Synthesis and Antimicrobial Activity of New Pyridothienopyrimidines and Pyridothienotriazines

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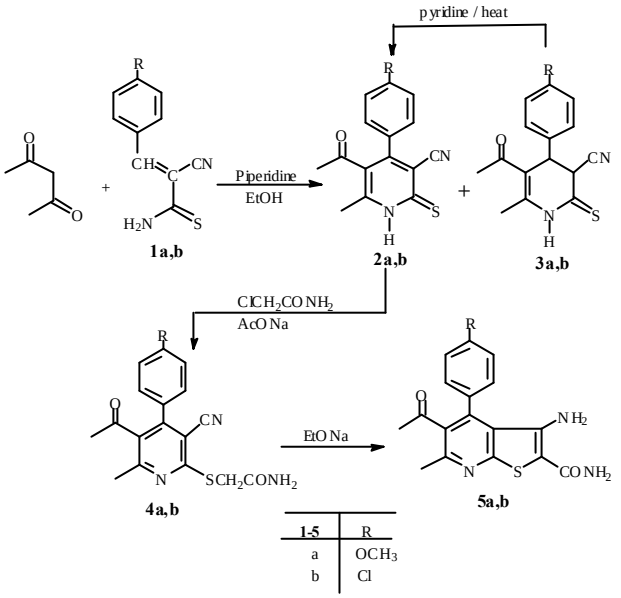
5-Acetyl-3-amino-4-aryl-6-methylthieno[2,3-b]pyridine-2-carboxamides (**5a,b**) were reacted with triethyl orthoformate or nitrous acid to give the corresponding pyrimidinones **6a,b** and triazinones **7a,b**. The reaction of **5a,b** with acetic anhydride was carried out and its products were identified as a mixture of 8-acetyl-9-aryl-2,7-dimethylpyrido[3′,2′:4,5]thieno[3,2-d]pyrimidine-4(3*H*)-one (**9a,b**) and related 5-acetyl-4-aryl-3-biacetylamino-6-methylthieno[2,3-b]pyridine-2-carbonitrile (**10a,b**). Reaction of **7a** with some halocompounds afforded the N-alkylated triazinones **8a-c**. Chlorination of **6a,b** and **9a,b** with phosphorus oxychloride produced 4-chloropyrimidines **11a-d** which were used as precursors for the rest of the target heterocycles. Some of the prepared compounds were tested *in vitro* for their antimicrobial activities.

INTRODUCTION

Thieno[2,3-b]pyridine ring systems have proved to be an interesting class of heterocycles. It has been reported that many of its derivatives possess good antibacterial,[1-3] antihypertensive[4] and gonadotropin-releasing hormone antagonizing[5,6] activity. Pyridothienopyrimidine derivatives have found applications as analgesics,[7] antipyretics[8] and anti-inflammatories.[9] Also, some pyridothienotriazines are known to exhibit antianaphylactic[10] and antiallergic[11] activity. In view of these benefits and as a continuation of our program directed towards the synthesis of new condensed thieno[2,3-b]pyridines,[12,13] we report herein the synthesis of the title compounds and their evaluation regarding antimicrobial activity.

Scheme I



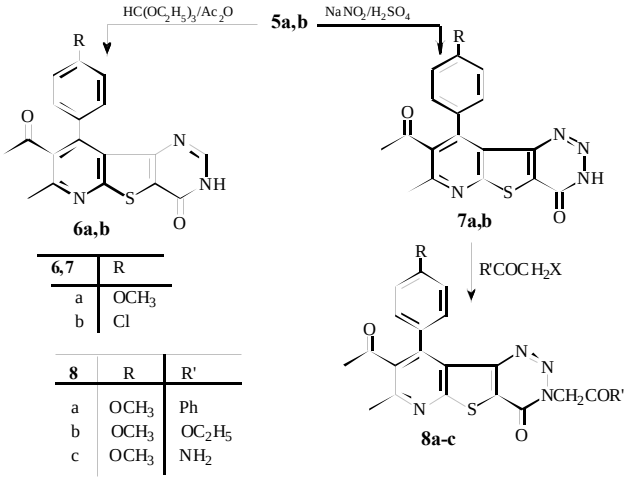
RESULTS AND DISCUSSION

Our approach to the synthesis of the target compounds started from the reaction of arylmethylene cyanothioacetamides (**1a,b**) with acetylacetone which gave a mixture of dihydrothioxopyridines **2a,b** and related tetrahydrothioxopyridines **3a,b**.[14] Dehydrogenation of **3a,b** to afford **2a,b** was achieved by heating in pyridine.[14] The reaction of **2a,b** with chloroacetamide by refluxing in ethanol containing sodium acetate gave the corresponding acetamide derivatives **4a,b**. The latter compounds (**4a,b**) were cyclized into the key intermediates, 5-acetyl-3-amino-4-aryl-6-methyl-thieno[2,3-b]-pyridine-2-carboxamides (**5a,b**) upon boiling with sodium ethoxide in ethanol (Scheme I).

The cyclocondensation of **5a,b** with triethyl orthoformate by refluxing in acetic anhydride led to the formation of pyrimidinones **6a,b** in excellent yields. The 1,2,3-triazinone analogs **7a,b** were obtained, in 85-87% yield, upon treatment of **5a,b** in concentrated sulfuric acid with sodium nitrite wherein diazotisation followed by self coupling took place. The reaction of **7a** with some halocompounds, namely phenacyl bromide, ethyl chloroacetate or chloroacetamide, afforded the corresponding N-alkylated triazinones **8a-c** in 84-92% yield (Scheme II).

