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# Zn(II) complex derived from bidentate Schiff base ligand: Synthesis, characterization, DFT studies and evaluation of anti-inflammatory activity



Mohammad Azam <sup>a, \*</sup>, Saud I. Al-Resayes <sup>a</sup>, Agata Trzesowska-Kruszynska <sup>b</sup>, Rafal Kruszynski <sup>b</sup>, Faiyaz Shakeel <sup>c</sup>, Saied M. Soliman <sup>d, e</sup>, Mahboob Alam <sup>f, \*\*</sup>, Mohammad Rizwan Khan <sup>a</sup>, Saikh Mohammad Wabaidur <sup>a</sup>

<sup>a</sup> Department of Chemistry, College of Science, King Saud University, P. O. Box 2455, Riyadh, 11451, Saudi Arabia

<sup>b</sup> Institute of General and Ecological Chemistry, Lodz University of Technology, Zeromskiego 116, 90-924, Lodz, Poland

<sup>c</sup> Department of Pharmaceutics, College of Pharmacy, King Saud University, P. O. Box 2457, Riyadh, 11451, Saudi Arabia

<sup>d</sup> Department of Chemistry, Rabigh College of Science and Art, King Abdulaziz University, P.O. Box 344, Rabigh, 21911, Saudi Arabia

<sup>e</sup> Department of Chemistry, Faculty of Science, Alexandria University, P. O. Box 426, Ibrahimia, Alexandria, 21321, Egypt

<sup>f</sup> Division of Chemistry and Biotechnology, Dongguk University, 123 Dongdae-ro, Gyeongju, Republic of Korea

# A R T I C L E I N F O

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# ABSTRACT

A novel zinc complex was prepared by the reaction of one equivalent of a bidentate Schiff base, N,N'bis(2-chlorobenzylidene)-2,2-dimethylpropane-1,3-diamine, L with one equivalent of zinc chloride in methanol, and characterized by elemental analyses, NMR, IR and single crystal X-ray crystallography. The crystallographic studies revealed that the zinc ion in the complex is coordinated to two imine nitrogen atoms of L and two chloride ions of zinc chloride. Furthermore, to obtain insights into the structure and bonding, density functional theory (DFT) calculations were performed. The obtained results were found to be similar with the results obtained from the experimental findings. In addition, the antiinflammatory activity of the studied zinc complex was also evaluated. The results obtained showed the studied complex could be a good candidate in treatment of inflammatory disorders.

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# 1. Introduction

Over the years, zinc based complexes have shown diverse medicinal applications such as anti-inflammatory, anticonvulsant, antimicrobial, antidiabetic, antioxidant and anti-proliferative activities [1–10]. In addition, several zinc complexes are used as a major ingredient of the medicine used in the treatment of skin diseases [11], and find significant use as a catalyst in various catalytic reactions [1]. In last few decades, Schiff bases have emerged as strong chelating ligands in coordination chemistry [12] due to their ease in synthesis, structural variation [13] and several biological, catalytic and industrial applications [14–16]. The zinc complexes

\*\* Corresponding author.

derived from Schiff bases are extensively studied due to their wide applications in material and biological science [17,18]. In recent years, the pioneer work of Chai and co-workers have explored various transition metal complexes based on Schiff bases and their applications [19–25].

Non-steroidal anti-inflammatory drugs (NSAIDs) are the frequently used analgesic, anti-inflammatory and antipyretic medicines [26]. However, the use of these medicines is associated to several side effects [26–28]. Therefore, to overcome these problems, there are many reports showing that the therapeutic behavior of the drug is improved upon coordination to the metal ions as the metal complexes have higher lipophilicity enabling them to pass quickly from cell membrane to exert their effect [29]. Therefore, considering the medicinal and biological properties of Schiff base and zinc ion, we are reporting here a novel zinc complex derived from L and its characterization by elemental analyses, Infrared spectroscopy (IR), Nuclear Magnetic Resonance (NMR) spectroscopy and single crystal X-ray crystallography. Furthermore,

<sup>\*</sup> Corresponding author.

