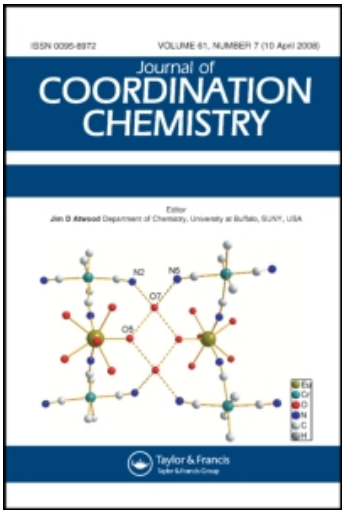

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Metal complexes of the third generation quinolone antibacterial drug sparfloxacin: preparation, structure, and microbial evaluation

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Metal complexes of the third generation quinolone antibacterial drug sparfloxacin: preparation, structure, and microbial evaluation

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The interactions of yttrium chloride, zirconium chloride, and uranium nitrate with sparfloxacin (SPAR) in ethanol, methanol, and acetone were studied. The isolated solid complexes were characterized by elemental analysis, infrared, ^{1}H-NMR and electronic spectra, and thermogravimetric analysis. The results support the formation of $[Y(SPAR)_2Cl_2]Cl \cdot 12H_2O$, $[ZrO(SPAR)_2Cl]Cl \cdot 15H_2O$, and $[UO_2(SPAR)_3](NO_3)_2 \cdot 5H_2O$. Infrared spectra of the isolated solid complexes indicate that SPAR is bidentate through the ring carbonyl oxygen and one oxygen of carboxylate. The calculated bond length and force constant, F(U=O), in the uranyl complex are 1.747 Å and 655.29 Nm^{-1}, respectively. The antimicrobial activities of the ligand and metal complexes have been tested against bacteria *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) and fungi *Penicillium rotatum* (*P. rotatum*) and *Trichoderma* sp., showing that the complexes exhibit higher antibacterial activity than SPAR.

Keywords: SPAR; IR spectra; Thermal analyses; ^{1}H-NMR; UV reflection; Biological activity

1. Introduction

Sparfloxacin (SPAR) is one of the third generation fluoroquinolone antibiotics used in the treatment of bacterial infections with trade names Zagam and Zagam Respipac. SPARs (scheme 1), like other quinolones and fluoroquinolones, are bactericidal drugs. Quinolones inhibit the bacterial DNA gyrase or the topoisomerase IV enzyme, thereby inhibiting DNA replication and transcription. Quinolones can enter cells easily and, therefore, are often used to treat intracellular pathogens, such as *Legionella pneumophila* and *Mycoplasma pneumoniae*. For many Gram-negative bacteria, DNA gyrase is the target, whereas topoisomerase IV is the target for many Gram-positive bacteria [1]. Eukaryotic cells do not contain DNA gyrase or topoisomerase IV.

The crystal structure, infrared (IR) spectroscopic and solid state paramagnetic resonance spectroscopy studies of various complexes synthesized from the interaction of

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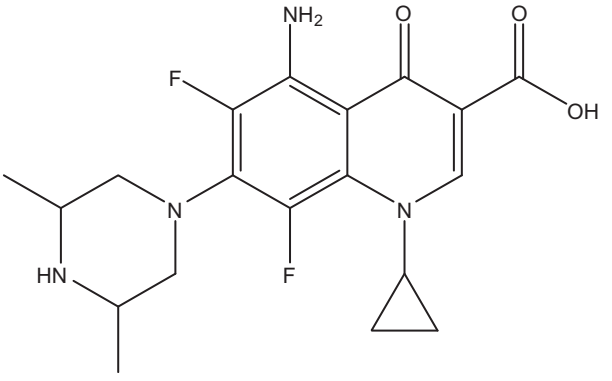


Scheme 1. SPAR, 5-amino-1-cyclopropyl-3-(3,5-dimethylpiperazin-1-yl)-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid.

metal ions with fluoroquinolones suggest that the fluoroquinolones are bidentate through carboxylate and carbonyl oxygens. The coordination of the fluoroquinolones with metallic ions by piperazine nitrogen is much less common. The literature contains some examples, such as complexes of zinc and platinum [2–13]. In most cases, the piperazine is coordinated through only one nitrogen (monodentate) or as a bridging ligand between two metal ions.

