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Synthesis of Mannich Bases of Benzimidazole as Possible Antiviral Agents

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The benzimidazolin-2-thione and formaldehyde stirred and added substituted-2-amino. benzothiazole in presence of traces of conc. HCl and refluxed for 1 h. to give 1,3-bis-[substituted amino benzothiazolyl]-methyl benzimidazolin-2-thione(III) by Mannich reaction. The antiviral screenings of all compounds were studied against tobacco mosaic virus (TMV) and cucumber green mottle mosaic virus (CGMMV) both *in vitro* and *in vivo*.

INTRODUCTION

Benzimidazole derivatives attract wide interest on account of their antiinflammatory[1–3], herbicidal[4], pesticidal[5], antimicrobial[6], anthelminthic[7] and antiviral[8] activities. While on the other hand several benzothiazole derivatives are useful as intermediates for dyes, plant protectants and pharmaceuticals[9, 10].

These findings prompted us to synthesise 1,3-bis-(N-substituted amino-benzothiazolyl) methyl benzimidazolin-2-thione (III) (Scheme-I), which can be prepared by taking benzimidazolin-2-thione on Mannich reaction with appropriate 2-amino-benzothiazole and formaldehyde in the presence of conc. HCl. These compounds were evaluated for antiviral activity against TMV and CGMMV both *in vitro* and *in vivo*.

EXPERIMENTAL

The instrumental details are same as in previous papers. The substituted 2-amino- benzothiazoles were prepared according to the procedure recorded in literature[11].

1,3-Bis-[6′-chloro-2′-amino-benzothiazolyl]-methyl benzimidazolin-2-thione (12)

The mixture of benzimidazolin-2-thione (0.01 mol) and formaldehyde (0.03 mol) in 20 mL ethanol was stirred for 30 min. To this solution 6-chloro-2-amino-benzothiazole (0.02 mol) in ethanol was added slowly with traces of conc. HCl and refluxed for 1 h. The reaction mixture was cooled and poured on crushed ice and neutralised by 10% $NaHCO_3$ solution; the separated solid was filtered, washed with cold water, dried and recrystallised from aqueous ethyl alcohol to

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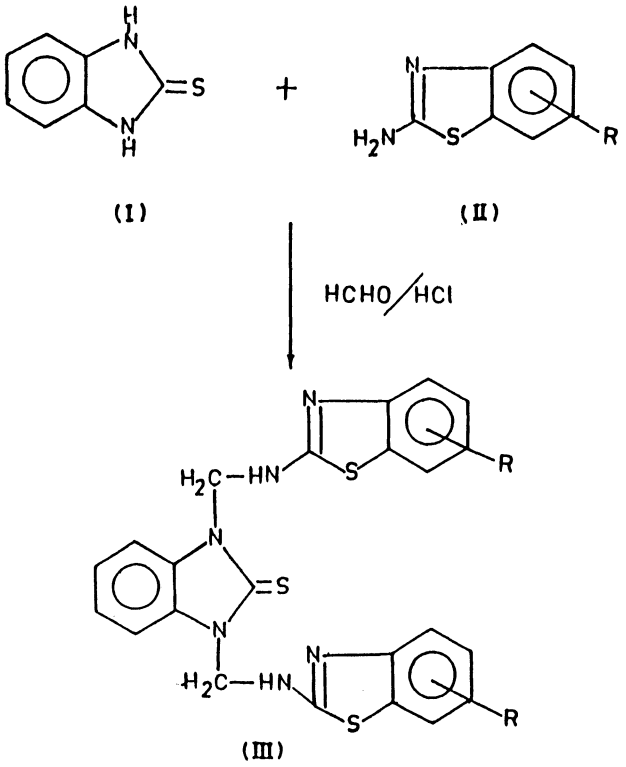

SCHEME I

give (12). m.p.: 163°C ; Yield: 76%; IR: 3350 (—NH), 2900 (—CH_2), 1635 (C=N) and 1240 cm^{-1} (C—N).

PMR: δ 5.05 (S, 4H, —N—CH_2—N), 6.7–7.9 (m, 12H, Ar—H and —NH).

The IR and PMR spectra of other members of the series were also in agreement with their structures assigned. Similarly all the compounds were synthesised and the physical data were recorded in Table-1.

