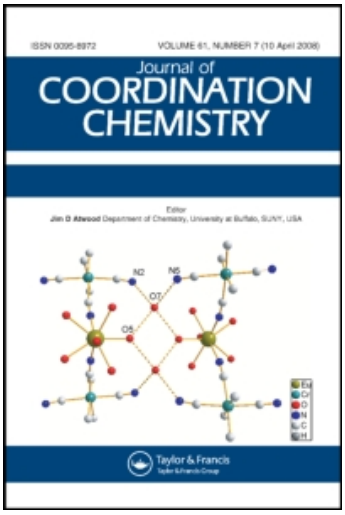

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Antimicrobial, antifertility, and antiradiation studies of Ga(III) and Tl(I) complexes with N^n^S and N^n^O donor systems

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Antimicrobial, antifertility, and antiradiation studies of Ga(III) and Tl(I) complexes with N⌒S and N⌒O donor systems

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New complexes of gallium(III) and thallium(I) derived from 5,6-dimethyl-1H-indol-2,3-dione hydrazinecarbothioamide (L^1H) and 5,6-dimethyl-1H-indol-2,3-dione hydrazinecarboxamide (L^2H) have been prepared and investigated using a combination of microanalytical analysis, melting point, molar conductance measurement, electronic, IR, ^1H NMR, and ^{13}C NMR spectral studies. Gallium isopropoxide interacts with the ligands in 1 : 1, 1 : 2, and 1 : 3 molar ratios resulting in the formation of colored products, whereas TlCl forms only unimolar products. The mono- and *bis*-alkoxy derivatives are dimeric, while the *tris* ligand metal complexes are monomeric. On the basis of conductance and spectral evidences, a pentacoordinate structure for gallium(III) 1 : 1 complexes, hexacoordinate structure for 1 : 2 and 1 : 3 complexes, and a bicoordinate geometry for thallium(I) complexes have been assigned. The ligands are coordinated to gallium(III) and thallium(I) via the azomethine nitrogen and the thiolic sulfur/enolic oxygen. The antimicrobial activities of the ligands and complexes have been screened *in vitro* against bacteria *Pseudomonas cepacicola* and *Bacillus subtilis* and fungi *Collectatrichum capsici* and *Fusarium oxysporum*. The complexes have higher activities than the free bases. *In vivo* studies of the ligands and their corresponding complexes have also been carried out to assess their antifertility and antiradiation activities. The results of these activities indicate the antiandrogenic and radiation protective nature of these complexes.

Keywords: 5,6-Dimethyl-1H-indol-2,3-dione hydrazinecarbothioamide; 5,6-Dimethyl-1H-indol-2,3-dione hydrazinecarboxamide; Antifertility; Antiradiation activity

1. Introduction

Schiff bases and their structural analogues, as ligating compounds containing acyclic and cyclic imine C=N bonds, are of great importance in modern coordination chemistry [1]. Schiff bases are superior reagents in biological, pharmacological, clinical, and analytical applications [2]. Schiff-base metal complexes are broad spectrum antimicrobial, antitumor [3], antiviral [4], and antifertility [5] agents. Ever since the discovery of radiation protection by cysteine, several synthetic compounds have been examined for their protective action on biological systems [6, 7].

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Coordination chemistry of Group 13 metal ions is of biochemical interest because of potential use in treatment and diagnosis of disease [8–10]. Gallium plays an important role as antitumor [11], antiviral [12], and anticoagulant agents and thallium as a probe for K^+ in biological systems [13]. Gallium(III) complexes of an aminophenol ligand are active against chloroquine-sensitive *Plasmodium falsiparum* strains [14]. The coordination chemistry and biological activity of gallium(III) and thallium(I) complexes of N∩S and N∩O donor ligands is interesting, so we are reporting herein complexes of these metal ions with hydrazinecarbothioamide and hydrazinecarboxamide.

2. Experimental

All the chemicals used in the synthesis of the complexes were of A.R. grade. The thallous chloride and isatin were purchased from BDH chemicals and S.D. fine chemicals, respectively, and used as received. Gallium isopropoxide was prepared in the laboratory. All the solvents were dried and distilled before use.

