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Synthesis and Antimicrobial Activity of Schiff Bases Derived from 5-Chlorosalicylaldehyde with Substituted Aniline

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ABSTRACT

Schiff bases (E)- 4- chloro-2- ((phenylimino) methyl) phenol, (E)- 4- chloro- 2- (((2-methoxyphenyl) imino) methyl) phenol, (E)- 4- chloro- 2-(((4-chlorophenyl) imino) methyl) phenol, (E)-4-chloro-2- (((5-chloro-2-methylphenyl) imino) methyl) phenol were synthesized from 5-chlorosalicylaldehyde and substituted aniline. The synthesized compounds were characterized by elemental analysis, IR, UV, ^{1}H, and ^{13}C NMR. The antibacterial studies revealed that the compounds exhibit broad spectrum antibacterial activity against *Escheriochia coli, Klebsiella pneumonia, proteus mirabilis, Pseudomonas aeruginosa* and *Salmonella typhimurium*. The antibacterial activities was affected by the substituent on the aniline part.

Introduction

Schiff base was first reported by Hugo Schiff [1, 2], when he reported the condensation of primary amines with carbonyl compounds [1, 2]. Schiff bases are condensation products of aldehydes or ketones with primary amines, they are compounds containing azomethine group (HC=N). They are also as imines or azomethines and are generally represented by the formula $R_1H=NR_2$ where R_1 and R_2 are alkyl or aryl groups [3].

Schiff bases as one of the most widely used organic compounds play important role in coordination chemistry. They exhibit biological activities including antifungal, antibacterial, antiviral, antipyretic, antimalarial, anti-inflammatory and antiproliferative properties [4-6]. Schiff bases play essential function in biological systems in combination of enzymes such as transaminases, tryptophan synthase etc. [7-9]. The imine group is significant in elucidating the mechanism of transamination and racemization reaction in biological system [1-4, 10, 11].

This study presents the effect of substituents on the antimicrobial activity of Schiff bases derived from substituted aniline and 5-chlosalicylaldehyde.

Materials and method

Reagents

5-chlorosalicyladehyde, aniline, 4-chloroaniline, o-anisidine, 5-chloro-2-methylaniline were purchased from Merck and used as supplied. The solvent DMSO (dimethylsulfoxide) and absolute ethanol were of analytical grade and were used without further purification. Elemental analysis was carried out with Finnigan Flash EA 1112 series. The electronic spectra were recorded on Shimadzu UV-2600 series in DMSO. The infrared spectra were recorded on a Perkin-Elmer 400 FT-IR/FT-FIR while the NMR spectra were obtained using a Bruker Avance 111 600 in chloroform ($CDCl_3$) - D_2 solution and DMSO-D_6 solution with tetramethylsilane (TMS) as internal standard. Melting points were taken on Stuart Melting point apparatus SMP-3 but were not correct.

Synthesis of the Schiff bases

0.015 mole (2.35 g) of 5-chlorosalicylaldehyde in 10 ml absolute ethanol was dispensed into a 0.015 mole of amine in 15 ml of absolute ethanol, which previously being stirred. Three drops of concentrated formic acid was added and the resulting mixture was stirred for 2 hrs. The precipitates were filtered and washed with cold ethanol, recrystallized from ethanol and dried in a desiccator over silica gel for two days.

Antimicrobial activity

The antibacterial potentials of the samples were evaluated by agar-well diffusion method against multi-drug resistance Gram-positive (*Streptococcus agalactiae and Staphylococcus aureus)*, and Gram-negative *(Escheriochia coli, Klebsiella pneumonia, proteus mirabilis, Pseudomonas aeruginosa and Salmonella typhimurium*) organisms. The bacteria isolates were sub-cultured in Nutrient agar and incubated at 37 ^{o}C for 24 hours. All the bacteria cultures were adjusted to 0.5 McFarland standards, 20 ml of sterilized Nutrient agar medium was dispensed into each Petri dish aseptically and allowed to gel and the plates were swabbed with inocula of the test organisms, and kept for 15 minutes for adsorption. Using sterile cork borer of 6 mm diameter, wells were bored into the seeded agar plates, and these were loaded with different concentrations of the samples. The plates were allowed to stand in the refrigerator for 1 hour to allow proper diffusion of the sample into the medium and incubated at 37 ^{o}C for 24 hours before visual assessment of the inhibition zones. Antimicrobial activities were expressed as inhibition diameter zones in millimeter (mm). Gentamicin (GEN) and Cloxicillin (CXC) were used as control.

