INTERNATIONAL JOURNAL OF ADVANCES IN PHARMACY, BIOLOGY AND CHEMISTRY

Research Article

Spectroscopic, thermal and antimicrobial studies on some metal complexes with indomethacin drug

Atiat S. Barakat [1,2], Mohamed S. El-Attar [1,3]*.

[1]Department of Chemistry, Faculty of Science,

Zagazig University, Zagazig, Egypt,

[2]Department of chemistry, Faculty of science, Taibah University,

Al-madinah Al-munawarah, Saudi Arabia,

[3]Medical Chemistry Dept., Preparatory Year Deanship,

Jazan University, Saudi Arabia.

ABSTRACT

In the study presented new metal complexes of indomethacin with Cr(III), Zr(IV), Cd(II), Ce(IV) and U(VI) were prepared and their structure was elucidated through melting point, molar conductivity, magnetic prosperities, elemental analysis, IR, UV-Vis., ^{1}H NMR, mass spectra as well as thermogravimetric analyses. The calculated bond length and force constant, F(U=O), in the uranyl complex are 1.735 Aº and 697.35 Nm^{-1}, respectively. The antibacterial and antifungal activities of the free ligand and their metal complexes were evaluated in vitro.

Keywords: Indomethacine; IR; Mass; Thermal; Antimicrobial activity.

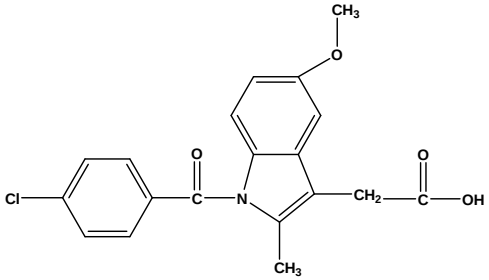
1. INTRODUCTION

indomethacin 2{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid (scheme 1) is a non-steroidal anti-inflammatory drug commonly used as a prescription medication to reduce fever, pain, stiffness, and swelling. It works by inhibiting the production of prostaglandins, molecules known to cause these symptoms. It is marketed under more than seventy different trade names. Indomethacin is one of the most potent of the clinically used non-steroidal anti-inflammatory drugs and interferes with prostaglandin synthesis by direct inhibition of the two cyclooxygenase enzyme systems, Cox-I and Cox-II. Inhibition of the Cox-II system results in anti-inflammatory action, while inhibition of the Cox-I enzyme system results in anti-inflammatory action as well as gastric irritation [1, 2].

Galani et al., [3] reported organotin adducts of indomethacin:

The complexes $[Me_2(Indo)SnOSn(Indo)Me_2]_2$, $[Bu_2(Indo)SnOSn(Indo)Bu_2]_2$ have been prepared.

The crystal structures of the complexes have been determined by X-ray crystallography. Each structure is centro-symmetric and features a central rhombus Sn_2O_2 unit with two additional tin atoms linked at the O atoms. Pairs of tin atoms are bridged by bidentate carboxylate ligands and by a monoatomic bridging oxygen. C–H π, π π, stacking interactions, inter and intramolecular hydrogen bonds stabilize.



Scheme 1. The formulas of 2{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1H-indol-3-yl}acetic acid

In this study, the new solid complexes of indomethacin with Cr(III), Zr(IV), Cd(II), Ce(IV) and U(VI) were prepared in ethanol as a solvent. The complexes were characterized through their melting point, molar conductivity, magnetic properties, elemental analysis, IR, UV-Vis., ^{1}H NMR, mass spectra as well as thermogravimetric analyses. The biological activity of the ligand and their metal chelates were measured against some selected Gram positive and Gram negative bacteria and two species of fungi.

2. MATERIALS

2.1. Chemicals

All chemicals used for the preparation of the complexes were of analytical reagent grade, commercially available from different sources and used without further purification. Indomethacin used in this study were purchased from the Egyptian International Pharmaceutical Industrial Company (EIPICO). $ZrOCl_2.8H_2O$ (99.9%), ethanol, acetone, NaOH, $FeCl_3.6H_2O$, $BaCl_2$, $FeSO_4$, K_2CrO_4 were purchased from Fluka Chemical Co. $Cr(CH_3COO)_3$, $CdCl_2$, $UO_2(CH_3COO)_2.2H_2O$, and $Ce(SO_4)_2$ from Aldrich Chemical Co. These materials used without further purification.

2.2. Synthesis of indomethacin metal complexes

An ethanolic suspended solution (50 mL) of indo. 2mmol (0.714 g) and NaOH 2mmol (0.08 g) added to 1mmol of $Cr(CH_3COOH)_3$ (0.329 g) and the reaction mixture was stirred at room temperature for 20 h. The solution was left for slow evaporation, after that the green $[Cr(Indo)_2(H_2O)_2](CH_3COO).2H_2O$ product was deposited.The solid obtained was filtered under vacuum, washed with ethanol and dried over anhydrous $CaCl_2$. In similar way described above, the yellow-green, white, yellow and yellow $[ZrO(Indo)_2(H_2O)].3H_2O$, $[Cd(Indo)_2(H_2O)_2].2H_2O$, $[Ce(Indo)_2(H_2O)_2](SO_4).2H_2O$ and $[UO_2(Indo)_2(H_2O)].2H_2O$ complexes were prepared by using ethanol as a solvent. Unfortunately we were not able to obtained appropriate monocrystals to perform X-ray diffraction analysis. The qualitative reactions revealed the presence of acetate and sulphate as counter ions.

2.3. Instruments

The infrared spectra of the five solid complexes and Indomethacine were recorded from KBr discs using FTIR 460 plus, ^{1}H NMR spectra were recorded on Varian Mercury VX-300 NMR Spectrometer using DMSO-d_6 as solvent. C, H and N elemental analysis were carried out on a Perkin Elmer CHN 2400. The percentage of metal ions were determined gravimetrically by transforming the solid products into oxide, and also determined by using atomic absorption method. A spectrometer model PYEUNICAMSP 1900 fitted with the corresponding lamp was used for this purposed. Electronic solid reflection spectra of Indomethacin and the isolated solid complexes were obtained in the region of 800–200 nm using UV-3101PC Shimadzu with a 1 cm quartz cell. Mass spectra were done on GCMS-QP-2010 plus Shimadzu(ESI-70 ev) in the range from 0-1090. Magnetic moment measurements were carried out at room temperature where $Hg[Co(SCN)_4]$ was used a calibrant by using Gouy method. Thermogravimetric (TG) and differential (DTG) thermogravimetric analyses were carried out under N -atmosphere using detectors model TGA 50H Shimadzu. The rate of heating of the sample was kept at10 °C/min. Molar conductivities in DMF at $1.0x10^{-3}$ M for all compounds were measured on CONSORT K410.

2.4. Antimicrobial activity

Antibacterial activity of the ligands and there metal complexes were investigated by a previously reported modified method of Beecher and Wong [4] against different bacterial species, such as *Staphylococcus aureus* (*S. aureus*), *Bacillus subtilis* (*B. subtilis)*, *Escherichia coli* (*E. coli*) and *Pseudomonas aeruginosa* (*P. aeruginosa*) and antifungal screening was studied against two species, *Candida Albicans (C. albicans)* and *Aspergillus fumigatus* (*A. fumigatus*). The tested microorganisms isolates were isolated from Egyptian soil and identified according to the standard mycological and bacteriological keys for identification of fungi and bacteria as stock cultures in the microbiology laboratory, Faculty of Science, Zagazig University. 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) and for antifungal (3% Sucrose, 0.3% $NaNO_3$, 0.1% K_2HPO_4, 0.05% KCl, 0.001% $FeSO_4$, 2% Agar-Agar) was prepared and then cooled to 47 ^oC 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 DMF at 1.0×10^{-3} M. These culture plates were then incubated at 37 ^oC for 20 h for bacteria and for seven days at 30 ^oC 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., (Ampicilin, Amoxycillin and Cefaloxin).

