International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 11 (7): 773-785, 2015
ISSN 1811-7775

RESEARCH ARTICLE OPEN ACCESS

DOI: 10.3923/ijp.2015.773.785

Structural, Conductometric and Antimicrobial Investigations of Ibuprofen Analgesic Drug Complexes with Certain Metal Ions

[1,2]Ahmed M. Naglah, [1]Mohamed A. Al-Omar, [3,4]Samy M. El-Megharbel and [4,5]Moamen S. Refat
[1]Department of Pharmaceutical Chemistry, Drug Exploration and Development Chair, College of Pharmacy, King Saud University, Riyadh, 11451, Saudi Arabia
[2]Department of Peptide Chemistry, Chemical Industries Research Division, National Research Centre, 12622, Dokki, Cairo, Egypt
[3]Department of Chemistry, Faculty of Science, Zagazig University, Zagazig, Egypt
[4]Department of Chemistry, Faculty of Science, Taif University, 888, Taif, Saudi Arabia
[5]Department of Chemistry, Faculty of Science, Port Said University, Port Said, Egypt

ARTICLE INFO
Article History:
Received: May 30, 2015
Accepted: September 09, 2015

Corresponding Author:
Ahmed M. Naglah
Department of Pharmaceutical Chemistry,
Drug Exploration and Development Chair, College of Pharmacy,
King Saud University,
Riyadh, 11451, Saudi Arabia

ABSTRACT
Metal complexes have been applied as medicinal agents in the treatment of different human infections and diseases. So, the aim of this study is focused on studying the spectroscopic, thermal and evaluating antimicrobial investigations of ibuprofen analgesic drug complexes formulas with Cu (II), Ni (II), Ag (I), Hg (II), UO_2 (II), Cd (II), Ba (II) and Al (III) metal ions. Complexes of Cu (II), Ni (II), Ag (I), Hg (II), UO_2 (II), Cd (II), Ba (II) and Al (III) with ibuprofen ligand as to evaluate the biological activity were synthesized and characterized by elemental analysis, conductometry, magnetic susceptibility, UV-VIS, IR, ^{1}H-NMR spectroscopy and thermal analysis. The IR spectral data suggested that the ibuprofen ligand behaves as a monobasic bidentate ligand towards the central metal ion with deprotonated of carboxylic group. From the microanalytical data, the stoichiometry of the complexes 1:1, 1:2 and 1:3 (metal: ligand) was found. The metal complexes were screened for antibacterial activity against Gram -ve organisms as *Escherichia coli* and *Pseudomonas aeruginosa*, Gram +ve organisms as *Bacillus subtilis* and *Bacillus cereus* and antifungal organisms such as *Aspergillus niger*, *Aspergillus flavus* and *Aspergillus oryzae*. The resulted Ibu compounds has proved the thermal stability feature. The antimicrobial activities of the metal complexes of Ibu recorded a significant effect against some bacteria and fungi.

Key words: Ibuprofen, transition metals, non transition metals, thermal analysis, spectroscopic, antimicrobial activity

INTRODUCTION

Metal complexes have been applied as medicinal agents in the treatment of different human infections and diseases. Currently, there are platinum (II) complexes that are being used clinically as antitumor drugs, silver and gold compounds are used as antibacterial and antiarthritic agents (Sadler and Sue, 1994). More recently, gold compounds are found to be considerable importance in the treatment of rheumatoid arthritis, with emphasis on uses of auranofin, solganol and miochrysine (Fricker, 2007; Youn *et al*., 2006). The current interest in metallotherapeutic drugs have been considered to be motivated in the design of anticancer ruthenium compounds. Several reports on this subject have been published and many of them are cited in most articles and reviews (Clarke, 2003; Dyson and Sava, 2006; Kostova, 2006; Zhang and Lippard,

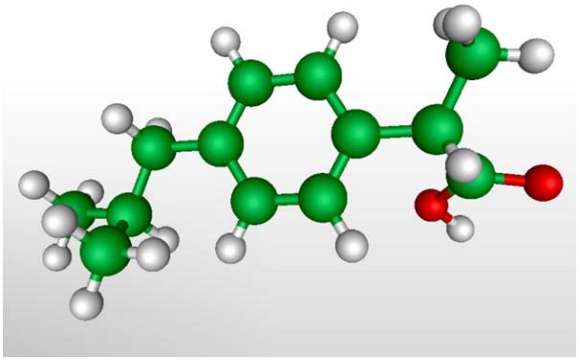

Fig. 1: 3D structure formula of ibuprofen analgesic drug

2003; Habtemariam *et al*., 2006; Ang and Dyson, 2006; Hartinger *et al*., 2006). Some ruthenium complexes exhibit antitumor activity which may be involved in the protein and DNA binding capacity of the metal (Zhang and Lippard, 2003; Habtemariam *et al*., 2006; Ang and Dyson, 2006; Hartinger *et al*., 2006; Grguric-Sipka *et al*., 2003; Djinovic *et al*., 2004; Zorzet *et al*., 2000; Sava *et al*., 2003). Due to the growth of antibiotic-resistant bacteria, new metallopharmaceuticals with antibacterial activities have been synthesized and described in the literature (Fox and Modak, 1974). The most remarkable example is the use of silver-sulfadiazine in the treatment of burns and wounds (Fox and Modak, 1974). Ibuprofen (Fig. 1) is a well known anti-inflammatory, analgesic and antipyretic drug that has been found recently to slow down the proliferation of colon cancer cells effectively (Zawidlak-Wegrzynska *et al*., 2010).

Solid-state compounds of general formula Ln(L)3, in which L is ibuprofen and Ln stands for trivalent La, Ce, Pr, Nd, Sm and Eu, have been synthesized. Simultaneous Thermogravimetry and Differential Thermal Analysis (TG-DTA), X-ray powder diffractometry (DRX), complexometry, fourier-transformed infrared spectroscopy (FTIR) and thermogravimetry coupled to fourier-transformed infrared spectroscopy (TG-FTIR) were used to characterize these compounds (Galico *et al*., 2014).

A novel gold (I) complex with ibuprofen was synthesized and characterized by chemical and spectroscopic measurements (Fiori *et al*., 2011), that elemental analysis led to the composition of $AuC_{14}H_{18}O_2N$. Infrared, ^1H and ^{13}C NMR data suggest that coordination of the ibuprofen ligand to Au(I) is carried out through the oxygen atom of the carboxylic group in a monodentate form. An antibiotic sensitive profile indicated the antibacterial activity *in vitro* of the complex against Gram-negative (*E. coli* and *P. aeruginosa*) and Gram-positive (*S. aureus*) microorganisms. So, the aim of this study is focused on studying the spectroscopic, thermal and evaluating antimicrobial investigations of ibuprofen analgesic drug complexes formulas with Cu (II), Ni (II), Ag (I), Hg (II), UO_2 (II), Cd (II), Ba (II) and Al (III) metal ions.

Experimental

Chemicals, reagents and instrumentals: All chemicals used in this study were of the purest laboratory grade (Merck) and ibuprofen drug was obtained from the Egyptian International Pharmaceutical Industrial Company (EIPICo.). Carbon and hydrogen contents were determined using a Perkin-Elmer CHN 2400. The metal content was found to be gravimetrically by converting the compounds into their corresponding stable oxide forms. The IR spectra were recorded on Bruker FT-IR spectrophotometer (4000-400 cm^{-1}) in KBr pellets. The UV-VIS spectra were studied in dimethylsulfoxide (DMSO) solvent with concentration (1.0×10^{-3} M) for the ibuprofen and their Cu (II), Ni (II), Ag (I), Hg (II), UO_2 (II), Cd (II), Ba (II) and Al (III) complexes by help of Jenway 6405 spectrophotometer with 1 cm quartz cell, in the range 800-200 nm. Molar conductivities of freshly prepared 1.0×10^{-3} mol dm^{-3} DMSO solutions were measured using Jenway. The proton NMR spectra were recorded on a Varian FT- 300 MHz spectrometer in DMSO-d_6 solvent, using TMS (Tetra methyl sillane) as internal standard. Stuart Scientific electrothermal melting point apparatus was used to measure the melting points of the ligands and their metal complexes in glass capillary tubes in degrees Celsius. The mass susceptibility (X_g) of the solid paramagnetic Cu (II) and Ni (II) complexes was measured at room temperature using Gouy's method by a magnetic susceptibility balance from Johnson Metthey and Sherwood model. The effective magnetic moment (μ_{eff}) values were obtained using the following Eq. 1-3 (Figgis *et al*., 1960).

$$X_g = \frac{C_{Bal} L (R - R_0)}{10^9 M} \quad (1)$$

Where:

R_o = Reading of empty tube
L = Sample length (cm)
M = Sample mass (g)
R = Reading for tube with sample
C_{Bal} = Balance calibration constant = 2.086

$$X_M = X_g \times M.Wt. \quad (2)$$

The values of X_M as calculated from Eq. 2 are corrected for the diamagnetism of the ligands using Pascal's constants and then applied in Curie's Eq. 3:

$$\mu_{eff} = 2.84 \sqrt{X_M \times T} \quad (3)$$

where, T is t (°C)+273.