2.1. *Synthesis of L^1H and L^2H*

5,6-Dimethyl-indol-2,3-dione has been prepared by the method reported earlier [15]. The ligands 5,6-dimethyl-1H-indol-2,3-dione hydrazinecarbothioamide (L^1H) and 5,6-dimethyl-1H-indol-2,3-dione hydrazinecarboxamide (L^2H) were prepared by condensation of 5,6-dimethyl-1H-indol-2,3-dione with thiosemicarbazide and semicarbazide hydrochloride (in the presence of sodium acetate) in 1 : 1 molar ratio in ethanol. The reaction mixture was refluxed over a water bath for 3–4 h and allowed to stand overnight. The products were recrystallized from ethanol and dried in *vacuum*. Their physico-chemical properties and analytical data are given in table 1. The parent ligands exist in the tautomeric forms (figure 1).

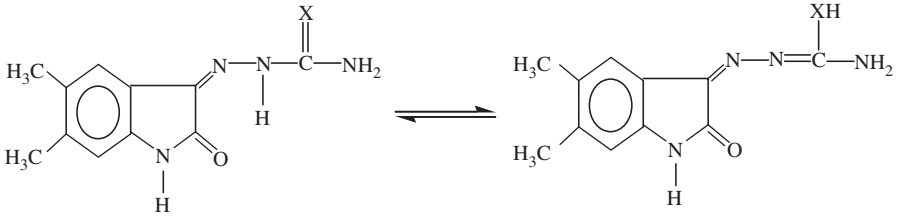
2.2. *Preparation of the complexes*

2.2.1. Preparation of thallium(I) complexes. To a methanolic solution of thallous chloride was added methanolic solution of the sodium salt of the ligands in 1 : 1 molar ratio. The resulting mixture was refluxed for 16–20 h. After completion of the reaction excess solvent was removed under reduced pressure and dried *in vacuo*. The physical properties and analytical data of the complexes are listed in table 1.

2.2.2. Preparation of gallium(III) complexes. Gallium(III) isopropoxide and the ligands were dissolved in dry benzene in 1 : 1, 1 : 2, and 1 : 3 molar ratios. The resulting mixtures were refluxed for 16–20 h; progress of the reaction was checked by measuring the amount of isopropanol in the azeotrope. After completion of the reaction, excess solvent was removed under reduced pressure and the complex dried *in vacuo*. The physical properties and analytical data are listed in table 1.

Table 1. Physical properties and analytical data for L^1H, L^2H and their metal complexes.

Compound	Color and state	Yield %	m.p. °C	Analysis found/(Calcd) % M	N	S	Mol. wt. found/(Calcd)
L^1H	Brown, solid	75	214	–	22.08 (22.56)	12.10 (12.91)	235.67 (248.30)
L^2H	Brown, solid	91	232	–	23.98 (24.12)	–	219.38 (232.24)
$Tl(L^1)$	Brown, solid	82	240 d	45.13 (45.25)	12.15 (12.40)	6.92 (7.10)	443.82 (451.68)
$Tl(L^2)$	Brown, solid	80	238 d	46.81 (46.92)	12.36 (12.86)	–	427.28 (435.62)
$\{Ga(OPr^i)_2(L^1)\}_2$	Yellow, solid	84	247 d	16.14 (16.02)	12.27 (12.87)	7.09 (7.37)	861.87 (870.38)
$\{Ga(OPr^i)(L^1)_2\}_2$	Yellow, solid	86	245 d	11.09 (11.18)	18.03 (17.97)	10.08 (10.29)	1235.90 (1246.79)
$Ga(L^1)_3$	Yellow, solid	87	253 d	8.67 (8.59)	20.31 (2071)	11.55 (11.85)	819.31 (811.60)
$\{Ga(OPr^i)_2(L^2)\}_2$	Yellow, solid	79	241 d	16.71 (16.64)	13.45 (13.37)	–	829.86 (838.26)
$\{Ga(OPr^i)(L^2)_2\}$	Yellow, solid	82	243 d	11.66 (11.79)	18.70 (18.95)	–	1189.51 (1182.55)
$Ga(L^2)_3$	Yellow, solid	83	250 d	9.20 (9.13)	22.13 (22.02)	–	752.95 (763.42)



where X = S (L^1H), X = O (L^2H)

Figure 1. Tautomeric forms of the ligands.

