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HETEROCYCLIC SYSTEMS CONTAINING BRIDGEHEAD NITROGEN ATOM: FACILE SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SPIRO [CYCLODODECANE-1, 7'(8'*H*)-[6*H*]-3',3'a-DIHYDROPYRAZOLO[3',4' : 4,5]THIAZOLO[3,2-*b*]-*s*-TETRAZINES]

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ABSTRACT
A facile synthesis of 3',3'a-dihydro-3'-arylspiro[cyclododecane-1,7'(8'*H*)-[6*H*]-pyrazolo[3',4' : 4,5]thiazolo[3,2-*b*]-*s*-tetrazines] **4** has been achieved by the condensation of 13, 14, 16, 17 - tetra azaspiro[5, 11]heptadecane-15-thione **1** with chloroacetic acid and then with aldehydes yielded7'-arylidene-6'(7'*H*)-oxospiro[cyclododecane-1,3'(4'*H*)-[2*H*]-thiazolo[3,2-*b*]-*s*-tetrazines] **3** followed by treatment with hydrazine hydrate. The antibacterial and antifungal activity of some of the compounds have also been evaluated.

KEYWORDS
3',3'a-dihydro-3'-arylspiro[cyclododecane-1,7'(8'*H*)-[6*H*]-pyrazolo[3',4':4,5]thiazolo[3,2-*b*]-*s*-tetrazines]**;** 13, 14, 16, 17 - tetra azaspiro[5, 11]heptadecane-15-thione; 7'-arylidene-6'(7'*H*)-oxospiro[cyclododecane-1,3'(4'*H*)-[2*H*]-thiazolo[3,2-*b*]-*s*-tetrazines] ;

INTRODUCTION
Thiazolo-s-tetrazines are of current interest in view of their reported antimicrobialactivity[i-iii]. In continuation of our earlier work on the synthesis of biologically active bridgehead nitrogen heterocyclic systems[iv-x] we report in this paper, the synthesis of pyrazoline fused thiazolo-s-tetrazines and the biological activity associated with them.

The required compound 13, 14, 16, 17 - tetra azaspiro [5,11]-heptadecane-15-thione **1** was synthesized by the reaction of cyclododecanone with thiocarbohydrazide following the method of Lamon[xi]. Treatment of **1** with chloroacetic acid and then with aldehydes afforded 7'- arylidene-6' (7'*H*)-oxospiro [cyclododecane-1,3' (4 *H*)-[2*H*]- thiazolo [3, 2-*b*]-*s*-tetrazines] **3** (Scheme-1, Table-1). The structures **3**were supported by the appearance of a band at 1690-1710 cm^{-1} in their IR spectra. Condensation of **3** with hydrazine hydrate yielded in one step the cyclized products 3',3'a-dihydro-3'-arylspiro [cyclododecane-1,7'(8'*H*)-[6*H*]-pyrazolo[3',4':4,5]thiazolo[3,2-*b*]-*s*-tetrazines] **4** (Scheme-1, Table-2). Lack of absorption in the IR spectra of **4** in the region 1690-1710 cm^{-1} showed the absence of a carbonyl group, thereby suggesting the cyclic structures for **4.** The structures **4** were further supported by their PMR spectral data (vide experimental). The appearance of two doublets at δ7.47 and 7.65 (J = 6.0 Hz) respectively for the protons at 3a and 3 positions in the **PMR** spectrum of **4a** corroborated the cyclic structure and *cis* configuration[xii].

ANTIMICROBIAL ACTIVITY

The compounds **4a** (Ar = *p*-ClC_6H_4) and **4b** (*p*-H_3CO-C_6H_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*by neat samples and serial plate dilution method[xiii]. The minimuum inhibitory concentrations (MIC) of compounds **4a** &**4b** against *E. coli* were found to be 125 and 250 µg/ml respectively. These compounds were found to be active against *C. albicans*when tested as neat samples. They may, therefore be used for local application in the form of powder or ointment, provided further studies indicate the absence of toxicity following local application.

