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Synthesis and antimicrobial testing of some new *S*-substituted-thiopyridines, thienopyridines, pyridothienopyrimidines and pyridothienotriazines

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The reaction of 5-acetyl-4-aryl-3-cyano-6-methylpyridine-2(1*H*)-thiones (**1a**, **b**) with 4-methylphenacyl bromide, chloro-*N*-arylacetamides or chloroacetonitrile gave the corresponding S-substituted thiopyridines **2a**–**c**, **4a**–**f** and **6a**–**c**, respectively. The latter compounds underwent intramolecular Thorpe-Ziegler cyclization to give 2-substituted 5-acetyl-3-amino-4-aryl-6-methylthieno[2,3-*b*]pyridines **3a**–**c, 5a**–**f** and **7a**–**c**. Compounds **5a**–**f** and **7b, c** are key intermediates in the synthesis of the target compounds. Some compounds showed remarkable antimicrobial activity.

1. Introduction

Many pyridines are useful as herbicidals [1], bactericidals [2], fungicidals [3], insecticidals [4] and pharmaceuticals [5–7]. In particular, some thieno[2,3-*b*]pyridine derivatives possess antibacterial [8, 9], antiviral [10], antihypertensive [11] and immunostimulating [12] activities. Others are used as gonadotropin-releasing hormone antagonists [13–18] and as lipoxygenases inhibitors [19]. Recently, certain thieno[2,3-*b*]pyridine derivatives were prepared as antinflammatory agents, particularly for treating arthritis and as bone resorption inhibiting agents [20]. Pyridothienopyrimidine derivatives have been found applications as analgesics [21], antipyretics [22] and anti-inflammatories [23]. Moreover, some pyridothienotriazines exhibit anti-anaphylactic [24] and antiallergic activity [25]. Encouraged by all these findings and as a continuation of our work on thieno[2,3-*b*]pyridines [26–28], we synthesized the title compounds which might show enhanced activities owing to the incorporation of different pharmacophores such as the thiopyridine, thienopyridine, pyridothienopyrimidine and/or pyridothienotriazine moiety into their structures. Some representative compounds were tested for antimicrobial activity.

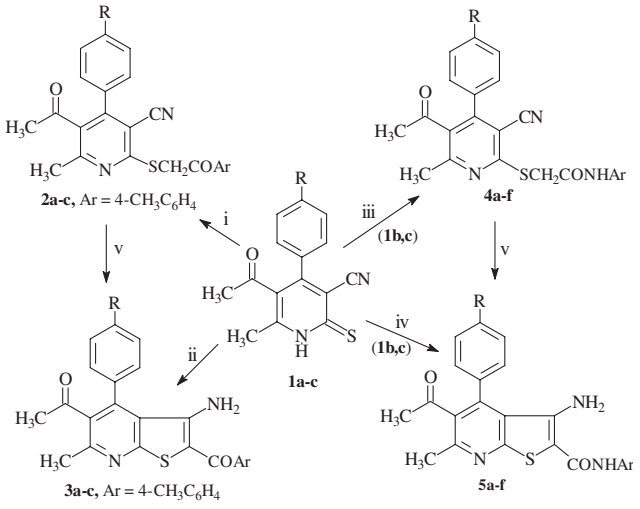
2. Investigations, results and discussion

2.1. Chemistry

The reaction of 5-acetyl-4-aryl-3-cyano-6-methylpyridine-2(1*H*)-thiones **1a**–**c** [28] with 4-methylphenacyl bromide or chloro-*N*-arylacetamides by refluxing in ethanol containing a slight excess of sodium acetate gave the corresponding S-substituted thiopyridines **2a**–**c** and **4a**–**f**, respectively. On heating these compounds in ethanol containing catalytic amounts of sodium ethoxide, they underwent intramolecular Thorpe-Ziegler cyclization to yield the thieno[2,3-*b*]pyridine derivatives **3a**–**c** and **5a**–**f**. The latter compounds were also synthesized by direct interaction of **1a**–**c** with the respective halo compounds in the presence of sodium ethoxide (Scheme 1).

In contrast, the reaction of pyridinethiones **1a**–**c** with chloroacetonitrile in the presence of a slight excess of sodium acetate afforded 5-acetyl-3-amino-4-aryl-6-methylthieno [2,3-*b*]pyridine-2-carbonitriles **7a**–**c** directly. This

Scheme 1

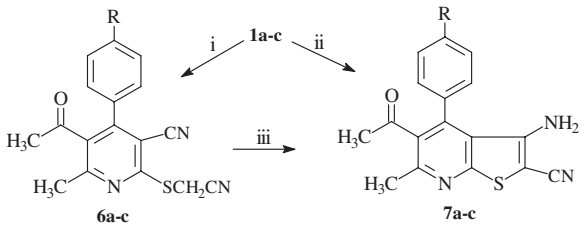


i: 4-$CH_3C_6H_4COCH_2Br$ / excess AcONa; ii: 4-$CH_3C_6H_4COCH_2Br$ / EtONa;
iii: $ArNHCOCH_2Cl$ / excess AcONa; iv: $ArNHCOCH_2Cl$ / EtONa; v: EtONa

1, 2, 3	R
a	H
b	OCH_3
c	Cl

4, 5	R	Ar
a	OCH_3	C_6H_5
b	OCH_3	4-$CH_3C_6H_4$
c	OCH_3	4-ClC_6H_4
d	Cl	C_6H_5
e	Cl	4-$CH_3C_6H_4$
f	Cl	4-ClC_6H_4

