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Synthesis of Certain N-Aryl-N'-(2-pyrimidinyl) guanidine Derivatives as Potential Antimicrobial Agents

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Abstract□N-Aryl-N'-(4-hydroxy-6-methyl-2-pyrimidinyl) guanidines (IIa-c) were prepared by cyclization of N-arylbiguanides (Ia-c) with ethyl acetoacetate. Coupling of compounds (IIa-c) with the appropriate diazotized arylamine gave N-aryl-N'-(5-arylhydrazono-6-methyl-4-oxopyrimidin-2-yl) guanidines (IIIa-f). Whereas, their chlorination with phosphorus oxychloride followed by treatment of N-aryl-N'-(4-chloro-6-methyl-2-pyrimidinyl) guanidines (IVa-c) with the appropriate arylamine afforded the corresponding 4-arylamino derivatives (Va-f). Compounds (IIIa-f) were also formed when compounds (Ia-c) were treated with ethyl 2-arylhydrazono-3-oxobutyrates. The antimicrobial testing of some of the prepared compounds against some pathogenic microorganisms revealed that only two have a marked effect against *Escherichia coli.*

Keywords□Antimicrobial testing, pyrimidinylguanidines.

Furukawa[1] studied on the reaction of 1-arylbiguanide with some carboxylic esters and infered that the product may be s-triazine or pyrimidine ring system. In previous publication[2], we reported the antimicrobial activities of certain s-triazines prepared by reaction of 1-(p-fluoro-m-nitrophenyl) biguanide with ethyl formate, ethyl cyanoacetate and diethyl oxalate. The present investigation dealt with the synthesis and antimicrobial activity of certain N-aryl-N'-(2-pyrimidinyl) guanidines. The preparation of these compounds was undertaken due to the fact that some pyrimidine[3,4] derivatives are reported to exhibit antimicrobial and antiviral activities.

RESULTS AND DISCUSSION

Synthesis

The desired compounds (II-V) were prepared as depicted in the Scheme. The arylbiguanides (Ia-c) were prepared according to the reported procedure[5]. Reaction of compounds (Ia-c) with ethyl 2-arylhydrazono-3-oxobutyrates gave N-aryl-N'-(5-arylhydrazono-6-methyl-4-oxo-pyrimidine-2-yl) guanidines (IIIa-f). Structural assignment of compounds (IIIa-f) was based on elemental and spectral analyses The IR data revealed that the compounds (IIIa-f) are existing mainly in the arylhydrazono rather than arylazo structure. Compounds (IIIa-f) were also obtained by an alternate route. Compounds (Ia-c) were treated with ethyl acetoacetate to give N-aryl-N'-(4-hydroxy-6-methyl-2-pyrimidinyl) guanidines (IIa-c) followed by coupling with diazotized arylamines. On the other hand, chlorination of compounds (IIa-c) with phosphorus oxychloride followed by condensation of N-aryl-N'-(4-chloro-6-methyl-2-pyrimidinyl) guanidines (IVa-c) with the appropriate arylamine afforded the corresponding 4-arylamino derivatives (Va-f).

Antimicrobial testing

Five representative compounds were evaluated for antimicrobial activity against *Bacillus subtilis, Staphylococcus aureus* and *Escherichia coli,* by using the agar diffusion[6] technique. Compounds IIIb and IIIc exhibited a marked activity against *E. coli* and a moderate activity against *B. subtilis.* While compound Vc showed a moderate activity against *B. subtilis.* Compound Vf had a moderate activity against *B. subtilis* and *St. aureus* and compound IVa showed no antimicrobial activity against the used microorganisms (Table I).

EXPERIMENTAL

Melting points were determined on a Fisher-Johns melting point apparatus and were uncorrected.

