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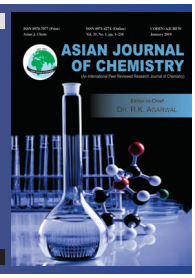

Synthesis, Spectral and Antimicrobial Studies of ((3E,4E)-3,4-*bis*((Pyridinyl)methyleneamino)phenyl)(phenyl)methanones

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A series of ((3E,4E)-3,4-*bis*((pyridin-2-yl)methyleneamino)phenyl)(phenyl)methanone compounds (**1-3**) were synthesized by a simple one-step condensation reaction of pyridinyl compounds. The synthesized compounds **1-3** were characterized by elemental, FTIR, ^{1}H and ^{13}C NMR spectral data. From IR and NMR spectra, the characteristic frequencies were assigned and the data used for confirmation of the formation pyridinyl methylene amino. All the compounds were screened for their preliminary antibacterial and antifungal activities. The antimicrobial activity of pyridinyl methylene amino and Schiff bases of pyridinyl substituted compounds were investigated against *Staphylococcus aureus*, *Bacillus cereus* and *Streptococcus mutans*. Gram-negative bacteria (*Proteus vulgaris*, *E. coli*, *Salmonella typhi*) and *Candida albicans* and *Candida tropicalis* (fungi). The results indicated that the antimicrobial activity of Schiff bases was stronger than that of pyridinyl compounds and dependent on the substituent group. The pyridinyl substituted compounds **1** and **2** show good antibacterial activity against their bacterial strains within the agreed mm of zone of inhibition. The compounds **1** and **2** substituted pyridinyl also showed good antifungal activities against their fungal strains.

Keywords: Schiff bases, Substituted pyridinyl, Antimicrobial activity.

INTRODUCTION

Schiff bases are easily synthesized and exhibit a large variety of structure. They are formed by a simple condensation reaction between primary amines and carbonyl compounds, either aldehydes or ketones. Consequently, they can be synthesized using various compounds as raw material. Schiff bases have received considerable interest because of their biodegradability, non-toxicity, antibacterial activity and biocompatibility. Therefore, the fields of applications of Schiff bases include agriculture, pharmaceuticals, cosmetics, food technology, environmental protection and biotechnology [1-11]. Antibacterial activity is one of the most salient bioactivities of Schiff bases; these compounds were demonstrated to effectively inhibit the growth of many common bacteria and fungi [12]. Moreover, chitosan is superior to other types of antimicrobial agents because it exhibits a higher antibacterial activity, broader activity spectrum, higher killing rate and lower toxicity rate toward mammalian cells than other types of antimicrobial agents [13].

The structure and activity relation of Schiff base ligands play a major effect in the research area since the activity varied based on structures [14-17]. The Schiff base ligands have various biological applications, such as antibacterial [18], anticancer [19], antifungal [20,21], herbicidal [22], antidiabetic [23], antiviral agents [24] and antiinflammatory activities [25]. Still, chemists have a great interest in the synthesis of Schiff base ligands for better stability and activity. Chemical modifications of the reactive amino and hydroxyl groups of Schiff bases require relatively mild reaction conditions. These modifications alter the chemical properties of the Schiff bases [26-30]. Synthesized derivatives exhibit superior processability, solubility, antimicrobial activity and interaction with other substances compared with the parent compounds [31-36].

Based on the above consideration, the modification of Schiff base with pyridinyl methylene amino as a substituent may improve some of the physical properties and antimicrobial activity of Schiff base. Therefore, the aim of the present study is to develop new Schiff bases with pyridinyl moiety. In this

TABLE-1
PHYSICAL CONSTANTS, YIELDS AND ANALYTICAL DATA OF COMPOUNDS **1-3**

Compd.	R	m.f.	m.w.	Yield (%)	m.p. (°C)	Elemental analysis (%): Found (calcd.)		
						C	H	N
1	R_1 = N	$C_{25}H_{18}N_4O$	390.44	88	187-192	76.86 (76.91)	4.59 (4.65)	14.80 (14.85)
2	R_2 = N	$C_{25}H_{18}N_4O$	390.44	91	124-127	76.89 (76.91)	4.54 (4.65)	14.79 (14.85)
3	R_3 = N	$C_{25}H_{18}N_4O$	390.44	95	218-222	76.86 (76.91)	4.56 (4.65)	14.83 (14.85)

article, we report the synthesis, characterization and antimicrobial studies of (((3E,4E)-3,4-bis((pyridin-2-yl)methyleneamino)-phenyl)(phenyl)methanone.