Scheme 2



i: $ClCH_2CN$ / equimolar ammount of AcONa; ii: $ClCH_2CN$ / excess AcONa; iii: AcONa

6, 7	R
a	H
b	OCH_3
c	Cl

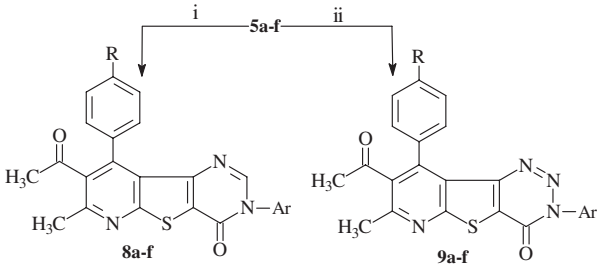
may be due to the high activity of the methylene group of their intermediates **6a**–**c** which can be isolated when an equimolar amount of sodium acetate was used. The compounds **6a**–**c** were easily cyclized into the corresponding thienopyridines **7a**–**c** upon heating in ethanol containing sodium acetate (Scheme 2).

The cyclocondensation of 5-acetyl-3-amino-4-aryl-2-(*N*-aryl)carbamoyl-6-methyl-thieno[2,3-*b*]pyridines **5a**–**f** with triethyl orthoformate by refluxing in acetic anhydride yielded 8-acetyl-3,9-diaryl-7-methylpyrido[3′,2′ : 4,5]thieno[2,3-d]pyrimidine-4(3*H*)-ones **8a**–**f**. Diazotization of **5a**–**f** using sodium nitrite and sulfuric-acetic acid mixture led to 8-acetyl-3,9-diaryl-7-methylpyrido[3′,2′ : 4,5]thieno-[3,2-d][1,2,3]triazine-4(3*H*)-ones **9a**–**f** (Scheme 3).

5-Acetyl-3-amino-4-aryl-6-methylthieno[2,3-*b*]pyridine-3-carbonitriles **7b, c** were also used as starting materials for other new pyridothienopyrimidines. Thus, the reaction of **7b** with CS_2 in hot pyridine gave 8-acetyl-2,4-dithioxo-9-(4′-methoxy-phenyl)-7-methyl-1,2,3,4-tetrahydropyrido[3′,2′ : 4,5]thieno[3,2-d]pyrimidine (**10**) which was reacted with methyl iodide in the presence of sodium hydroxide to afford the dimethylthiopyrimidine derivative **11**. Refluxing compound **7b** with phenyl isothiocyanate in pyridine led to 8-acetyl-4-imino-9-(4′-methoxyphenyl)-7-methyl-3-phenyl-2-thioxo-1,2,3,4-tetrahydropyrido-[3′,2′ : 4,5]thieno[3,2-*d*]pyrimidine (**12**). The reaction of **7b, c** with sodium azide in DMF containing ammonium chloride afforded the tetrazolyl derivatives **13a, b** which reacted with triethyl orthoformate to furnish the tetrazolo-pyridothienopyrimidines **14a, b**. The latter compounds were identical to those prepared by another method [28] in all aspects (Scheme 4).

Condensation of *o*-aminocarbonitriles **7b, c** with triethyl orthoformate by refluxing in acetic anhydride afforded ethyl *N*-[5-acetyl-4-aryl-2-cyano-6-methyl-thieno[2,3-*b*] pyridin-3-yl]methanimidates **15a, b**. On treatment of **15a, b** with hydrazine hydrate in dioxane at room temperature, 8-acetyl-3-amino-9-aryl-3,4-dihydro-4-imino-7-methyl-pyrido[3′,2′ : 4,5]thieno[3,2-*d*]pyrimidines **16a, b** were ob-

