

Synthesis and Reactions of New Thienopyridines, Pyridothienopyrimidines and Pyridothienotriazines

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4-Aryl-3-cyano-6-(2'-thienyl)-pyridine-2(1*H*)-thiones (**1a-c**) were reacted with phenacyl bromide, chloro-*N*-arylacetamides or 2-chloroacetylaminopyridine to furnish 2-functionalized 3-amino-4-aryl-6-(2'-thienyl)-thieno[2,3-*b*]pyridines **4a-c** and **5a-c** or **5d** respectively. The compounds **5a-d** underwent different sequence of reactions to produce a variety of thienylpyridothienopyrimidines and thienylpyridothienotriazines. Some of the prepared compounds were tested *in vitro* for their antimicrobial activities.

Key Words : Thienopyridines, Pyrimidines, Triazines

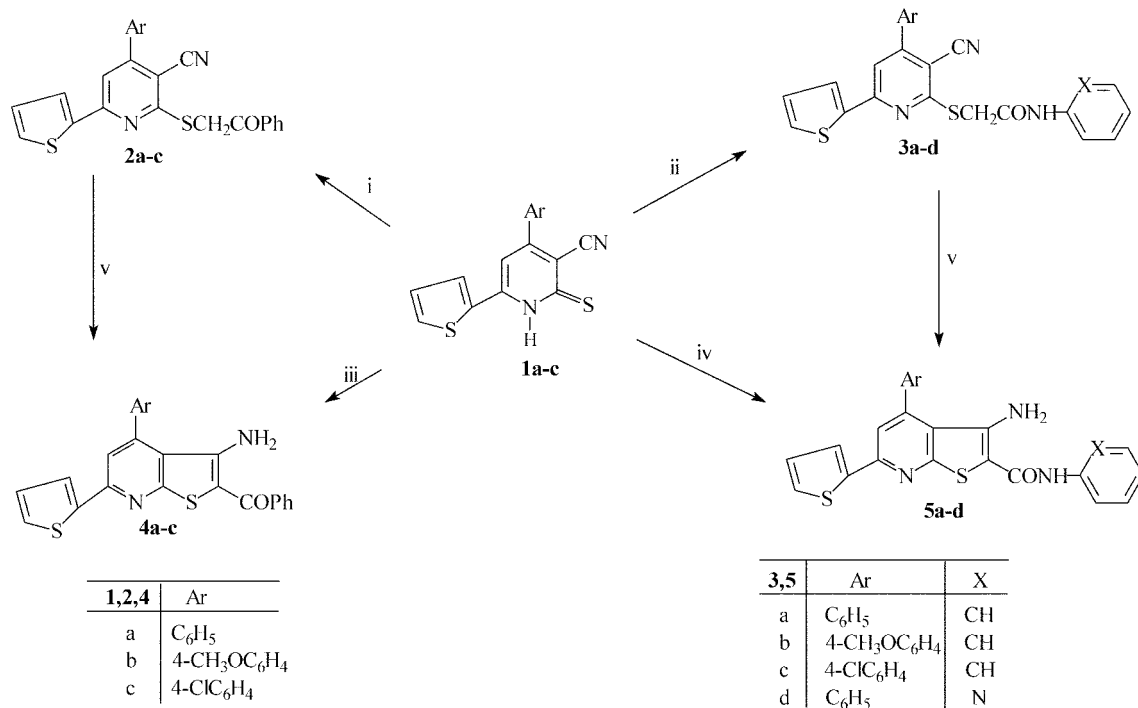
Introduction

The biological activities of condensed pyrimidines as sedatives, antibacterials and antimalarials are well documented.^{1,2} Several thieno[2,3-*b*]pyridine derivatives are known to possess antibacterial,³⁻⁵ antihypertensive⁶ and gonadotropin-releasing hormone antagonizing^{7,8} activity. Pyridothienopyrimidine derivatives have been found applications as analgesics,⁹ antipyretics¹⁰ and anti-inflammatories.¹¹ Moreover, some pyridothienotriazines are known to exhibit



antianaphylactic,¹² and antiallergic activity.¹³ In view of these facts and as a continuation of our previous work on thieno[2,3-*b*]pyridines,¹⁴⁻¹⁷ we report herein the synthesis of the title compounds and their evaluation regarding antimicrobial activities.

