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Synthesis and Antimicrobial Activities of Schiff Base from Nitrogen Containing Heterocycles

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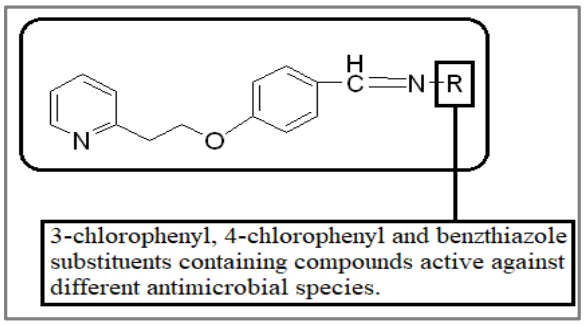
ABSTRACT

This article dealing with microwave assisted synthesis of Schiff base from pyridine clubbed heterocycles with their micro molar potency. MW stimulated synthetic route provides diverse advantages such as reaction rate acceleration, less by-product, higher yield and reproducibility of final product. Schiff base containing compounds have been an interesting field of study since long task, it constitutes a significant class of components for new drug development. Recently various Schiff base derivatives have been synthesized N-(4-substitutedphenyl)-1-(4-(2-(pyridin-2-yl)ethoxy)phenyl)methanimine(5a-j) from 4-(2-(pyridin-2-yl)ethoxy)benzaldehyde using catalytically amount of conc.H_2SO_4 at room temperature. The structure of final compounds has been established by elemental analysis such as IR, ^1H NMR, ^{13}C NMR & Mass spectroscopy and also evaluated for their antibacterial, antifungal potency. The result revealed that pyridine clubbed Schiff base shows promising antifungal activity against C. albicans. The biologically potent Schiff base 5i was found most active against S. aureus (MIC=25 µg mL^{-1}) with subjected to reference drug chloramphenicol and ciprofloxacin. The final compounds 5b, 5d, 5i displayed good antibacterial activity (MIC=50 µg mL^{-1}) with reference drug.

Graphical Abstract

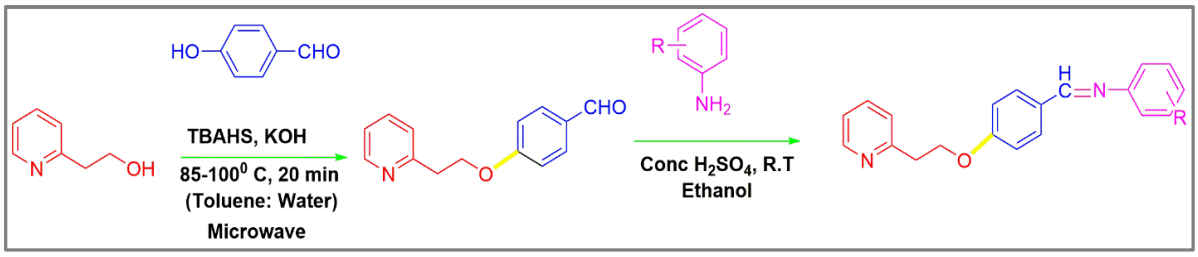


Keywords: Microwave irradiation, Schiff base, Antibacterial, Antifungal activity.

INTRODUCTION

Today's antibiotics are one of the most favorable medications for micro-organism in drug market. Microbial infection resistance to antibiotics drug, have been the biggest challenge nowadays, which threaten the health of society. In worldwide, millions of deaths were every year because of the microbial disease. About the 17 % of total death, in 2013, 9.2 million of deaths have been reported due to microbial disease. The incidence of evolution of the resistance has caused the extant antimicrobial medication to change into less effective or even infective. Today's diverse strategies have been suggested to overcome the resistance of antibiotic medication [**1-3**].

Hugo Schiff was the first who discovered the Schiff base in 1864. Schiff bases are prepared by reaction of amino and carbonyl group viz aldehyde and ketone by removal of H_2O [**4**]. It has been claimed that Schiff base containing N=C linkage is an essential structure responsible for medicinal potency [**5**]. Schiff bases play a vital role in the field of pharmaceutical and medical. Thus, development and synthesis of Schiff base derived from diverse heterocyclic moiety as a biologically potent candidate attracts the attention of medicinal and organic chemist [**6**]. Biologically potent Schiff base prepared from various heterocycles possess different kind of pharmacological potency namely antiviral [**7**], anticancer [**8**], cytotoxic [**9**], antimicrobial [**10**], antibacterial [**11, 12**], anticonvulsant [**13**]. Large number of substituted pyridines have been claimed to have several pharmacological applications including antibacterial, antifungal [**14-17**], analgesic and anti-inflammatory [**18-20**], antiparkinsonian [**21**], antimalarial [**22**]. Furthermore, MW assisted organic reaction enhancement gained favor as a non-conventional method for rapid synthesis could help to gain higher yield, short time duration and clean reaction outcome. This technique eliminates the circumstance related toxicity and flammability issue with the help of organic solvent free reaction conditions [**23-30**]. With organic reaction in solvent free environment assisted by microwave irradiation have being consider as environmentally benign methodologies [**31**].



