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SYNTHESIS, CHARACTERIZATION, AND ANTIMICROBIAL STUDIES OF NOVEL BIO-RELEVANT COMPOUNDS DERIVED FROM SUBSTITUTED BENZOTHIAZOLE

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ABSTRACT

Heterocyclic moieties containing heteroatoms nitrogen, sulfur, and oxygen, such as substituted benzothiazole, have great potential for biological and pharmaceutical importance due to their structural, binding affinity, and photophysical properties. Herein, we have synthesized novel compounds derived from substituted benzothiazole with 2-chloroacetophenone and comparative studies of their mixed ligand metal complexes having 8-hydroxyquinoline. These new compounds were characterized using elemental analysis, magnetic moment determination, molar conductance, melting point determination, and various spectral techniques (FTIR, mass, and ^{1}H NMR spectra). These synthesized compounds were also investigated for their *in vitro* antimicrobial bioactivity against two bacterial strains; one is gram-positive bacteria *Staphylococcus aureus* and the second is gram-negative bacteria *E. coli* and one fungal strain *Aspergillus niger* using agar well diffusion method and MIC (minimum inhibition concentration) were used to express their antimicrobial activity. Obtained results were compared with Ciprofloxacin and Ketoconazole. Metal complexes possess higher biological activity as compared to free Schiff base ligands in most cases.

Keywords: 8-Hydroxy Quinoline; Benzothiazole; Acetophenone; Schiff Base; Antimicrobial Activity.
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INTRODUCTION

Heterocyclic compounds containing sulphur, nitrogen, and oxygen play an essential role in the medicinal and pharmaceutical fields and various drug designs. The coordination affinity and binding to metals influence the potential effect of these types of compounds. Benzothiazole acts as a promising bioactive compound due to having sulfur heteroatom, with its remarkable achievements and fundamental building skeleton of various important therapeutic natural and synthetic compounds.[1,2] Benzothiazole scaffold having heteroatoms possess various remarkable activities such as antiviral[3], antimicrobial[4-9], anti-inflammatory[10], anticonvulsant[11], anticancer[12,13], antimalarial[14], and antioxidant.[15] In particular, acetophenone has emerged as a good pharmacophore on account of its pharmacological significance in medicinal and metal-based drug discovery fields. Recently, the inclusion of this moiety with other pharmacophores raised their bioactivity with the construction of new bioactive compounds. As a result, there are some reviews on the biological significance of acetophenone-appending compounds against antimicrobial[16], anti-inflammatory[17], and anticancer[18] activities. Schiff base and ternary metal complexes are more biologically potent and significant than their free Schiff bases.[19,20,21] Because of the pharmacophore mentioned above moieties and our previously reported work, attempts were made to synthesize and design a novel series of acetophenone with substituted benzothiazole.

EXPERIMENTAL

Material and Methods

Solvents, metal salts, reagents, and starting materials used for the synthesis, were purchased from Sigma Aldrich and used as such. The completion of the reaction and purity of synthesized compounds were confirmed by TLC using Silica Gel-G plates coated with aluminum. The melting point of bioactive compounds was calculated by open capillary electrothermal equipment. IR and NMR data were documented on a Perkin-Elmer spectrometer in the 4000cm^{-1} - 400cm^{-1} range and a Jeol Resonance ECS-400 Spectrometer used with 400 MHz operating frequency, respectively. Mass spectra were documented in TOF MS ES$^+$ mass spectrometer operating at 70 eV ionization potential.

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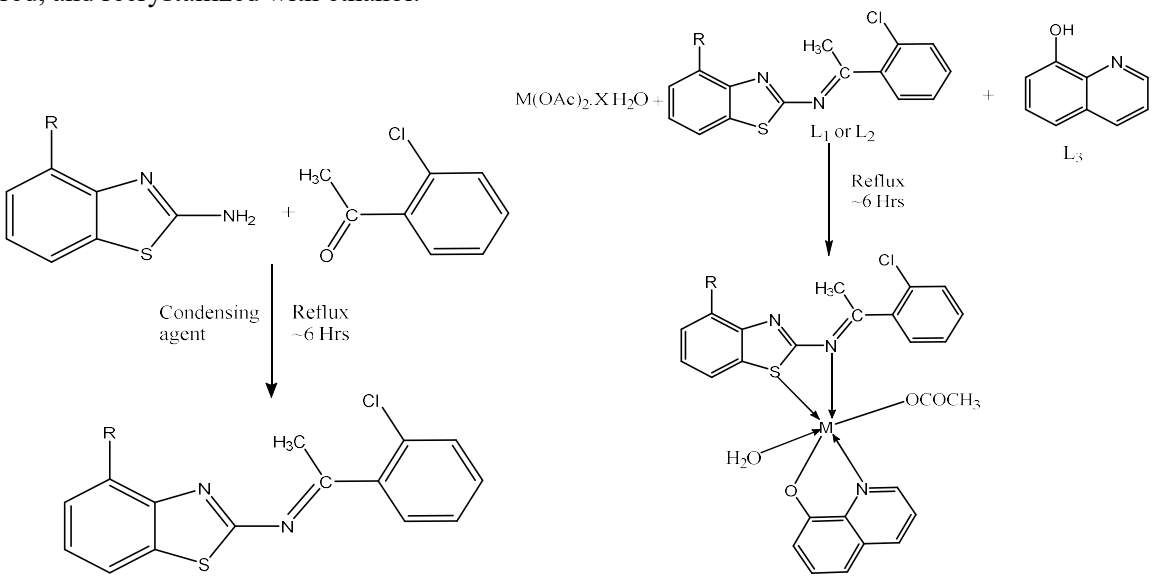
Synthesis of Schiff Bases L_1 and L_2

