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Research Article

MICROWAVE ASSISTED SYNTHESIS OF SCHIFF BASES COMPLEXES VIA ECO - FRIENDLY GREENER METHODOLOGY

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ABSTRACT

A new class of unsymmetrical organotitanium (IV) and organozirconium (IV) complexes of biologically potent ligands derived from heterocyclic ketones and semicarbazide hydrochloride/ thiosemicarbazide have been prepared by the microwave irradiations. The resulting new complexes have been characterized by elemental analyses, molar conductance and spectral studies including electronic, IR and ^{1}H NMR. Molecular weight determination by Rast Camphor Method indicated the monomeric nature of these complexes and conductance measurements showed their non-electrolytic behavior. Octahedral geometry has been proposed for the resulting complexes. The ligands act as monobasic bidentate with $\widehat{N\,O}H$ and $\widehat{N\,S}H$ as donor systems. A comparative study has been made between microwave assisted synthesis and the thermal synthesis. The Schiff bases and their complexes have been screened for their in-vitro antibacterial (*Escherichia coli and Staphylococcus aureus*) and antifungal (*Aspergillus niger and Pencillium chrysogenum*) activities and found active in this respect. The testicular sperm density, sperm morphology, sperm motility, density of cauda epididymis, spermatozoa and fertility in mating trials and the biochemical parameters of the reproductive organs of the rat were examined.

Keywords: *Microwave Assisted Synthesis, Thermal Synthesis Antifungal, Antibacterial, Antifertility*

INTRODUCTION

The coordination chemistry of schiff bases as multidentate ligands having delocalized π - orbitals gained importance for more than two decade because of their use as models of biological systems. Schiff bases derived from amines and aldehydes have a wide variety of applications in many fields, e.g., biological, inorganic and analytical chemistry (Ibrahim and Sharif, 2007; Cimerman *et al.*, 2000; Elmali *et al.*, 2000; Patel *et al.,* 1999). Among the organic reagents actually used, Schiff bases possess excellent characteristics, structural similarities with natural biological substances, relatively simple preparation procedures and the synthetic flexibility that enables design of suitable structural properties (Patai, 1970; Jungreis and Thabet, 1969). In recent years among the chemical compounds, some Schiff bases and their complexes because of their ability as biologically activities such as antimicrobial, antifungal, antivirial and antitumor have been found to be very important and usefulness of these compounds are not covered by anyone (Kumar *et al.,* 2009). Schiff bases usually have variable donation sites, e.g., nitrogen, sulfur and/or oxygen markedly affected the activity of the compounds. They could be monodentate, bidentate, tridentate or tetradentate forming mono- or polynuclear complexes (Singh *et al.*, 1997). Also for this class of compounds, many applications such as antidepressants, antiphlogogistic, antinematocide, and other medicinal agents have been reported (Tarafder *et al.,* 2000). Schiff base metal complexes have good ability to reversibly bind oxygen in epoxidation reactions, catalytic role in hydrogenation of olefins (Zhao *et al.*, 2001) and photochromic properties (Liu *et al.,* 2004). Schiff bases can be used to obtain optical materials and conducting polymers (Aly and El-Shaieb, 2004). In the present paper, preparation and identification of several new Schiff base ligands and their metal complexes by using microwave irradiation /thermal method have been discussed.

MATERIALS AND METHODS

All the chemicals and solvent used were dried and purified by standard method and reaction were carried out under strictly anhydrous conditions. All the reactions were carried out in a domestic microwave oven (Kenstar, Model No. OM-26 E 60, Power-1200 W), (Power-1200 W). The ligands were prepared by two methods. In first method microwave technique were used. In microwave method synthesis of ligands HL_1 2-[1(2 Pyridinyl) ethyledene] hydrazine carbothioamide, HL_2: 2-[1(2 Thienyl) ethyledene] hydrazine carboxamide, HL_3 2-[1(2 Naphthenyl) ethyledene] hydrazine carboxamide, HL_4 2-[1(2 Naphthenyl) ethyledene] hydrazine carbothioamide were prepared by condensation of respective ketones with thiosemicarbazide or semicarbazide presence of sodium acetate in eqimolar ratio (1.1.1) in alcoholic medium. The content was allowed to react in Teflon beaker in microwave oven using few ml of solvent. The reactions were completed in short time (4-8 min.). Their physical properties and analytical data are recorded in Table 1.

