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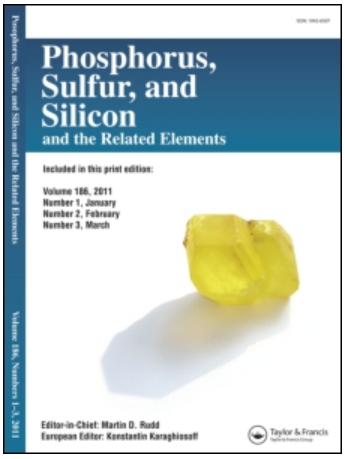

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ONE-FLASK SYNTHESES OF SOME NEW SPIROTHIAZOLOPYRANOPYRAZOLE, SPIROTHIAZOLODIHYDROPYRIDI-NOPYRAZOLE AND SPIROTHIAZOLOTHIOPY-RANOPYRAZOLE DERIVATIVES AS ANTIMICROBIAL AGENTS

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ONE-FLASK SYNTHESES OF SOME NEW SPIROTHIAZOLOPYRANOPYRAZOLE, SPIROTHIAZOLODIHYDROPYRIDINOPYRAZOLE AND SPIROTHIAZOLOTHIOPYRANOPYRAZOLE DERIVATIVES AS ANTIMICROBIAL AGENTS

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1-Thia-4-benzyl-4-azaspiro[4.4]nonan-3-one (2a) and/or 1-thia-4-benzyl-4-azaspiro[4.5]decan-3-one (2b) reacted with 4-arylidene-3-methylpyrazolin-5-ones (1a–f) in a mixture of ethanol/pyridine at reflux temperature to give spirothiazolopyranopyrazoles (3a–l) in one flask. The fusion of compounds 1a–f with 2a and/or 2b in the presence of ammonium acetate afforded spirothiazolodihydropyridinopyrazole derivatives (4a–l) in good yields. Also the reaction of compounds 1a–f with 2a and/or 2b with phosphorus pentasulfide in pyridine at reflux temperature yielded the spirothiazolothiopyranopyrazoles (5a–l). All the synthesized spiroheterocyclic derivatives were identified by conventional methods (IR, ^{1}H-NMR) and elemental analyses. All the prepared compounds were tested for their antimicrobial activities in comparison with tetracycline as a reference compound.

Keywords: Spiroheterocycles; spirothiazolopyranopyrazoles; spirothiazolodihydropyridinopyrazoles; spirothiazolothiopyranopyrazoles; antimicrobial; NMR

INTRODUCTION

Several authors have reported the synthesis and applications of spirocyclic derivatives.[1–10] The synthesis of spirocycles as class III antiarrhythmic agent was done.[18]. Synthesis of spiro[3H-indole-3,4(4H)pyran]-2-(1H)-ones having central nervous system activities were carried out.[12] Spirocycloalkylsubstituted azetidinones were used as hypocholesterolemic agents.[13] Spiro compounds showed photochromic properties.[14] The preparation of fluoran derivatives as

coloring agents for recording materials was carried out.[15] Also the preparation of spiroazafuranone derivatives to be used for the treatment of neurodegenerative disorders and as anxiolytics was achieved.[16] Spiro derivatives were used as herbicides, insecticides, acaricides and antivirals.[17] It is of interest to note that pyrazole derivatives are reported as well known pharmaceuticals.[18–20] From all of the forgoing facts and as a continuation of our previous works,[21–24] we report herein the synthesis and application of some new spirothiazolopyrazole derivatives.

