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Synthesis and Biological Evaluation of Novel Schiff Bases of Aryloxy Moiety

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ABSTRACT

Schiff's bases are condensation products of primary amines with carbonyl compounds. Schiff bases (imines) possess wide variety of biological activities that include antibacterial and antifungal activity. In present work, Schiff bases from 3,5- Dimethoxyphenol (aryloxy moiety) as starting material synthesized. Esterification of 3,5- Dimethoxyphenol led to formation of (3,5-Dimethoxy-phenoxy)-acetic acid ethyl ester (1). (3,5-Dimethoxy-phenoxy)-acetic acid hydrazide (2) is derived from Compound (1) by hydrazination. Compound (2) was reacted with different aromatic aldehydes to yield novel imines or Schiff bases (3A-I). The newly synthesized compounds were characterized on the basis of spectral studies and evaluated for antibacterial and antifungal activities. All the synthesized compounds had shown antibacterial and antifungal activity. Schiff bases **3C, 3D, 3E and 3I** had shown good antimicrobial activity among all newly synthesized compounds.

Keywords: Schiff base, aryloxy moiety, imines

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INTRODUCTION

The incidence of fungal and bacterial infections has increased dramatically in recent years [1]. Infection is a major category of human disease and skilled management of antimicrobial drugs is of the first importance. The accomplishment of antimicrobial agents, ranging from direct killing of invading pathogens to immune response modulation and other complex biological responses, has stimulated research and clinical interest for more than two decades. However the area is still flourishing due to emerging discoveries in the functions, roles and regulation of antimicrobial agents [2]. Schiff's bases are an important class of organic compounds [3]. They were first reported by Hugo Schiff in 1864 [4]. Structurally, a Schiff's base (also known as imine or azomethine) is a nitrogen analogue of an aldehyde or ketone in which the carbonyl group (>C = O) is replaced by an imine or azomethine group. Schiff's bases have also been shown to exhibit a broad range of biological activities, including antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic properties [5,6]. Imine or azomethine groups are present in various natural, naturally derived, and non-natural compounds. The imine group present in such compounds has been shown to be critical to their biological activities [7-10]. Kumar A *et al*. synthesized a series of Schiff bases of diphenylamine derivatives and evaluated *in vitro* for their antibacterial activity against pathogenic both Gram-positive bacteria *B. subtilis* and Gram-negative bacteria *E. coli* [11]. Azab ME *et al*. combined phthalazinones with 4-methoxybenzaldehyde to yield novel Schiff bases and tested against *Bacillus subtilis* and *Staphylococcus aureus* as Gram-positive bacteria, *Escherichia coli* and *Pseudomonas aurignosa* as Gram-negative bacteria, and *Candida albicans* and *Aspergillus niger* as fungi strains [12]. Sharif HMA *et al*. reported synthesis and spectral data of eight Schiff bases of salicylaldehyde with different amines, and evaluation of their anti-microbial activities against different bacterial strains. All the bases showed moderate to good activities against all the tested microorganisms [13]. Schiff bases of p-bromo-m-cresol were reported by Fuloria NK *et al*. The newly synthesized compounds were characterized on the basis of spectral studies and evaluated for antibacterial and antifungal activities [14]. It is clear from the literature review & market demand, that Schiff bases (imines) possesses wide variety of biological activities like antimicrobial, antitubercular, antimalarial and antiviral. Among various biological activities of several Schiff bases molecules synthesized in literature, the antimicrobial activity was found to be very prominent. According to literature it was also known that Esters, Hydrazides and Imines can be synthesized from different moieties. So, in the view of medicinal importance and synthetic routes to Schiff bases, it was thought worthwhile to study and synthesize compounds possessing

imino group. It was pertinent to investigate their structural modification. Hence the aim of present study was to synthesize and evaluate antimicrobial activity of Schiff bases of aryloxy Moiety.

EXPERIMENTAL

Melting points of newly synthesized compounds were determined in open capillary tubes. IR spectra were recorded (in KBr) on Schimadzu FTIR Spectrophotometer, ^{1}H NMR spectra on BRUKER Avance-II 400 MHz instrument using $CDCl_3$ solvent and mass spectra on LCMS 2010 EV SHIMADZU Mass spectrometer.

