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Synthesis of Benzofuran and Schiff's Base Derivatives and Its Biological Study

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Abstract – Schiff bases are very important class of ligands which can bind to the metal via azomethine nitrogen and have been extensively studied in the recent years. Benzofuranle Schiff base ligands acts as a scaffold for the synthesis of metal complexes, to fight against infectious diseases. the synthesis of 2-(1methyl-1-H-Benzofuranl-2-yl)phenyl)imino)methyl)phenol ligand and used it for the preparation of dicopper metal complexes. Both ligand and its complexes are characterized by various spectroscopic techniques including IR, NMR, ESI-MS and single crystal X-ray crystallography. As per the biological activity is concerned, binding study with DNA and BSA have been carried out, results are suggested that the metal complex bind in a partial intercalative/electrostatic interactions and was shown to have better binding affinity than ligand. Also, cytotoxic effects were studied on human breast cancer cells (MCF-7), IC50 values reveals that metal complex was found to be better cytotoxic activity than ligand. Besides the biological activity, the fluorescent property of Benzofuran [1,2-c] quinazoline have led researchers to explore the property for the welfare of mankind. One such advantage is the use of luminescent organic compound in the optoelectronic devices like solar cells and organic light emitting diodes (OLEDs). Synthesized monomeric and dimeric Benzofuran quinazoline derivatives and characterized by elemental analysis, IR, NMR, ESI-MS and single crystal X-ray crystallographic techniques. Photophysical properties were studied by UV-vis and fluorescence spectroscopic analysis. The compounds were doped with 1,3-bis(9-carbazolyl)benzene at different concentrations, which were made into thin films and then emission spectra were recorded. The results reveal that long range emission spectrum in the visible region and thermal stability of the synthesized compounds may act as promising molecules for OLED application.

Key Words – Synthesis, Benzofuran, Schiff's Base Derivatives, Biological Activity, Fluorescence Spectroscopic Analysis, Crystallographic Techniques

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INTRODUCTION

Heterocyclic bearing nitrogen atom like Benzofuranle plays significant role as a pharmaceutical and biological entity varying from antimicrobial to anticancer agents [1]. Benzofuranle is being one of the biological active components in albendazole, mebendazole and thiabendazoles which are widely used as anthelmintic agents contains Benzofuranle core as an active pharmacopore [2]. More importantly Benzofuranle derivative 5,6-dimethyl-1-(α-D-ribofuranosyl)Benzofuranle is a basic constituent of vitamin B12 [3]. A large spectrum of Benzofuranle derivatives have been studied for their antibacterial efficacy [4], antiviral [5], anticancer [6], antiprotozoal [7], analgesic [8], anti-inflammatory [9], antipyretic [10] and antiangeogenesis [11] activity. Quinazoline and its derivatives showed promising biological activity, acted as potent cytotoxic agents. Substituted quinazolines have exhibited anticancer, fungicidal, anti-inflammatory, anti-hypertensive and analgesic properties. Benzofuranles fused with quinazolines resulting in the formation of Benzofuran-quinazoline motifs are shown to exhibit enhanced biological activity of the latter.

DihydroBenzofuran [1,2-c] quinazoline (BIQ): structural isomers of Schiff base counterparts are generated by the reaction of 2- amino phenyl Benzofuranle (AMPB) with substituted aromatic aldehydes. During the course of synthesis of Schiff base, Benzofuranle with free NH groups undergoes oxidative cyclocondensation with azomethine of the Schiff base generated in situ via a prototropictautomerism [12] to yield BIQ (Scheme 2.1-2.4). Over the past few decades several attempts have been made for the synthesis of BIQ owing to their excellent biological activity and internal fluorescence property [13]. BIQ's is being a remarkable fluorophore used in various fields from heavy metal ion detection in water sources [14] to metal ion sensing in human

body [15]. BIQ's is acting as biosensors will be helpful in studying drug delivery and drug metabolism after its administration [16]. BIQ fluorescent sensors have many advantages like high selectivity, specificity and easy synthetic procedure [17]. Recent observations reveal the fact that selection of chemosensor for the detection of metal ions depending upon the nature of the metal ion and basicity of the fluorescence probe and also the pH and solvents [18]. The applicability of the fluorescent property of the BIQ's has been further explored for the intracellular detection of metal ions. The cells are pretreated with the metal ions, and after the addition of fluorescent probe, the cell lines are observed under fluorescence microscope. The absence of fluorescence indicated that the compounds can permeate through the cell wall and interact with metal ions [19].

