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Synthesis and Antiinflammatory Properties of N-Substituted Guanidines

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Various N[(*p*-substituted/unsubstituted)phenyl), (substituted thiazol-2-yl/oxazol-2-yl/naphthothiazol-2-yl)],N'-[N"',N"'-dimethyl/diethylaminoacetyl],N"-phenyl guanidines were prepared from corresponding N-substituted thiocarbamides and were evaluated for their antiinflammatory activity. All the substituted guanidines (100 mg/Kg) provided 1-79 % protection against carrageenin induced edema in rats. Phenyl butazone (100 mg/Kg) was used as a standard drug for comparative evaluation and showed greater antiinflammatory activity. The results suggest that the presence of methoxy group on phenyl nuclei at *para* position enhances antiinflammatory activity. The increase in chain length on alkyl group of N $(R)_2$ skeleton also cause some enhancement in activity. Among heterocyclic molecules maximum level of antiinflammatory activity is shown by oxazol-2-yl substituted guanidines.

Key Words: Synthesis, Antiinflammatory, Guanidines.

INTRODUCTION

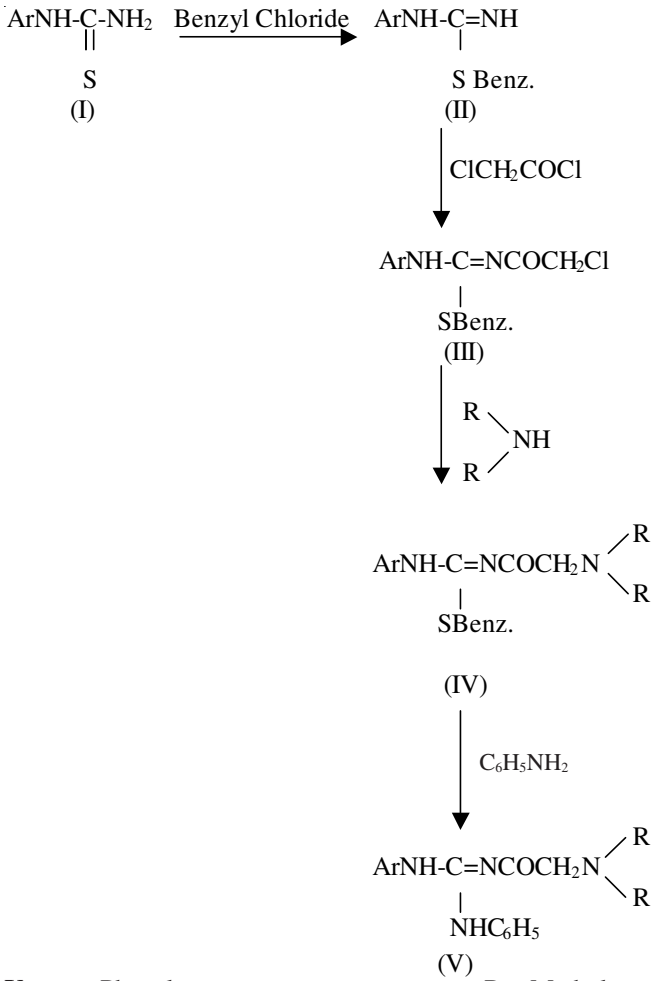
Occurrence of antimalarial activity in certain substituted diguanides[1] stimulated researchers to search for some other therapeutically useful members of this series and in due course led to the discovery of high antibacterial activity[2] more specially among a series of *bis* diguanides. At present guanidine derivatives are shown to possess diverse therapeutic values such as antiviral[3,4], adrenergic blocking agent[5] anthelmintics[6,7], antitumor[8], disinfectant[9] antifungal[10], cardiotonics[11], antiarrhythmines[12], *etc*. Guanidines derivatives have also shown marked antiinflammatory activity[13-19], considering the need of potent antiinflammatory agent and keeping in view the referred facts twenty new derivatives of guanidines were synthesized and evaluated for their antiinflammatory activity.

