

Synthetic, spectral, antimicrobial and plant growth regulatory activity of coordination compounds of N and S/O donor ligands with some rare earth elements

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ABSTRACT

Coordination complexes of La(III) and Yb(III) with Schiff bases namely 3-acetyl coumarin hydrazinecarbothioamide (ACTSZH), 3-acetylcoumarin hydrazinecarboxamide (ACSHZ), 3-formyl-4-chlorocoumarin hydrazinecarbothioamide (FCTSZH) and 3-formyl-4-chlorocoumarin hydrazinecarboxamide (FCSZH) have been synthesized. These complexes were prepared by the interaction of ligands in 1:3 molar ratios and the mixture was heated under reflux for about 13-16 h in methanol to yield the products. The characterization and nature of bonding of these complexes were elucidated by elemental analysis, melting point, molecular weight determinations, magnetic moment, molar conductance, IR, ¹H NMR and ¹³C NMR spectral studies. Spectral studies confirm the ligands to be monofunctional bidentate and an octahedral environment around the metal ions. The molar conductance values indicate the non-electrolytic behaviour of the metal complexes. The reported compounds are examined as antimicrobial agents by screening their biological interactions; they showed enhanced antimicrobial activity compared with that of the free ligands. Plant growth regulating activity of two ligands and their complexes has also been recorded on gram plant, and results have been discussed.

Keywords: Lanthanide(III) complexes, magnetic moment, spectral studies, biological studies.

1. INTRODUCTION

Schiff bases have played a marvelous role in the development of coordination chemistry [1,2]. Because of these, complexes of the rare earth ions are a subject of increasing interest in bioinorganic and coordination chemistry [3]. There is good prospectus of study on N and S/O donor systems concerning their biochemical properties that is N and S/O donor ligands possess a range of biological applications like antitumor activity [4], antibacterial [5], antifungal [6], and antifertility [7] activity. Schiff base complexes also exhibit anticoagulation and plant growth regulating activities [8-10]. In recent years, there is increasing interest in application of rare earth metal to medicinal plants, as it is able to affect the growth and/or development of such plants directly or indirectly. Application of adequate rare earth metal can promote the germination of seeds and roots development, increase plant biomass, and improve the quality of fruiting bodies. There is a certain critical level for absorption of rare earth elements in plants, and these elements can

improve growth and development of plants when supplied at a suitable concentration. However, if the concentration of these elements exceeds the optimum level, they can inhibit the plant growth and even cause mortality [11]. The metal complexes of hydrazinecarboxamides [12,13] and hydrazinecarbothioamides [14,15] have remarkable potential for inhibiting growth of various pathogenic microorganisms and this property has been exploited in pharmacological applications. An important role of lanthanide complexes in chemical, medical and industrial processes is enough to recognize them as worthwhile for synthesis of new complexes. Recently, coumarin derivatives have been evaluated in the treatment of human immunodeficiency virus, due to their ability to inhibit human immunodeficiency virus integrase [16,17]. Several authors have reported the use of 7-hydroxycoumarin as the treatment of human carcinomas [18] and the inhibition of growth of cell lines of various types of cancer [19-21]. Encouraged by the above findings and our

interest in the biological and chemical properties of such compounds, we envisioned to design and synthesize some coumarin based imines and their La(III) and Yb(III) complexes.

2. EXPERIMENTAL

Hydrated lanthanum(III) chlorides, ytterbium(III) chloride, 3-acetyl coumarin and 4-hydroxy coumarin were purchased from Alfa Aesar and used as received. All the chemicals and solvents used were of analytical grade. All the solvents were dried and distilled before use. The metal contents were estimated complexometrically with EDTA using Erichrome Black T as an indicator. Molecular weight determinations were carried out by the Rast Camphor Method [22]. Sulfur and nitrogen were estimated by the Messenger's [23] and Kjeldahl's [24] method, respectively. Melting points were determined by using capillaries in an electrical melting point apparatus. The conductivity values measured on 10^{-3} mol dm⁻³ solution in DMF at room temperature. Magnetic moment measurements were taken on a model 155 vibrating sample magnetometer. Infrared (IR) spectra of the ligands and their complexes were recorded on a Nicolet Magna FTIR-550 spectrophotometer as KBr pellets. ¹H and ¹³C NMR spectra were scanned on a 400MHz Advance III NMR, Spectrometer in DMSO-d₆ using TMS as an internal standard at room temperature.

