

Synthesis and Antibacterial Activity of 2-Phenyl Amino-4-(Aryl Thio Ureido/Aryl Ureido)-6-[[4'-(2'',4''-Dichloro-5''-Fluoro Phenyl)-6'-(3'',4'',5''-Trimethoxy Phenyl) Pyrimidine-2'-yl]Amino]-s-Triazine

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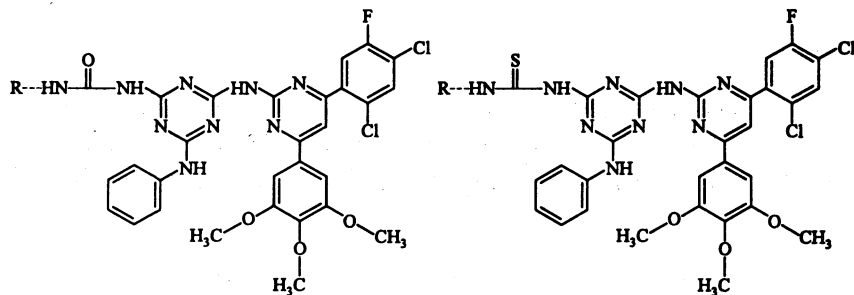
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Some new s-triazine derivatives have been prepared by the condensation of aniline and cyanuric chloride giving 2-phenyl amino-4,6-dichloro-s-triazine, which on reaction with aryl thio ureido/aryl ureido gives 2-phenyl amino-4-aryl thio ureido/aryl ureido-6-chloro-s-triazine which on further reaction with 2-amino-4-(2',4'-dichloro-5'-fluoro phenyl)-6-(3',4',5'-trimethoxy phenyl) pyrimidine gives the title compound. The structure of the product has been characterised by elemental analysis and spectral data. The products have been screened for their antibacterial activity against *Staphylococcus aureus* and *Escherichia coli*.

Key Words: Synthesis, Antibacterial activity, s-Triazine derivatives.

INTRODUCTION

Chalcone¹⁻³ has been associated with diverse antibacterial activity. The biological significance of the pyrimidine derivative⁴⁻⁶ has led us to the synthesis⁷⁻¹¹ of substituted pyrimidines. Pyrimidine is the basic nucleus in DNA and RNA. Urea¹² and thiourea¹³ of different aryl amines are associated with a wide range of pharmacological activities¹⁴. Several workers have investigated s-triazine nucleus as potential therapeutic agent for diseases due to bacteria¹⁵. s-Triazine derivatives show tubercular and diuretic¹⁶ properties too. In the present work we have reported the synthesis of s-triazine derivatives and their bacterial activities having the following general structures 1 and 2.



[1]

[2]

(1)

(2)

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. Purity of compounds was checked by TLC using silica gel-G. IR spectra were recorded on Perkin-Elmer-272 spectrophotometer. ^1H NMR spectra (CDCl_3) were recorded on Bruker Avance DPX-200 MHz instrument. (Chemical shifts are given in δ ppm). The physical and analytical data are given in Tables 1 and 2.

