ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

Preparation,Characterization and Microbial Evaluation of$[VO(GFLX)_2L]Cl_3.nH_2O$ (L,n=DMF,3; An,5; Py,3; o-Tol,1 and Et_3N,1)

Sadeek A. Sadeek[*1],Wael A. Zordk[1,2], Mohab H. Abd Allah[3]

1. Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt.
2. Chemistry department, collage of Quanfudha-umm Al-QuraUniversity, KSA.
3. Ridgewood for infrastructure project, Cairo, Egypt

Manuscript Info

Manuscript History:

Received: 19 July 2014
Final Accepted: 26 August 2014
Published Online: September 2014

Key words:

GFLX, IR, UV,^{1}H NMR, TGA and Antimicrobial activity

***Corresponding Author**

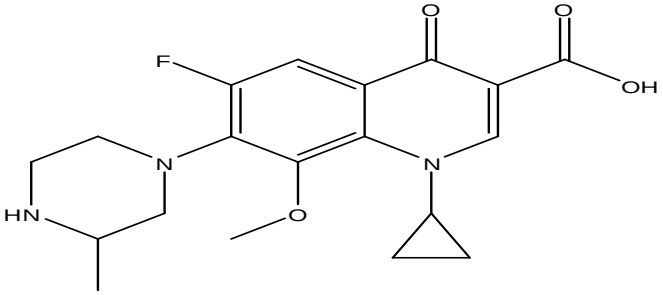
Sadeek A. Sadeek[*]

Abstract

Five new Vanadium (V) complexes $[VO(GFLX)_2DMF]Cl_3.3H_2O$, $[VO(GFLX)_2An]Cl_3.5H_2O$, $[VO(GFLX)_2Py]Cl_3.3H_2O$,$[VO(GFLX)_2o\text{-}Tol]Cl_3.H_2O$and $[VO(GFLX,)_2Et_3N]Cl_3.H_2O$have been synthesized. The isolated solid complexes have been characterized with elemental analysis, melting point, conductance measurements, IR spectroscopy, UV-Vis, ^{1}H NMR and thermal analysis. The results support the formation of the complexes and indicated that gatifloxacin reacts as a bidentate deprotonated ligand bound to the vanadium (V) through the ketone oxygen and a carboxylato oxygen. The antimicrobial activity of ligand and their complexes has been tested against microorganism, three Gram-negative, *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*) and*Klebsiella pneumonia* (*K.pneumonia*e)andthree Gram-positive,*Staphylococcus aureus(S. aureus), Staphylococcus epidermidis(S. epidermidis)*and *Bacillus pumilus (B. pumilus)*, the data showing that the complexes exhibit higher activity than free ligand.

Introduction

Gatifloxacin {±-1-cyclopropyl-6-fluoro-7-(3-methyl-1-piperaziny)-8-methoxy-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid sesquihydrate} (Scheme 1)is a new broad-spectrum 8-methoxy fluoroquinolone antibacterial agent.Gatifloxacin shown activity against both Gram (+), Gram (−) and is used in the treatment of a wide range of infections [1–3]. Gatifloxacin with a methoxy side chain at the C-8 position that not only seems to increase bactericidal action enhances the ability of drug to inhibit growth of mutants but also reduces the quinolone associated photo toxicity [4-7].



Scheme 1.

Uses of metal in medicines have become increasingly important over the last couple of decades resulting in a variety of exciting and valuable drugs [7-10]. The metal complexes are amenable to combinatorial synthetic methods, and an immense diversity of structural scaffolds can be achieved. Metal centers are capable of organizing surrounding atoms to achieve pharmacophore geometries that are not readily achieved by other means [11]. The mechanism of gatifloxacin action involves inhibition of bacterial DNA gyrase, which is essential for DNA replication, and it has been proposed that metal complex intermediates are involved in this process [12, 13]. A study on the structure and activity of certain fluoroquinolones and the interaction of their Cu(II) complexes on a DNA model, suggested that the intercalation of the fluoroquinolone complexes to a metal is an important step in the mechanism of action of these drugs [14]. Number of studies confirmed that DNA-affinity of the fluoroquinolone, modulated by Mg(II), plays an important role in poisoning the cleavable gyrase-DNA complex and, consequently, in eliciting antibacterial activity by this familyof drugs [15-19]. These results encouraged us to study the coordination chemistry of fluoroquinolones with transition metal ions in an attempt to determine the modes of binding in the solid state and to investigate biological activities.

In the present workwe describe the synthesis of gatifloxacinwith Vanadium (V) complexes, with the objective of better understanding the structure formed by these complexes. For the characterization of the complexes formed, the following techniques were employed: ^{1}HNMR, Infrared, UV spectroscopies, Elemental analysis, conductance measurements and thermal analysis.

Materials and methods

All chemicals used for the preparation of the complexes were of analytical reagent grade, commercially available from different sources. Gatifloxacin used in this study were obtained from EIPICO, $VOCl_3$ (99.9%) was purchased from Aldrich Chemical Co. and solvents were purchased from Merck.These materials used withoutfurther purification.

The infrared spectra of the five solid complexes and gatifloxacinwere recordedfrom KBr discs using FTIR 460 plus, ^{1}HNMR spectra wererecorded on Varian Mercury VX-300 NMR Spectrometer usingDMSO-d_6 as solvent. C, H and N elemental analysis werecarried out on a Perkin Elmer CHN 2400. The percentage of V(V) was determined gravimetrically bytransforming the solid products into vanadium(V)oxide, and also determinedby using atomic absorption method. A spectrometer model PYEUNICAMSP 1900 fitted with the corresponding lamp was usedfor this purposed. Electronic solid reflection spectra of gatifloxacinand the isolated solid complexes were obtained in the region of800–200 nm using UV-3101PC Shimadzu with a 1 cm quartz cell.Thermogravimetric (TG) and differential (DTG) thermogravimetricanalysis were carried out under N_2-atmosphere using detectorsmodel TGA-50H Shimadzu. The rate of heating of the sample waskept at 10 °C/min. Molar conductivities in DMSO at 1.0 x 10^{-3} M for all compounds were measured on CONSORT K410.

Synthesis of gatifloxacin metal complexes

An ethanolic suspended solution (20 mL) of Gatifloxacin (1.0 mmol, 0.375 g) was added to an ethanolic solution of $VOCl_3$ (0.5 mmol, 0.095 mL) and the reaction mixture was stirred at room temperature for 1h and then adding 1 mL dimethylformamide (0.5 mmol, d=0.949g/L) after that the mixture was stirred for 3 days at room temperature. The solution was left for slow evaporation, after that a faint greensolid product was deposited. The solid obtained was filtered under vacuum, washed with ethanol and dried over anhydrous $CaCl_2$.In a similar way described above,TheDark green,Brown,and Faint green$[VO(GFLX)_2An]Cl_3.5H_2O$, $[VO(GFLX)_2Py]Cl_3.3H_2O$$[VO(GFLX)_2$o-Tol$]Cl_3.H_2O$ and $[VO(GFLX)_2Et_3N]Cl_3.H_2O$complexes were prepared by using ethanol as a solvent and using Aniline, Pyridine, o-toluidine, triethylamine instead of DMF in 1:2:1 molar ratio.