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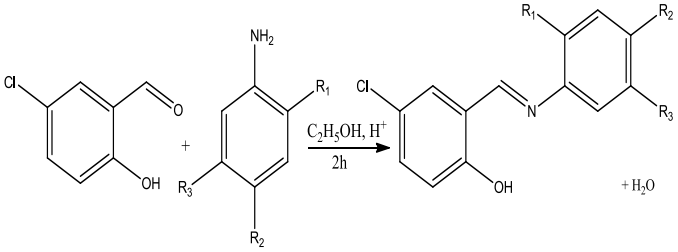
Result and Discussion

Synthesis

The condensation of 5-chlorosalicyladehyde and corresponding substituted aniline give the corresponding Schiff bases: I (E)-4-chloro-2-((phenylimino)methyl)phenol, II (E)-4-chloro-2-((2-methoxyphenylimino)methyl)phenol, III (E)-4-chloro-2-((4-chlorophenylimino)methyl)phenol, IV (E)-4-chloro-2-(((5-chloro-2-methylphenyl)imino)methyl)phenol.



R_1= H, R_2= H, R_3= H (I)

R_1= OCH_3, R_2= H, R_3= H (II)

R_1= H, R_2= Cl, R_3= H (III)

R_1= CH_3, R_2= H, R_3= Cl (IV)

Scheme 1. Synthetic route to compounds 1-4.

The compounds were obtained as light – deep yellow solids in good yields. They are stable. Their spectroscopic data are summarized below (Table 1). The IR spectra show the absence of the carbonyl band, C=O for the aldehydic group and the presence of band in the region 1617-1610 cm^{-1} attributed to HC=N, azomethine bond, indicate the formation of the Schiff bases. The Phenolic, (C−O) band is observed at 1282-1254 cm^{-1} while the O−H band appeared in the region 2980- 2400 cm^{-1}. The lower frequency of the OH band is due to the intramolecular hydrogen bonding. The NMR spectra further confirmed the formation of the compounds by the appearance of a singlet between 8.90-8.60 ppm in the ^1H NMR (Fig. 1-4) and 163.50-160ppm in the ^{13}C NMR spectra attributed to the azomethine, H−C=N protons and carbons respectively. The UV spectra of the Schiff bases show two absorption peaks at 286-260 and 346-360 nm. These are assigned to n-π * of the azomethine and π-π * of the aromatic ring in the Schiff bases. Important IR, NMR (^1H and ^{13}C) and UV peaks of the compounds are listed in (Table 2).

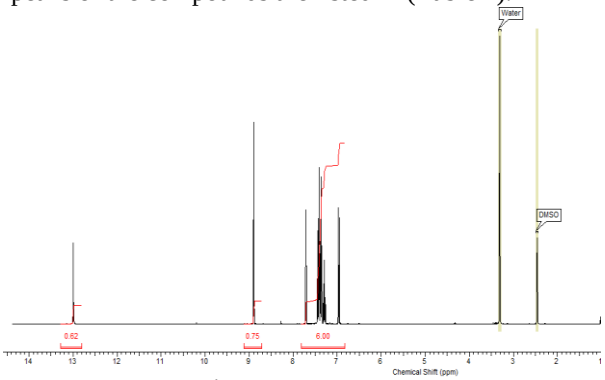


Fig 1a. ^1H NMR spectrum of I.

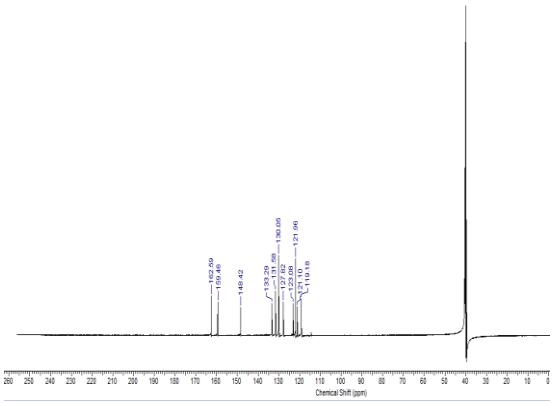


Fig 1b. ^{13}C NMR spectrum of I.

