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AN *IN VITRO* ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF COPPER (II) AND ZINC (II) COMPLEXES OF N^4-METHYL-3-THIOSEMICARBAZONES

Satheesh D.[1]* and Jayanthi K.[1]

[1]Department of Chemistry, L. N. Government College, Ponneri - 601 204, Tamilnadu, India.

Corresponding Author:** Email: **satheeshvdm@gmail.com

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ABSTRACT

Schiff bases (E)-2-(2-hydroxy-3-methoxybenzalidene)-N^4-methylhydrazinecarbothioamide (L^1), (E)-2-(2,4-dimethoxybenzalidene)-N^4-methylhydrazinecarbothioamide(L^2), (E)-2-(2,3-dichlorobenzalidene)-N^4-methylhydrazinecarbothioamide(L^3) derived from simple condensation of N^4-methyl-3-thiosemicarbazide with 2-hydroxy-3-methoxybenzaldehyde, 2,4-dimethoxybenzaldehyde and 2,3-dichlorobenzaldehyde respectively. Schiff base metal complexes of Cu(II) and Zn(II) derived from N^4-methyl-3-thiosemicarbazones (L^1, L^2 and L^3) with $CuCl_2.2H_2O$, $CuBr_2$ and $ZnCl_2.7H_2O$. All synthesized Schiff bases have been characterized by microanalysis, FT-IR, ^1H NMR and ^{13}C NMR and their metal complexes characterized by microanalysis and FT-IR. The Schiff bases and metal complexes showed good activity against the Gram-positive bacteria (Staphylococcus aureus and Bacillus subtilis) Gram-negative bacteria(Escherichia coli and Salmonella paratyphi) and fungi (Aspergillus niger and Candida albicans). The antimicrobial results also indicate that the copper complexes of L^1 are better antimicrobial agents as compared to other Schiff bases and their complexes.

Keywords: *Schiff base, Thiosemicarbazone, Metalcomplexes, Antimicrobial activity.*

1. INTRODUCTION

Thiosemicarbazone (TSC) based metal complexes have remarkable biological activities such as antitumor,[1–6] antiviral,[7,8] antibacterial,[9-12]antifungal,[11-13]antimalarial,[14]antileishmanial,[15] antioxidant,[16–18] antidiabetic[19] properties and different coordination structures.[20–27] The biological properties of thiosemicarbazones are often related to metal ion coordination. Most of the biological research carried out on metal complexes is related to bi- and tridentate thiosemicarbazones with palladium, platinum[28-35] and copper ions.[5,9,11,12,30-35]

The present paper describes the synthesis, characterization and *in vitro* evaluation of antibacterial and antifungal activity using nine new Cu(II) and Zn(II) complexes with the substitutedbenzalidene-N^4-methyl-3-thiosemicarbazones (**L^1–L^3**), obtained from the condensation reaction of N^4-methyl-3-thiosemicarbazide with 2-hydroxy-3-methoxybenzaldehyde, 2,4-dimethoxy benzaldehyde and 2,3-dichloro benzaldehyde. All ligands and metal complexes were tested for their *in vitro* antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* (Gram-positive), *Escherichia coli* and*Salmonella paratyphi* (Gram-negative) and antifungal activity against *Aspergillus niger, Candida albicans.*

2. MATERIALS AND METHODS

2.1 Materials

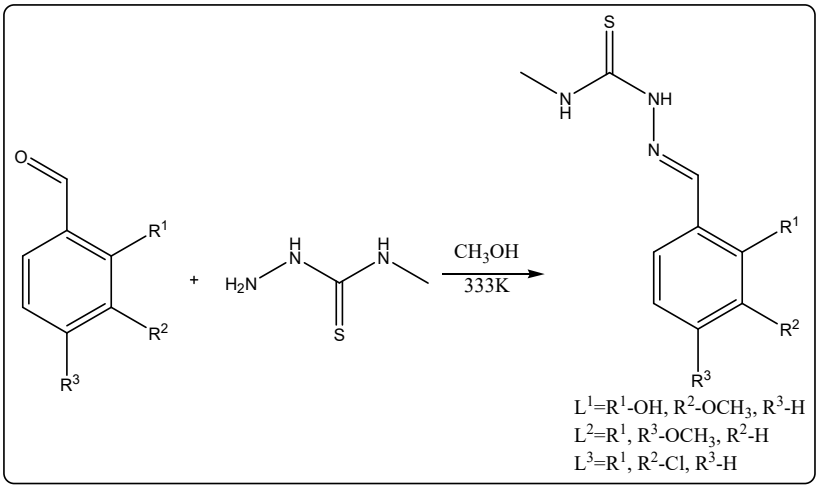
All chemicals and solvents were of reagent grade and were used as commercially purchased without further purification.

