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Structural And Antimicrobial Studies Of Some Lanthanide(III) Complexes Of 4-[[2-Hydroxyphenyl]Imino]Methyl}-1,5-Dimethyl-2-Phenyl-1,2-Dihydro-3H-Pyrazol-3-One

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ABSTRACT

La(III), Pr(III), Nd(III) and Sm(III) complexes of the Schiff base ligand 4-[[2-hydroxyphenyl]imino]methyl}-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one(L1) having general formula $[Ln(L_1)_2(ClO_4)_2]ClO_4$ ($Ln = La, Pr, Nd$ and Sm) were synthesized. These complexes were characterised on the basis of elemental analysis, molar conductance, magnetic susceptibility and spectral techniques (IR, ¹H NMR & UV-Visible). From the analytical data, the stoichiometry of the complexes was found to be 1:2 (metal: ligand). All the complexes were 1:1 electrolytes as established by their molar conductivities. From the IR spectral data it has been confirmed the tridentate nature of the Schiff base ligand and also bidentate coordinating behaviour of two of the perchlorate ions. The lanthanide ions exhibit coordination number ten in these complexes. The Schiff base and its metal complexes were screened for their in vitro antimicrobial activities against six human pathogenic bacteria viz. *Escherichia coli*, *Vibrio cholerae*, *Salmonella typhimurium*, *Aeromonas hydrophila*, *Staphylococcus aureus* and *Bacillus subtilis* and antifungal activities against three fungal strains *Aspergillus flavus*, *Aspergillus fumigatus* and *Candida albicans* in agar disc diffusion method. Most of the metal complexes showed significantly enhanced antimicrobial activity than the Schiff base.

Keyword: Lanthanide(III) complexes; Schiff bases; antimicrobial activity

INTRODUCTION

Infectious diseases are the leading cause of death world-wide. Antibiotic resistance has become a global concern. The clinical efficacy of many existing antibiotics is being threatened by the emergence of multidrug resistant pathogens. There is a continuous need to discover new antimicrobial compounds with diverse chemical structures and novel mechanism of action [1, 2]. Metals and metal complexes have played key

roles in the development of pharmacy and modern chemotherapy [3] has received much attention. Schiff bases were important class of organic compounds. Such ligands and their metal complexes had a variety of applications including biological, clinical, analytical and industrial in addition to their important roles in catalysis and organic synthesis [4,5]. Antipyrine (2,3-dimethyl-1-phenyl-3-pyrazolin-5-one), its derivatives and complexes with transition and

rare-earth metals are of considerable importance in the biological and pharmaceutical fields because of their broad bioactivities as antitumor, antimicrobial, antiviral, and analgesics [6-12]. Lanthanide complexes can be used as diagnostic tools for biology and medicine due to their special, photo physical [13-15] and biological properties [16, 17]. An interesting coordination chemistry of lanthanide Schiff base complexes and its role in chemical, medical and industrial processes are enough to recognize their importance and to synthesize new complexes. Therefore, attempt has been made to describe synthesis, characterization and biological evaluation of some lanthanide(III) Schiff base complexes.

In this context we have synthesized La(III), Pr(III), Nd(III) and Sm(III) complexes of the Schiff base 4-[(2-hydroxyphenyl)imino]methyl-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (**L₁**). These complexes have been characterized by using elemental analysis, thermal studies, FT-IR, ¹H NMR, UV-Visible and molar conductance data. All complexes were screened against six bacterial strains comprising gram positive and gram negative bacteria and three fungal strains for determining antimicrobial efficiency.

