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# Synthesis of Some New 5[[{(substituted amino) methyl} Benzimidazole-2-yl]thio] Methyl-N-[(substituted-phenyl) methylene]-1,3,4-Thiadiazoles-2-amino as Potential Anthelmintic Drugs

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The title compounds have been synthesised and screened for their anthelmintic activity against *Hymenolepsis nana* infection in mice and *Nippostrongylus brasiliensis* infection in rats. These compounds have also been tested for their *in vivo* and *in vitro* activity against tobacco mosaic virus (TMV) and cucumber green mottel mosaic virus (CGMMV).

## INTRODUCTION

Of the several approaches studied in medicinal chemistry, the drug hybridisation approach has been found to yield a variety of drugs possessing better activity than the hybridising pharmacophores[1]. With this view, compounds (5–15) have been synthesised which represent two pharmacological important pharmacophores *e.g.* benzimidazoles[2,3] and thiadiazol[4,5].

The 5-[(1H-benzimidazol-2-yl)-thio-methyl]-N-[(substituted-phenyl) methylene]-1,3,4-thiadiazoles-2-amine (4) have been synthesised by the condensation of 5-(1H-benzimidazol-2-yl)-thio-methyl-1,3,4-thiadiazol-2-amine[6] (3) with substituted aldehyde. The latter were prepared by the reaction of 2-carboxymethylthiobenzimidazol[7] (1) with thiosemicarbazide (2) in presence of sodium hydroxide. Compounds (4) have been characterised by their analytical and IR spectra data, max $cm^{-1}$ 1600–1580 (C–N); 1570–1500) C=C phenyl) and 3300–3250 ($NH_2$). The final compounds (5–15) have been prepared by the reaction of compounds (4) with secondary amine in presence of formaline (i.e. Mannich reaction). Compounds (5–15) have been characterised by their sharp melting point, analytical, IR and NMR data (Scheme 1).

## EXPERIMENTAL

Melting points were taken in open capillary tubes using sulphuric acid bath and are uncorrected. IR spectra in KBr were recorded on a Perkin Elmer 137