When **5a,b** were heated with acetic anhydride at reflux temperature for 8 hours, the products were identified as a mixture 8-acetyl-9-aryl-2,7-dimethylpyrido[3′,2′:4,5]thieno-

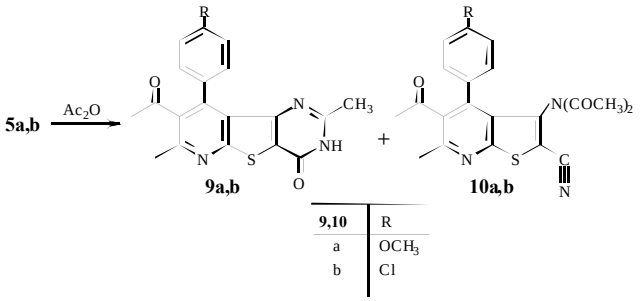
Scheme II



6,7	R
a	OCH_3
b	Cl

8	R	R'
a	OCH_3	Ph
b	OCH_3	OC_2H_5
c	OCH_3	NH_2

Scheme III



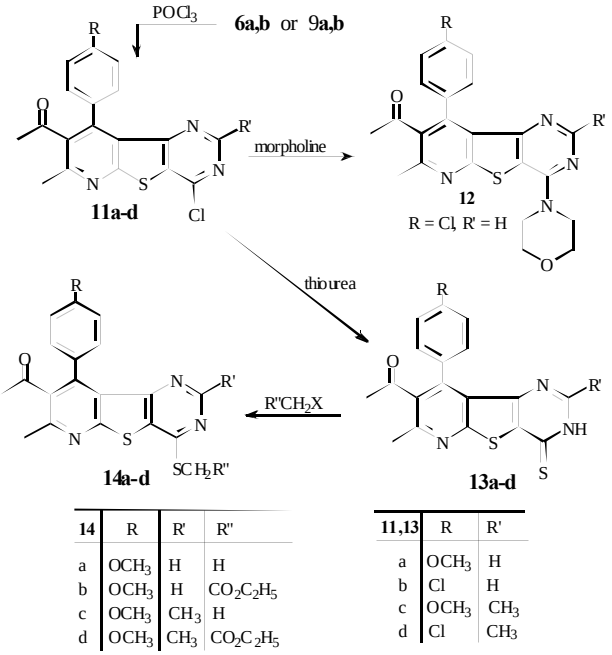
9,10	R
a	OCH_3
b	Cl

[3,2-d]pyrimidine-4(3*H*)-one (**9a,b**) and re lated 5-acetyl-4-aryl-3-biacetylamino-6-methylthieno[2,3-b]pyridine-2-carbonitrile (**10a,b**)[15] (Scheme III).

The chlo ri na tion of com pounds **6a,b** and **9a,b** with an ex cess amount of phos pho rus oxychloride re sulted in the for ma tion of the cor re spond ing 4-chloropyrimidine de riv a tives **11a-d** in high yields. Com pound **11b** un der went nucleophilic dis place ment when treated with morpholine to give mor-pholi no de riv a tive **12**. Com pounds **11a-d** were re acted smoothly with thiourea to fur nish the cor re spond ing pyrimidinthiones **13a-d**. When **13a,c** were al lowed to re act with methyl io dide or ethyl chloroacetate, the S-alkylated prod ucts **14a-d** were ob tained in 75-89% yield (Scheme IV).

On treat ment of **11a-d** with an ex cess amount of hydrazine hy drate, only nucleophilic dis place ment of la bile chlo rine at oms by the hydrazino group took place to give the cor re spond ing hydrazino com pounds **15a-d** in nearly quan ti-ta tive yield. It is im por tant to note that the acetyl group of com pounds **11a-d** or **15a-d** were not af fected by hydrazine

Scheme IV

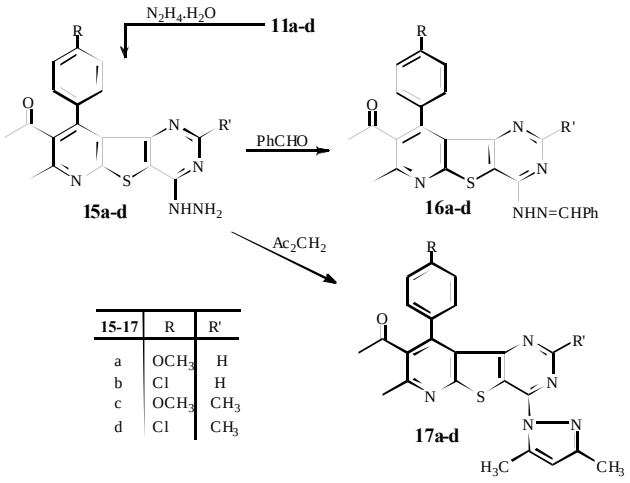


14	R	R'	R''
a	OCH_3	H	H
b	OCH_3	H	$CO_2C_2H_5$
c	OCH_3	CH_3	H
d	OCH_3	CH_3	$CO_2C_2H_5$

11,13	R	R'
a	OCH_3	H
b	Cl	H
c	OCH_3	CH_3
d	Cl	CH_3

hy drate in the lat ter re ac tion. This may be due to an elec tronic or a steric fac tor. Con den sa tion of **15a,b** with benzaldehyde gave the phenyl hy dra zones **16a,b**. The 3,5-dimethyl pyr-azolyl de riv a tives **17a-d** were pre pared, in 80-89% yield, by the re act ing of com pounds **15a-d** with acetylacetone un der neat con di tions (Scheme V).

