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Synthesis, Spectroscopic, Biological, and Theoretical Evaluation of Novel Zirconium (IV) N, O Donor Amino Acid Schiff Base Complexes

Hari S. Yadav[1]*, Gopal L. Kumawat[2]

[1]Department of Chemistry, SNKP Government P.G. College Neemkathana, Sikar-332713, (Raj.), India
[2]Department of Chemistry, SRK Government P.G. College Rajsamand -313324, (Raj.), India
Corresponding author's email address: harichem86@gmail.com

Abstract A series of novel dichlorozirconium (IV) Schiff bases complexes $[ZrCl_2 (L)_2]$ (LH = N, O donor Schiff base derived by the condensation of 2-Acetyl-5-methylfuran & 2-acetyl-4-methyl thiophene with amino acids) were synthesized by the reaction of zirconium (IV) chloride and sodium salt of an N, O donor Schiff base ligand and characterized. The authenticity of all the synthesized ligands and their Zr (IV) complexes had been elucidated by microanalysis, various spectroscopic techniques like FT-IR, ^{1}H NMR, ^{13}C NMR spectroscopic techniques, electrical conductance measurements, and elemental analysis (CHN). The ligand acts as a bidentate in which the carboxylate oxygen and the azomethine nitrogen of the ligand are involved in coordination. Both the ligands and their corresponding metal complexes have been tested for their antibacterial and antifungal activity. The activities of the samples have shown significant and noticeable changes in complexation. Experimental studies propose that metal chelates are more potent than their parent ligands.

Keywords Schiff base, Antibacterial, Antifungal activity, Metal chelates

Introduction

The research grounds in organometallic chemistry of Schiff bases are potentially biologically active and a peculiar type of ligands possessing a diversity of donor atoms and have been widely explored, through its use in antifungal [1-10], antitumor [11-12], antibacterial [13-15], and anticancer activities [16-17]. The chelating activity of the bidentate Schiff bases ligand with nitrogen-oxygen donor atoms gives it kinetic and thermodynamic stability, making it interesting for researchers. The impendence of nitrogen in the imine groups (C=N) in Schiff bases and their metallic complexes and their chelating properties are the reason for their many unique biological properties [18-19]. Recently, a noticeable effort has been intent to the potential potent properties, coordinating ability, spectral properties, and structural and biological aspects of Schiff base ligands and their relevant metal complexes [20-22]. Varshney S., *et al*. depict the complexes of the amino acids [23] and metal ions are a kind of important bioinorganic compounds due to being widely applied in biology and medicine, their derivatives have attracted a great deal of attention [24-25]. Strauch J., Warren T. H., *et al.* studied the high affinity for the chelation of the Schiff bases towards the zirconium metal ion utilized in preparing inorganic compounds [26] and coordination complexes [27-28]. Albeit the chemistry of zirconium complexes has been spaciously studied, particularly concerning their application in polymerization [29]. So introducing the variant class of amino acid Schiff bases incorporating metal-ligand as antibacterial and antifungal. All zirconium (IV) complexes were showed toxicity and more active than the

ligands but less active than these standard drugs [30]. Despite this, relatively less work has been issued on the complexes of zirconium metal ions. This is not more information on zirconium (IV) complexes from the existing literature.

So, keeping all these things in consideration I am very enthusiastic to synthesize dichlorozirconium (IV) Schiff bases complexes $[ZrCl_2(L)_2]$ with N, O donor Schiff bases (L^1H-L^4H) derived from 2-Acetyl-5-methylfuran & 2-acetyl-4-methyl thiophene and amino acids (Glycine & Leucine) were obtained. The antimicrobial activity of the Zr (IV) complex was investigated against the growth of Gram-positive *Staphylococcus aureus*, Gram-negative *Escherichia coli* bacteria, *Aspergillus niger*, *Rhizopus phaseoli* fungi. The ligand and its complexes showed varied activity against more strains and their activity was enhanced respectively on coordination/chelation due to their stability, electron-donating capacity, and biological activity.