Unfortunately we were not able to obtained appropriate monocrystals to perform X-ray diffractionanalysis. The qualitative reactions revealed the presence of chloride as counter ions.

Antibacterial activity

Antibacterial activity of the ligand and its metal complexes was investigated by a previously reported modified method of Beecher and Wong [20], against different bacterial species, such as three Gram-negative, Escherichia coli (E. coli), Pseudomonas aeruginosa (P. aeruginosa) and Klebsiella pneumonia(K.pneumoniae) and three Gram-positive, Staphylococcus aureus (S. aureus), Staphylococcus epidermidis (S. epidermidis) and Bacillus pumilus (B. pumilus) microorganisms. The nutrient agar medium for antibacterial was (0.5% Peptone, 0.1% Beef extract, 0.2% Yeast extract, 0.5% NaCl and 1.5% Agar-Agar) was prepared and then cooled to 47 °C and seeded with tested microorganisms. After solidification 5 mm diameter holes were punched by a sterile cork-borer. The investigated compounds, i.e., ligand and their complexes, were introduced in Petri-dishes (only 0.1 ml) after dissolving in DMSO at 1.0 x 10^{-3} M. These culture plates were then incubated at 37 °C for 20 h for bacteria. The

activity was determined by measuring thediameter of the inhibition zone (in mm). Growth inhibition wascalculated with reference to the positive control, i.e., gatifloxacin.

Result and disscusion

The infrared spectra of the five complexes $[VO(GFLX)_2DMF]Cl_3.3H_2O$, $[VO(GFLX)_2An]Cl_3.5H_2O$, $[VO(GFLX)_2Py]Cl_3.3H_2O$,$[VO(GFLX)_2o\text{-}Tol]Cl_3.H_2O$and $[VO(GFLX)_2Et_3N]Cl_3.H_2O$in pottasium bromide discs are shown in fig.1. The prepared complexes are hydrates with variousdegrees of hydration. The structures of the complexes suggestedfrom the elemental analysis agree well with their proposed formula(Table 1). The molar conductance values of the gatifloxacin and thier metal complexes in DMSO-$d_6$with standard reference, using 10^{-3}M solutions at room temperature were found to be in the range from 9.00 to305.90 S cm^2 mol^{-1}.The data indicated that the complexes are electrolyte and the chloride ion was found as counter ions at all five complexes.

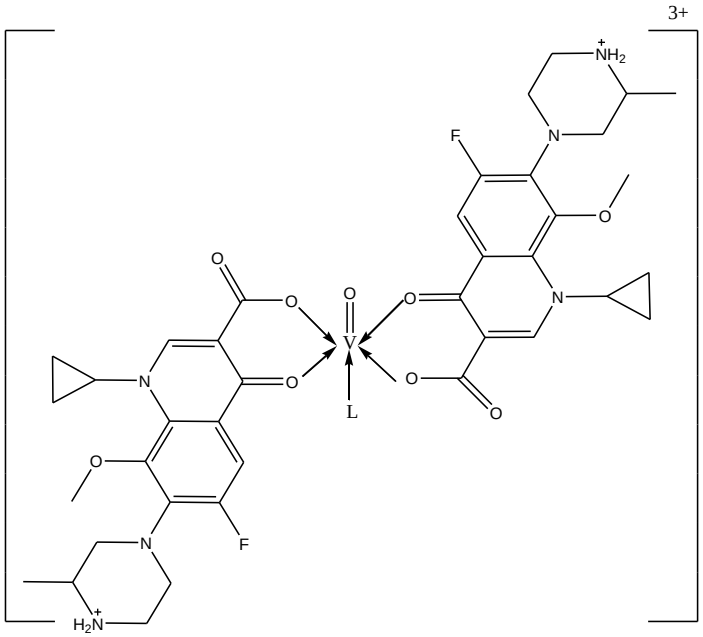
Table (1): Elemental analysis and Physico-analytical data for gatifloxacin and its metal complexes.

Compounds MWt. (M.F.)	Yield%	Mp/^{o}C	Color	Found (Calcd.) (%)				Λ (S cm^2 mol^{-1})
				C	H	N	M	
GFLX375.44 ($C_{19}H_{22}N_3O_4F$)	-	158	white	(60.78) 60.73	(5.98) 5.86	(11.19) 11.17	-	9.00
$[VO(GFLX)_2DMF]Cl_3.3H_2O$ 1051.34 ($VC_{41}H_{57}F_2N_7O_{13}Cl_3$)	90	221	faint green	(46.84) 46.89	(5.48) 5.43	(9.33) 9.27	(4.85) 4.80	293.01
$[VO(GFLX)_2An]Cl_3.5H_2O$ 1107.41 ($VC_{44}H_{61}F_2N_7O_{14}Cl_3$)	88	191	Dark green	(47.72) 47.69	(5.56) 5.50	(8.86) 8.87	(4.60) 4.61	282.12
$[VO(GFLX)_2Py]Cl_3.3H_2O$ 1057.34 ($VC_{43}H_{49}F_2N_7O_9Cl_3$)	81	207	Dark green	(48.57) 48.84	(5.33) 5.25	(9.30) 9.27	(4.89) 4.82	305.90
$[VO(GFLX)_2o\text{-}Tol]Cl_3.H_2O$ 1049.36 ($VC_{45}H_{55}F_2N_7O_{10}Cl_3$)	78	176	Brown	(51.50) 51.47	(5.29) 5.23	(9.35) 9.32	(4.85) 4.85	297.51
$[VO(GFLX)_2.Et_3N]Cl_3.H_2O$ 1043.41 ($VC_{44}H_{61}F_2N_7O_{10}Cl_3$)	87	200	Faint green	(50.65) 50.63	(5.90) 5.83	(9.40) 9.40	(4.88) 4.87	289.43

Infrared spectra

The vibrational assignments of all observed bands are given in table 2. Infrared spectrum of gatifloxacin is multifaceteddue to the presence of numerous functional groups and all bands wereassigned [21]. In the majority of the metal fluoroquinolone complexes described in the literature, the ligand coordinate in a bidentatemanner via the carboxylic and the ketone group, where the metallic ion forms a stable six-membered ring chelate. In these complexes it is possible to observe the disappearance of theabsorption band at 1724cm^{-1} due to the freecarboxylic acid indicating the formation of a bond between the metallic ion and the carboxylate oxygen [22]. For the V(V) complexes, two characteristic absorption bands around 1618 and 1385 cm^{-1} were observed which can be attributed to asymmetric and symmetric ν(O–C–O), respectively [22,23]. 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 [24, 25]. If Δν is greater than 200 cm^{-1}, this group is probably bound in amonodentate way, as was observed for the complexes reported herein. The absorption band at 1635 cm^{-1} attributed to the ketone group in the free ligand spectra is shifted to 1587– 1570 cm^{-1} in the complexes which is good indication that this group is coordinated to the V(V) ion [22]. The IR spectra of all complexes exhibit broad bandsin the range 3425-3418cm^{-1} which confirms the presence of water molecules, since, according to the elemental analysis and thermogravimetric studies, all the obtained complexes contain water of crystallization. The stretching vibration $\nu(-NH_2^+)$ observed in the spectra of free gatifloxacin and its complexes are at the same region, 2620-2419 cm^{-1}.