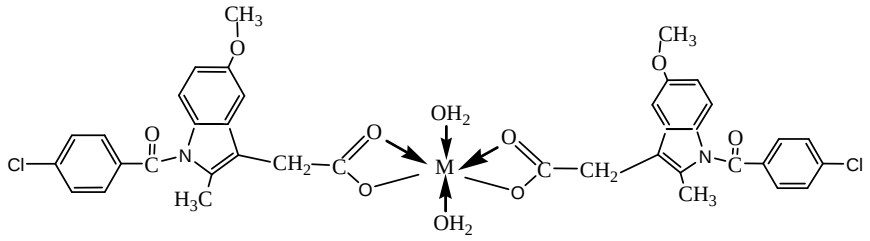
Table 1
Elemental analysis and physico-analytical data for Indo and its metal complexes

Compounds M.Wt. (M.F.)	Yield%	Mp/ °C	Color	Found (Calcd.) (%)				μ_{eff} (B.M.) Λ	S cm^2 mol^{-1}
				C	H	N	M		
Indomethacin 357.787 ($C_{19}H_{16}NO_4Cl$)	80.0	162	White	(63.67) 63.72	(4.51) 4.47	(3.70) 3.91	-	Diamagnetic	13.08
$[Cr(Indo)_2(H_2O)_2](CH_3COO).2H_2O$ 896.57 ($CrC_{40}H_{41}N_2O_{14}Cl_2$)	79.99	>300	Green	(53.24) 53.54	(4.02) 4.57	(3.01) 3.12	(5.78) 5.79	3.82	146.3
$[ZrO(Indo)_2(H_2O)].3H_2O$ 892.77 ($ZrC_{38}H_{38}N_2O_{13}Cl_2$)	80.14	>300	Yellow-Green	(50.98) 51.07	(4.12) 4.25	(3.09) 3.13	(10.18) 10.21	Diamagnetic	14.9
$[Cd(Indo)_2(H_2O)_2].2H_2O$ 897.97 ($CdC_{38}H_{38}N_2O_{12}Cl_2$)	73.52	>300	White	(50.92) 50.78	(4.00) 4.23	(3.23) 3.12	(12.45) 12.51	Diamagnetic	14.6
$[Ce(Indo)_2(H_2O)_2](SO_4).2H_2O$ 1021.69 ($CeC_{38}H_{38}N_2O_{16}Cl_2S$)	75.46	>300	Yellow	(44.58) 44.63	(3.68) 3.72	(2.67) 2.74	(13.80) 13.71	Diamagnetic	176.7
$[UO_2(Indo)_2(H_2O)].2H_2O$ 1037.60 ($UC_{38}H_{36}N_2O_{13}Cl_2$)	78.77	>300	Yellow	(44.01) 43.94	(3.33) 3.47	(2.70) 2.69	(22.87) 22.94	Diamagnetic	15.2

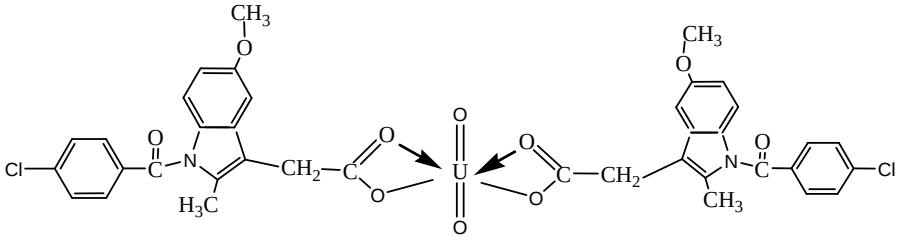
Table 2
The characteristic IR bands of ligand and their metal complexes.

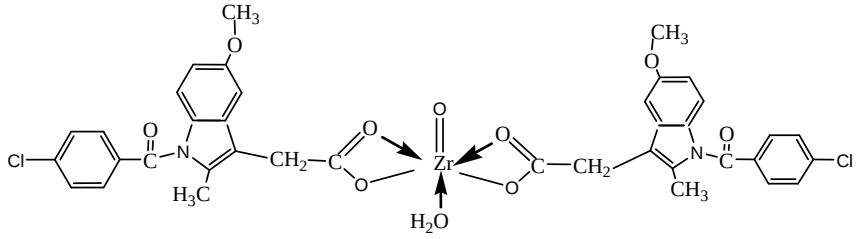
compund	ν(O-H); H_2O; COOH	ν(C=O); COOH	ν(C=O); keto group	$\nu_{as}(COO^-)$	$\nu_s(COO^-)$	ν_{as}(U=O) ν_s(U=O)	ν (Zr=O)	ν(M-O)
Indomethacin	3400w	1709vs	1693vs	1596vs	-	-	-	694s, 656s 594s, 563m 478ms, 436m
$[Cr(Indo)_2(H_2O)_2](CH_3COO).2H_2O$	3395m	-	1682sh 1647m	1585w	1423m	-	-	617w, 521m
$[ZrO(Indo)_2(H_2O)].3H_2O$	3395vs	-	1660vw	1585m	1450w	-	810ms	613m, 529s
$[Cd(Indo)_2(H_2O)_2].2H_2O$	3395m	-	1682vw	1586m	1445s	-	-	617m, 525m
$[Ce(Indo)_2(H_2O)_2](SO_4).2H_2O$	3383w	-	1674sh	1593m	1440s	-	-	617vs, 525m
$[UO_2(Indo)_2(H_2O)].2H_2O$	3380w	-	1624sh	1570vs	1425m	928m 849s	-	617w, 525m

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



M= Cr(III), Cd(II) and Ce(IV)





Scheme 2.

The coordination mode of Cr(III), Zr(IV), Cd(II), Ce(IV) and U(VI) with indomethacin.

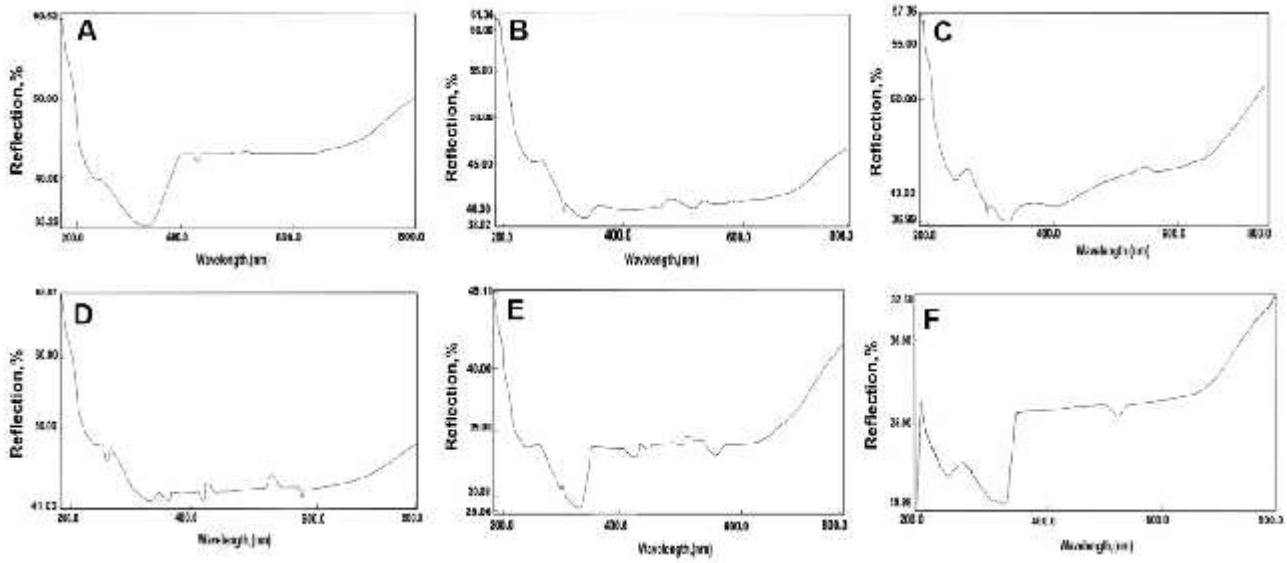


Fig. 1.

