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Utility of s-triazine nucleus in the synthesis of novel heterocyclic systems as potential antibacterial agents

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ABSTRACT

Chalcones, 2,4-bis-(4'-fluorophenylamino)-6-[4'-{3''-(substituted phenyl)-2''-propenon-1''-yl}phenylamino]-*s*-triazine **(6a-f)** have been prepared from ketone (5) on treatment with different aromatic aldehydes. These chalcones **(6a-f)** on cyclisation with guanidine nitrate and malono nitrile give the corresponding aminopyrimidine **(7a-f)** and cyanopyridine**(8a-f)** derivatives respectively. All the synthesized compounds have been screened for their antibacterial activities against *S.aureus* (MTCC 96), *B.subtilis*(MTCC 441), *E.coli* (MTCC 443) and *S.paratyphi-B* (MTCC 733), using cup-plate agar diffusion method. The structures of these compounds have been established on the basis of spectral studies and elemental analysis.

KEYWORDS

Chalcones;
Aminopyrimidines;
Cyanopyridines;
Antibacterial activity.

INTRODUCTION

Although a large number of *s*-triazine analogs have been synthesized, there still exists much scope for the synthesis of *s*-triazine derivatives possessing different pharmacophores[1-3].

Literature survey reveals that pyridine and pyrimidine is the parent of a series of compounds that are important in medicinal and industrial chemistry. These observation led us to synthesize some new *s*-triazinyl based chalcones[4,5] and its corresponding cyanopyridine and aminopyrimidine derivatives.

Chalcones constitute an important class of naturally occurring compounds, which occupy a central place in the biogenesis. They are also used as intermediate for the synthesis of various other compounds. Chalcones possess some interesting biological properties such as antibacterial[6], antifungal[7], insecticidal[8], anaesthetic[9], ulcerogenic[10] etc… Aminopyrimidine derivatives have been reported to possess hypnotic[11], antiulcer[12], anticonvulsant[13] and herbicidal[14] properties. While cyanopyridine derivatives possess wide range of therapeutic activities such as insecticidal[15], antitubercular[16], pesticidal[17] and analgesic[18].

In the present work, we report the reaction of cyanuric chloride **(1)** with 4-fluoroaniline 2 at 0-5 ºC 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'-fluorophenyl amino)-6-(4'-acetylphenyl amino)-*s*-triazine **(5)**. Compond **(5)** on reaction with different aromatic aldehydes to gives chalcones **6(a-f)**. Further these

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

Compd. no.	R	M.P. (°C)	Yield (%)	Mol. formula	Elemental analysis found/Calcd. %			
					C		N	
6a	2-Chlorophenyl	120	74	$C_{30}H_{21}ClF_2N_6O$	64.87	64.92	15.09	15.14
6b	3-Chlrophenyl	117	80	$C_{30}H_{21}ClF_2N_6O$	64.90	64.92	15.12	15.14
6c	3-Bromophenyl	120	78	$C_{30}H_{21}BrF_2N_6O$	60.08	60.10	14.00	14.02
6d	3-Methoxyphenyl	115	73	$C_{31}H_{24}F_2N_6O_2$	67.58	67.63	15.22	15.27
6e	3-Phenoxyyphenyl	116	68	$C_{36}H_{26}F_2N_6O_2$	70.56	70.58	13.70	13.72
6f	3,4-Dimethoxyphenyl	113	72	$C_{32}H_{26}F_2N_6O_3$	66.16	66.20	14.45	14.48
7a	2-Chlorophenyl	172	69	$C_{31}H_{22}ClF_2N_9$	62.63	62.67	21.20	21.22
7b	3-Chlrophenyl	176	70	$C_{31}H_{22}ClF_2N_9$	62.65	62.67	21.17	21.22
7c	3-Bromophenyl	155	64	$C_{31}H_{22}BrF_2N_9$	58.27	58.30	19.70	19.74
7d	3-Methoxyphenyl	161	62	$C_{32}H_{25}F_2N_9O$	63.42	63.47	20.77	20.82
7e	3-Phenoxyyphenyl	126	69	$C_{37}H_{27}F_2N_9O$	66.52	66.56	18.87	18.89
7f	3,4-Dimethoxyphenyl	121	70	$C_{33}H_{27}F_2N_9O_2$	63.91	63.94	20.32	20.35
8a	2-Chlorophenyl	165	67	$C_{33}H_{22}ClF_2N_9$	64.10	64.12	20.38	20.40
8b	3-Chlrophenyl	164	58	$C_{33}H_{22}ClF_2N_9$	64.09	64.12	20.36	20.40
8c	3-Bromophenyl	136	55	$C_{33}H_{22}BrF_2N_9$	59.78	59.81	19.01	19.03
8d	3-Methoxyphenyl	139	68	$C_{34}H_{25}F_2N_9O$	66.53	66.55	20.52	20.55
8e	3-Phenoxyyphenyl	189	70	$C_{39}H_{27}F_2N_9O$	69.31	69.33	18.63	18.66
8f	3,4-Dimethoxyphenyl	175	66	$C_{35}H_{27}F_2N_9O_2$	65.29	65.31	19.57	19.59

