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SYNTHESIS, ANTIBACTERIAL AND ANTIFUNGAL ACTIVITIES OF 2,4-DIETHYL-3,5-DIARYLIMINO-1,2,4-THIADIAZOLIDINES AND RELATED BENZOTHIAZOLYLGUANIDINES

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A series of 2,4-diethyl-3,5-diarylimino-1,2,4-thiadiazolidines (1a-k) and 1-(benzothiazol-2-yl)-1,3-diethyl-4-aryl guanidines (2a-k) were evaluated for their antibacterial and antifungal activities. Substitution of p-ethoxy (1d) and p-chloro (1f, 2f) in the aryl ring resulted in most active compounds of the series in both activities.

Keywords: *Thiadiazolidines; Benzothiazolylguanidines; Synthesis; Antibacterial activity; Antifungal activity*

Introduction

The thiadiazole and benzothiazole heterocyclic nuclei have been reported to exhibit diverse biological activities. 1-(Alkyl and substituted phenyl)-3-(5-alkoxypheyl-1,3, 4-thiadiazol-2-yl) ureas have been shown to exhibit potent and broad spectrum antibacterial and antimycotic activity(1). El Haddad et al.(2) screened a series of 2-(aminoacyl)-amino-6-halobenzothiazoles for their antimicrobial and antifungal activities. 2-[1-(4-piperonyl) piperazinyl]benzothiazoles as agents for stimulating gastrointestinal motility(3). Recently, a series of 1,2,4-thiadiazolidines and corresponding benzothiazole derivatives have been reported to possess antibacterial and antifungal activities(4). In order to study the structure-activity relationship in the series and the effect of carbon chain length the present ethyl substituted derivatives were synthesized.

Chemistry:

The synthesis of 2,4-diethyl-3,5-diaryl-imino-1,2,4-thiadiazolidines was completed by the method adopted by Christophersen et al.(5). The thiadiazolidines were converted to benzothiazole guanidines by their acid catalysed rearrangement (Scheme). The structures of the compounds were elucidated by spectral data and elemental analyses.

Materials and Methods

Melting points were determined in open capillaries and were uncorrected. UV, IR and ^{1}H NMR spectra were recorded on Jasco-J-0063 model Perkin Elmer 883 (KBr) and Jeol Fx 90 Q (Fourier Transform) instruments respectively and were consistent with the assigned structures. Elemental analyses were performed on Carlo Erba Strum DP 200 instrument and the results were within 0.4% of the theoretical values. Purity of the compounds was monitered by thin layer chromatography (solvent system $CHCl_3$:CH_3OH-(3:2). Partition coefficient was determined according to the medhod of Chandra et al.(6). The N-ethyl-N'-arylthio-ureas were prepared according to the method of Schroeder(7).

Synthesis of 2, 4 - diethyl - 3, 5 - di (4 - methoxyphenly)- imino-1,2,4 - thiadiazolidine (1c):

A solution of sodium nitrite (6.9 g, 0.1 M) in water (25 ml) was added dropwise under cold conditions and stirring to a mixture of N-ethyl-N'-(4-methoxyphenyl) thiourea (10.5 g, 0.05 M) and concentrated hydrochloric acid (36%, 12.9 ml, 0.15 M) in 50 ml ethanol. After one hour the precipitated sulfur was removed and the filtrate was basified with ammonia solution (25%, 11.2ml, 0.15M). The resulting precipitate was washed with water and recrystallized from ethanol. Yield: 4.28 g (44.6%), m.p.: 109-110°C. Calcd. for $C_{20}H_{24}N_4O_2S$: N,14.58; S,8.33, found: N,14.72;S,8.44. UV(MeOH,λ_{max} nm): 287; IR(KBr,ν_{max} cm^{-1}): 1600 (C=N), ^{1}HNMR, ($CDCl_3$, δ ppm) 1.05-1.25 (t, 6H, 2x CH_3); 3.65-3.75 (q 4H 2xCH_2); 3.75 and 3.80 (2s, 6H, 2x OCH_3); 6.80-7.45 (m, 8H, Ar).

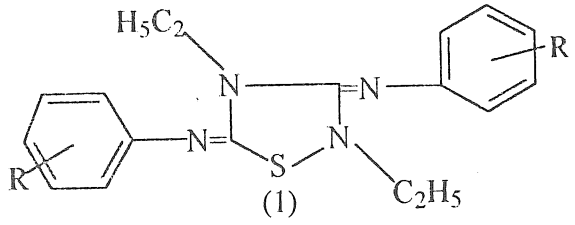
Other compounds of the series (1 a-k) were prepared in a similar manner and their physical properties are recorded in Table 1.