2.1. Preparation of the ligands

For the preparation of the ligands weighed amount of starting materials 3-acetylcoumarin (2.56 g, 10mmol) and 3-formyl-4-chlorocoumarin (2.68 g, 10mmol) with thiosemicarbazide (0.91 g, 10mmol) or semicarbazide hydrochloride (1.11 g, 10mmol) in the presence of sodium acetate in 1:1 molar ratio, in absolute alcohol. The reaction mixture was then refluxed over a water bath for 3-4 h and allowed to stand overnight. The products were recrystallized from the solvent ethanol and dried *in vacuo*. 3-Formyl-4-chlorocoumarin is prepared as described in the literature [25]. The synthetic route of the ligands is given in Scheme 1.

2.2. Synthesis of the sodium salt of the ligands

Sodium metal(0.35g-0.39g) was taken in equimolar ratio of the ligand. Now both the sodium metal and ligand were dissolved in minimum amount of methanol separately. Ultimately these two solutions had been dissolved to prepare sodium salt of the ligand. In this process the sodium metal first reacts with methanol and form sodium methoxide. This sodium methoxide in the next step reacts with the ligand and replaces acidic proton from the enolic

form of the ligand with the sodium metal and form sodium salt of the particular ligand.

2.3. Synthesis of the lanthanide (III) complexes

The methanolic solution of the hydrated lanthanide chloride LnCl₃.6H₂O(2g, 5.16-5.66mmol) was mixed with methanolic solution of the sodium salt of the ligand(3.79-5.12g, 15.48-16.98mmol) in 1:3 molar ratios. The mixture was then heated under reflux for about 13-16 hrs. On cooling, the sodium chloride which formed in this reaction was separated out by the alkoxy funnel and then filtrate was dried *in vacuo*. The purity was further checked by TLC using silica gel G. The physical properties and analytical data of these complexes are summarized in Table 1. Suggested structure of the complexes is given in Figure 1.

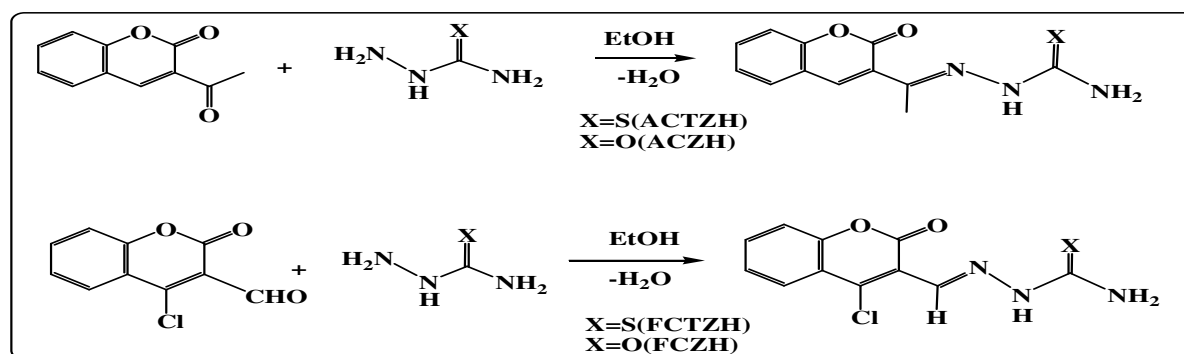
2.4. Biocidal screening

2.4.1 *In vitro* Antifungal Activity: Agar plate technique

Bioefficacies of the synthesized compounds were checked *in vitro*. The test fungi, namely *A. fumigates* and *Aspergillus niger* were obtained from the Seed Pathology Laboratory, Department of Botany, University of Rajasthan, Jaipur, India. The *in vitro* antifungal activities of the ligands and their complexes have been evaluated against two pathogenic fungi, by the agar plate technique [26]. The potato dextrose agar (PDA) medium was prepared in the laboratory to maintain fungal growth. Potato Dextrose Agar (PDA), medium was prepared by mixing 1000 mL of potato infusion to 20g each of agar and glucose followed by autoclaving as usual. Solutions of the test compounds in methanol at 50, 100 and 200 ppm were prepared and then mixed with the medium. The medium was then poured into Petri plates and spores of fungi were placed on the medium with the help of inoculum's needle. These Petri plates were wrapped in polythene bags containing a few drops of alcohol and were placed in an incubator at 25±2°C. The activity was determined after 96 h of incubation at room temperature (25°C). Controls were also run and three replicates were used in each case. The linear growth of fungus was obtained by measuring the diameter of the fungal colony after 4 days. The antifungal screening data (Graph - 1) of compounds were compared with the standard (Flucanazole). The linear growth of the fungus was recorded by measuring the diameter of the fungal colony after 96h and the percentage inhibition was calculated by the equation:

$$\% \text{ inhibition} = 100 (C - T) / C$$

Where C and T are the diameters of the fungal colony in the control and the test plates, respectively [27].