Scheme:

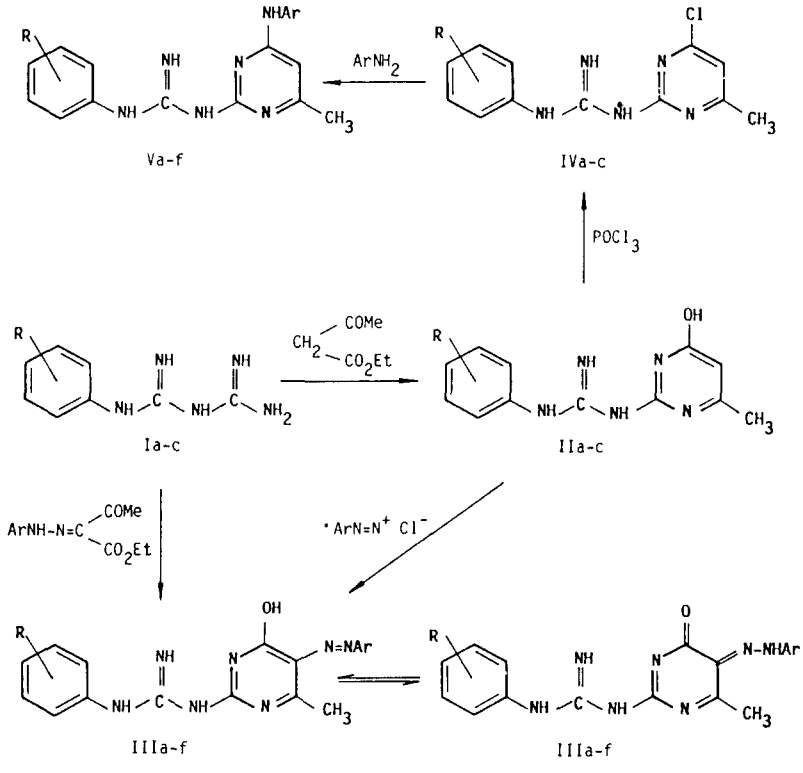

Table I. Antimicrobial activity of some representative compounds as 0.2% solutions in dimethylsulphoxide.

Comp. No.	*B. subtilis*	*St. aureus*	*E. coli*
IIIb	+	–	+ +
IIIc	+	–	+ +
IVa	–	–	–
Vc	+	–	–
Vf	+	+	–
DMSO	–	–	–

+, Moderate activity (inhibition zone 10-15 mm); + +, Marked activity (inhibition zone 16-20 mm); DMSO, Dimethylsulphoxide.

IR spectra were recorded on a Pye Unicam SP 1000 infrared spectrophotometer in KBr (ν in cm^{-1}). ^1H NMR spectra were recorded on an IBM FT-200 NMR spectrometer in DMSO-d_6 (chemical shifts in δ ppm).

N-Aryl-N'-(4-hydroxy-6-methyl-2-pyrimidinyl) guanidines (IIa-c)

A mixture of the appropriate 1-arylbiguanide (0.01 mol) and ethyl acetoacetate (1.43g, 0.011 mol) in methanol (20 m*l*) was heated under reflux for 2 h. The solid separated slowly from the reaction mixture during heating was collected, washed with hot ethanol and crystallized (Table II). ^1H NMR (DMSO-d_6) δ for compound (IIc): 2.1 (s, 3H,CH_3), 5.5 (s, 1H, H_5 of pyrimidine), 7.3-7.8 (m, 5H, ArH & OH), 8.1-8.9 (m, 3H, 3NH).

N-Aryl-N'-(5-arylhydrazono-6-methyl-4-oxopyrimidin-2-yl) guanidines (IIIa-f)

Method (A)

A solution of p-chloro or p-nitroaniline (5 mmol) in acetic acid (10 m*l*) and concentrated hydrochloric acid (15 m*l*) was cooled and diazotized with a solution of sodium nitrite (0.35g, 5 mmol) in water (25 m*l*). The cold diazonium salt was added gradually with continuous stirring to a cold solution of compounds (IIa-c) (5 mmol) in ethanol (50 m*l*), sodium acetate (5g) and water (5 m*l*). The solid products