*E-mail addresses:* mhashim@ksu.edu.sa, azam\_res@yahoo.com (M. Azam), mahboobchem@gmail.com (M. Alam).

to obtain insights into the structure, theoretical studies of the complex are also carried out. In addition, we are also reporting the anti-inflammatory efficacy of the studied Zn(II) complex.

# 2. Experimental

# 2.1. Materials and methods

All the chemicals used in the experiment were procured from commercial sources. The bidentate Schiff base ligand, L was prepared as cited in the literature [30].

Synthesis of bis(chloro)-(N,N'-(2,2-dimethylpropane-1,3-diyl) bis(1-(2-chlorophenyl)-methanimine))-zinc(II).

Zinc chloride (90 mg, 0.66 mmol) was added gradually into the methanolic solution of L (229 mg) [30] in equimolar ratio followed by the stirring of the resulting reaction mixture for 3 h [Scheme 1]. Slight turbidity appeared, which was removed by filtration. The colorless prismatic crystals were obtained by slow evaporation of filtrate at room temperature.

Yield 65%, mp 165 °C; Molecular Formula  $C_{19}H_{20}Cl_4N_2Zn$ ; Analytical Calc.: C, 47.19; H, 4.17; N, 5.79; Found: C, 47.11; H, 4.13; N, 5.75%; <sup>1</sup>H NMR (DMSO-*d*<sub>6</sub>): (ppm): 8.63 (2H, s, -CH=N), 7.99–7.46 (8H, m, Ar–H), 3.51 (4H, s,  $-CH_2$ ), 0.99 (6H, s, (CH<sub>3</sub>)<sub>2</sub>C-); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): (ppm) 157.3 (-CH=N), 133.8 (-C-CH=N), 132.7 (-C-Cl), 132–127.5 (Ar–C), 69.4 (-CH<sub>2</sub>-N), 36.6 (CH<sub>2</sub>)<sub>2</sub>–C-, 24.4 (-C(CH<sub>3</sub>)<sub>2</sub>).

# 2.2. Crystal structure determination

The single crystal for the complex was measured at 100.0 (1) K in the environment of helium using Bruker APEXII automatic diffractometer with CCD detector using graphite monochromated CuK<sub> $\alpha$ </sub> ( $\lambda$  = 1.54178) radiation. The crystal details are specified in Tables 1–3. The Lorentz, polarization and numerical absorption [31,32] corrections were performed during the data reduction. SHELXS [32], SHELXL [33] and SHELXTL programs [34] were used in solving the structure.

# 2.3. Computational studies

Geometry optimizations of the free ligand and its Zn(II) complex were performed using density functional method employing mPW1PW91 functional [35a] and TZVP basis sets [35b] with the aid of Gaussian 09 program package [36]. Atomic charges were calculated using the built in NBO 3.1 program [37] in the Gaussian 09 software. Moreover, atoms in molecules (AIM) topological parameters were computed [38] using Multwfn program [39,40].

# 2.4. Hirshfeld surface analysis

Crystal Explorer 3.1 software [41] was used to perform the Hirshfeld surface analysis [42–45]. The fingerprint (FP) plot [46] was used to summarize the intermolecular contacts in the crystal

### Table 1

Crystal and structure refinement data of Zn (II) complex.

Compound	1
Empirical formula	$C_{19}H_{20}Cl_4N_2Zn$
Formula weight	483.54
Crystal system, space group	monoclinic, $P2_1/c$ (No.14)
Unit cell dimensions [Å, °]	a = 10.0761 (3)
	b = 15.4015 (5)
	c = 13.8575 (4)
	$\beta = 103.1180$ (10)
Volume [Å <sup>3</sup> ]	2094.39 (11)
Z, Calculated density [Mg/m <sup>3</sup> ]	4, 1.534
F(000)	984
Crystal size [mm]	0.075, 0.069, 0.066
$\theta$ range for data collection [°]	4.356 to 72.572
Index ranges	$-12 \le h \le 12, -18 \le k \le 19, -17 \le 1 \le 17$
Reflections collected/unique	$23219/4142 [R_{(int)} = 0.0241]$
Completeness [%]	99.9 (to $\theta = 67^{\circ}$ )
Data/restraints/parameters	4142/0/237
Goodness-of-fit on F <sup>2</sup>	1.136
Final R indices $[I > 2\sigma(I)]$	R1 = 0.0229, w $R2 = 0.0559$
R indices (all data)	R1 = 0.0230, w $R2 = 0.0559$
Largest diff. Peak and hole [e•Å <sup>-3</sup> ]	0.396, -0.297

Table 2
Selected bond distances and angles for Zn(II) complex [Å,
°].

