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Full Length Research Paper

Synthesis, electronic spectra and inhibitory study of some Salicylaldehyde Schiff bases of 2-aminopyridine

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A series of Schiff bases namely N-(2-hydroxylbenzylidene)pyridin-2-amine (I), N-(5-nitro-2-hydroxylbenzylidene)pyridin-2-amine (II), N-(5-bromo-2-hydroxylbenzylidene)pyridin-2-amine (III) and N-(5-methoxy-2-hydroxylbenzylidene)pyridin-2-amine (IV) derived from 2-aminopyridine and substituted benzyaldehydes are reported and characterized by IR, ^{1}HNMR and elemental analysis. The electronic absorption spectra of the compounds were studied in ethanol, N, N- dimethylformamide (DMF) and 1, 4-dioxane. The observed absorption bands were assigned to corresponding electronic transitions. A band above 400 nm obtained in II reveals keto-enol tautomerisim in DMF. *In vitro* screening of the compounds on *Staphylococcus aureus* ATCC 25923*, Enterococcus feacalis* ATCC 29212, *Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922 in N, N- dimethylformamide (DMF) and 1,4-dioxane was studied using agar ditch method. The results indicate that the compounds have the capacity to inhibit the growth of *S. aureus* and *E. coli* in varying concentrations. The inhibitory ability was influenced by the solvent and substituent group on the salicyldene fragment.

Key words: Schiff base, 2,aminopyridine, keto-enol tautomerisim, inhibitory ability.

INTRODUCTION

During the past decade, life-threatening infectious diseases caused by gram positive and gram negative pathogenic bacteria have increased to an alarming level around the world. This increase coupled with emergence of bacteria resistant to commonly used antibiotics has resulted in the need to evolve new classes of antibacterial agents to combat infections. Understanding the chemistry of molecular biology has created a significant class of compounds that are now employed as antibacterial agents. A class of compounds that has shown great promise in this area are the Schiff bases (Fessenden and Fessenden, 1989). A Schiff base is the nitrogen analogue of aldehyde in which the C=O group is replaced by a C=N group.

Schiff bases are reported to exhibit antibacterial (Parekh et al., 2005; Sinha et al., 2008; Zhang et al., 2006; Hou et al., 2010), antifungal (Aggarwal et al., 2009) and antitumor activity (Adsule et al., 2006). In addition, the compounds and their metal complexes exhibit interesting photophysical properties (Hadjoudis, 1995).

The spectra behaviour of Schiff bases has been investigated for use in structure elucidation (Houlden and Csizmadia, 1969; Guha et al., 2000; Issa et al., 2003; Schiff et al., 2002). Salicylidimines show important photochromism where light absorption causes interconversion between enol-imine and keto-amine tautomers through intramolecular hydrogen transfer. They have also been shown to exhibit a variety of biological activities with substituted salicylaldehyde compounds possessing higher activities (Prisakar et al., 2005). This has led to intense research on this class of compounds (Pelttari et al., 2007) and their metal complexes (Chohan et al., 2007; Tsapkov et al., 2008). Similarly, the presence of hetero-atoms in the Schiff bases enhances activity (Shi et al., 2007).

As part of our efforts in understanding the role of subtle electronic variations on molecular activity, we report a study of the effect of substituent position in salicylidene-2-aminopyridine Schiff bases on the absorption spectra in organic solvents of varying polarities and their antibacterial activity against some common pathogens

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namely *Staphylococcus aureus*, *Entercoccus feacalis*, *Pseudomonas aeruginosa and Escherichia coli*.

MATERIALS AND METHODS

All chemicals were obtained commercially from Zayo-Sigma Chemicals Ltd. Solvents: ethanol, N, N-dimethylformamide (DMF), 1, 4-dioxane and hexane were of analytical grade and used without further purification. Melting points were determined on a Gallenkemp England melting point apparatus. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS/O analyzer. Infrared spectra were recorded on a FT-IR Perkin-Elmer 1600 spectrometer as nujol mulls. NMR spectra were performed in $CDCl_3$ on a Bruker AMX 400 spectrometer using tetramethylsilane (TMS) as internal standard. The electronic absorption spectra of the compounds were investigated in N, N-dimethylformamide (DMF) and 1, 4-dioxane and recorded on a PG T80/T80$^+$ UV-VIS Spectrophotometer using 1 cm quartz cell immediately after preparing the solutions.

