SYNTHESIS OF 3-(SUBSTITUTED AMINOMETHYL)-5-(NITROBEZYLIDENE)-4-THIAZOLIDINONE-2-THIONES AS POTENTIAL ANTIVIRAL AGENTS

ALKA PANDE and V. K. SAXENA
Department of Chemistry, Lucknow University, Lucknow 226007, India.

ABSTRACT

Twelve new title compounds (4–15) were synthesized by the Mannich reaction of 5-(nitrobenzylidene)-4-thiazolidinone-2-thiones (2 and 3) with appropriate amines in the presence of aq. HCHO. All the compounds were tested against sunnhemp rosette virus (SRV) and Ranikhet disease virus (RDV). Most of compounds exhibited significant protection against these viruses.

INTRODUCTION

4-THIAZOLIDINONE-2-THIONE derivatives have been reported to display remarkable antifungal[1], antibacterial[2], herbicidal[3] and insecticidal[4] activities. A survey of the recent work on 4-thiazolidinone-2-thiones revealed that it inhibited itself the multiplication of ECHO 12 virus[5] and some 5-benzylidene-4-thiazolidinone-2-thiones, obtained by the condensation of 4-thiazolidinone-2-thione with aldehydes, exhibited remarkable activity against vesicular virus[6]. These observations prompted us to synthesize some new thiazolidinone derivatives.

EXPERIMENTAL PROCEDURE

The melting points were determined in open capillaries in conc H_2SO_4 melting point bath and are therefore uncorrected. IR spectra were recorded on Perkin Elmer spectrophotometer using KBr. PMR spectra were recorded on Perkin Elmer spectrometer using TMS as internal reference (chemical shift in δ ppm). Purity of the compounds was checked on silica gel TLC plates and the spots were located by iodine vapours.

4-Thiazolidinone-2-thione (Rhodanine) (1) was prepared by the method of Campbell and McKail[7] and 5-(nitrobenzylidene)-4-thiazolidinone-2-thiones (2 and 3) were also prepared by known methods[8].

3-(Substituted aminomethyl)-5-(nitrobenzylidene)-4-thiazolidinone-2-thiones (4–15): To a suspension of 5-(nitrobenzylidene)-4-thiazolidinone-2-thione (0.005 mol) in 10 ml of warm methanol, were added 1 ml of 37% formalin and an appropriate amine (0.005 mol) under shaking. The reaction mixture was further stirred for 5 min with occasional warming after which it was allowed to stand overnight at room temperature. The solid, thus separated, was filtered, dried and recrystallized from chloroform/ethyl acetate. Compounds 4–15, thus synthesized, are recorded in table 1.

IR(KBr): Compounds showed IR spectral bands at 1710–1700 (C=O), 1210–1200 (C=S) and 1650–1640 (C=CH). PMR($CDCl_3$):

Compd. 9: 1.44 – 1.76 (m, 6H, CH_2), 3.38 – 3.74 (m, 4H, N-CH_2), 5.44 (s, 2H, N-CH_2-N), 6.90–7.64 (m, 9H, 8Ar-H and 1C = CH).

