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Formulation and antibacterial evaluation of some novel s-triazine based chalcones and their derivativees

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ABSTRACT

Some new chalcones, 2-(4'-chlorophenylamino)-4-(4'-flurophenylamino)-6-[4'-3{3"-(substituted phenyl/2-thienyl/2furanyl)-2"-propenon-1"-yl} phenylamino]-s-triazine (6a-e) have been acheived by the reaction between 2-(4'-chlorophenylamino)-4-(4'-flurophenylamino)-6-(4'-acetylphenylamino)-s-triazine (5) and differentt aromatic and heterocycli aldehydes, which on cyclisation with phenyl hydrazine hydrochloride in the presence of alkali give phenyl pyrazolines (7a-e). Chalcones (6a-e) on cyclisation with malononitrile in the presence of ammonium acetate give cyanopyridines (8a-e). The characterization of newly synthesized compounds has been done on the basis of IR, ^{1}H NMR spectral data as well as elemental analysis. The compounds have been evaluated for antibacterial activity against *E. coli* (MTCC 443), *S. paratyphi-B* (MTCC 733), *S. aureus* (MTCC 96) and *B. Subtilis* (MTCC 441)

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

INTRODUCTION

A number of triazine derivatives containing pharmacophoric group have been reported to possess antiviral activity[1] against Enecphalomycocarditics virus (EMCV) and Japaneses encephalitis virus (JEV) both in vivo and in vitro. The s-triazine based chalcones and their derivatives have their own importance in heterocyclic chemistry due to their good biological activities[2]. Chalcones have been studied extensively because of their wide range of biological activity. They are found to be effective as antibacterial[3], antifungal[4], antiinflammatory[5] and anticancer[6] agents. Synthesis and characterization of pyrazoline derivatives has been developing field with in the realm of the heterocyclic chemistry for the past several decades because of their ready accessibility through synthesis and wide range of chemical reactivity. Pyrazoline derivatives have been found to possess wide range of therapeutic activities as antibacterial, antifungal[7], anticancer[8]. In recents years, the chemistry of pyridines and their derivatives have gained increasing attention because substituted pyridines are associated with different types of biological activities. Cyanopyridines have attracted considerable attention as they appeared of interest to possess antitubecular[9], antibacterial[10] and anticancer, antifungal[11] activities. It was therefore considered to interest to synthesized some novel s-triazine based chalcones and their derivatives.

