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Green Synthesis and Evaluation of Novel Pyrimidine Incorporated Schiff Bases as Promising Antibacterial Agents

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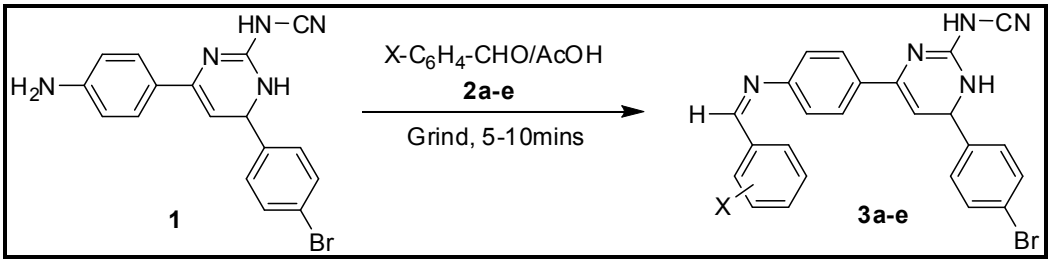
ABSTRACT

*Green and rapid synthesis of Novel N-(4-(4-(benzylideneamino)phenyl)-6-(4-chlorophenyl)-1,6 -dihydropyrimidin-2-yl)cyanamide derivatives (**3a-f**) from N-(4-(4-aminophenyl)-6-(4-chlorophenyl) -1,6-dihydropyrimidin-2-yl)cyanamide (**1**)have been described. All the compounds were obtained in very good yield within 5-10 min by using grinding method. The structures were confirmed using FT-IR, ^{1}H-NMR and ^{13}C-NMR spectra. The synthesized compounds were screened for their antibacterial activities and showed potential activities against tested bacterial strains.*

Graphical Abstract



Keywords: Antibacterial Activity, FT-IR, ^{1}H-NMR and ^{13}C-NMR spectra, Schiff bases.

INTRODUCTION

The condensation product between aryl amine and aryl aldehyde was first reported by Schiff in 1864 which is called as Schiff base [1-2]. This type of compounds containing -C=N moiety and plays important role in the realm of organic chemistry as synthons [3-4]. Apart from synthetic utility, they have gained importance in medicinal and pharmaceutical fields due to a broad spectrum of biological activities like antibacterial [5], antifungal [6] anti-inflammatory [7], analgesic [8], anticonvulsant [9], anticancer [10] and antioxidant [11]. On the other way, Pyrimidine is most important 1, 3-positional isomer of six membered heterocycles and is abundant in nature. Hence, their structural subunits present in natural products such as DNA, RNA, vitamins, amino acids and alkaloids they exhibit significant role in life. For instance, they have interesting biological, medicinal and therapeutic

applications [12-18]. Furthermore, these type of compounds have given attention from the last two decades due to their simple formation by combination of a reagent containing N-C-N skeleton with C-C-C unit [19-21] and their interesting chemical properties [22-24]. Medicinal chemistry concerns with the discovery and development of biologically active compounds at molecular level resulted by simple changes in the structural alignment of novel heterocyclic compounds, concern and continuation of my earlier work [25-26], here with synthesized a series of novel Schiff compounds by incorporating pyrimidine heterocycles in a simple and green manner.

MATERIALS AND METHODS

General: All the required chemicals for research were purchased from Avra, Loba, and S.D fine chemicals (India). Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrophotometer as KBr pellet. ^{1}H-NMR and ^{13}C-NMR spectra were obtained on a Brucker (300 MHz) instrument in $CDCl_3$ solvent using tetramethylsilane (TMS) as an internal standard and chemical shift values are given in δ ppm. Anti-bacterial studies were performed by using disc diffusion method where the inhibition values are given in mm in diameter and Gentamicin (20 µg) used as standard.

General procedure to synthesis of Schiff bases (3a-e): One equivalent of **1** and one equivalent of Benzaldehyde **2a** were taken in pestle and mortar. To this 3-5 drops of glacial acetic acid was added and mixture was grinded up to 5-10 min. While grinding, the solid mixture was started to melt and finally solidified. After completion of the reaction indicated by TLC, distilled water was added to solid mass, filtered and recrystallized from ethanol. The same procedure was followed to prepare remaining derivatives by changing aldehydes.