Studies on the reaction of SPAR with metal ions in the literature are quite limited [14–19] showing that SPAR is bound to metal ions *via* the pyridone oxygen and one carboxylate oxygen.

Continuing our investigation in this area [20–23], we present interactions of Y(III), Zr(IV), and U(VI) with SPAR in an attempt to examine the mode of coordination and the biological properties of the resultant complexes. The complexes have been synthesized and characterized with elemental analysis, spectroscopic techniques (UV-Vis, IR, and ^{1}H-NMR spectroscopies), and thermal analyses. The biological activities of the ligand and complexes have been evaluated against three bacterial species, *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*), and *Pseudomonas aeruginosa* (*P. aeruginosa*), and two fungi, *Penicillium rotatum* (*P. rotatum*) and *Trichoderma* sp.

2. Materials and methods

SPAR was purchased from Sigma, Metal salts, and solvents were purchased from Merck, Germany. All the chemicals were of reagent grade and used without purification.

Infrared spectra of the three complexes, SPAR, and the final products of the thermogravimetric (TG) analysis were recorded from KBr discs using a FT-IR 460 plus. ^{1}H-NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer using DMSO-d_6 as solvent. C, H, N, and halogen analyses were carried out on a Perkin Elmer CHN 2400. The percentages of Y(III), Zr(IV), and U(VI) were determined gravimetrically by transforming the solid products into oxide, and also determined by

using atomic absorption. A spectrometer model PYE-UNICAM SP 1900 fitted with the corresponding lamp was used for this purpose. Electronic spectra of SPAR and the isolated solid complexes were obtained from 800 to 200 nm using a UV-3101PC Shimadzu with a 1 cm quartz cell. TG and differential thermogravimetric (DTG) analyses were carried out under N_2 using detectors model TGA-50H Shimadzu. The rate of heating of the sample was kept at $10^{\circ}C\,min^{-1}$. Molar conductivities in DMSO at $1.0 \times 10^{-3}\,mol\,L^{-1}$ were measured on a CONSORT K410.

2.1. *Synthesis of SPAR metal complexes*

The light green $[Y(SPAR)_2Cl_2]Cl \cdot 12H_2O$ was prepared by adding 0.5 mmol (0.0977 g) of yttrium chloride (YCl_3) in 10 mL twice-distilled water dropwise to a stirred suspension of 1 mmol (0.39241 g) of SPAR in 50 mL ethanol. The reaction mixture was stirred for 15 h at 30°C in a water bath. The light green precipitate was filtered off and dried in vacuum over $CaCl_2$. The yellowish green and reddish brown solid complexes of $[ZrO(SPAR)_2Cl]Cl \cdot 15H_2O$ and $[UO_2(SPAR)_3](NO_3)_2 \cdot 5H_2O$ were prepared in a similar manner by using methanol and acetone as a solvent 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 molar ratios. Unfortunately, we were not able to obtain single crystals to perform X-ray diffraction analysis. Qualitative black ring test for ionic nitrate using freshly prepared $FeSO_4$ solution and concentrated sulfuric acid was conducted; a black ring of $FeSO_4 \cdot NO$ formed indicating the presence of free nitrate in the uranyl/SPAR complex; for the other complexes, the qualitative reactions revealed the presence of chloride. The three complexes were characterized by their elemental analysis, infrared, electronic, ^{1}H-NMR spectra, and thermal analyses.

2.2. *Antibacterial and antifungal activities*

Antibacterial activities of the ligand and complexes were investigated by a previously reported modified method of Beecher and Wong [24], against *S. aureus*, *E. coli*, and *P. aeruginosa*; antifungal screening was studied against *P. rotatum* and *Trichoderma* sp. The tested microorganism isolates were isolated from Egyptian soil and identified according to the standard mycological and bacteriological keys for the identification of fungi and bacteria as stock cultures in the microbiology laboratory, Faculty of Science, Zagazig University. The nutrient agar medium for bacteria was (0.5% peptone, 0.1% beef extract, 0.2% yeast extract, 0.5% NaCl, and 1.5% agar-agar) and for fungi (3% sucrose, 0.3% $NaNO_3$, 0.1% K_2HPO_4, 0.05% KCl, 0.001% $FeSO_4$, and 2% agar-agar) prepared, cooled to 47°C, and seeded with tested microorganisms. After solidification, 5 mm diameter holes were punched by a sterile cork borer. The SPAR and complexes were introduced in Petri dishes (only 0.1 mL) after dissolving in DMSO at $1.0 \times 10^{-3}\,mol\,L^{-1}$. These culture plates were then incubated at 37°C for 20 h for bacteria and for 7 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. SPAR.