Results and Discussion

Based on the important synthetic utility of many 3-cyanopyridine-2(1*H*)-thione derivatives,¹²⁻¹⁷ the 4-aryl-3-



i: PhCOCH₂Br/AcONa; ii: PhCOCH₂Br/EtONa

iii: ClCH₂CONH-/AcONa; iv: ClCH₂CONH-/EtONa; v: EtONa /EtOH

Scheme 1

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cyano-6-(2'-thienyl)-pyridine-2(1*H*)-thiones (**1a-c**) were used as starting materials in the synthesis of the target heterocycles. The reaction of **1a-c** with some halocompounds namely: phenacyl bromide, chloro-*N*-phenylacetamide or 2-chloroacetylaminopyridine in the presence of sodium acetate trihydrate gave 2-substituted methylthio-4-aryl-3-cyano-6-(2'-thienyl)-pyridines (**2a-c**, **3a-c** and **3d**). Upon treatment of these compounds with sodium ethoxide in ethanol, they underwent intramolecular *Thorpe-Ziegler* cyclization to furnish 2-functionalized 3-amino-4-aryl-6-(2'-thienyl)-thieno[2,3-*b*]pyridines (**4a-c**, **5a-c** and **5d**). The latter thienopyridine derivatives were also prepared *via* direct reaction of **1a-c** with the respective halocompounds in the presence of sodium ethoxide as a basic catalyst (Scheme 1).

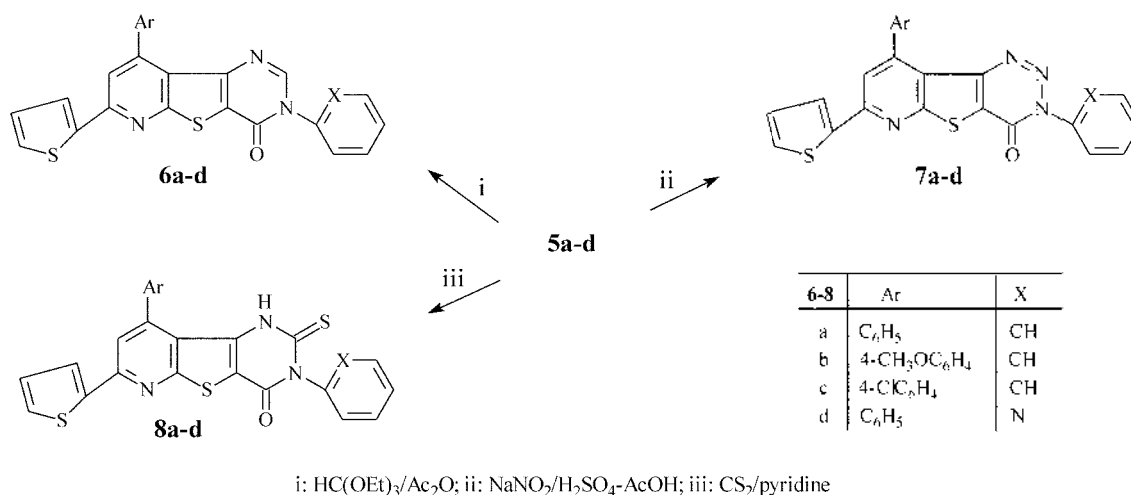
The cyclocondensation of **5a-d** with triethyl orthoformate in the presence of acetic anhydride afforded pyrido[3,2':4,5]thieno[3,2-d]pyrimidine-4(3*H*)-ones **6a-d**. The triazinone analogs **7a-d** were prepared by diazotisation of **5a-d** using sodium nitrite and acetic acid-sulfuric acid mixture. The interaction of **5a-d** with carbon disulfide in hot pyridine resulted in the formation of thioxopyrimidinone derivatives **8a-d** (Scheme 2).

The reaction of **8a** with methyl iodide in ethanolic sodium hydroxide solution gave 3,9-diphenyl-2-methylthio-7-(2'-