RESULTS AND DISCUSSION

The novel Schiff bases (**3a-e)** were obtained in very good yield by performed reaction between cyanopyrimidine **1** with different aromatic aldehydes **2a-e** in the presence of catalytic amount of AcOH. The synthesis of compound **1** was reported by me [25-26] using aldol condensation reaction and Michael type addition reaction where previous was used to make chalcone and later was used to make Cyanopyrimidine **1**.

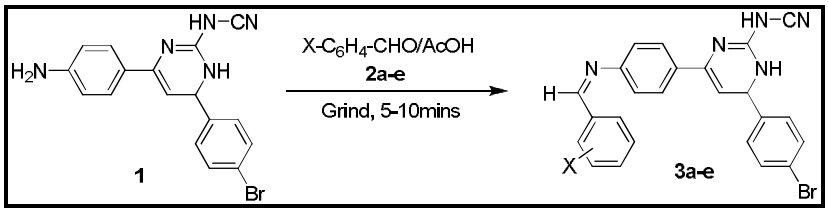


Table 1. Physical data of Schiff bases **3a-e.**

Comp.code	X	Time(Min)	Yield (%)	Mp (°C)	Rf value (Hex:EA, 2:1)
3a	H	5	70	136-138	0.50
3b	2-Cl	10	78	152-254	0.40
3c	2-F	5	80	144-146	0.42
3d	3-NO_2	10	85	150-152	0.38
3e	3-Br	5	88	148-150	0.41

The physical and spectral data such as, melting point, Rf value, FT-IR, ^{1}H-NMR and ^{13}C-NMR (Table 1 and 2) were well supported the formation of the desired products. The Antimicrobial activities of **3a-e** were examined using disc diffusion method (Fig 1). Among these five compounds,

3b, 3c, 3e were showed highest activities than standard against *Staphylococcus aureus*. The compounds **3b**, **3c** and **3d** showed almost equal activities as standard in case of *Escherichia coli*. However, all the compounds were in active against *Aspergillus niger* (Table 3). FT-IR, ^{1}H-NMR and ^{13}C-NMR spectra of compound 3a and 3b shown in figure 2a-2c.

