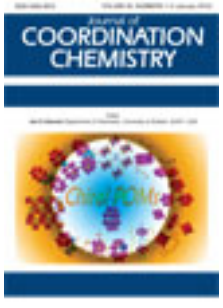


Journal of Coordination Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gcoo20

Spectroscopic, thermal analysis, and antimicrobial evaluation of new Y(III), Zr(IV), and U(VI) ibuprofen complexes

Wael A. Zordok [a], Sadeek A. Sadeek [a] & Walaa H. El-Shwiniy [a]
[a] Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt
Published online: 20 Jan 2012.

To cite this article: Wael A. Zordok, Sadeek A. Sadeek & Walaa H. El-Shwiniy (2012) Spectroscopic, thermal analysis, and antimicrobial evaluation of new Y(III), Zr(IV), and U(VI) ibuprofen complexes, Journal of Coordination Chemistry, 65:2, 353-369, DOI: 10.1080/00958972.2011.654203

To link to this article: http://dx.doi.org/10.1080/00958972.2011.654203

Journal of Coordination Chemistry
Vol. 65, No. 2, 20 January 2012, 353–369

Spectroscopic, thermal analysis, and antimicrobial evaluation of new Y(III), Zr(IV), and U(VI) ibuprofen complexes

WAEL A. ZORDOK, SADEEK A. SADEEK* and WALAA H. EL-SHWINIY

Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt

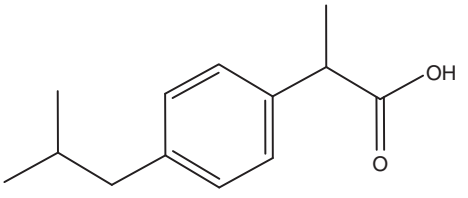
(*Received 23 August 2011; in final form 6 December 2011*)

New complexes of Y(III), Zr(IV), and U(VI) with the anti-inflammatory drug ibuprofen (IBU) have been synthesized and characterized by elemental analysis, spectroscopic techniques (UV-Visible, IR, and ^{1}H NMR), magnetic moment determination, conductance measurements, and thermal analyses (thermogravimetric and differential thermogravimetric). The anti-inflammatory drug acts as bidentate chelate bound to metal ions through the deprotonated carboxylate. The calculated bond length and force constant, F(U=O), in the uranyl complex are 1.815 Å and 671.69 Nm^{-1}, respectively. The metal–ligand binding of the Zr(IV) and Y(III) complexes is predicted using density functional theory at the B3LYP-CEP-31G level of theory and total energy, dipole moment estimation of different Zr(IV) and Y(III) ibuprofen structures. The antibacterial activity of the ligand, metal salts, and metal complexes have been tested, showing that the complexes are significant against all six bacterial species compared with IBU and metal salts.

Keywords: IBU; IR; TG; Antibacterial activity

1. Introduction

Ibuprofen is a phenyl propionic acid derivative (formula 1) and is a non-steroidal anti-inflammatory drug. Ibuprofen is sometimes used for treatment of acne, because of its anti-inflammatory properties [1] and has been sold in topical form for adult acne [2]. It functions by inhibiting the enzyme cyclooxygenase (COX), which converts arachidonic acid to prostaglandin H_2 (PGH_2). PGH_2, in turn, is converted by other enzymes to several other prostaglandins, which are mediators of pain, inflammation, and fever, and to thromboxane A_2, which stimulates platelet aggregation, leading to the formation of blood clots.



Formula 1. (RS)-2-(4-(2-methylpropyl)phenyl)propionic acid.

*Corresponding author. Email: sadeek59@yahoo.com

Journal of Coordination Chemistry
ISSN 0095-8972 print/ISSN 1029-0389 online
http://dx.doi.org/10.1080/00958972.2011.654203

Most anti-inflammatory drugs are carboxylic acids in which carboxylate is available for metal–ligand interaction [3–8]. Much work has focused on interactions of transition metal ions with nonsteroidal anti-inflammatory drugs such as ibuprofen, oxicams, and piroxicam [6–10]. Some studies suggest that regular ibuprofen intake may also be an effective chemopreventive against breast cancer and can decrease non-small cell lung cancer growth *in vitro* [6–10]. Complexation behavior of carboxylate ligands exhibits a variety of coordination modes and binding of the carboxylate groups to metal ions in a specific manner may be important [11–13].

Complexes of Zn(II), Cd(II), and Pt(II) with the anti-inflammatory drugs such as tolmetin, ibuprofen, naproxen, and indomethacin have been synthesized and characterized [14]. For Cd-(naproxen)$_2$ the anti-inflammatory drug is a bidentate ligand coordinatively bound to metal ions through the deprotonated carboxylate. For platinum(II) carboxylate compounds only unidentate and bidentate coordination modes [14–16] have been structurally detected.

In continuation of our interest on synthetic and structural characterization of some ibuprofen complexes of transition metals, this work describes the synthesis of new Y(III), Zr(IV), and U(VI) ibuprofen complexes. Characterization of the complexes was effected by elemental analysis, thermogravimetric and differential thermogravimetric (TG and DTG) analyses, magnetic properties, melting points, UV-Visible, IR, ^{1}H NMR, and biological studies. Density functional theory (DFT) was used to compute the cation influence on theoretical parameters of the Zr(IV) and Y(III) complexes of ibuprofen. Such computational characterization reduces time-consuming experiments for biomedical and pharmaceutical studies of the drugs and their complexes. Profiles of the optimal set and geometry of these complexes were simulated by applying the GAUSSIAN 98 W package of programs [17] at B3LYP/CEP-31G [18] level of theory.

2. Materials and methods

2.1. *Chemicals*

Ibuprofen was purchased from the Egyptian Company for Chemicals & Pharmaceuticals (ADWIA). YCl_3 was purchased from Aldrich Chemical Co. $ZrOCl_2 \cdot 8H_2O$, $UO_2(NO_3)_2 \cdot 6H_2O$ and all solvents were purchased from Fluka Chemical Co. All the chemicals and solvents were of analytical reagent grade and used as purchased.

2.2. *Synthesis*

An ethanolic solution (20 mL) of ibuprofen (2 mmol, 0.4126 g) and NaOH (2 mmol, 0.08 g) was added to an ethanolic solution of YCl_3 (1 mmol, 0.1953 g) and the reaction mixture was stirred at room temperature for 15 h. The solution was left for slow evaporation; the white precipitate formed was filtered off, washed with twice distilled water several times, and dried in a vacuum over $CaCl_2$ in a dessicator. The yellowish-white and yellow solid complexes of $[ZrO(IBU)_2H_2O] \cdot H_2O$ and $[UO_2(IBU)_2 H_2O] \cdot 4H_2O$ were prepared in a similar manner using methanol and acetone as solvents and using $ZrOCl_2 \cdot 8H_2O$ and $UO_2(NO_3)_2 \cdot 6H_2O$ in 1 : 2 and 1 : 3 molar

ratios, respectively. Unfortunately we were not able to obtain single crystals to perform X-ray diffraction analysis. To verify that the chloride is ionic and not coordinated, the complex solution was tested with an aqueous solution of $AgNO_3$ (precipitate was formed). The three complexes were characterized by elemental analyses, infrared (IR), electronic, ^{1}H NMR, and thermal analyses.

