Four monomeric copper(II) complexes of non-steroidal anti-inflammatory drug Ibuprofen and N-donor ligands: Syntheses, characterization, crystal structures and cytotoxicity studies.

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Abstract

Reaction of hydrated copper(II) ibuprofenate with various nitrogen donor ligands, *β*-picoline, *γ*-picoline, pyrrolidine and unsymmetrical ethylenediamine (*un-dmen*), at room temperature in methanol:water mixture (4:1 v/v) yielded four new complexes, [Cu(*Ibu*)$_2$(*β*-picoline)$_2$(H$_2$O)]; **1**, [Cu(*Ibu*)$_2$(*γ*-picoline)$_2$(H$_2$O)].H$_2$O; **2**, [Cu(*Ibu*)$_2$(*pyrrolidine*)$_2$].H$_2$O; **3** and [Cu(*un-dmen*)$_2$(H$_2$O)](*Ibu*)$_2$; **4** respectively, where *Ibu* = deprotonated Ibuprofen (H*Ibu*). The newly synthesized complexes have been characterized by elemental analyses, spectroscopic methods (FT-IR, UV-Vis and EPR), TGA and single crystal X-ray structure determination. Crystallographic investigations revealed that all the complexes are monomeric in nature, in contrast to dimeric nature of copper(II) ibuprofenate solvates. EPR studies clearly revealed that the chromophore present in all complexes (**1-4)** is consistent with structures determined by X-ray crystallography**.** The cytotoxic effects of all complexes were tested by a colorimetric assay on three human cell lines**;** though the activity resulted to be affected by the nature of the cell line, the newly synthesized complexes **1-4** showed higher cytotoxicity than parent molecule against all the tumoral cell lines.

Introduction

The common cancer forms affecting lives of human beings, (*i.e*. breast cancer, prostate cancer, gastric cancer etc.) need different types of treatment such as surgery, chemotherapy, radiation therapy, or a combination of these. Among the chemotherapeutic agents, cisplatin is still a drug of choice for 90% of different cancers, even though there are some severe side effects associated with its use [1-3]. A collaborative study of British and Chinese scientists discovered that cisplatin binds to proteins at positions occupied by zinc ions, which results in unwanted loss of zinc ions and wastage of drug [4]. Therefore, design and synthesis of cheap metal-based drugs that are able to overcome the problems associated with cisplatin (but more effective with less dose and minimal side effects) is a challenging task for inorganic, pharmaceutical and medicinal chemists. In this direction works on other bio-compatible metal complexes are of immense interest as they can be more effective and target-specific than cisplatin [5-11]; for example, $[Ag(tpp)_3(pHbza)]$, where tpp = triphenylphosphine, p-HbzaH = p-hydroxy-benzoic acid, exhibits a significantly higher *in-vitro* activity than cisplatin against LMS (leiomyosarcoma) and MCF-7 (human breast adenocarcinoma) [12]. As for copper(II) complexes, the pioneering work of Sorenson [13] provided a tremendous impetus to research aimed at exploring their biological, antiradiation and anticancer properties. Copper complexes are now widely studied for their potential effectiveness as antibacterial, antimalarial, and antifungal agents, in the treatment of Alzheimer's disease (due to its neuroprotective action), Parkinson's and many other diseases [14,15]. For example, halogen and piperonal substituted thiosemicarbazone Cu(II) complexes act as effective drugs against liver cancer cells and colon cancer cell lines [3, 15-18], while the performance of phenanthroline (nitrogen based donor ligand) complexes [19] in cancer treatment have catalysed the interest of synthetic chemists in the design and evaluation of new metal based anticancer drugs [20-24]. In spite of the large number of studies on their biological activity, however, these complexes display modes of action which are not yet fully understood and therefore deserve more attention.

In view of our long experience in structural chemistry of copper(II) carboxylates [25-29], we started a research programme aimed at: synthesizing and characterizing new copper(II) complexes of non-steroidal anti-inflammatry drugs (NSAIDs); - evaluating their biological activity and possibly assessing their structure-activity relationships, for potential useful pharmaceutical applications [30]. NSAIDs constitute a commercially important class of drugs to cure pain and inflammation associated with diseases or injuries, including intestinal disease and migraine. Moreover, from a metal-complexes synthetic point of view they are particularly interesting since most of them contain a carboxylic group –COOH which, when deprotonated, may exhibit a variety of coordination modes towards metal ions e.g. monodenatate, bidentate, bidentate chelating or bidentate bridging etc. as shown in Fig. 1

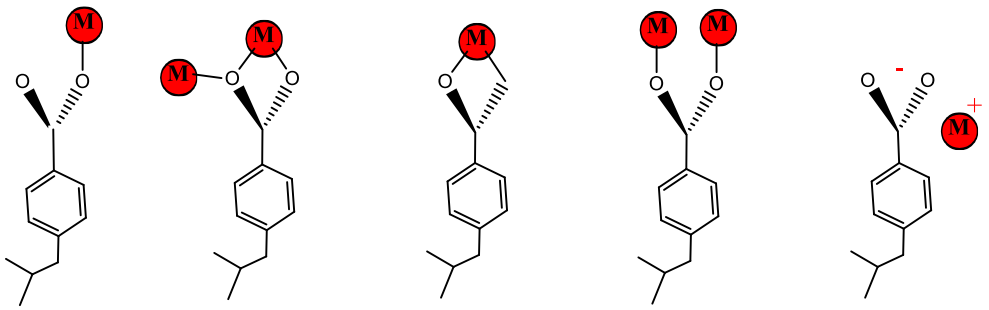
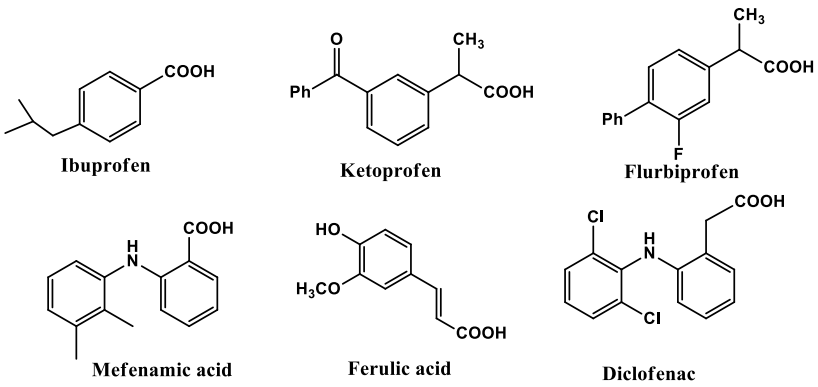


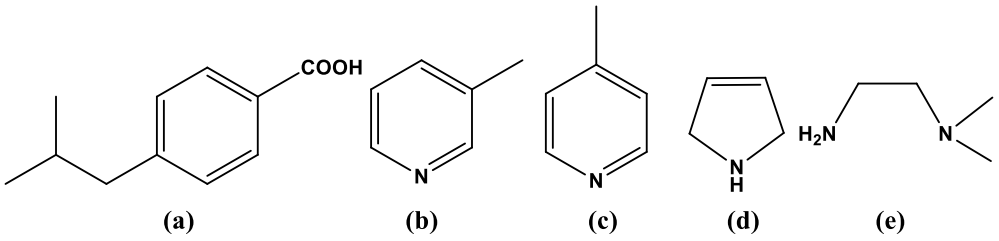
Fig. 1.Structural representation of diverse coordination modes of carboxylate group in ibuprofen available to the metal center.

In literature, there are several reports on the anticancer activities of NSAIDs, such as aspirin [31], indomethacin [32], celecoxib [33], naproxen [34] and ibuprofen [35a]; indeed, most of them were found to be effective against colorectal, colon, breast and pancreatic cancers. Different synthetic approaches have been developed to enhance the anticancer activity of NSAIDs, and complexation with metal have led to compounds exhibiting significant biological activity towards biomolecules such as DNA and proteins in human body, hence showing possible wide application as anticancer agents [35]. Some of the commercially used NSAIDs are reported in Scheme 1.



