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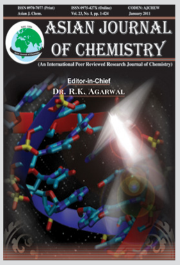

Synthesis, Characterization and *in vitro* Antimicrobial Activity of Co(II), Cu(II), Zn(II), Cd(II) and Sn(II) Ions with {[5-(4-Bromophenyl)-1,3,4-oxadiazol-2-yl]thio}acetic Acid

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In present studies, five metal complexes derivative of {[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]thio}acetic acid, HL with the metal ions [Co(II), Cu(II), Zn(II), Cd(II) and Sn(II)] have been successfully prepared in alcoholic medium. The complexes obtained are characterized quantitatively and qualitatively by using FTIR spectroscopy, electronic spectroscopy, mass spectroscopy ^{1}H and ^{13}C NMR, magnetic susceptibility and conductivity measurements. From the spectral study, all the complexes obtained as a monomeric structure and the metals centre moieties are four-coordinated and exhibited tetrahedral geometry except Cu(II) complex (square planar). Preliminary *in vitro* antimicrobial study indicated that all the compounds showed significant activity against the tested bacterial strains.

Key Words: Carboxylate, 1,3,4-Oxadiazole, Metal complexes, Antimicrobial activity.

INTRODUCTION

The synthesized and structural study of metal complexes with oxygen donor ligands have received considerable attention due to the physiological importance of oxygen donor and the biological active role of certain metal ions[1-3]. The ligands containing polyfunctional donors (S, O and N) also gained attention resulting from the interest of structural diversities as well as the biological study[1-7]. 1,3,4-Oxadiazoles are a class of heterocyclic compound, which has attracted significant interest in medicinal chemistry and have a wide range of pharmaceutical and biological activities including antimicrobial, antifungal, antiinflammatory and antihypertensive[4-8].

In this study, we reported the synthesis and characterization of metal complexes derivatives of 1,3,4-thiadizole ring system, which is similar to 1,3,4-oxadiazole compound. Moreover, *in vitro* antimicrobial screening activities of the complexes obtained are carried out and the results are reported.

EXPERIMENTAL

All the reagents, starting materials as well as solvents were purchased commercially and used without any further purification. The melting points were recorded on a hot stage Gallen Kamp melting point apparatus. Elemental C, H, N and S analysis were carried out on a Fison EA 1108 analyzer. The infrared spectra were recorded by using FTIR.8300 Shimadzu spectrophotometer as CsI disc in the frequency range of 4000-200 cm^{-1}. The ultraviolet-visible (UV-VIS) spectra were recorded by using Shimadzu UV-VIS. 160 A-Ultra-Violet spectrophotometer in the range of 200-1100 nm. The magnetic susceptibility values were obtained at room temperature using Magnetic Susceptibility Balance Bruke Magnet B.M.6. Conductivity measurements were carried out by using WTW conductivity meter, atomic absorption measurements were obtained by using Shimadzu 680cc-flame. The spectra of ^{1}H and ^{13}C NMR spectra were recorded on a Jeol 400 MHz spectrometer using deuterated DMSO as the solvent and tetramethylsilane, TMS as the internal standard. Mass spectra were recorded on a micromass UK PLATFORM II LC-MS spectrometer.

Synthesis of {[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]thio}acetic acid: A mixture of ethyl 4-bromobenzoate (0.1 mol) and hydrazine hydrate (0.1 mol) was heated under reflux for 2 h. Then, ethanol (50 mL) was added to the mixture and the heating under reflux was carried out for another 5 h. The precipitate of benzoyl hydrazine was filtered and washed with cold methanol. Later, carbon disulfide (0.04 mol) and potassium hydroxide (0.02 mol) were added to ethanol solution of 4-bromobenzoyl hydrazine (0.02 mol) at 273 K and the mixture was heating under refluxed for another 7 h. The solvent was evaporated and the residue dissolved in water and acidified with dilute hydrochloric acid. The precipitate was filtered and crystallized from ethanol to give 5-(4-bromophenyl)-1,3,4-

