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Synthesis and Antimicrobial Activity of Schiff Bases Derived from Substituted Salicylaldehyde with 2-aminophenol and 2-aminothiophenol

Fasina, T. M.*[1], Ejiah, F. N.[1]Dueke-Eze, C.U.[1] and Idika N[2]
[1]*Department of Chemistry, University of Lagos. Akoka.*
[2] *Department of Microbiology, Nigerian Institute of Medical Research, Yaba*

ABSTRACT

Schiff bases of substituted salicylaldehydes namely 5-bromosalicylaldehyde and 5-nitrosalicyladehyde with 2-aminophenol and 2-aminothiophenol have been synthesized and characterized by IR, NMR and elemental analysis. All synthesized compounds were screened for their antimicrobial activity against some clinically important bacteria; Escherichia coli ATCC 25922, Pseudomonas aeruginosa ATCC 27853, Staphylococcus aureus ATCC25923, Enterococcus feacalis ATCC 29212 by Agar ditch method using N,N'-dimethylformamide (DMF) and 1,4-dioxane as solvents. Activity data shows a higher activity of the compounds in DMF with the bromo substituted imines more potent than the nitro substituted compounds

Key words: Schiff base, 2-aminophenol, 2-aminothiophenol, antimicrobial activity

INTRODUCTION

Schiff bases are a class of important compounds owing to their wide range of properties and applications. These compounds have received much attention because of their use as models for biological system (Banik and Banik, 2003) and applications as catalysts in various chemical and photochemical reactions (Gao and Zheng, 2002). Schiff bases are reported to show antibacterial (da Silva *et al*., 2010; Shi *et al*., 2007), antifungal (Jarrahpour *et al*., 2007) anticancer (T'ang *et al*., 1885) and herbicidal (Aggarwal et al., 2009; Samadhiya. and Halve, 2001) activities. In addition, salicylaldimines exhibit interesting electronic properties due to close proximity of the hydroxyl and imine groups. These compounds show important photochromism where light absorption causes interconversion between the enol-imine and keto-amine tautomers (Guha *et al*., 2000). The biological activity of the compounds is mainly dependent on their molecular structure. It is known that the spectral behaviour is strongly related to the ground state and excited state structures of the compounds. Thus, spectra behaviour of Schiff bases has been investigated for use in structure elucidation (Schiff *et al*., 2002).

In this study, Schiff bases of 2-aminophenol and 2-aminothiophenol with 5-bromosalicyladehyde and 5-nitrosalicyladehyde have been synthesized and characterized to investigate the effect of substituent on the biological activity of the Schiff bases.

MATERIALS AND METHOD

All chemicals 2-aminophenol, 2-aminothiophenol, 5-bromosalicylaldehyde and 5-nitrosalicylaldehyde were obtained from Aldrich. The solvents: ethanol, methanol, N,N"-dimethylformamide (DMF) and acetonitrile were of spectroscopic grade and used without further purification.

IR spectra were recorded as nujol mulls on a Shimadzu FT-IR 157 Spectrophotometer. NMR Spectra were recorded in using dimethysulfoxide (DMSO-d_6) as solvent with TMS as internal standard on a Brucker 400 MHz spectrometer. Elemental analyses were determined at the Durham University elemental analysis service. Melting points were determined using a Gallenkamp melting point apparatus.

TYPICAL SYNTHESIS

Equimolar quantities (0.04 mol) of aldehyde and primary amine were dissolved in ethanol (45 ml) with the addition of 3 drops of formic acid. The mixture was heated under reflux at 70^{o}C for 4 hours. The precipitate formed was separated by filtration, re-crystallized from ethanol, and dried in a desiccator.

* *Corresponding Author: tofefash@yahoo.ca*

4-bromo-2-[(2-hydroxylphenyl)imino]methylphenol 1;
Yield 69%; I. R. (cm^{-1}) 3280, 2363.2, 2158, 2042,1984,1807, 1695, 1622, 1589, 1501, 1454, 1401, 1316, 1267, 1189, 1127, 1023, 920, 819, 747. 688. ^{1}H NMR (DMSO): 8.97 (s), 6.91-6.98 (m) 7.49-7.86(m). ^{13}C NMR: 160, 159.9, 151.3, 134, 134.4, 135.8, 126.5, 121.3, 119.6, 119.4, 119.1, 116.6, 109.9.
Anal calcd for $C_{13}H_{10}NBrO$: C 53.46; H 3.44; N4.43; found C 53.41; H 3.42; N 4.79.