2.1 Ethyl aryloxy acetate (1): A mixture of aryloxy compound (0.1mol), ethylchloro acetate (0.1 mol) and anhydrous potassium carbonate (0.15 mol) in dried acetone was refluxed for 24 h. Resultant mixture was distilled off and poured on to ice-cold water and stirred. Residue was extracted with ether and the extract was dried over anhydrous sodium sulphate and was purified under reduced pressure to yield compound **1**; yield (62.74%), b.p. (305^{0}c), IR 1745 C=O of ester, 1149 for C-O of ester.

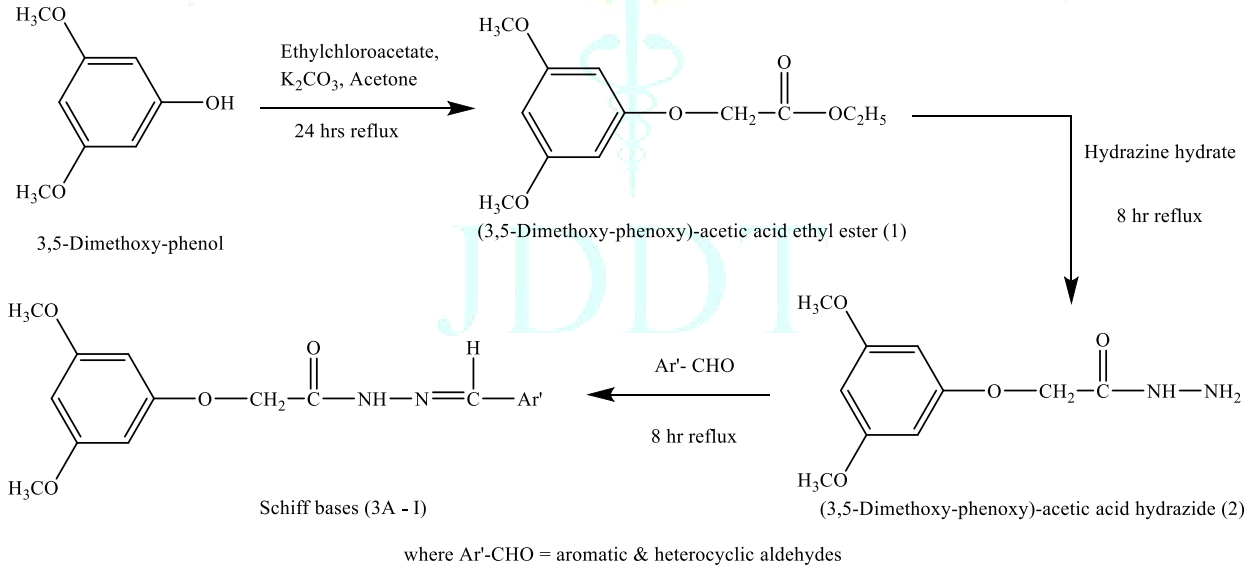
2.2 Acetohydrazide (2): A mixture of compound **1** (0.05mol) and hydrazine hydrate (0.075 mol) in ethanol was refluxed for 8 h and after distilling off the solvent the residue was recrystallized from methanol to yield compound **2**; yield (70.00%), m.p. (134^{0}c), IR 3306**,** 3198 for N-H and NH_2, 1674 for C=O of amide, 1524 for N-H bending of amide, 1250 and 1065 for C-O of phenyl ether.

2.3 Schiff bases (3A-I): A mixture of compound **2** (0.001 mol) and aromatic aldehyde (0.001 mol) was refluxed for 8 h using ethanol and glacial acetic acid. Crystals formed were washed with ice-cold water, dried and recrystallized from methanol to yield compounds **3A-I** [15,16].

2.4 Screening for biological activity: The synthesized compounds **3A-I** were screened for antibacterial activity using *Staphylococcus aureus* (MTCC 737), *Escherichia coli* (MTCC 452) and antifungal activity using *Candida albicans* (MTCC 227) by disk diffusion method at a concentration of 2 mg/mL using DMF as solvent. Ampicillin 1 mg/mL and fluconazole 2.5 mg/mL were used as standards [17]. The results were recorded using ampicillin and fluconazole as standards are given in Table-4.

