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Synthesis, Characterization and Antibacterial Activity Two New Schiff Bases derived from (E)-2-(((2-Aminoethyl) Amino) Methyl) Phenol (E)-2-(4-Aminobut-1-Enyl)-5-Methylbenzamine

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Abstract

In this study two new Schiff base ligands were synthesized, characterized and antibacterial activities were investigated against *Escherichia coli, Pseudomonas aeruginosa, Bacillus cereus, Salmonella typhimurium* and *Staphylococcus aureus*. (E)-2-(4-aminobut-1-enyl) phenol derived from ethylene diamine and salicyldehye. (E)-2-(4-aminobut-1-enyl)-5-methylaniline derived from 4-dimethyl amino benzaldehyde and ethylene di-amine. The Schiff bases were characterized by elemental analysis and FT-IR. The Schiff base ligands were screened *in vitro* for their antibacterial inhibiting potential by using disc diffusion method. The results indicated that the Schiff base I have showed biological activity against *E coli.* The main purpose of the study was to compare the inhibitory effect of these Schiff bases with commercial antibiotics Ciprofloxacin and Erythromycin to introduce new varieties of antibacterial agents.

Keywords: Schiff base; Antibacterial; FT-IR; Chemical synthesis

Introduction

In the last decades, the misuse, overuse, and uncontrolled prescriptions of antimicrobial drugs by population led to the increase of antimicrobial resistance to conventional drugs worldwide, representing, therefore, a serious threat to the current strategies employed to treat infectious diseases [1]. Resistant bacteria are causal agents of various infectious diseases that have led to increased mortality among patients. For instance, staphylococcal infection caused by the Grag positive bacteria *S. aureus* resulted in 11,000 fatal victims annually ranging from 10 to 25% depending on the immunological status of patients [2,3]. In addition, bacteria are economically important because, for example, it is responsible for bovine mastitis that leads to milk production losses [4].

To cope with this global health challenge, there is a clear need for the development of new and effective antimicrobial agents. Therefore, the success in designing antimicrobial agents which are distinct from those classical antibiotics is the key for treating such infectious diseases known for their chronicity and failure to treat with conventional antibiotics which will eventually lead to death. Synthetic molecules have emerged as potential substitutes for conventional drugs or even as and adjuvant to them [5]. Based on that, Schiff's bases have emerged as important antimicrobial molecules in the last years. Schiff bases have extensive applications in foodstuff manufacturing, pigment production, diagnostic chemistry, catalysis, antifungal, an agricultural chemical such as an herbicide or an insecticide as well as pharmacological activity or biological activities. Presently, the contemplation of Schiff bases along with their metal complexes is escalating outstanding to their marvelous biological and pharmacological usefulness. Schiff bases can play their important role as power storage space procedure, sensors, electrodes, planetary cells as well as biological sensor apart from its biological effectiveness [6,7].

Related to antimicrobial action, it´s been reported that Schiff bases present antibacterial [8,9]. In the last decades, scientists have expended expressive effort to use Schiff bases to target a condensing protein ketoacyl Acyl Synthase (KAS) from multi resistant gram positive and gram-negative bacteria [10,11]. In addition to that, the ability of Schiff bases to bind oxygen in redox systems and to oxidize DNA is also quite important to antibacterial activity [12]. These studies reinforce the importance of Schiff bases as possible antibiotic agent to treat bacterial infections.

Recently, our research group showed that a Schiff based complexes with cobalt has a great antibacterial activity against *Escherichia coli, Bacillus cereus, Klebsiella pneumoniae,* and *Staphylococcus aureus* at concentration of 32.2 µg. Here, we shown that a Schiff based derived from 4-dimethyl amino benzaldehyde and ethylene di-amine was analyzed by FT-IR possess antibacterial activity against *E. coli*.

Materials and Methods

General experimental condition

The chemicals salicyldehyde (Fluka), 4-dimethyl amino benzaldehyde (Fluka) and Ethylene-di-amine (Fluka) were used as received. All the solvents used in this study were obtained from Merck and used without any purification. The Infra-Red spectra of the synthesized compounds were recorded on on KBr pellets in the wave number range of 4000-400 cm^{-1} (PCSIR laboratories Peshawar). The elemental analysis (C, H and N) were carried out. The reactions were monitored by using TLC (Thin Layer Chromatography). TLC was performed on pre-coated silica gel plates (DC-Alugram 60 UV254 of. Merck), and the spots were observed firstly under UV (254 nm) and after that stained with cerium (IV) sulfate spray reagent and heated till coloration appeared.