Fused heterocyclic compounds such as Benzofuranle-quinazoline, indolequinazolines and many other moieties showed enhanced antimicrobial activity. Rohini et al. [20] synthesized various 6-arylBenzofuran [1,2-c] quinazoline and systematically characterized and studied their antimicrobial efficacy for six bacterial and fungal stains. Results reveals that all the synthesized compounds show moderate to good results against all the microbial strains. Bubbly et al. [21] have synthesized many Benzofuran [1,2-c] quinazoline derivatives and structurally characterized by various spectroscopic techniques and single crystal studies; biological efficacy for the synthesized compounds are also reported. 1H and 13C NMR spectra support for the formation of cyclized product and it is further confirmed by X- ray crystallographic study. Structural analysis reveals that dihydropyrimidine ring possess a skew- boat conformation with the phenyl ring attached to it. Antibacterial results suggest that high toxicity when compared to standard one, but showed moderate results against fungus yeast.

In the treatment of various diseases related to inflammation, Tumor Necrosis Factor –Alpha (TNF-α) a pro-inflammatory agent found to be associated with tumor cells growth. Galarce et al. [22] have synthesized 6-arylBenzofuran [1, 2-c] quinazoline derivatives as inhibitor for the TNF-α secretion with fewer toxic levels, thereby providing protein biologists a new potential alternatives in treatment of diseases associated with inflammation.

Y. A. Resto et al. [23] have screened medicines for malaria venture (MMA) box for identification of inhibitors of protozoan parasite Perknisusmarinus, which was responsible for dermo disease – main obstacle for the declining of oyster population. Results found, Benzofuran [1,2-c] quinazoline derivative with IC50 of 2.08 μM giving a moderate activity.

The ethidium bromide displacement assay is carried out to determine the competitive binding of synthesized compound to DNA. Lyakhova et al. [24] synthesized Benzofuran [1,2-c] quinazoline and phenylbenzoimidazole and checked for thier affinity to bind DNA by ethidium displacement assay. Log ka values for compounds containing Benzofuran [1,2-c] quinazoline are higher than that for the corresponding phenylBenzofuranle, due to the planar nature of the latter than the former.

EXPERIMENTAL

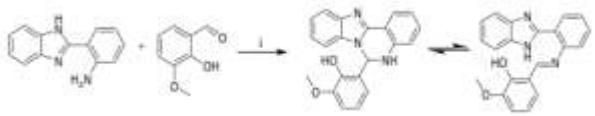
1. MATERIALS

2-(1H-benzoimidazol-2-yl)-phenylamine, ortho-vanillin, syringaldehyde, 5- chlorosalicylaldehyde and 5-bromo-2-hydroxy-3-methoxy-benzaldehyde were procured from Sigma Aldrich Chemicals Pvt. Ltd. Bengaluru. All the solvents used were of analytical grade. Solvents were dried and purified before their use according to the standard procedures.

2. SYNTHESIS OF LIGANDS L1-L4

2.1. Preparation of 2-(5,6-Dihydro-benzo[4,5]imidazo[1,2-c]quinazolin-6-yl)- 6-methoxy-phenol (L1)

To an ethanolic solution of 2-(1H-benzoimidazol-2-yl)-phenylamine (5 millimoles, 1.04 g) ortho-vanillin (5 millimoles, 0.76 g) and catalytic amount of glacial acetic acid were added, the reaction mixture was refluxed on a water bath for 4 h. The pale yellow solid that formed upon cooling, was filtered off and dried under vacuum at room temperature. The obtained compounds are in equilibrium. The synthetic route of Schiff base L1 is depicted in Scheme 2.1.