EXPERIMENTAL

All the chemicals and solvents used were of AnalaR grade. The melting points were taken in open capillaries in an electrical apparatus and are uncorrected. Elemental analyses were carried out on VARIOMICRO V2.2.0 CHN analyzer. The FT-IR spectrum of the synthesized compounds was taken in the range of 4000-400 cm^{-1} an AVATAR-330 FT-IR spectrometer (Thermo Nicolet) using KBr (pellet form). ^1H NMR was recorded on a Bruker 400 MHz NMR and ^{13}C NMR was recorded on a Bruker 100 MHz NMR using DMSO-d_6 as a solvent.

Antibacterial activity: The petri plates were prepared with 20 mL of Muller Hinton Agar (MHA-Hi-media), and the test cultures were swabbed on the top of the solidified media and allowed to dry for 10 min. The Gram-positive bacteria *S. aureus*, *B. cereus* and *S. mutans*. Gram-negative bacteria *P. vulgaris*, *E. coli* and *S. typhi* [37,38]. The sterile disc was dipped in compound solution 40 µg/mL concentration and placed on the agar plate and kept for incubation at 37 ºC for 24 h.

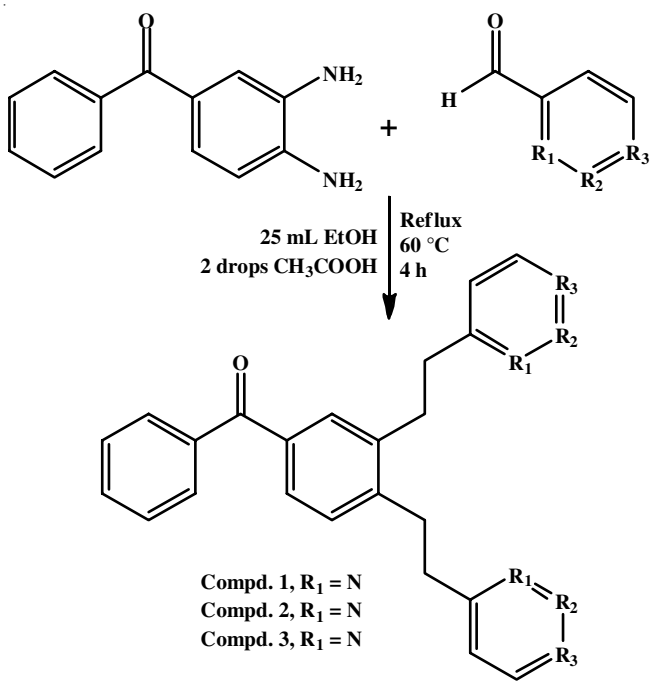
Antifungal activity: The antifungal activity of synthesized compounds **1-3** was evaluated using the disc diffusion method (CLSI 2004) with some modifications. The fungi *Candida albicans* and *Candida tropicalis* were used to antifungal activity. The synthesized compounds were loaded on the sterile disc which was placed on the surface of solidified agar medium [39]. Subsequently, 100 µL of fungal inoculums was uniformly spread onto the plates. Amphotericin-B was used as a positive control. The discs were applied to the plates, which were then incubated at 35 ºC for 24-48 h.

Synthesis: 3,4-Diaminobenzophenone (1 mmol) was added to picolinaldehyde, nicotinaldehyde and isonicotinaldehyde (2 mmol) and mixed in ethanol (25 mL) in the presence of two drops of glacial acetic acid. The resultant mixture was refluxed for 4 h and then cool the solution. The precipitate was poured into crushed ice. Solids thus obtained were filtered and washed several times with water, followed by ethanol and then dried in a vacuum. The crude products were crystallized in ethanol afford the compounds **1-3** (**Scheme-I**).

RESULTS AND DISCUSSION

The synthesized substituted pyridinyl Schiff base compounds were characterized by their elemental analysis and FT-IR, NMR spectral data. The physical constants, analytical and elemental analyses data of title compounds are given in Table-1.

IR analysis: The IR spectral data of compounds **1-3** are given in Table-2. The aromatic compounds commonly exhibit multiple weak bands in the region 3122-2971 cm^{-1} due to aromatic



Scheme-I: Synthesis of compounds **1-3**

C-H stretching vibrations. The band in the interval 3058.31-2971.58 cm^{-1} is attributed to aromatic C-H stretching vibration. As seen in Table-2, the band ascribed to C=N stretching vibration appears in the region 1602-1556 cm^{-1}. The C=O stretching vibration appears in the region 1739-1654 cm^{-1}. In cyanopyridine compounds, the C=N stretching frequency is observed as a very strong band at ~1660 cm^{-1} where as C=N stretching is assigned in the region 1579-1548 cm^{-1} in phenazine derivatives. In this case, carbonyl C=N stretching appeared in the region 1657.14-1597.43 cm^{-1}. The aromatic C=C stretches observed in the range of 1602.43-1405.17 cm^{-1}. The C-H in-plane bending vibration usually occurs in the region 1390-990 cm^{-1}. The aromatic C-H in-plane bending vibrations appear in the region 1397.67-1247.87 cm^{-1} while the bands at 1173.44-680.50 cm^{-1} are due to the aromatic C-H out-of-plane bending vibrations.