EXPERIMENTAL AND RESULTS

TLC was run on silica gel G plates using acetone-benzene (1:3) as irrigant. Melting points are uncorrected. IR (ν_{max} in cm^{-1}) and PMRspectra (chemical shifts, δppm downfield from TMS) were recorded on a Hitachi-215 and Varian VXR-200 MHz spectrometers respectively.

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13,14,16,17-Tetraazaspiro[5,11]heptadecane-15-thione 1

It was prepared in 37% yield by treating cyclododecanone with thiocarbohydrazide following the method of Lamon[xi], **m.p.** 220°C, (Lit[xiv], m.p. 260°C).

6'-(7'*H*)-Oxospiro[cyclododecane-1,3'(4'H)-[2'*H*]-thiazolo[3,2-*b*]-*s*-tetrazine] 2

A mixture of compound **1** (5.0g, 0.016 mole), chloroacetic acid (1.58g, .016 mole), anhyd. sodium acetate (1.31g, .016 mole) in absolute alcohol was heated under reflux for 5 hr on water bath. The reaction mixture was half concentrated, cooled and kept overnight. The solid thus separated was filtered, washed well with water and recrystallized with ethanol, m.p. 160°C, yield 3.5 g (63.52%). (Found : C, 56.53; H, 8.57; N, 18.49; S, 10.51. $C_{14}H_{26}N_4SO$ requires C, 56.37; H, 8.72; N, 18.79; S, 10.73%); IR : 1515 (C-N stretching), 1630 (C=N stretching), 1730 (C = O stretching), 3220 (N-H stretching).

7'-(*p*-chlorobenzylidene)-6'(7'*H*)-oxospiro[cyclododecane-1,3'(4'*H*)-[2'*H*]-thiazolo[3,2-*b*]-*s*-tetrazine]3a (Ar=*p*-Cl-C_6H_4)

A mixture of compound **2**(2.0g, .0067mole), *p*-chlorobenzaldehyde (0.941g, .0067 mole), anhyd. sodium acetate (0.549 g, .0067 mole) in gl. acetic acid (40 ml) was heated under reflux for 3 hr. The reaction mixture was half concentrated, cooled. The solid thus separated was filtered, washed well with water and crystallized from ethanol, yield 1.0 g (34.48%), m.p. 220°C. (Found : C, 61.34; H, 6.52;N, 12.78; S, 7.62. $C_{22}H_{29}N_4SClO$ requires C, 61.04; H, 6.70; N, 12.94; S, 7.39%); IR : 830 (1,4-disubstituted benzene ring), 1520 (C-N stretching), 1620 (C = N), 1700 (C = 0), 3180 (N-H stretching).

The characterization data of other compounds **3a, 3b, 3c, 3d & 3e** prepared similarly are given in **Table-1.**

3',3'a-Dihydro-2'(*H*)-3'-(*p*-chlorophenyl)spiro[cyclododecane-1,7'(8'H)-[6H]-pyrazolo[3',4': 4,5]thiazolo[3,2-*b*]-*s*-tetrazines] 4a (Ar=*p*-Cl-C_6H_4)

A mixture of **3a** (0.450g, .0010 mole), hydrazine hydrate (0.050g, .0010 mole), anhyd. sodium acetate (0.082g, .0010 mole) in gl. acetic acid (25ml) was heated under reflux for 6 hr. The reaction mixture was half

concentrated, cooled. The solid thus separated was filtered, washed well with water and recrystallized from gl. acetic acid, yield .225g(48.91%), m.p. 260°C. (Found : C, 59.37; H, 6.76; N, 18.62; S, 7.42. $C_{22}H_{31}N_6SCl$ requires C, 59.12; H, 6.94; N, 18.81; S, 7.16%); IR : 840 (1, 4-disubstituted benzene ring), 1525 (C-N stretching), 1600, 1620(C=C and C=N), 3040 (aromatic C-H stretching), 3320 (N-H stretching; ^{1}H NMR (DMSO) : 1.65-2.80 (22H, m, methylene protons of cyclododecane ring), 7.47 (1H, d(J=6.0Hz), C-3'a-H), 7.65 (1H, d (J=6.0Hz), C-3'-H), 7.98 (1H, s, -NH proton).