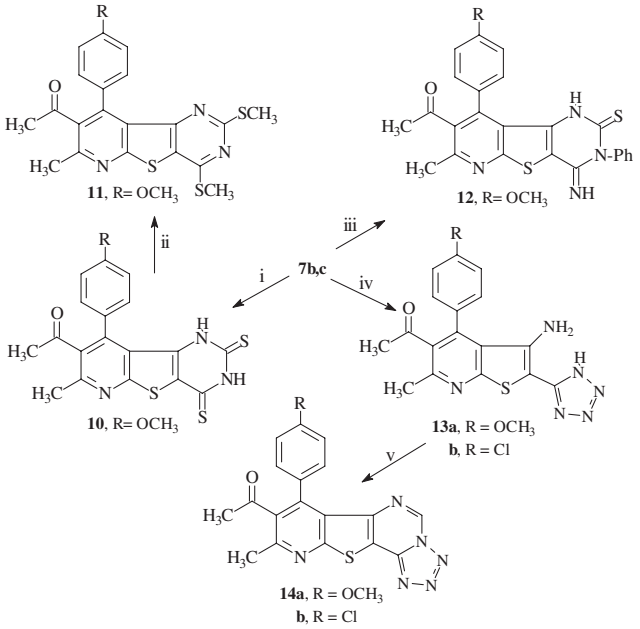
Scheme 3



i: $HC(OEt)_3$ / Ac_2O; ii: $NaNO_2$ / H_2SO_4 /AcOH

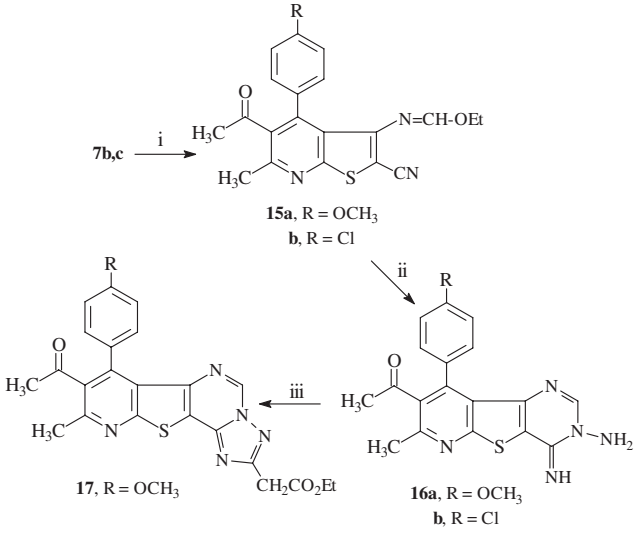
8, 9	R	Ar
a	OCH_3	C_6H_5
b	OCH_3	4-$CH_3C_6H_4$
c	OCH_3	4-ClC_6H_4
d	Cl	C_6H_5
e	Cl	4-$CH_3C_6H_4$
f	Cl	4-ClC_6H_4

Scheme 4



i: CS_2 /pyridine; ii: CH_3I / NaOH / EtOH; iii: PhNCS / pyridine; iv: NaN_3 / NH_4Cl / DMF v: $NaNO_2$ / AcOH

Scheme 5



i: $Hc(OEt)_3$ /Ac_2O; ii: NH_2-NH_2.H_2O / dioxane; iii: $CH_2(CO_2Et)_2$ / neat

tained. The interaction of **16a** with diethyl malonate afforded ethyl (8-acetyl-7-(4′-methoxyphenyl)-9-methyl-*S*-triazolo[2″,3″-*c*]pyrido[3′,2′ : 4,5]thieno[2,3-*e*]pyrimidin-2-yl)acetate (**17**) (Scheme 5).

The structural formulas of all newly synthesized compounds were confirmed by elemental and spectral analyses (Table 1).

2.2. Antimicobial activity

Compounds **2c**, **3c**, **4a**, **4f**, **5f**, **6b**, **7b**, **8d**, **8e**, **8f**, **9a**, **9e**, **10**, **11**, **13a**, **15b**, **16b** and **17** were tested *in vitro* for antimicrobial activity against three species of bacteria (*Bacillus cereus, Staphylococcus aureus* and *Proteus* sp.) and one fungal species, *Aspergillus fumigatus* using the filter paper disc method [29]. The results revealed that: (i) all the tested compounds showed moderate to very strong activity against *Bacillus cereus,* (ii) most of the tested compounds showed moderate to very strong activity against *Staphylococcus aureus* and *Proteus* sp., (iii) compounds **7b**, **13a** and **16b** inhibited the growth of *Aspergillus fumigatus* and (iv) the other compounds tested were inactive against the microorganisms under investigation (Table 2).

3. Experimental

Melting points are uncorrected and measured on a Gallankamp apparatus. IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; υ_{max} in cm^{-1}), ^1H 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 Jeol JMS-600 mass spectrometer. Elemental analyses: Elementar Analyses system GmbH VARIOEL $V_{2.3}$ CHNS Mode.

3.1. 5-Acetyl-4-aryl-3-cyano-6-methylpyridine-2(1H)-thiones (**1a–c**)

These compounds were prepared as described [28].

3.2. Reaction of compounds **1a–c** *with 4-methylphenacyl bromide or chloro-N-arylacetamides; formation of S-substituted thiopyridines* **2a–c** *and* **4a–f**

A mixture of compound **1a–c** (0.1 mol), the respective halo compound (0.1 mol) and $CH_3CO_2Na \cdot 3\,H_2O$ (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 white needles of **2a–c** or **4a–f**, respectively.

3.3. 2-Substituted 5-acetyl-3-amino-4-aryl-6-methylthieno[2,3-b]pyridines **3a–c** *and* **5a–f**

3.3.1. Method A

Compound **2a–c** or **4a–f** (0.01 mol) was suspended in C_2H_5ONa solution (0.12 g sodium in 3 ml of abs. C_2H_5OH) and heated under reflux for 5 min. The solid that formed after cooling was collected and recrystallized from C_2H_5OH to give canary yellow crystals of **3a–c** or **5a–f**, respectively.

3.3.2. Method B

To a suspension of compound **1a–c** (0.01 mol) in C_2H_5ONa solution (0.35 g Na in 30 ml of abs. C_2H_5OH), the respective halo compound (0.01 mol) was added. The resulting mixture was heated under reflux for 20 min and allowed to cool. The yellow precipitate that formed was collected and recrystallized from C_2H_5OH to give compounds **3a–c** or **5a–f** in 78–83% yield. These products were identical in all aspects to those received with method A.

3.4. 5-Acetyl-4-aryl-3-cyano-2-cyanomethylthio-6-methylpyridines (**6a–c**)

A mixture of compounds **1a–c** (0.1 mol), $ClCH_2CN$ (6.3 ml, 0.1 mol) and an equimolar quantity of $CH_3CO_2Na \cdot 3\,H_2O$ (13.6 g, 0.1 mol) in ethanol (300 ml) was heated under reflux for 2 h. The precipitate was collected and recrystallized from aq. C_2H_5OH to give white crystals of **6a–c**.

