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Synthesis, Characterization and Antibacterial Activities of Polydentate Schiff Bases, Based on Salicylaldehyde

Yosef Bayeh[1,2], Fekiya Mohammed[3], Mamo Gebrezgiabher[1,2], Fikre Elemo[1,2], Mesfin Getachew[1], Madhu Thomas[1,2*]

[1]Department of Industrial Chemistry, College of Applied Sciences, Addis Ababa Science and Technology University, Addis Ababa, Ethiopia
[2]Center of Excellence in Nanotechnology, Addis Ababa Science and Technology University, Addis Ababa, Ethiopia
[3]Department of Food Engineering, College of Biological and Chemical Engineering, Addis Ababa Science and Technology University, Addis Ababa, Ethiopia

Email: *madhu.thomas@aastu.edu.et

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Abstract

Three Schiff bases L_1, L_2 and L_3 were synthesized by condensing salicylaldehyde with 4-aminoantipyrine, ethylendiamine and 2-aminophenol respectively and subsequently characterized by various physicochemical investigations. All the three compounds were screened for their *In-vitro* antibacterial activity against two gram positive bacteria, *Staphylococcus aureus* (S.A), *Staphylococcus epidermidis* (S.E) and two gram negative bacteria *Klebsiella pneumoniae* (K.P) and *Pseudomonas aeruginosa* (P.A) by agar diffusion method. On comparing the results obtained with the activity of commercially available antibiotics such as Ciprofloxacin and Chloramphenicol, the newly synthesized compounds showed comparable antibacterial activities. The solvent methanol exhibit activity against all bacterial species with IZs ranging from 8 ± 0.25 to 17 ± 0.29 mm while the standard antibiotics Ciprofloxacin and Chloramphenicol exhibited an activities with IZs varying from 21.3 ± 0.31 to 28.3 ± 0.32 and 26.3 ± 0.24 mm to 32.3 ± 0.23 mm, respectively. However, the newly synthesized Schiff bases L_1, L_2 and L_3 showed IZs ranging from 7.4 ± 0.23 to 32.5 ± 0.14, 3 ± 0.57 to 12 ± 0.28 and 10 ± 0.20 to 32 ± 0.36 respectively. Among the Schiff bases, L_3 showed the activity (32 ± 0.36) against S.E and P.A which is higher than the activity of standard antibiotics Ciprofloxacin and Chloramphenicol against the same bacterial strains. The results obtained revealed that all the synthesized Schiff bases exhibit appreciable antibacterial activity against all the bacteria species which potentially makes them, to apply as wide range antibacterial drugs, after further *in-vivo* cytotoxicity investigations. Their activity can also be further modified by changing the functionali-

ty of precursors for Schiff base condensation.

Keywords

Schiff Bases, Salicyaldehyde, Antibacterial Activity, *In-Vitro*

1. Introduction

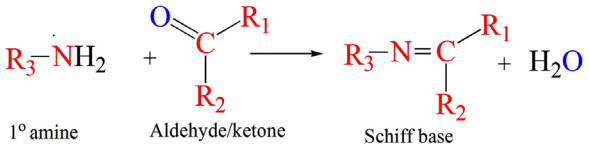
Schiff bases are the class of compounds, which are obtained by condensing primary amines and carbonyl compounds [1]. They are also known as an imine or azomethine, is an analogue of a ketone or aldehyde in which the carbonyl group (-C=O) is changed to imine or azomethine (-HC=N-) functionality on reacting with a primary amine (**Scheme 1**).

Since the discovery of Schiff base [2], it has drawn much attention due to the easy tailoring possibility of the compounds by incorporating different substituents in both amino and aldehydic precursors, which may bring about the variation in the fundamental properties of the synthesized products. The use of Schiff bases in biological or therapeutic applications as promising drug or biological probes has been investigated especially their antibacterial activities [3] [4] [5] [6].

There has been increasing interest on the binding ability of small molecules such as Schiff bases to DNA. Modern coordination chemistry is enriched by Schiff base ligands as metal complexes of Schiff bases are the most widely studied coordination compounds [7]. Increasing importance of Schiff bases as biochemical and analytical reagents are also well documented [8].

Many reports so far on Schiff bases have given rise to several new compounds, and some of them are biologically relevant. The ease with which the Schiff base are designed and prepared have made them to be referred as "fortunate ligands", with C=N linkage which is relevant for antibacterial, antifungal, antioxidant, anticancer, and diuretic activities [8] [9] [10] [11]. Schiff bases with various donor atoms (like N, O, S, etc.) exhibit broad biological activities and are of special interest due to variety of ways in which they can bind to metal ions, their stability and biological applications [12] [13] [14].