TABLE-1
ANALYTICAL AND PHYSICAL DATA OF THE COMPOUNDS

Compound No.	R	m.f.	m.p. (°C)	Elemental analysis %, Found (Calcd.)	
				C	N
Va	Phenyl	$\text{C}_{33}\text{H}_{28}\text{N}_9\text{O}_4\text{Cl}_2\text{F}$	265	57.66 (57.69)	17.30 (17.30)
Vb	2-Chloro phenyl	$\text{C}_{35}\text{H}_{27}\text{N}_9\text{O}_4\text{Cl}_3\text{F}$	136	55.05 (55.08)	16.50 (16.52)
Vc	3-Chloro phenyl	$\text{C}_{35}\text{H}_{27}\text{N}_9\text{O}_4\text{Cl}_3\text{F}$	117	55.06 (55.08)	16.51 (16.52)
Vd	4-Chloro phenyl	$\text{C}_{35}\text{H}_{27}\text{N}_9\text{O}_4\text{Cl}_3\text{F}$	183	55.06 (55.08)	16.50 (16.52)
Ve	3-Methoxy phenyl	$\text{C}_{36}\text{H}_{30}\text{N}_9\text{O}_5\text{Cl}_2\text{F}$	121	56.98 (56.99)	16.61 (16.62)
Vf	4-Methoxy phenyl	$\text{C}_{36}\text{H}_{30}\text{N}_9\text{O}_5\text{Cl}_2\text{F}$	119	56.99 (56.99)	16.60 (16.62)
Vg	2-Nitro phenyl	$\text{C}_{35}\text{H}_{27}\text{N}_{10}\text{O}_6\text{Cl}_2\text{F}$	98	54.30 (54.33)	18.10 (18.11)
Vh	4-Nitro phenyl	$\text{C}_{35}\text{H}_{27}\text{N}_{10}\text{O}_6\text{Cl}_2\text{F}$	119	54.31 (54.33)	18.10 (18.11)
Vi	4-Methyl phenyl	$\text{C}_{36}\text{H}_{30}\text{N}_9\text{O}_4\text{Cl}_2\text{F}$	117	58.21 (58.22)	16.96 (16.98)
Vj	4-Bromo phenyl	$\text{C}_{35}\text{H}_{27}\text{N}_9\text{O}_4\text{BrCl}_2\text{F}$	146	52.03 (52.04)	15.60 (15.61)
Vk	4-Phenoxy phenyl	$\text{C}_{41}\text{H}_{32}\text{N}_9\text{O}_5\text{Cl}_2\text{F}$	112	60.00 (60.00)	15.33 (15.36)
Vi	4-Sulphonic phenyl	$\text{C}_{35}\text{H}_{28}\text{N}_9\text{O}_7\text{SCl}_2\text{F}$	94	51.96 (51.98)	15.56 (15.59)
Vm	3-Chloro-4-fluoro phenyl	$\text{C}_{35}\text{H}_{26}\text{N}_9\text{O}_4\text{Cl}_3\text{F}_2$	103	53.80 (53.81)	16.14 (16.14)
Vn	3,4-Dichloro phenyl	$\text{C}_{35}\text{H}_{26}\text{N}_9\text{O}_4\text{Cl}_4\text{F}$	107	52.66 (52.69)	15.80 (15.80)

