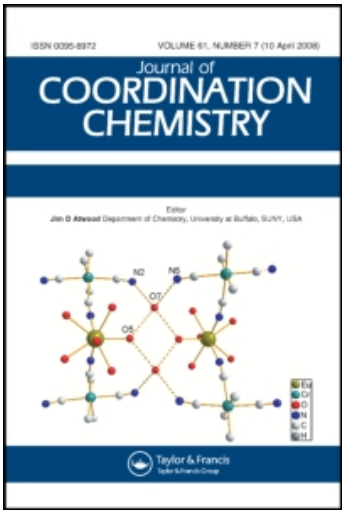

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Hydrothermal syntheses, crystal structures and antibacterial activities of two transition metal complexes with ciprofloxacin

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Hydrothermal syntheses, crystal structures and antibacterial activities of two transition metal complexes with ciprofloxacin

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Hydrothermal reactions of ciprofloxacin with $Co(OH)_2$, and with oxalate and $Fe(OH)_3$, yield $[Co(Cip)_2]\cdot 2H_2O$ (**1**) and $[Fe(H\text{-}Cip)\cdot(C_2O_4)]\cdot(H_2Cip)\cdot 5H_2O$ (**2**), which were characterized by elemental analysis, IR and single crystal diffraction analyses. Compounds **1** and **2** were screened for antibacterial activities against *Staphylococcus aureas*, *Escherichia coli*, *Candida albicans* and *Pseudomonas aeruginosa*.

Keywords: Ciprofloxacin; Iron; Cobalt; Crystal structure; Oxalate; Antibacterial activity

1. Introduction

The quinolones are a group of synthetic antibacterial agents structurally related to nalidixic acid, very active against aerobic Gram-negative microorganisms but less active against Gram-positive microorganisms [1]. They are extremely useful for the treatment of a variety of problems, including urinary tract infections, soft tissue infections, respiratory infections, bone-joint infections, sexually transmitted diseases, prostatitis, acute bronchitis and sinusitis [1]. The most active representatives of this class, designated as "fluoroquinolones," include ciprofloxacin [H-cip = 1-cyclopropyl-6-fluoro-1, 4-dihydro-4-oxo-7(1-piperazinyl)-3-quinolone carboxylic acid], ofloxacin, norfloxacin, enoxacin and perfloxacin. Many drugs possess modified pharmacological and toxicological properties when administered in the form of metal complexes. Metal complexes with quinolones have been extensively reported [2–19]. It was also established that some transition metal ions are effective in induction of cyotoxicity of quinolones against *leukemia in vitro*. In our previous paper, we described the syntheses and crystal structures of four metal complexes of the fluoroquinolone class [20–22]. Till now, the reports on the crystal structure of ciprofloxacin directly chelated to transition metals are rare. In continuation of our work, we report here the syntheses and crystal structures of $[Co(Cip)_2]\cdot 4H_2O$ (**1**) and $[Fe(H\text{-}Cip)\cdot(C_2O_4)]\cdot(H_2Cip)\cdot 5H_2O$ (**2**), see schemes 1(a)–1(d), and their bio-activity against certain bacteria.