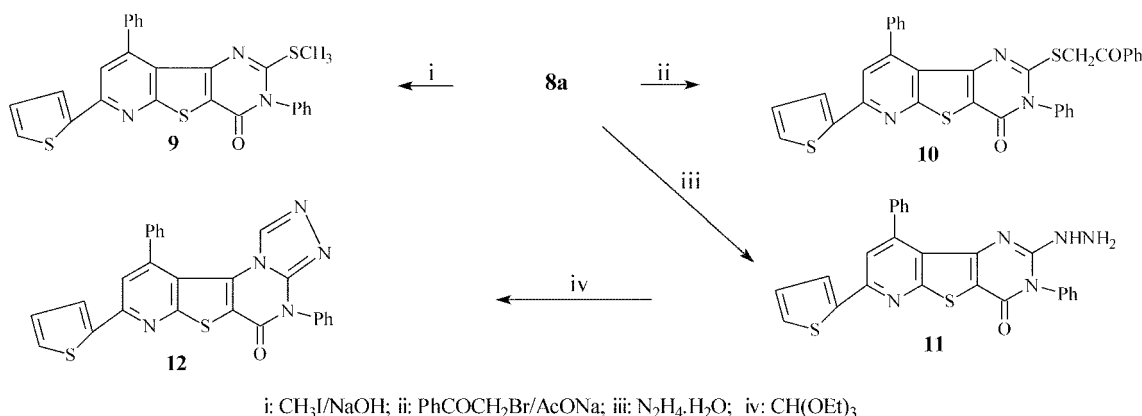
thienyl)-pyrido[3,2':4,5]thieno[3,2-d]pyrimidine-4(3*H*)-one (**9**). Compound **10** was synthesized through the reaction of **8a** with phenacyl bromide in the presence of sodium acetate. Heating **8a** with hydrazine hydrate in pyridine resulted in the formation of hydrazinopyrimidinone derivative **11** which underwent a cyclocondensation reaction upon heating with triethyl orthoformate under neat conditions to furnish 4,10-diphenyl-8-(2'-thienyl)-*s*-triazolo[4''3''-*a*]pyrido[3,2':4,5]-thieno[2,3-*e*]pyrimidine-5(4*H*)-one (**12**) (Scheme 3).

The structural formulas of all newly synthesized compounds were established and confirmed on the basis of their elemental analyses and spectral data (*cf.* Tables 1, 2 and experimental part).

Some of the synthesized compounds were evaluated *in-vitro* for their antimicrobial activities against three strains of bacteria and two fungal species (Table 3) using filter paper disc diffusion method.¹⁸ Tioconazole (Tyrosyde[®]) (**13**) which contains a thiophene moiety in its structure was used as a reference substance. The results indicated that most of the tested compounds exhibited moderate to strong activities against *Staphylococcus aureus*, *Bacillus cereus* and *Serratia rhodnii*. However, concerning the antifungal activity, all tested compounds showed no effects except for compounds **3a**, **3d**, **6a**, **7d**, **9** and **12** which showed considerable activity



Scheme 2



Scheme 3

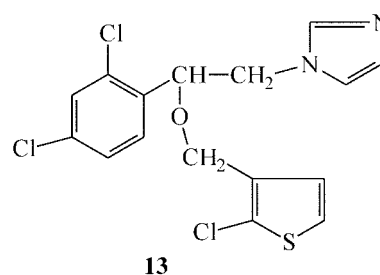
Table 1. Melting points, yields and analytical data of the synthesized compounds