EXPERIMENTAL

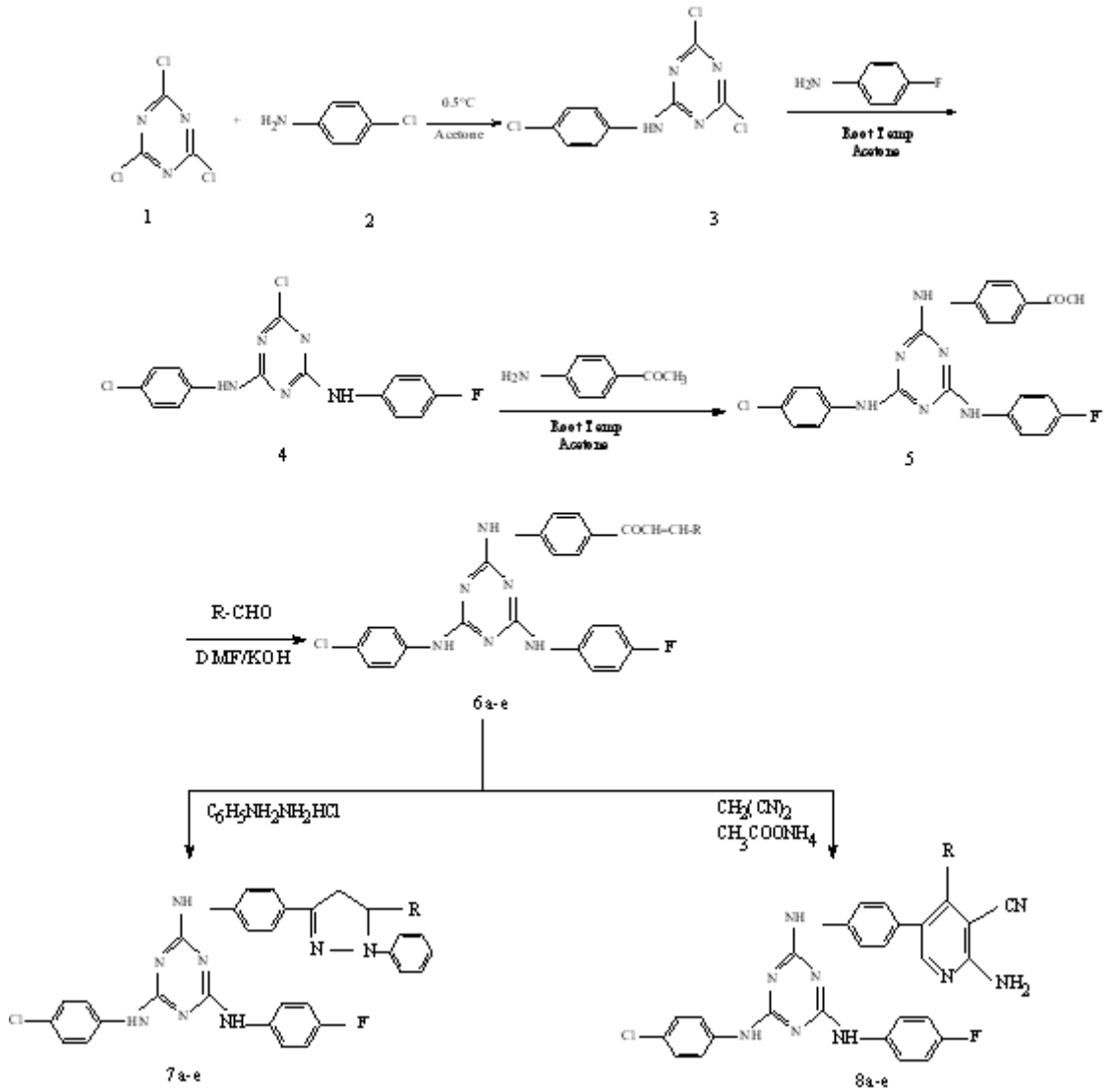
All the melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on Perkin-Elmer 237 spectrometer. ^{1}H NMR spectra on a Bruker Avance DPX 300 MHz spectrometer with $CDCl_3$ as a solvent and TMS as internal reference. Purity of the compounds was checked on TLC using silica gel-G.

Preparation of 2-(4'-chlorophenylamino)-4,6-dichloro-s-triazine (3)

4-Chloroaniline (0.01 mol in 10ml acetone) was added slowly to cyanuric chloride (0.01 mol in 30 ml acetone) with constant stirring for 4 hours at 0 to 5°C. Periodically sodium carbonate solution (0.005mol, 0.53g in 10ml 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 alcohol to give (3). Yield 90 % m.p. 220°C.

Preparation of 2-(4'-chlorophenylamino)-4-(4'-flurophenylamino)-6-chloro-s-triazine (4)

4-Fluoroanilin (0.01 mol in 10ml acetone) was added slowly compound (3) (0.01 mol in 30 ml acetone) with constant stirring for 6 hours at room temperature. Periodically sodium carbonate solution (0.005mol in 10ml 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 alcohol to give (3). Yield 85% m.p. 193°C, IR (KBr) cm^{-1}: 1035 (C-F), 805 (C-N, s-



Scheme 1:

triazine), 770 (C-Cl). ^{1}H NMR ($CDCl_3$): δ7.20-7.80 (m, 10H, Ar-H and (NH).