Differential Thermal Analysis (DTA) and Thermo Gravimetric Analysis (TGA) experiments were conducted by using Shimadzu DTA-50 and Shimadzu TGA-50H thermal analyzers, respectively. All experiments were performed by

using a single loose top loading platinum sample pan under nitrogen atmosphere at a flow rate of 30 mL min^{-1} and a 10°C min^{-1} heating rate for the temperature range 25-800°C.

The ibuprofen ligand and their metal complexes were tested for their antimicrobial activity against Gram -ve organisms as *Escherichia coli* and *Pseudomonas aeruginosa*, Gram +ve organisms as *Bacillus subtilis* and *Bacillus cereus* and antifungal organisms such as *Aspergillus niger*, *Aspergillus flavus* and *Aspergillus oryzae* using filter paper disc method (Oliver *et al*., 1959). The screened compounds were dissolved individually in DMSO (dimethyl sulfoxide) in order to make up a solution of 1000 μg mL^{-1} concentration for each of these compounds. Filter paper discs (Whatman No.1 filter paper, 5 mm diameter) were saturated with the solution of these compounds. The discs were placed on the surface of solidified Nutrient agar dishes and seeded by the tested bacteria or Czapek´s Dox agar dishes seeded by the tested fungi. The diameters of inhibition zones (mm) were measured at the end of an incubation period, which was 24 h at 37°C for bacteria and 4 days at 28°C for fungi.

Synthesis of ibuprofen complexes: The Cu (II), Ni (II), Ag (I), Hg (II), UO_2 (II), Cd (II), Ba (II) and Al (III) complexes were synthesized by reactions of $CuCl_2.5H_2O$, $NiCl_2$, $AgNO_3$, $HgCl_2$, $UO_2(NO_3)_2$, $6H_2O$, $CdCl_2$, $BaCl_2$ and $Al_2(SO_4)_3$ metal ions (1 mmol; 20 mL distilled water) to solution of ibuprofen (2 mmol, 20 mL 99% CH_3OH) with stiochiometric 1:2 for all complexes except for Al (III) is 1:3 ratio. The pH for ibuprofen metal ions mixtures was adjusted in between 7-9 using 5% NH_4OH/CH_3OH. The resulting solutions were stirred and refluxed on hot plate at 60°C for 1 h. The precipitations were obtained and then filtered, washed several times with distilled water and methanol. The precipitations were dried at 70°C and stayed under vacuum over anhydrous calcium chloride.

RESULTS AND DISCUSSION

The elemental analysis agrees quite well with the speculated structures of the solid ibuprofen complexes which are summarized in Table 1. The elemental analysis data of the complexes indicate that the 1:3 stoichiometry (metal: ligand) for the Al (III)and 1:2 (metal: ligand) stoichiometry for the Cu (II), Ni (II), Hg (II), UO_2(II), Cd (II) and Ba (II) while 1:1 (metal: ligand) ratio with Ag(I).

Conductivities and conductometric titrations of metal chelates: The molar conductivity values for ibuprofen complexes were measured in dimethylformamide (DMF) at room temperature (Table 1) and which existed in the range of non-electrolytes (Geary, 1971). The interpretation concerning decreasing of conductivity values back to the deprotonation of -OH carboxylic group for the ibuprofen ligand. This assumption proves that free ligand acts in a monodentate fashion via carboxylic group.

Nayar and Pandey (1948) have been performed Monovariation method, which is a complementary with the mole ratio method by Yoe and Jones (1944). To elucidation the ligand: metal ratio, conductometric titrations tool by using monovariation method were measured at room temperature. The 0.01 M solution of ibuprofen pure drug was prepared in 80:20 mixtures of methanol and water. In the same solvents, solutions of $CuCl_2.5H_2O$ and $HgCl_2$ metal salts were prepared with 0.02 M concentration. The 20 mL of ibuprofen drug was diluted to 200 mL with same solvent. The ibuprofen ligand was titrated against metal salts solution using Monovariation method. The conductance was recorded after each mL added from ibuprofen. The graphical diagram is plotted between corrected conductance and volume of mentioned metal salts added. From the equivalence point in the graph it has been concluded that the complex formation has taken place in the ratio of 2:1 (L:M) (Table 2 and 3).

Accordingly continuous variation method (Skoog and West, 1985), the composition of metal-chelation can be determined. Equimolar solutions of ibuprofen ligand and metal salt solutions were prepared with three series C1, C2, C3 of solutions. In set C1 metal salt solution was filled with volume 0.0-12 mL and total volume was made to 12 mL in each case. Similarly, in C2 ligand solution was filled and set C3 was prepared by mixing metal salt solution from 0.0-12 mL and ligand solution from 12.0-0.0 mL. Conductance was recorded for each solution and this was calculated using formula C1+C2-C3. The process was repeated by changing the

Table 1: Elemental analysis and physical data for ibuprofen complexes

			Content (found) calculated			
Complexes	Mwt.	Color	C /%	H/%	M/%	A/S (cm^2 mol^{-1})
$[Cu(Ibu)_2 (H_2O)_2].3H_2O$	569	Gray	54.31 (54.78)	7.26 (7.52)	11.32 (11.51)	25
$[Ag (Ibu) (H_2O)_3]. H_2O$	384	Black	40.83 (40.56)	6.79 (6.50)	27.86 (27.66)	20
$[Hg (Ibu)_2 (H_2O)_2].3H_2O$	702	White	44.93 (44.46)	6.31 (6.27)	28.79 (28.50)	33
$[UO_2 (Ibu)_2 (H_2O)_2].3H_2O$	770	White	40.62 (40.51)	5.39 (5.71)	31.01 (30.90)	29
$[Ba(Ibu)_2 (H_2O)_4]$	619	White	50.37 (49.55)	1.78 (1.76)	21.91 (22.18)	12
$[Al(Ibu)_3 (H_2O)_3].H_2O$	717	White	58.28 (58.45)	3.22 (3.93)	3.61 (3.76)	10
$[Cd(Ibu)_2 (H_2O)_4]$	594	White	50.40 (49.94)	2.06 (1.97)	18.65 (18.92)	11
$[Ni(Ibu)_2 (H_2O)_4].8H_2O$	683	Green	56.74 (57.29)	6.50 (6.60)	8.54 (8.59)	11

*Values without parenthesis are the calculated values, while the values between parenthesis are the experimental values

concentration of solutions of ligand and metal (Fig. 2). Graphs were plotted between corrected conductances versus mole metal: ligand ratio. The study was carried out using ibuprofen drug as ligand and both of Cu (II) and Hg (II) metal salts. The results are recorded in Table 4 and 5. The peak in the graph coincides with the ratio of metal and drug in solution, which comes out to be 1:2.

Table 2: Conductometric titration between ibuprofen and $CuCl_2.5H_2O$ (Monovariant method)

Volume of metal salt	Observed conductance (mS)	Corrected conductance (mS)
0	0.071	0.071
1	0.121	0.122
2	0.160	0.163
3	0.239	0.246
4	0.300	0.312
5	0.389	0.408
6	0.450	0.477
7	0.470	0.502
8	0.499	0.538
9	0.520	0.566
10	0.549	0.603
11	0.560	0.621
12	0.570	0.638

Table 3: Conductometric titration between ibuprofen and $HgCl_2$ (Monovariant method)

Volume of metal salt	Observed conductance (mS)	Corrected conductance (mS)
0	0.06	0.06
1	0.13	0.131
2	0.17	0.173
3	0.22	0.226
4	0.30	0.312
5	0.40	0.42
6	0.45	0.477
7	0.48	0.513
8	0.49	0.529
9	0.53	0.577
10	0.55	0.605
11	0.58	0.643
12	0.59	0.660

Infrared spectra: The infrared spectra of ibuprofen and its Cu (II), Ni (II), Ag (I), Hg (II), UO_2 (II), Cd (II), Ba (II) and Al (III) complexes were exhibited with the main coordination bands which reveal the mode of bonding and are summarized