chalcones on reaction with guanidine nitrate in the presence of alkali and with malononitrile in the presence of ammonium acetate to give aminopyrimidines **7(a-f)** and cyanopyridines **8(a-f)** respectively (SCHEME 1 TABLE 1). The structures of the newly synthesised compounds have been identified on the basis of their elemental analysis, IR spectra and ^{1}H NMR spectra.

EXPERIMENTAL

All the melting points were taken in an 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, using TMS as internal reference. TLCs were performed on precoated Merck Silica Gel 60 F_{254} Aluminium foil.

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

4-Fluoroaniline (0.01mole, 1.11g) was added slowly to cyanuric chloride (0.01 mole, 1.845g) in acetone (30ml) with constant stirring for 4 hours at 0-5 ºC. Periodically sodium carbonate solution (0.005 mole, 0.53g in 20ml water) was added drop wise to neutralized HCl evolved during the reaction. Finally the contents were poured into crushed ice. The solid separated out was filtered, washed with water and recrystallised from alcohol to give **(3)**, m.p. 224ºC.

Preparation of 2,4-bis-(4'-fluorophenylamino)-6-chloro-*s*-triazine (4)

4-Fluoroaniline (0.01mole, 1.11g) was added slowly to 2-(4'-fluorophenylamino)-4,6-dichloro-s-triazine (0.01mole, 2.59g) in acetone(35ml) with constant stirring for 6 hours at room temperature. Periodically sodium carbonate solution (0.005 mole, 0.53g in 20ml water) was added drop wise to neutralized HCl evolved during the reaction. Finally the contents were poured into crushed ice. The solid separated out was filtered, washed with water and recrystallised from alcohol to give **(4)**, m.p. 212°C. IR(KBr)cm^{-1}: 1010(C-F), 805 (C-N, s-triazine), 770(C-Cl)

Preparation of 2,4-bis-(4'-fluorophenylamino)-6-(4'-acetylphenylamino)-*s*-triazine(5)

4-Aminoaceto phenone (0.01mole, 1.35g) and 2,4-bis-(4'-fluoro phenylamino)-6-chloro-s-triazine (0.01mole, 3.335g) were dissolved in 40ml acetone. The reaction mixture was refluxed for 6 hours. Periodically sodium carbonate solution (0.005mole, 0.53g in 20ml 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)**, m.p.195°C.

