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Il Farmaco 55 (2000) 331–337

IL FARMACO

Synthesis and antimicrobial activity of 1-aryl-2-amino-3-(4-arylthiazol-2-yl)/(benzothiazol-2-yl)guanidines

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Received 10 January 1999; accepted 16 February 2000

Abstract

The synthesis of fifteen new 1-aryl-2-amino-3-(4-arylthiazol-2-yl)/(benzothiazol-2-yl)guanidines is described. They were screened for their antimicrobial susceptibility by the standard disc diffusion method of the World Health Organization (WHO) and the activities compared with that of standard strain of *Escherichia coli* NCTC 10418. The sensitive aminoguanidines were further subjected to the minimum inhibitory concentration (MIC) test.

Keywords: Antimicrobial activity; Minimum inhibitory concentration; Guanidines

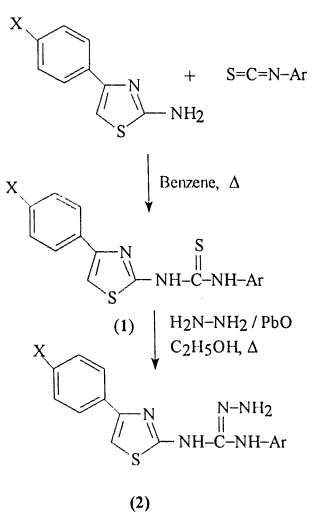
1. Introduction

A number of thiazolyl and benzothiazolyl guanidines have been reported to exhibit antitubercular, antimalarial, CNS depressant, analgesic [1–8] and antimicrobial activity against both Gram-positive and Gram-negative bacteria [9]. The related *N*-aminoguanidines are very scarcely reported in the literature; an exception being their report as tuberculostatic agents [10]. Therefore, we considered it interesting to synthesize and evaluate the antibacterial activity of some new 1-aryl-2-amino-3-(4-arylthiazol-2-yl)/(benzothiazol-2-yl)guanidines.

The synthetic approach to these compounds [2,4] is outlined in Schemes 1 and 2. The starting materials, 2-amino-4-arylthiazoles and 2-aminobenzothiazole were refluxed with substituted phenyl isothiocyanates in dry benzene. Subsequent desulfurization of the resulting thioureas **1** and **3** with yellow lead oxide in ethanol in the presence of hydrazine hydrate gave **2** and **4**, respectively, in 45–75% yields. The structure of the compounds **1**–**4** were confirmed by elemental analyses, IR and ^{1}H NMR spectral data.

2. Experimental

All melting points (m.p.) were determined in open capillaries on a Gallenkamp apparatus and are uncorrected. The purity of the compounds was routinely checked by thin layer chromatography (TLC) using



X = H, CH_3
Ar = 4-BrC_6H_4, $C_6H_5CH_2$, 2-ClC_6H_4, 3-ClC_6H_4, 4-$C_2H_5OC_6H_4$, 2-$NO_2C_6H_4$

Scheme 1.

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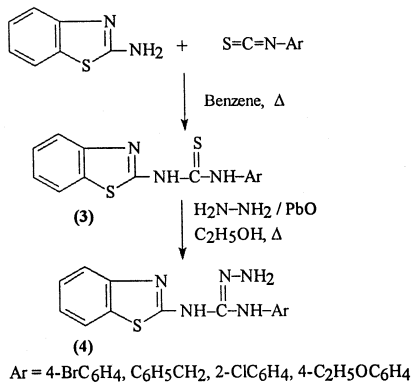

Scheme 2.

silica gel G (E. Merck). A Jeol FX-90Q Fourier transform spectrometer was used for recording ^{1}H NMR spectra at 27°C with TMS as an internal standard. A Jasco FT-IR 5300 spectrophotometer was used for IR spectra and a Perkin–Elmer CHN Analyzer 240C for elemental analyses. The analytical values for all the new compounds were within $\pm 0.3\%$ of the theoretical values.

