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Synthesis and in vitro Antibacterial Activity of Some Novel 2-Amino-4, 6-D Derivatives

S.A. Rahaman,[1,*] Y. Rajendra Prasad,[2] K. Phani Kumar,[1]
D. Hareesh,[2] and A. Prameela Rani[3]

[1]*Department of Pharmaceutical Chemistry, Nirmala College of Pharmacy, Mangalagiri-522503, India*
[2]*University College of Pharmaceutical Sciences, Andhra University, Visakhapatnam,India*
[3]*University College of Pharmaceutical Sciences, Acharya Nagarjuna University, Nagarjuna Nagar, Guntur (dt), Andhra Pradesh,India*

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Abstract

Heterocyclic systems are one of the most important classes of organic compounds present in nature or synthesized in laboratory. These compounds posses an array of biological activities and are employed in the treatment of commonly occurring diseases. Keeping this in view, some new 2-amino-4,6-diarylpyrimidine from chalcones were synthesized. Eight novel 2-amino-4,6-diarylpyrimidine derivatives have been prepared by condensation of chalcone derivatives with guanidine hydrochloride. The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR spectra, ^{1}H NMR and Mass spectral data. These compounds were screened for their antibacterial activity. The recorded zone of inhibition showed significant antibacterial activity when compared with reference standard Sparfloxacin.

Keywords: Pyrimidines; 4[1]-Piperazine acetophenone; Guanidine and Sparfloxacin

Introduction

Pyrimidines are an important group of heterocyclic compounds and some of them posess wide range of biological activities such as an antibacterial (1, 2), antiproliferative (3), anticancer (4,5), antifungal (6), antiviral (7), anti-inflammatory (8,9), etc. The presence of pyrimidine heterocyclic nucleus functional group in pyrimidine derivatives is found to be responsible for their antimicrobial activity, which may be altered depending on type and position of substituents attached. Pyrimidine derivatives were prepared by condensation of chalcone derivatives with guanidine hydrochloride. The structures of various synthesized pyrimidine compounds (Fig. 1) were assigned on the basis of elemental analysis (Table 2), IR and ^{1}HNMR (Table 3) spectral data. These compounds were also screened for their antimicrobial activity.

Materials and Methods

Experimental

All melting points were determined by digital melting point apparatus. The IR spectra (10) were recorded on perkin-Elmer 377 spectrophotometer and

* Corresponding author, Tel.: +9849702527, Fax: +8645236722, E-mail: rahaman_pharma@rediff.com

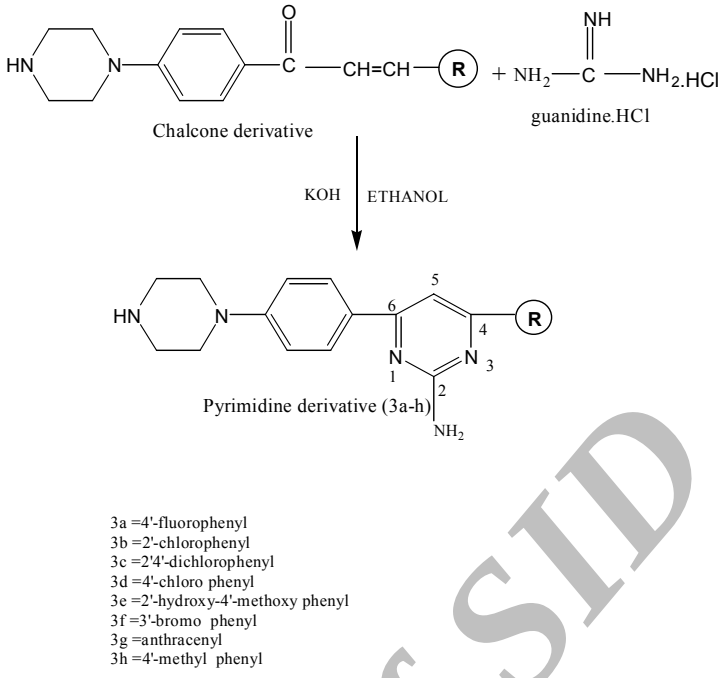

Figure 1. Scheme of the synthesis of novel pyrimidin derivative.

