Synthesis and Antimicrobial Activity of s-Triazine Based Chalcones, Pyrazolines and Amino Pyrimidines

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Some s-triazine based chalcones have been synthesized starting from ketone (D) and different aldehydes. Chalcones on cyclization with hydrazine hydrate and guanidine nitrate give the corresponding pyrazolines and amino pyrimidines. The synthesized compounds are screened for their antimicrobial activity. The structures of the synthesized compounds have been confirmed by elemental analysis, IR and NMR spectral studies.

Key Words: Synthesis, s-Triazine, Chalcones, Pyrazolines, Amino Pyrimidines, Antimocrobial activity.

INTRODUCTION

The s-triazine derivatives have their own importance in heterocyclic compounds due to their good biological activities[1–3]. There are many reports on the s-triazine derivatives substituted with a hetero ring as herbicidal active agents[4, 5]. The wide variety of heterocycles have been explored for developing pharmaceutically important molecules like chalcones[6, 7], pyrazolines and amino pyrimidines. The chemistry of chalcones has generated a lot of scientific studies with special reference of their biological application such as antiulcer[8], antitumour[9], antitubercular[10] and fungicidal[11]. The pyrazolines[12] and pyrimidines[13] play a vital role owing to their wide range of biological activities such as antibacterial[14, 15] anticonvulsant[16], herbicidal[17], anticancer[18], etc..

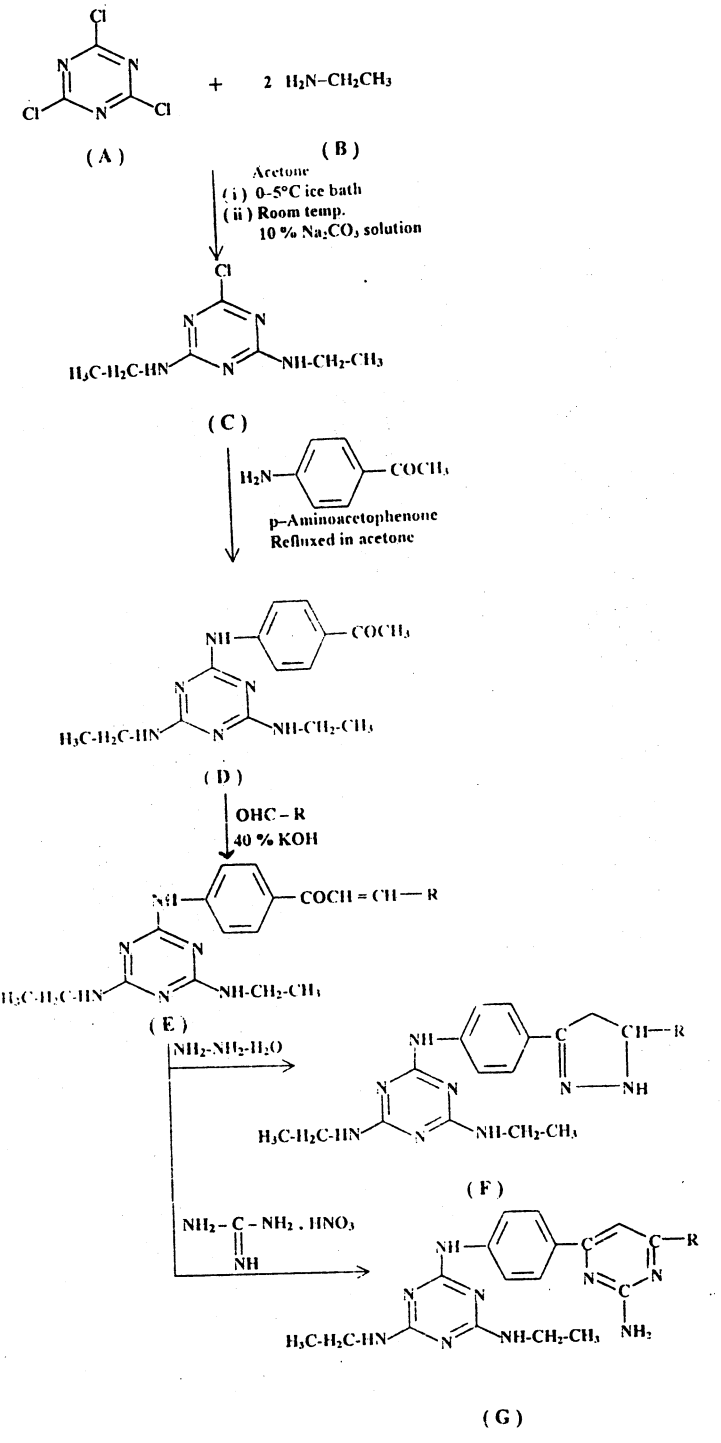
In the present work ketone (D) reacts with different aromatic aldehydes to form chalcones (E_1–E_9). Chalcones are cyclized with hydrazine hydrate and guanidine nitrate to form pyrazolines (F_1–F_9) and amino pyrimidines (G_1–G_9) respectively. The structures of newly synthesized compounds are confirmed by elemental analysis, IR and NMR spectra.