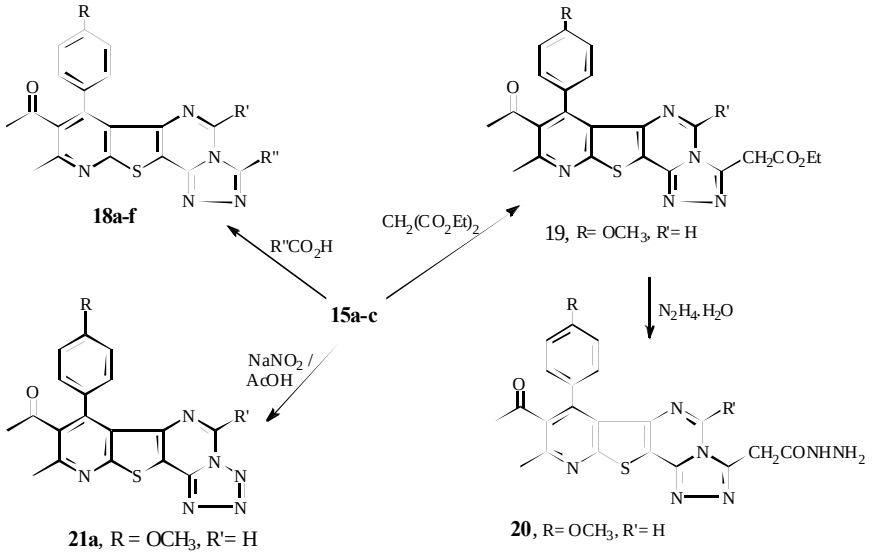
Scheme V



15-17	R	R'
a	OCH_3	H
b	Cl	H
c	OCH_3	CH_3
d	Cl	CH_3

Heating of **15a-c** with for mic or ace tic acid at re flux tem per a ture re sulted in the for ma tion of mod er ate yields of *s*-triazolopyridothienopyrimidines **18a-d**, re spec tively. An-

Scheme VI



18	R	R'	R''
a	OCH_3	H	H
b	Cl	H	H
c	OCH_3	CH_3	H

18	R	R'	R''
d	OCH_3	H	CH_3
e	Cl	H	CH_3
f	OCH_3	CH_3	CH_3

other *s*-triazolo de riv a tive **19** was ob tained upon fu sion of **15a** with di ethyl malonate. Hydrazinolysis of **19** pro duced the acethydrazide de riv a tive **20**. Di azo ti sa tion of **15a,b** in gla cial ace tic acid with so dium ni trite so lu tion pro duced the tetrazolo de riva tives **21a,b** in 73-76% yield (Scheme VI).

The struc tures of all newly syn the sized com pounds were elu ci dated and con firmed by el e men tal anal y ses, IR, ^{1}H NMR and mass spec tral data (Ta ble 1).

Six teen com pounds were screened *in vitro* for their antimicrobial activities against three strains of bacteria (*Serratia rhodenii, Echerichia coli* and *Micrococcus roseus*) and two fun gal spe cies (*Aspergillus fumigatus* and *Penicillium oxalicum*) us ing the fil ter pa per disc method.[16] The re sults revealed that all the tested com pounds ex hibit mod er ate to very strong ac tiv ity against *S. rhodenii* and are in ac tive against *E. coli*. Only six compounds (**5b, 6a, 9b, 10b, 13d** and **19**) showed mod er ate to very strong ac tiv ity against *M. roseus.* None of the tested com pounds were ac tive against the two fungal species used. However, concerning the structure-action re la tion ship, it is ob served that: (i) the cyclized compound **5b** ex hib ited more po tency than its open in ter me di ate **4b**; (ii) The pyrimidinone de riv a tive **6a** showed higher ac tivity than its triazinone an a logue **7a**; (iii) As the num ber of sulfur at oms in creases in the mol e cule the an ti bac te rial ac tiv ities in crease, i.e. com pound **13d** pos sesses higher ac tiv ity than the re lated oxo an a logue **9b** (Ta ble 2).

EXPERIMENTAL

All m.p.'s are un cor rected and mea sured on a Gallenkamp apparatus. IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; V_{max} in cm^{-1}); ^{1}H-NMR spec tra on a Varian EM-390, 90 MHz spec trom e ter with TMS as inter nal stan dard or on a Jeol LA 400 MHz FT-NMR spec trometer (δ in ppm); MS on a Jeol JMS-600 mass spec trom e ter and elemental analyses on a Perkin-Elemer 240C elemental analyser or on an Elementar Analysensystem GmbH VARIOEL V2.3 July 1998 CHNS Mode.

Reaction of arylmethylenecyanothioacetamides (1a,b) with acetylacetone; formation of com pounds 2a,b and 3a,b

This re ac tion was per formed ac cord ing to the re ported procedure.[14]

(5-Acetyl-4-aryl-3-cyano-6-methylpyridin-2-ylthio)-acetamides (4a,b)