4-bromo-2-[(2-suphanylphenyl)imino]methylphenol 2:
Yield 30%; I. R. (cm^{-1}) 2788, 2280, 1613, 1569, 1472, 1431, 1372, 1308, 1264, 1204, 1131, 1083, 1014, 976, 869, 815, 722. 622. ^{1}H NMR: 11.7 (s), 8.90 (s), 8.38 (s), 8.15(d, J=7.6), 8.08 (d, J=8), 7.56-7.45 (m), 7.07 (s). ^{13}C NMR: 162, 155.2, 151.3, 135.4, 134.4, 130.1, 126.4, 125.1, 122.4, 121.9, 120.9, 119.1, 110.8,
Anal calcd for $C_{13}H_{10}NBrS$: C 50.65; H 3.25; N4.55; found C 50.66; H 3.27; N 4.54.

4-nitro-2-[(2-hydroxylphenyl)imino]methylphenol 3: Yield 66%; IR (cm^{-1}) 3071; 2165, 1617,1577,1520,1483, 1329, 1278, 1210, 1101, 941, 815. ^{1}H NMR: 10.5, 9.4, 8.68, 8.55-8.22, 7.67-7.65 (d), 7.29-7.03, 6.98-6.95. ^{13}C NMR: 172.4, 159.2, 150.4, 136.8, 130.0, 129.8, 129.3, 128.7, 120.4, 119.8, 118.9, 116.6, 116.5.
Anal calcd for $C_{13}H_{10}N_2O$: C 60.47, H 3.88, N 10.85; found C 60.83, H 3.90, N 10.83.

4-nitro-2-[(2-suphanylphenyl)imino]methylphenol 4: yield 85%; IR (cm^{-1}); 3214.5, 2571.4, 1615, 1520. ^{1}H NMR: 9.18, 8.29-8.14(M), 7.58 -7.48 (m), 7.26(d). ^{13}C NMR: 161.4, 161.2, 151.2, 139.9, 127.1, 126.5, 125.3, 124.3, 122.6, 122.0, 119.6, 117.6.
Anal calcd for $C_{13}H_{10}N_2OS$: C 56.93, H 3.65, N 10.21; found C 57.47, H 3.22, O 10.20.

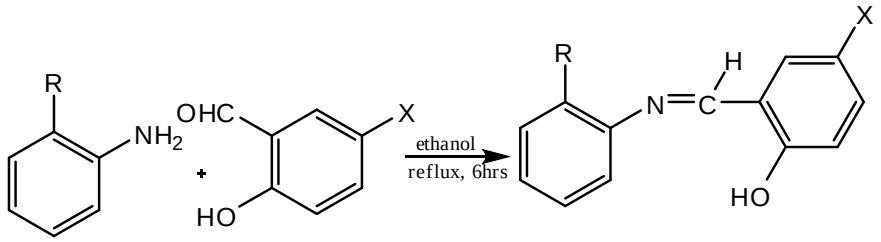
Biological Activity

The *in-vitro* antimicrobial activity of compounds **1-4** against *Staphylococcus aureus*, *Entercoccus feacalis*, *Pseudomonas aeruginosa* and *Escherichia coli* were determined using the agar ditch method (Parekh *et al*., 2005). The stock solution from which two- fold serial dilutions obtained was prepared by dissolving 40 mg of each compound in 1 mL of N,N-dimethylformamide (DMF) and 1,4-dioxane respectively.
A double layered Muller Hinton agar plate was aseptically prepared. The plate was flooded with standardized (0.5 McFarland) test microorganism and allowed to adjust to the environment for two minutes. A sterilized cork borer was used to make five wells radially. The wells were filled with the test compounds using a micropipette and incubated at 37 ^{o} C for 24 h. During this period, the test compounds 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 Schiff bases **1-4** were obtained in good yields from condensation reaction of 2-aminophenol or 2-aminothiophenol with the corresponding substituted salicylaldehyde (Scheme 1) and purified by successive recrystallization using ethanol. The purity of the compounds was checked by TLC. The compounds were characterized by ^{1}H NMR, infrared spectroscopy and elemental analysis.



