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Synthesis and antibacterial activity of chalcones, aminopyrimidines and pyrazolines

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ABSTRACT

Chalcones (E_1-E_5) have been prepared by the reaction between ketone (D) and different substituted aromatic aldehydes. These chalcones (E_1-E_5) were cyclized with guanidine nitrate and hydrazine hydrate to give aminopyrimidine (F_1-F_5) and pyrazoline (G_1-G_5) derivatives corresponding chalcones (E_1-E_5). The synthesized compounds were characterized by the spectral data and elemental analysis. These compounds were screened for their antibacterial activity by using ciprofloxacin as standard drug.

Key words: Chalcones, aminopyrimidines, pyrazolines, spectral data, antibacterial activity.

INTRODUCTION

The compounds with the backbone of chalcones have been reported to exhibit a wide variety of pharmacological effects, including antioncogenic[1], antimalarial [2], antiulcerative [3], analgesic [4] and anti-inflammatory [5] activities. Literature survey reveals that pyrimidine derivatives have attracted considerable attention as they are endowed with wide spectrum of activities like anticancer [6], CNS - stimulant [7], antiviral [8] and anti - HIV [9]. Synthesis and characterization of pyrazoline derivatives has been a developing field within realm of heterocyclic chemistry for the past several decades because of their ready accessibility through synthesis, wide range of chemical reactivity and broad spectrum of biological activity [10,11]. Pyrazoline derivatives have been found to possess antibacterial [12], antidepressant [13] activities and cerebroprotective effect [14]. Inspired from these observations and in a continuation of our work [15-18] on chalcones and its derivatives, it was planned to synthesize chalcones and their aminopyrimidine and pyrazoline derivatives. All the the synthesized compounds were tested for antibacterial activity. The synthesized compounds were characterized by mean of spectral data and elemental analysis.

EXPERIMENTAL

All melting points were determined in open capillary and are uncorrected. The IR spectra were recorded on Perkin-Elmer 237 spectrophotometer. ^{1}H NMR spectra on a Bruker Avance DPX 400 MHz spectrometer with $CDCl_3$ as a solvent and tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in part per million (ppm) downfield from the internal standard and signals are quoted as s (singlet), d (doublet) and m (multiplate). Thin Layer Chromatography (TLC) analytical separation was conducted with Silica Gel 60 F-254 (Merck) plates of 0.25mm thickness eluted with visualized with UV (254nm) or iodine to check the purity of the synthesized compounds.

Preparation of 2,4-bis-ethylamino-6-chloro-*s*-triazine (C)

Cyanuric chloride (A) (0.01 mol) was

dissolved in acetone (25 ml) and monoethyl amine (B) (0.02 mol) was added slowly to it at 0-5ºC with constant stirring for 6 hours at room temperature. Periodically, sodium carbonate solution (0.005 mol in10 ml water) was added dropwise to neutralized HCl evolved during the reaction. Finally the contents were poured into crushed ice. The solid separated out was filtered, washed with water, dried and recrystallized from ethyl alcohol to give (C). m.p. 112ºC; IR (KBr): 3370 (N-H str.), 805 (C-N, *s*-triazine), 772 (C-Cl str.); ^{1}H NMR ($CDCl_3$): δ 1.2 [t, 6H, - (-CH_2-C$\underline{H}_3$)$_2$], 4.1 [q, 4H, (-C$\underline{H}_2$-CH_3)$_2$], 6.9 [s. 2H, N$\underline{H}$].

