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Comparative Study of the Schiff Bases by Conventional and Green Method and Antimicrobial Activity

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Abstract
Green chemistry which is the latest and one of the most researched topics now days has been in demand since 1990's. Majority of research in green chemistry aims to reduce the energy consumption required for the production of desired products, whether it may be any drug, dyes and other chemical compounds. It aims to reduce or even eliminates the production of any harmful bi-products and maximizing the desired product without compromising with the environment. Schiff Bases are characterized by the –N=CH- (imine) group which works in elucidating the mechanism of transmination and rasmination reaction in biological system. The antibacterial activities have been studied more than antifungal activities because bacterium can achieve resistance to antibiotics through biochemical and morphological modifications. Schiff bases are used as substrate in the preparation of a large of bioactive and industrial compounds via ring closure, cycloaddition, replacement reactions etc. The synthesis of Schiff bases by conventional and microwave irradiation method. Aldehyde and amine were dissolved in ethyl alcohol with two drop of glacial acetic acid and the mixture was refluxed. The structure of the compounds had been established on the basis of IR, 1H NMR, and MS spectral data and by elemental analysis.The Schiff bases have been screened for their in vitro biological activities against bacteria, fungi.

In this study, it was concluded that microwave irradiation method has been proved here as a better method for the synthesis of Schiff bases and increase in percentage (%) yield. Schiff bases play an important role for the bactericidal and fungicidal action.

Keywords: green chemistry, microwave irradiation, Conventional heating, aldehyde, amine, anti-microbial activity.

Introduction
Schiff Bases are characterized by the –N=CH- (imine) group which works in elucidating the mechanism of transmination and rasmination reaction in biological system [1, 2]. Schiff bases are active against a wide range of organisms like Candida albicans, Escherichia coli, Staphylococcus aureus, Bacillus polymxa, Trychophyton, gypseum, Mycobacteria, erysiphe graminis and Plasmopora viticola [3,4]. Schiff bases have often been used a chelating ligands in the field of coordination chemistry for obtaining thermotropic liquid crystalline polymers and their metal complexes [5], which have been used as radiopharmaceuticals for cancer targeting, as dioxygen carriers and as model system for biological macromolecules [6]. Various novel Schiff base compounds have been synthesized by reaction of 2-hydroxy-4-pentadecylbenzaldehyde with substituted benzothiophene-2-carboxylic acid hydrazide and different substituted aromatic or heterocyclic amines in the presence of acetic acid in ethanol [7]. However most Schiff bases are chemically unstable and show a tendency to be involved in various equilibria, like tautomeric interconversions, hydrolysis, or formation of ionized species. Therefore, successful application of Schiff bases requires a careful study of their characteristics. Schiff bases prepared from salicyaldehyde have shown some activity against Sarcoma 180, Lewis

lung carcinoma, and L1210 leukemia of mice. The synthesis of two Schiff base derivatives of cefotaxime antibiotic (CFX) Metal complexes of the two Schiff bases ligands with Co(II), Ni(II), Cu(II), Cd(II), Pd(II) and Pt(IV) ions were prepared by reacting each ligand with the metal salts in refluxing ethanol [8]. Schiff bases are also used as catalysts, pigments and dyes, intermediates in organic synthesis, polymer stabilizers, and corrosion inhibitors [9].

Materials and methodology

4-fluoro-2-methyl aniline with other aromatic aldehydes used was of Sigma-Aldrich. Ethanol and other solvents of A. R. grade were used as received.

Synthesis of Schiff Bases

The following two methods are adopted for synthesis of Schiff bases.

Classical heating based synthesis (Method A)

4-fluoro-2-methyl aniline (0.001 mol) and substituted aldehyde (0.001 mol) were dissolved in ethyl alcohol (25 ml.). One drop glacial acetic acid was added and the mixture was refluxed for 1-2 hours. The resultant solution was cooled and poured in cold water. The separated solid was filtered and recrystallised from ethyl alcohol. The prepared product was identified to be N-(substituted) benzylidine-N-(4-fluoro-2-methyl) phenyl anilne (figure 1).

