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AN EXPEDITIOUS SYNTHESIS AND MICROBIAL STUDIES OF NOVEL *N*-(6-(4-CHLOROPHENYL) (SUBSTITUTED-BENZYLIDENEAMINO)PHENYL)-1,6-DIHYDROPYRIMIDIN-2-YL)CYANAMIDE

K. Babu

PG and Research Department of Chemistry, Rajah Serfoji Government College (Auto), Thanjavur, Tamil Nadu, India.
Email: kbabu.chemistry@gmail.com

ABSTRACT
A series of novel schiff bases incorporated with cyanopyrimidine heterocycles have been synthesized by applying simple methods. The structures were confirmed with the help of Melting point, TLC, FT-IR, ^{1}H-NMR and^{13}C-NMR spectra based on the agreement of observed signals with expected signals. The invitro antibacterial activities were examined by using disc diffusion method and observed very good response of the compounds against selective bacterial strains than fungus.

KEYWORDS: Pyrimidine, Schiff base, Aldol reaction, 4-Aminoacetophenone, 4-Cl-Benzaldehyde.

INTRODUCTION
Schiff bases were first reported by Schiff in 1864 and are containing carbon-nitrogen double bond formed by condensation reaction of primary amines with carbonyl compounds. They have been found to posses various pharmacological activities due to its imine functionality [i-x]. Furthermore, it plays a vital role in the progresses of chemistry and has been used as fine chemicals and medicinal substrates [xi-xiii]. Heterocyclic compounds are abundant in nature as vitamins, amino acids, alkaloids and etc. Particularly, pyrimidines based heterocycles are contribute to the society by helping in different life processes and play in cellular processes which made them valuable leads for drug discovery [xiv-xv]. Apart from that, these compounds show various medicinal activities such as, Antimicrobial [xvi-xix], Anti-HIV [xx], anti-tubercular [xxi], anti-tumor [xxii], anti-neoplastic [xxiii], anti-inflammatory [xxiv-xxvi], diuretic [xxvii], anti-malarial [xxviii-xxix] and cardiovascular [xxx]. By considering the application of both Schiff base and Pyrimidine, I attempted to synthesize a series of compounds by connecting these two moiety in order to improve their medicinal activities.

EXPERIMENTAL SECTION
General: Chemicals required for research was purchased from Merck (India), S.D fine and AVRA chemicals (India). Melting points are uncorrected. Infrared spectra were recorded on a

Perkin-Elmer Paragon 1000 FTIR spectrophotometer as potassium bromide discs unless otherwise indicated. ^{1}H NMR spectra were obtained on a Brucker (300 MHz) instrument in $CDCl_3$ solutions using tetramethylsilane as an internal standard. *J* Values are given in Hz. Antibacterial activities were checked by using disk diffusion method where Gentamicin used as standard.

General procedure for synthesis substituted chalcones (3):

A mixture of 0.01mol of *p*-NH_2-acetophenone **1**, (1 equiv) and *p*-Cl-benzaldehyde **2** (1 equiv) with 40% NaOH aqueous solution (2 mL) was stirred in ethanol (20 mL) for 2-3 hrs at room temperature. Progress of the reaction monitored by TLC and after completion of the reaction mixture was poured in to crushed ice and acidified with dilute hydrochloric acid. The solid was filtered, dried and recrystalyzed from ethanol.

General procedure for synthesis substituted pyrimidines (5)

A mixture of substituted chalcone **3** (1 equiv) and 2-cynoquanidine **4** (1 equiv) was refluxed for 2-3 hr in distilled ethanol (20 mL) with catalytic amount of NaOH. After completion of the reaction indicated by TLC, the mixture was poured in to ice-cold water. The solid formed was filtered, washed repeatedly with water, dried and finally recrystalyzed from ethanol.

General procedure for synthesis of schiff bases pyrimidines (7a-e):

One equivalent of **5** and one equivalent of *p*-OCH_3-benzaldehyde were taken in pestle and morter. To this 3-5 drops of glacial acetic acid was added and mixture grinded upto 10-20mins. During the grinding, the solid compounds were started to melt and finally solidified. Progress of the reaction monitored by TLC and after completion of the reaction mixture was poured in to crushed ice. The obtained solid mass was filtered and recrystalyzed from ethanol. The same procedure was followed to prepare remaining derivatives and all the products were obtained in very good yield.

