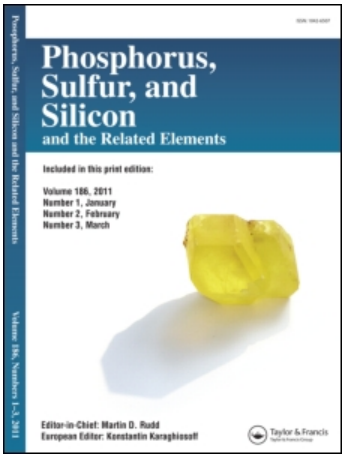

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW PYRIDO[3',2':4,5]THIENO[3,2-d]- PYRIMIDINE DERIVATIVES

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NEW PYRIDO[3′,2′:4,5]THIENO[3,2-d]-PYRIMIDINE DERIVATIVES

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*5-Acetyl-3-amino-4-aryl-6-methylthieno[2,3-b]pyridine-2-carboxamides (**1a**,**b**) were reacted with aromatic aldehydes or with some cycloalkanones to give the corresponding tetrahydropyridothienopyrimidinone derivatives **2a–f** and **4a–d**. The reaction of compound **1b** with urea and/or carbon disulfide has been carried out and their products were identified. Some representative compounds were screened in vitro for their antimicrobial activities.*

Keywords: Antimicrobial activity; pyridothienopyrimidines; spiro compounds; thieno[2,3-b]pyridines

In view of the wide spectrum of biological activity associated with many condensed pyrimidines.[1,2] thienopyridines,[3–7] and pyridothienopyrimidines,[8,9] and as a continuation of our work on pyridothienopyrimidines with anticipated biological activities,[10–12] we undertook the synthesis of the title compounds and their evaluation regarding antimicrobial properties.

RESULTS AND DISCUSSION

5-Acetyl-3-amino-4-aryl-6-methylthieno[2,3-b]pyridine-2-carboxamides (**1a**,**b**) were prepared following our previous method[12] and used as a starting materials in this investigation. Thus, when compounds **1a**,**b** were heated with aromatic aldehydes in acetic acid or in ethanol containing few drops of conc. HCl, a cyclocondensation reaction

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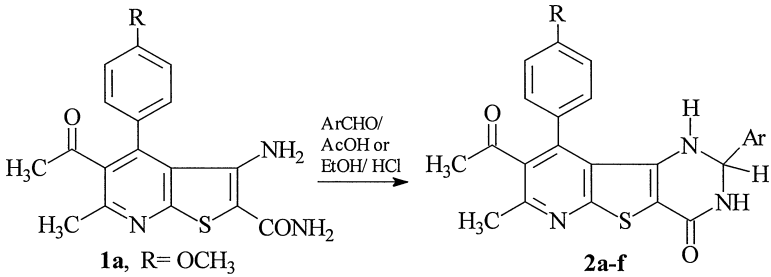
occurred and tetrahydropyridothienopyrimidines **2a–f** were obtained (Scheme 1).



