. [22] have shown that the complex of Cu(II) and ciprofloxacin presents a significant enhancement in antitubercular activity. Presumably, the formation of the complex facilitates the intracellular transport of the drug, while Cu(II) can be easily reduced to Cu(I) resulting in oxidized species which are lethal to the microorganism. Many other examples are available: the complex formed between norfloxacin and silver can prevent bacterial infection during the treatment of burned skin [23]; the inhibition of *E. coli* with ciprofloxacin was increased in the presence of Al(III) [24] as well as others.

Platinum complexes are well-known antitumor agents, cisplatin and carboplatin being first lines of treatment for many types of cancer. Numerous other platinum complexes have been synthesized and tested, including platinum(IV) and multinuclear complexes [25,26].

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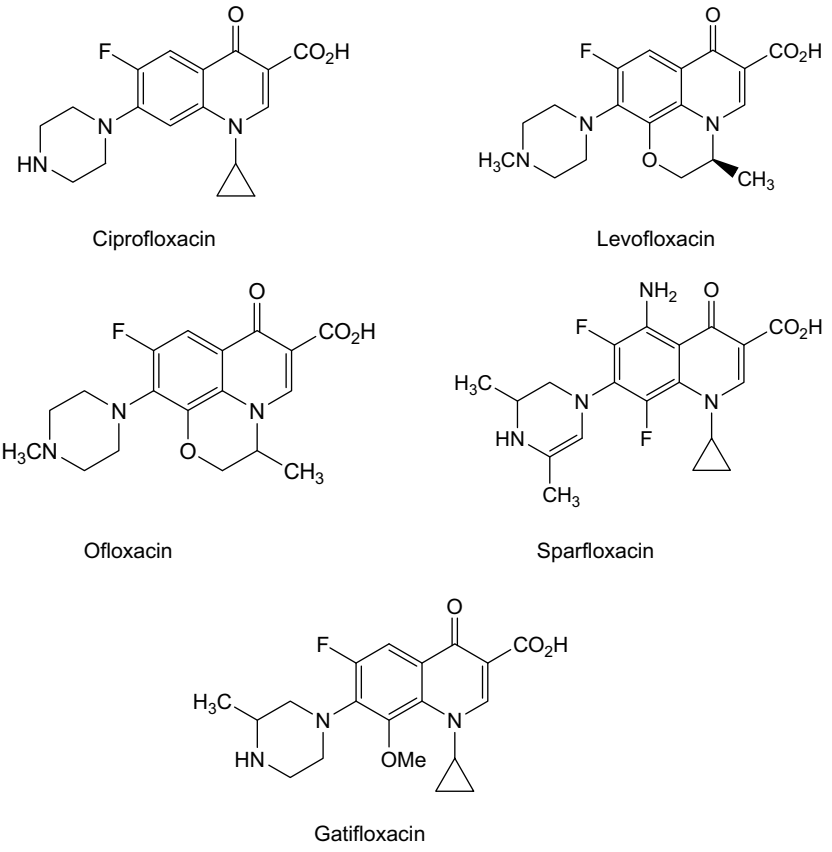

Fig. 1. Fluoroquinolones used as ligands.

The biological activity of palladium complexes has not been studied as exhaustively but can be exemplified with several literature reports. Palladium complexes with thiosemicarbazones have shown antitumor activity [27–30]. Some of them are active even in cell lines resistant to cisplatin and others present less nephrotoxicity than cisplatin.

Some palladium and platinum complexes also show antibacterial activity. For instance, recent studies report Pd(II) and Pt(II) complexes with tetracyclines that exhibit antibacterial activity. Interestingly, these complexes are active against tetracycline resistant bacteria [8].

The antibacterial and antifungal properties of palladium and platinum complexes with thiosemicarbazones have also been shown [31]. These complexes are lethal towards *Staphylococcus aureus* and *Candida albicans*.