Electronic reflection spectra for (A) Indomethacin, (B) $[Cr(Indo)_2(H_2O)_2](CH_3COO).2H_2O$**,** (C) $[Zr(Indo)_2(H_2O)].3H_2O$**,** (D) $[Cd(Indo)_2(H_2O)_2].\ 2H_2O$, (E) $[Ce(Indo)_2(H_2O)_2].2H_2O$**,** (F) $[UO_2(Indo)_2(H_2O)].2H_2O$.

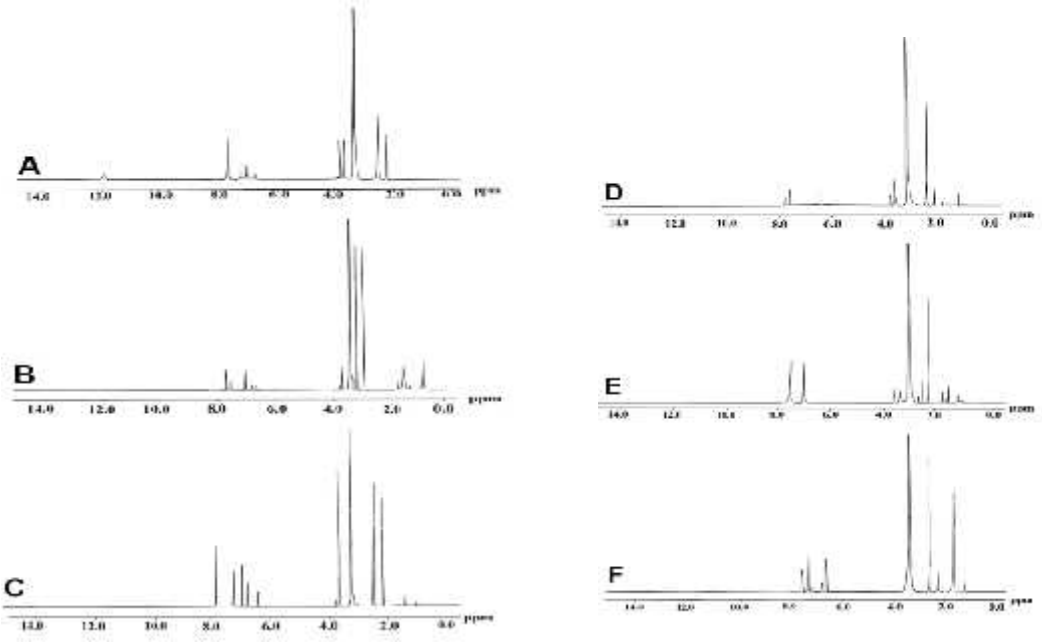
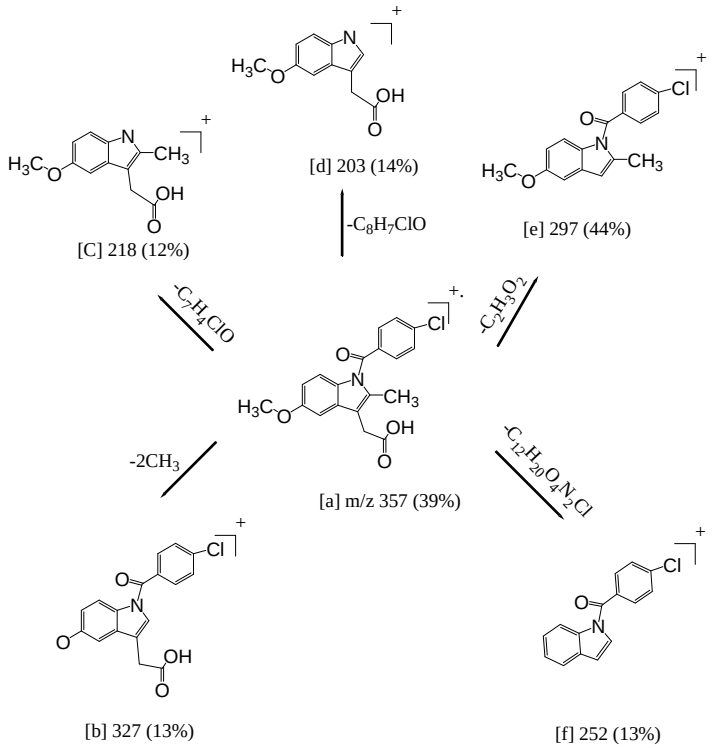
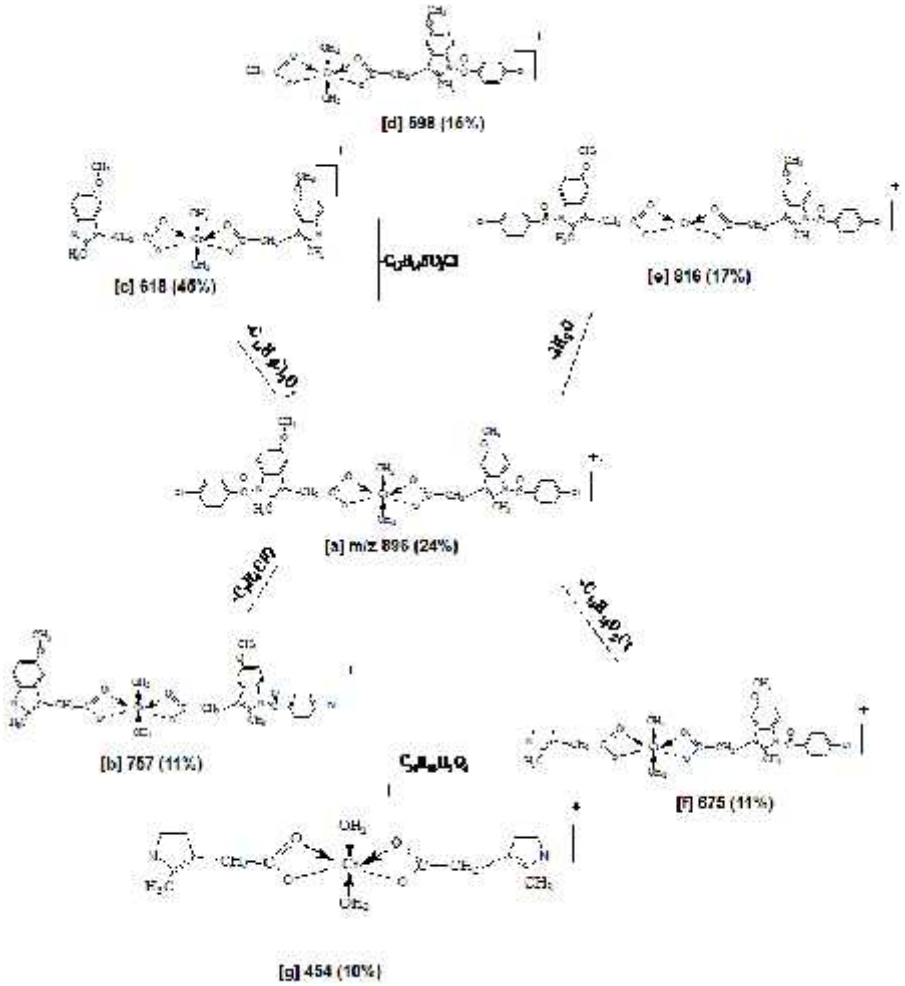


Fig. 2.
^{1}H NMR spectra for (A) Indomethacin, (B) $[Cr(Indo)_2(H_2O)_2](CH_3COO).2H_2O$, (C) $[Zr(Indo)_2(H_2O)].3H_2O$, (D) $[Cd(Indo)_2(H_2O)_2].2H_2O$, (E) $[Ce(Indo)_2(H_2O)_2].2H_2O$, (F) $[UO_2(Indo)_2(H_2O)].2H_2O$.



Scheme 3. Fragmentation pattern of free indomethacin.