In the present study, 20 substituted thiocarbamides *viz.*, N-[(*p*-substituted/unsubstituted)-phenyl), (substituted thiazol-2-yl/oxazol-2-yl/naphthothiazol-2-yl)]thiocarbamide (**I**) were benzylated in ethanol and were concentrated to obtain the solid (**II**) {N [(*p*-substituted/unsubstituted)phenyl), (substituted thiazol-2-yl/oxazol-2-yl/naphthothiazol-2-yl)] S-benzyl thiocarbamide} which on treatment with freshly distilled chloroacetyl chloride gave (**III**) {N-[(*p*-substituted/unsubstituted)phenyl), (substituted thiazol-2-yl/oxazol-2-yl/naphthothiazol-2-yl)],N'-choloroacetyl,S-benzyl thiocarbamide} (**III**) on treatment with diethyl/dimethyl amine in benzene was concentrated to give solid (**IV**) {N-[(*p*-substituted/unsubstituted)phenyl), (substituted thiazol-2-yl/oxazol-2-yl/naphthothiazol-2-yl)],N'-[N"',N"'-dimethyl/diethyl aminoacetyl], S-benzyl thiocarbamide. Which on subsequent treatment with aniline gave the targeted compounds (**V**) of {N-[(*p*-substituted/unsubstituted)phenyl),(substituted thiazol-2-yl/oxazol-2-yl/naphthothiazol-2-yl)],N'[N"',N"'-dimethyl/diethyl aminoacetyl],N"phenyl guanidine}. These compounds were characterized by their sharp melting points, IR and PMR spectra. The general sequence of scheme is shown in **Scheme-I**.

EXPERIMENTAL

Synthesis of N-phenyl, S-benzyl thiocarbamide: A mixture of phenyl thiourea (0.01 mol) and benzyl chloride (0.01) mol in ethanol (50 mL) in presence of K_2CO_3 was refluxed for 8 h on steam bath. The solvent was removed under reduced pressure and the solid obtained was treated with water and filtered. The residue was recrystallised from EtOH to obtain N-phenyl, S-benzyl thiocarbamide with yield 78 % (m.p. 82 ºC). IR (KBr, ν_{max}, cm^{-1}): 1410 (due to CH_2-S), 1590 (due to C=N), 3260 (due to NH) PMR = δ 7.3- 7.5 (10H, m, 2xAr-H), δ 4.1-4.3 (1H, b, NH), δ 2.7-2.9 (2H, s, S-CH_2), δ 9.3 (1H, s, C=NH). Similarly other N-[(*p*-substituted phenyl), (substituted thiazol-2-yl/oxazol-2-yl/naphthothiazol-2-yl)]thiocarbamide were synthesized using the similar procedure.

Synthesis of N-phenyl,N'-chloro acetyl,S-benzyl thiocarbamide: Freshly prepared chloroacetyl chloride (0.01 mol) in dry benzene was gradually added to N-phenyl,S-benzyl thiocarbamide dissolved in benzene containing potassium



Va$_1$	= Phenyl;	R = Methyl
Va$_2$	= *p*-Tolyl;	R = Methyl
Va$_3$	= *p*-Chloro phenyl;	R = Methyl
Va$_4$	= *p*-Ethoxy phenyl;	R = Methyl
Va$_5$	= *p*-Methoxy phenyl;	R = Methyl
Va$_6$	= Phenyl ;	R = Ethyl
Va$_7$	= *p*-Tolyl;	R = Ethyl
Va$_8$	= *p*-Chloro phenyl;	R = Ethyl
Va$_9$	= *p*-Ethoxy phenyl;	R = Ethyl
Va$_{10}$	= *p*-Methoxy phenyl;	R = Ethyl
Vb$_1$	= 4-Phenyl thiazol-2-yl;	R = Methyl
Vb$_2$	= 4-*p*-Hydroxy phenyl thiazol-2-yl;	R = Methyl
Vb$_3$	= 4-*p*-Tolyl thiazol-2-yl;	R = Methyl
Vb$_4$	= 4-*p*-Phenyl oxazol-2-yl;	R = Methyl
Vb$_5$	= Naphthathiazolyl;	R = Methyl
Vb$_6$	= 4-Phenyl thiazol-2-yl;	R = Ethyl
Vb$_7$	= 4-*p*-Hydroxy phenyl thiazol-2-yl;	R = Ethyl
Vb$_8$	= 4-*p*-Tolyl thiazol-2-yl;	R = Ethyl
Vb$_9$	= 4-*p*-Phenyl oxazol-2-yl;	R = Ethyl
Vb$_{10}$	= Naphthathiazolyl;	R = Ethyl

