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PAPER



# Structural features of mono- and tri-nuclear Zn(II) complexes with a non-steroidal anti-inflammatory drug as ligand†

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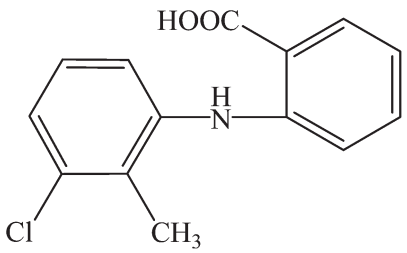
The interaction of Zn(II) with the non-steroidal anti-inflammatory drug tolfenamic acid leads to the formation of the structurally characterized trinuclear $[Zn_3(tolfenamato)_6(CH_3OH)_2]$ complex. In the presence of the *N*,*N*′-donor heterocyclic ligands 1,10-phenanthroline and 2,2′-bipyridine at a range of ratios, the mononuclear Zn complexes of the general formulae [Zn(tolfenamato)(*N*,*N*′-donor)Cl] and $[Zn(tolfenamato)_2(N,N'\text{-donor})]$ have been isolated and structurally characterized by X-ray crystallography. The deprotonated tolfenamato ligands are coordinated to the Zn(II) ion through carboxylato oxygen atoms. Tolfenamic acid and its complexes exhibit good binding propensity to human or bovine serum albumin protein having relatively high binding constant values.

## Introduction

Zinc is an element of great biological interest being the second most abundant trace element in the human body.[1] Its role is important in various biological systems since it is critical for numerous cell processes and is a major regulatory ion in the metabolism of cells.[2] The administration of zinc in children suffering from deadly diarrhoea in the form of the preparation "Baby Zinc" resulted in significant reduction of child mortality in underdeveloped countries.[3] In the literature, zinc complexes with drugs used for the treatment of Alzheimer's disease[4] and others showing antibacterial/antimicrobial,[5] anticonvulsant,[6] antidiabetic,[7] anti-inflammatory[8] or antiproliferative/antitumor[5,8] activity are structurally characterized. In addition, a number of workers have reported the structures of binuclear, trinuclear and polynuclear Zn(II) complexes containing carboxylato bridging ligands.[9–11]

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently used analgesic, anti-inflammatory and antipyretic agents.[12] NSAIDs inhibit the cyclo-oxygenase (COX)-mediated production of prostaglandins, have exhibited anti-tumorigenic activity by reducing the number and size of carcinogen-induced colon tumors or through inducing the apoptosis of several cancer cell lines as well as a synergistic role on the activity of certain antitumor drugs.[13] In this context, the direct interaction of NSAIDs and their metal complexes with DNA is of interest since their potential anticancer as well as anti-inflammatory activities may be explained.[14] The chemical classes of NSAIDs comprise salicylate derivatives, phenylalkanoic acids, oxicams, anthranilic acids, sulfonamides and furanones.[15] The NSAID tolfenamic acid (= Htolf, Scheme 1) belongs to the derivatives of *N*-phenylanthranilic acid and chemically resembles mefenamic and niflumic acid and other fenamates in clinical use.[15] Htolf is found in analgesic, anti-inflammatory, antipyretic and antirheumatoid drugs and is also used for veterinary purposes.[16] To the best of our knowledge, the crystal structures of two tin(IV),[17] two copper(II)[18] and two cobalt(II)[19] complexes have been reported in the literature.

Our recent studies have been focused on the coordination chemistry of carboxylate-containing anti-inflammatory[19–22] or antimicrobial[23,24] drugs with metal ions ($Co^{2+}$, $Ni^{2+}$, $Cu^{2+}$ and $Zn^{2+}$) in an attempt to examine their mode of binding and possible biological relevance. In addition, we have reported studies on the interaction of these metal complexes with biomolecules (nucleic acids and serum albumin proteins) as well as their tentative biological (antimicrobial, anticancer, antioxidant) activity. Taking into consideration the biological role and activity of zinc and its complexes as well as the significance of NSAIDs in




**Scheme 1** Tolfenamic acid.

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medicine, we present the synthesis and the structural characterization of neutral zinc(II) complexes with the NSAID tolfenamic acid in the presence of: methanol (complex **1**, $[Zn_3(tolf)_6(CH_3OH)_2]$); a nitrogen-donor heterocyclic ligand such as 1,10-phenanthroline (= phen) (complexes **2**, [Zn(tolf)(phen)Cl] and **4·Et$_2$O**, $[Zn(tolf)_2(phen)]\cdot Et_2O$); and 2,2′-bipyridine (= bipy) (complexes **3**, [Zn(tolf)(bipy)Cl] and **5**, $[Zn(tolf)_2(bipy)]$). The crystal structures of $[Zn_3(tolf)_6(CH_3OH)_2]$ (**1**), [Zn(tolf)(phen)Cl] (**2**), $[Zn(tolf)_2(phen)]\cdot Et_2O$ (**4·Et$_2$O**) and $[Zn(tolf)_2(bipy)]$ (**5**) complexes are also reported. Due to the biological impact of these compounds we plan to report later upon completion antioxidant and cytotoxicity studies along with the binding properties with calf-thymus DNA and DNA-competitive binding studies with ethidium bromide. In this report the affinity for bovine (BSA) and human serum albumin (HSA) proteins involved in the transport of metal ions and metal complexes with drugs through the blood stream, performed with fluorescence spectroscopy is also reported.

## Results and discussion

### Synthesis and spectroscopic study of the complexes

The synthesis of the complexes in high yield was achieved *via* the aerobic reaction of tolfenamic acid ($C_6H_3(Cl)(CH_3)$-NH-$C_6H_4(COOH)$) and KOH with $ZnCl_2$ or $Zn(NO_3)_2\cdot 6H_2O$ in the absence, (eqn (1)) for **1**, or presence of the corresponding *N*, *N*′-donor heterocyclic ligand (L = $C_{12}H_8N_2$ or $C_{10}H_8N_2$), (eqn (2) and (3)) for complexes **2**, **3** and **4**, **5**, respectively, according to the equations:

$$\begin{aligned} &3ZnCl_2 + 6C_6H_3(Cl)(CH_3) - NH - C_6H_4(COOH) \\ &\quad + 6KOH + 2CH_3OH \\ &\quad \rightarrow [Zn_3\{C_6H_3(Cl)(CH_3) - NH \\ &\qquad - C_6H_4(COO)\}_6(CH_3OH)_2] + 6KCl + 6H_2O \end{aligned} \quad (1)$$

$$\begin{aligned} &ZnCl_2 + C_6H_3(Cl)(CH_3) - NH - C_6H_4(COOH) \\ &\quad + KOH + L \\ &\quad \rightarrow [Zn\{C_6H_3(Cl)(CH_3) - NH - C_6H_4(COO)\}(L)Cl] \\ &\qquad + KCl + H_2O \end{aligned} \quad (2)$$

$$\begin{aligned} &Zn(X)_2 + 2C_6H_3(Cl)(CH_3) - NH - C_6H_4(COOH) \\ &\quad + 2KOH + L \\ &\quad \rightarrow [Zn\{C_6H_3(Cl)(CH_3) - NH - C_6H_4(COO)\}_2(L)] \\ &\quad + 2KX + 2H_2O \\ &(X = NO_3^- \text{ or } Cl^-, L = C_{12}H_8N_2 \text{ or } C_{10}H_8N_2) \end{aligned} \quad (3)$$

All complexes are soluble in DMSO, DMF and non-electrolytes (for 1 mM solutions, $\Lambda_M \leq$ 1–8 mho cm$^2$ mol$^{-1}$).