2.3. *Analytical methods and physical measurements*

The molecular weights were determined by the Rast camphor method. Conductivity measurements in dry dimethylformamide were performed with a conductivity bridge type 305. IR spectra of the ligands and their metal complexes were recorded on a Nicolet Megna FT IR 550 spectrophotometer using KBr pellets. The purities of these ligands and their metal complexes were checked by TLC on silica Gel-G using anhydrous DMSO and benzene (1 : 1) as solvent. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as standard on a JEOL AL 300 FT NMR spectrometer. Electronic spectra of the complexes were recorded in DMF on a UV-160A Shimadzu spectrophotometer from 200 to 600 nm. Nitrogen and sulfur were estimated by Kjeldahl and Messenger's methods, respectively [16]. Gallium(III) [17] and thallium(I) [18] were estimated gravimetrically.

2.4. *Antimicrobial assay*

2.4.1. Antifungal activity. The antifungal activity of the ligands and complexes have been evaluated by radial growth method [19] using Czapek's agar medium having composition, glucose 20 g, starch 20 g, agar–agar 20 g, and distilled water 1000 cm^3. Solutions of the test compounds in DMF at 50, 100, and 200 ppm concentrations were prepared. The medium was then poured into the petriplates and spores of fungi were placed on the medium with the help of an inoculum needle. The petriplates were wrapped in polyethylene bags containing a few drops of alcohol and were placed in an incubator at $30 \pm 1°C$. Controls were also run and three replicates were used in each case. The linear growth of the fungi was obtained by measuring the fungal colony diameter after 4 days and percentage inhibition calculated as $100(d_C - d_T)/d_C$, where d_C and d_T are the diameters of the fungus colony in the control and test plates, respectively. The organisms used in these investigations included *Collectatrichum capsici* and *Fusarium oxysporum*.

2.4.2. Antibacterial activity. Activity against bacteria was evaluated by the inhibition zone technique [20]. The nutrient agar medium having composition, peptone 5 g, beef extract 5 g, NaCl 5 g, agar–agar 20 g, and distilled water 1000 cm^3 was pipetted into the petridish. When it solidified, 5 cm^3 of warm seeded agar was applied. The seeded agar was prepared by cooling the molten agar to 40°C and then adding the amount of bacterial suspension.

The compounds were dissolved in DMF in 250, 500, and 1000 ppm concentrations. Paper discs of Whatmann No. 1 filter paper (5 mm) were soaked in these solutions of varied concentrations. The discs were dried and placed on the medium previously seeded with organisms in petriplates at suitable distance. The petriplates were stored in an incubator at $28 \pm 2°C$ for 24 h. The zone of inhibition thus formed around each disc containing the test compounds was measured in mm. Three replicates were used in each case. The organisms used in these investigations included *Pseudomonas cepacicola* and *Bacillus subtilis*.

2.4.3. Antifertility activity. In view of potential interest in biologically active compounds, the antifertility activity of selected compounds has been studied on male albino rats.

Sexually mature male albino rats of Wistar-Strain weighing 180–200 g (90–100 days old) were used for the experiment. They were housed in steel cases and maintained under standard conditions (12 h light/12 h dark; $25 \pm 3°C$; 35–60% relative humidity). Rat feed (Ashirwad Industries Ltd, Chandigarh, India) and water were provided *ad libitum*. The animals were randomly allocated into seven groups of five animals each. In the control group (I) only olive oil (0.5 m per animal per day) was orally administered for 60 days. In groups II and III ligands (L^1H and L^2H) 30 mg kg^{-1} body weight suspended in olive oil were given orally for a period of 60 days. The animals of groups IV and V received $Ga(OPr^i)_2(L^1)$ and $Tl(L^1)$, whereas animals of groups VI and VII received the same doses of compounds $Ga(OPr^i)_2(L^2)$ and $Tl(L^2)$, respectively, for the same period.

The rats were cohabited with proestrus females in 1 : 2 ratio to assess the fertility test by natural mating. The mating exposure tests of various compounds were performed

before and on the 55th day of treatment. The presence of spermatozoa in vaginal smear of cohabited females was used as evidence of mating. On day 16, laparotomy was performed to note the implantation sites, then females were allowed to complete the term. Numbers of litters were recorded. Treated animals were anesthesized on day 61 with ether and their testes, epididymis, ventral prostate, and seminal vesicles were dissected out and weighed. Sperm mobility in cauda epididymis and sperm density in testes and cauda epididymis were assessed. The protein, sialic acid, glycogen, fructose, and cholesterol were estimated in testes, epididymis, and accessory sex organs by using standard laboratory techniques. Results were analyzed statistically using Student's '*t*'-test.

2.4.4. Irradiation activity

2.4.4.1. *Animal*. Inbred 4–6 week old Swiss albino mice (25 ± 1 g) were purchased from inbreading station. They were kept in well-ventilated cages under standard conditions of temperature, pressure, and humidity. The animals were provided with normal mouse feed and water *ad libitum*.