Table 1. Characterization Data of Pyrimidine Derivatives 3(a-h)

Compound	Molecular Formula	Molecular Weight	Melting Point(°C)	Yield (%)
3_a	$C_{20}H_{20}N_5F$	348	110-112	72
3_b	$C_{20}H_{20}N_5Cl$	365.5	117-118	78
3_c	$C_{20}H_{19}N_5C_{l2}$	400	128-130	80.12
3_d	$C_{20}H_{20}N_5Cl$	365.5	124-126	84.5
3_e	$C_{21}H_{23}N_5O_2$	377	155-156	69
3_f	$C_{20}H_{20}N_5Br$	407	107-108	64.5
3_g	$C_{20}H_{25}N_5$	431	145-148	82
3_h	$C_{21}H_{23}N_5$	345	95-97	77.4

Table 2. Elemental analysis 3(a-h)

Compound		C	H	N	O	F	Cl	Br
3_a	Required	68.9	5.74	20.11	--	5.17	--	--
	found	69.12	5.8	20.34	--	5.40	--	--
3_b	Required	65.66	5.47	19.15	--	--	9.71	--
	found	65.9	5.8	19.32	--	--	9.85	--
3_c	Required	60.0	4.75	17.5	--	--	17.75	--
	found	60.24	4.91	17.34	--	--	17.65	--
3_d	Required	65.66	5.47	19.15	--	--	9.71	--
	found	65.9	5.82	19.17	--	--	10.04	--
3_e	Required	66.84	6.1	18.56	8.48	--	--	--
	found	67.23	6.14	18.4	8.65	--	--	--
3_f	Required	58.96	4.91	17.19	--	--	--	18.91
	found	59.16	4.78	17.50	--	--	--	18.72
3_g	Required	77.96	5.8	16.24	--	--	--	--
	found	78.12	5.85	16.34	--	--	--	--
3_h	Required	73.04	6.6	20.29	--	--	--	--
	found	73.24	6.54	20.45	--	--	--	--

Table 3. IR and ^{1}HNMR Spectral Data of Pyrimidine Derivatives 3(a-h)

Compound	IR (Cm^{-1}) (KBr)	H'NMR ($CDCl_3$) (δ PPM)
3_a	N-H -- 3356 C=N -- 1570.89 C=C -- 1601.89 C-F -- 1229.48	1.86(1H,s,aliphatic N-H) 2.5(4H,m,piperazinyl protons) 2.9(4H,m,piperazinyl protons) 4.19(2H,bs,1° NH_2) 7.6(1H,s,C-5H) 6.5-8.2(8H,m,aromatic protons)
3_b	N-H -- 3370.08 C=C --1683.49 C=N --1567.93 C-Cl -- 651.48	1.66(1H,s,aliphatic N-H) 2.5&2.8(8H,m,piperazinyl protons) 3.71(2H,1° NH_2) 7.63(1H,s,C-5H) 6.85-7.52(8H,m,aromatic protons)
3_c	N-H -- 3365.3 C=C -- 1594.2 C=N -- 1527.9 C-Cl -- 669.5	1.84(1H,s,aliphatic N-H) 2.50&2.9(8H,m,piperazinyl protons) 3.97(2H,1° NH_2) 7.22(1H,s,C-5H) 6.7-8.0(7H,m,aromatic protons)
3_d	N-H -- 3400.6 C=N -- 1574 C-Cl -- 653.8	1.74(1H,s,aliphatic N-H) 2.5&2.85(8H,m,piperazinyl protons) 3.61(2H,1° NH_2) 8.45(1H,s,C-5H) 6.9-8.2(8H,m,aromatic protons)
3_e	N-H -- 3407.1 C=C -- 1604.3 C=N --1572.5 C-O -- 1248.4	1.896(1H,s,aliphatic N-H) 2.5&2.93(8H,m,piperazinyl protons) 3.88(3H,s,-OCH_3) 4.1(2H,s,NH_2) 7.51(1H,s,C-5H) 6.88-8.11(8H,m,aromatic protons)
3_f	N-H -- 3341.4 C=C -- 1598.6 C=N -- 1564.8 C-Br -- 536.6	1.86(1H,s,aliphatic N-H) 2.5&2.8(8H,m,piperazinyl protons) 4.26(2H,1° NH_2) 8.42(1H,s,C-5H) 6.6(1H,s,C-2'H_2) 6.9-8.2(7H,m,aromatic protons)
3_g	N-H -- 3392.6 C=C -- 1602.1 C=N -- 1567.9	1.87(1H,s,aliphatic N-H) 2.5&2.8(8H,m,piperazinyl protons) 4.14(2H,1° NH_2) 7.20(1H,s,C-5H) 6.75-8.69(13H,m,aromatic protons)
3_h	N-H -- 3398.4 C=C -- 1603.1 C=N -- 1575.1	1.87(1H,s,aliphatic N-H) 2.5&2.87(8H,m, piperazinyl protons) 2.37(3H,s,benzylic protons) 3.74(2H,1°NH_2)