Compd.	M.p., °C yield, %	Formula (M.W.)	Calculated / Found				
			% C	% H	% N	% S	% Cl
2a	170	C ₂₄ H ₁₆ N ₃ OS ₂	69.88	3.91	6.79	15.54	
	90	(412.54)	69.91	3.85	6.74	15.29	
2b	165	C ₂₃ H ₁₈ N ₃ O ₂ S ₂	67.85	4.09	6.33	19.49	
	91	(442.55)	67.67	4.14	6.51	14.19	
2c	160	C ₂₄ H ₁₅ ClN ₃ O ₂ S ₂	64.49	3.38	6.27	14.35	7.93
	90	(446.97)	64.62	3.51	6.34	14.49	7.82
3a	200	C ₂₄ H ₁₇ N ₃ OS ₂	67.42	4.01	9.83	14.10	
	94	(427.55)	67.55	4.08	9.69	14.01	
3b	210	C ₂₅ H ₁₉ N ₃ O ₂ S ₂	65.62	4.19	9.18	14.02	
	95	(457.57)	65.59	4.00	9.07	14.32	
3c	210	C ₂₄ H ₁₆ ClN ₃ O ₂ S ₂	62.40	3.49	9.09	13.88	7.68
	92	(462.00)	62.64	3.62	9.39	14.03	7.90
3d	190	C ₂₃ H ₁₆ N ₄ O ₂ S ₂	64.47	3.76	13.07	14.96	
	85	(428.54)	64.65	3.86	13.03	15.01	
4a	180	C ₂₄ H ₁₆ N ₂ O ₂ S ₂	69.88	3.91	6.79	15.54	
	85	(412.54)	69.50	3.75	6.92	15.74	
4b	192	C ₂₃ H ₁₈ N ₂ O ₂ S ₂	67.85	4.09	6.33	14.49	
	87	(442.55)	67.79	4.04	6.52	14.61	
4c	275	C ₂₄ H ₁₅ ClN ₃ O ₂ S ₂	64.49	3.38	6.27	14.35	7.93
	87	(446.97)	64.69	3.53	6.12	14.40	7.95
5a	235	C ₂₄ H ₁₇ N ₃ OS ₂	67.42	4.01	9.83	14.10	
	88	(427.55)	67.35	4.14	9.90	14.12	
5b	220	C ₂₃ H ₁₉ N ₃ O ₂ S ₂	65.62	4.19	9.18	14.02	
	85	(457.57)	65.86	4.34	9.31	14.00	
5c	240	C ₂₄ H ₁₆ ClN ₃ O ₂ S ₂	62.40	3.49	9.09	13.88	7.68
	84	(462.00)	62.56	3.65	9.03	13.65	7.70
5d	130	C ₂₃ H ₁₆ N ₄ O ₂ S ₂	64.47	3.76	13.07	14.96	
	80	(428.54)	64.12	3.50	13.00	14.85	
6a	330	C ₂₅ H ₁₅ N ₃ OS ₂	68.63	3.46	9.60	14.66	
	95	(437.55)	68.43	3.34	9.55	14.72	
6b	190	C ₂₆ H ₁₇ N ₃ O ₂ S ₂	66.79	3.66	8.99	13.72	
	90	(467.56)	66.88	3.34	8.90	13.79	
6c	270	C ₂₅ H ₁₄ ClN ₃ O ₂ S ₂	63.62	2.99	8.90	13.59	7.51
	92	(471.98)	63.42	3.01	8.99	13.79	7.70
6d	325	C ₂₄ H ₁₄ N ₄ O ₂ S ₂	65.73	3.22	12.78	14.62	
	90	(438.53)	65.63	3.14	12.50	14.40	
7a	300	C ₂₄ H ₁₄ N ₄ O ₂ S ₂	65.73	3.22	12.78	14.62	
	92	(438.53)	65.59	3.13	12.70	14.68	
7b	285	C ₂₅ H ₁₆ N ₄ O ₂ S ₂	64.08	3.44	11.96	13.69	
	90	(468.55)	64.32	3.30	12.02	13.90	
7c	270	C ₂₄ H ₁₅ ClN ₄ O ₂ S ₂	60.95	2.77	11.85	13.56	7.50
	90	(472.97)	61.02	2.90	11.91	13.15	7.74
7d	280	C ₂₃ H ₁₃ N ₃ OS ₂	62.85	2.98	15.93	14.59	
	90	(439.52)	62.90	2.85	15.75	14.33	
8a	>360	C ₂₃ H ₁₅ N ₃ OS ₃	63.94	3.22	8.95	20.48	
	71	(469.61)	63.75	3.18	8.83	20.61	
8b	280	C ₂₆ H ₁₇ N ₃ O ₂ S ₃	62.50	3.43	8.41	19.25	
	70	(499.63)	62.75	3.29	8.34	19.11	
8c	345	C ₂₅ H ₁₄ ClN ₃ O ₃ S ₃	59.57	2.80	8.34	19.09	7.03
	66	(504.04)	59.41	2.87	8.18	19.02	6.80
8d	315	C ₂₄ H ₁₄ N ₄ O ₃ S ₃	61.25	2.99	11.91	20.44	
	71	(470.60)	61.12	3.16	11.78	20.63	
9	335	C ₂₆ H ₁₇ N ₃ OS ₃	64.57	3.54	8.69	19.89	
	97	(483.64)	64.65	3.36	8.49	19.71	

Table 1. Continued

Compd.	M.p., °C yield, %	Formula (M.W.)	Calculated / Found				
			% C	% H	% N	% S	% Cl
9	335	C ₂₆ H ₁₇ N ₃ OS ₃	64.57	3.54	8.69	19.89	
	97	(483.64)	64.65	3.36	8.49	19.71	
10	265	C ₃₃ H ₂₁ N ₃ O ₂ S ₂	67.44	3.60	7.15	16.37	
	80	(587.75)	67.65	3.43	7.00	16.02	
11	327	C ₂₅ H ₁₈ N ₄ OS ₂	64.08	3.87	14.95	13.69	
	47	(468.58)	64.13	3.68	14.86	13.53	
12	285	C ₂₆ H ₁₅ N ₅ OS ₂	65.39	3.17	14.66	13.43	
	55	(477.57)	65.12	3.01	14.42	13.35	

against *penicillium oxalicum* and/or *Aspergillus fumigatus*.

**13**

Experimental Section

All melting points are uncorrected and measured on a Gallan-Kamp apparatus. IR spectra: Shimadzu 470 IR-spectrophotometer (KBr; ν_{\max} in cm^{-1}). ¹H NMR spectra: Varian EM-390, 90 MHz ¹H NMR spectrometer using TMS as internal standard (δ in ppm); MS: Jeol JMS-600; elemental analyses: Elementar Analysensystem GmbH VARIOEL V2.3 July 1998 CHNS Mode: their results were in good agreement with the calculated values. Melting points, yields and analytical data of all newly synthesized compounds are listed in Table 1.