IR spectroscopy has been used in order to confirm the deprotonation and binding mode of tolfenamic acid. In the IR spectrum of Htolf, the observed absorption band at 3355(br,m) cm$^{-1}$, attributed to the $\nu$(H–O) stretching vibration has disappeared upon binding to the metal ion. The bands at 1661(s) cm$^{-1}$ and 1265(s) cm$^{-1}$ attributed to the stretching vibrations $\nu(C{=}O)_{carboxylic}$ and $\nu(C{-}O)_{carboxylic}$ of the carboxylic moiety (–COOH) respectively, have shifted in the IR spectra of complexes **1–5**, in the range 1578–1583 cm$^{-1}$ and 1375–1397 cm$^{-1}$ assigned to antisymmetric, $\nu_{asym}(C{=}O)$, and symmetric, $\nu_{sym}(C{=}O)$, stretching vibrations of the carboxylato group, respectively. The difference $\Delta$ [= $\nu_{asym}(C{=}O) - \nu_{sym}(C{=}O)$], a useful characteristic tool for determining the coordination mode of the carboxylato ligands, gives a value falling in the range 185–203 cm$^{-1}$ indicative for an asymmetrical binding mode of the tolfenamato ligand.[19,25]

The UV-vis spectra of the complexes have been recorded as nujol mull and in DMSO solution and are similar, suggesting that the complexes retain their structure in solution. In addition, the fact that complexes **1–5** have the same UV-Vis spectral pattern in nujol and in DMSO solution as well as in the presence of the buffer solution (150 mM NaCl and 15 mM trisodium citrate at pH 7.0) at ratios used in the biological experiments in combination with the fact that they are non-electrolytes in DMSO solution suggests that the compounds keep their integrity in solution. A thorough study of similar Cu(II) and Co(II) complexes with NSAIDs as ligands supporting the stability of those complexes in solution has been recently reported by our lab.[20a,21b]

### Description of the crystal structure of $[Zn_3(tolf)_6(CH_3OH)_2]$

The crystal structure of $[Zn_3(tolf)_6(CH_3OH)_2]$ is shown in Fig. 1, and selected bond distances and angles are listed in Table 1. Complex **1** is a centrosymmetric trinuclear double-wheel Zn complex with Zn(1) lying on the inversion center. The six tolfenamato ligands behave as deprotonated ligands in the bidentate mode and are coordinated *via* two carboxylato oxygen atoms to two zinc atoms, the central Zn, Zn(1), and a terminal one, Zn(2), forming six bidentate carboxylate bridges.

The central Zn atom, Zn(1), is six-coordinate with a distorted octahedral geometry. The basal plane of the octahedron is formed by four coordinated carboxylato oxygen atoms O(1), O(22), O(1)′ and O(22)′ of four different tolfenamato bridging ligands while at the axial positions the carboxylato oxygen atoms O(42) and O(42)′ of the remaining two tolfenamato bridging ligands are lying at further distances (Zn(1)–O(42) = 2.207 (3) Å) than O(1) (Zn(1)–O(1) = 2.110(3) Å) and O(22) (Zn–O(22) = 2.044(2) Å). The six coordinated tolfenamato ligands form *syn–syn* bidentate carboxylato bridges between the central zinc atom, Zn(1), and the two terminal zinc atoms, Zn(2) and Zn(2)′; three bridges between Zn(1) and each terminal zinc atom.

Each of the terminal zinc atoms, Zn(2) or Zn(2)′, is four-coordinate. It is coordinated to three oxygen atoms O(2), O(21) and O(41) from the three tolfenamato bridging ligands [Zn(2)–O(2) = 1.940(3) Å, Zn–O(21) = 1.901(3) Å and Zn(2)–O(41) = 1.913 (3) Å] and an oxygen atom from a terminal coordinated methanol [Zn(2)–O(1M) = 2.030(3) Å]. The tetrahedrality calculated for Zn(2) atoms gives a dihedral angle of 81.90° (the tetrahedrality for a four-coordinate metal complex can be determined from the angle subtended by two planes, each encompassing the metal and two adjacent atoms;[26a] for strictly square planar complexes with $D_{4h}$ symmetry, the tetrahedrality is 0°; for tetrahedral complexes with $D_{2d}$ symmetry, the tetrahedrality equals 90°) supporting a tetrahedral geometry for $ZnO_4$[26b] with the three tolfenamato oxygen atoms and the methanol oxygen lying at the

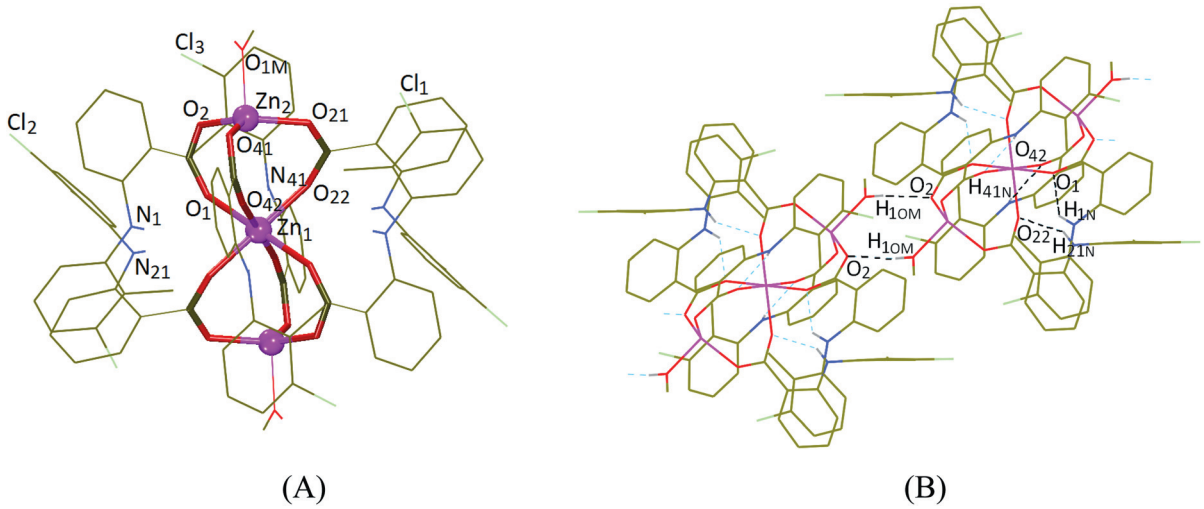


**Fig. 1** (A) The molecular structure and partial labeling of $[Zn_3(tolf)_6(CH_3OH)_2]$. (B) Intra- and inter-molecular H-bonding network in **1**.

**Table 1** Selected bond distances and angles for complex **1**

| Bond distance | (Å) | Bond distance | (Å) |
|---|---|---|---|
| Zn(1)–O(22) | 2.044(2) | Zn(2)–O(1M) | 2.030(3) |
| Zn(1)–O(1) | 2.110(3) | Zn(2)–O(41) | 1.913(3) |
| Zn(1)–O(42) | 2.207(3) | Zn(2)–O(2) | 1.940(3) |
| Zn(1)···Zn(2) | 3.515 | Zn(2)–O(21) | 1.901(3) |
| **Bond angle** | **(°)** | **Bond angle** | **(°)** |
| O(1)–Zn(1)–O(22)′ | 86.02(10) | O(22)–Zn(1)–O(42) | 98.11(10) |
| O(1)–Zn(1)–O(22) | 93.98(10) | O(22)–Zn(1)–O(42)′ | 81.89(10) |
| O(1)–Zn(1)–O(42)′ | 83.74(10) | O(2)–Zn(2)–O(41) | 117.06(12) |
| O(1)–Zn(1)–O(42) | 96.26(10) | O(2)–Zn(2)–O(21) | 123.01(13) |
| O(21)–Zn(2)–O(41) | 113.85(13) | O(2)–Zn(2)–O(1M) | 90.95(12) |
| O(21)–Zn(2)–O(1M) | 95.78(13) | O(41)–Zn(2)–O(1M) | 108.71(13) |

[a] Symmetry operation: (′) $2 - x, -y, 1 - z$.

vertices of the tetrahedron. The bond angles around Zn(2) lie in the range 90.95(12)°–123.01(13)°.

A thorough review of the literature has revealed the coordination number and modes of the carboxylato bridges in Zn complexes as given in Table 2. The number of the carboxylato bridges between Zn atoms varies from 1 to 4 while they are found as monodentate monoatomic coordinated groups or bidentate triatomic bridges as well as in diverse combinations of these two modes. In the case of one or two carboxylato groups, all the possible combinations have been reported, while four carboxylato bridges are arranged around Zn atoms according to the paddle-wheel pattern.