Scheme -1: Synthetic route of the ligands

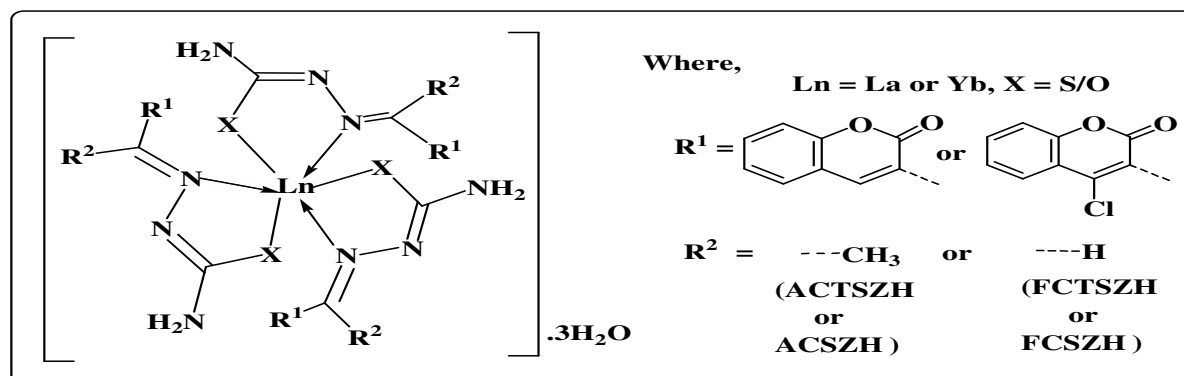
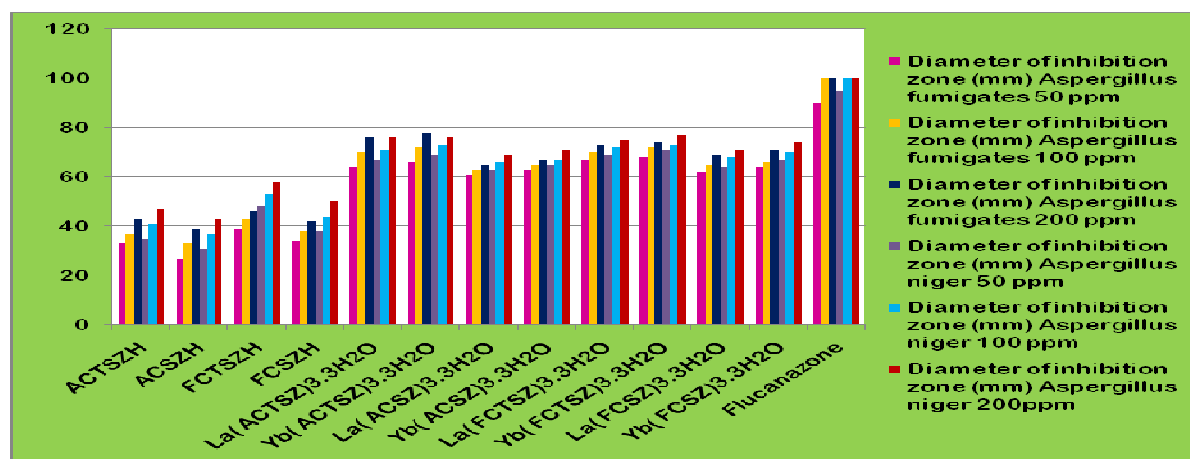


Figure- 1: Proposed structure of the synthesized metal complexes.



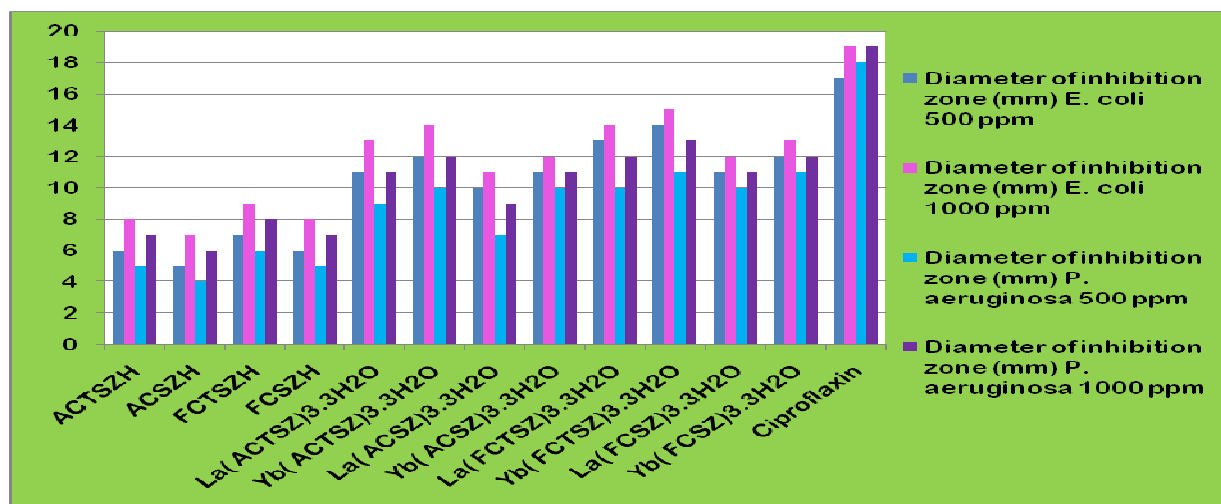
Graph- 1: Activity index of antifungal activity of the ligands and their complexes

