Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2013, 5(10):177-181

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Substituent effect on electronic absorption and biological properties of Schiff bases derived from aniline

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ABSTRACT

The effect of substituents on biological activity of Schiff bases was investigated using Schiff bases derived from the condensation of aniline with salicyaldehyde, 5-methoxysalicyaldehyde, 5-nitrosalicyladehyde and 2-hydroxynaphtaldehyde. The electronic absorption spectra of the compounds in DMF and ethanol reveal that compounds containing the electron withdrawing nitro or naphtyl groups exist in the keto-amine form in both solvents. The compounds were screened against some clinically important bacteria namely Escherichia coli (ATCC 25922), Proteus mirabilis (ATCC 13315), Enterococcus feacalis (ATCC 29212) and Staphylococcus aureus (ATCC25923) using the agar ditch method and results show that 5-methoxysalicyaldehyde Schiff base exhibited highest activity.

Keywords: Aniline, Schiff base, Substituent effect, biological activity, electronic spectra

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INTRODUCTION

The design of new ligands is crucial to formation of novel metal complexes with interesting properties and applications as the Chemistry of a metal complex is greatly influenced by the properties of the ligand. Since the electron donating and accepting properties of the ligand and presence of structural functional groups affects the nature of metal complex obtained, a knowledge of ligand properties can afford synthesis of metal complexes with tuneable properties.

Schiff bases are considered an important class of organic compounds, which have wide applications. In recent years, they have gained significant interest in the area of drug research and development owing to the broad bioactivities such as insecticidal[1], antibacterial[2], antituberculosis[3] and antimicrobial[4-5] reported for the compounds and their metal complexes. These compounds play an important role in biological systems and are observed in various enzymes such as transaminases, tryptophan synthase etc. The important physical and biological properties of these compounds are related to the presence of the intramolecular hydrogen bond and proton transfer equilibrium.

Schiff bases have also been utilized as ligands to synthesize metal complexes with interesting applications[6-7]. The steric and inductive effects introduced by substituents present on the aromatic portion of the Schiff base can influence the properties of the ligand significantly.

In continuation of our efforts in understanding the role of subtle electronic variations such as substituent effects on Chemistry and activity of Schiff bases and their metal complexes, we herein report the effect of substituents on the antimicrobial activity of Schiff bases derived from aniline and substituted salicyaldehyde.

EXPERIMENTAL SECTION

Chemicals used were purchased from Zayo-Sigma Chemicals Ltd. Solvents were of analytical grade and used without further purification.

Melting points were determined using the STUART SMP10 model Barnstead/Electrothermal digital melting point apparatus and are uncorrected. ^{1}HNMR was performed on a Bruker Avance 111 200MHz spectrophotometer using $CDCl_3$ as solvent with tetramethylsilane (TMS) as an internal standard. All chemical shifts are given in ppm referenced to TMS. Infrared spectra of the compounds were recorded as nujol mulls on a Perkin-Elmer Spectrum RX1 spectrophotometer in the range 4000 - 400 cm^{-1}. Microanalytical data were determined using a Perkin-Elmer automated model 2400 Series II CHNS/O analyzer. The electronic absorption spectra of the solutions were investigated in ethanol and N, N'-dimethylformamide. The spectra were recorded on a T80/T80$^+$ UV-VIS Spectrophotometer using 1 cm quartz cell at room temperature immediately after preparing the solutions.

Typical synthesis of Schiff bases

Synthesis of (z)-2-((phenylimino)methyl)phenol (L1)

To a solution of aniline (3.82 g, 41 mmol.) in hot absolute ethanol (20 ml) was added a solution of salicylaldehyde (5.02 g, 41 mmol.) in hot absolute ethanol (20 ml). The mixture was heated to reflux for 4 h, allowed to cool; the yellow solid obtained filtered, recrystallized from ethanol and dried in a dessicator. Yield: (5.55 g, 69.37 %); mp: 60 - 62^{o}C; ^{1}HNMR ($CDCl_3$) 6.94 (d, 1H, ArH), 7.03(d,.1H, ArH), 7.27-7.30 (m,.3H, ArH), 7.36 -7.44 (m, 4H, ArH), 8.62 (H, HC=N); ^{13}CNMR ($CDCl_3$): 117.25, 119.08, 121.15, 126.91, 129. 40, 132.38, 133.18, 162.65. IR (cm^{-1}**):** 1591, 1270. .Anal.Cald for $C_{13}H_{11}NO$ C: 79.16, H: 5.62, N: 7.10 found C: 79.15, H: 5.62, N: 7.15.

(Z)-4-methoxy-2-((phenylimino)methyl)phenol (L2)

Red crystalline solid (60.67 %); mp: 64 - 67^{o}C; ^{1}HNMR ($CDCl_3$) 3.80 (s, 3H, OMe), 6.89-6.96 (m,.3H, ArH), 7.26-7.29 (m, 3H, ArH), 7.40-7.44 (m, 2H, ArH), 8.58 (s, 1H, HC=N); ^{13}CNMR 55.92, 99.94, 115.29, 118.04, 118.77, 120.41, 121.14, 126.90, 129.38, 148.49, 152.22, 155.34, 162.36. IR (cm^{-1}**):** 1635, 1289. .Anal.Cald for $C_{14}H_{13}NO_2$ C: 73.99, H: 5.77, N: 6.16 found C: 73.17, H: 5.67, N: 6.06.