2.1. 1-p-Bromophenyl-3-(4-phenylthiazol-2-yl)-2-thiourea (**1a**)

An equimolecular mixture of 2-amino-4-phenylthiazole (4.0 g, 23 mmol) and *p*-bromophenyl isothiocyanate (5.3 g, 25 mmol) in 30 ml of dry benzene was refluxed in a water-bath for 10 h. After cooling, the solid product was filtered and washed with ether followed by dilute HCl. The product was finally washed with water and crystallized from ethanol to give colorless crystals; yield 73%, m.p. 255°C. Analysis: $C_{16}H_{12}BrN_3S_2$ (C, H, N, S). IR (Nujol, cm^{-1}): 3400 m, 3345 s (N–H str), 1640 s, 1590 m, 1460 m (aromatic ring), 1200 s (C=S str). NMR (DMSO-d_6): δ 3.50–3.89 (broad, 1H, NH, D_2O exchangeable), 6.90–8.00 (m, 10H, ar), 11.25–11.50 (broad, 1H, NH, D_2O exchangeable).

2.2. 1-p-Bromophenyl-3-(4-p-totylthiazol-2-yl)-2-thiourea (**1g**)

The compound was prepared by condensing 2-amino-4-*p*-tolylthiazole with *p*-bromophenyl isothiocyanate in dry benzene as above; yield 58%, m.p. 225°C. Analysis: $C_{17}H_{14}BrN_3S_2$ (C, H, N, S). IR (KBr, cm^{-1}): 3450 m, 3350 m (N–H str), 1660 m, 1600 m, 1540 s (aromatic ring), 1230 s (C=S str). NMR (DMSO-d_6): δ 2.20 (s, 3H, CH_3), 7.13–7.90 (m, 10H, 9 ar and one NH, D_2O exchange), 9.04 (s, 1H, NH, D_2O exchange). Other thioureas **1** were prepared similarly in 46–73% yields. Their m.p. and characteristic IR data (Nujol) are reported in Table 1.

2.3. 1-p-Bromophenyl-3-(benzothiazol-2-yl)-2-thiourea (**3a**)

The compound was prepared by refluxing 2-aminobenzothiazole with *p*-bromophenyl isothiocyanate in dry benzene as above; yield 95%, m.p. 231°C. Analysis: $C_{14}H_{10}BrN_3S_2$ (C, H, N, S). IR (KBr, cm^{-1}): 3480 m, 3340 w (N–H str), 1660 w, 1640 s, 1550 s (aromatic ring), 1240 (C=S str). NMR (DMSO-d_6): δ 6.50–8.45 (m, 8H, ar), 9.20 (broad, 1H, NH, D_2O exchange), 11.92 (broad, 1H, NH, D_2O exchange). By following this procedure, thioureas **3b**–**d** were also prepared. Their yields, m.p. and characteristic IR data (Nujol) are given in Table 2.

2.4. 1-p-Bromophenyl-2-amino-3-(4-phenylthiazol-2-yl)guanidine (**2a**)

A mixture of 1-*p*-bromophenyl-3-(4-phenylthiazol-2-yl)-2-thiourea (4.0 g, 0.01 mol), yellow lead oxide (2.2 g,

Table 1
Characterization data of 1-aryl-3-(4-arylthiazol-2-yl)-2-thioureas (**1**)