2.4.2. *In vitro* Antibacterial Activity: Disc diffusion method

The ligands and their corresponding metal complexes were tested for their antibacterial activity (Graph - 2) against *Echerichia coli* and *Pseudomonas aeruginosa* (obtained through the courtesy of SMS medical college, Jaipur, India) using the disc diffusion method^[28]. The nutrient agar medium having composition of peptone 5 g, beef extract 5 g, NaCl 5 g, agar-agar 20 g, and distilled water 1000 mL was pipetted into the Petri dish. When it solidified, 5 mL of warm-seeded agar was applied. The seeded agar was prepared by cooling the molten agar to 40°C and then adding 10 mL of bacterial suspension.

The compounds were dissolved in methanol in 500 and 1000 ppm concentrations. Paper discs of Whatman filter paper (No.1) measuring diameter of 6 mm were soaked in these solutions of varied concentrations. The discs were dried and placed on the medium previously seeded with organisms in Petri plates at suitable distance. The Petri plates were stored in an incubator at 37°C for 20-24 h. The antibacterial activity of a common standard antibiotic *Ciproflaxin* was also recorded using the same procedure as above at the same concentrations and solvent. The % Activity Index for the complex was calculated by the formula as under:

$$\% \text{ AI} = \text{IZ of compounds} \times 100 / \text{IZ of standard}$$

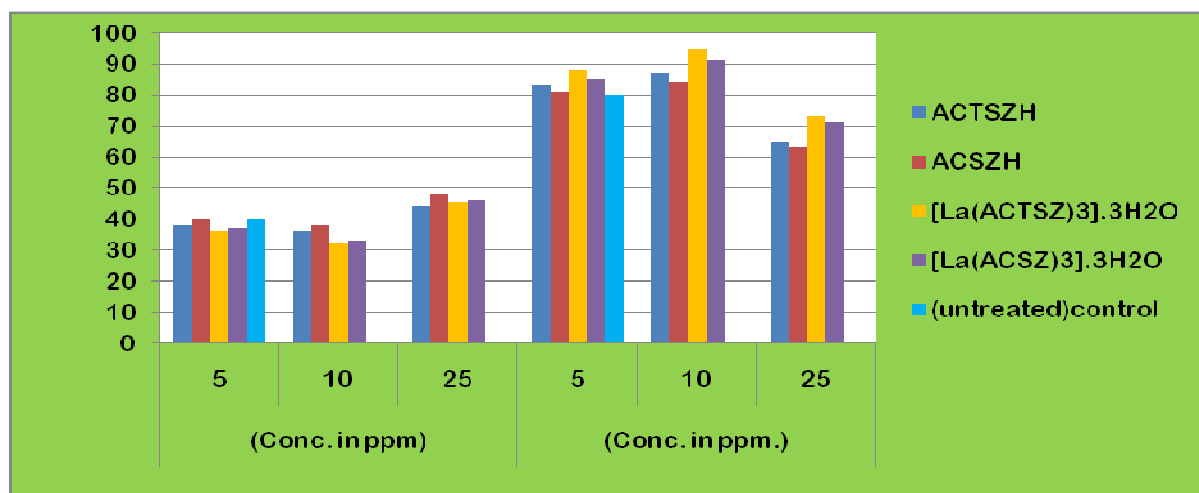


Graph- 2: Activity index of antibacterial activity of ligands and metal complexes

