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Synthesis, Spectroscopic Studies, and Biological Activity of Some New N_2O_2 Tetradentate Schiff Base Metal Complexes

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Abstract—The new tetradentate Schiff base *N*,*N*'-ethylene bis[1-ethyl-6-fluoro-4-imine-7-(piperazine-1-yl)-quinoline-3-carboxylic acid] (Nor-en) has been synthesized. Its chelated complexes with Co(II), Ni(II), Cu(II), Zn(II), Y(III), Zr(IV), La(III), and U(VI) are characterized using molar conductivity, magnetic moment, FT-IR, UV-Vis, ^{1}H NMR, and mass spectra, and thermal analysis. It is determined that the complexes have monomeric structures and exist in the octahedral configuration. The molar conductance values indicate the electrolytic nature of the complexes. According to the spectroscopic data, the complexes share the same coordination environment around the metal ions, consisting of N_2O_2 and one or two water molecules. The thermodynamic parameters (activation energy, E*, entropy, ΔS*, enthalpy, ΔH*, and Gibbs free energy, ΔG*) are calculated using Coats–Redfern and Horowitz–Metzger methods. The carried out tests indicate the compounds' high antibacterial activity against *Staphylococcus aureus*, *Bacillus cereus*, and *Salmonella typhi*. Anticancer activity of the ligand and its metal complexes is evaluated against HepG-2 cells (human Hepatocellular carcinoma) and determined to be very low.

Keywords: Nor-en, metal complexes, spectroscopy, thermal analysis, antimicrobial activity

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INTRODUCTION

Poly dentate Schiff bases ligands form stable complexes with transition metals. Such complexes have been used in catalysis [1], medicine [2], crystal engineering [3], and corrosion protection [4].

Fluoroquinolone norfloxacin is used in treatment of a wide range of infections. Norfloxacin can react with aliphatic or aromatic amines giving Schiff bases [5]. According to the literature survey highly limited attention has been paid to complexes of fluoroquinolones Schiff bases with transition metals [6, 7].

For filling in that gap, a series of metal complexes with norfloxacin Schiff base (Scheme 1) were synthesized and characterized by conductivity, magnetic susceptibility measurements, FT-IR, UV–Vis, ^{1}H NMR, and mass spectra, and thermal analysis. Antibacterial, antifungal and anticancer activities of the complexes were tested.

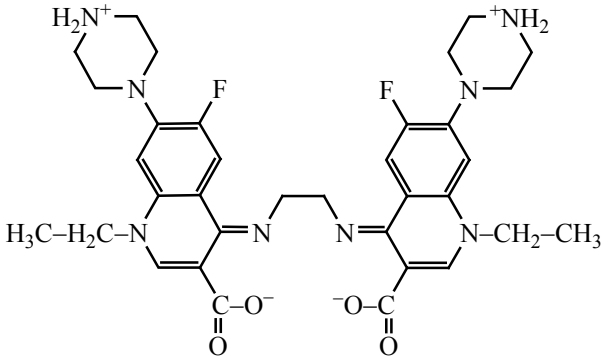
EXPERIMENTAL

All high purity chemicals were purchased from Aldrich Chemical Co., Fluke Chemical Co. and Egyptian International Pharmaceutical Industrial Company (EIPICO). The antibiotic discs were purchased from Hi-media Laboratories Ltd**.**

Synthesis of the ligand (Nor-en) Schiff base ($C_{34}H_{40}N_8O_4F_2$). An ethanolic solution of norfloxacin (2 mmol, 1.378 g) with ethylenediamine (1 mmol, 0.066 mL) was refluxed in the presence of 1 mL of glacial acetic acid for 4 h. The resulting mixture was concentrated on a water bath then cooled down to 0°C. White precipitate was filtered off, washed several times by ethanol and dried under vacuum over $CaCl_2$.

Synthesis of metal complexes. The solid complex $[Co(Nor\text{-}en)(H_2O)_2]Cl_2{\cdot}2H_2O$ (1) was prepared by adding dropwise 0.5 mmol (0.118 g) of $CoCl_2{\cdot}6H_2O$ dissolved in 20 mL of ethanol to a stirred suspension of Nor-en (0.5 mmol, 0.345 g) in 50 mL of ethanol. The reaction mixture was stirred at room temperature for 72 h, then left for slow evaporation. Thus formed precipitate was filtered off and dried under vacuum over anhydrous $CaCl_2$. The blue, white, faint brown, white and yellow solid complexes $[Ni(Nor\text{-}en)(H_2O)_2](CH_3COO)_2{\cdot}6H_2O$ (**2**), $[Cu(Nor\text{-}en)(H_2O)_2](CH_3COO)_2{\cdot}4H_2O$ (**3**), $[Zn(Nor\text{-}en)(H_2O)_2]$

Scheme 1. *N,N'*-ethylene bis[1-ethyl-6-fluoro-4-imine-7-(piperazine-1-yl)-quinoline-3-carboxylic acid] (Nor-en).