3. Results and discussion

SPAR complexes of Y(III), Zr(IV), and U(VI) were prepared as solids with colors characteristic of the metal ion. The prepared complexes are hydrates with various degrees of hydration and with a metal-to-ligand ratio of 1 : 2 for Y(III) and Zr(IV) and 1 : 3 for U(VI). The elemental analyses agree well with proposed formulae (table 1). The physical characteristics of these complexes are given in table 1 and the molar conductance values of the complexes were found to be in the range 114.4–264.2 $S\,cm^2\,mol^{-1}$ at 25°C.

3.1. *Infrared absorption studies*

Infrared spectra of SPAR and its complexes are listed in table 2. Infrared spectra of quinolones are quite complex due to the presence of numerous functional groups [1]. The infrared spectra of SPAR metal complexes exhibit a broad band between 3444 and 3335 cm^{-1}, which corresponds to ν(O–H) of water [25–28]. The N–H vibration of the piperazinyl appears at 2568–2363 cm^{-1}, indicating that the molecules exist in zwitterionic form [7].

The infrared spectrum of SPAR shows absorption at 1717 cm^{-1} [29] attributed to ν(C=O) which has been replaced with bands at ~1636 cm^{-1} assigned to the asymmetric stretching vibration (ν_{as}) and at 1395 cm^{-1} for Y(III), 1356 cm^{-1} for Zr(IV), and 1383 cm^{-1} for U(VI), assigned to the symmetric stretching vibration, respectively. The difference $[\Delta\nu = \nu_{as}(COO^-) - \nu_s(COO^-)]$ of 258 cm^{-1} indicates monodentate coordination of carboxylate [17, 30, 31]. The ν(C=O) of pyridone for free SPAR at 1638 cm^{-1} has a very strong intensity absorption but in the spectra of complexes, is a medium strong band at 1569 cm^{-1} for Y(III), 1590 cm^{-1} for Zr(IV), and 1565 cm^{-1} for U(VI). In the majority of the metallic complexes with fluoroquinolones in the literature, the ligands are bidentate *via* carbonyl and carboxylic oxygens, forming a stable six-member chelate. In our complexes, disappearance of the band at 1717 cm^{-1} due to free carboxylic group and shift of pyridone stretch to lower frequency indicate formation of bonds to these groups [32]. The spectra of the isolated solid complexes show a group of bands characteristic for ν(M–O). ν(Y–O) bands at 682 and 488 cm^{-1} and at 643, 486, and 461 cm^{-1} for Zr(IV), and 678 and 448 cm^{-1} for U(VI) (table 2) are absent in the spectrum of SPAR. Thus, the drug coordinates through its ketone and carboxylate.

The most probable structure of $[UO_2(SPAR)_3](NO_3)_2 \cdot 5H_2O$ is shown in scheme 2, where the six oxygens of SPAR occupy equatorial positions, forming a plane containing the six-membered rings and the two oxygens of uranyl occupy axial positions. The ν_{as}(U=O) is very strong at 915 cm^{-1} and ν_s(U=O) at 823 cm^{-1}, medium strong. The assignments for the uranyl group, UO_2, agree quite well with those known for dioxouranium(VI) complexes [22, 33, 34]. The ν_s(U=O) value was used to calculate both the bond length and force constant, F(U=O), for UO_2 in our complex [33, 35], as 1.747 Å and 655.29 Nm^{-1}.