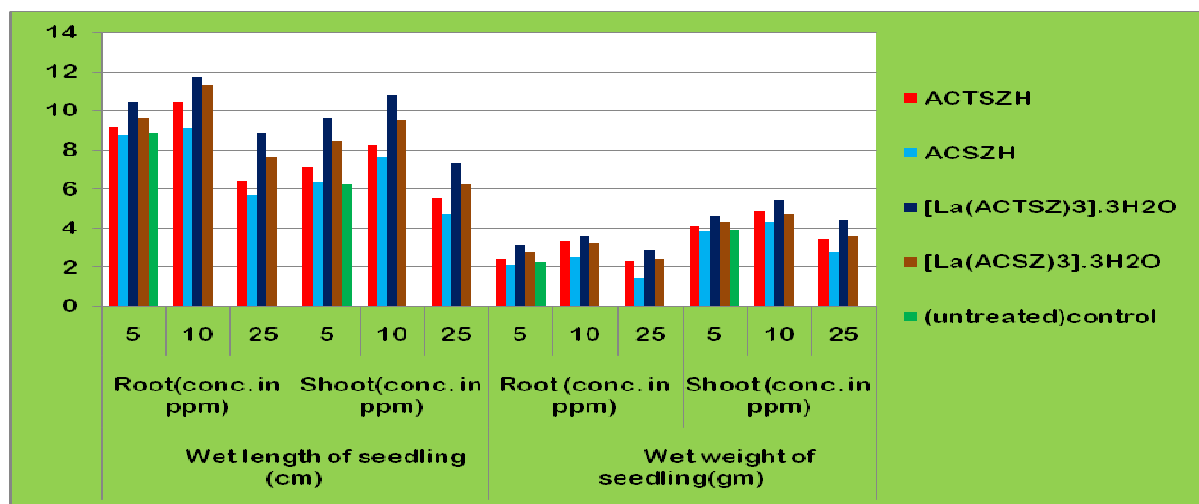
2.4.3. Plant growth regulating activity: Towel Paper method

The use of rare earth elements in agriculture to promote the growth of plants is well known. Keeping this fact in view, the ligands, ACTSZH and ACSZH and their La(III) complexes were used to carry out the germination study on *Cicer aretinum* (Gram plant). The germination was followed by the Towel Paper method. Two brown coloured towel papers of equal size (46cm×27 cm) for each test were jointly soaked in different concentrated (5, 10, and 25 ppm) ligands and their complexes for treated experiments and in water for controlled experiment for 4 h and placed over a butter paper (39 cm×25 cm). 100 seeds were placed at an equal distance over the towel papers, which were subsequently covered by another moist towel paper (46cm×27 cm). Then the towel paper was rolled up, two ends of the towel paper tied lightly with a rubber band and

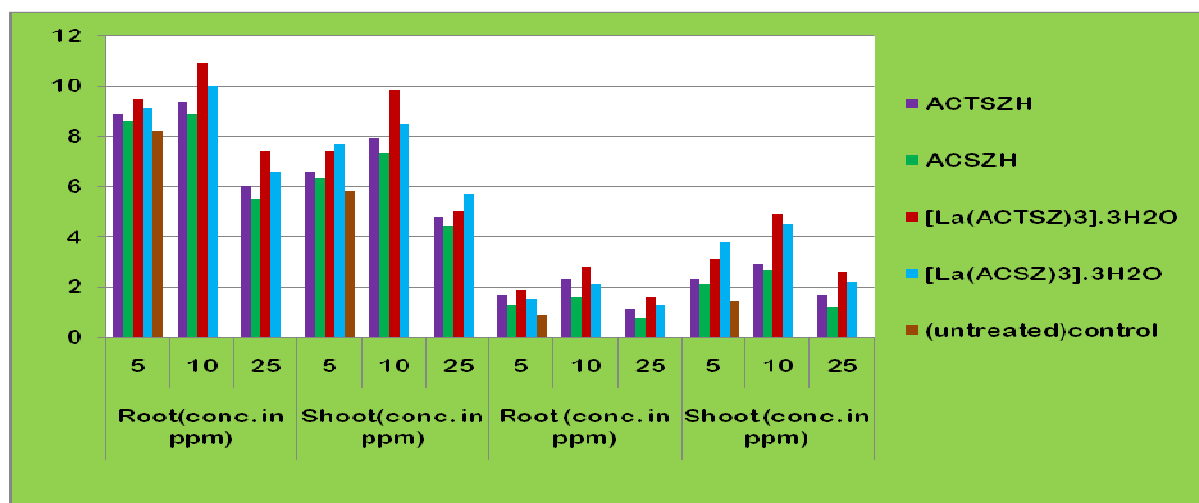
placed in a germination chamber at 25±1 °C. 100 seeds were used for each sample. The observations for percent germination and normal seedling were recorded on the 4th and 8th days. The seedlings, which possessed the ability to develop into fully normal and healthy plants, were considered as normal seedlings. In the second experiment, the seeds were treated with physiologically active concentration of the plant growth regulators solution for 6 h at room temperature and drying them to the original moisture level by a hot air circulating oven. After that, uniform size seeds were placed on Whatman No. 1 filter paper lying in the glass Petri plates. Each Petri plate has 15 seeds placed at equidistance. The filter papers were moistened with fresh solutions of required concentrations. The concentrations of the plant growth regulators used were 5, 10, and 25 ppm (Graph 3 to 5).