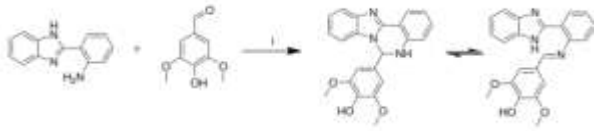
Scheme 2.1: Synthetic route of L1

Ligand (L1): yield: (89%). m.p 184-186 °C. IR ν (cm-1): 1713, m (C=N, Benzofuranle), 1360 (NH, Benzofuran [1, 2-c] quinazoline), 3386 (Ph-OH), ESI–MS m/z: 343.38 [M+1]+ . Anal.calcd. for [C21H17N3O2] (%) C, 73.46; H, 4.99; N, 12.24.Found C, 73.64; H, 5.12; N, 12.54. 1H NMR 9.364 (S, 1H, OH); 7.915(d, 1H, J= 7.5Hz, ArH); 7.60 (d, 1H, J= 7.5Hz ArH); 7.252-7.039 (m, 5H, ArH); 7.188(s, 1H, -NH-); 6.872-6.747 (m, 3H, ArH); 6.558 (t, 1H, J= 7.9Hz, ArH); 6.279 (d, 1H, J= 7.59 Hz, -CH-, sp 3); 3.777(s, 3H, OCH3).13C NMR 148.186, 147.564, 144.301, 143.800, 143.671, 133.297, 131.924, 127.988, 124.988, 122.529, 122.354, 119.691, 118.977, 118.249,

118.211, 115.138, 112.421, 111.844, 110.546, 63.072, 56.470.

2.2. Preparation of 4-(5,6-Dihydro-benzo[4, 5]imidazo[1,2-c]quinazolin-6-yl)- 2,6-dimethoxy-phenol (L2)

A catalytic amount of glacial acetic acid was added to a mixture of ethanolic solutions of 2-(1H-benzoimidazol-2-yl)-phenylamine (5 millimoles, 1.04 g) and syringaldehyde (5 millimoles, 0.91g); the reaction mixture was then heated on a water bath for 5 h. The pale yellow solid that formed upon cooling, was filtered off and dried under vacuum at room temperature. The synthetic route of new Schiff base ligand (L2) is depicted in Scheme 2.2. Single crystal suitable for X-ray was obtained from slow evaporation of methanol- dichloromethane solution.

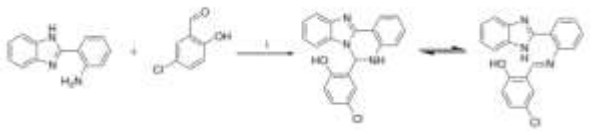


Scheme 2.2: Synthetic route of L2

Ligand (L2): yield: (85%). m.p 180-182 °C. IR v (cm-1): 1720, m (C=N, Benzofuranle), 1365 (NH, Benzofuran [1, 2-c] quinazoline), 3386 (Ph-OH), ESI– MS m/z: 374.03 [M+1]+ . Anal.calcd. for [C22H19N3O3] (%) C, 70.76; H, 5.13; N, 11.25; Found C, 70.64; H, 6.12; N, 11.54. 1H NMR 8.612 (s, 1H, OH); 7.943 (d, 1H, J=8Hz, ArH); 7.616 (d,1H,J= 8.8 Hz, ArH); 7.415 (s, 1H, J= 8.8Hz ArH); 7.261 (t, 1H, J= 7.2 Hz, ArH); 7.416 (t, 1H, J= 8.4Hz ArH); 7.053 (t, 1H, J=7.2 Hz, ArH); 6.882-6.787 (m, 4H, ArH); 6.699 (s, 1H, -CH-, sp 3); 4.077 (s, 1H, -NH-); 3.774 [s, 6H, 2(OCH3)]. 13C NMR 148.513, 147.784, 144.369, 144.225, 137.054, 133.487, 131.946, 130.080, 125.056, 122.445, 122.339, 119.046, 118.682, 115.229, 112.542, 111.290, 105.067, 111.844, 69.446, 56.530.