Preparation of 2-(4'-chlorophenylamino)-4-(4'-flurophenylamino)-6-acetylphenylamino-s-triazine (4)

4-Aminoacetophenone (0.01 mol) compound (4) (0.01 mol) were dissolved acetone (40ml). The reaction mixture was refluxed for 6 hours, cooled and poured into crushed ice. Periodically sodium carbonate solution (0.005mol in 10ml water) was added to neutralized HCl evolved during the reaction. The solid separated out was filtered, washed with water, dried and recrystallized from alcohol to give (5). Yield 79% m.p. 208°C, IR (KBr) cm^{-1}: 1658 (-C=O), 1020 (C-F), 800 (C-N, s-triazine), 786 (C-Cl). ^{1}H NMR ($CDCl_3$): δ2.6 s, (3H,-$CpCH_3$) δ 6.9-8.9 (m, 15H, Ar-H and (NH).

Preparation of 2-(4'-chlorophenylamino)-4-(4'-flurophenylamino)-6-[4-{3"-(3''',4'''-dimethoxyphenyl) 2-"-propenon-1"-yl} phenyl amino]-s-triazine (6a)

Compounds (5) (0.001 mol) was dissolved in DMF (30ml) and 3,4-dimethoxybenzaldehyde (0.01mol) was added to it. Then solution of KOH (5ml 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 alcohol to give (6a). Yield 71%, m.p. 230°C, IR (KBr) cm^{-1}: 1649 (-C=O), 1010 (C-F), 806 (C-N, s-triazine), 786 (C-H). ^{1}H NMR ($CDCl_3$): δ3.80 (s, 3H, m-OCH_3), δ3.84 (s, 3H, p-OCH_3), δ6.9 (d, IH,-CI-CH=) δ7.1-7.8 (m, 18H, Ar-H and NH), δ8.05 (d, 1H, Ar-CH=).

Similarly the remaining compounds (6b-e) were prepared by this method. Their physical data are given in Table 1.

Preparation of 2-(4'-chlorophenylamino) (4'-flurophenylamino)-6-[4'-{1"-phenyl-5"-(3"',4"'-dimethoxyphenyl) 2-"-pyrazolin-3"-yl} phenyl amino-s-triazine (7a)

Compounds (6a) (0.001mol) was dissolved in alcohol (30ml) and phenyl hydrazine hydrochloride (0.01mol) was added to it. Then solution of KOH (5ml of 40%) was added to the reaction mixture and refluxed for 6 hours. The reaction mixture was then cooled, poured into crushed ice and neutralized with

Table 1: Characterization data of compounds (6a-e), (7a-e) and (8a-e)

Compd.	R	m.p.°C	% Yield
6a	3,4-Dimethoxyphenyl	230	71
6b	4-N,N-dimehylamino phenyl amino	183	70
6c	4-N,N-dimehylamino phenyl amino	197	71
6d	2-Thienyl	180	69
6e	4-Furanyl	146	68
7a	3,4-Dimethoxyphenyl	120	67
7b	4-N,N-dimehylamino phenyl amino	135	61
7c	4-N,N-dimehylamino phenyl amino	95	62
7d	2-Thienyl	94	63
7e	4-Furanyl	100	63
8a	3,4-Dimethoxyphenyl	119	67
8b	4-N,N-dimehylamino phenyl amino	94	61
8c	4-N,N-dimehylamino phenyl amino	161	58
8d	2-Thienyl	150	60
8e	4-Furanyl	115	61

HCl. The product separated out was filtered, washed with water, dried and recrystallized from alcohol to give (7a). Yield 67%, m.p. 120°C, IR (KBr) cm^{-1}: 1573 (-C=N), 1225 (C-O-C), 1015 (C-F) 810(C-N, s-triazine), 785 (C-Cl). ^1H NMR ($CDCl_3$): δ3.1 (dd, 1G, $-CG_A$), δ3.3 (dd, 1H, $-CH_8$) δ3.80 (s, 3H, m-OCH_3), δ3.86 (s, 3H, p-OCH_3), δ5.72 (dd, 1H, -CH) δ6.8-7.8 (m, 23H, Ar-CH and NH).

Similarly the remaining compounds (7b-e) were prepared by this method. Their physical data are given in Table 1.