3.5. 5-Acetyl-3-amino-4-aryl-6-methylthieno[2,3-b]pyridine-2-carbonitriles (**7a–c**)

3.5.1. Method A

A mixture of compound **1a–c** (0.1 mol), $ClCH_2CN$ (6.3 ml, 0.1 mol) and $CH_3CO_2Na \cdot 3\,H_2O$ (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 yellow needles of **7a–c**.

3.5.2. Method B

A mixture of **6a–c** (0.01 mol) and a slight excess of $CH_3CO_2Na \cdot 3\,H_2O$ (1.36 g, 0.01 mol) in C_2H_5OH (50 ml) was heated under reflux for 2 h. After cooling, the yellow precipitate thus formed was collected and recrystallized from C_2H_5OH to give compounds **7a–c** in 92–95% yield. These products were identical in all aspects to those received with method A.

3.6. 8-Acetyl-3,9-diaryl-7-methylpyrido[3′,2′ : 4,5]thieno[3,2-d]pyrimidine-4(3H)-ones (**8a–f**)

A mixture of **5a–f** (0.001 mol) and $HC(OC_2H_5)_3$ (5 ml) in redistilled $(CH_3CO)_2O$ (20 ml) was refluxed for 2 h. The solid product was collected and recrystallized from C_2H_5OH to give colorless plates of **8a–f**.

3.7. 8-Acetyl-3,9-diaryl-7-methylpyrido[3′,2′ : 4,5]thieno[3,2-d]-1,2,3-triazine-4(3H)-ones (**9a–f**)

To a solution of **5a–f** (0.001 mol) in glacial CH_3CO_2H (5 ml) and conc. H_2SO_4 (5 ml) at 0 °C, a cold 10% solution of $NaNO_2$ in H_2O (7 ml; 0.01 mol) was added with stirring during 10 min. The precipitate that separated was filtered off, washed with water and crystallized from C_2H_5OH to give white needles of **9a–f**.

3.8. 8-Acetyl-2,4-dithioxo-9-(4′-methoxyphenyl)-7-methyl-1,2,3,4-tetrahydropyrido-[3′,2′ : 4,5]thieno[3,2-d]pyrimidine (**10**)

To a solution of **7b** (1.7 g, 0.005 mol) in pyridine (15 ml), CS_2 (2 ml) was added. The resulting mixture was heated under reflux on a water bath for 10 h. The precipitate was collected and recrystallized from CH_3CO_2H as orange crystals.

3.9. 8-Acetyl-2,4-dimethylthio-9-(4′-methoxyphenyl)-7-methylpyrido-[3′,2′ : 4,5] thieno[3,2-d]pyrimidine (**11**)

To a solution of **10** (0.4 g, 0.001 mol) in ethanolic NaOH 5% (10 ml), CH_3I (0.13 ml, 0.002 mol) was added. The resulting mixture was heated under reflux for 1 h. The product that formed on cooling was collected and recrystallized from C_2H_5OH as white needles.

3.10. 8-Acetyl-4-imino-9-(4′-methoxyphenyl)-7-methyl-3-phenyl-1,2,3,4-tetrahydro-2-thioxopyrido[3′,2′ : 4,5]thieno[3,2-d]pyrimidine (**12**)

A mixture of **7b** (3.37 g, 0.01 mol) and PhNCS (1.20 ml, 0.01 mol) in pyridine (20 ml) was heated on a water bath for 5 h. The mixture was cooled, poured into ice-H_2O (50 ml) and acidified with CH_3CO_2H. The precipitate was collected and recrystallized from $HCON(CH_3)_2$ to give **12** as yellow needles.

3.11. 5-Acetyl-3-amino-4-aryl-6-methyl-2-(1H-tetrazol-5-yl)-thieno[2,3-b]-pyridine (**13a, b**)

A mixture of compounds **7b, c** (0.088 mol), NaN_3 (1.5 g, 0.023 mol) and NH_4Cl (1.25 g, 0.023 mol) in $HCON(CH_3)_2$ (50 ml) was heated under reflux on a water bath for 21 h. The cooled mixture was added to 350 g ice-H_2O and acidified with 4N HCl. The product was collected and crystallized from C_2H_5OH to give yellow crystals of **13a, b**, respectively.

3.12. 8-Acetyl-7-aryl-9-methyltetrazolo[1″,5″-c]pyrido[3′,2′ : 4.5]thieno-[2,3-e]pyrimidines (**14a, b**)

Compounds **13a, b** (0.002 mol) in $HC(OC_2H_5)_3$ (10 ml) were heated under reflux for 2 h. The solid that formed after cooling was collected and recrystallized from C_2H_5OH to give **14a, b** (yield: 73–78%) which are identical to those reported above in all aspects.

3.13. Ethyl N-[5-acetyl-4-aryl-2-cyano-6-methylthieno[2,3-b]pyridin-3-yl]-methan-imidate (**15a, b**)

A mixture of **7b, c** (0.01 mol) and $HC(OC_2H_5)_3$ (7 ml) in redistilled $(CH_3CO)_2O$ (40 ml) was refluxed for 3 h. The crystalline product that separated on cooling was collected and recrystallized from C_2H_5OH as colourless plates of **15a, b**.