Scheme 4.
Fragmentation pattern of $[Cr(Indo.)_2(H_2O)_2](CH_3COO).2H_2O$

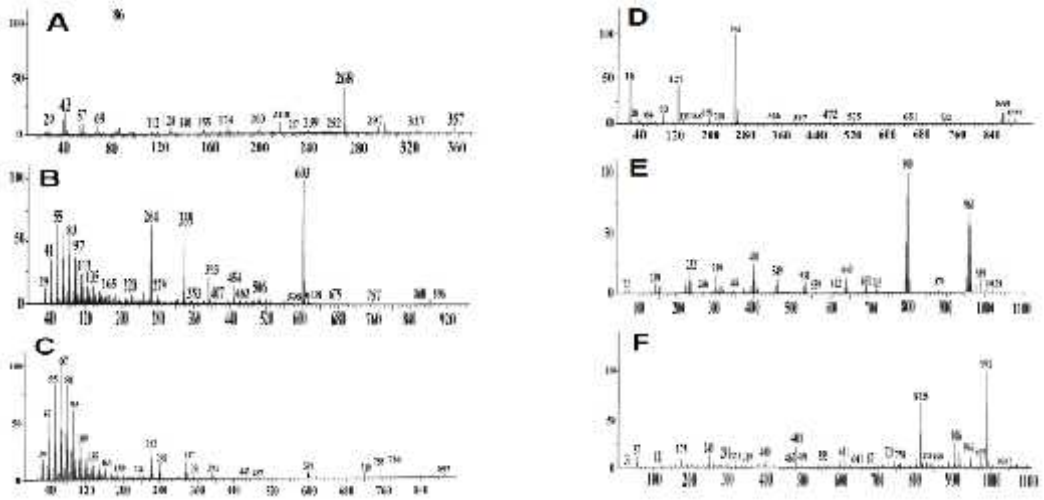


Fig. 3.
Mass spectra diagram of (A) Indomethacin, (B) $[Cr(Indo)_2(H_2O)_2](CH_3COO).2H_2O$, (C) $[Zr(Indo)_2(H_2O)].3H_2O$, (D) $[Cd(Indo)_2(H_2O)_2].2H_2O$, (E) $[Ce(Indo)_2(H_2O)_2].2H_2O$, (F) $[UO_2(Indo)_2(H_2O)].2H_2O$.

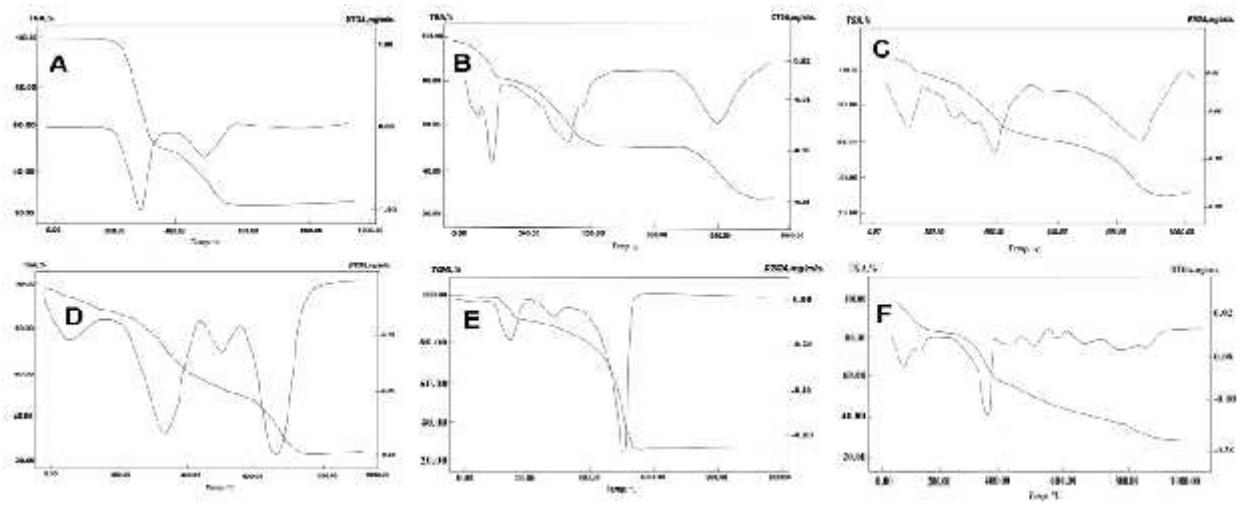


Fig. 4.
TGA and DTG diagram for (A) Indomethacin, (B) $[Cr(Indo)_2(H_2O)_2](CH_3COO).2H_2O$, (C) $[Zr(Indo)_2(H_2O)].3H_2O$, (D) $[Cd(Indo)_2(H_2O)_2].2H_2O$, (E) $[Ce(Indo)_2(H_2O)_2].2H_2O$, (F) $[UO_2(Indo)_2(H_2O)].2H_2O$.

Table 3
The maximum temperature T_{max} (°C) and weight loss values of the decomposition stages for Indomethacine, Cr(III), Zr(IV), Cd(II), Ce(IV) and U(VI) complexes

Compounds	Decomposition	T_{max}(°C)	Weight loss (%)		Lost species
			Calc.	Found	
Indomethacin ($C_{19}H_{16}NO_4Cl$)	First step Total loss Residue	325, 530	99.78 100	99.5 100	$8C_2H_2+3CO+NO+0.5Cl_2$
$[Cr(Indo)_2(H_2O)_2](CH_3COO).2H_2O$ ($C_{40}H_{37}N_2O_{12}Cl_2Cr$)	First step Second step Total loss Residue	116 380,977	4.01 83.31 87.32 12.68	4.00 83.2 87.2 12.8	$2H_2O$ $14C_2H_2+C_2H_4+2NO+2HCL+7CO+1.5H_2O$ $CrO_{1.5}+3C$
$[ZrO(Indo)_2(H_2O)].3H_2O$ ($C_{38}H_{32}N_2O_{10}Cl_2Zr$)	First step Second step Total loss Residue	55,100 271,355,446, 950,1181	6.04 65.19 71.23 28.77	6.1 65 71.1 28.9	$3H_2O$ $9C_2H_2+3C_2H_4+2NO+2HCL+3CO_2$ ZrO_2+11C
$[Cd(Indo)_2(H_2O)_2].2H_2O$ ($C_{38}H_{34}N_2O_{10}Cl_2Cd$)	First step Second step Total loss Residue	112 377,569,730	4.00 68.59 72.59 27.41	4.1 68.55 72.65 27.35	$2H_2O$ $15C_2H_2+CO_2+2NO_2+2HCl+H_2O$ $CdCO_3+6C$
$[Ce(Indo)_2(H_2O)_2]SO_4.2H_2O$ ($C_{38}H_{34}N_2O_{14}Cl_2SCe$)	First step Second step Total loss Residue	169 292,442	3.50 70.12 73.62 26.38	3.6 70 73.6 26.4	$2H_2O$ $8C_2H_2+4C_2H_4+6CO+2NO_2+2HCl+SO_2$ CeO_2+8C
$[UO_2(Indo)_2(H_2O)].2H_2O$ ($C_{38}H_{32}N_2O_{11}Cl_2U$)	First step Second step Total loss Residue	84 381,433,871, 1113	3.47 62.25 65.72 34.28	3.30 62.1 65.4 34.6	$2H_2O$ $14C_2H_2+2NO_2+2HCl+2CO+CO_2+H_2O$ UO_2+7C