Experimental

Analytical Methods and Physical Measurements

All chemicals and solvents used for the synthesis were of analytical grade. 2-Acetyl-5-methylfuran, 2-acetyl-4-methyl thiophene (Across) and amino acids (Aldrich), Zirconium (IV) chloride (Sigma Aldrich), and used as received. All the reactions were carried out under strictly anhydrous conditions. IR spectra were acquired using a model Shimadzu Spectrophotometer by preparing in KBr medium on an FT-IR spectrometer. Nitrogen was estimated by Kjeldahl's method. Molecular weights were determined by Rast's method. Molar conductance measurements were made in anhydrous DMF at 34±1° using a Systronics Model 305 conductivity bridge. Melting points were measured by the melting points apparatus.

Synthesis of Ligands

2-Acetyl-5-methylfuran and 2-acetyl-4-methyl thiophene were assorted with Glycine and Leucine in an equimolar ratio in presence of methanol. The solution was heated under reflux for 5-6 hours. On cooling, the solid product was separated, which was dried and further purified by recrystallization from the same solvent. The crystals finally dried under reduced pressure and yield, and m.p's was recorded. The structure of ligands (L^1H-L^4H) proposed in the present work is given in Figure 1.

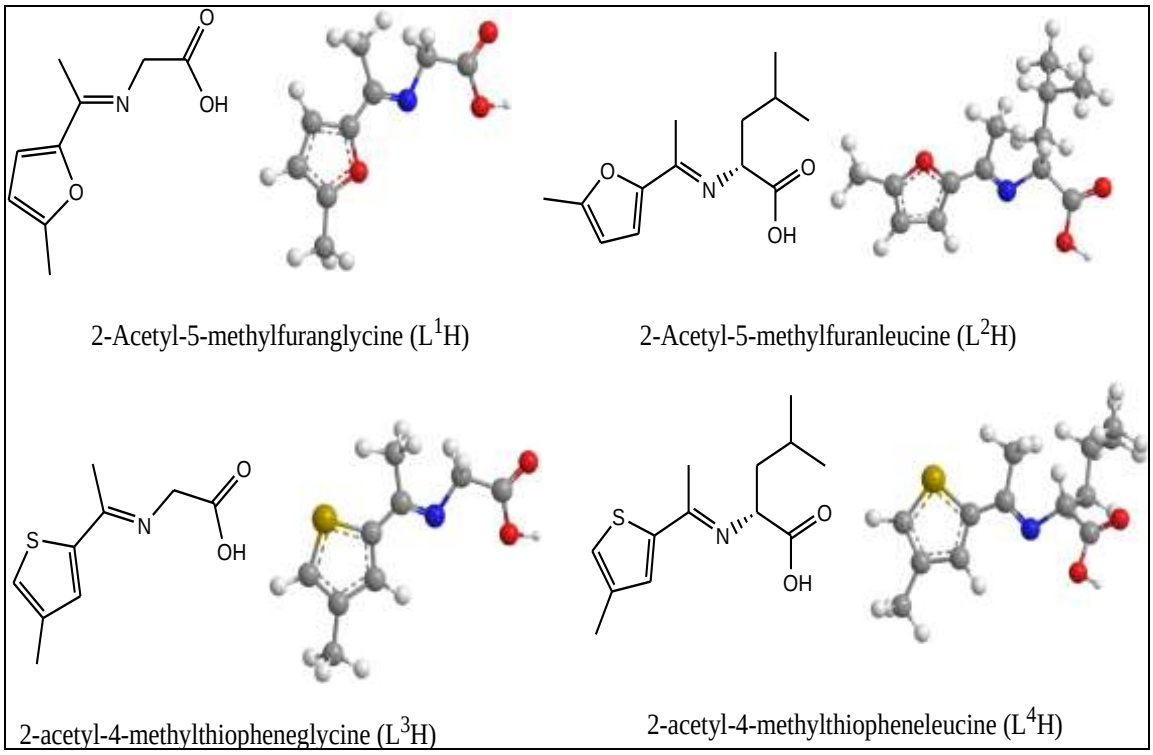


Figure 1: Structure of ligands (L^1H-L^4H)

2-Acetyl-5-methylfuranglycine $C_9H_{11}NO_3$ (L^1H), Yellow Solid, m.p. 192 ºC; 2-Acetyl-5-methylfuranleucine $C_{13}H_{19}NO_3$ (L^2H), Yellow Solid, m.p. 186 ºC; 2-Acetyl-4-methylthiopheneglycine $C_9H_{11}NO_2S$ (L^3H), Shining Yellow Solid m.p. 205 ºC; 2-Acetyl-4-methylthiopheneleucine $C_{13}H_{19}NO_2S$ (L^4H), Light Yellow Solid, m.p. 182 ºC.