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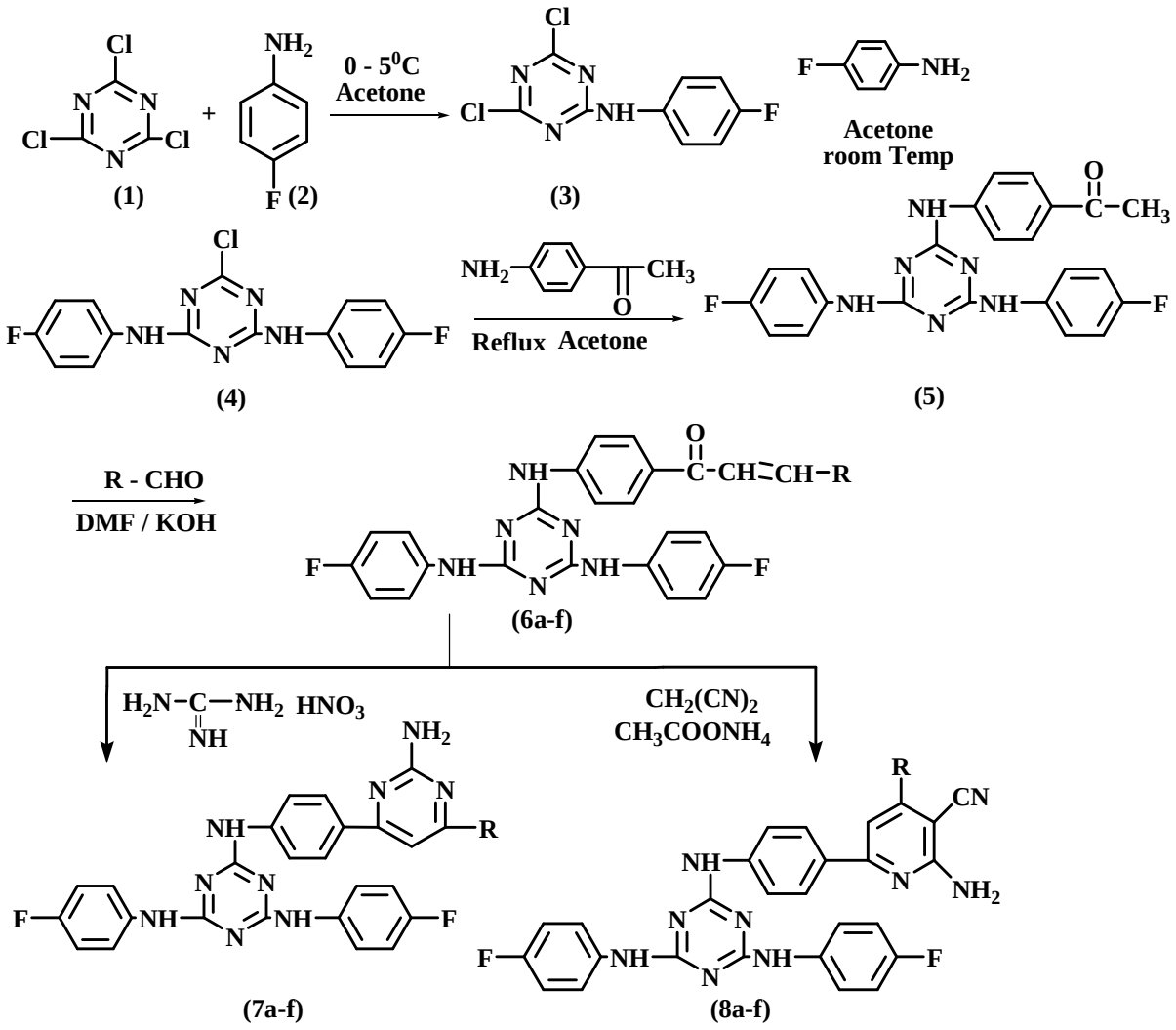

SCHEME 1

IR (KBr)cm^{-1} : 1662(C=O), 1055(C-F), 805(C-N, s-triazine); ^{1}H NMR ($CDCl_3$) δppm : 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''-(3'",4'"dimethoxyphenyl)-2''-propenon-1''yl} phenylamino]-*s*-triazine (6f)

2,4-Bis-(4'-fluorophenylamino)-6-(4'-acetyl phenylamino)-s-triazine(0.01mole, 4.32g) was dissolved in DMF (30ml) and 3,4-dimethoxybenzaldehyde (0.01mole, 1.66g) in DMF was added to the reaction mixture with constant stirring at room temperature. Then 40% KOH in distilled water 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 and recrystllised from alcohol to give **(6f)**, m.p. 113°C. Similarly remaining compounds were prepared by this method.

IR (KBr): cm^{-1} 1646 (C=O), 1089 (C-F), 1025 (C-O-C), 804(C-N, s-triazine); ^{1}H NMR ($CDCl_3$) δppm : 3.85(s, 3H, m-OCH_3), 3.96 (s, 3H, p-OCH_3), 6.90(d, 1H, -CO-CH=), 7.0 to 7.75(m, 15 Ar-H and 3 -NH), 8.1 (d, 1H, Ar-CH=).

Preparation of 2,4-bis-(4'-fluorophenylamino)-6-[4'-{2''amino-6''-(3'"-methoxyphenyl)-pyrimidine-4''-yl} phenylamino]-*s*-triazine (7d)

A mixture of 2,4-bis-(4'-fluorophenylamino)-6-[4'-{3''-(3'''-methoxyphenyl)-2''-propenone-1''-yl} phenylamino]-*s*-triazine **(6d)** (0.005 mole, 2.75g) in 25

