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ANTISPERMATOGENIC ACTIVITY OF LATER TRANSITION METAL COMPLEXES OF BENZOTHIAZOLINES DERIVED FROM SUBSTITUTED COUMARINS IN MALE RATS

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ABSTRACT

Biologically active sulfur donor ligands 3-acetylcoumarin benzothiazoline and 3-formyl-4-chlorocoumarinbenzothiazoline and their lanthanide metal complexes were synthesized, characterized and examined for their antifertility activities. The present investigation was conducted to reveal the effect of later transition metal complexes on the reproductive organs of male rats. In male rats, dose level of 30 mg/kg of ligands and their metal complexes was administrated for 60 days which caused a significant decline in the weight of reproductive organs. Negative fertility in treated rats was seen in fertility test .The treatment has also shown decline in the sperm motility and density significantly. A significant lowering in glycogen, protein and sialic acid and an increase in cholesterol content of testes were noticed. Present study indicated that ligands and their lanthanide metal complexes showed antifertility effects on male reproductive functions.

KEYWORDS:3-acetylcoumarinbenzothiazoline,3-formyl-4-chlorocoumarinbenzothiazoline, spectral studies, antifertility activity.

1. INTRODUCTION

Increasing population of India at an alarming rate and limited sources has become the major concern for the people of all the walks of life. Within few years of time span, India will be the leading country as far as the population growth is concerned. In view of the rapid development and challenging demands, it has become necessary to synthesize and screen newer compounds for antispermatogenic activity. Earlier, compounds of benzothiazolines have been tested for antifertility in male rats and were found to show significant antifertility

activity[1,2] but during literature survey it has been revealed that no attention has been paid to compare the effects of later transition metal complexes with benzothiazoline ligands derived from coumarins on the reproductive system of male rats. Such ligands continue to occupy an important position in metal coordination chemistry[3], even almost a century since their discovery. In the development of coordination chemistry, schiff base metal complexes has been playing a key role resulting in quality research, ranging from synthetic work to relevant studies of metal complexes. Moreover, Lanthanide coordination compounds are also the subject of concern due to their potential applications such as magnetic[4,5], fluorescent[6,7] and biological properties.[8-10] Coumarin chemistry has become important over the years, which is documented by thousands of papers and patents of coumarin. Coumarin (1, 2- benzopyrone) compounds are of a large family of organic compounds having a lactone structure and extensively used in many fields. The biological activities of coumarin and related compounds are multiple and include antimicrobial[11], DNA cleavage,[12] pesticidal[13], antioxidant[14], anti-inflammatory[15], antituberculosis[16], anticancer[17] and anti HIV[18] activities. In this context, the present communication deals with the synthesis, characterization and antifertility effect of later transition metal complexes derived from 3-acetylcoumarinbenzothiazolines and 3-formyl-4-chlorocoumarinbenzothiazolines. The aim of the antifertility activity was to assess the effect on fertility and to contribute to a better understanding of the reproductive function of male albino rats.

2. EXPERIMENTAL

2.1. MATERIALS AND METHODS

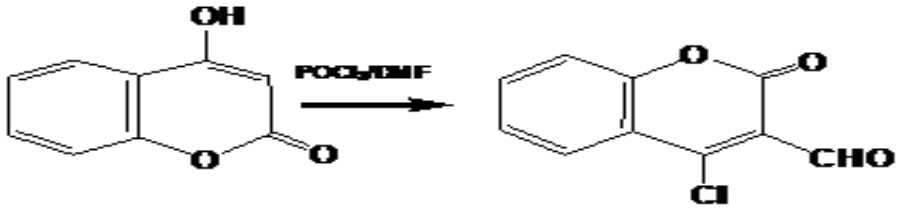
All the chemicals were of reagent grade and solvents of analytical grade were distilled from appropriate drying agents immediately prior to use. 3-Acetylcoumarin, 4-hydroxycoumarin, Samarium(III) and Neodymium(III) salts were purchased from Alfa Aesar, Gadolinium(III) salt was procured from Sigma Aldrich. The metal chlorides used were in hydrated form. Sulfur and nitrogen were estimated by the Messenger's and Kjeldahl's method, respectively. The metal contents were estimated complexometrically with EDTA using Erichrome Black T as an indicator. Melting point was determined by using capillaries in electrical melting point apparatus. Molecular weight determinations were carried out by the Rast Camphor Method. The conductivity values measured on 10^{-3}moldm^{-3} solution in DMF at room temperature on century digital conductivity meter model CC601. Infrared spectra of the ligands and their complexes were recorded with the help of Nicolet Megna FTIR-550 spectrophotometer on KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL-AL-300 FT NMR

spectrometer in DMSO-d_6 using TMS as the internal standard. EPR spectra of the complexes were monitored on Varian make E line century X-band EPR spectrometer (Model E-112).The electronic spectra were recorded on a Varian–Cary/5E spectrophotometer.