Compound No.	R	m.f.	m.p. (°C)	Elemental analysis %, Found (Calcd.)	
				C	N
Vo	4-(2'-propyl) phenyl	C ₃₈ H ₃₄ N ₉ O ₄ Cl ₂ F	274	59.05 (59.06)	16.56 (16.58)
VIa	Phenyl	C ₃₅ H ₂₈ N ₉ O ₃ SCl ₂ F	262	56.43 (56.45)	16.91 (16.93)
VIb	2-Chloro phenyl	C ₃₅ H ₂₇ N ₉ O ₃ SCl ₃ F	178	53.93 (53.94)	16.15 (16.18)
VIc	3-Chloro phenyl	C ₃₅ H ₂₇ N ₉ O ₃ SCl ₃ F	121	53.92 (53.94)	16.16 (16.18)
VI d	4-Chloro phenyl	C ₃₅ H ₂₇ N ₉ O ₃ SCl ₃ F	115	53.94 (54.94)	16.17 (16.18)
VIe	2-Methoxy phenyl	C ₃₆ H ₃₅ N ₉ O ₄ SCl ₂ F	122	55.80 (55.81)	16.25 (16.27)
VI f	3-Methoxy phenyl	C ₃₆ H ₃₀ N ₉ O ₄ SCl ₂ F	117	55.80 (55.81)	16.25 (16.27)
VI g	4-Methoxy phenyl	C ₃₆ H ₃₀ N ₉ O ₄ SCl ₂ F	108	55.81 (55.81)	16.27 (16.27)
VI h	4-Ethoxy phenyl	C ₃₇ H ₃₂ N ₉ O ₄ SCl ₂ F	132	56.33 (56.34)	15.98 (15.98)
VI i	4-Nitro phenyl	C ₃₅ H ₂₇ N ₁₀ O ₅ SCl ₂ F	108	53.23 (53.23)	17.73 (17.74)
VI j	2-Methyl phenyl	C ₃₆ H ₃₀ N ₉ O ₃ SCl ₂ F	252	56.98 (56.99)	16.61 (16.62)
VI k	3-Methyl phenyl	C ₃₆ H ₃₀ N ₉ O ₃ SCl ₂ F	158	56.98 (56.99)	16.60 (16.62)
VI l	4-Methyl phenyl	C ₃₆ H ₃₀ N ₉ O ₃ SCl ₂ F	118	56.99 (56.99)	16.61 (16.62)
VI m	4-Bromo phenyl	C ₃₅ H ₂₇ N ₉ O ₃ SBrCl ₂ F ₂	105	51.02 (51.03)	15.29 (15.30)
VI n	4-Phenoxy phenyl	C ₄₁ H ₃₂ N ₉ O ₄ SCl ₂ F ₂	159	58.83 (58.85)	15.06 (15.07)
VI o	3-Chloro-4-fluoro phenyl	C ₄₁ H ₂₆ N ₉ O ₃ SCl ₃ F ₂	120	52.71 (52.73)	15.80 (15.81)
VI p	3,4-Dichloro phenyl	C ₃₅ H ₂₆ N ₉ O ₃ SCl ₄ F	158	51.63 (51.66)	15.46 (15.49)
VI q	4-Fluoro phenyl	C ₃₅ H ₂₇ N ₉ O ₃ SCl ₂ F ₂	115	55.09 (55.11)	16.50 (16.53)
VI r	2,6-Dimethyl phenyl	C ₃₅ H ₃₂ N ₉ O ₃ SCl ₂ F	210	57.50 (57.51)	16.32 (16.32)

TABLE-2
ANTIBACTERIAL ACTIVITY OF THE SYNTHESIZED COMPOUNDS

Compd. No.	Diameter in mm		Compd. No.	Diameter in mm	
	<i>S. aureus</i>	<i>E. Coli</i>		<i>S. aureus</i>	<i>E. Coli</i>
Va	20	28	Vla	15	12
Vb	24	25	Vlb	18	14
Vc	15	24	Vlc	13	15
Vd	25	20	Vld	12	11
Ve	10	12	Vle	13	22
Vf	10	14	Vlf	20	15
Vg	19	17	Vlg	18	12
Vh	20	18	Vlh	12	14
Vi	20	18	Vli	19	17
Vj	24	18	Vlj	12	15
Vk	14	12	Vlk	20	21
VI	12	15	VIl	15	13
Vm	17	10	VIm	10	12
Vn	22	20	VIn	13	19
Vo	12	14	VIo	13	12
			VIp	14	13
			VIq	20	17
			VIr	12	17

[1] Procedure for the preparation of 2-amino-4-(2',4'-dichloro-5'-fluoro phenyl)-6-(3',4',5'-tr methoxy phenyl)pyrimidine (I)

1-(2'-4'-Dichloro-5'-fluoro phenyl)-3-(3',4',5'-trimethoxy phenyl)-2-propene-1-one (chalcone) was synthesised by reported method.³ A mixture of chalcone (0.01 mole) and guanidine nitrate (0.012 mole) was dissolved in ethanol (50 mL). Added 40% NaOH (2 mL) in it and refluxed for 36 h. The excess of solvent was distilled off and the obtained material was poured into ice-cold water, the solid obtained was filtered, washed with cold water and dried. It was recrystallised from ethanol, then checked TLC by using benzene : propanol (9 : 1) as mobile phase; yield 61%; ν_{\max} (cm⁻¹): 3250 ν (NH)₂, 1600 ν (C=N), 1060 ν (OCH₃), 1050 ν (C—F), 730 ν (C—Cl).