Table II. Characterization data of the synthesized compounds

Comp. No.	R	Ar	Cryst. solv.*	m.p. °C	Yield %	Mol. formula#
IIa	4-C_2H_5O	–	DMF	255	88	$C_{14}H_{17}N_5O_2$
b	2-Br	–	DMF	265	75	$C_{12}H_{12}BrN_5O$
c	3-NO_2	–	DMF	282	80	$C_{12}H_{12}N_6O_3$
IIIa	4-C_2H_5O	2-$CH_3OC_6H_4$	DMF/W	268	80	$C_{21}H_{23}N_7O_3$
b	4-C_2H_5O	2,4-$Cl_2C_6H_3$	DMF/W	260	75	$C_{20}H_{19}Cl_2N_7O_2$
c	2-Br	2-$CH_3OC_6H_4$	DMF	275	82	$C_{19}H_{18}BrN_7O_2$
d	2-Br	2,4-$Cl_2C_6H_3$	DMF	270	85	$C_{18}H_{14}BrCl_2N_7O$
e	3-NO_2	2-$CH_3OC_6H_4$	DMF/W	290	78	$C_{19}H_{18}N_8O_4$
f	3-NO_2	2,4-$Cl_2C_6H_3$	DMF/W	285	75	$C_{18}H_{14}Cl_2N_8O_3$
IVa	4-C_2H_5O	–	B	80	75	$C_{14}H_{16}ClN_5O$
b	2-Br	–	B	95	80	$C_{12}H_{11}BrClN_5$
c	3-NO_2	–	B	105	78	$C_{12}H_{11}ClN_6O_2$
Va	4-C_2H_5O	4-ClC_6H_4	Aq.E.	110	90	$C_{20}H_{21}ClN_6O$
b	4-C_2H_5O	4-$NO_2C_6H_4$	E	118	92	$C_{20}H_{21}N_7O_3$
c	2-Br	4-ClC_6H_4	Aq.E.	132	90	$C_{18}H_{17}BrClN_6$
d	2-Br	4-$NO_2C_6H_4$	Aq.E.	135	85	$C_{18}H_{16}BrN_7O_2$
e	3-NO_2	4-ClC_6H_4	E	160	88	$C_{18}H_{16}ClN_7O_2$
f	3-NO_2	4-$NO_2C_6H_4$	E	165	95	$C_{18}H_{16}N_8O_4$

*DMF = Dimethylformamide, DMF/W = Dimethylformamide/water, B = Benzene, Aq.E. = Aqueous ethanol, E = Ethanol.
#Elemental analyses for C, H and N were obtained for all compounds (±0.4%).

were collected by filteration, washed with water, dried and crystallized (Table II).

Method (B)

Compounds (IIIa-f) were also prepared by the same procedure employed for the preparation of compounds (IIa-c) using ethyl 2-arylhydrazono-3-oxobutyrates instead of ethyl acetoacetate. IR (KBr) ν cm^{-1} for compound (IIIc): 1590 (C=N), 1680 (C=O), 3200-3350 (NH). ^1H NMR (DMSO-d_6) δ for compound (IIIa): 1.2-1.45 (t, 3H, OCH_2CH_3), 2.05 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 3.85-4.2 (q, 3H, OCH_2CH_3), 6.8-7.3 (m, 8H, ArH), 7.5-8.3 (m, 4H, 4NH).

N-Aryl-N'-(4-chloro-6-methyl-2-pyrimidinyl) guanidines (IVa-c)

A mixture of compounds IIa-c (0.01 mol) and phosphorus oxychloride (3 m*l*) was heated at 110-120° for 2 h. Excess phosphorus oxychloride was distilled off under vacuo and poured onto ice (10g). The reaction mixture was extracted several times with ether and the combined ethereal extract washed with sodium bicarbonate solution (10%) then with water and dried over anhydrous sodium sulphate. The solid obtained after distillation of the solvent was crystallized (Table I).

N-Aryl-N'-(4-arylamino-6-methyl-2-pyrimidinyl) guanidines (Va-f)

A mixture of compounds IVa-c (0.01 mol), p-chloro or p-nitroaniline (0.01 mol) and aqueous hydrochloric acid (30 m*l*, 50%) was refluxed for 2 h. The solution was then neutralized with sodium hydroxide solution (10%), the separated solid filtered and crystallized (Table II). ^1H NMR (DMSO-d_6) δ for compound (Vf): 2.2 (s, 3H, CH_3), 5.6 (s, 1H, H_5 of pyrimidine), 7.1-7.4 (m, 8H, ArH), 7.5-8.3 (m, 4H, 4NH).

Antimicrobial testing

The tested compounds were prepared as 0.2% solutions in dimethylsulphoxide, which were allowed to fill the ditches made in 23 g/*l* nutrient agar plates before they were inoculated on the surface with streaks of the selected microorganisms, *Bacillus subtilis, Staphylococcus aureus* and *Escherichia coli.* The plates were subsequently incubated at 37° for 24 h and the areas of the growth inhibition zones were determined.

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