Materials and methods

4-antipyrine carboxaldehyde, 2-aminophenol (Sigma Aldrich) and nutrient agar (Himedia) were purchased and used without further purification. Lanthanide perchlorates were prepared by dissolving the respective metal oxides (99.95%) in 60% A.R. perchloric acid (Merck), followed by crystallization. The C, H and N contents in the complexes were determined using Heracus CHN rapid analyser. All complexes were analysed for their metal and chloride content by standard methods [18]. The molar conductivities of the complexes were measured in DMF (10⁻³M). The IR spectra were recorded in the range 4000–350cm⁻¹ on Shimadzu IR470 spectrophotometer. The electronic spectra in the range 190–900nm were

recorded using Shimadzu UV–160A. The ¹H NMR spectra were recorded on a Bruker DRX-500 spectrometer using DMSO-*d*₆ as solvent. The magnetic susceptibility measurements were performed on a Sherwood Scientific Gouy Balance.

Synthesis of the Schiff base: 4-[(2-hydroxyphenyl)imino]methyl-1,5-dimethyl-2-phenyl-1,2-dihydro-3H-pyrazol-3-one (**L₁**)

2-aminophenol (0.44g) was dissolved in 20ml ethanol and added to 4-antipyrine carboxaldehyde (0.86g) in 30 ml ethanol. The 1:1 mixture was refluxed on a boiling water bath for 4 hours and the orange red solid formed was washed with ether, recrystallized from ethanol and dried. Yield: 71%, mp 169°C.

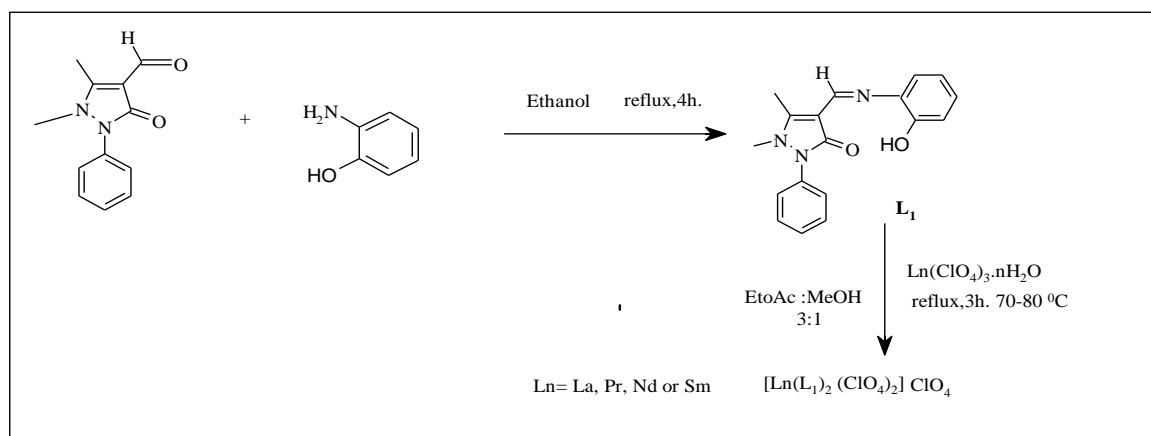
¹H NMR: (*d*₆-DMSO) (δ, ppm) : 8.76(s, 1H, phenolic), 8.3 (s, 1H, -CH=N-), 6.7-7.6(m, -Ph) 3.32(s, 3H, -N-CH₃), 2.72 (s, 3H, =C-CH₃). IR (cm⁻¹, KBr); ~3300 (ν OH), 1651(ν C=O), 1591 (ν C=N), 1272 (ν ph-O). Anal. Calcd for C₁₈H₁₇N₃O₂ (307.35) C, 70.34; H, 5.58; N, 13.67. Found: C, 70.1, H, 5.28; N 13.73%.