2.2 Methods

The elemental analyses were determined using a Perkin Elmer EA 2400 Series Elemental Analyzer. Infrared spectra of the compounds were recorded on KBr pellets using a Perkin Elmer FT-IR Spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance spectrometer (400 MHz) at 298 K. Chemical shifts δ in ppm were referenced to the solvent residual peak as an internal standard. ^{13}C NMR was recorded on a Bruker Avance spectrometer (400 MHz) and spectra was referenced to the solvent residual peak.

2.2.1 Synthesis of N^4-methyl-3-thiosemicarbazones

2-Hydroxy-3-methoxy-(L^1), 2,4-dimethoxy-(L^2) and 2,3-dicholoro-(L^3) substituted-N^1-benzalidene-N^4-methy-3-lthiosemicarbazones were synthesized from 10 mmol (1.05g) of N^4-methyl-3-thiosemicarbazide was dissolved in 20 ml of hot methanol and to this was added 10 mmol of the corresponding benzaldehydes in 10 ml of ethanol over a period of 10 mins with continuous stirring. The reaction mixture was refluxed for 2h and allowed to cool where by a compound began to separate (**Scheme 1**). This was filtered and washed thoroughly with ethanol and then dried in vacuum. The compounds were recrystallized from a hot ethanol solution. The compounds were checked using elemental analysis and characteristic spectroscopic data.



Scheme 1: Synthesis of N^4-methy-3-thiosemicarbazones

The color, yield (%), melting point (ºC), elemental analysis, IR (KBr, cm^{-1}), ^{1}H-NMR (DMSO-d6) and ^{13}C-NMR (DMSO-d6) data of L^1, L^2 and L^3 are given as follows:

L^1: pale yellow powder, yield (1. 8995 g, 79%), 164-167ºC, Anal. calc. for $C_{10}H_{13}N_3O_2S$, (239.38 g mol^{-1}): C, 50.19; H, 5.48; N, 17.56; S, 13.40, found: C, 50.23; H, 5.45; N, 17.60; S, 13.37%. IR (cm^{-1}): υ(OH) 3308, υ(NH) 3341,1387, 610,υ(N-N) 932, υ(C=N) 1556, 1527, 480, υ(C=S) 831, υ(ArC-OCH_3) 2844, 1216. ^{1}H NMR (δ in ppm): 11.42 (s, 1H, C**H**=N^1),9.17 (s, 1H, O**H**), 8.41 (s, 2H, Ar-**H**), 7.55 (s, 1H, Ar-**H**), 6.97, (s, 1H, N**H)**, 6.80 (s, 1H, N**H)**, 3.82 (s, 3H, OC**H_3**), 3.37, 3.28 (cis/trans ratio: 3/2, s, 3H, N^4–C**H_3**), 2.15-1.56 (N=C-S**H**).^{13}C NMR (δ in ppm): 149.46 (**C**=S), 146.64 (Ar**C_2**–OH), 142.20 (Ar**C_4**–OCH_3), 127.17 (**C**H=N), 119.99 (Ar**C_6**), 113.54 (Ar**C_5**), 113.19 (Ar**C_1**-CHN), 111.70 (Ar**C_3**–OCH_3), 55.66 (ArC_3–O**C**H_3), 30.74 (N^4–**C**H_3).