Table 1: Physical properties and analytical data of ligands

Ligand	Color	M.P. °C	Analysis % Found (Calcd.)		Mol. Wt. Found (Calc.)
			N	S	
2-AcThiop.SCZH $C_7H_oN_3SO[L_1H]$	White	188	22.81 (22.93)	17.23 (17.20)	205 (183)
2-AcPyd.TSCZH $C_8H_{10}N_4S[L_2H]$	Yellow	142	28.59 (28.84)	16.66 (16.51)	218 (194)
2-AcNaph.SCZH $C_{13}H_{13}N_3O[L_3H]$	White	214	18.57 (18.49)	–	248 (227)
2-AcNaph.TSCZH $C_{13}H_{13}N_3S[L_4H]$	White	144	17.13 17.27	13.05 (13.18)	268 (243)

In the second method the conventional heating technique was used. In this method the weight amount of thiosemicarbazide or semicarbazide hydrochloride and the respective ketones (in presence of sodium acetate) were mixed in 100ml of ethanol refluxed for 3 hrs. The crystalline products so obtained were filtered, recrystallized from the same solvent and dried. A comparison between thermal method and microwave method is given in Table 2.

Table 2: Comparison between microwave and thermal method

Compound	Yield (%)		Solvent (ml)		Time	
	Thermal	Microwave	Thermal	Microwave	Thermal (hrs.)	Microwave (min.)
L_1H	60	70	80	2	3	2
L_2H	80	90	85	2	4	6
L_3H	80	85	85	2	4	6
L_4H	75	85	95	2	4	4
$Cp_2Ti(L_1)(L_2)$	76	84	30	3	12	6
$Cp_2Ti(L_3)(L_4)$	75	88	40	2	17	6
$Cp_2Zr(L_1)(L_2)$	74	86	35	2	18	6
$Cp_2Zr(L_3)(L_4)$	76	84	35	2	16	5

The complexes were also synthesized by the above techniques. For the microwave assisted synthesis the reaction of metallocenes of titanium (IV) and Zirconium (IV) with L_1H and L_2 H. were carried out in 1:1:1 molar ratio in dry THF using triethyl amine as hydrogen chloride accepter. In the same way this reaction was also performed with ligands L_3H and L_4H. The resulting product were recovered from the microwave oven and dissolved in few ml of tetrahydrofuran, were the precipitate of triethyl amine hydrogen chloride formed during the course of the reaction was filtered off and the filtered dried in Vacuum. The products were purified by repeated washing with n- hexane and their purity was further checked by TLC using silica gel G.

The above complexes were also synthesis by thermal method where the refluxing time is longer and the yield was also low as compared to the microwave assisted synthesis. The physical properties and analytical data of these complexes are enlisted in Table 3.

Table 3: Physical-properties and analytical data of unsymmetrical complexes of Ti and Zr

