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SYNTHESIS OF 2-AMINOPYRIMIDINE DERIVATIVES AS ANTIMICROBIAL AGENTS

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ABSTRACT

Synthesis of some 2-aminopyrimidine **[1a-g]** have been synthesized by the condensation of chalcone with guanidine hydrochloride in ethanol, 2-aminopyrimidins were treated with acetic anhydride to gives 2-acetamidopyrimidine **[2a-g]**. The structural assignment of the compounds was based on elements analysis and IR, ^{1}H NMR data. All the synthesized compounds have been screened for their antibacterial activity and antifungal activity.

Key words: 2-aminopyrimidine, Antimicrobial agent.

INTRODUCTION

A large number of heterocycles compounds derived from chalcone group have been reported as active biological entities, where 2-aminopyrimidine play a vital role owing to their wide range of therapeutic activities. Thus significant biological properties associated with pyrimidine derivatives have aroused considerable interest to design the compound with better drug potential and to study their pharmacological profile.

Generally pyrimidine derivatives such as 2-hydroxy pyrimidine, 2-mercapto pyrimidine and 2-aminopyrimidine are studied. Pyrimidines have been isolated from the nucleic acid hydrolysates. The first primary synthesis from aliphatic fragments was carried out by Frankland and co-workers in 1848, since then a many distinct primary synthetic method have been devised[1-2]. It is also possible to prepare pyrimidines from other heterocyclic compounds such as pyrole[3], imidazole[4], isoxazoles and oxazoles[5-6], pyridines[7], pyrazines[8], 1,3,5-triazines[9], oxazines[10], thiazines[11] by variety of processes. 2-Aminopyrimidines exhibit a wide spectrum of pharmacological activities like, antimicrobial[12-17], antitumor[18], cardiovascular[19], inflammatory[20] and antiviral[21].

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Antimicrobial activity

The antibacterial activity of the synthesized compounds was screened by cup borer method[22]. The test contained 50 μg compound. The activity was shown against gram-positive bacteria *S. aureus* and *B. subtilis* and gram-negative bacteria *E. coli* and *S. typhi.* Similarly the antifungal activity of the compounds was also screened by cup borer method[17] and the test contained 100 μg compound. The activity was shown against fungus *A. niger*. The antimicrobial activities of the synthesized compounds have been compared with standard drugs like Amoxycillin, Ciprofloxecine and Griseofulvin. DMF was used as a solvent. The antimicrobial activities are summarized in the Table 2.

EXPERIMENTAL

General chemicals were purchased from Merck, SD Fine and commercial source were used. All non-aqueous reactions were performed in dry glass ware. Thin layer chromatography (TLC) was performed on pre-coated plates, silica gel 60-F254 (Merck 1.16834, layer thickness 0.25 mm) using Ethyl acetate : Benzene mixtures (1.5 : 8.5) as developing system. The detection of the products on TLC was carried out in iodine vapour.

Melting points were taken in open capillaries and are uncorrected. The IR spectra were recorded on a Shimadzu FTIR 8400 Spectrophotometer; PMR spectra were recorded on a BRUKER (300 MHz) Spectrometer using TMS as internal standard.

Preparation of 2-amino-4-(2'-hydroxy-3'-iodo-4'-ethoxy-5'-bromo phen-1' yl)-6-substituted pyrimidine : [1a-g]

2'-hydroxy-3'-iodo-4'-ethoxy-5'-bromo-substituted phenyl chalcone (0.01 mole) and guanidine hydrochloride (0.01 mole) in ethanol (25 mL) was refluxed on water bath at 65-70°C. An aqueous solution of NaOH (40%, 5 mL) added to the reaction mixture at certain intervals during 3 hrs. The mixture was refluxed continuously for further 9 hrs, then the mixture was cooled and the solid separated was washed with water, dried and crystallised from ethanol as dark yellow needles.

Similarly, all other compounds **[1a-g]** were synthesized. Their physical constant and antimicrobial activity are recorded in Table 1.

Spectroscopic data of synthesized compounds

IR (KBr) cm^{-1} 1 g: 2960 (C-H), 1577 (C=C), 1265 (C-O-C), 1635 (C=N), 3382 (Ar-OH), 3195 (NH_2), 1552 (N=O), 1312 ($-NO_2$), 610 (C-Br), 502 (C-I).

^{1}H NMR (δ ppm) 1a : 1.36-1.48 (t, 3H,CH_3-CH_2), 4.08-4.16 (q, 2H, CH_2-CH_3), 6.88 (s, 1H, Ar-OH), 7.56 (s, 2H, NH_2), 7.12-7.42 (m, 5H, Ar-H). **1c**: 1.43-1.58 (t, 3H,CH_3-CH_2), 4.10-4.20 (q, 2H, CH_2-CH_3), 6.88 (s, 1H,Ar-OH), 7.70 (s, 2H, NH_2), 3.84 (s, 6H, $(OCH_3)_2$), 3.92 (s, 3H, OCH_3), 7.12-7.52 (m, 5H, Ar-H).