Development of antibiotics against gram-positive and gram-negative bacteria such as *Staphylococcus aureus* (S.A), *Staphylococcus epidermidis* (S.E), *Klebsiella pneumonia* (K.P) and *Pseudomonas aeruginosa* (P.A) was a challenge, and their invention led successful achievements of modern science by controlling infectious bacterial decreases. Amoxicillin, Norfloxacin, Chloramphenicol, Ciprofloxacin are the most common antibiotics used for these bacterial infections but are associated with side effects such as neurological alterations generated by the interaction of the drug with the central nervous system [15]. Therefore, it is necessary to search for new alternative antibiotics with ease of synthesis and with relatively less side effects [16].



Scheme 1. General synthesis route for Schiff bases. R is -alkyl or -aryl functionality.

Aforementioned facts prompted us to synthesize Schiff bases (L_1, L_2 and L_3) characterize and further investigate for their antibacterial activity.

2. Methods

2.1. Materials

Salicylaldehyde, 2-aminophenol, 4-aminoantipyrine and ethylendiamine were supplied from Aldrich. All solvents were of analytical grade and used without any further purification.

2.2. Physical Methods of Analysis

IR spectra were recorded using KBr discs in the 4000 - 400 cm^{-1} range on Perkin Elmer IR 65 Spectrometer. ^1H NMR measurements were performed on a Bruker Avance 400 MHz using DMSO-d^6 as a solvent and TMS as an internal reference. The elemental analyses (C, H and N) were carried out on a Heraeus CHNO rapid analyzer. Agar diffusion method was used to investigate the antibacterial activities by disc diffusion.

2.3. Synthesis of the Compounds

2.3.1. Synthesis of L_1

The Schiff base ($\mathbf{L_1}$) (Scheme 2) was prepared according to the reported method [17] with modification by the 1:1 ethanolic condensation of 4-aminoantipyrine (2 mmol, 0.4064 g) with salicylaldehyde (2 mmol, 0.2443 g) in 100 ml of solvent. The reaction mixture was then refluxed for 2 h. On cooling, the yellow colored Schiff base was precipitated, which was collected by filtration after washing with diethyl ether and recrystallized from ethanol, which was subsequently dried over P_2O_5. (Yield = 88.84%).

2.3.2. Synthesis of L_2

L_2 was synthesized by the synthetic route as described by the reported method [18] with modifications by the Scheme 3. To an ethanolic (100 ml) solution of ethylendiamine (2 mmol, 0.120 g), (4 mmol, 0.977 g) salicylaldehyde was added under stirring. The resultant reaction mixture was then refluxed for 2 h. The Schiff base precipitated as yellow solid, was filtered, washed with diethyl ether and finally recrystallized from ethanol and dried under P_2O_5 (Yield = 82.90%).

2.3.3. Synthesis of L_3

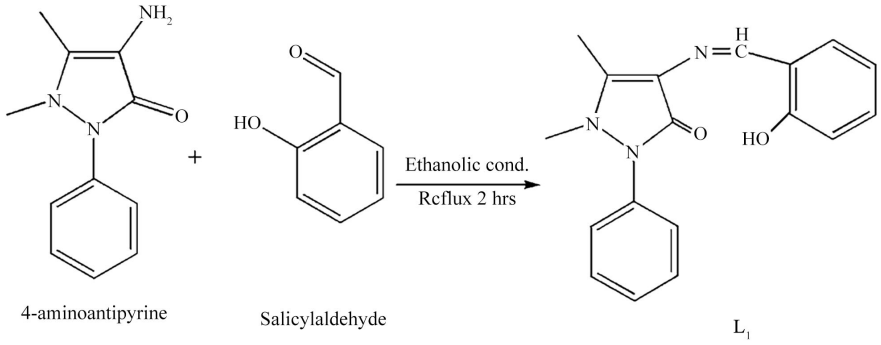
The Schiff base ligand L_3 was prepared as described in literature [19] with modified procedure as by the synthetic route shown in Scheme 4. To a stirred ethanolic solution (100 ml) of 2-amiophenol (2 mmol, 0.218 g), (2 mmol, 0.244 g) of

salicylaldehyde was added. The reaction mixture was then kept under reflux for 2 h. On cooling, the Schiff base was precipitated filtered, recrystallized from ethanol, dried under vacuum over P_2O_5 (Yield = 93.60%).