For three carboxylato groups, as found in **1**, two possible arrangements have been observed; one monodentate monoatomic coordinated carboxylato group and two bidentate triatomic carboxylato bridges (mode 6), or three bidentate triatomic carboxylato bridges (coordination mode 7) (Fig. 2). For coordination mode 6, a series of trinuclear Zn complexes of the general formula $[Zn_3(RCOO)_6(L)_2]$ (where RCOO and L = benzoate and nicotinamide;[11d] MeCH=CHCO$_2$ and $C_9H_7N$;[21] $O_2CCH_3$ and 2,5-bis(2-pyridyl)pyrazine[10d] or pyridine,[11a] respectively) have been reported but **1** is a rare example of the general formula

**Table 2** Coordination modes and Zn(II)···Zn(II) separation (Å) for zinc carboxylato-bridged complexes

| Coord. mode | Compound | Zn(II)···Zn(II) separation (Å) | Ref. |
|---|---|---|---|
| **1** | $[Zn(PTCH)(phen)(H_2O)]_2$ | 3.519 | 9*a* |
| | $[Zn_2(1,4\text{-}BDC)_2(IP)]$, 3D polymer | 4.39 | 9*b* |
| **2** | $[Zn(pht)A]_n$ | 3.467(2), 3.470(2) | 9*c* |
| **3** | $[Zn_2(oNBz)_4(AQ)_2(H_2O)_2]$ | 3.31 | |
| | $[Zn_2L^1(\mu_{1,3}\text{-}OAc)_2](ClO_4)$ | 3.281 | 9*d* |
| **4** | $[Zn_7(\mu_4\text{-}O)_2(OAc)_{10}(3pdb)]_n$ | 3.0016(8) | 10*a* |
| | $[Zn_7(\mu_4\text{-}O)_2(OAc)_{10}(4pdb)]_n$ | 2.9727(8) | |
| **5** | $[Zn_2L^2(\mu_{1,3}\text{-}OAc)_2](ClO_4)$ | 3.281 | 9*d* |
| **6** | $[Zn_3(benz)_6(nia)_2]$, | 3.1845(2) | 10*d* |
| | $[Zn_3(OAc)_6(bppz)_2](H_2O)$, | 3.347(1) | 10*d* |
| | $[Zn_3(MeCH{=}CHCO_2)_6(C_9H_7N)_2]$ | Not available | 11*b* |
| | $[Zn_3(O_2CCH_3)_6(py)_2]$ | Not available | 11*a* |
| **7** | $[Zn_3(tolf)_6(CH_3OH)_2]$ | 3.515 | This work |
| | $[Zn(L^3)_2(MeOH)_2]_3$ | 4.188 | 10*c* |
| **8** | $[Zn_2(Indo)_4(py)_2]$, | 2.969(1) | 8 |
| | $[Zn_2(\mu\text{-}oNBz)_4(AMP)_2]$ | 3.00 | 9*b* |
| | $[Zn_2(O_2CCH_3)_4(py)_2]$ | 2.8921(10) | 11*a* |
| | $[Zn_2(MeCH{=}CHCO_2)_4(C_9H_7N)_2]$ | Not available | 11*b* |

[a] 1,4-$H_2$BDC = 1,4-benzendicarboxylic acid; 3pdb = 1,4-bis(3-pyridyl)-2,3-diaza-1,3-butadiene; 4pdb = 1,4-bis(4-pyridyl)-2,3-diaza-1,3-butadiene; A = 4-methylpyridine; AQ = 8-aminoquinoline; AMP = 2-aminopyrimidine; benz = benzoate anion; bppz = 2,5-bis(2-pyridyl)pyrazine; $HL^3$ = 9-acridinecarboxylic acid; IndoH = 1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1*H*-indole-3-acetic acid); IP = 1*H*-imidazo[4,5-*f*][1,10]-phenanthroline; $L^1$ = 2,6-bis(*N*-2-(2′-pyridylethyl)-formimidoyl)4-methylphenol; $L^2$ = 2,6-bis(*N*-2-(2′-pyridylethyl)-formimidoyl)4-methylphenol; nia = nicotinamide; OAc = acetate; oNBz = 2-nitrobenzoato anion; phen = 1,10-phenanthroline; $pht^{2-}$ = dianion of *o*-phthalic acid; $PTCH_3$ = 3-propanetricarboxylic acid.

$[Zn_3(RCOO)_6(L)_2]$ that contains three bidentate triatomic carboxylato bridges per pair of Zn atoms. The distance Zn(1)···Zn(2) (3.515 Å) is the longest Zn···Zn distance found in the trinuclear complexes of this formula (Table 2). Three bidentate triatomic carboxylato bridge modes have been also reported for the compound $[Zn_3(9\text{-acridinecarboxylato})_6(MeOH)_6]$ with a Zn···Zn separation of 4.188 Å.[10c] Although the binding mode of

 

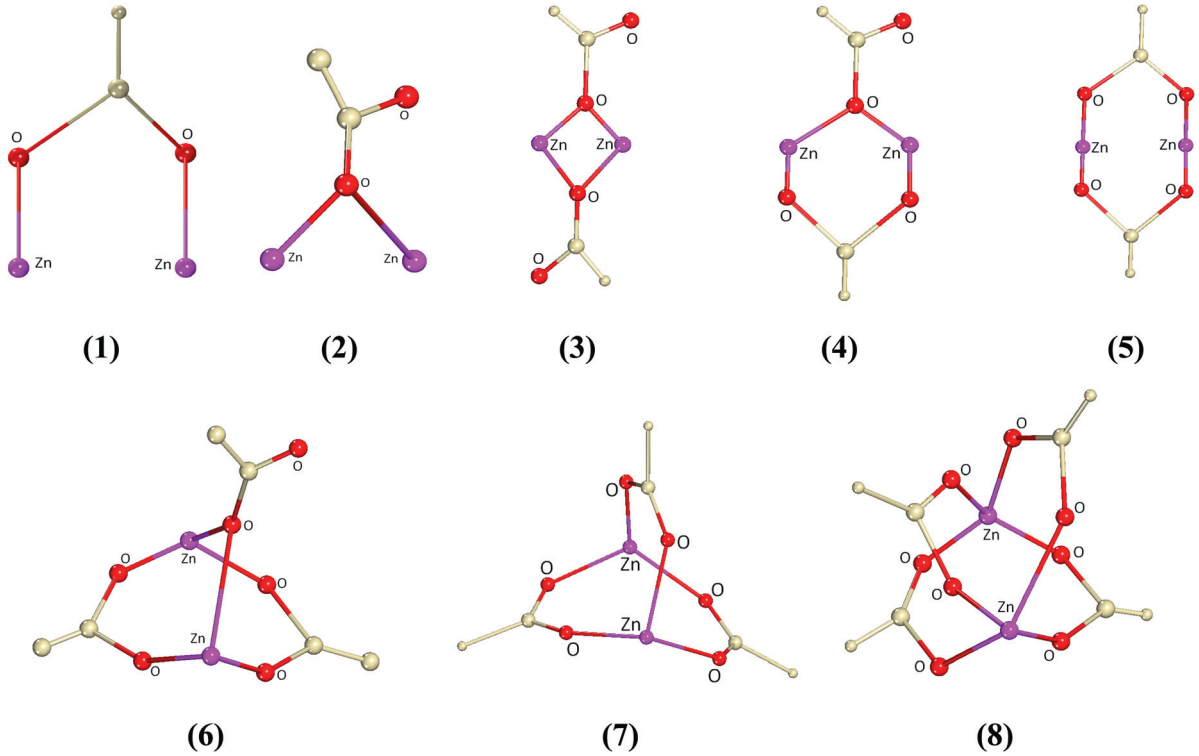


**Fig. 2** Coordination modes for zinc carboxylato-bridged complexes.

the carboxylato bridges is similar to **1**, the geometrical features around the Zn atoms are significantly different. In $[Zn_3(9\text{-acridinecarboxylato})_6(MeOH)_6]$, the central Zn atom exhibits almost perfect octahedral geometry and the terminal Zn atoms are six-coordinate, presenting a distorted octahedral geometry;[10c] in **1** the central Zn presents a distorted octahedral geometry with non-equal Zn–O distances, while the terminal Zn atoms are four-coordinate with a distorted tetrahedral geometry. The compound shows an extended intra- and inter-molecular H-bonding network creating an infinite chain consisting of trinuclear repeat units along the crystallographic *b*-axis (Fig. 1(B), Table S1†).

### Description of the crystal structure of [Zn(tolf)(phen)Cl]

The complex [Zn(tolf)(phen)Cl] **2**, is a mononuclear Zn(II) complex and the tolfenamato ligand behaves as a deprotonated ligand in the bidentate mode and is coordinated to zinc ions *via* two carboxylato oxygen atoms.

There are two crystallographically independent molecules in the asymmetric unit of **2**, denoted as **2A** and **2B** respectively, which may be considered as related through a 180° pseudo-rotation (Fig. S1†). A careful inspection of bond distances and angles (Table 3) reveals severe differences between **2A** and **2B** which along with an apparent rotation of the tolfenamato ligand around the $C_{carboxylato}$–$C_{phenyl}$ bond justify their simultaneous presence in the asymmetric unit of **2**. For clarity reasons, only the molecular structure of **2A** is shown in Fig. 3.

The zinc atom is five-coordinate and could be described as having a distorted square pyramidal geometry. The tetragonality[27a] $T^5$ = 0.953 (for **2A**) and 0.943 (for **2B**), based on the changes in bond lengths, along with the trigonality index[27b] [$\tau$ = ($\varphi_1$–$\varphi_2$)/60°, where $\varphi_1$ and $\varphi_2$ are the largest angles in the coordination sphere; $\tau$ = 0 for a perfect square pyramid, and $\tau$ = 1 for a perfect trigonal bipyramid] $\tau$ = (139.97–136.95)/60 = 0.05 (for **2A**) and $\tau$ = (148.51–135.28)/60 = 0.22 (for **2B**), show slight distortion from the regular square-based pyramidal geometry for **2A**[27c] and more severe distortion for **2B**, justifying the presence of the two crystallographically independent molecules.