Equimolar ethanolic solution of 2-aminobenzothiazole (1.50g, 10mmol) with 2-chloroacetophenone (1.54 g, 10mmol) and 2-amino-4-methylbenzothiazole (1.64g, 10mmol) with 2-chloroacetophenone (1.54 g, 10mmol) was taken separately and allowed to reflux for ~6 hours with a condensing agent (with a few drops of glacial acetic acid). The end product of the reaction was checked by TLC with suitable developing solvents. After completion of the reaction, the reaction mixture was kept for 24 hours at room temperature for evaporation of the solvent. A solid product was obtained, which was washed and recrystallized with ethanol and dried in a desiccator using silica gel.

Synthesis of Metal Complexes

The equimolar amount of primary ligand [L_1 (2.86g, 10mmol) or L_2 (3.01g, 10mmol)], secondary ligand (L_3, 1.45g, 10mmol) and metal salts [Fe(II), Ni(II), and Zn(II)] were used in 1:1:1 proportion for the synthesis of metal complexes. Firstly, the prepared solution of the primary ligand was heated in a round bottom flask, and added an aqueous solution of corresponding metal salt. After one hour of reflux, added a solution of 8-hydroxyquinoline and reflux continued for ~ 6 hours. All the reaction processes were monitored by TLC. Solid products obtained by evaporation of solvent at room temperature were washed, filtered, and recrystallized with ethanol.



[L_1& L_2] R = H for L_1
R = -CH_3 for L_2

Metal Complexes [Ni(II), Fe(II) & Zn(II)]

Scheme-1: Schematic Procedure of Synthesis of Schiff Bases and Metal Complexes

Ligand L_1 [N-(benzo[d]thiazol-2-yl)-1-(2-chlorophenyl)ethan-1-imine]

Yield = 72.19%, brown colour, M. P.- 118.2ºC; Elemental analysis[$C_{15}H_{11}N_2SCl$]: Calculated% (found%) C= 62.80 (62.21), H= 3.87 (3.14), N= 9.77 (9.71), S= 11.16(11.45) Cl= 12.39 (12.85);); IR (υ,cm^{-1}): 1426 (C-C_{str}), 781 (C-C_{bend}), 1560 (C=N), 2972 (C-H_{str}); ^{1}H NMR (DMSO-d_6): δ = 1.8 (CH_3, azomethine), 6.7 - 7.8 (Ar-H); Mass (70eV) calculated for [$C_{15}H_{11}N_2SCl$]: m/z 251.46[M-Cl]$^+$

Ligand L_2 [1-(2-chlorophenyl)-N-(4-methylbenzo[d]thiazol-2-yl)ethan-1-imine]

Yield = 75.57%, brown colour, M. P.- 126.5ºC; Elemental analysis[$C_{16}H_{13}N_2SCl$]: Calculated% (found%) C= 63.87 (63.61), H= 4.36 (4.74), N= 9.31 (9.83), S= 10.65(10.43) Cl= 11.81 (11.25); IR (υ,cm^{-1}): 1428 (C-C_{str}), 783 (C-C_{bend}), 1564 (C=N), 2975 (C-H_{str}); ^{1}H NMR (DMSO- d_6): δ = 1.8(CH_3, azomethine), 6.7-7.8 (Ar-H), 2.0 (CH_3, benzene ring); Mass (70eV) calculated for [$C_{16}H_{13}N_2SCl$]: m/z 266.35[M-Cl]$^+$

Compound A; [Ni(L_1)(8-HQ)(OAc)(H_2O)]

Yield = 57.18%, light green colour, M. P.- 168.2ºC, Elemental analysis[$C_{26}H_{22}N_3O_4SClNi$]; Calculated% (Found%) C= 55.09 (55.24), H= 3.91 (3.86), N= 7.42 (7.74), S = 5.65 (5.23), Cl= 6.27 (6.13), Ni= 10.36 (10.23);); IR (υ,cm^{-1}): 1422 (C-C_{str}), 778 (C-C_{bend}), 1558 (C=N), 2969 (C-H_{str}),1605 (C=O), 708 (M-O),