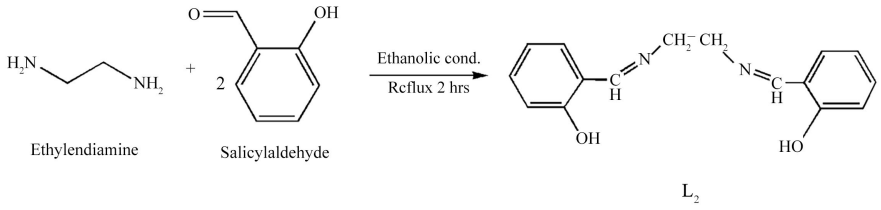
3. Result and Discussions

3.1. Synthesis and Characterization Studies

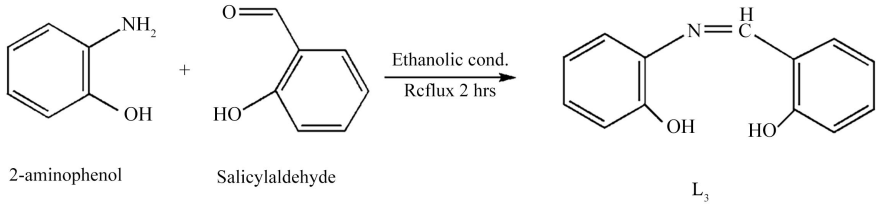
Analytical studies (Table 1) reveal that the formulations of L_1, L_2 and L_3 are $C_{18}H_{17}N_3O_2$, $C_{16}H_{16}N_2O_2$ and $C_{13}H_{11}N_1O_2$ respectively. L_1 and L_2 are yellow powders while L_3 is dark orange needle shape crystals. The molecular weights of the Schiff bases are shown in Table 1 and the compounds are synthesized in 88% - 92% yield.



Scheme 2. Synthetic route of L_1.



Scheme 3. Synthetic route of L_2.



Scheme 4. Synthetic route of L_3.

Table 1. Analytical data of the complexes.

Compound	Molecular formula	Molar mass (g/mol)	Color and appearance	Yield (%)	Elemental analysis Calculated (found) (%)		
					C	H	N
L_1	$C_{18}H_{17}N_3O_2$	307	Yellow powder	88.84	62.14 (62.08)	5.54 (5.51)	13.68 (13.62)
L_2	$C_{16}H_{16}N_2O_2$	268	Yellow powder	82.90	71.64 (71.60)	5.97 (5.92)	10.45 (10.41)
L_3	$C_{13}H_{11}N_1O_2$	213	Dark orange crystal	92.60	73.24 (73.20)	5.16 (5.05)	6.57 (6.50)

3.2. Spectroscopic Results

3.2.1. FT-IR Spectra of L_1

The IR spectra of L_1 (Figure 1) and the corresponding assignments (Table 2), reveal that the compound L_1 showed a weak broad band at 3505 cm^{-1}, which may be assigned to the ν (OH) vibration. The band at 1596 cm^{-1} corresponds to νC=N (of azomethine) stretching vibration. The C-O (phenolic) stretching mode appeared at 1362 cm^{-1}. The bands observed at 1676 cm^{-1}, 1505 cm^{-1} and 1324 cm^{-1} are stretching vibrations for νC=O, νC=C and νC-N respectively. The peak observed at 1425 cm^{-1} corresponds to N-CH_3 stretching vibration while the aromatic νC-H asymmetric and symmetric stretching bands are observed at 3085 cm^{-1} and 3075 cm^{-1} respectively. Additionally, stretching frequency corresponding to νC-H (CH_3) appeared at 2945 cm^{-1} [20] [21] [22].

3.2.2. ^{1}H NMR Spectra of L_1

The ^{1}H NMR spectra of the compound L1 is shown in Figure 2 and the corresponding chemical shifts are listed in Table 3. In the spectra, the phenyl multiplets are observed between δ 6.9 - 7.5. The = C-CH_3, and -N-CH_3 are observed at δ 2.4 and 3.2 ppm respectively. Also azomethine (−CH=N-) resonance is observed at δ 9.7, as a singlet [20] [22] [23].