R= NH_2, 3-Cl, 4-F, 4-Cl, 4- Br, 2,4-difluoro, 3-Chloro 4-fluoro, p-toluidine , 2 amino benzothiazole, 2 amino 6 methoy benzothiazole

Scheme. Preparation of Schiff's bases.

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MATERIALS AND METHODS

All solvents, chemicals and reagents were purchased from Sigma-Aldrich with the highest purity and used without further purification. Melting points were determined with open capillary method on 'Equiptronics' digital melting point apparatus, model no. EQ-730 and are uncorrected. IR spectra were recorded on a Perkin Elmer spectrophotometer (KBr pellets) instrument. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance II 500MHz NMR Spectrometer using DMSO- d6 as solvent and TMS as internal standard. All chemical shifts were reported as δ values (ppm). Mass spectra were recorded using Expression CMS from Advion, USA using ESI as ion source (mobile phase 0.1% Formic acid in 80:20, Methanol: Water). Analytical thin- layer chromatography (TLC) was performed with Merck silica gel plates and visualized with UV irradiation (254 nm) or iodine.

Procedure for the synthesis of 4-(2-(pyridin-2-yl)ethoxy)benzaldehyde: A mixture of pyridn-2 ethanol (820 mg, 6.66 mmol) and 4-Hydroxybenzaldehyde ware dissolved in toluene (3 mL) water (1 mL) mixture. To this mixture added TBAHS (tetra butyl ammonium hydrogen sulphate) (220 mg, 0.650 mmol) and KOH powder (1.10 gm, 19.6 mmol). Reaction mass was introduced in microwave assisted magnetic stirrer for 20 min at 85-100°C temperature. The completion of reaction was monitored by TLC (Hexene: Ethyl acetate) (4:1). The reaction mass was cooled down and extract in 25 mL toluene and dried over anhydrous Na_2SO_4 to give aldehyde.

General procedure for the synthesis of Schiff base from 4-(2-(pyridin-2-yl)ethoxy) benzaldehyde: In 100 mL beaker, take a 4-(2-(pyridin-2-yl)ethoxy)benzaldehyde (0.02 mol) and substituted amines (0.01 mol) in methanol. To this mixture added catalytical amount of conc. H_2SO_4 (1-2 mL). The product was instantly separates out at room temperature. Filter and dry it. The completion of reaction was monitored by TLC (Toluene: Ethyl acetate)(4:1)

Table 1. Characterization data of Compounds **5a-5j**

Compound No.	R	Molecular Formula	M.P/B. P °C	Yield%
5a	Aniline	$C_{20}H_{18}N_2O$	120	85
5b	3-Chloro aniline	$C_{20}H_{17}ClN_2O$	156	89
5c	4-Fluoro aniline	$C_{20}H_{17}FN_2O$	205	73
5d	4-Chloro aniline	$C_{20}H_{17}ClN_2O$	230	89
5e	4-Bromo aniline	$C_{20}H_{17}BrN_2O$	197	78
5f	2,4-difluoro aniline	$C_{20}H_{16}F_2N_2O$	134	82
5g	3-Chloro 4- Fluoro aniline	$C_{20}H_{16}ClFN_2O$	241	90
5h	p- toluidine	$C_{21}H_{20}N_2O$	162	74
5i	2- Amino benzothiazole	$C_{21}H_{17}N_3OS$	149	80
5j	2- Amino 6-methoxy benzothiazole	$C_{22}H_{19}N_3O_2S$	218	86