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

Compd. no.	R	Antibacterial activity Zone of Inhibition in mm			
		S.aureus(MTCC 96)	*B.subtilis*(MTCC 441)	*E.coli*(MTCC 443)	*S.paratyphi-B*(MTCC 733)
6a	2-Chlorophenyl	-	-	13	-
6b	3-Chlrophenyl	10	10	11	-
6c	3-Bromophenyl	11	13	11	-
6d	3-Methoxyphenyl	14	-	-	10
6e	3-Phenoxyyphenyl	14	12	12	-
6f	3,4-Dimethoxyphenyl	-	11	10	-
7a	2-Chlorophenyl	11	18	-	10
7b	3-Chlrophenyl	10	-	-	-
7c	3-Bromophenyl	10	-	-	10
7d	3-Methoxyphenyl	-	-	11	-
7e	3-Phenoxyyphenyl	14	-	-	-
7f	3,4-Dimethoxyphenyl	-	-	12	-
8a	2-Chlorophenyl	17	-	-	-
8b	3-Chlrophenyl	12	17	-	-
8c	3-Bromophenyl	12	-	-	-
8d	3-Methoxyphenyl	11	-	-	-
8e	3-Phenoxyyphenyl	-	-	-	-
8f	3,4-Dimethoxyphenyl	10	10	-	-
Standard drug	Ciprofloxacin	22	20	24	25

ml dioxane, guanidine nitrate (0.005 mole, 0.66g) and 40% KOH solution (1ml) was refluxed for 10 hours. Then the reaction mixture was cooled and poured into crushed ice. The product separated out was filtered, washed with water and recrystallised from alcohol to give **(7d)**, m.p. 117 °C. Similarly remaining compounds were prepared by this method.

IR (KBr)cm^{-1}: 3408(-NH), 1650(C=N), 1349(C-N), 1175(C-F), 1029(C-O-C); ^{1}H NMR ($CDCl_3$): δppm, 3.9(s, 3H, m-OCH_3), 5.1(s, 2H, -NH_2), 7.0 to 8.0(m, 17 Ar-H and 3 -NH).

Preparation of 2, 4-bis-(4'-fluorophenylamino)-6-[4'-{2''-amino-3''-cyano-4''-(2'''-chlorophenyl) pyridine-6''-yl} phenylamino]-*s*-triazine (8a)

A mixture of 2,4-bis-(4'-fluorophenylamino)-6-[4'-{3''-(2'''-chlorophenyl)-2''-propenone-1''yl} phenylamino]-s-triazine **(6a)** (0.005mole, 2.77g) in 40 ml alcohol, malanonitrile (0.01mole, 0.66g) and ammonium acetate was refluxed for 8 hours. Then the reaction mixture was cooled and poured into crushed ice. The product separated out was filtered, washed with water and recrystallised from alcohol to give **(8a)**, m.p. 165°C. Similarly remaining compounds were prepared by this method.

IR (KBr) cm^{-1}: 3406(-NH_2), 2200(C=N), 1180(C-F), 1029(C-O-C); ^{1}H NMR ($CDCl_3$) δ ppm : 5.2(s, 2H, -NH_2), 7.0 to 8.0 (m, 17 Ar-H and 3 -NH).

Antibacterial activity

All the synthesized compounds were screened for their antibacterial activity by using agar diffusion method[19] against *S.aureus* (MTCC 96), *B.subtilis* (MTCC 441) (Gram positive) and *E.coli* (MTCC 443), *S.paratyphi-B*(MTCC 733)(Gram negative) bacteria in nutrient agar medium. The sterilized agar media was poured into petridishes and allowed to solidify. On the surface of the agar media microbial suspension was spread over to solidify. A stainless steel cylinder (pre-sterilized) was used to bore the cavities. All the synthesised compounds (100μg/ml) in DMF were placed serially in the cavities, with the help of micropipette. It is then allowed to diffuse for 10 minutes in refrigerator. The plates were incubated at 37 °C for 24 hours. After incubation the diameter of zone of inhibition was measured in mm. Under similar conditions controlled experiment was carried out by using Ciprofloxacin as standard drug for comparison. All the antibacterial activity data are presented in TABLE 2.

RESULT AND DISCUSSION

From the antibacterial activity data it has been observed that the compound**(8a)** bearing R=2-chloro phenyl found active against *S.aureus*(MTCC 96); where as compounds **(6d)**, **(6e)** and **(7e)** bearing R=3-methoxyphenyl and 3-phenoxyphenyl respectively were

found to be moderately active against same bacteria. The remaining compounds are less active or inactive against *S.aureus*(MTCC 96).

Compound**(7a)** and **(8b)** bearing R=2-chlorophenyl and 3-chlorophenyl were found active against *B.subtilis* (MTCC 441). While remaining compounds were found to moderately active or inactive against the same bacteria.

In case of Gram-negative bacteria like *E.coli* (MTCC 443) compound**(6a)** contaning R=2-chloro phenyl was found moderate-y active. Where as remaining compounds were less active or inactive against same bacteria. In case of Gram-negative bacteria like *S.paratyphi-B*(MTCC 733) all the compounds were found less active or inactive.

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