The data given in table 2 showed that ν(V=O) is a very strong band in the region 972-941 cm^{-1}[26]. Also the infrared spectra of the prepared complexes display changes in the aromatic ring vibrations in comparison to the corresponding absorption bands for free ligand. Also, the spectra of the isolated complexes showed a group of bands with different intensities which characteristics for ν(M-O) and ν(M-N). The ν(M-O) and ν(M-N) bands observed at 598, 517 and 451 cm^{-1} for DMF, at 613, 529 and 475 cm^{-1} for An, at 606, 516 and 477 cm^{-1} for Py, at 664, 525 and 436 cm^{-1} for o-Tol, at 517, 478 and 438 cm^{-1} for Et_3N complexes. The proposed structure formula on the basis of the results discussed according to the infrared spectra located as follows (Scheme 2).



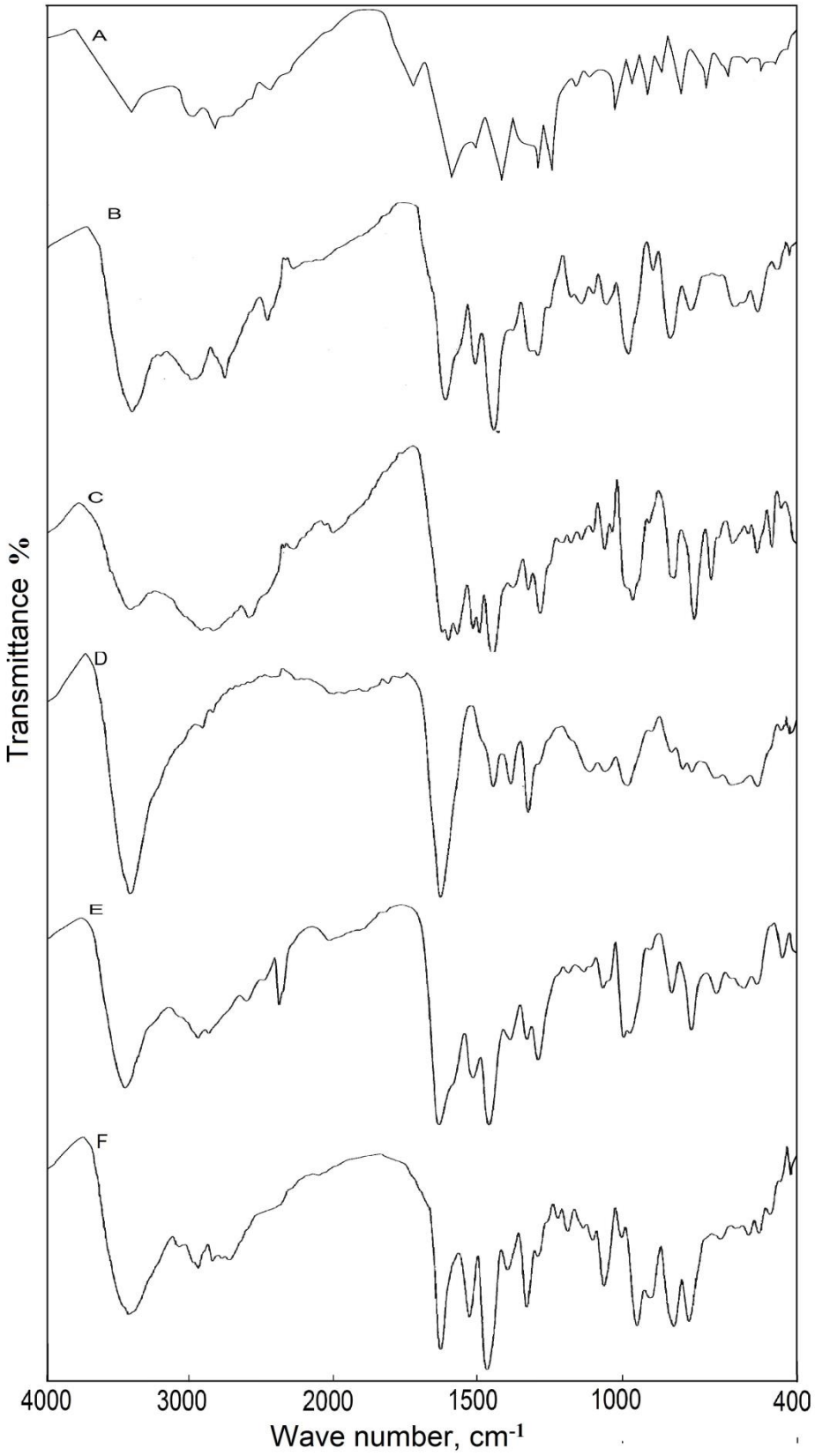
Scheme 2: The coordination mode of V(V) with gatifloxacin and L (L = DMF, An, Py, o-Tol and Et_3N).

Table (2): Infrared frequencies (cm^{-1}) and tentative assignments for (A) (GFLX), (B) $[VO(GFLX)_2DMF]Cl_3.3H_2O$,(C) $[VO(GFLX)_2An]Cl_3.5H_2O$, (D) $[VO(GFLX)_2Py]Cl_3.3H_2O$, (E) $[VO(GFLX)_2o\text{-}Tol]Cl_3.H_2O$ and (F) $[VO(GFLX)_2Et_3N]Cl_3.H_2O$.