Scheme 1. Structural formulae of some commonly used NSAIDs

In this work, for the synthesis of copper complexes we selected the NSAID Ibuprofen (H*Ibu*), a widely used drug that can exhibit some side effects like headache, diahorrea, vomiting *etc*. [36]. As additional ligands, in view of our expertise in Copper/N-donor ligands synthetic chemistry, as stated above, the molecules depicted in Scheme 2b-e have been chosen which have different chemical properties (such as aromaticity), different sizes or different flexibility features, in order to study the complexation behaviour of copper(II) towards ibuprofen drug in presence of these ligands**.**:



Scheme 2: Ligands used in the synthesis of complexes **1-4**; (a) Ibuprofen; (b) β-picoline, (c) γ-picoline (d) Pyrollidine(e) Un-symmetrical dimethylethylenediamine

With this view in mind, this paper reports the synthesis and characterization of four new ibuprofen copper(II) complexes, besides the evaluation of their anticancer properties. Although few papers on copper ibuprofenate complexes have been reported in the literature, no X-ray structural studies are available. During the progress of this work two papers on X-ray structural studies of ruthenuim(II, III) and zinc ibuprofenate have been reported [37].

Experimental

Materials and physical measurements

Analytical grade reagents were used throughout this work without any further purification. Elemental analysis was performed using an automatic Perkin Elmer 2400 CHN element analyzer and copper was determined by standard literature methods [38]. Fourier transform infrared spectra (FT-IR) were recorded (neat) on PERKIN ELMER SPECTRUM RX FT-IR system. UV-visible spectra were recorded using HITACHI 330 SPECTROPHOTOMETER.

Synthesis of [Cu(Ibu)$_2$(β-picoline)$_2$(H$_2$O)] (1). 0.50 g $CuSO_4.5H_2O$ (2 mmol) was dissolved in 10 mL of distilled water. Sodium salt of Ibuprofen was prepared in situ by dissolving 0.16 g (4 mmol) of NaOH and 0.82 g (4 mmol) of Ibuprofen in minimum amount of water. On mixing the two solutions, a green precipitated product of hydrated copper(II) Ibuprofenate resulted immediately which was filtered through a fine filter paper, washed with water followed by methanol and dried at room temperature (yield 90%). Hydrated copper(II) ibuprofenate was then suspended in methanol-water mixture (4:1 *v*/*v*) and β-picoline was added drop wise with stirring till a clear blue colored solution was obtained. When the reaction mixture solution was allowed to evaporate slowly at room temperature, blue shiny crystal appeared after few days, which were separated from the mother liquor and dried in air. Crystals of Complex **1** are soluble in methanol, insoluble in water and decomposes at 197 ^oC. FT-IR (neat) (ν_{max}, cm^{-1}): 3316(s), 2962(s), 2923(m), 2867(w), 1620(w), 1568(s), 1453(m), 1363(s), 1261(m), 1089(s), 1063(s), 593(m), 505(s). UV-vis in DMSO λ/nm (ε/ $L.mol^{-1}cm^{-1}$): 728 (45), Anal. Calcd. for $C_{38}H_{50}CuN_2O_5$ (MW = 678.34): Cal. C, 67.22; H, 7.37; N, 4.12; Cu, 9.36 %; Found: C, 67.01; H, 7.16; N, 3.98; Cu, 9.52 %.

Synthesis of [Cu(Ibu)$_2$(γ-picoline)$_2$(H$_2$O)].H$_2$O (2). Complex **2** was synthesized in a similar manner as complex **1** by adding γ-picoline instead of β-picoline till a clear blue color solution was obtained. When the reaction mixture was allowed to evaporate slowly at room temperature, blue crystals appeared after a few days, which were separated from the mother liquor and dried in air. Complex **2** is also soluble in methanol, insoluble in water and decomposes at 122 ^oC. FT-IR (neat) (ν_{max}, cm^{-1}): 3347(s), 2960(s), 2925(m), 2867(s), 1619(s), 1580(s), 1451(m), 1384(s), 1270(m), 1021(m), 791(m), 496(m). UV-vis in DMSO, λ/nm (ε/$L.mol^{-1}cm^{-1}$): 735(175). Anal. Calcd. for

$C_{38}H_{50}CuN_2O_5.H_2O$ (MW = 696.35): Cal. C, 65.48; H, 7.46; N, 4.02; Cu, 9.11 %; Found: C, 65.77; H, 7.36; N, 4.22; Cu, 9.24 %.

Synthesis of [Cu(Ibu)$_2$(pyrrolidine)$_2$].H$_2$O (3). Complex **3** was synthesized in a similar manner as complex **1** by adding *pyrrolidine* instead of *β*-picoline till a clear blue color solution was obtained. When the reaction mixture was allowed to evaporate slowly at room temperature, blue crystals appeared after a few days, which were separated from the mother liquor and dried in air. Complex **3** is also soluble in methanol, insoluble in water and decomposes at 172 ^{o}C. FT-IR (neat) (ν_{max}, cm^{-1}): 3508(s), 3244(s), 2956(s), 2844(m), 1567(s), 1462(m), 1381(s), 1279(s), 1095(m), 1067(m), 840(m), 607(m), 499(s). UV-vis in DMSO, λ/nm (ε/L.mol^{-1}cm^{-1}): 678 (228). Anal. Calcd. for $C_{34}H_{52}CuN_2O_4.H_2O$ (MW = 652.34): Cal. C, 62.57; H, 8.58; N, 4.29; Cu, 9.73 %; Found: C, 62.19; H, 8.55; N, 4.56; Cu, 9.80 %.

Synthesis of [Cu(un-dmen)$_2$(H$_2$O)](Ibu)$_2$ (4). Complex **4** was synthesized in a similar manner as complex **1** by adding unsymm-dimethylethylenediamine (*un-dmen*) in place of *β*-picoline till a clear blue color solution was obtained. When the reaction mixture solution was allowed to evaporate slowly at room temperature, blue crystals appeared after a few days, which were separated from the mother liquor and dried in air. Complex **4** is also soluble in methanol, insoluble in water and decomposes at 170 ^{o}C. FT-IR (neat) (ν_{max}, cm^{-1}): 3106(m), 2965(s), 2848(s), 1581(s), 1463(m), 1380(s), 1288(s), 1259(w), 1064(s), 1022(w), 506(s). UV-Vis in DMSO, λ/nm (ε/ L.mol^{-1}cm^{-1}): 608(108). Anal. Calcd. for $C_{34}H_{60}CuN_4O_5$ (MW = 685.50): Cal. C, 59.56; H, 9.05; N, 8.17; Cu, 9.26 %; Found: C, 59.40; H, 8.80; N, 8.27; Cu, 9.14 %.

EPR measurements

The anisotropic X-band (9.43 GHz) EPR spectra of frozen $CHCl_3$ solutions were recorded at 110 K using a Bruker ESP 300 spectrophotometer. The EPR spectra were referenced to 2,2-diphenyl-1-picrylhydrazyl (DPPH) (g=2.0037). All spectra were recorded using 100 kHz frequency modulation, 21.186 G amplitude modulation, and microwave power of 6 mW.

Biological activity

Cell lines were cultured in DMEM, Mc Coy's 5a modified or MEM culture medium (pH 7.4, controlled by the presence of the pH indicator (phenol red) in the medium) supplemented with 10 % fetal bovine serum (FBS). Initial stock solutions of complexes were prepared in dimethyl sulfoxide (DMSO) at a concentration of 10^{-1} M and used to achieve the several dilutions. A control experiment was achieved where cell lines were incubated with the same final concentration of DMSO without complexes to ensure the observed cytotoxicity is due to complexes rather than to DMSO. The effects of complexes on cell viability at 24h were measured using an MTT tetrazolium salt colorimetric assay (Sigma-Aldrich, Saint-Louis, Missouri, United States) according to the manufacturer's instructions. The pH was controlled with the dye indicator contained in the culture medium. Briefly, the cells (15000/well) were incubated in three replicates in a 96-well plate in the presence of various concentrations of complexes (0, 6.25, 12.5, 25, 50, 100, 200 µM in the wells). After 24 hours of treatments, cells were incubated for three hours after addition of 20% MTT then medium was removed and DMSO was added to dissolve formazan. A colorimetric assay was realized at 560nm using a plate reader Tecan F200 Pro (Tecan, Lyon, France).