2.3. *Instruments*

C, H, N, and halogen analyses were carried out on a Perkin Elmer CHN 2400. The percentages of metal were determined gravimetrically by transforming the solid products into oxide, and also determined by using atomic absorption. Spectrometer model PYE-UNICAM SP 1900 fitted with the corresponding lamp was used for this purpose. IR spectra were recorded on a FTIR 460 PLUS (KBr discs) from 4000 to 400 cm^{-1}; ^{1}H NMR spectra were recorded on a Varian Mercury VX-300 NMR spectrometer using DMSO-d_6. TG–DTG measurements were carried out under N_2 from room temperature to 800°C using a TGA-50H Shimadzu. Electronic spectra were obtained using a UV-3101PC Shimadzu. Solid reflection spectra were recorded with KBr pellets. Magnetic measurements were carried out on a Sherwood scientific magnetic balance using the Gouy method and Hg[Co(SCN)] as calibrant. Molar conductivities of solutions of the ligand and metal complexes in DMSO at 5.5×10^{-4} mol L^{-1} were measured on a CONSORT K410. All measurements were carried out at ambient temperature with freshly prepared solutions.

2.4. *Antimicrobial investigation*

Antibacterial activities of the ligand, metal salts, and complexes were investigated by a previously reported modified method of Beecher and Wong [19] against bacteria, *Staphylococcus aureus* K1, *Bacillus subtilis* K22, *Brevibacterium otitidis* K76, *Escherichia coli* K32, *Pseudomonas aeruginosa* SW1, and *Klebsiella oxytoca* K42. The tested microorganism's isolates were isolated from Egyptian soil and identified according to the standard bacteriological keys for identification of bacteria as stock cultures in the microbiology laboratory, Faculty of Science, Zagazig University. The Müller–Hinton agar (30.0% Beef extract, 1.75% Casein hydrolysate, 0.15% Starch, and 1.7% 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, metal salts, and their complexes, were introduced in holes (only 100 µL) after being dissolved in DMSO at 10^{-4} mol L^{-1}. These culture plates were then incubated at 37°C for 20 h. The activity was determined by measuring the diameter of the inhibition zones (in mm). Growth inhibition was calculated with reference to ibuprofen.

3. Results and discussion

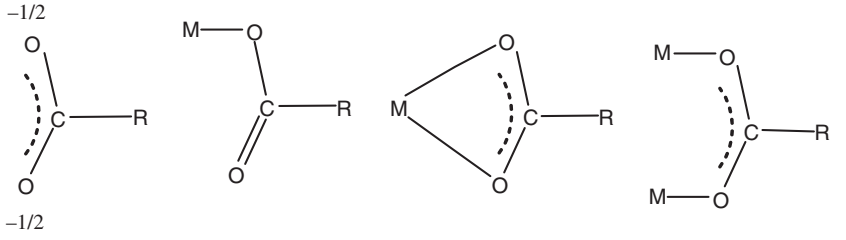
Ibuprofen reacts with Y(III), Zr(IV), and U(VI) in ethanol, methanol, and acetone at room temperature to form complexes with a color characteristic of the metal ions.

The molar ratio for all complexes is M : IBU = 1 : 2, established from chemical analysis (table 1); the complexes also contain water. Qualitative reactions revealed the presence of chloride as counter ion in the Y(III) complex. The molar conductance values of ibuprofen and Y(III), Zr(IV), and U(VI) complexes (DMSO) at room temperature were found at zero, 30.73, 8.28, and 7.69 $S\,cm^2\,mol^{-1}$, respectively. The non-electrolyte behavior is consistent with the presence of neutral species in DMSO. In contrast, the value for Y(III) agrees well with that expected for 1 : 1 electrolyte.

Magnetic moment measurements were carried out at 35.0°C using Gouy's method, where $Hg[Co(SCN)_4]$ was used as calibrant. The magnetic susceptibility measurements for the three ibuprofen complexes indicate that the complexes are diamagnetic.

3.1. *IR data and bonding*

The IR spectra of $[Y(IBU)_2(H_2O)_2]Cl$, $[ZrO(IBU)_2H_2O]\cdot H_2O$, and $[UO_2(IBU)_2H_2O]\cdot 4H_2O$, and free ibuprofen were measured as KBr discs and the assignments are given in table 2. The three complexes are compared with free ligand to determine the site of coordination. The ibuprofen complexes exhibit characteristic IR spectra due to ligand vibration modes. The $\nu_{as}(COO^-)$ and $\nu_s(COO^-)$ for carboxylate depend upon the coordination mode of the carboxylato ligand.



LI LII LIII LIV

In the free ion both CO bonds are equivalent, and the antisymmetric and symmetric COO^- stretches appear at 1582 and 1425 cm^{-1}, respectively. In LII, the antisymmetric and symmetric COO^- stretches will be shifted to higher and lower frequencies, respectively, with an average $\Delta\nu$ of 190 cm^{-1} [20–33]. If coordination occurs symmetrically (structures LIII and LIV), both COO^- stretches may be shifted in the same direction, since both CO bonds may be changed by the same amount. For most ibuprofen complexes bidentate coordination is found with average $\Delta\nu$ value 160 cm^{-1}.

In spectra of the complexes and ibuprofen, the O–H stretching due to water or carboxylic group can be observed at 3645–3332 cm^{-1}. The ν(C=O) of carboxylic acid appeared at 1720 cm^{-1} for the free ligand, but disappears in spectra of the complexes. Two very strong bands are present at 1551–1580 cm^{-1} and 1410–1420 cm^{-1} assigned to $\nu(COO^-)$ asymmetric and symmetric stretches, respectively, with an average $\Delta\nu$ of $\sim$160 cm^{-1}, indicating bidentate coordination of carboxylate [34–40]. The normal coordination number of Y(III) in carboxylate complexes varies from 6 to $\sim$10 [41, 42]. Also, the data given in table 2 show that ν(Zr=O) is a strong band at 849 cm^{-1} [43]. Coordination *via* oxygen of carboxylate is confirmed by ν(M–O) bands at 540 cm^{-1} for Y(III), 490 cm^{-1} for Zr(IV) and at 548 cm^{-1} for U(VI). Thus ibuprofen is coordinated with metal through oxygen of carboxylates.

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

Compounds M. Wt. (M.F.)	Yield (%)	M.p. (°C)	Color	Found (Calcd) (%)				μ_{eff} (B.M.)	Λ ($S\,cm^2\,mol^{-1}$)
				C	H	M	Cl		
IBU 206.28($C_{13}H_{18}O_2$)		70	White	75.62 (75.63)	17.41 (17.45)	–	–	Diamagnetic	0
$[Y(IBU)_2(H_2O)_2]Cl$ 572.4($YC_{26}H_{40}O_6Cl$)	98	<360	White	54.45 (54.51)	6.89 (6.99)	15.53 (15.53)	6.15 (6.20)	Diamagnetic	30.73
$[ZrO(IBU)_2H_2O]\cdot H_2O$ 555.22($ZrC_{26}H_{40}O_7$)	85.28	160	Yellowish-white	56.15 (56.19)	7.20 (7.20)	16.43 (16.43)	–	Diamagnetic	8.28
$[UO_2(IBU)_2H_2O]\cdot 4H_2O$ 772.00($UC_{26}H_{46}O_{11}$)	75.5	<360	Yellow	40.39 (40.42)	5.92 (5.96)	30.78 (30.83)	–	Diamagnetic	7.69

Table 2. IR frequencies (cm^{-1}) and tentative assignments for (A) ibuprofen; (B) $[Y(IBU)_2(H_2O)_2]Cl$, (C) $[ZrO(IBU)_2H_2O]\cdot H_2O$, and (D) $[UO_2(IBU)_2H_2O]\cdot 4H_2O$.