(Z)-4-nitro-2-(phenylimino)methyl)phenol (L3)

Orange crystals (83.47%); ^{1}HNMR($CDCl_3$) 7.07-7.48 (6H, ArH), 8.24-8.39 (2H, m, ArH), 8.71 (s, 1H, HC=N). ^{13}CNMR:118.08, 118.32, 121. 20, 128. 07, 128. 36, 129. 67, 139. 90, 146. 64, 160.59, 166.84. .IR (cm^{-1}**):** 1595, 1321.; Anal.Cald for $C_{17}H_{13}NO$: C: 64.46, H: 4.16, N: 11.56 found C: 63.94, H: 3.99, N: 11.47.

1-((phenylimino) methyl) naphthalen-2-ol (L4)

Yellow powder (98.95%);^{1}HNMR($CDCl_3$) 7.06 (d, 2H, ArH), 7.28-7.37 (m, 2H, ArH), 7.43-7.53 (m, 2H, ArH), 7.70 (d, 2H, ArH), 7.78 (d, 2H, ArH), 8.07(d, 2H, ArH), 9.31 (s, H, HC=N, 15.50 (s, H, OH). ^{13}CNMR: 108.67, 118.74, 120.15, 122.54, 123.52, 127.17,128.11, 129.38, 129.68, 133.24, 136.94, 144.79, 154.23, 171.16. IR(cm^{-1}**):** 1642, 1229.; Anal.Cald for $C_{17}H_{13}NO$: C: 82.57, H: 5.30, N: 5.66 found C: 81.84, H: 5.85, N: 5.29.

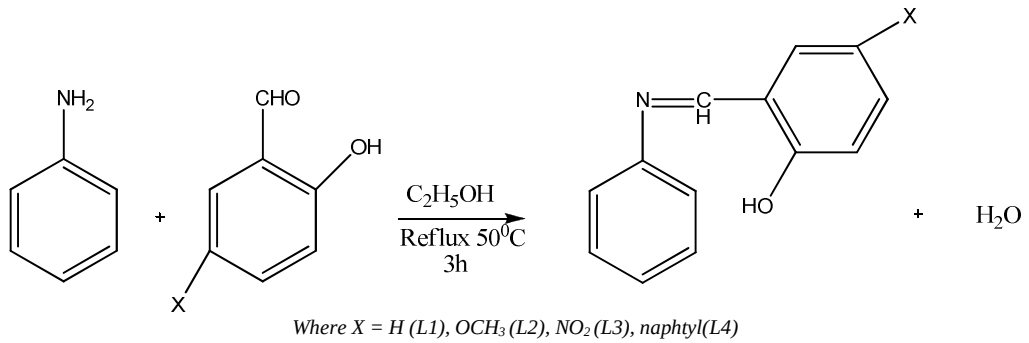
Determination of biological activity

In-vitro screening effect of the compounds was investigated using gram negative and gram positive bacteria namely *Staphylococcus aureus*, *Entercoccus feacalis*, *Escherichia coli* and *Proteus mirabilis* with solutions containing 5mg of each compound (L1-L4) in 1ml of dimethylformamide (DMF) using the Agar-ditch method [8]

The bacterial strain was inoculated in 25ml of McConkay agar and activated by incubation at 37^{o}C for 24 h. 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 four 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

The Schiff bases (**L1 - L4)** were obtained in moderate yields by condensation of aniline and the appropriate aldehyde namely salicyaldehyde (**L1**), 5-methoxysalicyaldehyde (**L2**), 5-nitrosalicyladehyde (**L3**) and 2-hydroxylnapthaldehyde (**L4**) under reflux condition (Scheme 1). The physical and analytical data of the Schiff bases are summarized in table 1. The compounds are air stable with sharp melting points indicating the purity of the compounds and microanalysis of the compounds are in agreement with the suggested composition.



Where X = H (L1), OCH_3 (L2), NO_2 (L3), naphtyl(L4)
Scheme 1: Synthetic route to Schiff bases L1-L4

Table 1: Physical and analytical data of L1-L4

Compound	Empirical Formula	Molecular Weight (g/mol)	Yield (%)	Melting Point (°C)	Colour	Microanalysis Found (Calculated)		
						%C	%H	%N
L1	$C_{13}H_{11}NO$	197	69.37	60 – 62	Yellow	79.15 (79.16)	5.62 (5.62)	7.15 (7.10)
L2	$C_{14}H_{13}NO_2$	227	60.67	64 - 66	Red	73.17 (73.99)	5.67 (5.77)	6.06 (6.16)
L3	$C_{13}H_{10}N_2O_3$	242.23	83.47	129-130	Orange	63.94 (64.46)	3.99 (4.16)	11.47 (11.56)
L4	$C_{17}H_{13}NO$	247.29	98.95	108-110	Yellow	81.84 (82.57)	5.85 (5.30)	5.29 (5.66)