BIOASSAY

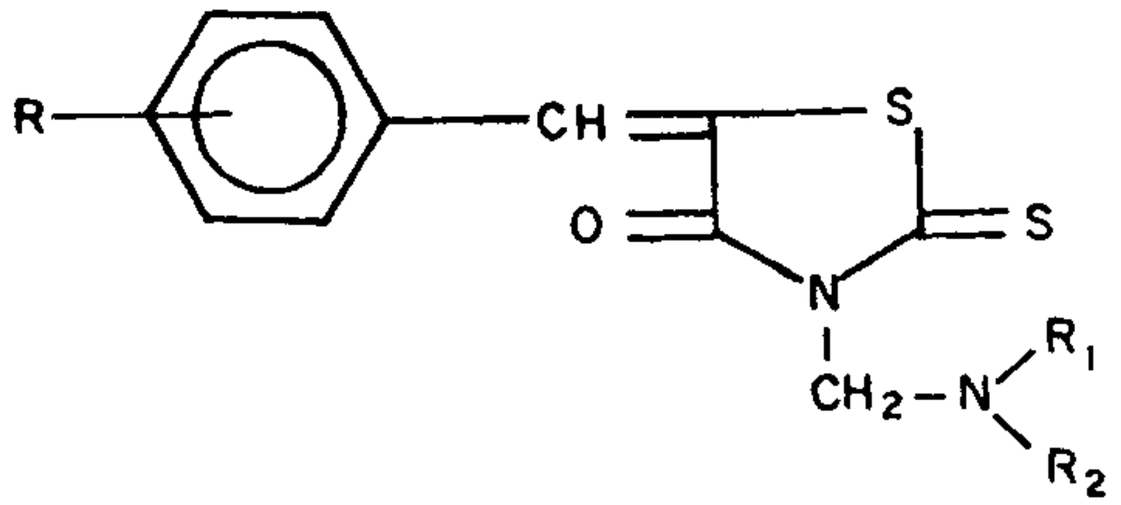
All the twelve compounds were screened against SRV, *in vitro* as well as *in vivo*, and against RDV. The results of screening are recorded in table 2.

a. *Antiviral activity against sunnhemp rosette virus*: The culture of sunnhemp rosette virus (SRV) was maintained by successive host innoculation (Cyamopsis tetragonoloba plants). The procedure of Mukerjee *et al*[9] was followed for *in vitro* and *in vivo* antiviral testing.

The solutions of test compounds were prepared by dissolving 5 mg of the compound in 1 ml of ethanol and making up the volume to 4 ml with distilled water. These solutions were termed 'test solutions'. The inhibition was expressed as % inhibition $= C - T/C \times 100$ where, C is the number of lesions on control leaves and T the number of lesions on treated leaves.

b. *Antiviral activity against Ranikhet disease virus*: All the compounds were tested against Ranikhet disease virus (RDV) in stationary culture of the chorioallantoic membrane of chick embryo. The strain of the Ranikhet disease virus was the same as employed by Babbar and Dhar[10]. Chorioallantoic membranes (CAM) of chick embryo (10 days old) were

Table 1. *3-(Substituted aminomethyl)-5-(nitrobenzylidene)-4-thiazolidinone-2-thiones (4–15).*