1a, R= OCH_3
b, R= Cl

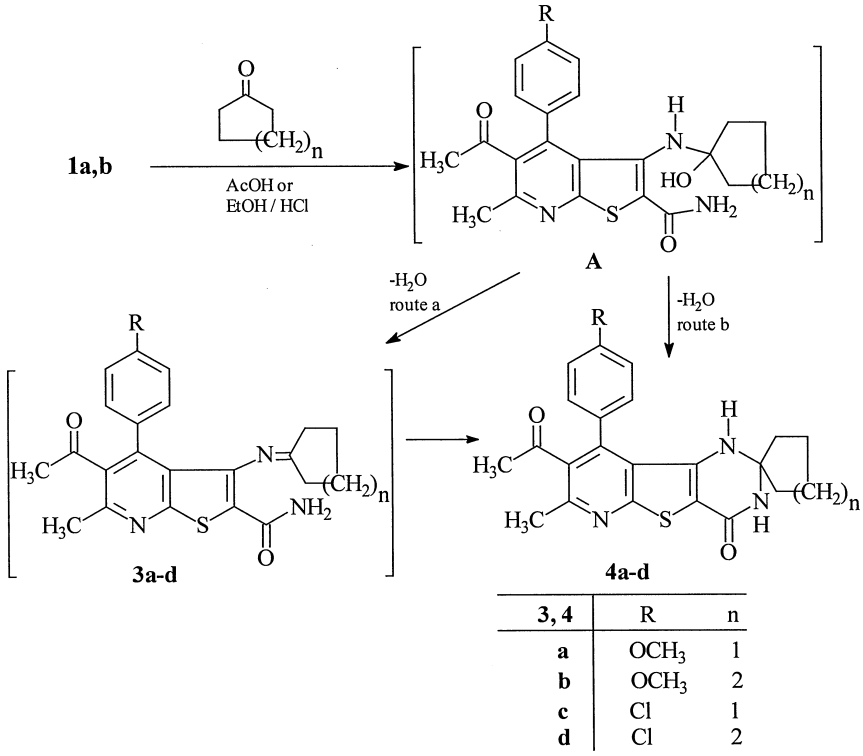
2a-f

2	R	Ar
a	OCH_3	C_6H_5
b	OCH_3	4-$CH_3OC_6H_4$
c	OCH_3	4-ClC_6H_4
d	Cl	C_6H_5
e	Cl	4-$CH_3OC_6H_4$
f	Cl	4-ClC_6H_4

SCHEME 1

The *o*-aminoamides **1a**,**b** also were reacted with cyclopentanone or cyclohexanone upon refluxing in glacial acetic acid or ethanol containing few drops of HCl. In view of the earlier reports,[13] the products of this reaction were identified as spiro compounds **4a–d** rather than Schiff's bases **3a–d**. The proposed pathway of this reaction is depicted in Scheme 2. Thus, this reaction involves the formation of addition product A which underwent spontaneous dehydration to give the expected products **3a–d** or **4a–d** via two probable routes (a and b). If compounds **3a–d** formed they may be underwent cycloaddition reaction to give **4a–d**.The reaction of compound **1b** with urea by refluxing in decalin led to the formation of pyridothieno-pyrimidindione **5**. The thioxo analogue **6** was prepared by heating **1b** with carbon disulfide in pyridine. Compound **6** was reacted with an equimolar quantity of 4-bromophenacyl bromide to give the *S*-alkylated product **7** which upon. with conc.H_2SO_4 furnished thiazolopyridothienopyrimidine **8**[14] (Scheme 3). The structures of all newly synthesized compounds were confirmed by elemental analyses (Table I) as well as spectroscopic data (Table II).

Finally, eight compounds were screened in vitro for their antimicrobial activity against three strains of bacteria (*Serratia rhodenii*, *Echerichia coli*, and *Micrococcus roseus*) and two fungal species (*Aspergillus fumigatus* and *Fusarium oxysporum*) using filter paper



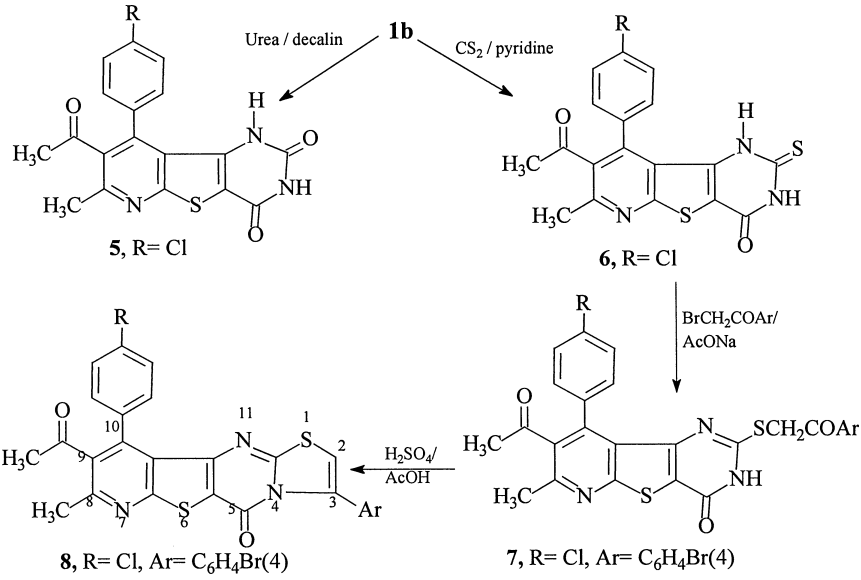
3, 4	R	n
a	OCH_3	1
b	OCH_3	2
c	Cl	1
d	Cl	2

SCHEME 2

disc method.[15] The results revealed that: (1) all tested compounds showed high activity against *Serratia rhodenii* and no activity against *Echerichia coli*; (2) most of the tested compounds exihibited considerable activity against *Micrococcus roseus*; (3) only compound **4b** inhibited the growth of *Aspergillus fumigatus*; and (4) Compounds **4b**, **4c**, **4d** showed moderate activity against *Fusarium oxysporum* (Table III).