Spectral characterization of the compounds 5a-5j

N-phenyl-1-(4-(2-(pyridin-2-yl)ethoxy)phenyl)methanimine (5a): IR (KBr) ν cm^{-1}: 2948 (-CH-,Ar), 2879 (-CH_2-), 1598 (CH=N), 1290, 1024 (-C-O-C-);^{1}H NMR (DMSO-d_6) δ (ppm): 8.48 (s, 1H, CH=N), 7.14-8.45(m, 4H, pyridine ring), 7.02-8.85(m, 9H, aromatic ring), 4.27 (t, 2H, -CH_2-O), 3.30 (t, 2H, CH_2);^{13}C NMR(500MHz, DMSO-d_6) δ (ppm):(C-2) 148.4, (C-3) 121.2, (C-4) 136.1, (C-5) 122.7, (C-6) 159.6, (C-7) 32.4, (C-8) 67.3, (C-10) 161.5, (C-11) 114.3, (C-12) 129.9, (C-13) 128.2, (C-14) 129.7, (C-15) 114.2, (C-16) 160.2, (C-18) 152.2, (C-19) 122.1, (C-20) 130.3, (C-21) 127.1, (C-22) 130.1, (C-23) 122.3; ESI–MS: m/z calculated 302.38, found [M+H] 303.15.

N-(3-chlorophenyl)-1-(4-(2-(pyridin-2-yl)ethoxy)phenyl)methanimine (5b): IR (KBr) ν cm^{-1}:3067 (-CH-, Ar) ,2846 (-CH_2-), 1599 (N=CH), 1227,1046 (C-O-C) ,778 (C-Cl);^{1}H NMR (DMSO-d_6) δ (ppm): 8.80 (s, 1H, CH=N), 7.12- 8.64 (m, 4H, pyridine ring), 6.8-8.55 (m, 9H, aromatic), 4.37 (t, 2H, -CH_2-O), 3.33 (t, 2H, CH_2); ^{13}C NMR(500MHz, DMSO-d_6) δ (ppm):(C-2) 148.1, (C-3) 121.1, (C-4) 136.2, (C-5) 122.6, (C-6) 159.8, (C-7) 32.1, (C-8) 67.2, (C-10) 161.4, (C-11) 114.1, (C-12) 129.5, (C-13) 128.1, (C-14) 129.8, (C-15) 114.2, (C-16) 160.1, (C-18) 156.3, (C-19) 122.5, (C-20) 134.2, (C-21) 127.3, (C-22) 131.2, (C-23) 120.3;ESI–MS:m/z calculated 336.82, found [M+H] 336.10.

N-(4-fluorophenyl)-1-(4-(2-(pyridin-2-yl)ethoxy)phenyl)methanimine (5c): IR (KBr) ν cm^{-1}: 3010 (-CH-, Ar), 2858 (-CH_2-), 1611 (N=CH), 1245, 1015 (C-O-C), 962 (C-F);^{1}H NMR (DMSO-d_6) δ (ppm): 8.65 (s, 1H, CH=N), 6.69-7.65 (m, 4H, pyridine ring), 6.45 -7.49 (m, 8H, aromatic), 4.45 (t, 2H, -CH_2-O), 3.40 (t, 2H, CH_2); ^{13}C NMR(500MHz, DMSO-d_6) δ (ppm):(C-2) 148. 4, (C-3) 121.3, (C-4) 136.3 (C-5), 122.8, (C-6) 159.6, (C-7) 32.5, (C-8) 67.5, (C-10) 161.4, (C-11) 114.4, (C-12) 129.6, (C-13) 128.4, (C-14) 129.5, (C-15) 114.2, (C-16) 160.1, (C-18) 147.5, (C-19) 123.8, (C-20) 116.5, (C-21) 161.2, (C-22) 116.7, (C-23) 123.5;ESI–MS:m/zcalculated 320.37, found [M+H] 320.13.

N-(4-chlorophenyl)-1-(4-(2-(pyridin-2-yl)ethoxy)phenyl)methanimine (5d): IR (KBr) ν cm^{-1}: 2989 (-CH-, Ar), 2853 (-CH_2-), 1616 (N=CH), 1280, 1067 (C-O-C), 817 (C-Cl); ^{1}H NMR (DMSO-d_6) δ (ppm):8.58 (s,1H,CH=N), 7.17-8.40 (m, 4H, pyridine ring), 7.04-8.7 (m, 8H, aromatic), 4.32 (t, 2H, -CH_2-O), 3.44 (t, 2H, CH_2); ^{13}C NMR(500MHz, DMSO-d_6) δ (ppm):(C-2) 148.6, (C-3) 121.5, (C-4) 136.1, (C-5) 122.6, (C-6) 159.4, (C-7) 32.1, (C-8) 67.2, (C-10) 161.1, (C-11) 114.5, (C-12) 129.4, (C-13) 128.1, (C-14) 129. 6, (C-15) 114.1, (C-16) 160.4, (C-18) 146.1, (C-19) 122.4, (C-20) 130.2, (C-21) 132.6, (C-22) 130.3, (C-23) 122.2; ESI–MS:m/z calculated 336.82, found [M+H] 336.10.

