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BRIDGEHEAD NITROGEN HETEROCYCLIC SYSTEMS : FACILE SYNTHESIS, STEREOCHEMISTRY AND ANTIMICROBIAL ACTIVITY OF *cis*-8,8a-DIHYDROPYRAZOLO[3',4':4,5]THIAZOLO[2,3-*b*]-*s*-TRIAZOLO[3,4-*b*]|[1,3,4]THIADIAZOLE

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ABSTRACT
A facile synthesis of 9a-aryl-7H-8-aryl-3-(*p*-nitrophenyl)-*cis*-8,8a-dihydropyrazolo[3',4' :4,5]thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4] thiadiazole**4** has been achieved. Condensation of 3-(*p*-nitrophenyl)-6-aryl-*s*-triazolo[3,4-*b*][1,3,4] thiadiazole**1** with thioglycollic acid yield 8a-aryl-3-(*p*-nitrophenyl)-thiazolo [2, 3-*b*]-*s*-triazolo [3,4-*b*] [1,3,4]-thiadiazol-6(7*H*)-one **2.** The thiazolidinones**2** on reaction with *p*-chlorobenzaldehyde yield 7-*p*-chlorobenzylidene-8a-aryl-3-(*p*-nitrophenyl)-thiazolo[2,3-*b*]-s-triazolo[3,4-*b*][1,3,4]-thiadiazol-6(7*H*)-one **3.** Condensation of **3** with hydrazine hydrate furnish **4.** The antibacterial and antifungal activity of some of the compounds have also been evaluated.

KEYWORDS
9a-aryl-7H-8-aryl-3-(*p*-nitrophenyl)-*cis*-8,8a-dihydropyrazolo[3',4':4,5]thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4] thiadiazole;3-(*p*-nitrophenyl)-6-aryl-*s*-triazolo[3,4-*b*][1,3,4] thiadiazole**;** 8a-aryl-3-(*p*- nitrophenyl)-thiazolo [2 , 3-*b*]-*s*-triazolo [3 ,4-*b*] [1,3, 4]-thiadiazol-6 (7*H*)-one ; 7-*p*-chlorobenzylidene-8a-aryl-3-(*p*-nitrophenyl)-thiazolo[2,3-*b*]-s-triazolo[3,4-*b*][1,3,4]-thiadiazol-6(7*H*)-one; antibacterial and antifungal activity

INTRODUCTION
In continuation of our earlier work on the synthesis of novel bridgehead nitrogen heterocyclic systems[i-viii] the author reports herein the synthesis of pyrazolo [3',4':4,5]thiazolo [2,3-*b*]-s-triazolo[3,4-*b*] [1,3,4] thiadiazole system.

3-(*p*-nitrophenyl)-6-(*p*-chlorophenyl)-*s*-triazolo[3,4-*b*][1,3,4] thiadiazole**1A,** obtained by the condensation of 3-(*p*-nitrophenyl)-4-amino- 5-mercapto- *s*-triazole with *p*-chlorobenzoic acid, oncondensation with thioglycollic acid afforded 8a-*p*-chlorophenyl-3-(*p*-nitrophenyl)-thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazol-6(7*H*)-one **2A.** Condensation of **2A** with *p*-chlorobenzaldehyde yielded 7-*p*-chlorobenzylidene-8a-*p*-chlorophenyl-3-(*p*-nitrophenyl)-thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazol-6-(7*H*)-ones **3A.** The structures **2A** and **3A** were supported by their IR spectra. The parent thiazolidinone showed a peak at 1720cm^{-1}(>N-C=O) but the exocyclic double bond at 7-position being in conjugation with the carbonyl group at 6-position produced a bathochromic shift[ix] in the carbonyl absorption of **3A.** The band appeared at 1700cm^{-1}in **3A** (Ar=*p*-Cl-C_6H_4). Condensation

of **3A** with hydrazine hydrate yielded the cyclized products, 9a-aryl-7H-8-aryl-3-(*p*-nitrophenyl)-*cis*-8,8a-dihydropyrazolo[3',4':4,5] thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles**4A.** The structures of **4** were supported by their ^{1}H NMR spectral data (vide Experimental). The appearance of two doublets at δ 7.83 &7.95 (J=10.0 Hz) respectively for the protons 8a and 8 corroborated the cyclic structure and *cis* configuration[x].

ANTIMICROBIAL ACTIVITY

The compounds **2** and **4** were evaluated for their antimicrobial activity against the gram-positive *Staphylococcus aureus,* gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* and the fungus *Candida albicans.* Neat samples and serial plate dilution method were used[xi].