Table 2. Spectral data of selective Schiff base compounds **3a, 3b** and **3d.**

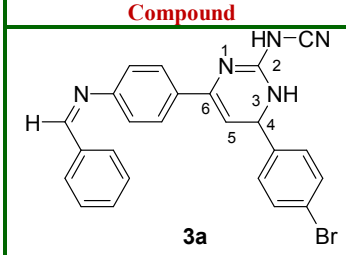
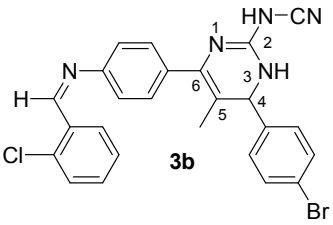
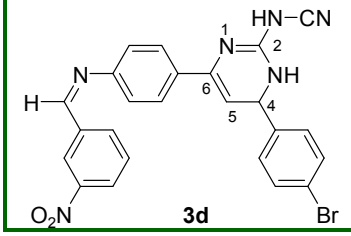
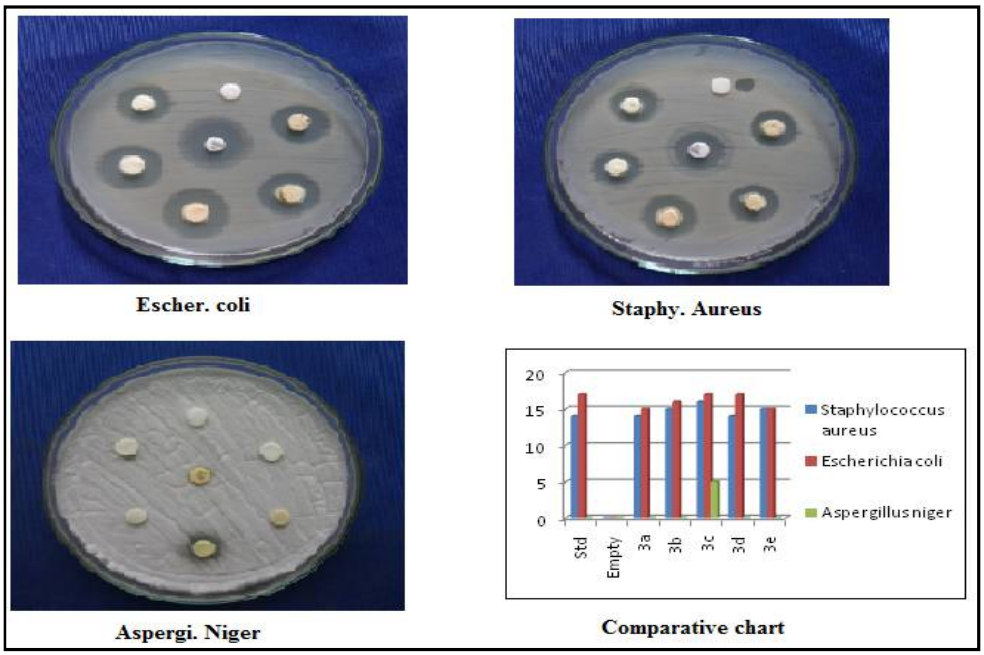
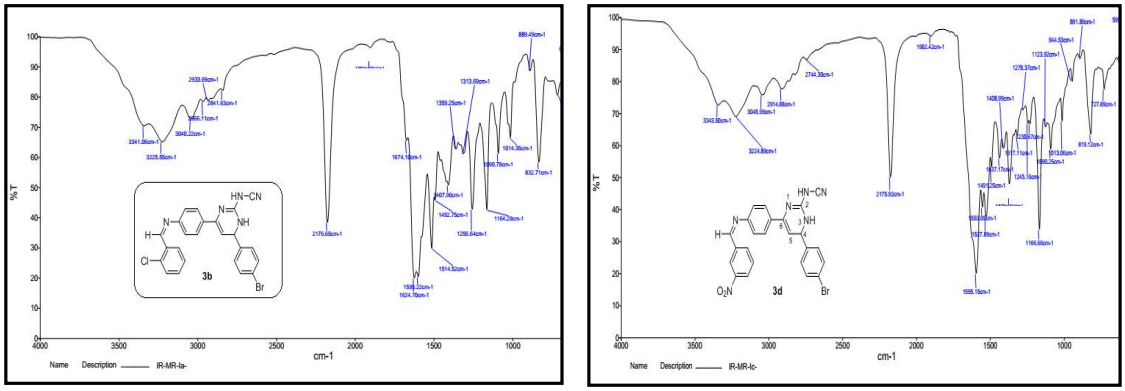
Compound	Spectral Data
 **3a**	**FT-IR:** 3341.06, 3225.55 (NH), 3040.22(Ar-CH), 2176.65(CN), 1599.22(HC=N), 1251.02(C-N), 1090.78(Ar-Br). **^{1}H-NMR:** 6.01(s, 2H, NH, broad), 5.16 (d, 1H, C_4-H), 5.32 (d, 1H, C_5-H), 7.02-7.86 (13Ar-CH), 8.35 (s, 1H, CH=N). **^{13}C-NMR:** 54.98 (C_4-Pyr), 99.05 (C_5 of Pyr), 132.80 (C-Br), 128.02, 136.57, 141.11, 152.32, 156.24 (5-Ar-QC) 119.23, 120.50, 125.93, 126.66, 127.62, 127.72, 128.30, 128.60, 129.36, 129.53, 133.14, 133.0(12Ar-CH), 162.05 (CH=N).
 **3b**	**FT-IR:** 3341.04, 3225.50(NH), 3040.22(Ar-CH), 2176.60 (CN), 1624.70(HC=N), 1256.64 (C-N), 1014.36 (Ar-Br). **^{1}H-NMR:** 6.64 (s,2H, NH, broad), 5.12 (d, 1H, C_4-H), 5.33 (d,1H, C_5-H), 6.97-7.86 (12Ar-CH), 8.33 (s, 1H, CH=N). **^{13}C-NMR:** 54.94 (C_4Pyr), 99.15 (C_5, Pyr), 135.08 (C-Br) 136.59 (C-Cl), 127.73, 133.62, 141.02, 152.53, 156.28 (5-Ar-QC) 119.62, 120.53, 125.73, 127.43, 127.62, 128.02, 128.25, 129.17, 129.36, 131.29, 132.80, 133.14, 133.62 (12Ar-CH), 160.15 (CH=N).
 **3d**	**FT-IR:** 3224.80 (NH), 3045.99, (Ar-CH), 2175.60 (CN), 1595.15(HC=N), 1527.89 (NO_2), 1245.16(C-N), 1013.06(Ar-Br). **^{1}H-NMR:** 6.64 (s,2H, NH, broad), 5.12 (d, 1H, C_4-H), 5.33 (d, 1H, C_5-H), 6.97-7.86(12Ar-CH), 8.33, (s, 1H, CH=N). **^{13}C-NMR:** 55.53 (C_4, Pym), 97.70 (C_5, Pym), 132.80 (C-Cl), 140.70 (C-NO_2), 128.31, 134.34, 141.68, 151.16, 151.28 (5-Ar-QC), 117.09, 121.64, 122.58, 126.22, 127.34, 127.52, 128.53, 128.82, 129.43, 129.95, 133.81, 134.34 (12Ar-CH), 159.74 (CH=N).