Synthesis of Lanthanide complexes (1) to (4)

The lanthanide complexes (**1**) to (**4**) were prepared according to the same procedure (**Scheme 1**). A hot methanolic solution (15ml) of **L₁** (0.615g, 2mmol) was refluxed with a solution of LaClO₄.6H₂O (0.544g, 1mmol) in ethyl acetate (25ml) at 70-80°C on a magnetic stirrer for 3 hours. The resulting solution was concentrated and cooled to room temperature. On cooling the colored complex (**1**) was precipitated, filtered and washed thoroughly with hot ethyl acetate to remove excess ligand. It was then dried in vacuum over anhydrous CaCl₂. Other complexes (**2**) to (**4**) were prepared in the same way by the reaction of **L₁** and corresponding Ln(ClO₄)₃.6H₂O (where Ln = Pr, Nd or Sm) in 1:2 (metal: ligand) ratio (**Scheme 1**). The yield and melting point of these complexes were found and tabulated in **Table 1**.

Table 1: Analytical and physical data of the ligand L₁ and its lanthanide complexes

Compound (Empirical formula)	Colour	Mol. Weight	mp °C	Yield (%)	% Observed(Calculated)					Λ_m Ω^{-1} mol ⁻¹ cm ²
					C	H	N	Cl	Ln	
L ₁ C ₁₈ H ₁₇ N ₃ O ₂	orange red	307.35	169	71	70.1 (70.34)	5.28 (5.58)	13.73 (13.67)	-	-	-
[La(L ₁) ₂ (ClO ₄) ₂]ClO ₄ (1)	Brown	1051.96	308	63	40.7 (41.1)	3.16 (3.23)	7.67 (7.98)	9.8 (10.1)	12.9 (13.2)	68
[Pr(L ₁) ₂ (ClO ₄) ₂]ClO ₄ (2)	Yellowish Brown	1053.96	324	66	40.8 (40.99)	3.15 (3.25)	7.6 (7.97)	9.9 (10.1)	13.1 (13.4)	77
[Nd(L ₁) ₂ (ClO ₄) ₂]ClO ₄ (3)	Brown	1057.29	328	61	40.48 (40.9)	3.08 (3.21)	7.5 (7.95)	9.76 (10.06)	13.3 (13.6)	74
[Sm(L ₁) ₂ (ClO ₄) ₂]ClO ₄ (4)	Yellowish Brown	1063.4	335	63	40.4 (40.6)	3.1 (3.2)	7.3 (7.9)	9.7 (10.03)	13.7 (14.1)	79

Scheme. 1. Synthesis of complexes [Ln(L₁)₂(ClO₄)₂]ClO₄

ANTIMICROBIAL ACTIVITY

The ligand and its lanthanide complexes were screened *in vitro* antimicrobial activity against the bacterial species viz. *Escherichia coli*, *Vibrio cholerae*, *Salmonella typhimurium*, *Aeromonas hydrophila*, *Staphylococcus aureus* and *Bacillus subtilis* and antifungal activities against three fungal strains *Aspergillus flavus*, *Aspergillus fumigatus* and *Candida albicans* by disc diffusion method [19]. The test organisms were grown on nutrient agar (muller hinton agar for bacteria and Sabouraud Dextrose agar for fungi) medium in petriplates. The test solutions were prepared in DMSO and soaked in filter paper discs of 5 mm diameter and 1mm thickness. 1mg of each of the test compounds were separately dissolved in 1ml dimethylformamide (DMF) to get stock solution. The filter paper disc (5mm diameter) impregnated with 20 μ L of each of the synthesized compound is placed on the seeded plates so that the amount of test material

present per disc is 20 μ g/disc. The plates were incubated at 37°C for 24 hours and the zones of inhibition were measured around the discs for bacterial and 72 hours for fungal species. Streptomycin (20 μ g /disc) and Amphotericin-B (20 μ g /disc) were used as antibacterial and antifungal standards respectively and DMF as control solvent. All the tests were performed three times simultaneously to check for consistency in the results and the mean was recorded.