FT-IR, ^{1}H-NMR and ^{13}C-NMR data of selected Schiff base derivatives:

N-(6-(4-chlorophenyl)-4-(4-(4-methoxybenzylideneamino)phenyl)-1,6-dihydropyrimidin-2-yl)cyanamide (7a):

FT-IR (KBr, cm^{-1}): 3341.06, 3225.55 (NH), 3040.22 (Ar-CH), 2966.11 (Aliphatic-CH), 2176.65 (CN), 1599.22 (HC=N), 1090.78 (Ar-Cl), ^{1}H-NMR ($CDCl_3$, δ): 3.89 (s, 3H, OCH_3), 4.5, 4.6 (s,2H, NH, broad & weak), 5.16 (d, 1H, C_4-H of Pyrimidine), 5.32 (d, 1H, C_5-H of Pyrimidine), 7.02, 7.05, 7.12, 7.19, 7.32, 7.34, 7.37, 7.39, 7.44, 7.48, 7.83, 7.86 (12Ar-CH), 8.35 (s, 1H, CH=N); ^{13}C-NMR ($CDCl_3$,δ), 52.53 (OCH_3), 54.98 (C_4 of Pyrimidine), 99.05 (C_5 of Pyrimidine), 132.80 (C-Cl), 128.02, 136.59, 141.11, 152.42, 156.28 (5-Aromatic quaternary carbons) 119.64, 120.55, 125.93, 126.66, 127.62, 127.73, 128.33, 128.60, 129.36, 129.53, 133.14, 133.62 (12Ar-CH), 163.95 (CH=N).

N-(6-(4-chlorophenyl)-4-(4-(4-(dimethylamino)benzylideneamino)phenyl)-1,6 5dihydropyrimidin-2-yl)cyanamide(7c):

FT-IR (KBr, cm^{-1}): 3343.50, 3224.85 (NH), 3045.99 (Ar-CH), 291488 (Aliphatic-CH), 2175.92 (CN), 1595.15 (HC=N), 1090.25 (Ar-Cl), ^{1}H-NMR ($CDCl_3$, δ): 3.03 (s, 6H, $N(Me)_2$), 4.2, 4.4 (s,2H, NH, broad & weak), 5.15 (d, 1H, C_4-H of Pyrimidine), 5.33 (d, 1H, C_5-H of Pyrimidine), 7.05, 7.08, 7.21, 7.23, 7.32, 7.34, 7.42, 7.40, 7.53, 7.54, 7.72, 7.75 (12Ar-CH), 8.28 (s, 1H, CH=N); ^{13}C-NMR ($CDCl_3$,δ), 44.61 ($N(CH_3)_2$), 55.35 (C_4 of Pyrimidine), 100.23 (C_5 of Pyrimidine), 132.79 (C-Cl), 125.25, 128.07, 129.14, 134.59, 140.39 (5-Aromatic quaternary carbons) 116.93, 125.23, 128.28, 128.61, 128.87, 129.14, 129.35, 129.83, 132.79, 133.20, 134.05 (12Ar-CH), 157.69 (CH=N).

N-(4-(4-(4-chlorobenzylideneamino)phenyl)-6-(4-chlorophenyl)-1,6-dihydropyrimidin-2-yl)cyanamide (7d):

FT-IR (KBr, cm^{-1}): 3225.48 (NH), 3048.67 (Ar-CH), 2924.09 (Aliphatic-CH), 2177.25 (CN), 1596.73 (HC=N), 1090.44 (Ar-Cl), ^{1}H-NMR ($CDCl_3$, δ): 4.40, 4.70 (s,2H, NH, broad