N-(4-bromophenyl)-1-(4-(2-(pyridin-2-yl)ethoxy)phenyl)methanimine (5e): IR (KBr) ν cm^{-1}: 3075 (-C-H-, Ar), 2820 (-CH_2-), 1648 (N=CH), 1208, 1056 (C-O-C), 650 (C-Br); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.28 (s, 1H, CH=N), 7.14-8.40 (m, 4H, pyridine ring), 7.02- 7.88 (m, 8H, aromatic), 4.62 (t, 2H, -CH_2-O), 3.14 (t, 2H, CH_2); ^{13}C NMR(500MHz, DMSO-d_6) δ (ppm):(C-2) 148.2, (C-3) 121.3, (C-4) 136.4, (C-5) 122.8, (C-6) 159.2, (C-7) 32.4, (C-8) 67.2, (C-10) 161.1, (C-11) 114.5, (C-12) 129.4, (C-13) 128.0, (C-14) 129.5, (C-15) 114.4, (C-16) 160.1, (C-18) 151.2, (C-19) 122.6, (C-20) 132.4, (C-21) 121.5, (C-22) 132.3, (C-23) 122.5;ESI–MS: m/zcalculated 381.27, found [M+H] 380.05.

N-(2,4-difluorophenyl)-1-(4-(2-(pyridin-2-yl)ethoxy)phenyl)methanimine (5f): IR (KBr) ν cm^{-1}: 3056 (-CH-, Ar), 2951 (-CH_2-), 1627 (N=CH), 1225, 1046 (C-O-C), 970 (C-F); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.24 (s, 1H, CH=N), 7.14-8.41 (m, 4H, pyridine ring), 7.05-7.86 (m, 7H, aromatic), 4.36 (t, 2H, -CH_2-O), 3.10 (t, 2H, CH_2); ^{13}C NMR(500MHz, DMSO-d_6) δ (ppm):(C-2) 148.6, (C-3) 121.4, (C-4) 136.1, (C-5) 122.6, (C-6) 159.4, (C-7) 32.1, (C-8) 67.0, (C-10) 161.4, (C-11) 114.1, (C-12) 129.5, (C-13) 128.3, (C-14) 129.2, (C-15) 114.2, (C-16) 160.6, (C-18) 135.7, (C-19) 155.4, (C-20) 107.2, (C-21) 159.4, (C-22) 112.2, (C-23) 125.3;ESI–MS: m/z calculated 338.36, found [M+H] 338.12.

N-(3-chloro-4-fluorophenyl)-1-(4-(2-(pyridin-2-yl)ethoxy)phenyl)methanimine (5g): IR (KBr) ν cm^{-1}: 3028 (-CH-, Ar), 2812 (-CH_2-), 1687 (N=CH), 1280, 1075 (C-O-C), 745 (C-Cl), 952 (C-F); ^{1}H NMR (DMSO-d_6) δ (ppm):8.69 (s, 1H, CH=N), 7.18-8.39 (m, 4H, pyridine ring),6.98-7.80 (m, 7H, aromatic), 4.60 (t, 2H, -CH_2-O), 3.22 (t, 2H, CH_2); ^{13}C NMR(500MHz, DMSO-d_6) δ (ppm):(C-2) 148.3, (C-3) 121.2, (C-4) 136.3, (C-5) 122.5, (C-6) 159.4, (C-7) 32.2, (C-8) 67.1, (C-10) 161.1, (C-11) 114.2, (C-12) 129.8, (C-13) 128.1, (C-14) 129.6, (C-15) 114.3, (C-16) 160.3, (C-18) 152.2, (C-19) 124.3, (C-20) 122.2, (C-21) 157.4, (C-22) 118.4, (C-23) 122.1;ESI–MS: m/z calculated 354.81,found [M+H] 354.09.