Preparation of 2,4-bis-ethylamino-6-(4'-acetylphenylamino)-*s*-triazine (D)

2,4-Bis-ethylamino-6-chloro-*s*-triazine (C) (0.01mol) and 4-amino acetophenone (0.01 mol) were dissolved in DMF (40 ml) and the reaction mixture was refluxed for 12 hours. Periodically, sodium carbonate solution (0.005 in 10 ml water) was added to neutralized HCl evolved during the reaction. Finally the contents were poured in to crused ice. The solid separated out was filtered, washed with water, dried and recrystallized from ethyl alcohol to give (D). m.p. 266ºC; IR (KBr): 3366 (N-H str.), 1660 (-C=O), 804 (C-N, *s*-triazine). ^{1}H NMR ($CDCl_3$): δ 1.26 [t, 6H, -(-CH_2-C$\underline{H}_3$)$_2$], 2.6 (s, 3H, -COC$\underline{H}_3$), 4.12 [q, 4H, (-C$\underline{H}_2$-CH_3)$_2$], 6.9 - 8.8 (m, 7H, Ar-$\underline{H}$ and N$\underline{H}$).

Preparation of 2,4-bis-ethylamino-6-[4'-{3''-(3''',4''',5'''-trimethoxyphenyl)-2''-propenon-1''-yl}phenylamino]-*s*-triazine (E_1)

2,4-Bis-ethylamino-6-(4'-acetylphenylamino)-*s*-triazine (D) (0.01mol) was dissolved in DMF (30 ml) 3,4,5-trimethoxy benzaldehyde (0.01 mol) was added to it. Then solution of KOH (5 ml of 40%) was added to the reaction mixture with constant stirring at room temperature. After 24 hours the reaction mixture was poured into crushed ice and neutralized with HCl. The product separated out was filtered, washed with water, dried and recrystallized from ethyl alcohol to give (E_1); IR (KBr) cm^{-1} : 3380 (N-H str.), 1682 (-C=O, chalcone moeity), 1222 (C-O-C str.), 804 (C-N, *s*-triazine); ^{1}H NMR ($CDCl_3$): δ 1.2 [t, 6H, - (-CH_2-C$\underline{H}_3$)$_2$], 3.80 (s, 6H, m-OC$\underline{H}_3$), 3.86 (s, 3H, p-OC$\underline{H}_3$), 4.1[q, 4H, (-C$\underline{H}_2$-CH_3)$_2$], 6.80 (d, lH, -CO-C$\underline{H}$=), 7.1-7.7 (m, 9H, Ar-$\underline{H}$ and N$\underline{H}$), 7.81 (d, 1H, Ar-C$\underline{H}$=).

Similarly the remaining compounds (E_2 – E_5) were prepared by this method. Their physical data and analytical data are given in Table-1