**Table 3** Selected bond distances and angles for **2**

| **2A** | | **2B** | |
|---|---|---|---|
| Bond distance | (Å) | Bond distance | (Å) |
| Zn(1)–O(21) | 2.343(2) | Zn(2)–O(62) | 2.184(2) |
| Zn(1)–O(22) | 2.003(2) | Zn(2)–O(61) | 2.095(2) |
| Zn(1)–N(1) | 2.095(2) | Zn(2)–N(41) | 2.084(2) |
| Zn(1)–N(2) | 2.056(2) | Zn(2)–N(42) | 2.082(2) |
| Zn(1)–Cl(1) | 2.2292(8) | Zn(2)–Cl(3) | 2.2395(8) |
| Bond angle | (°) | Bond angle | (°) |
| O(21)–Zn(1)–O(22) | 59.65(8) | O(61)–Zn(2)–O(62) | 61.28(8) |
| O(21)–Zn(1)–N(1) | 139.97(9) | O(61)–Zn(2)–N(41) | 148.51(9) |
| O(21)–Zn(1)–N(2) | 93.33(8) | O(61)–Zn(2)–N(42) | 92.79(9) |
| O(21)–Zn(1)–Cl(1) | 105.15(6) | O(61)–Zn(2)–Cl(3) | 102.73(7) |
| O(22)–Zn(1)–N(1) | 98.74(9) | O(62)–Zn(2)–N(41) | 102.92(8) |
| O(22)–Zn(1)–N(2) | 136.95(9) | O(62)–Zn(2)–N(42) | 135.28(9) |
| O(22)–Zn(1)–Cl(1) | 110.45(7) | O(62)–Zn(2)–Cl(3) | 105.61(6) |
| N(1)–Zn(1)–N(2) | 80.74(9) | N(41)–Zn(2)–N(42) | 80.16(9) |
| N(1)–Zn(1)–Cl(1) | 114.30(7) | N(42)–Zn(2)–Cl(3) | 115.88(7) |
| N(2)–Zn(1)–Cl(1) | 108.67(7) | N(41)–Zn(2)–Cl(3) | 107.97(7) |

The two carboxylate oxygen atoms O(21)/O(22) for **2A** and O(61)/O(62) for **2B** of the tolfenamato ligand and the nitrogen atoms N(1)/N(2) for **2A** and N(41)/N(42) for **2B** of the phen

ligand occupy the four positions in the basal plane around Zn(1) and Zn(2), respectively, while the Cl atom occupies the apical position. An arrangement similar to that of the *N*,*N*′-donor ligand has also been observed in [Zn(oxo)(bipy)Cl]·MeOH[23a] and in a series of copper compounds, $[Cu(L)_2(bipy)(H_2O)]$ and $[Cu(L)_2(phen)(H_2O)]$ (L = a monodentate phenoxyalkanoato ligand),[28] [Cu(oxolinato)(phen)Cl]·MeOH,[29a] [Cu(enrofloxacinato)(bipy)$(H_2O)$]Cl,[29b] [Cu(propyl-norfloxacinato)(bipy)Cl][29c] and [Cu(ciprofloxacinato)(phen)Cl][29d] with the $O_{water}$ or Cl atoms occupying the apical position, where oxolinic acid, enrofloxacin, propyl-norfloxacin and ciprofloxacin are bidentate quinolone antimicrobial drugs. The Zn–N distances, [Zn(1)–N(1) = 2.095(2) Å and Zn(1)–N(2) = 2.056(2) Å for **2A** and Zn(2)–N(41) = 2.084(2) Å and Zn(2)–N(42) = 2.082(2) Å for **2B**] are almost equal with those found in the five-coordinate complexes $[Zn(S_2CNMe_2)_2(py)]$ (2.079(6) Å),[30a] $[Zn(bipy)_2(pybet)](ClO_4)$ (2.081(5)–2.140(6) Å, $pybet^-$ = pyridinioacetate)[30b] and $[Zn(bipy)(CCl_3CO_2)_2(H_2O)]$ (2.086(2) and 2.151(2) Å).[30c]

In both **2A** and **2B**, the ligand atoms forming the basal plane are almost coplanar (for **2A**, N(2) and O(22) lie 0.018 Å and 0.024 Å above the plane towards the apex and O(21) and N(1) are at 0.023 Å and 0.024 Å below the plane; for **2B**, N(41) and O(61) lay above the plane towards the apex by 0.097 Å and 0.104 Å, respectively, and O(62) and N(42) are at 0.093 Å and 0.108 Å below the plane). The zinc atom is displaced towards the chlorine atom by 0.72 Å in **2A** and 0.66 Å in **2B**. The *trans* angles in the basal plane of **2B** [O(61)–Zn(2)–N(41) = 148.51(9)° and O(62)–Zn(2)–N(42) = 135.28(9)°] show significantly different values compared to those in **2A** [O(21)–Zn(1)–N(1) = 139.97(9)° and O(22)–Zn(1)–N(2) = 136.95(9)°], justifying the more distorted square pyramidal geometry around Zn(2). The N–Zn–N angle observed is 80.74(9)° and 80.16(9)° for **2A** and **2B**, respectively, and is similar to reported values of other chelating polycyclic diimines.[20] The phen ligands are planar with the zinc atoms almost lying in this plane (largest deviation 0.16 Å for Zn(1) and 0.09 Å for Zn(2)).

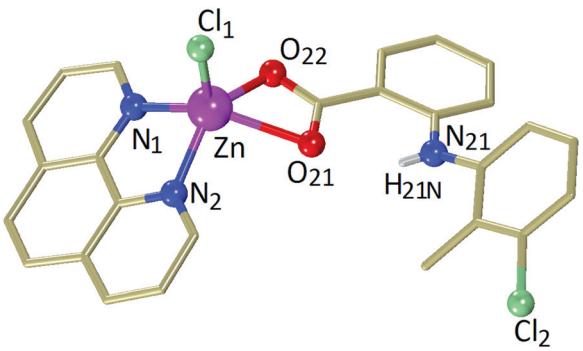


**Fig. 3** The molecular structure and partially labeling of **2A**.

### Crystal structure of $[Zn(tolf)_2(phen)]\cdot Et_2O$, $4\cdot Et_2O$ and $[Zn(tolf)_2(bipy)]$, 5

Diagrams of **4** and **5** are shown in Fig. 4(A) and 4(B), and selected bond distances and angles are listed in Table 4. Due to the similarities of the two structures we describe the structural features of compound **5** that also reflect analogous discussion of compound **4**. Complex **5** is mononuclear and the tolfenamato ligands behave as deprotonated ligands coordinated to the zinc atom *via* the carboxylato groups which adopt the asymmetric chelating mode (C(1)–O(1) = 1.254(4) Å and C(1)–O(2) = 1.269(3) Å, C(21)–O(21) = 1.271(3) Å and C(21)–O(22) = 1.262(3) Å).

In **5**, the zinc atom is six-coordinate and is surrounded by two tolfenamato ligands and a bidentate 2,2′-bipyridine ligand showing a distorted trigonal prismatic geometry, with the six vertices occupied by two nitrogen and four oxygen atoms, giving a $ZnN_2O_4$ chromophore. The plane of each trigonal base of the trigonal prism is formed by two oxygen atoms from the two tolfenamato ligands (O(1) and O(21) form participate in base 1 and O(2) and O(22) in base 2) and a nitrogen atom of bipy (N(41) and N(42), respectively) (Fig. S2†). The two almost parallel trigonal basal planes form an angle of 5.87° and lie at a distance of 2.197 Å with the zinc atom being closer to base 1 (1.095 Å) than to base 2 (1.136 Å).