Table 1: Characterization data of the synthesized compounds

Compd.	M.P. (°C) (yield: %)	Formula[a] (M.W.)	Spectral data
2a	169–170 (75)	$C_{24}H_{20}N_2O_2S$ (400.50)	IR: 2200 (C≡N); 1690 (2 C=O). ^{1}H-NMR ($CDCl_3$): 8.0–8.2 (d, 2 H, ArH's); 7.3–7.8 (m, 7 H, ArH's); 4.8 (s, 2 H, SCH_2); 2.6 (s, 3 H, $COCH_3$); 2.4 (s, 3 H, CH_3 of tolyl residue); 1.9 (s, 3 H, CH_3 at C-6)
2b	140–141 (73)	$C_{25}H_{22}N_2O_3S$ (430.52)	IR: 2200 (C≡N); 1690 (2 C=O). ^{1}H-NMR ($CDCl_3$): 7.0–7.8 (m, 8 H, ArH's); 4.7 (s, 2 H, SCH_2); 3.9 (s, 3 H, OCH_3); 2.6 (s, 3 H, $COCH_3$); 2.4 (s, 3 H, CH_3 of tolyl residue); 1.9 (s, 3 H, CH_3 at C-6)
2c	158–159 (70)	$C_{24}H_{19}ClN_2O_2S$ (434.94)	IR: 2200 (C≡N); 1690 (2 C=O)
3a	191–192 (89)	$C_{24}H_{20}N_2O_2S$ (400.50)	IR: 3500, 3300 (NH_2); 1690 (2 C=O). ^{1}H-NMR ($CDCl_3$): 7.2–7.9 (m, 9 H, ArH's); 6.6 (s, 2 H, NH_2); 2.6 (s, 3 H, $COCH_3$); 2.4 (s, 3 H,CH_3 of tolyl residue); 1.9 (s, 3 H, CH_3 at C-6)
3b	179–180 (82)	$C_{25}H_{22}N_2O_3S$ (430.52)	IR: 3500, 3300 (NH_2); 1690 (2 C=O). ^{1}H-NMR ($CDCl_3$): 7.0–7.8 (m, 8 H, ArH's); 6.7 (s, 2 H, NH_2); 3.9 (s, 3 H, OCH_3); 2.6 (s, 3 H, $COCH_3$); 2.4 (s, 3 H, CH_3 of tolyl residue); 2.0 (s, 3 H, CH_3 at C-6)
3c	206–207 (86)	$C_{24}H_{19}ClN_2O_2S$ (434.94)	IR: 3500, 3300 (NH_2); 1690 (2 C=O)
4a	184–185 (93)	$C_{24}H_{21}N_3O_3S$ (431.51)	IR: 3200 (NH); 2200 (C≡N); 1700 (C=O); 1660 (C=O)
4b	184–186 (90)	$C_{25}H_{23}N_3O_3S$ (445.54)	IR: 3200 (NH); 2200 (C≡N); 1700 (C=O); 1660 (C=O). ^{1}H-NMR ($CDCl_3$): 8.9 (s, 1 H, NH); 7.0–7.6 (m, 8 H, ArH's); 4.1 (s, 2 H, SCH_2); 3.9 (s, 3 H, OCH_3); 2.6 (s, 3 H, $COCH_3$); 2.4 (s, 3 H,CH_3 of tolyl residue); 1.9 (s, 3 H, CH_3 at C-6). MS: 445.6 ($M^{+\bullet}$, 63%); 339.5 ($M^{+\bullet}$-$NHC_6H_4CH_3^{\bullet}$, 100%); 311.5 ($M^{+\bullet}$-$CONHC_6H_4CH_3^{\bullet}$, 27%); 107.2 ($C_6H_4OCH_3^+$, 22%); 43.1(CH_3CO^+, 12%)
4c	192–193 (90)	$C_{24}H_{20}ClN_3O_3S$ (465.95)	IR: 3200 (NH); 2200 (C≡N); 1700 (C=O); 1660 (C=O)
4d	156–157 (89)	$C_{23}H_{18}ClN_3O_2S$ (435.93)	IR: 3200 (NH); 2200 (C≡N); 1700 (C=O); 1660 (C=O)
4e	223–224 (80)	$C_{24}H_{20}ClN_3O_2S$ (449.95)	IR: 3200 (NH); 2200 (C≡N); 1700 (C=O); 1660 (C=O). ^{1}H-NMR ($CDCl_3$): 8.8 (s, 1 H, NH); 7.3–7.7 (m, 8 H, ArH's); 4.0 (s, 2 H, SCH_2); 2.8 (s, 3 H, $COCH_3$); 2.4 (s, 3 H,CH_3 of tolyl residue); 2.2 (s, 3 H, CH_3 at C-6)