Preparation of 2-acetamido-4-(2'-hydroxy-3'-iodo-4'-ethoxy-5'-bromo phen-1' yl)-6-substituted pyrimidine

2-amino-4-(2'-hydroxy-3'-iodo-4'-ethoxy-5'-bromo phen-1'yl)-6-substituted pyrimidines (0.01 mole) and acetic anhydride (10 mL) in acetic acid (15 mL) was refluxed on a water bath at 70-80°C for 2 hrs. The resulting mixture was cooled and pour in ice water. The resulting solid obtained was filtered, washed with water, dried and crystallised from ethanol as black brown needles.

Similarly, all other compounds **[2a-g]** were synthesized. Their the physical constant and antimicrobial activity are recorded in Table 1 and 2, respectively.

Table 1: Physical constants of synthesized compounds

Comp. No.	R	Molecular formula	M. W.	M. P. (°C)	R_f	% of Yield	% of Halogen	
							Calcu.	Found
1a	2-Cl-C_6H_4	$C_{18}H_{14}O_2N_3ClBrI$	546.5	180	0.68	68 %	43.37	43.40
1b	4-CH_3-C_6H_4	$C_{19}H_{17}O_2N_3BrI$	526	130	0.64	66 %	39.35	39.38
1c	3,4-di OCH_3-C_6H_3	$C_{20}H_{19}O_4N_3BrI$	572	80	0.66	64 %	36.18	36.12
1d	2-OH-C_6H_4	$C_{18}H_{15}O_3N_3BrI$	528	90	0.67	60 %	39.20	39.24
1e	4-N-N-di CH_3-C_6H_4	$C_{20}H_{20}O_2N_4BrI$	555	72	0.69	65 %	37.29	37.25
1f	3,4,5-tri OCH_3-C_6H_2	$C_{21}H_{21}O_5N_3BrI$	602	95	0.65	66 %	34.38	34.35
1g	4-NO_2-C_6H_4	$C_{18}H_{14}O_4N_4BrI$	557	135	0.62	62 %	37.16	37.12
2a	2-Cl-C_6H_4	$C_{20}H_{16}O_3N_3ClBrI$	588.5	100	0.64	44 %	41.20	41.24
2b	4-CH_3-C_6H_4	$C_{21}H_{19}O_3N_3BrI$	568	80	0.66	46 %	36.44	36.40
2c	3,4-di OCH_3-C_6H_3	$C_{22}H_{21}O_5N_3BrI$	614	120	0.68	42 %	33.71	33.74
2d	2-OH-C_6H_4	$C_{20}H_{17}O_4N_3BrI$	570	100	0.60	40 %	36.31	36.34
2e	4-N-N-di CH_3-C_6H_4	$C_{22}H_{22}O_3N_4BrI$	597	-	0.62	44 %	34.67	34.70
2f	3,4,5-tri OCH_3-C_6H_2	$C_{23}H_{23}O_6N_3BrI$	644	80	0.64	45 %	32.14	32.15
2g	4-NO_2-C_6H_4	$C_{20}H_{16}O_5N_4BrI$	599	110	0.65	46 %	34.55	34.60

TLC Solvent system : Ethyl acetate : Benzene (1.5 : 8.5)

Table 2: Antimicrobial activity of synthesized compounds

Comp. No.	Antibacterial activity (zone of inhibition in mm)				Antifungal activity (mm)
	S. aureus	***B. subtilis***	***E. coli***	***S. typhi***	***A. niger***
1a	20	18	12	15	13
1b	20	18	13	15	12
1c	20	16	13	14	15
1d	18	15	11	13	19
1e	20	13	12	12	12
1f	19	12	10	11	13
1g	18	15	19	21	12
2a	12	12	12	12	13
2b	13	12	15	13	15
2c	15	12	12	14	23
2d	11	15	12	11	24
2e	12	13	13	12	13
2f	12	12	15	12	12
2g	13	13	15	13	13
Standard drugs					
Amoxicillin	22	23	24	24	-
Ciprofloxacin	26	25	24	25	-
Griseofulvin	-	-	-	-	26

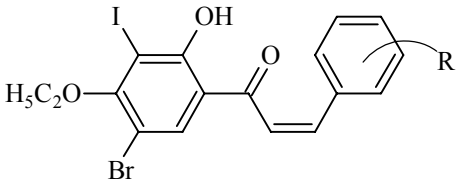
Spectroscopic data of synthesized compounds

IR (KBr) cm^{-1} 2a: 2961 (C-H), 1572 (C=C), 1262 (C-O-C), 1224 (C-O), 1525 (C=N), 3360 (Ar-OH), 840 (NH), 1742 (NH-$COCH_3$), 778 (C-Cl), 590 (C-Br), 518 (C-I).