EXPERIMENTAL

All melting points are uncorrected and measured on a Gallan-Kamp apparatus. IR spectra were recorded on a Shmiadzu 470 IR-spectrophotometer (KBr; υ_{max} in cm^{-1}). ^{1}H-NMR spectra on a Varian EM-390, 90 MHz spectrometer with TMS as internal standard or on a Jeol LA 400 MHz FT-NMR spectrometer (δ in ppm); MS on a



SCHEME 3

Jeol JMS-600 mass spectrometer. Elemental analyses on an Elementar Analyses system GmbH VARIOEL $V_{2.3}$ July 1998 CHNS Mode.

8-Acetyl-2,9-diaryl-7-methyl-4-oxo-1,2,3,4-tetrahydropyrido[3′,2′:4,5]thieno[3,2-d]pyrimidines (2a–f)

A mixture of **1a**,**b** (0.002 mmol) and the respective aldehyde (0.002 mmol) in glacial acetic acid (15 mL) or in ethanol (20 mL) containing few drops of HCl was heated under reflux for 3 h. The product was collected and recrystallized from acetic acid to give **2a–f** in the form of yellow needles.

Reaction of 1a,b with Cycloalkanones; Formation of Spiro Compounds 4a–d

A mixture of **1a**,**b** (0.002 mmol) and cyclopentanone or cyclohexanone (0.002 mmol) in glacial acetic acid (15 mL) or in ethanol (20 mL) containing a few drops of HCl was heated under reflux for 3 h. The precipitate that formed on cooling was collected and recrystallized from ethanol to give yellow crystals of **4a–d**.

TABLE I Melting Points, Yields, and Analytical Data of All Newly Synthesized Compounds

Comp. no.	m.p. (°C) (yield%)	Mol. formula (M.wt)	Analysis; calculated/found (%)				
			C	H	N	S	Cl
2a	>360	$C_{25}H_{21}N_3O_3S$	67.70	4.77	9.47	7.23	—
	(89)	(443.52)	67.89	4.58	9.41	7.00	—
2b	>360	$C_{26}H_{23}N_3O_4S$	65.95	4.90	8.87	6.77	—
	(82)	(473.55)	65.87	5.14	8.92	6.53	—
2c	225–226	$C_{25}H_{20}ClN_3O_3S$	62.82	4.22	8.79	6.71	7.42
	(80)	(477.97)	62.71	4.32	8.77	7.00	7.71
2d	322–323	$C_{24}H_{18}ClN_3O_2S$	64.35	4.05	9.38	7.16	7.91
	(85)	(447.94)	64.44	4.11	9.39	7.35	7.72
2e	>360	$C_{25}H_{20}ClN_3O_3S$	62.82	4.22	8.79	6.71	7.42
	(87)	(477.97)	63.18	4.18	8.36	6.91	7.25
2f	317	$C_{24}H_{17}Cl_2N_3O_2S$	59.76	3.55	8.71	6.65	14.70
	(83)	(482.38)	59.91	3.47	8.58	6.42	14.51
4a	268–270	$C_{23}H_{23}N_3O_3S$	65.54	5.50	9.97	7.61	—
	(90)	(421.51)	65.73	5.48	9.82	7.44	—
4b	323–224	$C_{24}H_{25}N_3O_3S$	66.19	5.79	9.65	7.36	—
	(94)	(435.54)	66.37	5.74	9.87	7.52	—
4c	278–279	$C_{22}H_{20}ClN_3O_2S$	62.04	4.73	9.87	7.53	8.32
	(92)	(425.93)	62.38	4.79	9.77	7.60	8.21
4d	338–339	$C_{23}H_{22}ClN_3O_2S$	62.79	5.04	9.55	7.29	8.06
	(91)	(439.96)	63.03	5.13	9.44	7.36	8.28
5	>360	$C_{18}H_{12}ClN_3O_3S$	56.04	3.13	10.89	8.31	9.19
	(73)	(385.82)	56.21	3.17	10.70	8.00	9.43
6	>360	$C_{18}H_{12}ClN_3O_2S_2$	53.80	3.01	10.46	15.95	8.82
	(78)	(401.89)	53.70	3.07	10.31	16.19	8.72
7	298–299	$C_{26}H_{17}BrClN_3O_3S_2$	52.14	2.86	7.02	10.71	—
	(69)	598.92	52.28	2.91	7.30	10.50	—
8	285–286	$C_{26}H_{15}BrClN_3O_2S_2$	53.76	2.60	7.23	11.04	—
	(66)	580.90	53.41	2.73	7.15	11.32	—

8-Acetyl-9-(4-chlorophenyl)-7-methylpyrido[3′,2′:4,5]-thieno[3,2-d]pyrimidine-2,4(1H,3H)-dione (5)

A mixture of **1b** (1.43 g, 0.004 mmol) and urea (0.3 g, 0.005 mmol) in decalin (30 mL) was refluxed for 4 h. The white product was collected and crystallized from chloroform to give **5**.