RESULTS AND DISCUSSION

Syntheses started with the reaction of 1-thia-4-benzyl-4-azaspiro[4.4]nonan-3-one (2a) and 1-thia-4-benzyl-4-azaspiro[4.5]decan-3-one (2b) with 4-arylidene-3-methylpyrazolin-5-ones (1a–f) in a mixture of ethanol/pyridine to yield spirothiazolopyranopyrazole derivatives (3a–l) in good yields in one flask and one step. The structures of compounds 3a–l were established from their elemental analyses and spectroscopic data (Table I).The IR spectrum of 3a showed characteristic strong absorption bands at 3150 cm^{-1} corresponding to the stretching vibration of NH group of the pyrazoline ring, 3050 cm^{-1} for aromatic carbon-hydrogen stretching, 2870 cm^{-1} for aliphatic carbon-hydrogen, 1600 cm^{-1} for the C=N bond of the pyrazoline moiety and 710 cm^{-1} for the C-S bond and no absorption bands for any carbonyl groups. The ^{1}H-NMR spectrum of 3a (DMSO-d_6) showed the following signals: δ 1.30–1.70 (4H, m, two methylene groups of cyclopentane ring), 1.90–2.20 (4H, m, two methylene groups of cyclopentane ring), 2.78(3H, s, for the methyl protons of the pyrazoline ring), 3.20(2H, s, the methylene of benzyl group), 3.40 (1H, s, the proton at C_4 of the pyran ring), 7.00–7.80(10H, m, for the aromatic protons) and 8.20 ppm (1H, s, the NH proton of the pyrazole ring). The fusion of the spiro derivatives 2a,b with 1a–f in the presence of ammonium acetate yielded the spirothiazolodihydropyridinopyrazole derivatives 4a–l in good yields (Scheme 1). The structures of compounds 4a–l were confirmed on the basis of their elemental analyses and spectroscopic data (Table I). Reactions of compounds 2a,b with 1a–f in the presence of phosphorus pentasulfide in pyridine afforded the spirothiazolothiopyranopyrazole derivatives 5a–l in good yields (Scheme 1, Table I). The structure assignment of the prepared spirocycles 5a–l were based on elemental and spectral analyses (Table I). The ^{1}H-NMR spectrum of 5a (DMSO-d_6) showed the following signals: δ 1.30–1.70 (4H, m, two methylene groups of the cyclopentane ring), 1.90–2.10 (4H, m, two methylene groups of the cyclopen-

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TABLE I Physical Data of Spirothiazolopyranopyrazoles (3a–l), Spirothiazolodihydropyridinopyrazoles (4a–l) and Spirothiazolothiopyranopyrazoles (5a–1).

