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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NEW FLUORINE CONTAINING *S*-TRIAZINE BASED CHALCONES AND ITS DERIVATIVES

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ABSTRACT

Chalcones, 2,4-bis-(4'-fluorophenylamino)-6-[4'-{3''-(phenyl / 4'''-substituted phenyl)-2''-propenon-1'-yl} phenylamino]-*s*-triazine (6a-f) have been prepared according to Claisen-Schmidt condensation. Further these chalcones (6a-f) on reaction with malononitrile gives cyanopyridines (7a-f) and on reaction with guanidine nitrate gives aminopyrimidines (8a-f). The structures of the newly synthesized compounds have been characterized on the basis of their IR and ^{1}H NMR spectral data. The synthesized compounds have been screened for their antibacterial and anticancer activities.

Keywords: Chalcones, cyanopyridines, aminopyrimidines, antibacterial activity, anticancer activity

INTRODUCTION

Chemistry of chalcone[1] has been recognized as a significant field of study. Chalcones possess analgesic[2], antiulcer[3] and antitumor[4] activities. Cyanopyridines have attracted considerable attention, as they possess antitubercular[5] and antihypertensive[6] activities, while amino pyrimidine derivatives possess antifungal[7], antiulcer[8] and antitumor[9] activities. In the present work, we report the reaction of cyanuric chloride **(1)** with 4-fluoroaniline **(2)** at 0-5ºC to give **(3)**, which reacts with 4-fluoroaniline at room temperature to give **(4).** Compound **(4)** is further treated with 4-aminoacetophenone to give 2,4-bis-(4'-fluorophenylamino)-6-(4'-acetylphenylamino)-*s*-triazine **(5)**. Compound **(5)** on reaction with different aromatic aldehydes to give chalcones **(6a-f)**. Further these chalcones on reaction with malononitrile in the presence of ammonium acetate and guanidine nitrate to give cyanopyridines **(7a-f)** and aminopyrimidines **(8a-f)** respectively (**SCHEME – I**).

EXPERIMENTAL

Melting points were taken in an open capillary and are uncorrected. The IR spectra were recorded on Perkin Almer 237 spectrometer. ^{1}H NMR spectra were recorded on the Bruker Avance 400 MHz spectrometer, using TMS as internal reference and $CDCl_3$ as a solvent. Purity of the compounds was checked on TLC using precoated Merck Silica Gel 60 F_{254} aluminium foil.

Preparation of 2-(4'-fluorophenylamino)-4,6-dichloro-*s*-triazine (3):

4-Fluoroaniline (0.01 mol, 1.11g) was added slowly to cyanuric chloride (0.01 mol, 1.845g) in acetone (30 mL) with constant stirring for 4 h at 0-5ºC. Periodically, sodium carbonate solution (0.005 mole, 0.53g in 20 mL water) was added drop wise to neutralized HCl evolved during the reaction. Finally, the content was poured into crushed ice. The solid separated out was filtered, washed with water and recrystallised from alcohol to give **(3)**.

IR (KBr) cm^{-1}: C-F (1067), C-N, s-triazine (807), C-Cl (769).

Preparation of 2,4-bis-(4'-fluorophenylamino)-6-chloro-*s*-triazine (4):
4-Fluoroaniline (0.01mol, 1.11g) was added slowly to 2-(4'-fluorophenylamino)-4,6-dichloro-s-triazine (0.01 mole, 2.59g) in acetone (35 mL) with constant stirring for 6 h at room temperature. Periodically, sodium carbonate solution (0.005 mole, 0.53g in 20 mL water) was added drop wise to neutralized HCl evolved during the reaction. Finally, the content was poured into crushed ice. The solid separated out was filtered, washed with water and recrystallised from alcohol to give **(4)**.
IR (KBr) cm^{-1}: C-F (1060), C-N, s-triazine (808), C-Cl (770).