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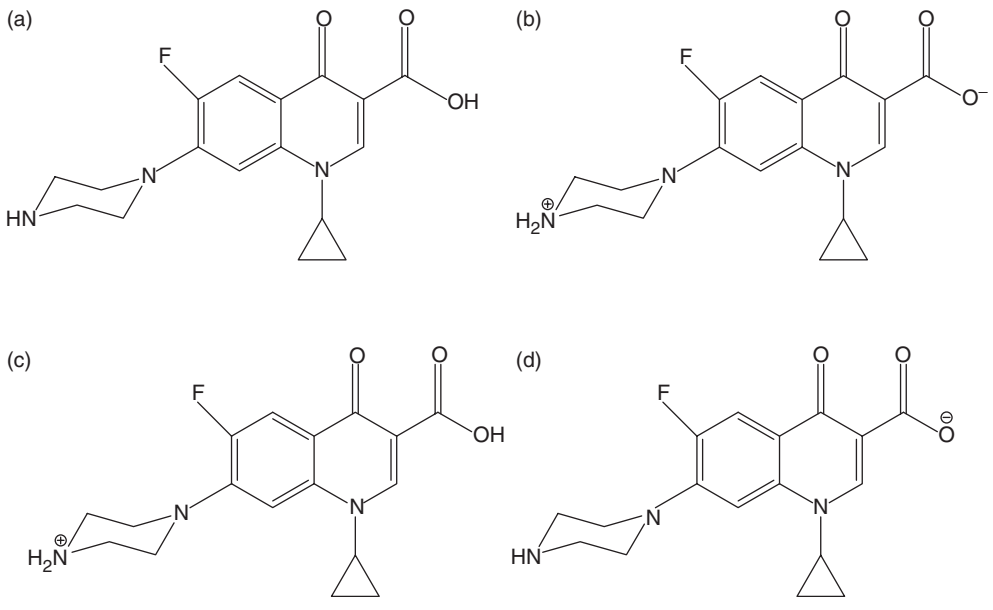


Scheme 1. (a) Ciprofloxacin, (b) Zwitterion of H-Cip, (c) H_2Cip cation, (d) Cip anion.

2. Experimental

2.1. *Materials and apparatus*

Ciprofloxacin was purchased from Fluka, and all other chemicals were purchased and used as received without purification. All solvents were of analytical grade. C, H and N data were obtained using an American PE 2400 II CHNS/O elemental analyzer. Infrared spectra were measured from KBr pellets using a Nicolet 5DXB system.

2.1.1. $[Co(Cip)_2]\cdot 4H_2O$ (1). An aqueous mixture (15 mL) containing ciprofloxacin (1 mmol, 0.2720 g) and $Co(OH)_2$ (0.5 mmol, 0.093 g) was placed in a Teflon-lined stainless steel vessel (25 mL). Ethanol (5.0 mL) was added to the mixture. The vessel was sealed and heated to 110°C for 4 days. Upon cooling to room temperature, yellow block-shaped crystals of **1** were obtained. Anal. Calcd for **$[Co(Cip)_2]\cdot 4H_2O$**: C, 54.18; H, 4.78; N, 11.15. Found: C, 54.12; H, 4.79; N, 11.12. IR data: (KBr pellet, cm^{-1}): 3419(s), 2972(w), 2850(w), 2536(w), 1628(s), 1576(s), 1554(s), 1524(s), 1489(s), 1385(m), 1354(m), 1338(m), 1306(s), 1272(s), 1226(m), 1184(w), 1114(m), 1031(w), 949(m), 897(m), 866(m), 842(m), 816(m), 787(w), 715(w), 627(s), 585(w), 557(w), 544(w), 513(w).

2.1.2. $[Fe(H\text{-}Cip)\cdot(C_2O_4)]\cdot(H_2Cip)\cdot 5H_2O$ (2). An aqueous mixture (15 mL) containing ciprofloxacin (1 mmol, 0.2720 g), oxalic acid (1.5 mmol, 0.1350 g) and $Fe(OH)_3$ (1 mmol, 0.1069 g) was placed in a Teflon-lined stainless steel vessel (25 mL). Ethanol (5.0 mL) was added to the mixture. The vessel was sealed and heated to 110°C for 4 days. Upon cooling to room temperature, pale yellow, block-shaped crystals of **2** were obtained. Anal. Calcd for **$[Fe(H\text{-}Cip)\cdot(C_2O_4)]\cdot(H_2Cip)\cdot 5H_2O$**: C, 46.50; H, 4.28;

Table 1. Summary of crystallographic data for **1** and **2**.