A	B	C	D	E	F	Assignment
3403m	3425mbr	3418mbr	3429vsbr	3425mbr	3425mbr	ν(O-H); H_2O, COOH
3091vw	3044sh	3048sh	3107vw	3071sh	3025m	ν(C-H); aromatic
3022vw	3009vw		3086w	3017sh		
2978vw	2970m	2971sh	2928w	2924w	2965vw	ν(C-H); aliphatic
2938vw	2777m	2924vw	2855m	2861m	2943w	
2842m		2843w			2845vw	
2591vw	2620w	2596vw	2596vw	2588m	2534w	$\nu(-NH_2^+)$
2475m,br	2476w	2572m	2515vw	2473m		
			2419vw			
1724s	-	-	-	-	-	ν(C=O); COOH
-	1612s	1620vw	1624vs	1620m	1624vs	$\nu_{as}(COO^-)$
1635vs	1573m	1570m	1487sh	1577s	1587w	ν(C=O)and phenyl
1547ms	1508m	1516w		1508m	1524s	breathing modes
		1493m				
1448vs	1447vs	1447vs	1443m	1450vs	1462vs	-CH ; deformations of $-CH_2$
-	1377m	1377m	1385s	1381m	1393m	$\nu_s(COO^-)$
1360ms	1324sh	1323w	1319s	1323w	1323s	$\delta_b(-CH_2)$
1321vs	1288s	1281s	1287m	1281vs	1288m	
1278vs	1248m	1255m			1249w	
1210ms	1173vw	1204vw	1165sh	1177vw	1215vw	ν(C-O),
1180vw	1134w	1173w	1107vw	1126vw	1180w	ν(C-N),
1143ms		1138w				ν(C-C)
1114vw	1096vw	1099m	1053w	1111vw	1096vw	$\delta_r(-CH_2)$
1096vw	1053w	1057m		1061vw	1057vs	
1061vs		1030s		1054m		
-	972vs	961vs	972s	964vs	941m	ν_{as}(V=O)
995s	883w	903m	891w	895w	895s	-CH bend; phenyl
938vs	826s	814s	818w	818m	814m	
888s						
775ms	752m	745vs	779w	752vs	760vs	$\delta_b(COO^-)$
733s	705vw		748w		718vw	
686ms,	598w	687s	606vw	664m	652w	ν(M-O), ν(M-N)+
651s	517m	660w	516m	618vw	552w	ring deformation
542s	451w	613w	477w	571w	517w	
487m		529m	436vw	525s	478m	
450vw		475vs	405vw	436m	438m	

Keys: s=strong, w=weak, v=very, m=medium, br=broad, sh=shoulder, ν=stretching, δ_b=bending

Figure. 1: Infrared spectra of (A) (GFLX),(B) $[VO(GFLX)_2DMF]Cl_3.3.5H_2O$, (C) $[VO(GFLX)_2An]Cl_3.5H_2O$, (D) $[VO(GFLX)_2Py]Cl_3.3H_2O$, (E) $[VO(GFLX)_2o\text{-}Tol]Cl_3.H_2O$ and (F) $[VO(GFLX)_2Et_3N]Cl_3.H_2O$.



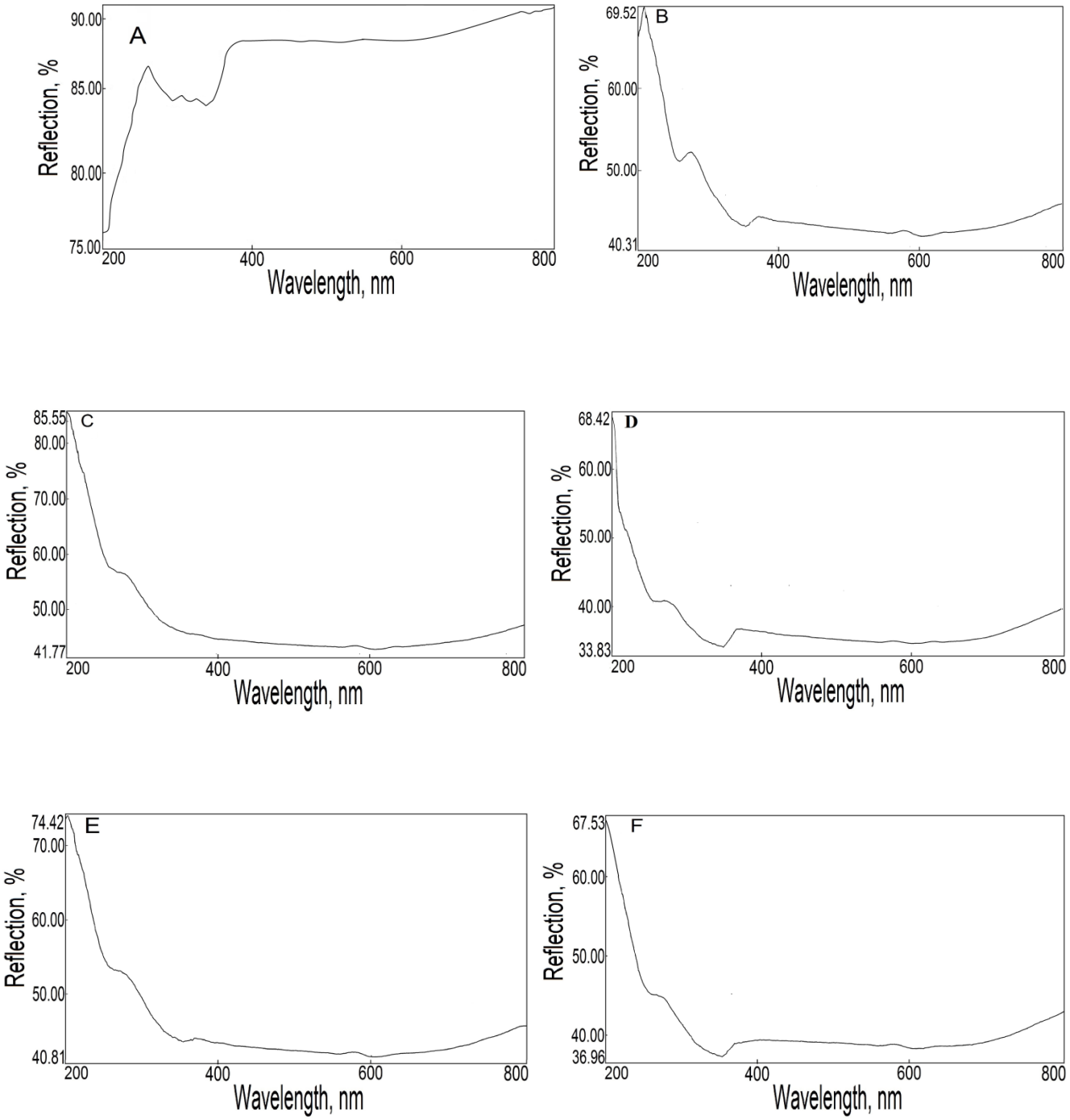
Electronic reflection spectra

The use of visible and ultraviolet spectroscopy to explain the structural aspects of chelates is a rather simple but powerful tool. The application of ultraviolet spectroscopy is more universal and can be useful in structural determinations of all chelates since they all absorb in this region [27]. Fig 2 showed the electronic solid reflection spectra of free gatifloxacin andtheir metal complexes. Table 3 reportedthe assignments of all observed bands from 800-200 nm. The reflection spectrum of free gatifloxacin showed bands at 260 and 280 nm which is assigned to π-π^* transitions, and at 308, 326 and 348 nm which is assigned to n-π^* transitions. For the five complexes the reflectance bands λ_{max} shifts to higher and to lower values attributed to complexation behavior of gatifloxacin towards metal ion.These complexes showed new band from 498 to 579 nm, which may be assigned to the ligand to metal charge-transfer [28, 29].

Table (3):UV-Vis. Spectra for (A) (GFLX), (B) $[VO(GFLX)_2DMF]Cl_3.3H_2O$, (C) $[VO(GFLX)_2An]Cl_3.5H_2O$, (D) $[VO(GFLX)_2Py]Cl_3.3H_2O$, (E) $[VO(GFLX)_2o\text{-}Tol]Cl_3.H_2O$ and (F) $[VO(GFLX)_2Et_3N]Cl_3.H_2O$.

