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Research Article

Synthesis And Microbial Evaluation of Copper(II) Complexes of Schiff Base Ligand Derived From 3-Methoxysalicylaldehyde With Semicarbazide and Thiosemicarbazide

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ABSTRACT

Three monobasic Schiff base ligands of (*E*)-2-(2-hydroxy-3-methoxybenzalidene)-*N*^{4}-methylhydrazinecarbothioamide (**HL$_1$**), (*E*)-2-(2-hydroxy-3-methoxybenzalidene)-hydrazinecarbothioamide (**HL$_2$**) and (*E*)-2-(2-hydroxy-3-methoxybenzalidene)-hydrazinecarboamide (**HL$_3$**) have been synthesized by simple condensation of 3-methoxy salicylaldehyde with *N*^{4}-methylthiosemicarbazide, thiosemicarbazide and semicarbazide respectively. The synthesized Schiff bases have been characterized by elemental analysis, FT-IR, ^{1}H-NMR and ^{13}C-NMR spectral studies. Three Schiff base copper(II) complexes [Cu(L$_3$)$_2$] (**1**), [Cu(L$_2$)$_2$] (**2**) and [Cu(L$_1$)$_2$] (**3**) have been synthesized and characterized by elemental analysis and FT-IR studies. The complexes exhibit coordination number six. The complexes are coloured and stable in air. Analytical data reveal that the copper (II) complexes (**1-3**) exhibit 1:2 (metal:ligand) ratio. FT-IR data show that the ligand coordinates with the metal ions in a tridentate manner through the phenolic oxygen, azomethine nitrogen and thiocarbamido/carbamido groups. The *in vitro* antimicrobial activity against *Staphylococcus aureus*, *Bacillus subtilis, Escherichia coli*, *Salmonella paratyphi*, *Aspergillus niger and Candida albicans* was studied and compared therewith of free Schiff base ligands. All the copper(II) complexes (**1-3**) showed a better antimicrobial activity than the Schiff base ligands against the microorganisms.

Keyword: Schiff base; salicylaldimine thiosemicarbazone; copper(II) complex; antimicrobial evaluation

INTRODUCTION

The chemistry of the transition metal complexes of thiosemicarbazones (TSCs) became mostly appealing owing to their broad profile of pharmacological activity and has a various kind of compounds with completely different activities. [1–4] TSCs are known as potent metal chelators with high affinity for first row transition metals. [5,6] A number of the detected biological activities of the thiosemicarbazones and their complexes with transition metal ions are antibacterial, [7-10] antifungal, [9-11] antiviral, [12,13] antimalarial, [14] antileishmanial, [15] antioxidant, [16–18]

antidiabetic [19] antitumor [20–25] properties and distinctive coordination structures. [26–33] Coordination of salicylaldehyde semicarbazone and thiosemicarbazone with metal, i.e., chelation causes drastic change in the biological property of the ligand and also the metal moiety. It has been reported that chelation is the cause for curing of many diseases including cancer. Schiff base of salicylaldehyde semicarbazone, thiosemicarbazone and their metal complexes have a variety of applications in biological, clinical, analytical and pharmacological areas. [34-40]

As the continuation interest of our study of transition metal complexes, [41,42] here we present the synthesis and characterization of new copper(II) complex derivatives of (*E*)-2-(2-hydroxy-3-methoxybenzalidene)-*N*⁴-methylhydrazinecarbothioamide (**HL₁**), (*E*)-2-(2-hydroxy-3-methoxybenzalidene)-hydrazinecarbothioamide (**HL₂**) and (*E*)-2-(2-hydroxy-3-methoxybenzalidene)-hydrazinecarboamide (**HL₃**). Moreover, the in vitro antimicrobial screening activities of the complexes obtained are carried out and the results are reported herein.