564 (M-N), 425 (M-S); ^{1}H NMR (DMSO- d_6): δ = 1.37 (CH_3, azomethine), 6.8-7.8 (Ar-H), 2.3 (CH_3, acetic acid), 3.28(H_2O); Mass (70eV) calculated for [$C_{26}H_{22}N_3O_4SClNi$]: m/z 563.91[M-2]$^+$

Compound B; [Fe(L_1)(8-HQ)(OAc)(H_2O)]
Yield = 70.85%, black colour, M. P.- 159.6ºC, Elemental analysis [$C_{26}H_{22}N_3O_4SClFe$]; Calculated% (Found%) C= 55.36 (55.18), H= 3.93 (3.63), N= 7.45 (7.67), S = 5.68 (5.21), Cl= 6.30 (6.21), Fe= 9.91 (9.43);); IR (υ,cm^{-1}): 1424 (C-C_{str}), 775 (C-C_{bend}), 1556 (C=N), 2970 (C-H_{str}), 1602 (C=O), 712 (M-O), 569 (M-N), 429 (M-S); ^{1}H NMR (DMSO- d_6): δ = 1.58 (CH_3, azomethine), 6.8-7.5 (Ar-H), 2.4 (CH_3, acetic acid), 3.3(H_2O); Mass (70eV) calculated for [$C_{26}H_{22}N_3O_4SClFe$]: m/z 561.57[M-2]$^+$

Compound C; [Ni(L_2)(8-HQ)(OAc)(H_2O)]
Yield = 59.18%, light green color, M. P.- 178.2ºC, Elemental analysis[$C_{27}H_{25}N_3O_4SClNi$]; Calculated% (Found%) C= 55.72 (55.29), H= 4.33 (4.81), N= 7.22 (7.74), S= 5.50 (5.76), Cl= 6.10 (6.13), Ni= 10.09 (10.23);); IR (υ,cm^{-1}): 1423 (C-C_{str}), 780 (C-C_{bend}), 1560 (C=N), 2971 (C-H_{str}), 1609 (C=O), 726 (M-O), 564 (M-N), 434 (M-S); ^{1}H NMR (DMSO- d_6): δ = 1.8 (CH_3, azomethine), 6.7-7.3 (Ar-H), 2.3 (CH_3, acetic acid), 2.2 (CH_3, benzene ring), 3.2 (H_2O); Mass (70eV) calculated for [$C_{27}H_{25}N_3O_4SClNi$]: m/z 580.82[M]$^+$

Compound D; [Fe(L_2)(8-HQ)(OAc)(H_2O)]
Yield = 71.85%, black color, M. P.-172.7ºC, Elemental analysis [$C_{27}H_{25}N_3O_4SClFe$]; Calculated% (Found%) C= 56.00 (56.18), H= 4.35 (4.63), N= 7.26 (7.67), S = 5.53 (5.68), Cl= 6.14 (6.21), Fe= 9.65 (9.43); IR (υ,cm^{-1}): 1420 (C-C_{str}), 774 (C-C_{bend}), 1554 (C=N), 2969 (C-H_{str}),1603 (C=O), 731 (M-O), 547 (M-N), 442 (M-S); ^{1}H NMR (DMSO- d_6): δ =1.35 (CH_3, azomethine), 6.7-7.3 (Ar-H), 2.3(CH_3, acetic acid), 2.2 (CH_3, benzene ring), 3.2 (H_2O); Mass (70ev) calculated for [$C_{27}H_{25}N_3O_4SClFe$]: m/z 578.51[M]$^+$

Compound E; [Zn(L_2)(8-HQ)(OAc)(H_2O)]
Yield = 52.43%, light greenish-yellow color, M. P.- 189.8ºC, Elemental analysis [$C_{27}H_{25}N_3O_4SClZn$]; Calculated% (Found%) C= 55.09 (55.27), H= 4.29 (4.18), N= 7.14 (7.69), S = 5.44 (5.92), Cl= 6.04 (6.17), Zn= 11.12 (11.43);); IR (υ,cm^{-1}): 1421 (C-C_{str}), 776 (C-C_{bend}), 1557 (C=N), 2968 (C-H_{str}), 1605 (C=O), 724 (M-O), 552 (M-N), 448 (M-S); ^{1}H NMR (DMSO- d_6): δ = 1.6 (CH_3, azomethine), 6.7-7.8 (Ar-H), 2.3 (CH_3, acetic acid), 2.0(CH_3, benzene ring), 3.3 (H_2O); Mass (70eV) calculated for [$C_{27}H_{25}N_3O_4SClZn$]: m/z 590.4[M-2]$^+$