Compound No.	*Yield (%)*	*M.P. (°C)*	*Molecular formula (Solvent of crystallization)*	*Microanalyses-Calculated/Found (%)*					*IR (KBr)(cm^{-1})*	*^{1}H-NMR (DMSO-d_6) δ (TMS) ppm*
				C	*H*	*N*	*S*	*Cl*		
3a	60	160–162	$C_{25}H_{25}ON_3S$ (ethanol)	72.28 72.10	6.02 6.00	10.12 10.00	7.71 7.60	– –	3150(NH), 3050(CH arom), 2870(CH aliph), 1600(C=N), 710(C-S)	1.30–1.70(4H,m), 1.90–2.20(4H,m), 2.78(3H,s) 3.20(2H,s), 3.40(1H,s), 7.00–7.80(10H,m), 8.20(1H,s).
3b	57	164–166	$C_{25}H_{24}ON_3SCl$ (ethanol)	66.81 66.70	5.34 5.25	9.35 9.20	7.12 7.00	7.79 7.60	3150(NH), 3050(CH arom), 2890(CH aliph), 1600(N=C), 720(C-S).	1.30–1.70(4H,m), 1.90–2.20(4H,m), 2.80 (3H,s), 3.20(2H,s), 3.40(1H,s), 7.00–7.80(9H,m), 8.20(1H,s).
3c	55	180–182	$C_{25}H_{24}O_3N_4S$ (methanol)	65.21 65.10	5.21 5.10	12.17 12.10	6.95 6.80	– –	3150(NH), 3070(CH arom), 2880(CH aliph), 1600(C=N), 1510(NO_2), 730(C-S).	1.30–1.70(4H,m), 1.90–2.20(4H,m), 2.80(3H,s), 3.20(2H,s), 3.40(1H,s) 7.00–7.80(9H,m), 8.20(1H,s).
3d	56	170–172	$C_{31}H_{29}N_3OS$ (methanol)	75.76 75.50	5.90 5.80	8.55 8.40	6.51 6.40	– –	3050(CH arom), 2870(CH aliph), 1600(C=N), 730(C-S) 7.00–7.90(15H,m).	1.30–1.70(4H,m), 1.90–2.20(4H,m), 2.80(3H,s), 3.20(2H,s), 3.40(1H,s),
3e	55	176–178	$C_{31}H_{28}N_3OSCl$ (ethanol)	70.85 70.70	5.33 5.20	8.00 7.90	6.09 6.00	6.66 6.50	3050(CH arom), 28990(CH aliph), 1600(C=N), 720(C-S) 7.00–7.90(14H,m).	1.30–1.70(4H,m), 1.90–2.20(4H,m), 2.80(3H,s), 3.20(2H,s), 3.40(1H,s),
3f	58	185–187	$C_{31}H_{28}N_4O_3S$ (methanol)	69.40 69.30	5.22 5.10	10.44 10.30	5.97 5.80	– –	3050(CH arom), 2890(CH aliph), 1600(C=N), 1510 NO_2), 730(C-S)	1.30–1.70(4H,m), 1.90–2.20(4H,m), 2.80(3H,s), 3.20(2H,s), 3.40(1H,s), 7.00–8.20(14H,m).
3g	60	190–192	$C_{26}H_{27}N_3OS$ (methanol)	72.72 72.60	6.29 6.20	9.79 9.60	7.45 7.10	– –	3150(NH), 3050(CH arom), 2900(CH aliph), 1600(C=N), 730(C-S).	1.40–1.80(6H,m), 1.90–2.10(4H,m), 2.75(3H,s), 3.20(2H,s), 3.40(1H,s), 7.00–8.10(10H,m), 8.30(1H,s).
3h	55	163–165	$C_{26}H_{26}N_3OSCl$ (ethanol)	67.38 67.20	5.61 5.40	9.07 9.00	6.91 6.70	7.55 7.40	3150(NH), 3070(CH arom), 2890(CH aliph), 1600(C=N), 710(C-S)	1.40–1.85(6H,m), 1.90–2.20(4H,m), 2.75(3H,s), 3.20(2H,s), 3.70(1H,s), 7.00–8.10(9H,m), 8.30(1H,s).

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TABLE I (continued)

