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Research Article

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Utility of Michael type addition on the synthesis of pyrimidines and antibacterial studies of 4,6-diaryl-3,4-dihydropyrimidin-2(1*H*)-ylidene) cyanamides

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ABSTRACT

Synthesis, characterization and antibacterial studies of newer 4,6-diaryl-3,4-dihydropyrimidin-2(1H)-ylidene) cyanamide derivatives are reported. The structures of all the synthesized compounds were elucidated by the value of spectral data; introduced against selective microorganism using disc diffusion method displayed comparatively good proposition.

Keywords: Cyanoquanidine, pyrimidine, bromocetophenone, chalcone and antibacterial activity.

INTRODUCTION

Heterocyclic compounds are abundant in nature. They exhibit significant role in life hence their structural subunits exist in natural products such as vitamins, amino acids, alkaloids and etc. In particular, pyrimidines are important nitrogen containing heterocycles where two nitrogen atoms occupy 1st and 3rdposition of the six-member ring. The pyrimidine exhibited extensive chemical and pharmacological properties [1-5]; furthermore these derivatives, especially with hydroxyl group at any position on the ring shows a unique consigns in medicinal chemistry [6, 7]. The extensive activities like anti-HIV [8], anti-tubercular [9], anti-tumor [10], anti-neoplastic [11], anti-inflammatory [12], diuretic [13], anti-malarial [14] and cardiovascular [15] of pyrimidine derivatives, promote to synthesize them with the active points against the parasites.

EXPERIMENTAL SECTION

General:
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 (400 MHz) instrument in $CDCl_3$ solutions using tetramethylsilane as an internal standard. *J* Values are given in Hz. Mass spectra were obtained at the Indian Institute of Chemical technology, Hyderabad, India. All the basic chemicals were purchased from Merck (India), *s.d* fine chemicals (India).

General procedure to synthesis substituted chalcones (3a-h):
A mixture of 0.01mol of *p*-bromoacetophenone**1**,0.01mol of aryl aldehyde **2a-h** and an aqueous solution of 40%

NaOH (5 mL) was stirred in ethanol (40 mL) for 2-3 hr continuously at room temperature. After completion of the reaction-monitored by TLC;the mixture was poured in to crushed ice and acidified with dilute hydrochloric acid. The solid was filtered, dried and recrystalyzed from ethanol. The spectral details coincide with the earlier literature values.

General procedure to synthesis substituted pyrimidines (5a-h)

A mixture of substituted chalcone **3a-h**(0.01mol) and 2-cynoquanidine **4**(0.01mol) 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 was filtered, washed repeatedly with water, dried and recrystalyzed from ethanol.The physical parameters are as shown in **Table 1**.

***N*-(6-(4-bromophenyl)-4-phenyl-1,4-dihydropyrimidin-2-yl)cyanamide (5a):**

IR(KBr, cm^{-1}): 3227.17, (N-H), 2174.03(C≡N), 1626.67 (C=N) and 708.43 (C-Br);^{1}H-NMR ($CDCl_3$, δ): 5.22-5.23 (d, 1H, *J* = 3.0Hz, C_4-H of pyrim), 5.41-5.43(d, 1H, *J* =3.0Hz, C_5-H of pyrim), 6.07 (N-H, 2H), 7.21-7.98 (m, 8H, Ar-H);^{13}C-NMR ($CDCl_3$,δ), 55.00, 99.65, 117, 124.91, 127.69, 127.97, 128.52, 129.06, 129.32, 129.84, 131.99, 132.35, 133.27,134.05,134.52, 140.29, 144.02, 155.79.

2. *N*-(6-(4-bromophenyl)-4-(4-chlorophenyl)-1,4-dihydropyrimidin-2-yl)cyanamide (5b):

IR (KBr, cm^{-1}): 3206.15, (N-H), 2172.65 (C≡N), 1627.35 (C=N), 699.74 (C-Br); ^{1}H-NMR ($CDCl_3$-d_6,δ): 5.16-5.17 (d, 1H, *J* = 3.0Hz, C_4-H of pyrim), 5.33-5.34(d, 1H, *J* =3.0Hz, C_5-H of pyrim), 6.72 (1NH), 7.21-7.98 (8Ar-H+1NH).^{13}C-NMR ($CDCl_3$,δ): 55.30, 100.23 116.93, 125.23, 128.07, 128.28, 128.61, 128.87, 129.14, 129.35, 129.83, 132.79, 133.20, 134.59, 140.39 155.94.

3. *N*-(6-(4-bromophenyl)-4-(3-nitrophenyl)-1,4-dihydropyrimidin-2-yl)cyanamide (5c):

IR (KBr, cm^{-1}): 3207.66, (NH), 2175.49 (C≡N), 1628.98 (C=N), 694.87 (C-Br); ^{1}H-NMR ($CDCl_3$,δ): 5.22-5.23(d, 1H, *J* = 3.0Hz, C_4-H of pyrim), 5.41-5.42(d, 1H, *J* =3.0Hz, C_5-H of pyrim), 6.11 (1NH), 7.21-8.00 (8Ar-H+1NH).^{13}C-NMR ($CDCl_3$,δ): 55.30, 100.21, 116.87, 125.23, 128.07, 128.28, 128.61, 128.85, 129.14, 129.35, 129.80, 132.79, 133.20, 134.05, 134.59, 140.35, 155.92.