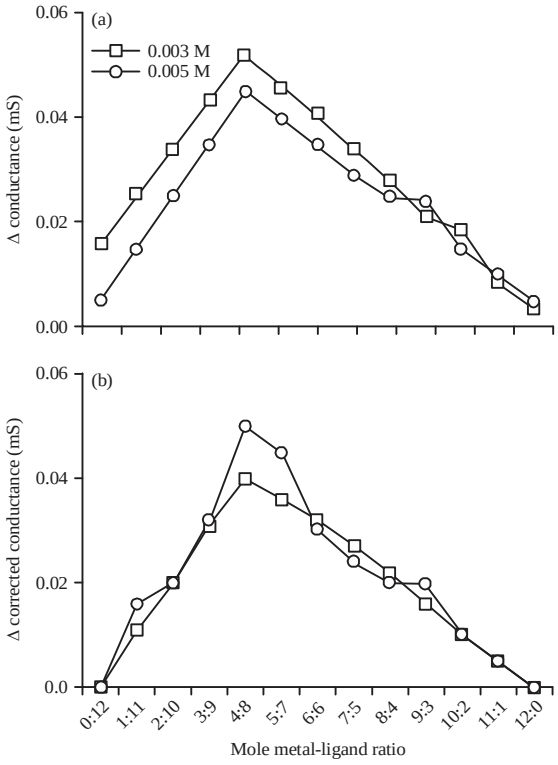

Fig. 2(a-b): Modified Job's Method, (a) Modified Job's Method (Concentration of ibuprofen: 0.005 M and concentration of $CuCl_2.5H_2O$: 0.005 M solvent: 80% ethanol) and (b) Modified Job's Method (Concentration of ibuprofen: 0.003 M concentration of $HgCl_2$: 0.003M solvent: 80% ethanol)

Table 4: Modified Job's method (Concentration of ibuprofen: 0.005 M and concentration of $CuCl_2.5H_2O$: 0.005 M solvent: 80% ethanol)

	Conductance (mS)				
Ratio	M:S (C1)	S:L (C2)	M:L (C3)	Δ conductance (C1+C2-C3)	Δ corrected conductance
0:12	0.005	0.010	0.0101	0.0049	0.0000
1:11	0.010	0.020	0.0152	0.0148	0.0160
2:10	0.015	0.030	0.0200	0.0250	0.0200
3:9	0.020	0.040	0.0251	0.0349	0.0320
4:8	0.025	0.050	0.0300	0.0450	0.0500
5:7	0.030	0.045	0.0352	0.0398	0.0449
6:6	0.050	0.030	0.0450	0.0350	0.0300
7:5	0.040	0.020	0.0310	0.0290	0.0240
8:4	0.035	0.015	0.0250	0.0250	0.0200
9:3	0.030	0.010	0.0210	0.0240	0.0199
10:2	0.020	0.010	0.0150	0.0150	0.0100
11:1	0.015	0.010	0.0150	0.0100	0.0050
12:0	0.010	0.005	0.0100	0.0050	0.0000

Table 5: Modified Job's method (Concentration of ibuprofen: 0.003 M concentration of $HgCl_2$: 0.003M solvent: 80% ethanol)

	Conductance (mS)				
Ratio	M:S (C1)	S:L (C2)	M: L (C3)	Δ Conductance (C1+C2 - C3)	Δ corrected conductance
0:12	0.0100	0.0159	0.010	0.01590	0.0000
1:11	0.0400	0.0155	0.030	0.02550	0.0110
2:10	0.0890	0.0142	0.069	0.03420	0.0200
3:9	0.1200	0.0136	0.090	0.04360	0.0310
4:8	0.1710	0.0121	0.130	0.05210	0.0400
5:7	0.2199	0.0160	0.190	0.04590	0.0390
6:6	0.2510	0.0105	0.221	0.04050	0.0320
7:5	0.2790	0.0142	0.259	0.03420	0.0270
8:4	0.0320	0.0181	0.310	0.02810	0.0220
9:3	0.0350	0.0110	0.340	0.02100	0.0160
10:2	0.3790	0.0085	0.369	0.01850	0.0100
11:1	0.4210	0.0084	0.420	0.00840	0.0050
12:0	0.4700	0.0032	0.471	0.00321	0.0000

Table 6: Main IR data of ibuprofen and its complexes

Compound	ν (O-H)	ν (C-O)	ν_{as} (COO)	ν_s (COO)	Δν (COO)	ν (M-O)
Cu (II)	3141	1284	1588	1405	183	547
Ag (I)	3406	1287	1562	1393	169	577
Hg (II)	3442	1280	1538	1402	136	566
UO_2 (II)	3468	1280	1530	1419	111	458
Ba (II)	3434	1266	1600	1410	190	561
Al (III)	3475	1285	1595	1466	129	617
Cd (II)	3445	1265	1547	1457	90	613
Ni (II)	3393	1265	1571	1458	113	542

in Fig. 3 and Table 6. Concerning the ibuprofen complexes, the most important region in the infrared spectra of all complexes as well as the Ibu free ligand is (1700-1300 cm^{-1}). This important region was selected and assigned in Table 2 as follows: In comparison between free Ibu ligand and their complexes, there is no any absorption band at 1720 cm^{-1}, which characteristic for the ν (C = O) vibration of carboxylic group in case of free Ibu ligand (Nakamoto, 1997). This is attributed to the involvement of the carboxylic group in the coordination with metal ion. The peaks at 1588, 1571, 1562, 1538, 1530, 1547, 1699 and 1595 cm^{-1}, for the Cu (II)/Ibu, Ni (II)/Ibu, Ag (I)/Ibu, Hg (II)/Ibu, UO_2 (II)/Ibu, Cd (II)/Ibu, Ba (II)/Ibu and Al (III)/Ibu complexes, respectively, are absent in the spectrum data of the free Ibu drug ligand which can be assigned to the asymmetric stretching vibration of the carboxylate group, ν_{as} (COO^-). The other interested band is exhibited within the range of 1393-1466 cm^{-1}, this band is absent in spectrum of Ibu and interpretive to the symmetric vibration of the ν_s (COO^-) group. Nakamato and McCarthy (1968) have been established that if the coordination is monodentate, the ν_{as} (COO^-) and ν_s (COO^-) will be shifted to higher and lower frequencies, respectively. Whereas, if the coordination is chelating bidentate or bridging bidentate both ν_{as} (COO^-) and ν_s (COO^-) frequencies will change in the same direction because the bond orders of both C = O bonds would change by the same amount. Based on these facts and comparison between the ν_{as} (COO^-) and ν_s (COO^-) frequencies of the ibuprofen complexes by the ν_{as} (COO^-) and ν_s (COO^-) frequencies of carboxylate group (Goto and Takenaka, 1963), as shown in Table 2, may can say that all the prepared complexes are chelating dependent on the monodentate fashion. The weak or medium intensity were observed in the wavenumbers range 600-500 cm^{-1} were assigned to ν (M-O) stretching vibration motions of metal-OOC of Ibu chelate. The absorption band corresponding to the ν_{as} (U = O) in the UO_2 group is observed at 895 cm^{-1} (Gandhi and Kulkarni, 1999). The O = U = O stretching force constant in UO_2/Ibu complex has been calculated using the G-F matrix method (Herzberg, 1951). The O = U = O bond distance (R) have been calculated using the Jones (1958) modification of Badger's formula (Badger,1935). The calculated values of the force constants (f_{U-O}) and bond lengths (R_{U-O}) of (O = U = O) in the uranyl moiety are 6.61 $mdyne^{-1}$ and 1.74, respectively. In the uranyl complex the very strong sharp band is observed corresponding to the ν_{as} (O = U = O). This band is singlet sharp, confirming the equivalence of the electronic environments around the uranyl centre. The coordination of Ibu moiety allows delocalisation possibility of the electron density and reduces the bond order, resulting in lengthening of the U = O bond (Gandhi and Kulkarni, 2001).