Compound No.	Yield (%)	M.P. (°C)	Molecular formula (Solvent of crystallization)	Microanalyses-Calculated/Found (%)					IR (KBr)(cm^{-1})	^{1}H-NMR (DMSO-d_6) δ (TMS) ppm
				C	H	N	S	Cl		
3i	60	172–175	$C_{26}H_{26}N_4O_3S$	65.82	5.48	11.81	6.75	–	3180(NH, 3050(CH arom),	1.35–1.75(6H,m), 1.90–2.20(4H,m),
			(methanol)	65.70	5.30	11.70	6.60	–	2870(CH aliph), 1600(C=N),	2.70(3H,s), 4.30(2H,s), 3.60(1H,s),
									1510(NO_2), 720(C-S).	7.00–8.10(9H,m), 8.20(1H,s).
3j	57	180–182	$C_{32}H_{31}N_3OS$	76.03	6.13	8.31	6.33	–	3070(CH arom), 2890(CH	1.40–1.80(6H,m), 1.90–2.10(4H,m),
			(ethanol)	76.00	6.00	8.20	6.20	–	aliph), 1600(C=N), 730(C-S)	2.70(3H,s), 3.25(2H,s), 3.40(1H,s),
									7.00–8.10(15H,m).	
3k	55	187–189	$C_{32}H_{30}N_3OSCl$	71.24	5.56	7.79	5.93	6.49	3050(CH arom), 2875(CH	1.40–1.80(6H,m), 1.90–2.20(4H,m),
			(methanol)	71.10	5.40	7.60	5.70	6.30	aliph), 1600(C=N), 720(C-S)	2.80(3H,s), 3.20(2H,s), 3.60(1H,s),
									7.00–8.10(14H,m).	
3l	56	194–196	$C_{32}H_{30}N_4O_3S$	69.81	5.45	10.18	5.81	–	3080(CH arom), 2870(CH	1.35–1.75(6H,m), 1.90–2.20(4H,m),
			(ethanol)	69.70	5.30	10.00	5.60	–	aliph), 1600(C=N), 730(C-S)	2.80(3H,s), 3.20(2H,s), 3.40(1H,s),
									1510(NO_2)	7.00–8.10(14H,m).
4a	60	162–164	$C_{25}H_{26}N_4S$	72.46	6.28	13.52	7.72	–	3150(NH, 3070(CH arom),	1.30–1.70(4H,m), 1.90–2.10(4H,m),
		(ethanol)	72.20	6.10	13.40	7.50	–	2870(CH aliph), 1600(C=N)	2.80(3H,s), 3.25(2H,s), 3.40(1H,s),
									720(C-S).	7.00–8.10(10H,m), 8.30(2H,s).
4b	55	190–192	$C_{25}H_{25}N_4SCl$	66.96	5.58	12.50	7.14	7.81	3180(NH), 3070(CH arom),	1.30–1.70(4H,m), 1.90–2.10(4H,m),
		(methanol)	66.70	5.30	12.40	7.00	7.60	2890(CH aliph), 1600(C=N),	2.80(3H,s), 3.20(2H,s), 3.60(1H,s),
									710(C-S).	7.00–8.10(9H,m), 8.30(2H,s).
4c	57	200–202	$C_{25}H_{25}N_5O_2S$	65.35	5.44	15.25	6.97	–	3150(NH), 3060(CH arom),	1.30–1.70(4H,m), 1.90–2.20(4H,m),
		(ethanol)	65.10	5.20	15.10	6.70	–	2860(CH aliph), 1600(C=N),	2.80(3H,s), 3.20(2H,s), 3.45(1H,s),
									1510(NO_2), 720(C-S).	7.00–8.10(9H,s), 8.20(2H,s)
4d	60	210–212	$C_{31}H_{30}N_4S$	75.91	6.12	11.42	6.53	–	3170(NH), 3080(CH arom),	1.30–1.70(4H,m), 1.90–2.20(4H,m),
		(methanol)	75.70	6.00	11.20	6.40	–	2900(CH aliph), 1600(C=N),	2.80(3H,s), 3.20(2H,s), 3.50(1H,s),
									730(C-S).	7.00–8.10(15H,m), 8.30(1H,s).

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TABLE I (continued)