Antibacterial screening was done at the Nigeria Institute of Medical Research (NIMR), Yaba, Lagos, Nigeria.

General procedure for preparation of Schiff bases

N-(2-hydroxylbenzylidene)pyridin-2-amine (I)

A solution of 2-hydroxybenzaldehyde (2.45 g, 20 mmol) in ethanol (10 ml) and two drops of formic acid were added to a stirred solution of 2-aminopyridine (1.88 g, 20 mmol) in ethanol (10 ml) . Thereafter, the reaction mixture was refluxed for 6 h, the precipitate collected by filtration and recrystallized from ethanol-hexane (1:1).

Yellow-orange crystal; yield 35%; mp 62-64°C. IR (cm^{-1}): 3434, 1613, 1589, 1278, 1256, 1148, 993, 915, 845, 790, 732, 578. ^{1}HNMR ($CDCl_3$, 400mHz): 6.91-8.49(m, 8H), 9.41(s,1H), 13.40(s,1H). Anal.calcd for $C_{12}H_{10}N_2O$: C,72.72, H,5.05, N,14.14.Found:C,72.33, H,5.03, N,14.0.

N-(5-nitro-2-hydroxylbenzylidene) pyridin-2-amine (II)

Yellow solid; yield 46%; mp 182-184°C. IR (cm^{-1}): 3053, 1615, 1585, 1527, 1430, 1289,1108, 1090, 992, 895, 829, 787, 706, 639. ^{1}HNMR ($CDCl_3$, 400 MHZ): 7.10 to 8.54 (m, 7H), 9.53(s, 1H), 14.56(s, 1H).

Anal.calcd for $C_{12}H_9N_3O_3$: C, 59.26, H, 3.70, N, 17.28. Found: C, 59.14, H, 3.56, N, 16.96.

N-(5-bromo-2-hydroxylbenzylidene) pyridin-2-amine (III)

Light-orange crystal; yield 81 %; mp 138-140°C; IR (cm^{-1}): 1607, 1582, 1431, 1341, 1271, 1179, 1073, 991, 915, 871, 812, 783, 739, 699, 624. ^{1}HNMR ($CDCl_3$, 400 MHZ): 6.89-8.49(m, 7H), 9.34(s,1H), 13.42(s,1H).

Anal.calcd for $C_{12}H_9N_2OBr$: C, 51.98, H, 3.24, N, 10.10. Found: C, 51.96, H, 3.21, N,9.88

N-(5-methoxy-2-hydroxylbenzylidene) pyridin-2-amine (IV)

Dark-orange crystals; yield 75%; mp 82-84°C. IR (cm^{-1})**:** 1609, 1575, 1549, 1484, 1325, 1271, 1143, 1027, 991,890, 830, 770, 623. ^{1}HNMR ($CDCl_3$, 400 MHZ): 3.77(s, 3H), 6.92 to 8.48(m,7H), 9.37(s, 1H), 12.93(s, 1H).

Anal.calcd for $C_{13}H_{10}N_2O_2$: C, 68.42, H,5.26, N,12.28. Found: C, 68.32, H, 5.28, N, 12.14.

Biological activity

The *in-vitro* effect of compounds I to IV were tested against *S. aureus*, *E.feacalis*, *P.aeruginosa* and *E.coli*. The stock solution from which two- fold serial dilutions were employed 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 for two minutes to adjust to the environment. 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°C for 24 to 48 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

Condensation of the 2-aminopyridine with the corresponding aldehyde readily gave rise to the corresponding Schiff bases N-(2-hydroxylbenzylidene)pyridine-2-amine (I), N-(5-nitro-2-hydroxylbenzylidene) pyridin-2-amine (II), N-(5-bromo-2-hydroxylbenzylidene) pyridin-2-amine (III) and N-(5-methoxy-2-hydroxylbenzylidene) pyridin-2-amine (IV) (Figure 1).