Starting Material (g)	Ligand (g)	Ligand (g)	Et_3N	Compound	Colour	M.P. °C	Analysis % Found (Caled.)			Mol. Wt. Found (Calcd.)
							N	S	M	
Cp_2TiCl_2	$C_7H_9N_3OS$	$C_8H_{10}N_4S$	Et_3N	$Cp_2Ti(C_7H_8N_3SO)(C_8H_9N_4S)$	Brown	100d*	17.67	11.24	8.58	509
0.53	0.39	0.41	0.43				(17.71)	(11.58)	(8.64)	(554)
Cp_2TiCl_2	$C_{13}H_{13}N_3O$	$C_{13}H_{13}N_3S$	Et_3N	$Cp_2Ti(C_{13}H_{12}N_3O)(C_{13}H_{12}N_3S)$	Light brown	170	13.05	5.03	7.46	602
0.76	0.69	0.74	0.61				(12.99)	(4.59)	(7.40)	(647)
Cp_2ZrCl_2	$C_7H_9N_3OS$	$C_8H_{10}N_4S$	Et_3N	$Cp_2Zr(C_7H_8N_3SO)(C_8H_9N_4S)$	Greenish Yellow	89	16.38	10.55	15.21	557
0.86	0.53	0.57	0.59				(16.42)	(10.74)	(15.28)	(597)
Cp_2ZrCl_2	$C_{13}H_{13}N_3O$	$C_{13}H_{13}N_3S$	Et_3N	$Cp_2Zr(C_{13}H_{12}N_3O)(C_{13}H_{12}N_3S)$	Brown	128	12.12	4.25	13.27	645
0.49	0.38	0.41	0.34				(12.18)	(4.64)	(13.22)	(690)

Physical Measurements and Analytical Methods

Nitrogen and Sulphur were determined by the Kjeldahl's (Vogel, 1991) and Messenger's (Mahajan *et al.*, 2007) method, respectively. Titanium (IV) and Zirconium (IV) were estimated gravimetrically as their oxide. The electronic spectra were recorded on a Hitachi- U-2000 spectrophotometer and IR spectra were recorded on a Perkin Elmer modal 577 gratting spectrophotometer in the range 4000 – 200 cm^{-1} in KBr discs. ^1H NMR spectra were recorded on a JEOL AL 300 FT NMR spectrophotometer in DMSO- d_6 using TMS as an internal standard.

RESULTS AND DISCUSSION

The stoichiometric reactions of Titanocenedichloride or Zirconocenedichloride with two different monofunctional bidentate ligands, resulting with the formation of unsymmetrical complexes which can be represented by the following reaction.

$$Cp_2MCl_2 + N\,OH + N\,SH \xrightarrow[T.H.F.]{Et_3N} Cp_2M(N\,O)(N\;\,S) + Et_3N.HCl$$

where N SH/N OH represent the donor-system of ligand molecule M = Ti and Zr

The resulting complexes are coloured solid, which exhibits their solubility in methanol, $CHCl_3$, DMSO, DMF and THF. Their molar conductivity values (10-15 ohm^{-1} cm^2 mol^{-1}) in dry DMF show that they are non electrolyte and their monomeric nature has been confirmed by the molecular weight determinations.

It is observed that, the reaction rate from microwave method was *ca*.100 times faster than the reaction rate in the conventional way. Under microwave irradiation, molecules with a permanent dipole moment become aligned to the electric field and their orientation changes as field oscillates. The reorientation of molecules in phase with the electrical field excitation causes an intense internal heating. Thus, reaction time is brought down from hours to seconds as compared to the conventional heating (Mistry and Desai, 2006), which is cleared from the Table 2.

The physical properties of the products obtained from thermal method and conventional method are almost the same. (Table 3)

Electronic Spectra

In the electronic spectra of the ligands the bands at ca 280 nm and 305 nm due to π- π^* transitions appear almost in the same region in the spectra of their complexes. Another band observed at ca 380 nm in the spectra of the ligands assigned to the n- π^* transitions of the azomethine moiety, gets shifted at lower wave length due to the polarization within the chromophore >C = N caused by the metal- ligand electron interaction.