$(NO_3)_2 \cdot 3H_2O$ (**4**), $[Y(Nor\text{-}en)(H_2O)_2]Cl_3 \cdot 10H_2O$ (**5**), $[ZrO(Nor\text{-}en)H_2O]Cl_2 \cdot H_2O$ (**6**), $[La(Nor\text{-}en)(H_2O)_2]Cl_3 \cdot 8H_2O$ (**7**), and $[UO_2(Nor\text{-}en)(H_2O)_2](CH_3COO)_2 \cdot 3H_2O$ (**8**) were prepared in a similar manner as described above using the respective salts $Ni(CH_3COO)_2 \cdot 2H_2O$, $Cu(CH_3COO)_2$, $Zn(NO_3)_2 \cdot 6H_2O$, $YCl_3 \cdot 6H_2O$, $ZrOCl_2 \cdot 8H_2O$, $LaCl_3 \cdot 7H_2O$, and $UO_2(CH_3COO)_2 \cdot 2H_2O$.

Elemental analysis was performed on a Perkin Elmer 2400 CHN elemental analyzer. The chlorides content in the complexes was determined according to the Volhard method [8]. The metal ions content was determined by atomic absorption on a Spectrometer PYE-UNICAM SP 1900 fitted with the corresponding lamp and gravimetrically by transforming the solid products into metal oxides. FT-IR spectra (KBr) were recorded on a FT-IR 460 PLUS spectrophotometer. ^1H NMR spectra were measured on a Varian Mercury VX-300 NMR Spectrometer using DMSO-d_6 as a solvent. UV-Vis spectra were recorded for DMSO-d_6 solutions on a Schimadzu UV-3101PC spectrophotometer. Mass spectra were measured on a GCMS-QP-1000EX Shimadzu (ESI-70ev) in the range of 0–1090. TG-DTG measurements were carried out under N_2 atmosphere within the temperature range 20–1000°C on a Shimadzu TGA-50H. Room temperature magnetic susceptibilities of the powdered samples were measured on a Sherwood scientific magnetic balance using $Hg[Co(CSN)_4]$ as a calibrant. All analytical measurements were carried out at Micro Analytical Center, Cairo University, Egypt. Molar conductance of the compounds (1×10^{-3} M) was measured in DMF on a CONSORT K410. Melting points were determined on a Buchi apparatus.

Antimicrobial activity. The ligand and its metal complexes were tested for antibacterial activity against Gram(+) *Staphylococcus aureus* (*S. aureus*) ATCC6538, *Bacillus cereus* (*B. cereus*) GST4, isolated in the Microbiology department, faculty of medicine, Zagazig University, Egypt, and Gram(–) *Escherichia coli* (*E. coli*) ATCC11229, *Salmonella typhi* (*S. typhy*) ATCC14028, isolated in El Ahrar Hospital, Zagazig, Egypt. Anti-fungal activity was studied against two species, *Aspergillus niger* (*A. niger*) OC10 and *Penicillium vulpinum* (*P. vulpinum*) CM1 (Faculty of Medicine, Zagazig University) [9]. The nutrient Müller–Hington agar medium for antibacterial and antifungal tests were prepared [10], then cooled down to 47°C and seeded with tested microorganisms. Sterile water agar layer was solidified, after which 5 mm diameter discs were aseptically placed over inoculated agar plates and incubation conditions were created. The disc diffusion method for measuring the inhibition zone diameters [11] was used. The tested compounds were introduced in petri dishes (0.1 mL) after dissolving in DMF (1.0×10^{-3} M). The culture plates were incubated at 37°C for 20 h for bacteria and for seven days at 30°C for fungi. The activity was determined by measuring the inhibition zone diameter (in mm). Bacterial growth inhibition was calculated with reference to the positive control, Amikacin (AK, 30 μg), Cefuroxime (CXM, 30 μg), Cefpodoxime (CPD, 30 μg), Ceftazidime (CAZ, 30 μg), and Ciprofloxacin (CIP, 5 μg). Antifungal antibiotics references used were dare Nystatin (NS, 100 μg), and Fluconazole (FU, 10 μg).

Anticancer activity. Human liver carcinoma cell line (HepG-2 cells) (human Hepatocellular carcinoma) was obtained from VACSERA Tissue Culture Unit. The mammalian cells were propagated in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% heat-inactivated fetal bovine serum, 1% L-glutamine, HEPES buffer and 50 μg/mL gentamycin. All cells were maintained at 37°C in a humidified atmosphere of 5% CO_2 and subcultured two times a week.