3.2. *UV-Vis spectra*

Electronic solid reflection spectra of free SPAR and its metal complexes from 200 to 800 nm, given in table 3, are practically identical with slight shifts to higher

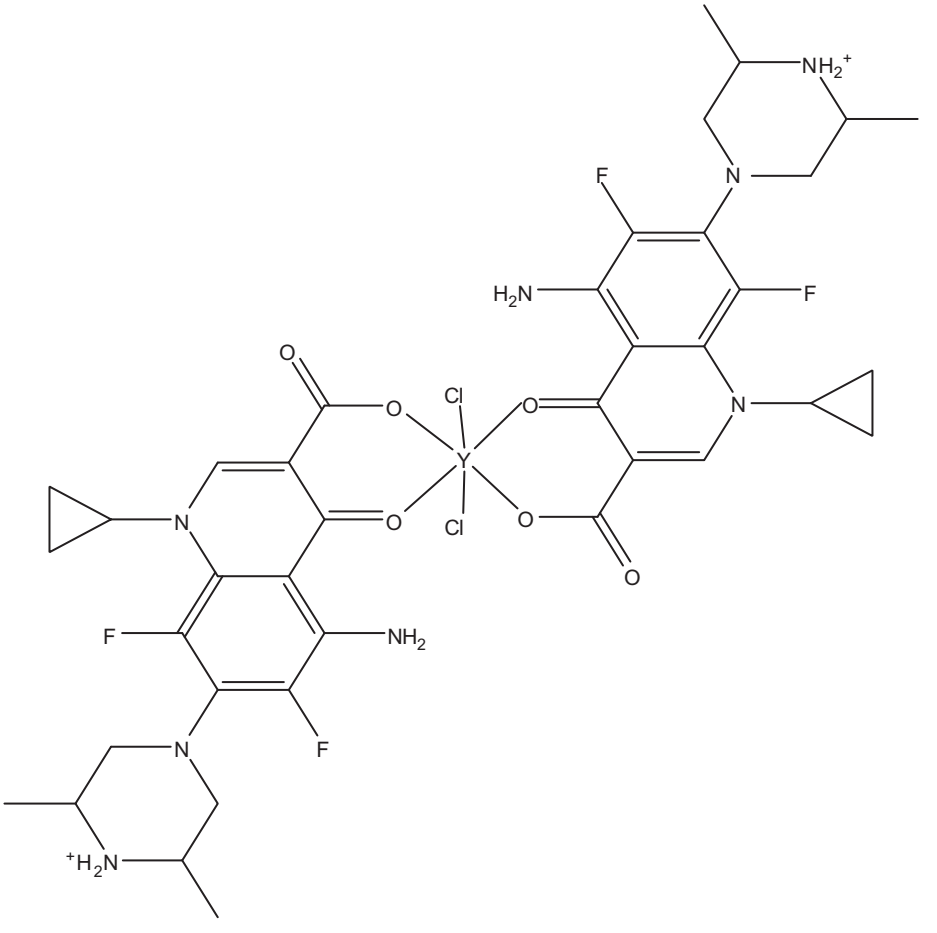
Table 1. Elemental analysis and physico-analytical data of SPAR and its metal complexes.

Complexes Molecular weight (molecular formula)	Yield%	m.p. (°C)	Color	Content ((Calcd) found)					Λ ($S cm^2 mol^{-1}$)
				%C	%H	%N	%Cl	%M	
SPAR	–	168	Yellow	(58.1)	(5.6)	(14.3)	–	–	−10.4
392.41 ($C_{19}H_{22}N_4O_3F_2$)				58.0	5.6	14.2			
$[Y(SPAR)_2Cl_2]Cl \cdot 12H_2O$	87.76	280	Light green	(38.1)	(5.6)	(9.4)	(8.91)	(7.45)	264.2
1195.4 ($C_{38}H_{68}N_8O_{18}F_4Cl_3Y$)				38.1	5.7	9.4	(8.89)	7.45	
$[ZrO(SPAR)_2Cl]Cl \cdot 15H_2O$	54.55	340	Yellowish green	(37.0)	(6.0)	(9.1)	(5.76)	(7.40)	213.2
1232.22 ($C_{38}H_{74}N_8O_{22}F_4Cl_2Zr$)				37.0	5.9	9.1	5.70	7.35	
$[UO_2(SPAR)_3](NO_3)_2 \cdot 5H_2O$	43.34	>360	Reddish brown	(41.2)	(4.6)	(11.8)	–	(14.34)	114.4
1660 ($C_{57}H_{76}N_{14}O_{21}F_6U$)				41.2	4.5	11.8		14.30	

Table 2. Infrared frequencies[a] (cm^{-1}) and tentative assignments[b] for (A) SPAR; (B) $[Y(SPAR)_2Cl_2]Cl \cdot 12H_2O$; (C) $[ZrO(SPAR)_2Cl]Cl \cdot 15H_2O$, and (D) $[UO_2(SPAR)_3](NO_3)_2 \cdot 5H_2O$.

