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Synthesis and Antimicrobial Activity of Some New 2-Amino Pyrimidine Derivatives from 1-(3, 5-Dibromo-2-Hydroxy-4 Methyl Phenyl) Ethanone

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ABSTRACT

The newly synthesized pyrimidine derivatives exhibited moderate to good antimicrobial activity respect to standard drugs. In present investigation, we report the synthesis of 2-amino pyrimidine from chalcones and guanidine hydrochloride using potassium tetr-butoxide as base. These synthesized compounds were characterized on the basis of IR, ^{1}HNMR, Mass spectroscopic data. All synthesized new 2-amino pyrimidine derivatives were screened for antibacterial and antifungal activity against different strains as compare to standard drugs Amoxicillin and Griseofulvin. Compound 3a, 3b, 3d, 3g and 3f were found to be active against selected antibacterial and antifungal strains.

KEYWORDS

2-amino pyridine, 1-(3,5-dibromo-2-hydroxy-4 methyl phenyl) ethanone, chalcone, Antimicrobial Activity.

INTRODUCTION

Infectious diseases caused by bacteria, fungi and other parasite are major threat for health of mankind. With availability of number of drugs in market, the problem is not solved but hastily increases with various cases of multi drug resistance parasites, bacteria and fungi. And this becomes major threat to health of humankind worldwide. So to come out from this budding problem, scientific community all over the world are trying to discover the new affordable and more active compounds which may cross all barrier and rapidly reach to the drug stages. 1,3-diaryl prop-2-en-1-one very well known as Chalcone, is the molecule which was known from many decades due to its wide range of biological activities such as analgesic[1], antiinflammatory[1], antiplatelet[2], antiulcer[3], antimalarial[4], antiparasitic[5], antioxidant[6], antituberculosis[7]. Chalcone exist as either E or Z isomer, but E isomer is most stable form and consequently major chalcone are isolated as E isomer.

From many years bromo acetophenone nucleus has received remarkable attention due to associated with various therapeutic activities like antibacterial[8], anticancer[9], anti-leishmanial[10] etc. Chalcones are intermediate for the synthesis of number of heterocycles for eg. pyridine, pyrimidine, pyrazoline, isooxazoline, flavanoid, benzodiazepine, indazole, azetidinone which also shown various pharmacological activities. While 2-amino pyrimidine also shown good number of biological activities like antitumor[11], anti AIDS agents[12] etc.

So with consideration of the activity of chalcones and 2-amino pyrimidine derivatives we decided to synthesize new derivatives of 2-amino pyrimidine, then characterized them and screened for antimicrobial activity.

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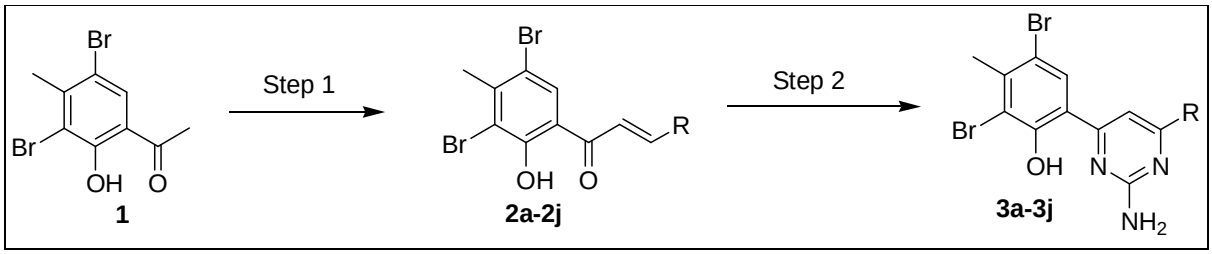
MATERIAL AND METHODS

The melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded on Shimadzu FT-IR-8400 spectrophotometer using KBr disc and ^{1}H NMR spectra in DMSO- d_6 or in $CDCl_3$ (Chemical shift in δ ppm) on Bruker spectrometer (400 MHz) using TMS as an internal standard. The results are in good agreement with the structure assigned. The purity of all compounds was checked by thin layer chromatography using TLC plates of silica gel (E.Merck G254) using Ethyl acetate : Hexane solvent system (7:3). Physical Constants and Spectral data of synthesized compounds (3a-3j) are recorded in Table – 1 and 2 respectively.