Scheme-I

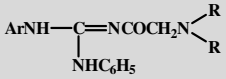
carbonate with constant stirring. The reaction mixture was stirred on the water bath at 70 ºC for 3 h. Excess benzene was distilled off and the residue was treated with water and filtered off to give yellow coloured solid N-phenyl, N'-chloro acetyl, S-benzyl thiocarbamide which was recrystallized from alcohol in the yield 69 % and m.p. 148 ºC. IR (KBr, ν_{max}, cm^{-1}) 1410 (due to CH_2-S), 1690 (due to C=O), 3260 (due to NH), 740 (due to C-Cl). PMR = δ 7.23-8.35 (10H, m, 2 × Ar-H), δ 4.1-4.3 (1H, b, NH), δ 2.45-3.2 (2H, s, S-CH_2), δ 9.3 (1H, s, C=NH) δ 3.4 (2H, s, CH_2-Cl). Similarly other{N-[(*p*-substituted phenyl), (substituted thiazol-2-yl/oxazol-2-yl/naphthothiazol-2-yl)],N'-choloroacetyl,S-benzyl thiocarbamide were prepared using the same reaction procedure.

Synthesis of N-phenyl, N'-(N''',N'''-diethyl aminoacetyl) S-benzyl thiocarbamide: Dietylamine (0.015 mol) in dry benzene was gradually added to N-phenyl, S-benzyl thiocarbamide dissolved in dry benzene containing triethylamine and the mixture was refluxed for 5 h. Excess of benzene and diethyl amine were recovered by distillation under reduced pressure and the residue was treated by $NaHCO_3$ solution, followed by water treatment and finally filtered. The solid so obtained was recrystallized from ethanol to give N-phenyl, N'-(N''',N'''-diethyl aminoacetyl) S-benzyl thiocarbamide in 62 % yield. (m.p. 125 ºC). IR (KBr, ν_{max}, cm^{-1}) 1420 (due to CH_2-S), 1690 (due to C=O), 3260 (due to NH). PMR = δ 7.1- 8.2 (10H, m, 2xAr-H), δ 2.6-3.1 (2H, s, CH_2-N), δ 1.4-1.8 (4H, q, 2 × CH_2-C), δ 9-1.1 (6H, t, 2 × CH_3-C). Similarly other {N-[(*p*-substituted phenyl), (substituted thiazol-2-yl/oxazol-2-yl/naphthothiazol-2-yl)],N'[N''',N'''-dimethyl/diethyl aminoacetyl], S-benzyl thiocarbamide were synthesized using the similar procedure.