Antiviral Activity

All compounds were evaluated for antiviral activity against TMV and CGMMV both *in vitro* and *in vivo* by the method of verma *et al.*[11]

Antiviral activity against tobacco mosaic virus (TMV)

The culture of TMV was maintained by successive host inoculation (*Datura stramonium* plants). The compounds were dissolved in their respective solvents. The solutiions were termed as "test solution". The % of inhibition was expressed as

$$\% \text{ inhibition} = \frac{(C - T) \times 100}{C}$$

where C = number of lesions on control leaves

and T = number of lesions on treated leaves.

TABLE-1
PHYSICAL CHARACTERISATION DATA OF SYNTHESISED COMPOUNDS

Comp. No	Substituent R	m.p. (°C)	Yield (%)	Mol. formula	% N	
					Found	(Calcd.)
1	H	62	70	$C_{23}H_{18}N_6S_3$	17.40	(17.72)
2	4′-CH_3	65	72	$C_{25}H_{22}N_6S_3$	16.38	(16.73)
3	5′-CH_3	70	65	$C_{25}H_{22}N_6S_3$	16.40	(16.73)
4	6′-CH_3	76	68	$C_{25}H_{22}N_6S_3$	16.64	(16.73)
5	4′-OCH_3	26	60	$C_{25}H_{22}N_6S_3O_2$	15.70	(15.73)
6	5′-OCH_3	98	62	$C_{25}H_{22}N_6S_3O_2$	15.56	(15.73)
7	6′-OCH_3	120	66	$C_{25}H_{22}N_6S_3O_2$	14.62	(15.94)
8	4′-OC_2H_5	102	59	$C_{25}H_{26}N_6S_3O_2$	14.74	(14.94)
9	5′-OC_2H_5	121	64	$C_{25}H_{26}N_6S_3O_2$	14.91	(14.94)
10	6′-OC_2H_5	138	72	$C_{25}H_{26}N_6S_3O_2$	15.30	(15.46)
11	5′-Cl	142	70	$C_{23}H_{16}N_6S_3Cl_2$	15.44	(15.46)
12	6′-Cl	164	76	$C_{23}H_{16}N_6S_3Cl_2$	13.10	(13.29)
13	5′-Br	152	61	$C_{23}H_{16}N_6S_3Br_2$	13.18	(13.29)
14	6′-Br	174	60	$C_{23}H_{16}N_6S_3Br_2$	13.18	(13.29)
15	5′-NO_2	141	60	$C_{23}H_{16}N_8S_3O_4$	19.39	(19.85)
16	6′-NO_2	169	78	$C_{23}H_{16}N_8S_3O_4$	19.68	(19.85)

*All compounds crystallised from aq. methanol and gives C and H analysis satisfactorily.

TABLE-2
ANTIVIRAL ACTIVITY DATA

Comp. No.	TMV/*D.s.**		CGMMV/*C.a.**	
	in vitro	*in vivo*	*in vitro*	*in vivo*
1	40	22	48	42
2	56	53	52	46
3	58	55	54	48
4	60	54	58	49
5	62	56	58	49
6	64	57	54	43
7	66	59	62	56
8	70	62	64	58
9	72	64	65	59
10	71	63	66	62
11	58	49	39	29
12	59	48	40	32
13	54	45	47	44
14	56	48	49	46
15	78	69	68	66
16	76	70	69	65

**D.s.* = *Datura stramonium* †*C.a.* = *Chenopodium amaranticolor*

It is evident that most of the compounds have shown significant activity against TMV *in vitro* and *in vivo* (Table-2).

Antiviral activity against cucumber green mottle mosaic virus (CGMMV)

The culture of CGMMV was maintained by successive host inoculation (*Chenopodium amaranticolor* plants). It is evident that most of the compounds have exhibited significant inhibition against CGMMV *in vitro* and *in vivo* (Table-2).

From the activity data, it was established that the benzothiazole moiety having —OCH_3, —OC_2H_5 and —NO_2 groups shows good activity against TMV and CGMMV *in vitro* and *in vivo*. The benzothiazole moiety having groups such as H, —CH_3, —Cl and —Br shows moderate activity.

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