4f	215–216 (78)	$C_{23}H_{17}Cl_2N_3O_2S$ (470.38)	IR: 3200 (NH); 2200 (C≡N); 1700 (C=O); 1660 (C=O)
5a	202–203 (95)	$C_{24}H_{21}N_3O_3S$ (431.51)	IR: 3500, 3300 (NH_2); 3200 (NH); 1690 (C=O); 1640 (C=O)
5b	148–149 (93)	$C_{25}H_{23}N_3O_3S$ (445.54)	IR: 3500, 3300 (NH_2); 3200 (NH); 1690 (C=O); 1640 (C=O). ^{1}H-NMR ($CDCl_3$): 9.3 (s, 1 H, NH); 7.0–7.6 (m, 8 H, ArH's); 5.8 (s, 2 H, NH_2); 3.9 (s, 3 H, OCH_3); 2.6 (s, 3 H, $COCH_3$); 2.4 (s, 3 H, CH_3 of tolyl residue); 2.1 (s, 3 H, CH_3 at C-6). MS: 445.6 ($M^{+\bullet}$, 55%); 339.5($M^{+\bullet}$-$NHC_6H_4CH_3^{\bullet}$, 100%); 107.2 ($C_6H_4OCH_3^+$, 12%); 43.1 (CH_3CO^+, 5%)
5c	160–161 (89)	$C_{24}H_{20}ClN_3O_3S$ (465.95)	IR: 3500, 3300 (NH_2); 3200 (NH); 1690 (C=O); 1640 (C=O)
5d	176–177 (92)	$C_{23}H_{18}ClN_3O_2S$ (435.93)	IR: 3500, 3300 (NH_2); 3200 (NH); 1690 (C=O); 1640 (C=O)
5e	153–154 (85)	$C_{24}H_{20}ClN_3O_2S$ (449.95)	IR: 3500, 3300 (NH_2); 3200 (NH); 1690 (C=O); 1640 (C=O). ^{1}H-NMR ($CDCl_3$): 9.2 (s, 1 H, NH); 7.2–7.7 (m, 8 H, ArH's); 5.7 (s, 2 H, NH_2); 2.7 (s, 3 H, $COCH_3$); 2.4 (s, 3 H,CH_3 of tolyl residue); 2.1 (s, 3 H, CH_3 at C-6)
5f	189–190 (80)	$C_{23}H_{17}Cl_2N_3O_2S$ (470.38)	IR: 3500, 3300 (NH_2); 3200 (NH); 1690 (C=O); 1640 (C=O)
6a	122–123 (94)	$C_{17}H_{13}N_3OS$ (307.37)	IR: 2220, 2200 (2 C≡N); 1690 (C=O). ^{1}H-NMR ($CDCl_3$): 7.3–7.7 (m, 5 H, ArH's); 4.2 (s, 2 H, SCH_2); 2.7 (s, 3 H, $COCH_3$); 1.9 (s, 3 H, CH_3 at C-6)
6b	163–164 (90)	$C_{18}H_{15}N_3O_2S$ (337.40)	IR: 2220, 2200 (2 C≡N); 1690 (C=O). ^{1}H-NMR ($CDCl_3$): 7.0–7.5 (2d, 4 H, ArH's); 4.2 (s, 2 H, SCH_2); 3.8 (s, 3 H, OCH_3); 2.6 (s, 3 H, $COCH_3$); 1.9 (s, 3 H, CH_3 at C-6)
6c	154–155 (89)	$C_{17}H_{12}ClN_3OS$ (341.81)	IR: 2220, 2200 (2 C≡N); 1690 (C=O)
7a	200–201 (95)	$C_{17}H_{13}N_3OS$ (307.37)	IR: 3450, 3300 (NH_2); 2200 (C≡N); 1690 (C=O). ^{1}H-NMR ($CDCl_3$): 7.3–7.7 (m, 5 H, ArH's); 4.4 (s, 2 H, NH_2); 2.7 (s, 3 H, $COCH_3$); 2.0 (s, 3 H, CH_3 at C-6)
7b	184–185 (92)	$C_{18}H_{15}N_3O_2S$ (337.40)	IR: 3450, 3300 (NH_2); 2200 (C≡N); 1690 (C=O). ^{1}H-NMR ($CDCl_3$): 7.27–7.29 (d, J = 8.5 Hz, 2 H, ArH's); 7.04–7.06 (d, J = 8.5 Hz, 2 H, ArH's); 4.00 (s, 2 H, NH_2); 3.89 (s, 3 H, OCH_3); 2.59 (s, 3 H, $COCH_3$); 2.00 (s, 3 H, CH_3 at C-6)
7c	187–188 (87)	$C_{17}H_{12}ClN_3OS$ (341.81)	IR: 3450, 3300 (NH_2); 2200 (C≡N); 1690 (C=O)