Infrared Spectra

On comparing the IR spectra of the ligands to that of the corresponding titanium and zirconium complexes, it has been confirmed that the formation of the complexes takes place through the bonding of nitrogen and sulfur/ oxygen of the ligands moieties. In the solid state IR spectra of the ligands, a broad band 3300-3100 cm^{-1} may be assigned to ν (NH) vibration. However, in their solution spectra an additional band due to ν (SH) also appears in the 2700-2500 cm^{-1} region due to tutomerization. The disappearance of these ν(NH)/(OH)or ν(SH) bands and presence of ν(M ←N), ν(M-S) and ν(M-O) vibrations at ca 525-425, 360-320 and 620-540 cm^{-1}in the complexes indicates the possible deprotonation of the functional groups on complexation. The medium intensity band appearing in the ligands due to ν (>C=N) shift to the lower frequency (ca.20 cm^{-1}) in the complexes indicating coordination of the azomethine nitrogen to the metal atom. However, two strong bands at ca 3490 and 3360 cm^{-1} due to the NH_2 group, remain unchanged in the spectra of the complexes showing thereby the non-involvement of this group in coordination. The bands due to ν (C=O) and ν (C=S) modes in the spectra of ligands were observed at ca 1680 and ca 1020 cm^{-1}, respectively. These bands disappear in the spectra of the metal complexes suggesting thereby inolization of the ligands and their chelation through the amido oxygen and thiolic sulpur. This fact is further corroborated with the observation of the bands due to ν(C-O) and ν (C-

S) modes at lower frequencies in the spectra of the metal complexes. In addition of these the characteristic bands at ca 3100 ν (C-H), ca 1450 ν(C-C) and 1020 and 810 cm^{-1} δ (C-H) in –plane and out – of – plane respectively, are of the cyclopentadienyl ring. The persistence of bands due to the cyclopentadienyl ring of the spectra of the complexes indicates that this group remains delocalized and π bonded (η^5) to the metal and retained its aromatic character.

NMR Spectral Studies

The ^{1}H NMR spectra of the ligands and their unsymmetrical complexes have been recorded in DMSO – d$_6$ Table 4-. The proton signal appearing at δ 9. 83 – 10.68 ppm in the spectra of the ligands is due to NH proton and it disappears in the spectra of the metal complexes thereby suggesting the deprotonation of NH group. The methyl proton signal of the azomethine moiety is observed at δ 1.68 – 2.30 ppm in the spectra of the ligands and gets schiffted downfield in the spectra of the metal complexes. The NH_2 proton signals remain at the same position in the ligand and its complexes. A sharp singlet in the δ 6.00 – 6.20 ppm range provides additional evidence for the presence of the (n-C_5H_5 group)

On the basis of the above evidences the following tentative structure can be proposed for the resulting hexa coordinated complexes.

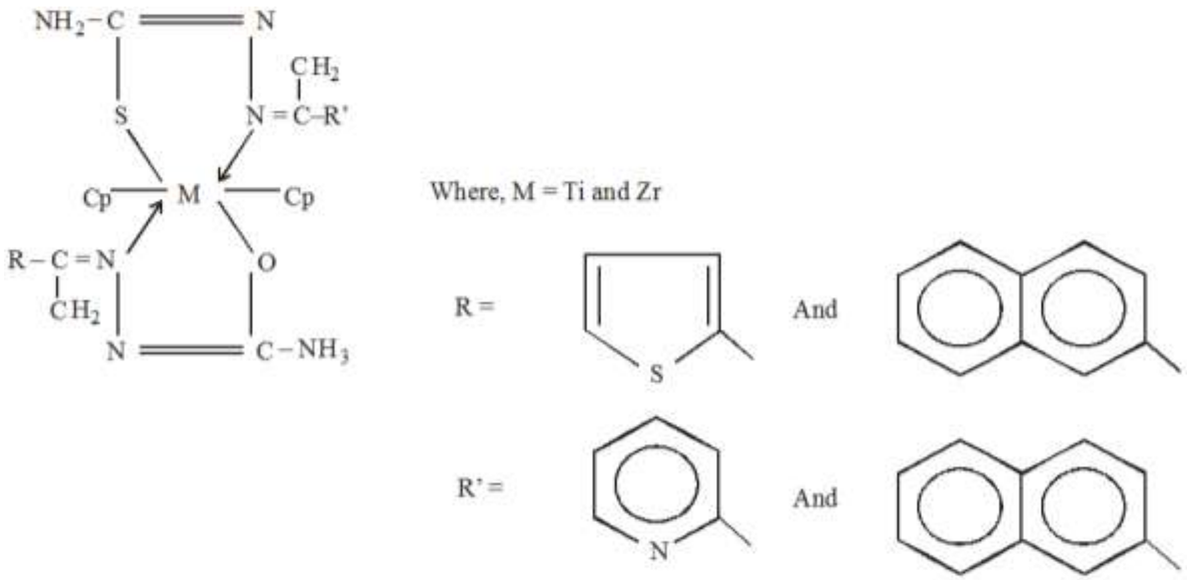

Table 4: ^{1}H NMR spectral data of ligands and their corresponding Ti and Zr complexes