Reaction Scheme



Reaction condition: step (1) substituted aldehyde, 40% KOH, 25^{0}C, 18hrs, (R= different substitution), step (2) guanidine hydrochloride, KOt-Bu, t-butanol, reflux, 4-5hrs

General procedure for synthesis of (2E)-1-(3, 5-dibromo-2-hydroxy-4-methylphenyl)-3-phenylprop-2-en-1-ones (2a-2j)

To a well stirred solution of 1-(3,5-dibromo-2-hydroxy-4 methyl phenyl) ethanone (1) (0.01 mol) and substituted aldehyde (0.01 mol) in ethanol (25 ml), 40% KOH solution was added till the solution become basic. The reaction mixture was stirred for 24 hrs at 25^{0}C. Completion of reaction was monitored by TLC. Reaction mass was poured onto crushed ice, acidified using concentrated HCl. The product was filtered, dried in vacuo and crystallized using an appropriate solvent.

General procedure for synthesis of 6-(2-amino-6-phenylpyrimidin-4-yl)-2, 4-dibromo-3-methylphenol (3a-3j)

To as stirred solution of 2a-2j (0.01 mol) and guanidine hydrochloride (0.01mol) in

t-Butanol, potassium-t-butoxide (0.01 mol) was added and reflux the solution on a water bath for 4-5 hours. The solvent was evaporated and the residue was neutralized with 20% HCl, the separated solid was filtered out and crystallized using an appropriate solvent.

Antimicrobial 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 such *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and fungi strain *Aspergillus niger* at 40 µg/mL concentration. Standard drugs like Amoxicillin and Griseofulvin were used for the comparison purpose. The obtained results for compounds 3a-3j are recorded table 2.

ANALYTICAL DATA OF THE COMPOUNDS 3a-3j

6-(2-amino-6-phenylpyrimidin-4-yl)-2,4-dibromo-3-methylphenol (3a)

^{1}H-NMR($CDCl_3$) δppm : 2.83(3H,s,-CH_3), 5.61(2H,br,-NH_2), 7.66-7.90(5H,m,Ar-H), 8.18(1H,s,Ar-H), 8.27(1H,s,Ar-H), 9.02(1H,s,-OH)

IR(KBr)υcm^{-1} : 3400-3600(Ar-OH), 3200(Ar-NH_2), 3120(Ar C-H str.), 2950(CH_3 str), 2850(-

Table: 1 Physical constants of 6-(2-amino-6-substituted phenylpyrimidin-4-yl)-2, 4-dibromo-3-methylphenol (3a-3j)

Sr No.	Compound Name	R	Molecular Formula	Molecular Weight	Yield	Melting Point	R_f
1	3a	C_6H_5-	$C_{17}H_{13}Br_2N_3O$	435	72%	220^0C	0.50
2	3b	3-Br-C_6H_4-	$C_{17}H_{12}Br_3N_3O_2$	514	60%	190^0C	0.57
3	3c	2-Cl-C_6H_4-	$C_{17}H_{12}Br_2ClN_3O$	469	68%	160^0C	0.59
4	3d	4-Cl-C_6H_4-	$C_{17}H_{12}Br_2ClN_3O$	469	70%	198^0C	0.52
5	3e	4-$N(CH_3)_2$-C_6H_4-	$C_{19}H_{18}Br_2N_4O$	478	65%	154^0C	0.67
6	3f	4-OCH_3-C_6H_4	$C_{18}H_{15}Br_2N_3O_2$	465	75%	140^0C	0.70
7	3g	3,4-OCH_3-C_6H_3	$C_{19}H_{17}Br_2N_3O_3$	495	60%	170^0C	0.45
8	3h	2-NO_2-C_6H_4-	$C_{17}H_{12}Br_2N_4O_3$	480	58%	182^0C	0.30
9	3i	3-NO_2-C_6H_4-	$C_{17}H_{12}Br_2N_4O_3$	480	60%	198^0C	0.38
10	3j	4-OH-C_6H_4-	$C_{17}H_{13}Br_2N_3O_2$	451	70%	167^0C	0.54