,	
Zn1-N2	2.0611 (12)
Zn1-N1	2.0682 (12)
Zn1–Cl4	2.2130 (4)
Zn1–Cl3	2.2140 (4)
C7-N1	1.275 (2)
N1-C8	1.4752 (18)
C12-N2	1.4745 (19)
N2-C13	1.276 (2)
N2-Zn1-N1	92.23 (5)
N2-Zn1-Cl4	115.83 (4)
N1–Zn1–Cl4	103.85 (4)
N2-Zn1-Cl3	101.78 (4)
N1–Zn1–Cl3	118.43 (4)
Cl4–Zn1–Cl3	121.378 (17)

# Table 3

Hydrogen bond lengths and angles for Zn(II) complex [Å,  $^\circ\mbox{]}.$ 

D—H•••A	d (D-H)	d (H•••A)	d (D•••A)	<(DHA)
C7–H7…Cl1	0.95	2.71	3.0197 (16)	99.5
C13–H13…Cl2	0.95	2.70	3.0180 (16)	100.6
C13–H13…Cl4 <sup>i</sup>	0.95	2.70	3.4534 (15)	136.2
C16–H16…Cl3 <sup>ii</sup>	0.95	2.64	3.5792 (17)	168.0

Symmetry transformations used to generate equivalent atoms: (i) x, -y+1/2, z+1/2; (ii) x-1, y, z.



Schiff base igand, L

Zinc chloride

Scheme 1. Synthesis of Zn(II) complex.

Zn(II) complex

a)

H16

# [20,22,47].

# 2.5. Pharmacodynamics studies in wistar rats

Pharmacodynamics studies in terms of anti-inflammatory efficacy were carried out on studied zinc(II) complex, and its results were compared with that of the standard diclofenac drug by the "Carrageenan-induced hind paw edema method" [48]. For these studies, eighteen male Wistar rats (200-250 g of weights) were taken from "Animal Care and Use Center of College of Pharmacy at King Saud University, Riyadh, Saudi Arabia" and kept under standard laboratory conditions of "temperature and relative humidity" in plastic cages (n = 6.0 rats in each cage), and fed to the "standard laboratory pellet diet and water ad libitum". The animals were divided into 3 groups (n = 6/group). The animals of group I were given Carrageenan only, and considered as control group. However, the animals of groups II and III were given the standard diclofenac and the studied Zn(II) complex, respectively. The doses for standard diclofenac and the studied Zn(II) complex were 4 mg/kg and 10 mg/ kg, respectively. Paw edema in all three groups was induced by injecting 0.1 ml suspension of Carrageenan (1% w/v). It was induced in right paw. Both compounds were administered orally 30 min before induction of paw edema. The initial and final paw volumes for each animal were estimated regularly at 1, 2, 3, 4, 5 and 6 h after injection using an electronic "Plethysmometer (Ugo Basile, Italy)". The anti-inflammatory efficacy in terms of % inhibition for the standard diclofenac drug and the studied zinc(II) complex treated groups was estimated as proposed in literature [48,49]. The results of anti-inflammatory efficacy were analyzed statistically by applying student t-set using MS Excel 2010 program. The value of P at 5% level of significance (P < 0.05) was proposed as significant value.

