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Synthesis, Spectral and Biological Studies of Schiff Bases Derived from 3-Aminophenol and Substituted Benzaldehydes

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Abstract

Increased reports of hospital acquired infections as a result of microbial resistance reported to known antimicrobial and antiseptic agents have led the search of new highly active agents. A series of Schiff bases (L^1-L^8) derived from 3-aminophenol and substituted benzaldehydes; 2-methoxybenzaldehyde, 2-hydroxybenzaldehyde, 2-chlorobenzaldehyde, 2-nitrobenzaldehyde, 4-methoxybenzaldehyde, 4-hydroxybenzaldehyde, 4-chlorobenzaldehyde and 4-nitrobenzaldehyde have been synthesized and characterized based on elemental analysis, FT-IR, ^{1}H NMR and UV-Vis spectroscopy. The Schiff base ligands were screened for their *in-vitro* antibacterial activity against six pathogenic bacteria; *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa, Bacillus cereus, Enterococcus faecalis and Klebsiella pneumoniae* using the disc diffusion method and 96-well micro-plate dilution method with ampicillin and sodium hypochlorite used as reference compounds. The antibacterial activity exhibit a dependence on both nature and position of substituent with compounds derived from 4- chlorobenzaldehyde (L^7) and 4-nitrobenzaldehyde (L^8) showing highest activity against the tested bacterial strains better than the reference compounds. These compounds can be employed as active ingredients in development of antibacterial/antispetic agents against these pathogenic organisms.

Keywords: 3-aminophenol, Schiff base, substituted benzaldehydes, antibacterial activity, antiseptic agent

1. Introduction

Hospital acquired infections (HAI) or nosocomial infections are a major cause of morbidity among hospitalized patients worldwide. It is generally acknowledged that inanimate surfaces in health care establishments act as reservoir of microbes such as door handles, sterile packaging, mops, ward fabrics, taps, plastics and so on (Page *et al.*, 2009; Russotto *et al.*, 2015). When touched by either healthcare workers or patients these surfaces could in turn lead to the spread of infection, hence the spread of HAI causative agents can be controlled by maintaining a rigorous hygiene regiment aimed at reducing contamination of inanimate surfaces in health care establishments.

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A growing approach to reduction of microbial contamination is the development of highly active antimicrobial agents applicable to surfaces (Hota, 2004; Borkow, 2014). These antimicrobial agents are commonly known as antiseptics and/or disinfectants. Some known antiseptic agents include Chlorhexidine, Sodium hypochlorite, phenol and quaternary ammonium compounds. Many hospitals in Nigeria use sodium hypochlorite solutions commonly called bleach for cleaning of surfaces. The active ingredient, sodium hypochlorite, denatures protein in micro-organisms making it effective in killing bacteria, fungus and viruses. Reports of antimicrobial resistance worldwide have shown that there is need to develop new antiseptic agents suitable for use in hospitals and health care institutions.

Aminophenols are antiviral agents used to treat various infections and the addition of aminophenol derivatives to biosystems can have stable antiviral effects (Valentovic *et al*., 1996; Racine *et al*., 2014). Thus, it is envisaged that compounds derived from aminophenols would have biocidal properties making them useful as antiseptic and disinfectants. These compounds could be used in formulation of antimicrobial cleaning agents for use in healthcare establishments. This prompted our investigation of antimicrobial properties of Schiff bases derived from aminophenols. The imine functional group present in Schiff bases confers on this class of compounds a wide range of interesting properties and applications. These compounds have received much attention because of their use as models for biological systems (Baluja *et al*., 2009) and are reported to show antibacterial (Da Silva *et al*., 2010; Ejiah *et al*., 2013; Azab *et al*., 2015) antifungal (Jarrahpour *et al*., 2007), anticancer (Kose *et al*., 2015) and herbicidal (Aggarwal *et al*., 2009) activities.

As part of our efforts to design new potent antiseptic agents to prevent hospital acquired infections, we herein report the synthesis and structure activity antibacterial relationship of Schiff base ligands derived from condensation of 3-aminophenol with some substituted benzaldehydes.