A mix ture of **2a,b** (0.1 mol), chloroacetamide (9.4 g,

Table 1. Characterization Data of the Prepared Compounds

Compd.	M.P (°C) Yield (%)	Formula* (M.W.)	Spectral data
4a	175-176 90	$C_{18}H_{17}N_3O_3S$ (355.4)	IR: 3400, 3300 (NH_2); 2200 (C≡N); 1690 (C=O, acetyl); 1650 (C=O, amide). ^{1}H NMR ($CDCl_3$): 7.26-7.28 (d, *J* = 8.5 Hz, 2H, ArH's); 6.98-7.00 (d, *J* = 8.5 Hz, 2H, ArH's); 6.16 (br, 2H, NH_2); 3.93 (s, 2H, SCH_2); 3.84 (s, 3H, OCH_3); 2.51 (s, 3H, $COCH_3$); 1.86 (s, 3H, CH_3 at C-6).
4b	198-199 93	$C_{17}H_{14}ClN_3O_2S$ (359.8)	IR: 3400, 3300 (NH_2); 2200 (C≡N); 1690 (C=O, acetyl); 1650 (C=O, amide).
5a	251-253 91	$C_{18}H_{17}N_3O_3S$ (355.4)	IR: 3450, 3400, 3300, 3200 ($2NH_2$), 1690 (C=O, acetyl); 1640 (C=O, amide). ^{1}H NMR ($CDCl_3$): 6.99-7.50 (dd, J_1, J_2 = 8.5 Hz, 4H, ArH's); 5.67, 5.79 (2s, 4H, two -NH_2 groups); 3.86 (s, 3H, OCH_3); 2.59(s, 3H, $COCH_3$); 1.97 (s, 3H, CH_3 at C-6).
5b	277-278 92	$C_{17}H_{14}ClN_3O_2S$ (359.8)	IR: 3450, 3400, 3300, 3200 ($2NH_2$); 1690 (C=O, acetyl); 1640 (C=O, amide).
6a	>360 85	$C_{19}H_{15}N_3O_3S$ (356.4)	IR: 3200-2000 (br, NH), 1690 (C=O, acetyl); 1650 (C=O, pyrimidinone).
6b	350-352 89	$C_{18}H_{12}ClN_3O_2S$ (369.8)	IR: 3200-2000 (br, NH), 1690 (C=O, acetyl); 1650 (C=O, pyrimidinone). ^{1}H NMR (DMSO): 12.87 (br, 1H, NH); 8.06 (s, 1H, CH pyrimidine); 7.51-7.53 (d, *J* = 8.0 Hz, 2H, ArH's); 7.35-7.37 (d, *J* = 8.0 Hz, 2H, ArH's); 2.57 (s, 3H, $COCH_3$); 2.04 (s, 3H, CH_3 at C-7). MS: 370 (M^+, 10%); 369 (M^+-1, 34%); 368 (M^+-2, 51%); 367 (M^+-1-2H, 83%); 354 (M^+-O, 39%); 352 (M^+-1-OH, 100%).
7a	269-271 85	$C_{18}H_{14}N4O_3S$ (366.4)	IR: 3200-2000 (br, NH); 1690 (C=O, acetyl); 1650 (C=O, triazinone). ^{1}H NMR ($CDCl_3$): 13.55 (br, 1H, NH); 7.02-7.34 (dd, J_1, J_2 = 8.0 Hz, 4H, ArH's); 3.88 (s, 3H, OCH_3); 2.69 (s, 3H, $COCH_3$); 1.99 (s, 3H, CH_3 at C-7).
7b	246-247 87	$C_{17}H_{11}ClN_4O_2S$ (370.8)	IR: 3200-2000 (br, NH), 1690 (C=O, acetyl); 1650 (C=O, triazinone).
8a	246-247 84	$C_{26}H_{20}N_4O_4S$ (484.5)	IR: 1690 (2 C=O, ketones); 1660 (C=O, triazinone).
8b	179-180 92	$C_{22}H_{20}N_4O_4S$ (452.5)	IR: 1740 (C=O, ester); 1690 (C=O, acetyl); 1650 (C=O, triazinone). ^{1}H NMR ($CDCl_3$): 7.31-7.33 (dd, *J* = 2 Hz, 2H, ArH's); 6.98-7.00 (dd, *J* = 2 Hz, 2H, ArH's); 5.17 (s, 2H, NCH_2); 4.21-4.26 (q, *J* = 7.0 Hz, 2H, OCH_2); 3.86 (s, 3H, OCH_3); 2.67 (s, 3H, $COCH_3$); 1.98 (s, 3H, CH_3 at C-7); 1.20-1.25 (t, *J* = 7.0 Hz, 3H, CH_3).
8c	276-277 85	$C_{20}H_{17}N_5O_4S$ (423.5)	IR: 3400, 3200 (NH_2), 1690 (C=O, acetyl); 1660 (C=O, triazinone and amide).
9a	>360 32	$C_{20}H_{17}N_3O_3S$ (379.4)	IR: 3200-2000 (br, NH); 1690 (C=O, acetyl); 1650 (C=O, pyrimidinone). ^{1}H NMR (DMSO): 12.73 (s, 1H, NH); 7.24-7.26 (d, *J* = 8.3 Hz, 2H, ArH's); 6.98-7.00 (d, *J* = 8.3 Hz, 2H, ArH's); 3.81 (s, 3H, OCH_3); 2.55 (s, 3H, $COCH_3$); 2.11 (s, 3H, CH_3 at C-2); 1.96 (s, 3H, CH_3 at C-7).
9b	>360 30	$C_{19}H_{14}ClN_3O_2S$ (383.8)	IR: 3200-2000 (br, NH); 1690 (C=O, acetyl); 1650 (C=O, pyrimidinone).
10a	203-204 47	$C_{22}H_{19}N_3O_4S$ (421.5)	IR: 2200 (C≡N), 1720 (2C=O, biacetylamino); 1690 (C=O, acetyl).
10b	201-202 48	$C_{21}H_{16}ClN_3O_3S$ (425.9)	IR: 2200 (C≡N), 1720 (2C=O, biacetylamino); 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 7.41-7.43 (d, *J* = 8.3 Hz, 2H, ArH's); 7.06-7.09 (d, *J* = 8.3 Hz, 2H, ArH's); 2.65 (s, 3H, $COCH_3$); 2.04 (s, 3H, CH_3 at C-6); 2.01(s, 6H, 2x$COCH_3$, biacetylamino group). MS: 427 (M^++1, 6%); 426 (M^+, 12%); 425 (M^+-1, 15%); 424 (M^+-2, 26%); 384 (M^++1-$COCH_3$, 94%); 383 (M^+- $COCH_3$ 62%); 382 (M^+-1-$COCH_3$, 100%); 340 (M^+-2$COCH_3$, 100%); 42.9 ($COCH_3^+$,75%).