# 3. Results and discussion

X-ray analysis revealed that the studied complex exits in 1:1 metal ligand stoichiometric ratio, which is contrary to the work of Chai et al. [19,20,22-24]. A perspective view of studied zinc(II) complex is shown in Fig. 1. The compound possesses complex molecules formed from bis(chloro)-(N,N'-(2,2-dimethylpropane-1,3-diyl)bis (1-(2-chlorophenyl)methanimine)) ligand, the Zn<sup>2+</sup> cation and two chloride anions and adopts slightly distorted tetrahedral geometry [50]. Oppositely to the work of Chai et al. [19–25], the two chloride ions are bonded to zinc ion in the studied complex. However, similar to the work of Chai et al. [19–25], zinc ion is coordinated to the imine nitrogen atoms in the title complex. The sum of interbond angles centred at metal atom is 653.5°, which is close to the sum of these angles ideal tetrahedron (657°) and differs from ideal values for square planar geometry (720°) and tshape geometry (630°). The 1-(2-chlorophenyl)methanimine) moieties are distinctly distorted from planarity (N=C-C<sub>Ph</sub>-C<sub>Ph</sub> torsion angles are -32.9(2) and  $-35.4(2)^{\circ}$ ), oppositely to the similar compound in which analogous moieties are planar [51]. The general molecular geometry of coordination moiety is similar to cadmium compound [30], however, the intermolecular interaction scheme is distinctly different in these compounds. In addition, the studied complex shows the coordination of two chloride ions to zinc ion. Nevertheless, similar to the work of Chai et al., zinc ion in this complex is coordinated to two imine nitrogen atoms [19–25].

The molecules of the studied complex are linked by two structurally different weak C-H···Cl intramolecular hydrogen bonding interactions [52] (Table 3) to the hydrogen bonded layers extending along crystallographic (010) plane (in above mentioned cadmium coordination compound, there are no distinguishable intermolecular hydrogen bonds, even the weak ones), and form the C(5) and C





H11A

H10A

H10C

H10B

H13

214

218

C19

H19

C15

C16

C17

H11C

Fig. 1. A ortep view with 50% probability of displacement ellipsoids showing (a) atoms connectivity (hydrogen atoms are drawn as spheres of arbitrary radii) (b) ligand conformation (hydrogen atoms are omitted for clarity).

(8) motifs of lowest degree of the unitary graph set [53,54].

# 3.1. Density functional theory (DFT) studies

The optimized molecular geometry of the ligand and its Zn(II) complex are shown in Fig. 2. The cartesian coordinates of the optimized structures are given in Supplementary data. The calculated Zn-Cl (2.221 Å) and Zn-N (2.133 Å) bond distances are slightly higher than the experimental findings (Table 2) by 0.007-0.008 Å and 0.065-0.072 Å, respectively. However, the ligand configuration changed very slightly due to its coordination to Zn(II) ion, indicating that the complexation between the ligand and zinc(II) ion produced slight lengthening in C=N bonds which doesn't exceed 0.007 Å (Table 2). The C-N bonds of the ligand optimized structure were calculated to be 1.264 Å while it was found to be 1.275 Å (calc. 1.271 Å) for the complex. However, the most noticeable changes occurred for the phenyl moieties attached to C=N groups. The N2-C13-C14-C19 and N1-C7-C1-C6 dihedral angles are only 4.8° in the free ligand. However, the value increased significantly to 37.0° (exp. 32.9-35.4°) in the complex. It is clear that the complexation with zinc chloride produced significant twist for the phenyl moieties via free rotation around the C13-C14 and C7-C1 bonds, respectively to minimize the steric repulsion obtained due to the complexation with zinc ion, and leave enough space for zinc(II) ion to bind with the donor atoms of ligand.

The atomic charges computed using NBO method are given in Table 4. The charge of the Zn(II) ion is reduced to 0.97 e due to its coordination with the ligand, and this value is very close to the value obtained from the single crystal X-ray structure (exp. 0.94 e). The two chloride anions reduced its charge by 0.75 e while the organic ligand transferred 0.27 e (exp. 0.31 e) to Zn(II) ion. Moreover, the charges of the donor atoms are shifted to higher negative

H3



Fig. 2. The optimized molecular geometry of the free ligand and its Zn(II) complex.