3.2.3. FT-IR Spectra of L_2

The Infrared spectra of L_2 are presented in (Figure 3) and the corresponding assignments in Table 2. L_2 show a weak broad band at 3499 cm^{-1}, which has assigned to the ν (OH) stretching vibration. Whereas the band at 1605 cm^{-1} corresponds to the azomethine (νC=N) stretching vibration. The C–O (phenolic) modes of L_2 appeared at 1230 cm^{-1}. The bands observed at 1500 cm^{-1} and 1330 cm^{-1} are stretching vibrations for νC=C and νC-N respectively. However, the aromatic νC-H asymmetric and symmetric stretching bands observed at 3092 cm^{-1} and 3005 cm^{-1} respectively [20] [21] [22].

3.2.4. ^{1}H NMR Spectra of L_2

The ^{1}H NMR spectra of the compound L_2 and corresponding chemical shift values are presented in Figure 4 and Table 3 respectively. L_2 displays phenyl multiplets between 6.8 - 7.4 δ while the -OH and -CH=N signals observed at 13.4 and 8.6 δ respectively as a singlet. In addition to this the -CH_2- δ value is observed at 3.9 δ [20] [22].

Table 2. Summary of characteristic IR absorption (cm^{-1}, KBr) of compounds L_1, L_2 and L_3.

Compound	$\nu_{(C=N)}$	$\nu_{(O-H)}$	$\nu_{(C-O)}$	$\nu_{(C=O)}$	$\nu_{(C=C)}$	$\nu_{(C-N)}$	ν_{N-CH3}	$\nu_{(CH)as}$(ar)	$\nu_{(CH)s}$(ar)	$\nu_{(CH)}$(CH_3)
L_1	1596 s	3505 w	1362 m	1676 s	1505 m	1324 m	1425 m	3085 w	3075 w	2945 w
L_2	1605 s	3499 w	1230 m	-	1500 m	1330 m	-	3092 w	3005 w	-
L_3	1633 s	3432 w	1274 m	-	1498 m	1315 m	-	3095 w	3080 w	-

w = weak; m = medium; s = strong.

Table 3. Summary of ^{1}H NMR spectral data (δ, ppm) of L_1, L_2 and L_3.

L_1	L_2	L_3	Assignments
6.9 - 7.5 (br, m)	6.8 - 7.4 (br, m)	6.8 - 7.6 (br, m)	Phenyl multiplet
2.4 (sh, s)	-	-	=C-CH_3
3.2 (sh, s)	-	-	-N-CH_3
9.7 (sh, s)	8.6 (sh, s)	8.9 (sh, s)	-CH=N-
-	13.4 (sh, s)	9.8, 13.8 (sh, s)	-OH
-	3.9 (sh, s)	-	-CH_2-

sh: sharp; br: broad; s: singlet; m:multiplet.

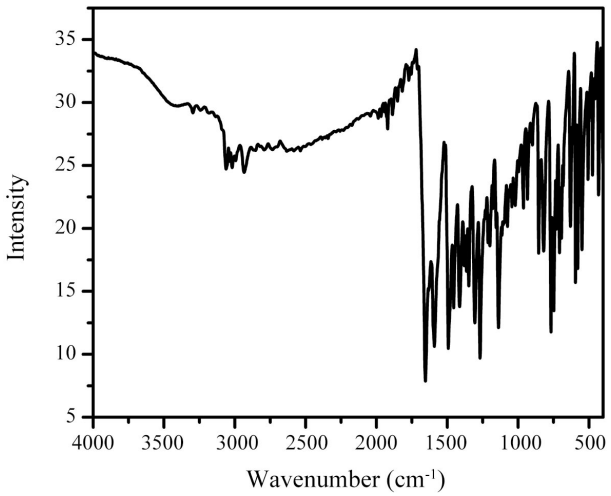


Figure 1. FT-IR spectra of L_1.