TABLE-1
MELTING POINTS, ELEMENTAL ANALYTICAL DATA (%) AND *m/e* VALUE OF COMPOUNDS

Compounds	colour	m.p. (ºC)	Elemental (%)					*m/z*
			C	H	N	S	M (metal)	
HL	White	158-160	37.88 (38.11)	2.11 (2.22)	8.76 (8.89)	10.06 (10.16)	-	314
Co(L)$_2$, 1	Blue	155-157	35.00 (34.95)	2.00 (2.04)	8.23 (8.15)	9.22 (9.32)	8.42 (8.58)	687
Cu(L)$_2$, 2	Green	152-155	34.87 (34.71)	2.13 (2.02)	8.02 (8.10)	9.13 (9.26)	8.20 (9.19)	691
Zn(L)$_2$, 3	White	100-112	34.55 (34.62)	2.07 (2.02)	8.18 (8.08)	9.09 (9.23)	9.33 (9.43)	693
Cd(L)$_2$, 4	White	110-113	32.44 (32.42)	1.77 (1.89)	7.44 (7.56)	8.45 (8.64)	15.24 (15.18)	740
Sn(L)$_2$, 5	White	205-208	32.11 (32.15)	1.90 (1.87)	7.77 (7.50)	8.47 (8.57)	16.01 (15.09)	746

oxadiazole-2-thiol and react with equivalent mole of chloroacetic acid in the presence of potassium hydroxide as a basic media to give {[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]thio}acetic acid, HL and finally recrystallized from methanol.

Preparation of complexes: An ethanol solution of the metal salt [cobalt(II) chloride hexahydrate, tin(II) chloride, copper(II) chloride dihydrate, cadmium(II) chloride dihydrate and zinc(II) chloride] was added to ethanol solution of {[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]thio}acetic acid, HL in 1:2 (metal : ligand) molar ratio. Then the mixture was heating under reflux for 1.5 h, colour precipitates were obtained at room temperature. The precipitates were filtered out, washed with distilled water and recrystallized from ethanol.

RESULTS AND DISCUSSION

In general, {[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]thio}acetic acid, HL was prepared by reacting 1 mol of 5-(4-bromophenyl)-1,3,4-oxadiazole-2-thiol with 1 mol of chloroacetic acid in the presence of potassium hydroxide. The complexes obtained by heating under reflux of respective metal salts with HL in the1:2 molar ratio. The purity of the acid, HL and complexes obtained were checked by TLC using silica gel-G as adsorbent. The micro-elemental analysis for C, H and N obtained were in agreement with the suggested formula for complexes **1-5**. Complexes **1-5** gave a sharp melting point indicated the isolation of fairly pure complexes. An outline of the proposed structure for complexes **1-5** and acid, HL are depicted in Fig. 1. The melting point, micro-elemental analysis and *m/z* are given in Table-1.

The infrared spectrum of HL showed some characteristic stretching bands at 3468, 1633, 1351,1606, 1187 and 1066 cm^{-1} assigned to ν(OH), ν(COO)as, ν(COO)s, ν(C=N) of the oxadiazole ring, $\nu(\text{C-O-C})_{as}$, $\nu(\text{C-O-C})_{s}$ respectively. The ν(O-H) band of the HL appeared at 3468 cm^{-1} was absent in the infrared spectra of complexes **1-5**, indicating the deprotonation and coordination of the carboxylate anions to the metal atom moiety. The infrared spectra of complexes **1-5** revealed that the $\nu(\text{COO})_{as}$ was shifted to a lower wavelength number compared to the parent acid signifying that the coordination took place *via* the oxygen atoms of the carboxylate anion. Generally, the $\Delta\nu = [\nu(\text{COO})_{as} - \nu(\text{COO})_{s}]$ value is used to determine the bonding properties of carboxylate anion to the metal atom. The values of $\Delta\nu$ could be divided into three categories. (a) When $\Delta\nu > 350$ cm^{-1}: the carboxylate anions bonded to the metal moiety in monodentate manner, however, other weak intra and intermolecular interactions could not be excluded. (b) When $\Delta\nu < 200$ cm^{-1}, the carboxylate anions exhibited bidentate bonding manner. (c) If the 350 cm$^{-1} > \Delta\nu > 200$ cm^{-1} an intermediate state between monodentate and bidentate (anisobidentate) occurs. Based on the infrared data in Table-2, all the complexes showed that the $\Delta\nu$ fall in the range of 350 cm$^{-1} > \Delta\nu > 200$ cm^{-1} indicated the carboxylate anions bonded to metal atom moiety in anisobidentate manner resulting the metal centre exhibited four coordination. In addition, the stretching of metal-oxygen bands of the complexes appeared in low frequency region in the range of 497-472 cm^{-1} also signifies the complexation through oxygen atom from the carboxylate anion[9].

