

Full Length Research Paper

# Lanthanide complexes of {(5-phenyl-1,3,4-oxadiazol-2-yl)thio}acetic acid: Synthesis, characterization and preliminary *in vitro* antibacterial screening activity

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A total of four new lanthanide complexes of {(5-phenyl-1,3,4-oxadiazol-2-yl)thio}acetic acid (ligand, HL) with the metal ions [La(III), Nd(III), Gd(III) and Dy(III)] have been successfully prepared in alcoholic medium. The complexes obtained are characterized quantitatively and qualitatively by using microelemental analysis, Fourier transform infrared spectroscopy (FTIR) spectroscopy, ultraviolet-visible spectroscopy, mass spectroscopy, <sup>1</sup>H & <sup>13</sup>C NMR, magnetic susceptibility and conductivity measurements. From the spectral study, all the complexes were obtained as monomeric structure and the metals centre moieties are six-coordinated with distorted octahedral geometry. The preliminary *in vitro* antibacterial screening activity revealed that complexes 1 to 4 showed a significant activity compared to the ligand, HL and all the complexes exhibited antimicrobial activity especially against *Escherichia coli*.

**Key words:** {(5-phenyl-1,3,4-oxadiazol-2-yl)thio}acetic acid, lanthanide complexes, *in vitro* antibacterial activity.

## INTRODUCTION

The preparation and the 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 (Fenton and Vigato, 1988; Devi and Singh, 2011; Singh et al., 2011). In addition, ligands containing polyfunctional donors (S, O and N) also gained tremendous attention resulting from the interest of structural diversities as well as the biological activities (Fenton and Vigato, 1988; Devi and Singh, 2011; Singh et al., 2011). Moreover, ligand such as 1,3,4-oxadiazoles are a class of heterocyclic compound which also has received significant interest in medicinal chemistry and biological activities including antimicrobial, anti-fungal,

anti-inflammatory, and antihypertensive (Wandiga, 1999; Yousif and Rentschler, 2010; Hasan et al., 2011; Kamal et al., 2011). As a result, the preparation and the biological activities of 1,3,4-oxadiazole derivatives with metal atoms are still extensively studied up till today.

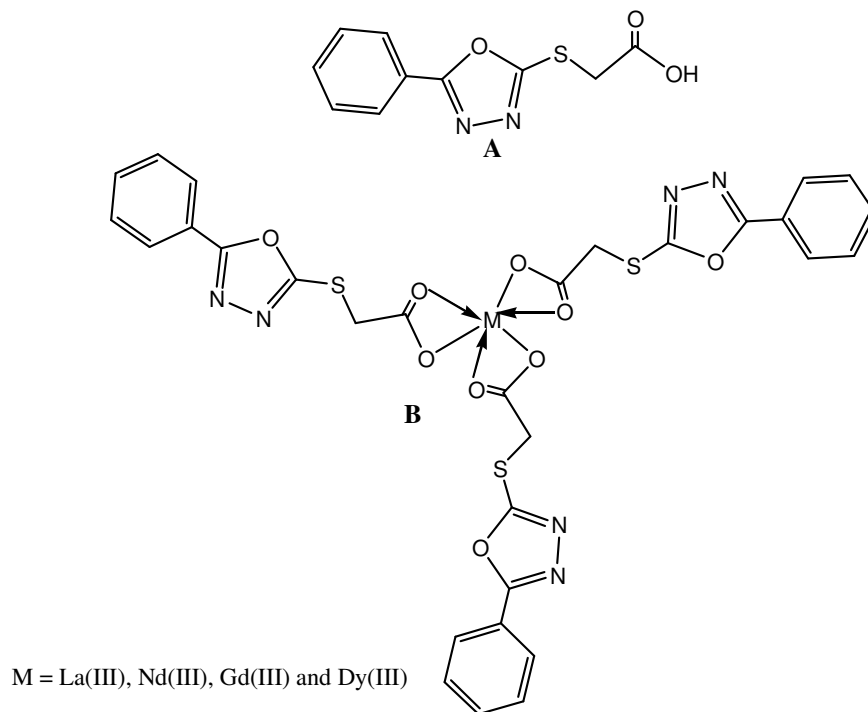
In this study, we report on the synthesis and characterization of {(5-phenyl-1,3,4-oxadiazol-2-yl)thio}acetic acid (ligand, HL) and its lanthanide complexes derivatives. Furthermore, the preliminary *in vitro* antibacterial screening activity of the ligand and complexes were carried out and the results are reported herein.

## MATERIALS AND METHODS

### General and instrumental

All the reagents, starting materials as well as solvents were purchased commercially and used without any further purification.

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**Figure 1.** The structure of HL and Complexes 1 to 4 (M= metal).