Synthesis of Complex

The zirconium (IV) chloride and sodium salt of ligand (prepared by adding the corresponding weight of sodium metal to Schiff bases of amino acids (L^1H-L^4H) were assorted in 1:2 molar ratios in dry methanol as the reaction medium. The mixture was heated under reflux for 8-10 hrs and the progress of the reaction was monitored by the estimation of sodium chloride. The white sodium chloride was removed by the filtration and the filtrate was dried under reduced pressure. The resulting product was repeatedly washed with dry cyclohexane to remove the unreacted reactants. The products so formed were finally dried in vacuo for 3-4 hrs. The purity of the compounds was checked by TLC using silica gel-G as an adsorbent. The main characteristic and analyses of these complexes are recorded and the structure of the complexes proposed in the present work is given in Figure 2.

[Zr ($C_{18}H_{20}Cl_2N_2O_6$)]: Light brown solid; yield 78%; m.p.192ºC; Calcd. : C, 41.380; H, 3.86; N, 5.36; Zr, 17.46 (%), Found: C, 41.32; H, 3.79; N, 5.26; Zr, 17.42 (%); Mol. wt. Calcd. : 522.49, Found: 520.36.

[Zr ($C_{26}H_{36}Cl_2N_2O_6$)]: Reddish Brown solid; yield 72%; m.p.172 ºC; Calcd. : C, 49.20; H, 5.72; N, 4.41; Zr, 14.37 (%), Found: C, 49.13; H, 5.66; N, 4.34; Zr, 14.26 (%); Mol. wt. Calcd. : 634.70, Found: 633.02.

[Zr ($C_{18}H_{20}Cl_2N_2O_4S_2$)]: Brown Solid; yield 76%; m.p.168 ºC; Calcd. : C, 38.98; H, 3.63; N, 5.05; S, 11.56; Zr, 16.45 (%), Found: C, 38.92; H, 3.57; N, 4.98; S, 11.51; Zr, 16.39 (%); Mol. wt. Calcd.: 554.62, Found: 551.32.

[Zr ($C_{26}H_{36}Cl_2N_2O_4S_2$)]: Light Brown Solid; yield 71%; m.p.188 ºC; Calcd. : C, 46.83; H, 5.44; N, 4.20; S, 9.62; Zr, 13.68 (%), Found: C, 46.71; H, 5.39; N, 4.16; S, 9.56; Zr, 13.68 (%); Mol. wt. Calcd.: 666.84, Found: 663.87.

Biological Activity

Antibacterial Activity

In vitro antibacterial activity of the ligands and their corresponding zirconium complexes were evaluated against *Escherichia coli* (-), *Proteus mirabilis* (-), *Bacillus thuringiensis* (+) *Staphylococcus aureus* (+) by using the paper

disc plate method [31-32]. The nutrient agar medium was used as a culture medium for bacterial growth. The compounds under investigation were dissolved in DMSO to get a final concentration of 500 and 1000 ppm. The paper disc (Whatman no.1) having a diameter of 5 mm was soaked in these solutions and placed in an appropriate medium previously seeded with the tested organism in Petri dishes. The plate was incubated for 24 h at 30±2°C. After inoculation, the diameter of the clear zone of inhibition surrounding each sample is taken as a measure against the particular test organism [33-35]. Streptomycin was used as a reference compound for antibacterial activities. The antibacterial activities displayed by ligands and their complexes are shown in Figure 3.

Antifungal Test

Antifungal activity of the ligands and their corresponding zirconium complexes is found in vitro against Aspergillus niger, Fusarium oxysporum, and Aspergillus flavus by the agar plate technique [36-37]. The solutions of the compounds in different concentrations (100 and 200 ppm) in DMF were then mixed with the medium. The linear growth of the fungus was recorded by measuring the diameter of the colony and the percent inhibition was calculated. Micostatin was used as a reference compound for antifungal activities (Figure 3).