2d: 2968 (C-H), 1587 (C=C), 1274 (C-O-C), 1164 (C-O), 1642 (C=N), 3436 (Ar-OH), 3357 (NH_2), 1758 (C=N), 612 (C-Br), 522 (C-I).

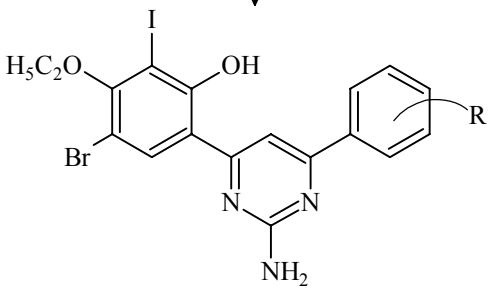
^{1}H NMR (δ ppm) 2a: 1.36-1.48 (t, 3H,CH_3-CH_2), 4.18-4.16 (q, 2 H, CH_2-CH_3), 7.68 (s, 3 H,NH), 2.85 (s, 3 H, CO-CH_3), 7.14 (s, 1 H,OH), 7.12-7.82 (m, 5 H,Ar-H).

Reaction scheme



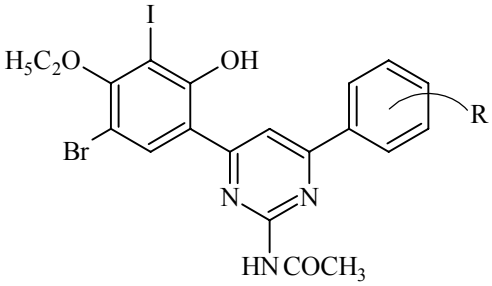
2'-hydroxy -3'-iodo-4'-ethoxy 5'-bromo substituted phenyl chalcone

Gaunidine hydrochloride | Ethanol 40% NaOH



2-Amino 4 -(2'-hydroxy -3'-iodo-4'-ethoxy 5'-bromo phen -1'-yl) 6-substituted phenyl pyrimidine**[1a-g]**

Acetic anhydride | Pyridine actic acid



2-Acetamido 4 -(2'-hydroxy -3'-iodo-4'-ethoxy 5'-bromo phen -1'-yl) 6-substituted phenyl pyrimidine **[2a-g]**

R=2-chloro, 4-methyl, 3,4-di methoxy, 2-hydroxyl, 4-N-N- di methyl, 3,4,5, tri methoxyl, 4-nitro

RESULTS AND DISCUSSION

IR spectra of 2-aminopyrimidine exbits strong bands of NH_2 function in region 3100-3500 cm^{-1} and > C=N band at 1500-1650 cm^{-1}. 2-acetamido derivative of 2-animopyrinidine showed characteristic-$NHCOCH_3$ stretching at above 1788 cm^{-1}. C=N 1620-1690 cm^{-1} and NH band 750-850 cm^{-1} were also observed.

NMR spectra of 2-aminopyrimidine gives singlet of -NH_2 proton at 7.1-8.0 δ ppm. In 2-acitamidopyrimidine derivatives -$NHCOCH_3$ proton gives singlet at 7.68 δ ppm and -$NHCOCH_3$ proton gives singlet at 2.85 δ ppm. The phenolic proton in 2-aminopyrimidine and their derivatives were appeared as a singlet at 6.0-7.20 δ ppm. Other PMR peaks of aromatics protons, OCH_2CH_3 protons are given in detail analysis.

The antimicrobial activity of synthesized compounds have been mentioned, which exhibited significant antibacterial activity. The observation of screening data suggest that the test compound **1 a**, **b**, **c**, **e** and **1f** with various substitution at the phenyl nucleus exhibited excellent antibacterial activity against gram positive bacterial strain *S. aureus* comparable to reference agent Gentamycin but 2-amino group is substituted by acetyl group compounds showed almost poor activity against gram positive bacterial strain *S. aureus.* Compound **1g** exhibited remarkable activity against both gram negative bacterial strains *E. coli* and *P. aeruginosa* and also against gram positive bacterial strain *S. aureus.*

Compound **1c** and **1f** with 3,4,-di-OCH_3 and 3,4,5-tri-OCH_3, respectively substituted to phenyl nucleus exhibited moderate antibacterial activity against gram negative bacterial strains *E. coli* and *S. typhi*.

Overall view of this series, compounds were selectively found active against gram positive strains, although some of the compound showed remarkable activity against gram negative strains. It was also observed that substitution with acetyl group at 2-amino pyrimidine nucleus does not enhance activity of **2a-g** compounds. While rest of the compounds showed poor activity even at concentration of 100 μg/mL.

All the synthesized compounds were screened for their antifungal activity and exhibited significant results however with a degree of variation.

The antifungal activity of the test compound **1d** with -OH group at phenyl nucleus exhibited excellent antifungal activity against *A. niger*. Compound **2c**, **f** with -OCH_3 substituted phenyl ring exhibited excellent antifungal activity. Rest of the compounds showed poor or no activity even at concentration of 200 μg/mL.

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