Procedure for synthesis of schiff bases

(E)-2-(((2-aminoethyl) imino) methyl)phenol (SBI): A solution of salicyldehyde 5 mM (6.11 g) in 15 ml ethyl acetate was added to a stirred solution of Ethylene-di-amine 5 mm (3.0 g) in 15 ml warm (temperature) ethyl acetate. The reaction mixture was refluxed in (Reflux condenser) at 150°C for 5 h. The solid product was filtered off and washed with ethanol and subsequently dried over anhydrous $CaCl_2$ in a desiccator. The pure Schiff base was isolated as a yellow crystalline solid. This ligand was insoluble in commonly used organic solvents such as diethylether, n-hexane, benzene, but soluble in polar solvents such as DMSO (Dimethylsulfoxide) and DCM (Dichloromethane).

(E)-2-(4-aminobut-1-enyl)-5-methylbenzamine (SBII): A solution of 4-dimethylamino benzaldehyde 5 mm (3.72 g) in 18 ml ethyl acetate was added to a stirred solution of ethylene-di-amine 5 mm (1.50 g) in 20 ml of ethyl acetate. The reaction mixture was refluxed at 150°C for 5 h. The solid product was filtered off and washed with cold ethanol and then dried over anhydrous $CaCl_2$ in a desiccator. The pure Schiff base was isolated as a yellow crystalline solid. This ligand was found insoluble in common organic solvents such as diethyl ether, n-hexane, benzene, etc and soluble in polar solvents such as DCM and DMSO.

Biological activity

Antibacterial (*Escherichia coli, Pseudomonas aeruginosa, Bacillus cereus, Salmonella typhimurium, Staphylococcus aureus* and *Klebsiella pneumoniae*) activity was evaluated by disc diffusion method. Nutrient ager was used as culture for antibacterial activity and DMSO was used to dissolve compounds. Nutrient agar it is used to grow the bacteria. Nutrient agar was prepared in a conical flask, by taking 1000 ml of distilled water in each flask and placed it over the electric heater for heating then added the powder media to each flask and shake it slowly until it become completely dissolved, then the entire media was sterilized by placed it in the autoclave at 121˚C, 15 psi for 15 min. The prepared media was stored in refrigerator for use.

Antibacterial assessed by disc diffusion method

The antibacterial activities of the Schiff bases were tested *in vitro* using disc diffusion method. Bacterial inoculums were prepared from overnight grown cultures (24 h) in Nutrient broth and turbidity was adjusted equivalent to 0.06 OD at 600 nm. The plates were incubated at 37°C for 48 h. The dried agar surface of each plate was stacked by a sterile cotton swab with reference bacterial strain (10 µl) with sterilized double autoclaved filter paper disc (5 mm diameter) were wetted with 100 µl of a solution of each compound to be tested, in the concentration of (6 µl and 12 µl) in DMSO. The plates were then incubated 20-24 h at 37°C. After 24 h the inhibition zones produced were measured and recorded in mm and converted to perceptual of inhibition by using the data from positive control. The values are reported at Table 2 as a mean of three replicates.

Results and Discussion

In this study, the Schiff bases were obtained by reacting ethylene-di-amine with different phenolic compounds. The reaction between salicyldehye and ethylene-di-amine produced Schiff Base 1 (SB-1), whereas the reaction between 4-dimethylamino benzaldehyde results in the Schiff Base 2 (SB-2)(Figure 1). The compounds were labeled as SB-1 and SB-2. The structures of compounds were characterized by FT-IR and elemental analysis. The properties of the Schiff bases are given in Table 1.

Table 1: The results of molecular formula and formula weight derived for Schiff base I and II.

S.No	Molecular formula	Formula weight	Elemental analysis			
			% of C	% of H	% of O	% of N
1	$C_9H_{12}ON_2$	164	73.61	7.97	9.81	8.58
2	$C_{12}H_{18}N_2$	190	73.17	9.75	--	17.03

The important IR absorption bands for the synthesized Schiff bases are listed. In the SB-1 and SB-2, the strong bands show at 1600 cm^{-1} and 1681 cm^{-1} are assigned to the v (C=N) stretching mode. The absence of a v (C=O) peak at around 1700 cm^{-1} is

indicative of Schiff base condensation. The bands show at 1505 cm^{-1} and 1502 cm^{-1} are assigned to the v (C=C) stretching mode in the SB-1 and SB-2. These bands prove the presence benzene. A medium band corresponding to phenolic Oxygen (C-O) is observed at 1239 and 1251 cm^{-1} for SB-1 and SB-2 respectively.