All the compounds are air stable with sharp melting points indicating the purity of the compounds. The elemental analyses of the compounds are in agreement with the composition suggested for the compounds. The IR of each compound confirms the formation of imine bond (–C=N-) and absence of the original aldehydic bond (-C=O). A band at 1607-1615 cm^{-1} is assigned to the stretching vibration of the imine group v (C=N). All the compounds displayed a band at 1271-1289 cm^{-1} which is assigned to v(C-O) stretching vibration of the Phenolic –OH, respectively. The *v*(OH) band at 3434-3438 cm^{-1} was observed only in compounds I and II. Proton NMR showed sharp singlet at 9.34-9.53 ppm which further confirmed the formation of –C=N- bonds.

Electronic absorption spectra

The electronic absorption spectra of the compounds (I to IV) were obtained in ethanol, DMF and 1,4-dioxane and are listed in Table 1. The spectra consist of several absorption bands in the 200 to 500 nm region. Molecular structure of compound and polarity of medium affect the spectral behaviour of Schiff base. The first one or two bands (Bands A and B) appearing within the 200 -270 nm region can be assigned to the π–π^* transition of the aromatic rings. These bands are sensitive to substitution on the aromatic ring and their positions are little

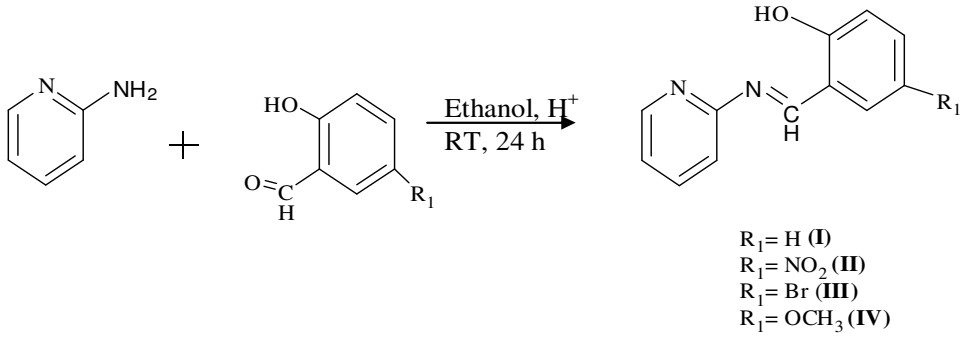

Figure 1. Reaction scheme for the synthesis of Schiff bases I to IV.

Table 1. Electronic absorption bands of Schiff bases.

Schiff bases	Solvent	Band A		Band B		Band C		Band D		Band E	
		λ_{max}	logε	λ_{max}	logε	λ_{max}	logε	λ_{max}	logε	λ_{max}	logε
	Ethanol	207	4.29	268	4.00	305	4.11	347	4.05	-	-
I	DMF	-	-	268	3.77	300	3.86	-	-	-	-
	Dioxane			269	3.91	305	4.01	351	3.97		
	Ethanol	233	4.38	300	4.05	348	3.85	387	3.77	-	-
II	DMF	209	4.18	-	-	-	-	377	3.93	429	4.57
	Dioxane			297	4.05						
	Ethanol	-	-	255	4.48	298	4.06	354	3.91	-	-
III	DMF	-	-	255	3.04	302	3.35	361	3.42	-	-
	Dioxane					306	4.01	360	3.92		
	Ethanol	230	4.29	268	4.11	302	4.23	379	4.02	-	-
IV	DMF	217	4.04	269	4.26	302	4.28	379	4.06	-	-
	Dioxane					304	3.90	380	3.66		

influenced by changing the solvent polarity (Hammud et al., 2006). The third band (Bands C) observed within the wavelength range 290-310 nm is due to transition between the π–orbital localized on the central azomethine (–CH=N-) bond (Soliman, 1997). The fourth band located within the 340 to 400 nm region can be ascribed to charge transfer within the entire Schiff base molecule. This band is commonly observed in o-hydroxyl Schiff bases (Gahr, 1990) and is based on strong intramolecular hydrogen bonding between the hydroxyl group of the salicylidene and the azomethine nitrogen (Sovilj et al., 1998).