MATERIALS AND METHODS

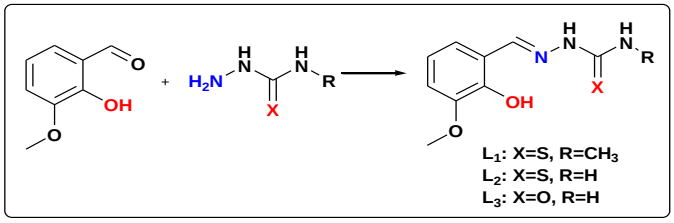
Materials

All chemicals and solvents were of reagent grade and were acclimated as commercially purchased without further purification. **Methods:** The elemental analyses were determined using a Perkin Elmer EA 2400 Series Elemental Analyzer. FT-IR spectra of the compounds were recorded on KBr pellets using a Perkin Elmer FT-IR Spectrophotometer and the characteristic bands obtained at the wave numbers are specific to the functional group of the molecular structure. [41,42] ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance spectrometer (400 MHz) at 298 K. Chemical shifts (δ, in ppm) were referenced to the residual proton signal of the solvent (DMSO-d⁶).

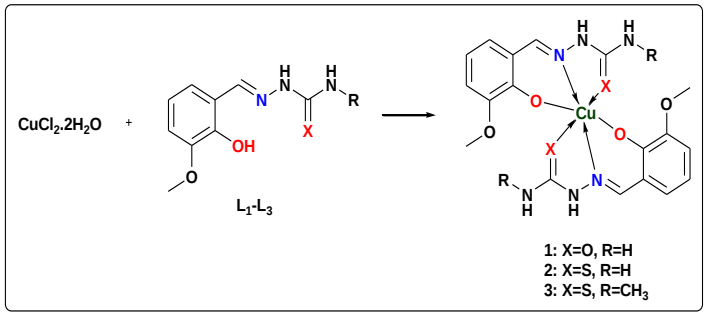
EXPERIMENTAL METHODS

Synthesis of Schiff base ligands L₁, L₂ and L₃

Schiff base ligand L_1 has been already synthesized in methanol as a solvent and characterized by analytical and spectral studies [41]. In the present work L_1 was synthesized from 0.01 mole of 2-Hydroxy-3-methoxybenzaldehyde (1.5215g) and 0.012 moles (1.2619g) of *N*⁴-methylthiosemicarbazide in 20mL of mixture of acetonitrile and ethanol (1:1). Added 1ml of acetic acid to this reaction mixture and continuously stirred using magnetic stirrer for about 2 hours at 80°C. The precipitate obtained was filtered, washed with methanol and diethyl ether (1:1, 3x2mL) and recrystallized with mixture of acetonitrile and ethanol (1:1). Schiff base ligands L_2 and L_3 were synthesized from thiosemicarbazide and semicarbazide instead of *N*⁴-methylthiosemicarbazide using the same method.



Scheme 1: Synthesis of Schiff base ligands L₁, L₂ and L₃



Scheme 2: Synthesis of copper(II) complex of 1, 2 and 3

Synthesis of copper(II) complexes 1, 2 and 3

Complex 1 was synthesized from 15mL of the 1:1 ratio of acetonitrile and ethanol mixture of 0.0011 mole (0.2301g) of Schiff base ligand L_3 and 10 mL of acetonitrile and ethanol the mixture of 0.0005 mole (0.0853g) $CuCl_2.2H_2O$. The reaction mixture was refluxed and continuously stirred using magnetic stirrer for about 6 hours at 100^0C and then allowed to cool. The precipitate was filtered off, washed with ethanol and ether mixture (1:1, 3x2 mL) and dried in vacuum over P_2O_5. Complexes 2 and 3 were synthesized by the reaction of 10 ml of acetonitrile and ethanol mixture of 0.0005 mole (0.0853g) $CuCl_2.2H_2O$ with 0.0011 mole of L_2 and L_1 instead of L_3 using the same method.

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_3** and their copper(II) complexes **1-3** are given as follows:

L_1 [41]: pale yellow powder, yield (2.2268g, 93%), 239-241ºC, Anal. calc. for $C_{10}H_{13}N_3O_2S$, (239.38g mol^{-1}): C, 50.19; H, 5.48; N, 17.56; S, 13.40, found: C, 50.33; H, 5.25; N, 17.70; S, 13.57%. **FT-IR** (cm^{-1}): υ(OH) 3308, υ(NH) 3341, υ(N-N) 1067, 932, υ(C=N) 1556, 1527, υ(C=S) 831. **^{1}H NMR** (DMSO-d^6, 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$_3$**). **^{13}C NMR** (DMSO-d^6, δ in ppm): 177.47 (**C**=S), 149.46 (**C**H=N), 146.64 (Ar**C$_2$**–OH), 142.20 (Ar**C$_4$**–OCH_3), 127.17 (Ar**C$_6$**), 119.99 (Ar**C$_5$**), 113.54, 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: dirty white crystal, yield (2.1628g, 96%), 232-234ºC, Anal. calc. for $C_9H_{11}N_3O_2S$ (225.27g mol^{-1}): C, 47.99; H, 4.92; N, 18.65; S, 14.23, found: C, 47.79; H, 5.12; N, 18.85; S, 14.03%. **FT-IR** (KBr, cm^{-1}): υ(OH) 3285, υ(NH) 3420, 3383, υ(N-N) 1082, υ(C=N) 1628, 1609, υ(C=S) 855. **^{1}H-NMR** (DMSO-d^6, δ in ppm): 9.17 (s, 1H, O**H**), 8.39 (s, 1H, C**H**=N^1), 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$_3$**). **^{13}C NMR** (DMSO-d^6, δ in ppm): 177.65 (**C**=S), 147.88 (**C**H=N), 145.96 (Ar**C$_3$**–OCH_3), 139.40 (Ar**C$_2$**–OH), 120.77 (Ar**C$_6$**), 118.86 (Ar**C$_5$**), 118.11 (Ar**C$_1$**-CHN), 112.78 (Ar**C$_4$**), 55.87 (ArC_3–O**C**H_3).

L_3: yellow crystal, yield (2.0558g, 98%), 226-228ºC, Anal. calc. for $C_9H_{11}N_3O_3$ (209.20g mol^{-1}): C, 51.67; H, 5.30; N, 20.09; O, 22.94, found: C, 51.87; H, 5.26; N, 20.19; O, 22.74%. IR(cm^{-1}): υ(OH) 3281, υ(NH) 3466, υ(N-N) 1005, 931, υ(C=N) 1586, 1515, υ(C=O) 1678. **^{1}H-NMR** (DMSO-d^6, δ in ppm): 10.25 (s, 1H, C**H**=N^1), 9.29 (s, 1H, O**H**), 8.17 (s, 1H, N**H)**, 6.42 (s, 1H, N**H$_2$)**, 7.39, 7.37 (d, 1H, Ar-**H^6**), 6.92, 6.90 (dd, 1H, Ar-**H^5**), 6.78, 6.76, 6.74 (m, 1H, Ar-**H^4**), 3.79, 3.38 (s, 3H, OC**H$_3$**). **^{13}C NMR** (DMSO-d^6, δ in ppm): 156.70 (**C**=O), 147.88 (**C**H=N), 145.31 (Ar**C$_3$**–OCH_3), 137.21 (Ar**C$_2$**–OH), 121.09 (Ar**C$_6$**), 118.96 (Ar**C$_5$**), 118.13 (Ar**C$_1$**-CHN), 112.18 (Ar**C$_4$**), 55.83 (ArC_3–O**C**H_3).

1: light green powder, yield (0.2168g, 90%), >300ºC, Anal. Calc. for $C_{18}H_{20}N_6O_6Cu$ (479.93g mol^{-1}): C, 45.05; H, 4.20; N, 17.51; O, 20.00; Cu, 13.24; found: C, 45.35; H, 4.29; N, 17.31; O, 20.20; Cu, 13.14%. IR (cm^{-1}): υ(NH) 3466, 3328, υ(N-N) 1065, 961, υ(C=N) 1603, 1586, υ(C=O) 1651.

2: dark green powder, yield (0.2274g, 89%), >300ºC, Anal. Calc. for $C_{18}H_{20}N_6O_4S_2Cu$ (512.07 g mol^{-1}): C 42.22; H, 3.94; N, 16.41; S, 12.52, Cu, 12.41; found: C 42.52; H, 3.84; N, 16.49; S, 12.47, Cu, 12.49%. IR (cm^{-1}): υ(NH) 3461, 3414, 3344, υ(N-N) 1112, 1059, υ(C=N) 1618, 1601, υ(C=S) 880, 822.

3: black powder, yield (0.4597 g, 85%), >300ºC, Anal. Calc. for $C_{20}H_{24}N_6O_4S_2Cu$ (540.12g mol^{-1}): C, 44.47; H, 4.48; N, 15.56; S, 11.87, Cu, 11.77; found: C 44.67; H, 4.45; N, 15.51; S, 11.93, Cu, 11.73%. IR (cm^{-1}): υ(NH) 3417, υ(N-N) 1082, 976, υ(C=N) 1609, 1548, υ(C=S) 890.