CH_3 str.), 1470(-CH_3 bend), 1380(-CH_3 bend.), 1575(C=N str.), 1529(C=C bend.), 596(C-Br str.)

Elemental Analysis (Calc.) C, 46.93; H, 3.01; N, 9.66; O, 3.68 % (Found) C, 46.95; H, 3.03; N, 9.67; O, 3.70 %

6-[2-amino-6-(3-bromophenyl) pyrimidin-4-yl]-2,4-dibromo-3-methylphenol (3b)

^{1}H-NMR($CDCl_3$) δppm : 2.83(3H,s,-CH_3), 5.61(2H,br,-NH_2), 7.66-8.40(4H,m,Ar-H), 8.18(1H,s,Ar-H), 8.34(1H,s,Ar-H), 9.02(1H,s,-OH)

IR(KBr)υcm^{-1} : 3400-3600(Ar-OH), 3200(Ar-NH_2), 3120(Ar C-H str.), 2950(CH_3 str), 2850(-CH_3 str.), 1470(-CH_3 bend), 1380(-CH_3 bend.), 1575(C=N str.), 1529(C=C bend.), 596(C-Br str.)

Elemental Analysis (Calc.) C, 39.72; H, 2.35; N, 8.17; O, 3.11 %

6-[2-amino-6-(2-chlorophenyl) pyrimidin-4-yl]-2,4-dibromo-3-methylphenol (3c)

^{1}H-NMR($CDCl_3$) δppm : 2.82(3H,s,-Ar-CH_3),7.25-7.70(4H,m,Ar-H) 8.18(1H,s,Ar-H), 8.23(1H,s,Ar-H),9.05(1H,s,Ar-OH)

IR(KBr)υcm^{-1} : 3400-3600(Ar-OH), 3200(Ar-NH2), 3120(Ar C-H str.), 2950(CH_3 str), 2850(-CH_3 str.), 1470(-CH_3 bend), 1380(-CH_3 bend.), 1575(C=N str.), 1529(C=C bend.), 740(C-Cl str.),596(C-Br str.),

Elemental Analysis(Calc.) C, 43.48; H, 2.58; Br, 34.03; Cl, 7.55; N, 8.95; O, 3.41 %

(Found) C, 43.46; H, 2.59; Br, 34.05; Cl, 7.58; N, 8.97; O, 3.42 %

6-[2-amino-6-(4-chlorophenyl) pyrimidin-4-yl]-2,4-dibromo-3-methylphenol (3d)

^{1}H-NMR($CDCl_3$) δppm : 2.82(3H,s,-Ar-CH_3), 8.18(1H,s,Ar-H), 8.22(1H,s,Ar-H),

7.62(2H,dd,Ar-H), 8.02(2H,dd, Ar-H),9.10(1H,s,Ar-OH)

IR(KBr)υcm^{-1} : 3400-3600(Ar-OH), 3200(Ar-NH_2), 3120(Ar C-H str.), 2950(CH_3 str), 2850(-CH_3 str.), 1470(-CH_3 bend), 1380(-CH_3 bend.), 1575(C=N str.), 1529(C=C bend.), 740(C-Cl str.), 596(C-Br str.)