2. Material and Methods

All reagents used were purchased from commercial sources (Sigma-Aldrich Co. Ltd, Germany and Merck Chemicals) and used without further purification. Solvents were of analytical or spectroscopic grade. Elemental analyses were performed using a Perkin Elmer 2400 series II CHNS/O elemental analyzer. Infrared (IR) spectra of the compounds were recorded on a Bruker FT-IR (ATR) tensor 27 spectrophotometer directly on samples of the

compounds in the range 4000 to 400 cm^{-1}. ^{1}H-NMR spectra were recorded on a Bruker Avance III 400 MHz in DMSO-d_6 solutions. Chemical shifts were reported relative to TMS as internal standard. Electronic absorption spectra of the complexes were recorded from 200 to 800 nm on freshly prepared chloroform solutions using a Cary Model 50 spectrophotometer. Melting points were determined on a Reichert Thermovar melting-point apparatus and are uncorrected.

Synthesis of 3-(2-methoxybenzylideneamino) phenol (L^1): Equimolar quantities of 3-aminophenol (10 mmol.) and 2-methoxybenzaldehyde (10 mmol.) were refluxed for 2 h in toluene (100 ml). The reaction mixture was filtered hot, the solid product obtained re-crystallized from toluene, dried and stored over silica gel in a desiccator.

Yield: 48 %. m.p.: 170-172 ^{o}C. Analyses: calculated: $C_{14}H_{13}NO_2$: C, 73.90; H, 5.77; N, 6.16. Found: C, 74.77; H, 6.07; N, 5.48. ^{1}H NMR ($CHCl_3$): δ 8.91 (1H, s, O–H), 8.11 (1H, s, -N=CH), 6.12-7.83 (8H, m, aromatic), 3.91 (3H, s, -OCH_3).

Synthesis of 3-(2-hydroxybenzylideneamino) phenol (L^2): Equimolar quantities of 3-aminophenol (10 mmol.) and 2-hydroxylbenzaldehyde (10 mmol.) were refluxed for 2 h in toluene (100 ml). The reaction mixture was filtered hot, the solid product obtained re-crystallized from toluene, dried and stored over silica gel in a desiccator.

Yield: 61 %. m.p.: 82-83 ^{o}C. Analyses: calculated: $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.01; H, 5.16; N, 6.57. ^{1}H NMR ($CHCl_3$): δ 8.77 (1H, s, O–H), 8.38 (1H, s, -N=CH), 6.73-7.38 (8H, m, aromatic).

Synthesis of 3-(2-chlorobenzylideneamino) phenol (L^3): Equimolar quantities of 3-aminophenol (10 mmol.) and 2-chlorobenzaldehyde (10 mmol.) were refluxed for 2 h in toluene (100 ml). The reaction mixture was filtered hot, the solid product obtained re-crystallized from toluene, dried and stored over silica gel in a desiccator.

Yield: 57 %. m.p.: 120 ^{o}C.: Analyses: calculated: $C_{13}H_{10}NOCl$; C, 67.39; H, 4.35; N, 6.05.Found: C, 66.67; H, 4.46; N, 5.61. ^{1}H NMR ($CHCl_3$): δ9.11 (1H, s, O–H), 8.23 (1H, s, -N=CH), 6.53-7.37 (8H, m, aromatic).

Synthesis of 3-(2-nitrobenzylideneamino) phenol (L^4): Equimolar quantities of 3-aminophenol (10 mmol.) and 2-nitrobenzaldehyde (10 mmol.) were refluxed for 2 h in

toluene (100 ml). The reaction mixture was filtered hot, the solid product obtained re-crystallized from toluene, dried and stored over silica gel in a desiccator.

Yield: 47 %. m.p.: 102-103 ^{o}C. Analyses: calculated: $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.57; H, 4.40; N, 11.54. ^{1}H NMR ($CHCl_3$): δ 8.91 (1H, s, O–H), 8.17 (1H, s, -N=CH), 6.24-7.79 (8H, m, aromatic).

Synthesis of 3-(4-methoxybenzylideneamino) phenol (L^5): Equimolar quantities of 3-aminophenol (10 mmol.) and 4-methoxybenzaldehyde (10 mmol.) were refluxed for 2 h in toluene (100 ml). The reaction mixture was filtered hot, the solid product obtained re-crystallized from toluene, dried and stored over silica gel in a desiccator.

Yield: 52 %. m.p.: 148-149 ^{o}C. Analyses: calculated: $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.32; H, 6.01; N, 5.40. ^{1}H NMR ($CHCl_3$): δ 8.47 (1H, s, O–H), 7.87 (1H, s, -N=CH), 6.24-7.24 (8H, m, aromatic), 3.33 (3H, s, -OCH_3).