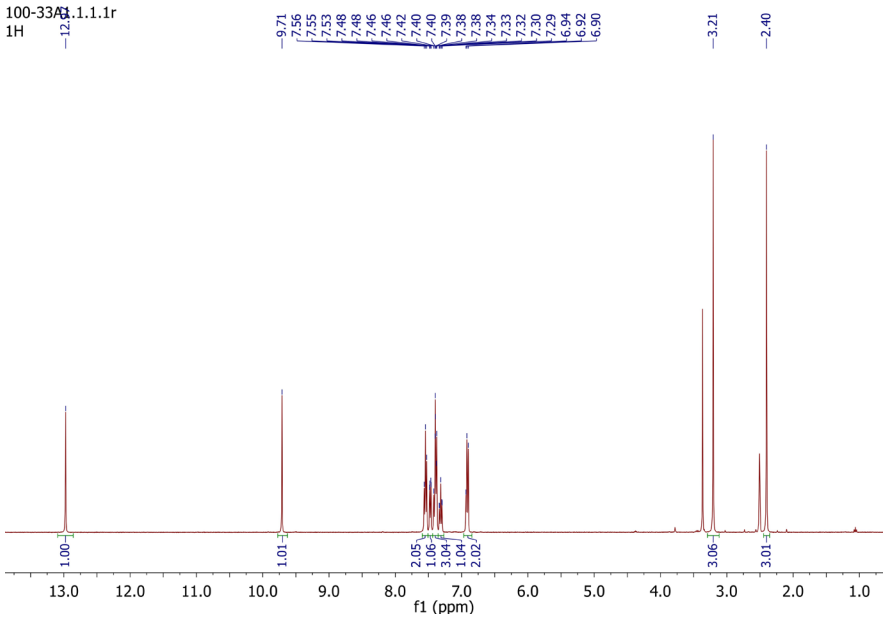


Figure 2. NMR spectra of L_1.

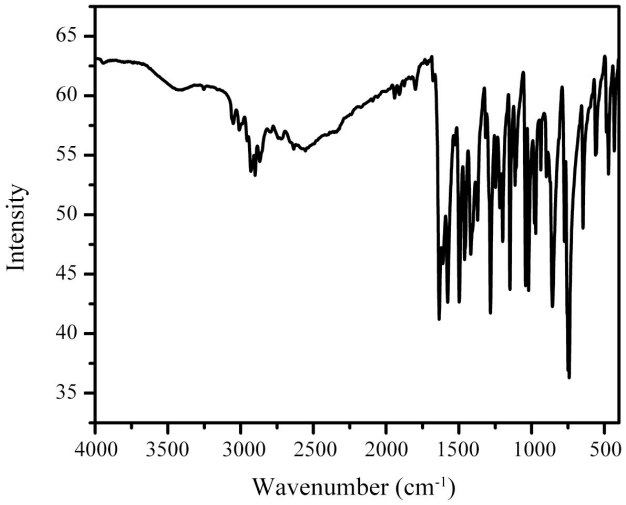


Figure 3. FT-IR spectra of L_2.

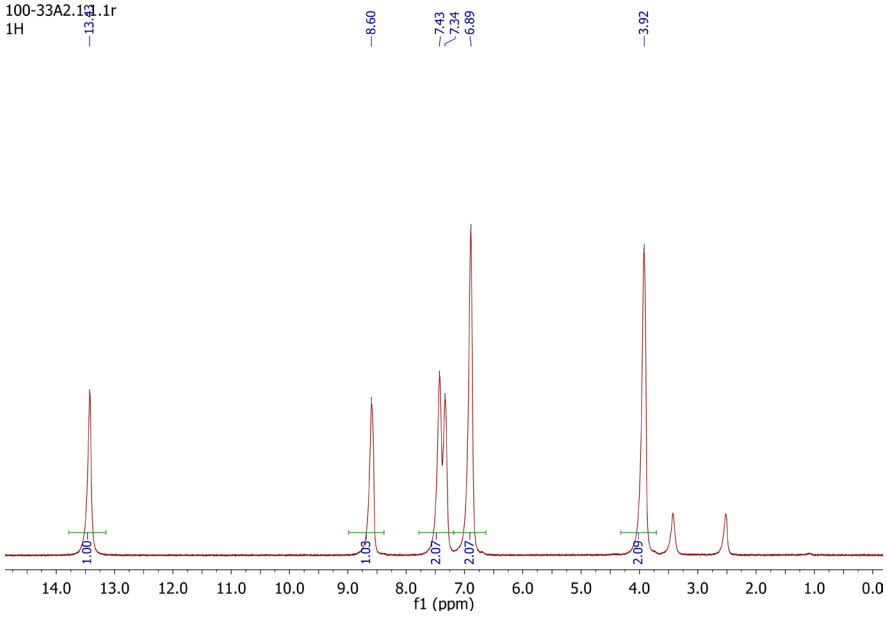


Figure 4. NMR spectra of L_2.

3.2.5. FT-IR Spectra of L_3

The IR spectra of L_3 (**Figure 5**) and the corresponding assignments (**Table 2**), reveal that the band at 3432 cm^{-1}, corresponds to ν (OH). While the band at 1633 cm^{-1} is characteristic of the azomethine (C=N), stretching vibration. The band at 1274 cm^{-1} in the IR-spectrum of L_3 is ascribed to the phenolic C-O stretching vibration.