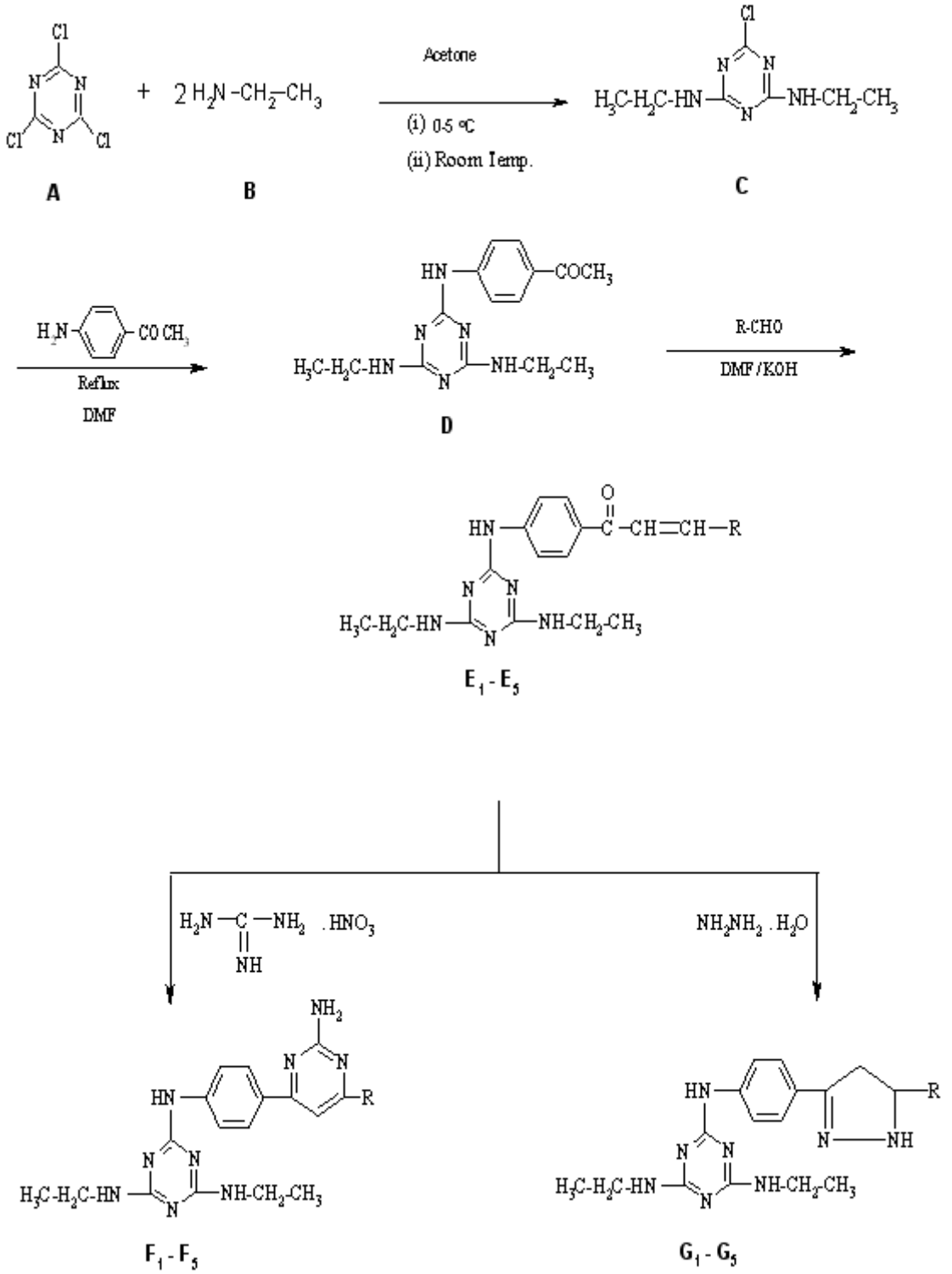
Preparation of 2,4-bis-ethylamino-6-[4'- {2"-amino-6"-(3''',4''',5'''-trimethoxy phenyl)-pyrimidin-4"-yl} phenylamino]-*s*-triazine(F_1)

2,4-Bis-ethylamino-6-[4'-{3''-(3''',4''',5'''-trimethoxyphenyl)-2''-propenon-1''-yl} phenylamino]-*s*-triazine (E_1) (0.01mol) was dissolved in 25 ml dioxane and guanidine nitrate (0.01 mol) was added to it. Then solution of KOH (5 ml of 40%) was added to the reaction mixture and refluxed for 15 hours. The reaction mixture was then cooled, poured into crushed ice and product separated out was filtered, washed with water, dried and recrystallized from ethyl alcohol to give (F_1). IR (KBr) cm^{-1} : 3393 (-NH_2 pyrimidine moiety), 1645 (-C=N str. pyrimidine moiety), 1253 (C-O-C str.), 804 (C-N, *s*-triazine); ^{1}H NMR ($CDCl_3$): δ 1.31 [t, 6H, -(-CH_2-C$\underline{H}_3$)$_2$], 3.78 [q, 4H, (-C$\underline{H}_2$-CH_3)$_2$], 3.86 (s, 6H, m-OC$\underline{H}_3$), 3.91 (s, 3H, p-OC$\underline{H}_3$), 5.50 (s,2H,-N$\underline{H}_2$), 6.31 (s, lH, -C$\underline{H}$), 7.2–7.8 (m, 9H, Ar-$\underline{H}$ and N$\underline{H}$).