11a	208-209 86	$C_{19}H_{14}ClN_3O_2S$ (383.9)	IR: 1690 (C=O, acetyl).
11b	192-193 87	$C_{18}H_{11}Cl_2N_3OS$ (388.3)	IR: 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 8.36 (s, 1H, CH pyrimidine); 7.37-7.39 (d, *J* = 8.0 Hz, 2H, ArH's); 7.23-7.26 (d, *J* = 8.0 Hz, 2H, ArH's); 2.60 (s, 3H, $COCH_3$); 1.92 (s, 3H, CH_3 at C-7).
11c	172-173 80	$C_{20}H_{16}ClN_3O_2S$ (397.9)	IR: 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 7.22-7.24 (d, *J* = 8.3 Hz, 2H, ArH's); 6.96-6.98 (d, *J* = 8.3 Hz, 2H, ArH's); 3.80 (s, 3H, OCH_3); 2.52 (s, 3H, $COCH_3$); 2.07 (s, 3H, CH_3 at C-2); 1.94 (s, 3H, CH_3 at C-7).
11d	220-221 77	$C_{19}H_{13}Cl_2N_3OS$ (402.3)	IR: 1690 (C=O, acetyl).
12	183-184 89	$C_{22}H_{19}ClN_4O_2S$ (438.9)	IR: 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 8.36 (s, 1H, CH pyrimidine); 7.37-7.39 (d, *J* = 8.0 Hz, 2H, ArH's); 7.23-7.26 (d, *J* = 8.0 Hz, 2H, ArH's); 3.89-3.92 (t, J_1J_2 = 5Hz, J_2J_3 = 4 Hz, 4H, $(CH_2)_2O$); 3.79-3.81 (t, J_1J_2 = 5Hz, J_2J_3 = 4 Hz, 4H, $(CH_2)_2N$); 2.60 (s, 3H, $COCH_3$); 1.92 (s, 3H, CH_3 at C-7).
13a	304-305 79	$C_{19}H_{15}N_3O_2S_2$ (381.5)	IR: 3200-2000 (br, NH); 1690 (C=O, acetyl).
13b	343-344 75	$C_{18}H_{12}ClN_3OS_2$ (385.9)	IR: 3200-2000 (br, NH); 1690 (C=O, acetyl).
13c	354-355 82	$C_{20}H_{17}N_3O_2S_2$ (395.5)	IR: 3200-2000 (br, NH), 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 13.6 (s, 1H, NH); 7.0-7.5 (dd, *J* = 8.0 Hz, 4H, ArH's); 3.8 (s, 3H, OCH_3); 2.7 (s, 3H, $COCH_3$); 2.2 (s, 3H, CH_3 at C-2); 1.9 (s, 3H, CH_3 at C-7).
13d	385-386 77	$C_{19}H_{14}ClN_3OS_2$ (399.9)	IR: 3200-2000 (br, NH); 1690 (C=O, acetyl).
14a	206-207 89	$C_{20}H_{17}N_3O_2S_2$ (395.5)	IR: 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 8.6 (s, 1H, CH pyrimidine);7.0-7.4 (dd, *J* = 8.5 Hz, 4H, ArH's); 3.8 (s, 3H, OCH_3); 2.8 (s, 3H, SCH_3); 2.5 (s, 3H, $COCH_3$); 2.0 (s, 3H, CH_3 at C-7).
14b	163-164 88	$C_{23}H_{21}N_3O_4S_2$ (467.6)	IR: 1730 (C=O, ester); 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 8.74 (s, 1H, CH pyrimidine); 7.31-7.33 (d, *J* = 8.5 Hz, 2H, ArH's); 6.99-7.01 (d, *J* = 8.5 Hz, 2H, ArH's); 4.19-4.24 (q, *J* = 7.0 Hz, 2H, OCH_2); 4.18 (s, 2H, SCH_2); 3.89 (s, 3H, OCH_3); 2.68 (s, 3H, $COCH_3$); 1.94 (s, 3H, CH_3 at C-7); 1.24-1.28 (t, *J* = 7.0 Hz, 3H, CH_3 of ester).
14c	198-199 75	$C_{21}H_{19}N_3O_2S_2$ (409.5)	IR: 1690 (C=O, acetyl).
14d	152-153 78	$C_{24}H_{23}N_3O_4S_2$ (481.6)	IR: 1730 (C=O, ester); 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 7.0-7.4 (dd, *J* = 9.0 Hz, 4H, ArH's); 4.1-4.3 (q, 2H, OCH_2); 3.9 (s, 2H, SCH_2); 3.7 (s, 3H, OCH_3); 2.5 (s, 3H, $COCH_3$); 2.2 (s, 3H, CH_3 at C-2); 1.9 (s, 3H, CH_3 at C-7); 1.1-1.3 (t, 3H, CH_3 of ester).
15a	289-290 93	$C_{19}H_{17}N_5O_2S$ (379.4)	IR: 3400-3200 ($NHNH_2$); 1690 (C=O, acetyl); 1640 (C=N).
15b	292-293 92	$C_{18}H_{14}ClN_5OS$ (383.9)	IR: 3400-3200 ($NHNH_2$); 1690 (C=O, acetyl); 1640 (C=N). ^{1}H NMR (DMSO): 9.12 (br, 1H, NH); 8.08 (s, 1H, CH pyrimidine); 7.49-7.51 (d, *J* = 8.0 Hz, 2H, ArH's); 7.33-7.35 (d, *J* = 8.0 Hz, 2H, ArH's); 4.96 (br, 2H, NH_2); 2.56 (s, 3H, $COCH_3$); 2.02 (s, 3H, CH_3 at C-7).
15c	297-298 95	$C_{20}H_{19}N_5O_2S$ (393.5)	IR: 3400-3200 ($NHNH_2$); 1690 (C=O, acetyl); 1640 (C=N).
15d	323-324 91	$C_{19}H_{16}ClN_5OS$ (397.9)	IR: 3400-3200 ($NHNH_2$), 1690 (C=O, acetyl), 1640(C=N). ^{1}H NMR (DMSO): 9.0 (br, 1H, NH); 7.2-7.6 (dd, *J* = 8.0 Hz, 4H, ArH's); 5.1 (br, 2H, NH_2); 2.6 (s, 3H, $COCH_3$); 2.1 (s, 3H, CH_3 at C-2); 1.9 (s, 3H, CH_3 at C-7).
16a	262-263 89	$C_{26}H_{21}N_5O_2S$ (467.5)	IR: 3200 (NH); 1690 (C=O, acetyl); 1640 (C=N).