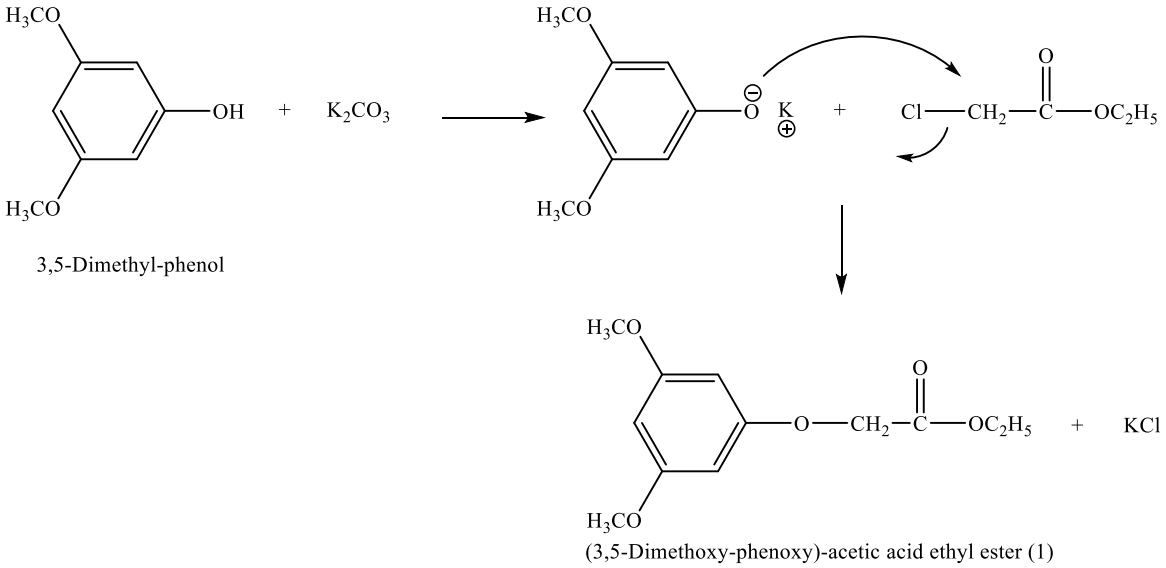
RESULTS AND DISCUSSION

The synthetic route is outlined in Scheme-I. (3,5-Dimethoxy-phenoxy)-acetic acid ethyl ester (**1**) was synthesized by refluxing 3,5-Dimethoxyphenol with ethylchloroacetate in dry acetone. Compound **1** on reacting with hydrazine hydrate gave (3,5-Dimethoxy-phenoxy)-acetic acid hydrazide (**2**). Condensation of **2** with various aromatic aldehydes afforded the potent antibacterial and antifungal Schiff bases (**3A-I**). Physical data of **3A-I** are given in Table-1. The structures of all compounds were characterized by spectral analysis. All the synthesized compounds **3A-I** had shown antibacterial and antifungal activity to certain extent. From the compounds synthesized, compounds **3C, 3D, 3E and 3I** had shown good antibacterial and antifungal activity and the remaining compounds have shown moderate activity on tested organisms **(Table-4).**

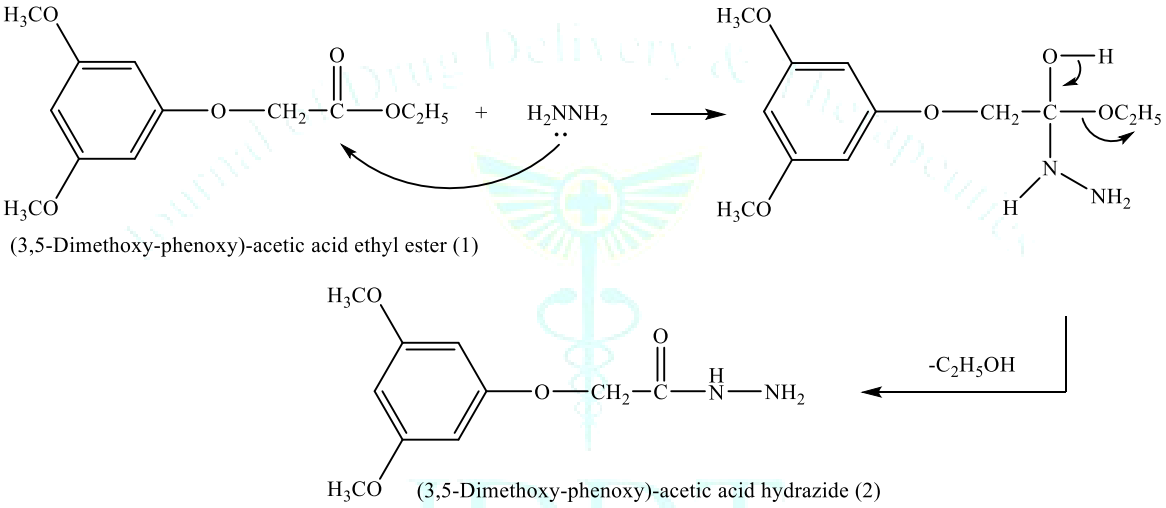


Scheme – I: Conversion of aryloxy moiety into Schiff bases

First of all nucleophilic substitution reaction take place between 3,5-Dimethoxyphenol and ethylchloroacetate in the basic medium to produce the corresponding ethyl ester **(1)**.