TABLE-2
FT-IR SPECTRAL DATA OF COMPOUNDS **1-3**

Assignments	Compd. **1**	Compd. **2**	Compd. **3**
	R_1 = N	R_2 = N	R_3 = N
ν(ArC-H)	3058	3063	3055
ν(C=O)	1739	1696	1721
ν(C=N)	1654	1647	1651
	1602	1608	1611
ν(C=C)	1563	1602	1597
β(C-H)	1316	1311	1367
γ(C-H)	1072-679	1104-661	1088-680

TABLE-3
THE CHEMICAL SHIFTS OF NMR (δ, ppm) SPECTRAL VALUES OF COMPOUNDS **1-3**

Compd.	R	^{1}H NMR		^{13}C NMR		
		Ar-H	HC=N	C=O	C=N	Ar-C
1	R_1=N	7.59-8.12	8.81	196.36	166.44	121.02-151.08
2	R_2=N	7.63-8.14	8.78	197.03	166.34	122.19-151.73
3	R_3=N	7.54-8.21	8.80	196.38	165.54	121.32-151.91

TABLE-4
ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF SYNTHESIZED COMPOUNDS **1-3** BY DISC DIFFUSION METHOD

Compound	Diameter of the zone of inhibition (mm)							
	Antibacterial activity						Antifungal activity	
	Staphylococcus aureus	*Bacillus subtilis*	*Streptococcus pyogens*	*Salmonella typhi*	*Escherichia coli*	*Proteus vulgaris*	*Candida albicans*	*Candida tropicalis*
1	13	12	12	11	12	13	15	14
2	9	6	15	7	10	11	19	13
3	10	12	9	10	5	5	13	10
Chloramphenicol	22	25	20	24	32	33	–	–
Amphotericin-B	–	–	–	–	–	–	23	18

NMR analysis: As seen in Table 3, the multiplet ranges from 7.59-813 ppm are due to aromatic protons. The ^{1}H chemical shifts values of compounds **1-3** are given in Table-3. In the ^{13}C NMR spectra of compounds **1-3**, the weak signal around 166.54 ppm is due to C=N of azomethine unit. The ipso attached carbon appeared in the region 166.34-165.54 ppm. The signals in the region 121.02-151.91 ppm are assigned to aromatic carbons while the signals in the region 196.03-197.03 ppm are assigned to C=O.

Antibacterial activity: Antibacterial activity of synthesized compounds **1-3** are significantly active against the test bacteria. The zone of inhibition ranged from 06-19 mm at 40 μg/mL concentration (Table-4). The compound **1** activity against *Staphylococcus aureus* and *Proteous vulgaris* recorded a wider zone of inhibition (13 mm) at 40 μg/mL. This was followed by *Escherichia coli*, *Bacillus subtilis* and *Streptococcus pyogens* (12 mm). *Salmonella typhi* was the lowest zone of inhibition (11 mm) at 40 μg/mL zone of inhibition, respectively. In compound **2**, the activity against *Streptococcus pyogens* is the highest as compared to other bacteria and *Bacillus subtilis* is the lowest activity. However in compound **3**, *Bacillus subtilis* has the highest activity (12 mm) *Escherichia coli* and *Proteou vulgaris* (5 mm) have lowest activity as compared to other compounds. The standard chloramphenicol recorded zone of inhibition ranged from 20 to 23 mm.

Antifungal activities: The antifungal activities of synthesized compounds **1-3** were determined against fungal pathogens. The results are shown in Table-4. Compound 2 has shown the highest activity among the synthesized compounds against *Candida albicans* (19 mm) at the concentration of 40 μg/mL, while the activity of compound **3** is lowest against *Candida tropicalis* (10 mm).

Conclusion

A series of ((3E, 4E)-3,4-*bis*((pyridinyl)methylene amino)-phenyl)(phenyl)methanones compounds are synthesized and characterized. The elemental, FT-IR, ^{1}H and ^{13}C NMR spectral data of all the synthesized compounds **1-3** suggest that the succcessful formation of compounds. The results of antimicrobial activity of Schiff bases of pyridinyl methylene amino had better antimicrobial activities than pyridinyl methylene amino. However, antibacterial and antifungal activities are significantly influenced by the substituents in the phenyl ring.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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