RESULTS AND DISCUSSION

Analytical and physical data

The data obtained from elemental analysis, metal analysis and some physical properties like colour, melting point etc. are listed in **Table 1**. The complexes (1) to (4) were stable in air at room temperature, coloured, non-hygroscopic, soluble in common organic solvents like methanol, ethanol, DMF, DMSO, sparingly

soluble in acetone, acetonitrile and ethyl acetate but insoluble in water, benzene and ether. The percentage of metal, anion, carbon, hydrogen and nitrogen were summarized in **Table 1**. The stoichiometries of the complexes prepared by both the methods were determined from elemental analysis data found to be 1:2 stoichiometry (metal: ligand) and the complexes.

Molar conductance

The molar conductance (in $\text{ohm}^{-1}\text{cm}^2\text{mol}^{-1}$) values for the complexes were measured in DMF (10^{-3}M) at room temperature and given in **Table 1**. The Λ_m values were in the range reported for 1:1 electrolytes suggesting two of the perchlorate ions are present inside the coordination sphere while one remains as ionic [20]. Hence the complexes (**1**) to (**4**) may be represented by the general formulae $[\text{Ln}(\text{L}_1)_2(\text{ClO}_4)_2]\text{ClO}_4$ ($\text{Ln} = \text{La, Pr Nd and Sm}$)

Infrared spectra

The selected FTIR spectra of the Schiff base ligand **L₁** and its lanthanide(III) nitrate complexes are listed in **Table 2**. The binding modes of ligand to metal ions can be understood on comparison of IR spectra of complexes with that of the free ligand. The IR spectral band found at 1652 cm^{-1} corresponding to characteristic C=O stretching vibration of the Schiff base **L₁** get shifted to the region $1636\text{--}1644\text{ cm}^{-1}$ in all the complexes indicate that the carbonyl oxygen is coordinated to the central metal ion. Also $-\text{CH}=\text{N}-$ stretching vibration of **L₁** observed at 1594 cm^{-1} also shifted to lower wavenumbers in the range $1568\text{--}1578\text{ cm}^{-1}$ indicating coordination via azomethine nitrogen atom. This is further supported by the appearance of two medium intensity bands at

low frequency region around $452\text{--}462\text{ cm}^{-1}$ and $500\text{--}504\text{ cm}^{-1}$ in all the complexes can be assigned to the stretching vibrations of M-N and M-O bonds respectively. The presence of a broad band at $\sim 3360\text{ cm}^{-1}$ in the ligand spectrum corresponds to the stretching frequencies of aromatic hydroxyl substituent. In all the complexes these OH band is also present at $3050\text{--}3382\text{ cm}^{-1}$ with an increase in intensity indicates the coordination of metal ion to the phenolic oxygen without proton displacement [21,22]. In addition to that, the stretching frequency of aromatic C-O at 1272 cm^{-1} of the ligand also get slightly shifted lower frequencies in the complexes ($1245\text{--}1258\text{ cm}^{-1}$) support the above observation [13-16]. Thus **L₁** acts as a neutral tridentate ligand coordinating through carbonyl oxygen, imine nitrogen and phenolic oxygen. In all the perchlorate complexes; the triply split band maxima at $\sim 1143, 1114,$ and 1022 cm^{-1} are due to the ν_8, ν_6 and ν_1 vibrations respectively of perchlorate ion (C_{2v} symmetry), indicating coordination of the perchlorate groups in a bidentate fashion. The bands observed at ~ 940 and 636 cm^{-1} due to the ν_2 and ν_3 vibrations respectively of the coordinated perchlorate group. The presence of a very strong band at 1089 cm^{-1} is attributed to the ν_3 vibration of uncoordinated ClO_4^- ion (Td symmetry). Also another band in the range $\sim 618\text{--}627\text{ cm}^{-1}$ attributed to ν_4 , the asymmetric bending vibration of ionic perchlorate group support the existence of uncoordinated perchlorate ion in the complexes. All these observations suggest that the coexistence of both ionic and bidentately coordinated perchlorate groups in the complexes [23].