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 (IR) spectra were recorded as KBr disc by using a FTIR.8300 Shimadzu Spectrophotometer in the frequency range of 4000 to 400  $\text{cm}^{-1}$ . The ultraviolet-visible (UV-Vis) spectra were recorded by using Shimadzu Uv-vis. 160 A-Ultra-violet Spectrophotometer in the range of 200 to 1100 nm. The magnetic susceptibility values were obtained at room temperature using a 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  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Jeol 400 MHz spectrometer using deuterated  $\text{d}_6$ -DMSO as the solvent and tetramethylsilane, TMS as the internal standard. Mass spectra were recorded on a Micromass UK PLATFORM II LC-MS spectrometer.

#### Preparation of {(5-phenyl-1,3,4-oxadiazol-2-yl)thio}acetic acid

A mixture of ethyl benzoate (0.1 mole) and hydrazine hydrate (0.1 mole) was heated under reflux for two hours. Then, ethanol (50 ml) was added to the mixture and the heating under reflux was continued for another five hours. The precipitate of benzoyl hydrazine (0.02 mole) was filtered and washed with cold methanol. Later, carbon disulfide (0.04 mole) and potassium hydroxide (0.02 mole) were added to ethanolic solution of benzoyl hydrazine (0.02 mole) at 273K and the mixture was heated under reflux for another seven hours. The solvent was evaporated and the residue dissolved in water and acidified with dilute hydrochloric acid. The precipitate obtained was filtered and crystallized from ethanol and then reacted with an equivalent mole of chloroacetic acid in the presence of potassium hydroxide as a basic media to give {(5-phenyl-1,3,4-oxadiazol-2-yl)thio}acetic acid, HL (Figure 1) and finally recrystallized from methanol.

#### Preparation of complexes

An ethanolic solution of the lanthanide compounds [ $\text{La}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{Nd}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ ,  $\text{Gd}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$  and  $\text{Dy}(\text{NO}_3)_3 \cdot 6\text{H}_2\text{O}$ ] was added to an ethanolic solution of {(5-phenyl-1,3,4-oxadiazol-2-yl)thio}acetic acid, HL in 1:3 (metal : ligand) molar ratio. Then the mixture was heated under reflux for ninety minutes and coloured precipitates were obtained. The precipitates were filtered out, washed with distilled water and finally recrystallized from ethanol.

#### Physical and elemental analysis

The {(5-phenyl-1,3,4-oxadiazol-2-yl)thio}acetic acid, HL and the complexes 1 to 4 were prepared by reactions mentioned previously. The complexes were obtained by heating under reflux of respective lanthanide compounds with HL in the 1:3 molar ratio. The purity of the ligand, HL and complexes obtained were checked by using TLC and silica gel-G as adsorbent. The micro-elemental analysis of C, H, N and S obtained were in agreement with the predicted formula for ligand, HL and complexes 1 to 4. complexes 1 to 4 gave a sharp melting point indicating the isolation of fairly pure complexes. The prominent molecular ion peaks in the mass spectra of complexes 1 to 4 established the molecular formula and supported the proposed structures of the complexes obtained. An outline of the proposed structure for complexes 1 to 4 and ligand, HL are depicted in Figure 1. The melting point, micro-elemental analysis and  $m/z$  are given in Table 1.

**Table 1.** Melting points, elemental analytical data (%) and  $m/z$  value of HL and complexes 1 to 4.

Compound	Physical appearance	Melting point (°C)	Elemental (%)				$m/z$
			C	H	N	S	
HL	White	162-164	50.84 (50.78)	3.41 (3.57)	11.14 (11.21)	13.17 (13.69)	230
La(L) <sub>3</sub> , 1	Pale yellow	283-285	42.20 (42.60)	2.80 (2.85)	9.90 (10.10)	11.30 (11.20)	844
Nd(L) <sub>3</sub> , 2	Pale orange	175-177	42.20 (42.26)	2.80 (2.88)	9.80 (9.93)	11.20 (11.34)	850
Gd(L) <sub>3</sub> , 3	Yellow	266-267	41.60 (41.73)	2.70 (2.76)	9.70 (9.65)	11.10 (11.23)	864
Dy(L) <sub>3</sub> , 4	Pale yellow	287-289	41.30 (41.54)	2.70 (2.77)	9.60 (9.85)	11.00 (10.90)	868

Calculated values are given in parentheses.