A	B	C	D	Assignments
3645m	3456m,br	3332w	3352m,br	ν(O–H); H_2O; COOH
3556m				
3070w	3171m,br	3088vw	3045vw	ν(C–H); aromatic
3045vw	3045sh	3045vw	3020vw	
3020vw		3022vw		
2956ms	2956vw	2955vs	2955vs	ν(C–H); aliphatic
2920m	2874vw	2928w	2928m	
2870ms		2870s	2870ms	
2731ms		2723m		
2631ms				
1720vs	–	–	–	ν(C=O); COOH
–	1636ms	1600sh	–	$\delta_b(H_2O)$; coordinated H_2O
–	1580vs	1560vs	1551s	$\nu_{as}(COO^-)$
1634w	–	1462s	1462ms	phenyl breathing modes
1622sh				
1508s				
1458s				
1418vs				
–	1410s	1420vs	1412s	$\nu_s(COO^-)$
1377s	1366w	1373m	1377vw	–CH; deformations of CH_2
1327vs	–	1285s	1288s	$\delta_b(-CH_2)$
1269s	1130vs,br	1202m	1260w	ν(C–C)
1231vs		1169m	1130w	
1180vs		1130w		
1123ms	1070sh	1080vs	1107w	$\delta_r(-CH_2)$
1069s		1055w		
1011s		1000vw		
937vs	991s	899vs	999s	–CH-bend; phenyl
868s				
	–	–	900vs	ν_{as}(U=O)
		–	849vs	ν_s(U=O)
		849s	–	ν(Zr=O)
779s	–	791s	770ms	$\delta_b(COO^-)$
745m		710m	702m	
667s	677vw	690m	621s	ν(M–O) + ring deformation
633m	613vs	602vs	548m	
590s	540s	490ms		
521s	440w	436ms		
482m	410ms	409s		
421s				

s = strong, w = weak, v = very, m = medium, br = broad, sh = shoulder, ν = stretching, δ_b = bending, δ_r = rocking.

The proposed structure for $[UO_2(IBU)_2H_2O]\cdot 4H_2O$ is represented by formula 2, the five donors of two ibuprofen and H_2O coordinated to U(VI) in a plane forming a pentagon with the two oxygen atoms of the uranyl, UO_2, axial [44–48]. The four vibrations of the uranyl unit, UO_2, under C_s symmetry are 3 A′ and A″, ν_s(U=O), A′; ν_{as}(U=O), A′; $\delta(UO_2)$, A′ and $\delta(UO_2)$, A″. The ν_{as}(U=O) occurs at 900 cm^{-1} as a very strong singlet and ν_s(U=O) is also very strong at 849 cm^{-1}. These assignments for uranyl agree with those for many dioxouranium(VI) complexes [49–54]. The ν_s(U=O) value was used as according to the known method [53, 54], 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 1.815 Å and 671.69 Nm^{-1}.

Table 3. UV-Vis spectra of ibuprofen (IBU) and its metal complexes.

		IBU complex with		
Assignments (nm)	IBU	Y(III)	Zr(IV)	U(IV)
$\pi-\pi^*$ transitions	217	260	253	223
	244	269	301	251
		284		303
		299		
		319		
$n-\pi^*$ transitions	412	339	327	324
		354	343	342
		370	354	410
		375	374	
		389	383	
		461	389	
Ligand–metal charge transfer	–	502	523	569
		523	539	
		543	550	
		567	568	

3.2. *UV-Vis spectra*

The application of ultraviolet spectroscopy can be useful in structural determinations of chelates since they all absorb in this region [55]. The formation of ibuprofen complexes was confirmed by electronic solid reflection spectra. The electronic solid reflection spectra of ibuprofen along with the Y(III), Zr(IV), and U(VI) complexes from 200 to 800 nm are listed in table 3. Free ibuprofen shows bands at 217, 244, and 412 nm assigned to $\pi-\pi^*$ and $n-\pi^*$ transitions. The bathochromic shift of the reflectance band and appearance of new bands for the complexes is attributed to complexation of ibuprofen. The complexes of Y(III), Zr(IV), and U(VI) show bands at 502–568 nm, which may be assigned to ligand–metal charge transfer.

3.3. *Thermal studies*

To confirm the proposed structure of $[Y(IBU)_2(H_2O)_2]Cl$, $[ZrO(IBU)_2H_2O]\cdot H_2O$, and $[UO_2(IBU)_2H_2O]\cdot 4H_2O$, TG and DTG analyses were carried out under nitrogen at $20\,mL\,min^{-1}$. The maximum temperature values for decomposition along with the corresponding lost species are given in table 4.

The data obtained indicate that decomposition of ibuprofen starts at 120°C and finishes at 305°C with one stage. The stage of decomposition occurs at 219°C and is accompanied by a weight loss of 99.62%, corresponding to the loss of $3C_2H_2 + 3C_2H_4 + CO_2$. The thermal decomposition for $[Y(IBU)_2(H_2O)_2]Cl$ exhibits one main degradation step starting at 50°C and finishing at 600°C with maxima at 308°C and 488°C, accompanied by weight loss of 46.86%, corresponding to the loss of $5C_2H_6 + 4.5H_2O + HCl$.

Thermal degradation for $[ZrO(IBU)_2H_2O]\cdot H_2O$ exhibits four main degradation steps. The first at 61°C with no weight loss indicates cleavage of solid–solid interactions. The second stage of decomposition at 80–175°C with a maximum at 97°C accompanied by weight loss of 3.21% corresponds to loss of one water molecule. The third step of

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

Compounds	Decomposition	T_{max} (°C)	Weight loss (%)		Lost species
			Calcd	Found	
IBU	First step	219	100.00	99.62	$3C_2H_2 + 3C_2H_4 + CO_2$
($C_{13}H_{18}O_2$)	Total loss, Residue		100.00, 0.00	99.62, 0.38	
$[Y(IBU)_2(H_2O)_2]Cl$	First step	308, 488	46.73	46.86	$5C_2H_6 + 4.5H_2O + HCl$
($YC_{26}H_{40}O_6Cl$)	Total loss, Residue		47.73, 53.27	46.86, 53.14	
$[ZrO(IBU)_2H_2O] \cdot H_2O$	First step	97	3.21	3.24	H_2O
($ZrC_{26}H_{40}O_7$)	Second step	210	3.22	3.24	H_2O
	Third step	304, 432, 497	66.92	67.00	$4C_2H_2 + 7C_2H_4 + CO + CO_2$
	Total loss, Residue		73.35, 26.65	73.48, 26.52	
$[UO_2(IBU)_2H_2O] \cdot 4H_2O$	First step	80	5.31	5.28	$4H_2O$
($UC_{26}H_{46}O_{11}$)	Second step	185, 356, 450	54.73	54.72	$10C_2H_2 + 3C_2H_4 + O_2 + 3H_2O$
	Total loss, Residue		60.04, 39.96	60.00, 40.00	

decomposition at 210°C accompanied by weight loss of 3.22% corresponds to loss of one coordinated water molecule. The next decomposition occurs with three maxima at 304°C, 432°C, and 497°C with a weight loss of 66.92%, in agreement with the calculated value 67.00%, corresponding to the loss of $4C_2H_2 + 7C_2H_4 + CO + CO_2$ giving $ZrO_2 + 2C$.

