Synthesis of 6-aryl-7-arylazo-4-(N-substituted aminomethyl)-2H-thiazolo-[3, 2-a]-1, 3, 5-triazino-2-thiones as Antiviral Agents

Dr. Archana Jyoti

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Abstract
2-amino-4-aryl thiazole was diazotised with different aromatic amines to give 2-amino-4-aryl-5-arylazo thiazoles. These compounds were refluxed with ammonium thiocyanate and chloroacetyl chloride in acetone to afford N1-chloroacetyl-N3-(4-aryl-5-arylazothiazol-2-yl)-thioureas. These thioureas were cyclized in presence of POCl3 and PCl5 to give 6-aryl-7-arylazo-4-chloromethyl-2H-thiazolo-[3, 2-a]-1, 3, 5-triazino-2-thiones. These compounds were reacted with secondary amines in methanol to give title compounds 6-aryl-7-arylazo-4-(N-substituted aminomethyl)-2H-thiazolo-[3,2-a]-1,3,5-triazino-2-thiones. Antiviral nature of these compounds was studied against Ranikhet Disease Virus (RDV), Vaccinia Virus (VV) and Sunnhemp Rosette Virus (SRV). Some of these compounds have been found to be active against RDV and Vaccinia Virus.

Keywords: Triazines, Thiones, Ranikhet Disease Virus, Vaccinia Virus, Sunnhemp Rosette Virus

Introduction
Triazine derivatives have been reported to exhibit pronounced antiviral activity against various strains of viruses [1-3]. 2-amino-4-arylamino-5-triazines have been found to possess promising antiviral activity [4]. Recently some substituted triazino-2-thiones have been found to be associated with antiviral activity against RDV. These varied

Scheme
observations led the author to synthesize twelve new title compounds and to study their pharmacological action.

**Methodology**

2-aminoo-4-aryl thiazole (1) was diazotised with different aromatic amines to give compounds (2-4). These compounds were refluxed with ammonium thiocyanate and chloroacetyl chloride in aceton to afford N1-chloroacetyl-N1-(3,4,5-aryaloxythiazol-2-yl)-thioureas (5-7). These thioeureas were cycled in presence of POCl3 and PCl5 to give 6-aryloxy-4-chloromethyl-2H-thiazolo-[3,2-a]-1,3,5-triazino-2-thiones (8-10). These compounds were reacted with secondary amines in methanol to give title compounds (11-22).

Melting points of the compounds were taken in a sulphuric acid bath in open capillaries. Structures of final compounds were confirmed by IR, PMR spectra and TLC.

2-aminoo-4-aryl thiazole (1) was prepared by the known method [9]. This thiaurea was converted into 2-aminoo-4-aryl-5-aryloxythiazoles (2-4) by known procedure [6].

**N1-chloroacetyl-N1-(4-aryl-5-aryaloxy thiazol-2-yl)-thiourea (5-7)**

To a mixture of ammonium thiocyanate (0.06 mole) and chloroacetylchloride (0.06 mole) in aceton (160 ml) heated under reflux for 30 min was added 2-aminoo-4-aryl-5-aryloxythiazoles (2-4) and the reaction mixture was further refluxed for 3-4 hrs. After this the reaction mixture was poured into excess water. The desired thioeurea thus precipitated was filtered, washed and recrystallized from DMF-ethanol mixture (1:1). Characterisation data of these compounds are as follows:

**N1-chloroacetyl-N1-(4-aryl-5-aryaloxy thiazol-2-yl)-thiourea (5)**

m.p. 118 °C Analysis for C13H12N3OS: Cl: Calc N 15.22; Found N 15.20; IR (KBr): 3490-3440 (N-H) 1680-1690 (C=O), 1610 (C=C), 1585-1580 (N=N), 1200 (C=S) and 705-700 (C=Cl).

**N1-chloroacetyl-N1-(4-aryl-5-chloroaryloxythiazol-2-yl)-thiourea (6)**

m.p. 198 °C Analysis for C17H14N3OS2Cl: Calc N 15.02; Found N 15.02; IR (KBr): 3490-3440 (N-H) 1680-1690 (C=O), 1585-1580 (N=N), 1200 (C=S) and 705-700 (C=Cl).

**N1-chloroacetyl-N1-(4-aryl-5-nitroaryloxythiazol-2-yl)-thiourea (7)**

m.p. 180 °C Analysis for C19H17N4OS2Cl: Calc N 18.24; Found N 18.20; IR (KBr): 3490-3440 (N-H) 1680-1690 (C=O), 1585-1580 (N=N), 1200 (C=S) and 705-700 (C=Cl).

6-aryloxy-4-chloromethyl-2H-thiazolo-[3,2-a]-1,3,5-triazino-2-thiones (8-10)

N1-chloroacetyl-N1-(4-aryl-5-aryloxythiazol-2-yl)-thiourea (0.015 mole) was refluxed with a mixture of POCl3 (15 ml) and PCl5 (0.015 mole) for 3-4 hrs. The excess POCl3 was removed under reduced pressure and crushed ice was added to the residue. The precipitate thus obtained was filtered, washed and recrystallized from ethanol.