EXPERIMENTAL

All the melting points are determined in an open capillary tube and are uncorrected. The IR spectra are recorded on Perkin-Elmer 237 spectrophotometer and NMR spectra on a Bruker Avarice DPX 200 MH_Z spectrophotometer with $CDCl_3$ as a solvent using TMS as internal reference (chemical shift in δ ppm). Purity of the compounds is checked on TLC using Silica gel-G. Physical and analytical data of all the synthesized compounds have been given in Table-1. The synthesized compounds are screened for their antimicrobial activity.

Preparation of 2,4-bis-ethylamino-6-chloro-s-triazine [C]: Cyanuric chloride (0.01 M; 1.845 g) was dissolved in acetone (25 mL) and monoethyl amine (0.02 M; 0.900 g) was added to it at 0–5°C temperature and stirred for 2 h. Then the reaction mixture was stirred at room temperature for 3 h. Sodium carbonate solution (10%) was added to neutralize hydrochloric acid evolved during the reaction. Then

REACTION :


Cl
N
N
Cl
N
Cl
+ 2 H₂N–CH₂CH₃
(A)
(B)
Acetone
(i) 0-5°C ice bath
(ii) Room temp.
10 % Na₂CO₃ solution
H₃C-H₂C-HN
NH-CH₂-CH₃
(C)
H₂N
COCH₃
p-Aminoacetophenone
Refluxed in acetone
NH
(D)
OHC – R
40 % KOH
COCH = CH — R
(E)
NH₂-NH₂-H₂O
CH—R
C
N
NH
(F)
NH₂ – C – NH₂ . HNO₃
NH
NH₂
(G)

the reaction mixture was poured into crushed ice. The solid separated out was filtered, washed with water and recrystallized from alcohol, m.p. 112°C.