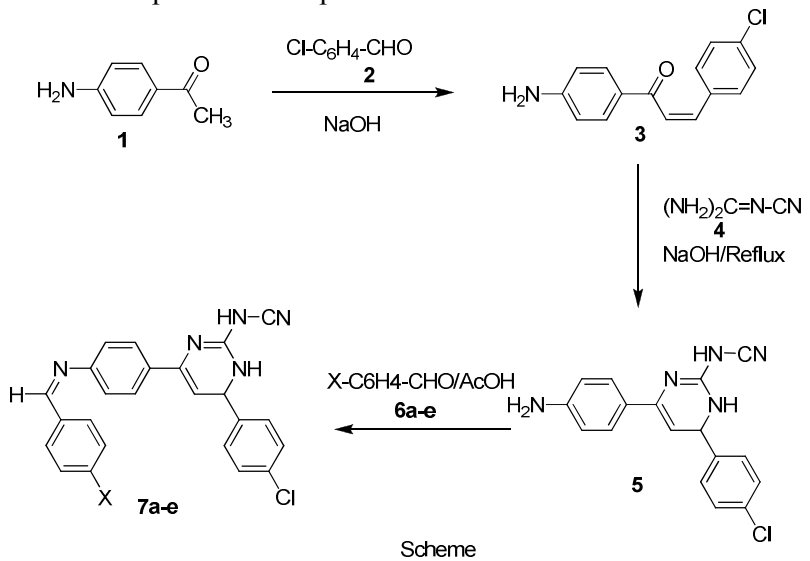
& weak), 5.18 (d, 1H, C_4-H of Pyrimidine), 5.33 (d, 1H, C_5-H of Pyrimidine), 7.00, 7.02, 7.18, 7.21, 7.32, 7.35, 7.44, 7.46, 7.78, 7.75, 7.81, 7.84 (12Ar-CH), 8.39 (s, 1H, CH=N); ^{13}C-NMR ($CDCl_3$,δ), 54.37 (C_4 of Pyrimidine), 99.42 (C_5 of Pyrimidine), 133.00, 133.37 (C-Cl), 129.64, 136.59, 141.06, 151.86 (5-Aromatic quaternary carbons) 119.75, 120.98, 126.09, 127.53, 128.19, 128.52, 129.64, 133.62, 130.40, 133.62, 136.59, 136.97 (12Ar-CH), 159.56 (CH=N).

N-(6-(4-chlorophenyl)-4-(4-(3-nitrobenzylideneamino)phenyl)-1,6-dihydropyrimidin-2-yl)cyanamide (7e):

FT-IR (KBr, cm^{-1}): 3348.29, 3224.05 (NH), 3039.76 (Ar-CH), 2900.44 (Aliphatic-CH), 2175.62(CN), 1622.38 (C=N), 1090.50 (Ar-Cl), ^{1}H-NMR ($CDCl_3$, δ): ^{1}H-NMR ($CDCl_3$, δ): 4.7, 4.77 (s,2H, NH, broad & weak), 5.00-5.01 (d, 1H, C_4-H of Pyrimidine), 5.29-5.30 (d, 1H, C_5-H of Pyrimidine), 7.16, 7.18, 7.23, 7.24, 7.32, 7.36, 7.43, 7.44, 7.47, 7.48, 7.53, 7.55 (12Ar-CH), 8.39 (s, 1H, CH=N); ^{13}C-NMR ($CDCl_3$,δ), 55.43 (C_4 of Pyrimidine), 97.67 (C_5 of Pyrimidine), 133.81 (C-Cl), 128.53, 129.18, 134.34, 140.70, 151.14 (5-Aromatic quaternary carbons), 115.11, 122.46, 122.38, 126.22, 126.37, 128.31, 130.09, 130.51, 131.14, 133.18, 134.34, 134.53 (12Ar-CH), 159.74 (CH=N).

RESULTS AND DISCUSSION

Present work begins with 4-NH_2-Acetophenone (**1**) which react with 4-Cl-Benzaldehyde aldehyde (**2**) produced corresponding chalcone (**3**). This chalcone further react with 2-cyanoguanidine (**4**) afforded Cyanopyrimidine derivative (**5**). Final products (**7a-e**) were obtained by reaction between **5** and various substituted benzaldehydes (**6a-e**) in the presence of catalytic amount of AcOH. Here in, Aldol condensation reaction was utilized to obtain the chalcone, Michael type addition reaction was performed to get pyrimidine and finally Schiff base reaction was used to produce final products.