Anti-microbial Screening

The anti-microbial activity of synthesized ligands **L_1-L_3** and their copper(II) complexes (**1a-b, 1-3**) were tested and the zone of inhibition calculated (**Table 1**) as described earlier. [41, 42]

Table 1: Anti- microbial Activity of Schiff bases and their Cu(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[41]	09	18	09	28	08	10
L_2	14	12	10	13	12	***
L_3	12	12	10	10	10	***
1	25	20	15	15	34	20
2	36	24	18	23	36	32
3	19	20	16	24	20	20
Ciprofloxacin	30	25	30	30	-	-
Clotrimazole	-	-	-	-	32	38
Flucanazole	-	-	-	-	30	34

***- Not active

RESULTS AND DISCUSSION

The synthesized Schiff base ligands **L_1-L_3** and copper(II) complexes **1-3** were identified by their spectral (^{1}H-NMR, ^{13}C-NMR and FT-IR spectra) data, physical data (melting point and elemental analysis), and comparison with authentic ones. The FT-IR spectra provide valuable information regarding the nature of the functional group attached to the metal atom. The infrared spectra of the ligands showed a band at 1515-1628 cm^{-1} which was attributed to mC=N- band at 1556 cm^{-1} in **L_1**, 1628 cm^{-1} in **L_2** and 1586, 1515 cm^{-1} in **L_3** due to the azomethine group which shows a shift to lower frequencies in all complexes almost between 06 and 10 cm^{-1} which may be indicating the involvement of -C=N- nitrogen in coordination to the Cu^{2+} ion. The FT-IR spectra of the new compounds showed a band in the region (1439–1469) cm^{-1} referring to mNCS band in **2** and **3** and the absence of this band in **1** which may be indicating absence of NCS. The frequencies of **L_1** and **L_2** that appeared at 755, 744 cm^{-1} and 831, 855 cm^{-1} regions are assigned to mC–S and mC=S bands respectively, which undergo a shift toward lower frequencies in all complexes. The infrared spectra of –C=O in the ligand **L_3** showed a band at 1678 cm^{-1} was observed due to the carbonyl group which shows a shift to lower frequencies by 27 cm^{-1} which may be indicating the involvement of -C=O nitrogen in coordination with the Cu^{2+} ion. Accordingly, the ligand acts as tridentate chelating agent, bonded to the metal ion via the *O*-atom in phenolic oxygen, N-atom of the azomethine nitrogen and as well as *S-/O*-atom of the thiocarbamido/carbamido groups [41, 42].

The ^{1}H-NMR and ^{13}C-NMR spectra of **L_1**, **L_2**, **L_3** showed one proton singlet at δ = 11.42, 8.39, 10.25 ppm and 149.46, 147.88, 147.88 ppm due to the **>CH**=N- respectively. The -OH signal of phenol appeared within 9.17-9.29 ppm as a broad singlet in all the ligands. The ^{13}C-NMR spectra of **L_1**, **L_2** and **L_3** showed at 177.47, 177.65 and 156.70 ppm due to the **>C=S** in **L_1**, **L_2** and **>C=O** in **L_3** respectively. In ^{13}C-NMR spectra, the one singlet observed within 55.66-55.87 ppm due to -O**C**H_3 in all the ligands. ^{13}C-NMR spectra showed at 30.74 ppm due to >N-**C**H_3 in only **L_1**.