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS

Compd.	R	m.f.	m.p. (°C)	Elemental analysis (%)			
				C		N	
				Calcd.	Found	Calcd.	Found
E_1	Phenyl	$C_{22}H_{24}N_6O$	195	68.04	68.0	21.64	21.60
E_2	2-Chlorophenyl	$C_{22}H_{23}N_6OCl$	185	62.48	62.40	19.88	19.80
E_3	3-Chlorophenyl	$C_{22}H_{23}N_6OCl$	180	62.48	62.45	19.88	19.85
E_4	4-Chlorophenyl	$C_{22}H_{23}N_6OCl$	200	62.48	62.40	19.88	19.80
E_5	3-Bromophenyl	$C_{22}H_{23}N_6OBr$	175	56.41	56.30	17.94	17.90
E_6	4-Fluorophenyl	$C_{22}H_{23}N_6OF$	112	65.02	64.95	20.68	20.60
E_7	2-Hydroxyphenyl	$C_{22}H_{24}N_6O_2$	220	65.34	65.30	19.35	19.30
E_8	4-Methylphenyl	$C_{23}H_{26}N_6O$	170	68.65	68.60	20.89	20.80
E_9	4-Methoxyphenyl	$C_{23}H_{26}N_6O_2$	155	66.02	65.95	20.09	20.0
F_1	Phenyl	$C_{22}H_{26}N_8$	135	65.67	65.60	27.86	27.80
F_2	2-Chlorophenyl	$C_{22}H_{25}N_8Cl$	140	60.48	60.40	25.65	25.55
F_3	3-Chlorophenyl	$C_{22}H_{25}N_8Cl$	173	60.48	60.45	25.65	25.60
F_4	4-Chlorophenyl	$C_{22}H_{25}N_8Cl$	143	60.48	60.40	25.65	25.55
F_5	3-Bromophenyl	$C_{22}H_{25}N_8Br$	152	54.88	54.80	23.28	23.20
F_6	4-Fluorophenyl	$C_{22}H_{25}N_8F$	129	62.85	62.75	26.66	26.60
F_7	2-Hydroxyphenyl	$C_{22}H_{26}N_8O$	162	63.15	63.10	26.79	26.70
F_8	4-Methylphenyl	$C_{23}H_{28}N_8$	130	66.34	66.30	26.92	26.85
F_9	4-Methoxyphenyl	$C_{23}H_{28}N_8O$	175	63.88	63.80	25.92	25.82
G_1	Phenyl	$C_{23}H_{25}N_9$	171	64.63	64.50	29.50	29.41
G_2	2-Chlorophenyl	$C_{23}H_{24}N_9Cl$	185	59.80	59.70	27.30	27.22
G_3	3-Chlorophenyl	$C_{23}H_{24}N_9Cl$	167	59.80	59.75	27.30	27.25
G_4	4-Chlorophenyl	$C_{23}H_{24}N_9Cl$	141	59.80	59.70	27.30	27.22
G_5	3-Bromophenyl	$C_{23}H_{24}N_9Br$	162	54.54	54.48	24.90	24.80
G_6	4-Fluorophenyl	$C_{23}H_{24}N_9F$	136	62.05	62.00	28.34	28.20
G_7	2-Hydroxyphenyl	$C_{23}H_{25}N_9O$	117	62.30	62.22	28.44	28.40
G_8	4-Methylphenyl	$C_{24}H_{27}N_9$	152	65.30	65.20	28.57	28.50
G_9	4-Methoxyphenyl	$C_{24}H_{27}N_9O$	146	63.01	63.00	27.57	27.50

Preparation of 2,4-bis-ethylamino-6-(4′-acetyl phenylamino)-s-triazine [D]: 2,4-Bis-ethylamino-6-chloro-s-triazine (0.01 M; 2.015 g) and *p*-amino acetophenone (0.01 M; 1.350 g) were dissolved in acetone (50 mL) and the reaction mixture was refluxed for 12 h. At a regular interval 10% sodium carbonate solution was added to neutralize hydrochloric acid evolved during the reaction. Then the reaction mixture was poured into crushed ice. The product separated was filtered, washed with water and recrystallized from alcohol, m.p. 266°C.

Preparation of 2,4-bis-ethylamino-6-[4′-{3″-(4‴-methoxyphenyl)-2″-propenon-1″-yl}-phenylamino]-s-triazine [E_9]: To a well stirred solution of 2,4-bis-ethylamino-6-(4″-acetylphenylamino)-s-triazine (0.01 M, 2.015 g), 4-methoxy benzaldehyde (0.01 M, 1.36 g) in DMF (30 mL), 40% KOH (10 mL) was added. The reaction mixture was stirred for 2 h and left overnight. Then the mixture was poured into ice water, neutralised with HCl, filtered, washed with water and recrystallised from alcohol to give E_9.

