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SYNTHESIS & ANTIMICROBIAL STUDIES ON NOVEL PYRIMIDINES DERIVED FROM PIPERAZINE CHALCONES

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ABSTRACT

Treatment of 3-substituted phenyl-1-(4-(4- hydroxyl phenyl)- piperzin-1-yl)-Prop-2-en-1-ones with guanidine hydrochloride in presence of ethanol and potassium hydroxide, formed 4- substituted phenyl-6-(4-(4- hydroxyl phenyl)- piperzin-1-yl)- Pyrimidinyl derivatives (RP-1 to RP-10). These are assayed for their antibacterial activity against Bacillus pumilus, Bacillus subtilis, Escherichia coli and Proteus vulgaris; for antifungal activity against Aspergillus niger and Candida albicans strains. Antibacterial assay revealed that, compounds RP-2, 3, 7, 8, 10 were highly effective against Bacillus subtilis and Proteus vulgaris and in the antifungal assay, compounds RP-3, 10 proved to be effective against Aspergillus niger.

KEYWORDS: 4- substituted phenyl-6-(4-(4- hydroxyl phenyl)- piperzin-1-yl)- Pyrimidinyl derivatives, antibacterial activity, assay, effective, antifungal activity.

INTRODUCTION

Chalcone[1] is an aromatic ketone and an enone that forms the central core for a variety of important biological compounds, which are known collectively as chalcones or chalconoids. Chalcones are bichromophoric[2] molecules separated by a keto vinyl chain and belong to the flavanoid family. Chemically they consist of open chain flavanoids in which the two aromatic rings are joined by a three carbon α, β- unsaturated carbonyl system, which is responsible for the wide spectrum of biological activities.

In the present study, a novel synthetic method has been designed for the preparation of new series of piperazine containing pyrimidines from the reaction between series of chalcones and guanidine hydrochloride. The synthesized compounds contain pyrimidine group along with 4-phenol piperzinyl ring. The piperzinyl[4] and pyrimidinyl[3] derivatives demonstrate wide range of biological activities such as anti-diabetic, anti-neoplastic, anti-hypertensive, anti-inflammatory, anti-parasitic, anti-histaminic, anti-malarial, anti-oxidant, anti-fungal, anti-tubercular[6], immunosuppressant, anti-nociceptive, hypolipidemic, anti-filarial, anti-angiogenic, anti-protozoal, anti-bacterial[and anti-steroidal properties. The synthesized compounds were purified and screened for the antimicrobial activity against various bacterial and fungal strains.[5]

MATERIALS AND METHODS

Antimicrobial Activity

The synthesized compounds were screened for antimicrobial activity against gram-positive bacteria like Bacillus pumilus, Bacillus subtilis and gram negative bacteria like Escherichia coli and Proteus vulgaris. Similarly the compounds were screened for antifungal activity against fungi like Aspergillus niger and Candida albicans by using cup-borer method. Ciprofloxacin and Miconazole nitrate were used as standard drugs. DMSO was used as solvent.

EXPERIMENTAL

Melting points of the synthesized compounds were determined by open capillary method and are uncorrected. Purity of the compounds was verified on TLC plates coated with silica gel. IR spectra were recorded on Thermo Nicolet IR 200 spectrometer using KBr disc method.

H^1NMR spectra were recorded on BRUKER amx-400 NMR spectrometer where $CDCl_3$ is used as internal standard. Results of combustion analysis were found to be within the limits of permissible errors.

Spectral Details

RP-1: 4-(4-(2- amino-6- phenyl pyrimidin-4-yl)- piperzin-1-yl) Phenol; Yield 72%; mp 110 - 112^{0}C; IR (KBr) νcm^{-1} 3346.29(-NH, str),1620.76 (-C=N, str), 1509.08(-C=C-, str); H^1 NMR δ(ppm) 1.246 & 2.993(8H, Piperzinyl protons), 3.763(2H, s, $-NH_2$), 6.004 & 8.472 (10H, aromatic protons), 7.068(1H, s, -C-5H), 10.420(1H, s, phenolic OH).

RP-2: 4-(4-(2- amino-6-(4-chloro phenyl) pyrimidin-4-yl)- piperzin-1-yl) Phenol; Yield 71%; mp 117 -119^{0}C; IR (KBr) νcm^{-1} 3432.48(-NH, str), 1634.34(-C=N, str), 1452.10(-C=C-, str); H^1 NMR δ(ppm)1.26 & 2.863(8H, Piperzinyl protons), 3.653(2H, s, -NH_2), 7.811(1H, s, -C-5H), 10.516(1H, s, phenolic OH).

RP-3: 4-(4-(2- amino-6-(4- fluoro phenyl) pyrimidin-4-yl)- piperzin-1-yl) Phenol; Yield 70.12%; mp 128 -130^{0}C; IR (KBr) νcm^{-1} 3433.72(-NH, str), 1636.63(-C=N, str), 1512.44(-C=C-, str); H^1 NMR δ(ppm) 1.289 & 2.902(8H, Piperzinyl protons), 3.563(2H, s, -NH_2), 7.088(1H, s, -C-5H), 9.976(1H, s, phenolic OH).