Hydrated U(VI) ibuprofen complex loses four water molecules in the first stage at 80°C. The second step of decomposition occurs from 150°C to 630°C accompanied by weight loss of 54.72%; this step is associated with loss of ibuprofen forming UO_2 as final product. The observed weight loss associated with each step of decomposition for our complexes agrees well with the calculated weight loss (table 4).

The decomposition mechanisms proposed for ibuprofen and complexes are summarized as follows:

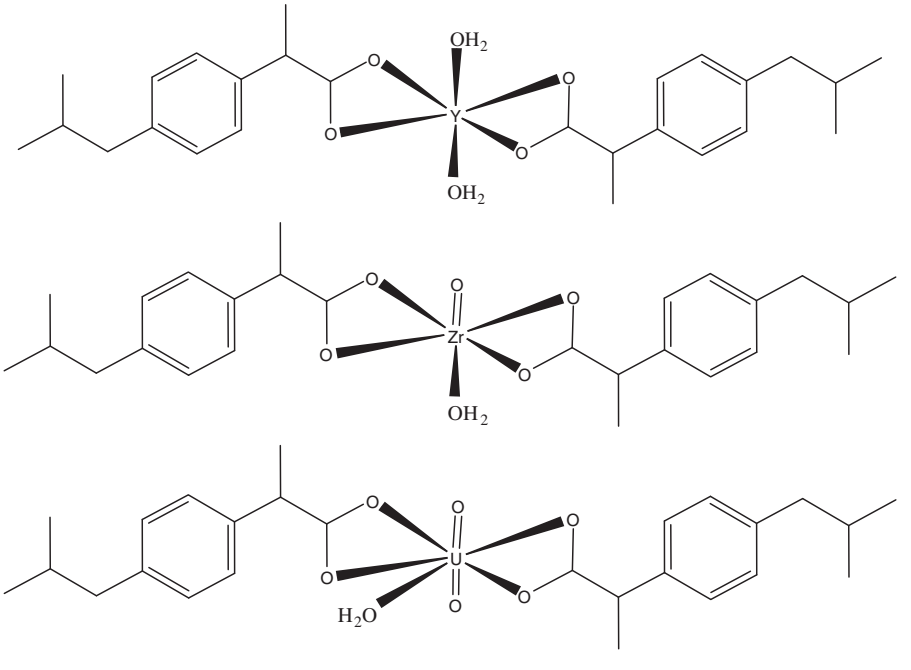
$$C_{13}H_{18}O_2 \xrightarrow{219^\circ C} 3C_2H_2 + 3C_2H_4 + CO_2, \tag{1}$$

$$\left[Y(C_{13}H_{18}O_2)_2(H_2O)_2\right]Cl \xrightarrow{308.488^\circ C} YO_{1.5} + 16C + 5C_2H_6 + 4.5H_2O + HCl, \tag{2}$$

$$\begin{aligned}
&\left[ZrO(C_{13}H_{18}O_2)_2H_2O\right]\cdot H_2O \xrightarrow{97^\circ C} \left[ZrO(C_{13}H_{18}O_2)_2H_2O\right] + H_2O,\\
&\left[ZrO(C_{13}H_{18}O_2)_2H_2O\right] \xrightarrow{210^\circ C} \left[ZrO(C_{13}H_{18}O_2)_2\right] + H_2O,\\
&\left[ZrO(C_{13}H_{18}O_2)_2\right] \xrightarrow{304,\ 432,\ 497^\circ C} ZrO_2 + 4C + 4C_2H_2 + 7C_2H_4 + CO + CO_2,
\end{aligned} \tag{3}$$

$$\begin{aligned}
&\left[UO_2(C_{13}H_{18}O_2)_2H_2O\right]\cdot 4H_2O \xrightarrow{80^\circ C} \left[UO_2(C_{13}H_{18}O_2)_2H_2O\right] + 4H_2O,\\
&\left[UO_2(C_{13}H_{18}O_2)_2H_2O\right] \xrightarrow{185,\ 356,\ 450^\circ C} UO_2 + 10C_2H_2 + 3C_2H_4 + O_2 + 3H_2O.
\end{aligned} \tag{4}$$

The proposed structures are shown in formula 2.



Formula 2. The coordination mode of Y(III), Zr(IV), and U(VI) with ibuprofen.

Table 5. ^{1}H NMR values (ppm) and tentative assignments for (A) ibuprofen; (B) $[ZrO(IBU)_2H_2O]Cl_2 \cdot H_2O$, and (C) $[UO_2(IBU)_2H_2O] \cdot 4H_2O$.

A		B	C	Assignments
0.91, 1.56		0.83–1.81	0.84–1.19	δH, –CH_3; methyl propyl and methyl adjacent to –COOH
1.82, 3.82	2.43	2.38–2.51	2.49–2.63	δH, different –CH δH, –CH_2
–		3.2–3.59	3.36	δH, H_2O
7.05, 7.24		7.06–7.19	7.32–8.06	δH, –CH aromatic
12.34		–	–	δH, –COOH

3.4. *The ^{1}H NMR spectra*

^{1}H NMR spectra of ibuprofen in DMSO-d_6 (table 5) show multiplets at δ: 0.91 and 1.56 ppm corresponding to methyl propyl and methyl adjacent to –COOH; singlets at δ: 1.82 and 3.82 ppm for –CH, a weak singlet at 7.05 and 7.24 ppm for –CH aromatic. The peak at 12.34 ppm can be assigned to carboxylic proton (COOH). ^{1}H NMR spectra of $[ZrO(IBU)_2H_2O]Cl_2 \cdot H_2O$ and $[UO_2(IBU)_2H_2O] \cdot 4H_2O$ in DMSO-d_6 exhibit new resonances at 3.2–3.59 and 3.36 ppm [56–58], due to the presence of water in the complexes. The carboxylic proton (COOH) is not detected in spectra of the complexes, suggesting coordination of ibuprofen through carboxylate [49]. On comparing ibuprofen with its complexes, all peaks of the free ligand are present in spectra of the complexes with some shifts from binding of the ligand to the metal.

3.5. *Biological activities test*

Antibacterial results are presented in table 6 and figure 1. All ibuprofen metal complexes show significant antibacterial activities. The chelation makes ibuprofen a more powerful bacteriostatic agent [59].

The three complexes are more active against Gram-positive bacteria than Gram-negative due to the presence of a double membrane surrounding each bacterial cell. Although all bacteria have an inner cell membrane, Gram-negative bacteria have a unique outer membrane. This outer membrane excludes certain drugs and antibiotics from penetrating the cell, partially accounting for why Gram-negative bacteria are more resistant to antibiotics than are Gram-positive bacteria. *Brevibacterium otitidis* is a more sensitive Gram-positive bacteria, so all of the complexes are more active toward *Br. otitidis*.

4. Computational details

4.1. *Computational method*

The geometric parameters and energies were computed by DFT at the B3LYP/CEP-31G level, using the GAUSSIAN 98W package of programs, on geometries that were optimized at CEP-31G basis set. The high basis set was chosen to detect the energies at a highly accurate level. The atomic charges were computed using natural atomic orbital

Table 6. The inhibition diameter zone values (mm) for IBU and complexes.