The bond distances around the Zn atom are not equal, with the carboxylate oxygen atoms O(2) and O(21) being closer to Zn (Zn–O(2) = 1.971(2) Å and Zn–O(21) = 2.0620(18) Å) than the bipy nitrogens (Zn–N(41) = 2.088(2) Å and Zn–N(42) =

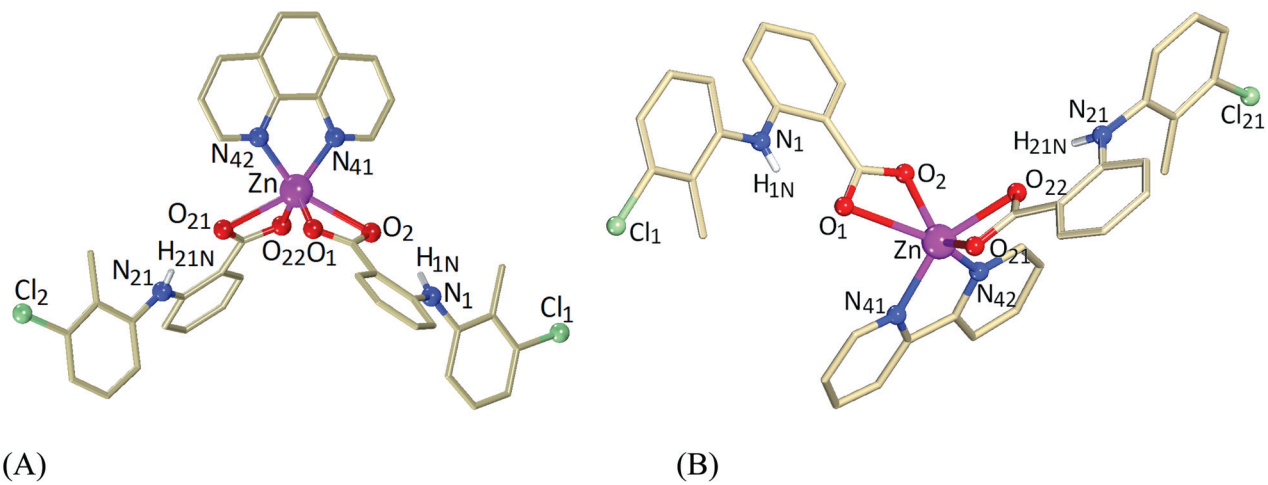


**Fig. 4** The molecular structures and partial labeling of (A) **4** and (B) **5**.

 

2.099(2) Å). These Zn–O and Zn–N bond distances are relatively shorter than those found in analogous six-coordinate complexes $[Zn(bipy)_2(ONO)](NO_2)$ (2.122(9) Å),[31a] $[Zn(phen)_2(MeCO_2)](ClO_4)$ (2.100(5)–2.160(5) Å)[30b] and $[Zn(pipdtc)_2(bipy)]$ (2.196(3) Å, $pipdtc^-$ = piperidine–carbodithioato anion).[31b] The two longer $Zn–O_{carboxylate}$ distances (Zn–O(22) = 2.269(2) Å and Zn–O(1) = 2.575(2) Å), Zn–O(1) are at the borderline of bond distances for Zn(II).

The N(41)–Zn–N(42) angle observed is 78.19(9)° and is similar to reported values of other chelating polycyclic diimines.[23,24] The bipy ligand is almost planar with the zinc atom lying ~0.25 Å out of this plane.

**Table 4** Selected bond distances and angles for **4** and **5**

| Bond distance | (Å) |
|---|---|
| Zn–O(1) | $\{1.966(2)\}^4$ or $\{1.970(2)\}^5$ |
| Zn–O(2) | $\{2.555(3)\}^4$ or $\{2.575(2)\}^5$ |
| Zn–N(41) | $\{2.083(3)\}^4$ or $\{2.088(2)\}^5$ |
| C(1)–O(1) | $\{1.287(4)\}^4$ or $\{1.269(3)\}^5$ |
| C(1)–O(2) | $\{1.249(4)\}^4$ or $\{1.254(4)\}^5$ |
| Zn–O(21) | $\{2.478(2)\}^4$ or $\{2.062(2)\}^5$ |
| Zn–O(22) | $\{1.973(2)\}^4$ or $\{2.269(2)\}^5$ |
| Zn–N(42) | $\{2.088(3)\}^4$ or $\{2.099(2)\}^5$ |
| C(21)–O(21) | $\{1.261(4)\}^4$ or $\{1.262(3)\}^5$ |
| C(21)–O(22) | $\{1.273(4)\}^4$ or $\{1.271(3)\}^5$ |
| **Bond angle** | **(°)** |
| O(1)–Zn–O(22) | $\{113.14(9)\}^4$ or $\{120.33(7)\}^5$ |
| O(1)–Zn–N(41) | $\{123.62(10)\}^4$ or $\{83.95(8)\}^5$ |
| O(1)–Zn–N(42) | $\{107.65(10)\}^4$ or $\{140.49(8)\}^5$ |
| O(1)–Zn–O(21) | $\{92.37(9)\}^4$ or $\{96.71(7)\}^5$ |
| O(1)–Zn–O(2) | $\{56.81(9)\}^4$ or $\{55.98(7)\}^5$ |
| O(21)–Zn–O(22) | $\{57.96(9)\}^4$ or $\{60.42(7)\}^5$ |
| O(22)–Zn–N(41) | $\{104.89(10)\}^4$ or $\{152.86(9)\}^5$ |
| N(41)–Zn–N(42) | $\{79.95(10)\}^4$ or $\{78.19(9)\}^5$ |
| O(2)–Zn–N(42) | $\{145.00(9)\}^4$ or $\{102.23(9)\}^5$ |
| O(2)–Zn–O(21) | $\{123.16(8)\}^4$ or $\{121.68(8)\}^5$ |
| O(2)–Zn–O(22) | $\{89.30(9)\}^4$ or $\{88.51(8)\}^5$ |
| O(2)–Zn–N(41) | $\{84.71(9)\}^4$ or $\{116.97(9)\}^5$ |
| O(21)–Zn–N(41) | $\{143.78(9)\}^4$ or $\{108.09(9)\}^5$ |
| O(21)–Zn–N(42) | $\{85.67(9)\}^4$ or $\{122.23(8)\}^5$ |
| O(22)–Zn–N(42) | $\{124.96(10)\}^4$ or $\{87.80(8)\}^5$ |

[a] $\{\}^4$: for compound **4**; $\{\}^5$: for compound **5**.

### Interaction of the compounds with serum albumins

Serum albumin (SA) is the most abundant protein in blood plasma. Therefore, it is important to consider the interactions of drugs with plasma proteins particularly with SA. Binding to these proteins may lead to loss or enhancement of the biological properties of the original drug, or provide paths for drug transportation. Bovine serum albumin (BSA) is the most extensively studied serum albumin, due to its structural homology with human serum albumin (HSA).[19–21] BSA and HSA solutions exhibit an intense fluorescence emission with a peak at 343 nm and 351 nm, respectively, due to the tryptophan residues (Trp-134 and Trp-212 in BSA and Trp-212 in HSA) when excited at 295 nm.[19,20] The changes and the quenching occurring in the fluorescence emission spectra of tryptophan in BSA or HSA upon addition of complexes **1–5** are primarily due to a change in protein conformation, subunit association, substrate binding or denaturation.[32a] Htolf and complexes **1–5** in buffer solutions exhibit a maximum emission at 330 nm under the same experimental conditions and the SA fluorescence spectra have been corrected before the experimental data processing.

The quenching provoked by Htolf and complexes **1–5** to the BSA fluorescence signal at 343 nm is significant (up to 12% of the initial fluorescence intensity for Htolf, 2.5% for **1**, 4% for **2**, 25% for **3**, 1% for **4** and 10% for **5**, Fig. 5(A)) because of possible changes in protein secondary structure leading to changes in tryptophan environment of BSA, and thus indicating the binding of each complex to BSA.[32b]

The Stern–Volmer and Scatchard graphs may be used in order to study the interaction of a quencher with serum albumins. According to the Stern–Volmer quenching equation:[33a]

$$\frac{I_0}{I} = 1 + k_q\tau_0[Q] = 1 + K_{SV}[Q] \quad (4)$$

where $I_0$ = the initial tryptophan fluorescence intensity of SA, $I$ = the tryptophan fluorescence intensity of SA after the addition

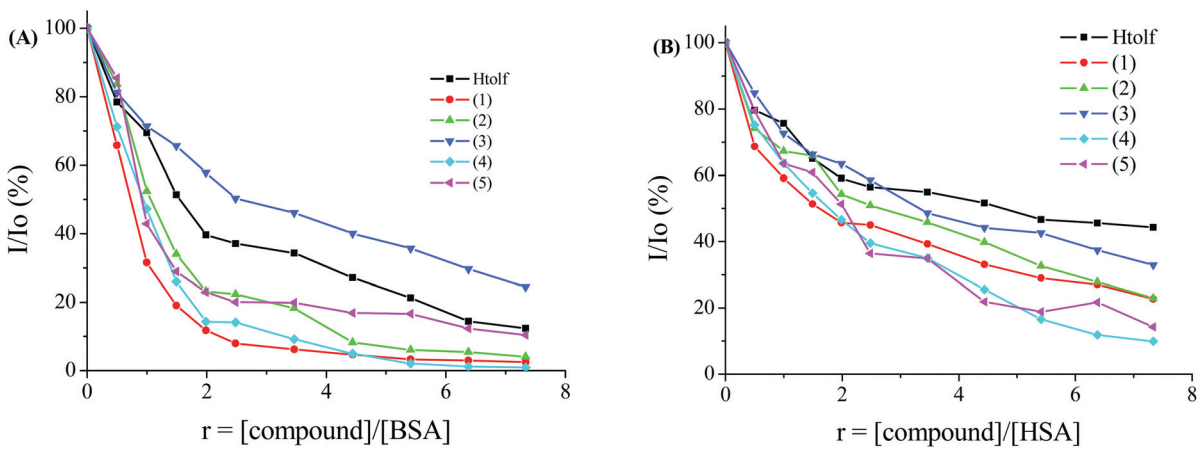


**Fig. 5** (A) Plot of % relative fluorescence intensity at $\lambda_{em}$ = 343 nm ($I/I_0$%) *vs.* $r$ ($r$ = [compound]/[BSA]) for Htolf and complexes **1–5** in buffer solution (150 mM NaCl and 15 mM trisodium citrate at pH 7.0). (B) Plot of % relative fluorescence intensity at $\lambda_{em}$ = 351 nm ($I/I_0$%) *vs.* $r$ ($r$ = [compound]/[HSA]) for Htolf and complexes **1–5** in buffer solution (150 mM NaCl and 15 mM trisodium citrate at pH 7.0).