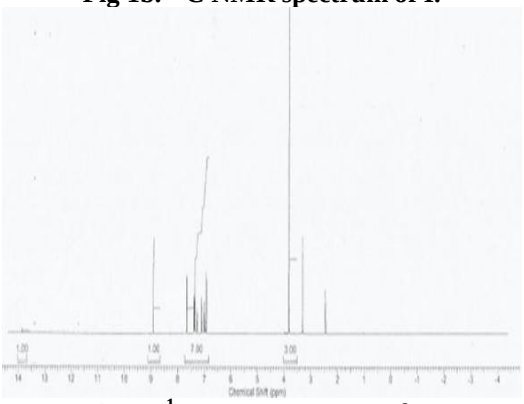


Fig 2a. ^1H NMR spectrum of II.

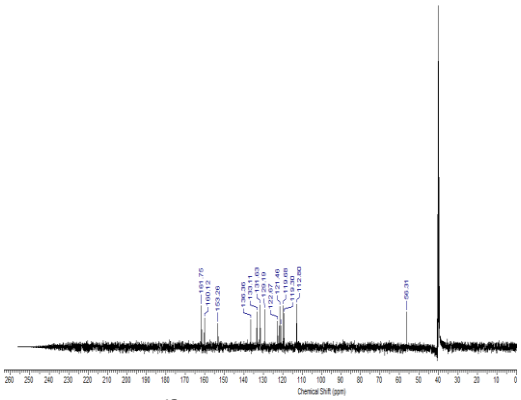


Fig 2b. ^{13}C NMR spectrum of II.

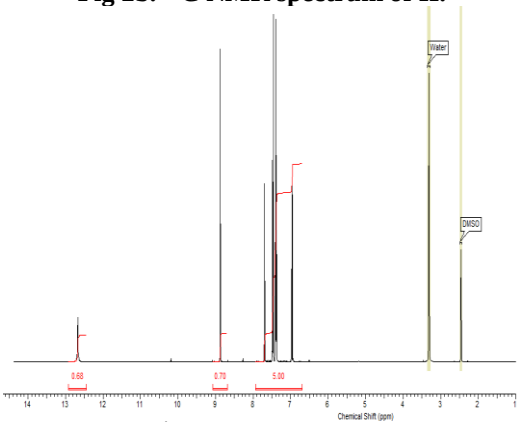


Fig 3a. ^1H NMR spectrum of III.

Table 1. Physical and analytical data of the Schiff bases.

Compounds	Empirical formula	Molecular weight (g/mol)	Yield (%)	Elemental analysis (calculated)		
				%C	%H	%N
I	$C_{13}H_{10}ClNO$	231.68	68.39	67.36(67.39)	4.34(4.35)	6.04(6.05)
II	$C_{14}H_{12}ClNO_2$	261.70	60.52	64.20(64.25)	4.59(4.62)	5.35(5.33)
III	$C_{13}H_9Cl_2NO$	266.12	83.27	58.65(58.67)	3.40(3.41)	5.24(5.26)
IV	$C_{14}H_{11}Cl_2NO$	280.15	96.54	59.99(60.02)	3.96(3.97)	5.00(5.00)

Table 2. Important IR, NMR (^{1}H and ^{13}C) and UV of the compounds.

Compounds	IR (cm^{-1})		NMR		UV-vis (nm)	
	C=N	C−O	δ(ppm)	Assignments	n-π*	π-π*
I	1613	1275	12.99	(s, 1H, −HO)	260	346
			8.89	(s, 1H, −HC=N)		
			7.71-6.83	(m, 6H, CH_{Ar})		
			162.59	(s, 1C, −CH=N)		
II	1615	1254	13.85	(s, 1H, −HO)	286	360
			8.91	(s, 1H, −HC=N)		
			7.70-6.80	(m, 7H, CH_{Ar})		
			3.81	(s, 3H, $CH_{methoxy}$)		
			161.75	(s, 1C, −CH=N)		
III	1610	1275	12.67	(s, 1H, −HO)	262	351
			8.87	(s, 1H, −HC=N)		
			7.69-6.95	(m, 5H, CH_{Ar})		
			162.85	(s, 1C, −CH=N)		
IV	1617	1282	12.87	(s, 1H, −HO)	263	353
			8.81	(s, 1H, −HC=N)		
			7.70-6.93	(m, 6H, CH_{Ar})		
			2.23	(s, 3H, CH_{methyl})		
			163.25	(s, 1C, −CH=N)		

Key: s = singlet, m = multiplet

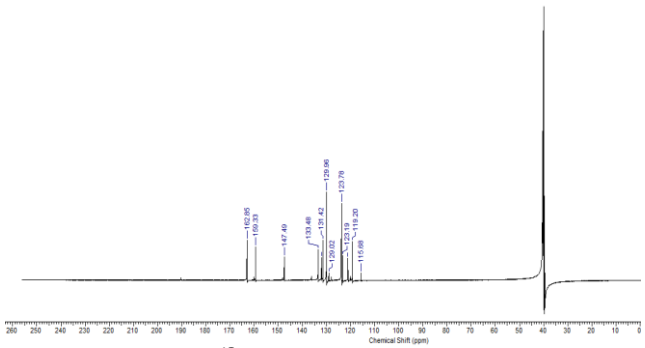


Fig 3b. ^{13}C NMR spectrum of III.

