Asian Journal of Chemistry Vol. 11, No. 1 (1999), 65–70

Synthesis and Antimicrobial Activity of Thiazole Derivatives

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Attempts have been made to prepare thiazole derivatives of type 1 and of type 2 by substitution at 2-amino group of 2-amino-4-phenylthiazole by substituted-s-triazine nucleus. The products were tested for antimicrobial activity against *E. coli*, *Salmonella typhi*, *Bacillus subtilis* spores and *Candida albicans*. Antimycobacterium testing was carried out against $H_{37}Rv$ organism. The constitution of these products have been confirmed by IR and PMR spectral studies.

INTRODUCTION

Thiazoles, which form a part of vitamin B_1, the penicillins and several bioactive agents, have been extensively studied and used for dverse applications. 2-Amino-4-arylthiazole and its derivatives are good antibacterial agents[1] and fungicides.[2] The presence of lyophilic and polar substituents like aryl and amino groups in the thiazole nucleus is expected to enhance the fungitoxic property.[3] 2-Amino-4-phenylthiazole has been found to posess antimicrobial, anthelmintic and insecticide activities.[4] Taking into consideration the wide range of therapeutic activity of s-triazine nucleus[5], arylurea[6] and arylthiourea derivatives[7], thiazole derivatives of type 1 and of type 2 have been synthesised.