Figure 1. Anti microbial activities images (Disc Diffusion Method) of Schiff bases **3a-e**.





igure 2a. FT-IR Spectra of **3b and 3d.**

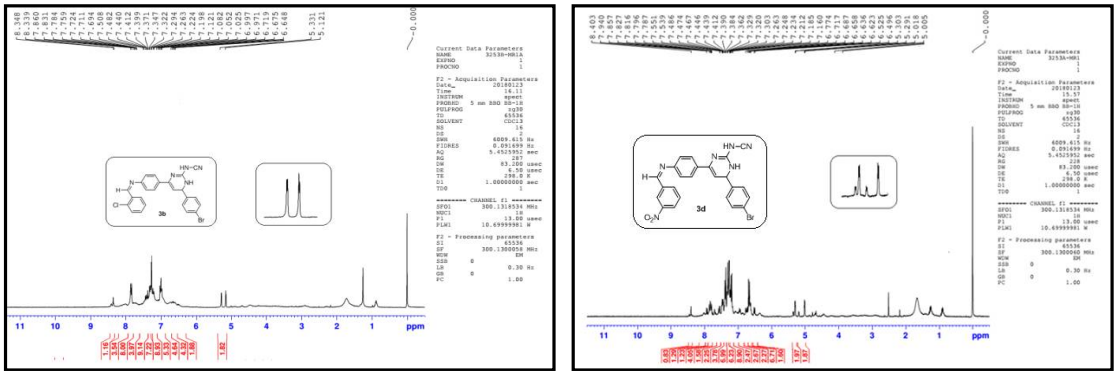


Figure 2b. ^{1}H-NMR Spectra of **3b and 3d.**

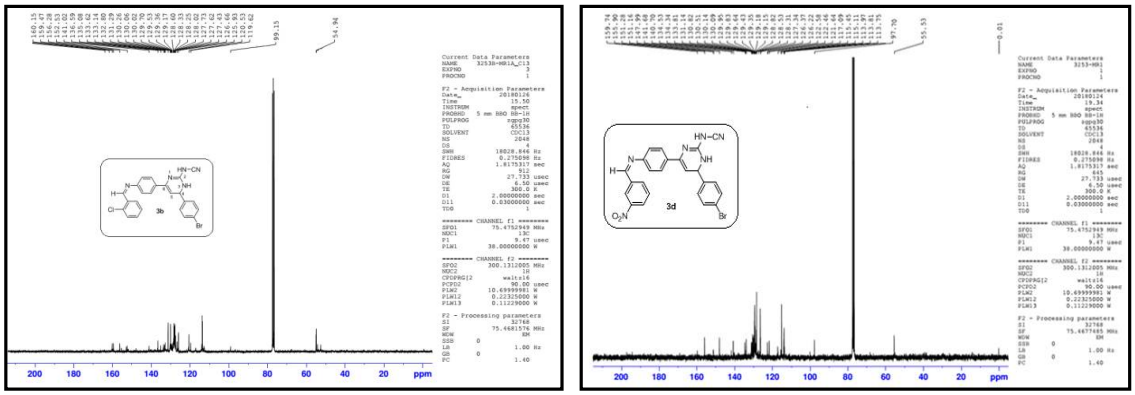


Figure 2c. ^{13}C-NMR Spectra of **3b and 3d.**

Table 3. Antimicrobial activities values of Schiff bases **3a-e**.

S. No.	Bacteria	Zone of inhibition (mm in diameter, 30µg disc^{-1})						
		Standard	Empty	3a	3b	3c	3d	3e
1	*Staphylococcus aureus*	14	-	14	15	16	14	15
2	*Escherichia coli*	18	-	15	16	17	17	15
3	*Aspergillus niger*	-	-	-	-	5	-	-

APPLICATION

Novel Schiff base compounds comprising pyrimidine heterocycles are potential antibacterial activities.

CONCLUSIONS

Above, described synthesis of some novel Schiff base compounds comprising pyrimidine heterocycles. The structures were proposed using different spectral studies and potential antibacterial activities were observed against tested bacterial strains than fungus.

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