Graph- 3: Effect of the ligands and their La(III) complexes on growing period and percent germination of *Cicer aretinum*



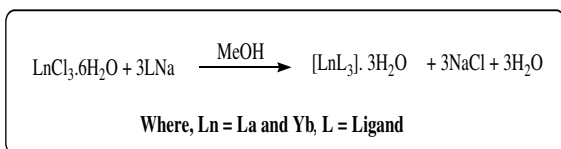
Graph - 4: Effect of the ligands and their La(III) complexes on Germination(wet length and wet weight) of *Cicer arretinum*.



Graph - 5: Effect of the ligands and their La(III) complexes on Germination (Dry length and dry weight of seedling) of *Cicer arretinum*

3. RESULTS AND DISCUSSION

The reactions of hydrated lanthanide chlorides with monobasic bidentate ligands have been shown by the following general equation:-



The newly synthesized complexes have been obtained as coloured solids which exhibit their solubility in methanol, DMSO and DMF. The monomeric nature of these products has been confirmed by the molecular weight determinations. Measured molar conductance in DMF shows the non electrolytic behaviour of metal complexes pointing towards non dissociation of complexes in DMF (Table 1).

3.1. IR spectra

IR spectra of the complexes (Table 2) show that ligands behave as monobasic bidentate ligands, coordinating through thiolic sulfur/ketonic oxygen and azomethine nitrogen while the carbonyl of lactone and -NH₂ remain free. IR spectra of the free ligands show a medium intensity band at 3150–3240 cm⁻¹ due to -NH, which is absent in the spectra of the complexes indicating the deprotonation of this group on coordination with the metal atom. The IR spectra of the free ligands display absorption bands at 1610–1635 assigned to (>C=N) bands. The marked shift of (>C=N) band observed in all the complexes indicates the involvement of azomethine nitrogen upon complexation. The bands at 1730-1735 cm⁻¹ due to (>C=O) of lactone moiety of the ligands remain almost unchanged in the complexes indicating their non-involvement in

complexation. The broad band, due to (-NH) vibrations, disappears in the spectra of the complexes, indicating the deprotonation of this group on coordination with the metal atom. The bands at 1080-1085 cm⁻¹ and 1690-1720 cm⁻¹ in the free ligands were attributed to (>C=S) and (>C=O), respectively and the appearance of new bands at 941-964 cm⁻¹ and 1022-1035 cm⁻¹ due to (C-S) and (C-O) were observed in metal complexes indicating coordination of sulfur and oxygen to the central metal atom. The spectra of the free ligands display two sharp bands at 3340-3500 and 3350-3490 cm⁻¹ due to $\nu_{\text{asym.}}$ and $\nu_{\text{sym.}}$ vibrations of NH₂ group, respectively, which remain at almost the same positions in the spectra of the complexes, suggesting that the -NH₂ group is not involved in chelation. Some new bands observed in the regions 508-556 and 411-429 cm⁻¹ for $\nu(\text{M-N})$, $\nu(\text{M-S})$, respectively. The band in 570-592 cm⁻¹ range may be assigned to $\nu(\text{M-O})$ vibrations in the respective complexes. The appearance of these bands further supports bonding of the ligands to the metal through nitrogen, sulfur and oxygen.

3.2. ¹H NMR spectra

The proton magnetic resonance spectral data of the ligands and their corresponding metal complexes (Table 3) have been recorded in DMSO-d₆ using TMS as internal standard. In the NMR spectra of the ligands, a complex pattern in the region δ 6.42-8.13 ppm due to aromatic protons, appears almost in the same position in their respective complexes. Ligands show singlets at δ 3.41- 3.46 ppm assigned to -NH₂ proton. In the spectra of Ln(III) complexes, the -NH₂ proton signal remains almost unperturbed indicating the non involvement of this group in the complexation. The ¹H NMR spectra of the ligands show a signal at δ 8.46-8.68 ppm which is due to -NH proton. The absence of this signal in the spectra of the complexes, suggests that this proton has been lost *via* thioenolization and ketoenolization of >C=S and >C=O groups and coordination of the sulfur and oxygen atom to the metal atom, respectively. Moreover, >C=N proton in ligands FCTSZH and FCSZH show singlet at δ 6.7-6.8 ppm, shifted to downfield in the metal complexes due to the coordination through metal atom.