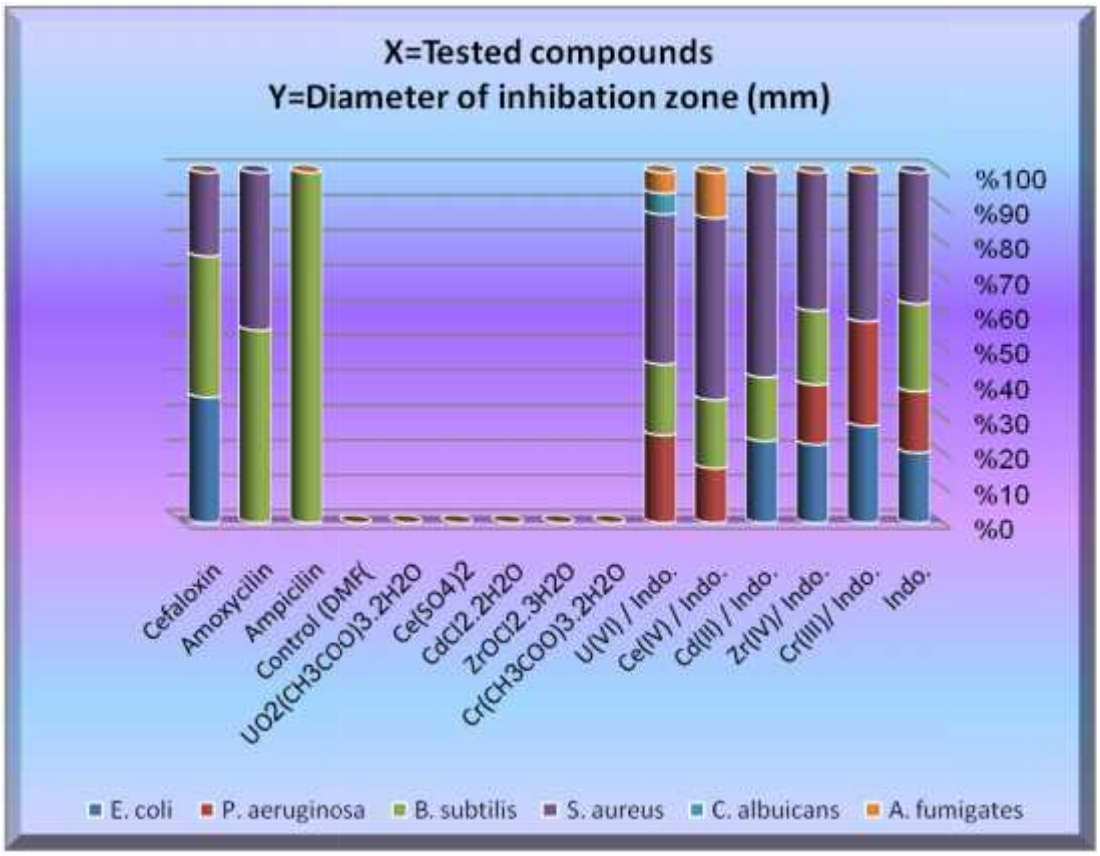


Fig. 5.
Statistical representation for biological activity of indomethacin and its metal complexes.

Table 4
The inhibition diameter zone values (mm) for indomethacin and its metal complexes

Tested compounds		Microbial species					
		Bacteria				Fungi	
		E. coli	*P. aeruginosa*	*B. subtilis*	*S. aureus*	*C. albicans*	*A. fumigatus*
Indomethacin		8 ±0.33	7 ±0.22	10 ±0.33	15 ±0.10	0	0
Cr(III)/ Indo.		$13^{+1} \pm 0.11$	$14^{+1} \pm 0.44$	0	$20^{+1} \pm 0.06$	0	0
Zr(IV)/ Indo.		$17^{+2} \pm 0.02$	$13^{+1} \pm 0.30$	$16^{+1} \pm 0.22$	$30^{+2} \pm 0.88$	0	0
Cd(II) / Indo.		$18^{+2} \pm 0.03$	0	$14^{NS} \pm 0.11$	$45^{+3} \pm 0.33$	0	0
Ce(IV) / Indo.		$23^{+3} \pm 0.04$	$12^{+1} \pm 0.02$	$15^{+1} \pm 0.22$	$40^{+3} \pm 0.11$	0	$10^{+2} \pm 0.11$
U(VI) / Indo.		0	$21^{+2} \pm 0.13$	$17^{+1} \pm 0.15$	$36^{+1} \pm 0.14$	$5^{+1} \pm 0.22$	$5^{+1} \pm 0.33$
$Cr(CH_3COO)_3.2H_2O$		0	0	0	0	0	0
$ZrOCl_2.3H_2O$		0	0	0	0	0	0
$CdCl_2.2H_2O$		0	0	0	0	0	0
$Ce(SO_4)_2$		0	0	0	0	0	0
$UO_2(CH_3COO)_3.2H_2O$		0	0	0	0	0	0
Control (DMF)		0	0	0	0	0	0
Standard	Ampicilin	0	0	28 ± 0.40	0	0	0
	Amoxycilin	0	0	22 ± 0.11	18 ± 1.73	0	0
	Cefaloxin	24 ± 0.34	0	27 ± 1.15	16 ± 0.52	0	0

Statistical significance P^{NS} P not significant, P >0.05; P^{+1} P significant, P<0.05; P^{+2} P highly significant, P <0.01; P^{+3} P very highly significant, P <0.001; student's, *t*-test (Paired).

3. RESULTS AND DISCUSSION

Indomethacin of Cr(II), Zr(IV), Cd(III), Ce(IV), and U(VI) were synthesized as solids of a color characteristics of the metal ion. Table 1 summarizes the carbon, hydrogen and nitrogen elemental analysis as well as melting points and magnetic properties of the isolated solid complexes. The results obtained indicated that all of the isolated complexes were formed from the reaction of the metal salt with indomethacine in 1:2 molar ratios in presence of NaOH for all the elements. All the complexes reported here in are hydrates with various degrees of hydration and air stable solids at room temperature. The structures of the complexes suggested from the elemental analysis agree quite well with their proposed formulas. The found values of elemental analysis agree quite well with the calculate percentage of C, H and N. The metal content is a well agreement with the molecular formulas of the prepared complexes. The molar conductance values of indo and its metal complexes were found in the range from 13.08 to 176.7 S cm^2 mol^{-1}. Conductance data showed that the Cr(III) and Ce(IV) complexes are electrolyte compared with indomethacine alone . The magnetic moments (as B.M.) of the complexes were measured at room temperature. The Zr(IV), Cd(II), Ce(IV) and U(VI) complexes are found in diamagnetic characters and octahedral geometry around the metal ion but the Cr(III) complex is found in paramagnetism with measured magnetic moment value at 3.82.

For $[Cr(Indo)_2(H_2O)_2](CH_3COO).2H_2O$ and $[Ce(Indo)_2(H_2O)_2](SO_4).2H_2O$ complexes. The complexes solutions were tested with an aqueous solutions of $FeCl_3$ and $BaCl_2$, a red brown color and a white precipitate were formed which indicated the presence of acetate and sulphate as counter ions (outside the complex sphere) [5].

3.1. Spectroscopic studies IR absorption spectra

The infrared spectra of the ligand and their complexes were measured as KBr discs. The infrared spectra of the five complexes are compared with this of the free indomethacin in order to determine the site of coordination that may be involved in chelation. There are some guide peaks in the spectrum of the ligand which are of good help for achieving this goal. These peaks are expected to be involved in chelation (Table 2).

The band observed at 1709 cm^{-1} in the spectrum of the free indomethacin have been assigned to the stretching vibration of carboxylic group ν(COOH), [6-15]. In the case of bidentate carboxylate ligand, the antisymmetric and symmetric COO^- stretches will be shifted to higher and lower frequencies, respectively, with an average $\Delta\nu < 200$ cm^{-1} [16-30]. The infrared spectra of indomethacin complexes showed the absence of the band attributable to ν(COO^-) of carboxylic group. Instead, newly formed bands in the ranges 1593-1570 and 1450-1423 cm^{-1} which assigned to the asymmetric and symmetric stretching vibrations of the ligated carboxylato group were obtained with $\Delta\nu < 200$ cm^{-1} indicated that the carboxylate group reacts as bidentate through the two oxygen atoms of carboxylic group (Scheme 5) [31-34].