2.4.4.2. *Irradiation*. The animals whole body was exposed to gamma radiation by a ^{60}Co source (dose rate is 0.98 Gy min^{-1}) at a distance of 101.98 cm from the source at the Department of Radiotherapy, SMS Medical College and Hospital, Jaipur, India.

2.4.4.3. *Drug*. 10 mg kg^{-1} body weight dissolved in distilled water (DDW).

2.4.4.4. *Experimental design*. Mice were divided into four groups: (1) Sham irradiation (normal), (2) drug orally (10 mg kg^{-1} body weight per day) for seven consecutive days, (3) DDW + irradiation (control), (4) drug + irradiation (drug alone). Thirty minutes after the last administration, animals were exposed with whole body to 6.0 Gy gamma radiation. Blood was collected from tail vein in a vial containing 0.5 EDTA. Lipid peroxidation (LPO) and reduced glutathione (GSH) were estimated after 24 h past irradiation in blood.

3. Results and discussion

The complexes are colored solids, soluble in alcohol, benzene, THF, DMF, and DMSO. All reactions can be completed within 16–20 h. The alkoxy derivatives are moisture sensitive, while the 1 : 3 metal : ligand complexes are quite stable. Molecular weight determinations reveal the dimeric nature of the mono- and *bis*-alkoxy gallium(III) complexes and the monomeric nature of the *tris* (ligand) metal derivatives. The low molar conductance (8–12 Ω^{-1} cm^2 mol^{-1} in DMF at 10^{-1} M concentration) indicates that all complexes are non-electrolytes. It has been observed that the order of the rate of reaction in (M : L) complexes is 1 : 1 > 1 : 2 > 1 : 3. However, there is no correlation between coordination numbers and melting points of the resulting complexes.

3.1. *Spectral studies*

Infrared spectra have bands at *ca* 3400 and 3320 cm^{-1} due to ν_{asym} and ν_{sym} NH_2 vibrations of the ligands, which remain almost unchanged in complexes indicating their

non-involvement in complexation. Ligands show broad bands in the regions 3250–3170 cm^{-1} due to νNH which disappear in spectra of the complexes indicating loss of a proton on chelation with the metal. On the basis of the shift observed for >C=N vibrations from 1610 cm^{-1} (L^1H) and 1590 cm^{-1} (L^2H) to higher wavenumber in the complexes, it can be deduced that the imine nitrogen atom is involved in coordination to the metal. The bands at 1062 cm^{-1} (L^1H) and 1690 cm^{-1} (L^2H) due to >C=S and >C=O vibrations, respectively, are observed in the spectra of the ligands, but disappear in the spectra of the complexes with appearance of >C–S and >C–O bands, support coordination of sulfur and oxygen. The complexes show new bands in the far IR region 660–600 cm^{-1}, 480–350 cm^{-1} and 320–280 cm^{-1} due to νGa–O, νGa–N, and νGa–S, respectively. The thallium complexes exhibit bands at ~440 cm^{-1}, 425 cm^{-1}, and 270 cm^{-1}, attributed to Tl–O, Tl–N, and Tl–S, respectively.

The UV spectra of the ligands and their metal complexes show bands at *ca* 270 and 300 nm assignable to π–π^* electronic transitions. The spectra of the ligands show a broad band at ~375 nm due to n–π^* transitions of the azomethine (>C=N). However, in the spectra of the complexes, this band shifts to the lower wavelength due to coordination of the azomethine nitrogen to the metal, indicating delocalization of electronic charge within the chelate ring stabilizing the resulting complexes.

