Synthesis of 1,2,4-triazolo-[3,2-b]-1,3,4-thiadiazolo-6-(5H) thione nucleoside analogues.

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Deparment of chemistry

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Abstract: 2-Amino-5aryl-1,3,4-thiazole undergoes regioselective condensation with KSCN to give N'(5-aryl-1,3,4-thiazole-2-yl) thioureas in ethanol. The ureas on treatment with $SOCl_2$ and pyridine afforded 2-aryl-1,3,4-triazolo[3,2,-b] thiadiazole-6-(5H)thione nucleobase, which on glycosylation with different sugar gave nucleoside analogues.

Key words:

A large number of thiadiazole derivatives including those where this ring system is a part of the nucleoside have been reported to display potential antiviral activities.[1-4] Virazole is 1,2,4-triazole derivative[5]. Various nucleosides incorporating fused thiazole nucleus have been reported to display potential biological activities like virucidal, egtostatic and antitumours[6-9].

1,3,4-thiadiazole **3** reacted with KSCN in ethanol for 5-6 hrs to give 5-aryl 1,3,4-thiadiazole-2-yl-thioureas **4a-c.** The thioureas 4a-c further reacted with $SOCl_2$ in pyridine to give 2-aryl-1,2,4-triazolo (3,2-b)-1,3,4-thiadiazole-6-(5H) thione. These on being treated with pentose and hexose sugar offerded the corresponding nucleosides.

2-amino-5-aryl 1,3,4-thiadiazole **3**and N' (5-aryl-1,3,4- thiadiazole-2-yl) thioureas **4** were synthesised according to the method reported in literatures.[10]

The structural assignment of all the synthesised compounds were based on elemental analyses, IR and ^{1}HNMR spectroscopy. Purity of compounds was checked by TLC (silica gel G). All the twentyseven compounds were evaluated for their antiviral activity *in vivo* against herpes simples virus according to the procedure described by Bajpai and Joshi[11]. In this method, compounds were dissolved in alcohol / DMSO and their solution (1 mg/mL) was made in PBS (pH 7.2) and kept at 4°C before use. Swiss albino mice of 30 days old (15-16g) were used for in vivo studies. The best compound was administered at the rate of 0.5 mg/mouse/dose by intraperitonial (ip) route for 18 hrs. before virus challenge, followed by two consecutive administration of the compound at 24hr intervals. After 18 hr of the first dose of the compound, animals were challenged with 5 LD_{50} concentration of virus by ip route for HSV-1. The animals were observed in the morning and evening for a period of 21 days to record their mortality with specified paralytic symptoms and Viremia. Treated animals were compared with that of untreated virus control, which were administered PBS in place of the compound. The mean survival times as well as percent protection of animals were calculated by standared methods. The antiviral activity of the compounds from5-11 is given in Table-1

The pattern of activity in Table 1 shows that all the nucleosides {6-11(a-c)} were far more active than their nucleobases and deacetylated nucleosides are more potent than acetylated nucleosides. The order to antiviral activity of these nucleosides {6-11 (a-c)} with respect to the sugar moiety present in them was found to be. β-D-xylopyranosyl >-β-Dglucopyranosyl >-β-D-galactopyranosyl. This shows that pentoses show more activity than hexoses. This is in keeping with the naturally occurring nucleosides.

It was however noteworthy that the introduction of a chloro or methyl group in the aryl moiety of these compounds tends to augment their antiviral activity.

Melting points were determined in open capillaries and are uncorrected. IR spectra in KBr were recorded on a Perkin Elmer infrared spectrophotometer and PMR spectra in $CDCl_3$ on a 300 MHz Brucker DRX-300 spectrophotometer using TMS as internal standard. The spectral data of only representative compounds are given in Table 1.

2-Amino-5-aryl-1,3,4-thiadiazoles (3a-c) : These were prepared by cyclodehydration of N'-benzolthiosemicarbazide**(2a-c)** with cone H_2SO_4 following the method of Maffii-et.al[12].

