SYNTHESIS AND ANTIBACTERIAL PROPERTY STUDIES OF THE N'-(4-SUBSTITUTED) ISONICOTINOHYDRAZIDES AND THEIR COPPER (II) COMPLEXES

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ABSTRACT

A series of Schiff base ligands (**L_1-L_4**) prepared by condensation of isonicotinic acid hydrazide with substituted benzaldehydes and their corresponding copper(II) complexes (**L_1A-L_4A**) had been synthesized and characterized based on IR, ^{1}H NMR and electronic absorption spectroscopy as well as by molar conductivity and elemental analyses. The *in-vitro* antimicrobial activity of the compounds against *Staphylococcus aureus, Enterococcus feacalis*, *Escherichia coli* and *Pseudomonas aeruginosa* studied using agar ditch method indicated that the copper complexes exhibited higher activity than the corresponding ligands. The antimicrobial activity of both the ligands and complexes was dependent on the electronic effect of the halogen substituent, which decreased in the order F > Cl > Br.

Keywords: *N*-(4-substitutedbenzylidene) isonicotinohydrazide, Halogen Schiff Bases, Copper (II) Complexes, Antimicrobial Activity.

INTRODUCTION

The coordination properties of acid hydrazides (R=CO-NH-NH$_2$) and their corresponding Schiff bases, *viz*, the aroylhydrazones (R-CO-NH-N=CH-R') with transition metals have been of interest due to the different bonding modes and the ready chelation displayed by the ligands with transition metals including transition metal ions present in the living system (Savini *et al.*, 2002; Abou-Melha 2008). These compounds also exhibit interesting biological properties and are useful in a wide range of biological applications as enzyme inhibitors, anti-depressants, anti-inflammatory, anti-mycobacterial and anti-cancer agents (Cui *et al.*, 2012; Swant *et al.*, 2013; Ramadevi *et al.*, 2014). Isonicotinic acid hydrazide (INH), a first line drug in the management of tuberculosis (Blair *et al.*, 1985) is of particular interest as it readily forms Schiff bases with aromatic aldehydes (Hearn and Cyanomon 2004; Lourenco *et al.*, 2008; Hearn *et al.*, 2009; Torres, *et al.*, 2011). The biological activities of the isonicotinoylhydrazones are further improved upon coordination with transition metal ions (Deepa and Aravindakshan, 2004; Kriza et al., 2010). The presence of a halogen atom in organic compounds has profound effect on the chemical, physical and biological properties of such compounds. For example, halogenation has been found to enhance the antagonistic or agnostic effects of drug candidates by improving their oral absorption and brain barrier permeability and therefore their medical application (Wong *et al.,* 2013). In continuation of efforts in understanding effects of subtle electronic variations on biological activity of Schiff base metal complexes, it is reported herein the effect of halogenation on the biological activity of isonicotinoylhydrazones and their corresponding copper (II) complexes.

MATERIALS AND METHODS

Experimental

All commercially available chemicals were obtained from Aldrich Chemical Ltd. Solvents such as ethanol and *N, N*-dimethylformamide (DMF) were of spectroscopic or analytical grade and used without further purification. Melting points were determined on a Stuart SMP3 melting point apparatus and are uncorrected. Conductivity measurements for 10^{-3} M solutions of the complexes in DMF were obtained using a digital conductivity meter DDS-307. IR spectra were recorded as powders on a FTS 7000 series Digilab Win-IR Pro ATR spectrometer with a diamond ATR (attenuated total reflectance)

accessory by using the thin-film method. ^{1}H NMR spectra were recorded on a Varian 300 MHz spectrometer as DMSO-d_6 solution and are referenced relative to the solvent peaks. Elemental analyses were performed with a Perkin -Elmer 2400 CHNS/O analyzer. Electronic spectra were recorded at room temperature using freshly prepared solutions of the Schiff bases on a Cecil Super Aquarius 9000 series UV-Vis spectrophotometer with a 1 cm quartz cell.

Typical Synthesis of Schiff Bases ($L_1 - L_4$)

To a solution of isonicotinic acid hydrazide (10 mmol.) in ethanol (20 mL) was added a solution of the desired benzaldehyde (10 mmol.) in ethanol (20 mL). The reaction mixture was left to stir at 60°C for 8 h and then allowed to cool to room temperature. The resulting precipitate was collected by filtration, and recrystallized from ethanol.