Electronic and magnetic measurements: The absorption of two bands (235 and 325 nm) with 200-400 nm region in the spectra of the Cu (II), Ni (II), Ag (I), Hg (II), UO_2 (II), Cd (II), Ba (II) and Al (III) complexes recorded in the DMF solvents, can be assigned to the π-π* and n-π* transitions within the ibuprofen ligand. Since the Ibu and aquo ligands occupying the coordination positions around metal ions, low energy

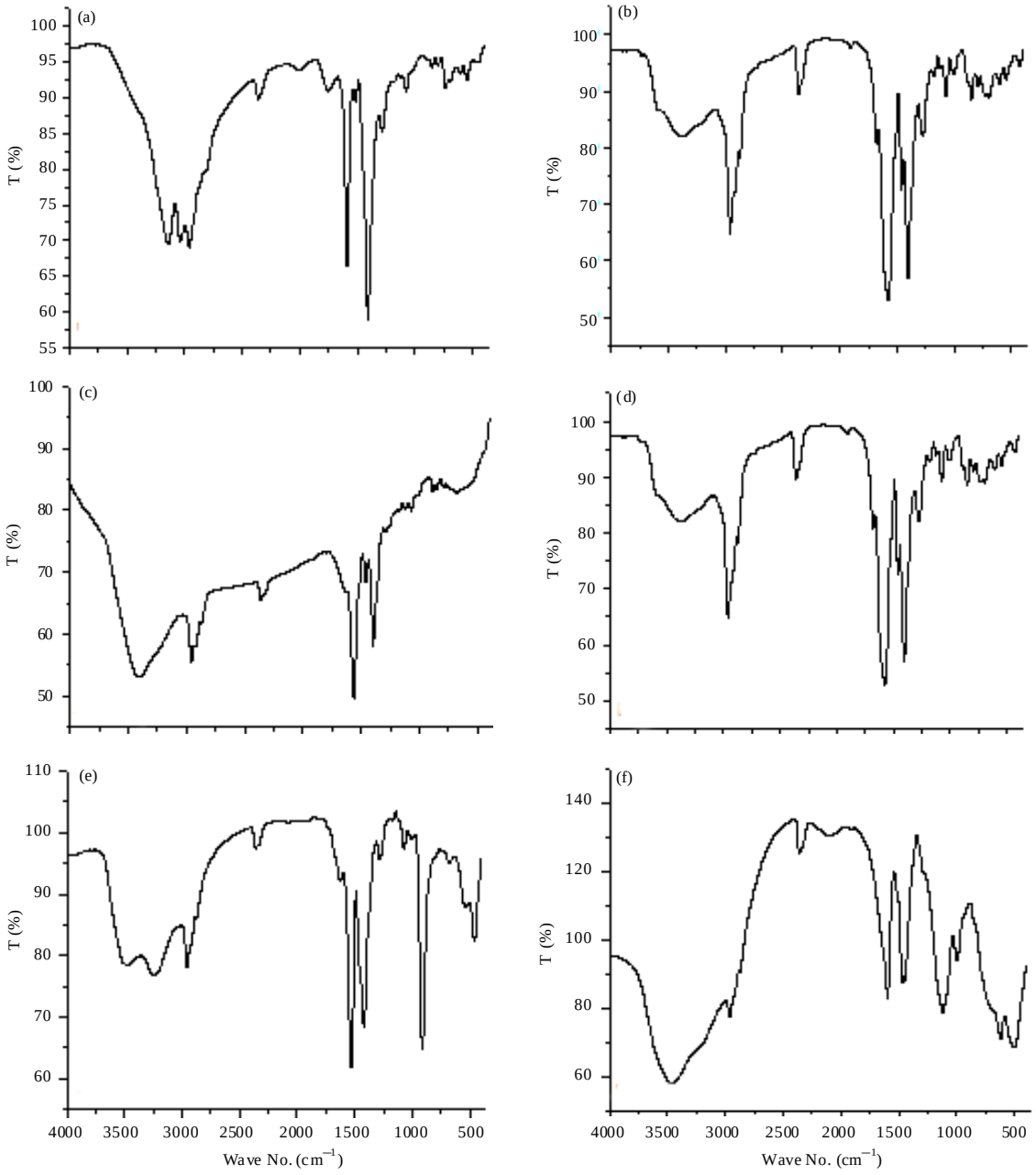

Fig. 3(a-f): Infrared spectra of, (a) Cu/ Ibu, (b) i/Ibu, (c) Ag/Ibu, (d) Hg/Ibu, (e) UO2/Ibu and (f) Al/Ibu

ligand-to-metal charge-transfer transition can take place in these complexes. In the spectra of the metal Ibu complexes, the two bands are bathochromically affected, suggesting the Ibu ligand has been changed to the deprotonated form. The results clearly indicate that the ibuprofen ligand coordinate to metal ions via carboxylic group which is in accordance with the results of the FTIR and ^{1}H-NMR spectra.

The solid reflectance spectrum of the 1:2 copper (II) complex has absorption band at 16129 cm^{-1} which assigned to the $^{2}A_{1g} \rightarrow {}^{2}B_{1g}$ transition and refereed to Cu (II) ion in a square-planar geometry (Gandhi and Kulkarni, 2001). The experimental magnetic moment value of copper (II) ion complex is 1.81 B.M, which is confirmed the square-planar geometry around Cu (II) ion. The coordination of two Ibu moieties as a monodentate and two coordinated water molecules toward the copper (II) ion (Figgis, 1966). The lower energy of the absorption band rather than the expected of square-planar geometry (Gruber *et al*., 1968) may be due to the distortion of the square-planar geometry towards tetrahedral (Gruber *et al*., 1968; Lever, 1984). The electronic reflectance spectrum of the monobasic nickel (II)/Ibu complex existed two identified absorption bands at 16949 and 22222 cm^{-1},

Table 7: Thermal data of ibuprofen complexes

Compound	DTG peak (°C)	TG Mass loss (%) Found	Calc.	Assignments
Cu (II)	136	41.43	41.13	$5H_2O+C_{11}H_{44}$
	186	34.24	34.26	$C_{11}H_5O_3$
	307	9.30	10.03	C_4H_5
Ag (I)	95	4.68	5.17	H_2O
	189	49.66	50.06	$3H_2O+C_9H_{13}O$
	300	9.36	8.83	$C_2H_4O_{0.5}$
Hg (II)	156	21.09	21.24	$5H_2O+C_4H_{10}$
	287	75.25	75.11	$Hg+C_{20}H_{24}O_4$
UO_2 (II)	96	9.35	9.20	$4H_2O$
	212	9.87	8.92	$H_2O+C_3H_6O$
	315	21.29	21.24	$C_6H_{28}O_3$
Ba (II)	150	5.80	6.63	$2H_2O$
	390	7.13	7.34	$2H_2O+5H_2$
	640	25.30	25.60	$C_7H_{24}O_2$
Al (III)	275	8.50	8.39	$3.5H_2O$
	400	5.04	5.34	$2H_2O+H_2$
	550	22.90	23.40	$C_8H_{21}O_3$
	620	18.20	17.80	C_9H_{22}
Cd (II)	240	4.60	4.60	$1.5H_2O$
	350	6.40	6.30	$2H_2O+H_2$
	500	43.70	43.70	$C_6H_{12}O_2+1/2H_2O$
	700	8.44	8.50	$C_2H_2+1/2CO+H_2$
Ni (II)	160	18.70	18.84	$7H_2O+H2$
	270	14.35	14.34	$5H_2O+4H_2$
	400	49.22	49.35	$C_{23}H_{12}O_3$
	650	7.00	6.70	C_3H_{12}

assigned to the transitions $^3A_{2g}(F)\rightarrow{}^3T_{1g}(F)$ and $^3A_{2g}(F)\rightarrow{}^3T_{1g}(P)$, respectively (Singh *et al*., 2010). This indicates that the nickel (II) ion coordinated with Ibu moieties in an octahedral geometry (Singh *et al*., 2010) and then Ni (II) ion complete its six-coordination sphere by four coordinated water molecules. The magnetic moment of the Ni (II)/Ibu complex is 3.11 B.M. which is different from the expected values, this can be attributed to the distorted octahedral geometry (Lever, 1984). The electronic absorption spectrum of the diamagnetic uranyl/Ibu complex show two bands at around 20000 and 25000 cm^{-1} due to charge-transfer transitions from both Ibu equatorial donating ligand to the UO_2 ion. The first absorption band at ~20000 cm^{-1} is due to charge-transfer from the uranyl oxygen to the uranium f orbitals. The shift of this transition towards lower energy compared to the free uranyl ion occurs because of the change in the U = O bond strengths as a result of the disturbed in the equatorial field (Badger, 1935).

HNMR spectra: The proton NMR spectra of the formed Hg (II) and Ba (II)/Ibu complexes were obtained using deuterated DMSO as a solvent. The proton NMR spectra of both Hg (II) and Ba (II) show the expected signals described for the free Ibu ligand around 2.50, 6.70, 707 and 7.24 ppm due to protons of CH_3 and aromatic ring, respectively. These signals are observed at nearly the same frequencies that were recorded for free Ibu ligand indicated that the magnetic environment associated with these protons has not been changed significantly with coordination. The proton NMR spectra for the Hg (II) and Ba (II) showed singlet peak at 3.54 and 3.75 ppm. These significant peaks are not observed in the free ligand spectrum and can be assigned due to protons of H_2O molecules, supporting the complex formulas. The singlet peak due to the proton of carboxylic acid group which was observed in the spectrum of the free ligand at above 9.00 ppm, did not observe in the complex spectrum. The disappearance of this proton comes in agreement with the coordination through the carboxylic group of ibuprofen. This conclusion support the suggestion that ibuprofen deprotonated during the reaction with Hg (II) and Ba (II) that come in consistence with the data previously obtained from the infrared spectra.