Elemental Analysis (Calc.) C, 43.48; H, 2.58; N, 8.95; O, 3.41%

(Found)C, 43.49; H, 2.59; N, 8.97; O, 3.43 %

6-{2-amino-6-[3 (dimethylamino)phenyl]pyrimidin-4-yl}-2,4-dibromo-3-methylphenol (3e)

^{1}H-NMR($CDCl_3$) δppm : 2.82(3H,s,Ar-CH_3),3.04(6H,s,-$N(CH_3)_2$), 6.67(1H,m,Ar-H), 7.05(1H,m,Ar-H), 7.68(1H,dt,Ar-H), 7.20(1H,m,Ar-H), 8.05(1H,s,Ar-H), 8.18(1H,s,Ar-H), 9.22(1H,s,Ar-OH)

IR(KBr)υcm^{-1} : 3400-3600(Ar-OH), 3200(Ar-NH_2), 3120(Ar C-H str.), 2950(CH3 str), 2850(-CH_3 str.), 1470(-CH_3 bend), 1380(-CH_3 bend.), 1575(C=N str.), 1529(C=C bend.), 596(C-Br str.)

Elemental Analysis(Calc.)C, 47.72; H, 3.79; N, 11.72; O, 3.35 %

(Found)C, 47.73; H, 3.81; N, 11.74; O, 3.36 %

6-[2-amino-6-(4-methoxyphenyl) pyrimidin-4-yl]-2,4-dibromo-3-methylphenol (3f)

^{1}H-NMR($CDCl_3$) δppm :2.82(3H,s,Ar-CH_3), 3.75(3H,s,-OCH_3), 7.07(2H,dd,Ar-H), 8.18(1H,s,Ar-H), 8.23(1H,s,Ar-H), 8.20(2H,dd,Ar-H), 9.10(1H,s,Ar-OH)

IR(KBr)υcm^{-1} : 3400-3600(Ar-OH), 3200(Ar-NH_2), 3120(Ar C-H str.), 2950(-CH_3 str), 2850(-CH_3 str.), 1470(-CH_3 bend), 1380(-CH_3 bend.), 1575(C=N str.), 1529(C=C bend.), 1261(C-O-C str.), 596(C-Br str.)

Elemental Analysis (Calc.) C, 46.48; H, 3.25; N, 9.03; O, 6.88 %

(Found) C, 46.49; H, 3.26; N, 9.05; O, 6.90 %

6-[2-amino-6-(3,4-dimethoxyphenyl) pyrimidin-4-yl]-2,4-dibromo-3-methylphenol (3g)

^{1}H-NMR($CDCl_3$) δppm :2.82(3H,s,Ar-CH_3), 3.90(6H,s,-OCH_3), 6.86(1H,m,Ar-H), 7.15(1H,m,Ar-H) 7.76(1H,dd,Ar-H), 8.18(1H,s,Ar-H), 8.30(1H,s,Ar-H), 9.10(1H,s,Ar-OH)

IR(KBr)υcm^{-1} : 3400-3600(Ar-OH), 3200(Ar-NH_2), 3120(Ar C-H str.), 2950(CH_3 str), 2850(-CH_3 str.), 1470(-CH_3 bend), 1380(-CH_3 bend.), 1575(C=N str.), 1529(C=C bend.), 1261(C-O-C str.), 596(C-Br str.)

Elemental Analysis (Calc.) C, 46.09; H, 3.46; N, 8.49; O, 9.69 %

(Found) C, 46.11; H, 3.48; N, 8.51; O, 9.70 %

6-[2-amino-6-(2-nitrophenyl) pyrimidin-4-yl]-2,4-dibromo-3-methylphenol (3i)

^{1}H-NMR($CDCl_3$) δppm :2.82(3H,s,Ar-CH_3), 7.36(1H,td,Ar-H), 7.54(1H,m,Ar-H), 7.56(1H,m,Ar-H),7.90(1H,m,Ar-H), 8.18(1H,s,Ar-H), 8.38(1H,s,Ar-H), 9.10(2H,br, -NH2), IR(KBr)υcm^{-1} : 3400-3600(Ar-OH), 3200(Ar-NH_2), 3120(Ar C-H str.), 2950(CH_3 str), 2850(-CH_3 str.), 1470(-CH_3 bend), 1380(-CH_3 bend.), 1575(C=N str.), 1529(C=C bend.), 1250(-NO_2 str.), 596(C-Br str.)