N-Benzylideneisonicotinohydrazide (L_1): White solid (52%), mp 201-203°C; ν_{max} (ATR): 3198, 1687, 1599, 1562 cm^{-1}; δ_H (300 Mz, DMSO-d_6): 7.46-7.51 (3H, m, 2H-pyridine, 1H-Ar), 7.74-7.84 (4H, m, H-Ar), 8.48 (1H, s, HC=N), 8.75-8.80 (2H, t, J = 3 Hz, H-pyridine), 12.09 (1H, s, H-NH).

Anal. calcd for $C_{13}H_{11}N_3O$: C, 69.32, H, 4.92, N, 18.66. Found: C, 69.62, H, 4.84, N, 18.84.

N-(4-Fluorobenzylidene) isonicotinohydrazide (L_2): Light Yellow (56%), mp. 197-199°C; ν_{max} (ATR): 3190, 1655, 1600 cm^{-1}; δ_H (300 MHz, DMSO-d_6): 7.34 (2H, d, J =*9.3* Hz, H-pyridine), 7.79-7.84 (4H, dd, J= *3.0* and 6.0 Hz, H-Ar), 8.47 (1H, s, HC=N), 8.78-8.80 (2H, d, J =6.0 Hz; H-pyridine), 12.07 (1H, s, H-NH).

Anal. calcd for $C_{13}H_{10}FN_3O$: C, 64.19, H, 4.14, N, 17.28. Found: C, 63.96, H, 4.20, N, 17.84.

N-(4-Chlorobenzylidene) isonicotinohydrazide (L_3): White solid (72%), mp. 224°C; ν_{max} (ATR): 3007, 1633, 1610 cm^{-1}; δ_H (300 MHz, DMSO-d_6): 7.53-7.56 (2H, d, J = 8.4 Hz, H-pyridine), 7.77-7.83 (4H, m, H-Ar), 8.46 (1H, s, HC=N), 8.78-8.80 (2H, d, J = 5.7 Hz, H-pyridine), 12.14 (1H, s, H-NH).

Anal.calcd for $C_{13}H_{10}ClN_3O$: C, 60.12, H, 3.88, N, 16.18. Found: C, 60.06, H, 4.18, N, 16.24

N-(4-Bromobenzylidene) isonicotinohydrazide (L_4): Light Yellow solid (52%), mp. 197-199°C; ν_{max} (ATR): 3194, 1665, 1589 cm^{-1}; δ_H (300 MHz, DMSO-d_6): 7.66-7.70 (4H, m, H-Ar), 7.72-7.83 (2H, d, J = 6 Hz, H-pyridine), 8.44 (1H, s, HC=N), 8.78-8.80 (2H, d, J = 5.1 Hz, H-pyridine), 12.14 (1H, s, H-NH).

Anal. calcd for $C_{13}H_{10}BrN_3O$: C, 51.34, H, 3.31, N, 13.82. Found: C, 51.99, H, 3.40, N, 13.67.

Typical Procedure for the Synthesis of Copper (II) Complexes $L_1A - L_4A$.

A solution of $CuCl_2.2H_2O$ (2.2 mmol) in ethanol (10 mL) was added dropwise to a hot solution of the desired ligand (4 mmol) in ethanol (30 mL) with constant stirring. The mixture was refluxed for 3 h and allowed to cool to room temperature. The resultant precipitate was collected by filtration, washed with cold ethanol and dried under *reduced pressure* over anhydrous $CaCl_2$.

The following complexes were prepared in this fashion:

L_1A: Green solid (41%), mp. 268-269°C; ν_{max} (ATR): 1669, 1604, 1521, 689, 587 cm^{-1}.

Anal. calcd for $C_{28}H_{26}CuN_6O_3$: C, 60.26, H, 4.97, N, 15.06. Found: C, 59.87, H, 5.86, N, 15.29

L_2A: Light green solid (44 %), mp. 296-299°C; ν_{max} (ATR): 1606, 1575, 1433, 640, 593 cm^{-1}.

Anal. calcd for $C_{28}H_{24}CuF_2N_6O_3$: C, 57.97, H, 4.07, N, 14.15. Found: C, 58.09, H, 4.01, N, 14.11.

L_3A: Deep green solid (46 %), mp, 289-290 °C; (270°C). ν_{max} (ATR): 1654, 1595, 1414, 701, 624 cm^{-1}.