Usually the fluoroquinolones act as bidentate ligands binding to the metallic ion through the carboxylate and carbonyl oxygens. The metallic ion can form a stable 6-member chelate ring with a slightly distorted octahedral geometry as was observed for complexes with metal ions such as Co(II), Ni(II), Zn(II), Cd(II), Mn^{II} and Cu^{II} [6,17,32,33]. This site seems to be preferred for most metal ions. Coordination of the fluoroquinolones with metal ions by way of the piperazine nitrogen atoms is much less common. Recently, our group described the synthesis of platinum complexes with fluoroquinolones as ligands [34]. We have shown that, contrary to most other known metal ion complexes, the fluoroquinolones ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, and gatifloxacin coordinate to platinum(II) ion in a bidentate fashion via the piperazine nitrogen atoms.

Palladium complexes with fluoroquinolones have not been reported yet, to the best of our knowledge.

In this context, the present work describes the synthesis of palladium(II) complexes having as ligands ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, and gatifloxacin. For the characterization of the compounds the following spectroscopic and analytical techniques were employed: IR and NMR spectroscopy, and thermogravimetric and elemental analyses.

2. Results and discussion

The complexes $[PdCl_2(L)]$ (where L = ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, and gatifloxacin) were obtained by reaction between the respective ligand and the palladium salt $K_2[PdCl_4]$ in aqueous medium. The desired product is immediately formed as an amorphous precipitate upon addition of the ligand to the palladium salt.

The platinum complexes were obtained in a similar fashion by reaction between the respective ligand and the platinum salt $K_2[PtCl_4]$, according to the previously reported procedure [34].

The elemental analyses were in good agreement with the proposed formulas for the five compounds.

The reactions involved in the formation of both palladium and platinum complexes are well-known substitution reactions of square-planar complexes which are favored by the trans effect of the chloride ligands. However, when comparing the formation of the complexes, it was observed that the palladium(II) complexes formed after a few minutes while the formation of platinum(II) complexes occurs more slowly. The coordination sites were found to be different for each metal, as is discussed within this paper and in previous work [34].

In the majority of the metal–fluoroquinolone complexes described in the literature, the ligands coordinate in a bidentate

manner via the carboxylic and the carbonyl oxygens, where the metallic ion forms a stable six-membered ring chelate. In these complexes it is possible to observe the disappearance of the absorption band in the region around 1700 cm^{-1} due to the free carboxylic acid indicating the formation of a bond between the metallic ion and the carboxylate oxygen [13]. This behavior was observed for the palladium(II) complexes as well, contrary to the platinum(II) complexes. For the Pd(II) complexes, two characteristic absorption bands around 1600 and 1400 cm^{-1} were observed which can be attributed to asymmetric and symmetric ν(O–C–O), respectively [13,35]. The carboxylate group can bind to metal ions in a monodentate, bidentate, or bridging manner. The frequency difference [$\Delta\nu = \nu_{as}(COO^-) - \nu_s(COO^-)$] can be used as an indication of the binding mode of the carboxylate [36,37]. If $\Delta\nu$ is greater than 200 cm^{-1}, this group is probably bound in a monodentate way, as was observed for the complexes reported herein.

The absorption band in the 1600 cm^{-1} region attributed to the ketone group in the free ligand spectra is shifted to 1580–1570 cm^{-1} in the palladium complexes which is good indication that this group is coordinated to the Pd(II) ion [13]. In the 3400 cm^{-1} region, one observes a broad absorption band due to the OH stretching of the water molecule, since, according to the elemental analysis and thermogravimetric studies, all the obtained complexes contain water of crystallization.

Table 1 presents the main IR absorption obtained for the palladium(II) complexes and Fig. 2 shows the IR spectra of free ciprofloxacin and its palladium complex.

^1H and ^{13}C NMR spectra were acquired for some of the synthesized palladium(II) complexes but were not very helpful since only small shifts were found in the spectra of the complexes compared to the free ligands. The same behavior was reported by Sánchez et al. [38] who found only small shifts in the ^1H NMR spectra of the Al(III), Mg(II), Ca(II), and Fe(II) complexes with ciprofloxacin and ofloxacin. In the study of Gao et al. [20] regarding the synthesis and characterization of norfloxacin complexes with Fe(III), Co(II), and Zn(II), it was reported that in all of the ^1H NMR spectra of the complexes, the chemical shift values were only slightly changed, being on the order of 0.2 ppm.