Table 2: Important IR spectral data (cm^{-1}) of ligand and its complexes

Complex	ν (O-H)	ν (C=O)	ν (C=N)	ν (C-O)	ν (M-N)	ν (M-O)	Coordinated perchlorate (C_{3v})					T_d Symmetry (Ionic perchlorate)	
							ν_8	ν_6	ν_1	ν_2	ν_3	ν_3	ν_4
L₁	3423 b	1651s	1591s	1272m	-	-	-	-	-	-	-	-	-
(1)	3363b	1638s	1575s	1251m	446w	501w	1143s	1114s	1022m	939s	636w	1086s	624s
(2)	3367b	1636s	1574s	1249m	449w	504w	1143s	1115s	1024m	943s	636w	1089s	627s
(3)	3320b	1644s	1576s	1245m	454w	505w	1139s	1113s	1023m	962s	639w	1080s	618s
(4)	3340b	1643s	1572s	1258m	461w	499w	1141s	1114s	1023m	958s	631w	1079s	621s

Electronic spectra

The UV-Visible absorption spectra of **L**₁ and the complexes (**1**) to (**4**) were recorded in DMF and the main bands were listed in **Table 3**. The ligand **L**₁ exhibits an intense absorption band at 294 and 375 nm that can be attributed to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of azomethine bond and carbonyl group respectively. The absorption bands of all the Ln(III) complexes show similarity which indicate similarity of their structures. In all the complexes both $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions are bands are shifted to lower wavelengths supporting the coordination of **L**₁ via the azomethine nitrogen and the carbonyl oxygen atoms to the central metal ion. In addition to these strong ligand bands, some weak *f-f* bands are identified in case of Pr(III), Nd(III), Sm(III) complexes [21,24]. The observed *f-f* transitions and their tentative assignments are given in the **Table 3**.

¹H NMR Spectra

The ¹H NMR spectra of the ligand **L**₁ and diamagnetic La(III) complex (**1**) were recorded in DMSO-d₆ solution. The ligand **L**₁ showed two singlet peaks at 8.76 and 8.3ppm (**Fig. 1**) were assigned to the phenolic hydroxyl proton and the azomethine proton (CH=N), respectively. A multiplet was observed in the range 6.7-7.5ppm were assigned to the protons of the aromatic rings. The other signals corresponding to methyl protons of the groups -N-CH₃ and =C-CH₃ were observed at 3.32 and 2.7 ppm respectively. In the ¹H NMR spectra of La(III) complex (**1**), peaks of azomethine proton showed a downfield shift to 8.4ppm and peak due to phenolic proton experienced a slight downfield shift to 8.85ppm compared to **L**₁ suggesting coordination of azomethine nitrogen and phenolic oxygen to the to the lanthanum ion [21,24]. In addition, the phenyl multiplet is slightly shifted upfield to 6.4-7.5ppm in complex(**1**) indicates due to change in chemical environment of the ring protons upon coordination.

Table 3: The UV-Visible absorption spectra of Schiff base ligand **L₁ and its Ln(III) complexes (**1**) to (**4**) in DMF solution at 25°C**

Compound	Wavelength λ_{\max} (nm)	Band Assignments	Magnetic moment μ (BM)
L ₁	294	$\pi \rightarrow \pi^*$	
	375	$n \rightarrow \pi^*$	
[La(L ₁) ₂ (ClO ₄) ₂]ClO ₄	322	$\pi \rightarrow \pi^*$	--
(1)	363	$n \rightarrow \pi^*$	
[Pr(L ₁) ₂ (ClO ₄) ₂]ClO ₄	474	³ H ₄ → ³ P ₁	3.41
(2)	484	³ H ₄ → ³ P ₀	
	325	$\pi \rightarrow \pi^*$	
	358	$n \rightarrow \pi^*$	
[Nd(L ₁) ₂ (ClO ₄) ₂]ClO ₄	471	⁴ I _{9/2} → ⁴ G _{11/2}	3.42
(3)	524	⁴ I _{9/2} → ⁴ G _{9/2}	
	581	⁴ I _{9/2} → ² G _{7/2} , ⁴ G _{5/2}	
	324	$\pi \rightarrow \pi^*$	
	363	$n \rightarrow \pi^*$	
[Sm(L ₁) ₂ (ClO ₄) ₂]ClO ₄	418	⁶ H _{5/2} → (⁶ P, ⁴ P) _{5/2}	1.3
(4)	451	⁶ H _{5/2} → ⁴ M _{17/2}	
	476	⁶ H _{5/2} → ⁴ I _{11/2}	
	498	⁶ H _{5/2} → ⁴ M _{15/2}	
	281	$\pi \rightarrow \pi^*$	
	335	$n \rightarrow \pi^*$	