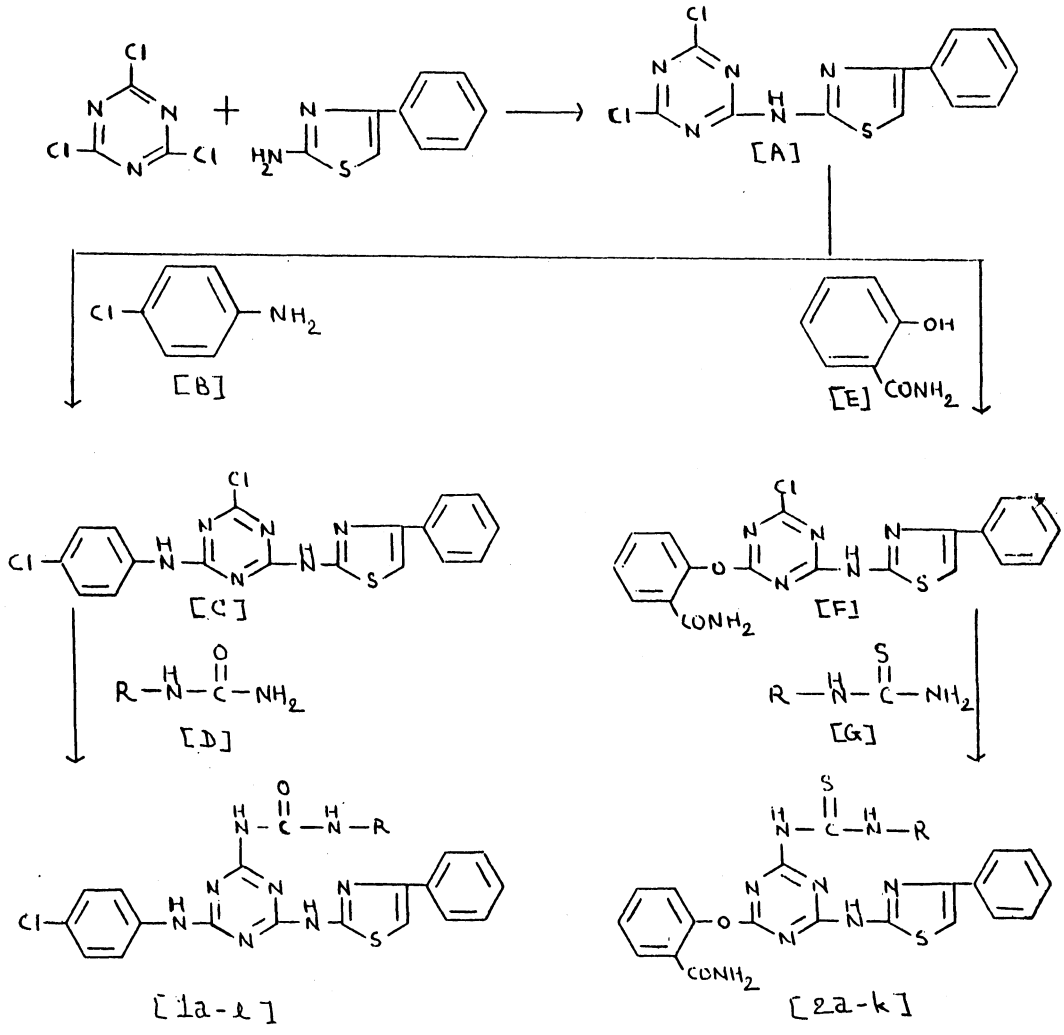
EXPERIMENTAL

All the melting points were determined by open capillary method and are not corrected. IR-spectra were recorded in KBr pellets on Perkin-Elmer spectrophotometer. PMR spectra (DMSO) were run on Varian-300 spectrometer using TMS as internal standard.

The required 2-amino-4-phenylthiazole was prepared by the method described in literature.[8]

Preparation of 2-(4′-phenylthiazol-2′-yl-amino)-4,6-dichloro-s-triazine (A)

To a stirred solution of cyanuric chloride (1.84 g, 0.01 mol) in acetone at 0–5°C, the solution of 2-amino-4-phenylthiazole (1.76 g, 0.01 mol) in acetone was added slowly and neutral pH was maintained. After complete addition, the stirring was continued at the same temperature for 2 h. Then the stirring was stopped and the solution was treated with crushed ice. The solid product thus obtained was filtered, dried and recrystallised from ethanol. (Yield 80%, m.p. 168°C. Found: N, 21.56%; $C_{12}H_7N_5SCl_2$, required: N, 21.60%.)



Preparation of 2-(4′-phenylthiazol-2′-yl-amino)-4-(4′-chlorophenylamino)-6-chloro-s-triazine (C)

To a well stirred solution of 2-(4′-phenylthiazole-2′-yl-amino)-4,6-dichloro-s-triazine (A) (3.24 g, 0.01 mol) in acetone at 35°C, the solution of *p*-chloroaniline (B) (1.28 g, 0.01 mol) in acetone was added slowly for 1/2 h. Neutral pH was maintained. The temperature was gradually raised to 45°C during stirring for 2h. The solution was poured in ice-cold water. The solid product thus obtained was filtered, dried and recrystallized from ethanol. (Yield: 70%; m.p. 259°C. Found: N, 20.21%; $C_{18}H_{12}N_6SCl_2$, required: N, 20.24%.)

Preparation of 2-(4′-phenylthiazol-2′-yl-amino)-4-(4′-chlorophenylamino)-6-(arylureido)-s-triazine (1a–*l*)

A mixture of 2-(4′-phenylthiazol-2′-yl-amino)-4-(4′-chlorophenylamino)-6-

chloro-s-triazine (C) (4.15 g, 0.01 mol) and arylurea (D) (0.01 mol) in acetone was refluxed for 3 h, cooled and poured into ice-cold water. The separated solid was filtered and recrystallised from ethanol to furnish 1a–*l*.

IR (KBr): ν_{max} (cm^{-1}) 825–800 ν(C_3N_3), 1540 ν(sec. amine NH), 1630–1620 ν(urea C=O), 1495–1490 ν(cyclic C=N).

PMR (DMSO) δ pm: 2.4901 (Ar—CH_3), 3.3343 (—NHAr), 7.3285 (—HCONH—), 7.3520 (—NHCONH—), 7.0990 (Ar—H), 7.7112 (Ar—H), 7.4633 (Ar—H), 7.9065 (Ar—H).