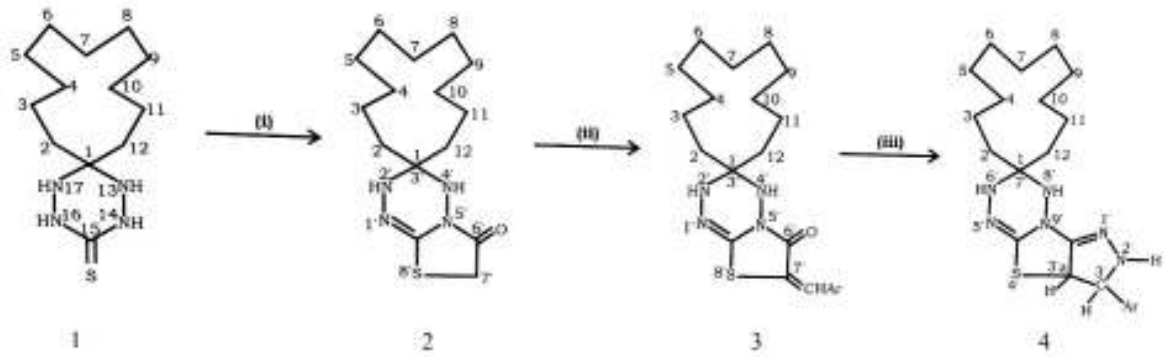
Similar method was adopted for the synthesis of compounds **4b, 4c, 4d** &**4e,** the characterization data of which are given in **Table-2.**

TABLE-1 Characterization data of 7'-arylidene-6'(7'*H*)-oxospiro[cyclododecane-1,3'(4'*H*)-[2*H*]thiazolo [3,2-*b*]-*s*-tetrazines]**3**

Compd.	Ar	m.p. °C	Yield %	Mol. formula	Found (%)/Calcd.			
					C	H	N	S
3b	*p*-CH_3O-C_6H_4	190	41.86	$C_{23}H_{32}N_4SO_2$	64.20 (64.48	7.29 7.47	13.31 13.08	7.61 7.47)
3c	*m*-NO_2-C_6H_4	240	47.29	$C_{22}H_{29}N_5SO_3$	59.32 (59.59	6.71 6.54	15.67 15.80	7.56 7.22)
3d	*p*-Me_2N-C_6H_4	200	36.19	$C_{24}H_{35}N_5SO$	65.57 (65.30	7.78 7.93	15.63 15.87	7.58 7.25)
3e	*o*-Cl-C_6H_4	180	44.82	$C_{22}H_{29}N_4SClO$	61.32 (61.04	6.58 6.70	12.75 12.94	7.67 7.39)

TABLE-2 Characterization data of 3', 3'a-dihydro-3'-arylspiro[cyclododecane-1,7'(8'*H*)-[6*H*]-pyrazolo[3',4' : 4,5] thiazolo[3,2-*b*]-*s*-tetrazines] **4**

Compd.	Ar	m.p. °C	Yield %	Mol. Formula	Found (%)/Calcd.			
					C	H	N	S
4b	*p*-CH_3O-C_6H_4	240	27.02	$C_{23}H_{34}N_6SO$	62.26 (62.44	7.83 7.69	18.85 19.00	7.53 7.23)
4c	*m*-NO_2-C_6H_4	>250	43.68	$C_{22}H_{31}N_7SO_2$	57.94 (57.76	6.49 6.78	21.65 21.44	6.83 7.00)
4d	*p*-Me_2N-C_6H_4	230	44.27	$C_{24}H_{37}N_7S$	63.57 (63.29	8.39 8.13	21.76 21.53	7.23 7.03)
4e	*o*-Cl-C_6H_4	210	42.32	$C_{22}H_{31}N_6SCl$	59.42 (59.12	6.73 6.94	18.69 18.81	7.42 7.16)



1 2 3 4

(i) $ClCH_2COOH$,anhyd. NaOAc(ii) ArCHO, anhyd. NaOAc, gl. AcOH(iii) $NH_2NH_2H_2O$

SCHEME-1

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