Table 2 Important I. R bands of the Ligands

Compound	Empirical formula	IR ν (cm^{-1})		NMR (δ)	Uv-vis	
		(C=N)	(C-O)	(HC=N)	$\lambda_{max\ Ethanol}$	$\lambda_{max\ DMF}$
L1	$C_{13}H_{11}NO$	1598	1270.	8.62	339, 318, 302, 278	415 337 323 307 274
L2	$C_{14}H_{13}NO_2$	1635	1289	8.57	359 312 282	439 368 276
L3	$C_{13}H_{10}N_2O_3$	1595	1321	8.70	437 374 280	462 313 280
L4	$C_{17}H_{13}NO$	1642	1229	9.30	437 382 319	459 316

Table 2 summarizes the spectroscopic data of the compounds. The absence of the carbonyl stretch for the aldehydic group and presence of an intense band in the region 1595 – 1642 cm^{-1} attributed to azomethine group (C=N) stretching vibration confirms the formation of the Schiff base. In addition, a band is observed in the range 1229 – 1321 cm^{-1}due to (C-O) stretching frequency of the phenolic group. The formation of the compounds was further confirmed by the observation of a singlet between 8.57 – 9.30 ppm in the ^{1}H NMR and 162.35 - 171.16 in the ^{13}C

NMR spectra assigned to the imine proton and carbon respectively. Chemical shifts of the azomethine proton and carbon experience a downfield shift for the electron withdrawing substituents *p*-NO_2 and naphthaldehyde and an upfield shift for electron donating *p*-OCH_3 group on the salicylaldehyde ring[9].

The electronic absorption spectra of the compounds (**L1-L4**) were studied in ethanol and DMF. Typical absorption spectra of salcylaldimines are composed of bands attributed to high energy $\pi-\pi^*$ and medium energy charge transfer transitions. In addition, absorption bands due to intramolecular charge transfer from solvent to the antibonding orbital of the salicyladehyde hydroxyl bond may be observed in polar solvents[10]. This charge transfer band is attributed to stabilization of the polar excited states of the molecule by polar solvents.

The spectra of the compounds (**Table 2)** consist of several absorption bands in the 200-500 nm region. It is known that molecular structure of compounds and polarity of the medium affect the spectral behaviour of Schiff bases. All compounds exhibit intramolecular charge transfer bands in the region 310- 360 nm. This solvent sensitive band is ascribed to charge transfer within the whole molecule could arise from strong intramolecular hydrogen bonding between the hydroxyl group of salicylidene and the azomethine nitrogen. The absorption maximum is shifted to lower wavelength in **L3** and **L4** which have electron withdrawing substituents and a hypochromic shift in **L2** containing an electron releasing substituent. The spectra in ethanol is characterized by existence of a band above 400 nm ascribed to intermolecular charge transfer from solvent to the antibonding orbital of the hydroxy bond in the salicylaldehyde unit. This band indicates the existence of keto-enol tautomerism in the Schiff base. Observation of the band above 400 nm in the spectra of DMF solutions of **L3** and **L4** suggests the more acidic hydroxyl favour keto formation, thus, tautomerism occurs readily with electron withdrawing substituents and naphthaldimine Schiff bases [11].

Biological activity

The compounds were evaluated for antimicrobial activity against four bacterial species namely E. *coli*, *P.mirabilis*, *S. aureus* and *E. feacalis* using a concentration of 5 mg mL^{-1} of each compound. The diameter (mm) of growth inhibition zones was measured and results are summarized in table 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 [12].

Results indicate that all the compounds exhibit highest activity against gram negative bacteria strains studied. All the studied compounds were active against *E.coli* but inactive against the *E. feacalis* bacteria strain used. The unsubstituted salicylaldimine **L1** was active only against *E. coli* while **L2** with the electron releasing methoxy group exhibited highest activity against E. *coli*, *P.mirabilis* and *S. aureus*. This is in line with previous results indicating that Schiff bases act by forming a chelate with the bacterial strain[13]. Both the unsubstituted salicylaldimine **L1** and naphthaldimine **L4** were inactive against both gram positive bacteria strains studied but L4 inhibited both E.*coli* and *P.mirabilis*. Thus, suggesting that the naphthalene ring enhances biological activity compared to benzene.

Table 3: Antimicrobial activity data of synthesized compounds L1-l4

Compound	E. *coli*	*P.mirabilis*	*S. aureus*	*E. feacalis*
L1	15	0	0	0
L2	33	30	32	0
L3	11	16	10	0
L4	14	10	0	0
DMF	-	-	-	-

CONCLUSION

Four Schiff bases derived from aniline and variously substituted salicyladehydes have been synthesized and characterized. The solution absorption studies reveal that electron withdrawing naphthyl and nitro substitutents enhance formation of keto-amine tautomer. However, the electron donating substituent enhanced biological activity against the bacteria species studied. Further work is on going on the metal complexes of the compounds.

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