2.3. Preparation of 4-Chloro-2-(5,6-dihydro-benzo[4,5]imidazo[1,2-c] quinazolin-6-yl)-phenol (L3)

To an ethanolic solution of 2-(1H-benzoimidazol-2-yl)-phenylamine (5 millimoles, 1.04 g), 5-chlorosalicylaldehyde (5 millimoles, 0.78 g) and a catalytic amount of glacial acetic acid were added; the reaction mixture was then heated on a water bath for 5 h. The pale yellow solid that formed upon cooling was filtered off and dried under vacuum at room temperature. The synthetic route of new Schiff base ligand (L3) is depicted in Scheme 2.3. Single crystal suitable for X-ray was obtained from slow evaporation of methanol- dichloromethane mixture.

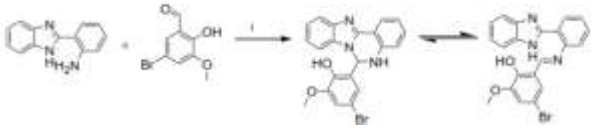


Scheme 2.3: Synthetic route of L3

Ligand (L3): yield: (89%). m.p 158-160 °C. IR v (cm-1): 1710, m (C=N, Benzofuranle), 1380 (NH, Benzofuran [1, 2-c] quinazoline), 3386 (Ph-OH), ESI– MS m/z: 347.99 [M+1]+ , 349.99 [M+2]+ . Anal.calcd. for [C20H14ClN3O] (%) C, 69.07; H, 4.06; N, 12.08; Found C, 69.43; H, 4.60; N, 12.93. 1H NMR 10.457 (s, 1H, OH);7.95 (d, 1H, J=6.8Hz, ArH); 7.646 (d, 1H, J=8Hz, ArH); 7.298 (s, 1H, -HN-); 7.236-7.085 (m, 6H, ArH); 6.933 (d, 1H, J= 8.8Hz ArH); 6.862 (d, 1H, J= 8 Hz, ArH); 6.798 (t, 1H, J= 7.6Hz, ArH); 6.648 (d, 1H, J=2.4 Hz, -CH-, sp 3); 13C NMR 153.893, 147.579, 144.253, 143.565, 133.123, 132.068, 130.194, 128.425, 126.384, 125.026, 122.931, 122.749, 122.590, 119.122, 118.446, 118.143, 115.176, 111.829, 110.546, 63.345.

2.4. Preparation of 4-Bromo-2-(5,6-dihydro-benzo[4,5]imidazo[1,2-c] quinazolin-6-yl)-6-methoxy-phenol (L4)

A catalytic amount of glacial acetic acid was added to an ethanolic solution of 2-(1H-benzoimidazol-2-yl)-phenylamine (5 millimoles1.04 g) and 5-bromo-2-hydroxy-3-methoxy-benzaldehyde (5 millimoles, 1.155g); the reaction mixture was then heated on a water bath for 5 h. The yellow solid that formed upon cooling was filtered off and dried under vacuum at room temperature. The synthetic route of new Schiff baseligand (L4) is depicted in Scheme 2.4. Single crystal suitable for X-ray was obtained from slow evaporation of methanol- acetonitrile mixture.



Scheme 2.4: Synthetic route of L4

Ligand (L4): yield: (85%). m.p 158-160 °C. IR v (cm-1): 1725, m (C=N, Benzofuranle), 1375 (NH, Benzofuran [1, 2-c] quinazoline), 3386 (Ph-OH), ESI– MS m/z: 422.27 [M]+ , 423.923 [M+2]+ . Anal.calcd. for [C21H16BrN3O2] (%) C, 59.73; H, 3.82; N, 9.95; Found C, 59.93; H, 4.02; N, 10.13. 1H NMR 9.689 (s, 1H, OH);7.92 (d, 1H, J=8.8Hz, ArH); 7.617 (d, 1H, J=8Hz, ArH); 7.278 (s, 1H, -HN-); 7.244-6.672 (m, 8H, ArH); 6.406 (d, 1H, J=2 Hz, -CH-, sp 3); 3.797 (s, 3H,OCH3) 13C NMR 149.370, 147.344, 144.248, 143.443, 143.329, 133.100, 132.053, 128.812, 125.010, 122.711, 122.544, 120.510, 119.076, 118.386, 115.365,

115.107, 111.586, 110.455, 110.433, 62.761, 56.796.