3.2.6. ^{1}H NMR Spectra of L_3

The ^{1}H NMR spectra of L_3 (**Figure 6**) and the corresponding chemical shifts (**Table 3**) show that the δ values between 6.8 - 7.6 δ correspond to phenyl multiplet resonance. The azomethine (-CH=N-) hydrogen resonance is observed at 8.9 δ while the -OH δ values are observed at 9.8 and 13.8 δ [20] [22].

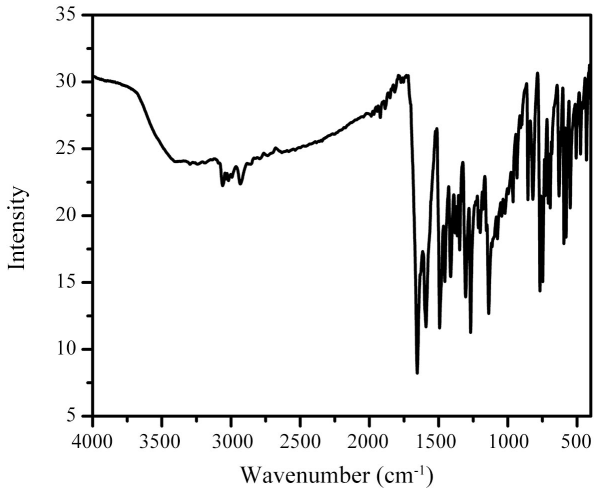


Figure 5. FT-IR spectra of L_3.

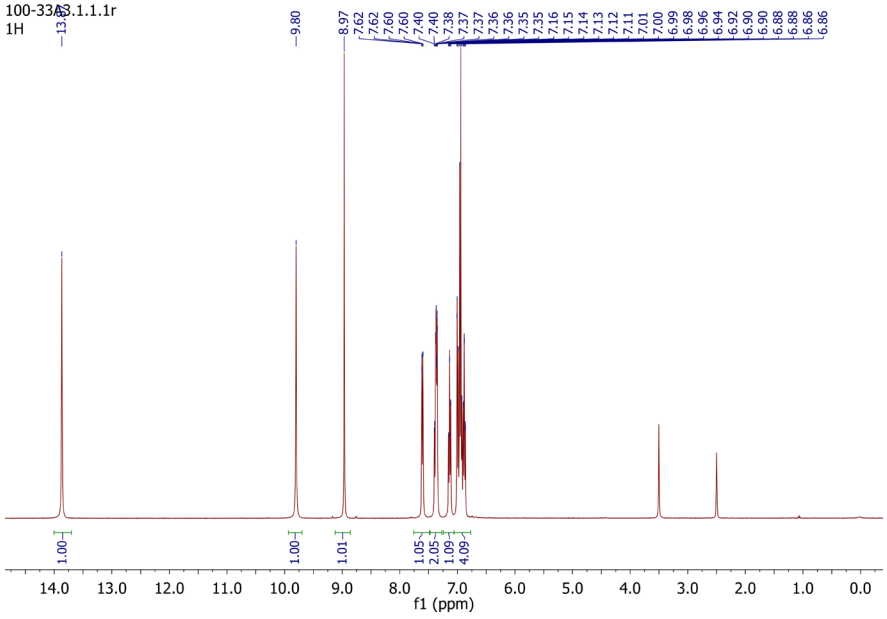


Figure 6. NMR spectra of L_3.

L_3 also showed a singlet at δ 9.857 ppm which was attributed to the azomethine (-CH=N-) proton. Also, ^{1}H NMR spectrum of L_3 revealed multiplets at 6.8 - 7.6 ppm, corresponding to aromatic protons.

Therefore, it is clear from these results that the data obtained from the elemental analyses; IR and ^{1}H NMR spectral measurements are in agreement with each other.