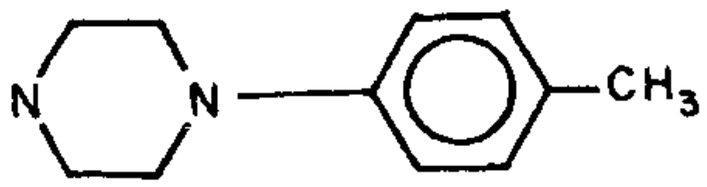
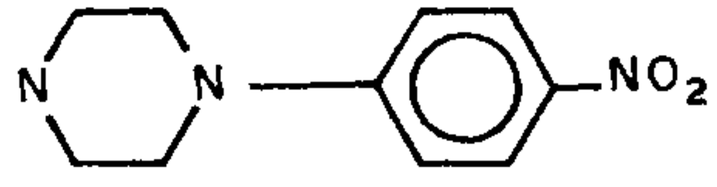
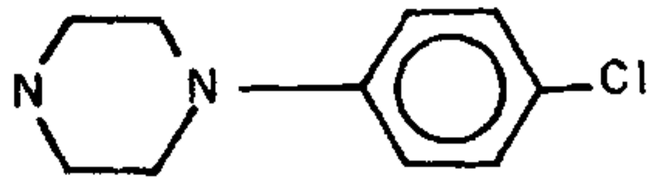
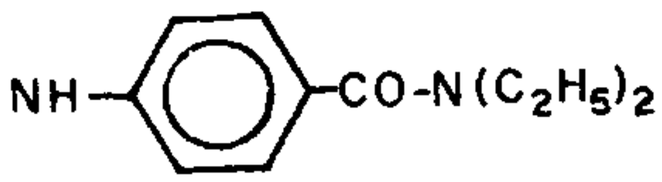
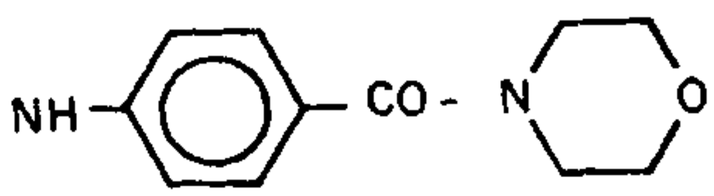
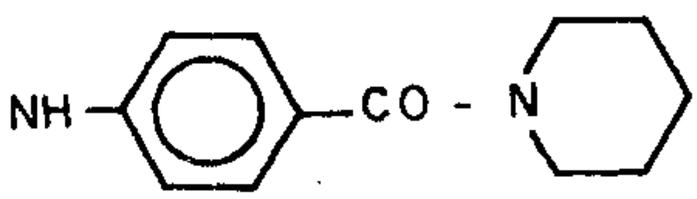
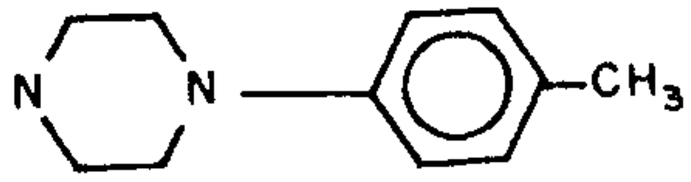
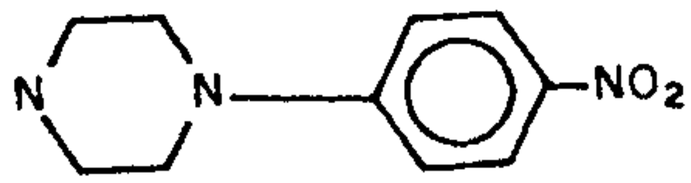
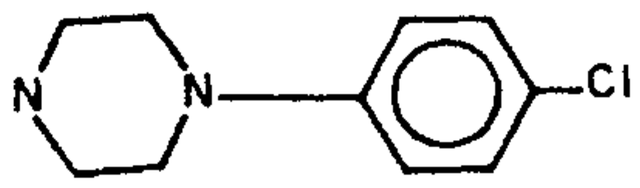
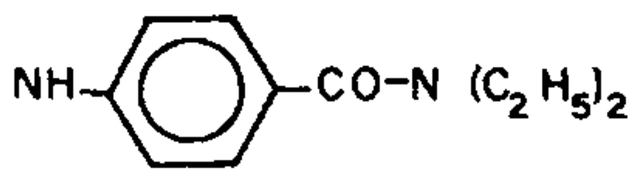
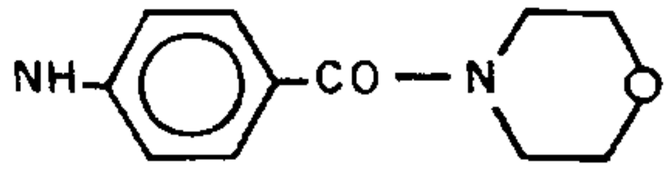