2.2. Preparation of the ligands

2.2.1. Synthesis of 3-formyl-4-chlorocoumarin

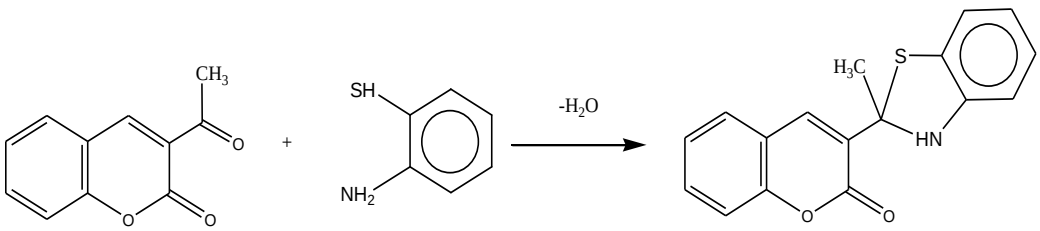
3-Formyl-4-chlorocoumarin is prepared as described in literature.[13] Phosphorus oxychloride (10 mL) was added drop wise to a solution of dimethylformamide (DMF) (20 mL) controlling the temperature below 50°C. Solution of 4-hydroxycoumarin (4.0 g) in DMF (10 mL) was then gradually added to the mixture with constant stirring and maintenance of the temperature of the reaction mixture below 5°C. The reaction mixture was then allowed to stand at room temperature for 2 h and then heated on a steam bath for 1 h. After cooling, the reaction mixture was poured onto crushed ice and neutralized with sodium carbonate. A solid product was immediately formed which was crystallized from ethanol to give a yellow solid m.p. 115°C, yield 3.2 g;80%.



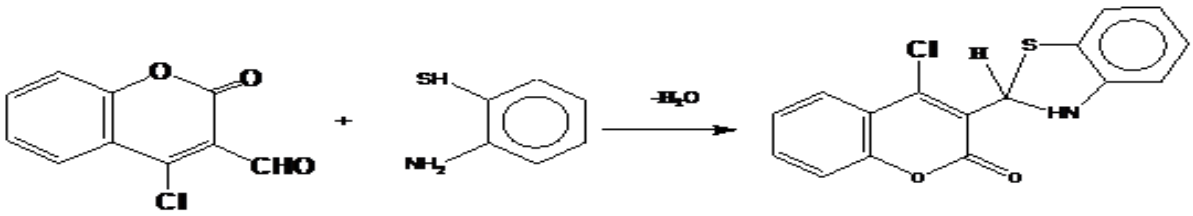
4- hydroxycoumarin **3-Formyl-4-chlorocoumarin**

2.2.2. Preparation of ligands 3-acetylcoumarinbenzothiazoline and 3-formyl-4-chlorocoumarinbenzothiazoline

The benzothiazolines were prepared by the condensation of 3-acetylcoumarin and 3-formyl-4-chlorocoumarin with o-aminothiophenol in 1:1molar ratio in ethanol(Figure 1). The reaction mixtures was stirred for 3–4 h, and the resulting products were filtered off, recrystallized from ethanol, and dried in vacuum.



3-acetylcoumarin **o-aminothiophenol** **3-acetylcoumarinbenzothiazoline**



3-formyl-4-chlorocoumarin **o-aminothiophenol** **3-formyl-4-chlorocoumarin benzothiazoline**

Preparation of 3-acetylcoumarinbenzothiazoline and 3-formyl-4-chlorocoumarin benzothiazoline

2.3. Synthesis of the sodium salt of the ligands

Sodium metal was taken corresponding to 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 forms 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 forms sodium salt of the particular ligand.