L^2: yellow crystal, yield (2.0519g, 81%),230-232ºC, Anal. calc. for $C_{11}H_{15}N_3O_2S$ (254.10 g mol^{-1}): C, 52.15; H, 5.97; N, 16.59; S, 12.66, found: C, 52.20; H, 6.03; N, 16.53; S, 12.64, IR (cm^{-1}): υ(NH) 3351, 3170, 1380, 618, υ(N-N) 924, 937, υ(C=N) 1554, 476, υ(C=S) 842, υ(ArC-OCH_3) 2838, 1211. ^{1}H-NMR: 11.32 (s, 1H, C**H**=N^1), 8.36, 8.31 (dd, 2H, Ar-**H**), 8.01, 8.03 (s, 1H, Ar-**H),** 6.57-6.61 (s, 2H, N**H**), 3.82, 3.84 (s, 6H, OC**H₃**), 3.06 (s, 3H, N^4–C**H₃**). ^{13}C NMR (δ in ppm): 177.40 (**C**=S), 162.20 (Ar**C₂**–OCH_3), 159.09 (Ar**C₄**–OCH_3), 137.55 (**C**H=N), 127.13 (Ar**C₆**H), 115.10 (Ar**C₁**-CHN), 106.32 (Ar**C₅**H), 97.99 (Ar**C₃**H), 55.74(ArC_4–O**C**H_3), 55.42 (ArC_2–O**C**H_3), 30.71 (N^4–**C**H_3).

L^3: yellow crystal, yield (2.2158 g, 84%),194-196ºC, Anal. calc. for $C_9H_9Cl_2N_3S$ (262.26 g mol^{-1}): C, 41.23; H, 3.46; N, 16.03; S, 12.23, found: C, 48.18; H, 4.92; N, 18.66; S, 14.27%. IR(cm^{-1}): υ(NH) 3317, 3155, 1407, 626, υ(N-N) 933, υ(C=N) 1585, 1543, 485, υ(C=S) 911, υ(ArC-Cl) 701. ^{1}H-NMR: 11.75 (s, 1H, C**H**=N^1), 8.66 (s, 1H, Ar-**H**), 8.49 (s, 1H, Ar-**H)**, 8.30, 8.28 (dd, 1H, Ar-**H)**, 7.68,7.66 (s, 1H, N^2**H**), 7.43-7.40 (s, 1H, N^4**H**), 3.06 (s, 3H, N^4–C**H₃**). ^{13}C NMR (δ in ppm): 177.93(**C**=S), 137.23 (**C**H=N), 134.09 (Ar**C₃**-Cl), 132.20 (Ar**C₂**-Cl), 131.07 (Ar**C₁**-CHN), 130.79 (Ar**C₄**H), 128.05 (Ar**C₆**H), 125.80 (Ar**C₅**H), 30.89 (N^4–**C**H_3).

For the synthesis of complexes 1a, 2a and 3a, compound L^1,L^2 and L^3 (1 mmol) were dissolved in 25 mL of hot water:ethanol (1:1) respectively. The mixture was added to a solution of 0.1705 g(1mmol) $CuCl_2.2H_2O$ in water:ethanol (25mL). The reaction mixture was refluxed for 6h and allowed to cool. The precipitate was filtered off, washed with ethanol–ether (1:1, 10 mL) and dried in vacuum over P_2O_5. Complexes1b, 2b and was synthesized by reaction of L^1, L^2 and L^3 (1 mmol) and$CuBr_2$ (1 mmol) using the same method. Complexes 1c, 2c and 3c were obtained by using $ZnCl_2$.6H2O instead of $CuCl_2.2H_2O$ in a similar manner.

The color, yield (g, %), melting point (ºC), elemental analysis, IR (KBr, cm^{-1} data of the complexes are given as follows:

1a: black powder, yield (0.1654 g, 46%), >230ºC, Anal. Calc. for $C_{10}H_{14}N_3O_3SCuCl$(355.46 g mol^{-1}): C 33.80; H, 3.97; N, 11.83; S, 9.02, Cu, 17.89; found: C 33.83; H, 3.95; N, 11.87; S, 9.01, Cu, 17.91. IR(cm^{-1}): υ(NH) 3371, 3224,1384, 609, υ(N-N) 974, υ(C=N) 1556, 1538, 473, υ(C=S) 852, υ(ArC-OCH_3) 2852, 1217.

1b: green powder, yield (0.1388 g, 35%), >230ºC, Anal. Calc. for $C_{10}H_{14}N_3O_3SCuBr$(399.69 g mol^{-1}): C, 30.05; H, 3.53; N, 10.51; S, 8.02; Cu, 15.90;found: C, 30.08; H, 3.51; N, 10.55; S, 8.04; Cu, 15.93. IR(cm^{-1}): υ(NH) 3417, 3354, 3275, 1395, 611, υ(N-N) 947, 973, υ(C=N) 1538, 1531, 455, υ(C=S) 853, υ(ArC-OCH_3) 2828.

