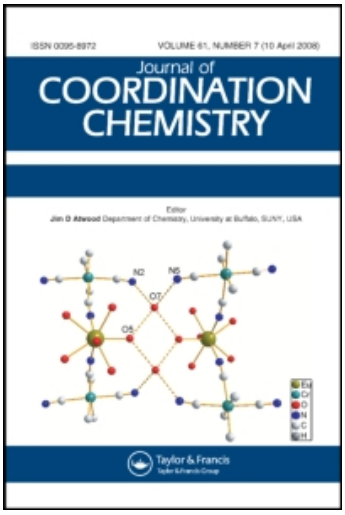

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Zinc(II) 5-(2'-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates and their adducts with N and P donor ligands: synthesis, spectral, biological, and anti-inflammatory investigations

K. V. Sharma[a]; Vandana Sharma[a]; U. N. Tripathi[b]
[a] Department of Engineering Chemistry, Mahakal Institute of Technology, Ujjain 456664, India [b] Department of Chemistry, D.D.U. Gorakhpur University, Gorakhpur 273001, India

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Zinc(II) 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates and their adducts with N and P donor ligands: synthesis, spectral, biological, and anti-inflammatory investigations

K.V. SHARMA*†, VANDANA SHARMA† and U.N. TRIPATHI‡

†Department of Engineering Chemistry, Mahakal Institute of Technology, Ujjain 456664, India
‡Department of Chemistry, D.D.U. Gorakhpur University, Gorakhpur 273001, India

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Synthesis, spectral, biological, and anti-inflammatory investigations of a series of complexes of zinc(II) with 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolines of the type $(C_{15}H_{12}N_2OX)_2Zn$ (where X = –H, –Cl, $–CH_3$, $–OCH_3$) are presented. The complexes were synthesized by reaction of anhydrous zinc(II) chloride with sodium salts of pyrazoline in 1 : 2 molar ratio. Adducts with N and P donor ligands (2,2′-bipyridine, 1,10-phenanthroline and triphenylphosphine) were prepared in 1 : 1 molar ratio. The complexes were characterized by elemental analyses, molecular weight, conductivity, IR, electronic, ^1H, ^{13}C, ^{31}P NMR, and FAB mass spectral studies. All complexes are amorphous. Tetrahedral geometry around zinc confirms the presence of two bidentate pyrazoline ligands in zinc(II) 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates. In adducts pyrazoline is monodentate. Bidentate and monodentate pyrazoline were confirmed by IR, ^1H, ^{13}C, and ^{31}P NMR spectral data. All metal complexes were tested for their antibacterial and antifungal activities. Anti-inflammatory activity was also carried out by the carrageenan-induced rat paw edema test. Brine shrimp bioassay was also carried out to study *in-vitro* cytotoxic properties.

Keywords: Anti-inflammatory activity; Biological activity; Cytotoxicity; Zinc(II) pyrazolinates; Pyrazoline; Triphenylphosphine; 1,10-Phenanthroline; 2,2′-Bipyridine

1. Introduction

Zinc is an essential element for function of more than 300 metalloenzymes, and the highly proliferative immune system is reliant on Zn-dependent proteins involved in general cellular functions such as replication, transcription and signal transduction [1]. Thus, coordination chemistry of zinc is of considerable interest [2]. Coordination chemistry of pyrazoline has also received attention, primarily due to biological implications. Binding of zinc with flexible biologically relevant ligands [3] can lead to an open position at the metal, beneficial for catalytic reactions [4]. About 20 zinc enzymes are known, in which zinc is tetrahedral [5, 6]. Zn(II) complexes with organic molecules were also used in clinical medicine, e.g., complex of zinc(II) acetate with erythromycin

*Corresponding author. Email: sharmak_v@yahoo.co.in

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acne therapy [7]. In general, organic ligands contribute to better transport of metal ions through the lipophillic regions of cell membranes; and antibacterial effects of various drugs can be enhanced when chelated to metal [8].

We have already drawn attention [9–13] to complexation of pyrazoline with metals, i.e., iron, cobalt, nickel, and copper. In this article, we describe the synthesis, spectral, antibacterial, antifungal, and anti-inflammatory investigations of zinc(II) 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazoline complexes (X = –H, –Cl, $–CH_3$, $–OCH_3$) and their adducts with N and P donor ligands.