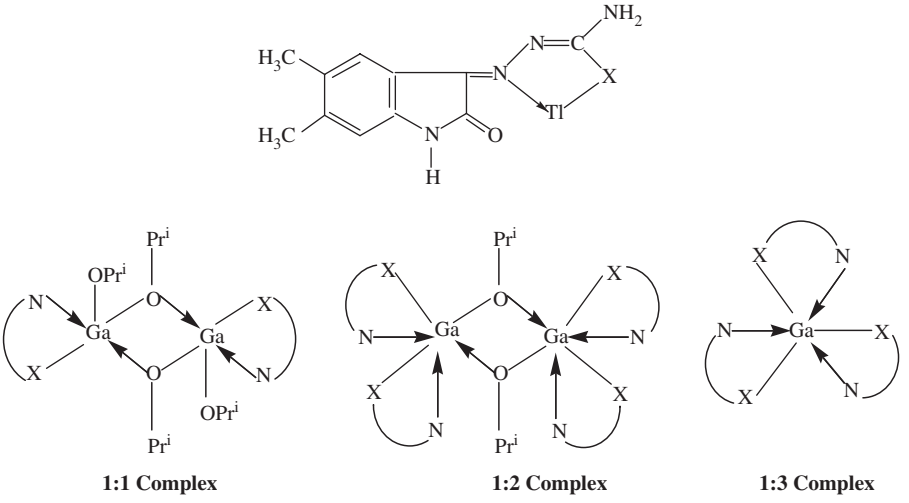
The mode of bonding and the geometry of the ligands and complexes were further confirmed by ^{1}H NMR spectra. The free ligands (L^1H) and (L^2H) exhibit singlets at δ 11.40 and δ 11.60 ppm due to –NH. The absence of these signals in the complexes suggests that these protons have been lost via thioenolization and ketoenolization of >C=S and >C=O groups and coordination of sulfur and oxygen to metal. The complexes show multiplets in the region δ 7.56–8.37 ppm due to the aromatic protons and a singlet due to $-NH_2$ at δ 3.26–3.42 ppm in both ligands. These signals remain unchanged in spectra of the complexes, suggesting their non-involvement in chelation. The spectra of $\{Ga(OPr^i)_2(L^1)\}_2$ and $\{Ga(OPr^i)_2(L^2)\}_2$ display two doublets and two fused septets which may be assigned to gem-dimethyl protons and methine protons of terminal and bridging isopropoxy groups, respectively; $\{Ga(OPr^i)(L^1)_2\}_2$ and $\{Ga(OPr^i)(L^2)_2\}_2$ exhibit a doublet and a fused septet due to bridging gem dimethyl protons and methine protons of bridging isopropoxy. The spectra of $Ga(L^1)_3$ and $Ga(L^2)_3$ show the absence of isopropoxy signals (Supplementary material).

^{13}C NMR spectra of L^1H and L^2H and their gallium(III) and Tl(I) complexes (Supplementary material) show the shifting of thiolic/amido and azomethine carbons, further confirming coordination of sulfur/oxygen and azomethine nitrogen to metal. The spectra of 1 : 1 complexes exhibit signals due to terminal and bridging isopropoxy, while spectra of the 1 : 2 complexes show signals only due to bridging isopropoxy.

For gallium(III) complexes pentacoordinate structure for 1 : 1 complex, hexacoordinate for 1 : 2, and 1 : 3 complexes and bicoordinate geometry for thallium(I) complexes have been assigned (figure 2).

3.2. *Antimicrobial assay*

Biological activities have been compared with the conventional fungicide bavistin and the conventional bactericide streptomycin and are listed in tables 2 and 3. The metal chelates are more active than the ligands for antimicrobial activity. Increased biocidal properties after complexation can be explained by chelation theory [21].



where N⌒X is donor system of the ligands, X = S (L^1H), O (L^2H)

Figure 2. Structures of the complexes.

Table 2. Fungicidal screening data for the ligands and their metal complexes (inhibition after 96 h (%) (conc. in ppm)).