Biological Studies
In vitro, all the newly synthesized bioactive compounds were examined for antimicrobial evaluation against two bacterial strains *S. aureus*, *E. coli,* and fungal strain *A. niger* using agar well diffusion methods at 20, 40, 60, and 80µl concentrations. Mueller Hinton agar no. 2 is used as a bacteriological cultural medium and Sabouraud's dextrose agar, SDA (Merck, Germany) is used as fungal cultural media. The compounds were diluted in DMSO solvent for antimicrobial assay. Sterilized Mueller Hinton agar (Hi, media, India) and poured into sterile Petri dishes. Wells were designed in the standardized agar plates and the target compound was inserted in the well (6mm) and incubated 24hrs at 37ºC. The bioactivity of compounds was determined in terms of zone size (diameter) around each well and calculated in mm. The bioactivity of these compounds compared with standard Ciprofloxacin and Ketoconazole control drugs. The bioactivity results of these compounds are summarized in Table-1, calculated in minimum inhibitory concentration (MIC) values.

RESULTS AND DISCUSSION

The experimental section summarizes the physiological analysis of the synthesized ligands (L_1 & L_2) and their ternary complexes. All the compounds are colored and soluble in various organic solvents such as methanol, ethanol, chloroform, DMF, and DMSO. Elemental analysis of these compounds has shown good agreement with obtained values. Magnetic moment (μ_{eff} in B. M.) for metal complexes is found to be approximately 2.89, 4.96, 2.98, 5.24, and zero for [Ni(L_1)(8-HQ)(OAc)(H_2O)], [Fe(L_1)(8-HQ)(OAc)(H_2O)], [Ni(L_2)(8-HQ)(OAc)(H_2O)], [Fe(L_2)(8-HQ)(OAc)(H_2O)] and [Zn(L_2)(8-HQ)(OAc)(H_2O)] metal complexes, respectively. This indicates the paramagnetic nature of Ni(II), Fe(II) metal ions with expected 2 and 4 unpaired electrons and the diamagnetic nature of Zn(II) metal ion with no unpaired electron. The molar conductivity of the metal complexes is found to be ~ 11-13ohm^{-1} cm^2 mol^{-1} which suggests the non-electrolytic nature of the complexes. FTIR spectra give some valuable information

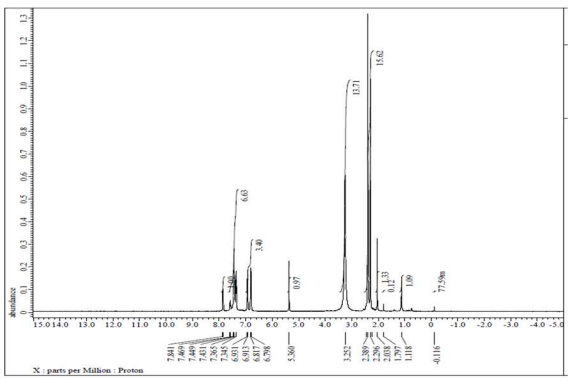
about the functional group present in the compounds, such as the nature of the azomethine linkage (C=N) of the synthesized Schiff base ligands and their metal chelates. All the metal compounds exhibit strong absorption bands lower than that obtained for Schiff bases (L_1 & L_2) at 1560 $cm^-$and and 1564 cm^{-1} respectively, which has shown the attachment of azomethine with metal ions.

Table-1: Bioactivity Results of Synthesized Compounds (MIC values)

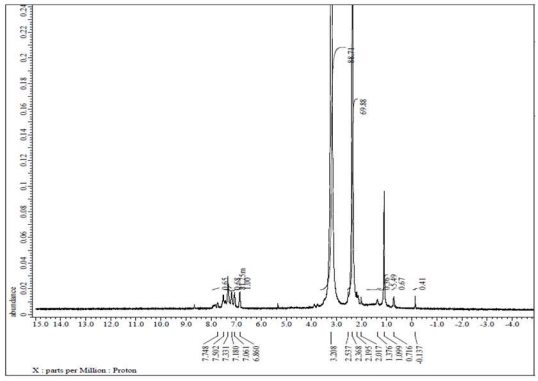
Comp. name	Bacterial strain								Fungal strain			
	Gram +ve				Gram -ve							
	S. aureus				*E. coli*				*A. niger*			
Concentration (µg/mL)	20	40	60	80	20	40	60	80	20	40	60	80
L_1	N	N	9	11	N	11	13	15	N	N	N	N
L_2	N	N	N	10	N	9	11	13	N	N	9	11
A	12	13	15	17	9	11	14	17	N	9	11	16
B	14	15	16	18	12	13	15	16	N	N	8	10
C	14	16	18	19	13	15	16	18	N	N	11	15
D	13	14	15	17	11	14	15	17	N	13	16	18
E	12	14	16	18	N	8	11	13	15	17	19	23
Standard(40µg/mL) Ciprofloxacin Ketoconazole	30				30				25			

[N=Nil]