Preparation of 2,4-bis-(4'-fluorophenylamino)-6-(4'-acetylphenylamino)-*s*-triazine (5):
4-Aminoacetophenone (0.01 mol, 1.35g) and 2,4-bis-(4'-fluorophenylamino)-6-chloro-s-triazine (0.01 mol, 3.335g) were dissolved in 40 mL acetone. The reaction mixture was refluxed for 6 h. Periodically, sodium carbonate solution (0.005 mol, 0.53g in 20 mL water) was added drop wise to neutralized HCl evolved during the reaction. Finally, the reaction mixture was cooled and poured into crushed ice. The solid separated out was filtered, washed with water and recrystallised from alcohol to give **(5)**.
IR (KBr) cm^{-1}: C=O (1665), C-F (1057), C-N, s-triazine (804); ^{1}H NMR ($CDCl_3$) δ ppm : 2.6 (s, 3H, -$COCH_3$), 7.20 to 7.90 (m, 13 Ar-H and 3-NH).

Preparation of 2,4-bis-(4'-fluorophenylamino)-6-[4'-{3''-(4'''-methoxyphenyl)-2''-propenon-1''-yl} phenylamino]-*s*-triazine (**6f**):
2,4-Bis-(4'-fluorophenylamino)-6-(4'-acetylphenylamino)-*s*-triazine **(5)** (0.01 mol) was dissolved in DMF (30 mL). Then 40% KOH solution and 4-methoxybenzaldehyde (0.01 mol) in DMF were added to the reaction mixture with constant stirring at room temperature. After 24 h the reaction mixture was poured into crushed ice and neutralized with HCl. The product separated out was filtered, washed with water and recrystallised from alcohol. Similarly remaining compounds **(6a-e)** were prepared by the above method.
IR (KBr) cm^{-1}: C=O (1663), C-N (1353), C-F (1160), C-O-C (1033); ^{1}H NMR ($CDCl_3$) δ ppm : 3.85 (s, 3H, -OCH_3), 6.90 (d, 1H, -CO-CH=), 7.0 to 7.75 (m, 19H, Ar-H and NH), 8.1 (d, 1H, Ar-CH=).

Preparation of 2,4-bis-(4'-fluorophenylamino)-6-[4'-{2"-amino-3"-cyano-4"-(4'"-methoxyphenyl) pyridine-6"-yl} phenylamino]-*s*-triazine (**7f**):
A mixture of 2,4-bis-(4'-fluorophenylamino)-6-[4'-{3"-(4'"-methoxyphenyl)-2"-propenon-1"-yl} phenylamino]-*s*-triazine **(6f)** (0.01 mol) in 40 mL alcohol, malononitrile (0.01 mol) and ammonium acetate (0.08 mol) was refluxed for 8 h. Then the reaction mixture was cooled and poured into crushed ice. The product separated out was filtered, washed with water and recrystallised from alcohol. Similarly remaining compounds **(7a-e)** were prepared by the above method.
IR (KBr) cm^{-1}: -NH_2 (3406), C≡N (2200), C-F (1180), C-O-C (1029); ^{1}H NMR ($CDCl_3$) δ ppm : 3.9 (s, 3H, -OCH_3), 5.2 (s, 2H, -NH_2), 7.0 to 8.0 (m, 20H, Ar-H and NH).

Preparation of 2,4-bis-(4'-fluorophenylamino)-6-[4'-{2"-amino-6"-(4'"-methoxyphenyl) pyrimidine-4"-yl} phenylamino]-*s*-triazine (8f):
A mixture of 2,4-bis-(4'-fluorophenylamino)-6-[4'-{3"-(4'"-methoxyphenyl)-2"-propenon-1"-yl} phenylamino]-*s*-triazine **(6f)** (0.01 mol) in 50 mL alcohol, guanidine nitrate (0.01 mol) and 40% KOH solution (2 mL) was refluxed for 10 h. Then the reaction mixture was cooled and poured into crushed ice. The product separated out was filtered, washed with water and recrystallised from alcohol. Similarly remaining compounds **(8a-e)** were prepared by the above method.
IR (KBr) cm^{-1}: -NH_2 (3408), C=N (1650), C-N (1349), C-F (1175), C-O-C (1029); ^{1}H NMR ($CDCl_3$) δ ppm : 3.9 (s, 3H, -OCH_3), 5.1 (s, 2H, -NH_2), 7.0 to 8.0 (m, 20H, Ar-H and NH).