3.3. Screening for Antimicrobial Activity

The *in vitro* antimicrobial activity of Schiff base compounds L_1, L_2 and L_3 towards gram positive bacteria *Staphylococcus aureus* (S.A), *Staphylococcus epidermidis* (S.E) and gram negative bacteria *Klebsiella pneumoniae* (K.P) and *Pseudomonas aeruginosa* (P.A) in Mueller Hinton Agar medium were investi-

gated by disc diffusion method [16]. The solutions of the intended compounds were prepared in methanol at a concentration of 500 μg/ml, 400 μg/ml, 300 μg/ml, 200 μg/ml and 100 μg/ml [24]. At general procedure, 100 μL of the test bacteria were grown in 10 mL of fresh media till they reach a growth of 1×10^8 cells/ml [25]. The microbial suspension was spread onto agar in petridish, which has been maintained in the same condition kept for bacterial growth. Then, methanolic solutions of the test solutions are spotted in the petridish with bacterial growth. It was then incubated for 24 h at 37˚C and then the diameters of the inhibition zones were measured in millimeters (**Figure 7**).

Standard antibiotics Chloramphenicol and Ciprofloxacin were used as positive control to evaluate the potency of the tested compounds under the same conditions. Activity was determined by measuring the diameter of the zone showing complete inhibition (mm). The same concentration and amount of solvent (methanol) was used as a negative control. Finally the activity results were calculated as a mean ± standard deviation of triplicates.

When compared with the commercially available Ciprofloxacin and Chloramphenicol, the newly synthesized compounds showed appreciable antibacterial activities (**Table 4**).

The solvent methanol exhibited activity against all bacterial species used with IZs ranging from 8 ± 0.25 to 17 ± 0.29 while the standard antibiotics Ciprofloxacin and Chloramphenicol exhibited high activities with IZs ranging from 21.3 ± 0.31 to 28.3 ± 0.32 and 26.3 ± 0.24 mm to 32.3 ± 0.23 mm, respectively. However, the newly synthesized Schiff base organic compounds L_1, L_2 and L_3 showed IZs ranging from 7.4 ± 0.23 to 32.5 ± 0.14, 3 ± 0.57 to 12 ± 0.28 and 10 ± 0.20 to 32 ± 0.36 respectively.

L_3 showed better activity compared to L_1 and L_2 for all strains of the bacteria studied except S.A for L_1. Furthermore, it is interesting to note that the antibacterial activity of L_1 and L_3 is higher than the activity of both standard antibiotics (Ciprofloxacin and Chloramphenicol) against S.A and S.E respectively, also L_3 showed higher activity against P.A than Ciprofloxacin.

Furthermore, the mode of action of the compounds may involve formation of a hydrogen bond through the azomethine group with the active centers of cell constituents, resulting in interference with the normal cell processes. The variation in the effectiveness of the different compounds against different organisms depends on the impermeability of the cells of the microbes or differences in ribosome of microbial cells [24]. Hence it has been inferred that antibacterial activity of the compounds is related to damage cell wall structure of the bacteria, which is essential for the survival of many bacteria and are able to destroy bacteria by inhibiting a step in the synthesis of peptidoglycan layer which is responsible for maintaining the shape of the organism [26].

The MIC is the lowest concentration of the test compound, which inhibits the visible growth of microorganisms after incubation and the MIC is an important diagnostic tool to confirm the resistance of microorganisms towards antimicrobial agents.

The MIC for L_3 is 300 µg/ml for S.E and K.P as well as 400 µg/ml for P.A and S.A respectively. However L_1 and L_2 showed MIC of 100 µg/ml for S.E, S.A and P.A and 200 µg/ml for K.P respectively which is better than L_3 (Table 5). In some cases zone overlapping occurs indicating good cleaning action of the tested samples (Figure 7).