the ^{1}HNMR (11, 12,13) spectra on Bruker AV 300 MHZ in DMSO using TMS as an internal standard.

General Procedure for the Preparation of Pyrimidines Derivatives 3(a-h)

A mixture of chalcone derivative (0.01ml) and guanidine hydrochloride (0.01ml) is stirred in methanol (30 ml) (14, 15). The mixture is kept overnight at room temperature and it is poured into crushed ice and then acidified with HCl. The solid separated is filtered and crystallized from ethyl acetate and methanol. The characterization data of these compounds are given in Tables 1-3.

Table 4. Zone of inhibition (mm) of synthesized Pyrimidine derivatives 3(a-h)

Compound code	Zone of inhibition (mm)							
	B. subtilis		*B. pumilis*		*E. coli*		*P. vulgaris*	
	50µg/ml	100µg/ml	50µg/ml	100µg/ml	50µg/ml	100µg/ml	50µg/ml	100µg/ml
3a	14	18	11	20	12	16	12	20
3b	17	20	12	20	13	15	12	24
3c	18	19	19	25	18	24	14	23
3d	12	18	12	20	12	16	12	20
3e	16	18	12	14	16	20	10	12
3f	16	18	18	25	12	18	15	23
3g	14	17	13	15	13	16	13	23
3h	12	15	12	16	11	15	12	18
Sparfloxacin	22	25	26	28	19	24	24	26
Control (DMF)	-	-	-	-	-	-	-	-

Antimicrobial Activity

The microbial assay medium was inoculated at 1% level with 18hrs old cultures of *Bacillus subtilis, Bacillus pumilis, Proteus vulgaris* and *E.coli* were transferred into sterile Petri dishes. The medium in the plates was allowed to stand at room temperature for 10 minutes and were set to solidify in a refrigerator for 30 minutes. Test solutions and standard solutions of Sparfloxacin at a concentration of 0.05% w/v and 0.1%w/v were prepared in DMF solvent. Then three discs were soaked in the above test and standard solutions .The discs so prepared were dried and placed in Petri plate with a sterile forceps. The plates thus prepared were left to stand in a refrigerator for about 1hr to allow the test solution for diffusion. After incubation for 24 hrs at 37°C, the plates were examined for their zone of inhibitions.

Results and Discussion

On comparing with the standard drug Sparfloxacin, the synthesized pyrimidine derivatives (3a-3h) showed a significant broad spectrum antibacterial activity at concentration levels 0.05% (50µg/ml) and 0.1 %(100µg/ml) respectively (Table 4). When an increase in concentration of all the synthesized pyrimidine derivatives (3a-3h) showed an increase in zone of inhibition.These measured zone of inhibitions suggested that the synthesized compounds exhibited a significant antibacterial activity. Among all the Pyrimidine derivatives particularly halogen substituted derivatives showed more activity than others.

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