Parameter	**1**	**2**
Empirical formula	$C_{34}H_{36}CoF_2N_6O_8$	$C_{38}H_{42}F_2FeN_6O_{19}$
Formula weight	753.62	980.63
Crystal size (mm^3)	$0.50 \times 0.26 \times 0.14$	$0.50 \times 0.37 \times 0.23$
Crystal system	Monoclinic	Triclinic
Space group	$P2_1/c$	$P\bar{1}$
Unit of cell dimenions (Å, °)		
a	5.95980(10)	10.343(2)
b	21.5779(5)	14.901(3)
c	13.3171(3)	15.684(3)
α	90	100.502(3)
β	101.443(2)	101.769(4)
γ	90	109.524(3)
V ($Å^3$)	1678.54(6)	2146.4(7)
Final R indices [$I > 2\sigma(I)$]	0.0429, 0.1288	0.0472, 0.1362
R indices (all data)	$R_1 = 0.0528$, $wR_2 = 0.1376$	$R_1 = 0.0542$, $wR_2 = 0.1438$
Completeness (%)	99.6	99.1
D_{Calcd} ($mg\,m^{-3}$)	1.491	1.517
$F(000)$	782	1016
Absorption coefficient (mm^{-1})	0.584	0.446
Max. and Min. transmission	0.9227 and 0.7588	0.9043 and 0.8076
h	$-7 \le h \le 7$	$-12 \le h \le 12$
k	$-26 \le k \le 26$	$-18 \le k \le 18$
l	$-16 \le l \le 15$	$-19 \le l \le 18$
Largest diff. peak and hole ($e\,Å^{-3}$)	1.224 and −0.379	1.127 and −0.570
Goodness-of-fit on F^2	1.053	1.040

N, 8.57. Found: C, 46.43; H, 4.30; N, 8.54. IR data: (KBr pellet, cm^{-1}): 3547(m), 3257(s), 2962(w), 2912(w), 1704(s), 1645(s), 1593(s), 1560(s), 1471(m), 1406(m), 1353(s), 1332(w), 1254(w), 1244(w), 1116(w), 945(w), 931(w), 912(w), 760(s), 743(m), 644(w), 621(w), 568(w), 549(w), 516(w), 413(w).

2.2. *Crystal structure determination*

The X-ray single crystal data collections for **1** and **2** were performed on a Bruker Smart CCD diffractometer equipped with graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å). Multi-scan absorption corrections were applied using the SADABS program. The structure was solved by direct methods using SHELXS-97. Refinement on F^2 was performed using SHELXL-97 by full-matrix least-squares with anisotropic parameters for all non-hydrogen atoms. The hydrogen atoms of Cip, Hcip and H_2cip were generated geometrically, while H atoms of coordinated water of **1** were located from difference Fourier synthesis, and were allowed to refine with isotropic displacement parameters. The H atoms of lattice water in **2** were not fixed. The crystal data are in table 1.

2.3. *Antibacterial tests*

Samples were suspended in distilled water and the orbicular filter scrip method was used for testing all samples. The process is similar to that of antibacterial tests of

Table 2. Comparative *in vitro* activities of tested compounds against four bacteria.

	Final concentrations of the tested substances ($\mu g\,mL^{-1}$)					
	Ciprofloxacin			**2**		
	0.5	0.25	0.125	0.5	0.25	0.125
Staphylococcus aureas	23	21	19	22	20	19
Escherichia coli	36	33	31	35	32	31
Pseudomonas aeruginosa	27	24	21	28	25	23
Candida albicans	12	10	9	11	9	7

bismuth(III)-quinolone against Helicobacter pylori and some other bacteria [23, 24]. All tested strains (*Streptococcus haemolyticus*, *Straphyloccus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*) were freshly isolated from clinical material, dissolved in 15 mL of sterilized agar culture media at 40°C and were inoculated to a sterilized culture dish. After being stirred to homodisperse, kept horizontal, and cooled, the culture medium of strains were obtained.