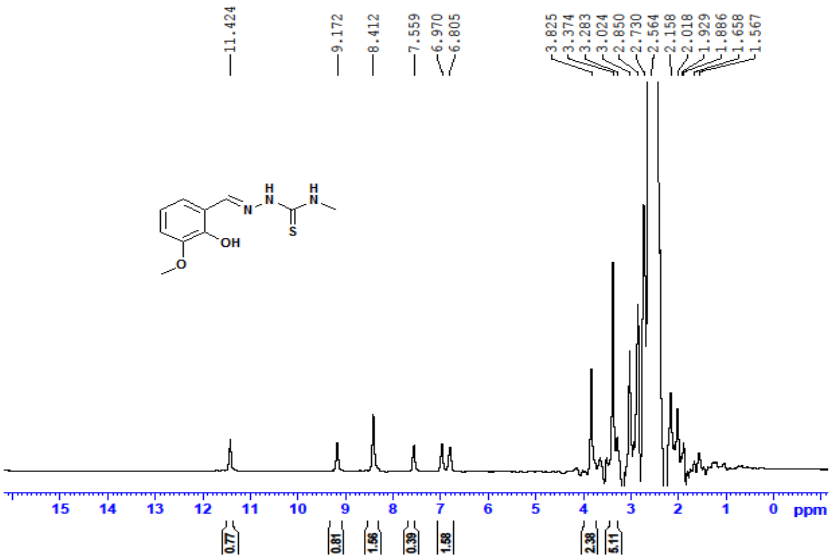


Fig. 1: ^{1}H-NMR spectrum of Schiff base L_1

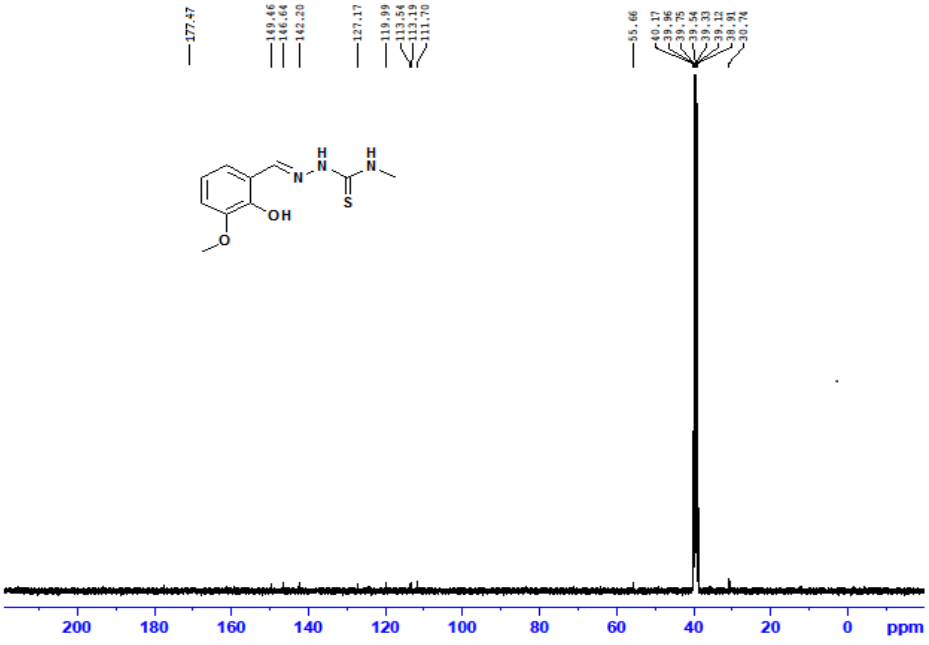


Fig. 2: ^{13}C-NMR spectrum of Schiff base L_1

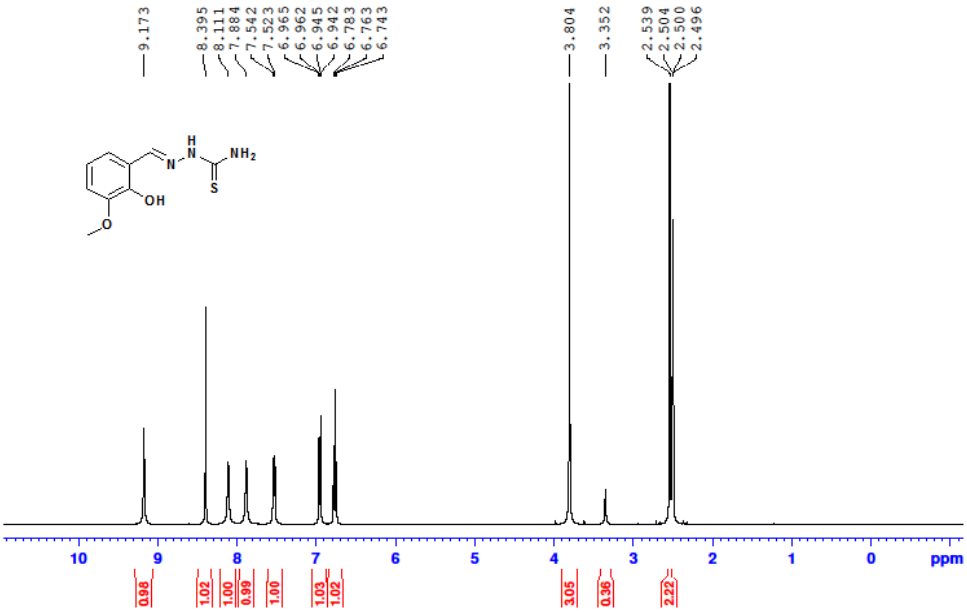


Fig. 3: ^{1}H-NMR spectrum of Schiff base L_2

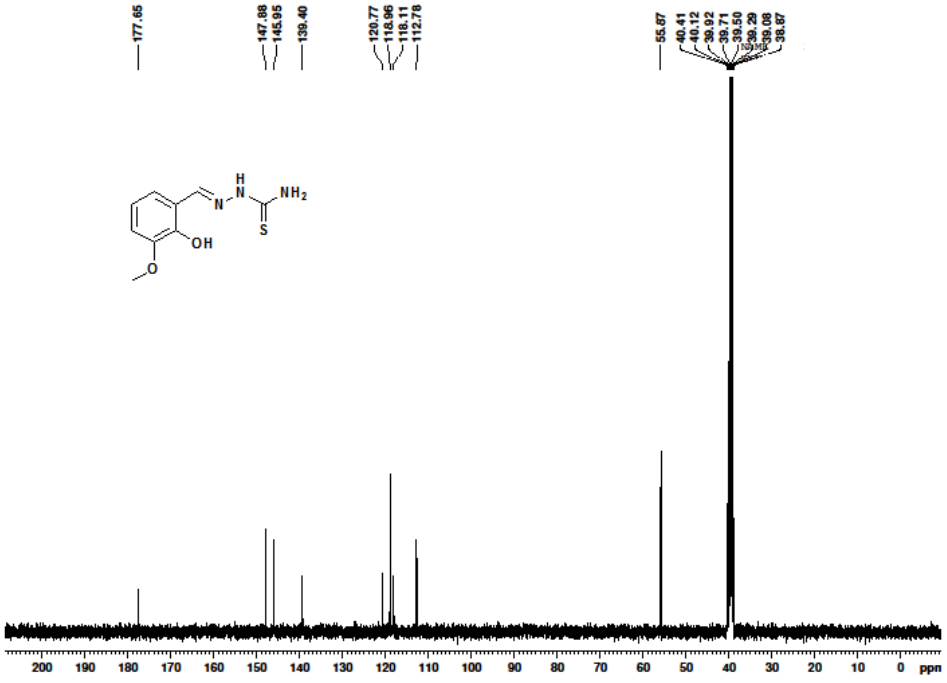


Fig. 4: ^{13}C-NMR spectrum of Schiff base L_2

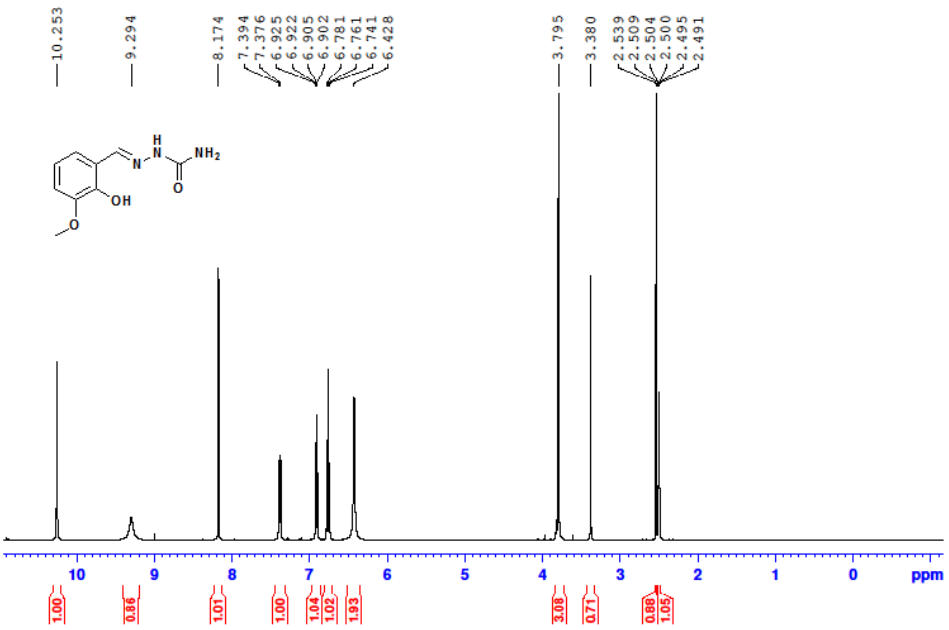


Fig. 5: ^{1}H-NMR spectrum of Schiff base L_3

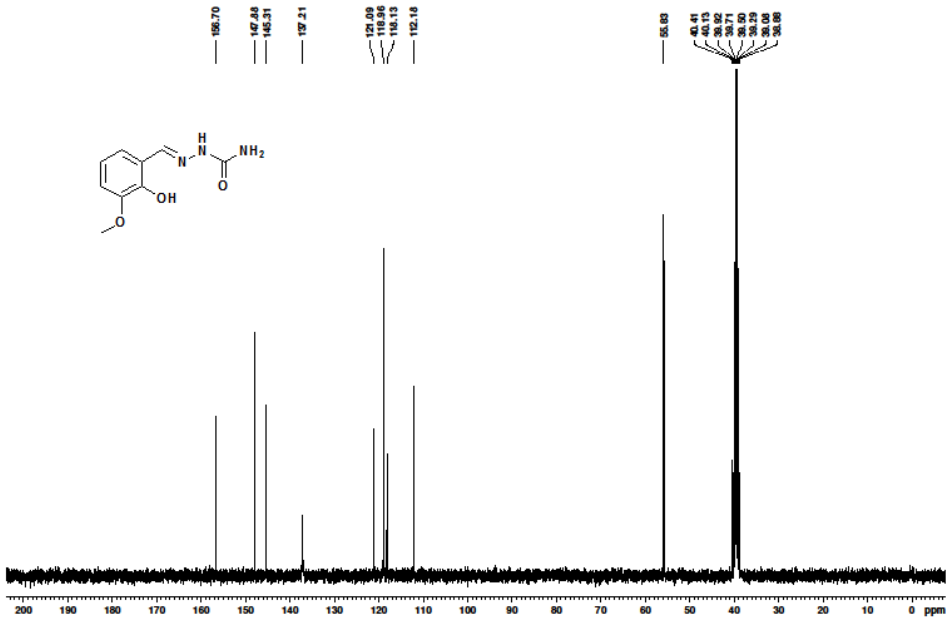