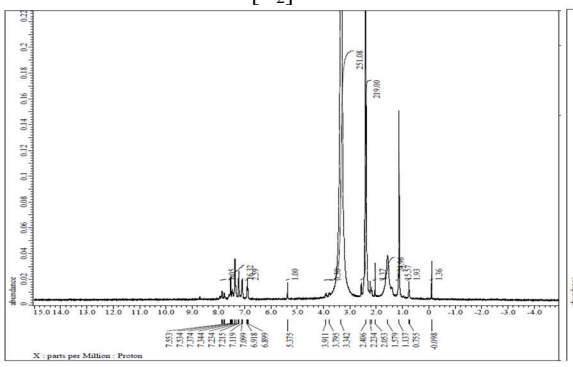
Some other absorption bands are also observed in metal complexes that range from 750 cm^- to 400 cm^-, which might be due to the formation of coordinate bonds between heteroatoms (N, O, S) and central metal ions. ^{1}H NMR spectra of above-synthesized compounds documented in d_6-DMSO solvent and data expressed in δ value (ppm) obtained downfield in reference to TMS (internal standard). In NMR spectra, all the compounds show a single peak at ~1.8 ppm due to methyl proton attached to azomethine. Ligand L_2 and its metal complexes exhibit a single peak at ~2.2 ppm for the methyl protons attached to the benzene ring of benzothiazole and a multiple at ~6.7 to 7.8 ppm for aromatic protons (Fig.-1).



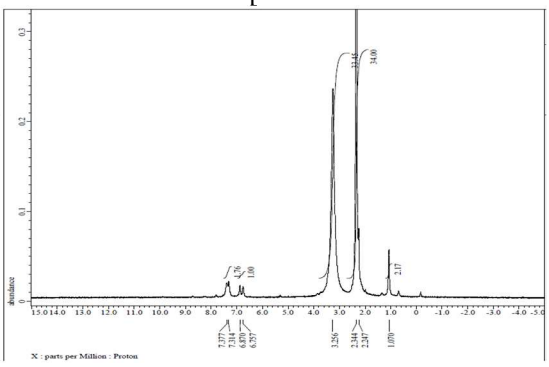
[L_2]