Comp.	Ar	X	m.p. (°C)	Molecular formula	Characteristic IR bands (cm^{-1})	
					νNH	νC=S
1a	4-BrC_6H_4	H	255	$C_{16}H_{12}BrN_3S_2$	3400 m, 3345 s	1200 s
1b	$C_6H_5CH_2$	H	178	$C_{17}H_{15}N_3S_2$	3350–3250 br	1210 m
1c	2-ClC_6H_4	H	148	$C_{16}H_{12}ClN_3S_2$	3250 s, 3240 s	1205 s
1d	3-ClC_6H_4	H	210	$C_{16}H_{12}ClN_3S_2$	3400 m, 3330 m	1205 s
1e	4-$C_2H_5OC_6H_4$	H	222	$C_{17}H_{17}N_3OS_2$	3460–3200 br	1200 s
1f	2-$NO_2C_6H_4$	H	120	$C_{16}H_{12}N_4O_2S_2$	3420 m, 3280 m	1205 m
1g	4-BrC_6H_4	CH_3	225	$C_{17}H_{14}BrN_3S_2$	3450 m, 3350 m	1230 s
1h	$C_6H_5CH_2$	CH_3	237	$C_{18}H_{17}N_3S_2$	3440–3350 br	1220 m
1i	2-ClC_6H_4	CH_3	194	$C_{17}H_{14}ClN_3S_2$	3480 s, 3320 m	1205 s
1j	3-ClC_6H_4	CH_3	228	$C_{17}H_{14}ClN_3S_2$	3400 m, 3200 m	1210 s
1k	4-$C_2H_5OC_6H_4$	CH_3	205	$C_{19}H_{19}NOS_2$	3400–3250 br	1210 s

Table 2
Characterization data of 1-aryl-3-(benzothiazol-2-yl)-2-thioureas (**3**)

Comp.	Ar	Yield (%)	m.p. (°C)	Molecular formula	Characteristic IR bands (cm^{-1})	
					νNH	νC=S
3a	4-BrC_6H_4	95	221	$C_{14}H_{10}BrN_3S_2$	3480 m, 3340 w	1240 m
3b	$C_6H_5CH_2$	55	181	$C_{15}H_{13}N_3S_2$	3300 s, 3280 m	1200 m
3c	2-ClC_6H_4	51	155	$C_{14}H_{10}ClN_3S_2$	3240 s, 3180 m	1210 m
3d	4-$C_2H_5OC_6H_4$	49	198	$C_{16}H_{15}N_3OS_2$	3440 s, 3280 m	1230 s

0.01 mol) and hydrazine hydrate (1.5 ml, 0.03 mol) in 30 ml of ethanol was heated in a sealed glass tube on a water-bath for 8 h. Lead sulfide was filtered while hot and the residue extracted with hot ethanol. The filtrates were concentrated to get the required guanidine, which was crystallized from ethanol to form light yellow crystals; yield 45%, m.p. 240°C. Analysis: $C_{16}H_{14}BrN_5S$ (C, H, N, S). IR (KBr, cm^{-1}): 3420 m, 3350 w (NH_2 and NH str), 1640 s, 1600 s, 1540 s, 760 m. NMR (DMSO-d_6): δ 5.27 (s, 2H, NH_2, D_2O exchange), 6.90–8.00 (m, 10H, ar), 8.85 (s, 1H, NH, D_2O exchange), 10.79–11.66 (broad, 1H, NH, D_2O exchange). By the above procedure, a series of 1-aryl-2-amino-3-(4-phenylthiazol-2-yl)guanidines (**2b**–**f**) were prepared and crystallized from ethanol. Their yields, m.p., characteristic IR and NMR data are recorded in Table 3.

2.5. 1-*p*-Bromophenyl-2-amino-3-(4-*p*-tolylthiazol-2-yl)guanidine (**2g**)

The guanidine was prepared from 1-*p*-bromophenyl-3-(4-*p*-tolylthiazol-2-yl)-2-thiourea by heating for 7 h; yield 48%, m.p. 114°C. Analysis: $C_{17}H_{16}BrN_5S$ (C, H, N, S). IR (KBr, cm^{-1}): 3450 m, 3350 m (NH_2 and NH str), 1640 m, 1600 m, 1540 s (aromatic ring), 760 s. NMR (DMSO-d_6): δ 2.35 (s, 3H, CH_3), 6.00 (s, 2H, NH_2, D_2O exchange), 7.12–7.90 (m, 10H, 9 ar and one NH, D_2O exchange), 9.00 (s, 1H, NH, D_2O exchange). Similarly, a series of 1-aryl-2-amino-3-(4-*p*-tolylthiazol-2-yl)guanidines (**2h**–**k**) were prepared and crystallized from ethanol. Their yields, m.p., characteristic IR and NMR (DMSO-d_6) data are given in Table 3.