The second step involves the synthesis of acid hydrazide through the reaction between hydrazine and the ethyl ester **(1)**. The reaction proceeds by nucleophilic substitution of hydrazine to the ethyl ester carbonyl group to give the corresponding hydrazide **(2)**.



The final step involves nucleophilic attack by the basic nitrogen compound on carbonyl carbon. Protonation of carbonyl oxygen in presence of acid makes carbonyl carbon more susceptible to nucleophilic attack. The addition product undergoes dehydration to produce Schiff bases **(3A-I)**.

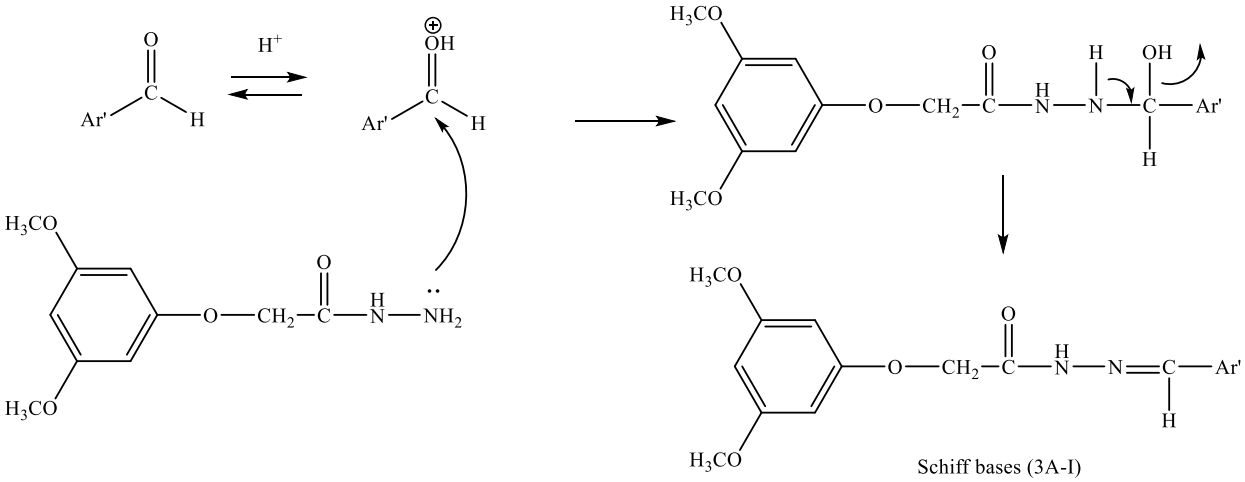


Table – 1: Physical characteristics of synthesized compounds 3A-I

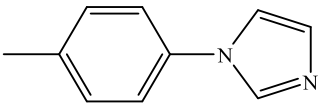
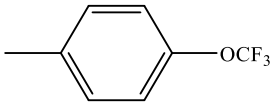
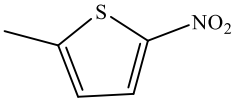
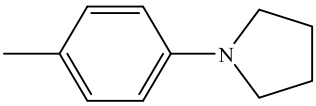
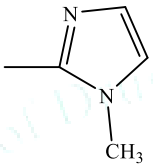
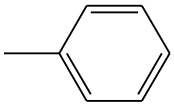
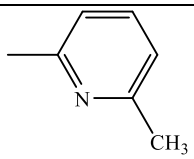
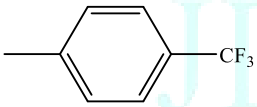
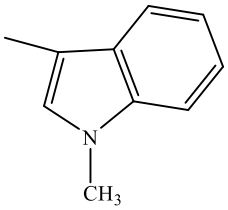
Compound (M.F.)	Ar' (aryl group)	Molecular Weight	Yield (%)	M.P. (^{0}c)
3A ($C_{20}H_{20}N_4O_4$)		380.41	72.00	134
3B ($C_{18}H_{17}F_3N_2O_5$)		398.34	78.22	144
3C ($C_{15}H_{15}N_3O_6S$)		365.37	69.48	150
3D ($C_{21}H_{25}N_3O_4$)		383.45	80.00	140
3E ($C_{15}H_{18}N_4O_4$)		318.34	80.60	130
3F ($C_{17}H_{18}N_2O_4$)		314.34	48.42	140
3G ($C_{17}H_{19}N_3O_4$)		329.36	70.82	156
3H ($C_{18}H_{17}F_3N_2O_4$)		382.34	86.24	124
3I ($C_{20}H_{21}N_3O_4$)		367.41	82.00	160