2.4. Preparation of the metal complexes

These complexes were synthesized by the condensation of the reaction mixture of $LnCl_3.6H_2O$ (0.01 mol) and respective sodium salt of the ligands (0.03 mol) in 1:3 molar ratios, reactions were completed in 13–15 h. The precipitate of sodium chloride formed during the course of the reaction was removed by filtration and the solvent was removed under reduced pressure. The product was dried in *vacuum*. The complexes were washed with dry n-hexane and recrystallized with cyclohexane. The physico-chemical properties and analytical data of the ligands (i,ii) as well as complexes(a,b,c) are listed below.

$$LnCl_3xH_2O + 3LNa \xrightarrow{MeOH} [Ln(L)_3].nH_2O + 3NaCl + (x-3)H_2O$$

(i). 3-Acetylcoumarinbenzothiazoline(L^1H)

($C_{17}H_{13}NSO_2$) Colour, Yellowish Brown, M. P., 77^oC , C, 68.68(69.13), H, 4.39 (4.44), N, 4.68 (4.74), S, 10.56(10.85), Mol. Wt., 293.158, (295.358), yield% 72(T).

(ii)3-Formyl-4-chlorocoumarinbenzothiazoline(L^2H): ($C_{16}H_{10}O_2NSCl$) Colour, Yellow, M. P., 150 ^oC, C, 60.18(60.86), H, 3.01 (3.19), N, 4.28(4.44), S, 9.84(10.15), Mol. Wt., 304.854 (315.7767), yield% 71(T).

a) Neodymium(III) Complex with monofunctional bidentate ligands 3-Acetylcoumarin benzothiazoline L^1H and 3-Formyl-4-chlorocoumarin benzothiazoline L^2H

$[Nd(L^1)_3].3H_2O$, Colour, Shiny Brown, M. P., 158 ^oC, C, 46.38 (46.45), H, 3.81 (3.90), N,3.56 (3.89),S, 8.65(8.90), Nd, 13.16 (13.34),Mol. Wt., 1067.459 (1081.329).

$[Nd(L^2)_3].3H_2O$, Colour, Orange, M. P., 102 ^oC, C, 50.18 (50.46), H, 2.81 (2.91), N,3.59(3.68),S, 8.145(8.42),Cl, 9.17(9.31), Nd, 12.56(12.62),Mol. Wt., 1137.58 (1142.591).

b) Samarium(III) Complex with monofunctional bidentate ligand 3-Acetylcoumarin benzothiazoline L^1H and 3-Formyl-4-chlorocoumarin benzothiazoline L^2H

$[Sm(L^1)_3].3H_2O$, Colour, Wooden Brown, M. P., 165 ^oC, C, 46.05 (46.14), H, 3.79 (3.87), N, 3.46 (3.86), S,8.65 (8.85) Sm, 13..55 (13.83), Mol. Wt., 1075.245 (1087.45).

$[Sm(L^2)_3].3H_2O$, Colour, Light Orange, M. P., 124 ^oC, C, 49.84 (50.19), H, 2.79 (2.90), N, 3.56 (3.66),S,8.24 (8.37), Sm, 12.84 (13.09), Mol. Wt., 1134.52 (1148.71).

c) **Gadolinium(III) Complex with monofunctional bidentate ligand 3-Acetylcoumarin benzothiazoline L^1H and 3-Formyl-4-chlorocoumarin benzothiazoline L^2H**

$[Gd(L^1)_3].3H_2O$, Colour, Brown, M. P., 175 ^oC, C, 45.75 (45.81), H, 3.77 (3.84), N, 3.69 (3.84), S,8.55(8.79), Gd, 14.26 (14.37), Mol. Wt., 1084.856 (1094.339).

$[Gd(^{L2})_3].3H_2O$, Colour, Brown, M. P., 94 ^oC, C, 49.75 (49.89), H, 2.77 (2.88), N, 3.69 (3.64), S,8.15(8.32), Cl,9.14(9.20), Gd, 13.26 (13.61) , Mol. Wt., 1148.657 (1155.601).

2.5. Pharmacology

Healthy adult male albino rats (Ratus norvegieus) of an average body weight 190-200 g were used for experimentation. The animals were kept in clean polypropylene cages covered with chrome plates grills and maintain in an airy room with controlled room temperature (20± 5℃) with 12:12 light and dark cycle. The animals were fed with food pellet procured from Ashirwad Industries, Chandigarh as well as germinated/sprouted gram and wheat seeds as an alternative feed. Tap water was supplied *ad libitum*. Animals were divided into nine groups containing 6 animals each. Group A animals were kept control and were administered olive oil only. The animals of groups B,C,D,E,F,G,H and I were treated with ligands and their complexes i.e. Nd(III), Sm(III) and Gd(III) metal complexes, respectively. The ligands and their complexes were dissolved in olive oil and administered to animals through oral intubations at the dose level of 30 mg/Kg weight for 60 days. At the end of experiment, the rats were weighed and scarified under light ether anesthesia. The male reproductive organs