Compound No.	Yield (%)	M.P. (°C)	Molecular formula (Solvent of crystallization)	Microanalyses-Calculated/Found (%)					IR (KBr)(cm^{-1})	^{1}H-NMR (DMSO-d_6) δ (TMS) ppm
				C	H	N	S	Cl		
4e	62	214–216 (ethanol)	$C_{31}H_{29}N_4SCl$ 70.70	70.99 5.30	5.53 10.50	10.68 6.00	6.10 6.50	6.67	3180(NH), 3060(CH arom), 2900(CH aliph), 1600(C=N), 730(C-S).	1.35–1.75(4H,m), 1.90–2.20(4H,m), 2.80(3H,s), 3.20(2H,s), 3.50(1H,s), 7.00–8.10(4H,m), 8.30(1H,s).
4f	58	160–162 (ethanol)	$C_{31}H_{29}N_5O_2S$ 69.30	69.53 5.30	5.42 13.00	13.08 5.80	5.98 –	–	3180(NH), 3050(CH arom), 2900(CH aliph), 1600(C=N), 1510(NO_2), 720(C-S).	1.40–1.75(4H,m), 1.90–2.20(4H,m), 2.75(3H,s), 3.20(2H,s), 3.40(1H,s), 7.00–8.10(14H,m), 8.30(1H,s).
4g	55	170–172 (methanol)	$C_{26}H_{28}N_4S$ 72.70	72.89 6.30	6.54 13.00	13.08 7.30	7.47 –	–	3180(NH), 3050(CH arom), 2900(CH aliph), 1600(C=N), 730(C-S).	1.30–1.70(6H,m), 1.90–2.20(4H,m), 2.80(3H,s), 3.20(2H,s), 3.50(1H,s), 7.00–8.10(10H,m), 8.30(2H,s).
4h	56	180–182 (methanol)	$C_{26}H_{27}N_4SCl$ 67.40	67.53 5.60	5.84 12.00	12.12 6.60	6.92 7.50	7.57	3170(NH), 3050(CH arom), 2900(CH aliph), 1600(C=N), 730(C-S).	1.30–1.70(6H,m), 1.90–2.20(4H,m), 2.80(3H,s), 3.20(2H,s), 3.60(1H,s), 7.00–8.10(9H,m), 8.40(2H,s).
4i	55	190–192 (ethanol)	$C_{26}H_{27}N_5O_2S$ 65.70	65.96 5.50	5.70 14.60	14.79 6.50	6.76 –	–	3180(NH), 3070(CH arom), 2900(CH aliph), 1600(C=N), 1510(NO_2), 710(C-S).	1.40–1.80(6H,m), 1.90–2.20(4H,m), 2.80(2H,s), 3.60(1H,s), 7.00–8.10(9H,m), 8.40(2H,s).
4j	60	87–189 (methanol)	$C_{32}H_{32}N_4S$ 76.00	76.19 6.20	6.34 11.00	11.11 6.20	6.34 –	–	3170(NH), 3060(CH arom), 2900(CH aliph), 1600(C=N), 710(C-S).	1.30–1.70(6H,m), 1.90–2.10(4H,m), 2.80(3H,s), 3.20(2H,s), 3.60(1H,s), 7.00–8.10(15H,m), 8.40(1H,s).
4k	56	194–196 (ethanol)	$C_{32}H_{31}N_4SCl$ 71.20	71.37 5.60	5.76 10.30	10.40 5.70	5.94 6.20	6.50	3170(NH), 3050(CH arom), 2900(CH aliph), 1600(C=N), 710(C-S).	1.40–1.80(6H,m), 1.90–2.20(4H,m), 2.80(3H,s), 3.20(2H,s), 3.40(1H,s), 7.00–8.10(14H,m), 8.50(1H,s).
4l	55	194–196	$C_{32}H_{31}N_5O_2S$ (ethanol)	69.94 69.70	5.64 5.50	12.75 12.50	5.82 5.60	– –	3180(NH), 3060(CH arom), 2900(CH aliph), 1600(C=N), 1510(NO_2), 730(C-S).	1.40–1.80(6H,m), 1.90–2.10(4H,m), 2.80(3H,s), 3.20(2H,s), 3.40(1H,s), 7.00–8.10(14H,m), 8.35(1H,s).

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TABLE I (continued)