2. Experimental

2.1. *Materials*

All solvents, i.e., ethanol, isopropanol, chloroform, dimethylformamide (DMF), dimethylsulphoxide (DMSO), pyridine, were of analytical grade quality and dried and distilled before use according to standard procedures [14]. Reagents zinc chloride(anhydrous), benzaldehyde, *p*-chlorobenzaldehyde, *p*-methylbenzaldehyde, *p*-methoxybenzaldehyde, *o*-hydroxyacetophenone, sodium hydroxide, hydrochloric acid, acetic acid, hydrazine hydrate, 2,2′-bipyridine, 1,10-phenanthroline, and triphenylphosphine were used as received without purification. The preparation of 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazoline ligand was carried out according to the reported method [15].

2.2. *Synthesis of 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of zinc*

Zinc(II) pyrazolinates were prepared by the following route:

$$ZnCl_2 + 2(C_{15}H_{12}N_2OX)Na \xrightarrow[\text{Room Temp.}]{\text{Isopropanol}} (C_{15}H_{12}N_2OX)_2Zn + 2\ NaCl$$
$$(X = -H, -Cl, -CH_3, -OCH_3)$$

Freshly cut sodium was taken in a flask containing isopropanol and refluxed (~0.5 h) until a clear solution of sodium isopropoxide was obtained. Solution of 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazoline (X = –H, –Cl, $–CH_3$, $–OCH_3$) in isopropanol was added and reaction was continued for 1 h until a constant yellow was obtained. The reaction mixture was cooled to room temperature and ethanolic solution of anhydrous zinc(II) chloride was added dropwise with constant stirring. The reaction mixture was further stirred for 20–24 h until the color changed from yellow to cream. The reaction mixture was filtered under vacuum and the solid was washed with hot water and alcohol, and then dried at 100°C. The data for synthesis of individual compounds are given in table 1.

2.3. *Synthesis of adducts of 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of zinc with N and P donors*

A weighed amount of zinc(II) pyrazolinate was dissolved in dry chloroform and to this a chloroform solution of 2,2′-bipyridine, 1,10-phenanthroline or triphenylphosphine

Table 1. Synthetic, analytical and physical data for 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of zinc.

Sl. no. (Compd. no.)	Reactants			Molar ratio	Product (color)	Yield %	m.p. (°C)	Mol. Wt. Found (Calcd)	Analysis, % Found (Calcd)			
	Anhydrous $ZnCl_2$ g (mmol)	Sodium g (mmol)	Ligand g (mmol)[a]						C	H	N	Zn
1	0.76 (5.56)	0.26 (11.12)	HPPP 2.64 (11.12)	1 : 2 : 2	$Zn(L_a)_2$ (Cream)	94	>360	538.23 (539.39)	66.45 (66.89)	4.45 (4.85)	10.58 (10.39)	12.38 (12.12)
2	0.67 (4.92)	0.23 (9.84)	HPCPP 2.69 (9.84)	1 : 2 : 2	$Zn(L_b)_2$ (Cream)	88	>360	609.10 (609.39)	59.37 (59.13)	3.67 (3.97)	9.18 (9.20)	10.69 (10.73)
3	0.72 (5.29)	0.24 (10.57)	HPMPP 2.66 (10.57)	1 : 2 : 2	$Zn(L_c)_2$ (Cream)	74	225	567.18 (567.39)	68.56 (67.74)	5.78 (5.33)	9.82 (9.87)	11.65 (11.52)
4	0.68 (5.00)	0.23 (10.01)	HPMeoPP 2.68 (10.01)	1 : 2 : 2	$Zn(L_d)_2$ (Cream)	84	>360	599.82 (599.39)	64.30 (64.12)	5.12 (5.05)	9.36 (9.35)	10.84 (10.91)

Note: [a]HPPP, L_a = 5-(2′-hydroxyphenyl)-3-phenylpyrazoline; HPCP, L_b = 5-(2′-hydroxyphenyl)-3-(4-chlorophenyl)pyrazoline; HPMPP, L_c = 5-(2′-hydroxyphenyl)-3-(4-methylphenyl)pyrazoline; HPMeoPP, L_d = 5-(2′-hydroxyphenyl)-3-(4-methoxyphenyl)pyrazoline.

was added dropwise with constant stirring for 24 h at room temperature. Reaction mixture was filtered under vacuum to collect the solid, which was first washed with distilled water and then with ethanol and dried at 100°C. The data for synthesis of individual compounds are given in tables 2–4.