were removed, washed with distilled water, dried, weighed and processed for biochemical studies. For mating exposure test, the animals were cohabitated with normal progestrous females in the ratio of 1:3. The vaginal plug and presence of sperms in the vaginal smear was checked for positive mating. Females were separated and resultant pregnancies were noted when dems gave birth. Sperm dynamics in Cauda epidydymis, density, testicular and cauda epidydymis, testicular protein, cholesterol, sialic acid, glycogen and serum testosterone. Concentrations were measured by standard laboratory techniques. The data were analyzed statistically by using student 'T' test and the significance of difference was set at P ‹ 0.01 and P‹ 0.001.

3. RESULTS AND DISCUSSION

Table I. Electronic spectral data of lanthanide (III) complexes

Complex	Assignment	V_{max} of Ln^{+3} ion (cm^{-1})	V_{max} of complexes (cm^{-1})	β	1-β	$b^{1/2}$	δ	η
Sm(L^1)$_3$.3H_2O	$6H_{5/2}$ – $4I_{13/2}$	21430	21250	0.9916	0.0084	0.0648	0.8500	0.0920
	- $4F_{9/2}$	25820	25640	0.9930	0.0070	0.0592	0.7049	0.0840
	- $4I_{9/2}$	26610	26410	0.9927	0.0073	0.0608	0.7354	0.0857
	- $6P_{3/2}$	28673	28515	0.9945	0.0055	0.0524	0.5530	0.0742
[Nd(L^2)$_3$].3H_2O	$4I_{9/2}$ -$4G_{5/2}$,$2G_{7/2}$	16822	16660	0.9904	0.0096	0.0693	0.9693	0.0985
	- $2G_{9/2}$	19813	19630	0.9908	0.0092	0.0678	0.9285	0.0964
	- $4G_{11/2}$	21915	21740	0.9920	0.0080	0.0632	0.8064	0.0897
[Sm(L^2)$_3$].3H_2O	$6H_{5/2}$ - $4I_{13/2}$	21596	21507	00.993	0.0041	0.0320	0.4116	0.0020
	- $4F_{9/2}$	24846	24724	0.9935	0.0049	0.0350	0.4924	0.0024
	- $4I_{9/2}$	24096	24038	0.9979	0.0024	0.0244	0.2405	0.0012

Table II:Effects of Ligands and Their Complexes on Body and Reproductive Organ Weight of Male Rats

Group	Treatment	Body Weight		Organ Weight (mg/100 g b.wt.)			
		Initial	Final	Testes	Epididymis	Seminal Vesicle	Ventral Prostrate
A	Control (olive oil)	220.0±16.4	230.0±14.5	1280.0±30.2	470.0±12.9	460.0±14.3	450.0±21.7
B	L^1H	225.0±10.3	238.0±13.3	1010.0±25.3	359.0±13.2	395.0±25.4	399.0±19.7
C	L^2 H	227.0±10.8	236.0±17.4	950.0±21.5	325.0±14.7	365.0±27.4	350.0±20.3
D	Nd(L^1)$_3$.3H_2O	210.0±9.7	228.0±14.3	750.0±30.7	290.0±13.3	225.0±30.3	280.0±22.4
E	Sm(L^1)$_3$.3H_2O	205.0±11.3	220.0±12.7	700.0±17.9	295.0±11.7	240.0±32.5	285.0±21.3
F	Gd(L^1)$_3$.3H_2O	200.0±12.4	227.0±11.9	720.0±15.8	280.0±11.2	250.0±26.5	275.0±17.9
G	Nd(L^2)$_3$·3H_2O	215.0±13.4	232.0±16.3	800.0±19.4	293.0±14.1	230.0±27.3	250.0±30.3
H	Sm(L^2)$_3$.3H_2O	217.0±15.4	239.0±16.5	710.0±20.4	270.0±14.3	220.0±26.9	260.0±30.2

M Av 6 determination
a = p‹ 0.01
b= p‹ 0.001

ns = p= Non Significant
Group B compared with Group A
Group C,D,E,F,G,H,I compared with Group

Table III. Altered Sperm Dynamics and Fertility of Ligands and Their Various Complexes Treated Male Rats