RESULTS AND DISCUSSION

Antibacterial activity

All the synthesized compounds have been screened for their antibacterial activity against *S. aureus* (MTCC 96), *B. subtilis* (MTCC 441) (Gram-positive bacteria) and *E. coli* (MTCC 443), *S. paratyphi-B* (MTCC 733) (Gram- negative bacteria) by using agar diffusion method[10]. The zone of inhibition was measured in mm. Under similar conditions, controlled experiment was carried out using Ciprofloxacin as a standard drug for comparison **(Table-No. 2)**.

In the series of aminopyrimidine **(8a-f)**, it has been observed that the compound **(8f)** containing R = 4-methoxyphenyl showed remarkable activity against *E. coli* and *S. paratyphi-B* (Gram-negative bacteria); where as the same compound was found to be inactive against (Gram-positive bacteria). In the series of chalcones **(6a-f)** compound **(6c)** containing R = 4-ethoxyphenyl and compound **(6f)** containing R = 4-methoxyphenyl were found to be moderately active against (Gram-negative bacteria), while in cyanopyridines **(7a-f)** compound **(7d)** containing R = 4-fluorophenyl found to be moderately active against (Gram-negative) bacteria. Remaining all compounds were found to be less active or inactive against all bacterial strain.

Anticancer activity

Total 4 compounds were selected for their primary anticancer assay against a panel of 3 cell line MCF-7, NCI-H460 and SF-268 i.e. Breast, Lung and CNS cancer **(Table-No. 3)**. The compounds **(5)**, **(6b)**, **(6e)** and **(6f)** are further selected for the testing against a panel of 60 human cancer cell lines.

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Table-1: Physical data of compounds (6a-f), (7a-f) and (8a-f)

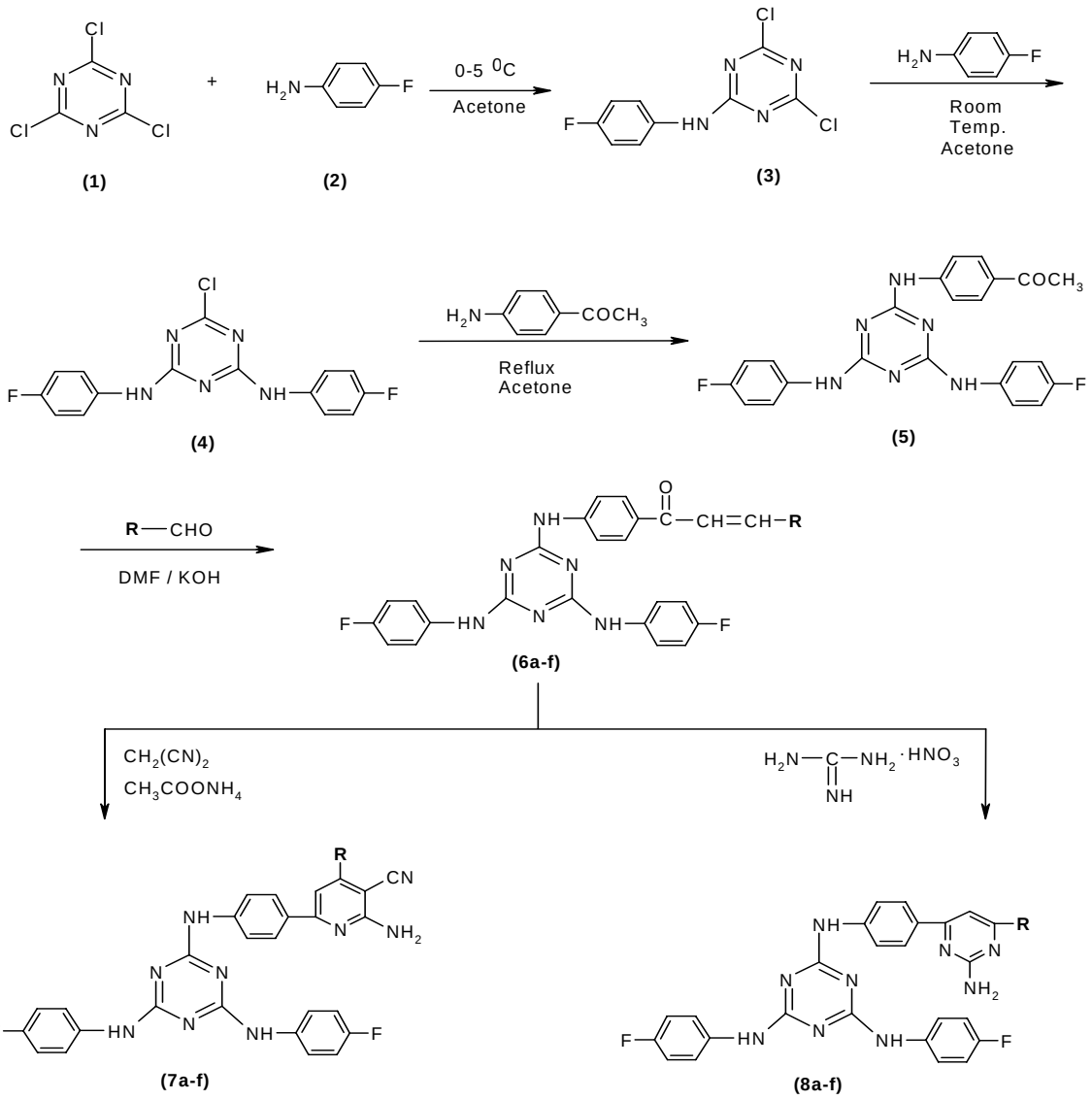
Comp.	R	MP (˚C)	Yield (%)
6a	Phenyl	136	78
6b	4-Chlorophenyl	119	76
6c	4-Ethoxyphenyl	129	70
6d	4-Fluorophenyl	130	68
6e	4-N,N-dimethylaminophenyl	190	72
6f	4-Methoxyphenyl	176	82
7a	Phenyl	260	69
7b	4-Chlorophenyl	158	64
7c	4-Ethoxyphenyl	273	62
7d	4-Fluorophenyl	272	65
7e	4-N,N-dimethylaminophenyl	226	70
7f	4-Methoxyphenyl	258	70
8a	Phenyl	189	67
8b	4-Chlorophenyl	173	55
8c	4-Ethoxyphenyl	161	68
8d	4-Fluorophenyl	195	70
8e	4-N,N-dimethylaminophenyl	219	66
8f	4-Methoxyphenyl	218	58