Anticancer activity. The extracts or pure compounds were tested against human liver carcinoma cell line

Table 1. Analytical and physical data for Nor-en and metal complexes **1**–**8**

Compound	M_w	Yield,%	mp, °C	Color	Calculated, % / Found, %					μ_{eff}, B.M.	Λ, S cm^2 mol^{-1}
					C	H	N	M	Cl		
Nor-en, $C_{34}H_{40}N_8O_4F_2$	689	82.5	220	White	59.22 59.10	6.24 6.03	16.26 16.11	–	– –	–	15.30
1, $CoC_{34}H_{48}N_8O_8F_2Cl_2$	863.93	85.31	335	Faint	47.23 47.20	5.56 5.53	12.96 12.92	6.82 6.78	8.22 8.19	4.60	157.13
2, $NiC_{38}H_{62}N_8O_{16}F_2$	982.69	78.69	350	Faint blue	46.40 46.10	6.31 6.27	11.39 11.34	5.97 5.95	–	3.11	148.16
3, $CuC_{38}H_{58}N_8O_{14}F_2$	951.54	68.52	240	Blue	47.92 47.89	5.67 5.65	11.77 11.72	6.68 6.66	–	2.40	142.22
4, $ZnC_{34}H_{50}N_{10}O_{15}F_2$	941.39	72.49	310	White	43.34 43.31	5.31 5.27	14.87 14.83	6.95 6.91	–	–	141.31
5, $YC_{34}H_{64}N_8O_{16}F_2Cl_3$	1073.4	76.45	340	White	38.01 38.00	5.96 5.94	10.43 10.41	8.28 8.27	9.92 9.91	–	155.34
6, $ZrC_{34}H_{44}N_8O_7F_2Cl_2$	876.224	64.30	210	Faint brown	46.56 46.54	5.02 5.01	12.76 12.74	10.41 10.32	8.10 7.96	–	166.17
7, $LaC_{34}H_{60}N_8O_{14}F_2Cl_3$	1087.4	72.52	290	White	37.52 37.41	5.52 5.23	10.30 10.10	12.77 12.55	9.79 9.71	–	205.67
8, $UC_{38}H_{56}N_8O_{15}F_2$	1140.02	68.46	300	Yellow	39.99 39.97	4.91 4.85	9.83 9.81	20.88 20.86	–	–	135.42

(HepG-2 cells) (human Hepatocellular carcinoma). All cytotoxicity tests were carried out in Tissue culture unit at the Regional Center for Mycology and Biotechnology RCMB, Al-Azhar University, Cairo, Egypt.

The cell lines were seeded in 96-well plate at cell concentration of 1×10^4 cells per well in 100 μL of growth medium. After 24 h of seeding, the monolayers were washed with sterile phosphate buffered saline (0.01 M, pH 7.2), and simultaneously the cells were treated with 100 μL from different dilutions of the test sample in fresh maintenance medium and incubated at 37°C. Different two-fold dilutions of the tested compound (500, 250, 125, 62.5, 31.25, 15.6, 3.9, and 0.0 μg/mL) were added to the confluent cell monolayer dispensed into 96-well, flat-bottomed microtiter plates (Falcon, NJ, USA) using a multichannel pipette. The microtiter plates were incubated at 37°C in a humidified incubator in 5% CO_2 atmosphere for 24 h. Untreated cells were served as controls. Three independent experiments were performed, each containing six replicates for each concentration of the tested samples. The cytotoxic effect of the compounds was measured using crystal violet staining viability assay. Briefly, after 24 h of treatment, the medium was removed, 100 μL of 0.5% of crystal violet in 50% methanol was added to each well and incubated for 30 min at room temperature, and subsequently excess dye was washed out gently by distilled water. The plate was allowed to dry, then the viable crystal violet-stained cells were lyses using 30% glacial acetic acid solution [12]. Optical density was measured on a Sun Rise, TECAN micro plate reader. Cisplatin was used as a positive control. The absorbance was proportional to the number of surviving cells in the culture plate. Thus, using this colorimetric procedure, the tested compounds-mediated cell lyses and the cytotoxic effect of Cisplatin (positive control) were measured and compared with the viability of untreated cells. The solutions of different concentrations of the tested compounds were solubilized in DMSO. Controls with DMSO alone were performed in parallel for each concentration.