Microwave "Jump Start" synthesis (Method B)

The reaction mixture of 4-fluoro-2-methyl aniline (0.001 mol) and substituted aldehyde (0.001 mol) were dissolved in ethyl alcohol (10 ml). One drop glacial acetic acid was taken in a borosil beaker and irradiated in a microwave at a power of 60W for 2-3 minutes. The resultant solution was cooled and poured in cold water. The separated solid was filtered and recrystallised from ethyl alcohol. The prepared product was identified to be N-(substituted) benzylidine-N-(4-fluoro-2-methyl) phenyl anilne (figure 1).

Antibacterial activity

Antibacterial activity was evaluated by the paper disc method. The Müller-Hinton agar (beef infusion, casein hydrolyzate, starch, agar) and 5 mm diameter paper discs of whatman No. 1 were used. The compound was dissolved in DMSO. The filter paper discs were soaked in different solutions of the compounds, dried and then placed in the petriplates previously seeded with the test organisms E. coli and S. aureus. The plates were incubated for 24–30 hours at 28±2°C and the inhibition zone around each disc was measured.

Antifungal screening

The antifungal activity of the compounds was evaluated against Aspergillus niger by the agar plate technique. The Sabouraud dextrose agar (dextrose, peptone, agar) and 5 mm diameter paper discs of whatman No. 1 were used. The compounds were dissolved in DMSO and then were mixed with in the medium. These petriplates were wrapped in the polythene bags containing a few drops of alcohol and were placed in an incubator at 25±2°C. The activity was determined after 96 hours of incubation at room temperature (25°C).

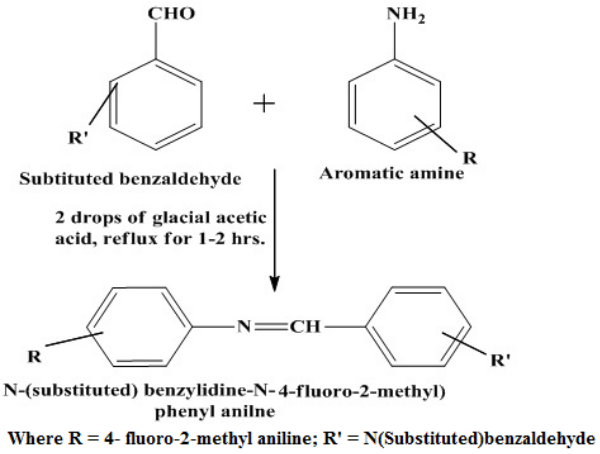


Figure 1: Chemical reaction of N-(substituted) benzylidine-N-(4-fluoro-2-methyl) phenyl anilne

Results and Discussion

Physical measurements and analytical data

Melting points were determined in open capillary tubes and are uncorrected (Table 1). The purity of the compound was checked by on TLC. The structures of the compounds are confirmed on the basis of their IR, 1H NMR and MS spectral. All the compounds gave satisfactory microanalysis (Table 2). Microwave irradiations were carried out in an unmodified IFB domestic microwave oven. All the chemicals were of analytical grade.

Infrared spectra

Infrared spectra of the substituted Schiff bases show medium intensity bands at 1179-1064 cm^{-1} dueto υ C-

F vibrations. A sharp bands found at 1314–1255 cm^{-1} due to υ=C-N. υ CH=N- stretching bands in the Schiff bases appeared at 1380–1259 cm^{-1}. In the IR spectra of the substituted Schiff bases the band appeared at 1597–1330 cm^{-1} due to the υ Ar-(C-C). υ C=N band appeared at 1685–1488 cm^{-1} in the compounds. A sharp and medium band of υ -OCH_3 showed at 2931 cm^{-1} and υ NH showed at 3312 cm^{-1}. The band appeared at 2976–1313 cm^{-1} due to the υ CH_2.

^{1}H NMR

The bonding patterns of these compounds are further supported by the proton magnetic resonance spectral studies in (400 MHz) DMSO-d6. The compounds exhibit a singlet at δ 4.6–3.13 ppm due to NH and singlet at δ 4.12-3.84 ppm due to CH_3. This compound shows multiplet in the region at δ 7.23-7.45 ppm attributable to the aromatic protons. Another singlet appearing at δ 4.22–3.30 ppm due to the CH_2 and singlet at δ 7.53-8.93 ppm due to -CH. A singlet due to the –OH group appears around δ 6.206.89 ppm.

Mass spectra

The base peak m/z appeared at 213.25-310.14.