The minimum inhibitory concentration (MIC) of the compounds **2** and **4** against *P. aeruginosa* and *S. aureus* were found to be 250 μg/ml and 500 μg/ml respectively. These compounds were also found tobe active against *C. albicans,* when tested as neat samples.

EXPERIMENTAL AND RESULTS

TLC was run on silica gel G plates using acetone-benzene (1:3) as irrigant. Melting points are uncorrected. IR (KBr)(cm^{-1}) and ^{1}H NMR ($CDCl_3$) (δ ppm downfield from TMS) spectra were recorded on a Hitachi-215 and Varian VXR-200 MHz spectrometers respectively. C, H and N analyses were carried out on a Yanaco MT-3 (Japan) analyser.

3-(*p*-Nitrophenyl)-6-*p*-chlorophenyl-*s*-triazolo[3,4-*b*]|[1,3,4] thiadiazole 1A

A mixture of 4-amino-5-mercapto-3-(*p*-nitrophenyl)-*s*-triazole (5.0g, 0.02mole) and *p*-chlorobenzoic acid (3.2g, 0.02mole) in $POCl_3$ (20ml) was heated under reflux in an oil bath at 120°C for one hour. The reaction mixture was cooled, poured into ice and neutralized with aq. K_2CO_3 solution. The solid thus separated was filtered, washed thoroughly with water and recrystallized from gl. acetic acid, yield 3.0g (39.78%), m.p.>250°C. (Found: C, 50.63; H, 2.48; N, 19.23; S, 8.76. $C_{15}H_8N_5O_2SCl$ requires C, 50.34; H, 2.23; N, 19.58; S, 8.95%); IR : 830, 840 (1,4-disubstituted benzene ring), 1355, 1535 (Nitro group), 1525 (C-N stretching), 1610, 1625 (C=C & C = N), 3040 (aromatic C-H stretching).

A similar method was adopted for the synthesis of compound 3-(*p*-nitrophenyl)-6-*p*-nitrophenyl-*s*-triazolo[3,4-*b*][1,3,4]thiadiazole **1B** (Ar=*p*-O_2N-C_6H_4) having m.p. 230°C, yield 3.0g(38.65%). (Found: C,48.71; H,2.47; N, 22.67; S, 8.43. $C_{15}H_8N_6SO_4$ requires C, 48.91; H, 2.17; N, 22.80; S, 8.69%); IR: 820, 840 (1,4-disubstituted benzenering), 1345, 1540 (NO_2 group), 1525 (C-N stretching), 1600, 1620 (C = C and C = N), 3050 (aromatic C - H stretching).

Also3-(*p*-nitrophenyl)-6-*m*-chlorophenyl-*s*-triazolo [3,4-*b*][1,3,4]thiadiazole**1C** (Ar=*m*-Cl-C_6H_4) was prepared having m.p. 200°C, yield 2.9g (38.46%) (Found : C, 50.67; H, 2.52; N, 19.32; S, 8.67 $C_{15}H_8N_5SO_2Cl$requires C, 50.34; H, 2.23; N, 19.58; S, 8.95%); IR : 770, 840, 880 (1,3 and 1,4-disubstituted benzene ring), 1350, 1530 (Nitro group), 1515 (C - N stretching), 1620 (C = C and C = N), 3040 (aromatic C-H stretching).

8a-*p*-Chlorophenyl-3-(*p*-nitrophenyl)-thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*] [1,3,4]thiadiazol-6(7*H*)-one 2A

A mixture of 1A (3.0g, .008mole), thioglycollic acid(0.77g, .008mole) in dry toluene (40ml) was heated under reflux using Dean-Stark water separator for 10-12 hr., concentrated & cooled. The solid thus separated was filtered, washed with water and crystallized from gl acetic acid, m.p. 115°C, yield (27.70%). (Found : C, 47.62; H, 2.33; N, 16.48; S, 14.52. $C_{17}H_9N_5S_2ClO_3$ requires C, 47.38; H, 2.09; N, 16.26; S, 14.86%); IR : 835, 845 (1,4-disubstituted benzene ring), 1520 (C - N stretching), 1600,

1620 (C = C & C = N), 1715 (C = O), 3040, 3060 (aromatic C-H stretching).