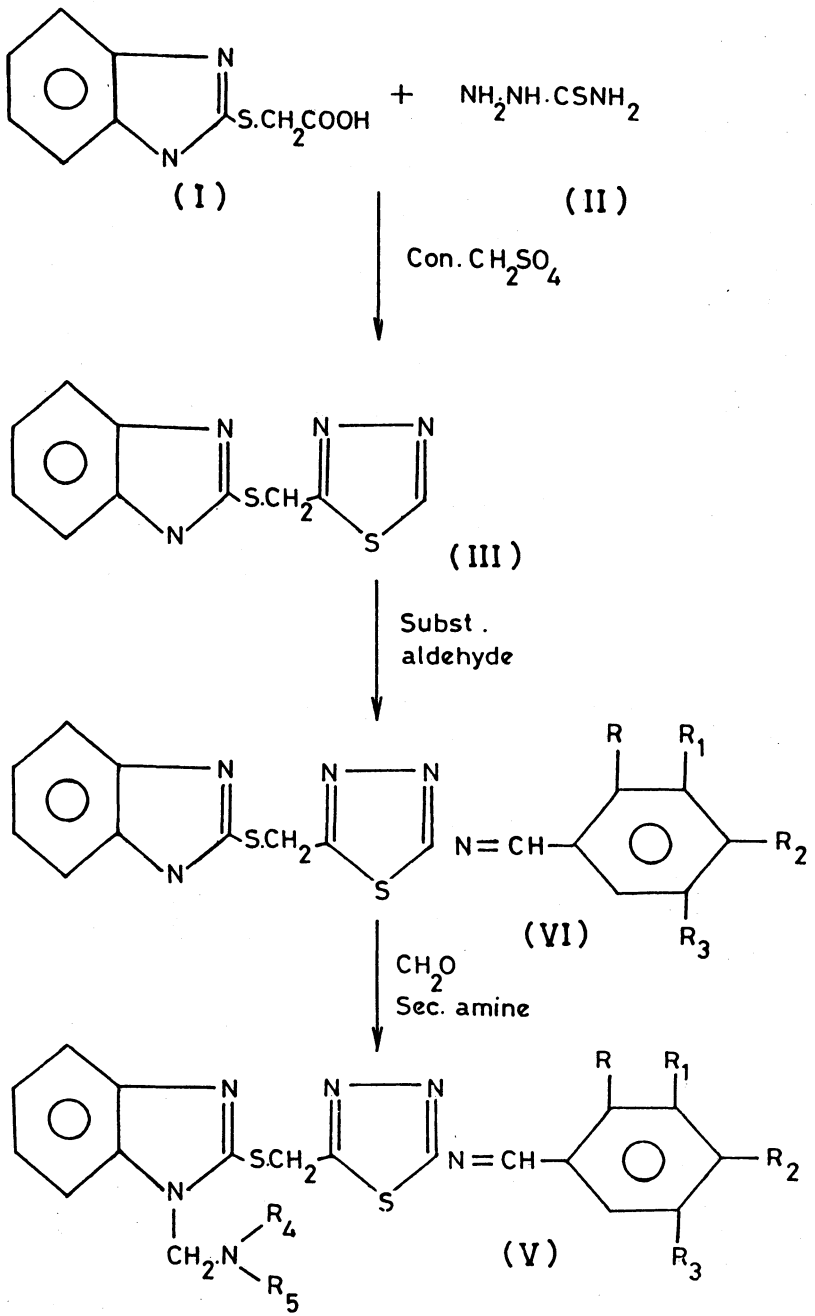



Fig. 1 Scheme-1

R–32 spectrometer; purity of compounds was checked by TLC on silica gel G plates and spots were located by iodine vapour.

**5-[(1 H-benzimidazol-2-yl)-thio-methyl]-N-[(substituted-phenyl) methylene]-1,3,4-thiadiazoles-2-amine (4)**

Compound (3, 0.01 mol) and substituted aldehydes (0.01 mol) in dry alcohol (30 ml) were refluxed for 8 hrs. in presence of glacial acetic acid, excess of alcohol was distilled off, the product thus formed was filtered, dried and crystallised from suitable solvent.

When R = $R_1$ = $R_2$ = $R_3$ = H, Yield 70%, m.pt. 151°C, $C_{17}H_{13}N_5S_2$.

Found: C, 57.5; H, 35; N, 19.7%.

Required: C, 58; H, 37; N, 19.94%.

IR(KBr) max $cm^{-1}$: 3300–3200 (NH); 1600–1580 (C=N); 1570–1500 (C=C phenyl).

PMR (Chloroform–$d_6$): 3.5–4.5 (s, 2H, $CH_2$), 6.3–7.5 (m, 10H, Ar–H, N–CH), 7.9–8.5 (m, 1H, NH) mass; M at m/z 351.

**5-[[{(substituted amino) methyl-benzimidazol-2-yl}-thio]-methyl]-N-[(substituted-phenyl)-methylene]-1,3,4-thiadiazoles-2-amine (5–15)**

Compound (4, 0.01 mol) suspended in DMF (20 ml) was warmed on a water bath; then formalin (1 ml) and morpholine etc. (1 ml) were added to it with vigorous stirring and the mixture was then left at room temperature. The resulting crystals were filtered, washed with methanol, dried at room temperature, recrystallized from chloroform-pet. ether (40–70)%.

Compound 9: Yield: 65%, M.pt.: 175°C

Molecular formula: $C_{28}H_{22}N_8O_2S$

IR(KBr) max $cm^{-1}$: 1620–1680 (C=N); 1550–1500 (C=C phenyl).