Thermogravimetric analysis: The heating rates were controlled at 10°C min^{-1} under nitrogen atmosphere and the mass loss was measured from ambient temperature up to at 800°C. The data are listed in Table 7 and shown in Fig. 4. The mass losses for each chelate calculated within the corresponding temperature ranges.

$[Cu(Ibu)_2(H_2O)_2].3H_2O$: The thermal decomposition of $[Cu(Ibu)_2(H_2O)_2].3H_2O$ complex occurs at three thermal degradation steps. The first degradation step takes place in the range of 15-150°C and its corresponds to the elimination of $5H_2O+C_{11}H_{14}$ (organic moiety) with an observed mass loss of (obs. = 41.13%) (calc. = 41.43%). The second step falls in the range of 150-200°C which is assigned to the loss of $C_{11}H_5O_3$ (organic moiety) with a mass loss (obs. = 34.26%, calc. = 34.24%). The third decomposition step within the temperature range 200-300°C was accompanied by mass loss of (obs. = 9.30%) (calc. = 10.03%), which is assigned to the loss of C_4H_5 (organic moiety). The CuO is the final products remain stable till 800°C.

$Ni(Ibu)_2(H_2O)_4].8H_2O$: The $[Ni(Ibu)_2(H_2O)_4].8H_2O$ complex is decomposed in four thermal steps. The first step occurs at 80-160°C and corresponds to the loss of $7H_2O+H_2$ molecules with obs. = 18.64% and calc. = 18.7%. The second step tale place in the range of 160-270°C and representing to the loss of $5H_2O+4H_2$ molecules with obs. = 14.34 and calc. = 14.35%. The third step occurs within range of 270-400°C and assigned to the loss of $C_{23}H_{12}O_3$ molecule with obs. = 49.35 and calc. = 49.22%. The fourth step occurs at 400-650°C with representing to the loss of C_3H_{12} molecule with obs. = 6.7 and calc. = 7.03. The final residue is NiO.

$[Ag(Ibu)(H_2O)_3].H_2O$: The Ag (I) ibuprofen complex is decomposed in three decomposition steps. The first step occurs at 55-100°C and corresponds to the loss of H_2O molecule representing an observed mass loss of (obs. = 5.17%) and

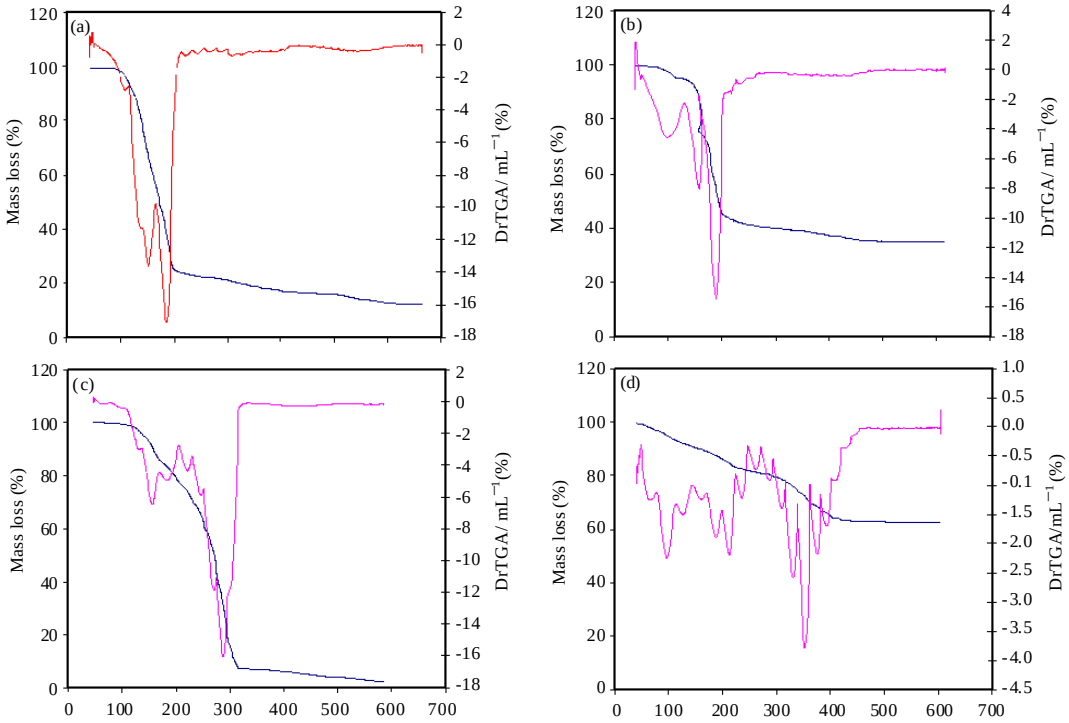

Fig. 4: TGA/DTG curves of a-Cu (II)/Ibu, b-Ag (I)/Ibu, c-Hg (II)/Ibu and d-UO_2/Ibu complexes

(calc. = 4.68%). The second step occurs at 100-200°C which corresponding to the loss of 3 H_2O+$C_9H_{13}O$ molecules where the mass loss associated with this stage (obs. = 50.06%) and (calc. = 49.66%). The third step takes place within the temperature range 200-310°C and can be assigned to the loss of $C_2H_4O_{0.5}$ molecule and the mass loss due to this step was (obs.= 8.83%) and (calc. = 9.36%). The final residue at the end of this stage is ½Ag_2O and residual carbon atoms.

[Hg(Ibu)$_2$(H$_2$O)$_2$].3H$_2$O: The thermal decomposition of mercury (II)/Ibu complex with the general formula [Hg(Ibu)$_2$(H$_2$O)$_2$].3H$_2$O is thermally decomposed in a successive two decomposition steps. The first estimated mass loss of (obs. = 21.24 %) within the temperature range of 50-190°C may be attributed to the loss of (5H_2O+C_4H_{10}) molecules of mass loss of (calc = 21.09%). The second step occurs within the temperature range 190-300°C with a mass loss (obs = 75.11%) and (calc = 75.25%) is probably accounted for the decomposition of $C_{20}H_{24}O_4$ and evaporation of Hg metal as vapor. The final residue at the end of this stage is residual carbon atoms.

[UO$_2$(Ibu)$_2$(H$_2$O)$_2$].3H$_2$O: [UO_2(Ibu)$_2$(H_2O)$_2$].3H_2O complex is decomposed in three definite steps. The first step occurs at 70-120°C and corresponds to the loss of 4H_2O molecules. It represents a mass loss of (obs. = 9.20%) and (calc. = 9.35%). The second step takes place in the range of 120-250°C and corresponds to the elimination of H_2O and C_3H_6O molecules with a mass loss of (obs. = 8.92%) which is in good matching with theoretical value (calc. = 9.87%). The third step takes place within the temperature range 250-400°C and can be assigned to the loss of $C_6H_{28}O_4$ molecules and the mass loss due to this step was (obs. = 21.24%, calc. = 21.29%). The UO_2 and residual carbon atoms are the final product remains stable till 800°C.

[Cd(Ibu)$_2$(H$_2$O)$_4$]: [Cd(Ibu)$_2$(H_2O)$_4$] complex is decompose with four thermal steps. The first step occur at 80-240°C and corresponding to the loss of 1½ H_2O, it represent mass loss of obs. = 4.6% and calc. = 4.6%. The second step take place in range 240-350°C and corresponds to the elimination of H_2 and 2H_2O molecules with mass loss of obs = 6.3% and calc. = 6.4%. The third step take place in the range 350-500°C and representing to the loss of ½H_2O+$C_{16}H_{26}O_2$ molecules with obs. = 43.7% and calc. = 43.7%. The fourth step takes places within the range 500-700°C and can be assigned due to the loss of C_2H_2+H_2+½CO molecules with obs. = 8.5 and calc. = 8.44%. The final residue is CdO and residual carbon atoms.

[Ba(Ibu)$_2$(H$_2$O)$_4$]: The thermal decomposition of [Ba(Ibu)$_2$(H_2O)$_4$] complex occurs at three steps. The first degradation step take place in the range of 50-150°C and it corresponds to the elimination of 2H_2O molecules with an observed mass loss 5.63% (calc. = 5.8%). The second step take place in the range of 150-390°C which is corresponds to the

loss of $2H_2O$ and $5H_2$ molecules with mass loss observed 7.34% (calc. = 7.13%). The third decomposition step take place in the range 390-640°C and was accompanied by mass loss of 25.6% (calc. = 25.3%) which is assigned due to the loss of ($C_7H_{24}O_3$). The BaO and few contaminated carbon atoms is the final product that remains stable till 790°C.