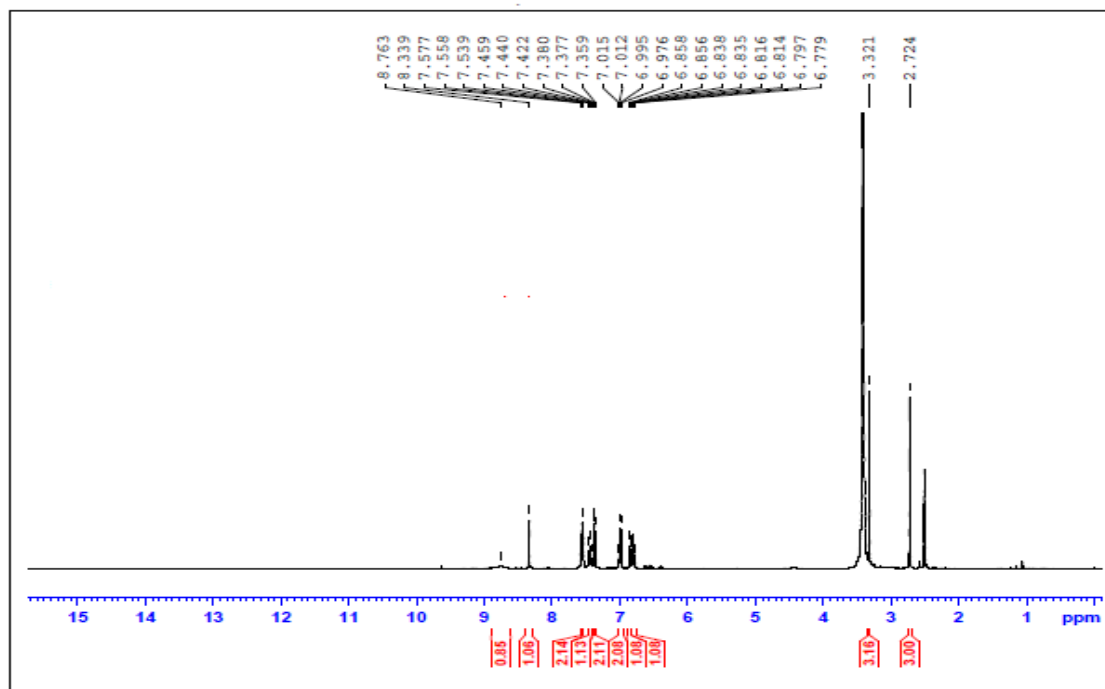


Fig.1: the ^1H NMR spectra of L_1

Magnetic susceptibility measurements

The magnetic moments data are listed in **Table 3**. The lanthanum complex (**1**) was found to be diamagnetic as expected while all other complexes (**2**) to (**4**) exhibit paramagnetic behaviour. The observed magnetic moment values of Ln(III) complexes are very close to the theoretical values calculated for the free lanthanide(III) ions. It suggest that there is

only very little interaction of the 4f electrons in metal-ligand bond formation, since these electrons are so screened that they are least affected by external ligand field [25].