Preparation of 2-(4'-chlorophenylamino)-4-(4'-flurophenylamino)-6-[4'-{2"-amino-3"-cyano-4"-(3''',4'''-dimethoxyphenyl) -pyridine-6"-yl} phenylamino-s-triazine (8a)

Compounds (6a) (0.001mol) was dissolved in alcohol (25ml), malanonitrile (0.01 mol, 0.66g) and ammonium acetate (0.08mol, 6.16g) was added to it and refluxed for 8 hours. The reaction mixture was then cooled, poured into crushed ice and product separated out was filtered, washed with water, dried and recrystallized from alcohol to give (8a). Yield 66%, m.p. 119°C, IR (KBr) cm^{-1}: 3468 ($-NH_2$), 2207 (C=N), 1227 (C-O-C). 1013 (C-F), 803 (C-N, s-triazine), 776 (C-Cl), ^1H NMR ($CDCl_3$): δ3.82 (s,3H, m-OCH_3): δ3.86 (s, 3H, p-COH_3), 6.8 (s, 2H, -NH_2), 7.0 to 8.2 (m, 20H, Ar-H and NH).

Similarly the remaining compounds (8b-e) were prepared by this method. Their physical data are given in Table 1.

RESULTS AND DISCUSSION

All the synthesized compounds were screened for their antibacterial activity by using agar diffusion method[12] against *S. aureus* (MTCC 96) and *B. subtilis* (MTCC 441) Gram positive data and *E. coli* (MTCC 443) and *S. paratyphi-B* (MTCC 773) Gram negative bacteria in nutrient agar medium.

Table 2: Antibacterial activity data of compound 2a-e and 3a-e

S. No	R	Antibacterial Activity Diameter of zone of inhibition (in mm)			
		S. aureus **MTCC 96**	***B. subtilis*** **MTCC 441**	***E.coli.*** **MTCC 443**	***S.parathyphi-B*** **MTCC 773**
6a	3,4-Dimethoxy phenyl	17	10	13	10
6b	4-N,N-dimetylamino phenyl amino	17	13	14	12
6c	4-N,N-dimetylamino phenyl amino	17	15	14	11
6d	2-Thienyl	13	17	10	14
6e	2-Furanyl	-	15	16	-
7a	3,4-Dimethoxy phenyl	-	20	16	20
7b	4-N,N-dimetylamino phenyl amino	-	21	17	17
7c	4-N,N-dimetylamino phenyl amino	19	20	19	20
7d	2-Thienyl	15	20	18	20
7e	2-Furanyl	14	20	19	20
8a	3,4-Dimethoxy phenyl	16	18	18	19
8b	4-N,N-dimetylamino phenyl amino	17	20	17	17
8c	4-N,N-dimetylamino phenyl amino	15	19	15	15
8d	2-Thienyl	15	15	16	18
8e	2-Furanyl	16	15	16	15
	Ciprofloxacin (Standard Drug)	22	24	27	28

Ciprofloxacin was used as standard drugs for the comparison of antibacterial activity.

Bu visualizing activity data, it could be observed that compounds (6a), (6b), (6c), (7c), (7d), (7e), (8a), (8b), (8c), (8d) and (8e) showed moderately against *S. aureus* (MTCC 96). Compounds (6e), (7a) and (7b) were found to be inactive against *S. aureus* (MTCC 96). Compounds (6d) was found to be less active *S. aureus* (MTCC 96). Compounds (7a), (7b), (7c), (7d), (7e), (8a), (8b) and (8c) were found to be active against *B. subtilis* (MTC 441). Compounds (6c), (6d), (6e), (8d) and (8e) were found to be moderately active against *B. subtilis* (MTCC 441), where as compound (6a) and (6b) were found to be less active against *B. subilis* (MTCC 441). Compounds (6e), (7a), (7b), (7c), (7d), (7e), (8a), (8b), (8c), (8d) and (8e) were found to be moderately active against *E. coli* (MTCC 443). Compounds (6a), (6b), (6c) and (6d) were found to be less active against *E. coli* (MTCC 443). Compounds (7a), (7c), (7d) and (7e) were found to be active against *S. paratyphi-B* (MTCC 733). Compounds (6a), (6b), (6c) and (6d) were found to be less active against *S. paratyphi-B* (MTCC 733). where as compound (6e) was found to be inactive against *S. paratyphi-B* (MTCC 733).

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