#### Table 4

Natural atomic charges in the free ligand and its Zn(II) complex.

Atom	Zn(II) complex <sup>a</sup>	Free ligand
Zn1	0.9725 (0.9412)	_
Cl1	-0.6233(-0.6244)	
Cl2	-0.6234(-0.6231)	
N1	-0.4640(-0.4444)	-0.3847
N2	-0.4640(-0.4465)	-0.3847
Ligand	0.2742 (0.3063)	_

<sup>a</sup> Values inside parentheses at the experimental geometry.

charge of 0.079 e due to the complexation between zinc(II) ion and the ligand. Another significant observation noticed is the large change in the dipole moment of Zn(II) complex in comparison to the free ligand. The former has dipole moment of 4.53 D compared to 1.15 D for the latter. Electron density mapped over molecular electrostatic potential (MEP) maps for the studied compounds showing the orientation of the dipole moment vector are shown in Fig. 3.

The frontier molecular orbitals of the studied compounds are shown in Fig. 4. The highest occupied molecular orbital (HOMO) and Lowest unoccupied molecular orbital (LUMO) of the free ligand are distributed over its delocalized  $\pi$ -system, and their calculated energies are -7.076 and -1.596 eV, respectively. In case of Zn(II) complex, the LUMO is almost the same while the HOMO is localized over the coordinated chloride ion. Both of the HOMO (-7.178 eV) and LUMO (-2.087 eV) frontier molecular orbitals are stabilized in the complex compared to the free ligand. It is clear that the

complexation between Zn(II) ion and the ligand reduced the HOMO-LUMO energy gap from 5.467 eV to 5.091 eV.

# 3.2. AIM study

AIM topological parameters were applied to predict the nature and strength of Zn–N and Zn–Cl bonds by using the electron density ( $\rho(r)$ ), its laplacian ( $\nabla^2 \rho(r)$ ), the total energy density H(r), and the ratio of electron potential to kinetic energy density (|V(r)|/G(r)|) (Table 5). It is worth mentioning that the  $\rho(r)$  values are around  $10^{-2}$  a. u for the Zn–N and Zn–Cl bonds in the studied complex, suggesting the dominance of closed shell interactions [55]. Furthermore, these values agree with the positive  $\nabla^2 \rho(r)$  ones [56]. Thus, it can be concluded that all the Zn–N and Zn–Cl bonds have positive H(r) values and  $|V(r)|/G(r)^{<1}$  [40]. In addition, values of the interaction energies [57] listed in table 5 conform that the studied complex has almost two equivalent Zn–N and two equivalent Zn–Cl interactions.

## 3.3. The hirshfeld surfaces analyses

The results of the Hirshfeld analysis are shown in Fig. 5. The decomposed FP plots were employed to quantitatively investigate the intermolecular interactions (Fig. 6). The results shed the light on the significance of H…H (40.2%), C…H (12.8%), Cl…H (34.2%) and Cl…C (8.3%) contacts. The shortest contact distances for these interactions are 2.347, 3.476, 2.515, and 3.532 Å, respectively. The non-covalent bonding interactions have shorter contact distances in comparison to the sum of the van der Waals radii of C1 .... H



Fig. 3. MEP maps of the free ligand and its Zn(II) complex.



Fig. 4. The frontier molecular orbitals of the studied compounds.

Table 5 The topological data at the bond critical points for the Zn–N and Zn–Cl interactions.

Bond	$\rho(r)^{a}$	G(r) <sup>a</sup>	V(r) <sup>a</sup>	H(r) <sup>a</sup>	$\nabla^2 \rho(r)$	V(r) /G(r)	Eint <sup>b</sup>
Zn-N	0.0512	0.1029	-0.0985	0.0044	0.4291	0.96	30.91
Zn-N	0.0523	0.1053	-0.1010	0.0042	0.4380	0.96	31.70
Zn-Cl	0.0427	0.0914	-0.0841	0.0073	0.3947	0.92	26.39
Zn-Cl	0.0428	0.0917	-0.0844	0.0073	0.3959	0.92	26.49

<sup>a</sup> a.u.