**Table 5** The BSA and HSA binding constants and parameters ($K_{sv}$, $k_q$, $K$, $n$) derived for Htolf and complexes **1–5**

| | Compound | $K_{sv}$ ($M^{-1}$) | $k_q$ ($M^{-1}$ $s^{-1}$) | $K$ ($M^{-1}$) | $n$ |
|---|---|---|---|---|---|
| BSA | Htolf[19] | $2.18(\pm0.12) \times 10^5$ | $2.18(\pm0.12) \times 10^{13}$ | $1.60 \times 10^5$ | 1.11 |
| | $[Zn_3(tolf)_6(CH_3OH)_2]$ | $1.87(\pm0.06) \times 10^6$ | $1.87(\pm0.06) \times 10^{14}$ | $2.07 \times 10^5$ | 1.44 |
| | [Zn(tolf)(phen)Cl] | $9.99(\pm0.60) \times 10^5$ | $9.99(\pm0.60) \times 10^{13}$ | $5.70 \times 10^4$ | 2.09 |
| | [Zn(tolf)(bipy)Cl] | $1.15(\pm0.04) \times 10^5$ | $1.15(\pm0.04) \times 10^{13}$ | $1.81 \times 10^5$ | 0.84 |
| | $[Zn(tolf)_2(phen)]$ | $1.00(\pm0.01) \times 10^6$ | $1.00(\pm0.01) \times 10^{14}$ | $1.88 \times 10^5$ | 1.31 |
| | $[Zn(tolf)_2(bipy)]$ | $3.67(\pm0.15) \times 10^5$ | $3.67(\pm0.15) \times 10^{13}$ | $6.20 \times 10^4$ | 1.70 |
| HSA | Htolf[19] | $0.61(\pm0.04) \times 10^5$ | $0.61(\pm0.04) \times 10^{13}$ | $3.12 \times 10^5$ | 0.63 |
| | $[Zn_3(tolf)_6(CH_3OH)_2]$ | $1.39(\pm0.05) \times 10^5$ | $1.39(\pm0.05) \times 10^{13}$ | $4.12 \times 10^5$ | 0.79 |
| | [Zn(tolf)(phen)Cl] | $1.41(\pm0.07) \times 10^5$ | $1.41(\pm0.07) \times 10^{13}$ | $4.37 \times 10^5$ | 0.65 |
| | [Zn(tolf)(bipy)Cl] | $0.86(\pm0.03) \times 10^5$ | $0.86(\pm0.03) \times 10^{13}$ | $1.43 \times 10^5$ | 0.86 |
| | $[Zn(tolf)_2(phen)]$ | $4.27(\pm0.28) \times 10^5$ | $4.27(\pm0.28) \times 10^{13}$ | $1.36 \times 10^5$ | 1.20 |
| | $[Zn(tolf)_2(bipy)]$ | $2.84(\pm0.12) \times 10^5$ | $2.84(\pm0.12) \times 10^{13}$ | $1.49 \times 10^5$ | 1.16 |

of the quencher, $k_q$ = the quenching rate constants of SA, $K_{SV}$ = the dynamic quenching constant, $\tau_o$ = the average lifetime of SA without the quencher, [Q] = the concentration of the quencher respectively,

$$K_{SV} = k_q \tau_o \quad (5)$$

and, taking as fluorescence lifetime ($\tau_o$) of tryptophan in SA at around $10^{-8}$ s,[33b] the dynamic quenching constant ($K_{SV}$, $M^{-1}$) can be obtained by the slope of the diagram $I_0/I$ *vs.* [Q], and subsequently the approximate quenching constant ($k_q$, $M^{-1}$ $s^{-1}$) may be calculated. The values of $K_{sv}$ and $k_q$ for the interaction of Htolf and complexes **1–5** with BSA have been calculated from (Fig. S4†) according to eqn (5). They are given in Table 5 and indicate good BSA binding propensity of the complexes with **1** exhibiting the highest quenching ability ($k_q = 1.87(\pm0.06) \times 10^{14}$ $M^{-1}$ $s^{-1}$). The $k_q$ values (>$10^{13}$ $M^{-1}$ $s^{-1}$) are higher than diverse kinds of quenchers for biopolymer fluorescence ($2.0 \times 10^{10}$ $M^{-1}$ $s^{-1}$) indicating the existence of static quenching mechanism.[32]

Using the Scatchard equation:[33]

$$\frac{\Delta I/I_0}{[Q]} = nK - K\frac{\Delta I}{I_0} \quad (6)$$

where $n$ is the number of binding sites per albumin and $K$ is the association binding constant, $K$ ($M^{-1}$), may be calculated from the slope in plots $(\Delta I/I_0)/[Q]$ *versus* $\Delta I/I_0$ and $n$ is given by the ratio of the $y$ intercept to the slope.[33a] $K$ and values for Htolf and complexes **1–5** have been obtained from the corresponding Scatchard plots (Fig. S5†) and are given in Table 5. It is obvious that Htolf exhibits a lower $K$ value than its complexes, suggesting that its coordination to Zn(II) results in an increased affinity for BSA. Additionally, the $n$ value of Htolf increases when it is coordinated to Zn(II).

Addition of Htolf or complexes **1–5** to HSA leads to a moderate decrease of the fluorescence signal at 351 nm (Fig. 5(B)) (up to 44% of the initial fluorescence intensity for Htolf, 23% for complexes **1** and **2**, 33% for **3**, 10% for **4** and 14% for **5**) which indicates that their binding to HSA quenches the intrinsic fluorescence of the single tryptophan in HSA.[32]

The calculated values of $K_{SV}$ and $k_q$ as obtained by the slope of the Stern–Volmer diagram (Fig. S6†), eqn (4) and (5), Htolf and **1–5** are given in Table 5 and indicate their good HSA binding propensity and complex **4** exhibits the highest quenching ability. The $k_q$ values (>$10^{12}$ $M^{-1}$ $s^{-1}$) are higher than diverse kinds of quenchers for biopolymer fluorescence ($2.0 \times 10^{10}$ $M^{-1}$ $s^{-1}$) suggesting a static quenching mechanism. From the Scatchard graph (Fig. S7†) and eqn (6), the association binding constant of each compound has been calculated (Table 5) with complexes **2** and **1** exhibiting the highest $K$ values. A comparison of the $n$ values shows that the $n$ value of Htolf increases when it is coordinated to Zn(II) in complexes **1–5**.

Comparing the affinity of the compounds for BSA and HSA ($K$ values), it can be concluded (Table 5) that complexes **3** and **4** show higher affinity for BSA than HSA, while Htolf and complexes **1**, **2** and **5** exhibit higher binding constants for HSA than for BSA. Considering that the binding constant ($K$) between a compound and BSA/HSA should be at an optimum and less than one of the highest protein–ligand binding affinity ($K_{avidin-ligands}$) $\approx 10^{15}$ $M^{-1}$ observed, it is obvious that $K$ values, between $5.70 \times 10^4$ and $4.37 \times 10^5$ (Table 5) are quite below this value suggesting a possible release from the serum albumin to the target cells. If $K$ is too high, the compound won't get released from the SA to the target cells.[34] Therefore, the interaction of tolfenamic acid and its complexes with SA provides useful information concerning their potential application.

In relation to previously reported Cu(II)[20a] and Co(II) mefenamato[20b] as well as the Co(II)-tolfenamato[19] complexes, the Zn(II)-tolfenamato complexes **1–5** present similar or lower $K$ values for BSA and similar or higher $K$ values for HSA.