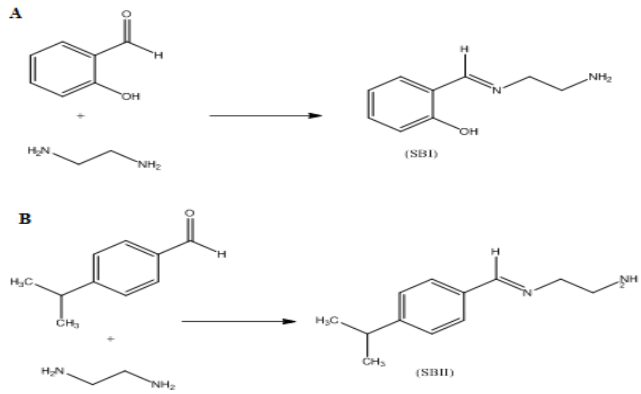

Figure 1: Synthesis of Schiff bases. The scheme shows the synthesis of Schiff base I (A) by the combination of salicyldehye 5 mm and ethylene-di-amine 5 mm and the Schiff base II (B) is synthesized by the addition of 4-dimethylamino benzaldehyde 5 mm with ethylene-di-amine 5 mm and the mixture was refluxed at 150°C for 5 h to obtain the Schiff basses I and II.

Antibacterial activities

The antibacterial activities of the synthesized compounds were evaluated *in vitro* using disc diffusion method against *E. coli, P. aeruginosa, B. cereus, S. typhimurium, S. aureus* and *K. pneumonia.* The antibacterial activities data are given in Tables 2-3. Erythromycin was used as a positive control. The Schiff Base SB-2 showed no antibacterial activity against any bacteria tested by applying the 6 µl (0.7 µM) and 12 µl (1.4 µm). Whereas, SB-I show inhibitory effect against the *E. coli* at very low concentration. The measured zone of inhibition of SB-I against *E. coli* was 8.5 and 13 mm for 6 µl (0.7 µM) and 12 µl (1.4 µm), respectively (Tables 2 and 3). These are great results compared to those presented by Sheheryar, et al. using the Schiff bases against *E. coli.*

Table 2: Bacterial growth inhibition shown by applying 6 µL of Schiff base I and II.

Samples	*E. coli* (-ve)	*B. cereus* (+ve)	*S. typhimurium* (-ve)	*K. pneumoniae* (-ve)	*P. aeruginosa* (-ve)	*S. aureus* (+ve)
Schiff base I	28.3% 8.5 mm	--	--	--	--	--
Schiff base II	--	--	--	--	--	--
Positive control (Ciprofloxacin)	100%	100%	100%	100%	100%	
	31 mm	30 mm	29 mm	18 mm	26.5 mm	
Positive control (erythromycin)						100%
	--	--	--	--	--	26.5 mm
Negative control (DMSO)	0%	0%	0%	0%	0%	0%

Table 3: Bacterial growth inhibition shown by applying 12 µL of Schiff base and II.

Samples	*E. coli* (-ve)	*B. cereus* (+ve)	*S. typhimurium* (-ve)	*K. pneumoniae* (-ve)	*P. aeruginosa* (-ve)	*S. aureus* (+ve)
Schiff base I	13 mm 43.33%	--	--	--	--	--
Schiff base II	--	--	--	--	--	--
Positive control (Ciprofloxacin)	30 mm	30 mm	35 mm	19.5 mm	35 mm	--
	100%	100%	100%	100%	100%	
Positive control (erythromycin)	--	--	--	--	--	31 mm
						100%

Negative control (DMSO)	--	--	--	--	--	--

However, in the present study the cell permeability was perhaps not affected and hence lower activity of the metal complexes is visualized. *E. coli* specie cause stubborn and dangerous inflammations. From any focus of inflammation, they can enter the blood stream and can produce septicemia. They can also cause meningitis and urinary tract infection. As the results in this study show that the Schiff base, I have the ability to inhibit the growth of *E. coli* to some extent. This shows that Schiff base has the tendency against the above bacteria as shown in the Table 1. The commonest infections caused by *E. coli* are the skin infection, urinary infection, cutaneous infection and infect the valve prosthesis.

Conclusion

The present research study showed the successful synthesis of two new Schiff bases. Schiff bases were characterized physically and chemically by the help of elemental analysis and IR spectral data. The antibacterial activity of the Schiff bases was tested on the bacterial strains of *E. coli, P. aeruginosa, B. cereus, S. typhimurium, S. aureus* and *K. pneumoniae,* it was compared to the standard Erythromycin. The tested compound SB-I have showed biological activity against two bacterial strains *E. coli* . While compound SB-2 showed no remarkable activity.

Conflict of interest

The authors have no conflicts of interest to declare.

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