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# SPECTRAL, MECHANISTIC, AND BIOLOGICAL STUDIES OF SYMMETRICAL TRIAZINES

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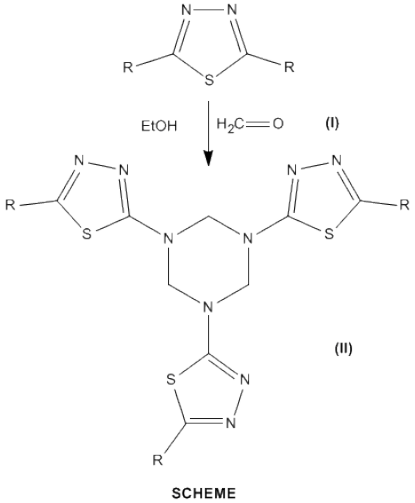
**Abstract- 2-Aminio-5-substituted -1, 3, 4-thiadiazoles (I) on reaction with formalin in ethanol solvent yielded 2, 2, 2-(1, 3, 5- triazinone- 1, 3, 5-tri-yl)- tris (5-substituted 1, 3, 4-thiadiazoles) (II) in moderate to excellent yields.**

## I. INTRODUCTION

Symmetrical triazines have been extensively investigated for their antiviral and anticancer activities. These compounds are capable of protecting mice infected with type-II influenza virus at a significant high level[1]. Some such compounds were found to suppress the enlargement of spleen in *Rouscher virus* leukemia[2] and were the most active in increasing the survival time of mice infected with *Moloney virus* leukemia[3]. Recent studies have demonstrated that triazines with suitable substituents in their molecular architecture were antivirally active against *Herpes Simplex virus type* I (HSV-I) and *Influenza virus* (IV) as well as against *Tobacco mosaic virus* (TMV), a plant virus. A part of biological study of triazine compounds was also devoted to the bioevaluation of these compounds for their antibacterial and antifungal activities[4]. This prompted the author to undertake the synthesis of some symmetrical triazines for studying their antiviral and antibacterial and properties. It is expected that the incorporation of 1, 3, 4-thiadiazole nucleus in the symmetrical triazine molecule would result in better therapeutic results.




SCHEME

## II. EXPERIMENTAL

Melting points of the synthesized compounds were taken in open capillary tubes in the Toshniwal electric apparatus and hence the values reported herein are uncorrected. The IR spectra of the compounds were recorded in the region 4000-400cm$^{-1}$ range using KBr discs on FTIR 8201 VC Perkin Elmer Spectrophotometer model 337(USA). $^{1}$HNMR and $^{13}$CNMR spectra were recorded on Brucker DRX 200 MHz spectrometer using $CDCl_3$ as solvent. TMS was used as an internal standard and the values of chemical shift are given in δ scale. Mass spectra (FAB) were recorded on JOEL SX 102/ DA-600 mass/data system using Argon/ Xenon (6KV 10mA) as the FAB gas. The accelerating voltage was 10KV and the spectra were recorded at room-temperature. m-Nitrobenzylalcohol was used as the matrix unless specified otherwise the matrix peaks have appeared at m/z 136, 137, 154, 289, 307 in the absence of any metal ions. The purity of target compounds was checked by thin layer chromatography (TLC).

**2-Amino-5-substituted-1, 3, 4-thiadiazoles (I)**

2-Amino-5-substituted-1, 3, 4-thiadiazoles were obtained following the literature method[5, 6].

**2, 2, 2-(1, 3, 5-Triazinane-1, 3, 5-tri-yl)- tris-(5-substituted)1, 3, 4-thiadiazoles (II)**

2-Amino-5-substituted-1, 3, 4-thiadiazole (I) (0.05mole) was dissolved in ethanol (50 ml) by warming gently and to this solution was added a solution of formaldehyde (1.14 mole) slowly in instalments. After each addition the reaction mixture was stirred, when the addition was completed, the resultant reaction mixture was vigorously stirred for half an hour and left undisturbed as such. A solid mass separated out, which was filtered off and washed with cold ethanol. The resulting product was purified by rapidly extracting with boiling petroleum ether (b.p. 80-100°C, 60 ml). After removal of the insoluble high polymer by hot filtration, the filtrate was cooled at room-temperature and the product was filtered off.