Group	Treatment	Sperm Mortility(%)	Sperm Density(million/ml)		Fertility(%)
		Cauda Epidydymis	Testes	Cauda Epidydymis	
A	Control (olive oil)	70.5±4.5	4.78±0.7	60.4±3.70	100(+ve)
B	L^1H	59.5±4.7	3.20±0.5	51.4±2.90	40(-ve)
C	L^2 H	55.0±5.7	3.00±0.4	49.1±2.70	45(-ve)
D	$Nd(L^1)_3.3H_2O$	42.0±6.3	2.60±0.3	30.0±2.60	75(-ve)
E	$Sm(L^1)_3.3H_2O$	39.0±7.3	1.90±0.4	29.0±3.10	79(-ve)
F	$Gd(L^1)_3.3H_2O$	35.0±6.5	1.97±0.3	25.0±2.10	82(-ve)
G	$Nd(L^2)_3.3H_2O$	30.0±5.4	1.80±0.3	27.0±2.20	85(-ve)
H	$Sm(L^2)_3.3H_2O$	32.0±5.1	1.50±0.4	20.0±1.90	88(-ve)
I	$Gd(L^2)_3.3H_2O$	31.0±3.9	1.30±0.3	21.3±2.10	85(-ve)

Values are mean± SEM Av 6 determination
a = p‹ 0.01
b= p‹ 0.001
ns = p= Non Significant
Group B compared with Group A
Group C,D,E,F,G,H,I compared with Group B

Table IV: Testicular Biochemistry and Serum Testosterone Levels of Ligands and Their Various Complexes Treated Rats

Group	Treatment	Protein	Sialic Acid	Cholestrol	Glycogen	Acid Phosphatase	Alkaline Phosphatase	Serum Testosterone (mg/ml)
A	Control (olive oil)	227.5± 10.5	4.25±0.70	8.0±0.90	3.25±0.39	3.20±0.19	10.3±0.60	2.90±0.67
B	L^1H	280.0±5.3	3.19±0.75	11.1±0.70	2.70±0.19	4.80±0.20	14.0±0.20	2.20±0.72
C	L^2 H	325.0±3.4	2.50±0.60	13.2±0.40	1.70±0.20	5.70±0.10	17.0±0.10	1.20±0.32
D	$Nd(L^1)_3.3H_2O$	330.0±3.7	2.10±0.71	12.3±0.30	1.50±0.10	5.90±0.11	16.0±0.20	1.10±0.30
E	$Sm(L^1)_3.3H_2O$	340.0±3.9	2.00±0.81	13.7±0.41	1.55±0.21	5.95±0.15	16.8±0.30	1.25±0.20
F	$Gd(L^1)_3.3H_2O$	335.0±2.9	1.90±0.72	13.9±0.39	1.49±0.11	5.35±0.16	17.1±0.20	1.35±0.10
G	$Nd(L^2)_3.3H_2O$	331.0±3.6	1.80±0.69	13.3±0.35	1.40±0.17	6.10±0.32	17.7±0.30	1.60±0.30
H	$Sm(L^2)_3.3H_2O$	338.0±4.3	1.7±0.75	13.6±0.31	1.30±0.13	6.20±0.39	17.2±0.40	1.28±0.10
I	$Nd(L^2)_3.3H_2O$	328.0±4.5	1.6±0.60	13.8±0.43	1.35±0.14	5.75±0.12	16.6±0.35	1.15±0.15

Values are mean± SEM Av 6 determination
a = p‹ 0.01
b= p‹ 0.001
ns = p= Non Significant
Group B compared with Group A
Group C,D,E,F,G,H,I compared with Group B

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

$$LnCl_3xH_2O + 3LNa \xrightarrow{MeOH} [Ln(L)_3].nH_2O + 3NaCl + (x-3)H_2O$$

Where, LNa is the sodium salt of the ligand molecule, Ln = Nd, Sm and Gd, n=3 and x=6. The newly synthesized complexes have been obtained as colored solids which exhibit their solubility in methanol, DMSO and DMF. The molar conductance values of 10^{-3} M solutions of metal complexes lie in the range 10–14 ohm^{-1} cm^2 mol^{-1} in dry DMF indicating their non electrolytic behavior. The complexes are monomers as revealed by their molecular weight determinations.