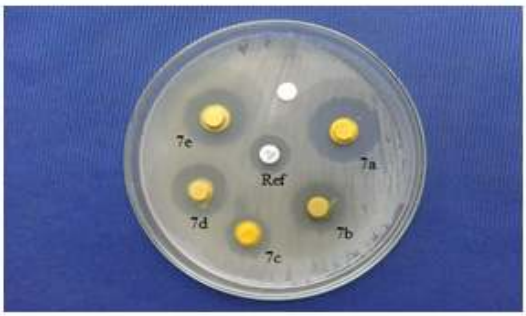


Scheme

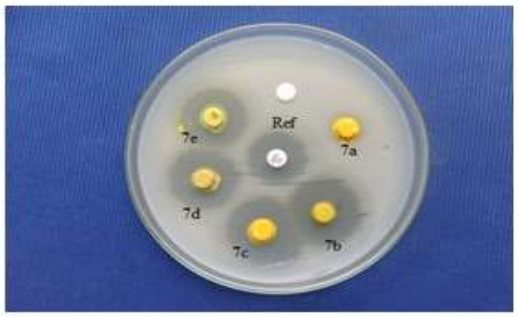
Table-1: Physical data of Pyrimidine incorporated Schiff bases **7a-e**

Comp.code	X	Yield (%)	Mp (°C)	Color	Rf value (Hex:EA, 2:1)
7a	*P*-OCH_3	65	144	Yellow	0.62
7b	*P*-CH_3	72	120	Yellow	0.60
7c	*P*-$N(Me)_2$	85	154	Orange	0.67
7d	*P*-Cl	80	160	Pale yellow	0.62
7e	*p*-NO_2	82	166	Brown	0.55

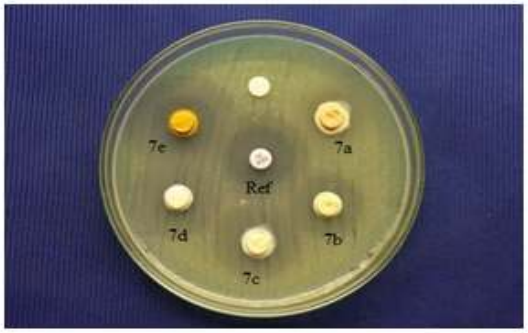
Figure-1: Anti microbial activities images of Schiff bases **7a-e**:



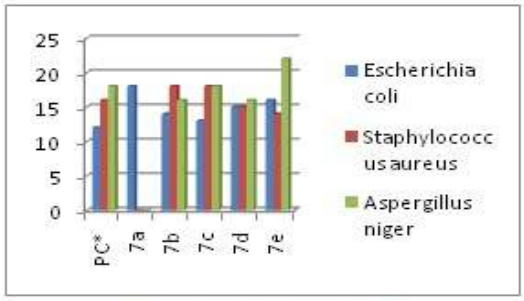
Escherchia coli



Pseud Aeruginosa



Aspergillus niger



Correlation chart

Table-2: Antimicrobial activity data of Schiff bases **7a-e**:

Sample	Zone of Inhibition (mm in diameter, 20 µg/disc)		
	Escherichia coli	*Pseudomonas aeruginosa*	*Aspergillus niger*
PC*	12	18	8
7a	18	-	8
7b	14	18	8
7c	13	18	8
7d	15	16	11
7e	16	15	-

The physical data such as, melting point, Color, Rf value (Table-1) and spectral data such as, FT-IR, ^{1}H-NMR and ^{13}C-NMR were well supported the formation of the desired products by producing characteristic signals. Antimicrobial activities of compounds **7a-e** were examined by using disc diffusion method. The compound **7a** showed maximum inhibition zone against *Escherchia coli* and compound **7c** showed minimum inhibition zone. The compounds **7a, 7b, 7c, 7d** showed very good activity against *Pseudomonas aeruginosa* except **7a**. The moderate to poor activity observed for all the tested compounds against *Aspergillus niger* (Table-2).

CONCLUSION

I have reported synthesis of some novel 4,6-aryl substituted 3,4-dihydropyrimidin-2(1*H*)-ylidene)cyanamide derivatives in a simple manner with very good yield. All the synthesized compounds were characterized by using analytical and spectral data and are aligned with

observed values. The very good antibacterial activity was observed against selective bacterial strains and moderate to poor activity was observed against fungal strains.

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