Compound	-NH (bs)	-NH_2 (bs)	-CH_3 (s)	Aromatic (m)	Ti-Cp/Zr-Cp (s)
L_1H	9.83	2.80	2.32	7.84-7.20	-
L_2H	10.64	2.84	1.68	8.92-7.48	-
L_3H	9.84	2.80	2.36	7.84-7.20	-
L_4H	10.68	2.90	1.91	8.90-7.55	-
$Cp_2Ti(L_1)(L_2)$	-	2.86	2.24	9.36-8.32	6.20
$Cp_2Ti(L_3)(L_4)$	-	2.84	2.26	9.42-8.26	6.18
$Cp_2Zr(L_1)(L_2)$	-	2.87	2.25	9.34-8.30	6.00
$Cp_2Zr(L_3)(L_4)$	-	2.82	2.23	9.31-8.36	6.15

Antimicrobial Studies

Antifungal Activity

The ligands and their metal complexes have been screened for their antifungal activities by the radial growth method using potato dextrose agar medium. The pathogenic fungi used during the investigations are *Fusarium oxysporum and Aspergillus niger*. The compounds were directly mixed with the medium in 50, 100 and 200 ppm concentrations. Controls were also run and three replicates were used in each case. The linear growth of the fungus was obtained by measuring the diameter of the fungal colony after four days. The percent growth inhibition was calculated by using the following formula:

$$\% \text{ Growth inhibition} = \frac{dc - dt}{dc} \times 100$$

where, dc = diameter of the fungal colony in the control plate.

dt = diameter of the fungal colony in the test plate.

The experimental results show that there is an increase in the toxicity of the complexes as compared to the ligands. The evaluation of antifungal studies further revealed that fungi toxicity of the complexes also depends on the nature of the metal ion. In general, the activity of these metal complexes increases as their concentration is increased in the test solution.

Antibacterial Activity

The ligands and their complexes were screened for their antimicrobial activity against gram negative as well as gram positive microorganisms such as *E.coli* and *S.aureus*. For antibacterial activity inhibition zone technique (Chaudhary *et al.*, 2002) was used. Solution of the test compounds in methanol in 500 and 1000 ppm concentrations were prepared in which discs were dipped in solution of the test sample and then placed on seeded plates. The petri plates having these discs on the seeded agar is placed at low temperature for 2 - 4 hours to allow for the diffusion of chemicals before being incubated at suitable optimum temperature 28 ± 2ºC for 24 - 30 hours. After the expiry of their incubation period, the zone of inhibition associated with the treated disc was measured in mm.

The data reveal that the antibacterial activity of the complexes is superior to that of the ligands. Further, on the basis of chelation theory (Sharma *et al.*, 2010), antibacterial activity of the metal chelates can be explained. Chelation may enhance the biochemical potential of bioactive species. Because on chelation, the polarity of the metal ion will be reduced due to the overlap of the ligand orbital and partial sharing of the positive charge of the metal ion with donor groups. Hence complexes become very stable due to delocalisation of π-electrons. It enhance the penetration of the complexes into lipid membranes and blocking of the metal binding sites in the enzymes of microorganisms. These complexes also disturb the respiration process of the cell thus block the synthesis of the proteins, which restricts further growth of organisms. Fungicidal and bactericidal activities of ligands and their corresponding titanium and zirconium complexes against different pathogenic fungi and bacteria have been recorded in Tables 5and 6

Table 5: Antifungal screening data of the ligands and their titanium and zirconium complexes (percent inhibition after 4 days at 25 ± 2ºC)