### Infrared, ultraviolet-visible and NMR spectral studies

The infrared spectrum of HL showed some characteristic stretching bands at 3468, 1633, 1351, 1606, 1187 and 1066  $\text{cm}^{-1}$  assigned to  $\nu(\text{OH})$ ,  $\nu(\text{COO})_{\text{as}}$ ,  $\nu(\text{COO})_{\text{s}}$ ,  $\nu(\text{C}=\text{N})$  of the oxadiazole ring,  $\nu(\text{C}-\text{O}-\text{C})_{\text{as}}$  and  $\nu(\text{C}-\text{O}-\text{C})_{\text{s}}$  respectively. The  $\nu(\text{O}-\text{H})$  band of the HL appeared at 3468  $\text{cm}^{-1}$  was absent in the infrared spectra of complexes 1 to 4, indicating the deprotonation and coordination of the carboxylate anions to the metal atom moiety. The infrared spectra of complexes 1 to 4 revealed that the  $\nu(\text{COO})_{\text{as}}$  was shifted to a lower wave length number compared to the ligand signifying that the coordination took place via the oxygen atoms of the carboxylate anion. Generally, the  $\Delta\nu = [\nu(\text{COO})_{\text{as}} - \nu(\text{COO})_{\text{s}}]$  value is useful to determine the bonding properties of carboxylate anion to the metal atoms. The values of  $\Delta\nu$  could be divided into three categories. (a) When  $\Delta\nu < 200 \text{ cm}^{-1}$ ; the carboxylate anions exhibited bidentate bonding manner. (b) When  $\Delta\nu > 350 \text{ cm}^{-1}$ ; the carboxylate anions bonded to the metal moiety in monodentate manner, however, other weak intra- and intermolecular interactions could not be excluded. (c) If the  $350 \text{ cm}^{-1} > \Delta\nu > 200 \text{ cm}^{-1}$  an intermediate state between monodentate and bidentate (anisobidentate) occurs (Win et al., 2011). Based on the infrared data in Table 2, all the complexes showed that the  $\Delta\nu$  fall in the range of  $350 \text{ cm}^{-1} > \Delta\nu > 200 \text{ cm}^{-1}$  which thus indicated that the carboxylate anions bonded to metal atom moiety in anisobidentate manner resulting in the metal centre exhibiting six coordination. In addition, the stretching of metal-oxygen bands of the complexes appeared in low frequency centering at  $\approx 480 \text{ cm}^{-1}$  also signifies the complexation through oxygen atom from the carboxylate anion (Yousif et al., 2010).

The ultraviolet visible electronic spectrum of the ligand, HL and complexes 1 to 4 in ethanol solution are given in Table 3. From Table 3, complexes 1 to 4 showed slightly different absorptions from the ligand, HL which the  $n \rightarrow \pi^*$  bands were shifted to higher wavelength in the range of 390 to 410 nm compared to the ligand, HL and the  $f-f$  orbital transitions appeared in the visible region in the range of 420 to 458 nm (Barraclough et al., 1977).

The  $^1\text{H}$  NMR spectra of complexes 1 to 4 gave an additional support for the formation of the complexation. The spectra of ligand, HL showed a sharp peaks,  $\delta(\text{OH})$  at 9.58 ppm which was absent in the spectra of the complexes 1 to 4, and indicated the deprotonation and complexation of carboxylate anions to metal ions (Yousif and Rentschler, 2010). From the  $^{13}\text{C}$  NMR spectra study, all the complexes exhibited a  $\delta(\text{COO})$  signal in the range of 169.70 to 170.77 ppm which were shifted to downfield region compared to that of the ligand, HL (168.69 ppm) indicating the participation of the carboxylate anions in the coordination to the lanthanide atom. This shifting was due to the decrease of the electron density in the carboxylate anions upon been coordinated to the lanthanide atom moiety during complexation (Yousif and Rentschler, 2010). Based on NMR spectra study of ligand and complexes 1 to 4, there was no additional uncharacterized peak indicating that the ligand and complexes obtained are pure.

### Magnetic susceptibility, conductivity measurement and complex formation in solution

Magnetic moment measurements are widely used in studying magnetic properties of lanthanide metal complexes and the magnetic moment of complexes 1 to 4 are given in Table 4. The magnetic properties are due to the presence of unpaired electrons in the partially filled  $f$ -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 of complexes 1 to 4 was calculated and falls in the range of 0.83 to 4.87 B.M. led to the suggestion of an octahedral structure (Patil et al., 2011). The magnetic moment of complex 1 at 0.83 B.M. could be regarded as a high spin octahedral complex. Based on the molar conductivity measurements study of complexes 1 to 4 (Table 4), all the prepared complexes were found to be non-electrolytes (Yousif and Rentschler, 2010; Win et al., 2011).