16b	282-283 85	$C_{25}H_{18}ClN_5OS$ (472.0)	IR: 3200 (NH); 1690 (C=O, acetyl); 1640 (C=N).
17b	244-245 89	$C_{23}H_{18}ClN_5OS$ (447.9)	IR: 1690 (C=O, acetyl).^{1}H NMR ($CDCl_3$): 8.7 (s, 1H, CH pyrimidine); 7.4-7.8 (dd, *J* = 9.0 Hz, 2H, ArH's); 6.1 (s, 1H, CH pyrazole); 2.7 (s, 3H, $COCH_3$); 2.8, 2.4 (2s, 6H, two -CH_3 attached to pyrazole ring); 2.0 (s, 3H, CH_3 at C-7).
17c	247-248 80	$C_{25}H_{23}N_5O_2S$ (457.6)	IR: 1690 (C=O, acetyl).^{1}H NMR ($CDCl_3$): 7.1-7.6 (dd, *J* = 9.0 Hz, 4H, ArH's); 6.3 (s, 1H, CH pyrazole); 3.9 (s, 3H, OCH_3); 2.7 (s, 3H, $COCH_3$); 2.5, 2.9 (2s, 6H, two -CH_3 attached to pyrazole ring); 2.2 (s, 3H, CH_3 at C-2); 2.0 (s, 3H, CH_3 at C-7).
17d	209-210 83	$C_{24}H_{20}ClN_5OS$ (462.0)	IR: 1690 (C=O, acetyl).
18a	282-283 76	$C_{20}H_{15}N_5O_2S$ (389.4)	IR: 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 9.08 (s, 1H, CH pyrimidine); 8.43 (s, 1H, CH triazole); 7.45-7.47 (d, *J* = 8.0 Hz, 2H, ArH's); 7.31-7.33 (d, *J* = 8.0 Hz, 2H, ArH's); 3.91 (s, 3H, OCH_3); 2.66 (s, 3H, $COCH_3$); 2.05 (s, 3H, CH_3 at C-9).
18b	275-276 79	$C_{19}H_{12}ClN_5OS$ (393.9)	IR: 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 9.10 (s, 1H, CH pyrimidine); 8.46 (s, 1H, CH triazole); 7.47-7.49 (d, *J* = 8.0 Hz, 2H, ArH's); 7.33-7.35 (d, *J* = 8.0 Hz, 2H, ArH's); 2.69 (s, 3H, $COCH_3$); 2.04 (s, 3H, CH_3 at C-9).
18c	233-234 70	$C_{21}H_{17}N_5O_2S$ (403.5)	IR: 1690 (C=O, acetyl).
18d	252-253 77	$C_{21}H_{17}N_5O_2S$ (403.5)	IR: 1690 (C=O, acetyl).
18e	279-280 79	$C_{20}H_{14}ClN_5OS$ (407.9)	IR: 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 8.98 (s, 1H, CH pyrimidine); 7.47-7.49 (d, *J* = 8.5 Hz, 2H, ArH's); 7.33-7.35 (d, *J* = 8.5 Hz, 2H, ArH's); 2.69 (s, 3H, $COCH_3$); 2.68 (s, 3H, CH_3 at C-3); 2.04 (s, 3H, CH_3 at C-9).
18f	268-269 74	$C_{22}H_{19}N_5O_2S$ (417.5)	IR: 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 7.1-7.5 (dd, *J* = 8.0 Hz, 4H, ArH's); 3.8 (s, 3H, OCH_3); 2.8 (s, 3H, $COCH_3$); 2.6 (s, 3H, CH_3 at C-3); 2.1 (s, 3H, CH_3 at C-2); 2.0 (s, 3H, CH_3 at C-9).
19	192-193 78	$C_{24}H_{21}N_5O_4S$ (475.5)	IR: 1730 (C=O); 1690 (C=O, acetyl).^{1}H NMR ($CDCl_3$): 9.04 (s, 1H, CH pyrimidine); 7.32-7.34 (d, *J* = 8.5 Hz, 2H, ArH's); 7.00-7.02 (d, *J* = 8.5 Hz, 2H, ArH's); 4.20-4.26 (q, *J* = 7.0 Hz, 2H, OCH_2); 4.05 (s, 2H, CH_2); 3.91 (s, 3H, OCH_3); 2.67 (s, 3H, $COCH_3$); 1.97 (s, 3H, CH_3 at C-9); 1.24-1.28 (t, *J* = 7.0 Hz, 3H, -CH_3 of ester). MS: 476 (M^++1, 30%); 475 (M^+, 100%); 474 (M^+-1, 16%); 460 (M^+-CH_3, 94%); 432 (M^+-$COCH_3$, 9%); 388 (M^+- $CH_2CO_2C_2H_5$ 11%).
20	213-214 87	$C_{22}H_{19}N_7O_3S$ (461.5)	IR: 3450, 3300 ($NHNH_2$); 1690 (C=O, acetyl); 1650 (C=O, hydrazide).
21a	210-211 73	$C_{18}H_{14}N_4O_3S$ (366.4)	IR: 1690 (C=O, acetyl). ^{1}H NMR ($CDCl_3$): 8.8 (s, 1H , CH pyrimidine); 7.0-7.5 (dd, *J* = 9.0 Hz, 4H, ArH's); 4.0 (s, 3H, OCH_3); 2.7 (s, 3H, $COCH_3$); 2.1 (s, 3H, CH_3 at C-9).
21b	223-224 76	$C_{17}H_{11}ClN_4O_2S$ (370.8)	IR: 1690 (C=O, acetyl).