Based upon the results of above physicochemical studies tentative structure of the lanthanide(III) perchlorate complexes $[\text{Ln}(\text{L}_1)_2(\text{ClO}_4)_2]\text{ClO}_4$ (where Ln = La, Pr, Nd and Sm) may be assigned as shown in **Fig.2**

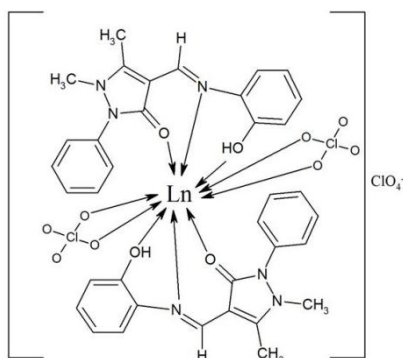


Fig 2: Tentative structure of complex $[\text{Ln}(\text{L}_1)_2(\text{ClO}_4)_2]\text{ClO}_4$, where Ln = La, Pr, Nd or Sm

Antimicrobial studies

The *in vitro* antimicrobial activity of the synthesised Schiff base ligand and their metal complexes against selected six human pathogenic bacteria viz. *Escherichia coli*, *Vibrio cholerae*, *Salmonella typhimurium*, *Aeromonas hydrophila*, *Staphylococcus aureus* and *Bacillus subtilis* and three fungi *Candida albicans*,

Aspergillus flavus and *Aspergillus fumigatus* by disc diffusion method. The antimicrobial screening data of compounds are summarised in **Table 4**. The Schiff base and its metal complexes varying degree of inhibitory effect on the growth of the tested bacterial and fungal strains. *In vitro* antibacterial studies indicate that the ligand (L_1) showed moderate activity

against three of the tested bacteria- *S.typhimurium*, *A.hydrophila* and *B. subtilis* with inhibition zone in the range 9-13mm. However the most of the metal complexes showed better antibacterial activity than compared to the Schiff base, with only slight exception in few cases. All the perchlorate complexes showed activity against *E.coli* and *S.typhimurium*. Among other complexes, Pr(III) complex (2) showed exceptionally higher activity against *E.coli*, *A.hydrophila* and *V.cholerae* in the range 22-31mm which is much higher than that of parent ligand and standard drug. The zone of inhibition exhibited by Pr(III) complex (2) against *V.cholerae* is shown in Fig.3. The other perchlorate complexes showed moderate activity against *E.coli*, *S.typhimurium*, *A.hydrophila*, *V.cholerae* with an inhibition zone of 8-13mm. The complexes (1), (2) and (4)

exhibited minimum to moderate activity with an inhibition zone of 7-14mm against Gram positive species *S.aureus* and *B. Subtilis*. Pr(III) complex (2) showed the maximum activity against both these species.

The ligand L₁ exhibited greater activity against one of the tested species *C.albicans* with a larger inhibition zone of 21mm while no activity against *A.flavus* and *A.fumigatus*. Against *C.albicans*, the Pr(III) complex (2) exhibited exceptionally high activity with an inhibition zone of 26mm while other complexes showed nil activity Against *A.flavus* and *A.fumigatus*, the complexes showed moderate activity with an inhibition zone in the range 9-16mm and complex (2) showed highest inhibition zone against both species. A graph showing the activity of ligand and complexes is depicted in Fig.4.

Table 4: Mean diameter of zone of inhibition (mm) for the antimicrobial activity of L₁ and its Ln(III) complexes using agar disc diffusion method(20µg/disc)

Compound	Diameter of zone of inhibition (mm)								
	Anti Bacterial activity						Anti fungal activity		
	<i>E.coli</i>	<i>S.typhi</i>	<i>V.cholera</i>	<i>A.hydrophilia</i>	<i>S.aureus</i>	<i>B.subtilis</i>	<i>C.albicans</i>	<i>A.flavus</i>	<i>A.fumigatus</i>
L ₁	-	13	-	10	-	10	21	-	-
(1)	11	10	12	12	8	9	-	10	9
(2)	22	16	31	23	14	10	26	16	15
(3)	14	10	10	12	-	-	-	-	-
(4)	13	9	-	-	7	8	-	14	13
DMF	0	0	0	0	0	0	0	0	0
Streptomycin (Std.)	18	20	6	18	21	23	-	-	-
Amphotericin -B	-	-	-	-	-	-	18	16	15