Table- 1: Analytical data and physical properties of the ligands and their complexes

Compound	Colour	Melting Point (°C)	Found (Calcd.) (%)				μ_{eff} (B.M)	Molar Cond. (cm ² mol ⁻¹) DMF	Mol.Wt. Found (Calcd.)	Yield (%)
			N	S	Cl	Ln				
(ACTSZH)	Cream Yellow	210	16.01 (16.08)	12.11 (12.27)	-	-	-	-	261.21 (261.31)	81
(ACSZH)	Cream	233	17.00 (17.13)	-	-	-	-	-	245.64 (245.23)	78
(FCTSZH)	Brown	127	14.70 (14.92)	11.08 (11.38)	12.03 (12.58)	-	-	-	281.34 (281.71)	81
(FCSZH)	Yellow	133	14.50 (14.82)	-	13.05 (13.35)	-	-	-	261.28 (261.32)	80
[La(ACTSZ) ₃].3H ₂ O	Pale Yellow	198-202d	11.65 (11.76)	9.67 (9.87)	-	14.23 (14.26)	0.00	10.8	973.34 (973.86)	75
[Yb(ACTSZ) ₃].3H ₂ O	Brown	218-222d	14.23 (14.47)	9.34 (9.50)	-	17.03 (17.16)	4.52	11.4	1007.71 (1007.96)	72
[La(ACSZ) ₃].3H ₂ O	Orange	180-184d	8.78 (8.85)	-	-	14.80 (14.95)	0.00	10.2	928.32 (928.59)	70
[Yb(ACSZ) ₃].3H ₂ O	Cream	230-234d	8.96 (8.83)	-	-	17.98 (18.02)	4.49	11.3	959.65 (959.76)	69
[La(FCTSZ) ₃].3H ₂ O	Dark Brown	245-249d	12.14 (12.17)	9.11 (9.29)	10.13 (10.28)	13.12 (13.42)	0.00	10.5	1035.01 (1035.08)	74
[Yb(FCTSZ) ₃].3H ₂ O	Chocolate Brown	256-260d	11.64 (11.79)	8.68 (8.99)	9.40 (9.96)	16.09 (16.12)	4.47	11.6	1069.18 (1069.21)	75
[La(FCSZ) ₃].3H ₂ O	Cream	230-234d	12.63 (12.77)	-	10.35 (10.79)	13.97 (14.07)	0.00	10.7	986.36 (986.89)	73
Yb(FCSZ) ₃ .3H ₂ O	Light Green	205-209d	12.13 (12.34)	-	10.27 (10.43)	16.65 (16.94)	4.44	11.9	1020.98 (1021.03)	69

Table- 2: IR (cm⁻¹) spectral data of the ligands and their corresponding complexes

Compounds	$\nu(\text{NH})$	$\nu(\text{C=S})/\nu(\text{C=O})$	$\nu(\text{C-S})/\nu(\text{C-O})$	$\nu(\text{C=N})$	$\nu(\text{M}\rightarrow\text{N})$	$\nu(\text{M}\rightarrow\text{O})$	$\nu(\text{M}\rightarrow\text{S})$
(ACTSZH)	3210	1080	-	1620	-	-	-
(ACSZH)	3190	1690	-	1610	-	-	-
(FCTSZH)	3150	1085	-	1630	-	-	-
(FCSZH)	3240	1720	-	1635	-	-	-
[La(ACTSZ) ₃].3H ₂ O	-	-	941	1630	508	-	411
[Yb(ACTSZ) ₃].3H ₂ O	-	-	949	1634	517	-	419
[La(ACSZ) ₃].3H ₂ O	-	-	1022	1622	532	570	-
[Yb(ACSZ) ₃].3H ₂ O	-	-	1028	1524	538	572	-
[La(FCTSZ) ₃].3H ₂ O	-	-	960	1640	512	-	426
[Yb(FCTSZ) ₃].3H ₂ O	-	-	964	1644	516	-	429
[La(FCSZ) ₃].3H ₂ O	-	-	1030	1646	553	589	-
[Yb(FCSZ) ₃].3H ₂ O	-	-	1035	1651	556	592	-

Table- 3: ¹H NMR(δ , ppm) spectra of the ligands and their La(III) complexes

Compounds	-NH	-NH ₂	Aromatic proton
ACTSZH	8.65	3.43	6.44-8.10
ACSZH	8.46	3.41	6.42-8.04
FCTSZH	8.68	3.46	6.71-7.73
FCSZH	8.48	3.45	6.69-8.11
[La(ACTSZ) ₃].3H ₂ O	-	3.42	6.65-8.22
[La(ACSZ) ₃].3H ₂ O	-	3.40	6.55-8.12
[La(FCTSZ) ₃].3H ₂ O	-	3.44	6.84-7.77
[La(FCSZ) ₃].3H ₂ O	-	3.43	6.92-8.18