RESULTS AND DISCUSSION

All the prepared compounds are stable at room temperature, non-hygroscopic, insoluble in water but soluble in methanol, ethanol, DMF and DMSO.

1. IR spectral studies

The important diagnostic bands in the IR spectra were assigned and the bands positions were compiled in the synthesis part. The infrared spectra for the ligands L1-L4 are as shown in Figure 1-4. A medium band at 1710-1725 cm-1 for ligands was assigned to the C=N of Benzofuranlering. A characteristic peak for Benzofuran [1,2-c] quinazoline ring with the tertiary nitrogen atom was appeared in the region 1360-1380 cm^{-1} and the absence of signals corresponding to –NH of imidazolyl ring and CH=N group were supports the Benzofuranquinazoline ring structure in the infrared spectra of L1-L4. A broad peak in the range 3300-3400 cm^{-1} indicates the presence of hydroxyl group. The peak corresponding to phenolic v(C-O) stretching frequency was occurred at 1270 cm-1 for all the ligands.

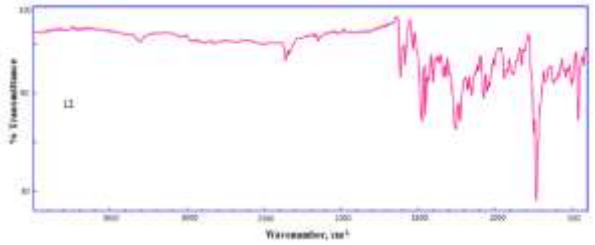


Figure 1: IR spectrum of L1

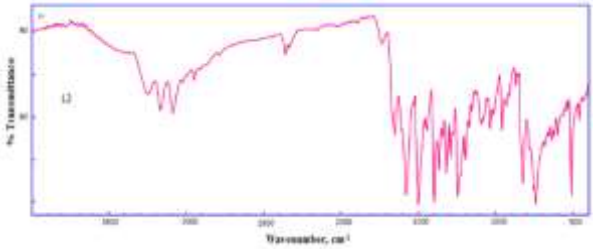


Figure 2: IR spectrum of L2

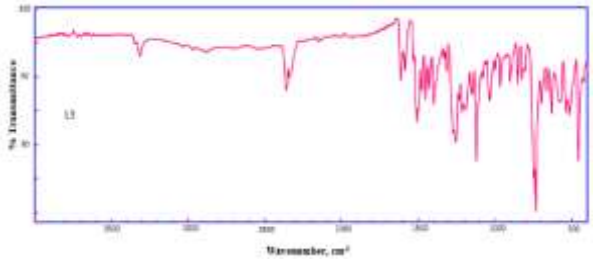


Figure 3: IR spectrum of L3

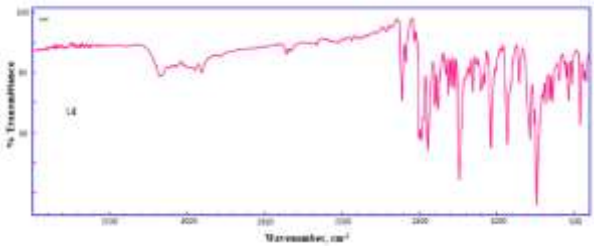


Figure 4: IR spectrum of L4

2. NMR investigations

^{1}H NMR and ^{13}C NMR spectral results of the ligands L1- L4 gives an insight into the structure and are in close agreement with the results obtained from IR and X-ray crystal studies. The 1H NMR spectrum of each ligand (L1-L4) (Figure 5, 7, 2.9 and 11), show signals at δ 6.279, 6.699, 6.648 and 6.406 ppm respectively corresponding to the sp^{3} carbon atom and the signals at δ 7.188, 4.077, 7.298 and 7.278 ppm for ligands L1 - L4 corresponds to NH of Benzofuran [1,2-c]quinazoline or dihydropyrimidine ring. A broad singlet peak at δ 9.364, 8.612, 10.457 and 9.689 ppm (s, OH) corresponds to OH proton in L1 - L4. The sharp signals at δ 3.777, 3.774, 3.797 ppm corresponding to methoxy groups for ligands L1, L2 and L4, respectively. The aromatic protons were appeared in the region between δ 7.92-6.270, 7.943-6.787, 7.95-6.798 and 7.92-6.672 ppm for L1–L4, respectively. Furthermore, 1H NMR results are supported by 13C-NMR spectrum which displays the signals corresponding to the different non-equivalent carbon atoms. In the 13C-NMR of L1-L4 (Figure 6, 8, 10 and 12), show a signal at δ 63.072, 69.446, 63.345 and 62.761 ppm corresponding to sp 3 carbon in Benzofuran [1, 2-c]quinazoline ring in L1–L4, respectively and a signal at δ 56.470, 56.530 and 56.796 ppm due to methoxy group in L1, L2 and L4.