8-Acetyl-9-(4-chlorophenyl)-7-methyl-4-oxo-1,2,3,4-tetrahydro-2-thioxopyrido[3′,2′:4,5]-thieno[3,2-d]pyrimidine (6)

A mixture of **1b** (1.79 g, 0.005 mmol) and carbon disulfide (6 mL) in dry pyridine (30 mL) was heated under reflux on a water bath for 48 h.

TABLE II Spectral Data of All Newly Synthesized Compounds

Comp. no.	Spectral data
2a	IR: 3400, 3200(2NH); 1690, 1640(2C═O). ^{1}H-NMR ($CDCl_3$): 7.73 (d, J = 4.0 Hz, 1H, CONH); 6.98–7.53 (m, 9H, ArH's); 5.89 (d, J = 4.0 Hz, 1H, NH); 5.79 (t, J = 4.0 Hz, 1H, CH at C-2); 3.91 (s, 3H, OCH_3); 2.74 (3H, $COCH_3$); 2.07 (s, 3H, CH_3 at C-7).
2b	IR: 3400, 3200(2NH); 1690, 1640(2C═O).
2c	IR: 3400, 3200(2NH); 1690, 1640(2C═O). ^{1}H-NMR (DMSO-d_6)): 8.43 (d, J = 4.0 Hz, 1H, CONH); 7.09–7.41 (m, 8H, ArH's); 5.74 (t, J = 4.0 Hz, 1H, CH at C-2); 5.18(d, J = 4.0 Hz, 1H, NH); 3.82(s, 3H, OCH_3); 2.49 (3H, $COCH_3$); 1.96 (s, 3H, CH_3 at C-7). MS: 479.7 ($M^+ + 2$, 11%); 478.7 ($M^+ + 1$, 38%); 477.6 (M^+, 41%); 476.6 ($M^+ - 1$, 37%); 475.6 ($M^+ - 2$, 100%); 364.9 ($M^+ - 2$-C_6H_4Cl, 91%).
2d	IR: 3400, 3200(2NH); 1690, 1640(2C═O).
2e	IR: 3400, 3200(2NH); 1690, 1640(2C═O). ^{1}H-NMR ($CDCl_3$)): 7.85 (d, J = 4.0 Hz, 1H, CONH); 6.87–7.44 (m, 8H, ArH's); 6.08 (d, J = 4.0 Hz, 1H, NH); 5.70 (t, J = 4.0 Hz, 1H, CH at C-2); 3.86 (s, 3H, OCH_3); 2.64 (3H, $COCH_3$); 2.05 (s, 3H, CH_3 at C-7).
2f	IR: 3400, 3200(2NH); 1690, 1640(2C═O).
4a	IR: 3400, 3200(2NH); 1690, 1640(2C═O).
4b	IR: 3400, 3200(2NH); 1690, 1640(2C═O). ^{1}H-NMR ($CDCl_3$)): 7.31–7.33 (d, J = 8.5 Hz, 2H, ArH's); 7.06–7.08 (d, J = 8.5 Hz, 2H, ArH's); 6.18 (s, 1H, CONH); 4.09 (s, 1H, NH); 3.88 (s, 3H, OCH_3); 2.62 (3H, $COCH_3$); 2.06 (s, 3H, CH_3 at C-7); 1.90–1.96 (m, 2H, CH_2 of cyclohexylidene ring; 1.13–1.49 (m, 6H, 3 CH_2 of cyclohexylidene ring); 0.81–0.83 (m, 2H, CH_2 of cyclohexylidene ring).
4c	IR: 3400, 3200(2NH); 1690, 1640(2C═O). ^{1}H-NMR ($CDCl_3$)): 7.52–7.54 (d, J = 8.3 Hz, 2H, ArH's); 7.32–7.34 (d, J = 8.3 Hz, 2H, ArH's); 6.17 (s, 1H, CONH); 3.64 (s, 1H, NH); 2.62 (3H, $COCH_3$); 2.10 (s, 3H, CH_3 at C-7) 1.29–1.77 (m, 8H, 4CH_2 of cyclopentylidene ring).
4d	IR: 3400, 3200(2NH); 1690, 1640(2C═O). ^{1}H-NMR ($CDCl_3$)): 7.56–7.58 (d, J = 8.0 Hz, 2H, ArH's); 7.41–7.43 (d, J = 8.0 Hz, 2H, ArH's); 6.42(s, 1H, CONH); 3.85 (s, 1H, NH); 2.66 (3H, $COCH_3$); 2.15 (s, 3H, CH_3 at C-7); 1.92–1.95 (m, 2H, CH_2 of cyclohexylidene ring; 1.17–1.54 (m, 6H, 3 CH_2 of cyclohexylidene ring); 0.78–0.80 (m, 2H, CH_2 of cyclohexylidene ring). MS: 441 ($M^+ + 2$, 1%); 440 ($M^+ + 1$, 5%); 439 (M^+, 18%); 438 ($M^+ - 1$, 13%); 437 ($M^+ - 2$, 42%); 396 (M^+-$COCH_3$, 41%); 394 ($M^+ - 2$-$COCH_3$, 100%).
5	IR: 3500–3200 (2NH); 1750-1650 (3C═O). MS: 387 ($M^+ + 2$, 9%); 386 ($M^+ + 1$, 3%); 385 (M^+, 26%); 370 (M^+ -CH_3, 38%); 369 ($M^+ - 1$-CH_3, 63%); 354.9 ($M^+ - 1$-$2CH_3$, 100%).
6	IR: 3400, 3100(2NH); 1690, 1650(2C═O).
7	IR: 3250 (NH); 1690, 1650 (2C═O).). ^{1}H-NMR (CD_3CO_2D): 7.1–7.6 (m, 8H, ArH's); 5.0 (s, 2H, SCH_2); 2.8 (s, 3H, CH_3); 2.2 (s, 3H, CH_3 at C-7).). MS: 598 (M^+, 28%); 594 ($M^+ - 4$, 100%); 592 (M^+-6, 70%); 570 (M^+ -CO, 30%).
8	IR: 1690 (2C═O). ^{1}H-NMR ($CDCl_3$)): 7.46–7.56 (dd, J = 8.0 Hz, 4H, ArH's); 7.28–7.36 (dd, J = 8.0 Hz, 4H, ArH's); 6.76 (s, 1H, CH-thiazole); 2.68 (3H, $COCH_3$); 2.03 (s, 3H, CH_3 at C-8).