The suspensions of the samples and orbicular filter scrip with diameter of 6 mm were sterilized at 120°C under high pressure. The minimum of suspensions were dropped in filter scrip and put into a culture dish containing culture medium of strains after drying at room temperature. Then the culture dish was placed into a culture box at 37°C for 18 h. The results showed the average ranges (mm) of inhibiting bacteria and are listed in table 2.

3. Results and discussion

3.1. *Spectroscopic properties*

IR spectra show two very strong peaks at 1628 and 1489 cm^{-1} for **1**, indicating that carboxylic acid of quinolones are deprotonated and coordinate to the metal due to the absence of a strong ν(COOH) band above 1704 cm^{-1} for ciprofloxacin. Compound **2** exhibits a broad split band between 3600 and 2900 cm^{-1}, which can be assigned to the O–H stretching vibration of water and also includes the N–H stretching vibration of the protonated piperazinyl moiety. Furthermore, the carboxylate stretching mode for **2** is observed at 1704 cm^{-1} while the pyridone carbonyl stretch is at 1645 cm^{-1}. Upon Fe^{3+} conjugation the former band disappears while the latter is found to be shifted to lower energy side, which is indicative of these two as the donors involved in metal coordination. The oxalate stretching vibrations appear at 1593 cm^{-1} $\upsilon_{as}(COO^{-})$, 1353 cm^{-1} $\upsilon_{s}(COO^{-})$.

3.2. *Crystal structures of 1 and 2*

The X-ray crystal analysis of **1** revealed that Co(II) has a distorted octahedral geometry with an equatorial plane composed of four oxygens [O(1), O(2), O(1C), and O(2C)], see figure 1. Two of the oxygens are from the quinolone ring and the others from

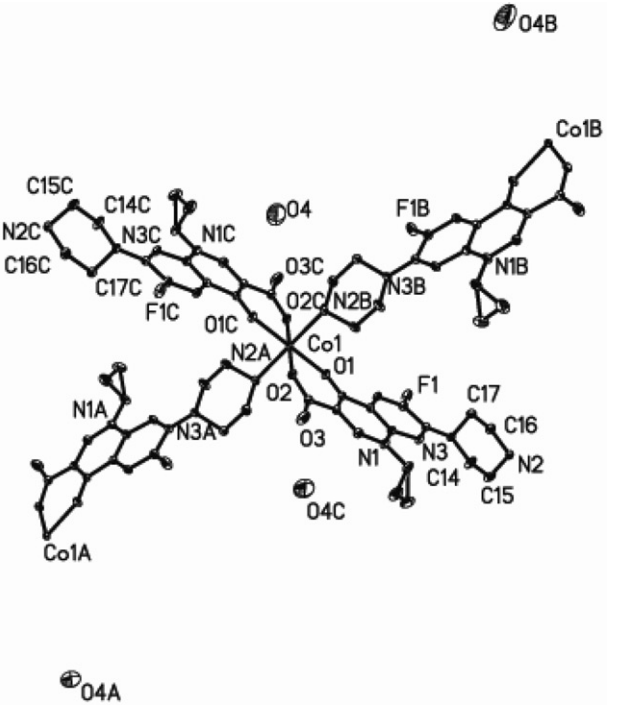


Figure 1. The coordination environment of Co^{2+} in **1**. The thermal ellipsoids are drawn at 30% probability level. H atoms were deleted for clarity.

Table 3. Selected bond lengths (Å) and bond angles (°) for complex **1**.