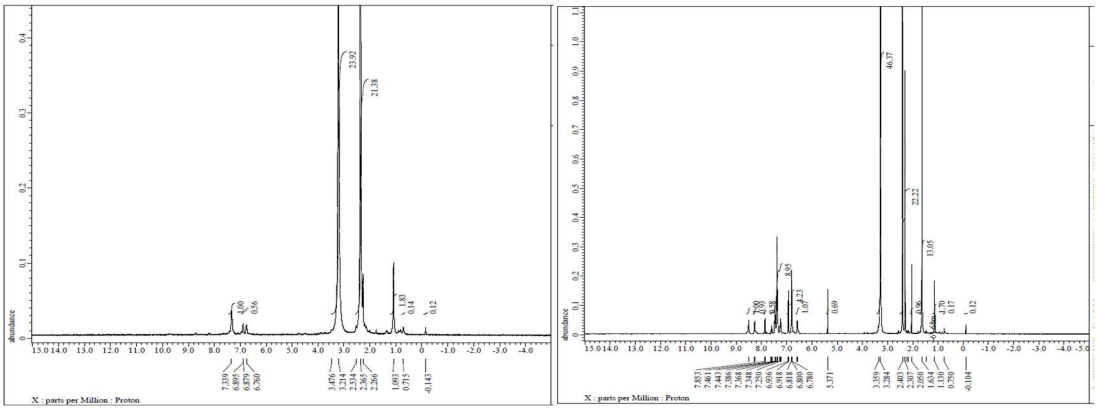
Comp. A



Comp. B



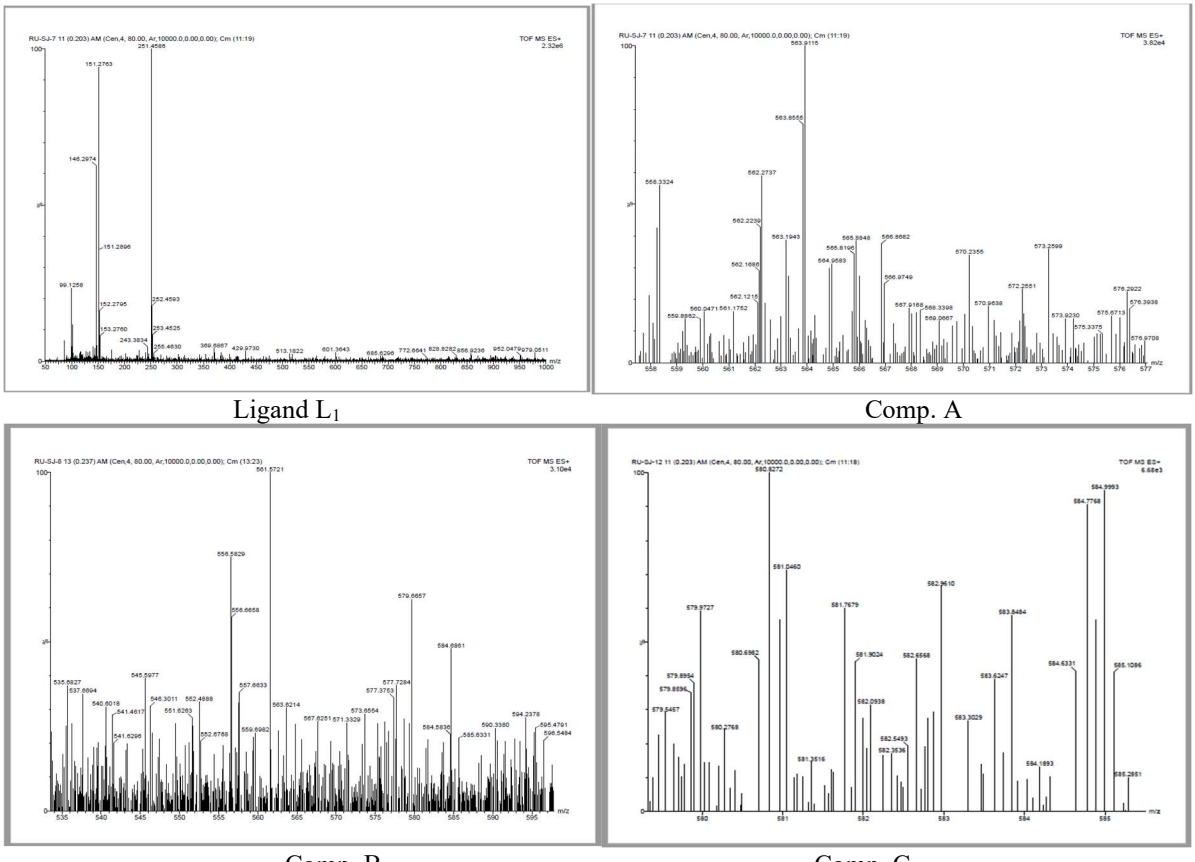
Comp. C



Comp. D Comp. E

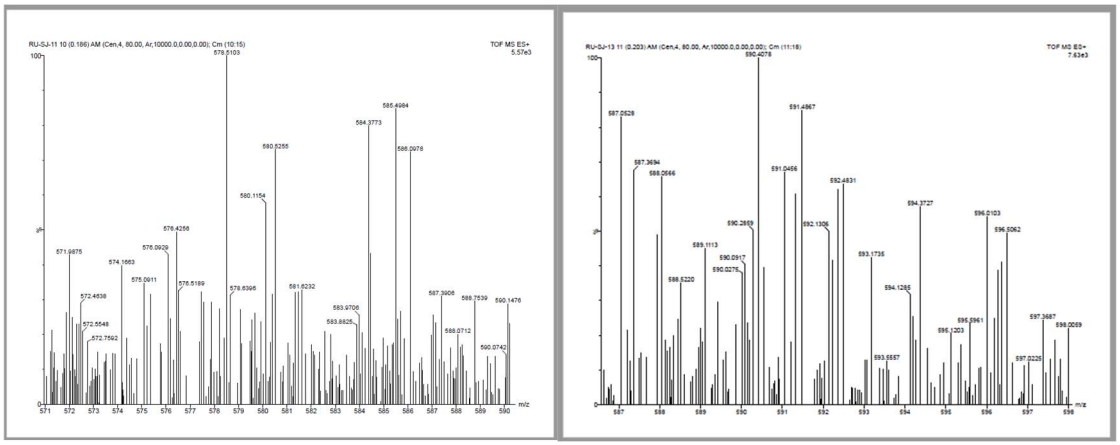
Fig.-1 ^{1}H NMR Spectra of Synthesized Compounds

The mass spectrum of the newly synthesized biologically active compounds described their molecular weight, which in turn is good evidence for confirmation of the synthesis of new organic compounds and their metal complexes. The MS ESI +ve of ligands (L_1&L_2) shows the parent ion peaks and base peak m/z at 251.46 and 266.35 for $[M\text{-}Cl]^+$, respectively, which are very close to the molecular weight (251.23 & 266.13) of the synthesized ligands$C_{15}H_{11}N_2SCl$ and $C_{16}H_{13}N_2SCl$, respectively. In addition, some other prominent peaks are observed at 146.29, and 151.27 for fragments of the ligands, which are closely identical to the plausible structure of the synthesized ligands. Metal compounds also have shown the parent ion peak m/z at 563.91 $[M\text{-}2]^+$, 561.57 $[M\text{-}2]^+$, 580.82 $[M]^+$, 578.51 $[M]^+$ & 590.4 $[M\text{-}2]^+$ for $[Ni(L_1)(8\text{-}HQ)(OAc)(H_2O)]$, $[Fe(L_1)(8\text{-}HQ)(OAc)(H_2O)]$, $[Ni(L_2)(8\text{-}HQ)(OAc)(H_2O)]$, $[Fe(L_2)(8\text{-}HQ)(OAc)(H_2O)]$, and $[Zn(L_2)(8\text{-}HQ)(OAc)(H_2O)]$, respectively (Fig.-2).