Anal. calcd for $C_{28}H_{28}CuCl_2N_6O_5$: C, 50.72, H, 4.26, N, 12.68. Found: C, 51.05, H, 4.73, N, 12.76.

L_4A: Deep green solid (50%), mp. 290-292°C; ν_{max} (ATR): 3343, 1659, 1612, 1419, 651, 620 cm^{-1}.

Anal. calcd for $C_{28}H_{28}CuBr_2N_6O_5$: C, 44.73, H, 3.75, N, 11.18. Found: C, 44.14, H, 3.42, N, 10.32.

Biological Activity

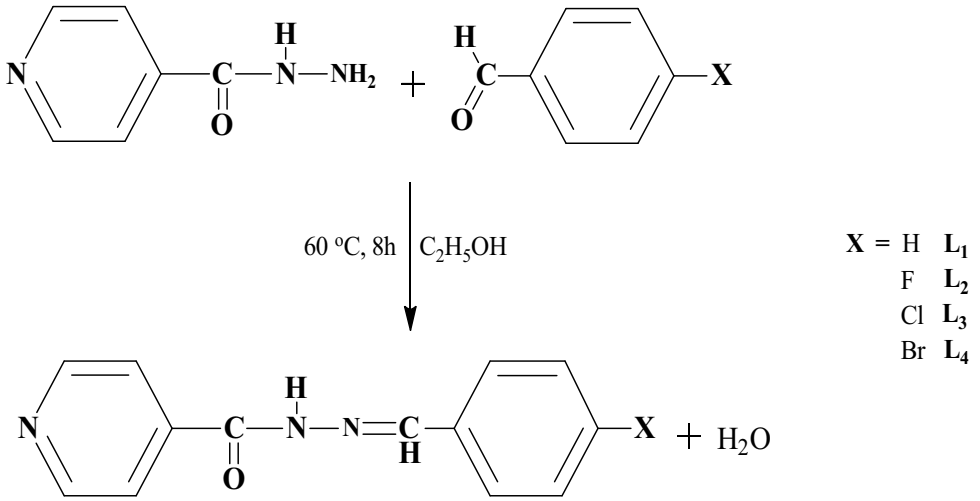
The *in-vitro* antimicrobial activity of the compounds prepared in this study was investigated against standard strains of *Staphylococcus aureus* (ATCC 25923), *Entercoccu*s

feacalis (ATCC 29212), *Pseudomonas aeruginosa* (ATCC 27853) and *Escherichia coli* (ATCC 25922) using a stock solution containing 5 mg of each compound dissolved in 1 mL *N,N*-dimethylformamide (DMF) from which serial dilutions were made. A double layered aseptically prepared Muller Hinton agar plate was flooded with standardized (0.5 McFarland) test microorganism and allowed to stand for two minutes. A sterilized cork borer (1 mm) was used to make four radial wells, which were filled with the test compounds using a micropipette and then incubated at 37°C for 24 h. During this period, the test compound diffused and the growth of the inoculated microorganism was affected. The diameter of the zone of inhibition surrounding each well was measured and recorded. In order to clarify any participating role of the solvent in the biological screening, control test was included using the solvent alone to fill the control well.

RESULTS AND DISCUSSION

Synthesis

The isonicotinohydrazone ligands $\mathbf{L_1}$–$\mathbf{L_4}$ were synthesized by condensation reaction of isonicotinic acid hydrazide and the corresponding benzaldehyde namely: benzaldehyde **(L_1),** 4-fluorobenzaldehye **(L_2)**, 4-chlorobenzaldehyde **(L_3)** and 4-bromobenzaldehyde **(L_4)** in ethanol at 60ºC (Scheme 1).



Scheme 1: Synthesis of ligands L_1 - L_4

Reaction of the ligands with copper (II) chloride in ethanol afforded the desired complexes $\mathbf{L_1A}$ – $\mathbf{L_4A}$. The purity of the compounds was confirmed by sharp melting points and micro-analytical data.