N'-(5-Aryl-1,3,4-thiadiazole-2yl) thioureas (4a-c) : These were prepared according to the method of Viswanathan et.al.[13] Reported thioureas were prepared by refluxing **3(a-c)**, potassium thiocyanate and conc. HCl in ethanol.

2-Aryl-1,2,4-triazolo[3,2-b]-1,3,4-thiadiazole-6-(5H)thione(5-a-c) : A mixture of **4a-c** (0.02 mole) and thionyl chloride (0.025 mole) in pyridine was refluxed for 8-10 hrs Pyridine was evaporated under pressure and the residue was washed with water and recrystallised from ethanol to furnish **5a-c.**

2-Aryl-5-(β-2,3,4,6-tetra-O-acetyl glucopyranosyl or β-D-2,34-tri-O-acetylxylopyranosyl or β-D-2,3,4,6-tetra-O-acetylgalactopyranosyl)1,2,4-triazolo-[3,2-b]-1-3,4-thiadiazole-6-(5H, 6H) thiones {6-8(a-c)} : Equimolar of above nucelobase and 1,2,3,4,6 penta-O-acetyl–β–D-glucopyranose and 1.5 molar of iodine, were dissolved in minimum amount of dioxane. This was refluxed for 3 hrs. and was poured in to an aqueous solution of sodium thiosulphate, after cooling to remove excess of iodine. The product was washed with water and recrystallised from ethanol.

2-Aryl-5- (β-D-gulcopyranosyl or β-Dxylopyranosyl or β-Dgalactopyranosyl)-1,2,4-triazolo-[3,2-b]-1,3,4-thiadiazole-6-(5H,6H) thiones {9-11(a-c)} : The above acetylated compounds in dry ethanol and solution of NaOMe were taken in a stoppered flask. The mixture was allowed to sand for 1hr. with occasional shaking. This was neutralised with dil HCl. The product thus prepared was filtered and recrystallised from ethanol.

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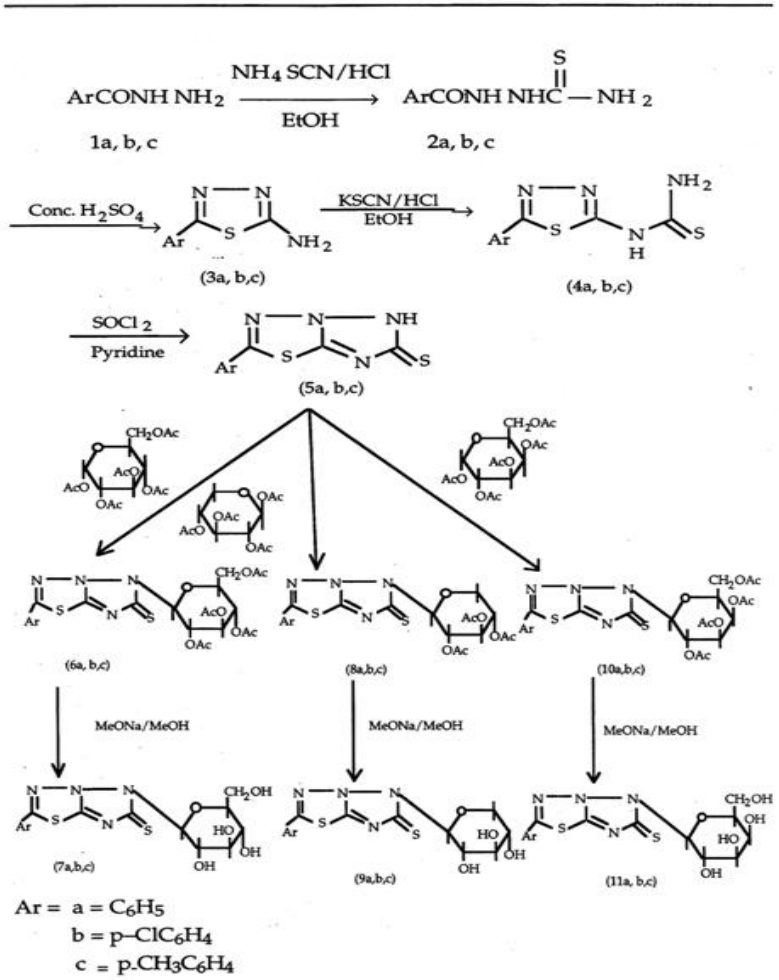
Table - I Characterization data of various compound prepared