Ligand L_1 Comp. A

Comp. B Comp. C



Comp. D Comp. E

Fig.-2: Mass Spectra of Synthesized Compounds

The biological evaluation shows that ligands and their metal complexes can inhibit particular bacterial and fungal strains. Among all the metal complexes, Compound E possesses excellent inhibition capacity and Compound A and Compound D also show moderate inhibition capacity for *A. niger* fungal strain. All metal complexes exhibit good potency against *S. aureus* and *E. coli*. The biological results indicated that ligands are less bioactive than metal complexes. Metal complexes exhibit good to moderate activity against all selective strains. (Fig.-3 and 4)

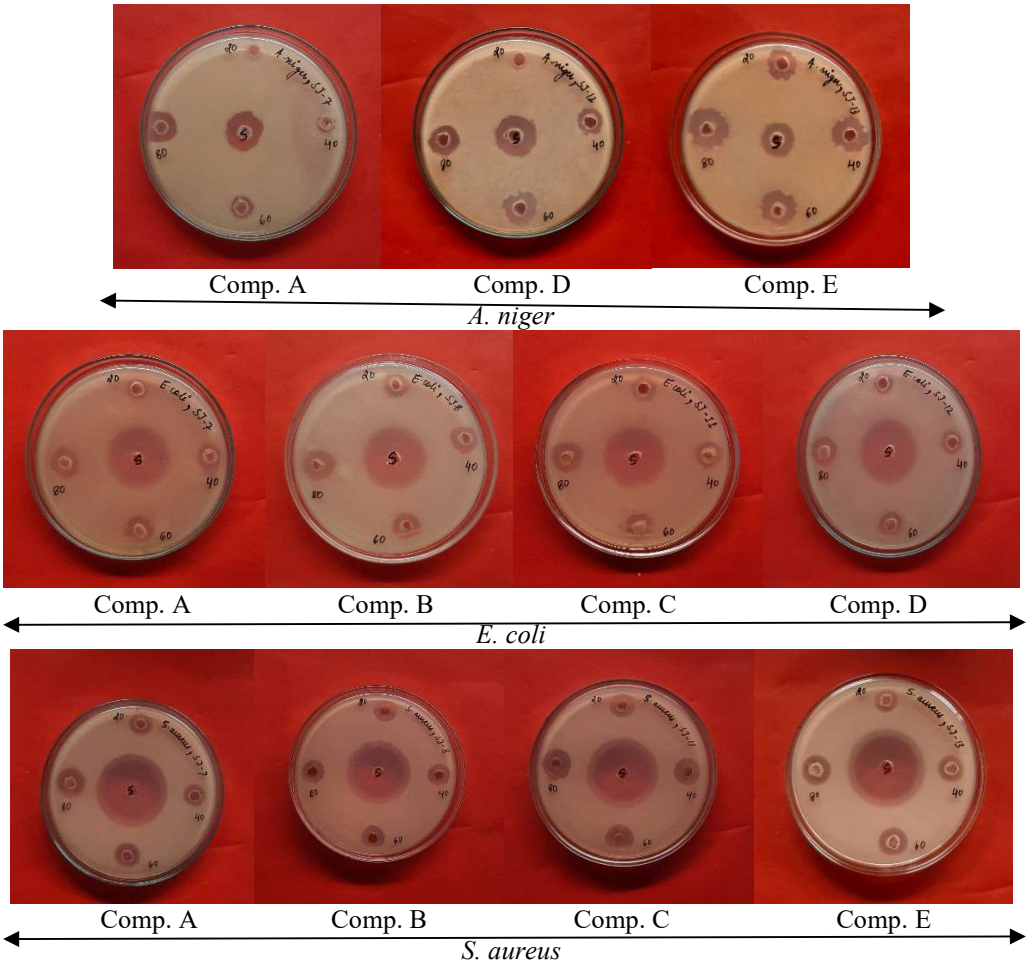


Fig.-3: Antimicrobial Studies of Compounds

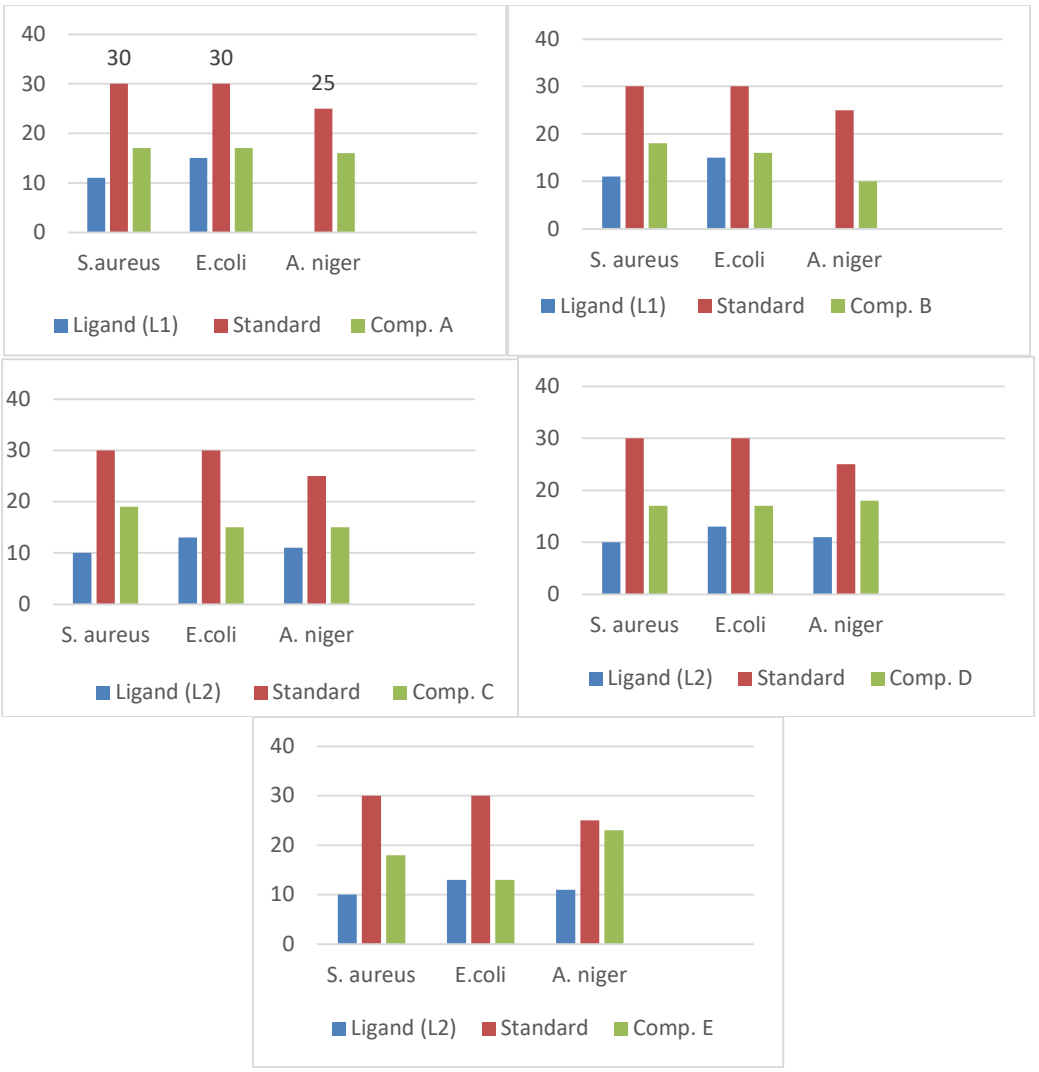


Fig.-4: Bar Diagram for Showing the Maximum MIC Value of the Antimicrobial Activity of the Synthesized Compounds

CONCLUSION

Two new Schiff base ligands were prepared by using 2-chloroacetophenone with 2-aminobenzothiazole; and 2-chloroacetophenone with 2-amino-4-methylbenzothiazole. Further, ternary metal complexes of transition metal ions [Ni(II), Fe(II), and Zn(II)] were prepared with these Schiff bases and 8-hydroxyquinoline. All the synthesized compounds were analyzed with elemental analysis and various spectral techniques. An octahedral geometry has been proposed for each of the metal complexes on the basis of the above analysis. Both Schiff base ligands act as bidentate with azomethine nitrogen and sulphur atom of benzothiazole ring as donor moieties. All the newly prepared compounds were evaluated for antimicrobial activity against *S. aureus*, *E. coli* bacterial strains, and *A. niger* fungal strains. Ligands, L_1 is comparatively more effective for bacterial strains whereas L_2 is for fungal strains. Ligands were found to be less potent than their metal complexes against all selective pathogens. Especially when L_2 is the primary ligand, then the metal complex having Zn(II) as the central metal ion shows the maximum inhibitory effect for *A. niger* fungal strain, whereas Compound C (Ni metal ion) and Compound D (Fe metal ion)exhibited moderate bioactivity against *A. niger*. When L_1 is a primary ligand, Compound B having Fe as a central metal ion, shows a prominent inhibitory effect compared to Compound A (having Ni metal ion) in the case of both bacterial strains. All the metal complexes exhibited good bioactivity against *S. aureus* and *E. coli* bacterial strains. All the results suggest that the bioactivity of metal complexes can be enhanced by changing substituents on heterocyclic moieties, which can be helpful for new drug development.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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