4. *N*-(6-(4-bromophenyl)-4-(4-nitrophenyl)-1,4-dihydropyrimidin-2-yl)cyanamide (5d):

IR (KBr, cm^{-1}): 3203.23, (NH), 2174.87 (C≡N), 1627.27 (C=N), 697.20(C-Br); ^{1}H-NMR ($CDCl_3$,δ): 5.28-5.29(d, 1H, *J* = 3.0Hz, C_4-H of pyrim), 5.63-5.64(d, 1H, *J* =3.0Hz, C_5-H of pyrim), 6.77 (1NH), 9.93-7.99 (8Ar-H+1NH).^{13}C-NMR ($CDCl_3$,δ): 55.82, 100.99, 117.05, 125.27, 126.87, 128.61, 129.13, 129.21, 129.49, 129.68, 129.87, 133.06, 133.67, 138.67, 139.01 156.00.

5. *N*-(6-(4-bromophenyl)-4-(4-bromophenyl)-1,4-dihydropyrimidin-2-yl)cyanamide(5e):

IR (KBr, cm^{-1}): 3334.51, (NH), 2192-29 (C≡N), 1652-25 (C=N), 742.41(C-Br); ^{1}H-NMR ($CDCl_3$,δ): 5.16-5.17 (d, 1H, *J* = 3.0Hz, C_4-H of pyrim), 5.33-5.34(d, 1H, *J* =3.0Hz, C_5-H of pyrim), 6.20 (1NH), 6.68-7.92(8Ar-H+1NH).^{13}C-NMR ($CDCl_3$,δ): 55.00, 99.62, 117.20, 124.90, 127.23,128.19, 128.70, 129.22, 129.83, 131.95, 132.35, 133.78, 134.05, 135.54140.27, 143.31 152.79.

6. *N*-(6-(4-bromophenyl)-4-p-tolyl-1,4-dihydropyrimidin-2-yl)cyanamide (5f):

IR (KBr, cm^{-1}): 3213. 83, (NH), 2193.95 (C≡N), 1628.43 (C=N), 742.41 (C-Br); ^{1}H-NMR ($CDCl_3$,δ): 2.31 (s,3H), 5.17-5.19(d, 1H, *J* = 6Hz, C_4-H of pyrim), 5.30-5.32(d, 1H, *J* =6Hz, C_5-H of pyrim), 6.50 (1NH), 7.05-7.96(8Ar-H+1NH).^{13}C-NMR ($CDCl_3$,δ): 22.15 (-CH_3), 55.31, 100.20, 116.91, 125.20, 128.07, 128.28, 128.60, 128.85, 129.14, 129.36, 129.83, 132.74, 133.20, 134.04, 134.59, 140.37, 155.80.

7. *N*-(6-(4-bromophenyl)-4-(4-methoxyphenyl)-1,4-dihydropyrimidin-2-yl)cyanamide (5g):

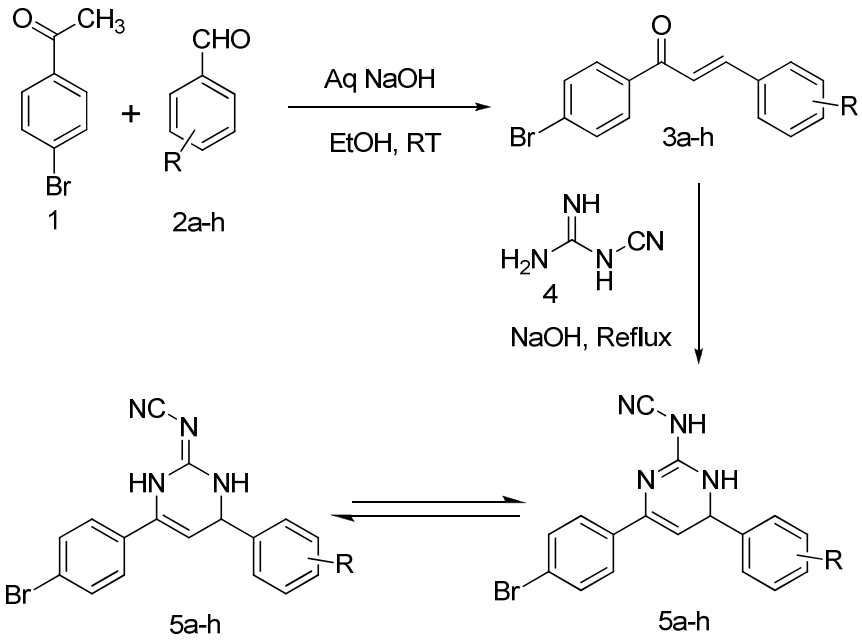
^{1}H-NMR ($CDCl_3$,δ): 3.81, 5.16-5.17 (d, 1H, *J* = 3.0Hz, C_4-H of pyrim), 5.29-5.30 (d, 1H, *J* =3.0Hz, C_5-H of pyrim), 6.10 (1NH), 6.67-7.95 (8Ar-H+1NH).^{13}C-NMR ($CDCl_3$,δ): 55.24, 100.98, 117.17, 125.19, 126.11, 127.28, 127.93, 128.04, 128.18, 128.30, 128.48, 128.95, 129.23, 132.94, 135.67, 136.78, 158.07.