S.No.	Compound Ar	Yield %	MP°C	M.formula	found/ (Calculated)			^{1}HNMR $CDCl_3$ δ J (Hz)	Mass m/z	Activity
					C	H	N			
5a	C_6H_5	72	145	$C_9H_6N_4S_2$	46.1 (46.0	2.5 2.5	23.39 23.40)	7.25-7.74 (5H,m,ArH); 9.30 (1H,brs, NH)	$(M)^+$234	07
5b	C_6H_4Cl(p)	62	136	$C_9H_5N_4S_2Cl$	40.29 (40.26	1.86 1.84	20.89 20.95)	7.25-7.75 (4H,m Ar H); 9.32(1H,brs, NH)	$[M]^+$268 & 270 [M+2]	18
5c	$C_6H_4CH_3$(p)	58	152	$C_{10}H_8N_4S_2$	48.38 (48.35	3.22 3.20	22.56 22.61)	2.32 (3H,s,CH_3); 7.00-8.02 (4H,m,Ar H) 9.30 (1H,brs,NH)	$[M]^+$248	22
6a	C_6H_5	74	110-112	$C_{23}H_{24}N_4O_9S_2$	48.93 (48.90	4.25 4.26	9.92 9.89)	2.10, 2.12, 2.15, 2.17(each 3H,s,Ac); 3.88-4.26 (2H,m,6'H) 4.39(1H,m,5'H); 4.74(1H d,J=7.0,1'H); 4.87-5.00(3H,m,2',3',4'H) 7.21-7.51 (5H,m,Ar H)	$[M]^+$564	10
6b	C_6H_4Cl(p)	68	95-96	$C_{23}H_{23}N_4S_2O_9Cl$	46.15 (46.10	3.84 3.86	9.36 9.38)	2.12, 2.14, 2.17, 2.19 (each 3H,s,Ac); 3.86-4.24(2H,m,6'-H),;4.37 (1H,m,5'H); 4.78 (1H,d,J=7.0,1'H); 4.89-5.02(3H,m, 2', 3',4 'H);7.24-7.57(4H,m,Ar H)	$[M]^+$598 & 600 [M+2]	22
6c	$C_6H_4CH_3$(p)	73	105	$C_{24}H_{26}N_4S_2O_9$	49.82 (49.80	4.49 4.48	9.68 9.65)	2.11, 2.14, 2.17, 2.19 (each 3H,s, Ac); 2.39 (3H,s,CH_3); 3.87-4.27(2H,m,6'H) ; 4.40 (1H,m,5'H);4.74(1H,d,J=7.0 1'H); 4.87-5.02 (3H,m,2',3',4'H);7.18-7.49 (4H,m, Ar H)	$[M]^+$578	23
7a	C_6H_5	76	110	$C_{20}H_{20}N_4O_7S_2$	45.26 (45.60	4.06 4.06	11.38 11.36)	2.17, 2.10, 2.05 (each 3H,s,Ac); 3.90-4.26 (2H,m,5'-H); 4.56 (1H,d,J=6, 1'H);5.00-5.37(3H,m, 2',3',4'H); 7.21-7.73(5H,m,Ar H)	$[M]^+$492	15