Assignments (nm)	GFLX	GFLX complex with				
	A	B	C	D	E	F
π-π^* transitions	260,280	208,275	209,272	211,272	211,273	212,269
n-π^* transitions	308,326, 348	377,431	372	375,416	368,368	402,414,424,476
Ligand-metal charge transfer	-	576	579	577	501,556, 575	498,540,577

Figure 2: UV-Vis.Spectrafor (A) (GFLX); (B) $[VO(GFLX)_2DMF]Cl_3.3H_2O$, (C) $[VO(GFLX)_2An]Cl_3.5H_2O$, (D) $[VO(GFLX)_2Py]Cl_3.3H_2O$, (E) $[VO(GFLX)_2o\text{-}Tol]Cl_3.H_2O$ and (F) $[VO(GFLX)_2Et_3N]Cl_3.H_2O$.



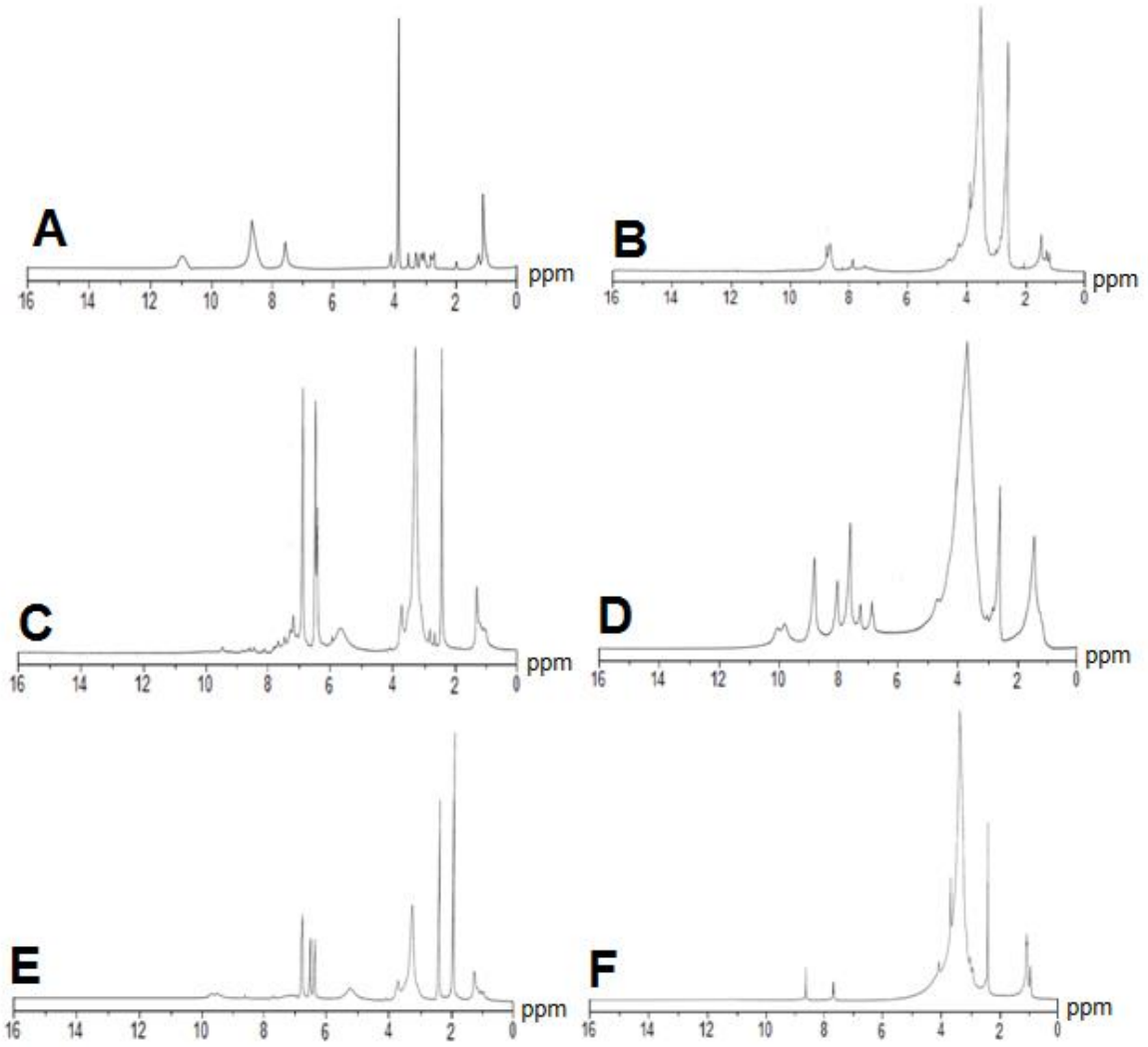
The ^{1}H NMR spectra

The ^{1}H NMR spectra for gatifloxacin and their isolated solid complexes in DMSO-d_6 as a solvent were recorded. The ^{1}H NMR spectra of parent molecule(Fig. 3) showed a multiplet at δ:0.97–1.23 ppm corresponding to cyclopropane protons; doublet at δ:1.44–1.46 ppm for CH_3 of piperazine ring; multiplet at δ:2.90–3.39 ppm for protons of piperazine ring; singlet at δ:3.72 ppm for methoxy group; multiplet at δ:3.98–4.01 ppm for –NCH_2; a weak singlet at 7.50 ppm for $^{+}NH_2$; doublet at δ:7.84- 8.79 ppm for CH aromatic and singlet at 10.80 ppm for carboxylic proton (COOH)Table 4 summarizes the assignments of ^{1}H NMR spectral data of free gatifloxacin and its complexes. On comparing main peaks of gatifloxacin with its complexes, it is observed that all the signals of the free ligand are present in the ^{1}H NMR spectra of the complexes. The signals for the aliphatic and piperazine protons are practically unchanged since they lie far from the binding site of the ligand [30, 31].The resonance of the carboxylic proton (COOH) is not detected in the spectra of the complexes that further suggest the coordination of gatifloxacin through its carboxylate oxygen atoms [32]and due to different chemical environments signals are recorded for the quaternized nitrogen (-$^{+}NH_2$). The (OH) proton peak appears near 4.62–5.2 ppm, adjacent to the piperazine protons, due to the presence of lattice water.

Table (4): ^{1}H NMR values (ppm) and tentative assignments for (A) (GFLX), (B) $[VO(GFLX)_2DMF]Cl_3.3H_2O$, (C) $[VO(GFLX)_2An]Cl_3.5H_2O$, (D) $[VO(GFLX)_2Py]Cl_3.3H_2O$, (E) $[VO(GFLX)_2o\text{-}Tol]Cl_3.H_2O$ and (F) $[VO(GFLX)_2Et_3N]Cl_3.H_2O$.