Table 2: Mass and ^{1}H-NMR data of 3A-3I

Compd.	Mass (M/Z)	^{1}H-NMR (ppm)
3A	380.2[M+], 381.2 [M+1]	3.71-3.73 (6H, s, for OCH_3), 5.13 (2H, s, for O-CH_2-CO), 6.10-6.19 (3H, m, for Ar-H), 7.47 (1H, dd, for imidazole-H), 7.82-7.84 (2H, ddd, for Ar-H), 7.88-7.90 (1H, dd, for imidazole-H), 8.04-8.07 (2H, ddd, for Ar-H), 8.41 (1H, s, for N=CH), 8.93-8.95 (1H, dd, for imidazole-H), 11.71 (1H, s, for NH).
3B	398.2[M+], 399.2 [M+1]	3.70-3.72 (6H, s, for OCH_3), 5.10 (2H, s, for O-CH_2-CO), 6.08-6.18 (3H, m, for Ar-H), 7.42-7.50 (2H, m, for Ar-H), 8.06-8.08 (2H, m, for Ar-H), 8.38 (1H, s, for N=CH), 11.67 (1H, s, for NH)
3C	365.3[M+], 366.3 [M+1]	3.74 (6H, s, for OCH_3), 5.10 (2H, s, for O-CH_2-CO), 6.26-6.28 (3H, m, for Ar-H), 7.55-7.58 (2H, d, for thiophene-H), 8.07 (1H, s, for N=CH), 11.08 (1H, s, for NH)
3D	383.2[M+], 384.2 [M+1]	1.88 (4H, m, for pyrazolidine-H), 3.46-3.48 (4H, m, for pyrazolidine-H), 3.70-3.72 (6H, s, for OCH_3), 5.10 (2H, s, for O-CH_2-CO), 6.20-6.30 (3H, m, for Ar-H), 6.71 (2H, ddd, for Ar-H), 7.38 (2H, ddd, for Ar-H), 8.05 (1H, s, for N=CH), 11.54 (1H, s, for NH)
3E	318.3[M+], 319.3 [M+1]	3.59 (3H, s, for N-CH_3), 3.74-3.76 (6H, s, for OCH_3), 5.10 (2H, s, for O-CH_2-CO), 6.20-6.23 (3H, m, for Ar-H), 7.30 (1H, d, for imidazole-H), 7.40 (1H, d, for imidazole-H), 7.78 (1H, s, for N=CH), 10.58 (1H, s, for NH)
3F	314.2[M+], 315.2[M+1]	3.74-3.76 (6H, s, for OCH_3), 5.13 (2H, s, for O-CH_2-CO), 6.26-6.32 (3H, m, for Ar-H), 7.20-7.42 (5H, m, for Ar-H), 8.12 (1H, s, for N=CH), 10.88 (1H, s, for NH)
3G	329.2[M+], 330.2[M+1]	2.52-2.54 (3H, s, for pyridine-CH_3), 3.70-3.72 (6H, s, for OCH_3), 5.12 (2H, s, for O-CH_2-CO), 6.19-6.24 (3H, m, for Ar-H), 7.19-7.52 (3H, m, for pyridine-H), 7.98 (1H, s, for N=CH), 10.10 (1H, s, for NH)
3H	382.2[M+], 383.2 [M+1]	3.74 (6H, s, for OCH_3), 5.08 (2H, s, for O-CH_2-CO), 6.20-6.22 (3H, m, for Ar-H), 7.41-7.66 (4H, m, for Ar-H), 8.02 (1H, s, for N=CH), 10.58 (1H, s, for NH)
3I	367.3[M+], 368.3 [M+1]	3.67-3.69 (3H, s, for N-CH_3), 3.72-3.74 (6H, s, for OCH_3), 5.13 (2H, s, for O-CH_2-CO), 6.20-6.23 (3H, m, for Ar-H), 7.21 (1H, t, for pyrrole-H), 7.38-7.54 (4H, m, for Ar-H), 8.10 (1H, s, for N=CH), 11.28 (1H, s, for NH)