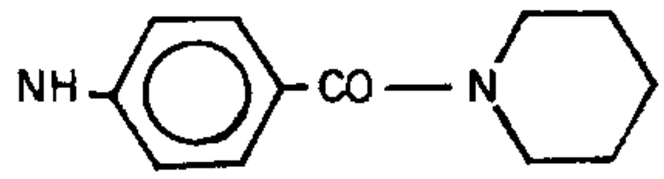
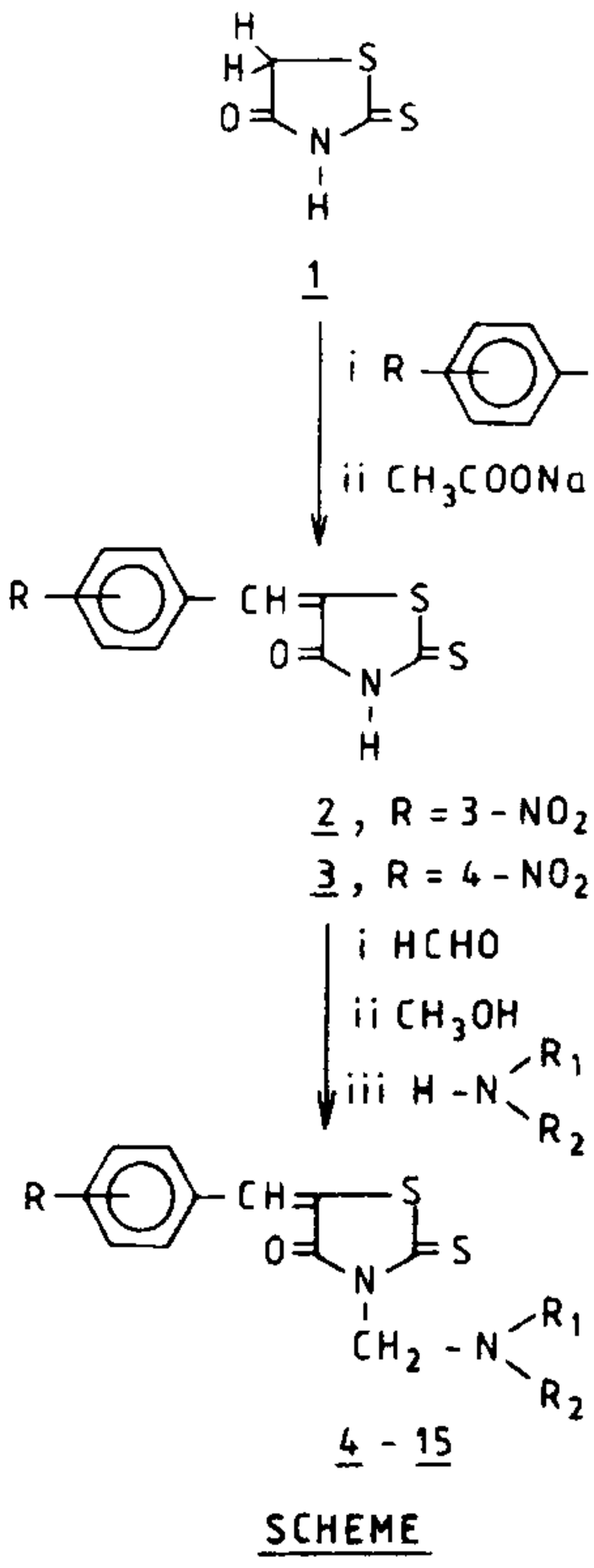
Compd. No.	$N\begin{matrix}R^1\\R^2\end{matrix}$	M.P. °C	Molecular formula
	R = 3 - NO_2		
4		172	$C_{22}H_{22}N_4O_3S_2$
5		160	$C_{21}H_{19}N_5O_5S_2$
6		181	$C_{21}H_{19}ClN_4O_3S_2$
7		203	$C_{22}H_{22}N_4O_4S_2$
8		177	$C_{22}H_{20}N_4O_5S_2$
9		219	$C_{23}H_{22}N_4O_4S_2$
	R = 4 - NO_2		
10		163	$C_{22}H_{22}N_4O_3S_2$
11		198	$C_{21}H_{19}N_5O_5S_2$
12		149	$C_{21}H_{19}ClN_4O_3S_2$