A	B	C	D	Assignment
3460 vs	3335 m, br	3411 w	3444 m, br	ν(O–H); H_2O, COOH
3336 s		3335 vw	3341 m, br	ν(N–H); NH_2
		3273 w		
		3132 w		
3092 m	3091 vw	3003 vw	3087 vw	ν(C–H); aromatic
3026 w	3000 vw			
2964 s	2977 vw	2978 vw	2986 m	ν(C–H); aliphatic
2928 vw	2942 vw	2941 vw	2932 w	
2839 m	2842 vw	2822 vw	2851 m	
2723 vw	2740 w	2736 vw	2753 w	
2614 vw	2557 w	2530 vw	2492 w	$\nu(-NH_2^+)$
2568 vw	2468 ms	2486 w	2125 vw	
2500 vw	2363 m	2363 m	1977 vw	
2455 vw	2148 w			
2360 w				
1921 w				
1717 vs	–	–	–	ν(C=O); COOH
–	1636 ms	1636 s	1637 s	$\nu_{as}(COO^-)$
1638 vs	1569 ms	1590 s	1565 m	ν(C=O) and phenyl breathing
1585 s		1518 s	1531 w	modes
1562 vw				
1529 vs				
1438 vs	1450 s	1439 vs	1438 s	–CH; deformations of $–CH_2$
1373 w				
–	1395 w	1356 w	1383 w	$\nu_s(COO^-)$
1327 m	1299 vs, sh	1297 vs	1289 vs	$\delta_b(–CH_2)$
1291 vs		1234 vw		
1226 m	1178 s	1180 vs	1176 ms	ν(C–O),
1179 m	1138 w	1117 vw	1090 vw	ν(C–N),
1150 w	1092 w	1103 s	1020 s	ν(C–C)
1107 vw	1020 vs, sh	1046 vw	936 vw	$\delta_r(–CH_2)$
1084 s		1024 s		
1026 s				
963 w	952 w	966 s	860 vw	–CH bend; phenyl
914 s	918 s	918 s		
861 vw	844 vw	898 ms		
841 w	821 vs	888 vw		
812 m		844 m		
–	–	–	915 vs	ν_{as}(U=O)
–	–	–	823 ms	ν_s(U=O)
–	–	813 ms	–	ν(Zr=O)
756 vs	741 m, sh	753 ms	744 ms, sh	$\delta_b(COO^-)$
		706 w		
668 ms	682 ms	663 vw	678 ms	ν(M–O) + ring deformation
59 vw	521 w	643 vw	522 m	
	488 vw	486 vw	448 m	
		461 w		
522 s				
445 s				
405 m				

[a]s, strong; w, weak; sh, shoulder; v, very; br, broad.
[b]ν, stretching; δ, bending.