The IR spectra of all complexes containing hydration and coordination water molecules display bands at 3395-3380 cm^{-1} due to ν(O-H) vibration mode of the water molecules [30] and this was confirmed by the results of thermal analysis. The stretching vibrations ν(C-H) of phenyl and $-CH_2$, $-CH_3$ units were observed in the range 3167-2527 cm^{-1} The assignments of all the C–H stretching vibrations agree quite well with the expected in the literature [35-37].

The proposed structures for complexes are shown in Scheme 2, the indomethacin ligand coordinated to metal ions in such a way that the four oxygen atoms of their indomethacin ligand occupy equatorial positions forming a plane containing four-membered rings. For Zr(IV) and U(VI) complexes possesses a one plane of symmetry and belongs to C_s point group. The complex is expected to display 255 and 258 vibrational fundamentals which all are monodegenerate and distributed between $A^{\backslash}$ and $A^{\backslash\backslash}$ motions. The four vibrations of the uranyl unit, UO_2, in the complex are of the type ν_s(U=O), $A^{\backslash}$; ν_{as}(U=O), $A^{\backslash}$; $\delta(UO_2)$, $A^{\backslash}$ and $\delta(UO_2)$, $A^{\backslash\backslash}$ [38, 39].

The data given in Table 2 shows that the ν_{as}(U=O) occurs at 928 cm^{-1} and corresponding ν_s(U=O) is observed as strong band at 849 cm^{-1}. These assignments for the stretching vibrations of the uranyl group agree quite well with those known for many dioxouranium(VI) complexes [36-38]. The ν_s(U=O) value was used as according to the known method [40, 41], to calculate both the U=O bond stretching force constant, F(U=O), and bond length. The calculated bond length and force constant values are 1.735 Å and 697.35 Nm^{-1}, respectively. For Cr(III), Cd(II) and Ce(IV) complexes may belong to C_{2v} symmetry. The C_{2v} complexes , $[M(Indo)_2(H_2O)_2]^{n+}$ are expected to display 261 vibrational fundamentals which all are monodegenerate and distributed between A_1, A_2, B_2 and B_2 motions .

The spectra of the isolated solid complexes showed a group of bands with different intensities which characteristics for (M-O). The (M-O) bands observed for Cr(III), at 617 and 521 cm^{-1} for Zr(IV), at 613 and 529 cm^{-1} and at 617 and 525 cm^{-1} for Cd(II), Ce(IV) and U(VI) (Table 2) which are absent in the spectrum of indomethacin. This indicated the coordination of indomethacin through carboxylic groups.

3.2. UV-Visible solid reflection Spectra

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 [42]. The formation of the metal indomethacin complexes was also confirmed by the electronic solid reflection spectra. The electronic solid reflection spectra of (Indomethacin) along with Cr(III), Zr(IV), Cd(II), Ce(IV) and U(VI) complexes in the wavelength interval from 200 to 800 nm range are shown in Fig. 1. It can be seen that free indomethacin reflected at 280, 347, 430 and 455 nm. The first band at 280 nm may be attributed to π-π^* transition and the other bands observed at 347, 430 and 455 nm are assigned to n-π^* transitions, these transitions occur in case of unsaturated hydrocarbons which contain ketone groups [43, 44]. The shift of the reflection bands to higher values (bathochromic shift) and the absence of the band at 347 nm in case of Cr(III), Zr(IV), Cd(II), Ce(IV) and U(VI) complexes and presence of new bands in the reflection spectra of complexes indicated the formation of their metal complexes [44]. Also,The five complexes have bands in the range from 514 to 580 nm which may be assigned to the ligand to metal charge-transfer [45].

3.3. ^{1}H NMR studies

To make sure about the proposed structure of the isolated metal complexes, ^{1}H NMR spectra were carried out (Fig. 2). Fig. 2 showed the characteristic singlet at δ:12 ppm to the proton of carboxylic (COOH). The resonance of the carboxylic proton (COOH) is not detected in the spectra of the isolated solid complexes that suggest the coordination of indomethacin through its carboxylato oxygen atoms [46]. On comparing main peaks of indomethacin with its complexes, it is observed that , the values of protons of -CH aliphatic observed in the range of 0.78-2.65 ppm (s, 12H, -CH_3) and those of aromatic ring in the range of 7.03-7.97 ppm (δ: CH aromatic). From ^{1}H NMR and FT-IR results, it was proposed that the indomethacin coordinated to the central metal ion as bidentate ligand through the oxygen atom of carboxylic group [47].

3.4. Mass spectra

The idea of mass spectrometer builds up on the separation of fragments ions dependent to the variation of these ions with the ratio of mass to charge (m/z). Mass spectrum of the free indomethacin (Fig. 3) showed molecular ion peak at m/z=357 (39%). The molecular ion peak [a] gave fragment which refer to base peak [b] at m/z=327 (13%) (Scheme 3). The molecular ion peak [a] losses C_7H_4ClO to give fragment [c] at m/z=218 (12%) and it losses C_8H_7ClO to give fragment [d] at m/z=203 (14%). It loses $C_2H_3O_2$ to give [e] at m/z=297 (44%). The molecular ion peak [a] gave fragment [f] at m/z=252 (13%). The fragmentation patterns of our studied complexes were obtained from mass spectra (Fig. 3). The mass spectrum of Cr(III) complex displayed molecular peak at m/z 896 (24%) suggesting that the molecular weight of the assigned product matching with elemental analysis calculated. Fragmentation pattern of the complex $[Cr(Indo)_2(H_2O)_2](CH_3COO).2H_2O$ is given as an example (Scheme 4). The molecular ion peak [a] appeared at m/z=896 (24%) losses C_7H_4ClO to give [b] at m/z=757 (11%) and it also loses $C_{14}H_8Cl_2O_2$to give [c] at m/z=618 (45%). The molecular ion peak [a] losses $C_{17}H_{14}NO_2Cl$ to give [d] at m/z=598 (15%) and it losses two molecules of water to give [e] at m/z=860 (17%). The parent peak also losses $C_{12}H_{10}ClO_2$ to give [f] at m/z=675 (11%) and it losses $C_{24}H_{20}Cl_2O_4$ to give [g] at m/z=454 (10%). The mass spectra of Zr(IV), Cd(II), Ce(IV) and U(VI) complexes displayed molecular peaks at 892.774, 897.974, 1021.69 and 1037.604 which refer to M.Wt. of these complexes with the abundance at 19%, 21%, 27% and 17%, respectively.

3.5. Thermal analysis

Thermogravimetric (TGA) and differential thermogravimetric (DTG) analyses for indomethacin and its isolated solid complexes, were carried out to get information about the thermal stability of these new complexes and to suggest a general scheme for thermal decomposition as well as to ascertain the nature of associated water molecules. In the present investigation, heating rates were suitably controlled at 10 ^oC min^{-1} under nitrogen atmosphere and the weight loss is measured from room temperature to 1200 ^oC. Fig. 4 represent the TGA and DTG curves and Table 3 gives the maximum temperature values for decomposition along with the corresponding weight loss values for each step of the decomposition reaction. These data support the proposed complexes chemical formulae. Indomethacin is thermally stable at room temperature. Decomposition of the indo started at 21 ^oC and finished at 998 ^oC with one stage at two maxima 325 and 530 ^oC and is accompanied by a weight loss of 99.78%.

The thermal degradation for $[Cr(Indo)_2(H_2O)_2](CH_3COO).2H_2O$ complex exhibits two degradation steps. Hydrated Cr(III) complex loss upon heating two water molecules in the first stage at maximum temperature 116 ^oC. The second step of decomposition occurs at two maxima temperature at 380 and 977 ^oC. This step is associated with the loss of indomethacine forming $CrO_{1.5}$ +3C as a final product.

The $[ZrO(Indo)_2(H_2O)].3H_2O$ complex decomposes in two steps within the temperature range 30-1181 ^oC with total mass loss 71.23% leaving ZrO_2 as residue.