1c: yellow powder, yield (0.1255 g, 33%), >230ºC, Anal. Calc. for $C_{10}H_{13}N_3O_2SZnCl_2$(339.27 g mol^{-1}): C, 31.98; H, 3.49; N, 11.19; S, 8.54; Zn, 17.41;found: C, 32.02; H, 3.47; N, 11.21; S, 8.55; Zn, 17.45. IR(cm^{-1}): υ(NH) 3340, 1387, 611, υ(N-N) 932, υ(C=N) 1555, 1526, 479, υ(C=S) 831, υ(ArC-OCH_3) 2844.

2a: green powder, yield (0.1706 g, 44%), >250ºC, Anal. Calc. for $C_{11}H_{15}N_3O_2SCuCl_2$(387.89 g mol^{-1}): C, 34.07; H, 3.90; N, 10.84; S, 8.27: Cu, 16.39; found: C, 34.10; H, 3.91; N, 10.82; S, 8.25; Cu, 16.35. IR(cm^{-1}): υ(NH) 3451, 1417, 639, υ(N-N) 935, υ(C=N) 1580, 474, υ(C=S) 830, υ(ArC-OCH_3) 2838, 1209.

2b: black powder, yield (0.1573 g, 33%), >250ºC, Anal. Calc. for $C_{11}H_{15}N_3O_2SCuBr_2$(476.79 g mol^{-1}): C, 27.72; H, 3.17; N, 8.82; S, 6.73; Cu, 13.33; found: C, 27.79; H, 3.16; N, 8.85; S, 6.74; Cu, 13.33. IR(cm^{-1}):υ(NH) 3445, 3354, 1416, 634, υ(N-N) 915, 933, υ(C=N) 1581, 1537, 455, υ(C=S) 823, υ(ArC-OCH_3) 2838, 1210, 1207.

2c: pale yellow crystals, yield (0.1176 g, 30%), >250ºC, Anal. Calc. for $C_{11}H_{15}N_3O_2SZnCl_2$ (389.94 g mol^{-1}): C, 31.98; H, 3.49; N, 11.19; S, 8.54; Zn, 17.41 found: C, 32.03; H, 3.51; N, 11.21; S, 8.55; Zn, 17.39. IR(cm^{-1}): υ(NH) 3350, 3167, 1381, 617, υ(N-N) 924, 937, υ(C=N) 1543, 477, υ(C=S) 842, υ(ArC-OCH_3) 2838, 1211.

3a: yellow powder, yield (0.2197 g, 53%), >250ºC, Anal. Calc. for $C_9H_{11}Cl_2N_3OSCuCl_2$ (414.78 g mol^{-1}): C 33.80; H, 3.97; N, 11.83; S, 9.02, Cu, 17.89; found: C 33.83; H, 3.96; N, 11.86; S, 9.01, Cu, 17.86. IR(cm^{-1}): υ(NH) 3375, 3276, 1399, 628, υ(N-N) 938, υ(C=N) 1561, 485, 451, υ(C=S) 908, υ(ArC-Cl) 704.

3b: yellow powder, yield (0.2507 g, 50%), >250ºC, Anal. Calc. for $C_9H_{11}Cl_2N_3OSCuBr_2$ (503.69 g mol^{-1}): C, 30.05; H, 3.53; N, 10.51; S, 8.02; Cu, 15.90; found: C, 30.09; H, 3.55; N, 10.50; S, 8.04; Cu, 15.86. IR(cm^{-1}): υ(NH) 3283, 1395, 623, υ(N-N) 933, υ(C=N) 1585, 1543, 485, υ(C=S) 911, υ(ArC-Cl) 703.

3c: pale yellow powder, yield (0.1530 g, 38%),>250ºC, Anal. Calc. for $C_9H_9Cl_2N_3OSZnCl_2$ (398.61 g mol^{-1}): C, 31.98; H, 3.49; N, 11.19; S, 8.54; Zn, 17.41 found: C, 32.03; H, 3.47; N, 11.18; S, 8.56; Zn, 17.39. IR(cm^{-1}): υ(NH) 3313, 3156, 1407, 635, υ(N-N) 933, υ(C=N) 1585, 1539, 486, υ(C=S) 911, υ(ArC-Cl) 701.