Compound No.	Yield (%)	M.P. (°C)	Molecular formula (Solvent of crystallization)	Microanalyses-Calculated/Found (%) C	H	N	S	Cl	IR (KBr)(cm^{-1})	^{1}H-NMR (DMSO-d_6) δ (TMS) ppm
5a	56	220–222 (methanol)	$C_{25}H_{25}N_3S_2$ 69.30	69.60 5.60	5.80 9.48	9.74 14.70	14.84 –	–	3150(NH), 3050(CH arom), 2890(CH aliph), 1600(C=N), 730(C-S).	1.30–1.70(4H,m), 1.90–2.10(4H,m), 2.80(3H,s), 3.20(2H,s), 3.40(1H,s), 7.00–8.10(10H,m), 8.30(1H,s).
5b	58	230–232 (methanol)	$C_{25}H_{24}N_3S_2Cl$ 64.40	64.51 5.00	5.16 9.00	9.03 13.50	13.76 7.30	7.52	3170(NH), 3050(CH arom), 2900(CH aliph), 1600(C=N), 720(C-S).	1.30–1.70(4H,m), 1.90–2.10(4H,m), 2.80(3H,s), 3.20(2H,s), 3.40(1H,s), 7.00–8.10(9H,m), 8.50(1H,s).
5c	60	240–242	$C_{25}H_{24}N_4O_2S_2$	63.02	5.04	11.76	13.44	–	3160(NH), 3050(CH arom), 2900(CH aliph), 1600(C=N), 730(C-S).	1.30–1.70(4H,m), 1.90–2.10(4H,m), 2.80(3H,s), 3.20(2H,s), 3.40(1H,s), 7.00–8.10(9H,m), 8.50(1H,s).
5d	62	247–249	$C_{31}H_{29}N_3S_2$ (methanol)	73.37 73.10	5.71 5.60	8.28 8.10	12.60 12.40	– –	3070(CH arom), 2900(CH aliph), 1600(C=N), 710(C-S)	1.30–1.70(4H,m), 1.90–2.20(4H,m), 2.75(3h,s), 3.20(2H,s), 3.50(1H,s), 7.00–8.10(15H,m).
5e	60	250–252	$C_{31}H_{28}N_3S_2Cl$ (methanol)	68.76 68.50	5.17 5.00	7.76 7.50	11.82 11.60	6.46 6.20	3060(CH arom), 2890(CH aliph), 1620(C= N), 720(C-S)	1.30–1.70(4H,m), 1.90–2.20(4H,m), 2.75(3H,s), 3.30(2H,s), 3.50(1H,s), 7.00–8.10(14H,m).
5f	62	210–212 (methanol)	$C_{31}H_{28}N_4O_2S_2$ 67.10	67.39 5.00	5.07 10.00	10.14 11.20	11.59 –	–	3050(CH arom), 2890(CH aliph), 1600(C= N), 1510(NO_2), 720(C-S)	1.30–1.70(4H,m), 1.90–2.20(4H,m), 2.75(3H,s), 3.30(2H,s), 3.60(1H,s), 7.00–8.00(14H,m).
5g	60	230'232 (methanol)	$C_{26}H_{28}N_4O_2S_2$ 70.00	70.11 70.00	6.06 6.00	9.43 9.20	14.10	14.38 –	–3180(NH), 3060(CH arom), 2900(CH aliph), 1600(C= N), 730(C-S).	1.40–1.80(6H,m), 1.90–2.20(4H,m), 2.70(3H,s), 3.30(2H,s), 3.60(1H,s), 7.00–8.00(10H,m), 8.50(1H,s).
5h	63	240–242	$C_{26}H_{26}N_3S_2Cl$ (methanol)	65.13 65.00	5.42 5.20	8.76 8.60	13.36 13.20	7.30 7.10	3170(NH), 3050(CH arom), 2900(CH aliph), 1600(C= N), 730(C-S).	1.40–1.70(6H,m), 1.80–2.20(4H,m), 2.70(3H,s), 3.30(2H,s), 3.50(1H,s), 7.00–8.10(9H,m), 8.60(1H,s).

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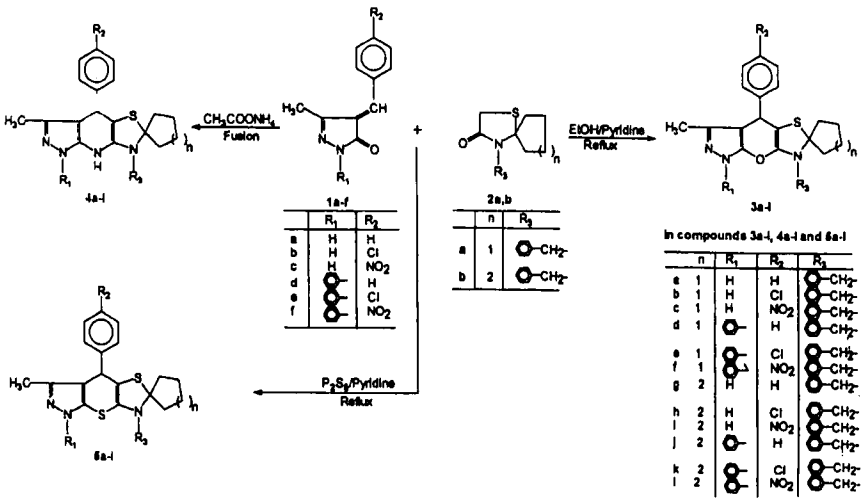
TABLE I (continued)