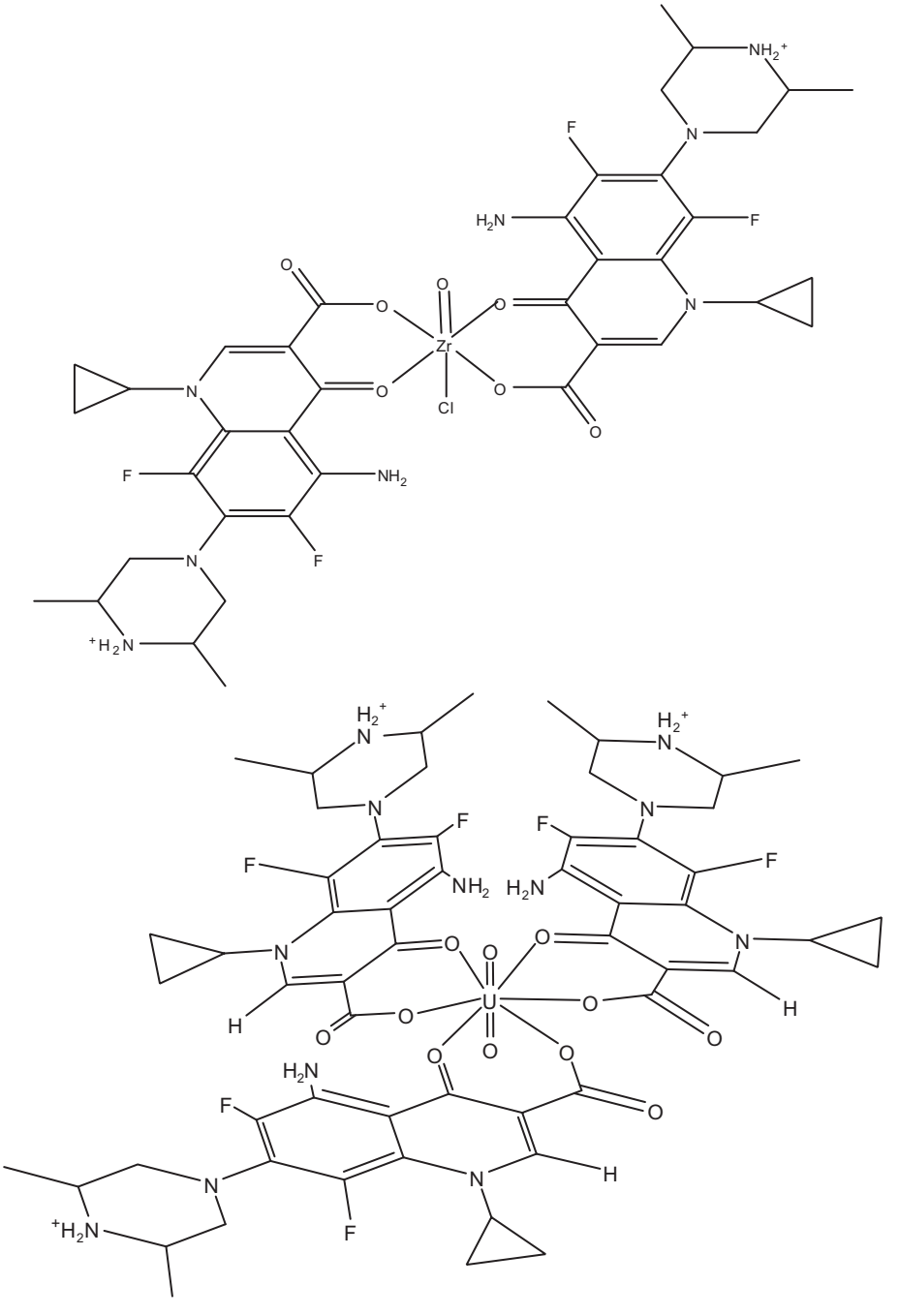


Scheme 2. The coordination mode of Y(III), Zr (IV) and U(VI) SPAR complexes.

(bathochromic shift) and to lower values (hypsochromic shift), indicative of coordination through the pyridone oxygen and one carboxylate oxygen. The complexes also exhibit an absorption band from 516–570 nm which can be assigned to the ligand-to-metal charge transfer transition for the quinolone ligand, as observed in a series of other quinolone complexes [7].

3.3. *TG analysis*

To confirm the proposed structure of the three prepared complexes, the TG and DTG analyses have been carried out in the temperature range between 25 and 800°C under N_2 flow with heating rates controlled at $10^{\circ}C\,min^{-1}$ (table 4). The SPAR had a characteristic one-step thermal decomposition pattern at temperature 320°C with a mass loss of 99.620% and it may be attributed to loss of $9C_2H_2 + CH_4 + 3NO + F_2 + 0.5N_2$.



Scheme 2. Continued.

Table 3. UV-Vis spectra of SPAR and its metal complexes (200–800 nm).

		SPAR complex with		
Assignments (nm)	SPAR	Y(III)	Zr(IV)	U(VI)
π–π^* transitions	239 338	238 334	235 312, 323	236, 252 292, 301, 319, 327
n–π^* transitions	351, 390	386	343	358, 379
Ligand–metal charge transfer	–	516, 570	524, 552	522, 543

Table 4. The maximum temperature T_{max} (°C) and weight loss values of the decomposition stages for Y(III), Zr(IV), and U(VI) SPARs.