Compounds	Microbial bacteria species					
	E. coli	*K. oxytoca*	*P. aeruginosa*	*B. subtilis*	*Br. otitidis*	*S. aureus*
IBU	0	0	0	9 ± 0.3	0	0
Y(III)/IBU	$15^{+2} \pm 0.6$	$8^{+1} \pm 1.2$	$21^{+2} \pm 1.5$	$26^{+2} \pm 0.2$	$31^{+3} \pm 0.3$	ND
Zr(IV)/IBU	$28^{+3} \pm 0.2$	$12^{+2} \pm 0.9$	$30^{+3} \pm 1.7$	$33^{+3} \pm 1.2$	$38^{+3} \pm 0.2$	$41^{+3} \pm 1.5$
U(VI)/IBU	$19^{+3} \pm 0.5$	$10^{+2} \pm 0.9$	$25^{+3} \pm 1.2$	$29^{+2} \pm 0.1$	$36^{+3} \pm 0.8$	ND
YCl_3	0	0	0	0	14 ± 0.7	10 ± 0.1
$ZrOCl_2 \cdot 8H_2O$	0	0	0	0	0	0
$UO_2(NO_3)_2 \cdot 6H_2O$	0	0	0	0	7 ± 0.5	0
Control (DMSO)	0	0	0	0	0	0
Standard						
Moxifloxacin	22 ± 1.7	14 ± 0.1	22 ± 0.3	36 ± 1.2	26 ± 0.1	40 ± 0.5
Lomefloxacin	17 ± 0.1	12 ± 0.1	13 ± 0.3	25 ± 0.5	27 ± 0.1	24 ± 0.2
Ciprofloxacin	27 ± 0.4	18 ± 0.4	23 ± 0.1	34 ± 1.2	28 ± 0.1	26 ± 0.3

ND: Non-detectable, i.e., the inhibition zones exceeds the plate diameter.
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).

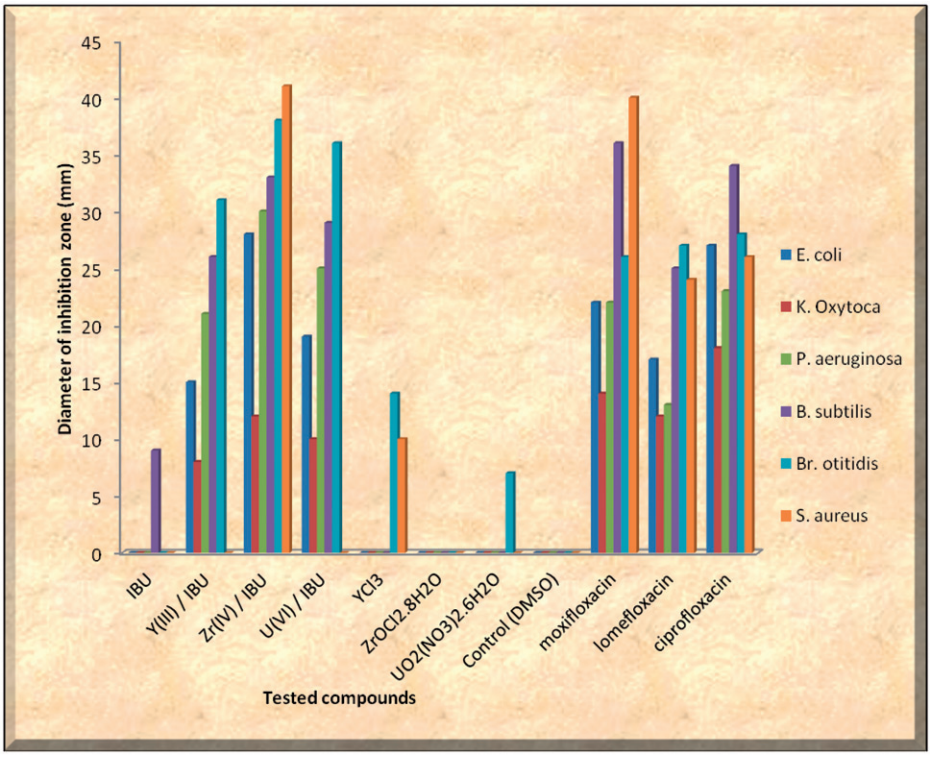


Figure 1. Statistical representation for biological activity of ibuprofen and its metal complexes.

populations. The B3LYP is the hybrid functional [60], which is a linear combination of the gradient functionals proposed by Becke [61] and Lee *et al*. [62], together with the Hartree–Fock local exchange function [63].

The geometry pre-optimizations of ibuprofen as free ligand and its complexes with Zr(IV) and Y(III) were carried out by applying the molecular mechanics method with MM+ force field using the HyperChem-7.5 software [64]. Pre-optimization performed makes it easier to perform full optimization using extended methods. Thereafter, the optimized equilibrium structures of complexes have been calculated at the B3LYP/CEP-31G level of theory, using the GAUSSIAN 98W package of the programs, on geometries that were optimized at CEP-31G basis set.

4.2. *Structural parameters and models*

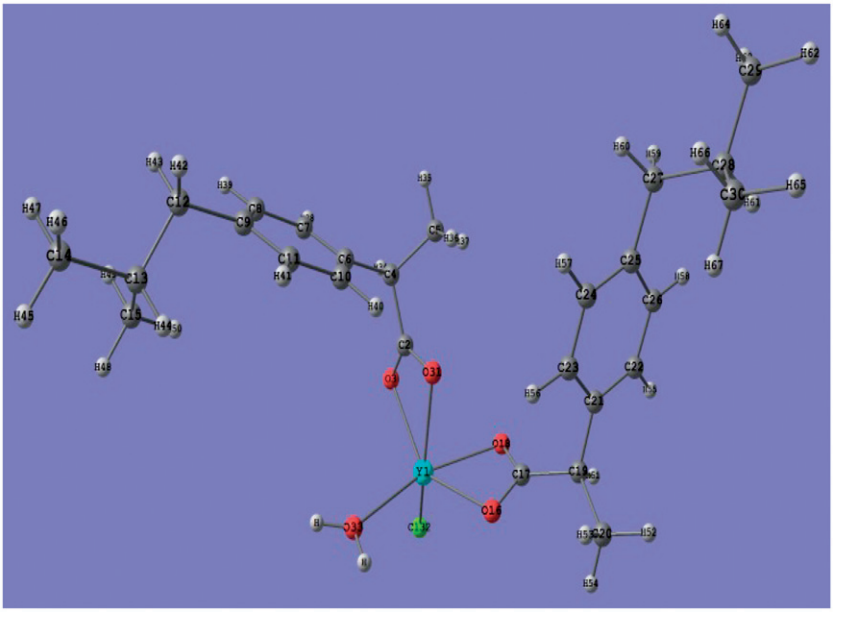
4.2.1. Ibuprofen. The biological activity of ibuprofen is determined by its structure. Complexation of carboxylates becomes significant for many non-steroidal drugs like ibuprofen [11, 12]. Values of geometric parameters (bond lengths and bond angles) of ibuprofen are calculated by using B3LYP/CEP-31G and compared with parameters experimentally obtained from both crystal geometries [65]. The calculated parameters give bond lengths slightly larger than the experimental values, due to theoretical calculations being in the gaseous phase and experimental results in the solid state.