2.4. *Physical measurements*

The IR spectra were recorded as KBr pellets on a Perkin–Elmer Spectrum RX1 spectrophotometer. Molecular weights were determined on a Knoauer Vapour pressure Osmometer in $CHCl_3$ at 45°C. Elemental analysis of zinc was done gravimetrically by standard procedure [16]. Carbon, hydrogen and nitrogen were estimated on an Elementor Vario ELIII Carlo1108 elemental analyzer. The molar conductivities of the complexes were determined in DMSO (1.0×10^{-3} M) at room temperature using a Systronics conductivity meter model-303. Electronic absorption spectra were recorded in chloroform/pyridine solution on a Perkin–Elmer Lambda 15 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DRX-300 spectrometer at room temperature. FAB mass spectra were recorded on a JEOL SX 102/DA-6000 mass spectrometer. The ^{31}P NMR spectra were recorded in solid state on a Bruker Advance DRX-300 spectrometer at room temperature. The complexes were examined for crystalline/amorphous nature through XRD on a Philips compact X-ray diffraction analyzer model PW 1710.

2.5. *Biological activity*

All biological activity studies (antibacterial, antifungal, and cytotoxicity) were conducted as previously reported [11–13].

2.6. *Anti-inflammatory activity*

Anti-inflammatory activity was determined by the carrageenan-induced rat paw method of Winter *et al*. [17]. Adult male wister albino rats (90–125 g) were fasted for 18 h, but with access to water. Each treatment, i.e., standard drug and Zn(II) complexes of 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazoline was administered at a dose of $100\,mg\,kg^{-1}$ body weight orally in 0.2% CMC suspension. Acute edema was induced in the right hind paw of rats by injecting 0.1 mL of freshly prepared 1% w/v of aqueous solution of carrageenan (Sigma, USA) in the subplanter region of right hind paw. After carrageenan injection the paw volume was measured before and after 1, 2, and 3 h by plethysmometer (UGO-Basile, Italy). The difference between the left and right paw was taken as a measure of edema. Any significant reduction in the volume of the paw compared to the control group was considered as anti-inflammatory response. The percent inhibition of inflammation after 3 h was calculated by applying the Newbould [18] formula:

$$\%\ \text{Inhibition}, I = 100[1 - (a - x/b - y)]$$

where x = mean paw volume of rats before the administration of carrageenan injection in the test and standard group, a = mean paw volume of rats after the administration of

Table 2. Synthetic, analytical and physical data for adducts of 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of zinc with 2,2′-bipyridine.

Sl. no. (Compd. no.)	Reactants: Complex g (mmol)	Reactants: 2,2′-Bipyridine $C_{10}H_8N_2$ g (mmol)	Molar ratio	Product (color)	Yield %	m.p. (°C)	Mol. Wt. Found (Calcd)	Analysis, % Found (Calcd): C	H	N	Zn
5	$Zn(L_a)_2$ 1.55 (2.87)	0.44 (2.87)	1 : 1	$Zn(L_a)_2$(bipy) (Cream)	90	> 360	694.32 (695.58)	69.28 (69.07)	4.96 (4.93)	12.02 (12.08)	9.85 (9.91)
6	$Zn(L_b)_2$ 1.59 (2.61)	0.40 (2.61)	1 : 1	$Zn(L_b)_2$(bipy) (Cream)	83	> 360	762.98 (765.58)	62.45 (62.76)	4.23 (4.21)	10.54 (10.98)	8.37 (8.54)
7	$Zn(L_c)_2$ 1.56 (2.76)	0.43 (2.76)	1 : 1	$Zn(L_c)_2$(bipy) (Cream)	84	> 360	725.25 (723.58)	69.57 (69.72)	5.49 (5.30)	11.59 (11.61)	9.10 (9.04)
8	$Zn(L_d)_2$ 1.58 (2.64)	0.41 (2.64)	1 : 1	$Zn(L_d)_2$(bipy) (Cream)	88	> 360	755.12 (755.58)	66.85 (66.76)	5.01 (5.07)	11.10 (11.12)	8.62 (8.65)

Table 3. Synthetic, analytical and physical data for adducts of 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of zinc with 1,10-phenanthroline.