R=OH, X=5-bromosalicyladehyde (1)

R=SH, X=5-bromosalicylaldehyde (2)

R=OH, X=5-nitrosalicylaldehyde (3)

R=SH, X=5nitrosalicylaldehyde (4)

Scheme 1: Synthetic route to Schiff bases 1-4

The important IR and ^{1}H NMR spectral bands for the compounds are listed in Table I.

Table 1: Important IR and NMR data of Schiff bases **1-4**

Compd	**IR(□ □ cm^{-1})**				**^{1}H NMR**
	OH	(C=N)	(SH)	(CO)str.	□ □ (HC=N)
1	3280	1622	-	1316	□□ □□
2	-	1613	2728	-	□ □ □ □
3	3037	1617	-	1307	□ □□ □
4	3214	1615	2571	-	□ □ □□

The infrared spectra of the compounds reveals the disappearance of the band about 1700 cm^{-1} attributed to the carbonyl group(C=O) and appearance of a band in the region 1622 -1613 cm^{-1} assigned to the azomethine (HC=N) bond thereby indicating formation of the Schiff base in all cases. The bands in the phenolic compounds **1** and **3** occur at lower wavenumbers to those of the thiol compounds **2** and **4**, in line with the higher polarity of the hydroxyl group compared to the thiol group. The formation of the Schiff base was further confirmed by appearance of a singlet at 8.96-9.38 in the ^{1}H NMR spectra characteristic of the azomethine proton.

Antimicrobial Activity

The *in vitro* antimicrobial activity of the compounds against some clinically important gram positive and gram negative bacteria in DMF and dioxane are reported in Table 2.

The activity of antibacterial agents is influenced by the morphology of the bacteria cell wall. The cell wall is composed of peptidoglycan which is thicker in the Gram positive bacteria and this usually poses a barrier to the degree of diffusion of antibacterial agents into the enzyme (Mims *et al*., 2004).

Table 2: Antibacterial screening data of Schiff bases **1-4**

Compd	**Solvent**	***S.aureus***			***P. aueroginosa***			***E. Feacalis***			***E.coli***		
		40	10	2.5	40	10	2.5	40	10	2.5	40	10	2.5
1	DMF	3+	3+	3+	-	-	-	3+	3+	3+	3+	3+	-
	Dioxane	3+	3+	2+	3+	-	-	-	-	-	-	-	-
2	DMF	3+	3+	+	2+	-	-	3+	3+	2+	2+	+	-
	Dioxane	3+	3+	3+									
3	DMF	3+	3+	3+	-	-	-	-	-	-	+	-	-
	Dioxane	-	-	-	-	-	-	-	-	-	-	-	-
4	DMF	3+	3+	+	2+	-	-	-	-	-	2+		
	Dioxane	-	-	-	-	-	-	-	-	-	-	-	-

Concentration in mg/ml

Activity key: + = 0.1 -0.5 cm beyond control (less active); 2+ = 0.6 -1.1cm beyond control (moderately active); 3+ = ≥1.2 cm beyond control (highly active) All compounds were active against *S.aureus* in DMF to varying extents. The bromo substituted imines **1** and **2** were highly active against the gram positive bacteria *S.aureus* and *E. Feacalis* at all concentrations studied. In addition, these compounds also showed high activity against *S.aureus* in dioxane. Thus indicating that the activity of bromo substituted imines **1** and **2** were selective activity against gram positive bacteria irrespective of the substituent on the amine component of the imine. The nitro substituted compounds **3** and **4** exhibited decreased activity against all bacteria strains studied with no activity against *E. Feacalis* in both solvents used. This correlates with observation that *p*-nitro substitution decreases antibacterial activity (Halve *et al*., 2006).

The different effect of the compounds against bacteria screened may be due to substituent on either the aldehyde or amine, and solvent utilized in the study. The diffusion capacity of the imines seems to increase with increased polarity of solvent. Minimal activity at highest concentration used was observed for *P. aueroginosa*. This bacterium thus appears to be the most resistant in this study.

CONCLUSION

Antibacterial activity of the synthesized compounds **1-4** studied in DMF and 1,4-dioxane was found to be dependent on both the substituent on the Schiff base and nature of solvent medium. DMF appears to be a better solvent than dioxane with the studied compounds, since it had higher inhibitory activity at lower concentrations studied. Compounds **1** and **2** were active at inhibiting Gram–positive bacteria. Hence, these compounds can be used in formulation of narrow spectrum antibiotics for treatment of infections caused by gram positive bacteria particularly *S.aureus*.

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