Results and Discussion

The zirconium (IV) chloride and sodium salt of ligand (prepared by adding the corresponding weight of sodium metal to Schiff bases of amino acids) were mixed in 1:2 molar ratios in dry methanol as the reaction medium. Schiff bases (L^1H-L^4H) are derived by the condensation of 2-acetyl-5-methylfuran and 2-acetyl-4-methyl thiophene with glycine and leucine. These reactions can be represented by the following general equations.

$$ZrCl_4 + 2NaN\overset{\frown}{O} \xrightarrow[\text{Methanol}]{1:2} Cl_2Zr(N\overset{\frown}{O})_2 + 2NaCl$$

Where $NaO\overset{\frown}{N}$ represents sodium salt of monofunctional bidentate amino acids Schiff bases

The newly synthesized zirconium complexes are colored solid crystals susceptible to hydrolysis and soluble in common organic solvents viz. THF, acetone, chloroform, etc. The complexation occurs through the loss of a proton from the ligands. The molecular weight determination shows that these complexes are monomeric. The lower value of molar conductivity (~16-18$ohm^{-1}cm^2mol^{-1}$) of the complexes in DMF shows them to be non-electrolytes [38].

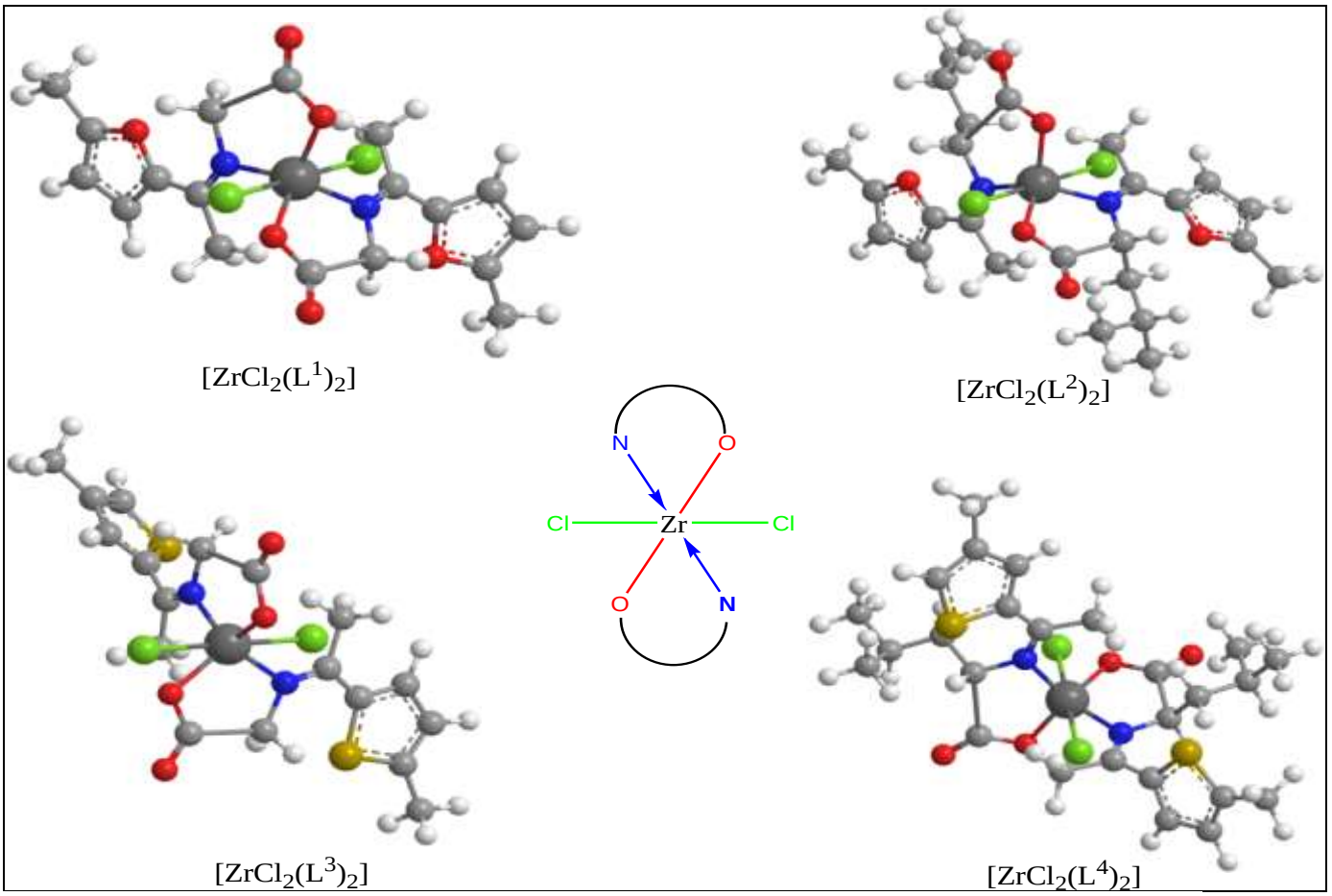


Figure 2: Structure of Zr (IV) Complexes

Spectroscopic Characterization

Electronic Spectra

The spectra of the ligands and their metal complexes were recorded in dry methanol. The electronic spectra of the ligands show two bands at around ~300 nm, 264nm, and 370nm. The first band may be assigned to л→ л* transition within the aromatic ring and remains almost unchanged in the spectra of complexes. Another two bands due to л → л* transition and n→л* transition of the azomethine group respectively [39-40] shift towards the higher wavelength in the metal complexes, which is attributed to the coordination of azomethine nitrogen to zirconium atom [41].

Significance IR Bands of Starting Material, Ligand, and Complex