X-ray Crystallography

The crystallographic data for complexes **1-4** were collected on a Nonius Kappa CCD diffractometer at room temperature using graphite-monochromated Mo-Kα radiation (λ= 0.71073 Å) with a φ scan followed by ω scan to fill the sphere. The low quality of the crystals of complex **4** precluded the possibility to reach a data completeness >82%, however not jeopardising the structure solution and refinement. All intensities were corrected for Lorentz, polarization and absorption effects [39]. The structures were solved by direct methods with the SIR97 program [40] and refined on F^2 by full-matrix least-squares methods with anisotropic non-H atoms. In complexes **1, 3** and **4** the methylpropyl groups of the ibuprofen ligands were found to be disordered; for **1**, however, any attempt to model such a disorder did not made significant improvements to the structure quality, while in **3** and **4** the atoms belonging to the methylpropyl group have been refined over two almost equivalent positions. The hydrogen atoms linked to the coordinated O1w atom in complexes **1** and **2**

were found in the Difference Fourier map and refined isotropically. In complex **2**, conversely, it was impossible to locate the hydrogens belonging to the free water molecule. In complexes **3** and **4** the hydrogen atoms linked to N or O atoms were found in the Difference Fourier map and refined isotropically. All other hydrogen atoms were included on calculated positions, riding on their carrier atoms. All other calculations were accomplished using SHELXL-2014/7 [41] and WingX [42]. Crystal data of all complexes **1-4** are given in Table 1. A selection of bond distances and angles is reported in Table 2 and hydrogen bonding contacts parameters are reported in Table S1 of the Supplementary Information (SI)**.**

Table 1. Data collection, structural refinement and crystallographic details for complexes 1-4

Compound	**1**	**2**	**3**	**4**
Chemical formula	$C_{38}H_{50}CuN_2O_5$	$C_{38}H_{50}CuN_2O_5 \cdot H_2O$	$C_{34}H_{52}CuN_2O_4 \cdot 2(H_2O)$	$2(C_{13}H_{17}O_2) \cdot C_8H_{26}CuN_4O$
M_r	678.34	696.35	652.34	668.40
Crystal system, space group	Triclinic, $P\bar{1}$	Triclinic, $P\bar{1}$	Monoclinic, $P2_1/c$	Monoclinic, $P2/c$
a, b, c (Å)	9.4147 (2), 11.8811 (3), 17.5005 (4)	10.2706 (2), 11.8221 (3), 17.2366 (3)	16.5388 (4), 6.1918 (1), 17.4653 (4)	9.6804 (8), 6.7371 (4), 29.453 (3)
α, β,γ (°)	95.564 (1), 103.187 (1), 103.464 (1)	104.3850 (14), 95.6170 (14), 109.5680 (13)	90, 94.8030 (14), 90	90, 92.188 (3), 90
V (Å^3)	1830.12 (7)	1872.19 (7)	1782.25 (7)	1919.5 (3)
Z	2	2	2	2
Radiation type	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$	Mo $K\alpha$
μ(mm^{-1})	0.64	0.63	0.66	0.61
Crystal size (mm)	0.47 × 0.35 × 0.17	0.41 × 0.38 × 0.23	0.47 × 0.20 × 0.09	0.35 × 0.14 × 0.10
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	34072, 8751, 7084	29871, 8977, 7084	24641, 4282, 3371	5584, 2773, 2162
R_{int}	0.052	0.055	0.040	0.064
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.056, 0.170, 1.08	0.049, 0.145, 1.04	0.055, 0.157, 1.06	0.064, 0.149, 1.06
No. of reflections	8751	8977	4282	2773
No. of parameters	423	432	235	230
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.92, -0.53	0.63, -0.52	0.92, -0.64	0.30, -0.41

Table 2. Selected bond distances and angles (Å, °) for complexes **1-4**

Complex 1

Cu1 - O1W	2.287(2)	Cu1 - N1	2.024(2)
Cu1 - O1	1.964(2)	Cu1 - N2	2.031(2)
Cu1 - O3	1.965(2)		
O1W - Cu1 - O1	90.21(7)	O1 - Cu1 - N1	89.06(8)
O1W - Cu1 - O3	97.89(8)	O1 - Cu1 - N2	91.24(8)
O1W - Cu1 - N1	92.90(8)	O3 - Cu1 - N1	89.42(9)
O1W - Cu1 - N2	98.58(8)	O3 - Cu1 - N2	88.65(9)
O1 - Cu1 - O3	171.83(8)	N1 - Cu1 – N2	168.50(8)

Complex 2

Cu1 - O1W	2.326(2)	Cu1 - N1	2.021(2)
Cu1 - O1	1.979(2)	Cu1 - N2	2.015(2)
Cu1 - O3	1.986(2)		
O1W - Cu1 - O1	97.63(7)	O1 - Cu1 - N1	88.18(7)
O1W - Cu1 - N1	99.48(7)	O1 - Cu1 - N2	89.92(7)
O1W - Cu1 - N2	92.04(7)	O3 - Cu1 - N1	90.83(7)
O1W - Cu1- O3	91.07(6)	O3 - Cu1 - N2	89.32(7)
O1 - Cu1 - O3	171.28(7)	N1 - Cu1 – N2	168.47(7)

Complex 3

Cu1 - N1	1.998(2)	Cu1 - O1	1.937(2)
Cu1...O2	2.985(3)		
N1 - Cu1 - O1	90.51(9)		
N1 - Cu1 - O1^{i}	89.49(9)		

Symmetry code: (i) –x,-y,-z

Complex 4

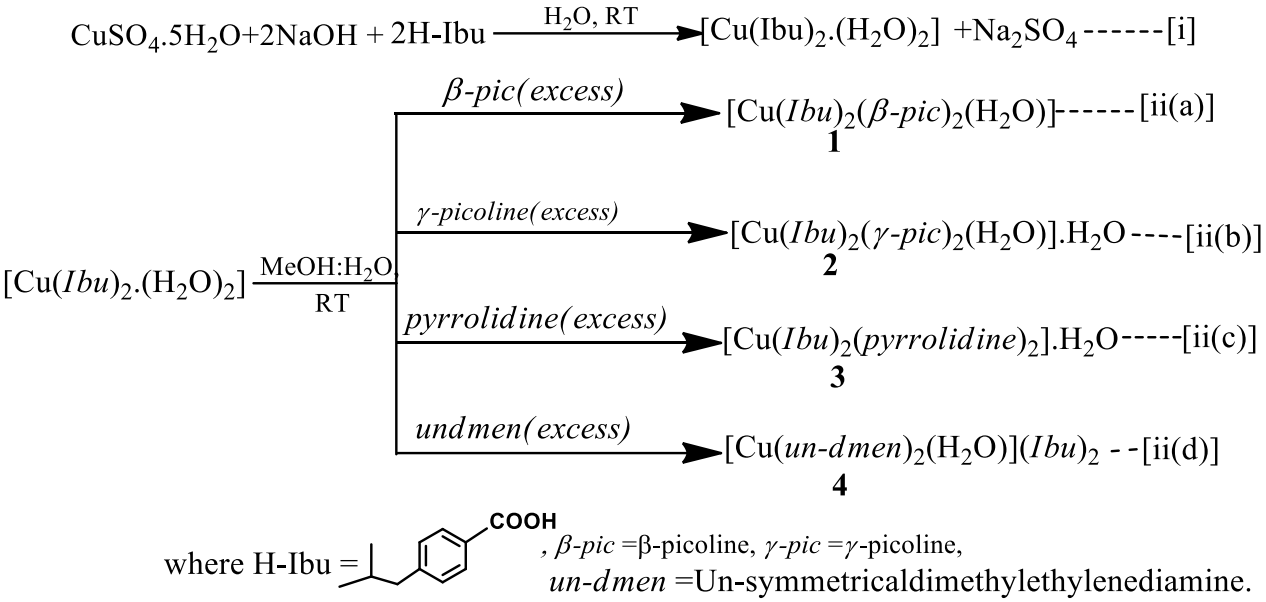
Cu1- O1w	2.216(5)	Cu1- N2	2.075(4)
Cu1- N1	1.989(4)		
O1 - Cu1 - N1	96.8(1)	N1 - Cu1 - N2	83.6(1)
O1 - Cu1 - N2	94.6(1)	N1 - Cu1 - N2^{i}	95.3(1)
N1 - Cu1 - N1^{i}	166.4	N2 - Cu1 – N2^{i}	170.7

Symmetry code: (i) 1-x,y,1/2-z

Results and Discussions

Synthesis and spectroscopic characterization

The hydrated copper(II) ibuprofenate was obtained by reacting hydrated copper sulfate with sodium salt of ibuprofen as shown in Scheme 3 (eq. (i)). The precipitated product was then suspended in methanol-water mixture (4:1, v/v) followed by the addition of different nitrogen-donor ligands (*β-pic, γ-pic, pyrrolidine, un-dmen*) with continuous stirring until a clear solution was observed in each case. Upon slow evaporation of respective resultant reaction mixtures at room temperature, four complexes **1-4** were isolated in good yields from respective solutions as shown in Scheme 3.