IR (cm^{-1}) (KBr): 805 ν(C—N, s-triazine), 1325 ν(C—N, aromatic), 1220 ν(C—O—C), 1675 ν(C=O, chalcone moiety).

NMR ($CDCl_3$): 1.15 δ ppm [t, 6H, —(CH_2—$\underline{CH_3}$)$_2$], 3.9 δ ppm (s, 3H, —$O\underline{CH_3}$), 4.1 δ ppm [q, 4H, —($\underline{CH_2}$—CH_3)$_2$], 6.9 δ ppm (d, 1H, —CO—$\underline{CH}$=), 7.25 to 7.7 δ ppm (m, 11 $\underline{H}$, Ar—H + N$\underline{H}$), 7.8 δ ppm (d, 1H, Ar—$\underline{CH}$=).

Similarly other compounds (E_1–E_8) were prepared by the above method.

Preparation of 2,4-Bis-Ethylamino-6-[4′-{5″-(4‴-Methoxyphenyl)-Pyrazolin-3″-yl}-Phenylamino]-s-Triazine [F_9]: A mixture of 2,4-bis-ethylami- no-6-[4′-{3″-(4‴-methoxyphenyl)-2″-propenon-1″-yl}-phenylamino]-s-triazine (0.01 M, 4.18 g) in 25 mL dioxane, hydrazine hydrate (0.02 M, 1.0 gm) was added and refluxed for 15 h. Then the reaction mixture was cooled and poured into ice-cold water. The product separated out was filtered, washed with water and recrystallised from alcohol to give F_9.

IR (cm^{-1}) (KBr): 805 ν(C—N, s-triazine), 1348 ν(C—N, aromatic), 1235 ν(C—O—C), 1620 ν(C=N, pyrazoline moiety), 2985 ν(=CH, aromatic)

NMR ($CDCl_3$): 1.3 δ ppm [t, 6H, —(CH_2—$\underline{CH_3}$)$_2$], 3.8 δ ppm (m, 2H, —$\underline{CH_2}$), 3.9 δ ppm (s, 3H, —$O\underline{CH_3}$), 4.1 δ ppm {q, 4H, —($\underline{CH_2}$—$\underline{CH_3}$)$_2$], 5.3 δ ppm (s, 1H, —$\underline{CH}$—), 6.9 to 7.8 δ ppm (m, 12H, Ar—$\underline{H}$ + N$\underline{H}$).

Similarly other compounds (F_1–F_8) were prepared by the above method.

Preparation of 2,4-bis-ethylamino-6-[4′-{2″-amino-6″-(3‴-bromo phenyl)-pyrimidin-4″-yl}-phenylamino]-s-triazine [G_5]: A mixture of 2,4-bis-ethyl-amino-6-[4′-{3″-(3‴-bromophenyl)-2″-propenon-1″-yl}-phenylamino]-s-triazine (0.01 M, 4.67 g) in 25 mL dioxane, guanidine nitrate (0,01 M, 1.22 g), 40% KOH (2 mL) was added and refluxed for 15 h. Then the reaction mixture was cooled and poured into ice water. The product was separated, filtered, washed with water and recrystallized from alcohol to give G_5.

IR (cm^{-1}) (KBr): 805 ν(C—N, s-triazine), 1345 ν(C—N, aromatic), 1650^{-1} ν(C=N, —NH_2, pyrimidine moiety) 1260 ν(C—O—C), 2995 ν(=CH, aromatic).

NMR ($CDCl_3$): 1.3 δ ppm [t, 6H, —(CH_2—$\underline{CH_3}$)$_2$], 3.8 δ ppm [q, 4H, —($\underline{CH_2}$—CH_3)$_2$], 3.9 δ ppm (s, 3H, *p*-$O\underline{CH_3}$), 4.0 δ ppm (q, 6H, *m*-O—$\underline{CH_3}$), 5.5 δ ppm (s, 2H, —N$\underline{H_2}$—), 6.3 δ ppm (s, 1H, —CH—), 7.2 to 7.8 δ ppm (m, 9H, Ar—$\underline{H}$ + N$\underline{H}$).