The carboxylate is out of the plane of benzene and the angle of C5C11C13 is 110.94° and dihedral angles of C6C5C11C13 and C1C5C11C13 are 64.29° and −117.43°. The isopropyl also is out of the plane of benzene and in the same plane as carboxylate, the angle of C3C7C8 is 114.08° and the dihedral angles of C8C7C3C2 and C8C7C3C4 are 103.83° and −74.97°. "Supplementary material" shows the optimized structure of ibuprofen, the dihedral angles of C5C11C13O14 and C5C11C13O15 are 104.31° and −75.61°, confirming that the two oxygen atoms of carboxylate do not lie in the plane of benzene. The values of bond distances are compared nicely with that obtained from experimental data [65].

There is significant build up of charge density on oxygen atoms, so ibuprofen is bidentate (O14 and O15 atoms) and the molecule is not highly dipole $\mu = 2.22$. A system with a larger highest occupied molecular orbital–lowest unoccupied molecular orbital (HOMO–LUMO) gap should be less reactive than one having smaller gap [66]. The HOMO–LUMO gap value is 0.208 eV, so electron movement between these orbitals could easily occur.

4.2.2. The yttrium-ibuprofen complexes. Y(III) binds two molecules of ibuprofen through four oxygen atoms of carboxylates. The complex is six-coordinate with four coordinate bonds from two ibuprofens and water or chlorides. We studied $[Y(IBU)_2(H_2O)Cl]$ and $[Y(IBU)_2(H_2O)_2]^+$.

4.2.2.1. *Description of the structure of* $[Y(IBU)_2(H_2O)Cl]$. Scheme 1 shows the optimized geometry of $[Y(IBU)_2(H_2O)Cl]$ with atomic-numbering. The yttrium, at a crystallographic inversion center, is in a distorted octahedral environment. The equatorial plane coordinated by two oxygen atoms (O3 and O31) of ibuprofen and their plane is perpendicular (91.52°) to the plane occupied by O16 and O18 of the other



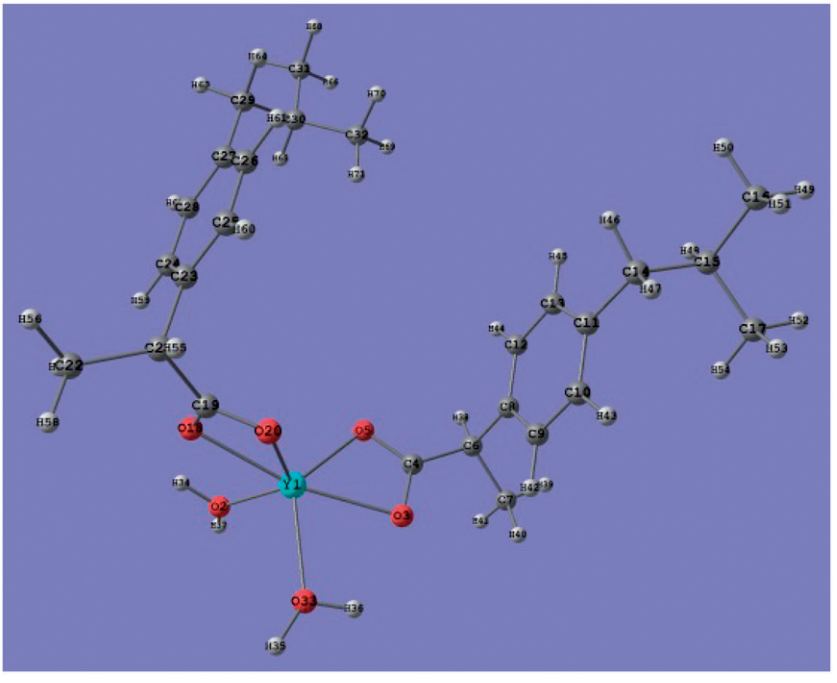
Scheme 1. Optimized geometrical structure of $[Y(IBU)_2(H_2O)Cl]$ by using B3LYP/CEP-31G.

ibuprofen. The bond lengths of 2.333 Å to 2.479 Å are similar to those observed in related compounds [67]. There is no large difference between the C–O distances of carboxylate group, confirming that ibuprofen chelates through the two oxygen atoms. The octahedral coordination is completed by two chlorides. The bond distances between Y–O3, Y–O31 are (2.333 Å, 2.479 Å) [68] and Y–O16, Y–O18 (2.374 Å, 2.407 Å) [69] while the Y–Cl distance is 2.607 Å [69]. The bond angles O18–Y–O33, 149.976°, and O31–Y–Cl32, 156.158°, deviated from linearity. The bond angles around Y(III) vary from 56.153° to 111.174°, differing significantly from a regular octahedron.

The distances and angles within the ligand are similar to those of free ibuprofen [65]. In the complex, C2–O3 and C2–O31 become equal (1.334 Å and 1.309 Å, respectively) and slightly longer than those found in free ibuprofen (1.251 Å). The energy of this complex is −299.479 au and the dipole moment is large 13.44D, so this complex is less stable.

4.2.2.2. *Description of the structure of* $[Y(IBU)_2(H_2O)_2]^+$. The structure of the complex with atomic-numbering is shown in scheme 2. The complex consists of two ibuprofens and two water molecules with Y(III). The complex is six-coordinate with a distorted octahedron. The Y(III) is coordinated with four oxygen atoms of carboxylates of ibuprofen and two water molecules. The Y–O3 and Y–O18 bond lengths (2.382 Å and 2.375 Å, respectively) are longer than Y–O5 and Y–O20 (2.239 Å and 2.246 Å, respectively). Both are similar to related Y(III) compounds [69]. Angles around Y(III) vary from 57.976° to 125.735°, differing from a regular octahedron. The distances and angles in ibuprofen are similar to those found in free ibuprofen [65].

The bond distances between Y(III) and oxygen are shorter than that in the chloride complex, so that the Y(III) is strongly bonded with surrounding oxygen atoms of

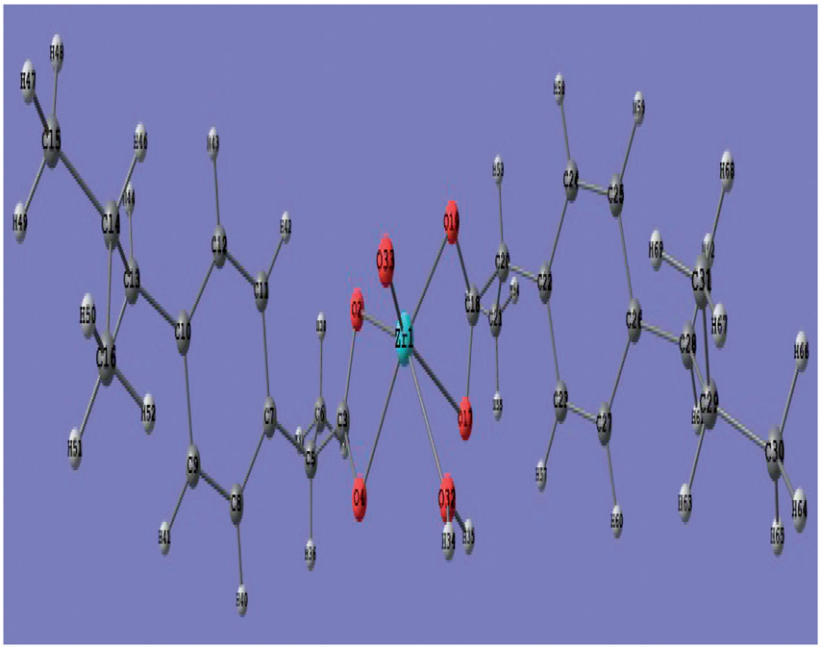


Scheme 2. Optimized geometrical structure of $[Y(IBU)_2(H_2O)_2]^+$ by using B3LYP/CEP-31G.

ibuprofen in the water complex. The charge accumulated on oxygen of carboxylates varies between −0.256 and −0.291 in the water complex while in the chloride complex the charge on oxygen atoms varied between −0.243 and −0.301. There is a strong interaction between Y(III) which has a charge equal to +1.159 and more negative oxygen atoms in the water complex; Y(III) has less positive charge (+1.096) in the chloride complex. The energy of this complex is −303.588 au and a dipole of 18.45D. For all these reasons the water complex is more stable than chloride complex and Y(III) favors coordinating two molecules of water more than chloride to complete the octahedral structure.