Table 3: IR spectral data of compounds 3A-I

Compd	IR (cm^{-1})
3A	3113 for N-H, 2970 for aliphatic C-H, 1697 for C=O of amide, 1609 for C=N of imines, 1524 for N-H bending of amide, 1261 and 1061 for C-O of phenyl ether
3B	3198 for N-H, 3082 for aromatic C-H, 2970 for aliphatic C-H, 1693 for C=O of amide, 1605 for C=N of imines, 1508 for N-H bending of amide, 1261 and 1072 for C-O of phenyl ether
3C	3113 for N-H, 3048 for aromatic C-H, 2963 for aliphatic C-H, 1686 for C=O of amide, 1612 for C=N of imines, 1528 for N-H bending of amide, 1281 and 1042 for C-O of phenyl ether
3D	3202 for N-H, 3044 for aromatic C-H, 2967 for aliphatic C-H, 1674 for C=O of amide, 1609 for C=N of imines, 1524 for N-H bending of amide, 1246 and 1053 for C-O of phenyl ether
3E	3132 for N-H, 3102 for aromatic C-H, 2994 for aliphatic C-H, 1701 for C=O of amide, 1609 for C=N of imines, 1524 for N-H bending of amide, 1285 and 1069 for C-O of phenyl ether
3F	3190 for N-H, 3028 for aromatic C-H, 2916 for aliphatic C-H, 1686 for C=O of amide, 1597 for C=N of imines, 1555 for N-H bending of amide, 1292 and 1030 for C-O of phenyl ether
3G	3059 for N-H, 2997 for aromatic C-H, 2947 for aliphatic C-H, 1717 for C=O of amide, 1624 for C=N of imines, 1539 for N-H bending of amide, 1250 and 1080 for C-O of phenyl ether
3H	3202 for N-H, 2986 for aromatic C-H, 2963 for aliphatic C-H, 1701 for C=O of amide, 1605 for C=N of imines, 1516 for N-H bending of amide, 1242 and 1069 for C-O of phenyl ether
3I	3102 for N-H, 3044 for aromatic C-H, 2943 for aliphatic C-H, 1690 for C=O of amide, 1620 for C=N of imines, 1524 for N-H bending of amide, 1254 and 1076 for C-O of phenyl ether

Table 4: Antimicrobial activity of compounds 3A-I

Compound number	Zone of inhibition in mm		
	Antibacterial activity		Antifungal activity
	S. aureus	*E. coli*	*C. albicans*
3A	15	16	10
3B	18	19	12
3C	25	26	17
3D	21	22	14
3E	24	24	15
3F	20	18	13
3G	18	18	12
3H	16	16	10
3I	22	22	15
Ampicillin	25	24	---
Fluconazole	---	---	17

CONCLUSION:

Antibiotic resistance is a serious and growing phenomenon in contemporary medicine and has emerged as one of the eminent public health concerns of the 21st century, particularly as it pertains to pathogenic organisms. Hence in recent years, there has been a growing interest in researching and developing new antimicrobial agents from various sources to combat microbial resistance. Schiff bases (imines) possess wide variety of biological activities like antimicrobial, antitubercular, antimalarial and antiviral. Among various biological activities of several Schiff bases molecules synthesized in literature, the antimicrobial activity was found to be very prominent. It was also observed that Esters, Hydrazides and Imines can be synthesized from different moieties. From FTIR spectroscopy, it was concluded that the compounds were synthesized successfully as spectra includes different stretching bands for characteristics functional groups. The structures of Schiff bases were further confirmed by their ^{1}H-NMR and mass spectroscopy. After carrying out the antimicrobial studies of newly synthesized compounds it was found that each compound 3A to 3I possesses antibacterial and antifungal activities to certain extent. Among newly synthesized derivatives, compound **3C** was found to be more potent than ampicillin when tested against the strains of *Escherichia coli*, whereas compounds **3E** was found to be equipotent to ampicillin and fluconazole when tested on *Staphylococcus aureus*, *Escherichia coli* and *Candida albicans*. Schiff bases containing nitro thiophene nucleus has exhibited highest antimicrobial activity among all newly synthesized compounds.

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