8.*N*-(6-(4-bromophenyl)-4-(4-(dimethylamino)phenyl)-1,4-dihydropyrimidin-2yl)cyanamide (5h):^{1}H-NMR ($CDCl_3$,δ): 3.29-3.35 (2s, $N(CH3)_2$), 4.10-4.41 (d, 1H, *J* = 3.0Hz, C_4-H of pyrim), 5.36-5.37(d, 1H, *J* =3.0Hz, C_5-H of pyrim), 6.50 (1NH), 6.95-8.08 (8Ar-H+1NH).^{13}C-NMR ($CDCl_3$,δ): 45.00, 55.00, 99.69, 117.27,

124.91, 126.25, 127.83, 127.97, 128.27, 128.90, 129.14, 129.06, 131.99, 133.27, 134.05, 135.19, 140.29, 155.70.

RESULTS AND DISCUSSION

This present work begins with the reaction of 4-bromo-acetophenone (**1**) with various substituted aromatic aldehydes (**2a-h**) to produce their corresponding chalcones (**3a-h**). The further introduction of chalcones (**3a-h)** with 2-cyanoguanidine (**4**) yields pyrimidine derivatives (**5a-h**).Claisen-Schmidt condensation reaction procedures are utilized to obtain the chalcones (**3a-h**) and their spectral data are resembled with the reported values.[Ref] 1,4-Michael type addition [Ref] of 2-cyanoguanidine (**5a-h**) with chalcones(**3a-h)** and the successive cyclisation gave the pyrimidines (**5a-h**).



SCHEME-1

Table-1: Physical data of 3,4-dihydropyrimidine-2(1*H*)ylidene)cyanamidederivatives (5a-h)

Comp	R	Yield (%)	mp (°C)	R_f value
5a	H	75	110-112	0.56
5b	4-Cl	90	104-106	0.60
5c	3-NO_2	82	118-120	0.50
5d	4-NO_2	75	124-126	0.54
5e	4-Br	85	120-122	0.56
5f	4-CH_3	80	174-176	0.52
5g	4-OCH_3	78	178-180	0.55
5h	4-N$(Me)_2$	70	120-124	0.54

The mixture of **3a** with cyanoguanidine **4** and sodium hydroxide in ethanol refluxed for 2 hours; thin layer chromatography analysis showed a procession in the reaction. After completion the reaction mixture was poured in to the ice-cold water, filtered, washed, dried and recrystallised from ehanol. Pyrimidine derivative **5a** showed strong bands around 2174.03 cm^{-1}in IR spectrum indicates that presence of C≡N; N-H stretching adsorption are recorded around 3227.17cm^{-1}; the characteristic C=N and C-Br stretching are sticking around 1626.67$cm^{-1}$and 708.43 cm^{-1}respectively. The ^{1}H-NMR and ^{13}C-NMR spectra of all the pyrimidine derivatives shows some characteristic signals and these are well supported for our proposed structure. The compound 5a shows two doublets at 5.20-5.21 and 5.27-5.28 are corresponding to protons attached with C-4 and C-5 of pyrimidine ring respectively. The two NH protons are not clearly observed in all the compounds but in 5a which observed at 6.09ppm as broad signal. In the ^{13}C-NMR spectra of **5a**, C-4 and C-5 carbons appeared 55.00 and 99.65ppm respectively. The -CN carbon signal

appeared at 117.27ppm and C-Br carbon appeared at 124.91ppm. These characteristic signals are also observed in remaining prrimidines derivatives 5b-h around their respective regions.

The antibacterial activity of some compounds tested against selective pathogens and all the derivatives **5a-e** shows very good activity. The detailed physical and antibacterial activity data are given in Table-1 and 2 respectively.

Table-2: Antimicrobial activity data 3,4-dihydropyrimidine-2(1*H*)ylidene)cyanamide(5a-e)

S. No.	Sample	Zone of Inhibition (mm in diameter)			
		Bacillus subtilis	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*
1	**PC***	19	15	17	18
2	**C**	-	-	-	-
3	**5a**	15	14	16	19
4	**5b**	12	13	15	22
5	**5c**	17	18	20	23
6	**5d**	17	19	16	22
7	**5e**	15	18	13	14

** Gentamicin (10 µg) for Bacteria*

CONCLUSION

We have synthesized a series of 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 such as Mp, Rf value, FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. All the compounds have been well supported our proposed structure and very good antibacterial activities were observed for tested pyrimidine derivatives against selective pathogens.

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