Co(1)–O(2)	2.0610(19)	Co(1)–O(1)	2.0733(17)
Co(1)–O(2)#1	2.0610(19)	Co(1)–O(1)#1	2.0733(17)
Co(1)–N(2)#2	2.247(2)	Co(1)–N(2)#3	2.247(2)
O(2)–Co(1)–O(2)#1	180.0	O(2)–Co(1)–O(1)#1	93.20(7)
O(2)#1–Co(1)–O(1)#1	86.80(7)	O(2)–Co(1)–O(1)	86.80(7)
O(2)#1–Co(1)–O(1)	93.20(7)	O(2)–Co(1)–N(2)#2	91.53(8)
O(2)#1–Co(1)–N(2)#2	88.47(8)	O(1)#1–Co(1)–N(2)#2	93.77(8)
O(1)–Co(1)–N(2)#2	86.23(8)	O(2)–Co(1)–N(2)#3	88.47(8)
O(2)#1–Co(1)–N(2)#3	91.53(8)	O(1)#1–Co(1)–N(2)#3	86.23(8)

Symmetry transformations used to generate equivalent atoms: #1 −x, −y + 1, −z + 1; #2 −x + 1, y − 1/2, −z + 3/2; #3 x − 1, −y + 3/2, z − 1/2; #4 −x + 1, y + 1/2, −z + 3/2.

carboxylate, which forms a stable six-membered chelating ring. The Co–O distances are in the range 2.0610(19)–2.0733(17) Å and the O–Co–O bond angles are in the range 86.80(7)–180.0° (table 3). The apical positions are occupied by two N atoms [N(2A)] and N(2B)] of the piperazinyl rings, resulting in formation of a two-dimensional neutral square grid with a cavity of 13.435 $Å^2$ (the distances of Co1–Co1A and Co1–Co1E equal to 13.435 Å), see figure 2. The carboxylate of ciprofloxacin in **1** is monodentate with one oxygen of the carboxylate group uncoordinated (scheme 2). The uncoordinated carbonyl oxygen of carboxylate is strongly hydrogen bonded to water. The uncoordinated carbonyl oxygen points up and is almost perpendicular to the molecular square cavity; water molecules are thus not enclathrated in the cavity but

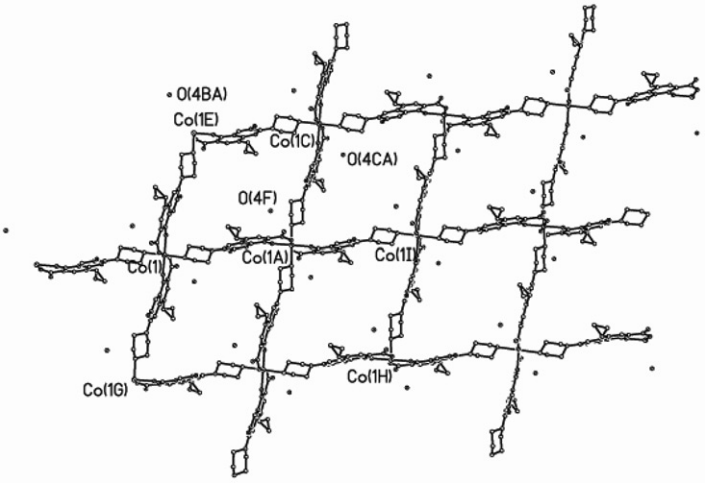
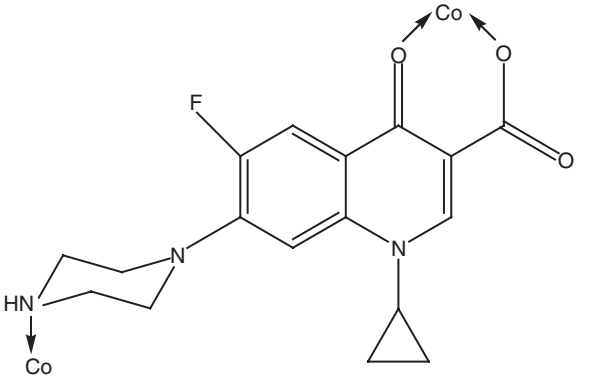


Figure 2. An extended two-dimensional network perspective view of **1**.