Sl. no. (Compd. no.)	Reactants: Complex g (mmol)	Reactants: 1,10-Phenanthroline $C_{12}H_8N_2$ g (mmol)	Molar ratio	Product (color)	Yield %	m.p. (°C)	(Mol. Wt. Found Calcd)	Analysis, % Found (Calcd): C	H	N	Zn
9	$Zn(L_a)_2$ 1.49 (2.77)	0.50 (2.77)	1 : 1	$Zn(L_a)_2$(phen) (Cream)	88	>360	718.3 (719.6)	70.25 (70.10)	4.65 (4.76)	11.65 (11.68)	9.04 (9.08)
10	$Zn(L_b)_2$ 1.54 (2.53)	0.45 (2.53)	1 : 1	$Zn(L_b)_2$(phen) (Cream)	87	340	788.2 (789.6)	63.74 (63.89)	4.10 (4.08)	10.60 (10.64)	8.45 (8.28)
11	$Zn(L_c)_2$ 1.51 (2.67)	0.48 (2.67)	1 : 1	$Zn(L_c)_2$(phen) (Cream)	89	>360	746.9 (747.6)	70.54 (70.69)	5.27 (5.12)	11.29 (11.24)	8.74 (8.75)
12	$Zn(L_d)_2$ 1.53 (2.56)	0.46 (2.56)	1 : 1	$Zn(L_d)_2$(phen) (Cream)	80	>360	778.1 (779.6)	67.77 (67.79)	4.86 (4.91)	10.69 (10.78)	8.39 (8.38)

Table 4. Synthetic, analytical and physical data for adducts of 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of zinc with triphenylphosphine.

Sl. no. (Compd no.)	Reactants: Complex g (mmol)	Reactants: Triphenylphoshine $C_{18}H_{15}P$ g (mmol)	Molar ratio	Product (color)	Yield %	m.p. (°C)	Mol. Wt. Found (Calcd)	Analysis, % Found (Calcd): C	H	N	Zn
13	$Zn(L_a)_2$ 1.34 (2.49)	0.65 (2.49)	1 : 1	$Zn(L_a)_2(PPh_3)$ (Cream)	88	>360	801.25 (801.68)	71.55 (71.91)	4.88 (4.90)	6.98 (6.99)	8.15 (8.16)
14	$Zn(L_b)_2$ 1.39 (2.29)	0.60 (2.29)	1 : 1	$Zn(L_b)_2(PPh_3)$ (Cream)	92	>360	871.58 (871.68)	66.87 (66.14)	4.49 (4.51)	6.45 (6.43)	7.48 (7.50)
15	$Zn(L_c)_2$ 1.36 (2.41)	0.63 (2.41)	1 : 1	$Zn(L_c)_2(PPh_3)$ (Cream)	86	>360	829.65 (829.68)	72.15 (72.38)	5.19 (5.10)	6.72 (6.75)	7.86 (7.88)
16	$Zn(L_d)_2$ 1.39 (2.32)	0.60 (2.32)	1 : 1	$Zn(L_d)_2(PPh_3)$ (Cream)	90	>360	861.54 (861.68)	69.21 (69.69)	5.89 (5.91)	6.58 (6.50)	7.52 (7.59)

carrageenan injection in the test and standard group, y = mean paw volume of rats before the administration of carrageenan injection in the control group, and b = mean paw volume of rats after the administration of carrageenan injection in the control group.

3. Results and discussion

The 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of zinc and their adducts with 2,2′-bipyridine, 1,10-phenanthroline and triphenylphosphine are nonhygroscopic and stable at room temperature. These zinc(II) complexes are soluble in organic (chloroform and dichloromethane) and coordinating (pyridine, DMSO, and tetrahydrofuran) solvents on slight heating. Molecular weight measurements and FAB mass spectral data show that complexes are monomers. Elemental analyses (C, H, N, and Zn) are in agreement with the stoichiometry proposed. The data are presented in tables 1–4.