The percentage cell viability was calculated using the Microsoft Excel. Cells viability was calculated:

$$\text{Cell viability} = [1 - (OD_t/OD_c)]\times100\%,$$

where OD_t is the mean optical density of wells treated with the tested compound and OD_c is the mean optical density of untreated cells. The test results were estimated

Table 2. IR spectra of Nor-en and metal complexes **1**–**8**

Compound	ν(O-H); H_2O; COOH	ν(C=O); COOH	$\nu_{as}(COO^-)$	ν(C=N)	$\nu_s(COO^-)$	$\nu_{as}(U=O)$ $\nu_s(U=O)$	ν(Zr=O)	ν(M–O) ν(M–N)
Nor-en·1.5H_2O	3420 w.br	1712 s	–	1628 v.s	–	–	–	632 w, 588 w, 508 w
1	3464 w	–	1628 v.s	1560 m.s	1385 m.s	–		624 m,5 21 m.s
2	3410 s.br	–	1625 v.s	1574 s	1395 s	–	–	621 m.s, 566 w, 521 w
3	3409 s.br	–	1625 ms	1577 s	1332 m	–	–	695 sh, 625 w, 580 w, 526 m
4	3429 m.br	–	1629 v.s	1564 m.s	1353 v.s		–	632 w, 588 w, 508 w
5	3413 w.br	–	1632 v.s	1572 s	1396 m.s	–		623 m, 564 w, 515 m
6	3410v s.br	–	1631 v.s	1587 w	1483 v.s	–	809 w	626 m, 565 w, 510 m
7	3435v s.br	–	1629 v.s	1563 s	1343 m	–	–	622 w, 560 w, 513 m
8	3426 m.br		1631 s	1571 m	1389 m.s	902 s 819 m		676 w, 622 v w, 563 w, 514 w

using IC_{50} values derived from graphical plots of surviving cells vs compound concentration.

RESULTS AND DISCUSSION

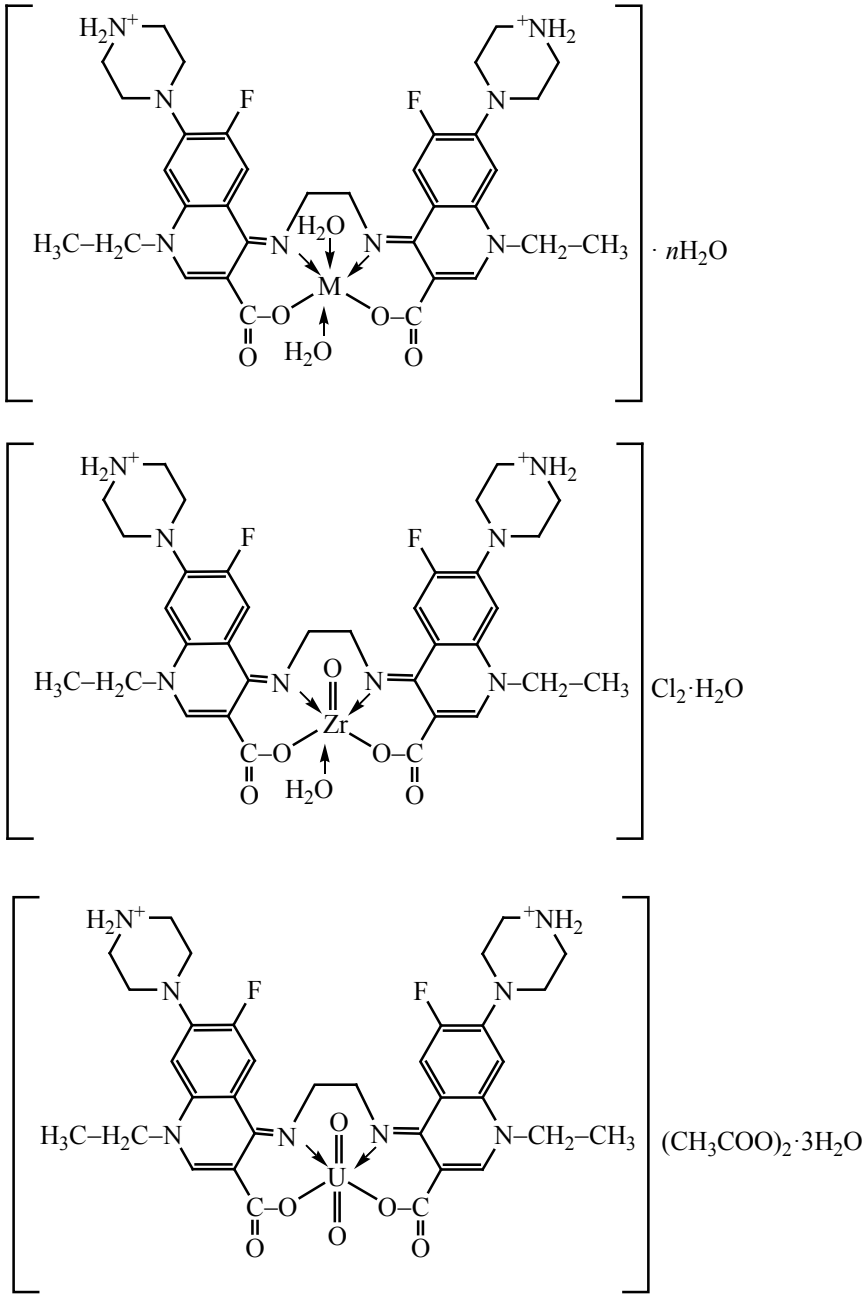
Molar conductivity of the compounds was measured in DMF at room temperature: Nor-en 15.30 S cm^2/mol and for complexes to be in the range of 135.42–205.67 S cm^2 mol^{-1}. The data indicated that the complexes **5** and **7** were 1 : 3 electrolytes while the other complexes were 1 : 2 electrolytes. The magnetic properties of the complexes have been measured at 295 K. The effective magnetic moment (4.6 B.M.) was determined for the complex **1**, suggesting the octahedral arrangement around the metal ion. The similar geometry could be assigned to complex **2** based on the magnetic moment (3.11 B.M.). For Cu-Nor-en (**3**), μ_{eff} = 2.4 B.M. corresponded to the presence of one unpaired electron [8]. Complexes **4**–**8** were determined to be diamagnetic (Table 1).