1-(4-(2-(pyridin-2-yl)ethoxy)phenyl)-N-(p-tolyl)methanimine (5h): IR (KBr) ν cm^{-1}: 3052 (-CH-, Ar), 2914 (-CH_2-), 1612 (N=CH), 1209, 1036 (C-O-C);^{1}H NMR (DMSO-d_6) δ (ppm): 8.72 (s, 1H, CH=N), 7.20-8.49 (m, 4H, pyridine ring), 7.05-7.82 (m, 8H, aromatic), 4.21 (t, 2H, -CH_2-O), 3.67 (t, 2H, CH_2); ^{13}C NMR(500MHz, DMSO-d_6) δ (ppm):(C-2) 148.5, (C-3) 121.2, (C-4) 136.6, (C-5) 122.6, (C-6) 159.0, (C-7) 32.4, (C-8) 67.2 (C-10) 161.7, (C-11) 114.7, (C-12) 129.8, (C-13) 128.5, (C-14) 129.7, (C-15) 114.6, (C-16) 160.5, (C-18) 149.2, (C-19) 122.1, (C-20) 130.3, (C-21) 136.8, (C-22) 130.1, (C-23) 122.3;ESI–MS:m/z calculated 316.40,found [M+H] 316.16.

N-(benzo[d]thiazol-2-yl)-1-(4-(2-(pyridin-2-yl)ethoxy)phenyl)methanimine (5i): IR (KBr) ν cm^{-1}**:** 2980 (-CH-, Ar), 2908 (-CH_2-), 1654 (N=CH), 1235, 1074(C-O-C);^{1}H NMR (DMSO-d_6) δ (ppm): 8.95 (s, 1H, CH=N), 7.18-8.45 (m, 4H, pyridine ring), 7.06 - 7.90 (m, 4H, aromatic), 7.51-8.20 (m, 4H, benzothiazole ring),4.61 (t, 2H, -CH_2-O), 3.25 (t, 2H, CH_2);^{13}C NMR(500MHz, DMSO-d_6) δ (ppm): (C-2) 148.1, (C-3) 121.5, (C-4) 136.2, (C-5) 122.4, (C-6) 159.8, (C-7) 32.1, (C-8) 67.2, (C-10) 161.3, (C-11) 114.3, (C-12) 129.6, (C-13) 128.3, (C-14) 129.7, (C-15) 114.3, (C-16) 160.1, (C-18) 174.5, (C-20) 148.5, (C-21) 125.6, (C-22) 121.8, (C-23) 124.6, (C-24) 125.2, (C-25) 121.4;ESI–MS:m/z calculated 359.45, found [M+H] 359.11.

N-(6-methoxybenzo[d]thiazol-2-yl)-1-(4-(2-(pyridin-2-yl)ethoxy)phenyl)methanimine (5j): IR (KBr) ν cm^{-1}: 3072 (-CH-, Ar), 2915 (-CH_2-), 1614 (N=CH), 1278, 1045 (C-O-C); ^{1}H NMR (DMSO-

d_6) δ (ppm):9.01 (s, 1H, CH=N), 7.16-8.45 (m, 4H, pyridine ring), 7.03-7.83 (m, 3H, aromatic), 7.02-7.53 (m, 3H, benzothiazole ring), 4.34 (t, 2H, -CH_2-O), 3.79 (s, 1H, OCH_3), 3.32 (t, 2H, CH_2); ^{13}C NMR(500MHz, DMSO-d_6) δ (ppm):(C-2) 148.3, (C-3) 121.2, (C-4) 136.5, (C-5) 122.8, (C-6) 158.6, (C-7) 32.2, (C-8) 67.1, (C-10) 161.8, (C-11) 114.5, (C-12) 129.6, (C-13) 128.1, (C-14) 129.8, (C-15) 114.3, (C-16) 160.0, (C-18) 174.7, (C-20) 141.2, (C-21) 136.2, (C-22) 104.8, (C-23) 156.9, (C-24) 114.5, (C-25) 122.5, (C-26) 55.6;ESI–MS: m/z calculated 389.47, found [M+H] 389.12

Table 2. Antimicrobial data of Compounds **5a-5j**

Code No.	Minimal Inhibition Concentration [Microgram mL^{-1}]						
	E. Coli	*P. Aeruginosa*	*S. Aureus*	*S. Pyogenes*	*C. Albicans*	*A. Niger*	*A. Clavatus*
	MTCC 443	MTCC 1688	MTCC 96	MTCC 442	MTCC 227	MTCC 282	MTCC 1323
5a	250	100	250	500	1000	1000	1000
5b	100	50	250	125	1000	1000	1000
5c	250	125	250	250	500	>1000	>1000
5d	50	62.5	100	125	250	1000	1000
5e	250	100	125	250	250	500	500
5f	100	100	500	250	1000	250	250
5g	62.5	100	250	250	500	1000	1000
5h	100	125	100	62.5	1000	>1000	>1000
5i	100	50	25	125	250	1000	1000
5j	100	100	125	100	500	500	500
Gentamycin	**0.05**	**1**	**0.25**	**0.5**	-	-	-
Chloramphenicol	**50**	**50**	**50**	**50**	-	-	-
Ciprofloxacin	**25**	**25**	**50**	**50**	-	-	-
Norfloxacin	**10**	**10**	**10**	**10**	-	-	-
Nystatin	-	-	-	-	**100**	**100**	**100**
Griseofulvin	-	-	-	-	**500**	**100**	**100**