RP-4: 4-(4-(2- amino-6-(4- nitro phenyl) pyrimidin-4-yl)- piperzin-1-yl) Phenol; Yield 64.5%; mp 124 -126^{0}C; IR (KBr) νcm^{-1} 3428.75(-NH, str), 1642.28(-C=N, str), 1541.41(-C=C-, str); H^1 NMR δ(ppm) 1.241 & 2.514(8H, Piperzinyl protons), 3.315(2H, s, -NH_2), 7.313(1H, s, -C-5H), 6.814 & 8.403(9H, aromatic protons), 10.214(1H, s, phenolic OH).

RP-5: 4-(4-(2- amino-6-(4- methoxy phenyl) pyrimidin-4-yl)- piperzin-1-yl) Phenol; Yield 69%; mp 155 -157^{0}C; IR (KBr) νcm^{-1} 3437.75(-NH, str), 1641.11(-C=N, str), 1459.27(-C=C-, str); H^1 NMR δ(ppm) 1.248 & 2.511(8H, Piperzinyl protons), 3.305(2H, s, -NH_2), 7.306(1H, s, -C-5H), 9.894(1H, s, phenolic OH).

RP-6: 4-(4-(2- amino-6-(3-ethoxy-4- hydroxy phenyl) pyrimidin-4-yl)- piperzin-1-yl) Phenol; Yield 64.5%; mp 137 -139^{0}C; IR (KBr) νcm^{-1} 3435.06(-NH, str), 1640.24(-C=N, str), 1456.07(-C=C-, str); H^1 NMR δ(ppm) 1.248 & 2.312(8H, Piperzinyl protons), 3.301(2H, s, -NH_2), 7.114(1H, s, -C-5H), 10.127(1H, s, phenolic OH).

RP-7: 4-(4-(2- amino-6-(3,4-dimethoxy phenyl pyrimidin-4-yl)- piperzin-1-yl) Phenol; Yield 62%; mp 145 -148^{0}C; IR (KBr) νcm^{-1} 3361.86(-NH, str), 1622.10(-C=N, str), 1532.86(-C=C-, str); H^1 NMR δ(ppm) 1.244 & 2.516(8H, Piperzinyl protons), 3.304(2H, s, -NH_2), 6.648 & 8.317(8H, aromatic protons),7.132(1H, s, -C-5H), 10.416(1H, s, phenolic OH).

RP-8: 4-(4-(2- amino-6-(4-(dimethyl amino) phenyl) pyrimidin-4-yl)- piperzin-1-yl) Phenol; Yield 67.4%; mp 135 -137^{0}C; IR (KBr) νcm^{-1} 3320.75(-NH, str), 1621.52(-C=N, str), 1516.19(-C=C-, str); H^1 NMR δ(ppm) 2.513 & 2.913(8H, Piperzinyl protons), 3.359(2H, s, -NH_2), 7.357(1H, s, -C-5H), 6.746 & 7.357(9H, aromatic protons), 9.465(1H, s, phenolic OH).

RP-9: 4-(4-(2- amino-6-(napth-1-yl) pyrimidin-4-yl)- piperzin-1-yl) Phenol; Yield 61.5%; mp 244 -246^{0}C; IR (KBr) νcm^{-1} 3431.44(-NH, str), 1688.19(-C=N, str), 1507.69(-C=C-, str); H^1 NMR δ(ppm) 1.241 & 2.518(8H, Piperzinyl protons), 3.314(2H, s, -NH_2), 7.798(1H, s, -C-5H), 7.117 & 9.171(12H, aromatic protons), 10.431(1H, s, phenolic OH).

RP-10: 4-(4-(2- amino-6-(2,4-dicholro phenyl) pyrimidin-4-yl)- piperzin-1-yl) Phenol; Yield 65.7%; mp 135 -137^{0}C; IR (KBr) νcm^{-1} 3384.31(-NH, str), 1619.84(-C=N, str), 1569.43(-C=C-, str); H^1 NMR δ(ppm) 1.218 & 2.576(8H, Piperzinyl protons), 3.375(2H, s, -NH_2), 7.623(1H, s, -C-5H), 6.056 & 7.944(8H, aromatic protons), 9.571(1H, s, phenolic OH).

RESULTS AND DISCUSSION

From the results mentioned in Table 2, it is evident that the synthesized pyrimidinyl derivatives i, e. compounds RP-1-10 showed significant antibacterial activity at two concentrations 0.5 mg/ml and 1 mg/ml. In particular, the compounds RP 3, 7 and 10 proved to be highly effective against the gram positive bacterial strains while the compound RC-4, 10 is lethal against the gram negative strains. When the compounds were evaluated for antifungal activity, compounds RC- 3 &10 exhibited considerable results.