$[Al(Ibu)_3(H_2O)_3].H_2O$: The Al (III) ibuprofen complex is decomposed in four steps. The first step occurs at 60-275°C and corresponds to the loss of 3½ H_2O molecules representing an observed mass loss of 8.39% (calc. = 8.5%). The second step occurs at 275-400°C which corresponding to the loss of $2H_2O$ and H_2 molecules the mass loss associated with mass loss (obs = 5.4%, calc. = 5.04%). The third step takes place within temperature range 400-550°C and corresponding to the loss of $C_8H_{21}O_3$ and the mass loss due to this step was obs. = 23.4 and (calc. = 22.9%), the fourth step at 550-620°C and correspond to the loss of C_9H_{22} and representing mass loss of obs. = 17.8 and calc. = 18.2%. The final result is ½Al_2O_3 and residual carbon atoms.

Kinetic studies: The kinetic analysis parameters such as activation energy (E*), enthalpy of activation (ΔH*), entropy of activation (ΔS*) and free energy change of decomposition (ΔG*) were evaluated graphically by employing the (Coats and Redfern, 1964; Horowitz and Metzeger, 1963) relations.

Coats-redfern equation:

$$Ln[- \ln(1-\alpha)/T^2] = -E^*/RT+\ln [AR/\varphi E] \quad (4)$$

A plot of Left-Hand Side (LHS) against 1/T was drawn. E* is the energy of activation in kJ mol^{-1} and calculated from the slop and A in (sec^{-1}) from the intercept. The entropy of activation ΔS* in (JK^{-1} mol^{-1}) was calculated by using the equation:

$$\Delta S^* = R \ln(Ah/kT_s) \quad (5)$$

where, k is the Boltzmann constant, h is the Plank's constant and T_s is the DTG peak temperature.

Horowitz-metzger equation: The Horowitz-Metzger (Eq. 6) was written in the form as follows:

$$Log[\log(w_\alpha / w_\gamma)] = E^*\theta/2.303RT_s^2-\log 2.303 \quad (6)$$

where, $\theta = T-T_s$, $w_\gamma = w_\alpha-w$, w_α = mass loss at the completion of the reaction, w = mass loss up to time t. The plot of $Log[\log(w_\alpha/w_\gamma)]$ versus θ was drawn and found to be linear from the slope E* was calculated. The pre-exponential factor, A, was calculated from the Eq. 7:

$$E^*\theta/RT_{s2} = A/[\varphi \exp(-E^*/RT_s)] \quad (7)$$

The entropy of activation, ΔS*, enthalpy activation, ΔH* and Gibbs free energy, ΔG*, were calculated from the following relations:

$$\Delta H^* = E^*-RT$$

$$\Delta G^* = \Delta H^*-T\,\Delta S^*$$

The calculated values of E*, ΔH*, ΔS* and ΔG* for the decomposition steps are given in Table 8. The kinetic data that obtained with the two methods are in harmony with each other. The ΔS* values were found to be negative, which indicate a more ordered activated state or more rigid structure than the reactants or intermediates and the reactions are slower than normal (More *et al*., 2001; Thankamony *et al*., 2009). It is clear that the thermal decomposition process of all ibuprofen complexes is non-spontaneous, i.e., the complexes are thermally stable. From the kinetic and thermodynamic data that resulted from the TGA curves and listed in Table 8, the following outcome can be discussed as follows: (1) Thermodynamic data obtained with the two methods are in harmony with each other, (2) High values of activation energies of the ibuprofen complexes led to thermal stability of the studied complexes., (3) Activation energy of Cu (II), Ni (II), Ag (I), Hg (II), UO_2 (II), Cd (II), Ba (II) and Al (III) complexes is expected to increase in relation with decrease in their radii (Refat and Mohamed, 2011), the smaller size of the ions permits a closer approach of the ligand and (4) Correlation coefficients of the Arrhenius plots of the thermal decomposition steps were found to lay in the range ~0.99 nearly one value, showing a good fit with linear function.

Structure of the Ibuprofen complexes: Structures of the ibuprofen complexes with from the IR spectra it is clear that ibuprofen behaves as monobasic monodentate ligand coordinated to the metal ion via the deprotonated carboxylate -OH atom. From the molar conductance data, it is found that the complexes are non-electrolyte because of the above observations Cu (II), Ni (II), Ag (I), Hg (II), UO_2 (II), Cd (II), Ba (II) and Al (III) ions have been confirmed from the elemental analysis, IR, ^{1}H-NMR, molar conductance, UV-VIS, solid reflectance, magnetic properties and thermal analysis data. Thus. Suggested structures for the investigated complexes were given in Fig. 5.

Antimicrobial investigation: Antibacterial and antifungal activities of ibuprofen complexes are carried out against the Gram-ve organisms as *Escherichia coli* and *Pseudomonas aeruginosa*, Gram +ve organisms as *Bacillus subtilis* and *Bacillus cereus* and antifungal organisms such as