[2] Procedure for the preparation of 2-phenyl amino-4,6-dichloro-s-triazine (II)

Cyanuric chloride (0.01 mole) was dissolved in acetone. Then aniline (0.01 mole) in acetone was added with constant stirring. Reaction was carried out at 0–5°C. During reaction pH was maintained neutral by adding 10% Na₂CO₃ solution. The reaction mixture was stirred for further 4 h. After completion of reaction (checked by TLC) the reaction mixture was poured on crushed ice. The

solid separated was filtered, washed and dried, then recrystallised in ethanol; m.p. 198°C; yield 86%.

[3] General procedure for the preparation of 2-phenyl amino-4-aryl ureido-6-chloro-s-triazine III (a-o) and 2-phenyl amino-4-aryl thio ureido-6-chloro-s-triazine IV (a-r))

The compound II (0.01 mole) was dissolved in acetone; then different aryl ureido aryl thio ureido (0.01 mole) in acetone was added with constant stirring. Reaction was carried out at room temperature. During the reaction pH was maintained neutral by adding 10% Na₂CO₃ solution. The reaction mixture was stirred for further 8 h. After completion of reaction (checked by TLC) the reaction mixture was poured on crushed ice. The solid separated was filtered, washed and dried and then recrystallised in ethanol; yield 75–80%.

[4] General procedure for the preparation of 2-phenyl amino-4-aryl ureido-6-[[4'-(2'',4''-dichloro-5'''-fluoro phenyl)-6'-(3'',4'',5'''-trimethoxy phenyl)-pyrimidine-2'-yl]amino]-s-triazine V(a-o) and 2-phenyl amino-4-aryl thioureido-6-[[4'-(2'',4''-dichloro-5'''-fluoro phenyl)-6'-(3'',4'',5'''-trimethoxy phenyl)pyrimidine-2'-yl]amino]-s-triazine VI (a-r))

The compound III/IV (0.01 mole) was dissolved in DMF and compound I also in DMF was refluxed for 10 h. During the reaction pH was maintained neutral by adding 10% Na₂CO₃ solution. After completion of reaction (checked by TLC) the reaction mixture was poured on crushed ice. The solid separated was filtered, washed and dried and then recrystallised in suitable solvent; yield 70–75%.

ν_{\max} (cm⁻¹): 1600 ν (C=N), 1060 (ν —OCH₃), 750–700 ν (—C—Cl), 1630–1590 ν (—NH), 1375 ν (>C=S)

NMR (CDCl₃) of compound No. V (f): 3.89 (s, 3H, —OCH₃ of *p*-anisidine); 3.8 (s, 9H, —OCH₃ of TMBA); 6.4–7.8 (m, 13H, Ar—H); 7.55 (s, 1H, —CH of pyrimidine ring).

NMR (CDCl₃) of compound No. V (l): 3.80 (s, 9H, Ar—OH₃); 6.4–7.8 (m, 13H, Ar—H); 1.25 (s, 3H, Ar—CH₃); 7.55 (s, 1H, —CH of pyrimidine ring).

Antibacterial activity

All the synthesised compounds were screened for their anti-bacterial activity against *Staphylococcus aureus* and *Escherichia coli* using agar cup method.¹⁷ The zone of inhibition was measured in m.m. All the compounds reported in Table-2 were tested at 100 μ g concentration. Under similar conditions control experiment was carried out by using chloramphenicol (18 mL) and ampicillin (15 mL) as a standard for comparison. Compounds Vp, Ve, Vf, Vk, Vl, Vo and Vid, Vih, VIj, VIm, VIo, VIp were found less active and compounds Vc, Vm, VIa, VIc, VIg, Vli, VII, VIn, VIr were found moderately active, while compounds Va, Vb, Vd, Vg, Vh, Vi, Vj, Vn, VIb, VIe, Vif, VIk, VIq were found more active against both microbes.

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