FT-IR spectra of complexes were compared with that of Nor-en. The IR spectrum of Nor-en demonstrated absence of the bands characteristic for NH_2 group of ethylenediamine and C=O of pyridone group of norfloxacin. The strong band recorded at 1628 cm^{-1} was attributed to C=N and it indicated condensation of the amino groups with the pyridone group, hence formation of the Schiff base linkage [13]. The spectra of all complexes contained bands in the range of 3409–3464 cm^{-1} originated from O-H vibrations indicating the presence of water molecules in all complexes [14]. The bands of different intensities in the range of 2870–1966 cm^{-1} were assigned to the quaternized nitrogen of the piperazine group, assigned to the zwitterionic form of Nor-en. Interaction of the carbonyl group oxygen with metal ions was recorded by absence of the band at 1712 cm^{-1} and the presence of the band at ca 1628 cm^{-1} in all complexes spectra [15]. Presence of the asymmetric stretching vibration band in 1625-1632 cm^{-1} region and ν_{sym} in the region of 1332–1483 cm^{-1} with $\Delta\nu > 200$ cm^{-1} for the ligated carboxylate group indicated the carboxylate group monodentate interaction via one of oxygen atoms [14,15]. Also, the shift of the characteristic band of azomethine group from 1560 cm^{-1} to 1587 cm^{-1} in all complexes spectra indicated involvement of C=N group in interaction with metal ions [15].

Spectra of the complexes demonstrated a new group of bands with different intensities that were attributed to M-O and M-N (Table 2, Scheme 2).

UV-Vis spectra. The bands of UV-Vis spectra for Nor-en and its complexes (Table 3) were assigned to π–π* and *n*–π* transitions [15]. The bathochromic shift of the bands and absence of the band at 340 nm in spectra of

Scheme 2. Coordination mode of Ni(II), Co(II), Cu(II), Zn(II), Zr(IV), Y(III), La(III), and U(VI) with Nor-en.



M = Co(II), Ni(II), Cu(II), Zn(II), Y(III), La(III). X = Cl^- for Co(II), Y(III) and La(III). X = CH_3COO^- for Ni(II) and Cu(II), X = NO_3^- for Zn(II); n = 2 for Co(II), n = 6 [Ni(II)], 4 [Cu(II)], 3 [Zn(II)], 10 [Y(III)], 8 [La(III)].

complexes as well as the new bands recorded indicated formation of the metal complexes. The bands recorded in the range of 437–473 nm could be assigned to the ligand to metal charge-transfer [13]. In case of complexes **1**–**3** the new bands observed in the range of 547–578 nm were assigned to d-d transition and indicated chelation of the ligand with metal ions [16]. The bands recorded for Co(II), Ni(II) and Cu(II) complexes at 552, 578, and 547 nm, respectively, were assigned to $^4T_{1g}$(F) $^4T_{1g}$(P), $^3A_{2g}$(F) $^3T_{2g}$, and $^2B_{1g}{}^2E_g$ transitions, respectively [17].