6-aryloxy-4-chloromethyl-2H-thiazolo-[3, 2-a]-1,3,5-triazino-2-thione (8)

m.p. 190 °C Analysis for C19H17N4OS2Cl: Calc N 17.61; Found N 17.62; IR (KBr): 1610 (C=N) 1580 (N=N), 1200 (C=S), 710-700 (C=Cl). The absence of conspicuous bands at 3450-3440 and 1690-1680 cm⁻1 showed the absence of N-H and C=O groups respectively.

6-aryloxy-7-p-chloroaryloxy-4-chloromethyl-2H-thiazolo-[3,2-a]-1,3,5-triazino-2-thione (9)

m.p. 182 °C Analysis for C19H17N4Cl3: Calc N 16.20; Found N 16.12.

6-aryloxy-7-p-nitroaryloxy-4-chloromethyl-2H-thiazolo-[3, 2-a]-1, 3, 5-triazino-2-thione (10)

m.p. 175 °C Analysis for C19H17N5O2Cl: Calc N 18.98; Found N 18.20.

6-aryloxy-7-aryloxy-4-(N-substitutedaminomethyl)-2H-thiazolo-[3, 2-a]-1, 3, 5-triazino-2-thiones (11-22)

A mixture of 8-10 (0.01 mole) and an appropriate secondary amine (0.01 mole) in methanol (25 ml) was refluxed on water bath for 6-8 hrs. After that the reaction mixture was poured on ice cooled water. The solid thus separated was filtered, washed with water and recrystallized from methanol. All the compounds (11-22) thus prepared are listed in table-1. IR (KBr): 2780-2775 (N-CH2), 1610 (C=)= 1580-1575 (N=N) 1210 (C=S). Appearance of peak for N-CH2 group and disappearance of peak for C-Cl group confirmed the structures of compounds. The PMR (CDC13) spectrum of compound No.13 exhibited signals at 1.50-1.68 (t, 6H, C-CH3). 3.62-3.75 (t, 6H, N-CH2) and 7.42-8.21 (10, 10H, Ar-H).

**Antiviral activity against rsv**

Compounds were tested against RDV in a stationary culture of minced chorioallantoic membrane of chick embryo. The strain of the Ranikhet Disease Virus was the same as employed by Babber and Dhar [7]. Chorioallantoic membrane (CAM) of 10 days old chick embryos were taken and the culture prepared according to the method of Babbar [8, 9]. The soluble compounds were dissolved in a nutrient fluid and the insoluble compounds were susptended in it in the presence of Tween 80 and the pH adjusted to 7.2 before sterilization. The solutions were then sterilized by autoclaving at 15 lbs pressure for 15 min. Two fold serial dilutions were then made and 1 ml of each dilution added to each of the test tubes containing the CAM culture. The dilution of a compound causing toxic symptoms in 50% of the CAM culture was taken as the end point. The highest nontoxic dose was given to each culture along with the virus (0.64 HA units/ml). Virus multiplication was measured by the haem agglutination (HA) titre (mean of log2) of the culture collected after 48 hrs of incubation at 37 °C. Inhibition in virus multiplication was obtained by subtracting this titre from that of the control. The mean difference (d) of 2 log2 HA units is significant at 50% or more than 50% level.

**Antiviral activity against vaccinia virus**

All the eighteen compounds were also tested [10] against Vaccinia Virus on chick embryo fibroblast monolayers. 0.05 mg/ml compound were given along with Vaccinia virus (50 p/ml) and incubated at 37 °C for 72 hrs. After 72 hrs the monolayers were strained and the numbers of plaques/monolayers were counted. The activity was calculated by the formula C-T/C×100.
Antiviral activity against sunnhemp rosette virus (srv)
The culture of Sunnhemp Rosette Virus was maintained by successive host inoculation (Cyamopsis tetragonoloba plants). The procedure of Mukherjee et al [11] was followed for antiviral testing.

Results and discussion
It is apparent from table-2 that compounds 16 and 22 exhibited 65% and 60% inhibition respectively against RDV. Thus insertion of N-methyl piperazino and morpholino groups in compounds enhances the antiviral activity of compounds. Further compounds 11, 14 and 17 have been found to be toxic. Remaining compounds showed varying degree of antiviral activity ranging from 0 to 40%. The order of antiviral activity of various values of R was found to be nitro chloro H.
The results of the antiviral activity against Vaccinia Virus given in table-2 shows that only compound 13 has showed pronounced antiviral activity, whereas compound no. 16 was found to possess mild antiviral activity (50%). These results indicate that probably substitution by piperidino and N-methyl piperazino group may be responsible for the antiviral nature of the compound. The results of activity against SRV show that all the compounds were found to be toxic in nature and possess no antiviral effect. However, compound 12, 14, 21 and 22 were found to possess comparatively less toxic effects.

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