Synthesis of 3-(4-hydroxybenzylideneamino) phenol (L^6): Equimolar quantities of 3-aminophenol (10 mmol.) and 4-hydroxylbenzaldehyde (10 mmol.) were refluxed for 2 h in toluene (100 ml). The reaction mixture was filtered hot, the solid product obtained re-crystallized from toluene, dried and stored over silica gel in a desiccator.

Yield: 64 %. m.p.: 193-195 ^{o}C. Analyses: calculated: $C_{13}H_{11}NO_2$: C, 73.23; H, 5.20; N, 6.57. Found: C, 72.82; H, 5.08; N, 6.61. ^{1}H NMR ($CHCl_3$): δ 8.71 (1H, s, O–H), 8.33 (1H, s, -N=CH), 6.88-7.83 (8H, m, aromatic).

Synthesis of 3-(4-chlorobenzylideneamino) phenol (L^7): Equimolar quantities of 3-aminophenol (10 mmol.) and 4-chlorobenzaldehyde (10 mmol.) were refluxed for 2 h in toluene (100 ml). The product obtained was filtered hot, re-crystallized from toluene, dried and stored in a desiccator over silica gel.

Yield: 47 %. m.p.: decomp.: Analyses: calculated: $C_{13}H_{10}NOCl$; C, 67.39; H, 4.35; N, 6.05. Found: C, 67.65; H, 4.52; N, 5.69. ^{1}H NMR ($CHCl_3$): δ8.57 (1H, s, O–H), 7.95 (1H, s, -N=CH), 6.24-7.63 (8H, m, aromatic).

Synthesis of 3-(4-nitrobenzylideneamino) phenol (L^8): Equimolar quantities of 3-aminophenol (10 mmol.) and 4-nitrobenzaldehyde (10 mmol.) were refluxed for 2 h in toluene (100 ml). The product obtained was filtered hot, re-crystallized from toluene, dried and stored in a desiccator over silica gel.

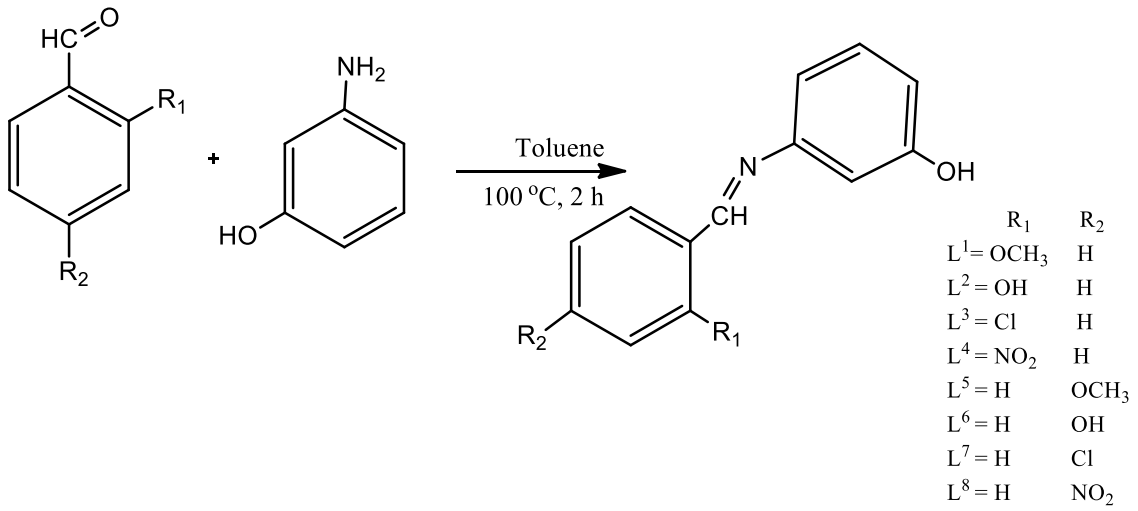
Yield: 52 %. m.p.: decomp. Analyses: calculated: $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.86; H, 4.42; N, 11.53. ^{1}H NMR ($CHCl_3$): δ 8.71 (1H, s, O–H), 8.39 (1H, s, N=CH), 6.20-8.11 (8H, m, aromatic).