4-Aryl-3-cyano-6-(2'-thienyl)-pyridine-2(1H)-thiones (1a-c). These compounds were prepared in analogy to the method described before.¹⁷

Reaction of 1a-c with phenacyl bromide, chloro-N-phenylacetamide or 2-chloroacetylaminopyridine: Formation of S-substituted thiopyridines 2a-c and 3a-c or 3d. To a suspension of compound 1a-c (20 nmol) and sodium acetate trihydrate (3.0 g, 22 mmol) in ethanol (50 mL), the respective halocompound (20 nmol) was added. The resulting mixture was refluxed for 2 hrs. The precipitate that formed on cooling was collected and recrystallized from ethanol as pale yellow needles of 2a-c, 3a-c or 3d respectively. (Tables 1, 2)

2-Functionalized 3-amino-4-aryl-6-(2'-thienyl)-thieno[2,3-b]pyridines 4a-c and 5a-d

Method A: Compounds 2a-c or 3a-d (10 mmol) were suspended in sodium ethoxide solution (0.12 g sodium in 30 mL abs. ethanol) and heated under reflux for 5 mins. The solid that formed while hot was collected and recrystallized from ethanol-chloroform mixture to give canary yellow

Table 2. IR, ¹H NMR and MS spectral data of compounds **2a-8d**

Compd. No.	Spectral data
2a	IR: $\nu = 2200$ (C≡N), 1670 (C=O) cm^{-1} . ¹ H NMR (DMSO- <i>d</i> ₆): $\delta = 7.1$ - 8.2 (m, 14H: 10ArH's, 3CH thienyl and CH pyridine), 5.0 (s, 2H, SCH ₂) ppm.
2b	IR: $\nu = 2200$ (C≡N), 1670 (C=O) cm^{-1} .
2c	IR: $\nu = 2200$ (C≡N), 1670 (C=O) cm^{-1} . ¹ H NMR (T.F.A): $\delta = 7.5$ - 8.5 (m, 13H: 9ArH's, 3CH thienyl and CH pyridine), 5.1 (s, 2H, SCH ₂) ppm.
3a	IR: $\nu = 3300$ (NH), 2200 (C≡N), 1660 (C=O) cm^{-1} . ¹ H NMR (DMSO- <i>d</i> ₆): $\delta = 10.7$ (s, 1H, NH), 8.2 (d, 1H, CH thienyl), 7.0 - 7.8 (m, 12H: 9ArH's, 2CH thienyl and CH pyridine), 4.3 (s, 2H, SCH ₂) ppm.
3b	IR: $\nu = 3300$ (NH), 2200 (C≡N), 1660 (C=O) cm^{-1} .
3c	IR: $\nu = 3300$ (NH), 2200 (C≡N), 1660 (C=O) cm^{-1} .
3d	IR: $\nu = 3300$ (NH), 2200 (C≡N), 1660 (C=O) cm^{-1} . ¹ H NMR (DMSO- <i>d</i> ₆): $\delta = 11.2$ (s, 1H, NH), 8.5 (m, 1H, CH thienyl), 8.2 (m, 1H, CH thienyl), 7.6 - 8.0 (m, 10H, aryl and pyridyl protons), 7.2 (m, 1H, CH thienyl), 4.4 (s, 2H, SCH ₂) ppm.
4a	IR: $\nu = 3490$, 3300 (NH ₂), 1620 (C=O) cm^{-1} .
4b	IR: $\nu = 3490$, 3300 (NH ₂), 1620 (C=O) cm^{-1} . ¹ H NMR (DMSO- <i>d</i> ₆): $\delta = 8.4$ (m, 1H, CH thienyl), 8.1 (d, 1H, CH thienyl), 7.6 - 7.9 (m, 10H: 9ArH's and CH pyridine), 7.1 - 7.3 (m, 1H, CH thienyl), 7.0 (s, 2H, NH ₂), 3.4 (s, 3H, OCH ₃) ppm.
4c	IR: $\nu = 3490$, 3300 (NH ₂), 1620 (C=O) cm^{-1} . ¹ H NMR (DMSO- <i>d</i> ₆): $\delta = 7.5$ - 8.5 (m, 13H: 9ArH's, 3CH thienyl and CH pyridine), 7.1 (s, 2H, NH ₂) ppm.