Antimicrobial activity

The data in Table 3, showing zone of inhibition against the bacterium Gram-positive *S. aureus*, Gram-negative *E. coli* and fungus *Aspergillus niger* due to the different substituted Schiff bases (figure 2 & 3). A & I compound of Schiff bases were found to be weak in activity against *E.coli* and compound A & B against *S. aureus.* Highest antimicrobial potential was observed with compound F & K against *E. coli* and compound J & L against *S. aureus.* Compound C & K showed highest antifungal potential against *Aspergillus niger.*

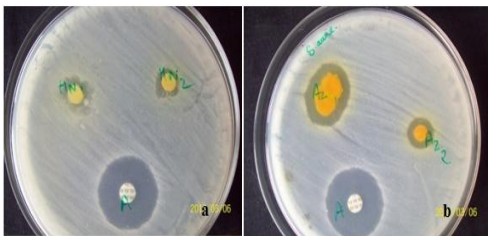


Figure 2: Antibacterial activity of N-(substituted) benzylidine-N-(4-fluoro-2-methyl) phenyl anilne against **(a)** Escherichia coli and **(b)** Staphylococcus aureus

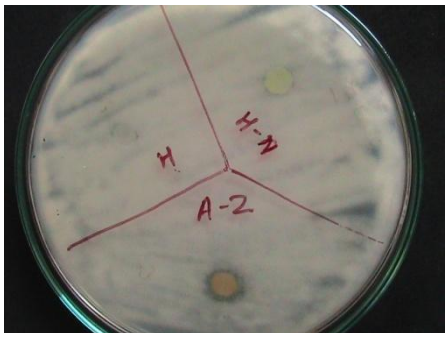
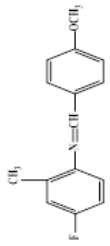
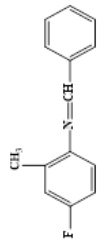
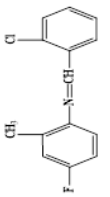
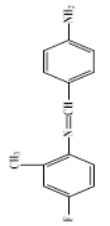
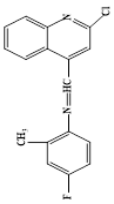
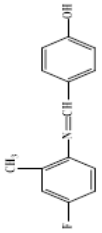
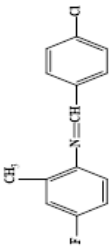
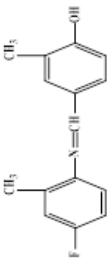
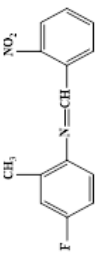
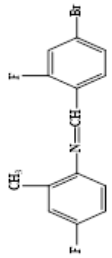


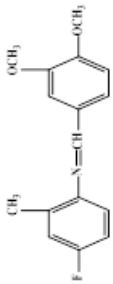
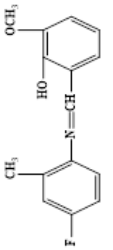
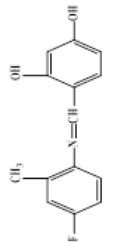
Figure 3: Antifungal activity of N-(substituted) benzylidine-N-(4-fluoro-2-methyl) phenyl anilne against Aspergillus niger

Table 1: Schiff Bases obtained by the condensation of substituted aldehydes with 4-fluoro-2-methyl aniline

S. No.	Substituted aldehyde (R')	Molecular Formula	Colour	M. P.(° C)	% Yield	
					Convection Heating	MWI
1	p-anisaldehyde	$C_{15}H_{14}FNO$	White	196	69.28	90.18
2	Benzaldehyde	$C_{14}H_{12}FN$	White	184	72.38	92.26
3	o-chloro	$C_{14}H_{11}ClFN$	White	187	70.03	90.31
4	o-amino	$C_{14}H_{13}FN_2$	White	191	73.65	93.75
5	2-chloroquinoline-3-caboxaldehyde	$C_{17}H_{12}ClFN_2$	White	197	73.45	94.74
6	p-hydroxy	$C_{14}H_{12}FNO$	Yellow	169	71.62	90.01
7	p-chloro	$C_{14}H_{11}ClFN$	White	185	72.87	94.11
8	3-methyl-4-hydroxy	$C_{15}H_{14}FNO$	White	192	76.96	95.23
9	2-nitro	$C_{14}H_{11}FN_2O_2$	White	172	71.94	90.15
10	4-brom-2-fluoro	$C_{14}H_{10}BrF_2N$	Yellow	178	72.46	93.57
11	Vertaldehyde	$C_{16}H_{16}FNO_2$	White	180	71.87	91.27
12	o-vanallin	$C_{15}H_{14}FNO_2$	orange	179	67.84	88.58
13	β-Resorcylaldehyde	$C_{14}H_{12}FNO_2$	Greenish Yellow	166	72.28	94.14