The thermal decomposition of $[Cd(Indo)_2(H_2O)_2].2H_2O$ complex in inert atmosphere proceeds approximately with two main degradation steps. The first step of decomposition occurs at maximum temperature of 112 ^oC and is accompanied by a weight loss of 4.00%, corresponding to the loss of two water molecules. The second stage of decomposition occurs at three maxima temperature of 377, 569 and 730 ^oC. The weight loss at this step is 68.59 %, corresponding to the loss of $15C_2H_2+2HCl+CO_2+2NO_2+H_2O$ as will be described by the mechanism of the decomposition. The final thermal decomposition product is $CdCO_3+6C$.

For Ce(IV) complex $[Ce(Indo)_2(H_2O)_2](SO_4).2H_2O$ the thermal decomposition exhibits two main degradation steps. The step of decomposition occurs at maximum temperature of 169 ^oC and is accompanied by weight loss of 3.50%, corresponding to the loss of two water molecules. The second stage of decomposition occurs at maxima temperature of 292 and 442 ^oC and is accompanied by a weight loss of 70.12%, corresponding to the loss of $4C_2H_4+8C_2H_2+2NO_2+6CO+SO_2+2HCl$, the final product obtained at 722 ^oC is CeO_2+8C.

The thermal decomposition of $[UO_2(Indo)_2(H_2O)].2H_2O$ exhibits two main degradation steps with maxima at 84, 381, 433, 871 and 1113 ^oC and is accompanied by a weight loss of 65.72%, corresponding to the loss of $14C_2H_2+2NO_2+2HCl+CO_2+H_2O+2CO$ giving UO_2 as a final product [48-50]

3.6. Antimicrobial activity

The antibacterial activity of the indomethacin ligand and its metal complexes, was studied against four bacterial species such as *S. aureus, E. coli, P. aeruginosa* and *B. subtilis* and two antifungal screening C. *albicans and A. fumigatus* (Fig. 5). Screening was performed by determining the inhibition zone values (mm) (Table 4).

A comparative study of ligand and its metal complexes showed that the Cr(III) complex showed significant difference for all types of bacteria except *B. subtilis* than free ligand. The Zr(IV) complex showed highly significant for *S. aureus* and *E. coli* and significant for *P. aeruginosa* and *B. subtilis*. Cd(II) showed highly significant against *E. coli* and very highly significant against *S. aureus* and not significant for *P. aeruginosa*. The Ce(IV) showed very highly significant against *S. aureus* and *E. coli* and significant difference for *P. aeruginosa* and *B. subtilis* and highly significant against *A. fumigatus*. U(VI) showed highly significant for *P. aeruginosa, and significant for S. aureus, B. subtilis, C. albicans and A. fumigatus* and not significant for *E. coli*.

The results were promising compared with the previous studies [51-53]. The metal ions are increasing the solubility of indomethacin, this increase of hydrophilicity can enhance the ability of drug molecules in crossing the membrane of a cell, and hence raise the biological utilization ratio and activity of the drug on the basis of the oxidation state of the metal ion, overtone concept and chelation theory Also, the chelation reduces the polarity of the metal ions, mainly because of the partial sharing of its positive charge with the donor groups and possibly the π-electron delocalization within the whole chelate ring system thus formed during coordination. Such chelation increase the lipophilic character of the central metal ion [49]. 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.

REFERENCES

1. Dukes MNG, Meyler's Side Effects of Drugs, An Encyclopedia of Adverse Reactions and Interactions, 13th ed., Elsevier, Amsterdam, 1996.
2. Vane JR, Botting RM. Mechanism of action of aspirin-like drugs.Semin. Arthritis Rheum., 1997, 26: 2-10.
3. Galani A, Demertzi D, Kourkoumelis N, Koutsodimou A, Dokorou V, Ciunik Z, Russo U, Demertzis M. Organotin adducts of indomethacin: synthesis, crystal structures and spectral characterization of the first organotin complexes of indomethacin. Polyhedron, 2004, 23: 2021-2030.
4. Beecher DJ, Wong AC. Identification of hemolysin BL-producing *B. cereus* by a discontinuous hemolytic pattern in blood agar. Appl. Environ. Microbial., 1994, 60:1646-1651.
5. Saif M, Mashaly MM, Eid MF, Fouad R. Synthesis, characterization and thermal studies of binary and/or mixed ligand complexes of Cd(II), Cu(II), Ni(II) and Co(III) based on 2-(Hydroxybenzylidene) thiosemicarbazone: DNA binding affinity of binary Cu(II) complex. Spectrochim.Acta Part A, 2012, 92: 347-356.
6. Silverstein RM, Bassler GC, Morril TC. Spectroscopic Identification of Organic Compounds, 5th Ed., Wiley, New York, 1991.
7. Sadeek SA. Synthesis, thermogravimetric analysis, infrared, electronic and mass spectra of

Mn(II), Co(II) and Fe(III) norfloxacin complexes. J. Mol. Struct., 2005, 753: 1-12.
8. Sadeek SA, Refat MS,Hashem HA. Complexation and thermogravimetric investigation on tin(II) and tin(IV) with norfloxacin as antibacterial agent. J. Coord. Chem., 2006, 59:759-775.
9. Sadeek SA, EL-Shwiniy WH. Metal complexes of the fourth generation quinolone antimicrobial drug gatifloxacin: Synthesis, structure and biological evaluation. J. Mol. Struct., 2010, 977: 243-253.
10. Sadeek SA, EL-Shwiniy WH. Preparation, structure and microbial evaluation of metal complexes of the second generation quinolone antibacterial drug lomefloxacin. J. Mol. Struct., 2010, 981: 130-138.
11. Sadeek SA, EL-Shwiniy WH. Metal complexes of the third generation quinolone antibacterial drug sparfloxacin: preparation, structure, and microbial evaluation. J. Coord. Chem., 2010, 63: 3471-3482.
12. Sadeek SA, Zordok WA, El-Attar MS, Ibrahim MS. spectroscopic, structural, thermal and antimicrobial studies of 4,6-bis (4-chlorophenyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile with some transition metals. Bull. Chem. Soc. Ethiop., 2015, 29(1): 75-94.
13. Sadeek SA, EL-Shwiniy WH, Zordok WA, EL-Didamony AM. synthesis, spectroscopic, thermal and biological activity investigation of new Y(III) and Pd(II) norfloxacin complexes. J. Argent. Chem. Soc., 2009, 97: 128-148.
14. Sadeek SA, EL-Didamony AM, EL-Shwiniy WH, Zordok WA. Uranium (VI) and zirconium (IV) of the second generation quinolone antimicrobial drug norfloxacin: structure and biological activity. J. Argent. Chem. Soc., 2009, 97: 51-76.
15. Gao F, Yang P, Xie J, Wang H. Synthesis, characterization and antibacterial activity of novel Fe(III), Co(II), and Zn(II) complexes with norfloxacin. J. Inorg. Biochem., 1995, 60: 61-67.
16. Dendrinou-Samara C, Kessissoglou DP, Manoussakis GE, Mentzafos D, Terzis A. Copper(II) complexes with antiinflammatory drugs as ligands. Molecular and crystal structure of bis(dimethylsulfoxide)tetrakis(6-methoxy-α-methyl-2-naphthalene-acetato)dicopper(II) and bis(dimethylsulfoxide)tetrakis(1-methyl-5-(toluolyl)-1H-pyrrole-2-acetato)dicopper(II) compounds. J. Chem. Soc., Dalton. Trans., 1990, 959-965.
17. Dendrinou-Samara C, Jannakoudakis PD, Kessissoglou DP, Manoussakis GE, Mentzafos D, Terzis A. Copper(II) complexes with antiinflammatory drugs as ligands solution behaviour and electrochemistry of mono and bi nuclear complexes. J. Chem. Soc., Dalton. Trans., 1992: 3259-3264.
18. Kessissoglou DP, Manoussakis GE, Hatzidimitriou AG, Kanatzidis MG. Synthesis and Characterization of Sulfonylurea Complexes With Cd_2+, Hg_2+ and Ag+. Crystal and Molecular Structures of K[Cd(Chlorpropamide)$_3$] and Hg(Tolbutamide)$_2$. Inorg. Chem. 1987, 26: 1395-1402.
19. Sadeek SA, Zordok WA, El-Farargy AF, El-Desoky SI. Synthesis, spectral, characterization, DFT and biological studies of new 3-[(3-chlorophenyl)-hydrazono]-pentane-2,4-dione metal complexes. J. Kor. Chem. Soc., 2014, 58(2): 169-178.
20. Hatzidimitriou AG, Manoussakis GE, Kessissoglou DP, Kourounakis PN, Economidis G. Solid and solution behavior of sulphonylurea complexes with ions of IIA group metals. Molecular modeling of K[Zn($ClCH_4SO_2NCONHC_3H_7$)$_3$] and action of zinc-sulphonylurea complexes as hypoglycemic agents. J. Inorg. Biochem., 1990, 39: 263-276.
21. Xanthopoulos CE, Sigalas MP, Katsoulos GA, Tsipis CA, Terzis A, Hountas A. crystal structure, magnetic properties and orbital interactions of the binuclear fumaratobridged bis[(*N*-(2-diethylamino)ethyl)-salicylidenaminato)copper(II)]complex. *Inorg. Chim. Acta*, 1993, 214,: 153-157.
22. Davies JA, Eagle CT, Pinkerton AA, Syed R Carbonatobis(triethylphosphine)platinum(II) Acta. Cryst., 1987, 43: 1547-1549.
23. Gregg MR, Powell J, Sawyer JF. Carbonatobis(triphenylphosphine)platinum(II) tetrahydrofuran solvate. Acta. Cryst., 1988, 44: 43-46.
24. Cariati F, Mason R, Robertson GB, Ugo R. The structure of bis(triphenylphosphine)carbonatoplatinum(II). J. Chem. Soc., Chem. Commun., 1967, 408.
25. Robertson GB, Tucker PA. Carbonatobis(triisopropylphosphine)platinum(II), $C_{19}H_{42}O_3P_2Pt$. Acta. Cryst., 1983, 39: 858-860.
26. Bryndza HE, Calabrese JC, Marsi M, Roe DC, Tam W, Bercaw JE. β-Hydride elimination from methoxo vs. ethyl ligands: thermolysis of $(DPPE)Pt(OCH_3)_2$, $(DPPE)Pt(CH_2CH_3)(OCH_3)$ and $(DPPE)Pt(CH_2CH_3)_2$. Journal of American Chemical Society, 1986 108: 4805-4813.