PMR: 3.2–4.5 (s, 4H, $CH_2$), 6.2–7.5 (m, 18H, N–CH, Ar–H)

## RESULTS AND DISCUSSION

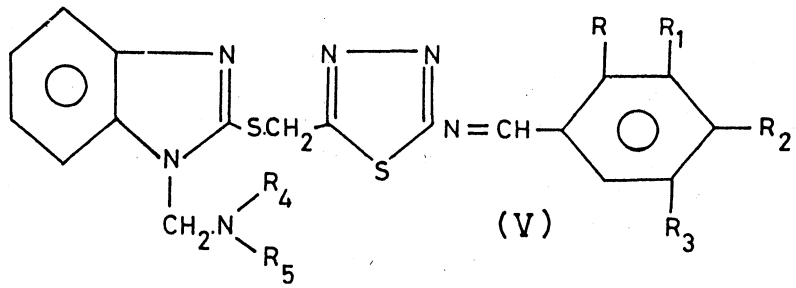
The compounds were obtained in about 60–70% yield; results are summarised in Table 1.

**Biological activity**

All the compounds were screened for their anthelmintic activity against *H. nana* infection in mice, using the technique of Steward[8]. The oral dose was 250 mg/kg given for 3 days. None of the compounds showed any activity.

Against *N. brasiliensis* infection in rats at the same oral dose, using standard methods[9]. The compounds exhibited the activity in range of 28–58%. The results are given in Table 1.

TABLE 1
PHYSICAL DATA OF COMPOUNDS (5–15)




| Compd. No. | R | $R_1$ | $R_2$ | $R_3$ | $N\langle^{R_4}_{R_5}$ | M. pt. °C | Yield% | Anthelmintic *H. nana* n.b. | *N. brasiliensis* |
|---|---|---|---|---|---|---|---|---|---|
| 5 | H | H | H | H | Phenyl piprazine | 155 | 60 | Inactive | 47 |
| 6 | H | H | OH | H | " | 224 | 50 | " | 43 |
| 7 | OH | H | H | H | " | 168 | 50 | " | 37 |
| 8 | H | H | $OCH_3$ | H | " | 152 | 70 | " | 35 |
| 9 | H | $NO_2$ | H | H | " | 175 | 65 | " | 58 |
| 10 | H | H | Cl | H | " | 180 | 55 | " | 49 |
| 11 | H | $OCH_3$ | OH | H | " | 220 | 42 | " | 45 |
| 12 | OH | H | OH | H | " | 265 | 50 | " | 37 |
| 13 | OBz | H | OBz | H | " | 240 | 40 | " | 36 |
| 14 | H | $OCH_3$ | $OCH_3$ | $NO_2$ | " | 190 | 48 | " | 48 |
| 15 | H | H | $N(CH_3)_2$ | H | " | 170 | 50 | " | 28 |

TABLE 2
ANTIVIRAL SCREENING

| Compd. No. | TMV/NC | | CGMMV/CA | |
|---|---|---|---|---|
| | *in vitro* | *in vivo* | *in vitro* | *in vivo* |
| 5 | $54^a$ | $47^b$ | $53^a$ | $48^b$ |
| 6 | $49^b$ | $43^b$ | $53^a$ | $42^b$ |
| 7 | $68^a$ | $48^b$ | $50^a$ | $46^b$ |
| 8 | $60^a$ | $35^b$ | $51^a$ | $48^b$ |
| 9 | $51^a$ | $42^b$ | $52^a$ | $51^a$ |
| 10 | $59^a$ | $45^b$ | $63^a$ | $42^b$ |
| 11 | $60^a$ | $54^a$ | $53^a$ | $48^b$ |
| 12 | $58^a$ | $35^b$ | $57^a$ | $42^b$ |
| 13 | $53^a$ | $48^b$ | $55^a$ | $46^b$ |
| 14 | $50^a$ | $46^b$ | $50^a$ | $32^b$ |
| 15 | $65^a$ | $43^b$ | $48^b$ | $37^b$ |

All the compounds have also been tested for their *in vitro* and *in vivo* activity against plant virus using standard method[10]. The host plants used were *Nicotiana glutinosa* for tobacco mosaic virus (TMV) and *Chenopodium amaranticolor* for cucumber green mottel mosaic virus (CGMMV). The compounds (Table 2) exhibited activity in the range of 49–68% *in vitro* and 42–54% *in vivo* against tobacco mosaic virus and 48–63% *in vitro* and 32–51% *in vivo* against cucumber green mottel mosaic virus inhibition.

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