TABLE III The Antimicrobial Activities of Some Representative Compounds

Compd. no.	**2f**	**4b**	**4c**	**4d**	**5**	**6**	**7**	**8**	Tioconazole tyrosyd
S. rhodenii	++	+++	+++	+++	++	+++	++	+++	++
E. coli	−	−	−	−	−	−	−	−	++
M. roseus	+	−	++	−	−	+++	+	++	+
A. fumigatus	−	++	−	−	−	−	−	−	+++
F. oxysporum	−	+	+	+	−	−	−	−	+++

−: No activity; +: moderate activity (inhibition zone 7–10 mm); ++: strong activity (inhibition zone 11–15 mm); +++: very strong activity (inhibition zone 16–20 mm).

During reaction time H_2S evolved. The solvent was removed by distillation under reduced pressure and the residue was crystallized from acetic acid as yellow crystals of **6**.

8-Acetyl-2-(4-bromophenacylthio)-9-(4-chlorophenyl)-7-methylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3H)-one (7)

To a mixture of **6** (0.8 g, 0.002 mmol), 4-bromophenacyl bromide (0.55 g, 0.002 mmol) and sodium acetate trihydrate (0.27 g, 0.002 mmol) in ethanol (30 mL) were then added. The mixture was refluxed for 3 h. The precipitate which formed on cooling was filtered off and recrystallized from ethanol to give pale yellow crystals of **7**.

9-Acetyl-3-(4-bromophenyl)-10-(4-chlorophenyl)-8-methylthiazolo[3′′,2′′-a]pyrido[3′,2′:4,5]thieno[3,2-d]-pyrimidine-5-one (8)

To a sample of **7** (0.59 g, 0.001 mmol) in acetic acid (10 mL), conc. sulfuric acid (3 mL) was added and the mixture was gently heated for 6 h. After cooling, the reaction mixture was poured onto ice-water (30 mL) and neutralized with $NaHCO_3$ solution. The precipitate was collected and crystallized from ethanol to give compound **8**.

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