Key to interpretation: (-)=no inhibition zone; 1-5 mm = less active; 5-10 mm = minimum activity; 10-15 mm = moderate activity; >15= high activity

- DMSO: negative control
- Streptomycin: antibacterial standard
- Amphotericin-b : antifungal standard



Fig.3. Photo of inhibition zone shown by [Pr(L₁)₂(ClO₄)₂]ClO₄ against *V.cholera*

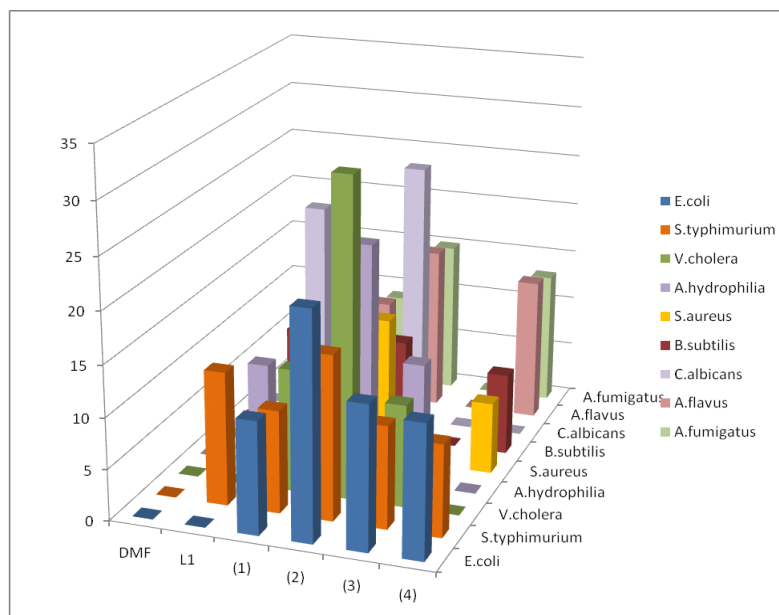


Fig.4: Graph Showing the Antimicrobial activity of Schiff base L₁ and its Ln(III)complexes

The *in vitro* antimicrobial screening of compounds and observed findings indicate that the ligand shows considerable antipathogenic behavior and its therapeutic action is considerably enhanced by coordination to certain metal ions. A likely explanation for higher activity of the metal complexes compared to free ligand has been suggested in the light of overtone's concept and Tweedy's chelation theory [26]. The polarity of the metal ion will be reduced upon chelation primarily because of partial sharing of its positive charge with the donor groups. Further it also increases π -electron delocalization over the entire chelate ring [27]. This increases the lipophilic character of the metal chelates which favours the penetration of the complexes into lipid membranes and blocks the metal binding sites in the enzymes of microorganisms which inhibits the further growth. According to overtone's concept of cell permeability, the lipid membrane that surrounded cell favours only lipid soluble materials so that liposolubility is an important factor that controls antimicrobial activity [28-29].

CONCLUSION

In the present work the lanthanide(III) complexes of the tridentate ligand L₁ of the type $[\text{Ln}(\text{L}_1)_2(\text{ClO}_4)_2]\text{ClO}_4$ (Ln = La, Pr, Nd and Sm) were synthesized and characterized by a variety of physicochemical methods. The lanthanides

exhibit a coordination number ten in these complexes. The ligand and the complexes were analyzed for their antimicrobial activities. The metal complexes have appreciably improved antibacterial and antifungal activity against microbial strains in compared with the free ligand. Thus, they may find application as a new antimicrobial agent after further study of their biological properties. Among the tested complexes Pr(III) complex showed exceptional high activity against most of the tested species.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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