Elemental Analysis (Calc.) C, 42.53; H, 2.52; Br, 33.29; N, 11.67; O, 10.00 %

(Found) C, 42.54; H, 2.53; Br, 33.31; N, 11.68; O, 10.02 %

6-[2-amino-6-(3-nitrophenyl) pyrimidin-4-yl]-2,4-dibromo-3-methylphenol (3j)

^{1}H-NMR($CDCl_3$) δppm :2.82(3H,s,Ar-CH_3), 7.49(1H,m,Ar-H), 7.98(1H,m,Ar-H), 8.00(1H,m,Ar-H), 8.13(1H,m,Ar-H), 8.18(1H,s,Ar-H), 8.41(1H,s,Ar-H), 9.10(1H, br, Ar-OH)

IR(KBr)υcm^{-1} : 3400-3600(Ar-OH), 3200(Ar-NH_2), 3120(Ar C-H str.), 2950(-CH_3 str), 2850(-CH_3 str.), 1470(-CH_3 bend), 1380(-CH3 bend.), 1575(C=N str.), 1529(C=C bend.), 1250(-NO_2 str.), 596(C-Br Str.)

Elemental Analysis(Calc.) C, 42.53; H, 2.52; N, 11.67; O, 10.00 %

(Found) C, 42.54; H, 2.53; N, 11.66; O, 10.02 %

6-[2-amino-6-(4-hydroxyphenyl)pyrimidin-4-yl]-2,4-dibromo-3-methylphenol (3k)

^{1}H-NMR($CDCl_3$) δppm :2.82(3H,s,Ar-CH_3), 6.86(2H,dd,Ar-H), 8.03(2H,dd,Ar-H), 8.18(1H,s,Ar-H), 8.29(1H,s,Ar-H), 9.10(1H,br, Ar-OH)

IR(KBr)υcm^{-1} : 3400-3600(Ar-OH), 3200(Ar-NH_2), 3120(Ar C-H str.), 2950(CH_3 str), 2850(-CH_3 str.), 1470(-CH_3 bend), 1380(-CH_3 bend.), 1575(C=N str.), 1529(C=C bend.), 596(C-Br str.)

Elemental Analysis (Calc.) C, 45.26; H, 2.90; N, 9.31; O, 7.09 % (Found) C, 45.27; H, 2.91; N, 9.33; O, 7.11 %

RESULTS AND DISCUSSION

From the results of antimicrobial data, compounds 3a and 3f were found to be active and compounds 3b, 3d, 3g were found to be moderately active against bacterial strain. While 3d, 3i and 3j were shown good activity against *A.niger*. The structure activity relationship data table, we find that phenyl ring substituted with methoxy substitution at 3 and 4 (3f and 3g respectively) shown as excellent result compare to standard drug amoxicillin at a scale of 40µg/ml. While phenyl ring substituted with nitro (3h and 3i) substituted not shown good antibacterial activity as compare to other substitutions.

Table 2 - Antimicrobial screening results of compounds 3a-3j

Compound No.	R Substitution	Antibacterial activity (%)				Antifungal activity (%)
		S. aureus	***S. epidermidis***	***E. coli***	***P. aeruginoa***	***A. niger***
3a	C_6H_5-	80	33	50	67	50
3b	3-Br-C_6H_4-	70	71	55	67	63
3c	2-Cl-C_6H_4-	60	54	86	48	67
3d	4-Cl-C_6H_4-	68	69	68	81	83
3e	3-N(CH_3)$_2$-	65	75	77	43	50
3f	4-OCH_3-	85	83	45	95	46
3g	3,4-di-OCH_3-C_6H_3-	75	54	70	86	38
3h	2-NO_2-C_6H_4-	65	38	77	67	54
3i	3-NO_2 -	50	45	55	52	75
3j	4-OH-C_6H_4-	65	62	74	77	71
Amoxicillin	-	100	100	100	100	-
Griseofulvin	-	-	-	-	-	100

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