3.1. *Conductivity measurements*

Conductances of the synthesized complexes are in the range 11.4–12.8 $\Omega^{-1}\,cm^2\,mol^{-1}$ (Supplementary Material), indicating nonelectrolytes [19].

3.2. *Electronic absorption spectra*

Electronic spectral data of pyrazolinates of zinc(II) (Supplementary Material) show intense bands in the range 29,228–26,730 cm^{-1} assigned to intraligand O → Zn ligand-to-metal charge transfer (LMCT). The spectrum shows no bands in the region below 23,000 cm^{-1}, typical for d^{10} Zn(II) [20–23]. Tetrahedral geometry is most likely in four-coordinate (two phenolate + two N donors) zinc(II) complexes. In adducts, two pyrazoline ligands are bonded with phenolic oxygen and two coordination sites are satisfied with nitrogens of 2,2′-bipyridine and 1,10-phenanthroline. For adducts with PPh_3, two coordination sites are phenolic oxygen of pyrazoline, one coordination site is triphenylphosphine and one occupied through solvent.

3.3. *Infrared spectra*

Assignments of infrared spectral bands for zinc(II) pyrazolinates and their adducts are given in Supplementary Material. The band due to υ(OH) in spectra of ligand in the region 3080–3050 cm^{-1} is absent in spectra of complexes, indicating involvement of phenolic OH. The band in the region 3432–3417 cm^{-1} assigned due to υ(N–H) is found at almost the same position with respect to the spectra of ligand suggesting noninvolvement of N–H in complexes. The υ(C=N) group in the region 1618–1607 cm^{-1} in ligand is shifted to higher wavenumber in complexes suggesting coordination through nitrogen of C=N [24], confirming bidentate ligand. In adducts, bands at 3436–3415 and 1607–1588 cm^{-1} are assigned to υ(N–H) and υ(C=N),

respectively, the same position as the ligand, suggesting noninvolvement of N–H and C=N in adducts, indicating monodentate pyrazoline. New bands in the region 545–465 and 415–390 cm^{-1} are υ(M–O) and υ(M–N) stretching vibrations, respectively. For PPh_3 adducts, only the band due to υ(M–O) is found in 538–524 cm^{-1} [25].

3.4. *^{1}H NMR spectra*

The ^{1}H NMR spectra of zinc(II) pyrazolinates (Supplementary Material) were recorded at 300 MHz in $CDCl_3$ and DMSO-d_6. Aromatic protons were observed as a multiplet in the region 6.45–8.07 ppm. The hydroxyl proton (present at 10.8–11.15 ppm in ligand) is absent from spectra of the complexes suggesting bonding through phenolate. The unaffected peak of N–H as a broad singlet at 4.40–5.10 ppm (originally present at 5.4–5.0 ppm in free pyrazolines) suggests noninvolvement of N–H in bond formation. The skeletal protons of the five-membered ring are observed as a triplet at 3.10–3.26 ppm and doublet at 2.00–2.50 ppm assigned to CH and CH_2, respectively [26–28].

3.5. *^{13}C NMR spectra*

The ^{13}C NMR spectra of zinc(II) pyrazoline complexes in $CDCl_3$ and DMSO-d_6 on a DRX 300 instrument are given in Supplementary Material. Assignments have been made on the basis of available literature and the spectrum of ligand. The zinc(II) complexes show the presence of all important signals for ligand. The signal in the region 122–138 ppm as a broad singlet was assigned to aromatic carbon. The signal at 146–160 ppm in the spectrum of the ligand assigned to C=N shifts to 157–176 ppm in the spectrum of the complexes, indicating involvement of imino nitrogen in coordination [26–28]. All other signals were at their respective positions as in ligands.

3.6. *^{31}P NMR spectra*

The ^{31}P NMR spectra of triphenylphosphine adducts of zinc(II) pyrazolinates in solid state exhibit a broad singlet in the range δ 35.7–31.6 ppm, indicating coordinaton between Zn(II) and triphenylphosphine [29–31]. Phosphorus donor ligands modify the electronic characteristics of a metallic center [32–35].