Scheme 3: Schematic representation of synthesis of Complexes **1-4**

Infrared spectra of complexes **1-4** were recorded in the region 4000-400 cm^{-1} and tentative bands assignments has been made on the basis of earlier reports in literature [43,44]. In solid state IR-spectra, complexes **1-4**, significant broad peaks observed in the region 3500-31000 cm^{-1} indicating the O-H and stretching frequency of water molecule in all complexes. The absorption bands observed in the region 3100- 2900 cm^{-1} were assigned to C(sp^2)-H stretching vibration of ibuprofen moieties in all complexes. For complex **4**, other peaks in the region 3300-3100 cm^{-1} might be

assigned to N-H stretching frequency of NH_2- group of unsymm-dimethylethylenediamine. The absorption peaks in the region near 1650-1600 cm^{-1} were assigned to C=C stretching vibration of ibuprofen molecule. The sharp absorption peak observed for free acid group of ibuprofen in region 1710-1650 cm^{-1} was absent in all cases indicated the carboxylate formation and two new bands appeared in the region 1612-1575 cm^{-1} and 1395-1350 cm^{-1} corresponding to $\nu_{as(COO)}$ and $\nu_{s(COO)}$ stretching vibrations of carboxylate group of ibuprofen [45,46]. The parameter $\Delta\nu$ ($\nu_{as(COO)}$-$\nu_{s(COO)}$) can be used as important tool in assigning the mode of coordination of carboxylate ligand in metal-carboxylates complexes. From various coordination modes of carboxylate coordination, i) ionic, ii) unidentate, iii) bidentate chelating are the most common. In complex **4**, the $\Delta\nu_{(COO)}$ value of 189 cm^{-1} falls in the range (210-160 cm^{-1}) observed for various ionic complexes e.g. sodium formate ($\Delta\nu$=201cm^{-1}), sodium acetate ($\Delta\nu$=164 cm^{-1}), sodium ibuprofenate ($\Delta\nu$=190 cm^{-1}) *etc.* For all other complexes the value of $\Delta\nu$ is higher indicated the covalent nature of resulted complexes **1-3.** The symmetric deformation vibrations of the $-CH_3$ group of ibuprofen in all complexes **1-4** were observed in the region 1300-1100 cm^{-1}, while the absorption peaks observed in the region 1000-620 cm^{-1} might be assigned to in-plane bending and out-of-plane deformation vibrations of hydrogen atoms on aromatic rings. The absorption peaks observed around 500 cm^{-1} in complexes **1-4** are within the range reported for Cu-O and Cu-N stretching frequencies in the literature. The FT-infrared spectra for complexes **1-4** are shown in Fig.S1 of the SI**.**

The UV-Visible spectra of complexes **1-4** were recorded using different solvents (methanol and DMSO, DMSO-H_2O (2:1) dilution) (Fig. S2-S4) exhibit very broad d-d bands in the visible region from 500-800 nm corresponded to octahedral complex or a combined merged broad peak corresponded to square pyramidal or square planar geometry. So, the exact geometry of resulted complex could not be predicted from solution state UV-Vis spectra. UV-Vis spectra of complexes **1-4** showed broad absorption band at 728 (ε= 45 $L.mol^{-1}.cm^{-1}$), 735(ε= 175 $L.mol^{-1}.cm^{-1}$), 678 (ε= 228 $L.mol^{-1}.cm^{-1}$), 608 (ε= 108 $L.mol^{-1}.cm^{-1}$) nm for complexes **1-4** respectively indicated different coordination environment of copper in complexes **1-4**. Moreover, the absorbance peaks for all

complexes **1-4** appeared at almost same wavelength even after dilution indicated that the chromophoric group remain intact in different solvents (no solvato-chromic effect). The observed electronic spectral bands for complexes **1** and **2** are in good agreement with literature data *e.g.* [Cu(*p*-hydroxybenzoate)$_2$) (β-pic)$_2$] [47] [Cu(py)$_2$(pfb)$_2$(H$_2$O)] [47], [Cu(2-Br/Cl-benzoate)$_2$ (β/γ-picoline)$_2$(H$_2$O)]$_n$ [25, 26]. Complexes **3** and **4** showed quite varied absorption wavelength indicated different geometries than complexes **1** and **2**. The solution state UV-Vis spectra for complexes **1-4** is given in Fig. S2 of the SI. In order to find out variation in coordination in solution with respect to solid state diffuse reflectance spectra of complexes **1-4** have been recorded. A comparative table of spectroscopic data of complexes **1-4** with related copper(II) complexes is given in Table 3 [25, 26, 47-49]. Complexes **1** and **2** showed similar absorption maxima at. 549 and 555 nm, respectively, whereas complexes **3** and **4** showed absorption maxima at lower wavelength, 520 and 515 nm respectively. It is worth noting that, for all complexes **1-4**, the observed values in the solid state spectra are different than those in solution; such a difference could be ascribable to a change in the coordination environment in solution state. The solid state reflectance spectra for complexes **1-4** was given in Fig. S3 of S1.

Table 3. A comparison of spectroscopic data of complexes **1-4** with related copper(II) complexes

Complex	**FT-IR spectral peaks**			**Mode of coordination of carboxylate**	**Geometry**	**UV-Vis (Solution state)**	**UV-Vis(Solid state)**	**Ref.**
	$\Delta\nu_{coo(asym)}$	$\Delta\nu_{coo(sym)}$	$\Delta\nu_{coo(asym)} - \nu_{coo(sym)}$					
$[Cu(L\text{-}Arg)_2(H_2O)]SO_4.\ 5H_2O$	-	-	-	Chelating	Square pyramidal	-	619	49(a)
$[Cu(L\text{-}Arg)_2(H_2O)](m\text{-pa}).\ 5H_2O$	-	-	-	Chelating	Square pyramidal	-	620	49(a)
$[Cu(L\text{-}Arg)_2(H_2O)]C_2O_4.\ 6H_2O$	-	-	-	Chelating	Square pyramidal	-	598	49(a)
Cu(*p*-hydroxybenzoato)$_2$(*β*-picoline)$_2$.H_2O	1598	1368	230	Monodentate	Square pyramidal	723	-	47
$Cu(py)_2(pfb)_2(H_2O)]$	1590	1375	215	Monodentate	Distorted octahedral	728	-	48
[Cu(2-Br/Cl-benzoate)$_2$(*β*-picoline)$_2$(H_2O)]	1595	1363	232	Monodentate	Distorted octahedral	726, 735	-	25,26
[Cu(2-Br/Cl-benzoate)$_2$(*γ*-picoline)$_2$(H_2O)]	1578	1371	207	Monodentate	Distorted octahedral	718, 720	-	25,26
[Cu(3-Br-benzoate)$_2$(*β*-/*γ*-picoline)$_2$(H_2O)]	1592	1380	212	Monodentate	Square pyramidal or octahedral	728, 738	635, 555	49(b)
[Cu(3-Cl-benzoate)$_2$(*β*-/*γ*-picoline)$_2$(H_2O)]	1595	1384	211	Monodentate	Square pyramidal or octahedral	721, 707	549, 654	49(b)
Complex **1**	1590	1388	202	Monodenatate	Square pyramidal	728	549	This work
Complex **2**	1585	1368	217	Monodentate	Square pyramidal	735	555	This work
Complex **3**	1595	1374	221	Monodenate	Square planar	678	520	This work
Complex **4**	1575	1398	177	Ionic	Square pyramidal	608	515	This work
where; L-Arg= L-Arginine, py= pyridine, pfb= pentaflouorobenzoate, C_2O_4= oxalate and m-pa= isophthalate								

EPR spectroscopy

Fig. 2 displays EPR spectra of Cu(II) complexes **1-4** obtained in $CHCl_3$ solution at 110 K. The three equally spaced ESR peaks are related to the hyperfine coupling of Cu^{2+} electron spin (S=1/2) with its nuclear spin (I=3/2). The parallel components $g_{//}$ and $A_{//}$ were determined from the spectrum at low temperature. The perpendicular region cannot be precisely determined from experimental spectrum. However, the simulated spectrum gave the spin-Hamiltonian parameters reported in Table 5. The results are consistent with a $d_{x^2-y^2}$ ground state for Cu^{2+} ions with an octahedral configuration geometry around the central ion. According to the Peisach-Blumberg diagram [50], the obtained values of $g_{//}$ and $A_{//}$, reported in Table 4, are consistent (in the equatorial plane) with a four oxygens coordinated (CuO_4 chromophore) complex for $Cu(Ibu)_2.xH_2O$, and with a two oxygens and two nitrogens coordinated (CuN_2O_2 chromophore) complex for compounds **1-4**. One can notice that no half-field signal was observed meaning that only monomeric species are present.