Based upon analysis of the results obtained, it was possible to identify that in the palladium(II) complexes with the fluoroquinolones used in this work, the coordination of the ligand to the metal occurs in the most usual way, i.e., via the ketonic and carboxylic oxygen atoms. Fig. 3 shows the proposed structure for complex **1**. Complexes **2**–**5** should present similar structures.

Thermogravimetric studies were performed for the complexes reported herein and they agree with the proposed formulas.

The t.g. curve for complex **2** shows three weight losses. The first, in the 40–140 °C range, corresponds to the loss of two water molecules (Calcd: 6.28%, Found: 6.75%). The second and the third inflections, near 400 and 480 °C, respectively, are attributed to complex thermal decomposition. The final mass of the residue agrees with 1 mol of PdO (Calcd: 21.29%, Found: 21.89%). The identity of the residue was confirmed through X-ray powder diffraction at 750 °C and compared to data available at the International Center for Diffraction Data (PdO ICDD number 41-1107). The t.g. curves for the other complexes follow a very similar pattern.

Table 1
Main IR absorptions (cm^{-1}).

Complex	ν_{COOH}	ν_{C-Oas}	$\nu_{C=O}$	ν_{C-Os}
1	–	1628	1581	1384
2	–	1624	1579	1397
3	–	1624	1586	1401
4	–	1635	1578	1372
5	–	1629	1574	1322

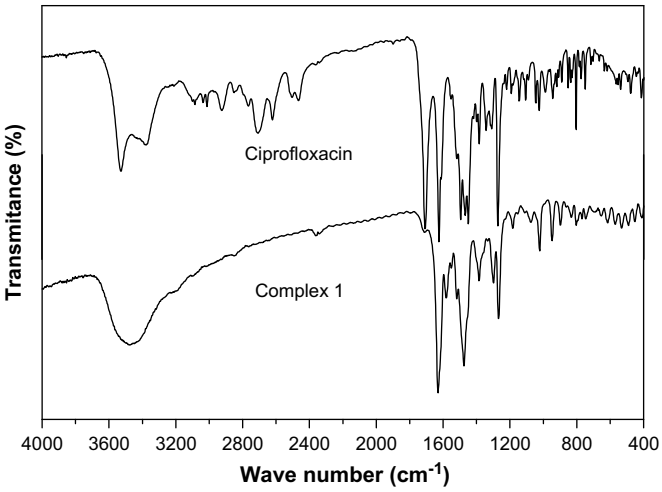

Fig. 2. IR spectra of free ciprofloxacin and its palladium complex.

The activity of the complexes against *Mycobacterium tuberculosis* virulent strain $H_{37}Rv$ was determined. The minimum inhibitory concentration (MIC) against *M. tuberculosis* was determined and results are presented in Table 2. Both, Pd(II) and Pt(II) complexes with sparfloxacin (**4** and **9**), were the most active within each series inhibiting bacterial growth at 0.31 μg/mL. The same MIC was found for the Pt(II) complex with gatifloxacin. On the other hand, the least active complexes of the series were the Pd(II) complex with ciprofloxacin and the Pt(II) complex with ofloxacin, which exhibited MIC = 1.25 μg/mL. Although the complexes have not shown better antitubercular activity than free gatifloxacin, in general all of the complexes exhibited good activity and, except complex **1**, all of them were more active than rifampicin.

Platinum complexes are well-established medicinal agents as anticancer agents and several palladium complexes have also been investigated for their antitumor properties. The use of palladium in medicinal chemistry could be interesting as a potentially less toxic alternative to platinum. The results reported herein indicate that both platinum and palladium complexes show potential antibacterial activity and their activity against other microorganisms should be investigated in order to collect more data that could allow the establishment of structure–activity relationships.

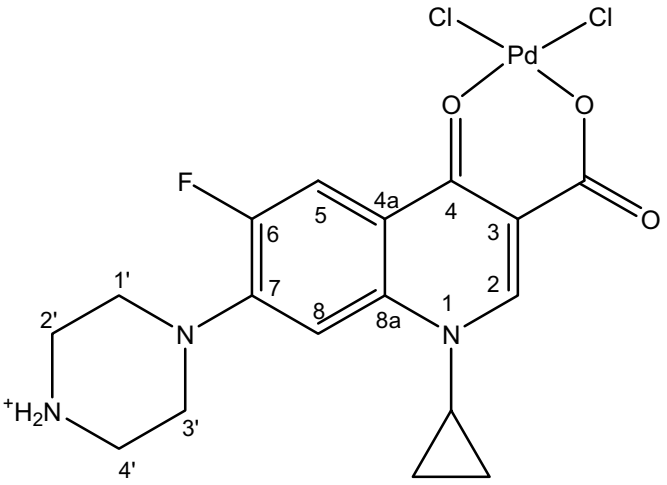

Fig. 3. Proposed structure for complex **1**.