TABLE-2
SELECTED INFRARED DATA OF COMPOUNDS

Compounds	Wavelength (cm^{-1})			
	ν(OH)	$\nu(\text{COO})_{as}$	$\nu(\text{COO})_{s}$	$\Delta\nu$
HL	3468	1630	1350	280
Co(L)$_2$, 1	-	1591	1348	243
Cu(L)$_2$, 2	-	1590	1348	242
Zn(L)$_2$, 3	-	1592	1348	244
Cd(L)$_2$, 4	-	1590	1349	241
Sn(L)$_2$, 5	-	1600	1344	256

$\Delta\nu = [\nu(\text{COO})_{as} - \nu(\text{COO})_{s}]$

The ^{1}H NMR spectra of complexes **1-5** gave an additional support for the formation of the complexation. The spectra of acid, HL showed a sharp peaks, δ(OH) at 9.55 ppm, which was absent in the spectra of the complexes **1-5** indicated deprotonation and complexation of carboxylate anions to metal ions. From the ^{13}C NMR study, all the complexes exhibited a δ(COO) signal in the range of 169.69-170.78 ppm. The chemical shift of the δ(COO) signal in each complex was shifted downfield compared to that of their parent acid (168.11 ppm) indicating the participation of the carboxylate anions in the coordination to the metal atom. This shift is due to the decrease of the electron density in the carboxylate anions upon coordinated to the metal atom moiety during complex formation[10].

The ultraviolet visible electronic spectrum of the acid and complexes **1-5** in ethanol solution are given in Table-3. The acid showed two bands at 205 and 276 nm attributed to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ electronic transition respectively. From Table- 3, complexes **1-5** showed significant different absorptions from the free acid, HL. Complex **1** existed in a divalent state with symmetrical tetrahedral geometry. This hypothesis is supported by the number of maxima observed bands in the UV-VIS spectra of complex **1**. These three maxima bands (Table-3) have been assigned to the transition $^4A_2 \rightarrow {}^4T_{2(F)}$, $^4A_2 \rightarrow {}^4T_{1(F)}$ and $^4A_2 \rightarrow {}^4T_{1(P)}$.

The value of υ_2 have been calculated and found at 1070 nm, while the value of υ_1 was expected to the transition of $^4A_2 \rightarrow {}^4T_{2(F)}$ at 1596 nm, which could not be observed in the spectrum of the complex **1**. These calculations were based on Tanabe-Sugano diagram for d^7 system[11].

TABLE-3
ELECTRONIC SPECTRA DATA OF COMPOUNDS IN ETHANOL

Compounds	Absorption bands (nm)	Assigned transition
HL	205, 276	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$
Co(L)$_2$, 1	1596, 1070 (calc), 634 (av.)	$^4A_2 \rightarrow {}^4T_{2(F)}$, $^4A_2 \rightarrow {}^4T_{1(F)}$, $^4A_2 \rightarrow {}^4T_{1(P)}$
Cu(L)$_2$, 2	904, 679, 502, 440	$^2B_{1g} \rightarrow {}^2E_g$, $^2B_{1g} \rightarrow {}^2B_{2g}$ $^2B_{1g} \rightarrow {}^2A_{1g}$, HL $\rightarrow$ Cu$_{(C.T.)}$
Zn(L)$_2$, 3	230, 258	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$
Cd(L)$_2$, 4	225, 300	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$
Sn(L)$_2$, 5	225, 279	$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$

Magnetic moment measurements are widely used in studying transition metal complexes and the magnetic moment of complexes **1-5** are given in Table-4. The magnetic properties are due to the presence of unpaired electrons in the partially filled *d*-orbital in the outer shell of these elements. These magnetic measurements give an idea about the electronic state of the metal ion in the complexes. The magnetic moment for complex **1** was *ca.* 4.35 BM and referred as paramagnetic and the geometry of cobalt metal centre was tetrahedral. Complex **2** showed that the magnetic moment was 1.67 BM and believed that the copper metal moiety exhibited square planar geometry[11]. Complexes **3-5** are diamagnetic and there were no magnetic moment recorded in this study. Based on the molar conductivity measurements study of complexes **1-5** (Table-4), all the prepared complexes were found to be non-electrolyte.