Table 1. (*continued*)

Compd. No.	$N<^{R^1}_{R^2}$	M.P. °C	Molecular formula
13		211	$C_{22}H_{22}N_4O_4S_2$
14		186	$C_{22}H_{20}N_4O_5S_2$
15		223	$C_{23}H_{22}N_4O_4S_2$

Yields ranged between 60–70%.
All the compounds gave satisfactory analyses for C, H, N and S.



SCHEME

Table 2 *Antiviral activity of compounds 4–15 against SRV and RDV.*

Compd. No.	Antiviral activity against SRV: Per cent inhibition *In-vitro*	Antiviral activity against SRV: Per cent inhibition *In-vivo*	Antiviral activity against RDV: Per cent inhibition
4	48[b]	54[a]	25
5	55[a]	46[b]	0
6	52[a]	40[b]	0
7	78[a]	64[a]	50
8	68[a]	75[a]	40
9	70[a]	68[a]	50
10	56[a]	49[b]	25
11	40[b]	52[a]	25
12	48[b]	54[a]	0
13	68[a]	60[a]	50
14	62[a]	69[a]	55
15	59[a]	65[a]	50

Results significant: a = at 1% level, b = at 5% level.

taken and the culture prepared according to the method of Babbar[11,12].

RESULTS AND DISCUSSION

The results of antiviral activity against SRV reveal that these compounds *in vitro* exhibited significant inhibitory effect in a range of 52–78% except com-

pounds 4, 11 and 12 which showed mild activity, compound 7 being the most active (78%). However, all of them *in vivo* showed significant inhibition of SRV ranging from 52–75% except compounds 5, 6 and 10 which showed less activity, the maximum inhibition of 75% being caused by Compound 8.

It appears from table 2 that compounds containing diethyl-, morpholino- and piperidino carbamoyl phenylamino-methyl substituents at position 3- of 4-thiazolidionone-2-thione nucleus develop significant activity *in vitro* as well as *in vivo*. The 4-nitro analogs have shown less inhibitory efficacy than those of 4-nitro derivatives.

Among the twelve compounds tested against RDV, six compounds 7, 8, 9, 13, 14 and 15 were active and the rest were inactive.

It can thus be inferred that the presence of diethyl-, morpholino- and piperidino carbamoyl phenylaminomethyl substituents at position 3- of 4-thiazolidinone-2-thione moiety makes the compounds significantly active against SRV as well as against RDV.

ACKNOWLEDGEMENT

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NEWS

NATIONAL SYMPOSIUM ON PHYTOBACTERIOLOGY

The Centre for Advanced Study in Botany, University of Madras, Madras, organized the National Symposium on Phytobacteriology during March 14–15, 1986. The symposium which attracted several distinguished phytobacteriologists from different states was inaugurated by Prof. G. Rangaswami, former Vice-Chancellor, Tamil Nadu Agricultural University, Coimbatore. Presentations included 5 special talks, 35 papers on the ecology, control and genetics of phytopathogenic bacteria and a special address by Dr D. N. Srivastava, Asst. Director-General of Indian Council of Agricultural Research. The University Grants Commission sponsored the symposium.

One of the important highlights of the symposium was the report on isolation of plasmids from *Xanthomonas* spp and *Pseudomonas solanacearum*. For the control of major bacterial pathogens it was recommended that emphasis be laid on looking into the feasibility of biological control particularly by bacteriophages and antagonistic rhizobacteria. At the conclusion of the symposium the delegates made the following recommendations for follow-up: 1. Conducting a workshop on bacterial plant pathology; 2. Publishing a bulletin, twice a year, to publish short reports, focus on research findings and news item; 3. Starting a culture collection to store freeze-dried cultures of plant pathogenic bacteria; and 4. Conducting an International symposium on Phytobacteruology (after a period of 3–4 years).