3.7. *FAB mass spectra*

The FAB mass spectra of 5-(2′-hydroxyphenyl)-3-(4-methylphenyl)pyrazoline and adduct complexes give tentative idea about the molecular weights. The mass spectra of $Zn(L_c)_2$ (L_c = 5-(2′-hydroxyphenyl)-3-(4-methylphenyl)pyrazoline) exhibited molecular ion peak at $m/z = 567$ and peaks at 474, 381, 290, 199, 160 and 121 m/z after successive removal of $-C_6H_5O^{\cdot}$, $-C_6H_5O^{\cdot}$, $-C_7H_7^{\cdot}$, $-C_3H_3^{\cdot}$, and $-C_3H_3^{\cdot}$, respectively. $Zn(L_a)_2$bipy shows molecular peak at $m/z = 696$ and peaks observed at 618, 540, 463, 386, 293, 200, 161 and 122 m/z after successive removal of $-C_5H_4N^{\cdot}$, $-C_5H_4N^{\cdot}$,$-C_6H_5^{\cdot}$, $-C_6H_5^{\cdot}$, $-C_6H_5O^{\cdot}$, $-C_6H_5O^{\cdot}$, $-C_3H_3^{\cdot}$, and $-C_3H_3^{\cdot}$, respectively. Mass spectra indicate monomers.

3.8. *Biological activity*

Complexes of zinc and adducts were screened for their antibacterial activity against *Escherichia coli, Shigella flexenary, Pseudomonas aeruginosa, Salmonella typhi, Staphylococcus aureus* and *Bacillus subtilis* and for antifungal activity against *Trichophyton* sp., *Candida albicans, Aspergillus flavus, Fucerium* sp., *Aspergillus niger, and Mucor* sp. Growth inhibition was compared with standard drugs Imipenem and Miconazole for antibacterial and antifungal activity, respectively. Each inhibition zone was measured as diameter in millimeter and activity was calculated as a mean of three replicates. The results are listed in tables 5 and 6.

The complexes have higher activity than the free ligand, explained on the basis of Overtone's concept and chelation theory [36]. These complexes disturb respiration of the cell and thus block the synthesis of proteins, restricting further growth of organisms. Different ligands provide variation in observed biological activity.

3.9. *Cytotoxic bioassay*

All complexes were screened for cytotoxicity (brine shrimp bioassay) using the protocol of Meyer *et al.* [37]. From data recorded in table 7, it is evident that all complexes and adducts displayed potent cytotoxic activity as $LD_{50} = 7.113–8.849 \times 10^{-4}$ against *Artemia salina*, while ligands were almost inactive for this assay.

Table 5. Antibacterial bioassay data of free pyrazoline ligands, 5-(2′-hydroxyphenyl)-3-(4-X-phenyl) pyrazolinates of zinc and their adducts.

	Gram(−ve) bacteria				Gram(+ve) bacteria	
Compounds	*E. coli*	*S. flexenari*	*P. aeruginosa*	*S. typhi*	*S. aureus*	*B. subtilis*
L_a*	00	00	00	00	08	09
L_b*	00	00	00	00	07	08
L_c*	00	00	00	00	07	07
L_d*	00	00	00	00	06	07
1	19	15	17	19	19	17
2	18	14	16	18	18	16
3	16	12	14	17	16	14
4	15	11	13	16	15	13
5	22	20	20	23	24	21
6	21	18	19	22	23	20
7	19	16	16	20	21	17
8	18	14	15	18	20	16
9	23	22	21	22	23	21
10	22	20	20	21	22	19
11	20	17	19	20	21	18
12	19	19	17	19	20	17
13	21	20	20	23	22	21
14	20	18	19	21	20	20
15	19	16	18	19	20	17
16	18	15	17	18	20	17
Standard drug (Imipenem)	30	27	27	26	30	28

Note: Diameter of inhibition zone measured in mm, paper disc 5 mm, inhibition zone measured excluding paper disc diameter, amount of complexes taken from 1 mg mL^{-1} of DMSO.

Table 6. Antifungal bioassay data of free pyrazoline ligands, 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of zinc and their adducts.