3.1. IR Spectral Studies

The general feature of the ligands ($L^{1,2}H$) that seems to be important is the absence of the *v*(SH) band at 2600– 2500 cm^{-1} and *v*(C=N)band at 1610–1600 cm^{-1} which is a strong evidence for the existence of benzothiazoline structure. A strong and sharp band in the region 1600–1620 cm^{-1} ascribed to *v* (C=N), is observed in the metal complexes, confirming that the ligand adopts the Schiff base form in complexes. The –NH stretching and deformation bands appear at 3290-3310 cm^{-1} and 1675–1700 cm^{-1}, respectively in free benzothiazolines. In the spectra of metal complexes, *v*(NH) bands disappear, suggesting the deprotonation of the ligand on chelation. Bands at 1725-1710 cm^{-1} was attributed to lactonic carbonyl *v*(C=O). The lactone carbonyl frequency of the complexes remained unchanged in the position and intensity, indicating the non coordination of the lactonic oxygen. The appearance of bands in 510–548 and 369–418 $cm^{-1}$for *v*(M-N) and *v*(M–S) vibrations, respectively further support the coordination of the ligands to the metal ions through the azomethine nitrogen and thiolato sulfur atoms.

3.2. ^{1}H NMR and ^{13}C NMR Spectra

The spectra of free ligands show the –NH protons signals at δ4.26-4.30 ppm. The free ligands show a complex multiplet at δ 6.50-8.85 for the aromatic protons. In^{13}C NMR spectrum of benzothiazolines the signal observed at *δ* 162.56-165.42 ppm in the spectrum of free benzothiazolines has been assigned to >C(R)N− group.. The aromatic carbon signals are observed in the range *δ* 120.31–149.97 ppm. Thus, the ^{1}H and ^{13}C NMR spectra, confirms the

monobasic bidentate nature of the ligands, which has already been suggested by the IR spectral studies, discussed above.

3.3. EPR Spectra

The EPR spectra of some of the Lanthanide compounds (both at RT and LNT) were recorded and similar g value of 1.99 was observed, which is nearly equal to the free electron value (g=2.00277). Similar line widths at both the temperatures indicate spin–lattice and spin–spin relaxation processes contribute equally to line width. Further, the complete absence of zero-field hyperfine splitting and the presence of broad bands indicate that the Ln^{+3} (where Ln^{+3} = Sm^{+3} and Gd^{+3}) ion is located in a rather disordered environment caused by strain.

3.4. Electronic Spectra

Electronic spectral studies of lanthanide (III) metal complexes are significant and are important tool for the measurement of covalency in complexes. The shift of hypersensitive bands has been utilized to calculate the nephelauxetic effect (β), Sinha's covalency parameter (δ%) (metal ligand covalency percentage) and the covalency factor ($b^{1/2}$) along with covalency angular overlap parameter (η) these parameters have been calculated using the following expressions.[13]

$b^{1/2} = [(1- \beta_{av})/2]^{1/2}$

$\delta\% = (1- \beta_{av})/ \beta_{av} .100$

$(\eta) = (1-\beta_{av})^{1/2}/ \beta_{av}^{1/2}$

The electronic spectral studies of lanthanide (III) metal complexes yield positive value for ($1-\beta_{av}$) and (δ%) which suggest that the bonding between metal and ligand is covalent in the complexes. The values of parameter of bonding (b½) and angular overlap parameter (η) are also found to be positive indicating covalent bonding in complexes. The electronic spectral data are presented in Table I.

3.5 Antifertility Activity

Treatment with ligands and their metal complexes at the dose level of 30 mg/Kg body weight for 60 days showed following variations in end points.

Weight Response(Table II): A significant reduction in the weight of testes, epidydymis, seminal vesicle and ventral prostate was observed after ligands and their metal complexes.

Sperm Motility and Density(Table III)

A significant decrease in motility of spermatozoa in cauda epidymis and sperm density in cauda epidydymis and testes have been observed in ligands and their metal complexes treated rats.

Testicular Biochemistry(Table IV)

Oral administration of ligands and their metal complexes caused a significant reduction in testicular glycogen and sialic acid contents where as cholesterol, acid and alkaline phosphatase contents of testes were increased after treatment with various complexes.

Sperm Testosterone(Table IV)

The serum testosterone concentrations were decreased significantly ($P \leq 0.01$ to 0.001) after treatment with ligands and their various complexes.