^{1}H NMR spectra. ^{1}H NMR spectra of Nor-en and its complexes supported formation of the complexes. The signal at 11 ppm (COOH) in the spectrum of the ligand was not recorded in those of the complexes indicating deprotonation and complexation of the ligand with metal

Table 3. UV-Vis spectra of Nor-en and metal complexes **1**–**8**

Compound	Band, nm			
	π–π* transitions	*n*–π* transitions	ligand-metal charge transfer	*d*–*d* transition
Nor-en	288	340		
1	283	336	473	552
2	268	330	442	578
3	287	324	438	547
4	284	317, 336	469	
5	283	321, 336	440	
6	281	321, 340	483	
7	285	318, 336	437	
8	284	322, 338	472	

Table 4. T_{max} and weight loss values of the decomposition stages for Nor-en and metal complexes **1**, **2**

Compound	Lost species	Weight loss, %		T_{max}, °C	Decomposition
		found	calculated		
Nor-en·1.5H_2O	1.5H_2O	3.571	3.92	64	First step
	3C_2H_4 + N_2	16.15	16.26	153	Second step
	3CO + 12C_2H_2 + 2HF + NO + 2.5N_2	77.84	78.10	320, 410, 670	Third step
		97.56	98.26		Total loss
	C	2.43	1.74		Residue
1	2H_2O	4.03	4.16	71	First step
	16C_2H_2 + 4NO + 2HF + N_2 + 2NH_4Cl + H_2O	84.12	84.38	334, 411, 655, 708	Second step
		88.15	88.55		Total loss
	CoO + 2C	11.85	11.45		Residue
2	6H_2O	10.63	10.99	63	First step
	2H_2O	3.21	3.66	113,159	Second step
	19C_2H_2 + 4NO + 2HF + 3H_2O + 2N_2	77.51	77.74	354,752	Third step
		91.35	92.39		Total loss
	NiO	8.64	7.60		Residue

ions [18]. Also, there were measured new signals in the range of 4.10–4.63 ppm (Table 4), assigned to water molecules in the complexes. ^{1}H NMR spectra of the paramagnetic complexes **1**–**3** have been reported [19].

Mass spectra. Mass spectrum of the synthesized free Nor-en was in good agreement with the suggested structure. Fragmentation pattern of complexes is illustrated by that of Nor-en–Zn(II) (Scheme 3).

Thermal studies. Thermal behavior of the solid compounds was studied using TG technique. Nor-en was thermally stable up to 41°C and then decomposed in three steps (Table 4).

Thermal decomposition of complexes **1**, **4**, and **6** took place in two steps. The first step corresponded to elimination of hydrated water molecules. The second step indicated degradation of the organic ligand and leaving CoO, ZnO, or ZrO_2 as a final product. The complexes **2**, **3**, **5**, **7**, and **8** degraded in three steps. The first step corresponded to elimination of the hydrated water. The second step represented elemination of the coordinated water molecules. Accordingly, the third step appeared due to degradation of the organic ligand and leaving NiO, CuO, $YO_{1.5}$, $LaO_{1.5}$, and UO_2 as final products.

Activation thermodynamic parameters. Kinetic

Scheme 3. Fragmentation pattern of Nor-en–Zn(II) complex.