3. RESULTS AND DISCUSSION

The synthesized Schiff bases and their complexes were checked by comparing the TLC with the starting materials, which resulted in a single spot different from the starting materials. The Synthesis achieved in high yields**.** The structures of all synthesized compounds (**Figure 1**) were confirmed on the basis of elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectral data.

3.1 Infrared Spectra and Coordination Mode

The ligand and complexes have been characterized in detail by recording their IR spectra. The phenolic υ(C–O) stretching vibrations in the free **L^1** is observed at 1110 cm^{-1}, which is shifted by 14–27 cm^{-1} towards lower wave numbers in the complexes and υ(O-H) at3308 cm^{-1}in free **L^1**is disappeared in copper complexes, thus indicating coordination of the phenolic oxygen to the Cu^{2+} ion. But these bands are remains unchanged in zinc complex, thus indicating an absence of coordination of the phenolic oxygen to the Zn^{2+} ion.

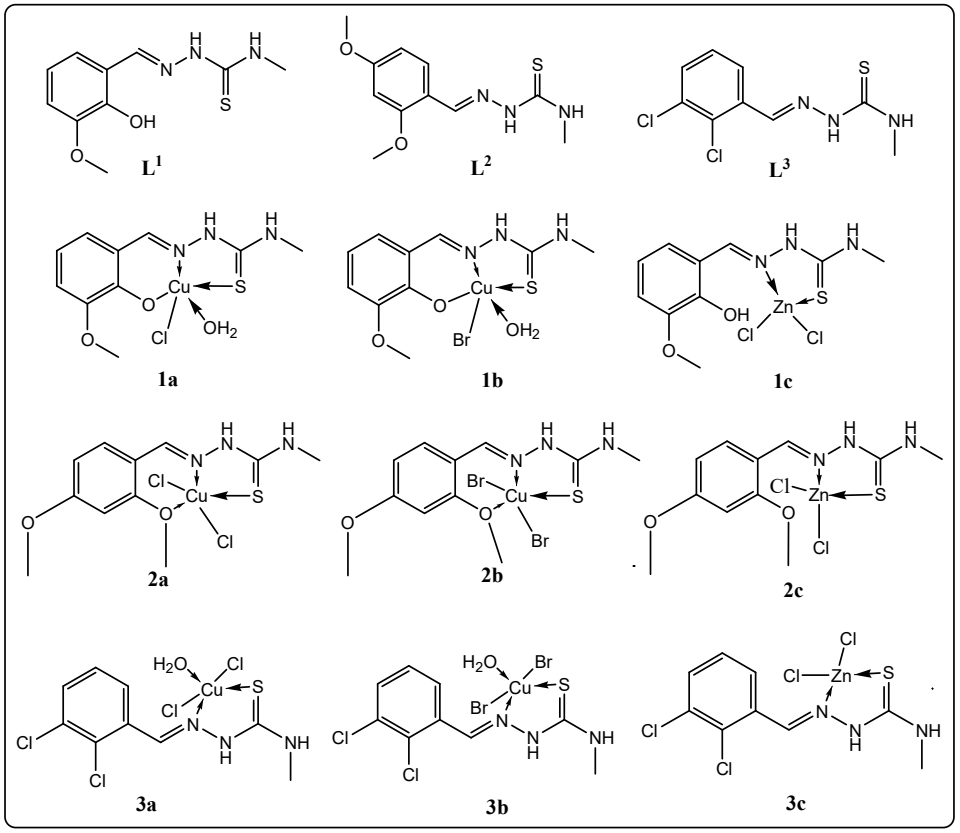


Fig. 1: Structures of Schiff bases and their copper (II) and zinc (II) complexes

The three bands appearing in the region 3351-3158, 1615-1585 and 882-785 cm^{-1} in the ligands spectra, were assigned to stretching vibration modes υNH,υC=N and υC=S respectively. The υ(C=N) band of the ligands in the region1606-1585 and 882-785 $cm^{-1}$is found to

be shifted to lower energies (1596–1538and 867-756 cm^{-1})in the spectra of the complexes, indicating coordination via the azomethine nitrogen and thioimidosulphur atom respectively. The formation of M-O and M-N bonds is further supported by the appearance of υM-O and υM-N in the regions 605-555 and 504-455 cm^{-1} respectively in the spectra of chelates.