Similarly the remaining compounds (F_2 - F_5) were prepared by this method. Their physical data and analytical data are given in Table 1

Preparation of 2,4-bis-ethylamino-6-[4'-{5''-(3''',4''',5'''-triiethoxyphenyl)-pyrazolin-3''-yl}phenyl amino]-*s*-triazine (G_1)

2,4-Bis-ethylamino-6-[4'-{3''-(3''',4''',5'''-trimethoxyphenyl)- 2'' -propenon-1''-yl} phenyl amino]-*s*-triazine (E_1) (0.01mol) was dissolved in 25 ml dioxane and hydrazine hydrate (0.02mol) was added to it. Then the reaction mixture was refluxed for 15 hours. The reaction mixture was then cooled, poured into crushed ice and product separated out was filtered, washed with water, dried and recrystallized from ethyl alcohol to give (G_1). IR (KBr) cm^{-1} : 3410 (N-H str.), 3325 (N-N, pyrazoline moiety), 1632 (-C=N, pyrazoline moeity), 1243 (C-O-C str.) 803 (C-N, *s*-triazine); ^{1}H NMR ($CDCl_3$): δ 1.34 [t, 6H, -(-CH_2-C$\underline{H}_3$)$_2$], 3.80 (m,2H,-CH_2), 3.84 (s, 6H, m-OC$\underline{H}_3$), 3.89 (s, 3H, p-OC$\underline{H}_3$), 4.0 [q, 4H, (-C$\underline{H}_2$-CH_3)$_2$], 5.3 (s, lH, -CH), 6.9 – 7.9 (m, 10H, Ar-$\underline{H}$ and N$\underline{H}$).


Cl
N
N
Cl
N
Cl
+ 2 H2N-CH2-CH3
Acetone
(i) 0-5 °C
(ii) Room Temp.
Cl
N
N
H3C-H2C-HN
NH-CH2-CH3
N
A
B
C
H2N
COCH3
Reflux
DMF
HN
COCH3
N
N
H3C-H2C-HN
NH-CH2-CH3
N
D
R-CHO
DMF/KOH
O
C
CH
CH
R
E1 - E5
H2N
C
NH2
NH
. HNO3
NH2NH2 . H2O
NH2
R
F1 - F5
N
NH
G1 - G5

Scheme 1

Similarly the remaining compounds (G_2 - G_5) were prepared by this method. Their physical data and analytical data are given in Table-1.

RESULTS AND DISCUSSION

The IR spectrum of compounds (E_1) shows the characteristic band in the region of 1682 cm^{-1}

Table 1: Physical and Analytical data of compounds (E_1-E_5), (F_1-F_5) and (G_1-G_5)

Compd.	R	M.P °C	% CCal / Found	%NCal / Found
E_1	3,4,5-Trimethoxyphenyl	140	62.76 / 62.70	17.57 / 17.50
E_2	3-Methoxy-4-hydroxyphenyl	215	63.59 / 63.50	19.35 / 19.37
E_3	3-Ethoxy-4-hydroxyphenyl	208	64.28 / 64.20	18.75 / 18.65
E_4	3-Phenoxyphenyl	135	70.00 / 69.95	25.00/ 24.95
E_5	4-N,N-dimethylaminophenylamino	193	66.82 / 66.80	22.73 / 22.70
F_1	3,4,5-Triimethoxyphenyl	139	60.34 / 60.30	24.37 / 24.30
F_2	3-Methoxy-4-hydroxyphenyl	222	60.88 / 60.80	26.63 / 26.60
F_3	3-Ethoxy-4-hydroxyphenyl	217	61.60 / 61.50	25.87 / 25.80
F_4	3-Phenoxyphenyl	176	67.05 / 67.00	24.27 / 24.20
F_5	4-N,N-dimethylaminophenylamino	182	63.82 / 63.72	29.78 / 29.70
G_1	3,4,5-Trimethoxyphenyl	180	60.97 / 60.90	22.76 / 22.70
G_2	3-Methoxy-4-hydroxyphenyl	150	61.60 / 61.50	25.00 / 24.90
G_3	3-Ethoxy-4-hydroxyphenyl	170	62.33 / 62.30	24.24 / 24.20
G_4	3-Phenoxyphenyl	145	68.07 / 68.0	22.67 / 22.60
G_5	3-Phenoxyphenyl	132	64.71 /64.65	28.31 / 28.23