All the ligands display a strong and sharp band in the region 1620±10 cm^{-1} which is due to the ν(>C=N-) stretching frequency in the free ligand [42], get split into two sharp bands appearing one at a lower frequency and another higher frequency in complexes. This splitting of bands suggests that the azomethines group is in different chemical environments. In the IR spectra of the Schiff bases, the strong absorption at 1720-1705 cm^{-1} and 1365-1380 cm^{-1} are attributed to the asymmetric and symmetric carboxyl group. The IR spectra of the complexes showed strong bands in the region 1665-1670 and 1415-1395 cm^{-1}, which can be attributed to the carboxyl group. The $\Delta\nu = \nu_{as}(CO_2)$-$\nu_s(CO_2)$ value is used to determine the nature of the bonding of carboxylate to the zirconium atom. It is generally that the difference in Δν between asymmetric $\nu_{as}(CO_2)$ and symmetric $\nu_s(CO_2)$ absorption frequencies above 210 cm^{-1} for the carboxylate moiety. These data suggest that the carboxylate-O group is involved in coordination with the zirconium in complexes. The new strong and medium intensity bands in the regions 630-580 cm^{-1} and 545-525 cm^{-1} in the spectra of the complexes may be assigned to ν(Zr-O) and ν(Zr←N) respectively (Table 1).

^{1}H NMR Spectra

To confirm the bonding pattern in the complexes proton magnetic resonance spectra of the ligands and their metal complexes were recorded in DMSO-d_6 using TMS as an internal reference. ^{1}H NMR spectra of Schiff bases show the -COOH proton signal at δ 11.10 ppm and it disappears in the spectra of the corresponding zirconium complexes showing thereby chelation of the ligand moiety through the deprotonated carboxylic oxygen. In the case of the ligands, a sharp proton signal at δ 1.80 ppm is observed due to [-C(CH_3)=N-] shifted downfield (δ1.99 ppm) showing the donation of the lone pair of the electron by azomethine nitrogen to the zirconium atom. The ^{1}H NMR spectral data are recorded in Table 2.

Table 1: IR spectral data (in cm^{-1}) of the ligands and their Zirconium complexes

Compound	ν(>C=N-)	ν(COO^{-1}) (asym)	ν(COO^{-1}) (sym)	ν(Zr←N)	ν(Zr←O)
(L^1H)	1612	1720	1367	-	-
(L^2H)	1615	1712	1365	-	-
(L^3H)	1610	1705	1365	-	-
(L^4H)	1620	1715	1370	-	-
[$ZrCl_2(L^1)_2$]	1592	1655	1330	545	630
[$ZrCl_2(L^2)_2$]	1598	1655	1345	535	585
[$ZrCl_2(L^3)_2$]	1596	1650	1345	540	595
[$ZrCl_2(L^4)_2$]	1590	1665	1375	540	610

Table 2: ^{1}H NMR spectral data (in δ ppm) of the ligands and their Zirconium complexes