3.2 ^{1}H-NMR and ^{13}C-NMR spectra

The ^{1}H-NMR and ^{13}C-NMR spectra of **L^1**, **L^2**,**L^3** show a low field one proton singlet at δ = 11.42, 11.32 and 11.75 (1H) ppm and 149.46, 177.40, 177.93 ppm due to the –**CH**=N respectively. The lower value of ^{13}C-NMR in **L^1** indicates intramolecular hydrogen bonding due to phenolic proton with azomethine nitrogen atom (-O-**H····N**=CH-). The O–H proton signal is observed at 9.17(1H) ppm and ^{13}C-NMR at 146.64ppm in **L^1**.The methyl proton signals are observed as a doublet at 3.37-3.03 (3H) ppm due to N-CH_3 group in the all ligands and singlets at 3.82 (3H) and 3.84-3.82 (6H) due to OCH_3 protons in **L^1**and **L^2** respectively. The methyl carbon ^{13}C-NMR signals appeared at30.74, 30.71 and 30.89 ppm in all ligands and O**C**H_3observed as a singlet at 55.66 ppm in **L^1** and two singlets at 55.42, 55.74 ppm in **L^2**.

3.3 Antibacterial Screening

The antibacterial activity of the ligands and its metal complexes were tested by using paper doc diffusion method against *Staphylococcus aureus* and *Bacillus subtilis* (Gram positive) and *Escherichia coli* and *Salmonella paratyphi* (Gram negative) At concentration of compound 100µg/ml(discs are soaked overnight in sample solution) and standard Ciprofloxacin 10µg, are placed with the help of sterile forceps. Then Petri dishes are placed in the refrigerator at 4ºC or at room temperature for 1 hour for diffusion. Incubate at 37ºC for 24 hours. The zone of inhibition was calculated (**Table 1**).

3.4 Antifungal Screening

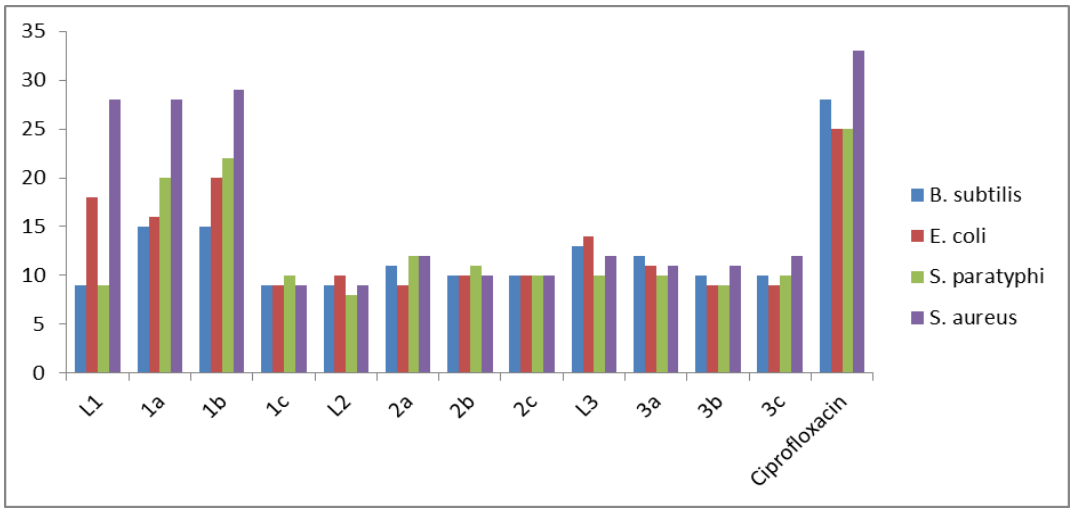
The antifungal activity of ligands and their metal complexes were tested against two pathogenic fungi, *Aspergillus niger* and *Candida albicans.* The compounds having concentration 100µg/ml and standard Ciprofloxacin 10µg, are placed with the help of sterile forceps. Then Petri dishes are placed in the refrigerator at 4ºC or at room temperature for 1 hour for diffusion. Incubate at 28ºC for 48 hours. The zone of inhibition was calculated (**Table 1**).