Synthesis of 1-(6-methoxybenzothiazol-2-yl)-1,3-diethyl-4-(4-methoxyphenyl) guanidine (2c):

A mixture of 2,4-diethyl-3,5-di(4-methoxyphenyl) imino-1,2,4-thiadiazolidine (1c) (3.38 g, 0.01M) and hydrochloric acid (50 ml) was refluxed for two hours.

On addition of sodium hydroxide solution (1M) at 0°C the crude benzothiazolylguanidine was obtained which was recrystallized from ethanol. Yield: 1.97 g (51.2%), m.p.: 122-124°C. Calcd. for $C_{20}H_{24}N_4O_2S$: N,14.58; S,8.33, found: N,14.64; S,8.28. UV (MeOH, λ_{max} nm) : 284; IR (KBr, ν_{max} cm-1): 3286 (NH); 1602 (C=N); ^{1}HNMR($CDCl_3$, δ ppm): 1.00-1.20 (t, 6H, 2xCH_3); 3.60-3.75 (q. 4H 2x CH_2); 3.75 and 3.85 (2s, 6H, 2xOCH_3); 5.65-5.80 (broad singlet, 1H, NH, D_2O exchangeable); 6.75-4.45 (m, 7H, Ar).

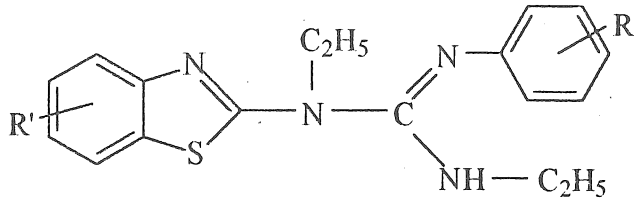
Table 1. Physical constants of 2,4-diethyl-3,5-diarylimino-1,2,4-thiadiazolidines.



(1)

Comp.	R	M.p. (oC)	Yield (%)	Mol. formula	Analysis % Calcd.	Found	Patition Coefficient (P)
a	H	82-84	58.2	$C_{18}H_{20}N_4S$	C H N	66.67 6.17 17.28	66.58 6.24 17.19	5.89
b	4-CH_3	129-130	51.6	$C_{20}H_{24}N_4S$	C H N S	68.18 6.82 15.91 9.09	68.10 15.82 9.15	2.62 6.64
c	4-OCH_3	109-110	44.6	$C_{20}H_{24}N_4O_2S$	N S	14.58 8.33	14.72 8.44	5.02
d	4-OC_2H_5	106-109	51.2	$C_{22}H_{28}N_4O_2S$	C H N	64.07 6.79 13.59	64.16 6.52 13.74	2.72
e	4-$CO.CH_3$	117-119	30.3	$C_{22}H_{24}N_4O_2S$	C H	64.70 5.88	64.58	3.89 5.72
f	4-Cl	138-139	52.4	$C_{18}H_{18}Cl_2N_4S$	N Cl	14.29 17.86	14.37 17.58	4.76
g	4-Br	148-150	46.5	$C_{18}H_{18}Br_2N_4S$	Br	33.20	33.08	2.64
h	3-CH_3	132-133	40.5	$C_{20}H_{24}N_4S$	N	15.91	15.97	2.12
i	3-OCH_3	121-123	40.3	$C_{20}H_{24}N_4O_2S$	C H	62.50 6.25	62.42 6.04	2.42
J	3-Cl	136-138	36.7	$C_{18}H_{18}Cl_2N_4S$	C H	55.10 4.58	55.22 4.35	3.04
k	2-OCH_3	107-109	39.2	$C_{20}H_{24}N_4O_2S$	N	14.58	14.62	2.10

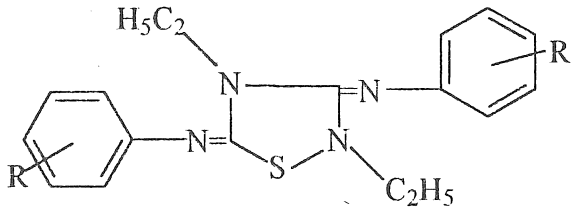
Table 2. Physical constants of 1-[2-(substituted benzothiazolyl)]-1,3-diethyl-4-arylguanidines.