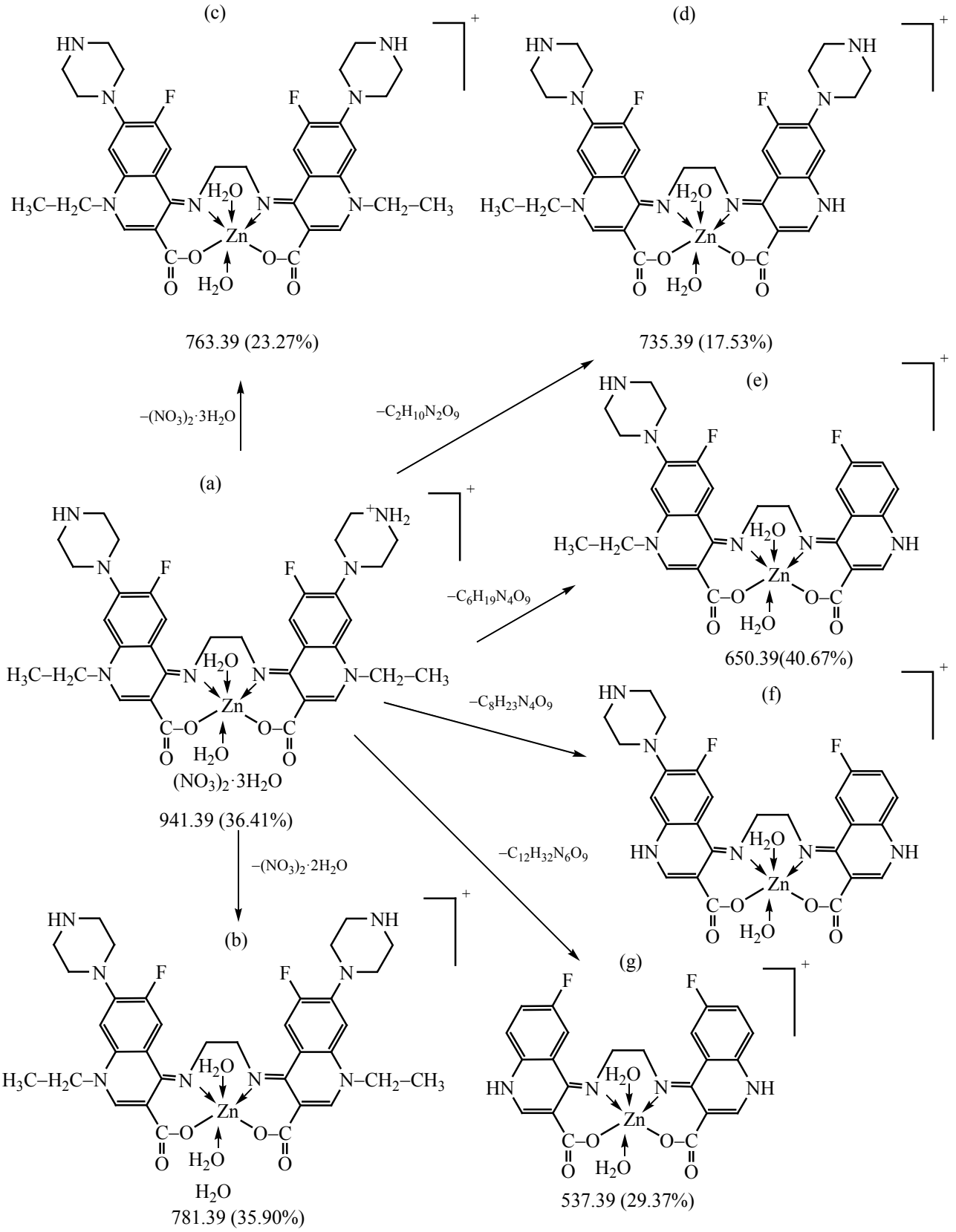


Table 5. Thermal behavior and kinetic parameters (Coats–Redfern and Horowitz–Metzger) for Nor-en and metal complexes **1–8**

Compound	Decomposition range, K	T_s, K	Method	Parameter					R^a	SD[b]
				E^*, kJ/mol	A, s^{-1}	ΔS^*, kJ mol^{-1} K^{-1}	ΔH^*, kJ/mol	ΔG^*, kJ/mol		
Nor-en	495–645	593	CR	126.460	639107.5	–0.0820	121.530	170.190	0.990	0.153
			HM	137.440	10019265	–0.0590	132.510	167.597	0.985	0.203
1	312–410	344	CR	55.820	2369.33	–0.1240	52.960	95.630	0.999	0.004
			HM	61.420	22085.93	–0.0196	58.560	65.303	0.999	0.034
	410–658	607	CR	122.070	105695.5	–0.0972	117.003	176.030	0.987	0.228
			HM	127.980	718993.6	–0.0810	122.940	172.270	0.986	0.256
2	311–356	336	CR	77.510	6437324	–0.0580	74.720	94.250	0.986	0.172
			HM	81.390	6.52×10^{10}	–0.0390	78.603	91.665	0.992	0.144
	470–792	627	CR	52.802	0.0298	–0.2230	47.590	187.320	0.997	0.251
			HM	56.450	0.1450	–0.2090	51.230	182.717	0.995	0.348
3	310–355	330	CR	68.680	664.67	–0.1340	65.940	110.250	0.998	0.075
			HM	44.020	75.29	–0.1520	41.277	91.570	0.999	0.048
	526–695	603	CR	103.240	3247.54	–0.1260	98.230	174.270	0.993	0.118
			HM	111.130	25936.85	–0.0131	106.114	114.010	0.989	0.163
4	452–657	569	CR	94.780	116.837	–0.1533	6.669	93.880	0.986	0.285
			HM	96.260	4092.86	–0.1240	91.520	161.910	0.984	0.333
	741–940	810	CR	176.043	637114.8	–0.0850	169.310	237.890	0.985	0.344
			HM	186.282	5867813.0	–0.0660	179.550	233.180	0.983	0.395
5	308–409	345	CR	45.610	54.580	–0.1550	42.737	96.426	0.993	0.115
			HM	51.660	565.137	–0.1360	48.792	95.770	0.989	0.165
	524–1129	594	CR	61.870	0.113	–0.2650	54.680	218.310	0.994	0.132
			HM	80.670	3.250	–0.1730	75.370	209.314	0.987	0.142
6	333–616	338	CR	37.000	8.905	–0.175	32.160	134.105	0.981	0.066
			HM	48.580	0.065	–0.216	43.730	169.560	0.994	0.046
	616–930	796	CR	68.090	0.087	–0.216	61.470	61.296	0.988	0.146
			HM	94.290	4.599	–0.183	87.680	233.310	0.989	0.165
7	332–497	339	CR	44.480	17.796	–0.165	41.660	97.460	0.983	0.147
			HM	48.730	274.12	–0.142	45.910	94.004	0.983	0.164
	693–820	758	CR	169.400	1642376	–0.076	163.100	220.895	0.996	0.088
			HM	181.760	21285381	–0.055	175.460	217.105	0.994	0.117
8	354–447	322	CR	98.620	6.85×10^{10}	–0.823	95.940	169.177	0.999	0.003
			HM	98.930	2.14×10^{11}	–0.029	96.250	86.980	0.999	0.005
	573–923	724	CR	63.890	0.102	–0.214	57.867	212.720	0.996	0.082
			HM	83.760	3.54	–0.184	77.740	211.206	0.989	0.165