7b	C_6H_4Cl (p)	69	120-122	$C_{20}H_{19}N_4S_2O_7Cl$	45.26 (45.60	3.61 3.58	10.64 10.68)	2.12, 2.06, 2.00 (each 3H, s, Ac); 3.91-4.26 (2H,m, 5'-H); 4.57 (1H,d,J=6, 1'H), 5.00-5.36 (3H,m, 2',3',4'H); 7.22-7.64 (4H, m, Ar H)	$[M]^+$526 & 528 [M+2]	24
7c	$C_6H_4CH_3$	64	130-131	$C_{21}H_{22}N_4S_2O_7$	49.80 (49.81	4.34 4.30	11.06 11.10)	2.12, 2.10, 2.05 (each 3H, s, Ac); 2.42, (3H, s, CH_3); 3.96-4.25 (2H,m,5'H); 4.55 (1H, d, J=6,1'H); 4.99-5.37 (3H,m, 2',3',4'H), 7.20-7.52 (4H,m, Ar H).	$[M]^+$506	26
8a	C_6H_5	72	99-101	$C_{23}H_{24}N_4O_9S_2$	48.92 (48.89	4.26 4.24	9.93 9.95)	2.11, 2.10, 2.08, 2.07 (each 3H, s, Ac); 3.88- 3.98 (1H,m,6'H); 4.25 (2H,m, 5'-H); 4.52 (1H,d,J=8, 1'-H); 4.89-5.28 (3H,m, 2',3',4' H) 7.27-7.65 (5H,m, Ar H)	$[M]^+$564	10
8b	C_6H_4Cl	69	102	$C_{23}H_{23}N_4S_2O_9Cl$	46.17 (46.15	3.83 3.84	9.35 9.38)	2.12, 2.09, 2.04 (each 3H,s, Ac); 3.82-3.93 (2H,m,6'H); 4.20(2H,m, 5'H); 4.59 (1H,d, J=8, 1'H); 5.00-5.38 (3H,m,2',3',4' H); 7.25-7.55 (4H,m, Ar H).	$[M]^+$598 & 600 [M+2]	20
8c	$C_6H_4CH_3$	76	101-103	$C_{24}H_{26}N_4S_2O_9$	49.80 (49.82	4.50 4.48	9.68 9.65)	2.12, 2.08, 2.05, 2.03 (each 3H, s, Ac); 2.52 (3H, s, CH_3); 3.87-3.98 (1H,m, 6'H), 4.32 (2H,m, 5'H); 4.62 (1H,d,J=8, 1'H); 5.00-5.40 (3H,m, 2',3','4H); 7.20-7.40 (4H,m, Ar H)	$[M]^+$578	21
9a	C_6H_5	67	101-103	$C_{15}H_{16}N_4O_5S_2$	45.45 (45.43	4.04 4.06	14.14 19.10)	3.37 (1H,m,2'H); 3.64-3.68 (2H,m, 6'H); 3.73-3.98 (3H,m,2',3',4' H); 4.74(1H,d,J=6, 1'H); 5.32 (4H,brs 4xOH); 7.27-7.76 (5H,m, Ar H)	$[M]^+$396	15
9b	C_6H_4Cl	62	110	$C_{15}H_{15}N_4S_2O_5Cl$	41.86 (41.87	3.48 3.48	13.02 13.00)	3.36 (1H,m,2'H); 3.61-3.67 (2H,m,6'H); 3.70-4.00(3H,m,3',4',5' H); 4.70 (1H,d,J=6, 1'H); 5.32 (4H, brs, 4xOH); 7.20-7.45 (4H, m, Ar H)	$[M]^+$430 & 432 [M+2]	26