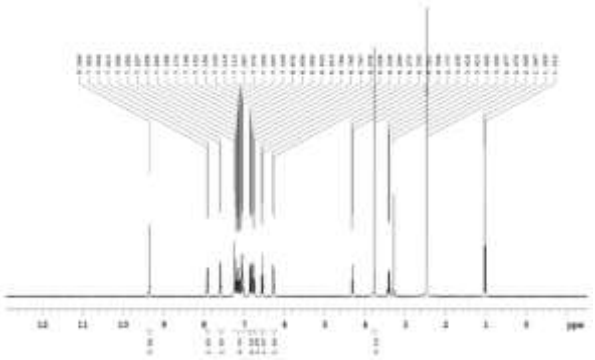


Figure 5: ^{1}H NMR spectrum of L1

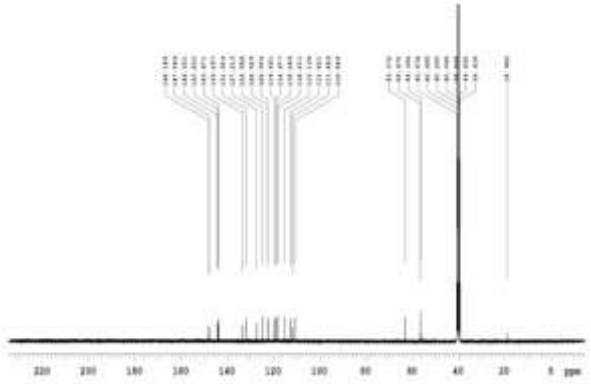


Figure 6: ^{13}C NMR spectrum of L1

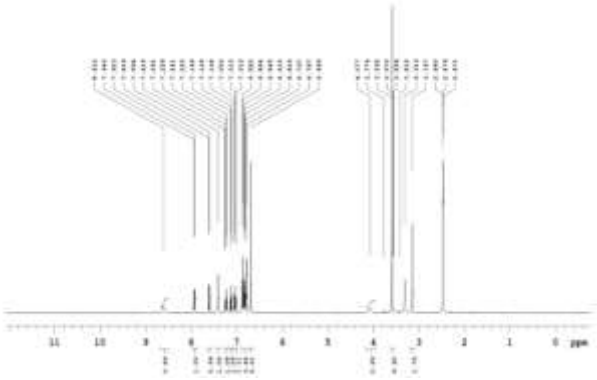


Figure 7: ^{1}H NMR spectrum of L2

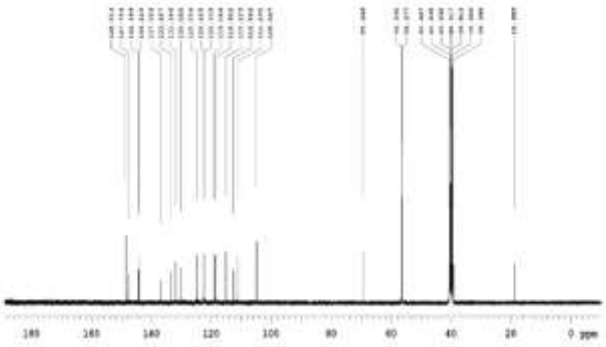


Figure 8: ^{13}C NMR spectrum of L2

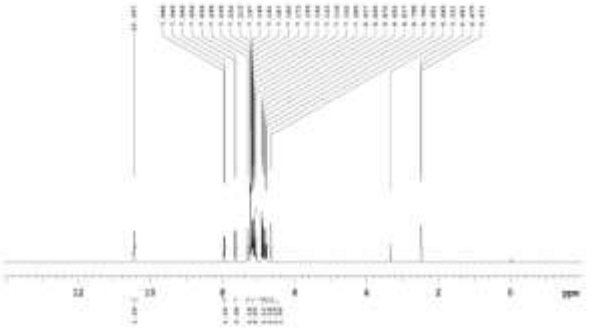


Figure 9: ^{1}H NMR spectrum of L3

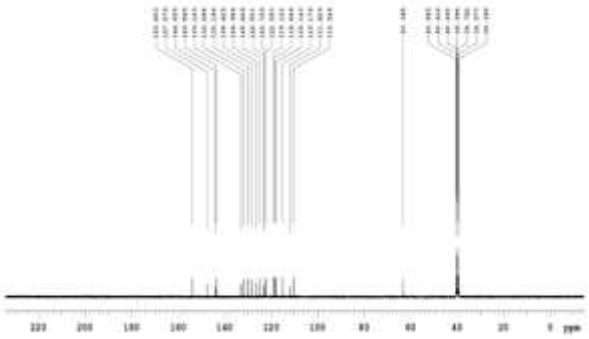


Figure 10: ^{13}C NMR spectrum of L3

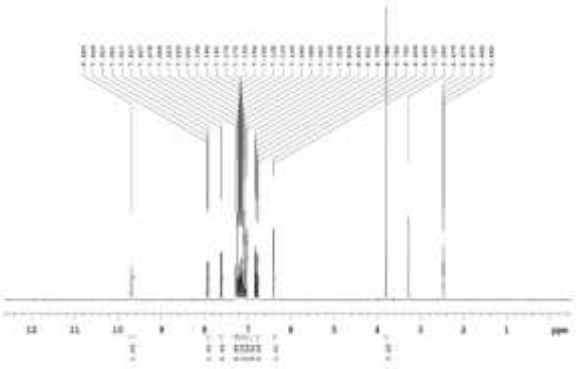


Figure 11: ^{1}H NMR spectrum of L4

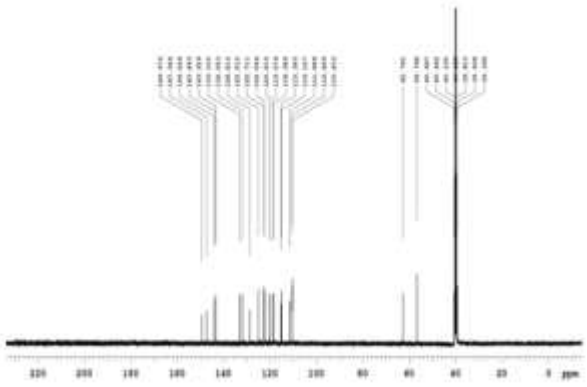


Figure 12: ^{13}C NMR spectrum of L4

BIOLOGICAL ACTIVITY

1. Antioxidant results: DPPH - Scavenging activity

The free radical scavenging activity of the new ligands L1-L4 was assessed by the DPPH assay. In the DPPH assay, the ability of the investigated BIQ ligand, to act as hydrogen atom donor or electron transfer in conversion of DPPH radical into its reduced form DPPH-H was investigated. The ability of the compounds to effectively scavenge DPPH radical, that was measured and it is compared with that of ascorbic acid as standard. A change in color of the reaction mixture from deep purple (DPPH radical) into the yellow colored (reduced DPPH-H) indicates its antioxidant activity, and its potency was screened

by measuring the absorbance at 517 nm. The smaller the absorbance values of the reaction mixture indicates a higher free radical scavenging activity. The IC50 value of the L1-L4 was comparable to the standard, ascorbic acid. However, the activity is highest for L4 and lowest for L1 following the order L4>L2>L3>L1, higher activity for L4 is due to the presence of electron donating methoxy (-CH_3) group along with phenolic group and bromine in its structure. Several studies suggested that the presence of halogens enhances the cellular antioxidant activity by increasing lipophilicity and cell membrane solubility of a drug. However, the least activity for L1 is due to the absence of any halogens in it. The IC50 values of all the ligands are presented in Table 1.