Table-2: Antibacterial activity data of compounds (6a-f), (7a-f) and (8a-f)

Sr. No.	R	Antibacterial Activity			
		Diameter of zone of inhibition (in mm)			
		S. aureus **MTCC 96**	***B. subtilis*** **MTCC 441**	***E. coli*** **MTCC 443**	***S. paratyphi-B*** **MTCC 733**
6a	Phenyl	10	14	16	14
6b	4-Chlorophenyl	10	-	16	14
6c	4-Ethoxyphenyl	-	13	17	-
6d	4-Fluorophenyl	-	11	11	-
6e	4-N,N-dimethylaminophenyl	-	12	10	-
6f	4-Methoxyphenyl	-	12	17	13
7a	Phenyl	-	-	10	12
7b	4-Chlorophenyl	-	-	11	10
7c	4-Ethoxyphenyl	-	-	-	13
7d	4-Fluorophenyl	-	10	-	19
7e	4-N,N-dimethylaminophenyl	-	14	16	10
7f	4-Methoxyphenyl	-	12	-	-
8a	Phenyl	-	11	10	-
8b	4-Chlorophenyl	-	10	-	-
8c	4-Ethoxyphenyl	-	-	10	-
8d	4-Fluorophenyl	-	10	-	-
8e	4-N,N-dimethylaminophenyl	-	-	12	12
8f	4-Methoxyphenyl	-	-	20	19
Ciprofloxacin (Standard Drug)		22	20	24	25

Table-3: Anticancer activity data of compounds

Compd. No.	R	% Growth			Selected for 60 cell testing
		(Breast) MCF-7	(Lung) NCI-H460	(CNS) SF-268	
5	Ketone	56	5	19	Y
6b	4-Chlorophenyl	20	43	57	Y
6e	4-N,N-dimethylaminophenyl	40	10	49	Y
6f	4-Methoxyphenyl	10	1	28	Y



SCHEME-I

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"We can't solve problems by using the same kind of thinking we used when we created them."

- **Albert Einstein**