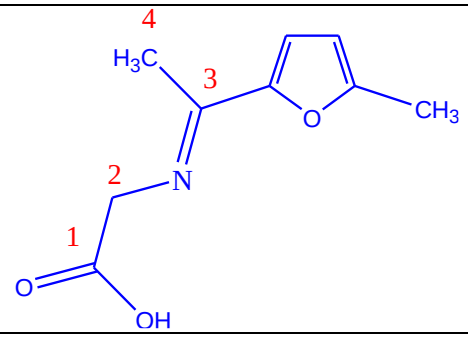
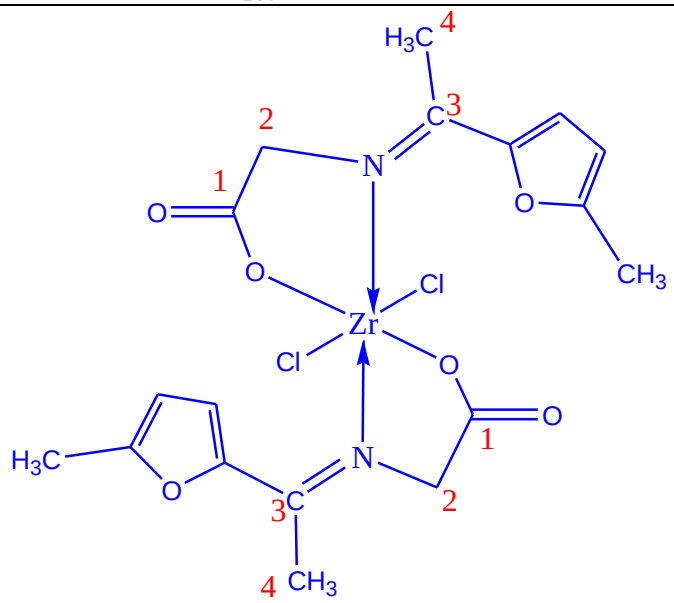
Compound	-COO**H**	-C(C**H**$_3$)=N-	Aromatic protons
(L^1H)	11.10	1.80(s)	(6.86-8.14) (m)
(L^2H)	11.52	1.94(s)	(6.80-8.12)(m)
(L^3H)	11.08	1.83(s)	(6.92-8.16)(m)
(L^4H)	11.10	1.88(s)	(6.86-7.96)(m)
[$ZrCl_2(L^1)_2$]	-	1.90(s)	(6.88-8.12)(m)
[$ZrCl_2(L^2)_2$]	-	1.98(s)	(6.85-8.10) (m)
[$ZrCl_2(L^3)_2$]	-	1.96(s)	(6.80-8.14) (m)
[$ZrCl_2(L^4)_2$]	-	1.96(s)	(6.82-8.10)(m)

^{13}C NMR Spectra

The ^{13}C NMR spectra of a few representative ligands (L^1H-L^4H) and their corresponding coordination compounds have been recorded in dry DMSO. A considerable shift in the position of carbon attached to the different participating groups indicates the bonding of azomethine nitrogen to the metal atom. The signal for >C=N was present in the spectra of ligands at δ 164.67–165.97 ppm and appears at δ 166.29–167.01 ppm in the complexes. The downfield shifting of δ ~2–3 ppm clearly defined that the azomethine moiety has been involved during the complexation. Thus based on the above spectral evidence, the following structures can be assigned to zirconium (IV) complexes. (Table 3)

Table 3: ^{13}C NMR spectral data (in δ ppm) of the ligands and their Zirconium complexes

Compound	Chemical shift value in δ ppm				
	C-1	C-2	C-3	C-4	Aromatic carbon

	175.8	62.2	164.6	13.2	111.3, 107.9, 154.3,141.2
	168.7	62.3	167.0	12.4	110.9, 106.4, 153.9, 140.2

Antimicrobial results

The results of the antimicrobial screening of the Schiff bases and zirconium complexes against Gram-negative (*Escherichia coli*, *Proteus mirabilis)* and Gram-positive (*Staphylococcus aureus Bacillus thuringiensis*,) bacteria and some selected fungi (*Aspergillus flavus*, *Fusarium oxysporum*, and *Aspergillus niger)* have been found. The inhibition zones were measured in mm and results have been recorded in Figure 3. The experimental data indicate that the metal complexes have more potent activity in inhibiting the growth of microorganisms than the ligands. The results further conclude that the antimicrobial activity of the complexes increases due to the metallation of its ligands [43]. The ligand and its metal complexes exhibit highly active at higher concentrations.