2.6. 1-*p*-Bromophenyl-2-amino-3-(benzothiazol-2-yl)guanidine (**4a**)

The compound was prepared from 1-*p*-bromophenyl-3-(benzothiazol-2-yl)-2-thiourea as above. The heating period was 6 h; yield 75%, m.p. 190°C. Analysis: $C_{14}H_{12}BrN_5S$ (C, H, N, S). IR (KBr, cm^{-1}): 3600–3200 broad (NH_2 and NH str), 1620 m, 1600 m, 1560 s (aromatic ring), 740 m. NMR (DMSO-d_6): δ 6.83–8.39 (m, 10H, 8 ar and NH_2, D_2O exchange), 9.35 (s, 1H, NH, D_2O exchange), 11.35–11.88 (broad, 1H, NH, D_2O exchange).

Similarly, a series of 1-aryl-2-amino-3-(benzothiazol-2-yl)guanidines (**4b**–**d**) were prepared. Their yields, m.p. and characteristic IR and NMR data are recorded in Table 4.

3. Antimicrobial screening results

The 1-aryl-2-amino-3-(4-arylthiazol-2-yl)guanidines (**2**) and 1-aryl-2-amino-3-(benzothiazol-2-yl)guanidines (**4**) were screened for their antimicrobial activity against seventeen different pathogenic strains of microorganisms such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Citrobacter freundii*, *Proteus vulgaris*, *Providencia rettgeri*, *Edwardsiela tarda*, *Salmonella typhi*, *Salmonella typhimurium*, *Strigella dysenteriae*, *Vibrio cholerae* 01 classical, *Vibrio cholerae* non 01, *Vibrio parahaemolyticus*, *Aeromonas hydrophila* and *Plesimonas shigelloides*. The antimicrobial susceptibility was determined by the Stokes disc diffusion technique [11] whereas minimum inhibitory concentration (MIC) was determined by the Stokes and Ridgeway plate dilution method [11]. Zones of inhibition of the test microorganisms were compared with that of the control NCTC strain of *E. coli* 10418.

The antimicrobial susceptibility was measured at a concentration of 40 μg/disc. The analysis of various patterns of susceptibility is shown in Table 5. The results reveal that there are a wide variety of combinations of the synthesized compounds to which strains were sensitive. The synthesized *N*-aminoguanidines are most active against *S. epidermidis*, *K. pneumoniae*, *S. dysenteriae*, *V. cholerae* 01 classical, *V. cholerae* non 01 and *A. hydrophila*. In general, those aminoguanidines which have *para or meta* halogen substituent in the phenyl ring show remarkable antibacterial activity.

The sensitive aminoguanidines from antimicrobial susceptibility test were further subjected to the MIC test as follows. Freshly prepared solutions of synthesized compounds diluted to different concentrations were

Table 3
Characterization data of 1-aryl-2-amino-3-(4-arylthiazol-2-yl)guanidines (**2**)