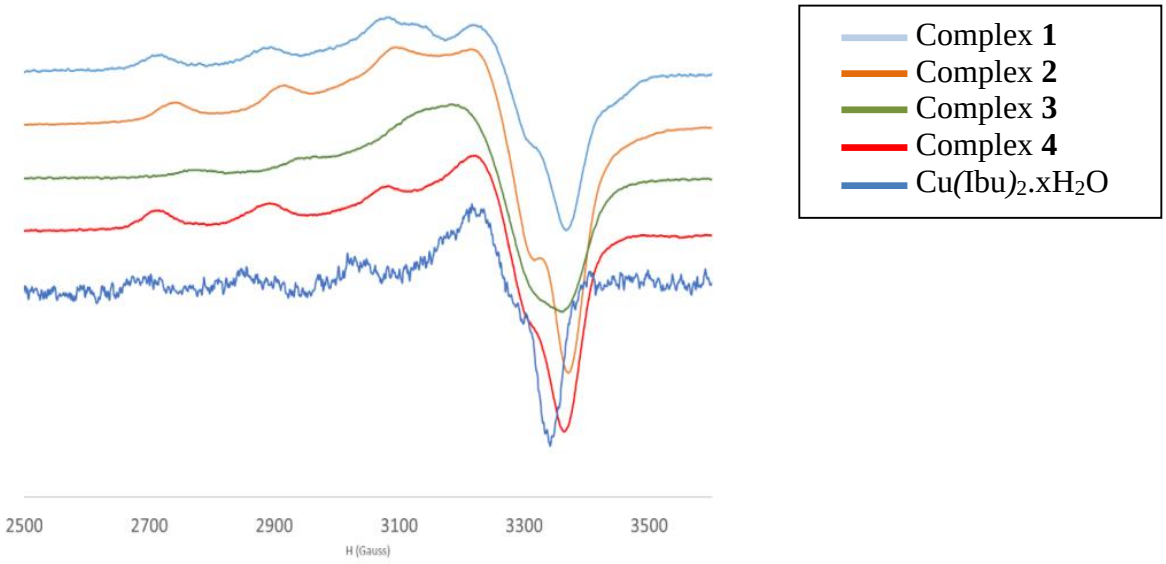


Figure 2. EPR spectra of the complexes in $CHCl_3$. Recording conditions: T = 110 K, modulation frequency: 100 kHz, modulation amplitude: 21.186 G, microwave power: 6mW. The weak solubility of $Cu(Ibu)_2.xH_2O$ explains its poor resolved spectrum.

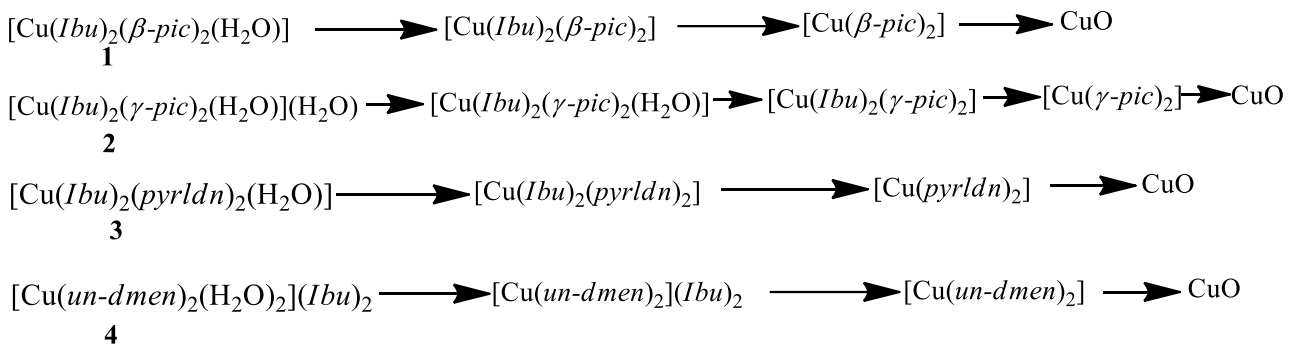
Moreover, the EPR parameters of Cu(*Ibu*)$_2$.xH$_2$O, **1, 2**, and **4** are typical of a strong tetragonally elongated octahedral Cu(II) compound. These results seems to indicate that the solid state structure (see RX section) are held in solution.

Table 4 EPR parameters for all copper complexes **1-4**

Complex	Tensor	10^{-4} cm^{-1}	10^{-4} cm^{-1}
Cu(*Ibu*)$_2$.xH$_2$O	$g_\perp$ = 2.060 $g_{//}$ = 2.285	$A_\perp$ = 18 $A_{//}$ = 176	$LW_\perp$ = 30 $LW_{//}$ = 40
Complex **1**	$g_\perp$ = 2.045 $g_{//}$ = 2.240	$A_\perp$ = 16 $A_{//}$ = 180	$LW_\perp$ = 30 $LW_{//}$ = 30
Complex **2**	$g_\perp$ = 2.045 $g_{//}$ = 2.240	$A_\perp$ = 20 $A_{//}$ = 182	$LW_\perp$ = 30 $LW_{//}$ = 30
Complex **3**	$g_\perp$ = 2.045 $g_{//}$ = 2.260	$A_\perp$ = 23 $A_{//}$ = 174	$LW_\perp$ = 30 $LW_{//}$ = 30
Complex **4**	$g_\perp$ = 2.070 $g_{//}$ =2.215	$A_\perp$ =21 $A_{//}$ = 181	$LW_\perp$ = 50 $LW_{//}$ = 40

Thermo gravimetric analyses (TGA)

Thermogravimetric curves for complexes **1-4** (Fig. 3) were recorded under nitrogen atmosphere to study the thermal stability of all newly synthesized complexes**.** TGA profiles for complexes **1-4** (Fig. S2 of the Supplementary Material) clearly revealed that complexes **1** and **4** are quite stable up to 100^{o}C. The first step of thermogravimetric curves for all complexes corresponds to loss of water molecules 70-150^{o}C. In complex **2**, lattice water molecule lost first and then after 120 ^{o}C coordinated water molecule is removed. Thereafter all complexes showed steep loss in the therogravimetric curves indicated the loss of loosely bonded arylcarboxlate group in the temperature range 150-300 ^{o}C. There is no sharp decomposition curves have been observed for all cases after 350 ^{o}C. After 350 ^{o}C all complexes **1-4** showed slow degradation of nitrogen donor ligands i.e. β-picoline, γ-picoline, pyrrolidine and ethylenediamine respectively. After 600 ^{o}C there is no weight loss observed for all complexes **1-4** indicated the formation of stable cupric oxide residue. Thermal decomposition of complexes **1-4** are given in equation (i).



All the complexes showed endothermic weight losses as clearly revealed from combined TGA-DTA diagram (see Fig.S4 of the Supplementary Material)

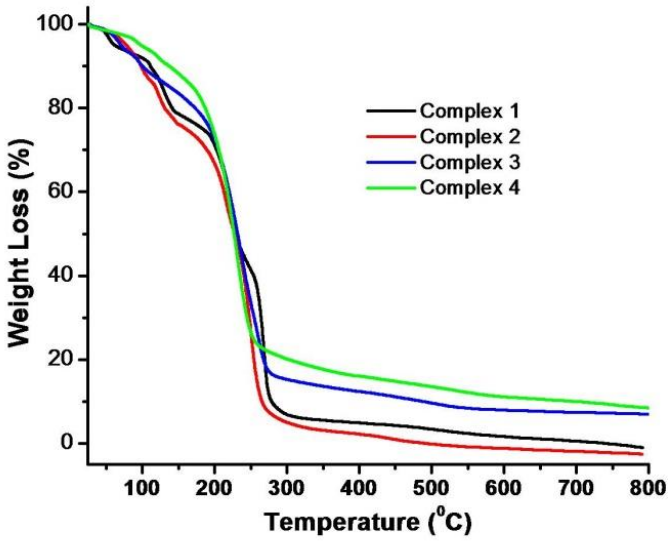


Figure 3. Thermogravimetric curves for complexes **1-4**

Structures description

The ORTEP diagrams of complexes **1-4** are given in Figs. 4-7, respectively. Selected bond lengths and bond angles are summarized in Table 2. The coordination geometry around the copper in complexes **1, 2** and **4** is square-pyramidal; in complex **1** and **2** the central atoms are bonded to two picoline ligands, two ibuprofen molecules acting as monodentate ligands and one water molecule in apical position (Figs. 4A and 5A, respectively). In complex **4**, the Cu and Ow atoms are located on a twofold axis and the basal plane is formed by the four nitrogen of two dimethylethylenediamine molecules, while one water molecule is at the apex of the pyramid; the ibuprofen anion is outside

the Cu-first coordination sphere resulting into ionic complex formation (Fig. 7A). The geometrical index τ can be used to evaluate the distortion of the coordination polyhedra in **1**, **2** and **4.** [51]. Such a parameter, useful to distinguish whether the geometry of the coordination center is trigonal bipyramidal or square pyramidal, is calculated as $\tau = (\varphi_1 - \varphi_2)/60$, where φ_1 and φ_2 are the largest and second largest X1-Cu-X2 angles. The value of $\tau = 1$ corresponds to trigonal bipyramidal, while $\tau = 0$ to square pyramidal geometry. For the structure **1**, **2** and **4** reported here (see Table 2), the τ values are 0.055, 0.46 and 0.071, respectively, which are close to the square pyramidal limit.