TABLE-4
CONDUCTIVITY MEASUREMENTS AND MAGNETIC MOMENT OF COMPOUNDS IN DMF

Compounds	Conductivity (μs.cm^{-1})	Magnetic moment (B.M.)	Proposed structure
HL	-	-	-
Co(L)$_2$, 1	20	4.35	Tetrahedral
Cu(L)$_2$, 2	15	1.67	Square planar
Zn(L)$_2$, 3	18	0.00	Tetrahedral
Cd(L)$_2$, 4	8	0.00	Tetrahedral
Sn(L)$_2$, 5	25	0.00	Tetrahedral

All the complexes obtained were studied in ethanol solution to determine the [M/L] ratio in the complex by molar ratio method[7]. A series of solutions were prepared with a constant concentration (10^{-3}M) of the metal ion and ligand, L.The [M/L] ratio was determined from the relationship between the absorption of the absorbed light and the mole ratio of [M/L]. The study showed that the metal to ligand ratio was [1/2] for complexes **1-5** and found to be similar to the solid state. Based on the spectral study, complexes **1-5** exhibited tetrahedral geometry except complex **2** (square planar). The proposed structures of complexes **1-5** are depicted in Fig. 1.

The *in vitro* antimicrobial screening activity of acid, HL and complexes **1-5** are given in Table-5. The synthesized complexes and acid, HL were screened for their *in vitro* antimicrobial activity against *Staphylococcus aureus, Escherishia coli, Pseudomonas aeroginosa* and *Candida albicans* bacterial strains, by inhibition zone method using agar diffusion method[12]. In this method a standard 5 mm diameter sterilized filter paper disc impregnated with the compound (1 mg/mL in acetone) was placed on an agar plate seeded with the test bacterial strains. The plates were incubated for 24 h at 37 ºC. The activity was determined by measuring the diameter of the inhibition zone (in mm). The preliminary screening results revealed that complexes **1-5** showed a significant activity compared to the acid, HL and all the complexes exhibited antimicrobial activity against *E. coli*. In addition, complex **1** and **5** consist of Co(II) and Sn(II) metal ions respectively exhibited greater activity against *E. coli* compared to complexes **2-4**. Based on this preliminary study, complex **2** with the square planar geometry was found to be active to all the four tested bacterial strains compared to complexes obtained in tetrahedral geometry.

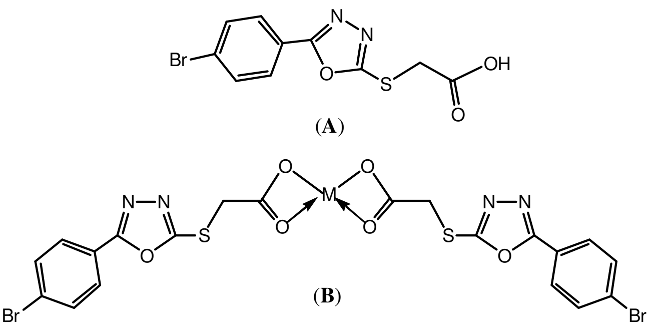

Fig. 1. The structure of acid (HL) and the proposed structure of complexes (M = metal).

TABLE-5
In vitro ANTIBACTERIAL SCREENING ACTIVITY OF COMPOUNDS

Compounds	Inhibition zone (mm)			
	Staphylococcus aureus	*Escherichia coli*	*Pseudomonas aeruginosa*	*Candida albicans*
HL	-	+	-	-
Co(L)$_2$, 1	-	+++	++	+
Cu(L)$_2$, 2	+	++	+	++
Zn(L)$_2$, 3	-	++	-	-
Cd(L)$_2$, 4	+	++	-	+
Sn(L)$_2$, 5	+	+++	-	+

= 5-10 mm, ++ = 11-20 mm, +++ = larger than 20 mm, - = no inhibition

Conclusion

The ligand {[5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl]thio}acetic acid was successfully synthesized. The ligand was treated to different metal ions salts to afford the corresponding complexes. The carboxylate anions coordinated to the metal atom *via* oxygen atoms resulting all the metal centre were four-coordinated. All the complexes exhibited tetrahedral geometry except complex **2** (square planar). Preliminary *in vitro* antimicrobial study indicated that all the compounds obtained showed significant activity against the tested bacterial strains. From the biological screening study, complex **2** with the square planar geometry was found to be active to all the four tested bacterial strains compared to complexes obtained in tetrahedral geometry.

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