A	B	C	D	E	F	Assignments
0.97-1.23	1.00-1.27	1.00-1.20	1.32	1.00	0.97-1.12	δH,-CH_2: cyclopropane
1.44-1.46	1.51-1.87	1.31	1.75	1.31	1.30	δH,-CH_3: piperazine
2.90-3.39	2.85	2.85-3.32	2.70	2.47-3.34	2.96-3.41	δH, -NH: piperazine
3.72	3.76	3.76	3.50	3.76	3.75	δH,-CH_3: methoxy
3.98-4.01	4.13	4.13	4.05	4.13	4.13	δH, -N-CH_2
-	4.50	5.74	4.60	5.33	4.61-5.07	δH, H_2O
7.50	7.75-7.78	7.55-6.99	7.39	7.34	7.25	δH, -$^{+}NH_2$
7.84-8.79	8.69-8.57	7.76-7.3	7.8-8.55	7.78	7.74-8.67	δH, -CH aromatic
10.80	-	-	-	-	-	δH, -COOH

Figure 3: ^{1}H NMR spectra of (A) (GFLX), (B) [VO(GFLX)$_2$DMF]Cl$_3$.3H$_2$O, (C) [VO(GFLX)$_2$An]Cl$_3$.5H$_2$O, (D) [VO(GFLX)$_2$Py]Cl$_3$.3H$_2$O, (E) [VO(GFLX)$_2$o-Tol]Cl$_3$.H$_2$O and (F) [VO(GFLX)$_2$Et$_3$N]Cl$_3$.H$_2$O.



Thermal analysis

Thermogravimetric studies for the ligand and their metal complexes were performed in the temperature range 25–1000 °C in N_2 atmosphereat a rate of 10 °C per min. Also, the thermal analysis used to ascertainthe nature of associated water molecules and compositional difference of complexes. Figure4 represented the TGA and DTG curves forgatifloxacin and their isolated solid complexes.Table 5 gives the maximum temperature values for decomposition along with the corresponding weight loss values for each step of the decomposition reaction.

Gatifloxacin is thermally stable in the temperature range 25-50^{o}C. Decomposition of the gatifloxacin started at 50 ^{o}C and finished at 800 ^{o}C with two stages, the first step at a maxima temperature 80 ^{o}Ccorresponding to the loss ofC_2H_2 molecule with a mass loss of 6.921%. The second stage of decomposition occurat two maxima 292 and 566 ^{o}C with the total weight loss accompanyingthese stage was 93.079% and may be attributed to the loss of $CO+8C_2H_2+3NO+HF+1.5H_2$.

The [VO(GFLX)$_2$DMF]Cl$_3$.3H$_2$O complex started at 25 ^{o}C and finished at 955^{o}C with three decomposition steps, the first stage with a maxima temperature50^{o}C accompined by weight loss of 5.32%and may be attributed to the loss of 3H$_2$O molecules which is in good agreement with the calculated values of 5.14%. The second stage occurs at maximum temperature 186 ^{o}C corresponds to the loss of dimethylformamide molecule with mass loss of 7.03% (6.95%). The third stageof decomposition occurs at two maxima 314 and 613 ^{o}C and the weight loss found at this stage equals to 69.14%corresponding to loss $14C_2H_2+2HF+HCl+2.5H_2O+3NO+0.5N_2+2NH_4Cl+CO$molecules. This step is associated with the loss of residue gatifloxacinate forming vanadium pentoxide $0.5V_2O_5+9C$ as a final solid product [32,33].

The thermal decompostion of $[VO(GFLX)_2An]Cl_3.5H_2O$ complex involved in three steps, the first stage indicated loss of five water molecules at maximum temperature 121^oC, while second loss was observed at 192-305 ^oC range corresponds to loss aniline molecule. The third stage of decomposition occurs at maximum temperature 679^oC giving residue. At final step the end products stable metal oxide $0.5V_2O_5$+6C was found at 900-1000 ^oC.

The TGA curve of $[VO(GFLX)_2Py]Cl_3.3H_2O$ complex exhibits two main degradation steps. The first step of decomposition occurs from 36 to 237 ^oC at temperature maximum of 135 ^oC is accompanied by a weight loss of 12.63% in agreement with the theoretical values 12.83% for the loss of $3H_2O+2.5C_2H_2+ 0.5N_2$molecules [29]. The second step observed at four maxima 363, 521, 687 and 887^oC with a weight loss of 66.28% this associated with the loss of $13C_2H_2+CO+2HF+HCl+2.5H_2O+2NH_4Cl+4NO+H_2$molecules,giving the final product $0.5V_2O_5$+11C.

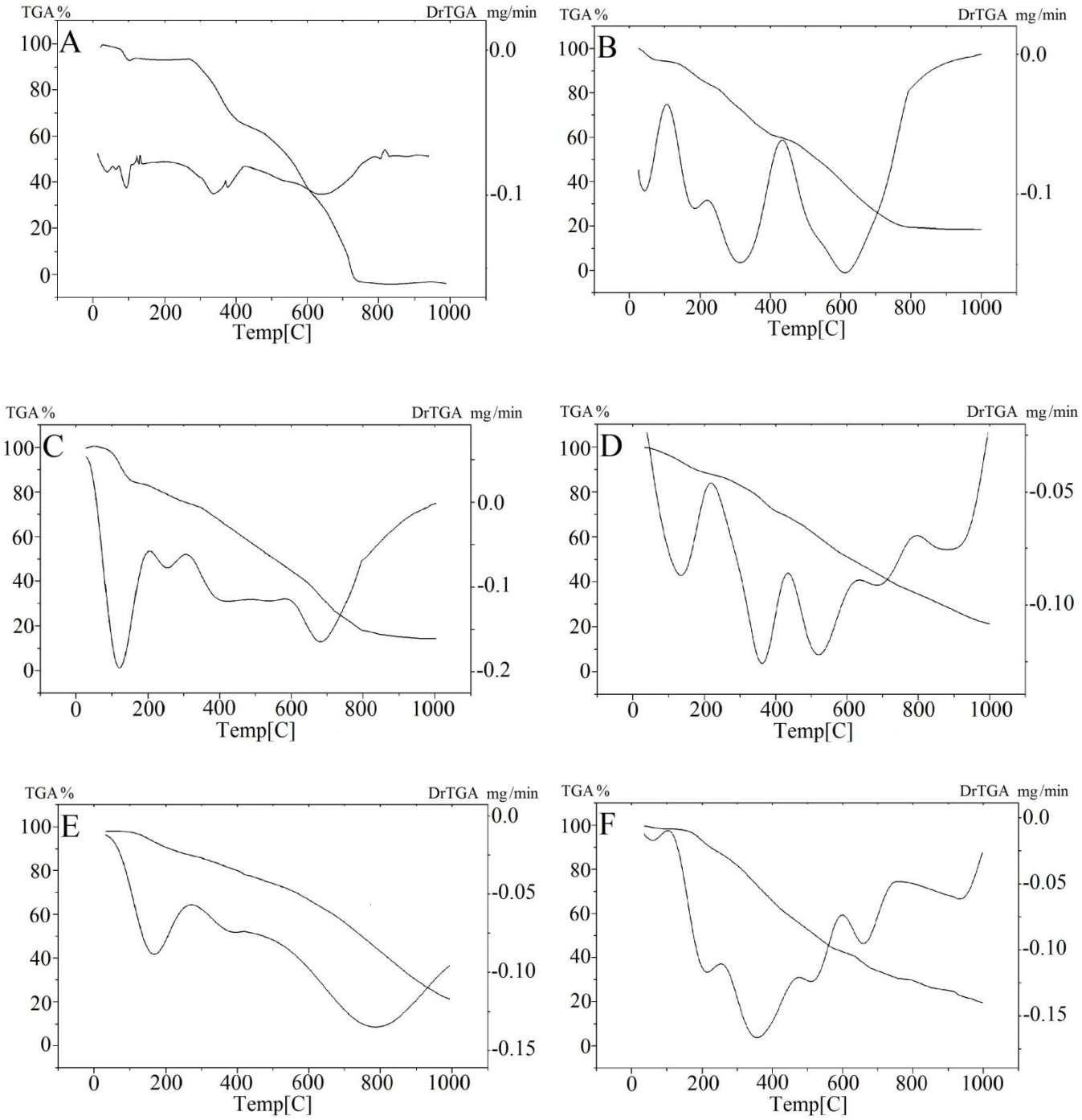
For $[VO(GFLX)_2o\text{-}Tol]Cl_3.H_2O$ complex exhibits two main degradation steps. The first step of decomposition occurs from 35 to 237 ^oC at temperature maximum of 171^oC is accompanied by a weight loss of 12.01% in agreement with the theoretical values 11.84% for the loss of$3C_2H_2+H_2+NH_3+CO$molecules. The second step of decompostion occurs at two maxima 384 and 791 ^oC with a weight loss of 69.96% , this associated with the loss of$15C_2H_2+2HF+2HCl+NH_4Cl+5NO+1.5H_2+1.5H_2O$molecules,giving the final product $0.5V_2O_5$+8C.