Conversely, in complex **3**, the coordination is square planar, since the co-crystallized water molecule is more than 4 Å away from Cu1; the Cu atom, located on a symmetry center, is connected to two monodentate ibuprofen molecules and two pyrrolidine ligands (Fig. 6A). The Cu-O, Cu-Ow and Cu-N bond distances of all complexes are in the range 1.937(2)-1.986(2) Å, 2.216(5)-2.326(2) Å and 1.989(4)-2.030(2) Å, respectively, in line with those reported in literature for similar compounds.

For all compounds the packing pattern is mainly determined by the formation of O/N-H…O hydrogen bonds (Table S1 of SI). In complexes **1** and **2** the coordinated water molecule is involved in both intramolecular (with the free carboxylate oxygen) and intermolecular (with the coordinated oxygen of the adjacent complex) interactions, giving the supramolecular dimer shown in Figs. 4B and 5B. In complex **1** these dimeric units are interacting with each others *via* weak van der Waals forces. Conversely, in **2** the non-coordinated solvent bridges two dimers (Fig. 5B) leading to the formation of ribbons running parallel to the *c* direction. In complex **3**, the co-crystallized water molecule acts as a H-bond donors towards the O2 atoms belonging to two adjacent molecules, in such a way to form a bifurcated hydrogen bonding on O2, and accepts another H-bond from N1. The resulting pattern is the zig-zag chain shown in Fig. 6B. Finally, in **4**, each Cu complex is surrounded by four ibuprofen anions, linked through N/O-H…O bonds involving the NH_2 groups and the water molecule as donors, and the carboxylate oxygen atoms as acceptors (Fig. 7B). The result is a layered structure made of alternating organic-inorganic layers.

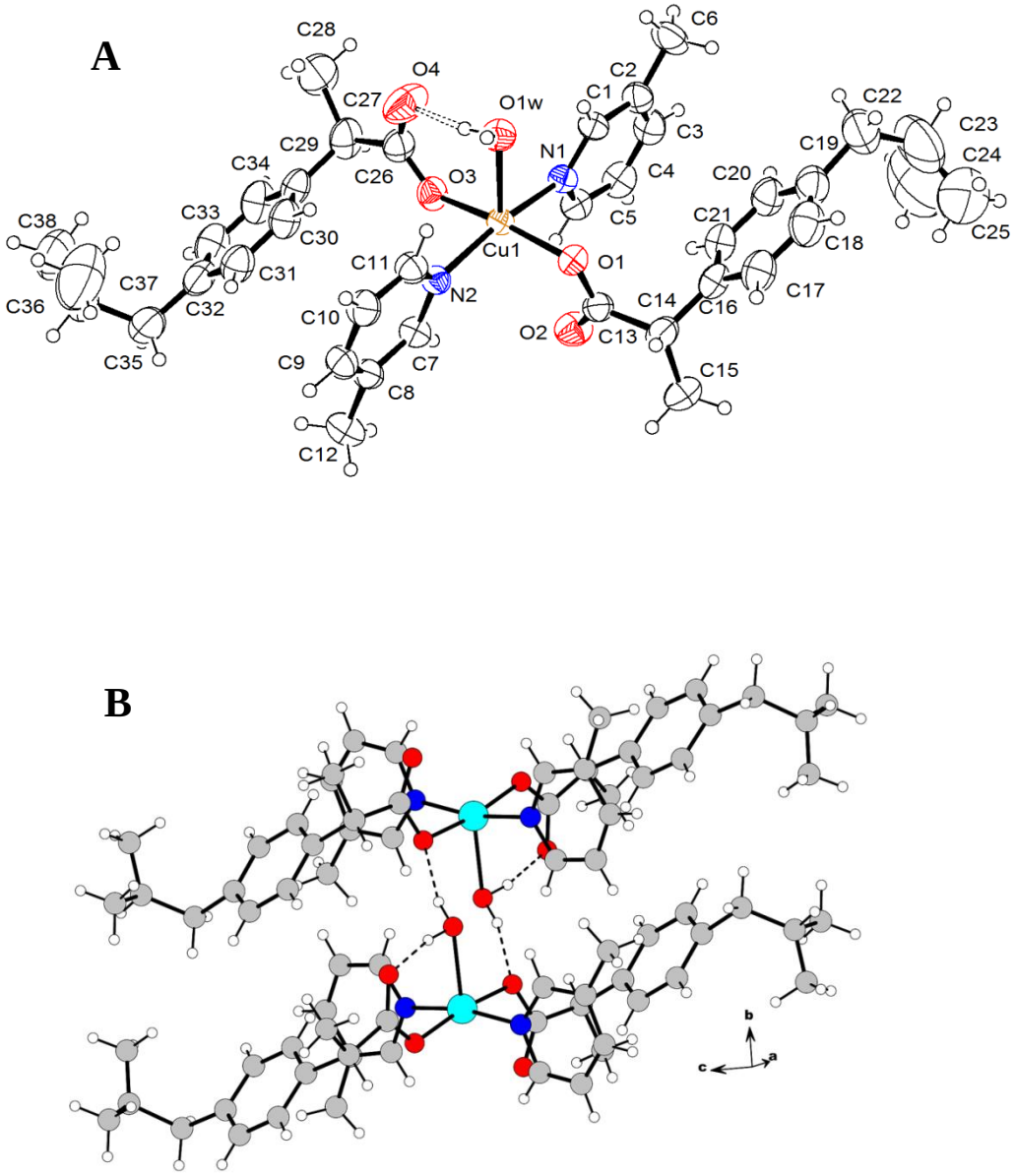


Figure 4. A) ORTEPIII view and atom numbering scheme for complex **1**. Thermal ellipsoids are drawn at the 40% probability level. Hydrogen bonds are drawn as dashed lines; B) Dimeric units formed via O-H…O hydrogen bonding

