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Synthesis and antimicrobial screening of some new pyrimido[1,2-a]benzimidazole derivatives

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ABSTRACT

Some new pyrimido[1,2-a]benzimidazole derivatives were synthesized by reacting 2-amino benzimidazole and chalcones in n-butanol at reflux temperature. In our present study we have used various heterocyclic chalcones derived from furfural and substituted acetophenones. All synthesized compounds were characterized by IR, ^{1}H NMR and Mass spectroscopy. All synthesized compounds were screened for their antimicrobial activity against gram positive and gram negative bacteria which showed moderate to good activity.

***Keywords*:** 2-amino benzimidazole; pyrimido[1,2-a]benzimidazole; chalcone; antimicrobial activity azoloazine

1. INTRODUCTION

In recent years, organic research for synthesis of novel nitrogen containing heterocyclic ring system is emerging. Over the years of active research, benzimidazole pharmacophore in many major drugs like albendazole, mebendazole, thiabendazole as antihelmintics; omeprazole, lansoprazole, pantoprazole as proton pump inhibitors; astemizole as antihistaminic; enviradine as antiviral; candesarten cilexitil and telmisartan as antihypertensives and many lead compounds in a wide range of other therapeutic areas[1-7].

Pyrimidine ring and its derivatives have been studied for therir chemical and biological singnificance from several decades. Pyrimidine derivatives have been reported as antibacterial, antiviral, and antitumor agents[8].Various fused heterocyclic ring system with pyrimidine nucleus are known for their significant biological activities[9].

Binucleophiles of aminoazole type are quite important reagents in modern heterocyclic chemistry, and their reactions with electrophiles are the most widespread and facile synthetic approach for obtaining diverse heterocyclic systems containing azole moiety. The most investigated area of aminoazole chemistry is their two-component reactions with ketoesters, β-dicarbonyls or α,β-unsaturated aldehydes and ketones yielding fused azoloazines[10-11].

Our research group is associated with synthesis and evaluation of biological activities of pyrimidine, pyridine and related nitrogen containing heterocyclic ring system from last decade[12-16]. As from the above facts of medicinal importance of benzimidazole and pyrimidine ring system, we have planned to synthesized some new derivatives of pyrimido[1,2-a]benzimidazole and evaluate its antimicrobial activities as compare to standard drugs.

In present research work, we submitted simple, rapid and catalyst free synthesis of some new derivatives of 1,4-dihydro pyrimido[1,2-a]benzimidazole by reacting 2-amino benzimidazole and various α,β-unsaturated ketone (chalcone) in n-butanol solvent at reflux temperature[17-21].

2. EXPERIMENTAL

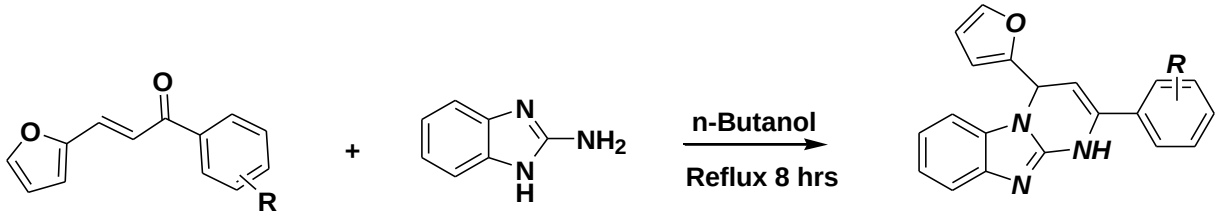
All chemicals and solvents were purchased from Spectrochem Pvt Ltd., Mumbai of AR grade and were used without further purification. Melting points were taken in open capillary method and are uncorrected. IR spectra were recorded on FTIR-8400 spectrophotometer (Shimadzu, Kyoto, Japan), using DRS prob KBr pallet. ^{1}H-NMR spectra of the synthesized compounds were recorded on a Bruker-Avance-II (400MHz) $DMSO_6$ solvent. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu, Kyoto, Japan).

2. 1. General procedure for synthesis of (2E)-1-(furan-2-yl)-3-substituted phenyl prop-2-en-1-one (1a-i)

A solution of substituted acetophenones (0.01 mol) in ethanol (10 ml) was added to a solution of furfural (0.01 mol) in ethanol (10 ml). To this mixture 40 % NaOH solution was added drop wise as to make it just alkaline (pH 10 ~ 11). The reaction mass was stirred for 18 hrs at room temperature. The product was isolated by filtration and crystallized using appropriate solvent.