Compound No.	Yield (%)	M.P. (°C)	Molecular formula (Solvent of crystallization)	Microanalyses-Calculated/Found (%)					IR (KBr)(cm^{-1})	^{1}H-NMR (DMSO-d_6) δ (TMS) ppm
				C	H	N	S	Cl		
5i	60	250–252	$C_{26}H_{26}N_4O_2S_2$ (methanol)	63.67 63.50	5.30 5.16	11.42 11.20	13.06 13.00	– –	3180(NH), 3060(CH arom), 2900(CH aliph), 1600(C= N), 1520(NO_2), 730(C-S).	1.40–1.70(6H,m), 1.90–2.10(4H,m), 275(3H,s), 3.20(2H,s), 3.60(1H,s), 7.00–8.10(9H,m), 8.50(1H,s).
5j	62	260–262 (methanol)	$C_{32}H_{31}N_3S_2$ 73.50	73.70 5.70	5.95 8.00	8.06 12.10	12.28 –	–	3070(CH arom), 2900(CH aliph), 1620(C=N), 720(C-S)	1.40–1.70(6H,m), 1.90–2.20(4H,m), 2.70(3H,s), 3.30(2H,s), 3.60(1H,s), 7.00–8.00(15H,m).
5k	61	257–259 (methanol)	$C_{32}H_{30}N_3S_2Cl$ 69.00	69.18 5.30	5.40 7.30	7.56 1.30	11.53 6.10	6.30	3070(CH arom), 2900(CH aliph), 1620(C=N), 710(C-S)	1.40–1.75(6H,m), 1.90–2.20(4H,m), 2.75(3H,s), 3.30(2H,s), 3.60(1H,s), 7.00–8.00(14H,m).
5l	60	270–272 (methanol)	$C_{32}H_{30}N_4O_2S_2$ 67.60	67.84 5.20	5.30 9.70	9.89 11.10	11.30 –	–	3050(CH arom), 2900(CH aliph), 1600(C=N), 1510 (NO_2), 710(C-S).	1.40–1/70(6H,m), 1.90–2.20(4H,m), 2.75(3H,s), 3.20(2H,s), 3.50(1H,s), 7.00–8.10(14H,m).



SCHEME 1

tane ring), 2.80 (3H, s, the methyl group protons of the pyrazole ring), 3.20 (2H, s, the methylene protons of the benzyl group), 3.40 (1H, s, the proton at C_4 of the thiopyran ring), 7.00–8.10 (10H, m, the aromatic protons) and 8.30 (1H, s, the NH proton of the pyrazole ring).

Antimicrobial Activity

The antimicrobial activity of the newly synthesized compounds were tested against representative organisms of the different categories of -pathogenic microorganisms such as *Escherichia coli, Pseudomonas aeruginosa* as Gram-negative bacteria, *Staphylococcus aureus, Bacillus cereus* as Gram-positive bacteria, *Aspergillus nigar, Aspergillus clavatus, Aspergillus fumigatus* from the moulds, and Candida albicans as yeast organism using the agar cup diffusion technique.[27] Each compound was tested on the various organisms and the inhibition of growth observed against controls.

Tested Miroorganisms

Aspergillus Spps: representative of the moulds that cause generalized toxicosis and pulmonary aspergillosis.

Candida albicans: representive yeast that causes thrush (oral candidosis), infection of the esophagus, intestine, vagina, skin, nails and other sites and organs of the body.

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Culture medium

1-Nutrient agar medium used for bacteria. 2-Sabaurounds dextrose agar medium for moulds. 3-Sabourauds maltose agar medium for yeast.

Environmental conditions for optimal growth were as follows:

1) 35–37°C incubation temperature for both Gram-negative and Gram-positive bacteria and the incubation period was 48 hrs., 28°C incubation temperature was used for moulds and yeast. The incubation period for moulds was 4–6 days, while 2–3 days for yeast.

Results of antimicrobial activity

The biological activities of the synthesized compounds were studied at two different concentrations A: 50 $\mu g/cm^{-3}$, B: 100 $\mu g/cm^{-3}$. Results of the biological activities are shown in Table (II).