Compounds	Organism					
	Trichophyton sp.	*C. albicans*	*A. flavus*	*Fucerium* sp.	*A. niger*	*Mucor* sp.
L_a*	00	00	10	00	08	00
L_b*	00	00	10	00	07	00
L_c*	00	00	07	00	05	00
L_d*	00	00	07	00	05	00
1	19	15	24	16	18	17
2	20	14	23	15	17	16
3	18	12	21	12	14	11
4	17	10	22	10	12	10
5	25	22	26	20	22	23
6	24	21	25	18	21	21
7	22	18	22	15	19	16
8	23	16	23	12	17	15
9	24	21	25	21	21	22
10	23	20	24	19	20	20
11	23	18	23	16	19	17
12	22	18	22	23	18	16
13	25	22	26	20	22	23
14	23	21	24	18	21	22
15	21	18	23	16	19	16
16	22	16	22	15	18	16
Standard drug (Miconazole)	32	28	34	30	31	34

Note: Diameter of inhibition zone measured in mm, paper disc 5 mm, inhibition zone measured excluding paper disc diameter, amount of complexes taken from 200 μg mL^{-1}.

Table 7. Brine shrimp bioassay data of free pyrazoline ligands, 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of zinc and their adducts.

Compounds	LD_{50} ($M\,mL^{-1}$)[a]
L_a	1.112×10^{-3}
L_b	1.609×10^{-3}
L_c	1.750×10^{-3}
L_d	1.246×10^{-3}
1	7.175×10^{-4}
2	7.220×10^{-4}
3	7.839×10^{-4}
4	7.113×10^{-4}
5	8.849×10^{-4}
6	8.725×10^{-4}
7	7.884×10^{-4}
8	7.732×10^{-4}
9	8.625×10^{-4}
10	8.831×10^{-4}
11	8.696×10^{-4}
12	8.321×10^{-4}
13	8.556×10^{-4}
14	7.938×10^{-4}
15	8.734×10^{-4}
16	8.423×10^{-4}

Note: [a]Average of four readings.

Table 8. Anti-inflammatory activity data of 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of zinc and their adducts.

Compounds	No. animals used	Dose ($mg\,kg^{-1}$) body wt.	Initial volume[a] 0.0 h	Final volume[a] after 3 h	Volume of edema[a]	% Inhibition
Control	8	100	0.575	1.105	0.530	-
Standard drug (Diclofenac)	8	100	0.540	0.905	0.365	31.13
1	8	100	0.821	0.950	0.119	75.56
2	8	100	0.826	0.950	0.124	76.60
3	8	100	0.815	0.938	0.123	76.79
4	8	100	0.831	0.950	0.119	77.55
5	8	100	0.826	0.950	0.124	76.60
6	8	100	0.831	0.950	0.119	77.55
7	8	100	0.817	0.935	0.118	77.74
8	8	100	0.826	0.935	0.109	79.43
9	8	100	0.805	0.912	0.107	79.81
10	8	100	0.809	0.915	0.106	80.00
11	8	100	0.819	0.921	0.102	80.75
12	8	100	0.809	0.911	0.102	80.75
13	8	100	0.819	0.931	0.112	78.87
14	8	100	0.826	0.935	0.109	79.43
15	8	100	0.805	0.912	0.107	79.81
16	8	100	0.809	0.915	0.106	80.00

Note: [a]Average of four readings.

3.10. *Anti-inflammatory activity*

The 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of zinc and their adducts were tested for anti-inflammatory activity. Differences between the complexes and standard drug (table 8) suggest that at equal doses the 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of Zn(II) were more effective than the standard drug. 5-(2′-Hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates have clinical usefulness [38–42], perhaps from zinc complexes responsible for anti-inflammatory activity of the clinically used anti-inflammatory agents.

4. Conclusion

Tetrahedral geometry [43–45] around zinc(II) with two bidentate pyrazoline ligands $(C_{15}H_{12}N_2OX)_2Zn$ is indicated. In adducts, pyrazoline is monodentate. Antimicrobial studies show that the 5-(2′-hydroxyphenyl)-3-(4-X-phenyl)pyrazolinates of zinc(II) and their adducts have greater activity towards all tested bacteria than free pyrazolines and exhibited greater antifungal and anti-inflammatory activity. Generally, complexes deactivate various cellular enzymes, which play a vital role in metabolic pathways of the microorganisms. Structures of the complexes which exhibit antimicrobial activity indicate that the ligands and metal play roles in the antimicrobial activity.

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