The thermal decompostion of $[VO(GFLX)_2Et_3N]Cl_3.H_2O$complex proceeds with three main degradation steps. The first stage of decomposition occurs at temperature maximum of 60 ^oC. The found weight loss associated with step is 1.71% and may be attributed to the loss of H_2Omoleculesin agreement with the theoretical values 1.73%.The second stage of decomposition occurs at maximum temperature 217 ^oC and the weight loss found at this stage equals to 9.81% corresponds to loss triethylamin. The third stage of decomposition occurs at fourth maxima 356,511,661and940^oC and the weight loss found at this stage equals to 69.28% corresponds to loss $14C_2H_2+CO+2HF+HCl+2NH_4Cl+4No+1.5H_2O+H_2$molecules,giving the final product $0.5V_2O_5$+9C.

Table (5): The maximum temperature T_{max} (^{o}C) and weight loss values of the decomposition stages for GFLX and V(V) complexes.

Compounds	Decomposition	T_{max}(^{o}C)	Weight loss (%)		Lost species
			Calc.	Found	
GFLX($C_{19}H_{22}N_3O_4F$)	First step	80	6.94	6.92	C_2H_2
	Second step	292,566	93.06	93.08	$8C_2H_2$+HF+CO+3NO+1.5H_2
	Total loss		100.00	100.00	
	Residue				
[VO(GFLX)$_2$DMF]Cl_3.3H_2O	First step	50	5.14	5.32	3H_2O
($VC_{41}H_{57}F_2N_7O_{13}Cl_3$)	Second step	186	6.95	7.03	C_2H_6+CO+0.5N_2+0.5H_2
	Third step	314,613	68.97	69.14	$14C_2H_2$+CO+2HF+HCl+2NH_4Cl+3NO+2.5H_2O+0.5N_2
	Total loss		81.06	81.49	
	Residue		18.93	18.51	0.5V_2O_5+9C
[VO(GFLX)$_2$An]Cl_3.5H_2O	First step	121	16.27	16.32	5H_2O
($VC_{44}H_{61}F_2N_7O_{14}Cl_3$)	Second step	252	8.41	8.34	$3C_2H_2$+0.5N_2+0.5H_2
	Third step	679	60.60	60.27	$16C_2H_2$+2HF+3HCl+2.5H_2O+4NO+H_2+N_2
	Total loss		85.28	84.93	
	Residue		14.72	15.07	0.5V_2O_5+6C
[VO(GFLX)$_2$Py]Cl_3.3H_2O	First step	135	12.83	12.63	3H_2O+2.5C_2H_2+0.5N_2
($VC_{43}H_{55}F_2N_7O_{12}Cl_3$)	Second step	363,521,687,887	65.89	66.28	$13C_2H_2$+CO+2HF+HCl+2.5H_2O+2NH_4Cl+4NO+H_2
	Total loss		78.72	78.90	
	Residue		21.28	21.10	0.5V_2O_5+11C
[VO(GFLX)$_2$o-Tol]Cl_3.H_2O	First step	171	11.84	12.01	$3C_2H_2$+H_2+NH_3+CO
($VC_{45}H_{55}F_2N_7O_{10}Cl_3$)	Second step	384,791	70.34	69.96	$15C_2H_2$+2HF+2HCl+NH_4Cl+5NO+1.5H_2+1.5H_2O
	Total loss		82.18	81.97	
	Residue		17.82	18.03	0.5V_2O_5+8C
[VO(GFLX)$_2$.Et_3N]Cl_3.H_2O	First step	60	1.73	1.71	H_2O
($VC_{44}H_{61}F_2N_7O_{10}Cl_3$)	Second step	217	9.70	9.81	$3C_2H_4$+NH_3
	Third step	356,511,661,940	69.50	69.28	$14C_2H_2$+CO+2HF+HCl+2NH_4Cl+4NO+H_2+1.5H_2O
	Total loss		80.93	80.80	
	Residue		19.07	19.20	0.5V_2O_5+9C

Figures 4: The TGA and DTG curves for (A) (GFLX); (B) $[VO(GFLX)_2DMF]Cl_3.3H_2O$, (C) $[VO(GFLX)_2An]Cl_3.5H_2O$, (D) $[VO(GFLX)_2Py]Cl_3.3H_2O$, (E) $[VO(GFLX)_2o\text{-}Tol]Cl_3.H_2O$ and (F) $[VO(GFLX)_2Et_3N]Cl_3.H_2O$.



Antimicrobial activity

The efficiencies of gatifloxacin and their metal complexes have been investigated against three Gram-negative, *Escherichia coli* (*E. coli*), *Pseudomonas aeruginosa* (*P. aeruginosa*) and*Klebsiella pneumonia*(*K.pneumoniae*)andthree Gram-positive, *(S. epidermidis), (B. pumilus)* and*(S. aureus)*microorganisms(Fig. 5).The results of the antibacterial study of the gatifloxacin and the five complexes have inhibitory action against all the three types of Gram-positive bacteria and Gram-negative bacteria (Table 6). All complexes showed a good activity against Gram-negative and Gram-positive microorganisms when compared with the free gatifloxacin. On the other hand, $[VO(Gat)_2Py]Cl_3.3H_2O$ complex and $[VO(Gat)_2Et_3N]Cl_3.H_2O$ exhibit excellent activity against all bacterial species. Such increased activity of metal chelate can be explained on the basis of the overtone concept and chelation theory.

