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SYNTHESIS, CHARACTERIZATION AND MICROBIAL STUDIES OF FEW SCHIFF BASES SYNTHESIZED FROM N-ETHYLPIPERAZINE

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ABSTRACT

Schiff bases have been prepared from N-ethylpiperazine on condensation with p-chloroaniline in absolute alcohol in presence of K_2CO_3 and subsequent reaction with various aromatic aldehydes (4e-4j). The structures of the synthesized compounds were assigned on the basis of elemental and spectral analysis and the same were evaluated for their growth inhibiting activities against strains of various microbes.

KEYWORDS: Antibacterial activity, antifungal activity, piperazine, schiff base.

1. INTRODUCTION

Literature reveals that Schiff bases are condensation products of primary amines and carbonyl compounds and they were discovered by a German chemist, Nobel Prize winner, Hugo Schiff in 1864. Structurally, Schiff base (also known as imine or azomethine) is an analogue of a ketone or aldehyde in which the carbonyl group (C=O) has been replaced by an imine or azomethine group.[1-3]

Schiff bases have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like anti-inflammatory,[4–7] analgesic,[5–8] antimicrobial,[9, 10] anticonvulsant,[11] antitubercular,[12] anticancer,[13, 14] antioxidant,[15] anthelmintic,[16] and so forth. The nitrogen atom of azomethine may be involved in the formation of a hydrogen bond with the active centers of cell constituents and interferes in normal cell processes.[17, 18]

Schiff bases have been utilized as synthons in the preparation of a number of industrial and biologically active compounds like formazans,[19, 20] 4-thiazolidinines,[21, 22] 2-azetidinones,[23,

[24] benzoxazines,[25] and so forth, via ring closure, cycloaddition, and replacement reactions. Their metal complexes have been widely studied because they have anticancer and herbicidal applications.[26, 27] They serve as modals for biologically important species.

Considering the numerous applications of Schiff bases in various fields of chemistry, there has been tremendous interest in developing efficient methods for their preparation. The principles of Green chemistry apply to most of the synthetic routes with microwave irradiation. Microwave assisted reactions are cleaner, last only very few minutes, have high yield and produced minimum waste.[28]

As is obvious from literature survey, it was thought-provoking to synthesise some Schiff bases from N-ehtylpiperazine and study the microbial activities of the same.

2. MATERIALS AND METHODS

2.1 General

The chemicals used were of Laboratory Grade procured from Sigma Aldrich, Merck and Fluka. The reactions were routinely checked by TLC. TLC was performed on aluminum-backed silica gel plates (silica gel 60 F254 grade, Merck DC) with spots visualized by UV light. Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on KBr on a Shimadzu 8400S FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Hitachi 300 MHz using TMS as an internal standard and elemental analysis had been carried out on Perkin-Elmer CHNS-2400.

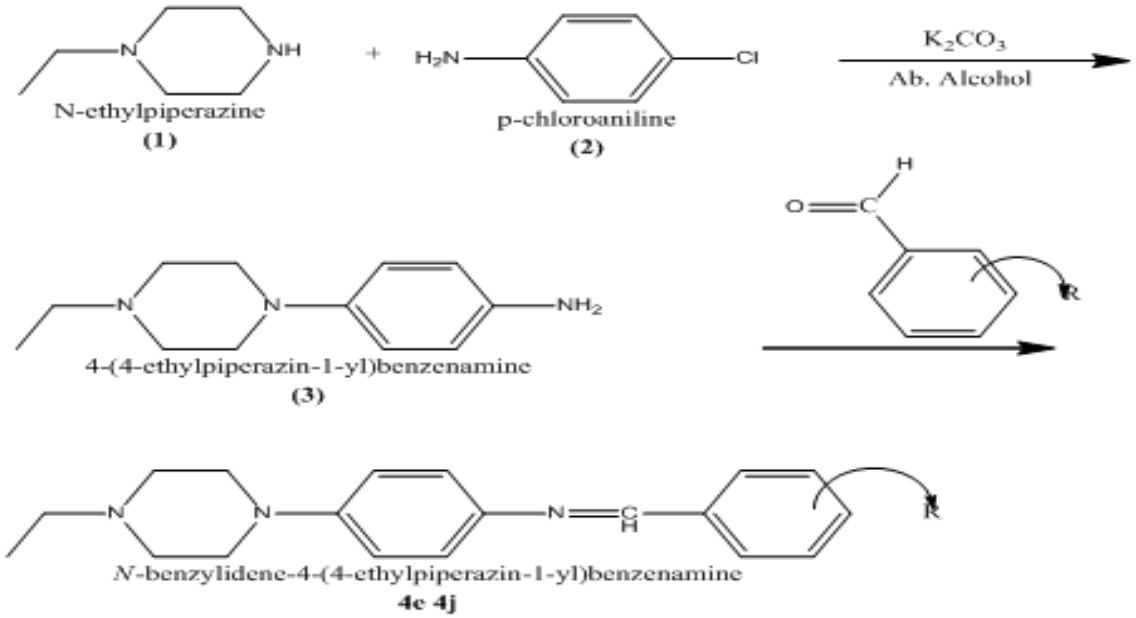
2.2 Synthesis of 4-(4-ethylpiperazin-1-yl)benzenamine(3)