The antibacterial sensitivity of the compounds were carried out in triplicate against a panel of Gram positive and Gram negative microorganisms, namely *Enterococcus faecalis* (ATCC 29212), *Bacillus cereus* (ATCC 10702), *Staphylococcus aureus* (ATCC 6538), *Echeriachia coli* (ATCC 8739), *Psuedomonas aeruginosa* (ATCC 19582), and *Klebsiella pneumonia (ATCC* 10031) using the disc diffusion method (Bauer *et al*., 1996; Laith and Najiah 2014). Molten Mueller-Hinton agar was inoculated with the bacteria suspension which had been adjusted to the 0.5 McFarland standards and poured into sterile 90 mm Petri dishes. Schiff bases were dissolved in DMSO to obtain a final concentration of 10 mg/ml. Sterile Whatman No. 1 (6 mm) discs were separately impregnated with each sample to be tested and placed on the inoculated agar. The plates were incubated at 37 ^{o}C for 24 h and the zones of inhibition measured at the end of the incubation period. Ampicillin and sodium hypochlorite were used as reference compounds however, the restriction on the purchase of sodium hypochlorite which is the active ingredient in Jik® necessitated the use of Jik® in 1:10 dilution in the study.

The minimum inhibitory concentration was obtained using the 96 micro-dilution plate method (Eloff 1998; Perumal *et al*., 2012). Serial plate concentrations of 5.0, 2.5, 1.25, 0.625, 0.312, and 0.157, 0.078 and 0.039 mgmL^{-1} were prepared for each compound. Each was inoculated with 1.5x10^8 CFU/mL of 0.5 McFarland standard bacteria suspension and incubated for 24 h at 37 ^{o}C. As an indicator of bacterial growth, 20 µL of 0.2 mgmL^{-1} *p*-iodonitrotetrazolium solution (a colourless tetrazolium) was added to each well and incubated at 37 ^{o}C for 30 min. Growing bacteria metabolise this salt to give a red product (formazan). Inhibition prevents this conversion resulting in a clear well. MIC values were recorded as the lowest concentration of compound preventing bacterial growth. .

3. Results and Discussion

The Schiff bases L^1-L^8 were obtained in moderate to good yields from the reactions of 3-aminophenol with 2-substituted-benzaldehydes (L^1–L^4) and 4-substituted-benzaldehydes (L^5-L^8) under reflux conditions as shown in Scheme 1.



	R_1	R_2
L^1	OCH_3	H
L^2	OH	H
L^3	Cl	H
L^4	NO_2	H
L^5	H	OCH_3
L^6	H	OH
L^7	H	Cl
L^8	H	NO_2

SCHEME 1: Synthetic route to Schiff bases L^1 - L^8

Analytical data for the compounds are summarized in **Table 1.**

TABLE 1: Physical and analytical data of Schiff bases

Compound	R_1	R_2	Empirical Formula (M.wt)	Yield (%)	Color	M.pt (ºC)	% Found (cacld) C	H	N
L^1	OMe	H	$C_{14}H_{13}NO_2$ (227)	48	Yellow	170-172	74.77 (73.90)	6.07 (5.77)	5.48 (6.16)
L^2	OH	H	$C_{13}H_{11}NO_2$(213)	61	Orange	82-83	73.01 (73.23)	5.16 (5.20)	6.57 (6.57)
L^3	Cl	H	$C_{13}H_{10}NOCl$ (231)	57	Red	120	66.67 (67.39)	4.46 (4.35)	5.61 (6.05)
L^4	NO_2	H	$C_{13}H_{10}N_2O_3$ (242)	47	Brown	102-103	64.57 (64.46)	4.40 (4.16)	11.54 (11.56)
L^5	H	OMe	$C_{14}H_{13}NO_2$ (227)	52	Orange	148-149	74.32 (73.99)	6.01 (5.77)	5.40 (6.16)
L^6	H	OH	$C_{13}H_{11}NO_2$(213)	64	Yellow	193-195	72.82 (73.23)	5.08 (5.20)	6.61 (6.57)
L^7	H	Cl	$C_{13}H_{10}NOCl$ (231)	47	Brown	dec.	67.65 (67.39)	4.52 (4.35)	5.69 (6.05)
L^8	H	NO_2	$C_{13}H_{10}N_2O_3$ (242)	52	Red	dec.	64.86 (64.46)	4.42 (4.16)	11.53 (11.56)