	C. capsici			*F. oxysporum*		
Compound	50	100	200	50	100	200
L^1H	43.0 ± 1.0	51.0 ± 1.0	59.0 ± 0.5	41.0 ± 1.0	44.0 ± 1.0	50.0 ± 2.0
L^2H	39.0 ± 1.0	48.0 ± 1.0	53.0 ± 0.9	39.0 ± 0.6	42.0 ± 0.8	47.0 ± 0.2
$TI(L^1)$	47.0 ± 0.6	53.0 ± 0.7	62.0 ± 0.2	48.0 ± 0.2	52.0 ± 0.4	57.0 ± 0.7
$TI(L^2)$	45.0 ± 2.0	52.0 ± 0.5	56.0 ± 0.6	42.0 ± 0.4	47.0 ± 0.9	56.0 ± 0.5
$\{Ga(OPr^1)_2(L^1)\}_2$	51.0 ± 0.6	55.0 ± 0.2	64.0 ± 0.3	51.0 ± 0.6	56.0 ± 0.6	61.0 ± 0.3
$\{Ga(OPr^1)(L^1)^2\}_2$	55.0 ± 0.2	60.0 ± 0.8	66.0 ± 0.9	53.0 ± 0.4	59.0 ± 0.6	67.0 ± 0.5
$Ga(L^1)_3$	61.0 ± 0.9	63.0 ± 0.4	70.0 ± 0.6	57.0 ± 0.9	63.0 ± 0.8	72.0 ± 0.6
$\{Ga(OPr^1)_2(L^2)\}_2$	46.0 ± 1.0	54.0 ± 0.6	58.0 ± 0.3	44.0 ± 0.3	51.0 ± 0.4	59.0 ± 0.3
$\{Ga(OPr^1)(L^2)_2\}_2$	49.0 ± 0.8	58.0 ± 0.7	61.0 ± 0.9	49.0 ± 0.7	57.0 ± 0.5	62.0 ± 0.4
$Ga(L^2)_3$	57.0 ± 0.4	61.0 ± 0.5	65.0 ± 0.6	53.0 ± 0.7	61.0 ± 0.5	67.0 ± 0.9
Standard (bavistin)	97.0 ± 2.0	100.0 ± 1.0	100.0 ± 2.0	91.0 ± 1.0	95.0 ± 1.0	100.0 ± 1.0

3.3. *Antifertility activity*

3.3.1. Body and organ weights. Administration of L^1H and L^2H and their complexes $\{Ga(OPr^i)_2(L^1)\}_2$, $\{Tl(L^1)\}$, $\{Ga(OPr^i)_2(L^2)\}_2$, and $\{Tl(L^2)\}$ did not bring about any significant change in the body weights of treated rats. The weights of testes, epididymis, seminal vesicle, and ventral prostate were recorded significantly in all experimental groups when compared with the control (Supplemental material).

3.3.2. Sperm motility and sperm density. A significant ($p \leq 0.001$) decline in sperm density in testes and cauda epididymis occurred in rats treated with L^1H and L^2H and their complexes. Sperm motility in cauda epididymis also decreased significantly ($p \leq 0.001$) in experimental animals (table 4).

Table 3. Antibacterial screening data for the ligands and their metal complexes (diameter of inhibition zone (mm) (conc. in ppm)).

	P. cepacicola			*B. subtilis*		
Compound	250	500	1000	250	500	1000
L^1H	4.00 ± 0.06	6.00 ± 0.02	9.00 ± 0.03	3.00 ± 0.02	5.00 ± 0.09	8.00 ± 0.08
L^2H	3.00 ± 0.04	5.00 ± 0.04	8.00 ± 0.09	2.00 ± 0.01	4.00 ± 0.04	6.00 ± 0.04
$Tl(L^1)$	5.00 ± 0.03	8.00 ± 0.05	10.00 ± 0.02	4.00 ± 0.06	6.00 ± 0.14	9.00 ± 0.03
$Tl(L^2)$	4.00 ± 0.01	7.00 ± 0.06	9.00 ± 0.07	3.00 ± 0.04	5.00 ± 0.08	7.00 ± 0.01
$\{Ga(OPr^1)_2(L^1)\}_2$	7.00 ± 0.10	9.00 ± 0.07	11.00 ± 0.04	6.00 ± 0.05	7.00 ± 0.06	10.00 ± 0.06
$\{Ga(OPr^1)(L^1)^2\}_2$	8.00 ± 0.09	10.00 ± 0.08	12.00 ± 0.03	7.00 ± 0.06	9.00 ± 0.03	11.00 ± 0.02
$Ga(L^1)_3$	9.00 ± 0.07	11.00 ± 0.03	13.00 ± 0.14	8.00 ± 0.03	10.00 ± 0.01	12.00 ± 0.07
$\{Ga(OPr^1)_2(L^2)\}_2$	5.00 ± 0.02	8.00 ± 0.04	10.00 ± 0.06	5.00 ± 0.07	6.00 ± 0.02	8.00 ± 0.04
$\{Ga(OPr^1)(L^2)_2\}_2$	7.00 ± 0.03	9.00 ± 0.10	11.00 ± 0.05	6.00 ± 0.02	8.00 ± 0.03	10.00 ± 0.02
$Ga(L^2)_3$	8.00 ± 0.06	10.00 ± 0.07	12.00 ± 0.03	7.00 ± 0.01	9.00 ± 0.07	11.00 ± 0.07
Standard (streptomycin)	15.00 ± 0.05	16.00 ± 0.08	17.00 ± 0.02	14.00 ± 0.11	15.00 ± 0.12	16.00 ± 0.10

Table 4. Effect of the ligands and their gallium and thallium complexes on sperm dynamics of male rats.