**2, 2, 2-(1, 3, 5-Triazinane-1, 3, 5-tri-yl) tris (5-phthalimidomethyl-1, 3, 4- thiadiazole) (IIa)**

White crystalline solid, m.p. 240-241°C, IR (KBr, in cm$^{-1}$) 1700 (ter. Amide C=O), 1645 (C=N), 2950 (C-H str. In $CH_2$), 1435 (C-H def. in $CH_2$), $^{1}$HNMR ($CDCl_3$ δppm) 6.50-7.75 (m, 12H, ArH), 3.75(s, 6H, C-$CH_2$-N) $^{13}$CNMR ($CDCl_3$, δppm) 45.7 (C-$CH_2$-N), 49.5 (N-$CH_2$-N) 111.2-137.7 (ArC), 165.7 (C=N) 171.6 (C=O), Mass: $M^+$ 816, base peak: m/z 160

Anal. For $C_{30}H_{24}N_{12}O_6S_3$; N calcd. 20.58%; N found 20.18%

**2, 2, 2-(1, 3, 5)- Triazinane-1, 3, 5-tri-yl) tris (5-phthalimido-α-methyl-methyl-1, 3, 4-thiadiazole) (IIb)**

White crystalline mass, m.p., 255°C IR (KBr, in cm$^{-1}$) 1705 (ter. Amide C=O), 1639 (C=N), 2947 (C-H str. In $CH_2$), 1435(C-H def. in $CH_2$); $^{1}$HNMR ($CDCl_3$, δppm): 6.65-7.82(m, 12H, ArH), 1.50 (d, 9H, $CH_3$), 3.25 (q, 3H, CH), 4.15 (s, 6H, N-$CH_2$-N), $^{13}$CNMR ($CDCl_3$, δppm), 22.5 ($CH_3$), 42.2 (CH), 111.5-139.5 (ArC), 166.2 (C=N), 174.6 (C=O) Mass: $M^+$ 858, base peak 105

Anal. For $C_{39}H_{30}N_{12}O_6S_3$; N calcd. 19.58%; N found 19.25%

**2, 2, 2-(1, 3, 5-Triazinane-1, 3, 5- tri- yl) tris (5-phthalimido- ethyl-1, 3, 4- thiadiazole (IIc)**

White needles, m.p. 245°C IR (KBr, $cm^{-1}$) 1710 (ter amide C=O), 1637 (C=N), 2945 (C-H str. In $CH_2$), 1440 (C-H def. in $CH_2$); $^1$HNMR ($CDCl_3$, δppm): 6.55-7.77 (m, 12H, ArH), 3.75 (t, 6H, C-$CH_2$), 4.15(t, 6H, N-$CH_2$); $^{13}$CNMR ( $CDCl_3$, δppm): 41.5 (C-$CH_2$), 42.6 (N-$CH_2$), 114.2-141.5 (ArC), 164.6 (C=N), 170.5 (C=O); Mass: $M^+$+/859, base peak 174

Anal. for $C_{39}H_{30}N_{12}O_6S_3$; N calcd. 19.58%; N found 19.25%

**2, 2, 2-(1, 3, 5-Triazinate-1, 3, 5-tri- yl) tris (benzamidomethyl)- 1, 3, 4- thiadiazole) (IId)**

White crystalline mass, m.p. 220°C, IR (KBr, $cm^{-1}$): 1680 (sec. amide C=O), 1632 (C=N), 2932 (C-H str. in $CH_2$), 1432 (C-H def. in $CH_2$); $^1$HNMR ($CDCl_3$, δppm): 6.45-7.92 (m, 15H, ArH), 3.95 (s, 6H, $NHCH_2$), 4.20 (s, 6H, N-$CH_2$-N), 8.75 (brs, 3H, CONH); $^{13}$CNMR ($CDCl_3$, δppm): 42.0 (N-$CH_2$-C), 44.5 (N-$CH_2$-N), 165.0(C=N), 172.4 (C=O); Mass: $M^+$738 base peak 129;