5a	IR: $\nu = 3490$ - 3350 (NH ₂), 3150 (NH), 1620 (C=O) cm^{-1} . ¹ H NMR (DMSO- <i>d</i> ₆): $\delta = 9.7$ (s, 1H, NH), 8.1 (d, 1H, CH thienyl), 7.2 - 7.9 (m, 13H, 10ArH's, 2CH thienyl, CH pyridine), 6.0 (br, 2H, NH ₂) ppm.
5b	IR: $\nu = 3490$, 3350 (NH ₂), 3150 (NH), 1620 (C=O) cm^{-1} .
5c	IR: $\nu = 3490$, 3350 (NH ₂), 3150 (NH), 1620 (C=O) cm^{-1} .
5d	IR: $\nu = 3490$, 3350 (NH ₂), 3150 (NH), 1620 (C=O) cm^{-1} . ¹ H NMR (DMSO- <i>d</i> ₆): $\delta = 10.2$ (s, 1H, NH), 8.5 (m, 1H, CH thienyl), 8.2 (m, 1H, CH thienyl), 7.6 - 8.0 (m, 10H, aryl and pyridyl protons), 7.2 (m, 1H, CH thienyl), 6.2 (s, 2H, NH ₂) ppm. MS: 428 (M ⁺ , 100%), 412 (M ⁺ -NH ₂ , 6%), 335 (M ⁺ -NH pyridyl, 57%), 308 (M ⁺ -CONH pyridyl, 61%).
6a	IR: $\nu = 1680$ (C=O) cm^{-1} . ¹ H NMR (CDCl ₃): $\delta = 8.6$ (s, 1H, CH pyrimidine), 8.2 (d, 1H, CH thienyl), 8.0 (s, 1H, CH pyridine), 7.9 (m, 1H, CH thienyl), 7.5 - 7.8 (m, 9H, ArH's), 7.4 (m, 1H, CH thienyl) ppm.
6b	IR: $\nu = 1680$ (C=O) cm^{-1} . ¹ H NMR (T.F.A): $\delta = 9.0$ (s, 1H, CH pyrimidine), 8.1 - 8.3 (m, 3H, 2CH thienyl and CH pyridine), 7.3 - 8.0 (m, 9H, 8ArH's and CH thienyl), 4.2 (s, 3H, OCH ₃) ppm
6c	IR: $\nu = 1680$ (C=O) cm^{-1} .
6d	IR: $\nu = 1680$ (C=O) cm^{-1} .
7a	IR: $\nu = 1670$ (C=O) cm^{-1} . ¹ H NMR (T.F.A): $\delta = 8.2$ (d, 1H, CH thienyl), 8.0 (s, 1H, CH pyridine), 7.9 (m, 1H, CH thienyl), 7.5 - 7.8 (m, 9H, ArH's), 7.4 (m, 1H, CH thienyl) ppm.
7b	IR: $\nu = 1670$ (C=O) cm^{-1} . ¹ H NMR (T.F.A): $\delta = 7.2$ - 8.3 (m, 12H: 8ArH's, 3CH thienyl and CH pyridine), 4.0 (s, 3H, OCH ₃) ppm.
7c	IR: $\nu = 1670$ (C=O) cm^{-1} .
7d	IR: $\nu = 1670$ (C=O) cm^{-1} .
8a	IR: $\nu = 3350$ (NH), 1680 (C=O) cm^{-1} . ¹ H NMR (CDCl ₃): $\delta = 8.3$ (d, 1H, CH thienyl), 8.0 (s, 1H, CH pyridine), 7.9 (m, 1H, CH thienyl), 7.5 - 7.8 (m, 9H, ArH's), 7.4 (m, 1H, CH thienyl) ppm.
8b	IR: $\nu = 3300$ (NH), 1680 (C=O) cm^{-1} . ¹ H NMR (T.F.A): $\delta = 7.2$ - 8.3 (m, 12H: 8ArH's, 3CH thienyl and CH pyridine), 4.0 (s, 3H, OCH ₃) ppm.
8c	IR: $\nu = 3300$ (NH), 1680 (C=O) cm^{-1} .
8d	IR: $\nu = 3350$ (NH), 1690 (C=O) cm^{-1} .

crystals of **4a-c** and **7a-d** respectively (Tables 1, 2).

Method B: To a suspension of compound **1a-c** (10 mmol) in sodium ethoxide solution (0.35 g sodium in 40 mL abs. ethanol), the respective halocompound (10 mmol) was added. The resulting mixture was refluxed for 20 mins. The formed yellow precipitate was collected and recrystallized from ethanol-chloroform mixture to give compounds **4a-c** and **5a-d** in 76-82% yield. These products were identical in all aspects to those described in method A.