			Sperm density (million mL^{-1})		
Group	Treatment	Sperm motility (%) Cauda epididymis	Testes	Epididymis	Fertility (%)
I	Control	69 ± 1	4.2 ± 0.5	48 ± 0.9	100 (+ve)
II	L^1H	45 ± 2^b	3.7 ± 0.3^a	20 ± 1^b	70 (−ve)
III	L^2H	38 ± 2^b	3.4 ± 0.4^a	21 ± 1^b	74 (−ve)
IV	$\{Ga(OPr^i)_2(L^1)\}_2$	27 ± 1^b	2.2 ± 0.1^b	10 ± 0.9^b	95 (−ve)
V	$Tl(L^1)$	21 ± 1^b	2.1 ± 0.1^b	10 ± 0.7^b	98 (−ve)
VI	$\{Ga(OPr^i)_2(L^2)\}_2$	17 ± 1^b	1.8 ± 0.2^b	9.6 ± 0.7^b	92 (−ve)
VII	$Tl(L^2)$	19 ± 1^b	1.7 ± 0.2^b	9.1 ± 0.6^b	96 (−ve)

Values means ± SE of six determinations.
[a] $p = 0.01$ Groups II and III compared with Group I.
[b] $p < 0.001$ Groups IV and V compared with Group II and Groups VI and VII compared with Group III.

3.3.3. Biochemical changes. Protein contents of testes, epididymis, ventral prostate, and seminal vesicle were reduced after treatment with the ligands L^1H and L^2H and their gallium and thallium complexes (table 5). Sialic acid contents of testes, epididymis, ventral prostate, and seminal vesicle were decreased in various experimental animals. A significant increase in testicular content was noticed in animals treated with ligands and their complexes, whereas testicular glycogen was decreased. Fructose content of seminal vesicles was reduced after treatment with the ligands L^1H and L^2H and their metal complexes.

Oral administration of L^1H, L^2H, $\{Ga(OPr^i)_2(L^1)\}_2$, $Tl(L^1)$, $\{Ga(OPr^i)_2(L^2)\}_2$, and $Tl(L^2)$ reduced the fertility in treated rats. A significant reduction was observed in the weights of testes, epididymis, and sex accessory organs (seminal vesicle and ventral prostate) in treated rats. Reduction in weights may reflect a declining amount and synthesis of androgen within these organs [22, 23]. Decrease in sperm motility and density could compromise the fertility [24]. These depletions suggest alterations in sperm maturation and sperm production [25]. Protein content in testes and other sex accessories significantly decreased after administration of L^1H and L^2H and their complexes, probably due to the absence of the spermatogenesis stages [26] in the testes.

Table 5. Effect of the ligands and their gallium and thallium complexes on tissue biochemistry of male rats.

		Protein ($mg\,g^{-1}$)				Sialic acid ($mg\,g^{-1}$)						
Group	Treatment	Testes	Epididymis	Seminal vesicle	Ventral prostate	Testes	Epididymis	Seminal vesicle	Ventral prostate	Glycogen ($mg\,g^{-1}$)	Cholesterol ($mg\,g^{-1}$)	Fructose ($mg\,g^{-1}$)
I	Control	250 ± 8	225 ± 3	215 ± 4	217 ± 3	5.7 ± 0.4	6.2 ± 0.3	5.8 ± 0.3	5.9 ± 0.4	3.70 ± 0.2	5.7 ± 0.5	4.80 ± 0.2
II	L^1H	195 ± 7^a	175 ± 4^a	167 ± 2^b	170 ± 2^a	4.7 ± 0.2^a	5.3 ± 0.2^a	4.6 ± 0.2^b	4.3 ± 0.1^b	2.90 ± 0.2	7.1 ± 0.3	4.0 ± 0.1^a
III	L^2H	194 ± 7^a	168 ± 4	172 ± 2	163 ± 2^a	4.6 ± 0.1^a	5.1 ± 0.1^b	4.2 ± 0.1^b	4.1 ± 0.2^b	2.72 ± 0.1^b	8.1 ± 0.3^b	4.1 ± 0.1^a
IV	$\{Ga(OPr^i{}_2(L^1)\}_2$	130 ± 3	125 ± 3^b	123 ± 2^b	128 ± 2	2.7 ± 0.2^b	3.7 ± 0.3^b	3.4 ± 0.1^b	2.9 ± 0.2^b	2.0 ± 0.2^b	12.0 ± 0.4^b	2.7 ± 0.1^b
V	$Tl(L^1)$	120 ± 6	115 ± 2	109 ± 2	118 ± 3	2.2 ± 0.3^b	2.3 ± 0.4^b	2.4 ± 0.2^b	2.1 ± 0.1^b	1.9 ± 0.1^b	13.8 ± 1	2.4 ± 0.1^b
VI	$\{Ga(OPr^i)_2(L^2)\}_2$	110 ± 3^b	121 ± 3^b	107 ± 2	112 ± 2	2.4 ± 0.1^b	2.2 ± 0.1^b	2.4 ± 0.2^b	2.1 ± 0.3^b	2.1 ± 0.1^b	13.1 ± 1^b	2.09 ± 0.1^b
VII	$Tl(L^2)$	104 ± 4	101 ± 3^b	100 ± 1^b	101 ± 3^b	2.2 ± 0.2^b	2.1 ± 0.2^b	2.1 ± 0.1^b	2.3 ± 0.1^b	1.6 ± 0.2^b	14.6 ± 2	2.0 ± 0.1^b