Table 6. Inhibition zone diameter for Nor-en, its metal complexes **1**–**8**, and standard drugs

Compounds	Inhibition zone diameter, mm					
	Bacteria				Fungi	
	E. coli	*Salomonella*	*S.aures*	*B.Cerusus*	*A. niger*	*P. vulpinum*
Nor-en	0	28.6±1.0[c]	24.6±0.8[b]	12.0±0.5[a]	0	0
1	0	23.6±1.0[b]	30.3±0.8[c]	15.6±0.8[a]	0	0
2	0	32.3±1.0[c]	27.0±1.0[c]	12.3±1.0[a]	0	0
3	0	24.6±0.8[b]	29.3±0.6[c]	13.6±0.8[a]	0	0
4	0	28.0±1.0[c]	32.3±0.8[c]	14.3±1.0[a]	0	0
5	0	30.3±0.8[c]	29.0±0.5[c]	7.0±0.5[a]	0	0
6	0	30.3±0.8[c]	27.0±1.0[c]	17.0±1.0[a]	0	0
7	0	28.6±1.0[c]	30.0±1.0[c]	19.6±0.8[a]	0	0
8	0	28.6±0.8[c]	25.6±1.0[b]	11.0±0.5[a]	0	0
Amikacin	14±0.5	14.6±1.0	8.6±0.8	19.3±0.8	0	0
Cefuroxime	0	7.0±0.5	18.3±0.8	0	0	0
Cefpodexime	0	15.3±1.0	19.0±1.0	4.0±0.5	0	0
Ceftazidime	0	15.0±0.5	3.0±0.5	0	0	0
Ethylenedi amine	0	0	0	0	0	0
DMF	0	0	0	0	0	0

Statistical significance: [a] p not significant, $p < 0.05$; p significant, $p > 0.05$; [b] p highly significant, $p > 0.01$; [c] p very highly significant, $p > 0.001$.

thermodynamic characteristics were calculated according to the developed earlier methods [20, 21] (Table 5). The high values of the activation energies indicated thermal stability of the complexes [22]. Negative values of entropy of activation indicated low rate of the decomposition reactions. Also, the correlation coefficients of Arrhenius plots of the thermal decomposition steps were found to lie in the range of 0.983–0.991, demonstrating a good fit with the linear function.

Antibacterial activity. Antimicrobial activity of Nor-en and its complexes was tested against a number of bacteria and fungi using the disc diffusion method [23]. Nor-en was characterized by good to excellent activity against Gram(+) bacteria *Staphylococcus aureus* (*S. aureus*) ATCC6538, *Bacillus cereus* (*B. cereus*) GST4, and Gram(-) *Escherichia coli* (*E. coli*) ATCC11229, *Salmonella typhi* (*S. typhy*) ATCC14028 (Table 6). Nor-en and its metal complexes demonstrated inhibiting of three types of bacteria, while *E. Coli* recorded no effect. Action of the complex **2** against *Salmonella typhi* (32.33±1 mm) was the most active followed by complex **6**. The complex **4** exhibited the highest activity followed by complex **7**. According to the accumulated data complexes were determined to be efficient against the tested organisms and more efficient that the ligand alone.

Antifungal activity. The preliminary fungi treatment by Nor-en and its complexes was performed against *Aspergillus niger* (*A. niger*) OC10 and *Penicillium vulpinum* (*P. vulpinum*) CM1 *species in vitro* by the diffusion agar technique [24]. Nor-en and all its metal complexes demonstrated no fungal growth inhibition.

Anticancer activity. Anticancer activity of the ligand and its metal complexes of Ni(II), Zn(II), Zr(IV), and La(III) was tested against HepG-2 cells (human Hepatocellular carcinoma). Cisplatin was used as a positive control. The *in vitro* action of the compounds on the HepG-2 cells line was estimated on the basis of the selectivity index. All complexes demonstrated weak anticancer activity but one, Zr(IV) complex.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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