Table 1: Antioxidant capacity (IC_{50}) of all the synthesized ligands

Compounds	IC_{50} (µg mL^{-1}) ± S.D*
AA	25 ± 0.54
L1	98 ± 0.60
L2	74 ± 0.34
L3	82 ± 0.45
L4	65 ±0.64

2. Antimicrobial results

In the present study, in vitro antibacterial activity for the synthesized compounds was evaluated against one Gram-negative bacteria E.coli, and three Grampositive bacteria's such as S. aureus, B. subtilis and L. monocytogenes and in vitro antifungal activity by treating two fungi niger, and flavus. A significant range of zone of inhibition was observed around individual wells. The zone of inhibition around each well was measured upon zone size in millimeter (mm). The measured growths of inhibitions against both Gram negative and positive microorganisms are listed in Table 2.

Table 2: Results of antimicrobial activity of L1-L4

Compound	Zone of inhibition (mm)*					
	Bacteria				Fungi	
	S. aureus	*B. subtilis*	*L. monocytogenes*	*E. coli*	*A. niger*	*A. flavus*
L1	8	6	8	10	13	10
L2	10	8	10	11	16	13
L3	11	10	12	12	15	12
L4	**14**	**11**	**14**	**15**	**17**	**14**
Ampicillin	24	25	28	27	-	-
Fluconazole	-	-	-	-	20	20

Minimum inhibitory concentration (MIC) value of synthesized compounds was determined. The bacterial cultures were grown overnight; the concentration was adjusted and determined by McFarland turbidity standard. Serial dilution method was carried out to investigate MIC of L1-L4 in microtitre plate assay. All the synthesized compounds exhibited observable range of MIC against all Gram positive and negative bacteria Table 3. Of all the synthesized ligands, L4 showed better antimicrobial activity may be due to the presence of –bromo group in its structure. Higher activity of the ligands may be explained by Overtones concept of cell permeability the lipid layer surrounding the cell allows only lipid soluble compound to pass through it. The above results are suggested that the following compounds can be used in the treatment of resistant bacteria, towards the development of novel antimicrobial drug.

Table 3: Minimum inhibitory concentration results

Compound	Range of concentration (µg/mL)*					
	Bacteria				Fungi	
	S. aureus	*B. subtilis*	*L. monocytogenes*	*E. coli*	*A. niger*	*A. flavus*
L1	110	120	130	120	115	124
L2	92	95	100	100	113	110
L3	98	95	90	95	99	102
L4	**75**	**80**	**91**	**93**	**80**	**75**
Ampicillin	25	25	25	25	-	-
Fluconazole		-	-	-	45	45

CONCLUSION

The synthetic procedure followed herein for the synthesis of Schiff base analogues is clean, high yield and high purity. The structures of the synthesized ligands L1, L2, L3 and L4 were determined by various spectroscopic techniques. Infra-red spectroscopy gives the details about the presence of functional groups. 1H and 13C NMR spectroscopy are useful in understanding the electronic environment around hydrogen and carbon atoms, which will be helpful in prediction of structure. UV-vis spectroscopy is a powerful tool to give the various transitions present in the synthesized compounds. The details about the presence of halogen in synthesized compounds by showing isotopic peaks in case of L3 and L4 are obtained by mass spectroscopy. However, the study of crystal structure for L2, L3 and L4 gives more structural insights and the results are matches with all other studied spectroscopic techniques. As per the biological activity is concerned, the synthesized ligands showed promising results as a good antimicrobial agents; good antioxidant agents as revealed by the DPPH scavenging assay. Of all the ligands under study, L4 was found to be a good candidate for further study for its use in medicinal field.

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