Table 1: (Continued)

Compd.	M.P. (°C) (yield: %)	Formula[a] (M.W.)	Spectral data
8a	300–301 (92)	$C_{25}H_{19}N_3O_3S$ (441.50)	IR: 1690, 1670 (2 C=O). ^{1}H-NMR (CF_3CO_2D): 8.8 (s, 1 H, CH pyrimidine), 7.3–7.8 (m, 9 H, ArH's); 4.2 (s, 3 H, OCH_3); 3.2 (s, 3 H, $COCH_3$); 2.3 (s, 3 H, CH_3 at C-7)
8b	339–340 (87)	$C_{26}H_{21}N_3O_3S$ (455.53)	IR: 1690, 1670 (2 C=O)
8c	309–310 (94)	$C_{25}H_{18}ClN_3O_3S$ (475.95)	IR: 1690, 1670 (2 C=O). MS; 475 ($M^{+\bullet}$, 100%); 460 (M^+-$CH_3^\bullet$, 100%)
8d	242–243 (92)	$C_{24}H_{16}ClN_3O_2S$ (445.92)	IR: 1690, 1670 (2 C=O). ^{1}H-NMR ($CDCl_3$): 8.3 (s, 1 H, CH pyrimidine), 7.3–7.7 (m, 9 H, ArH's); 2.7 (s, 3 H, $COCH_3$); 2.0 (s, 3 H, CH_3 at C-7)
8e	284–285 (89)	$C_{25}H_{18}ClN_3O_2S$ (459.95)	IR: 1690, 1670 (2 C=O)
8f	268–269 (90)	$C_{24}H_{15}Cl_2N_3O_2S$ (480.37)	IR: IR: 1690, 1670 (2 C=O). ^{1}H-NMR ($CDCl_3$): 8.3 (s, 1 H, CH pyrimidine), 7.3–7.7 (m, 8 H, ArH's); 2.8 (s, 3 H, $COCH_3$); 2.1 (s, 3 H, CH_3 at C-7)
9a	253–254 (80)	$C_{24}H_{18}N_4O_3S$ (442.49)	IR: IR: 1690, 1670 (2 C=O). ^{1}H-NMR ($CDCl_3$): 7.1–7.6 (m, 9 H, ArH's); 3.9 (s, 3 H, OCH_3); 2.7 (s, 3 H, $COCH_3$); 2.0 (s, 3 H, CH_3 at C-7). MS: 442 ($M^{+\bullet}$, 81%); 322 ($M^{+\bullet}$-$COCH_3^\bullet$-$C_6H_5^\bullet$); 414 (M+-N_2, 15%); 399 (M^+-$COCH_3^\bullet$, 40%); 43 ($COCH_3^+$, 20%)
9b	234–235 (83)	$C_{25}H_{20}N_4O_3S$ (456.52)	IR: 1690, 1670 (2 C=O). ^{1}H-NMR ($CDCl_3$): 7.0–7.7 (m, 8 H, ArH's); 3.9 (s, 3 H, OCH_3); 2.8 (s, 3 H, $COCH_3$); 2.5 (s, 3 H, CH_3 of tolyl residue); 2.1 (s, 3 H, CH_3 at C-7)
9c	261–262 (90)	$C_{24}H_{17}ClN_4O_3S$ (476.94)	IR: 1690 (C=O); 1670 (C=O)
9d	241–242 (87)	$C_{23}H_{15}ClN_4O_2S$ (446.92)	IR: 1690, 1670 (2 C=O). ^{1}H-NMR ($CDCl_3$): 7.3–7.7 (m, 9 H, ArH's); 2.7 (s, 3 H, $COCH_3$); 2.0 (s, 3 H, CH_3 at C-7)
9e	225–226 (94)	$C_{24}H_{17}ClN_4O_2S$ (460.94)	IR: 1690, 1670 (2 C=O)
9f	256–257 (85)	$C_{23}H_{14}Cl_2N_4O_2S$ (481.36)	IR: 1690, 1670 (2 C=O). ^{1}H-NMR ($CDCl_3$): 7.3–7.7 (m, 8 H, ArH's); 2.7 (s, 3 H, $COCH_3$); 2.0 (s, 3 H, CH_3 at C-7)
10	>360 (80)	$C_{19}H_{15}N_3O_2S_3$ (413.55)	IR: 3330 (NH); 1690 (C=O)
11	158 (86)	$C_{21}H_{19}N_3O_2S_3$ (441.60)	IR: 1690 (C=O). ^{1}H-NMR ($CDCl_3$): 7.26–7.28 (d, J = 8.6 Hz, 2 H, ArH's); 6.96–6.98 (d, J = 8.6 Hz, 2 H, ArH's); 3.84 (s, 3 H, OCH_3); 2.68 (s, 3 H, SCH_3); 2.67 (s, 3 H, $COCH_3$); 1.97 (s, 3 H, SCH_3); 1.96 (s, 3 H, CH_3 at C-7)
12	353–354 (77)	$C_{25}H_{20}N_4O_2S_2$ (472.59)	IR: 3350, 3250 (2 NH); 1700 (C=O); 1640 (C=N). MS: 472 ($M^{+\bullet}$, 100%); 457 ($M^{+\bullet}$-$CH_3^\bullet$, 9%); 414 ($M^{+\bullet}$-CH_3-$COCH_3^\bullet$, 22%); 77 ($C_6H_5^+$, 15%); 43 ($COCH_3^+$, 15%)
13a	264–265 (78)	$C_{18}H_{16}N_6O_2S$ (380.42)	IR: 3500, 3400, 3300 (NH_2, NH); 1690 (C=O). MS: 380 ($M^{+\bullet}$, 100%); 352 ($M^{+\bullet}$-N_2, 90%); 337 ($M^{+\bullet}$-N_2-$CH_3^\bullet$, 57%); 77 ($C_6H_5^+$, 15%); 43 ($COCH_3^+$, 15%)
13b	270–271 (80)	$C_{17}H_{13}ClN_6OS$ (384.84)	IR: 3500, 3400, 3300 (NH_2, NH); 1690 (C=O)
14a	210–211 (73)	$C_{19}H_{14}N_6O_2S$ (390.42)	IR: 1690 (C=O). ^{1}H-NMR ($CDCl_3$): 8.8 (s, 1 H, CH pyrimidine); 7.0–7.5 (2d, J = 9.0 Hz, 4 H, ArH's); 4.0 (s, 3 H, OCH_3); 2.7 (s, 3 H, $COCH_3$); 2.1 (s, 3 H, CH_3 at C-7)
14b	223–224 (76)	$C_{18}H_{11}ClN_6OS$ (394.84)	IR: 1690 (C=O)
15a	187–188 (88)	$C_{21}H_{19}N_3O_3S$ (393.46)	IR: 2200 (C≡N); 1700 (C=O)
15b	196–197 (90)	$C_{20}H_{16}ClN_3O_2S$ (397.88)	IR: 2200 (C≡N); 1700 (C=O). ^{1}H-NMR ($CDCl_3$): 7.7 (s, 1 H, N=CH); 7.2–7.6 (2d, J = 9.0 Hz, 4 H, ArH's); 3.5–3.7 (q, J = 7.0 Hz, 2 H, OCH_2); 2.6 (s, 3 H, $COCH_3$); 2.0 (s, 3 H, CH_3 at C-6); 1.0–1.3 (t, J = 7.0 Hz, 3 H, CH_3 of ethoxy group)
16a	234–235 (91)	$C_{19}H_{17}N_5O_2S$ (379.44)	IR: 3300, 3270, 3200 (NH, NH_2); 1690 (C=O), 1620 (C=N). ^{1}H-NMR ($CDCl_3$): 7.82 (s, 1 H, CH pyrimidine); 7.14–7.16 (d, J = 8.3 Hz, 2 H, ArH's); 6.83–6.85 (d, J = 8.3 Hz, 2 H, ArH's); 5.38 (s, 2 H, NH_2); 3.77 (s, 3 H, OCH_3); 2.49 (s, 3 H, $COCH_3$); 1.81 (s, 3 H, CH_3 at C-7)
16b	254–256 (87)	$C_{18}H_{14}ClN_5OS$ (383.86)	IR: 3300, 3270, 3200 (NH, NH_2); 1690 (C=O), 1620 (C=N)
17	194–195 (89)	$C_{24}H_{21}N_5O_4S$ (475.53)	IR: 1730 (C=O); 1690 (C=O). ^{1}H-NMR ($CDCl_3$): 9.06 (s, 1 H, CH pyrimidine); 7.34–7.36 (d, J = 8.8 Hz, 2 H, ArH's); 7.02–7.04 (d, J = 8.8 Hz, 2 H, ArH's); 4.22–4.28 (q, J = 7.0 Hz, 2 H, OCH_2); 4.02 (s, 2 H, CH_2CO); 3.92 (s, 3 H, OCH_3); 2.70 (s, 3 H, $COCH_3$); 1.99 (s, 3 H, CH_3 at C-9; 1.24–1.28 (t, J = 7.0, Hz, 3 H, CH_3 of ester). MS: 475 ($M^{+\bullet}$, 100%); 460 ($M^{+\bullet}$-$CH_3^\bullet$, 87%); 402 ($M^{+\bullet}$-$CO_2C_2H_5^\bullet$, 19%); 388 ($M^{+\bullet}$-$CH_2CO_2C_2H_5^\bullet$, 34%)