Analytical and spectroscopic data for the compounds are summarized in Tables 1-3. An earlier report of the template synthesis of L_1 by Ramadevi and coworkers (2014) used $NiCl_2$ as template agent. However, it is known that template reactions produce complexes containing the template agents (Hossein *et al.*, 2008, Kaczmarek *et al.*, 2011), hence the compound obtained in the report should be the nickel complex of the Schiff base and not the Schiff base as reported by the authors. Also, the synthesis of L_3 and one-pot synthesis of copper acetate complex of L_3 were reported by Ababei *et al.* (2011) but the Schiff base was not characterized. In this paper, all the Schiff bases are obtained from the direct condensation reaction of the aldehydes and isonicotinic acid hydrazide and the compounds characterized using spectroscopic methods.

Table 1: Physical and analytical data of L_1-L_4 and L_1A-L_4A

Compound	Empirical formula	Mp. (°C)	Yield(%)	Elemental analysis Found/(Calculated)		
				C	H	N
L_1	$C_{13}H_{11}N_3O$	201-203	52	70.62 (70.91)	5.02 (5.00)	16.69 (16.54)
L_1A	$Cu(L_1A)_2.EtOH$	268-269	41	59.87 (60.26)	5.86 (4.70)	15.29 (15.06)
L_2	$C_{13}H_{10}FN_3O$	197-199	56	63.96 (64.19)	4.20 (4.14)	17.84 (17.28)
L_2A	$Cu(L_2A)_2.EtOH$	296-299	44	58.09 (58.61)	4.01 (4.07)	14.11 (14.15)
L_3	$C_{13}H_{10}ClN_3O$	224-226	72	60.06 (60.12)	4.18 (3.88)	16.24 (16.18)
L_3A	$Cu(L_3A)_2.EtOH$	289-290	46	51.05 (50.72)	4.73 (4.26)	12.76 (12.68)
L_4	$C_{13}H_{10}BrN_3O$	227-229	76	51.99 (51.34)	3.42 (3.31)	13.67 (13.82)
L_4A	$Cu(L_4A)_2.EtOH$	290-292	50	44.14 (44.73)	3.42 (3.75)	10.32 (11.18)

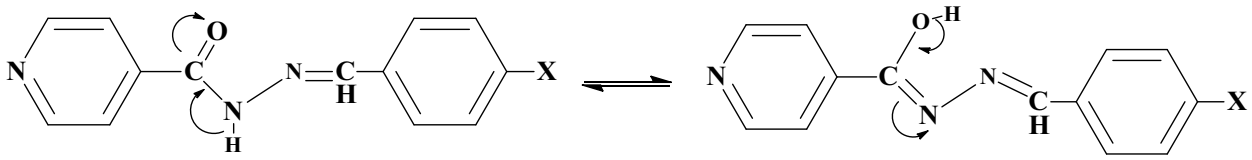
Table 2: Diagnostic IR (cm^{-1}) data for L_1-L_4 and L_1A-L_4A

Compound	υ **(NH)**	υ **(C=O)**	υ **(C=N)**	υ **(>C=N-N=C<)**	υ **(M-O)**	υ **(M-N)**
L_1	3198	1687	1599	-		-
L_1A	-	1669	1604	1521	689	587
L_2	3190	1665	1600	-	-	-
L_2A	-	1606	1575	1433	640	593
L_3	3007	1633	1610	-	-	-
L_3A	-	1654	1595	1414	701	624
L_4	3194	1655	1589	-	-	-
L_4A	-	1659	1612	1419	651	620

Table 3: Diagnostic ^{1}HNMR peaks for L_1-L_4

Compound	δ_H **(NH)**	δ_H **(H-pyridine)**	δ_H **(CH=N)**	δ_H **(H-Ar)**
L_1	12.09	8.75-8.80	8.48	7.74-7.84
L_2	12.07	8.78-8.80	8.47	7.79-7.84
L_3	12.14	8.78-8.80	8.46	7.77-7.83
L_4	12.14	8.78-8.80	8.44	7.66-7.70

The ligands prepared in this investigation have a potential to exist in tautomeric equilibrium (Figure 1). The ^{1}H NMR spectra of the Schiff base ligands in DMSO (DMSO-d_6) exhibit a singlet in the range 8.44–8.48 ppm assigned to the azomethine proton (HC=N-) group based on the literature precedent (Jain and Mishra, 2012). In addition to the pyridine proton signals which resonate as doublet at *ca.* 8.80 ppm (Deepa and Aravindakshan, 2004), the proton NMR spectra of compounds **L_1–L_4** reveal the presence of a signal in the region 12.07–12.14 ppm, which is attributed to the amide NH proton (Lourenco *et al.*, 2007). Based on the observed analytical data and literature precedents for the analogous systems, we envision that the compounds exist predominantly as the amide tautomer in the polar medium.