Anal. for $C_{33}H_{30}N_{12}O_3S_3$; N calcd. 22.76%; N found 22.50%

**Biological activity**[7]

The target compounds (IIa-IId) were evaluated for their antiviral activity against two human viruses viz; *Japanese Encephalitis virus* and *Herpes Simplex virus* Type-I *in vitro*. The biological activity data was incorporated in **Tables I** and **Tables II**.

| Compound No. | R | Dose | *In Vitro* | | TI | % CPE Inhibition |
|---|---|---|---|---|---|---|
| | | | $CT_{50}$(µg/ml) | $EC_{50}$(µg/ml) | | |
| **IIa** | Phthalimidomethyl | 500-4 | 500 | 250 | 2 | 20 |
| **IIb** | Phthalimido-α-methyl | 500-4 | 500 | __ | __ | __ |
| **IIc** | Phthalimidoethyl | 500-4 | 500 | 125 | 4 | 40 |
| **IId** | Benzamidomethyl | 500-4 | 500 | 62.5 | 8 | 50 |

**Table I**

CT = Cytotoxic, EC = Effective Concentration, TI = Therapeutic Index, CPE = Cytopathic Effect

| Compound No. | R | Dose | *In Vitro* | | TI | % CPE Inhibition |
|---|---|---|---|---|---|---|
| | | | $CT_{50}$ (µg/ ml) | $EC_{50}$ (µg/ml) | | |
| **IIa** | Phthalimidomethyl | 500-4 | 500 | 125 | 4 | 10 |
| **IIb** | Phthalimido-α-methyl-methyl | 500-4 | 500 | 250 | 2 | __ |
| **IIc** | Phthalimidoethyl | 500-4 | 500 | 125 | 4 | 40 |
| **IId** | Benzamidomethyl | 500-4 | 500 | 62.5 | 8 | 20 |

**Table II**

CT = Cytotoxic; EC = Effective concentration; TI = Therapeutic index; CPE = Cytopathic effect

**Antibacterial Activity**[8, 9]

All the four symmetrical triazines were evaluated for their antibacterial activity invitro involving broth dilution technique as recommended by the National Committee for clinical laboratory standards. The antibacterial activity data are incorporated in Table III.

**Table III**

Antibacterial activity data of 2, 2, 2-(1, 3, 5-triazinate-1, 3, 5-tri-yl) tris (5-substituted-1, 3, 4-thiadiazoles)

| Compound No. | R | Minimum Inhibitory Concentration (MIC) IN µg/ml | | | | |
|---|---|---|---|---|---|---|
| | | Sf | Kp | Ec | Pa | Sa |
| **1** | Phthalimidomethyl | >50 | >50 | 50 | 25 | 25 |
| **2** | Phthalimido-α-methyl-methyl | 50 | 50 | >50 | >50 | 50 |
| **3** | Phthalimidoethyl | >50 | >50 | >50 | 50 | 25 |
| **4** | Benzamidomethyl | 6.25 | 6.25 | 25 | 1.56 | 1.56 |

Sf = Streptococcus faecalis; Kp = Klebsiella pneumoniae; Ec = Escherichia coli; Pa = Pseudomonas aeruginosa; Sa = Staphylococcus aureus

## III. RESULTS AND DISCUSSION

Antiviral activity data presented in Tables II and III clearly indicate that these compounds exhibit only measurable level of antiviral activity. One compound (compound II) was found completely inactive against both the viruses. Out of four triazines, only one was found to display antibacterial activity against four bacterial strains. Thus, the compound IId bearing a benzamidomethyl substituent provoked satisfactory antiviral activity against Sf, Kp, Pa and Sa. These results undoubtedly indicate that the substituents have greater role to play in eliciting desired biological effects.

## IV. ACKNOWLEDGEMENT

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