4.2.3. The zirconium(IV)-ibuprofen complex. The Zr(IV) complex is six-coordinate, with four bonds with two ibuprofens and one water molecule besides oxygen of ZrO ion, $[ZrO(IBU)_2H_2O]$.

4.2.3.1. *Description of the structure of* $[ZrO(IBU)_2(H_2O)]$. The structure with atomic-numbering is shown in scheme 3. The complex consists of two ibuprofens and one water molecule with ZrO^{2+}. The complex is six-coordinate with distorted octahedral environment with Zr(IV) coordinated with two oxygen atoms with each ibuprofen and water. Zr–O4 and Zr–O17 bond lengths are 2.306 Å and 2.645 Å, respectively, longer than Zr–O2 and Zr–O19 (2.264 Å and 2.196 Å, respectively), and the bond distance between $Zr–O_{H2O}$ is 2.235 Å [70].



Scheme 3. Optimized geometrical structure of $[ZrO(IBU)_2H_2O]$ by using B3LYP/CEP-31G.

Table 7. Calculated energy values (HOMO, LUMO, and energy gap ΔE in eV) obtained by using DFT/B3LYP/CEP-31G.

	HOMO	LUMO	Energy gap, ΔE
IBU	−0.237	−0.028	0.208
$[Y(IBU)_2Cl_2]^+$	−0.148	0.060	0.207
$[Y(IBU)_2(H_2O)]^{3+}$	−0.305	−0.240	0.065
$[ZrO(IBU)_2Cl]^-$	−0.082	0.061	0.143
$[ZrO(IBU)_2(H_2O)]$	−0.235	−0.113	0.122

4.2.4. Electronic properties of studied molecules. The HOMO energies, the LUMO energies, and energy gap for the molecules are given in table 7. An electronic system with larger HOMO–LUMO gap should be less reactive than one having a small gap [65]. The HOMO–LUMO gap values are between 0.065 and 0.208 eV, so electron movement between these orbitals should easily occur; we observe a peak around 250 nm in UV-Vis spectra. The molecular orbital energy diagram in "Supplementary material" shows that the complexes which are most favored by interaction energy have lower energy barrier (table 7); however, the HOMO of these complexes is most stable and responsible for the low value in the interaction energy.

5. Conclusion

Three new Y(III), Zr(IV), and U(VI) complexes with ibuprofen were synthesized and characterized by means of elemental analyses, thermal analyses, UV-Vis, IR, ^{1}H NMR

as well as their magnetic behavior. The ibuprofen has two donating centers, oxygen atoms of carboxylate; when chelated with Y(III) there are six bonds formed, four with two ibuprofens and two water molecules. The Zr(IV) complex is coordinated with one water molecule to complete the octahedral structure. The biological activity of these compounds was tested against different bacterial species, such as *E. coli* K32 and highly significant for *S. aureus* K1, *B. subtilis* K22, *Br. otitidis* K76, *P. aeruginosa* SW1, and *K. oxytoca* K42. The biological assays show that all complexes are active compared with free ibuprofen and metal salts.

References

[1] A. van Esch, H.A. van Steensel-Moll, E.W. Steyerberg, M. Offringa, J.D. Habbema, G. Derksen-Lubsen. *Arch. Pediatr. Adolesc. Med.*, **149**, 632 (1995).
[2] J.R. Sorenson. *J. Med. Chem.*, **19**, 135 (1976).
[3] US Patent No. 5 082 834 (1992).
[4] J.R. Sorenson. In *Metal Ions in Biological Systems*, H. Sigel (Ed.), Vol. 14, pp. 77–124, Marcel Dekker, New York (1982).
[5] A. Goodman Gilman (Ed.). *Las Bases Farmacológicasde la Terapéutica*, Vol. II, 9th Edn, pp. 661–706, McGraw-Hill Interamericana, Méjico (1996).
[6] D.W. Gilroy, A. Tomlinson, K. Greenslade, M.P. Seed, D.A. Willoughby. *Inflammation*, **22**, 509 (1998).
[7] J.P. Pelletier. *Osteoarthritis Cartilage*, **7**, 374 (1999).
[8] S.B. Etcheverry, D.A. Barrio, A.M. Cortizo, P.A.M. Williams. *J. Inorg. Biochem.*, **88**, 94 (2002).
[9] R.P. Sharma, S. Singh, A. Singh, V. Ferretti. *J. Mol. Struct.*, **918**, 188 (2009).
[10] N.E.A. El-Gamel. *J. Coord. Chem.*, **62**, 2239 (2009).
[11] R.C. Malhotra, R. Bohra. *Metal Carboxylates*, Academic Press, London (1983).
[12] A.M. Greenaway, T.P. Dasgupta, K.C. Koshy, G.G. Sadler. *Spectrochim. Acta A*, **42**, 949 (1986).
[13] C. Dendrinou-Samara, G. Tsotsou, L.V. Ekateriniadou, A.H. Kortsaris, C.P. Raptopoulou, A. Terzis, D.A. Kyriakidis, D.P. Kessissoglou. *J. Inorg. Biochem.*, **71**, 171 (1998).
[14] F.D. Rochon, R. Melanson, J.P. Macouet, F. Belanger-Gariepy, A.L. Beauchamp. *Inorg. Chim. Acta*, **108**, 17 (1985).
[15] T.G. Appleton, J.R. Hall, S.F. Ralph. *Inorg. Chem.*, **24**, 673 (1985).
[16] M.A. Bennett, G.B. Robertson, A. Rokicki, W.A. Wickramasinghe. *J. Am. Chem. Soc.*, **110**, 7098 (1988).
[17] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery Jr, R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M.W. Gill, B. Johnson, W. Chen, M.W. Wong, J.L. Andres, C. Gonzalez, M. Head-Gordon, E.S. Replogle, J.A. Pople. *Gaussian 98, Revision A.6*, Gaussian, Inc., Pittsburgh, PA (1998).
[18] W.J. Stevens, M. Krauss, H. Bosch, P.G. Jasien. *Can. J. Chem.*, **70**, 612 (1992).
[19] D.J. Beecher, A.C. Wong. *Appl. Environ. Microbiol.*, **60**, 1646 (1994).
[20] C. Dendrinou-Samara, D.P. Kessissoglou, G.E. Manoussakis, D. Mentzafos, A. Terzis. *J. Chem. Soc., Dalton Trans.*, 959 (1990).
[21] C. Dendrinou-Samara, P.D. Jannakoudakis, D.P. Kessissoglou, G.E. Manoussakis, D. Mentzafos, A. Terzis. *J. Chem. Soc., Dalton Trans.*, 3259 (1992).
[22] D.P. Kessissoglou, G.E. Manoussakis, A.G. Hatzidimitriou, M.G. Kanatzidis. *Inorg. Chem.*, **26**, 1395 (1987).
[23] A.G. Hatzidimitriou, G.E. Manoussakis, D.P. Kessissoglou, P.N. Kourounakis, G. Economidis. *J. Inorg. Biochem.*, **39**, 263 (1990).
[24] A.G. Hatzidimitriou, D.P. Kessissoglou, G.E. Manoussakis. *J. Inorg. Biochem.*, **47**, 157 (1993).
[25] J.A. Davies, C.T. Eagle, A.A. Pinkerton, R. Syed. *Acta Cryst. C*, **43**, 1547 (1987).
[26] M.R. Gregg, J. Powell, J.F. Sawyer. *Acta Cryst. C*, **44**, 43 (1988).
[27] F. Cariati, R. Mason, G.B. Robertson, R. Ugo. *J. Chem. Soc., Chem. Commun.*, 408 (1967).
[28] G.B. Robertson, P.A. Tucker. *Acta Cryst. C*, **39**, 858 (1983).