TABLE 2: Spectroscopic data of Schiff bases

Compound	R_1	R_2	ν(O-H)	ν(C=N)	ν(C-O)	ν(C-Cl)	HC=N (s,1H)	OH (s, 1H)	OCH_3 (s, 3H)
L^1	OMe	H	3365	1586	1238	-	8.11	8.91	3.91
L^2	OH	H	3298	1583	1223	-	8.38	8.77	
L^3	Cl	H	3325	1617	1217	346	8.23	9.11	-
L^4	NO_2	H	3360	1606	1211	-	8.17	8.91	-
L^5	H	OMe	3330	1612	1280	-	7.87	8.47	3.33
L^6	H	OH	3339	1609	1275	-	8.33	8.71	
L^7	H	Cl	3351	1616	1219	326	7.95	8.57	-
L^8	H	NO_2	-	1603	1195	-	8.39	8.71	-

The Schiff bases showed the diagnostic ^{1}H NMR singlet in range 7.87-8.39 ppm for the azomethine proton. The appearance of IR bands in the region 1586 -1617 cm^{-1} characteristic of the imine functional group coupled with disappearance of the band at *ca* 1700 cm^{-1} for the carbonyl group and appearance of a band in 1195-1280 cm^{-1} for the phenolic oxygen in all compounds confirmed the formation of the Schiff base.

TABLE 3: Electronic spectra data of Schiff bases

Compound	R_1	R_2	$CHCl_3$(ν/ cm^{-1})(logε)	Assignment
L^1	OMe	H	260 (3.93) 339 (3.63)	π→π* n→π*
L^2	OH	H	270 (2.76) 345(2.85)	π→π* n→π*
L^3	Cl	H	274 (3.97) 356 (3.94	π→π* n→π*
L^4	NO_2	H	270 (3.09) 328 (2.55	π→π* n→π*
L^5	H	OMe	288 (3.96) 337 (3.92)	π→π* n→π*
L^6	H	OH	283 (2.83) 328 (2.86)	π→π* n→π*
L^7	H	Cl	272 (3.61) 356 (2.89	π→π* n→π*
L^8	H	NO_2	287 (3.29) 353 (2.96)	π→π* n→π*

The electronic spectra of freshly prepared chloroform solutions of the Schiff bases were studied from 200 – 800 nm and results summarized in **Table 3**. The spectra of the ligands comprises of absorption bands in the region 260 – 288 nm and 328 – 356 nm assigned to π→π* and n→π* transitions respectively. The absorption spectra showed a dependence on both the nature and position of the ring substituent. Compounds with 2-substituted benzaldehydes L^1-L^4 gave better resolved absorption bands (Figure 1) over the 4-substituted benzaldehydes L^5-L^8 (Figure 2). An overlap of absorption bands was observed for compounds containing the electron-withdrawing chloro L^3 & L^7 and nitro L^4 & L^8 substituents. This observation suggests that resonance of the *para*-substituents with the aromatic rings of the Schiff base, lowers the energy of the π* orbital making it less anti-bonding in character hence, different transition energies become averaged together in the spectra giving broad absorption bands (Pavia *et al*., 2000).

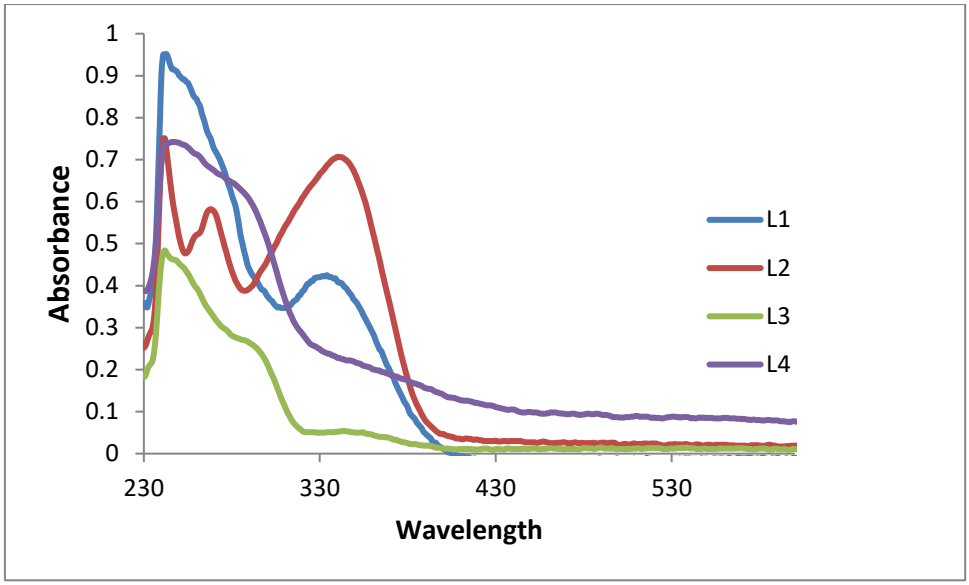


Figure1: Electronic absorption spectra of *o*- substituted Schiff bases $L^1 – L^4$