A mixture of N-ethylpiperazine (1) (0.1 mole) and p-chloroaniline (2) (0.1 mole) and anhydrous K_2CO_3 in absolute alcohol (20 ml) was refluxed for 4 hrs. The resultant mixture was cooled to room temperature and poured into ice-cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol.Yield 90%; m.p. 110°C.

2.3 N-substitutedbenzylidene-4-(4-ethylpiperazin-1-yl) benzenamine (4e-4j)

A mixture of 4-(4-ethylpiperazin-1-yl)benzenamine (3) (0.01 mole), aromatic aldehyde (0.01 mole) and 2-3 drops of glacial acetic acid in absolute alcohol (30 ml) was refluxed for 2 hrs. After the completion of reaction it was poured into ice-cold water with stirring. The solid product obtained was filtered, washed with water and recrystallized from ethanol to give compounds 4e-4j.

Scheme



Substituents of compounds **4 e – 4 j.**

4 e. 3-OCH_3
4 f. 4-OH
4 g. 2-Cl
4 h. 2-OH
4 i. 3,4,5-OCH_3
4 j. 3,4-OCH_3

3. RESULTS

Table 1: Characterization data of the synthesized compounds (4e-4j).

Compound No.	R	Molecular Formula	M.P. (°C)	Yield (%)	Elemental analysis (%)					
					C		H		N	
					Calcd	Found	Calcd	Found	Calcd	Found
4e	3-OCH3	$C_{20}H_{25}N_3O$	145-146°C	81%	74.27	74.29	7.79	7.81	12.99	13.01
4f	4-OH	$C_{19}H_{23}N_3O$	125-127°C	72%	73.76	73.78	7.49	7.53	13.58	13.59
4g	2-Cl	$C_{19}H_{22}ClN_3$	98-99°C	81%	69.61	69.64	6.76	6.77	12.82	12.84
4h	2-OH	$C_{19}H_{23}N_3O$	130-135°C	79%	73.76	73.77	7.49	7.52	13.58	13.59
4i	3,4,5-OCH_3	$C_{22}H_{29}N_3O_3$	150-151°C	81%	68.90	68.93	7.62	7.63	10.96	10.98
4j	3,4-OCH_3	$C_{21}H_{27}N_3O_2$	142-145°C	75%	71.36	71.37	7.70	7.71	11.89	11.90

Table 2: Spectral data of compounds (4e-4j).

Compound No.	IR (KBr, cm-1)	^{1}H NMR (400 MHz, Me_2SO–d_6)
4e	3280 (N–H), 3027 (C–H), 1522 (C=N), 1230 (C–O–C)	δ 8.41 (s, 1H, N=CH), 6.83 (m, Ar-H, 8H), 3.81 (s, 3H, -OCH_3), 3.67 (4H, br s, piperazine), 3.21 (4H, br s, piperazine), 2.41 (m, 2H, -$C\underline{H_2}CH_3$), 1.05 (t, 3H, -$CH_2C\underline{H_3}$)
4f	3423 (O–H), 3238 (N–H), 2937 (C–H), 1520 (C=N)	δ 8.32 (s, 1H, N=CH), 6.69 (m, Ar-H, 8H), 5.23 (br s, 1H, -OH), 3.57 (4H, br s, piperazine), 3.28 (4H, br s, piperazine), 2.37 (m, 2H, -$C\underline{H_2}CH_3$), 1.08 (t, 3H, -$CH_2C\underline{H_3}$)
4g	3255 (N–H), 2989 (C–H), 1547 (C=N), 625 (C–Cl)	δ 8.47 (s, 1H, N=CH), 6.73 (m, Ar-H, 8H), 3.60 (4H, br s, piperazine), 3.33 (4H, br s, piperazine), 2.45 (m, 2H, -$C\underline{H_2}CH_3$), 1.13 (t, 3H, -$CH_2C\underline{H_3}$)
4h	3446 (O–H), 3230 (N–H), 2968 (C–H), 1535 (C=N)	δ 8.46 (s, 1H, N=CH), 6.51 (m, Ar-H, 8H), 5.44 (br s, 1H, -OH), 3.49 (4H, br s, piperazine), 3.25 (4H, br s, piperazine), 2.29 (m, 2H, -$C\underline{H_2}CH_3$), 1.25 (t, 3H, -$CH_2C\underline{H_3}$)
4i	3319 (N–H), 2993 (C–H), 1528 (C=N), 1208 (C–O–C)	δ 8.35 (s, 1H, N=CH), 6.46 (m, Ar-H, 8H), 3.70 (s, 9H, -OCH_3), 3.71 (4H, br s, piperazine), 3.25 (4H, br s, piperazine), 2.25 (m, 2H, -$C\underline{H_2}CH_3$), 1.03 (t, 3H, -$CH_2C\underline{H_3}$)
4j	3302 (N–H), 3018 (C–H), 1533 (C=N), 1205 (C–O–C)	δ 8.29 (s, 1H, N=CH), 6.57 (m, Ar-H, 8H), 3.83 (s, 6H, -OCH_3), 3.50 (4H, br s, piperazine), 3.19 (4H, br s, piperazine), 2.38 (m, 2H, -$C\underline{H_2}CH_3$), 1.15 (t, 3H, -$CH_2C\underline{H_3}$)