(2)

Comp.	R	R'	M.p. (°C)	Yield (%)	Mol. formula	Analysis Calcd.	Found	Partition Coefficient (P)
a	H	H	126-127	68.4	$C_{18}H_{20}N_4S$	C H N	66.67 6.17 17.28	66.72 6.11 17.19	5.81
b	4-CH_3	6-CH_3	149-150	49.6	$C_{20}H_{24}N_4S$	C H N S	68.18 6.82 15.91 9.09	68.21 6.54 15.86 9.12	2.60
c	4-OCH_3	6-OCH_3	122-124	51.2	$C_{20}H_{24}N_4O_2S$	N S	14.58 8.33	14.64 8.28	4.91
d	4-OC_2H_5	6-OC_2H_5	119-121	56.2	$C_{22}H_{28}N_4O_2S$	C H N	64.07 6.79 13.59	64.02 6.62 13.48	2.61
e	4-CO.CH_3	6-CO.CH_3	121-123	32.3	$C_{22}H_{24}N_4O_2S$	N S	13.72 7.84	13.84 7.89	3.68
f	4-Cl	6-Cl	129-131	42.4	$C_{18}H_{18}Cl\,N_4S$	N H C	14.29 4.58 55.10	14.38 4.45 55.04	4.82
g	4-Br	6-Br	155-156	44.8	$C_{18}H_{18}Br_2N_4S$	N Br	11.62 33.20	11.52 33.24	2.70
h	3-CH_3	5CH_3	139-141	40.2	$C_{20}H_{24}N_4S$	C H	68.18 6.82	68.21 6.89	2.00
i	3-OCH_3	5-OCH_3	117-118	43.6	$C_{20}H_{24}N_4O_2S$	N	14.58	14.51	2.20
j	3-Cl	5-Cl	140-142	38.9	$C_{18}H_{18}Cl\,N_4S$	N	14.29	14.20	3.00
k	2-OCH_3	4-OCH_3	120-121	38.7	$C_{20}H_{24}N_4O_2S$	N	14.58	14.65	2.00

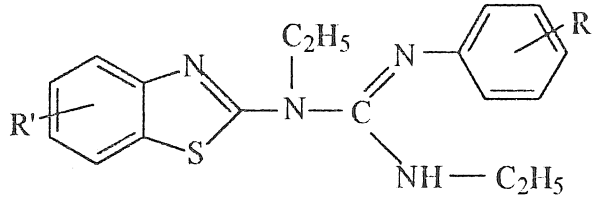
Table 3. Antibacterial and antifungal activities of 2,4-diethyl-3,5-diarylimino-1,2,4-thiadiazolidines.



(1)

Comp. No.	R	Anti-bacterial activity MIC (µg/ml)		Anti-fungal activity MIC (µg/ml)	
		S.aureus	*E.coli*	*P.citrinum*	*A.niger*
a.	H	200-250	150-200	80-100	80-100
b.	4-CH3	250-300	250-300	120-150	100-120
c.	4-OCH3	60-100	60-100	60-80	40-60
d.	4-OC2H5	40-60	20-40	20-40	20-40
e.	4-CO.CH3	100-150	100-150	100-120	80-100
f.	4-Cl	40-60	40-60	40-60	20-40
g.	4-Br	60-100	60-100	60-80	60-80
h.	3-CH3	250-300	250-300	150-200	120-150
i.	3-OCH3	100-150	60-100	80-100	60-80
j.	3-Cl	40-60	60-100	40-60	40-60
k.	2-OCH3	150-200	150-200	100-120	100-120
Miconazole-		15-20	15-20	5-8	4-6
Sulfamethizole		5-8	5-8		

Table 4. Anti-bacterial and Anti-fungal activities of 1-[2-(substituted benzothiazolyl)]-1,3-diethyl-4-arylguanidines



(2)

Comp. No.	R	R'	Anti-bacterial activity MIC (µg/ml)		Anti-fungal activity MIC (µg/ml)	
			S.aureus	*E.coli*	*P.citrinum*	*A.niger*
a.	H	H	200-250	150-200	100-120	100-120
b.	4-CH_3	6-CH_3	250-300	200-250	100-120	100-120
c.	4-OCH_3	6-OCH_3	100-150	100-150	60-80	60-80
d.	4-OC_2H_5	6-OC_2H_5	40-60	40-60	40-60	20-40
e.	4-$CO.CH_3$	6-$CO.CH_3$	150-200	150-200	100-120	100-120
f.	4-Cl	6-Cl	60-100	40-60	40-60	40-60
g.	4-Br	6-Br	100-150	60-100	60-80	60-80
h.	3-CH_3	5-CH_3	250-300	250-300	120-150	120-150
i.	3-OCH_3	5-OCH_3	100-150	100-150	100-120	80-100
j.	3-Cl	5-Cl	100-150	60-100	60-80	60-80
k.	2-OCH_3	4-OCH_3	200-250	150-200	120-150	100-120
Miconazole-		-	15-20	15-20	5-8	4-8
Sulfamethizole-		-	5-6	5-8	-	-