All the complexes obtained were studied in ethanolic solution to determine the  $[\text{M}/\text{L}]$  ratio in the complexes by Job's method (Bukhari et al., 2008; Harris, 2010). A series

**Table 2.** Selected infrared data of HL and complexes 1 to 4.

Compound	Wavelength (cm <sup>-1</sup> )			$\Delta\nu$
	$\nu(\text{OH})$	$\nu(\text{COO})_{\text{as}}$	$\nu(\text{COO})_{\text{s}}$	
HL	3468	1633	1351	282
La(L) <sub>3</sub> , 1	-	1598	1345	253
Nd(L) <sub>3</sub> , 2	-	1593	1346	247
Gd(L) <sub>3</sub> , 3	-	1591	1348	243
Dy(L) <sub>3</sub> , 4	-	1588	1349	239

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

**Table 3.** Electronic spectra data of HL and complexes 1 to 4 in ethanol.

Compound	Absorption bands (nm)	Assigned transition
HL	276	$n \rightarrow \pi^*$
La(L) <sub>3</sub> , 1	207, 250, 315, 420	$\pi \rightarrow \pi^*$ , $n \rightarrow \pi^*$ charge transfer, $f \rightarrow f$
Nd(L) <sub>3</sub> , 2	215, 249, 321, 423	$\pi \rightarrow \pi^*$ , $n \rightarrow \pi^*$ charge transfer, $f \rightarrow f$
Gd(L) <sub>3</sub> , 3	208, 248, 316, 420	$\pi \rightarrow \pi^*$ , $n \rightarrow \pi^*$ charge transfer, $f \rightarrow f$
Dy(L) <sub>3</sub> , 4	209, 253, 421, 458	$\pi \rightarrow \pi^*$ , $n \rightarrow \pi^*$ charge transfer, $f \rightarrow f$

**Table 4.** Conductivity measurements and magnetic moment of HL and complexes 1 to 4 in DMF.

Compound	Conductivity ( $\mu\text{S/cm}$ )	Magnetic moment (B.M.)	Proposed structure
HL	-	-	-
La(L) <sub>3</sub> , 1	19	0.83	Octahedral
Nd(L) <sub>3</sub> , 2	14	4.87	Octahedral
Gd(L) <sub>3</sub> , 3	12	3.56	Octahedral
Dy(L) <sub>3</sub> , 4	11	3.43	Octahedral

series of solutions were prepared with a constant concentration ( $10^{-3}\text{M}$ ) of the metal ion and ligand, HL. 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 indicated that the metal to ligand ratio was [1/3] for complexes 1 to 4 and found to be similar to the solid state. As a result, the metal ions of complexes 1 to 4 are six-coordinated and possessed distorted octahedral geometry. The proposed structures of complexes 1 to 4 are depicted in Figure 1.

#### Preliminary *in vitro* antibacterial screening activity

The preliminary *in vitro* antibacterial screening activity of

ligand, HL and complexes 1 to 4 are given in Table 5. The synthesized complexes and ligand, HL were screened for their *in vitro* antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Candida albicans* bacterial strains, by inhibition zone method using agar diffusion method (Yousif et al., 2009). 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°C. The activity was determined by measuring the diameter of the inhibition zone (in mm). The preliminary *in vitro* antibacterial screening revealed that complexes 1 to 4 showed a significant activity compared to the ligand, HL and all the

**Table 5.** Preliminary *in vitro* antibacterial screening activity of HL and complexes 1 to 4.

Compound	Inhibition Zone (mm)			
	<i>S. aureus</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>
HL	-	+	-	-
La(L) <sub>3</sub> , 1	++	+++	+	+
Nd(L) <sub>3</sub> , 2	-	++	+	-
Gd(L) <sub>3</sub> , 3	-	++	-	+
Dy(L) <sub>3</sub> , 4	+	++	-	-

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

complexes exhibited antimicrobial activity against *E. coli*. Moreover, complex 1 obtained showed some inhibition activity towards all the four bacterial strains although the activity were in the range of minimum 5 to 10 mm to larger than 20 mm. Based on the data obtained from Table 5, it clearly indicated that the complexes obtained were selective toward certain bacterial strains. As an example, complexes 1 and 3 showed some activity against *C. albicans* whereas complexes 1 and 4 performed some activity against *S. aureus*.

## Conclusion

The ligand, {(5-phenyl-1,3,4-oxadiazol-2-yl)thio}acetic acid was successfully synthesized. The ligand was treated to different lanthanide metal compounds to afford the corresponding complexes 1 to 4. The carboxylate anions coordinated to the metal atom via oxygen atoms resulting in the entire metal centre being six-coordinated and possessed distorted octahedral geometries. Preliminary *in vitro* antibacterial screening study indicated that all the complexes 1 to 4 obtained showed some comparable activity against *E. coli* and only complex 1 performed some activity to all four tested bacterial strains. Based on this preliminary *in vitro* antibacterial screening study, complexes 2 to 4 was found to be selective towards certain bacterial strains.

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