4. Microbiology

The antimicrobial activity of synthesized analogs has been carried out against two gram-positive bacteria (s. Aureus atcc 6538p and s. Pyrogenus atcc 8668), two gram-negative bacteria (e. Coli. Atcc 8739 and p.aeruginosa atcc 9027) and against three fungal species (c. Albicans atcc 10231, a. Niger atcc16404 and a. Clavatus atcc 9600). Here, ampicilline, chloramphenicol, ciprofloxacin (100 µg/disk) were used as control drugs for antibacterial activity while nystatin and griesofulvin for antifungal activity.[29, 30, 31]

Table 3: In-vitro antibacterial and antifungal activity of compounds 4e-4j.

Table 3: Antibacterial and antifungal activity of compounds 4a-4j								
Compound No.	R	Minimum Inhibitory Concentrations (µg/ml)				Minimum Inhibitory Concentrations (µg/ml)		
		Gram positive bacteria		Gram negative bacteria		Fungus		
		S. aureus ATCC 6538P	*S. pyogenus* ATCC 8668	*E. coli* ATCC 8739	*P.aeruginosa* ATCC 9027	*C.albicans* ATCC 10231	*A. niger* ATCC 16404	*A.clavatus* ATCC 9600
4e	3-OCH_3	512	256	256	512	512	512	512
4f	4-OH	256	256	128	128	256	512	512
4g	2-Cl	512	512	512	512	512	512	256
4h	2-OH	512	128	128	128	256	256	256
4i	3,4,5-OCH_3	512	512	256	256	512	256	256
4j	3,4-OCH_3	512	512	256	512	512	512	512
Ampicilin	-	250	100	100	100	-	-	-
Chloramphenicol	-	50	50	50	50	-	-	-
Ciprofloxacin	-	50	50	25	25	-	-	-
Norfloxacin	-	10	10	10	10	-	-	-
Nystatin	-	-	-	-	-	100	100	100
Griesofulvin	-	-	-	-	-	500	100	100

5. CONCLUSION

5.1 Antifungal activity

The results showed that Schiff bases compounds 4e,4g,4i and 4j displays moderate activity (MIC 512 µg/ml)against C. albicans while compounds 4f and 4h having 4-hydroxy substituent and 2-hydroxy substituent respectively exhibited good activity (MIC 256 µg/ml) against C. albicans when compared with Griseofulvin. All other compounds showed weak activity against A. niger and A. clavatus when compared with Griesofulvin and Nystatin.

5.2 Antibacterial activity

Antibacterial activities of N- (substitutedbenzylidene)- 4- (4-ethylpiperazin-1-yl) benzenamineacetamidehave been described here. Compound 4f having 4-hydroxy substituent showed moderate activity (MIC 256 µg/ml) against S. aureus when compared with Ampicillin. Compound 4h having 2-hydroxy substituents showed good activity (MIC 128 µg/ml) againstS. Pyogenus when compared with Ampicillin. Compounds 4f and 4hhaving, 4-hydroxy substituent and 2-hydroxy substituents respectively showed moderate activity (MIC 128 µg/ml) against E. coli when compared with Ampicillin. All Schiff base

compounds showed weak activity (MIC 128-512µg/ml) against *E. coli* when compared with Chloramphenicol. Compound 4f and 4h having 4-hydroxy and 2-hydroxy substituents respectively showed moderate activity (MIC 128 µg/ml) against *P.aeruginosa* when compared with Ampicillin. Whereas, other displayed weak activity against *P. aeruginosa*. Other compounds displayed weak activity against the different bacteria when compared with Chloramphenicol, Ciprofloxacin and Norfloxacin.

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