A similar method was adopted for the synthesis of compound 8a-*p*-nitrophenyl-3-(*p*-nitrophenyl)-thiazolo [2,3-*b]*-*s*-triazolo [3, 4-*b*] [1,3,4]thiadiazol-6(7*H*)-one **2B**(Ar=*p*-O_2N-C_6H_4) having m.p. 220°C, yield 1.5g (41.66%). (Found : C, 46.37; H, 2.42; N, 18.89; S, 14.26. $C_{17}H_{10}N_6O_5S_2$ requires C, 46.15; H, 2.26; N, 19.00; S, 14.47%); IR : 830, 840 (1,4-disubstituted benzene ring), 1515 (C-N stretching), 1610,1625 (C = C and C = N), 1720 (C = O), 3050 (aromatic C - H stretching).

Also 8a-*m*-chlorophenyl-3-(*p*-nitrophenyl)-thiazolo[2,3-*b*]-*s*-triazolo [3,4 -*b]* [1,3,4] thiadiazol-6(7*H*)-one **2C** (Ar=*m*-Cl-C_6H_4) was prepared having m.p. 195°C, yield 1.0g(27.70%). (Found : C, 47.56; H, 2.29; N, 16.47; S, 14.63. $C_{17}H_9N_5S_2ClO_3$ requires C, 47.38; H, 2.09; N, 16.26; S, 14.86%); IR : 710, 775, 835, 875 (1,3 and 1,4-disubstituted benzene ring), 1520 (C-N stretching), 1355, 1535 (NO_2 group), 1600, 1620 (C = C and C = N), 1715(C = O), 3040 (aromatic C - H stretching).

7-*p*-Chlorobenzylidene-8a-*p*-chlorophenyl-3-(*p*-nitrophenyl)thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazol-6(7*H*)-ones $3A_1$

A mixture of **2A**(1.5g, .002mole), *p*-chlorobenzaldehyde (0.39g, .002mole), anhyd. sodium acetate (0.22g, .002mole) in gl aceticacid (30ml) was heated under reflux for 5 hr, concentrated, cooled and poured into crushed ice. The solid thus separated was filtered,washed with water and crystallized from glacial acetic acid, yield 1.0g(51.81%), m.p. 220°C. (Found : C, 51.73; H, 2.61; N, 12.39; S, 11.37. $C_{24}H_{13}N_5S_2Cl_2O_3$ requires C, 51.98; H, 2.34; N, 12.63; S, 11.55%); IR :825, 840 (1,4-disubstituted benzene ring), 1360, 1530 (NO_2 group), 1600, 1630 (C=C and C = N), 1515 (C-N stretching), 1690 (C=O), 3040 (aromatic C-H stretching).

Similar method was adopted for the synthesis of compounds **$3A_2$, $3B_1$, $3B_2$, $3C_1$& $3C_2$**. Their characterization data is given in Table-1.

9a-(*p*-Chlorophenyl)-7*H*-8-(*p*-chlorophenyl)-3-(*p*-nitrophenyl)-*cis*-8,8a-dihydropyrazolo[3',4':4,5]thiazolo[2,3-*b*]-*s*-triazolo[3,4-*b*][1,3,4]thiadiazoles $4a_1$

A mixture of $3A_1$ (.330g,.0006mole), hydrazine hydrate (0.03g, .0006mole), anhydrous sodium acetate (.049g, .0006mole) in gl acetic acid (30ml) was heated under reflux for 6 hr. The reaction mixture was half concentrated, cooled. The solid thus separated was filtered and recrystallized from gl acetic acid, yield .150g(43.60%), m.p. 180°C. (Found: C, 49.62; H, 2.29; N, 16.71; S, 11.32. $C_{24}H_{15}N_7S_2Cl_2O_2$ requires C, 49.82; H, 2.59; N, 16.95; S, 11.07%); IR : 810, 825, 840 (1,4-disubstituted benzene ring), 1350, 1535 (NO_2 group), 1525 (C-N stretching), 1600, 1620 (C = C & C = N), 3040 (aromatic C-H stretching) ^{1}H NMR(DMSO) : 7.62(1H,d(J=10.0 Hz), C-8a-H), 7.72(1H,d(J=10.0 Hz), C-8-H), 7.95-8.15(12H, m, aromatic protons), 8.34 (1H, s, -NH group).

A similar method was adopted for the synthesis of compds**$4a_2$, $4b_1$, $4b_2$, $4c_1$,** &**$4c_2$** respectively, their characterization data isgiven in Table-2.