The data showed that all the synthesized compounds have a remarkable effect against the tested microorganisms (both Gram-negative and Gram-positive bacteria as well as moulds and yeast. Compounds 5c, 5d, 5f, 5i and 5l (at the concentrations A and B) showed highly significant effects against bacteria, moulds and yeast as indicated from the inhibition zones of 21 mm up to 27 mm range. *Aspergillus niger* has a resistant effect against compounds 3c, 3e, 3k, 3l (at the concentration A). The same compounds (at the concentration B) gave promising results against *Aspergillus niger* as well as moderate effect against bacteria.

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EXPERIMENTAL

The time required for completion of the reaction was monitored by thin layer chromatography (TLC). Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded on a Pye-Unicam Sp200G spectrophotometer. ^{1}H-NMR spectra were measured on an EM 360 90 MHz NMR spectrophotometer. Microanalyses were determined on a Perkin-Elmer 240 C microanalyser.

Preparation of 3-methyl-4-arylidine-2-pyrazoline-5-one drivatives (1a–f).

These compounds were prepared according to the reported procedure.[25]

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TABLE II In-vitro Antimicrobial screening of compounds 3–5 (inhibition zones mm) at concentration A = 50 μg/cm^{-3}, (B = 100μg/cm^{-3})

Compound No.	*Bacteria*				*Mould*			*Yeast*
	Escherichia coli	*Pseudomonas aeruginosa*	*Staphylococcus aureus*	*Bacillus cereus*	*Asp. niger*	*Asp. clavatus*	*Asp. fumigatus*	*Candida albicans*
3c	20	20	17	15	-ve	-ve	-ve	15
	(22)	(22)	(20)	(19)	(-ve)	(-ve)	(-ve)	(20)
3e	18	21	19	20	-ve	20	20	15
	(17)	(17)	(17)	(18)	(-ve)	(22)	(20)	(20)
3h	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
	(18)	(24)	(-ve)	(13)	(20)	(-ve)	(-ve)	(-ve)
3k	25	30	19	22	-ve	22	20	30
	(21)	(20)	(20)	(20)	(25)	(25)	(22)	(22)
3l	18	20	17	15	-ve	22	20	-ve
	(14)	(17)	(17)	(19)	(-ve)	(24)	(20)	(15)
4i	23	25	22	22	22	27	20	20
	(-ve)	(19)	(-ve)	(14)	(20)	(22)	(20)	(22)
5a	20	18	17	20	-ve	-ve	-ve	-ve
	(22)	(20)	(20)	(20)	(27)	(20)	(15)	(27)
5c	23	21	22	22	25	25	20	20
	(23)	(22)	(24)	(25)	(27)	(20)	(21)	(22)
5d	23	21	22	20	25	20	20	20
	(23)	(23)	(22)	(21)	(27)	(25)	(22)	(25)
5f	23	25	23	20	25	20	23	20
	(25)	(25)	(24)	(22)	(27)	(27)	(24)	(22)
5i	25	25	20	19	25	22	20	22
	(24)	(22)	(20)	(22)	(25)	(25)	(24)	(22)
5l	25	21	20	22	-ve	20	20	20
	(24)	(22)	(24)	(22)	(27)	(20)	(20)	(22)
Tetracyclina	8	10	8	7	8	10	9	7

*-ve means inactive.

Preparation of 1-thia-4-benzyl-4-azaspiro[4.4] nonan-3-one (2a) and 1-thia-4-benzyl-4-azaspiro[4.5]decan-3-one (2b):

These compounds were prepared according to the reported procedure.[26]

Synthesis of Spiroheterocycles Derivatives 3a-1–5a-1:

General Procedure

A mixture of 1-thia-4-benzyl-4-azaspiro[4.4]nonan-3-one (2a) and/or 1-thia-4-benzyl-4-azaspiro[4.5]decan-3-one (2b) (0.001 mole) and 4-aryl-methylpyrazolin-5-ones (1a–f) was refluxed in 25 cm^3 of ethanol/pyridine mixture (1 : 1) or fused with 0.0012 mole of ammonium acetate and/or refluxed with 0.001 mole of phosphorus pentasulfide in 25 cm^3 of pyridine. The reaction was heated at reflux temperature for 10 h, then cooled to room temperature and poured in 50 ml of dilute HCl (10%) whereby the target products were precipitated, filtered off and crystallized from the appropriate solvent (Table I).

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