Table 2: Antibacterial activity data of compounds (E_1-E_5), (F_1-F_5) and (G_1-G_5)

Compd.	*R*	Antibacterial Activity Diameter of zone of inhibition (in mm)			
		S.aureus **MTCC-96**	***B.subtilis*** **MTCC-441**	***E.coli*** **MTCC-443**	***S.paratyphi A*** **MTCC-733**
E_1	3,4,5-Trimethoxy phenyl	14	10	-	-
E_2	3-Methoxy-4-hydroxy phenyl	-	09	-	-
E_3	3-Ethoxy-4-hydroxy phenyl	-	-	-	-
E_4	3-Phenoxy phenyl	12	-	-	14
E_5	4-N,N-dimethylamino phenyl amino	11	10	15	11
F_1	3,4,5-Triimethoxy phenyl	08	-	08	10
F_2	3-Methoxy-4-hydroxy phenyl	-	-	09	-
F_3	3-Ethoxy-4-hydroxy phenyl	13	-	-	-
F_4	3-Phenoxy phenyl	10	-	08	-
F_5	4-N,N-dimethylamino phenyl amino	15	12	-	-
G_1	3,4,5-Trimethoxy phenyl	-	-	-	-
G_2	3-Methoxy-4-hydroxy phenyl	09	10	-	10
G_3	3-Ethoxy-4-hydroxy phenyl	10	14	-	-
G_4	3-Phenoxy phenyl	10	09	-	10
G_5	3-Phenoxy phenyl	12	15	-	-

which indicate the presence of -C=O group. The IR spectrum of compounds (F_1) shows the characteristic band in the region of 3393 cm^{-1} which indicate the presence of (-NH_2) primary amine. The IR spectrum of compounds (G_1) shows characteristic band in region the of 1632 cm^{-1} due to –C=N group. The IR spectrum of compounds (F_1) and compounds (G_1) does not show any absorption band in the region of 1700- 1647 cm^{-1} which indicate the absence of -C=O group. ^{1}H NMR spectrum of compounds (E_1) shows doublet of -CO-CH= at ä 6.8 confirmed the presence of chalcone moeity. The ^{1}H NMR spectrum of compounds (F_1) shows a sharp singlet near about δ 5.50 due to –NH_2 protons, it also give a sharp singlet of –CH near about δ 6.3 which confirmed the presence of aminopyrimidine derivatives. The ^{1}H NMR spectrum of compounds (G_1) shows multiplate of –CH_2 near about δ 3.80 confirmed the cyclisation in pyrazoline moiety.

Antibacterial activity

All the synthesized compounds were screened for their antibacterial activity by using agar diffusion method[21] against *S.aureus* and *B. subtilis* Gram-positive bacteria and *E-coli*, *S. paratyphi-A* Gram-negative bacteria in nutrient agar medium. Ciprofloxacin was used as standard drugs for the comparison of antibacterial activity.