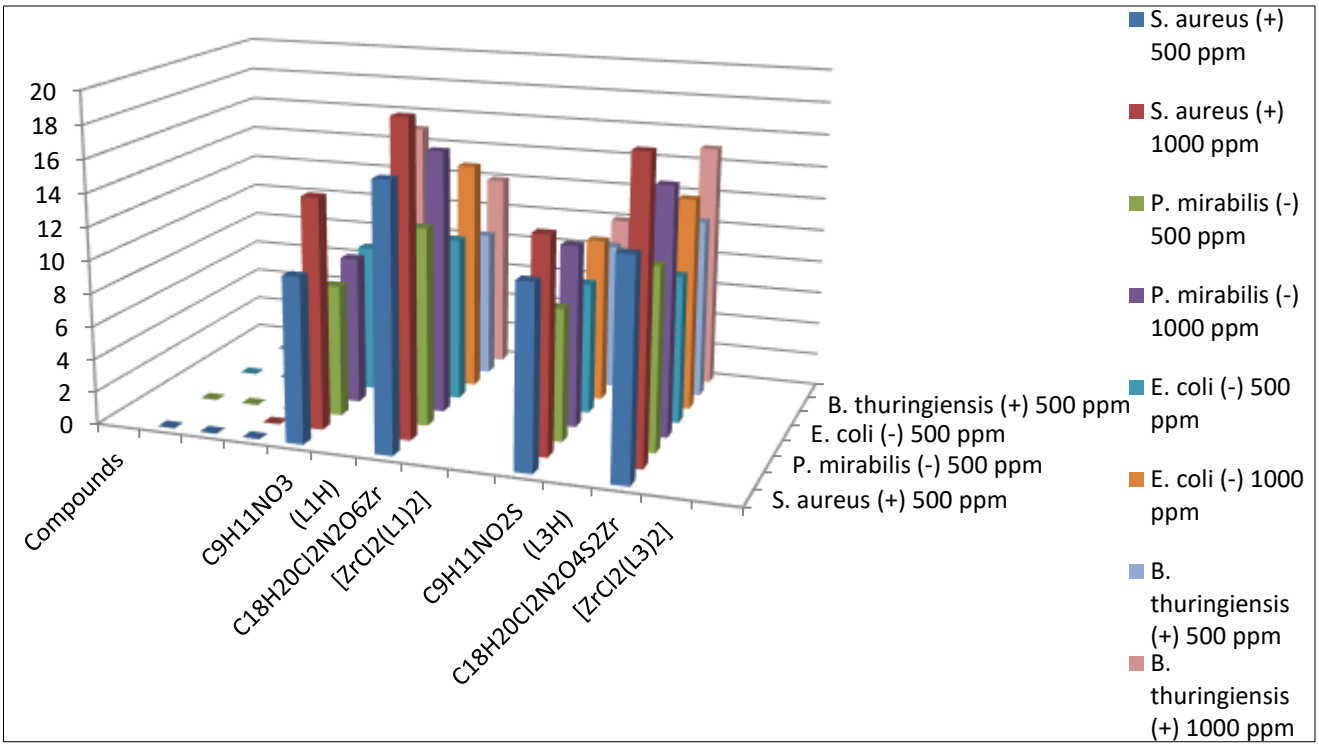


Figure 3: Antibacterial screening data of the azomethine derivatives of amino acid and their Zr(IV) complexes. Inhibition zone (mm) after 24 h (concentration in ppm).