2. 2. General procedure for the synthesis of 4-(furan-2-yl)-2-substituted phenyl-1,4-dihydro pyrimido[1,2-a]benzimidazole (3a-i)

To a solution of chalcone **(1a-i)** in n-butanol, 2-amino benzimidazole **(2)** was added and reflux the reaction mixture at reflux temperature for 8-10 hrs. After cool down the reaction mixture at room temperature, filtered the solid crude product. Wash the crude product with diethyl ether and dried in vacuo to obtained analytical pure grade compounds 3a-i. Physical Constants newly synthesized of pyrimidine derivatives 3a-3i are recorded in Table 1.



1a-i **2** **3a-i**

2. 3. Spectral characterization

4-(furan-2-yl)-2-(4-chlorophenyl)-1,4-dihydro pyrimido[1,2-a]benzimidazole (3b) IR (KBr) ν(cm^{-1}): 3047, 2945, 2874, 2818, 1620, 1560, 1508, 1460, 1276, 1172, 1008, 910, 796, 742, 662, 601, 501 cm^{-1}, ^1H NMR (DMSO-D_6) δ 9.76 (s, 1H), 7.73 (dd, 1H), 7.58 (dd, 1H), 7.50 – 7.39 (m, 5H), 7.24 (td, 1H), 7.15 (td, 1H), 6.38 (t, 1H), 6.37 – 6.29 (m, 2H), 5.20 (d, 1H); $M^+ = 348$.

Table 1. Physical Constant table of pyrimido[1,2-a]benzimidazole derivatives (3a-3i).

No	Comp.	R	Molecular Formula	Molecular Weight	Yield (%)	M.P. (^{0}C)
1	3a	H	$C_{20}H_{15}N_3O$	313	60	192
2	3b	4-Cl	$C_{20}H_{14}ClN_3O$	348	75	213
3	3c	4-Br	$C_{20}H_{14}BrN_3O$	392	70	225
4	3d	4-OCH_3	$C_{21}H_{17}N_3O_2$	343	78	185
5	3e	4-CH_3	$C_{21}H_{17}N_3O$	327	82	178
6	3f	4-NO_2	$C_{20}H_{14}N_4O_3$	358	55	230
7	3g	2-Cl	$C_{20}H_{14}ClN_3O$	348	70	240
8	3h	3-Br	$C_{20}H_{14}BrN_3O$	392	77	198
9	3i	3,4-$(OCH_3)_2$	$C_{22}H_{19}N_3O_3$	373	60	227

4. ANTI MICROBIAL ACTIVITY

The antimicrobial activity was assay by using the disc diffusion method. Newly synthesized compounds were screened *in vitro* for their antimicrobial activity against four bacterial strains, i.e. two gram +ve baceteria *Staphylococcus aureus and Staphylococcus epidermidis* and two gram –ve bacteria *Escherichia coli and Pseudomonas aeruginosa* and fungi strain *Aspergillus niger*. Standard drug Cephalexin and Greseofulvin were used for the comparison purpose. The obtained results for compounds 3a-3i are recorded Table 2.

Table 2. Antimicrobial activity of pyrimido[1,2-a]benzimidazole derivatives (3a-3i).

Compound No. (substitution)	Antibacterial activity (%)				Antifungal activity (%)
	S. aureus	*S. epidermidis*	*E. coli*	*P. aeruginosa*	*A. niger*
3a (H)	80	33	50	67	50
3b (4-Cl)	70	71	55	67	63

3c (4-Br)	60	54	86	48	67
3d (4-OCH_3)	68	69	68	81	83
3e (4-CH_3)	85	83	45	89	46
3f (4-$NO_{2)}$	75	54	85	86	38
3g (2-Cl)	90	38	77	80	54
3h (3-Br)	50	79	55	52	75
3i (3,4-$(OCH_3)_2$	45	42	64	67	71
Amoxicillin	100	100	100	100	-
Greseofulvin	-	-	-	-	100

5. CONCLUSION

In present report, we submitted very efficient method for the synthesis of some new pyrimido[1,2-a]benzimidazole derivatives without use of any catalyst. All synthesized compounds were obtained in good to moderate yield. The synthesized compounds were characterized by ^{1}H NMR, Mass and IR spectroscopy and the obtained results are showing good agreement with the synthesized structures.

From the results of antimicrobial data, compounds 3e and 3g were shown good activity against bacterial pathogens while compounds 3d, 3h and 3i were found good active against fungi pathogens as compare to the standard drugs.

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