[29] H.E. Bryndza, J.C. Calabrese, M. Marsi, D.C. Roe, W. Tam, J.E. Bercaw. *J. Am. Chem. Soc.*, **108**, 4805 (1986).
[30] G. Manoussakis, C. Bolos, L. Ekateriniadou, C. Sarris. *Eur. J. Med. Chem.*, **22**, 421 (1987).
[31] A. Kortsaris, D. Kyriakidis. *Microbiologica*, **11**, 347 (1988).
[32] G.M. Sheldrick. *SHELX 86*, University of Gottingen, Germany (1986).
[33] G.M. Sheldrick. *SHELXL 93: Crystal Structure Refinement*, University of Gottingen, Germany (1993).
[34] G.B. Deacon, R.J. Phillips. *Coord. Chem. Rev.*, **33**, 227 (1980).
[35] D.R. Frazier, S.K. Lynch, G.O. Carlisle. *J. Inorg. Nucl. Chem.*, **43**, 2747 (1981).
[36] C. Dendrinou-Samara, D.P. Kessissoglou, G.E. Manoussakis, D. Mentzafos, A. Terzis. *J. Chem. Soc., Dalton Trans.*, 959 (1990).
[37] Z.N. Chen, R.W. Deng, J.G. Wu. *J. Inorg. Biochem.*, **47**, 81 (1992).
[38] A.L. Abuhijleh. *J. Inorg. Biochem.*, **55**, 255 (1994).
[39] S.B. Etcheverry, D.A. Barrio, A.M. Cortizo, P.A.M. Williams. *J. Inorg. Biochem.*, **88**, 94 (2002).
[40] G. Ribeiro, M. Benadiba, A. Colquhoun, D.O. Silva. *Polyhedron*, **27**, 1131 (2008).
[41] M.J. Cai, J.D. Chen, M. Taha. *Inorg. Chem. Commun.*, **13**, 199 (2010).
[42] M.J. Cai, J.D. Chen, M. Taha. *J. Coord. Chem.*, **64**, 314 (2011).
[43] S.A. Sadeek, W.H. El-Shwiniy. *J. Coord. Chem.*, **63**, 3471 (2010).
[44] H. Almadfa, A.A. Said, E.M. Nour. *Bull. Soc. Chim. Fr.*, **128**, 137 (1991).
[45] E.M. Nour, I.S. Alnaimi, N.A. Alem. *J. Phys. Chem. Solids*, **53**, 197 (1992).
[46] E.M. Nour, A.A. Taha, I.S. Alnaimi. *Inorg. Chim. Acta*, **141**, 139 (1988).
[47] S.A. Sadeek, W.H. EL-Shwiniy, W.A. Zordok, A.M. El-Didamony. *J. Argent. Chem. Soc.*, **97**, 128 (2009).
[48] S.A. Sadeek, W.H. El-Shwiniy. *J. Mol. Struct.*, **977**, 243 (2010).
[49] S.A. Sadeek, W.H. El-Shwiniy. *J. Mol. Struct.*, **981**, 130 (2010).
[50] S.A. Sadeek, S.M. Teleb, M.S. Refat, M.A.F. Elmosallamy. *J. Coord. Chem.*, **58**, 1077 (2005).
[51] E.M. Nour, A.M. AL-Kority, S.A. Sadeek, S.M. Teleb. *Synth. React. Inorg. Met.-Org. Chem.*, **23**, 39 (1993).
[52] G. Bandoli, D.A. Clemente, U. Croatto, M. Vidali, P.A. Vigato. *Chem. Commun.*, 1330 (1971).
[53] S.P. McGlynn, J.K. Smith, W.C. Neely. *J. Chem. Phys.*, **35**, 105 (1961).
[54] L.H. Jones. *Spectrochim. Acta*, **15**, 409 (1959).
[55] K. Nakamoto, P.J. McCarthy, S. Fujiwara, Y. Shimura, J. Fujita, C.R. Hare, Y. Saito. *Spectroscopy and Structure of Metal Chelate Compounds*, Wiley & Sons, New York, London, Sydney (1968).
[56] N. Sultana, M.S. Arayne, S. Guland, S. Shamin. *J. Mol. Struct.*, **975**, 285 (2010).
[57] S.A. Sadeek, A.W.H. El-Shwiniy, W.A. Zordok, E. Kotb. *J. Mol. Struct.*, **1006**, 192 (2011).
[58] S.A. Sadeek, A.W.H. El-Shwiniy, M.S. El-Attar. *Spectrochim. Acta, Part A*, **84**, 99 (2011).
[59] M. Imaran, J. Iqbal, S. Iqbal, N. Ijaz. *Turk. J. Biol.*, **31**, 67 (2007).
[60] W. Kohn, L.J. Sham. *Phys. Rev. A*, **140**, 1133 (1965).
[61] A.D. Becke. *Phys. Rev. A*, **38**, 3098 (1988).
[62] C. Lee, W. Yang, R.G. Parr. *Phys. Rev. B*, 37 (1988).
[63] R.L. Flurry Jr. *Molecular Orbital Theory of Bonding in Organic Molecules*, Marcel Dekker, New York (1968).
[64] *HyperChem 7.5 Release for Windows*, Hypercube Inc., USA (2003).
[65] S. Sagdinc, H. Pir. *Spectrochim. Acta A*, **73**, 181 (2009).
[66] R. Kurtaran, S. Odabasoglu, A. Azizoglu, H. Kara, O. Atakol. *Polyhedron*, **26**, 5069 (2007).
[67] R. Khoshnavazi, A. Salimi, A. Ghiasi Moaser. *Polyhedron*, **27**, 1303 (2008).
[68] L.L. Shen, D.C. Hopper, J.S. Wolfson. *Quinolone Antimicrobial Agents*, 2nd Edn, p. 77, American Society for Microbiology, Washington, DC (1993).
[69] P.C. Andrews, T. Beck, B.H. Fraser, P.C. Junk, M. Massi. *Polyhedron*, **26**, 5406 (2007).
[70] G. Paolucci, M. Vignola, L. Coletto, B. Pitteri, F. Benetollo. *J. Organomet. Chem.*, **687**, 161 (2003).