Compound	*F.oxysporum*			*A. niger*		
	50 ppm	100 ppm	200 ppm	50 ppm	100 ppm	200 ppm
L_1H	7	16	29	28	40	48
L_2H	30	55	61	25	42	48
L_3H	20	41	56	-	-	-
L_4H	32	54	58	29	46	51
$Cp_2Ti(L_1)(L_2)$	34	45	68	43	61	75
$Cp_2Ti(L_3)(L_4)$	45	56	75	-	-	-
$Cp_2Zr(L_1)(L_2)$	38	50	74	47	66	81
$Cp_2Zr(L_3)(L_4)$	49	61	81	-	-	-

Table 6: Antibacterial screening data of the ligands and their titanium and zirconium complexes (percent growth inhibition after 24 hours at 30q±1°C)

Compound	*E.coli*		*S.aureus*	
	500 ppm	1000 ppm	500 ppm	1000 ppm
L_1H	3	5	4	7
L_2H	3	5	4	7
L_3H	2	5	3	6
L_4H	3	5	4	8
$Cp_2Ti(L_1)(L_2)$	7	13	6	13
$Cp_2Ti(L_3)(L_4)$	7	13	6	15
$Cp_2Zr(L_1)(L_2)$	6	11	5	12
$Cp_2Zr(L_3)(L_4)$	6	11	5	14

Antifertility Activity

The antifertility activity of the ligands and their complexes was studied on the adult male albino rats of sprague dawley strain. The rats were divided into five groups of five animals each.

The group A received the vehicle (Olive oil) only. Animals of groups B and C received ligands L_3Hand L_4H respectively. (20 mg/kg.b.wt.) orally for 60 days whereas the animals of groups Dand E received titanium and zirconium complexes respectively (20 mg/kg.b.wt.) orally for a period of 60 days. The animal were screened for fertility test and autopsied for detailed pathological and biochemical studies.

The sperm motility in cauda epididymis and density of testicular and cauda epididymis in suspended sperm were calculated. Reproductive organs were excised, blotted free of blood and weighed. The testes were frozen for biochemical estimations. Total protein, glycogen, total cholesterol, sialic acid, acid and alkaline phosphatase activities were estimated by using the standard laboratory techniques. Student's 't' test was applied in comparing the means.

Sperm Motility and Density

Oral administration of the ligands and their metal complexes resulted in a significant decline in the sperm motility in cauda epididymis and sperm density in testes and cauda epididymis. Table7

Fertility Test

A sharp decline in the fertility of male rats was observed after treatment with ligands and their complexes.

Biochemical Findings

Sialic acid and total protein content of testes, epididymis, seminal vesicle and ventral prostate were reduced significantly after treatment with ligands and their complexes. Cholesterol contents of testes and seminal vesicular fructose were reduced significantly in all treated groups. Our study indicated that oral administration of ligands and their titanium and zirconium complexes leads to a significant reduction in the weight of reproductive organ and sharp decline in sperm motility and sperm counts. The result indicates an inhibitory effect of test substances on testicular sperm production /epididymal sperm maturation, which consequently resulted in the gradual decline in the fertility rate. Alterations in the sperm motility, viability and morphology suggest a disturbed testicular and epididymal microenvironment due to treatment as evidenced by significant reduction in tissue weights (Craft *et al.,* 1993). The secretion of male sex accessory glands are known to have a variety of action on gametes and male reproductive tract (Mann and Mann, 1981). Seminal fluid contain fructose and protein that serve as energy source for maturation and motility of sperms (Curry and Artherton, 1990). Since the optimum level of protein and sialic acid are necessary for sperm maturation, capicitation and fertilization and all these are regulated by androgens (Sharp, 1987). Therefore, the decrease activity of biochemical constituents of testes and sex accessories (Lohiya and Ansari, 1999) suggest antiandrogenic effects of these compounds. In conclusion addition of titanium or zirconium moiety to the ligands enhance their activities. However, compounds of ligand 2 AcThiop.SczH with titanium or zirconium moiety seems to be more effective in reducing fertility (Table 8 and 9).