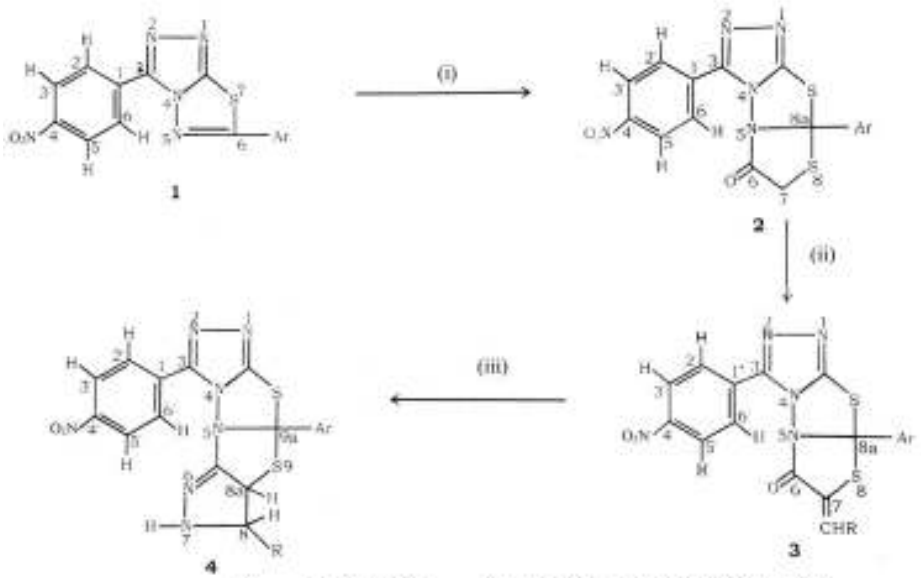
TABLE-1 Characterization data of compounds $3A_2$, $3B_1$, $3B_2$, $3C_1$, & $3C_2$

Compd.	Ar	R	m.p. °C	Yield %	Mol. Formula	Found (%)/Calcd.			
						C	H	N	S
$3A_2$	*p*-Cl-C_6H_4	*p*-H_3CO-C_6H_4	250	58.82	$C_{25}H_{16}N_5S_2ClO_4$	54.31 (54.59	2.73 2.91	12.92 12.73	11.37 11.64)
$3B_1$	*p*-O_2N-C_6H_4	*p*-Cl-C_6H_4	240	39.37	$C_{24}H_{13}N_6S_2ClO_5$	51.47 (51.20	2.09 2.31	14.69 14.93	11.56 11.37)

$3B_2$	*p*-O_2N-C_6H_4	*p*-H_3CO-C_6H_4	220	39.68	$C_{25}H_{16}N_6S_2O_6$	53.49 (53.76	2.61 2.86	15.31 15.05	11.67 11.46)
$3C_1$	*m*-Cl-C_6H_4	*p*-Cl-C_6H_4	200	46.63	$C_{24}H_{13}N_5S_2Cl_2O_3$	51.73 (51.98	2.58 2.34	12.39 12.63	11.29 11.55)
$3C_2$	*m*-Cl-C_6H_4	*p*-H_3CO-C_6H_4	195	52.28	$C_{25}H_{16}N_5S_2ClO_4$	54.38 (54.59	2.76 2.91	12.94 12.73	11.34 11.64)

TABLE-2 Characterization data of compounds $4a_2$, $4b_1$, $4b_2$, $4c_1$, & $4c_2$

Compd.	Ar	R	m.p. °C	Yield %	Mol. Formula	Found (%)/Calcd.			
						C	H	N	S
$4a_2$	*p*-Cl-C_6H_4	*p*-H_3CO-C_6H_4	120	48.89	$C_{25}H_{18}N_7S_2ClO_3$	53.61 (53.33	2.81 3.02	17.76 17.42	11.52 11.37)
$4b_1$	*p*-O_2N-C_6H_4	*p*-Cl-C_6H_4	190	47.84	$C_{24}H_{15}N_8S_2ClO_4$	48.69 (48.93	2.78 2.54	19.31 19.03	10.68 10.87)
$4b_2$	*p*-O_2N-C_6H_4	*p*-H_3CO-C_6H_4	160	48.78	$C_{25}H_{18}N_8S_2O_5$	52.52 (52.35	2.65 2.96	19.72 19.54	11.40 11.16)
$4c_1$	*m*-Cl-C_6H_4	*p*-Cl-C_6H_4	140	36.33	$C_{24}H_{15}N_7S_2Cl_2O_2$	49.63 (49.82	2.76 2.59	16.64 16.95	11.31 11.07)
$4c_2$	*m*-Cl-C_6H_4	*p*-H_3CO-C_6H_4	120	61.12	$C_{25}H_{18}N_7S_2ClO_3$	53.67 (53.33	2.79 3.02	17.20 17.42	11.07 11.37)



(i). $HSCH_2COOH$; (ii) ArCHO, anhyd. NaOAC, gl. AcOH;
(iii) Hydrazine hydrate , anhyd. NaOAc, AcOH.

SCHEME-I

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