			Weight loss (%)	
Compounds	Decomposition	T_{max} (°C)	Calcd	Found
SPAR ($C_{19}H_{22}N_4O_3F_2$)	First step Total loss, residue	320	100 100, 0.0	99.62 99.62, 0.38
$[Y(SPAR)_2Cl_2]Cl \cdot 12H_2O$ ($C_{38}H_{68}N_8O_{18}F_4Cl_3Y$)	First step Second step Total loss, residue	68 291, 519	15.05 60.44 75.49, 24.50	15.02 60.78 75.80, 24.19
$[ZrO(SPAR)_2Cl]Cl \cdot 15H_2O$ ($C_{38}H_{74}N_8O_{22}F_4Cl_2Zr$)	First step Second step Total loss, residue	84 342, 520	10.22 71.98 82.21, 17.79	10.22 71.97 82.2, 17.80
$[UO_2(SPAR)_3](NO_3)_2 \cdot 5H_2O$ ($C_{57}H_{76}N_{14}O_{21}F_6U$)	First step Second step Total loss, residue	58 343, 472, 551	5.42 78.31 83.73, 16.26	5.41 78.33 83.74, 16.25

Thermal degradation of $[Y(C_{19}H_{22}N_4O_3F_2)_2Cl_2]Cl \cdot 12H_2O$ exhibits two steps: the first step from 25°C to 171°C, with a maximum at 68°C, is accompanied by weight loss of 15.02% corresponding to a loss of 10 water molecules. The second step of degradation occurs with two maxima at 291°C and 519°C and is accompanied by a weight loss of 60.78%, corresponding to the loss of $7C_2H_2 + 4C_2H_4 + 3NH_4Cl + 4HF + CO + 5NO + 0.5H_2O + 0.5H_2$. The actual weight loss from these two steps is 75.80%, close to the calculated value 75.49%.

$[ZrO(C_{19}H_{22}N_4O_3F_2)_2Cl]Cl \cdot 15H_2O$ also decomposes in two steps with mass loss 71.97%, leaving ZrO_2 as residue; the activation energies were from 23.19 to 89.39 and 25.7 to 116.02 kJ mol^{-1} according to the Coats–Redfern [36] and Horowitz–Metzger equations [37], respectively (Supplementary material).

The thermal decomposition of $[UO_2(C_{19}H_{22}N_4O_3F_2)_3](NO_3)_2 \cdot 5H_2O$ exhibits two steps: the first at 58°C is accompanied by a weight loss of 5.41%, corresponding to a loss of five water molecules (theoretical value of 5.42%). The second step of decomposition with maxima at 343°C, 472°C, and 551°C is accompanied by a weight loss of 78.33%, corresponding to the loss of $18C_2H_2 + 6C_2H_4 + 6HF + 9CO + 6N_2O + N_2$, giving UO_2 as a final product. The infrared spectra of the final products show only the bands associated with the oxide and the absence of all bands associated with SPAR.

Table 5. ^{1}H-NMR values (ppm) and tentative assignments for (A) SPAR, (B) $[Y(SPAR)_2Cl_2]Cl \cdot 12H_2O$, and (C) $[ZrO(SPAR)_2Cl]Cl \cdot 15H_2O$ complexes.

A	B	C	Assignments
1.08, 1.12	1.12–1.14	1.10–1.12	δH, $–CH_2$; cyclopropane
1.33	1.29–1.31	1.24–1.26	δH, $–CH_3$
2.00	3.33–3.42	3.16–3.32	δH, –NH; piperazine
4.12	3.46	3.44–3.48	δH, $–N–CH_2$
–	3.97	4.00	δH, H_2O
5.90	7.45	7.29	δH, $–^+NH_2$, $–NH_2$
8.66	8.55	8.51	δH, –CH aromatic
15.12	–	–	δH, –COOH

Table 6. The inhibition diameter zone values (mm) for SPAR and its compounds.

	Microbial species				
	Bacteria		Fungi		
Compounds	*E. coli*	*P. aeruginosa*	*S. aureus*	*P. rotatum*	*Trichoderma* sp.
SPAR	22.5 ± 0.3	25 ± 0.4	29 ± 0.4	0	0
$[Y(SPAR)2Cl_2]Cl \cdot 12H_2O$	$25.5 + 1 \pm 0.3$	$32 + 2 \pm 0.8$	$35 + 2 \pm 0.2$	0	0
$[ZrO(SPAR)2Cl]Cl \cdot 15H_2O$	$24.5 + 1 \pm 0.2$	$34 + 2 \pm 0.2$	$46 + 3 \pm 0.2$	0	0
$[UO2(SPAR)3](NO_3)2 \cdot 5H_2O$	$24 + 1 \pm 0.5$	$32 + 2 \pm 0.7$	$40.5 + 3 \pm 0.3$	0	0
Control (DMSO)	0	0	0	0	0

The proposed structural formulae are shown in scheme 2.