By visualizing activity data, it could be observed that compounds E_1, E_4, E_5, F_3, F_5 and G_5 were found to be less active against *S.aureus*, whereas remaining compounds E_2, E_3, F_1, F_2, F_4, G_1, G_2, G_3 and G_4 were found to be inactive against *S.aureus.* Compounds E_1, E_5, F_5, G_2, G_3 and G_5 were found to be less active against *B. subtilis;* whereas remaining compounds E_2, E_3,E_4, F_1, F_2, F_3,F_4, G_1 and G_4 were found to be in active against *B. subtilis*. Compound E_5 was found to be moderately active against *E-coli;* whereas remaining compounds E_1, E_2, E_3, E_4, F_1, F_2, F_3, F_4, F_5, G_1, G_2, G_3, G_4 and G_5 were found to be in active against *E-coli*. Compounds E_4, E_5, F_1, G_2 and G_4 was found to be less active against *S. paratyphi-A*. Compounds E_1, E_2, E_3, F_2, F_3, F_4, F_5, G_1, G_3 and G_5 were found to be in active against *S. paratyphi-A*.

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REFERENCES

1. Kumar, S. K., Hager, E., Pettit, C., Gululingappa, H., Devidson, N. E. and Khan, S. R., *J. Med. Chem.*, **46** : 2813 (2003).
2. Liu, M., Wilairat, P. and Go, M. L., *J. Med. Chem.*, **44**: 4443 (2001).
3. Murakami, S., Muramatsu, M., Aihara, H. and Otomo, S., *Biochem. Pharmacol.*, **42**: 1447 (1991).
4. Viana, G. S., Banderi, M. A. and Matos, F. J., *Phytomedicine*, **10** : 189 (2003).
5. Hsieh, H. K., Lee, T. H., Wang, J. P., Wang, J. J. and Lin, C. N., *Pharm. Res.*, **15** : 39 (1998).
6. Yoshioka, H., Obata, T., Fujii, K., Yoshiya, H., Tsutsumiuchi, K. and Shikata, Shoji, *Eur. Pat. Appl. EP* 323, 757 (C1. C07239 / 42) 12 Jul 1984, *JP Appl*, 88 / 662, 07 Jan 1988 : 36pp ; *Chem. Abstr.*, **112** : 21012b (1990).
7. Tomino, Takesue, M., Kihara, N., Kihara, T.,Awaya, A., Horikomi, K., Sasaki, T. and Mizuchi A., *Eur. Pat*. EP 379, 806 (C1. C07239 / 48) 01 Aug (1990) *JP* Appl. 88 / 333, 670, 29 Dec (1988) : 154pp; *Chem. Abstr.*, 114 ; 23983j (1991).
8. Sanghvi, Y. S., Larson, S. B., Smee, D. F., Revankar, G. R. and Robinse, R. K., *Nucleosides, Nucleotides*, **10**(6): 1417 (1991).
9. Okabe, M., Sun, R. C. and Zenchoff G. B., *J. Org. Chem.*, **56**: 4393 (1991).
10. Rao, K. S. and Subbaraju, G. V., *Indian J. Heterocycl. Chem.*, **4**: 19 (1994).
11. Herman, E. R. and Gablines, J., *Cancer Chemotherapy Report*, **14**: 85 (1961).

12. Das, N.B.and Mitra, A.S., *Indian. J. Chem*., **16**B: 638 (1978).
13. Erol, D. and Pallaska, E., *Eur. J. Med. Chem*., **36**: 539 (2001).
14. Ohto, N. and Shigo, Y*., Jpn. J. Pharmacol*., **73** : 317 (1997).
15. Solankee, A., Kapadia, K., Solankee, P., Prajapati, Y., Patel, H., and Solankee, S., *Organic CHEMISTRY An Indian Journal*, **3**(4): 224 (2007).
16. Solankee, A., Kapadia, K., Solankee, P., Prajapati, Y., Patel, H., and Solankee, S., *Indian. J. Chem*., **46**B: 1707 (2007).
17 Solankee, A., Solankee, S. and Patel, G., *Orient. J. Chem*., **24**(1): 277 (2008).
18. Solankee, A., Kapadia, K., Solankee S., Prajapati Y., Patel H., Solankee, P., and Patel G., *Acta Ciencia Indica*, **XXXIVC**(1): 121 (2008).