## Conclusions

The synthesis and characterization of the neutral zinc(II) complexes with the non-steroidal anti-inflammatory drug tolfenamic in the absence or presence of the *N*,*N*′-donor heterocyclic ligands 2,2′-bipyridine or 1,10-phenanthroline has been achieved. The interaction of Zn(II) with the non-steroidal anti-inflammatory drug tolfenamic acid in the absence of the *N*,*N*′-donor ligands leads to the formation of the trinuclear Zn complex $[Zn_3(tolfenamato)_6(CH_3OH)_2]$ where all the tolfenamato ligands act as bidentate ligands forming three asymmetric triatomic carboxylato bridges between the central octahedral Zn and each terminal tetrahedral Zn atom. This arrangement of the carboxylato bridging ligands around the central Zn atom is unique for complexes bearing the formula $[Zn_3(carboxylato)_6(ligand)_2]$. Of course it must be noted that the existence of three symmetric triatomic carboxylato bridges between Zn atoms has been reported once in a complex of the type $[Zn_3(carboxylato)_6(CH_3OH)_6]$ where all the Zn atoms are octahedral.

 

The interaction of equimolar quantities of $ZnCl_2$, tolfenamato and *N*,*N*′-donor ligand results in the formation of complexes of the formula [Zn(tolfenamato)(*N*,*N*′-donor)Cl], while when double molar quantity of the tolfenamato ligand is used, complexes of the formula [Zn(tolfenamato)$_2$(*N*,*N*′-donor)] have been isolated. The crystal structures of the complexes [$Zn_3$(tolf)$_6$-($CH_3OH$)$_2$] **1**, [Zn(tolf)(phen)Cl] **2**, [Zn(tolf)$_2$-(phen)]·$Et_2O$, **4·Et$_2$O** and [Zn(tolf)$_2$(bipy)], **5** have been determined by X-ray crystallography. Comparing the affinity of the compounds for BSA and HSA (*K* values), it can be concluded that complexes **3** and **4** show a higher affinity for BSA than HSA, while Htolf and complexes **1**, **2** and **5** exhibit higher binding constants for HSA than for BSA. Considering that the binding constant (*K*) between a compound and BSA/HSA should be at an optimum and less than one of the highest protein–ligand binding affinities ($K_{avidin-ligands}$) ≈ $10^{15}$ $M^{-1}$ observed, it is obvious that the *K* values observed are quite below suggesting a possible release from the serum albumin to the target cells. If *K* is too high, the compound won't get released from the SA to the target cells. Therefore, the interaction of tolfenamic acid and its complexes with SA provide useful information concerning their potential application.

## Experimental

### Materials: instrumentation and physical measurements

Tolfenamic acid, $ZnCl_2$, $Zn(NO_3)_2·6H_2O$, bipy, phen, KOH, trisodium citrate, NaCl, BSA and HSA were purchased from Sigma-Aldrich Co. and all solvents were purchased from Merck. All the chemicals and solvents were reagent grade and were used as purchased.

Infrared (IR) spectra (400–4000 $cm^{-1}$) were recorded on a Nicolet FT-IR 6700 spectrometer with samples prepared as KBr pellets. UV-visible (UV-vis) spectra were recorded as nujol mulls and in solution at concentrations in the range $10^{-5}$–$10^{-3}$ M on a Hitachi U-2001 dual beam spectrophotometer. C, H and N elemental analysis were performed on a Perkin-Elmer 240B elemental analyzer. Molar conductivity measurements were carried out in 1 mM DMSO solution of the complexes with a Crison Basic 30 conductometer. Fluorescence spectra were recorded in solution on a Hitachi F-7000 fluorescence spectrophotometer.

### Synthesis of the complexes

**[$Zn_3$(tolf)$_6$($CH_3OH$)$_2$], 1.** A methanolic solution (20 mL) containing tolfenamic acid (1 mmol, 260 mg) and KOH (1 mmol, 56 mg) was stirred for 1 h and then was added dropwise to a methanolic solution (10 mL) of $ZnCl_2$ (0.5 mmol, 68 mg). The reaction mixture was stirred for 1 h, filtered and left for slow evaporation. Colorless crystals of [$Zn_3$(tolf)$_6$($CH_3OH$)$_2$], **1** (215 mg, 65%) suitable for X-ray structure determination were deposited after a few days. (Found C, 56.28; H, 4.28; N, 4.38; $C_{86}H_{74}Cl_6N_6O_{14}Zn_3$ (MW = 1824.32) requires C, 56.62; H, 4.09; N, 4.61%). IR: $\nu_{max}/cm^{-1}$ $\nu_{asym}(CO_2)$, 1582 (vs); $\nu_{sym}(CO_2)$, 1397 (vs); $\Delta$ = $\nu_{asym}(CO_2)$–$\nu_{sym}(CO_2)$: 185 $cm^{-1}$ (KBr disk); UV-vis: $\lambda$/nm ($\varepsilon/M^{-1}$ $cm^{-1}$) as nujol mull: 339, 305 (sh(shoulder)); in DMSO: 337(sh) (3400), 303 (15 700). Soluble in DMSO ($\Lambda_M$ = 4 mho $cm^2$ $mol^{-1}$, 1 mM in DMSO), DMF, $CH_3CN$ and ethanol.

**[Zn(tolf)(phen)Cl], 2 and [Zn(tolf)(bipy)Cl], 3.** Tolfenamic acid (0.4 mmol, 105 mg) was dissolved in methanol (15 mL) followed by the addition of KOH (0.4 mmol, 22 mg). After 1 h stirring, the solution was added slowly and simultaneously with a methanolic solution of phen (0.4 mmol, 72 mg) or bipy (0.4 mmol, 62 mg) to a methanolic solution (10 mL) of $ZnCl_2$ (0.4 mmol, 54 mg) and stirred for 30 min. The solutions were left for slow evaporation. Pale yellow crystals of [Zn(tolf)-(phen)Cl], **2** (120 mg, 57%) suitable for X-ray structure determination or microcrystalline product [Zn(tolf)(bipy)Cl], **3** (140 mg, 70%) were deposited after a few days.

[Zn(tolf)(phen)Cl], **2** (Found C, 57.54; H, 3.80; N, 7.47; $C_{26}H_{19}Cl_2N_3O_2Zn$ (MW = 541.71) requires C, 57.65; H, 3.54; N, 7.76%). IR: $\nu_{max}/cm^{-1}$; $\nu_{asym}(CO_2)$: 1578 (vs); $\nu_{sym}(CO_2)$: 1375 (vs); $\Delta$ = 203 $cm^{-1}$ (KBr disk); UV-vis: $\lambda$/nm ($\varepsilon/M^{-1}$ $cm^{-1}$) as nujol mull: 340, 307(sh); in DMSO: 339(sh) (2150), 309 (13 400). Soluble in DMSO ($\Lambda_M$ = 1 mho $cm^2$ $mol^{-1}$, 1 mM in DMSO), DMF, $CH_3CN$, ethanol and $CHCl_3$.

[Zn(tolf)(bipy)Cl], **3** (Found C, 55.40; H, 3.83; N, 7.95; $C_{24}H_{19}Cl_2N_3O_2Zn$ (MW = 517.72) requires C, 55.08; H, 3.70; N 8.12%). IR: $\nu_{max}/cm^{-1}$; $\nu_{asym}(CO_2)$: 1582 (vs); $\nu_{sym}(CO_2)$: 1397 (vs); $\Delta$ = 185 $cm^{-1}$ (KBr disk); UV-vis: $\lambda$/nm ($\varepsilon/M^{-1}$ $cm^{-1}$) as nujol mull: 336(sh), 306; in DMSO: 337(sh) (4900), 304(sh) (15 400). Soluble in DMSO ($\Lambda_M$ = 7 mho $cm^2$ $mol^{-1}$, 1 mM in DMSO), DMF and ethanol.

**[Zn(tolf)$_2$(phen)]·Et$_2$O, 4·Et$_2$O.** The complex was prepared by the addition of a methanolic solution (20 mL) of Htolf (0.4 mmol, 105 mg) and KOH (0.4 mmol, 22 mg), after 30 min of stirring, to a methanolic solution (10 mL) of $Zn(NO_3)_2·6H_2O$ (0.2 mmol, 59 mg) followed by the addition of 20 mL of diethylether and the solution was stirred for 30 min. The resultant precipitate of $KNO_3$ was removed by filtration. In the solution, a methanolic solution (5 mL) of phen (0.2 mmol, 36 mg) was added and the mixture was left for slow evaporation. Colorless crystals of [Zn(tolf)$_2$(phen)]·$Et_2O$, **4·Et$_2$O** (97 mg, 65%) suitable for X-ray structure determination, were deposited after a week. (Found C, 62.53; H, 4.88; N, 7.05; $C_{44}H_{40}Cl_2N_4O_5Zn$ (MW = 841.07) requires C, 62.83; H, 4.79; N, 6.66%). IR: $\nu_{max}/cm^{-1}$; $\nu_{asym}(CO_2)$: 1583 (vs); $\nu_{sym}(CO_2)$: 1387 (vs); $\Delta$ = 196 $cm^{-1}$ (KBr disk); UV-vis: $\lambda$/nm ($\varepsilon/M^{-1}$ $cm^{-1}$) as nujol mull: 337, 303(sh); in DMSO: 335(sh) (3100), 305 (18 500). Soluble in DMSO ($\Lambda_M$ = 8 mho $cm^2$ $mol^{-1}$, 1 mM in DMSO), DMF, $CH_3CN$, ethanol and $CHCl_3$.