3.4. *The ^{1}H-NMR studies*

To confirm the structures, studies of ^{1}H-NMR spectra of SPAR, $[Y(SPAR)_2Cl_2]Cl \cdot 12H_2O$ and $[ZrO(SPAR)_2Cl]Cl \cdot 15H_2O$ were carried out (table 5). SPAR showed a peak at δ 15.12 ppm, which is assigned to proton of carboxylic (COOH). The ^{1}H-NMR spectra of the two complexes in DMSO-d_6 exhibit O–H proton at δ 3.97–4.00 ppm, due to water in the complexes. The resonance of COOH is not detected in the spectra of the complexes suggesting coordination through carboxylate [38]. Peaks of the free ligand are present in spectra of the complexes, but shifted upon coordination of the quinolones to metal [39].

3.5. *Antimicrobial activity*

The efficiencies of the ligand and the complexes have been investigated against two Gram-negative *E. coli* and *P. aeruginosa*, and one Gram-positive *S. aureus*; antifungal screening was studied against *P. rotatum* and *Trichoderma* sp. The results are presented in table 6 and figure 1.

The antibacterial study of SPAR and the three complexes (table 6) show inhibitory action against all three bacteria and no antifungal activity for the ligand or its

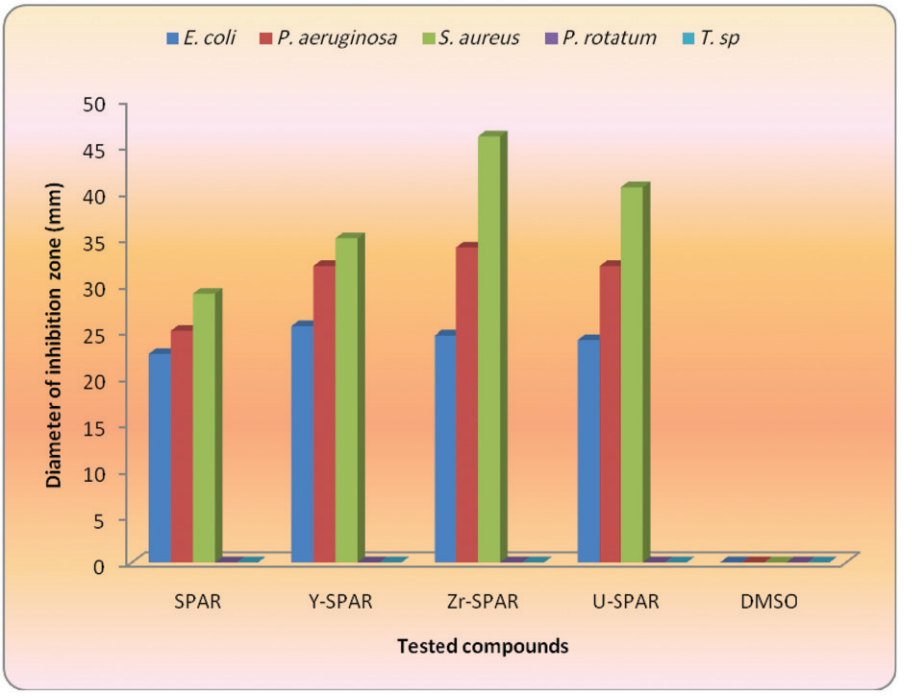


Figure 1. Statistical representation for biological activity of SPAR and its complexes.

metal complexes. The complexes show better activity against Gram-negative *P. aeruginosa* and Gram-positive *S. aureus* microorganisms than SPAR with moderate activity against *E. coli*. The nature of metal coordination to a drug may have a significant role in activity. In general, for metal complexes showing antimicrobial activity, the following five principal factors [40–43] should be considered: (1) the chelate effect; (2) the nature of the ligands; (3) the total charge of the complex; (4) the nature of the ion neutralizing the ionic complex; and (5) the nuclearity of the metal center in the complex. All the factors are present in our compounds except (2).

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