Table 2
In vitro antitubercular activities.

Complex	MIC (μg/mL)
1	1.25
2	0.62
3	0.62
4	0.31
5	0.62
6	0.62
7	0.62
8	1.25
9	0.31
10	0.31
Rifampicin	1.0
Gatifloxacin	0.1

3. Conclusions

The fluoroquinolones react with Pd(II) and Pt(II) ions furnishing compounds *cis*-[MCl_2(L)]. The ligands coordinate to the palladium in the most common manner, i.e., in a bidentate fashion via the carboxylic and the carbonyl oxygens. Coordination to platinum occurs in a bidentate fashion via the piperazine nitrogen atoms, this type of coordination being considerably rare. Complexes with both metallic ions show good antitubercular activity.

4. Experimental

4.1. Materials and methods

All reagents and solvents were reagent grade unless otherwise stated and were used without prior purification.

Elemental analyses were performed at the State University of São Paulo, Brazil. Molar conductivity measurements were performed at RT in DMF 10^{-3} mol/L using a Digimed DM 31 conductivity meter. The IR spectra were acquired on a Bomen FT IR MB – 102 spectrophotometer using KBr pellets. ^{1}H NMR (300 MHz), and ^{13}C NMR (75 MHz) spectra were recorded on Bruker spectrometer and were obtained by dissolving the complexes in DMSO-d_6 or DMF-d_7. The chemical shifts were expressed as δ (ppm) from internal reference standard TMS (^{1}H NMR). Thermogravimetric analyses were performed at the Federal University of Minas Gerais on a TG-50 Mettle STARE, using 6 mg samples packed in an aluminum crucible. Samples were heated at 10 °C/min from room temperature to 800 °C, in a dynamic N_2 atmosphere (flow rate = 200 cm^3/min). The t.g. residues were analyzed in a Siemens D5000 X-ray diffractometer using a copper tube and radiation Cu Kα = 1.54178 Å, angle 2θ, ranging from 0 to 90 °C.

4.2. Synthesis of the complexes

Complexes **1**–**5** presenting the general formula [$PdCl_2$(L)] were prepared with L = ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, and gatifloxacin, respectively.

Appropriate quantities of the ligands (0.3 mmol) were dissolved or suspended in distilled water (5 mL) which were then added to solutions of $K_2[PdCl_4]$ (0.3 mmol; 0.097 g) in distilled water (5 mL). The ligands as the hydrochlorides (ciprofloxacin and levofloxacin) were completely soluble in water, while the other ligands (ofloxacin, sparfloxacin, and gatifloxacin) formed an aqueous suspension. For complexes **1** and **2**, a triethylamine solution (1 mol/L) was added dropwise, maintaining the pH around 7. Immediately after addition of the ligand, a precipitate formed. The reaction mixture remained stirring at room temperature for 48 h. The solids obtained were filtered under vacuum, washed with water, methanol and then dried. Yields: **1**: 0.14 g (86%), **2**: 0.15 g (87%), **3**: 0.13 g (78%), **4**: 0.14 g (80%), **5**: 0.13 g (76%).

1: Yellow solid. IR: (KBr, cm^{-1}) 3473, 3418, 1628, 1581, 1473, 1384, 1266, 1019, 947, 316, 302. Anal. Calc. For $C_{17}H_{18}N_3Cl_2FO_3Pd\cdot 2H_2O$: C, 37.50; H, 4.04; N, 7.72. Found: C, 37.05; H, 3.48; N, 7.21.