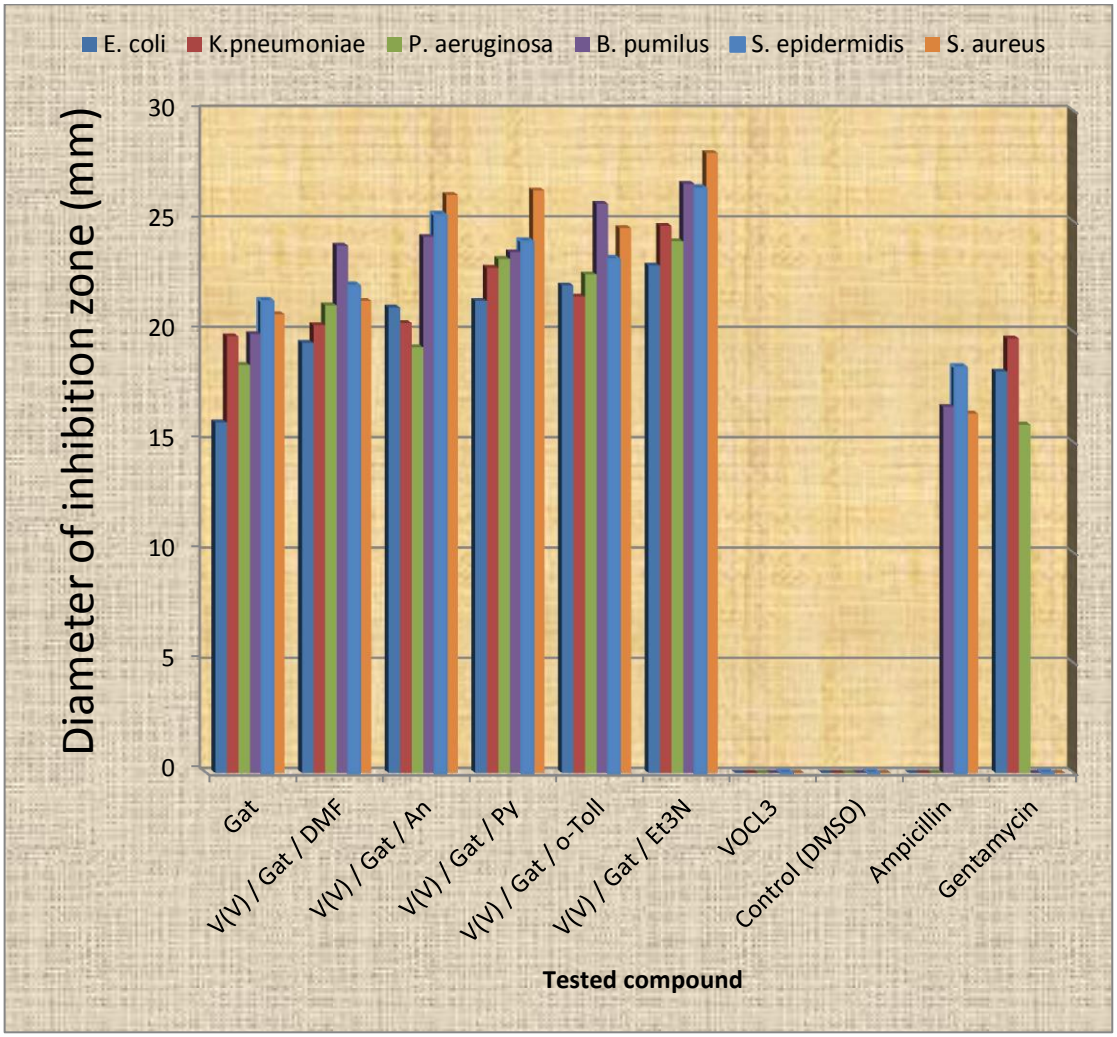
According to the overtone concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipid-soluble materials in which liposolubility is an important factor that controls the antimicrobial activity. On chelation the polarity of the metal ion will be reduced to a greater extent due to overlap of ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Further it increases the delocalization of π-electrons over the whole chelate ring and enhances the lipophilicity of the complexes [31]. This increased lipophilicity enhances the penetration of complexes into the lipid membranes and blocks the metal binding sites in enzymes of microorganisms. These complexes also disturb the respiration process of the cell and thus block the synthesis of proteins, which restricts further growth of the microorganisms [25, 34].

Table (6): The inhibition diameter zone values (mm) for Gatifloxacin and their complexes.

compounds	Microbial Bacteria species					
	E. coli	*K.pneumoniae*	*P. aeruginosa*	*B. pumilus*	*S. epidermidis*	*S. aureus*
GFLX	15.9 ±0.3	19.8 ±0.2	18.5 ±0.2	19.9 ±0.3	21.4 ±0.4	20.8 ±0.4
V(V)/GFLX/DMF	19.5^{NS} ±0.1	20.3^{NS} ±0.1	21.2^{+1} ±0.1	23.9^{+1} ±0.1	22.1^{NS} ±0.1	21.4^{NS} ±0.1
V(V)/ GFLX /An	21.1^{+1} ±0.1	20.4^{NS} ±0.1	19.3^{NS} ±0.1	24.3^{+1} ±0.1	25.3^{+1} ±0.2	26.2^{+2} ±0.3
V(V)/ GFLX /Py	21.4^{+1} ±0.1	22.9^{+1} ±0.1	23.3^{+1} ±0.2	23.6^{+1} ±0.3	24.1^{+1} ±0.1	26.4^{+2} ±0.1
V(V)/ GFLX /o-Tol	22.1^{+1} ±0.1	21.6^{NS} ±0.1	22.6^{+1} ±0.2	25.8^{+2} ±0.3	23.3^{+1} ±0.1	24.7^{+1} ±0.3
V(V)/ GFLX /Et_3N	23.0^{+1} ±0.3	24.8^{+1} ±0.3	24.1^{+1} ±0.4	26.7^{+2} ±0.3	26.5^{+1} ±0.4	28.1^{+2} ±0.4
$VOCl_3$	0	0	0	0	0	0
Control (DMSO-d_6)	0	0	0	0	0	0
Standard Ampicillin	0	0	0	16.6 ±0.06	18.4 ±0.2	16.3 ±0.08
Gentamycin	17.2 ±0.04	19.7 ±0.09	15.8 ±0.08	0	0	0

NA: No activity, data are expressed in the form of mean ± SD.Statistical significance $^{(NS)}$ not significance, $p > 0.05$; $^{(+1)}$ significant, $p < 0.05$; $^{(+2)}$ highly significant, $p < 0.01$; $^{(+3)}$ very highly significant, $p < 0.001$; student's t-test.

Figure. 5: Statistical representation for biological activity of gatifloxacin and its complexes.



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