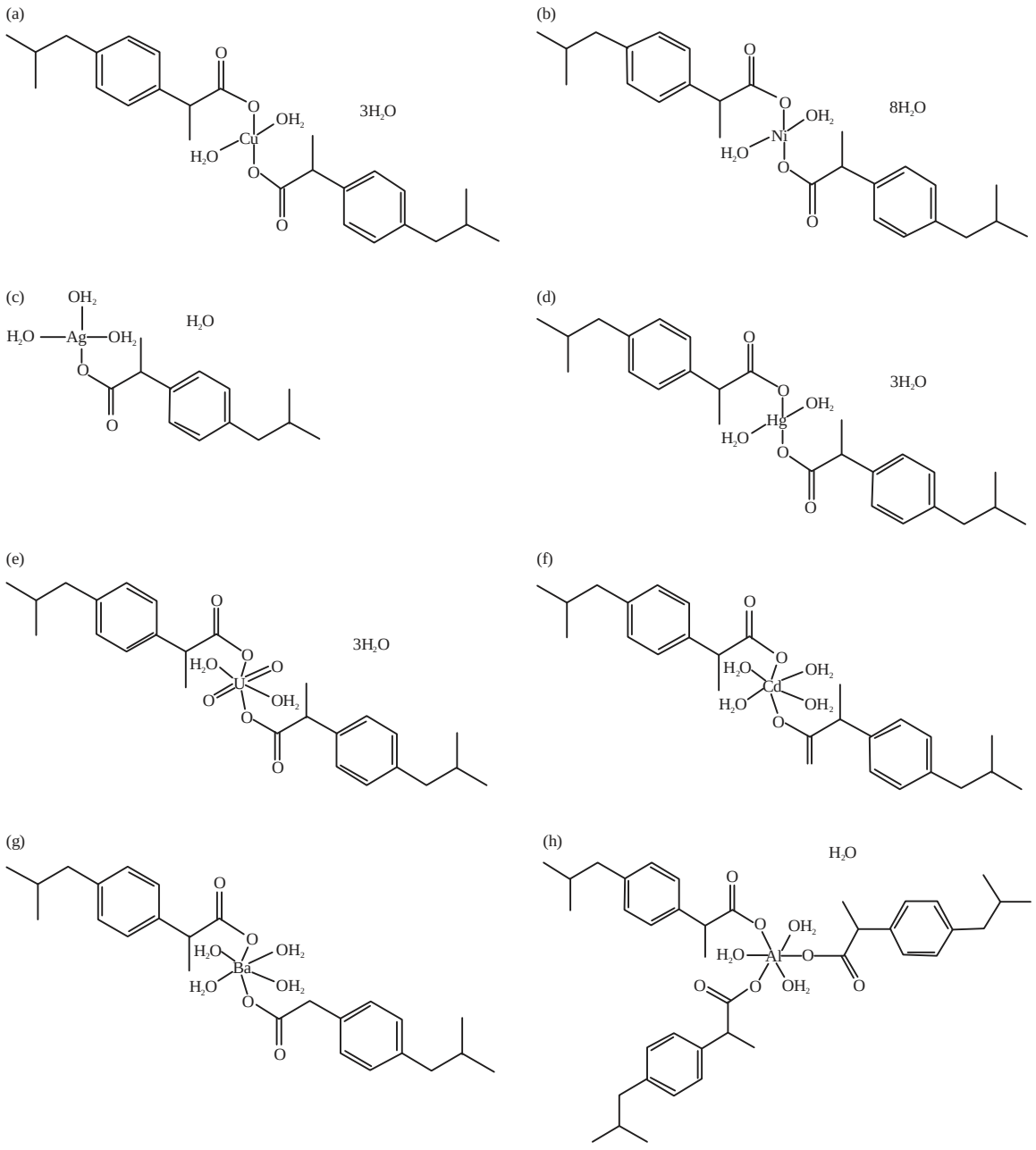

Fig. 5(a-h): Suggested structure of ibuprofen complexes

Aspergillus niger, *Aspergillus flavus* and *Aspergillus oryzae*. It is the fact that the complexation led to action more powerful than free ligand and potency as antimicrobial agent (Gupta *et al*., 1995). The inhibition zone data gave an idea about the effective role of metal ions within complexes against antibacterial activity. Such increased activity of the metal complexes can be explained on the basis of the overtone concept (Anjaneyulu and Rao, 1986) and chelation theory (Mishra and Singh, 1993). According to the overtone concept of cell permeability, the lipid membrane that surrounds the cell favors the passage of only lipid soluble materials, due to the liposolubility which is an important factor controlling the antimicrobial activity. On chelation, the polarity of the metal ion is reduced to a great extent due to the overlap of the ligand orbital and the partial sharing of the positive charge of the metal ion with donor groups. Furthermore, it increases the delocalization of electrons over the whole chelate ring and enhances the lipophilicity of the complex. This increased lipophilicity enhances the penetration of the complex into the lipid membrane and blocks the metal binding sites on the enzymes of the microorganism. The antimicrobial activity estimated based on the size of inhibition zone around dishes. The complexes are found to have high activity against bacteria especially *Escherichia coli* (Gram -ve) and two kinds of fungi,

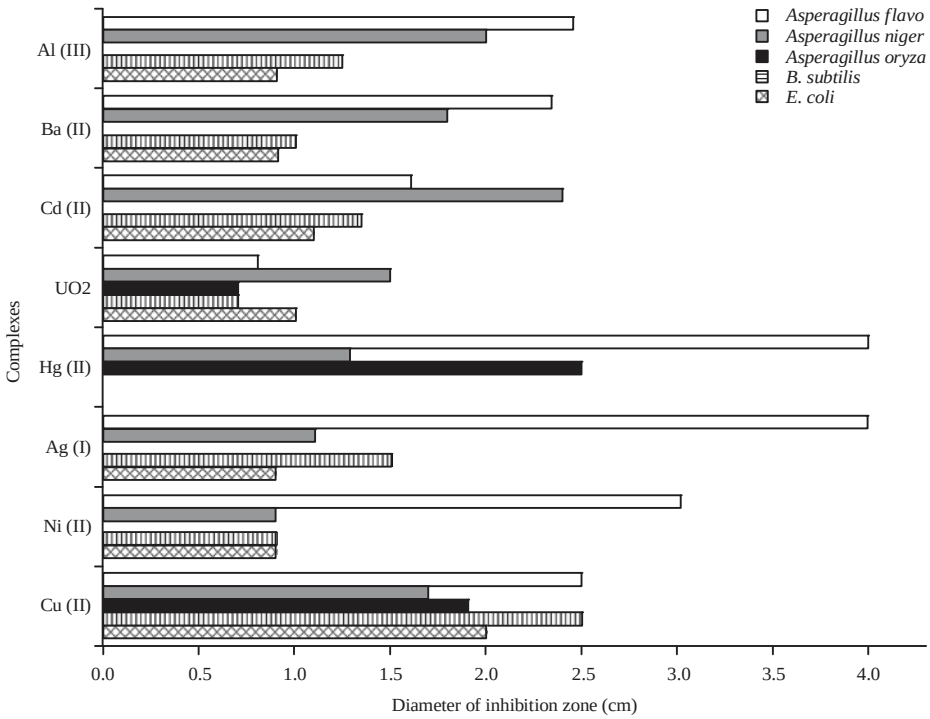

Fig. 6: Statistical representation for antimicrobial activity of ibuprofen complexes

Table 8: Kinetic parameters using the Coats–Redfern (CR) and Horowitz–Metzger (HM) equations for the ibuprofen complexes

			Parameters					
Complex	Stage	Method	E (J mol^{-1})	A (sec^{-1})	ΔS (J mol^{-1} K^{-1})	ΔH (J mol^{-1})	ΔG (J mol^{-1})	r
Cu (II)	2nd	CR	1.15E+05	1.30E+017	8.23E+01	1.13E+05	8.65E+04	0.9972
		HM	1.20E+05	1.13E+019	1.20E+02	1.20E+05	8.40E+04	0.9970
Ni (II)	2nd	CR	1.06E+05	5.60E+09	-6.40E+01	1.05E+05	1.35E+05	0.9965
		HM	1.16E+05	7.00E+10	-4.14E+01	1.12E+05	1.32E+05	0.9992
Ag (I)	2nd	CR	7.00E+04	1.12E+09	-7.18E+01	6.70E+04	8.77E+04	0.9960
		HM	7.21E+04	2.82E+10	-4.42E+01	7.32E+04	8.65E+04	0.9934
Hg (II)	2nd	CR	9.00E+04	3.41E+09	-6.42E+01	8.22E+04	1.03E+05	0.9984
		HM	9.11E+04	2.56E+10	-4.87E+01	9.06E+04	1.02E+05	0.9967
UO_2 (II)	2nd	CR	8.00E+04	7.80E+10	-3.74E+01	8.00E+04	8.95E+04	0.9955
		HM	8.51E+04	2.40E+12	-2.74E+01	8.32E+04	8.76E+04	0.9923
Cd (II)	2nd	CR	8.03E+04	2.81E+03	-1.64E+02	7.11E+04	2.59E+05	0.9994
		HM	1.01E+05	2.31E+05	-1.46E+02	6.92E+04	2.09E+05	0.9980
Ba (II)	2nd	CR	4.34E+04	9.90E+04	-1.53E+02	4.21E+04	8.86E+04	0.9997
		HM	4.98E+04	2.21E+06	-1.43E+02	4.43E+04	8.55E+04	0.9977
Al (II)	2nd	CR	7.24E+04	3.20E+07	2.15E+07	6.89E+04	1.11E+05	0.9542
		HM	7.01E+04	3.20E+07	-1.09E+02	6.72E+05	1.04E+05	0.9553

where as the Hg (II) complex is more active than the Cu (II), Ag (I) and UO_2 (II) complexes against *Aspergillus niger*, also, Ni (II) complex is more active against *Aspergillus flavous* and Cd (II) is more active against *Aspergillus niger*. The data were shown in Fig. 6.

CONCLUSION

The complexation between metal ions like Ag (I), Cu (II), Ni (II), Hg (II), UO_2 (II), Cd (II), Ba (II) and Al (III) with Ibu produced 1:1, 1:2 and 1:3 (metal: Ibu) molar ratio as a monobasic bidentate via carboxylic group. The resulted Ibu compounds were assigned by infrared and 1HNMR spectroscopy. Thermogravimetric analysis has proved the thermal stability feature of Ibu complexes. The antimicrobial activities of the metal complexes of Ibu recorded a significant effect against some bacteria and fungi.

ACKNOWLEDGMENT

The project was financially supported by King Saud University, Vice Deanship of Research Chairs.

REFERENCES

Ang, W.H. and P.J. Dyson, 2006. Classical and non-classical ruthenium-based anticancer drugs: Towards targeted chemotherapy. Eur. J. Inorg. Chem., 20: 4003-4018.

Anjaneyulu, Y. and R.P. Rao, 1986. Preparation, characterization and antimicrobial activity studies on some ternary complexes of Cu (II) with acetylacetone and various salicylic acids. Syn. Reac. Inorg. Metal-Org. Chem., 16: 257-272.

Badger, R.M., 1935. The relation between the internuclear distances and force constants of molecules and its application to polyatomic molecules. J. Chem. Phys., 3: 710-714.

Clarke, M.J., 2003. Ruthenium metallopharmaceuticals. Coord. Chem. Rev., 236: 209-233.

Coats, A.W. and J.P. Redfern, 1964. Kinetic parameters from thermogravimetric data. Nature, 201: 68-69.

Djinovic, V., M. Momcilovic, S. Grguric-Sipka, V. Trajkovic, M.M. Stojkovic, D. Miljkovic and T. Sabo, 2004. Novel ruthenium complex $K_2[Ru(dmgly)Cl_4]\bullet 2H_2O$ is toxic to C6 astrocytoma cell line, but not to primary rat astrocytes. J. Inorg. Biochem., 98: 2168-2173.