Similarly other compounds (G_1-G_9) were prepared by the above method.

RESULTS AND DISCUSSION

The synthesized compounds are tested for their antibacterial activity against *S. aureus, E. coli, S. paratyphi A.* and *B. subtilis* using agar cup method at concentration of 40 μg/mL. The zone of inhibition with respect to controlled medium is given in Table-2.

TABLE-2
ANTIMICROBIAL ACTIVITY OF COMPOUNDS

Compd.	R	Antifungal activity	Antibacterial activity			
			Zone of inhibition in mm			
		% inhibition	*S. aureus*	*E. coli*	*S.P.A.*	*B. subtilis*
E_1	Phenyl	23	—	—	18	18
E_2	2-Chlorophenyl	42	15	25	12	—
E_3	3-Chlorophenyl	33	9	—	—	—
E_4	4-Chlorophenyl	54	10	—	9	—
E_5	3-Bromophenyl	56	—	—	13	10
E_6	2-Hydroxyphenyl	52	12	—	10	14
E_7	4-Methylphenyl	36	—	—	10	12
E_8	4-Methoxyphenyl	34	—	—	9	9
F_1	Phenyl	25	12	—	11	9
F_2	2-Chlorophenyl	26	14	—	—	12
F_3	3-Chlorophenyl	42	10	—	10	—
F_4	4-Chlorophenyl	54	21	—	16	10
F_5	3-Bromophenyl	50	13	—	—	—
F_6	4-Fluorophenyl	52	8	11	—	—
F_7	2-Hydroxyphenyl	36	10	8	—	8
F_8	4-Methylphenyl	56	14	—	10	14
F_9	4-Methoxyphenyl	37	9	—	—	—
G_1	Phenyl	23	10	12	10	9
G_2	2-Chlorophenyl	33	—	10	—	8
G_3	3-Chlorophenyl	52	—	10	—	—
G_4	4-Chlorophenyl	42	9	—	—	—
G_5	3-Bromophenyl	61	12	—	—	—
G_6	4-Fluorophenyl	56	9	9	—	—
G_7	2-Hydroxyphenyl	26	12	8	8	—
G_8	4-Methylphenyl	50	10	—	—	—
G_9	4-Methoxyphenyl	25	11	12	—	—
	Ciprofloxacine	—	25	24	20	23
	Fusarium solani	83	—	—	—	—

The activity is compared with standard drug as ciprofloxacine at the same concentration. From the experimental data it has been observed that the compounds of the type E_2–E_4, E_6, E_9, F_1–F_3, F_6–F_9, G_1, G_4 and G_5–G_9 show poor activity against *S. aureus* bacteria. The remaining compounds are inactive against the same.

In case of Gram negative bacteria like *E. coli*, the compound of type E_2 is active. The compounds of the type F_6, F_7, G_1–G_4, G_7 and G_9 show poor activity, but the remaining compounds are inactive against the same bacteria.

The compound of type E_1 is active against *S. paratyphi A.*, whereas the compounds containing R = 3-bromophenyl and 4-chlorphenyl are moderately active. The compounds of type E_2, E_4, E_6–E_8, F_1, F_3, F_8, G_1 and G_7 are poorly active. The remaining compounds are inactive against the same.

In case of Gram positive bacteria like *B. subtilis* the compound of type E_1 is active, whereas the compounds of the type E_6 and F_8 exhibit moderate activity. The compounds of the type E_5, E_7, E_8, F_1, F_2, F_4, F_7, G_1 and G_2 possess poor activity. The remaining compounds are inactive against the same bacteria.

The compounds are also screened for their antifungal activity by using *Fusarium solani*. The zones of incubation are measured and the percentage inhibition is calculated. For standard, griseofulvin is used and the percentage inhibition obtained is 83.

From the experimental data it is observed that the compounds of type E_5, F_8, G_4 and G_5 showed considerable inhibition.

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