* Satisfactory elemental analyses were obtained for all compounds.

0.1 mol) and $CH_3CO_2Na.3H_2O$ (15.0 g, 0.11 mol) in C_2H_5OH (300 mL) was heated under reflux for 2 h. The precipitate that formed on cooling was collected and recrystallized from C_2H_5OH to give fine white needles of **4a,b**.

5-Acetyl-3-amino-4-aryl-6-methylthieno[2,3-b]pyridine-2-carboxamides (5a,b)

A suspension of compound **4a,b** (0.03 mol) in C_2H_5OH (100 mL) containing dissolved Na (0.46 g, 0.02 mol) was

Table 2. The Antimicrobial Activities of Some Representative Compounds (diameter of inhibition zones)

Compd. No.	*S. rhodenii*	*E. coli*	*M. roseus*	*A. fumigatus*	*P. oxalicum*
4b	++	–	–	–	–
5b	+++	–	++	–	–
6a	++	–	++	–	–
7a	+	–	–	–	–
8c	+	–	–	–	–
9b	++	–	+	–	–
10b	++	–	+	–	
11c	+	–	–	–	–
12	+	–	–	–	–
13d	+++	–	+++	–	–
14b	++	–	–	–	–
15c	+	–	–	–	–
17d	+	–	–	–	–
18a	+	–	–	–	–
19	+	–	++	–	–
21	+	–	–	–	–
Tioconazole (Tyrosyde)®	+	+	+++	++	+++

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

heated un der re flux for 20 min. The pre cip i tated solid was col lected and recrystallized from C_2H_5OH to give yel low crys tals of **5a,b**.

8-Acetyl-9-aryl-7-methylpyrido[3′,2′:4,5]thieno[3,2-d]-pyrimidine-4(3*H*)-ones (6a,b)

A mix ture of **5a,b** (0.01 mol) and $HC(OC_2H_5)_3$ (4 mL) in redistilled $(CH_3CO)_2O$ (20 mL) was heated un der re flux for 3 h. The solid that formed on cool ing was col lected and recrystallized from C_2H_5OH as colour less plates of **6a,b**.

8-Acetyl-9-aryl-7-methypyrido[3′,2′:4,5]thieno[3,2-d]-1,2,3-triazine-4(3*H*)-ones (7a,b)

So dium ni trite so lu tion (12 mL, 10%, 0.015 mol) was added to a so lu tion of **5a,b** (0.01 mol) in conc. H_2SO_4 (5 mL) and gla cial CH_3CO_2H (5 mL) at 0 °C over 5 min utes with stir-ring. The solid thus pre cip i tated was col lected and crys tal-lized from C_2H_5OH as white crys tals of **7a,b**.

Reaction of 7a with some halocompounds; for ma tion of triazinones 8a-c

A so lu tion of **7a** (0.36 g, 0.001 mol) in $HCON(C_2H_5)_2$ (7 mL) was stirred for a while with an hy drous K_2CO_3 (0.4 g), and then the respective halocompound (0.001 mol) was added. The mix ture was stirred at 80 °C for 2 h and then di-luted with H_2O (10 mL). The pre cip i tate was col lected and crys tal lized from C_2H_5OH to give **8a-c**.

Reaction of 5-acetyl-3-amino-4-aryl-6-methylthieno[2,3-b]-pyridine-2-carboxamides (5a,b) with ace tic an hy dride; for ma tion of com pounds 9a,b and 10a,b

Com pounds **5a,b** (0.005 mol) in redistilled $(CH_3CO)_2O$ (20 mL) was heated un der re flux for 8 h. The solid that pre-cip i tated af ter cool ing was fil tered off and recrystallized from C_2H_5OH. This compound was identified as 8-acetyl-9-aryl-2,7-dimethylpyrido[3′,2′:4,5]thieno[3,2-d]pyrim i-dine-4(3*H*)-one (**9a,b**). The mother li quor of the above crude prod uct was di luted with H_2O (20 mL) to give a pre cip i tate which was col lected and crys tal lized from aque ous C_2H_5OH. This prod uct was as signed as 5-acetyl-4-aryl-3- biacety ami-no-6-methylthieno[2,3-b]pyridine-2-carbonitrile (**10a,b**).

Chlorination of 6a,b and 9a,b; formation of 4-chloropyrimidines 11a-d; general procedure

Com pound **6a,b** or **9a,b** (0.005 mol) in an excess amount of $POCl_3$ (15 mL) was heated un der re flux for 4 h. The cooled re ac tion mix ture was poured with vig or ous stir-ring onto ice H_2O. The solid that sep a rated was col lected and crys tal lized from C_2H_5OH as white nee dles of **11a-d**.