2: Brownish-yellow solid. IR: (KBr, cm^{-1}) 3466, 1624, 1579, 1515, 1462, 1397, 1271, 1089, 981, 800, 748, 328, 326. ^{1}H NMR (DMSO-d_6) δ: 8.97 (s, 1H, H-2); 7.54 (d, 1H, H-5); 4.90 (m, 1H, NH^+); 4.59 (m, 1H, CH_2–O); 4.39 (m, 1H, CH_2–O); 3.92 (m, 1H, CH); 3.41 (s, 4H, CH_2-1′; CH_2-3′); 2.85 (m, 1H, CH_2-4′); 2.77 (m, 1H, CH_2-4′); 2.61 (s, 3H, CH_3–N); 2.36 (s, 2H, CH_2-2′); 1.44 (d, 3H, CH_3–CH). ^{13}C NMR (DMSO-d_6) δ: 176.3 (C4); 166.1 (COOH); 157.2 (C2); 153.8 (C6); 146.2 (C8); 124.8 (C7); 120.0 (C8a); 106.7 (C4a); 103.3 (C3 and C5); 68.2 (O–*CH_2*); 59.8 (CH); 54.9 (C2′ and C4′); 49.5 (C1′ and C3′); 44.6 (N–*CH_3*); 17.9 (CH_3). Anal. Calc. For $C_{18}H_{20}N_3Cl_2FO_4Pd\cdot 2H_2O$: C, 37.63; H, 4.18; N, 7.32. Found: C, 38.28; H, 4.09; N, 6.96.

3: Yellow solid. IR: (KBr, cm^{-1}) 3474, 3031, 2851, 2751, 1624, 1586, 1515, 1465, 1401, 1275, 1091, 980, 799, 325, 322. ^{1}H NMR (DMSO-d_6) δ: 8.95 (s, 1H, H-2); 7.53 (d, 1H, H-5); 4.90 (m, 1H, NH^+); 4.56 (m, 1H, CH_2–O); 4.39 (m, 1H, CH_2–O); 4.15 (m, 1H, CH); 3.42 (m, 4H, CH_2-1′; CH_2-3′); 2.77 (m, 4H, CH_2-2′; CH_2-4′); 2.47 (s, 3H, CH_3–N); 1.46 (d, 3H, CH_3–CH). ^{13}C NMR (DMSO-d_6) δ: 176.3 (C4); 166.1 (COOH); 157.1 (C2); 153.8 (C6); 146.1 (C8); 124.7 (C7); 120.0 (C8a); 106.7 (C4a); 103.2 (C3 and C5); 68.2 (O–*CH_2*); 54.8 (C2′ and C4′); 54.5 (CH); 48.8 (C1′ and C3′); 44.6 (N–*CH_3*); 17.9 (CH_3). Anal. Calc. For $C_{18}H_{20}N_3Cl_2FO_4Pd\cdot H_2O$: C, 38.85; H, 3.96; N, 7.55. Found: C, 39.68; H, 4.29; N, 7.34.

4: Brownish-red solid. IR: (KBr, cm^{-1}) 3425, 3035, 2047, 1635, 1578, 1539, 1452, 1372, 1291, 826, 677, 354, 332. Anal. Calc. For $C_{19}H_{20}N_4Cl_2F_2O_3Pd\cdot H_2O$: C, 38.97; H, 3.76; N, 9.57. Found: C, 39.02; H, 3.28; N, 9.58.

5: Brown solid. IR: (KBr, cm^{-1}) 3419, 2974, 2041, 1629, 1574, 1512, 1445, 1322, 1281, 1062, 997, 938, 821, 541, 391, 327, 323. Anal. Calc. For $C_{19}H_{22}N_3Cl_2FO_4Pd\cdot H_2O$: C, 40.00; H, 4.21; N, 7.37. Found: C, 39.15; H, 4.53; N, 7.15.

Complexes **6**–**10** presenting the general formula [$PtCl_2$(L)] were prepared with L = ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin, and gatifloxacin, respectively, according to the previously reported procedure [34].

4.3. Determination of minimal inhibitory concentration

The activity of the complexes against *M. tuberculosis* virulent strain H_{37}Rv was determined in vitro as previously described [39]. The minimum inhibitory concentration (MIC), concentration that inhibits the colony forming ability of *M. tuberculosis* was determined by incorporating decreasing concentrations of the test compounds dissolved in dimethylsulfoxide in Middlebrook 7H9 agar medium. MIC values represent mean of three separate experiments.

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