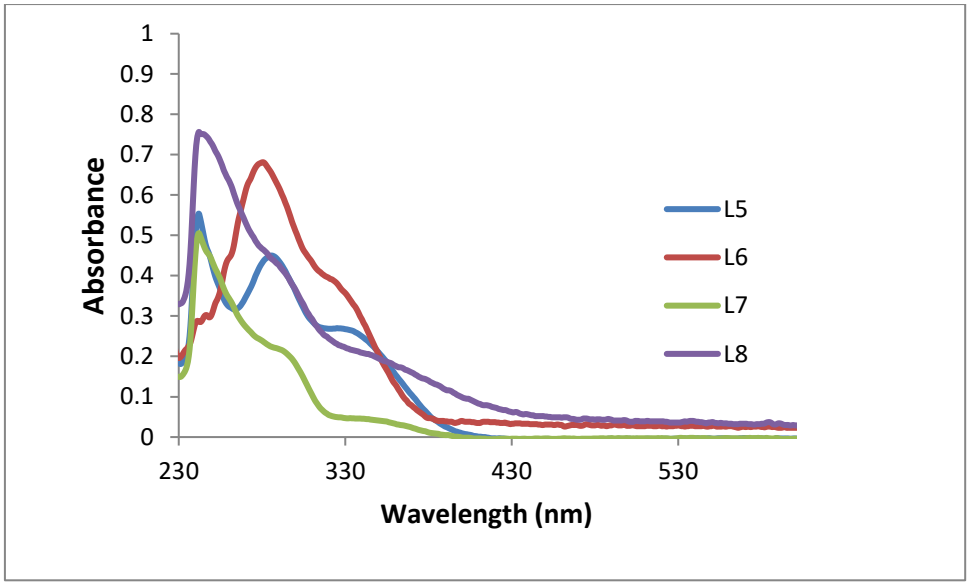


Figure2: Electronic absorption spectra of *p*- substituted Schiff bases $L^5 – L^8$

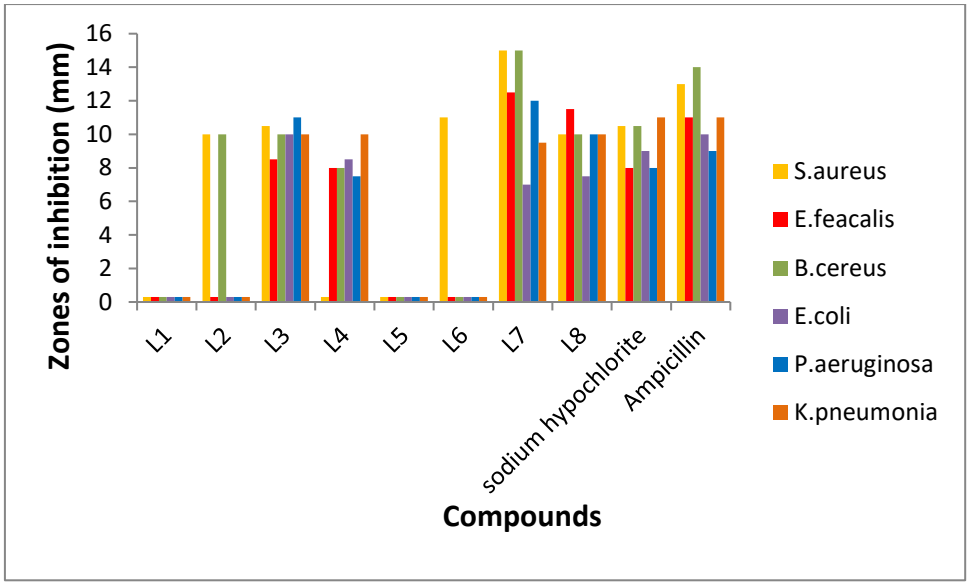


Figure 3: Bar chart of zones of inhibition for Schiff bases (10mg/ml).