Pyrido[3',2':4,5]thieno[3,2-d]pyrimidine-4(3H)-one derivatives 6a-d. A mixture of **5a-d** (5 mmol) and triethyl orthoformate (2 mL) in acetic anhydride (20 mL) was refluxed for 4 hrs. The solid thus formed while hot was

collected and recrystallized from ethanol-chloroform mixture to give white crystals of **6a-d** (Tables 1, 2).

Pyrido[3',2':4,5]thieno[3,2-d][1,2,3]triazine-4(3H)-one derivatives 7a-d. Sodium nitrite solution 10% (5 mL) was added to a solution of compound **5a-d** (2 mmol) in concentrated sulphuric acid (5 mL) and glacial acetic acid (5 mL) at 0 °C during 5 mins. with stirring. The mixture was allowed to stand at room temperature for 30 mins. The solid that precipitated on dilution with water was collected and recrystallized from ethanol as white needles of **7a-d** (Tables 1, 2).

4-Oxo-1,2,3,4-tetrahydro-2-thioxopyrido[3',2':4,5]thieno[3,2-d]pyrimidine-4(3H)-one derivatives 8a-d. A mixture

Table 3. The antimicrobial activities of some representative compounds

Compd. No.	<i>Staphylococcus aureus</i>	<i>Bacillus cerus</i>	<i>Serratia rhodenii</i>	<i>Penicillium oxalicum</i>	<i>Aspergillus fumigatus</i>
2c	+	-	-	-	-
3a	-	++	+	-	+
3d	+	-	++	+	+
4c	++	++	-	-	-
5a	+	+	+	-	-
5d	-	+	+	-	-
6a	+	-	-	+	+
6c	++	+	+	-	-
7b	-	++	++	-	-
7d	+	-	-	++	-
8a	++	+	-	-	-
8b	+	++	++	-	-
9	++	+	++	+	+
10	++	+	-	-	-
12	+	++	+	++	+
Tyrosyde [®]	+	+	+	++	+++

-: No activity; +: moderate activity (inhibition zone: 5-10 mm); ++: strong activity (inhibition zone: 11-15 mm); +++: very strong activity (inhibition zone: 16-20 mm).

of **5a-d** (3 mmol) and carbon disulphide (3 mL) in dry pyridine (25 mL) was refluxed on a water bath for 48 hrs. During reaction time hydrogen sulphide evolved. The solvent was removed by distillation under reduced pressure and the residue was crystallized from acetic acid as yellow crystals of **8a-d** (Tables 1, 2).

2-Methylthio-3,9-diphenyl-7-(2'-thienyl)-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine-4(3H)-one (9). Compound **8a** (0.93 g, 2 mmol) was dissolved in 4% (10 mL, 10 mmol) ethanolic sodium hydroxide solution. To this solution methyl iodide (0.2 mL, 3 mmol) was added. The reaction mixture was refluxed for 2 hrs. The precipitate was filtered off and recrystallized from ethanol as white needles of **9** IR: $\nu = 1670$ (C=O) cm^{-1} . $^1\text{H NMR}$ (TFA): $\delta = 8.0-8.3$ (m, 3H, 2CH thienyl and CH pyridine), 7.3-7.8 (m, 11H: 10 ArH's and CH thienyl), 2.0 (s, 3H, SCH_3) ppm.

3,9-Diphenyl-2-phenacylthio-7-(2'-thienyl)-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine-4(3H)-one (10). To a suspension of compound **8a** (0.94 g, 2 mmol) and sodium acetate trihydrate (0.54 g, 4 mmol) in ethanol (20 mL), phenacyl bromide (0.4 g, 2 mmol) was added. The resulting mixture was refluxed for 2 hrs. The precipitate that formed while hot was collected and recrystallized from ethanol-chloroform mixture as yellow needles of **10**. IR: $\nu = 1660$ (C=O) cm^{-1} . $^1\text{H NMR}$ (TFA): $\delta = 8.3-7.3$ (m, 19H, 15ArH's, 3CH thienyl and CH pyridine), 4.3 (s, 2H, SCH_2) ppm.

3,9-Diphenyl-2-hydrazino-7-(2'-thienyl)-pyrido[3',2':4,5]thieno[3,2-d]pyrimidine-4(3H)-one (11). A mixture of **8a** (1.9 g, 4 mmol) and hydrazine hydrate 99% (4.0 mL, 80 mmol) in pyridine (20 mL) was heated under reflux for 7 hrs. The product which precipitated while hot was collected and recrystallized from dioxane as pale yellow crystals of **11**. IR: $\nu = 3300, 3200$ (NHNH₂), 1670 (C=O) cm^{-1} . MS: 467.97 (M^+ , 10%), 376 (M^- -PhN, 100%), 332.89 (M^+ -PhN-

CS, 38%), 304 (M^+ -PhN-CS-CO, 45%), 77 (C_6H_5^+ , 90%).