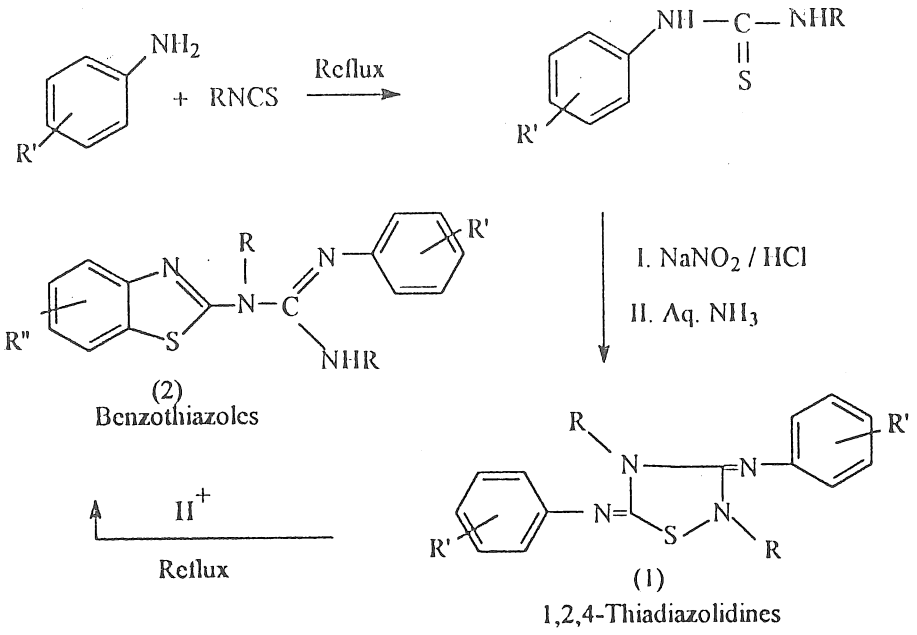
Other compounds of the series (2 a-k) were prepared in a similar manner and their physical parameters are recorded in Table2.

Antibacterial activity:

The pure bacterial cultures of *Staphylococcus aureus* (S.a.) and *Escherichia coli* (E.c.) were obtained from the Department of Microbiology, I.M.S., B.H.U., India. Nutrient broth and nutrient agar were procured from Hi media Pvt.Ltd. Bombay, India, Suitable dilutions of the synthesized compounds in propylene glycol were pepared in such a way that 0.1 ml of the suspension contained 20,40,60,100,150,200,300 and 400 g of the compounds. The determination of MICs was done by the plate bore method(8). MIC of the compounds were compared with standard drug sulfamethoxazole. The results are summarised in Table 3 and 4.

Antifungal activity:

The pure fungal strains of *Penicillium citrinum* and *Aspergillus niger* were obtained on agar slants from the Department of Botany, B.H.U. India. Solutions of the compounds of different concentrations in one ml were prepared in propylene glycol. Potato dextrose agar medium was used for the determination of MIC values of the compounds on the growth of the above two fungi. The agar disc method of Jackson(9) was followed. MIC values of the compounds were compared with standard drug Miconazole. The results are given in Table 3 and 4.



Scheme

R = Ethyl

R' = H, 4-CH_3, 3-CH_3 4-OCH_3, 3-OCH_3, 2-OCH_3, 4-Cl, 3-Cl, 4-Br, 4-$COCH_3$, 4-OC_2H_5

R" = H, 6-CH_3, 6-OCH_3, 6-OC_2H_5, 6-$COCH_3$, 6-Cl, 6-Br, 5-CH_3, 5-OCH_3, 5-Cl, 4-OCH_3

Results and Discussion

In the 1,2,4-thiadiazolidine series, the 4-ethoxy derivative (1 d) was found to be the most potent antibacteria and antifungal agent. This compound was more effective against gram negative bactireal than the gram positive ones. Other effective groups were 4-chloro and 3-chloro. The unsubstituted and methyl substituted compounds showed lower anti-bacterial activity than others. These compounds showed more antifungal and especially 4-ethoxy, 4-chloro, 4-methoxy, 4-bromo and 3-chlor substituted derivatives were highly effective antifungal agents. In this, the methyl substituted derivatives were less potent as compared to other groups described above.

Although the benzothiazolylguanidines were less active than the corresponding thi-adiazolidines, the 4-ethoxy and 4-chloro derivatives were the most potent compounds in the series. The antifungal activity is more pronounced in benzothiazolylguanidines as compared to antibacterial activity.

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