3.3. ¹³C NMR spectra

¹³C NMR spectra of the ligands and their corresponding metal complexes have been recorded in DMSO-d₆ using TMS as internal standard. The conclusions drawn from the IR and ¹H NMR spectra are concurrent with the ¹³C NMR spectral data regarding the confirmation of the proposed structure. In the case of ¹³C NMR spectra, the considerable shifts in the position of the carbon atoms attached to the different participating groups clearly indicate the bonding of azomethine nitrogen to the metal atom. The signal due to lactone >C=O carbon atoms remains almost in same position in the ¹³C NMR spectra of the metal complexes while marked shifts in the position of the carbon atoms attached to the sulphur/oxygen atom shows that proton is lost via thioenolization and ketoenolization. Thus, a

considerable change in the chemical shifts of the carbons attached to nitrogen, oxygen and sulphur is indicative of the role of these elements in coordination. Spectral data of the ligands and their metal complexes are given in table 4.

3.4. Magnetic properties

The observed magnetic moment data are summarized in Table 1. The paramagnetic behaviour of the lanthanide complexes is consistent with the presence of unpaired electrons. The La(III) complexes are diamagnetic as expected due to the absence of unpaired electrons. The magnetic moment of Yb(III) complexes were in the range of 4.44 - 4.52. The magnetic moments of the complexes do not deviate much from Van Vleck values^[29], indicating that there is no significant participation of the 4f

Table - 4: ^{13}C NMR (δ , ppm) spectral data of ligands and their La(III) complexes

Compounds	C=S/C=O	>C=N	Aromatic proton
ACTSZH	163.49	154.37	160.73,128.12,101.41,114.63,157.70,154.11,127.24, 132.77,125.30
ACSZH	170.55	153.33	161.92,129.52,100.35,115.37,158.95,154.36,127.54, 133.52,125.35
FCTSZH	171.85	165.65	160.34,127.56,116.78,130.42,146.48,152.56,128.25.135.69,123.51
FCSZH	176.56	162.45	158.68,127.47,119.69,123.23,146.76,152.57,128.54,135.41,128.41
[La(ACTS ₃)] ₃ .3H ₂ O	166.32	158.57	161.94,128.48,101.56,115.45,157.50,156.51,129.14,133.77, 127.48
[La(ACS ₃)] ₃ .3H ₂ O	173.57	157.54	162.42,130.62,102.33,115.67,159.35,155.76,127.64, 134.32,125.78
[La(FCTS ₃)] ₃ .3H ₂ O	179.58	167.36	162.25,129.36,118.18,131.52,148.67,153.76,130.35.137.62,124.11
[La(FCS ₃)] ₃ .3H ₂ O	182.12	166.51	169.18,127.67,120.59,123.63,147.66,153.27,129.64,136.41,129.71

electrons in bonding. The magnetic moment values agree with those reported for typical lanthanide complexes and indicate the non involvement of 4f electrons in bonding due to their very effective shielding by the electrons in $5s^2 5p^6$ orbitals.

3.5. Biological aspects

In the present study, the ligands and their lanthanide(III) complexes were evaluated for their antifungal activity against two fungi, *A. fumigates* and *Aspergillus niger* and two bacteria, *Echerichia coli* and *Pseudomonas aeruginosa*. The results are summarized in graph 1 and 2. The results were compared with those of the standard drug Flucanazole for fungi and Ciproflaxin for bacteria. All the ligands and their respective lanthanide(III) complexes were found to be sensitive against all the fungal and bacterial strains. The antimicrobial screening data indicate that the lanthanide complexes are more potent antimicrobial agents than the free ligands. The ligands ACTSZH and ACSZH and their La(III) complexes show positive or beneficial effect plant growth only at optimum concentrations. Ligands(ACTS₃H and ACS₃H) and La(III) complexes at higher concentration(25 ppm) are toxic whereas lower concentration(10 ppm) promote plant growth action, called the Hormesis effect[30] and this optimum concentration level is called hormetic threshold level. The activity has been recorded in terms of a decrease in the growing period and an increase in the wet and dry length and the weight of seedling. The activity of the ligand increases on complexation because lanthanide metal increase

the production of secondary metabolites via promoting the transcriptions of essential biosynthetic genes^[31].

4. CONCLUSION

On the basis of the analytical data and spectral studies, it has been observed that the ligands coordinated to the metal atoms in a monobasic bidentate manner and thus possess octahedral geometry. The complexes showed better antimicrobial activities as compared to the parent ligands but less active than Flucanazole and Ciprofloxacin as standard drugs. The ligands ACTSZH and ACSZH and their La(III) complexes show positive or beneficial effect on the growth of seeds of *Cicer aretinum* plant.

Acknowledgments

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