Synthesis of N-phenyl,N'[N''',N'''-diethyl aminoacetyl], N''-phenyl guanidine: Aniline (0.015 mol) was gradually added to the solution of N-phenyl, N'-(N''',N'''-diethyl aminoacetyl) S-benzyl thiocarbamide (0.01 mol) in benzene and the mixture was refluxed for 10 h. Excess of benzene was recovered by distillation under reduced pressure and the residue was treated first with petroleum ether and then with solvent ether. So formed N-phenyl,N'-[N''',N'''-diethyl aminoacetyl], N''-phenyl guanidine was recrystallised with alcohol in the yield 56 % (m.p. 210 ºC). IR (KBr, ν_{max}, cm^{-1}): 1660 (due to C=O), 754 and 696 (due to C_6H_5), 3240 (due to NH),1200 due to (N-(C=N)-N). PMR δ 7.1-8.6 (10H, m, 2 × Ar-H), δ 2.6-3.1 (2H, s, CH_2-N), δ 1.4-1.8 (4H, q, 2 × CH_2-C), δ 9-1.1 (6H, t, 2 × CH_3-C) δ 4.1-4.4 (2H, b, 2 × NH). Similarly, other N'-(*p*-substituted phenyl), (substituted thiazol-2-yl/ oxazol-2-yl/naphthothiazol-2-yl)], N'-[N''',N'''-dimethyl/ diethyl aminoacetyl], N''-phenyl guanidine were synthesized using the same reaction procedure. The physical characteristic data of the synthesized compounds are given in Table-1.

Antiinflammatory screening: The prepared compounds were tested for antiinflammatory screening by carrageenin induced edema in rats by the method of Winter *et al.*[20]. Albino rats weighing 80-120 g were allowed food, water and libitum, were used in this study, the rats were divided in the groups of 5-6 animals each. A suspension of carrageenin (1 %) in distilled water was prepared fresh 1 h before use and 0.1 mL was injected under the plantar aponeurosis of right hand paw. The various substituted guanidines were prepared in Tween-80 and were injected intraperitonially in the dose 100 mg/Kg to a group of five rats 1 h before injection of carrageenin. The control of 5 rats received an equivalent amount of Tween 80/suspension in water. The mean increase in the paw volume, due to carrageenin induced oedema was measured by the method of Bhatt *et al.*[21] before and 3 h after carrageenin treatment and was used to calculate the antiinflammatory activity of substituted

TABLE-1
PHYSICAL CHARACTERISTIC DATA OF {N-[(*p*-SUBSTITUTED/UNSUBSTITUTED)PHENYL), (SUBSTITUTED THIAZOL-2-YL/OXAZOL-2-YL/NAPHTHOTHIAZOL-2-YL)], N'[N"',N"'-DIMETHYL/DIETHYL AMINOACETYL], N"-PHENYL GUANIDINES



Compound No.	Ar	R	m.p. (ºC)	Yield (%)	m.f.
Va_1	Phenyl	Methyl	207	55	$C_{17}H_{20}N_4O$
Va_2	*p*-Tolyl	Methyl	209	57	$C_{18}H_{22}N_4O$
Va_3	*p*-Chloro phenyl	Methyl	227	58	$C_{17}H_{19}N_4OCl$
Va_4	*p*-Ethoxy phenyl	Methyl	224	59	$C_{19}H_{24}N_4O_2$
Va_5	*p*-Methoxy phenyl	Methyl	216	55	$C_{18}H_{22}N_4O_2$
Va_6	Phenyl	Ethyl	210	56	$C_{19}H_{24}N_4O$
Va_7	*p*-Tolyl	Ethyl	214	59	$C_{20}H_{26}N_4O_2$
Va_8	*p*-Chloro phenyl	Ethyl	235	58	$C_{19}H_{23}N_4OCl$
Va_9	*p*-Ethoxy phenyl	Ethyl	231	60	$C_{21}H_{28}N_4O_2$
Va_{10}	*p*-Methoxy phenyl	Ethyl	219	53	$C_{20}H_{26}N_4O$
Vb_1	4-Phenyl thiazol-2-yl	Methyl	221	52	$C_{20}H_{21}N_5OS$
Vb_2	4-*p*-Hydroxy phenyl thiazol-2-yl	Methyl	227	57	$C_{20}H_{21}N_5O_2S$
Vb_3	4-*p*-Tolyl thiazol-2-yl	Methyl	223	51	$C_{21}H_{23}N_5OS$
Vb_4	4-*p*-Phenyl oxazol-2-yl	Methyl	217	56	$C_{20}H_{21}N_5O_2$
Vb_5	Naphthathiazolyl	Methyl	225	57	$C_{22}H_{21}N_5OS$
Vb_6	4-Phenyl thiazol-2-yl	Ethyl	224	53	$C_{22}H_{25}N_5OS$
Vb_7	4-*p*-Hydroxy phenyl thiazol-2-yl	Ethyl	230	56	$C_{22}H_{25}N_5O_2S$
Vb_8	4-*p*-Tolyl thiazol-2-yl	Ethyl	225	50	$C_{23}H_{27}N_5OS$
Vb_9	4-*p*-Phenyl oxazol-2-yl	Ethyl	220	57	$C_{22}H_{25}N_5O_2$
Vb_{10}	Naphthathiazolyl	Ethyl	228	56	$C_{24}H_{25}N_5OS$