Dyson, P.J. and G. Sava, 2006. Metal-based antitumour drugs in the post genomic era. Dalton Trans., 16: 1929-1933.

Figgis, B.N., J. Lewis and R.G. Wilkins, 1960. The Magnetochemistry of Complex Compounds. In: Modern Coordination Chemistry: Principles and Methods, Lewis, J., S.J. Lewis and R.G. Wilkins (Eds.). Interscience Publishers Inc., New York, USA., pp: 400-454.

Figgis, B.N., 1966. Introduction to Ligand Field. John Wiley and Sons, New York, USA., Pages: 351.

Fiori, A.T.M., W.R. Lustri, A. Magalhaes and P.P. Corbi, 2011. Chemical, spectroscopic characterization and antibacterial activities *in vitro* of a novel gold(I)-ibuprofen complex. Inorg. Chem. Commun., 14: 738-740.

Fox, C.L. Jr. and S.M. Modak, 1974. Mechanism of silver sulfadiazine action on burn wound infections. Antimicrob. Agents Chemother, 5: 582-588.

Fricker, S.P., 2007. Metal based drugs: From serendipity to design. Dalton Trans., 43: 4903-4917.

Galico, D.A., B.B.C. Holanda, R.B. Guerra, A.O. Legendre, D. Rinaldo, O. Treu-Filho and G. Bannach, 2014. Thermal and spectroscopic studies on solid ibuprofen complexes of lighter trivalent lanthanides. Thermochimica Acta, 575: 226-232.

Gandhi, J.B. and N.D. Kulkarni, 1999. Study of uranyl complexes with new binucleating ligands involving amide and imine coordinating sites. Polyhedron, 18: 1735-1742.

Gandhi, J.B. and N.D. Kulkarni, 2001. Binuclear complexes with uranyl ions in non-equivalent coordination environments-2. Synthesis and electrochemistry of the complexes with binucleating aroyl hydrazones and 1,10-phenanthroline. Transition Met. Chem., 26: 96-99.

Geary, W.J., 1971. The use of conductivity measurements in organic solvents for the characterization of coordination compounds. Coord. Chem. Rev., 7: 81-122.

Goto, R. and T. Takenaka, 1963. Infrared absorption spectra of some monovalent metal salts of fatty acids. J. Chem. Soc. Jpn., 84: 392-402.

Grguric-Sipka, S.R., R.A. Vilaplana, J.M. Perez, M.A. Fuertes and C. Alonso *et al*., 2003. Synthesis, characterization, interaction with DNA and cytotoxicity of the new potential antitumour drug cis-$K[Ru(eddp)Cl_2)]$. J. Inorg. Biochem., 97: 215-220.

Gruber, S.J., C.M. Harris and E. Sinn, 1968. Metal complexes as ligands-IV [1,2,3]: Bi- and Tri-nuclear complexes derived from metal complexes of tetradentate salicylaldimines. J. Inorg. Nuclear Chem., 30: 1805-1830.

Gupta, R., R.K. Saxena, P. Chaturvedi and J.S. Virdi, 1995. Chitinase production by *Streptomyces viridificans*: Its potential in fungal cell wall lysis. J. Applied Bacteriol., 87: 378-383.

Habtemariam, A., M. Melchart, R. Fernandez, S. Parsons and I.D. Oswald *et al*., 2006. Structure-activity relationships for cytotoxic ruthenium(II) arene complexes containing N,N-, N,O- and O,O-chelating ligands. J. Med. Chem., 49: 6858-6868.

Hartinger, C.G., S. Zorbas-Seifried, M.A. Jakupec, B. Kynast, H. Zorbas and B.K. Keppler, 2006. From bench to bedside-preclinical and early clinical development of the anticancer agent indazolium *trans*-[tetrachlorobis (1*H*-indazole) ruthenate(III)] (KP1019 or FFC14A). J. Inorg. Biochem., 100: 891-904.

Herzberg, G., 1951. Molecular Spectra and Molecular Structure-II: Infrared and Raman Spectra of Polyatomic Molecules. van Nostrand, New York, USA., Pages: 558.

Horowitz, H.H. and G. Metzeger, 1963. A new analysis of thermogravimetric traces. Anal. Chem., 35: 1464-1468.

Jones, L.H., 1958. Systematics in the vibrational spectra of uranyl complexes. Spectrochimica Acta, 10: 395-403.

Kostova, I., 2006. Ruthenium complexes as anticancer agents. Curr. Med. Chem., 13: 1085-1107.

Lever, A.B.P., 1984. Inorganic Electronic Spectroscopy. 2nd Edn., Elsevier, Amsterdam, The Netherlands, ISBN-13: 9780444423894, pp: 31.

Mishra, L. and V.K. Singh, 1993. Synthesis, structural and antifungal studies of Co(II), Ni(II), Cu(II) and Zn(II) complexes with new schiff bases bearing benzimidazoles. Indian J. Chem., 32A: 446-457.

More, P.G., R.B. Bhalvankar and S.C. Pattar, 2001. Synthesis and biological activity of Schiff bases of aminothiazoles. J. Indian Chem. Soc., 78: 474-475.

Nakamato, K. and P.J. McCarthy, 1968. Spectroscopy and Structure of Metal Chelate Compounds. John Wiley and Sons, New York, USA., ISBN-13: 978-0471629818, pp: 268.

Nakamoto, K., 1997. Infrared and Raman Spectra of Inorganic and Coordination Compounds: Applications in Coordination, Organometallic and Bioinorganic Chemistry. 5th Edn., John Wiley and Sons, New York, USA., ISBN-13: 9780471163923, pp: 59-62.

Nayar, M.R. and C.S. Pande, 1948. Formation of complex compounds between lead nitrate and alkali nitrates. Proc. Indian Acad. Sci.-Sect. A, 27: 349-353.

Oliver, A.J., J. Stainton and P.J. Taylor, 1959. A simple filter-paper disc method for determining the sensitivity of *Myco. tuberculosis*. J. Clin. Pathol., 12: 444-447.

Refat, M.S. and S.F. Mohamed, 2011. Spectroscopic, thermal and antitumor investigations of sulfasalazine drug *in situ* complexation with alkaline earth metal ions. Spectrochimica Acta Part A: Mol. Biomolec. Spectrosc., 82: 108-117.

Sadler, P.J. and R.E. Sue, 1994. The chemistry of gold drugs. Met.-Based Drugs, 1: 107-144.

Sava, G., S. Zorzet, C. Turrin, F. Vita and M. Soranzo *et al*., 2003. Dual action of NAMI-A in inhibition of solid tumor metastasis: Selective targeting of metastatic cells and binding to collagen. Clin. Cancer Res., 9: 1898-1905.

Singh, D.P., K. Kumar and C. Sharma, 2010. Synthesis, characterization and antimicrobial activities of macrocyclic complexes of divalent transition metal ions. Synthesis Reactivity Inorganic Metal-Organic Nano-Metal Chem., 40: 378-385.

Skoog, D.A. and D.M. West, 1985. Principles of Instrumental Analysis. 3rd Edn., Saunders College Publishing, NewYork, USA., ISBN-13: 9780030012297, pp: 182-224.

Thankamony, M., B.S. Kumari, G. Rijulal and K. Mohanan, 2009. Lanthanum(III) chloride complexes with heterocyclic Schiff bases. J. Thermal Anal. Calorimetry, 95: 259-266.

Yoe, J.H. and A.L. Jones, 1944. Colorimetric determination of iron with disodium-1,2-dihydroxybenzene-3,5-disulfonate. Ind. Eng. Chem. Anal. Edn., 16: 111-115.

Youn, H.S., J.Y. Lee, S.I. Saitoh, K. Miyake and D.H. Hwang, 2006. Auranofin, as an anti-rheumatic gold compound, suppresses LPS-induced homodimerization of TLR4. Biochem. Biophys. Res. Commun., 350: 866-871.

Zawidlak-Wegrzynska, B., M. Kawalec, I. Bosek, M. Luczyk-Juzwa and G. Adamus *et al*., 2010. Synthesis and antiproliferative properties of ibuprofen-oligo (3-hydroxybutyrate) conjugates. Eur. J. Med. Chem., 45: 1833-1842.

Zhang, C.X. and S.J. Lippard, 2003. New metal complexes as potential therapeutics. Curr. Opin. Chem. Biol., 7: 481-489.

Zorzet, S., A. Bergamo, M. Cocchietto, A. Sorc and B. Gava *et al*., 2000. Lack of *in vitro* cytotoxicity, associated to increased G2-M cell fraction and inhibition of matrigel invasion, may predict *in vivo*-selective antimetastasis activity of ruthenium complexes. J. Pharmacol. Exp. Therapeut., 295: 927-933.