Table 1: Antibacterial and antifungal activity of ligands and their copper (II) and zinc (II) complexes

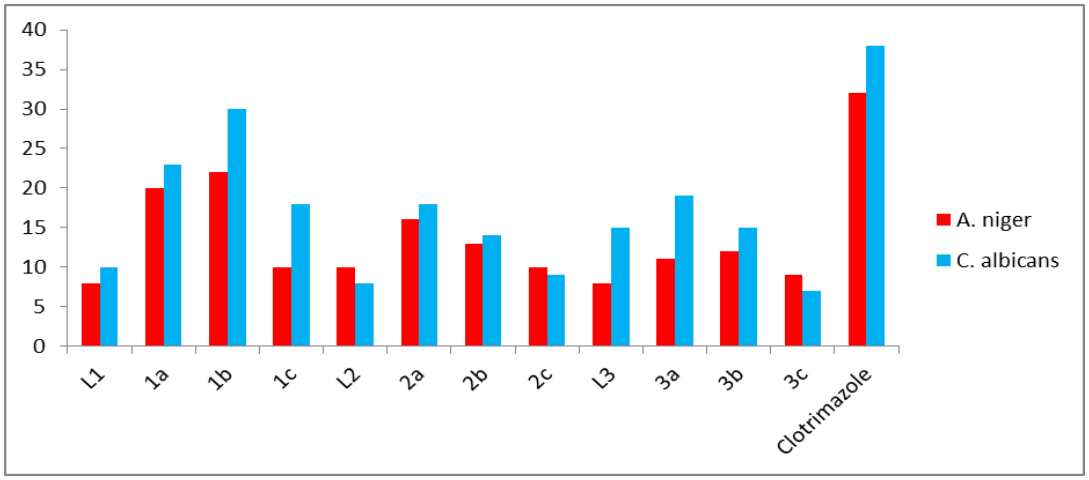
Ligand/ Complex	Inhibition zone (mm)					
	Antibacterial activity				Antifungal activity	
	B. subtilis	*E. coli*	*S. paratyphi*	*S. aureus*	*A. niger*	*C. albicans*
L^1	09	18	09	28	08	10
1a	15	16	20	28	20	23
1b	15	20	22	29	22	30
1c	09	09	10	09	10	18
L^2	09	10	08	09	10	08
2a	11	09	12	12	16	18
2b	10	10	11	10	13	14
2c	10	10	10	10	10	09
L^3	13	14	10	12	08	15
3a	12	11	10	11	11	19
3b	10	09	09	11	12	15
3c	10	09	10	12	09	07
Ciprofloxacin	28	25	25	33	-	-
Clotrimazole	-	-	-	-	32	38

All the new complexes showed a remarkable biological activity against bacteria and fungus. From the results, it is clear that the metal complexes are found to have biological activity than the parent ligands (**Graph 1 and Graph 2**).

Graph 1: Antibacterial activity of Schiff bases and their copper (II) and zinc (II) complexes



Graph 2: Antifungal activity of Schiff bases and their copper (II) and zinc (II) complexes



4. CONCLUSION

This work shows that complexes formed between thiosemicarbazone Schiff bases and Cu^{2+} and Zn^{2+} ions. All synthesized ligands and complexes were characterized by spectroscopic methods and evaluate the anti-bacterial and anti-fungal activities. The results generated in this study lead to the following conclusions. (a) Tested compounds **1a**,**1b, L^3** were found to possess moderate anti-bacterial activity against *Bacillus subtilis.* While that compounds **L^1, 1a, 1b, L^3**were found to possess good anti-bacterial activity against *Escherichia coli.* (b) The compounds **1a, 1b** were found very good activity against *Salmonella paratyphi* and **L^1, 1a, 1b** very good against *Staphylococcus aureus*. (c) Test compounds **1a, 1b, 1c, 2a, 3a** were found to possess good anti-fungal activity against *Aspergillus niger* and **1a, 1b, 2a** were found good activity against *Candida albicans*.

(d) Compared to other Schiff's bases, **L^1**possess very good anti-bacterial activity against *Escherichia coli* and *Staphylococcus aureus*. (e) The synthesized complexes, the copper (II) complexes with **L^1**only lead to a promising tool for extrapolating the biological activities as well as complex **1b**had highest activity than others.

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