Fig. 6: ^{13}C-NMR spectrum of Schiff base L_3

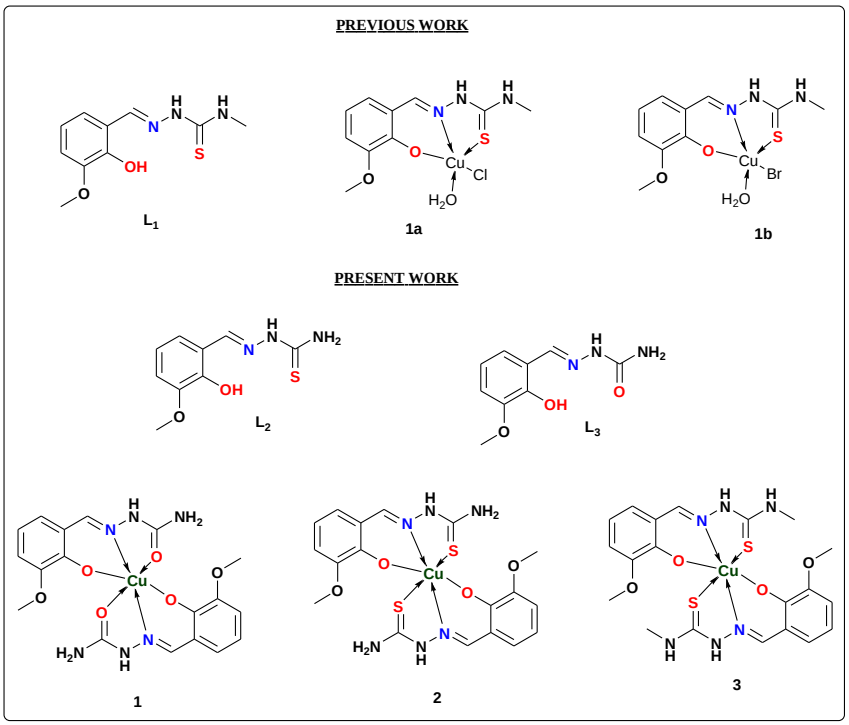
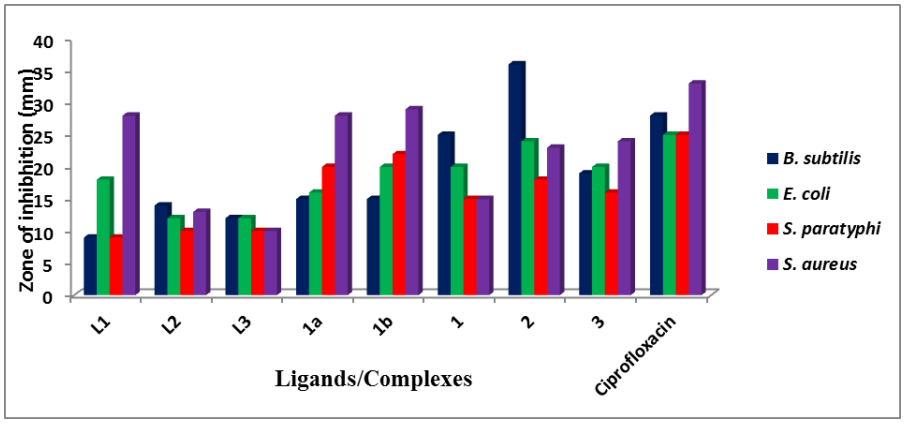


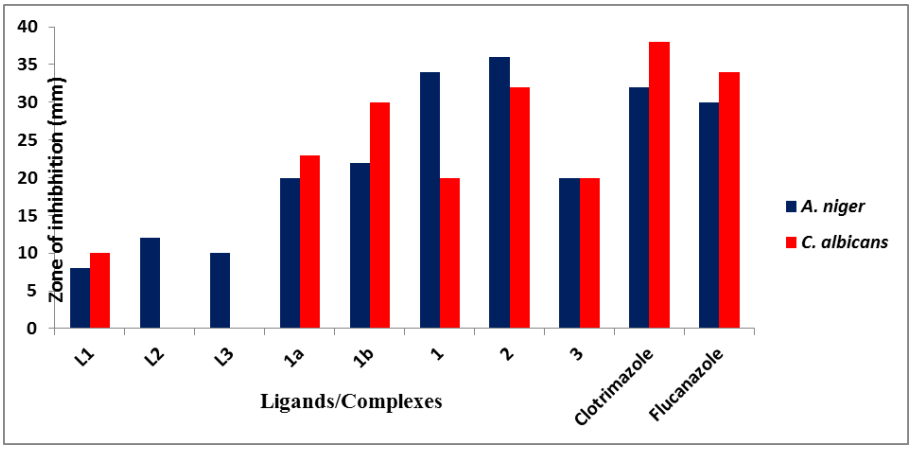
Fig. 7: Structure of Schiff base ligand L_1-L_3 and their copper(II) complex (1a-b and 1-3)

Anti-microbial Screening

All the new complexes showed a remarkable microbial activity against bacteria and fungi. From the results it is clear that the copper(II) complexes **1-3** are found to have microbial activity than the parent ligands (Graph 1 and Graph 2).



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



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

CONCLUSION

In conclusion, we synthesized three monobasic Schiff base ligands and there Cu(II) complexes with good to excellent yield (**85-98%**). The FT-IR results exhibits that the synthesized ligand binds with Cu^{2+} ions in tridentate coordination through the *O*-atom in phenolic oxygen, *N*-atom of the azomethine nitrogen and as well as *S*-/*O*-atom of the thiocarbamido / carbamido groups. The antibacterial data show that all the Cu(II) complexes have an excellent biological activity compared to that of parent ligands against all the microorganisms.

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CONFLICT OF INTEREST

The authors confirmed that there is no conflict of interest for this research paper.

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