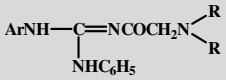
guanidines. In present study, phenyl butazone (100 mg/kg i.p.) was used as the standard reference drug for comparative evaluation the percentage of inhibition was calculated between substance treated and vehicle treated groups from the mean oedema value. The significance of the results was calculated by student's 't' test.

RESULTS AND DISCUSSION

From the **Va** series compounds **Va_2**, **Va_5** and **Va_{10}** have shown noteworthy antiinflammatory activity, whereas the antiinflammatory activity of compounds **Va_1**, **Va_4**, **Va_8** is not significant. **Vb** series provided encouraging results as **Vb_4** exhibited maximum antiinflammatory potency. Some antiinflammatory activity is also shown by **Vb_1**, **Vb_2**, **Vb_9**, **Vb_{10}** whereas **Vb_5**, **Vb_8** are found insignificant (Table-2).

The results indicate that although no clear structure activity relationship is observed yet the eligible facts suggest that in **Va** series presence of methoxy group on phenyl nuclei at *p*-position enhances antiinflammatory activity. Also the increase in chain length of alkyl group of amine skeleton causes some improvement in antiinflammatory activity. Next level of activity is shown by *p*-tolyl nucleous. Also it is clear from

TABLE-2
ANTIINFLAMMATORY SCREENING OF {N-[(*P*-SUBSTITUTED/UNSUBSTITUTED)PHENYL), (SUBSTITUTED THIAZOL-2-YL/OXAZOL-2-YL/NAPHTHOTHIAZOL-2-YL)], N'[N"',N"'-DIMETHYL/DIETHYL AMINOACETYL],N"PHENYL GUANIDINES



S. No.	Compound No.	Increase in paw volume (mean + SE)	Inhibition (%)	*p*-Value
1	Vehicle control	0.384 + 0.062	–	–
2	**Va_1**	0.302 + 0.420	25.54	N.S
3	**Va_2**	0.122 + 0.020	68.056	< 01
4	**Va_4**	0.226 + 0.046	40.99	N.S
5	**Va_5**	0.105 + 0.034	72.48	< 0.01
6	**Va_8**	0.253 + 0.069	34.037	N.S
7	**Va_{10}**	0.790 + 0.040	79.37	< 0.01
8	**Vb_1**	0.319 + 0.012	51.032	< 0.025
9	**Vb_2**	0.299 + 0.022	54.130	< 0.01
10	**Vb_4**	0.170 + 0.014	73.96	< 0.01
11	**Vb_5**	0.366 + 0.010	44.04	N.S.
12	**Vb_8**	0.381 + 0.034	41.670	N.S
13	**Vb_9**	0.280 + 0.055	63.55	< 0.01
14	**Vb_{10}**	0.333 + 0.099	57.032	< 0.025
15	Phenyl butazone	0.072 + 0.084	90.625	< 0.001

the results that *p*-chloro and *p*-ethoxy substitution lowers the activity of the compound. The results of $\mathbf{V_b}$ series shows the maximum level of activity in oxazol-2-yl substituted guanidines.

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