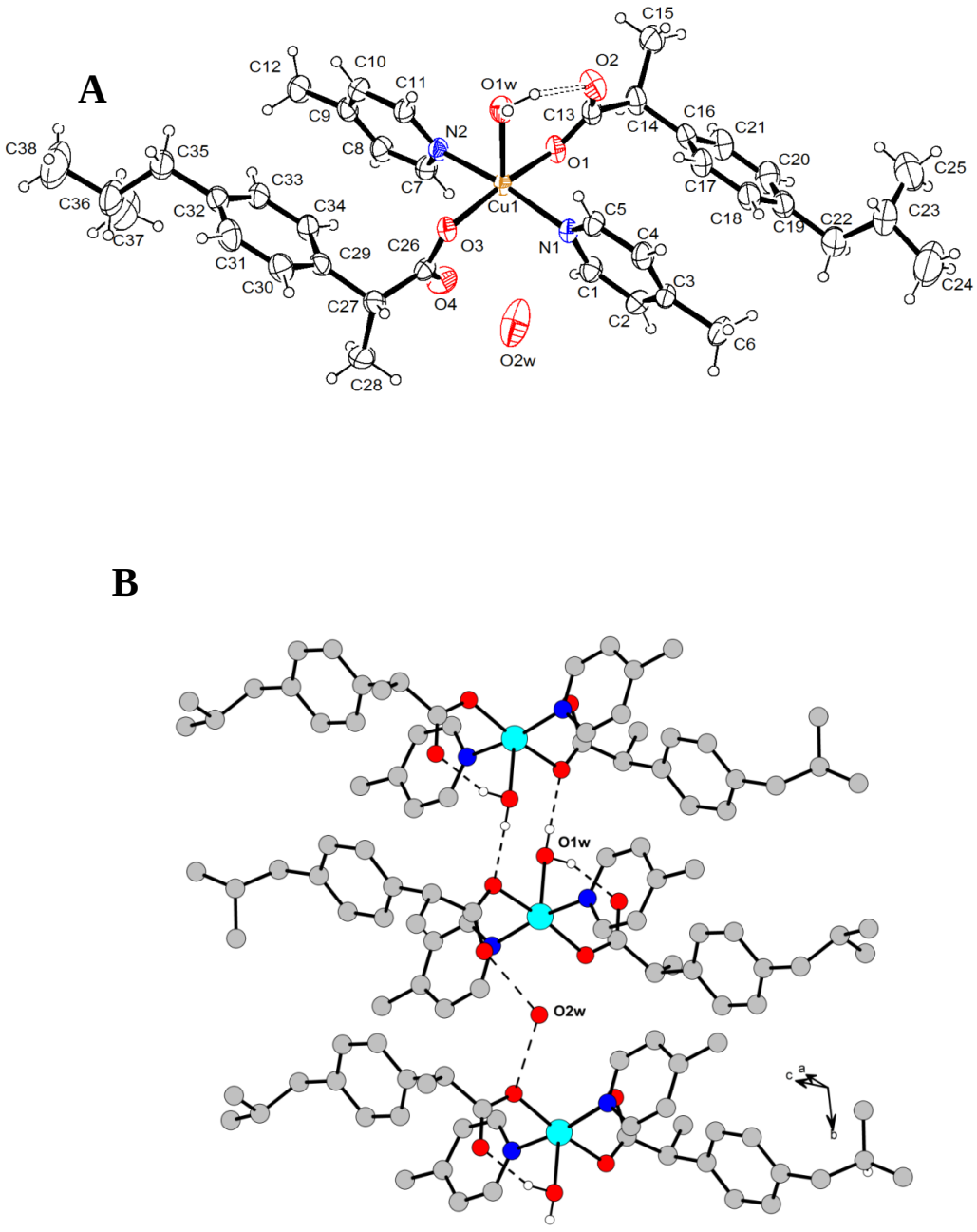


Figure 5. A) ORTEPIII view and atom numbering scheme for complex **2**. Thermal ellipsoids are drawn at the 40% probability level. Hydrogen bonds are drawn as dashed lines. B) Dimeric units formed via O-H…O hydrogen bonding (C-H hydrogens have been omitted for clarity)

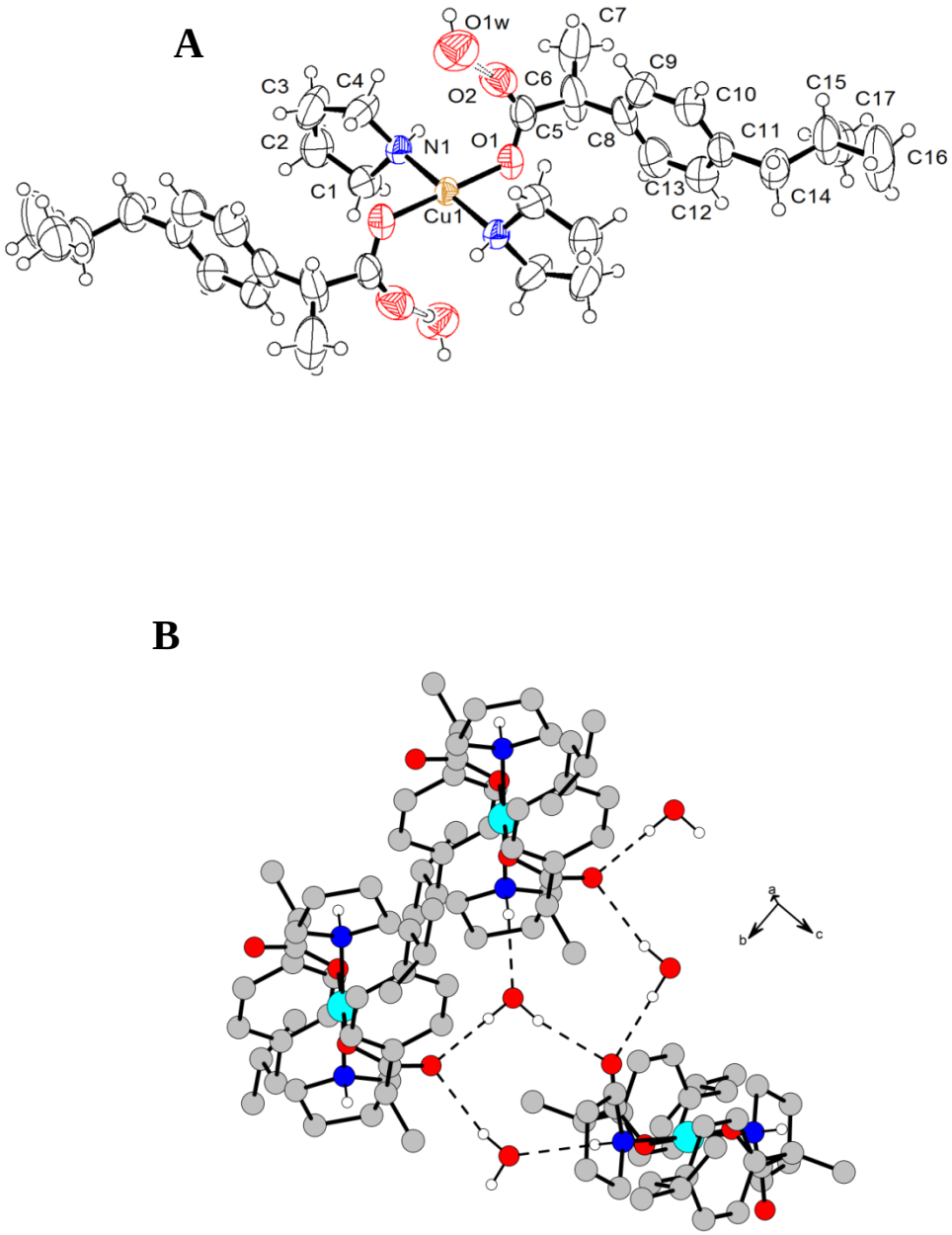


Figure 6. A) ORTEPIII view and atom numbering scheme for **3**. Thermal ellipsoids are drawn at the 40% probability level. Hydrogen bonds are drawn as dashed lines. B) O-H…O hydrogen bonding scheme (C-H hydrogens have been omitted for clarity)