Scheme 2. Coordination mode of **1**.

intercalated between two adjacent layers. The adjacent layers almost perfectly overlap so that the cavity looks like a non-interpenetrating open channel. Furthermore, nanosized squares are interlinked by intercalated water, resulting in formation of a nanosized hydrophobic tube (or tunnel), see figure 3. The two-dimensional nanosized neutral cavity without any interpenetration is, to our knowledge, rare and should be useful for host-guest chemistry. Complex **1** is almost insoluble in most common solvents such as ethanol, chloroform, ethyl acetate, acetone, acetonitrile, benzene and water.

As illustrated in figure 4, the asymmetric unit of **2** consists of $[Fe(H\text{-}Cip)\cdot(C_2O_4)]$, protonated ciprofloxacin cation (H_2Cip) and five water molecules. The Fe^{3+} in **2** is linked with two oxalates and a zwitterion of ciprofloxacin. The carboxylic acid of quinolones are deprotonated and coordinated to iron, while the terminal N of the piperazyl ring of ciprofloxacin is protonated, and not coordinated. The Fe^{3+} is distorted octahedral, surrounded by four oxalate oxygens O(O1, O2, O5, O6) and two oxygens (O9, O10) from ciprofloxacin. The Fe–O_{cip} bond distances Fe(1)–O(9) and Fe(1)–O(10) are 1.9989(16)–1.9678(18) Å. The Fe–O_{ox} bond distances Fe(1)–O(1),

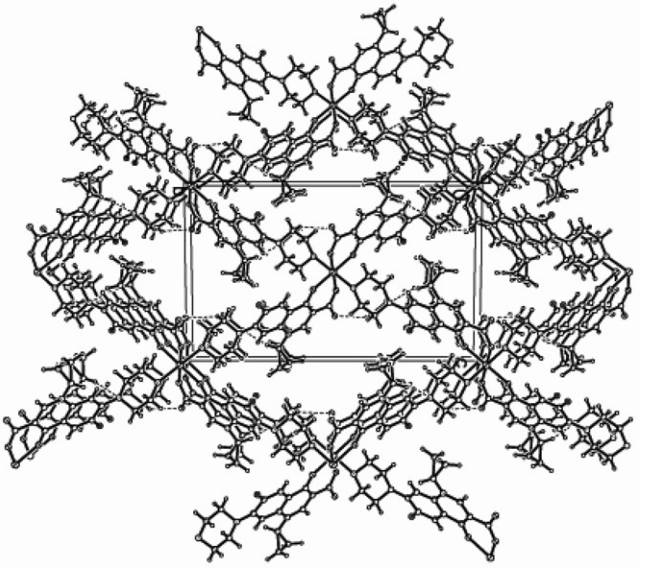


Figure 3. Crystal packing view of **1** along the *b* axis.

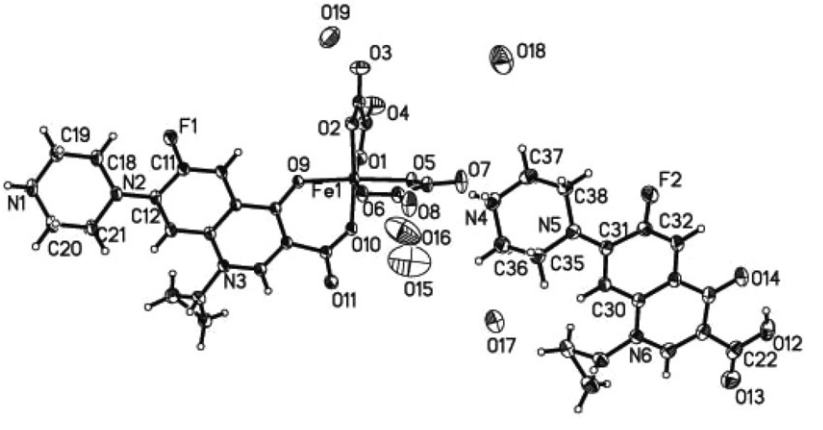


Figure 4. The crystal structure of **2**. The thermal ellipsoids are drawn at 30% probability level.