4,10-Diphenyl-8-(2'-thienyl)-s-triazolo[4'',3''-a]pyrido[3',2':4,5]thieno[3,2-e]pyrimidine-5 (4H)-one (12). A mixture of hydrazino compound **11** (0.4 g, 1 mmol) and triethyl orthoformate (7 mL) was heated under reflux for 4 hrs. The precipitate that formed while hot was filtered off and recrystallized from DMF to give pale yellow crystals of **12**. IR: $\nu = 1670$ (C=O) cm^{-1} . $^1\text{H NMR}$ (TFA): $\delta = 9.3$ (s, 1H, CH triazole), 7.4-8.5 (m, 14H: 10 ArH's, 3CH thienyl and CH pyridine). MS: 477 (M^+ , 5%).

Biological screening. The filter paper disc method was performed in Nutrient agar for bacteria and Dox agar for fungi. These agar media were inoculated with 0.5 mL of the 24 h. liquid cultures. Filter paper discs (5 mm diameter) saturated with each compound solution (10 mg/mL of DMSO) were placed on the indicated agar media. The incubation time was 48 h (at 37 °C for bacteria and at 28 °C for fungi). Discs saturated with DMSO were used as control. The diameter of inhibition zones (mm) were measured and recorded.

References

- Eichenberger, K.; Schweizer, E.; Schmidt, P. *U.S. Patent 2,627,766* 1971; *Chem. Abstr.* 1971, 74, 88638w.
- Burger, A. *Medicinal Chemistry*, 3rd Ed.; Wiley-Intersciences: New York (N.Y.), 1970; Vol 72, p 544, p 719.
- Shraideh, Z.; Sallal, A.-K. *Biomed. Lett.* 1997, 54, 233.
- Gilis, P. M.; Haemers, A.; Bollaert, W. *Eur. J. Med. Chem.* 1980, 15, 185.
- Bompert, J.; Giral, L.; Malicome, G.; Puygrenier, M. *Eur. J. Med. Chem.* 1987, 22, 139.
- Adachi, I.; Hiramatsu, Y. *Jap. Pat.*, 03,52,890; *Chem. Abstr.* 1991, 115, 71573.
- Furuya, S.; Takeyru, N.; Matsumoto, H. *Jap. Pat.*, 09,169,766; *Chem. Abstr.* 1997, 127, 176416.

8. Furuya, S.; Choh, N.; Suzuki, N.; Imada, T. *PCT Int. Appl. WO*, 000,00,493; *Chem. Abstr.* **2000**, 132, 64179.
 9. Dave, C. G.; Shah, P. R.; Dave, K. C.; Patel, V. J. *J. Indian Chem. Soc.* **1989**, 66, 48.
 10. Bousquent, E.; Romero, G.; Guerrero, F.; Caruso, A.; Roxas, M. A. *Farmaco Ed. Sci.* **1985**, 40, 869.
 11. Leistner, S.; Wagener, G.; Guesterscharo, M.; Glusa, E. *Pharmazie* **1986**, 41, 54.
 12. Wagner, G.; Leistner, S.; Vieweg, H.; Krasselt, U.; Prantz, J. *Pharmazie* **1993**, 48, 514.
 13. Youssefyeh, R. D.; Brown, R. E.; Wilson, J.; Shah, U.; Jones, H.; Loev, B.; Khandwala, A.; Leibowitz, M. J.; Sonnino-Goldman, P. *J. Med. Chem.* **1984**, 27, 1639.
 14. Bakhite, E. A.; Abdel-Rahman, A. E.; Mohamed, O. S.; Thabet, E. A. *Pharmazie* **2000**, 55, 577.
 15. Abdel-Rahman, A. E.; Bakhite, E. A.; Mohamed, O. S.; Thabet, E. A. *Phosphorus, Sulfur and Silicon* **2000**, 166, 149.
 16. Abdel-Rahman, A. E.; Bakhite, E. A.; Al-Taifi, E. A. *J. Chin. Chem. Soc.* **2002**, 49, 223.
 17. Abdel-Rahman, A. E.; Bakhite, E. A.; Mohamed, O. S.; Thabet, E. A. *Phosphorus, Sulfur and Silicon* **2002** (acceptance).
 18. Kalyoncuoglu, N.; Rollas, S.; Sur-Altiner, D.; Yegenoglu, Y.; Ang, O. *Pharmazie* **1992**, 47, 769.
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