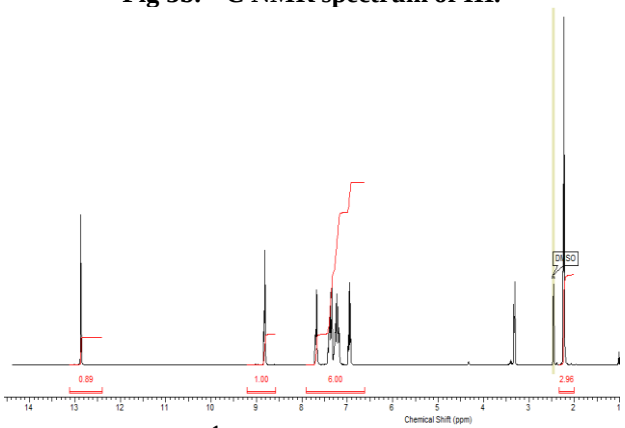


Fig 4a. ^{1}H NMR spectrum of IV.

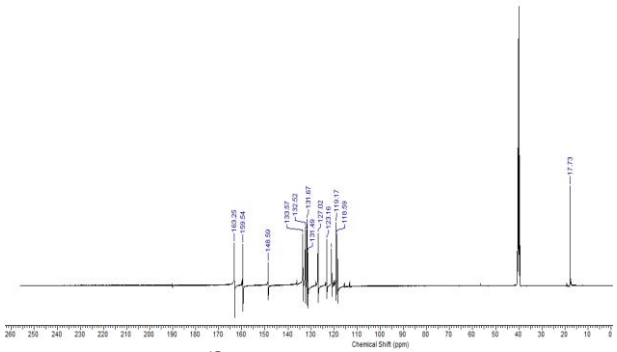


Fig 4b. ^{13}C NMR spectrum of IV.

Antimicrobial activity

The result of the antimicrobial activity of the compounds (Table 3) indicate that I and II are active against all the bacteria strains (positive and negative) at varying degrees. Compound II with the electron releasing methoxy group exhibited the highest activity. Compound IV showed activity against all the bacteria except *S. agalactiae* and also inactive against *S. typhimurium* and *P.mirabilis* at 10mg/ml. Compound III showed activity against *K. pneumonia, P. aeruginosa, S. aureus* and *S. typhimurium* with no activity against *E.coli, S. agalactiae and P.mirabilis*. The resistance of the pathogens towards the tested compounds can be attributed to the existence of cell wall in gram positive bacteria which reduces the permeability of the tested compounds, while the activity against them can be attributed to the greater lipophilicity of the compounds.

Table 3. Zone of inhibition showing the antimicrobial potentials of compounds (1-4).

Bacteria	Concentration of compounds / Zones of inhibition											
	I			II			III			IV		
	40 mg/ml	20 mg/ml	10 mg/ml	40 mg/ml	20 mg/ml	10 mg/ml	40 mg/ml	20 mg/ml	10 mg/ml	40 mg/ml	20 mg/ml	10 mg/ml
E. coli	13	13	12	30	30	30	0	0	0	22	20	20
K. pneumonia	14	14	14	30	30	30	12	11	10	15	12	10
P. aeruginosa	30	30	30	30	30	30	12	12	10	18	18	18
S. agalactiae	14	14	14	30	30	30	0	0	0	0	0	0
S. aureus	18	18	14	30	30	30	14	14	14	14	14	14
S. typhimurium	13	13	12	30	30	30	10	10	10	10	10	0
P.mirabilis	14	14	14	30	30	30	0	0	0	10	10	0

The difference between compounds III and IV with electron withdrawing chloro groups might be due to the effect of the electron donating methyl group on IV.

Conclusion

Four Schiff bases from 5-chlorosalicyladehyde and variously substituted aniline have been synthesized and characterized. The antimicrobial result reveals the order of activity of the compounds as II > I > IV > I II. This shows that the antimicrobial activity of the compounds depends on the nature of the substituent on the aniline.

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