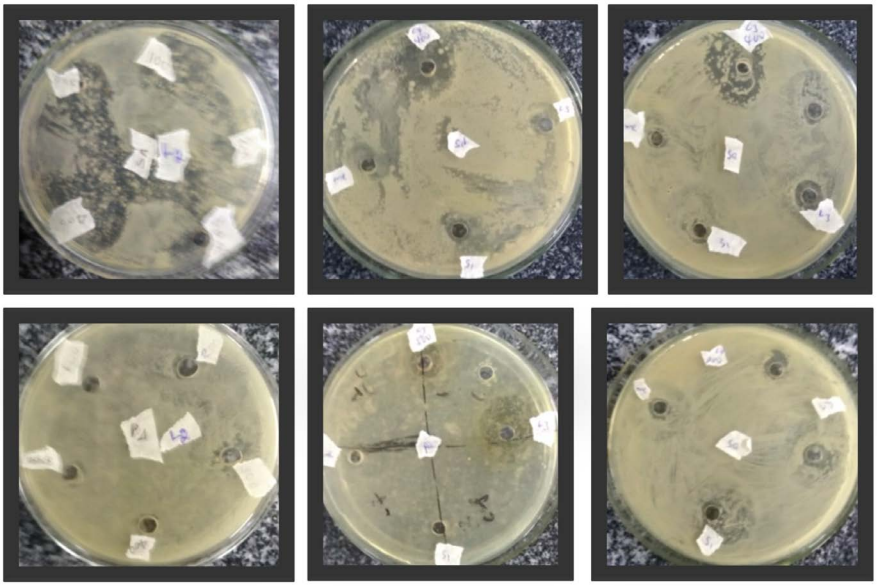


Figure 7. Inhibition zones of L_1, L_2 and L_3 at different concentrations.

Table 4. Antibacterial activity of ligand, (L_1, L_2, L_3), negative control (Methanol) and positive controls Chloramphenicol and Ciprofloxacin.

Compound	Antimicrobial activity (mean IZ diameter (mm) ± SD)			
	S.E	S.A	K.P	P.A
L_1	14 ± 0.33	32.5 ± 0.14	7.4 ± 0.23	12 ± 0.33
L_2	3 ± 0.57	12 ± 0.28	11 ± 0.29	8 ± 0.29
L_3	32 ± 0.36	10 ± 0.20	19 ± 0.29	23 ± 0.30
Methanol	8 ± 0.25	11 ± 0.58	12 ± 0.29	17 ± 0.29
Chloramphenicol	26.7 ± 0.35	26.3 ± 0.24	27.3 ± 0.21	27.3 ± 0.21
Ciprofloxacin	24.0 ± 0.21	24.0 ± 0.32	28.3 ± 0.32	21.3 ± 0.31

Table 5. MIC. assay of L_1, L_2 and L_3 against bacterial pathogens.

Name of Bacterial Pathogens	Observation of growth		
	L_1	**L_2**	**L_3**
S.E	100 µg/ml	100 µg/ml	300 µg/ml
S.A	100 µg/ml	100 µg/ml	400 µg/ml
K.P	200 µg/ml	200 µg/ml	300 µg/ml
P.A	100 µg/ml	200 µg/ml	400 µg/ml

Based on the MIC values presented we can conclude that, the newly synthesized Schiff base compounds L_1, L_2 and L_3 have appreciable MIC when compared with the commercially available antibiotics, Ciprofloxacin and Chloramphenicol with a potency of 5 μg/ml and 30 μg/ml respectively [27].

All the Schiff bases were synthesized by ethanolic condensation reaction and subsequently characterized by elemental analysis, IR and NMR spectra. They are soluble in most polar solvents like methanol and insoluble in almost all non-polar solvents. Based on the analytical and spectroscopic results discussed, the formation of Schiff base compounds has been confirmed. On comparing the antibacterial activities of the synthesized compounds, L_3 shows better activity than L_1 and L_2 against all pathogens, which is higher than the activity of standard antibiotics, Chloramphenicol and Ciprofloxacin for S.E and P.A. Also, it is interesting to note that, all the synthesized compounds exhibited antibacterial activity against all species of bacterium under study, which makes them ideal candidates as antibacterial drugs, after *in vivo* studies. The major limitations of these synthesized compounds are that in some of the bacterial strains, they showed less activity than the standard antibiotics Ciprofloxacin and Chloramphenicol. However, their antibacterial activity can be improved by tuning their functionality during Schiff base synthesis.

4. Conclusions

Three Schiff base compounds were synthesized, characterized and screened for their antibacterial activity by *in-vitro* investigations. The antibacterial activities of these compounds were examined using different cultures of bacteria and the results revealed that all the Schiff bases of current study showed appreciable activity.

Among the three compounds, L_3 showed the better antibacterial activity for both types of bacteria (gram-positive and gram-negative) as compared to the reference antibiotics Ciprofloxacin and Chloramphenicol. This approach can open new vistas in the chemotherapy of the infectious diseases. The field is further open for pharmacokinetics and clinical trials to establish these molecules as drugs in the market. From the results obtained, we concluded that the newly synthesized compounds could be used as good drug of choice to manage diseases caused by the investigated four bacterial pathogens after evaluating the *in-vitro* effect on experimental animals and clinical trials. Since all the Schiff bases in the present study show appreciable antibacterial activity, it will be interesting to check the activity of the corresponding metal complexes derived from them, and which is underway. Moreover, the newly synthesized compounds are organic molecules; they may have less side effects to the environment and human being.

Acknowledgements

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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