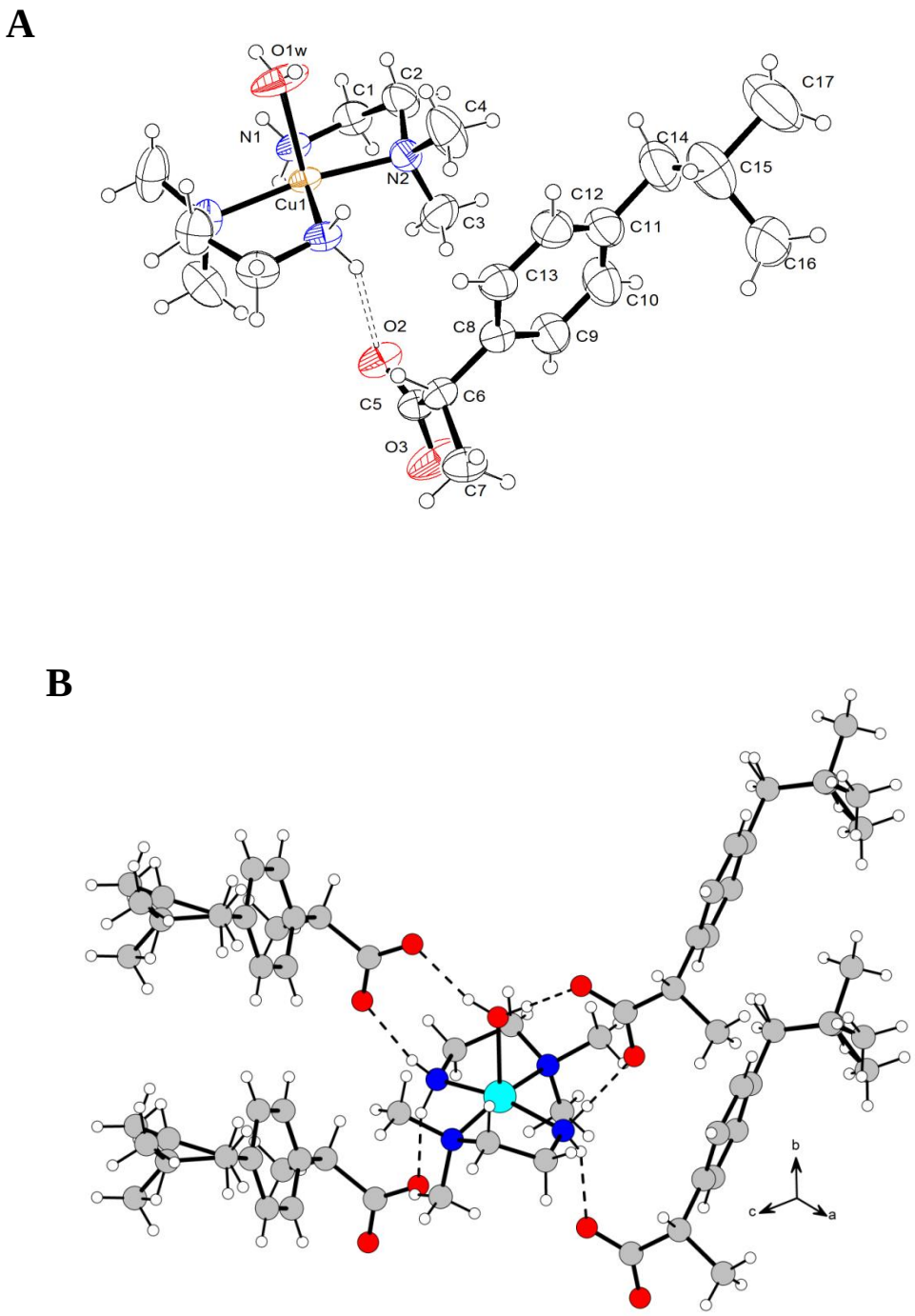


Figure 7. A) ORTEPIII view and atom numbering scheme for[Cu(*un-dm-en*)$_2$(H_2O)](*Ibu*)$^+$ cation in **4**. Thermal ellipsoids are drawn at the 40% probability level. B) Hydrogen bonding scheme

Biological activity

In vitro assays using mammalian cell cultures provide valuable information about the toxicity of compounds. The determination of the basal cytotoxicity of the compounds is a first step for further toxicity studies. Human cell cultures can be used as an approach to estimate acute toxicity [52]. The cytotoxicity of the copper complexes **1-4** was determined on healthy human dermal fibroblast (HDF) and two human melanoma cell lines, HT-144 and SKMEl-28. Cell viability was determined by means of the MTT reduction assay (Fig. 8). These cytotoxicity results are the mean of 3 independent experiments performed over a period of 15 days. The small standard error underlines that the cytotoxic activity of the complexes is reproducible under the testing conditions, which shows that the complexes dissolution always produces the same species in culture medium. Whereas newly synthesized monomeric copper complexes **1-4** showed higher cytotoxicity than parent molecule (IC50 > 500 μM) against various human cell cultures [53, 54], comparison of cytotoxic activities of the Cu(II) complexes did not vary substantially. Nevertheless, the most cytotoxic complex was **3**, which underlines a cytotoxicity activity slightly higher than the other complexes on the HDF and SKMEI-28 cell lines. Indeed, the toxicity reaches 20% at 25μM, whereas it is less than 10% for the other complexes at the same concentration. The square planar geometry of complex **3** compared to the square pyramidal geometry of the other complexes could explained this difference. The former being less sterically hindered could be more effective towards cell lines but further experiments are needed to have an in-depth understanding of the mechanisms involved. Of course, other parameters such as electronic and lipophilic properties should also be taken into account to have a better understanding of the observed difference.

The cytotoxic activity of the complexes is also different depending on the cell lines. Cu(II) complexes induces a significant cytotoxicity on the human melanoma cell line HT-144 with a mean IC_{50} of 120μM. Whereas as weak cytotoxic activity of the complexes is observed on the healthy human dermal fibroblast HDF cells, and the human melanoma cell line SKMEl-28 with a mean IC_{50} higher than 200μM.

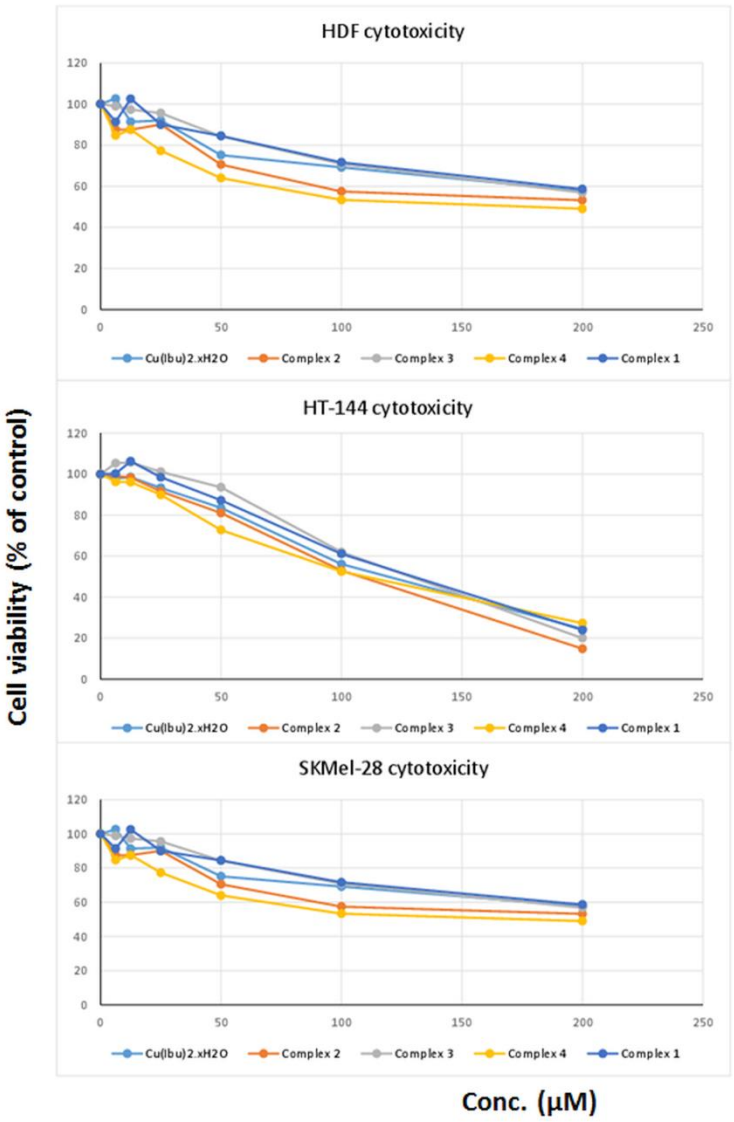


Figure 8. Cytotoxic effects of the complexes on healthy (Human Dermal Fibroblasts (HDF) and tumoral (human melanoma cell lines HT-144 and SKMEI-28) human cell lines. Each cell line was treated (0-200 µM) with Cu(II) complexes for 24h and viable cells were determined using a colorimetric assay.

Conclusions

Four new copper(II) ibuprofenate complexes with various nitrogen donor ligands, *β*-picoline, *γ*-picoline, pyrrolidine and unsymmetrical-dimethylethylenediamine (*un-dmen*) have been synthesized and characterized by spectroscopic and thermogravimetric methods. Crystallographic investigations revealed that copper(II) Ibuprofenate with aliphatic and aromatic nitrogen donor ligands are monomeric in nature in contrast to dimeric nature of copper(II) ibuprofenate solvates. EPR studies clearly revealed the chromophore present in all complexes **1-4** is consistent with X-ray crystallography**.** All the newly synthesized monomeric copper complexes **1-4** showed higher cytotoxicity than parent molecule against various tumoral cell lines. In general, also in view of their low toxicity to humans, such metal based drugs could be a good starting point for the development of promising therapeutic agents with possibly reduced side effects and enhanced bioavailability and selectivity.

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Supplementary data

The following is the supplementary data related to this article: Tables S1,S2, S3, S4 and checkcif reports for complexes **1-4.** Crystallographic data for the structural analysis of the four new compounds have been deposited at the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK, and are available free of charge from the Director on request quoting the deposition number CCDC **1509591-1509594** for complexes **1-4**, respectively.

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