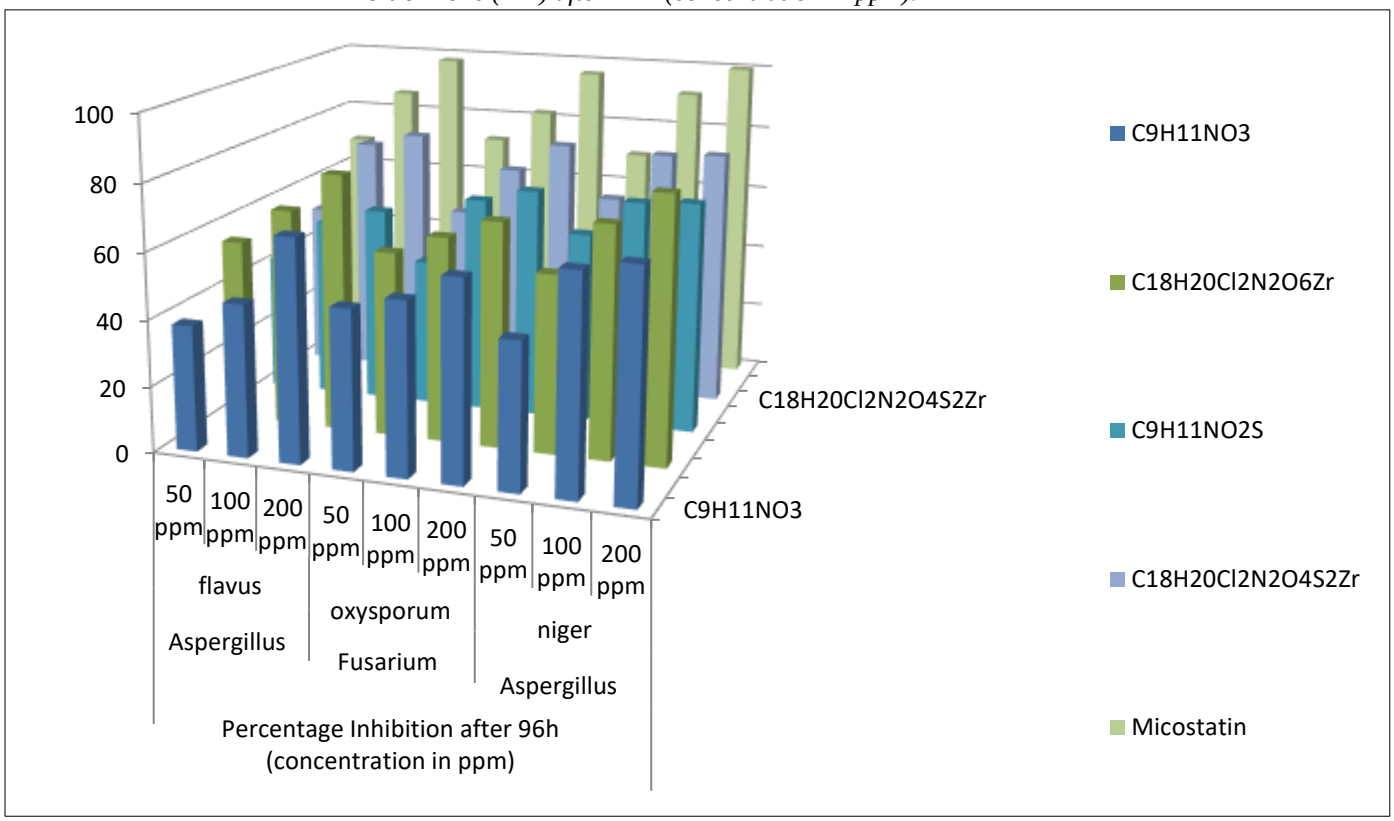


Figure 4: Antifungal screening data of azomethine derivatives of amino acid and their Zr(IV) complexes. Inhibition (%) after 96 h concentration 50, 100, and 200 ppm at 25 ± 2°C.

Conclusion

The present work reported the synthesis of new Zr (IV) complexes with amino acids Schiff bases are prepared and characterized by elemental analyses (CHN) and IR spectral data. The results showed that the Schiff base functions as a bi-dentate ligand through azomethine nitrogen and carboxylate oxygen. The IR spectra of the complexes indicate the presence of a deprotonated form of chelating ligand and ^{1}H NMR spectra showed that the calculated number of protons for each functional group in the complexes is equal to the number predicted from the molecular formula. The complexes showed better antimicrobial activities than parent ligands. The compounds showed toxicity against all species of fungi and the inhibition zone growth of fungi depends on the concentration of the compounds. In the present case, we have used *E. coli, S. Aureus, P. mirabilis* & *B. thuringiensis* for antibacterial activity and *A. niger, F. oxysporum & A. flavus* for antifungal activity against tested microorganisms of the studied complexes. The results showed that the compounds are more active than the ligands but less active than these standard drugs.

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