8-Acetyl-9-(4′-chlorophenyl)-7-methyl-4-morpholinopyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine (12)

A mix ture of **11b** (0.39 g, 0.001 mol) and morpholine (2 mL) was heated gently for 1 h. and then triturated with C_2H_5OH (10 mL). The pre cip i tate which formed af ter cool ing was col lected and recrystallized from CH_3OH to give white nee dles of **12**.

Reaction of 11a-d with thiourea; formation of pyrimidinethiones 13a-d

A mix ture of **11a-d** (0.003 mol) and thiourea (0.38 g, 0.005 mol) in C_2H_5OH (20 mL) was heated un der re flux for 3 h. The pre cip i tated solid was col lected, dis solved in warm 10% NaOH so lu tion and fil tered. The clear fil trate was acid i-fied with CH_3CO_2H whereby a yel low pre cip i tate sep a rated. It was col lected and crys tal lized from C_2H_5OH-$CHCl_3$ mix-ture to give yel low nee dles of **13a-d**.

Alkylation of 13a,c; formation of thioethers 14a-d

To a sus pen sion of **13a,c** (0.002 mol) and $CH_3CO_2Na.3H_2O$ (0.4 g, 0.003 mol) in C_2H_5OH (20 mL), methyl io dide or ethyl chloroacetate (0.002 mol) was added. The re sult ing

mixture was heated under reflux for 1 h. The solid that formed on cool ing was col lected and recrystallized from C_2H_5OH as colour less nee dles of **14a-d**.

Reaction of 11a-d with hydrazine hydrate; formation of 4-hydrazinopyrimidines 15a-d; general procedure

A mix ture of **11a-d** (0.02 mol) and hydrazine hy drate (2 mL, 0.04 mol) in C_2H_5OH (50 mL) was heated un der re flux for 2 h. The sep a rated prod uct was col lected and recrys tallized from dioxane to give white crys tals of **15a-d**.

8-Acetyl-9-aryl-4-benzylidenehydrazino-7-methylpyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidines (16a,b)

A mixture of **15a,b** (0.002 mol) and benzaldehyde (0.02 mL, 0.002 mol) in C_2H_5OH (25 mL) was refluxed for 3 h. The solid that pre cip i tated on cool ing was col lected and recrystallized from dioxane to give white crys tals of **16a,b**.

Cyclocondensation of 15a-d with acetylacetone; formation of 3,5-dimethylpyrazole deriv a tives 17a-d

Com pounds **15a-d** (0.001 mol) in acetylacetone (5 mL), were gently heated un der re flux for 4 h. The re ac tion mix ture was triturated with C_2H_5OH (5 mL) and then left to cool. The pre cip i tate was col lected and recrystallized from C_2H_5OH as white nee dles of **17a-d**.

Reaction of 15a-c with formic or ace tic acid; for ma tion of s-triazolopyridothienopyrimidines 18a-f

Com pounds **15a-c** (0.001 mol) in for mic acid 85% or gla cial ace tic acid (15 mL) was heated un der re flux for 5 h. The solid that pre cip i tated on cool ing was col lected and crystal lized from C_2H_5OH to give white nee dles of **18a-f**.

Ethyl (8-acetyl-7-(4′-methoxyphenyl)-9-methyl-*s*-triazolo-[4″,3″-c]pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-3-yl)-acetate (19)

Com pound **15a** (1.52 g, 0.004 mol) in di ethyl malonate (15 mL) was heated un der re flux for 2 h. The re ac tion mix ture was triturated with C_2H_5OH (20 mL) whereby a white solid pre cip i tated. It was col lected and recrystallized from C_2H_5OH to give **19**.

Reaction of 19 with hydrazine hy drate; for ma tion of acethydrazide 20

A mix ture of **19** (0.48 g, 0.001 mol) and hydrazine hydrate (0.5 mL, 0.01 mol) in C_2H_5OH (15 mL) was heated under re flux for 2 h and then left to cool. The pre cip i tated solid was col lected and recrystallized from C_2H_5OH to give **20**.

8-Acetyl-7-aryl-9-methyltetrazolo[1″,5″-c]pyrido[3′,2′:4,5]-thieno[3,2-e]pyrimidines (21a,b)

To a so lu tion of **15a,b** (0.001 mol) in gla cial CH_3CO_2H (15 mL) at 0 °C, a cold so lu tion of $NaNO_2$ 10% (7 mL, 0.01 mol) was added with stir ring over 10 mins. The pre cip i tate that sep a rated was col lected and crys tal lized from C_2H_5OH to give white crys tals of **21a,b**.

Biological Screening

The fil ter pa per disc method was per formed in Nu tri ent agar for bac te ria and Dox agar for fungi. These agar me dia were in oc u lated with 0.5 mL of the 24 h. liq uid cul tures. Filter pa per discs (5 mm di am e ter) sat u rated with each compound so lu tion (10 mg/mL of DMSO) were placed on the indi cated agar me dia. The in cu ba tion time was 48 h (at 37 °C for bac te ria and at 28 °C for fungi). Discs sat u rated with DMSO were used as con trol. Tioconazole (Tyrosyde®) was used as a ref er ence sub stance. The di am e ter of in hi bi tion zones (mm) were mea sured and re corded.

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Key Words

Thienopyridines; Pyridothienopyrimidines; Pyridothienotriazines; Triazolopyridothienopyrimidines; Tetrazolopyridothienopyrimidines; Antimicrobial activity.

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