Table 7: Effect of ligands and their metal complexes on body and reproductive organ weights of male rats

Groups	Treatment	Body Weight (gm)		Organ Weight (mg)			
		Initial	Final	Testes	Epididymis	Seminal Vesicle	Ventral Prostate
A	Control	225±15	240±.1^{a}	1350±70	515±30	435±16	340±17
B	L_3H	210±17	220±15^{a}	1010±90^{b}	430±10^{b}	330±20^{b}	260±15^{b}
C	L_4H	212±17	222±15^{a}	1014±90^{b}	434±10^{b}	334±20^{b}	260±15^{b}
D	$Cp_2Ti(L_3)(L_4)$	205±10	216±14^{a}	820±50^{b}	280±15^{c}	225±28^{c}	200±14^{b}
E	$Cp_2Zr(L_3)(L_4)$	212±18	228±11^{a}	840±60^{b}	290±30^{c}	250±18^{b}	165±10^{b}

= $p\leq0.01$ Group B and C compared with group A (Mean ± SEM of 5 animals)

Table 8: Altered sperm dynamics and fertility after treatment with various test compounds

Group	Treatment	Sperm Motility (%) (Cauda epididymics)	Sperm Density (million/ml)		Fertility (%)
			Testes	Cauda epididymis	
A	Control (Vehicle Only)	82.0±4.5	4.5.0±0.31	65.0±4.8	100% positive
B	L_3H	65.2±4.3^{b}	3.4±0.32^{b}	52.0±2.5^{c}	72% negative
C	L_4H	68.1±3.9^{c}	3.9±0.17^{c}	58.0±2.9^{c}	74% negative
D	$Cp_2Ti(L_3)(L_4)$	50.0±4.8^{b}	2.2±0.21^{b}	40.0±2.8^{b}	82% negative
E	$Cp_2Zr(L_3)(L_4)$	52.5±2.3^{b}	2.3±0.25^{b}	42.1±2.6^{b}	80% negative

a = p = non-significant, b = $p \leq 0.05$, c = $p \leq 0.001$
Groups B and C compared with Group A, Groups D and E compared with Groups B and C, Groups D and E compared with Group A

Table 9: Biochemical changes after treatment with various test compounds

Group	Treatment	Total cholesterol (mg/gm) Testes	Fructose (mg/gm) seminal Vesicle	Sialica acid (mg/gm)				Total protein (mg/gm)			
				Testes	Epididymis	Ventral prostate	Seminal Vesicle	Testes	Epididymis	Ventrial prostate	Seminal vesicle
A	Control (Vehicle only)	8.9±0.5	435±15	8.2±0.4	7.4±0.5	8.6±0.6	7.7±0.4	170±25	250±2.0	237±19	256±28
B	L_3H	62.±0.6^{b}	352±10^{b}	6.6±0.4^{b}	6.1±0.3^{b}	6.4±0.5	6.2±0.6^{b}	170±15	190±15	185±17	200±10^{a}
C	L_4H	5.2±0.4^{c}	380±12 ^{b}	4.6±0.2^{c}	4.2±0.4^{c}	4.9±0.3^{c}	4.8±0.4^{c}	147±11^{c}	138±14^{c}	121±20^{c}	180±15^{c}
D	$Cp_2Ti(L_3)(L_4)$	4.3±0.5^{b}	200±11^{c}	5.0±0.2^{b}	4.9±0.2^{b}	4.8±0.4^{b}	4.6±0.3^{b}	120±10^{c}	125±12^{c}	130±11^{c}	125±10^{c}
E	$Cp_2Zr(L_3)(L_4)$	4.9±0.6^{b}	220±15^{c}	5.2±0.1^{b}	5.0±0.1^{b}	5.8±0.1^{h}	4.9±0.2^{b}	130±10^{b}	130±20^{b}	138±13^{b}	139±18^{b}

a = p = non significant, b = $p \leq 0.05$, c = $p \leq 0.001$
Groups B and C compared with Group A, Groups D and E compared with Groups B and C, Groups D and E compared with Group A.

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