Table 2: Structures & C, H, N, O of Schiff Bases obtained by the condensation of substituted aldehydes with 4-fluoro-2-methyl aniline

S. No.	Structure of Compound	Name of Compounds	C% Found/Cal	H% Found/Cal	N% Found/Cal	O% Found/Cal
1		4-fluoro-N-(4-methoxybenzylidene)-2-methyl aniline	74.07/ 74.06	5.83/ 5.80	5.78/ 5.76	6.59/ 6.58
2		N-benzylidene-4-fluoro-2-methylaniline	78.87/ 78.85	5.69/ 5.67	6.60/ 6.57	----
3		N-(2-chlorobenzylidene)-4-fluoro-2-methyl aniline	67.93/ 67.89	4.51/ 4.48	5.67/ 5.65	----
4		N-(4-aminobenzylidene)-4-fluoro-2-methyl aniline	73.67/ 73.66	5.77/ 5.74	12.29/ 12.27	----
5		N-((2-chloroqui nolin-4-yl)methylene)-4-fluoro-2-methylaniline	68.39/ 68.35	4.08 / 4.05	9.39/ 9.38	----
6		4-(((4-fluoro-2-methylphenyl)imino)methyl)phenol	73.38/ 73.35	5.30/ 5.28	6.15/ 6.11	7.01/ 6.98
7		N-(4-chlorobenzylidene)-4-fluoro-2-methyl aniline	67.91/ 67.89	4.49/ 4.48	5.69/ 5.65	----
8		4-(((4-fluoro-2-methylphenyl)imino)methyl)-2-methylphenol	74.08/ 74.06	5.85/ 5.80	5.79/ 5.76	6.60/ 6.58
9		4-fluoro-2-methyl-N-(2-nitrobenzylidene)aniline	65.13/ 65.11	4.30/ 4.29	10.88/ 10.85	12.41/ 12.39
10		N-(4-bromo-2-fluorobenzylidene)-4-fluoro-2-methylaniline	54.25/ 54.22	3.27/ 3.25	4.55/ 4.52	----

11		N-(3,4-dimethoxybenzylidene)-4-fluoro-2-methylaniline	70.35/ 70.31	5.91/ 5.90	5.14/ 5.12	11.75/ 11.71
12		2-(((4-fluoro-2-methylphenyl)imino)methyl)-6-methoxyphenol	69.51/ 69.49	5.47/ 5.44	5.43/ 5.40	12.39/ 12.34
13		4-(((4-fluoro-2-methylphenyl)imino)methyl)benzene-1,3-diol	68.58/ 68.56	4.96/ 4.93	5.73/ 5.71	13.08/ 13.05

Conclusion

Microwave irradiation method has been proved here as a better method for the synthesis of Schiff bases and increase in percentage (%) yield is in following order: Method-1(Classical heating synthesis) < Method-2 (Microwave "jump start" synthesis). Schiff Bases obtained by the condensation of substituted aldehydes with 4-fluoro-2-methyl aniline were proved to have some antibacterial activity against Gram-negative E. coli & Gram-positive Staphylococcus aureus bacteria and Schiff bases also showed antifungal activity against Aspergillus niger.

Acknowledgements

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Table 3: Zone of inhibition against the bacterium Gram-positive *S. aureus*, Gram-negative *E. coli* and fungus *Aspergillus niger* due to the different substituted Schiff bases

S. No.	Compounds	Zone of inhibition (in mm)			
		E.coli	***S.aureus***	**Positive control (Amikacin)**	***Aspergillus niger* (Fungus)**
1	(A)	7	9	25	9
2	(B)	10	7	25	11
3	(C)	13	11	23	17
4	(D)	17	10	25	12
5	(E)	9	12	25	2
6	(F)	20	13	25	7
7	(G)	9	15	25	11
8	(H)	11	16	24	15
9	(I)	7	17	25	9
10	(J)	13	18	25	3
11	(K)	19	12	23	16
12	(L)	8	20	25	11
13	(M)	16	11	25	13

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