Values means $\pm$ SE of six determinations.
[a] $p = 0.01$ Groups II and III compared with Group I.
[b] $p < 0.001$ Groups IV and V compared with Group II and Groups VI and VII compared with Group III.

Table 6. Irradiation activity of the ligand.

	Group of mice	LPO	GSH
1.	Normal	0.95 ± 0.03	3.02 ± 0.01
2.	Drug (L^1H) alone	0.82 ± 0.05	3.3 ± 0.2
3.	DDW + radiation (control)	1.17 ± 0.04	2.69 ± 0.01
4.	Drug (L^1H) + radition (experiment)	1.12 ± 0.01	2.83 ± 0.04

Table 7. Irradiation activity of the metal complex.

	Group of mice	LPO	GSH
1.	Normal	0.95 ± 0.03	3.02 ± 0.01
2.	Drug $Ga(L^1)_3$ alone	0.82 ± 0.06	3.3 ± 0.2
3.	DDW + radiation (control)	1.17 ± 0.04	2.69 ± 0.01
4.	Drug $Ga(L^1)_3$ + radiation (experiment)	1.12 ± 0.01	2.83 ± 0.05

LPO = lipid peroxidation; GSH = reduced glutathione.

Cholesterol is a precursor for androgen biosynthesis and its level in testes is closely related to fertility and sperm output. Accumulation of cholesterol indicates reduced conversion to androgen [27]. Sialic acid is concerned with charging the membrane surface of maturing spermatozoa and with the development of their fertilizing capacity [28]. Thus, decreased sialic acid after treatment with the ligands L^1H and L^2H and their complexes may inhibit the fertility capacity of the sperm. The results from our study indicated that the ligands L^1H and L^2H and their complexes reduced the seminal vesicular fructose levels supporting inhibition of fructose and decrease in sperm motility [29]. Further, reduction in testicular glycogen after treatment with ligands and their complexes subsequently inhibit spermatogenesis.

3.4. *Irradiation activity*

One gallium complex of L^1H shows radiation protection action in mice after administration of drug followed by gamma radiation by a ^{60}Co source; complex is more protective than ligand. The GSH content in blood was measured spectrophotometrically using Ellman reagent (DTNA) as coloring reagent with the method described by Beutler *et al.* [30]. The absorbance was recorded at 432 nm (tables 6 and 7). The LPO level in serum was measured in terms of thiobarbituric acid reactive substance by the method of Ohkhawa *et al.* [31]. The absorbance was read at 532 nm (tables 6 and 7). The LPO has been suggested as one of the main causes of radiation induced membrane damage [32].

The GSH and LPO assays revealed that gallium complex shows radiation protection action in mice after administration of drug followed by gamma radiations by a ^{60}Co source. The application of this complex as a radioprotective drug in clinical radiotherapy needs further investigation.

4. Conclusion

The ligands L^1H and L^2H coordinate in 1 : 1, 1 : 2, and 1 : 3 metal : ligand ratio as monobasic bidentate. The analytical and spectral studies suggest structures shown

in figure 2. The antimicrobial, antifertility, and antiradiation activities of the complexes are higher than the parent ligands. Based on the above studies Schiff bases are versatile ligands that can coordinate virtually any metal ion with interesting bioactivities.

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