Amide tautomer Imidol tautomer

Figure. 1: Tautomeric equilibrium of the *N*-(4-substitutedbenzylidene)isonicotinohydrazide

The bonding mode of the ligands was elucidated by the comparison of IR spectra of the ligands with those of the corresponding Cu (II) complexes. The carbonyl absorption bands observed at ν_{max} 1633–1687 cm^{-1} in the IR spectra of the ligands shifted by a frequency ± 6–59 cm^{-1} upon coordination with the metal. This observation confirms involvement of the carbonyl oxygen in coordination to the metal (Joseph *et al*., 2012). The N-H bands observed in the region $\nu_{(NH)}$ 3007–3198 cm^{-1}, which are observed in the IR spectra of the free ligands are absent in the spectra of all the complexes and this observation in our view, suggest coordination of the potentially tautomeric ligands to the metal through the imidol oxygen as observed for the analogous N-isonicotinamido-2-furanketimine and N-isonicotinamido-5-methyl-2-furanketimine with the literature precedents (Singh and Kumar 2006; Wu *et al*., 2007). This is further supported by the presence of a new band in the region ν_{max} 1414–1521 cm^{-1} of the spectra of the complexes attributed to the azine group > C=N-N=C< (Sharma *et al*., 2010). The band observed in the region ν_{max} 1575–1612 cm^{-1}, due to the azomethine group of the ligands experienced a shift in frequency of about 5–25 cm^{-1} in the complexes thus suggesting metal–ligand bond formation through the azomethine nitrogen (Figure 2). The new bands in the region ν_{max} 640–701 and 587–624 cm^{-1}, which are assigned to $\nu_{(M-O)}$ and $\nu_{(M-N)}$ respectively (Usharani *et al*., 2012) further confirm the bidentate nature of the ligands with carbonyl-oxygen (C=O) and azomethine nitrogen (C=N-) as coordination sites.

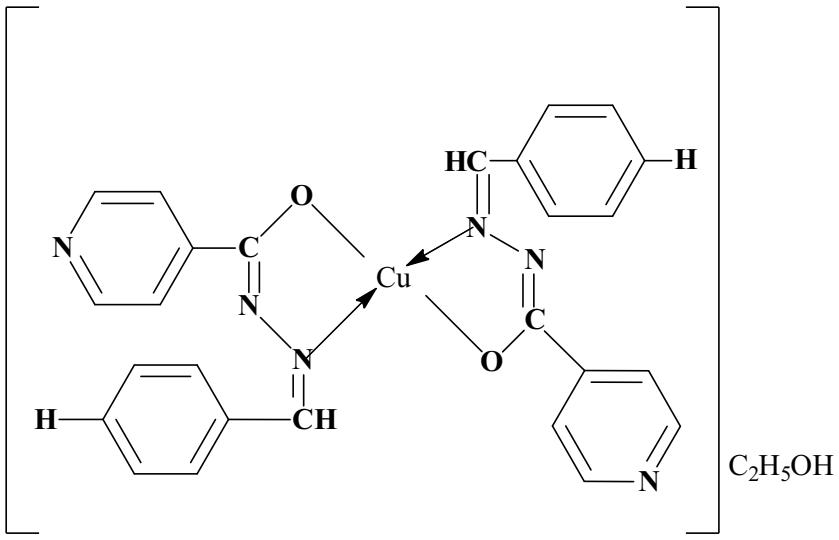


Figure 2: Proposed structure for compound [Cu $(L_1)_2$].EtOH **(**L_1A)

Electronic Absorption Spectra

The electronic absorption spectra of compounds **L_1–L_4** in DMF (Table 4) indicate that all Schiff base ligands exhibit the n-π*/ π- π*transition within the azomethine chromophore (-C=N-) at 32258–35088 cm^{-1} in line with literature precedent (Al-Sha'alan, 2007). The spectra of **L_1A** and **L_2A**, on the other hand, reveal the presence of bands in the region at 12675 - 18519 cm^{-1} due to the ^2A_1g–^2B_1g transitions characteristic of Cu(II) ion in a square-planar environment (Valent 2002; Mostafa and Haifaa 2007; Vanco *et al.,* 2008). The absorption bands 25253 cm^{-1} and 23810 cm^{-1} in the spectra of **L_3A** and **L_4A** are presumed to comprise of a series of overlapping absorption bands with the band due to d-d transition being completely concealed and essentially not easy to discern (Chohan *et al.*, 2006). However, based on available data a square planar geometry has been proposed for the complexes.