**[Zn(tolf)$_2$(bipy)], 5.** A methanolic solution (10 mL) of tolfenamic acid (0.4 mmol, 105 mg) and KOH (0.4 mmol, 22 mg) after 1 h stirring was added dropwise slowly and simultaneously with a methanolic solution (10 mL) of bipy (0.2 mmol, 31 mg) to a methanolic solution (10 mL) of $ZnCl_2$ (0.2 mmol, 27 mg). The resultant solution was left for slow evaporation. Colorless crystals of [Zn(tolf)$_2$(bipy)], **5** (90 mg, 60%) suitable for X-ray structure determination, were collected after a few days. (Found C, 61.05; H, 4.25; N, 7.42; $C_{38}H_{30}Cl_2N_4O_4Zn$ (MW = 742.93) requires C, 61.43; H, 4.07; N, 7.54%). IR: $\nu_{max}/cm^{-1}$; $\nu_{asym}(CO_2)$: 1583 (vs); $\nu_{sym}(CO_2)$: 1394 (vs); $\Delta$ = 189 $cm^{-1}$ (KBr disk); UV-vis: $\lambda$/nm ($\varepsilon/M^{-1}$ $cm^{-1}$) as nujol mull: 333, 304 (sh); in DMSO: 329(sh) (5100), 307(sh) (6400). Soluble in DMSO ($\Lambda_M$ = 3 mho $cm^2$ $mol^{-1}$, 1 mM in DMSO) and DMF.

**Table 6** Crystallographic data for complexes **1**, **2**, **4·Et$_2$O** and **5**

| | **1** | **2** | **4·Et$_2$O** | **5** |
|---|---|---|---|---|
| Formula | $C_{86}H_{74}Cl_6N_6O_{14}Zn_3$ | $C_{26}H_{19}Cl_2N_3O_2Zn$ | $C_{44}H_{40}Cl_2N_4O_5Zn$ | $C_{38}H_{30}Cl_2N_4O_4Zn$ |
| Fw | 1824.32 | 541.71 | 841.07 | 742.93 |
| $T$ (K) | 160(2) K | 160(2) K | 160(2) K | 180(2) K |
| Crystal system | Monoclinic | Monoclinic | Monoclinic | Triclinic |
| Space group | $P2_1/n$ | $P2_1/n$ | $P2_1/c$ | $P\bar{1}$ |
| $a$ (Å) | 14.3955(2) | 9.2336(1) | 12.9035(2) | 10.4238(2) |
| $b$ (Å) | 11.1192(2) | 16.8821(3) | 22.1385(4) | 10.7481(2) |
| $c$ (Å) | 24.9784(4) | 30.6278(5) | 14.6228(2) | 15.3980(3) |
| $\alpha$ (°) | 90.00 | 90.00 | 90.00 | 102.937(1) |
| $\beta$ (°) | 97.750(1) | 95.596(1) | 108.377(1) | 99.004(1) |
| $\gamma$ (°) | 90.00 | 90.00 | 90.00 | 92.532(1) |
| Volume (Å$^3$) | 3961.7(1) | 4751.6(1) | 3964.2(1) | 1654.99(5) |
| $Z$ | 2 | 8 | 4 | 2 |
| D(calc), Mg m$^{-3}$ | 1.529 | 1.514 | 1.409 | 1.491 |
| Abs. coef., $\mu$, mm$^{-1}$ | 3.503 | 3.746 | 2.519 | 2.914 |
| GOF on F$^2$ | 1.054 | 1.034 | 1.134 | 1.166 |
| $R_1$ = | 0.0609[a] | 0.0429[b] | 0.0531[c] | 0.0420[d] |
| w$R_2$ = | 0.1335[a] | 0.1083[b] | 0.1429[c] | 0.1124[d] |

[a] 4420 reflections with $I > 2\sigma(I)$; [b] 7291 reflections with $I > 2\sigma(I)$; [c] 5119 reflections with $I > 2\sigma(I)$; [d] 4260 reflections with $I > 2\sigma(I)$.

### Albumin binding experiments

The protein binding study was performed by tryptophan fluorescence quenching experiments using bovine (BSA, 3 μM) or human serum albumin (HSA, 3 μM) in buffer (containing 15 mM trisodium citrate and 150 mM NaCl at pH 7.0). The quenching of the emission intensity of tryptophan residues of BSA at 343 nm or HSA at 351 nm was monitored using Htolf or complexes **1–5** as quenchers with increasing concentration.[19–21] Fluorescence spectra were recorded from 300 to 500 nm at an excitation wavelength of 295 nm. The fluorescence spectra of Htolf and complexes **1–5** in buffer solutions were recorded under the same experimental conditions and exhibited a maximum emission at 330 nm. Therefore, the quantitative studies of the serum albumin fluorescence spectra were performed after their correction by subtracting the spectra of the compounds.

### X-Ray crystal structure determination

A crystal of **1** (0.05 × 0.14 × 0.18 mm), **2** (0.12 × 0.44 × 0.49 mm), **4** (0.09 × 0.11 × 0.58 mm) and **5** (0.07 × 0.25 × 0.40 mm) was taken from the mother liquor and immediately cooled to −113 °C (for **1**, **2** and **4**) and to −93 °C (for **5**). Diffraction measurements were made on a Rigaku R-AXIS SPIDER Image Plate diffractometer using graphite monochromated Cu Kα radiation (Table 6). Data collection ($\omega$-scans) and processing (cell refinement, data reduction and empirical absorption correction) were performed using the CrystalClear program package.[35] The structures were solved by direct methods using[36] SHELXS-97 and refined by full-matrix least-squares techniques on $F^2$ with SHELXL-97.[37] Further experimental crystallographic details for **1**: $2\theta_{max}$ = 130°; reflections collected/unique/used, 26 010/6453 [$R_{int}$ = 0.0896]/6453; 623 parameters refined; $(\Delta/\sigma)_{max}$ = 0.001; $(\Delta\rho)_{max}/(\Delta\rho)_{min}$ = 0.755/−1.273 e Å$^{-3}$; $R_1$/w$R_2$ (for all data), 0.0863/0.1512. Further experimental crystallographic details for **2**: $2\theta_{max}$ = 130°; reflections collected/unique/used, 33 486/8014 [$R_{int}$ = 0.0439]/8014; 765 parameters refined; $(\Delta/\sigma)_{max}$ = 0.001; $(\Delta\rho)_{max}/(\Delta\rho)_{min}$ = 1.232/−1.319 e Å$^{-3}$; $R_1$/w$R_2$ (for all data), 0.0463/0.1109. Further experimental crystallographic details for **4·Et$_2$O**: $2\theta_{max}$ = 130°; reflections collected/unique/used, 27 185/6546 [$R_{int}$ = 0.0493]/6546; 613 parameters refined; $(\Delta/\sigma)_{max}$ = 0.003; $(\Delta\rho)_{max}/(\Delta\rho)_{min}$ = 1.670/−0.599 e Å$^{-3}$; $R_1$/w$R_2$ (for all data), 0.0653/0.1562. Further experimental crystallographic details for **5**: $2\theta_{max}$ = 130°; reflections collected/unique/used, 19 749/5367 [$R_{int}$ = 0.0272]/5367; 537 parameters refined; $(\Delta/\sigma)_{max}$ = 0.002; $(\Delta\rho)_{max}/(\Delta\rho)_{min}$ = 0.525/−0.451 e Å$^{-3}$; $R_1$/w$R_2$ (for all data), 0.0521/0.1213. Hydrogen atoms were located by difference maps and were refined isotropically or were introduced at calculated positions as riding on bonded atoms. All non-hydrogen atoms were refined anisotropically.

## Abbreviations:

| | |
|---|---|
| bipy | 2,2′-bipyridine |
| BSA | bovine serum albumin |
| COX | cyclo-oxygenase |
| DMF | *N*,*N*-dimethylformamide |
| DMSO | dimethylsulfoxide |
| Et$_2$O | diethylether |
| HSA | human serum albumin |
| Htolf | Tolfenamic acid = 2-[(3-Chloro-2-methylphenyl)-amino]benzoic acid |
| NSAID | non-steroidal anti-inflammatory drug |
| phen | 1,10-phenanthroline |
| SA | serum albumin |
| sh | shoulder |
| vs | very strong |

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