DISCUSSION

The present study revealed that administration of ligands and their various complexes at the dose level of 30 mg/Kg body weight for 60 days resulted in a significant reduction in weight of testes and sex accessory organs. The decrease in testicular weight may be due to reduced tubule size, spermatogenic arrest and inhibition of steroid biosynthesis of leydig cells.[19] Reduction in weight of accessory reproductive organs directly support the reduced availability of androgen.[20] The decreased testosterone levels supports this view.[21] The low sperm density in Cauda epidydymis is caused by the alternation in androgen level. The negative fertility test may be attributed to lack of forward progression and reduction in density of spermatozoa and altered biochemical milieu of cauda epididymis.[22] Increased concentration of testicular cholesterol may be the result of non-utilization leading to the reduction of production of T, the main hormone involved in the control of fertility of animals including rats.[23] In present study, the elucidation in testicular protein content may be due to hepatic detoxification, which results in inhibitory effect on the activities of enzymes involved in androgen biotransformation.[24] Glycogen is an energy source for the general metabolism and constant supply of glucose is essential for the proper functioning of the testes. Similarly reduction in testicular sialic acid content may be due to absence of spermatozoa.[25] The increase in acid phosphatase in treated rats suggest that these compounds are acting as labializing agent and releasing the enzyme that degenerates the tissue resulting in reduction of various micromolecules including reduction in sperm count.[24] Further, reduced alkaline phosphatase activity indicates reduction in cellular permeability in gonadal cell as the enzyme

plays a significant role in transport.[26] Our study demonstrated that ligands and their metal complexes are effective in reducing the fertility and addition of metals moiety to the ligand enhanced its activity.

4. CONCLUSION

We have described the synthesis, characterization, and biological activity of benzothiazoline ligands and their Ln (III) complexes. 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 octahedral geometry have been assigned for Ln(III) complexes. Antifertility activities of the ligands and complexes showed that the Ln(III) complexes are more active than the parent ligands. Thus, it may be concluded that orally administered ligands and their complex produced antifertility effects or may be a potential source for the development of an antifertility drug for males because of their antispermatogenic nature and some antifertility effects on reproductive organs.

REFERENCES

1. Fahmi N, Meena R, Mitharwal P, Shrivastava S, Singh R V. (A study to evaluate the in vitro antimicrobial activity and antiandrogenic effects on rats of Cr (III) complexes of S∩N donor ligands). Int J Pharma Sci Res, 2014; 5(7): 2821-2833.
2. Sharma K, Singh R V, Fahmi N. (Palladium(II) and Platinum(II) derivatives of benzothiazoline ligands: synthesis, characterization, antimicrobial and antispermatogenic activity). Spectrochimica Acta Part A, 2011; 78 (1):80–87.
3. Zhong G Q, Zhong Q. (Solid–solid synthesis, characterization, thermal decomposition and antibacterial activities of Zinc(II) and Nickel(II) complexes of glycine–vanillin Schiff base ligand). Green Chem Lett Rev, 2014; 7: 236–242.
4. Gao F, Yao M, Yi-Zhi L, You S, Jing-Lin Z. (Syntheses, structures, and magnetic properties of seven-coordinate lanthanide porphyrinate or phthalocyaninate complexes with kläui's tripodal ligand). Inorg Chem, 2013; 52 (11): 6407–6416.
5. Vanco J, Travnicek Z, Kozak O, Boca R. (Structural, magnetic and luminescent properties of lanthanide complexes with N-salicylideneglycine). Int J Mol Sci, 2015; 16: 9520-9539.
6. Mutali V, Phaniband M A.(Synthesis, characterization, fluorescent and antimicrobial properties of new Lanthanide(III) complexes derived from coumarin Schiff base). J Chem Pharma Res, 2011; 3(2): 313-330.