<sup>b</sup>  $E_{int}$ =-V(r)/2 in kcal/mol.

hydrogen bonding interactions and displayed as red dots on the  $d_{norm}$  map and gave sharp spikes in the fingerprint plot of the studied compound. Intermolecular contacts such as  $H \cdots H$  and Cl

 $\cdots$  C have interaction distances somewhat higher than the sum of the van der Waals radii of the two elements and appear in the corresponding d<sub>norm</sub> map as white regions. The interactions occurring in the blue regions of the d<sub>norm</sub> map represent weak C  $\cdots$ H interactions, and have considerably greater contact than the vdW radii sum of the C and H atoms. The  $\pi$ - $\pi$  stacking interactions that occur in aromatic rings in general are not specified by the use of shape index and curvature maps.

<sup>1</sup>H NMR spectrum of Zn(II) complex revealed the presence of imine proton at 8.63 ppm. The proton resonances attributed to methyl and methylene protons were found at 0.99 and 3.51 ppm, respectively. The multiplet due to aromatic protons (m, 8H, Ar–H) is noticed at 7.46–7.99 ppm. The <sup>13</sup>C NMR spectrum exhibited the



Fig. 5. Hirshfeld surfaces and decomposed fingerprint plots of the most important intermolecular interactions in the studied compound.



Fig. 6. All possible intermolecular contacts and their percentage.

carbon signal due to -**C**H=N at 157.35 ppm [Supporting Information Fig. S1]. The carbon signals due to Ar-**C**-Cl and Ar-**C**-CH=N appeared at 132.7 ppm and 133.8 ppm, respectively, while the remaining aromatic carbon signals appeared at 132, 129.8, 128.2 and 127.5 ppm. The appearance of signal at 69.4 ppm is assigned to -CH<sub>2</sub> carbon. Furthermore, the quaternary and methyl carbon signal appeared at 36.6 ppm and 24.4 ppm, respectively [Supporting Information Fig. S2].

The anti-inflammatory efficacy of the studied Zn(II) complex was compared with that of the standard diclofenac drug and their

results are given in Fig. 7. The anti-inflammatory efficacy of the standard diclofenac drug increased (82.31%) with respect to time for up to 5 h. However, after 5 h, there was noticed slight decrease in the anti-inflammatory efficacy of the standard diclofenac drug (Fig. 7). On the other hand, the studied zinc complex showed increase in the anti-inflammatory efficacy for up to 6 h as shown in Fig. 7. But this is worth to mention that the increase in the antiinflammatory efficacy of the zinc(II) complex was significant for up to 4h(P < 0.05). However, after 4h, the enhancement in antiinflammatory efficacy of the studied zinc(II) complex was not significant (P > 0.05). Thus, it can be concluded that the antiinflammatory efficacy of the standard diclofenac was significant on comparing with that of the studied Zn(II) complex at each time interval (P < 0.05). Although, the anti-inflammatory efficacy of studied Zn(II) complex was not statistically significant as compared with that of the standard diclofenac drug (P > 0.05), but the studied compound showed good anti-inflammatory efficacy in Wistar rats, which is likely due to the inhibition of various inflammatory mediators. However, on comparing the anti-inflammatory efficacy of the studied zinc complex with that of ketoprofen complexed with Zn(II) ions after 3 h of oral administration [58], we found that the anti-inflammatory efficacy of the studied Zn(II) complex was 42.8% at 10 mg/kg dose, whereas the Zn(II) ion complexed with ketoprofen showed 62.5% at 10 mg/kg dose [58], thus suggesting the low anti-inflammatory efficacy for the studied zinc complex than that of the ketoprofen-Zn(II) complex.

# 4. Conclusion

A novel zinc(II) complex with slight distorted tetrahedral geometry derived from a bidentate Schiff base ligand was investigated. The studied complex exhibited good *in vivo* antiinflammatory activity when tested in Wistar rats.



Fig. 7. In vivo anti-inflammatory effects of studied Zn(II) complex and standard diclofenac in Wistar rats.

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# Appendix A. Supplementary data

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