Comp.	Ar	X	Yield (%)	m.p. (°C)	Molecular formula	Characteristic IR bands (cm^{-1})		^1H NMR in δ (DMSO-d_6)
						νNH_2, NH	$\nu C{=}N$	
2a	4-BrC_6H_4	H	45	240	$C_{16}H_{14}BrN_5S$	3420 m, 3350 w	1640 s	5.27 (s, 2H, NH_2, D_2O exchange), 6.90–8.00 (m, 10H, ar), 8.85 (s, 1H, NH, D_2O exchange), 10.79–11.66 (br, 1H, NH, D_2O exchange)
2b	$C_6H_5CH_2$	H	60	142	$C_{17}H_{17}N_5S$	3440 s, 3260 m	1620 s	2.83 (s, 1H, NH, D_2O exchange), 4.52 (d, 2H, CH_2), 4.53–5.22 (br, 2H, NH_2, D_2O exchange), 7.00–8.00 (m, 11H, ar), 10.13 (br, 1H, NH, D_2O exchange)
2c	2-ClC_6H_4	H	62	182	$C_{16}H_{14}ClN_5S$	3410 s, 3260 m	1610 m	3.40 (s, 2H, NH_2, D_2O exchange), 6.00 (s, 1H, NH, D_2O exchange), 6.66–8.32 (m, 11H, 10 ar and NH, D_2O exchange)
2d	3-ClC_6H_4	H	60	102	$C_{16}H_{14}ClN_5S$	3450 s, 3225 s	1640 m	5.98 (s, 2H, NH_2, D_2O exchange), 6.71–7.85 (m, 10H, ar), 9.00 (s, 1H, NH, D_2O exchange), 11.00–11.66 (br, 1H, NH, D_2O exchange)
2e	4-$C_2H_5OC_6H_4$	H	63	145	$C_{18}H_{19}N_5OS$	3480–3250 br	1630 s	–
2f	2-$NO_2C_6H_4$	H	46	150	$C_{16}H_{14}N_6O_2S$	3440 s, 3250 s	1610 s	–
2g	4-BrC_6H_4	CH_3	48	114	$C_{17}H_{16}BrN_5S$	3450 m, 3350 m	1640 m	2.35 (s, 3H, CH_3), 6.00 (s, 2H, NH_2, D_2O exchange), 7.12–7.90 (m, 10H, ar and NH, D_2O exchange), 9.00 (s, 1H, NH, D_2O exchange)
2h	$C_6H_5CH_2$	CH_3	49	178	$C_{18}H_{19}N_5S$	3400 s, 3300 s	1640 m	2.30 (s, 3H, CH_3), 4.52 (d, 2H, CH_2), 4.79 (s, 2H, NH_2, D_2O exchange), 7.00–8.00 (m, 11H, ar and NH, D_2O exchange), 10.12 (s, 1H, NH, D_2O exchange)
2i	2-ClC_6H_4	CH_3	58	84	$C_{17}H_{16}ClN_5S$	3450–3100 br	1630 s	1.28 (s, 3H, CH_3), 3.39 (s, 2H, NH_2, D_2O exchange), 6.70 (s, 1H, NH, D_2O exchange), 6.70–8.44 (m, 10H, ar and NH, D_2O exchange)
2j	3-ClC_6H_4	CH_3	68	136 (dec.)	$C_{17}H_{16}ClN_5S$	3400 m, 3325 m	1635 m	–
2k	4-$C_2H_5OC_6H_4$	CH_3	45	65	$C_{19}H_{21}N_5OS$	3400–3310 br	1620 s	1.33 (t, 3H, CH_3), 2.21 (s, 3H, CH_3), 3.90 (q, 2H, CH_2), 4.52–5.31 (br, 2H, NH_2, D_2O exchange), 5.66 (s, 1H, NH, D_2O exchange), 6.50–8.00 (m, 9H, ar), 8.26 (s, 1H, NH, D_2O exchange)

Table 4
Characterization data of 1-aryl-2-amino-3-(benzothiazol-2-yl)guanidines (**4**)