The use of freshly prepared solutions allows a study of solvent and substituent effect on the shift in absorption maxima for the enol-imine tautomer with minimum interference from the keto-amine tautomer. Furthermore, aminopyridine Schiff bases exhibit a reduced tendency to tautomeric interconversion as a result of the decreased basicity of the imino nitrogen group due to electron delocalization (Galic et al., 1997; Nazir et al., 2000). However, the electron-withdrawing nitro group in II increases the acidity of the salicylaldehyde OH thereby favouring keto-amine tautomer formation (Figure 2).

This is reflected in the band at 429 nm observed in the more polar solvent DMF (dielectric constant (ε) =36.7). This band probably arises from inter-molecular charge transfer from solvent to the anti-bonding orbital of the OH bond belonging to the salicylaldehyde moiety and is more sensitive to solvent polarity than bands resulting from local transitions (Ayad and Mansour, 1995). The solvent stabilizes intramolecular proton transfer in the compound resulting in existence of keto-enol tautomerism.

The charge transfer band (Band D) shifts to longer wavelength with a change in ring substituent in the order H<Br<OMe<NO_2, this parallels the electron-withdrawing nature of the substituent. The red shift indicates a decrease in HOMO-LUMO energy gap, probably as a result of destabilization of the HOMO by the electron withdrawing groups on the aldehyde.

The spectra data are good evidence for the presence of solute-solvent interactions. The absorption spectrum is affected by the nature of solvent used with changes in intensity and displacement of absorption band being observed. This effect is due to several solvent properties

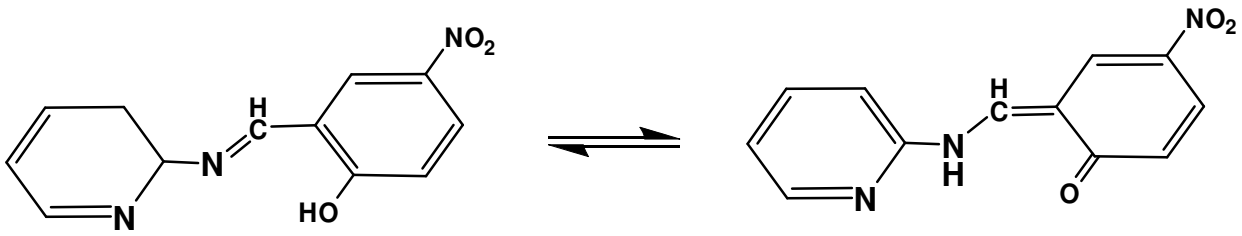

Figure 2. Keto-enol tautomerism in N-(5-nitro-2-hydroxylbenzylidene) pyridin-2-amine (II).

Table 2. Antibacterial activity of the Schiff bases in DMF.

Compounds		*S. aureus*							*E. feacalis*				*E. coli*			*P. aeruginosa*
	Concentration (mg/ml)	**40**	**20**	**10**	**5**	**2.5**	**1.25**	**0.62**	**40 - 1.25**	**40**	**20**	**10**	**5**	**2.5**	**1.25**	**40 - 1.25**
I		3+	3+	1+	0	0	0	0	0 - 0	2+	2+	1+	0	0	0	0 - 0
II		3+	3+	3+	3+	3+	2+	0	0 - 0	3+	2+	0	0	0	0	0 - 0
III		3+	3+	3+	3+	3+	2+	1+	0 - 0	3+	3+	3+	2+	1+	0	0 - 0
IV		3+	2+	2+	1+	0	0	0	0 - 0	3+	2+	0	0	0	0	0 - 0

Inhibition values = 1 - 5 mm = 1+ (less active); 6 - 11 mm = 2+ (moderate active); >12 mm = 3+ (highly active), 0 = not detected.

such as dipole moment, dielectric constant, refractive index and capability of hydrogen bonding. The solvent effect is thus the sum of several individual factors which may be additive or cancel out such that an accurate method to measure this effect is difficult.