[a] Satisfactory elemental analyses were obtained for all compounds

Table 2: Antimicrobial activity of some representative compounds

Compd.	*B. cereus*	*S. aureus*	*Proteus* sp.	*A. fumigatus*
2c	+	+++	−	−
3c	++	++	++	−
4a	++	+	+	−
4f	+	++	−	−
5f	++	−	−	−
6b	++	++	+	−
7b	++	+	−	++
8d	+	−	+++	−
8e	++	+++	−	−
8f	+	+	+	−
9a	+++	++	+++	−
9e	+++	+	++	−
10	++	++	−	−
11	+	+	++	−
13a	++	+++	++	++
15b	+	++	+	−
16b	+++	+++	−	++
17	++	+	++	−
Streptomycin®	+++	++	+++	+
Tyrosyd®	+	+	+	+++

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

3.14. 8-Acetyl-3-amino-9-aryl-3,4-dihydro-4-imino-7-methylpyrido-[3′,2′:4,5]thieno[3,2-d]pyrimidine (16a, b)

To a stirred suspension of **15a, b** (0.03 mol) in dioxane (100 ml), $NH_2NH_2 \cdot H_2O$ 80% (5 ml, 0.08 mol) was added. The reaction mixture was stirred at room temperature for 2 h. The precipitate which formed was collected and recrystallized from C_2H_5OH as white needles of **16a, b**.

3.15. Ethyl (8-acetyl-7-(4'methoxyphenyl)-9-methyl-S-triazolo[2″,3″-c]-pyrido[3′,2′:4,5]thieno[2,3-e]pyrimidine-2-yl)acetate (17)

A suspension of **16a** (1.9 g, 0.005 mol) in $CH_2(CO_2C_2H_5)_2$ (20 ml) was gently refluxed for 4 h, then cooled and triturated with C_2H_5OH (15 ml). The separated product was collected and recrystallized from C_2H_5OH as pale yellow needles.

3.16. Biological screening

The screened compounds were dissolved in DMSO to get a solution of 0.03 molar. Filter paper discs (Whatman No. 1 filter paper, 5 mm diameter) were saturated with this solution. The discs were placed on the surface of solidified Nutrient agar dishes seeded by the tested bacteria or Czapek′s Dox agar dishes seeded by the tested fungi. The diameters of inhibition zones (mm) were measured after 48 h of incubation (37 °C for bacteria; 28 °C for fungi). Discs saturated with DMSO were used as control. Streptomycin was used as a reference substance for testing antibacterial activity. Tioconazole (Tyrosyd®) was used as a reference substance for testing antifungal activity.

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