Comp.	Ar	Yield (%)	m.p. (°C)	Molecular formula	Characteristic IR bands (cm^{-1})		^1H NMR in δ (DMSO-d_6)
					νNH_2, NH	$\nu C{=}N$	
4a	4-BrC_6H_4	75	190	$C_{14}H_{12}BrN_5S$	3600–3200 br	1620 m	6.83–8.39 (m, 10H, ar and NH_2, D_2O exchange), 9.35 (s, 1H, NH, D_2O exchange), 11.35–11.88 (br, 1H, NH, D_2O exchange)
4b	$C_6H_5CH_2$	70	85–88 (dec.)	$C_{15}H_{15}N_5S$	3400–3100 br	1640 m	1.31 (s, 1H, NH, D_2O exchange), 3.11–3.79 (br, 2H, NH_2, D_2O exchange), 4.44 (d, 2H, CH_2), 6.53–8.35 (m, 10H, ar and NH, D_2O exchange)
4c	2-ClC_6H_4	70	210	$C_{14}H_{12}ClN_5S$	3400 br, 3200 br	1640 s	–
4d	4-$C_2H_5OC_6H_4$	59	115	$C_{16}H_{17}N_5OS$	3600–3100 br	1640 s	–

added to Mueller–Hinton agar (Hi-Media), at 45–50°C. It was mixed well and poured into 100-mm petridishes; 20 ml gave a depth of about 4 mm. Plates were dried prior to experiment and each plate was divided into equal sections. Overnight broth cultures of the test strains and control of *E. coli* NCTC 10418 were diluted to 1:1000 in phosphate buffer solution PBS (pH 7.4) to a concentration of about 10^4–10^5 viable cells/ml.

Aliquots of 0.01 ml of the diluted cultures were spotted on the different sectors on the agar plates containing the serial dilutions 2.0, 1.0, 0.5, 0.25 and 0.125 mg/ml of the synthesized compounds. Inocula were allowed to dry and the plates were incubated at 30°C overnight. All the test strains were also inoculated on a control plate containing no synthesized compound. The MIC of the synthesized compound was the lowest concentration of the compound per milliliter of medium that completely inhibited visible growth of the corresponding test strain.

The MIC of the various antimicrobial agents for species tested is shown in Table 6. The MIC values for the compounds showed a range from 0.125 to 2 mg/ml.

Table 5
Antimicrobial screening results of 1-aryl-2-amino-3-(4-arylthiazol-2-yl)guanidines (**2**) and 1-aryl-2-amino-3-(benzothiazol-2-yl)guanidines (**4**)[a]

Microorganisms	Comp. no.														
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**	**2i**	**2j**	**2k**	**4a**	**4b**	**4c**	**4d**
S. aureus	S	R	R	S	R	R	S	R	S	R	R	R	R	S	S
S. epidermidis	S	R	R	S	R	R	S	R	S	R	S	S	S	S	S
E. coli	S	R	R	S	R	R	S	R	R	R	R	S	S	S	R
K. pneumoniae	S	R	R	S	R	R	S	R	S	S	R	S	R	S	S
P. aeruginosa	R	R	R	S	R	R	R	R	R	S	R	S	R	R	R
C. freundii	R	R	R	S	R	R	S	R	R	R	S	R	S	R	S
P. vulgaris	S	R	R	S	R	R	S	R	R	S	S	R	S	R	R
P. rettgeri	S	R	R	S	R	R	S	R	R	S	R	S	S	S	R
E. tarda	S	R	R	R	R	R	S	R	R	R	S	R	R	R	S
S. typhi	S	S	R	S	R	R	S	R	R	S	S	R	R	R	R
S. typhimurium	R	S	R	S	R	R	S	R	R	S	R	R	S	S	R
S. dysenteriae	S	R	R	S	R	R	S	R	R	S	S	S	S	S	S
V. cholerae 01 classical	S	R	R	S	R	R	S	R	S	R	R	S	S	S	S
V. cholerae non 01	S	R	S	S	R	R	S	R	S	R	S	S	R	R	S
V. parahaemolyticus	S	R	R	S	R	R	R	R	S	S	S	R	R	S	S
A. hydrophila	S	R	R	S	R	R	S	R	S	R	S	S	R	S	S
P. shigelloides	S	R	R	S	R	R	S	R	R	S	S	R	R	R	S

[a] S = sensitive; R = resistant.