Preparation of 2-(4′-phenylthiazol-2′-yl-amino)-4-(benzamido-2′-yl-oxy)-6-chloro-s-triazine (F)

To a well stirred solution of 2-(4′-phenylthiazol-2′-yl-amino)-4,6-dichloro-s-triazine (A) (3.24 g, 0.01 mol) in acetone at 35°C, the solution of salicylamide (E) (1.37 g, 0.01 mol) in acetone was added slowly for 1/2 h. Neutral pH was maintained. The temperature was gradually raised to 45°C during the stirring for 2 h. The solution was poured in ice-cold water. The solid product thus obtained was filtered, dried and recrystallized from ethanol. (Yield 78%; m.p. 188°C. (Found: N, 19.75%; $C_{19}H_{13}O_2N_6SCl$, required: N, 19.79%.)

Preparation of 2-(4′-phenylthiazol-2′-yl-amino)-4-(benzamido-2′-yl-oxy)-6-(arylthioureido)-s-triazine (2a–k)

A mixture of 2-(4′-phenylthiazol-2′-yl-amino)-4-(benzamido-2′-yl-oxy)-6-chloro-s-triazine (F) (4.24 g, 0.01 mol) and arylthiourea (G) (0.01 mol) in acetone was refluxed for 3 h, cooled and poured into ice-cold water. The separated solid was filtered and recrystallized from ethanol to furnish 2a–k.

IR (KBr): ν_{max} (cm^{-1}) 800 ν(C_3N_3); 1540 ν(sec-amine NH), 1610 ν(1° amide NH), 1670 ν(primary amide C=O), 1070 ν(thiourea C=S), 1510 ν(cyclic C=N), 1225 and 1020 ν(C—O—C).

RESULTS AND DISCUSSION

The *in-vitro* screening for antibacterial activity of the compounds 1a–*l* and 2a–k is undertaken by different concentration methods.[9] Samples were dissolved in DMSO and subsequent dilution was done in distilled water to obtain two test concentrations, 50 mcg/mL and 500 mcg/mL. The organisms used for antimicrobial tests were *Escherichia coli*, *Salmonella typhi*, *Bacillus subtilis* spores and *Candida albicans*.

For antimycobacterium testing, $H_{37}Rv$ organism was used.

The results are given in Tables 3 and 4. Compound Nos. 1c, 1d, 1f and 1i do not have any antibacterial activity at the concentration of 50 mcg/mL. Compound 1d has moderate activity against *Escherichia coli* at the concentration of 500 mcg/mL and it shows slight inhibition of *Salmonella typhi*, *Bacillus subtilis* and *Candida albicans*, while compound 1c showed slight inhibition of *Escherichia coli*, at the concentration of 500 mcg/mL and compound 1f showed slight activity against *Candida albicans* only at 500 mcg/mL concentration and compound 1i showed slight activity against *Escherichia coli* and *Candida albicans* both at the concentration of 500 mcg/mL.

TABLE-1
PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS 1a–*l*

Compd No.	R	Molecular formula	m.p. (°C)	Yield (%)	% of nitrogen found (calcd.)
1a	—C_6H_5	$C_{25}H_{19}ON_8SCl$	298	48	21.72 (21.77)
1b	2′-$CH_3C_6H_4$	$C_{26}H_{21}ON_8SCl$	267	52	21.15 (21.19)
1c	4′-$CH_3C_6H_4$	$C_{26}H_{21}ON_8SCl$	278	54	21.14 (21.19)
1d	2′-$OCH_3C_6H_4$	$C_{26}H_{21}O_2N_8SCl$	274	49	20.53 (20.57)
1e	4′-$OCH_3C_6H_4$	$C_{26}H_{21}O_2H_8SCl$	285	59	20.55 (20.57)
1f	2′-$NO_2C_6H_4$	$C_{25}H_{18}O_3N_9SCl$	297	43	22.57 (22.52)
1g	3′-$NO_2C_6H_4$	$C_{25}H_{18}O_3N_9SCl$	312	56	22.50 (22.52)
1h	4′-$NO_2C_6H_4$	$C_{25}H_{18}O_3N_9SCl$	264	45	22.54 (22.52)
1i	2′-ClC_6H_4	$C_{25}H_{18}ON_8SCl_2$	259	54	20.35 (20.40)
1j	3′-ClC_6H_4	$C_{25}H_{18}ON_8SCl_2$	270	48	20.42 (20.40)
1k	4′ClC_6H_4	$C_{25}H_{18}ON_8SCl_2$	258	71	20.37 (20.40)
1*l*	—$C_{10}H_7$	$C_{29}H_{21}ON_8SCl$	272	55	19.89 (19.84)