Fe(1)–O(2), Fe(1)–O(5), and Fe(1)–O(6) are in the range 1.9952(19)–2.0368(17) Å. The average Fe–O_{ox} distance is 2.011(4) Å, longer than that of Fe–O_{cip}. The main distortion from ideal octahedral geometry is due to the reduced bite angle of the oxalate ligand [80.45(7)° for O(1)–Fe(1)–O(2) and 79.78(7)° for O(5)–Fe(1)–O(6)]. The other O–Fe–O bond angles are in the range 79.78(7)–169.26(7)°. The C–O bond distance and O–C–O bond angle of oxalate and the geometrical parameters of ciprofloxacin are as expected. Selected bond distances and angles are presented in table 4. The uncoordinated H_2Cip is composed of essentially planar quinoline systems, whereas the piperazine ring has a chair conformation. The N4 of the piperazine ring is protonated, while the carboxyl group is not dissociated. The cyclopropyl group plane is not orthogonal to the mean

Table 4. Selected bond lengths (Å) and angles (°) for **2**.

O(1)–Fe(1)	2.0042(19)	O(2)–Fe(1)	2.0097(18)
O(5)–Fe(1)	2.0368(17)	O(6)–Fe(1)	1.9952(19)
O(9)–Fe(1)	1.9989(16)	O(10)–Fe(1)	1.9678(18)
O(1)–Fe(1)–O(2)	80.45(7)	O(6)–Fe(1)–O(5)	79.78(7)
O(10)–Fe(1)–O(9)	88.20(7)	O(6)–Fe(1)–O(1)	163.85(8)
O(9)–Fe(1)–O(5)	169.26(7)	O(10)–Fe(1)–O(2)	167.62(8)
O(1)–Fe(1)–O(5)	86.59(7)	O(9)–Fe(1)–O(1)	104.14(8)
O(6)–Fe(1)–O(9)	89.55(7)	O(10)–Fe(1)–O(6)	100.39(8)
O(10)–Fe(1)–O(1)	88.73(8)	O(6)–Fe(1)–O(2)	91.54(8)

plane of the quinolone system; the corresponding dihedral angle is 125.6°. The hydrogen bond O12–H12···O14 involving the carboxyl OH group and the quinolone oxo form a six-membered pseudo ring. The 3-D supramolecular structure is generated through π–π stacking interactions of quinoline rings with a centroid–centroid distance of 3.845 Å between planes and strong intermolecular hydrogen bonds involving piperazyl terminal N–H, carboxylate and water.

3.3. *Antibacterial activities*

As shown in table 2, the activity of **2** was similar to that of ciprofloxacin, displaying almost the same antibacterial abilities as ciprofloxacin against *S. aureas*, *E. coli* and *C. albicans*. However, **2** showed stronger antibacterial activity against *P. aeruginosa* at any concentration. Complex **1** is insoluble and shows no bio-activity against the four bacteria. It is difficult to compare these results for the antibacterial activities with those reported by other authors because of the different methodology and strains assayed. Generally, the action mechanism proposed that the transition metal complex with quinolones interferes with the transport of substrates and ions through the cell membrane resulting in antibacterial activity [25]. The synergistic enhancement of the ligand activity upon metal coordination from increased liposolubility of the ligand may contribute to the facile transport into the bacterial cell [26]. The better activity of **2** than **1** is related to the different solubility. However, at this stage it was impossible to find a simple explanation for the antibacterial effect of metal-ciprofloxacin, and further studies will be needed to elucidate this phenomenon.

Supplementary material

Crystallographic data for **1** and **2** were deposited to the Cambridge Crystallographic Data Centre with deposition numbers CCDC 614257 and 666458, respectively.

Acknowledgement

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