Table 6
MIC of 1-aryl-2-amino-3-(4-arylthiazol-2-yl)guanidines (**2**) and 1-aryl-2-amino-3-(benzothiazol-2-yl)guanidines (**4**)[a]

Microorganisms	Comp. no.														
	2a	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**	**2h**	**2i**	**2j**	**2k**	**4a**	**4b**	**4c**	**4d**
S. aureus	2			2			1								1
S. epidermidis	0.125			1			0.125		0.125		2	0.125	1	0.125	1
E. coli	2						2					1	2		1
K. pneumoniae	1			1					2			1		2	
P. aeruginosa				0.5						2					1
C. freundii							2				1		2		
P. vulgaris										1					
P. rettgeri										2			2		
E. tarda															
S. typhi											2				
S. typhimurium										0.5					
S. dysenteriae				1			1			2	2		1		0.5
V. cholerae 01 classical				2					2			2	2	2	1
V. cholerae non 01	1			0.5					2		1	2			0.5
V. parahaemolyticus	2			2					2					2	1
A. hydrophila	2			1					2		1	2		2	1
P. shigelloides	2			2			1				1				1

[a] MIC = minimum inhibitory concentration. The figures are in mg/ml.

In the present study, all seventeen isolates were resistant to one or more antimicrobial agents while the MIC values did not exceed 0.125 mg/ml for any bacterial pathogens tested.

Acknowledgements

The authors wish to thank Professor R. Balaji Rao, Head of the Department of Chemistry and to the Head of the Department of Microbiology, IMS, Banaras Hindu University for providing the necessary facilities. The financial assistance by the Tribhuvan University, Kathmandu, Nepal, for the award of a Teacher Research Fellowship under the Faculty Development program to B.P.S. is also gratefully acknowledged.

References

[1] B.N. Jayasimha, S.C. Bhattacharyya, P.C. Guha, Biguanido derivatives of diaryl-sulfones and sulfides, Curr. Sci. 20 (1951) 158.

[2] F.H.S. Curd, F.L. Rose, Synthetic antimalarials. Part X. Some aryl-diguanide derivatives, J. Chem. Soc. (1946) 729.

[3] P.N. Bhargava, R. Lakhan, Synthesis of benzothiazolyl guanidines as antibacterials and antituberculars, Agric. Biol. Chem. 32 (1968) 1392.

[4] P.N. Bhargava, M.R. Chaurasia, Some new potential antituberculars: benzothiazolyl guanidines, Curr. Sci. 37 (1968) 347.

[5] P.N. Bhargava, H. Singh, Search for new antituberculars and CNS depressants, Indian J. Pharm. 31 (1969) 158.

[6] P.N. Bhargava, S.N. Singh, *N*-(2-Benzothiazolyl)-*N′*-benzylguanidine analogs, Indian J. Pharm. 33 (1971) 36.

[7] P.N. Bhargava, I.C. Tiwari, 2-Substituted acetamido-α-naphtho[2,1-*d*]thiazole as local anaesthetics, Egypt. J. Chem. 17 (1974) 915.

[8] P.R. Naik, S.N. Pandeya, A. Pandey, Synthesis, antiinflammatory and analgesic activities of 1-[2-(substituted) benzothiazolyl]-1,3-di-*n*-butyl-4-arylguanidines, Indian J. Heterocycl. Chem. 5 (1995) 73.

[9] P.N. Bhargava, S. Prakash, Synthesis and antibacterial activity of thiazolyl guanidines, J. Indian Chem. Soc. 56 (1979) 937.

[10] E. Jeney, T. Zsolnai, Tuberculostatic agents, I. Hydrazine derivatives, carbon acids, phenols, and quaternary ammonium compounds and their intermediates, Zentr. Bakteriol. Parasitenk. Abt. I Orig.167 (1956) 55; Chem. Abstr. 51 (1957) 7579f.

[11] E.J. Stokes, G.L Ridgeway, Clinical Bacteriology, 5th ed., Arnold, London, 1980, pp. 200–254.