The electronic absorption spectra of the investigated Schiff bases show a shift in λ_{max} in different solvents. There is a slight shift to longer wavelengths for low energy bands (Band C) with increasing solvent polarity. This suggests that the band arises from intramolecular charge transfer with the azomethine group being the primary center contributing to CT.

The peaks due to π–π^* transition (Band B) is insensitive to solvent polarity in all compounds except II indicating no contribution by hydrogen bonding to stabilization of both ground and excited states. The nitro substituent however, alters the resonance effect on the ring with hydrogen bonding effect stabilizing the ground state more than the excited states (Hammud et al., 2006).

Antibacterial activity

Antimicrobial activity of the compounds in DMF and dioxane are reported in Tables 2 and 3. The morphology of the cell wall is a key factor that influences the activity of antibacterial agents. The cell wall of the bacteria 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). Four standard bacteria strains screened were gram positive *S. aureus* (ATCC 25923) and *E. feacalis* (ATCC 29212), and gram negative *E. coli* (ATCC 25922) and *P. aeruginosa* (ATCC 27853).

All compounds were active against *S. aureus* and *E. coli* and inactive against *E. feacalis* and *P.aeruginosa.* The unsubstituted salicylaldehyde Schiff base I had minimal activity against bacteria studied in both solvents. Inhibitory studies of *S. aureus* in DMF revealed that III containing the bromo substituent exhibited activity at lowest concentration studied (0.625 mg/ml) with the electron-donating OMe Schiff base IV having the

Table 3. Antibacterial activity of the Schiff bases in 1, 4-dioxane.

Compounds		*S. aureus*							*E. feacalis*				*E. coli*				*P. aeruginosa*
	Concentration (mg/ml)	40	20	10	5	2.5	1.25	0.62	40 - 1.25	40	20	10	5	2.5	1.25	40 - 1.25
I		3+	2+	0	0	0	0	0	0 - 0	3+	2+	2+	0	0	0	0 - 0
II		3+	3+	3+	3+	3+	3+	2+	0 - 0	3+	2+	1+	1+	0	0	0 - 0
III		2+	2+	0	0	0	0	0	0 - 0	3+	3+	3+	3+	2+	0	0 - 0
IV		3+	3+	3+	2+	0	0	0	0 - 0	3+	3+	2+	1+	0	0	0 - 0

Inhibition values = 1 - 5 mm = 1+ (less active); 6 - 11 mm = 2+ (moderate active); >12 mm = 3+ (highly active) , 0 = not detected.

Least activity at the highest concentration (5 mg/ml). The electron-withdrawing NO_2 compound, II was moderately active at (1.25 mg/ml). Solvent change to less polar dioxane reported a higher activity with the minimum inhibitory concentration unaffected, except for III which showed lower activity. This, coupled with the electronic absorption suggests that the keto-amine form which exists in DMF is less active compared to the enol-imine tautomer that exists in dioxane. Screening against the gram negative *E. coli* in DMF revealed that III showed activity at concentration of 2.5 mg/ml and both II and IV were active at 20 mg/ml The change of solvent to less polar dioxane, II and IV were active at lower concentrations of 5 mg/ml respectively. The higher activity reported in less polar solvent may be due to easier diffusion across the cell wall.

Conclusion

In conclusion, the absorption spectra of Schiff bases of 2-aminopyridine and substituted salicylaldehydes show both substituent and solvent effects. While the solvent has little effect on the π–π^* electronic absorption, the intra-molecular charge transfer band undergoes bathochromic shift with increased electron-withdrawing nature of the substituent.

The compounds have the capacity of inhibiting metabolic growth of *S. aureus* and *E. coli* to different extent. The antibacterial activity of the compounds depends on the nature of substituent present on the aldehyde. The importance of this lies in the potential use of the compounds as narrow spectrum antibiotics in treatment of some common diseases.

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