TABLE-2
PHYSICAL AND ANALYTICAL DATA OF COMPOUNDS 2a–k

Compd. No.	R	Molecular formula	m.p. (°C)	Yield (%)	% of nitrogen found (calcd.)
2a	—C_6H_5	$C_{26}H_{20}O_2N_8S_2$	182	63	20.72 (20.74)
2b	2′-$CH_3C_6H_4$	$C_{27}H_{22}O_2N_8S_2$	190	70	20.25 (20.22)
2c	3′-$CH_3C_6H_{14}$	$C_{27}H_{22}O_2N_8S_2$	221	69	20.20 (20.22)
2d	4′-$CH_3C_6H_4$	$C_{27}H_{22}O_2N_8S_2$	189	68	20.24 (20.22)
2e	2′-$OCH_3C_6H_4$	$C_{27}H_{22}O_3N_8S_2$	191	73	19.67 (19.65)
2f	4′-$OCH_3C_6H_4$	$C_{27}H_{22}O_3N_8S_2$	231	63	19.61 (19.65)
2g	2′-ClC_6H_4	$C_{26}H_{20}O_2N_8S_2Cl$	194	83	19.47 (19.50)
2h	3′-ClC_6H_4	$C_{26}H_{20}O_2N_8S_2Cl$	215	77	19.49 (19.50)
2i	4′-ClC_6H_4	$C_{26}H_{20}O_2N_8S_2Cl$	196	61	19.52 (19.50)
2j	4′-BrC_6H_4	$C_{26}H_{20}O_2N_8S_2Br$	185	52	18.11 (18.09)
2k	—$C_{10}H_7$	$C_{30}H_{22}O_2N_8S_2$	219	50	18.95 (18.98)

TABLE-3
ANTIMICROBIAL ACTIVITY OF COMPOUNDS 1 AND 2

Compd No.	Concentration in mcg/mL							
	E. coli		*S. typhi*		*B. subtilis*		*C albicans*	
	50	500	50	500	50	500	50	500
1c	–	+	–	–	–	–	–	–
1d	–	++	–	+	–	+	–	+
1f	–	–	–	–	–	–	–	+
1i	–	+	–	–	–	–	–	+
2a	–	–	–	–	–	++	–	++
2b	–	–	–	–	–	++	–	++
2e	–	–	–	–	–	++	–	++
2h	–	–	–	–	–	++	–	++

– = No inhibition + = Slight inhibition + + = Moderate inhibition

TABLE-4
ANTIMYCOBACTERIAL ACTIVITY OF COMPOUNDS 1 AND 2

Compd No.	M.I.C. mcg/mL
1b	100.00
1k	50.00
2a	12.50
2c	100.00
Isonicotinic acid hydrazide	0.04
Streptomycin	1.00

Compound Nos. 2a, 2b, 2e and 2h do not have any antibacterial activity at a concentration of 50 mcg/mL but they show moderate activity at a concentration of 500 mcg/mL against *Bacillus subtilis* and *Candida albicans*. All the four compound sare not effective against *Escherichia coli* and *Salmonella typhi* even at a concentration of 500 mcg/mL.

In anti-T.B. testing against $H_{37}Rv$ organism, compounds 1b and 1k were found active at 100 mcg/mL and 50 mcg/mL concentration respectively and compound 2a and 2c were found active against $H_{37}Rv$ organism at concentrations of 12.5 mcg/mL and 100 mcg/mL respectively.

The physical and analytical data of compounds 1a–*l* and 2a–k are presented in Table-1 and Table-2 respectively.

ACKNOWLEDGEMENTS

The authors are thankful to authorities of B.K.M. Science College, Valsad for facilities, I.I.T., Bombay for NMR spectra and M.J. Institute of Research, Baroda and Haffkine Institute, Bombay for antimicrobial testing.

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(*Received*: 27 June 1998; *Accepted*: 21 September 1998) AJC-1569