Results of the antibacterial screening of the compounds shown in Figure 3 reveals that all compounds evaluated except those bearing the electron-donating methoxy group (L^1 & L^5) showed moderate activity against all the bacterial strains tested. Compounds with electron-withdrawing substituent's Cl and NO_2 (L^3 L^4 $L^7$and L^8) were highly active against the bacterial strains tested. Studies have shown that some antiseptics/disinfectants and antibiotics have similar effects on bacteria (Russell, 2002) hence a evaluation of the antibacterial activity potential antiseptic agents can be achieved by comparison with activity of known antibiotics.

The activities of compounds (L^3 and L^4) were comparable to those of the reference compounds ampicillin and sodium hypochlorite while compounds (L^7 and L^8) were better than sodium hypochlorite. The high activity of the chloro (L^3, L^7) and nitro (L^4, L^8) substituted compounds could be attributed to the inductive electron withdrawing effect of chlorine which promotes ionization (Benarde *et al*., 1967; Yeap *et al*., 2016) and ability of nitro group to interfere with normal breakdown of microtubules during cell division of globular proteins (Giannicchi *et al*., 2013).

Antibacterial activity is also affected by position of substituent. Results show that *para* substituted compounds exhibit higher activity compared to the corresponding *ortho* compounds. This is in line with previous study on DNA modification that reveal position of substituent play an important role in modifying DNA adducts with highest antibacterial activity reported in *para*-substituted compounds (Trumpp-Kallmeyer *et al*., 1992; Ahmed *et al*., 2015).

TABLE 4: Minimum inhibitory concentration (MIC) of Schiff bases

MIC (mg/mL)								
Compound	R_1	R_2	*S.aureus* (ATCC 6538)	*E.feacalis* (ATCC 29212)	*B.cereus* (ATCC 10702)	*E.coli* (ATCC 8739)	*P.aeruginosa* (ATCC 19582)	*K.pneumonia* (ATCC 10031)
L^1	OMe	H	5.00	5.00	5.00	2.50	5.00	5.00
L^2	OH	H	2.50	2.50	5.00	2.50	2.50	2.50
L^3	Cl	H	5.00	5.00	2.50	2.50	1.25	2.50
L^4	NO_2	H	2.50	2.50	2.50	2.50	2.50	2.50
L^5	H	OMe	>5.00	>5.00	>5.00	>5.00	>5.00	>5.00
L^6	H	OH	2.50	>5.00	>5.00	>5.00	>5.00	>5.00
L^7	H	Cl	1.25	1.25	1.25	5.00	1.25	1.25
L^8	H	NO_2	1.25	1.25	2.50	5.00	1.25	1.25
Ampicillin			2.50	5.00	5.00	1.25	5.00	2.50

The minimum inhibitory concentration (MIC) values of the Schiff bases against the tested bacterial strains are summarized in **Table 4**. A minimum inhibitory concentration value of 0.28-1.27 mg/ml has been attributed with extremely strong activity while MIC values of 1.81-8.85 mg/ml are attributed with weak activities (Aligiannis *et al.,* 2001; Gul and Bakht, 2015). The 2-hydroxybenzaldehyde Schiff base L^2 showed activity comparable to the reference compound ampicillin. Previous reports indicate that chelation makes a ligand a more powerful and potent bactericidal agent (Kothari and Sharma, 2013). The higher activity of L^2 can be attributed to the chelate effect as close proximity of the hydroxyl group to the imine nitrogen provides a suitable environment for chelate formation.

The electron- withdrawing *para* substituted compounds L^7 and L^8 were more active having lower MIC values compared to the reference compound. Highest antibacterial activity has been reported in *para*-substituted compounds due to interaction with specific amino acid residue or lie in a hydrophobic pocket in the binding site of the receptor (Trumpp-Kallmeyer *et al*., 1992). Such increased activity could be due to its ability to prevent interaction with cellular DNA due to the position of substituent group.

4. Conclusion

In the present study, eight Schiff bases derived from 3-aminophenol and substituted benzaldehydes have been synthesized, characterized and biological activity evaluated. The compounds bearing the electron-withdrawing substituent in the *para* position exhibited better activity against the bacterial strains tested. The minimum inhibitory concentration values indicate that compounds L^7 and L^8 were more active compared to the reference compounds hence, can be explored as active ingredients in development of new antiseptic agents.

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