9c	$C_6H_4CH_3$	72	106-108	$C_{16}H_{18}N_4S_2O_5$	46.82 (46.84	4.39 4.40	13.65 13.60)	2.72(3H, s,CH_3); 3.36 (1H,m, 2'H); 3.60-3.67 (2H, m, 6'H); 3.70-4.00 (3H, m, 3',4',5' H); 4.73(1H,d,J=6, 1'H); 5.34 (4H, brs, 4x OH); 7.25-7.57 (4H,m, Ar H).	$[M]^+$ 410	28
10a	C_6H_5	70	102	$C_{14}H_{13}N_4S_2O_4$	45.90 (45.89	3.55 3.51	15.30 15.32)	3.42-3.51 (3H, m, 2',3',5' H); 3.68-3.76 (2H, m, 6'H); 3.80 (1H, m, 4'H); 4.34 (1H,d, J=7, 1'H); 5.68 (4H,brs,3 c OH); 7.21-7.68 (5H,m, Ar H)	$[M]^+$364	20
10b	C_6H_4Cl	68	104-105	$C_{14}H_{14}N_4S_2O_4Cl$	42.00 (42.01	3.50 3.52	14.00 13.98)	3.40-3.49 (3H, m, 2',3',5'H); 3.70-3.78 (2H, m,6'H); 3.82 (1H,m,4'H); 4.36 (1H,d, J=7,1'H); 5.76 (4H,brs, 3 c OH) 7.20-7.58 (4H,m, Ar H)	$[M]^+$ 392 & 394 [M + 2]	28
10c	$C_6H_4CH_3$	74	110-112	$C_{15}H_{17}N_4S_2O_4$	47.36 (47.38	4.47 4.48	14.73 14.70)	2.75(3H, s,CH_3); 3.42-3.54 (3H,m,3',3',5'H); 3.68-3.78 (1H,m, 4'H); 3.68-3.78 (1H, m,4'H); 4.38 (1H,d,J=7, 1'H); 5.70 (4H,brs,3 x OH); 7.25-7.76 (4H,m, Ar H).	$[M]^+$ 378	31
11a	C_6H_5	72	107-108	$C_{15}H_{16}N_4O_5S_2$	45.47 (45.45	4.02 4.00	14.14 14.16)	3.45-3.52 (3H,m, 2',3',5'H); 3.68-3.78 (2H,m, 6'H); 3.83 (1H,m, 4'H); 4.36 (1H,d, J=7.5, 1'H); 5.67 (4H, brs 4 x OH) 7.28-7.52 (5H, m,Ar, H)	$[M]^+$ 396	12
11b	C_6H_4Cl	69	110	$C_{15}H_{15}N_4S_2O_5Cl$	41.84 (41.86	3.51 3.52	13.01 13.00)	3.43-3.56 (3H,m, 2',3',5'H); 3.68-3.78 (2H, m, 6'H) 3.85 (1H,m, 4'H); 4.36 (1H, d,J=7.5, 1'H); 5.65 (4H,brs, 4 x OH); 7.20-7.60 (4H, m, Ar H).	$[M]^+$430 & 432 [M + 2]	21
11c	$C_6H_4CH_3$	64	112	$C_{16}H_{18}N_4S_2O_5$	46.80 (46.81	4.41 4.42	13.67 13.65)	2.78 (3H,s, CH_3); 3.42-3.60 (1H,m, 2',3',5' H); 3.68-3.76 (2H, m, 6'H), 3.80 (1H, m,4'H); 4.36(1H,J=7.5, 1'H); 5.65 (4H, brs 4 x OH); 7.27-7.58(4H,m, Ar H).	$[M]^+$410	23

3(a-c): 1200 (C=S), 1625 (C=N); 4-6 (a-c): 1210(C=S), 1650 (C=N) 1750 (ester C=O); 7-9 (a-c): 1205(C-S), 1635 (C=N), 3455 (O-H).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KSCN/HCl
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SOCl 2
Pyridine
(5a, b,c)
(6a, b,c)
(8a,b,c)
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MeONa/MeOH
MeONa/MeOH
MeONa/MeOH
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(11a, b,c)
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b = p–ClC6H4
c = p.CH3C6H4