27. Manoussakis G, Bolos C, Ekateriniadou L, Sarris C. Synthesis, Characterization and Anti-Bacterial Studies of Mixed-Ligand Complexes of Dithiocarbamato Thiocyanato and Iron(III), Nickel(II), Copper(II) and Zinc(II). European Journal of Medicinal Chemistry, 1987, 22: 421-425.
28. Kortsaris AE, Kyriakidis DA. Ornithine decarboxylase and phosphatase activity can be stimulated by low concentrations of interferon in human breast cancer cell lines. Microbiologica, 1988, 11:347-353.
29. Sheldrick GM. SHELX86, University of Gottingen, Germany, 1986.
30. Sheldrick GM. SHELXL93, Crystal Structure Refinement, University of Gottingen, Germany, 1993.
31. Pasomas G, Tarushi A, Efthimiadou EK. Synthesis, characterization and DNA-binding of the mononuclear dioxouranium(VI) complex with ciprofloxacin. Polyhedron, 2008, 27: 133-138.
32. Nakamoto K. Infrared and Raman Spectra of Inorganic and Coordination Compounds, 4th Ed., Wiley, New York, 1986.
33. Nakamoto K. Infrared Spectra of Inorganic and Coordination Compounds, Wiley, New York, 1963.
34. Deacon GB, Phillips R. Relationships between the carbon-oxygen stretching frequencies of carboxylato complexes and the type of carboxylate coordination. Coordination Chemistry Reviews, 1980, 33: 227-250.
35. Almodfa H, Said AA, Nour EM. preparation and infrared and thermal studies of [UO_2(salen)(DMF)]. Bull. Soc. Chem. Fr., 1991, 128: 137-139.
36. Sadeek SA, Teleb SM, Refat MS, Elmosallamy MAF. Preparation, thermal and vibrational studies of UO_2(acac-o-phdn)(L) (L=H_2O, py, DMF and Et_3N). Journal of Coordination Chemistry, 2005, 58: 1077-1085.
37. Silverstein RM, Bassler GC, Morril TC. Spectroscopic Identification of Organic Compounds, 5th Ed., Wiley, New York, 1991.
38. Patil SA, Naik VH, Kulkarni AD, Badami PS. DNA cleavage, antimicrobial, spectroscopic and fluorescence studies of Co(II), Ni(II) and Cu(II) complexes with SNO donor coumarin Schiff bases.Spectrochim. Acta A, 2010, 75: 347-354.
39. Nour EM, Taha AA, Alnaimi IS, Infrared and Raman studiesof [UO(salen)(L)](L=H2O and CH_3OH). Inorg. Chim. Acta, 1988, 141: 139-140.
40. Jones LH. Determination of U–O bond distance in uranyl complexes from their infrared spectra. Spectrochim. Acta, 1959, 15: 409-411.
41. Nour EM, Al-kority AM, Sadeek SA, Teleb SM. Synthesis and spectroscopic of NN/-O-phenylene bis (salicylideneiminato) dioxouranium (VI) solvates (L) (L=DMF and PY). Synth. React. Inorg. Met.-Org. Chem., 1993, 23: 39-52.
42. Nakamoto K, Mccarthy, PJS, Fujiwara, Shimura Y, Fujita J, Hare CR, Saito Y. Spectroscopy and structure of metal chelate compounds, John Wiley & Sons, New York, London, Sydney, 1968.
43. Refat MS. Synthesis and characterization of norfloxacin-transition metal complexes (group 11, IB): Spectroscopic, thermal, kinetic measurements and biological activity. Spectrochimica Acta Part A, 2007, 68: 1393-1405.
44. EL-Shwiniy WH, Sadeek SA. Synthesis and characterization of new 2-cyano-2-(p-tolyl-hydrazono)thioacetamide metal complexes and a study on their antimicrobial activities. Spectrochimica Acta Part A, 2015, 137: 535-546.
45. Cotton FA, Wilkinson G, Murillo CA, Bochmann M. Advanced Inorganic Chemistry, 6th Ed., Wiley, New York, 1999.
46 Muhammad I, Javed I, Shahid I, Nazia I. In vitro antibacterial studies of Ciprofloxacin-imines and their complexes with Cu(II), Ni(II), Co(II) and Zn(II). Turkish Journal of Biology, 2007, 31: 67-72.
47. Skauge T, Turel I, Sletten E. Interaction between ciprofloxacin and DNA mediated by Mg^{2+} ions. Inorganica. Chimica Acta, 2002, 339: 239-247.
48. Bandoli G, Clemente DA, Croatto U, Vidali M, Vigato PA. Preparation and crystal molecular structure of N'-o -phenylene-bis (salicylideneiminato) $U0_2$(EtOH)]. Chem. Commun., 1971, 1330.
49 Sadeek SA, EL-Shwiniy WH, Zordok WA, EL-Didamony AM. Spectroscopic, structure and antimicrobial activity of new Y(III) and Zr(IV) ciprofloxacin. Spectrochimica Acta Part A, 2011, 78: 854-867.
50. Brzyska W, Hakim M. Hippurates of Mn(II), Cd(II) and Ag(I). Polish Journal of Chemistry, 1992, 66: 413-418.
51. Hughes MN. The inorganic chemistry of biological processes, 2nd Ed., Wiley Interscience, New York, 1981.
52. Anacona JR, Toledo C. Synthesis and antibacterial activity of metal complexes of

ciprofloxacin. Trans. Met. Chem., 2001, 26: 228-231.
53. Efthimiadou EK, Karaliota A, Pasomas G. Metal complexes of the third-generation quinolone antimicrobial drug sparfloxacin: Structure and biological evaluation. J. Inorg. Biochem., 2010, 104: 455-466.