These results were compared against a standard anti bacterial agent Ciprofloxacin and standard anti fungal agent Miconazole nitrate to assess the relative efficacy and potency of the compounds.

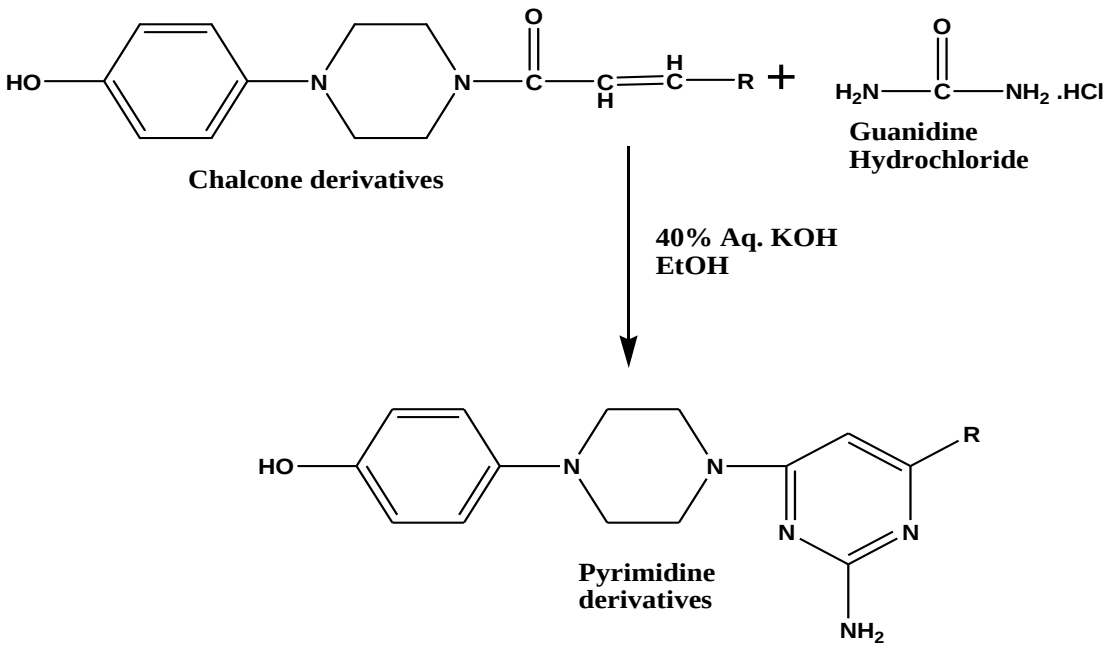

Fig 1: Scheme of piperazine containing pyrimidine derivatives.

Table 1: Compound code of pyrimidine derivatives.

Compound code	R
RP-1	Phenyl
RP-2	4-cholro phenyl
RP-3	4- fluoro phenyl
RP-4	4- nitro phenyl
RP-5	4- methoxy phenyl
RP-6	2- ethoxy-4- hydroxy phenyl
RP-7	2,4- di methoxy phenyl
RP-8	N,N- di methyl amino phenyl
RP-9	Napthyl
RP-10	2,4-dichloro phenyl

Table 2: Anti bacterial activity by cup-borer method.

Compound code	Anti bacterial activity (Zone of inhibition mm)							
	B.subtilis		B.pumilis		E.coli		P.Vulgaris	
	0.5 (mg/mL)	1 (mg/mL)	0.5 (mg/mL)	1 (mg/mL)	0.5 (mg/mL)	1 (mg/mL)	0.5 (mg/mL)	1 (mg/mL)
RP-1	10	12	-	10	8	12	12	16
RP-2	15	20	15	18	10	14	16	19
RP-3	16	23	13	19	13	18	18	21
RP-4	10	13	13	18	14	23	14	24
RP-5	11	14	10	13	-	12	-	11
RP-6	12	14	-	12	-	11	-	10
RP-7	17	23	14	19	10	14	10	13
RP-8	10	16	10	12	-	8	-	11
RP-9	-	10	-	-	-	-	-	8
RP-10	20	25	18	21	16	20	19	25
Ciprofloxacin	28		32		24		30	
Control(DMSO)	-		-		-		-	

Table 3: Anti fungal activity by cup-borer method.

Compound code	Zone of inhibition (mm)	
	1(mg/mL)	
	A. niger	C. albicans
RP-1	13	11
RP-2	12	10
RP-3	18	16
RP-4	8	11
RP-5	-	-
RP-6	8	-
RP-7	-	-
RP-8	12	8
RP-9	-	-
RP-10	18	17
Miconazole nitrate	30	27
Control(DMSO)	-	-

CONCULSION

At the end of the study it is learnt that the prepared pyrimidinyl derivatives possessed significant anti bacterial activity and anti fungal activity, although not as intense as the tested standards.

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