7. Rao N V S, Choudhury T D, Deb R, Paul M K , Rao T R , Francis T , Smalyukh I I. (Fluorescent lanthanide complexes of Schiff base ligands possessing N-aryl moiety: influence of chain length on crossover (calamitic to discotic) phase behavior). Liq Cryst, 2010; 37(11): 1393–1410.
8. Singh J, Agarwal S. (Lanthanide (III) complexes of schiff Bases of Dithiocarbazate Derivatives: Synthesis, Spectral Characterization and Biological Evaluation). Int J Adv Eng Glo Tech, 2015; 3(3): 387-397.
9. Reji T F A F , Pearl A J, Rosy B A . (Synthesis, characterization, cytotoxicity, DNA cleavage and antimicrobial activity of homodinuclear lanthanide complexes of phenylthioacetic acid). J Rare Earths, 2013; 31(10): 1009–1016.
10. Wang Q, Huang Y , Zhang J S , Yang X B. (Synthesis, characterization, dna interaction, and antitumor activities of La (III) complex with schiff base ligand derived from kaempferol and diethylenetriamine). Bioinorg Chem App, 2014; 2014(Article ID 354138):1-9.
11. Kapoor P, Fahmi N, Singh R V. (Microwave assisted synthesis, spectroscopic, electrochemical and DNA cleavage studies of Lanthanide(III) complexes with coumarin based imines).Spectrochimica Acta Part A, 2011;83:74–81.
12. Kapoor P, Singh R V, Fahmi N. (Coordination chemistry of rare earth metal complexes with coumarin based imines: ecofriendly synthesis,characterization, antimicrobial, DNA cleavage, pesticidal and nematicidal activity evaluations). J Coord Chem, 2012; 65(2): 262-277.
13. Dawara L, Singh R V. (Synthesis, spectroscopic characterization, antimicrobial, pesticidal and nematicidal activity of some nitrogen-oxygen and nitrogen-sulfur donor coumarins based ligands and their organotin(IV) complexes). App Organomet Chem, 2011; 25(9): 643–652.
14. Rajeshirke M, Shah R, Yadav P, Purohi N V. (Synthesis and antioxidant activity of Metal (II) complexes of isocoumarin derivatives). Der Pharma Sin, 2012; 3(2): 239-248.
15. Singh A K, Lohani M, Parthsarthy R. (Synthesis, characterization and anti-inflammatory Activity of Some 1,3,4 -Oxadiazole Derivatives). Iran J Pharm Res. 2013; 12(2): 319–323.
16. Cardoso S H, Barreto M B,Lourenço M C S, Henriques M G M O, Candea A L P, Kaiser C R, DeSouza M V N .(Antitubercular activity of new coumarins).Chem Biol Drug Design, 2011; 77: 489–493.

17. Zhu T, Wang Y, Ding W, Xu J, Chen R, Xie J, Zhu W, Jia L, Ma T.(Anticancer activity and DNA-binding investigations of the Cu(II) and Ni(II) complexes with coumarin derivative). Chem Biol Drug Des, 2015; 85(3): 385-93.
18. Manolov I , Raleva S , Genova P , Savov A , Froloshka L , Dundarova D , Argirova R. (Antihuman immunodeficiency virus type 1 (HIV-1) activity of rare earth metal complexes of 4-Hydroxycoumarins in cell culture). Bioinorg Chem App, 2006; 2006(Article ID 71938):1- 7.
19. Joshi S C, Tibrewal P, Sharma A, Sharma P. (Evaluation of toxic effect of 2,4-D (2,4-Dichlorophenoxyacetic acid) on fertility and biochemical parameters of male reproductive system of albino rats). Int J Pharm Pharm Sci, 2012; 4(3): 338-342.
20. Joshi S C, Mathur R, Gajraj A, Sharma T. (Influence of methyl parathion on reproductive parameters in male rats). Environ Toxicol Pharma, 2003; 14 (3): 91–98.
21. Joshi S C, Bansal B, Jasuja N D.(Evaluation of reproductive and developmental toxicity of cypermethrin in male albino rats).Toxicol Environ Chem, 2011; 93(3): 593–602.
22. Joshi S C, Mathur R, Gulati N.(Testicular toxicity of chlorpyrifos (an organophosphate pesticide) in albino rat). Toxicol Industrial Health, 2007; 23(7): 439–444.
23. Ngoula F, Watcho P, Dongmo M, Kenfack A, Kamtchouing P. (Tchoumboué effects of pirimiphos-methyl (an organophosphate insecticide) on the fertility of adult male rats). J Afr Health Sci, 2007; 7(1): 3-9.
24. Choudhary N, Goyal R, Joshi S C. (Effect of malathion on reproductive system of male rats). J Environ Bio, 2008; 29(2): 259-262.
25. Singh N, Watts S, Joshi S C, Singh R V. (Pesticidal and antifertility activities of triorganogermanium(IV) complexes synthesized using a green chemical approach).App Organomet Chem, 2013; 27 (5): 269-278.
26. Bhowal S K, Lala S, Hazra A, Paira P, Banerjee S, Mondal N B, Chakraborty S. (Synthesis and assessment of fertility-regulating potential of 2-(2''-chloroacetamidobenzyl)-3-(3'-indolyl) quinoline in adult rats as a male contraceptive agent). Contraception, 2008; 77(3): 214-222.