RESULTS AND DISCUSSION

The synthesis of final product Schiff base and an intermediate stage is given in the scheme.4-(2-(pyridin-2-yl)ethoxy)benzaldehyde was synthesized by reaction of pyridin-2 ethanol with 4-Hydroxybenzaldehyde using microwave assisted organic synthesis and followed by Schiff base formation at room temperature. Final compounds Schiff base [5a-j] were synthesized by using 4-(2-(pyridin-2-yl) ethoxy) benzaldehyde with different substituted amines using catalytically amount(1-2 drops) of Conc.H_2SO_4 at room temperature. The purity of compounds was checked by TLC and other spectroscopic technique. The reaction protocol is illustrated in the scheme.

The final compounds were confirmed by IR and ^{1}H NMR, ^{13}C NMR, Mass spectroscopy. In the IR spectrum of Schiff base, the symmetrical and asymmetrical band of C-O-C observed at 1288 cm^{-1} and 1055 cm^{-1} and band for -CH=N observed at 1625 cm^{-1}. In NMR a single observed at δ 8.80 and triplet observed at δ 4.45 confirmed the CH_2-O which confirmed the structure of **5c**.

Biological Assay: Broth dilution method was used to determine the MIC of the final compounds. Each of the tested samples were dissolved in DMSO to perform the desire drug concentration to test standard bacterial strains. Screening of biologically potent samples were against diverse strain, viz two-gram positive bacteria *S. aureus* (MTCC 96), *S. pyogenes* (MTCC 442) and two-gram negative bacteria *E. coli* (MTCC 443) and *P. aeruginosa* (MTCC 1688) and *C. albicans*(MTCC 227), *A. niger* (MTCC 282), *A. clavatus* for fungi and compare with standard drug chloramphenicol, ciprofloxacin, nystatin, griseofulvin. Schiff base **5i** was found most potent against *S. aureus* (MIC= 25 µg mL^{-1}) with reference drug ciprofloxacin. The final compound **5d** showed remarkable activity against *E. coli* (MIC = 50 µg mL^{-1}) compared with chloramphenicol. The biologically active Schiff base **5b, 5i** displayed good activity with MIC value 50 µg mL^{-1} against *P. aeruginosa* using chloramphenicol drug as a standard. The **5g** demonstrated moderately active against *E. coli* (MIC= 62.5 µg mL^{-1}) to chloramphenicol and ciprofloxacin. The Schiff base **5d, 5j** displayed poor activity against *P. aeruginosa* (MIC= 62.5 µg mL^{-1}) in comparison with reference drug ciprofloxacin and

chloramphenicol. Compound **5h** was found moderately active against *S. pyogenes* with MIC value 62.5 µg mL^{-1} to chloramphenicol and ciprofloxacin. Other compounds in the series were given very poor antibacterial potency.

From the antifungal assay of the Schiff base, it was found that compounds **5d, 5e, 5i** were exhibited good antifungal properties against *C. albicans* (MIC= 250 µg mL^{-1}) with griseofulvin. Amongst the other final compounds, the Schiff base **5c, 5g, 5j** demonstrated remarkable pharmacological potency against *C. albicans* (MIC= 500 µg mL^{-1}) griseofulvin. Other compounds were found moderately pharmacological properties.

APPLICATION

The freshly prepared Schiff's base bearing with thiophene derivatives which gave promising antibacterial and antifungal activity as compare with their standard control drug.

CONCLUSION

The newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and Mass analaysis techniques and also screened against various strains of Gram-Positive and Gram-nagative bacteria and antifungal applications. The result revealed that pyridine clubbed azomethine group displayed promising antifungal activity against *C. albicans*. The biologically potent schiff base**5i** was found most active against *S. aureus*. The azomethine products **5b, 5d, 5i** demonstrated good antibacterial activity.In which some therapuetically potent compounds gives exellent to moderate medicinal potent.

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