Table 4: Electronic spectra (cm^{-1}) and molar conductance of L_1 – L_4 and L_1A – L_4A

Compound	λ_{max}	Band assignment	Molar conductance
L_1	33003		-
	26738	n –π*	-
L_1A	12674	^2A_1g-^2B_1g	14
L_2	35088	n –π*	-
L_2A	18518	^2A_1g-^2B_1g	45
L_3	32355	n –π*	-
L_3A	29851	n –π*	36
	25253	CT	
L_4	32363	n –π*	-
L_4A	26462	n –π*	34
	23810	CT	

Biological Activity

The antimicrobial activities of the synthesized compounds were assayed in DMF solutions using the agar ditch method (Parekh *et al.*, 2005) with the solvent used as a negative control. The antibacterial results summarized in Table 5 show clearly that all the compounds (**L_1–L_4 and**

Table 5: Antibacterial activity of L1-L_4 and L_1A-L_4A

Compound	*S. aureus*				*E. feacalis*		*E. coli*				*P. aeruginosa*
	5[a]	2.5	1.25	0.62	5[a]	2.5-0.62	5[a]	2.5	1.25	0.62	5-0.62
L_1	12	10	9	0	0	0	0	0	0	0	0-0
L_1A	18	16	13	0	0	0	12	5	0	0	0-0
L_2	25	15	9	0	9	0	10	0	0	0	0-0
L_2A	30	15	9	0	13	0	16	12	11	0	0-0
L_3	11	5	0	0	0	0	0	0	0	0	0-0
L_3A	15	10	9	0	0	0	0	0	0	0	0-0
L_4	0	0	0	0	0	0	17	7	0	0	0-0
L_4A	7	7	5	0	0	0	10	6	0	0	0-0

Key: Inhibition values: 0 = not active; 1–5mm = less active; 6–11mm = moderately active; >12mm = highly active. concentration unit = mg/ml

L_1A-L_4A) exhibited some level of activity against *S. aureus* and none was active against *P. aeruginosa*. The metal complexes exhibit enhanced activity against the Gram positive and Gram negative bacteria studied except for **L_4A** which showed a slight decrease in activity against E. *coli*. The increased activity of the metal chelates can be explained on the basis of overtone's concept (Dharamraj *et al*., 2001) and chelation theory (Siddappa and Sunilkumar, 2013). The lipid membrane that surrounds the cell favours the passage of only lipid soluble materials which means lipophilicity is an important factor controlling the antimicrobial activity. Chelation of the ligands to the metal involves overlap of the ligand orbitals and partial sharing of the positive charge of the metal ion with the ligands thereby reducing the polarity of the metal ion. This interaction enhances the liposolubility of the complexes and allows for easy penetration of the complexes into the lipid membrane. The presence of a halogen substituent increases lipophilicity thereby improving bioavailability of the compound within the bacterial cell (Wong *et al*., 2013). The antibacterial activity of the compounds decreases in the order $L_2A > L_1A > L_3A > L_4A$. The decreasing electronegativity of the halogen with increase in size is reflected in lipophilicity of the complexes in order F > H > Cl > Br.

The increased antibacterial activity of the fluorinated compounds **L_2** and **L_2A** against *S. aureus, E. feacalis* and E. *coli* at all concentrations studied is in line with the high biological activity of fluorinated compounds. (Isanbor and O'Hagan, 2006). The small size and high electronegativity of the fluorine atom in a molecule decreases the basicity of fluorinated compounds thereby improving bioavailability (Rowley *et al*., 2001).

CONCLUSION

A series of halogenated Schiff bases of isoniazid and the corresponding copper (II) complexes have been prepared and their inhibitory activity against both Gram positive and Gram negative bacteria studied in this investigation. The copper (II) complexes have showed enhanced inhibitory activity towards bacterial strains studied compared to the free ligands. The biological activity of the compounds showed dependence on the nature of halogen substituent present with the fluorinated compounds exhibiting highest inhibitory effect. Further investigation of the fluorinated Schiff base and copper complex as promising compounds in the development of new anti-bacterial agents is on-going.

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