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Synthesis of Novel Thieno[2,3-*c*]pyridazines and Related Heterocycles

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Summary. The reaction of ethyl 2,3-dihydro-5,6-diphenyl-3-thioxopyridazine-4-carboxylate with ω-bromoacetophenones, chloro-*N*-arylacetamides, chloroacetonitrile, ethyl chloroacetate, or chloroacetone furnished the corresponding 4,5-diphenyl-3-hydroxy thieno [2,3-*c*]pyridazines. 2-Cyano-, 2-ethoxycabonyl-, and 2-acetyl-4,5-diphenyl-3-hydroxythieno[2,3-*c*]pyridazines were employed as precursors in the synthesis of some novel furo [2′,3′:4,5]thieno[2,3-*c*]pyridazines, pyrano-[2′,3′:4,5]thieno[2,3-*c*]pyridazines, and thieno[2,3-*c*]pyridazines. The antibacterial and antifungal activities of some of the compounds are reported.

Keywords. Biological activity; Furo[2′,3′:4,5]thieno[2,3-*c*]pyridazines; Pyrano[2′,3′:4,5]thieno[2,3-*c*]pyridazines; Thieno[2,3-*c*]pyridazines.

Synthese neuer Thieno[2,3-*c*]pyridazine und verwandter Heterocyclen

Zusammenfassung. Die Reaktion von Ethyl-2,3-dihydro-5,6-diphenyl-3-thioxo-pyridazin-4-carboxylat mit ω-Bromacetophenon, Chlor-*N*-arylacetamiden, Chloracetonitril, Ethylchloracetat oder Chloraceton ergab die entsprechenden 4,5-Diphenyl-3-hydroxythieno[2,3-*c*]pyridazine. 2-Cyano-, 2-Ethoxycabonyl- und 2-Acetyl-4,5-diphenyl-3-hydroxythieno[2,3-*c*]pyridazine wurden als Vorläufer neuer Furo[2′,3′:4,5]thieno[2,3-*c*]pyridazine, Pyrano[2′,3′:4,5]thieno[2,3-*c*]pyridazine und Thieno[2,3-*c*]pyridazine eingesetzt. Die antibakteriellen und fungistatischen Eigenschaften einiger Verbindungen werden mitgeteilt.

Introduction

Pyridazine derivatives and heterocyclic annelated pyridazines continue to attract interest due to a wide spectrum of biological activities [1–6]. In particular, some thienopyridazines have been reported to possess considerable antiasthmatic [7] and fibrinolytic activities [8]. In view of the above facts and in continuation of our program directed towards the synthesis of new polyheterocyclic systems containing a thiophene moiety with potential biological properties [9–12], we synthesized the title compounds and evaluated their antimicrobial properties.

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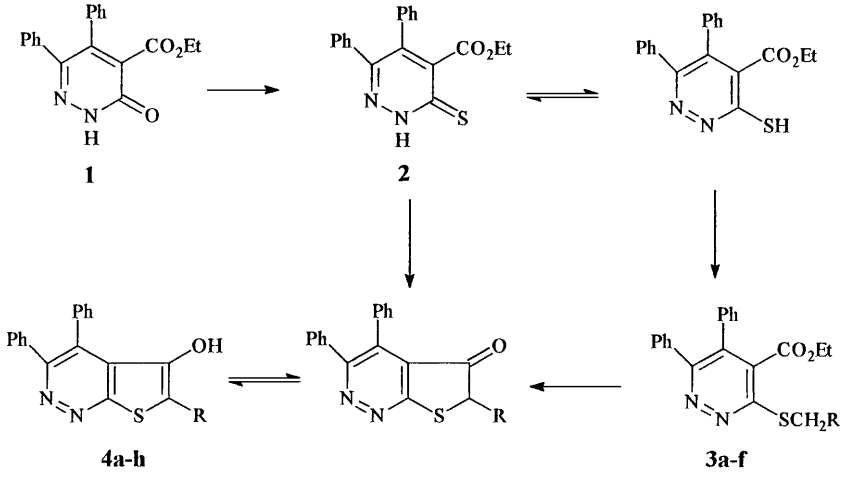
Results and Discussion

Syntheses

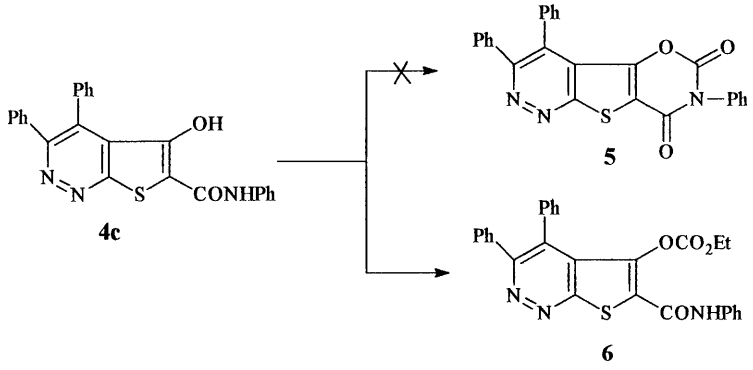
The thiation of ethyl 2,3-dihydro-5,6-diphenyl-4-oxopyridazine-4-carboxylate (**1**) [13] using P_2S_5 in dry pyridine resulted in the formation of thioxo derivative **2** which was used as a starting material in the synthesis of the target heterocycles. Thus, the reaction of **2** with halocompounds like ω-bromo-acetophenones, chloro-*N*-arylacetamides, or chloroacetonitrile in refluxing ethanol containing an equimolar quantity of sodium acetate gave the corresponding S-alkylated products **3a–f**. Cyclization of **3a–f** to the corresponding thienopyridazines **4a–f** was achieved by refluxing the educts in ethanol containing an excess of fused sodium acetate or catalytic amounts of sodium ethoxide. Compound **2** was also reacted with ethyl chloroacetate and/or chloroacetone in the presence of fused sodium acetate to give the thienopyridazines **4g**, **h**. (Scheme 1). Reaction of the vicinal hydroxycarbamoyl derivative **4c** with ethyl chloroformate afforded the thienopyridazine derivative **6** instead of the expected oxazine-2,4-dione **5** (Scheme 2).

An attempt to synthesize novel heterocyclic systems containing the furo-[2′,3′:4,5]thieno[2,3-*c*]pyridazine moiety involved reaction of **4f** with ethyl chloroacetate in *DMF* at 100°C for 2 h in the presence of K_2CO_3 to give ethyl-(2-cyano-4,5-diphenylthieno[2,3-*c*]pyridazin-3-yloxy)-acetate (**7**); the reaction of **4f**

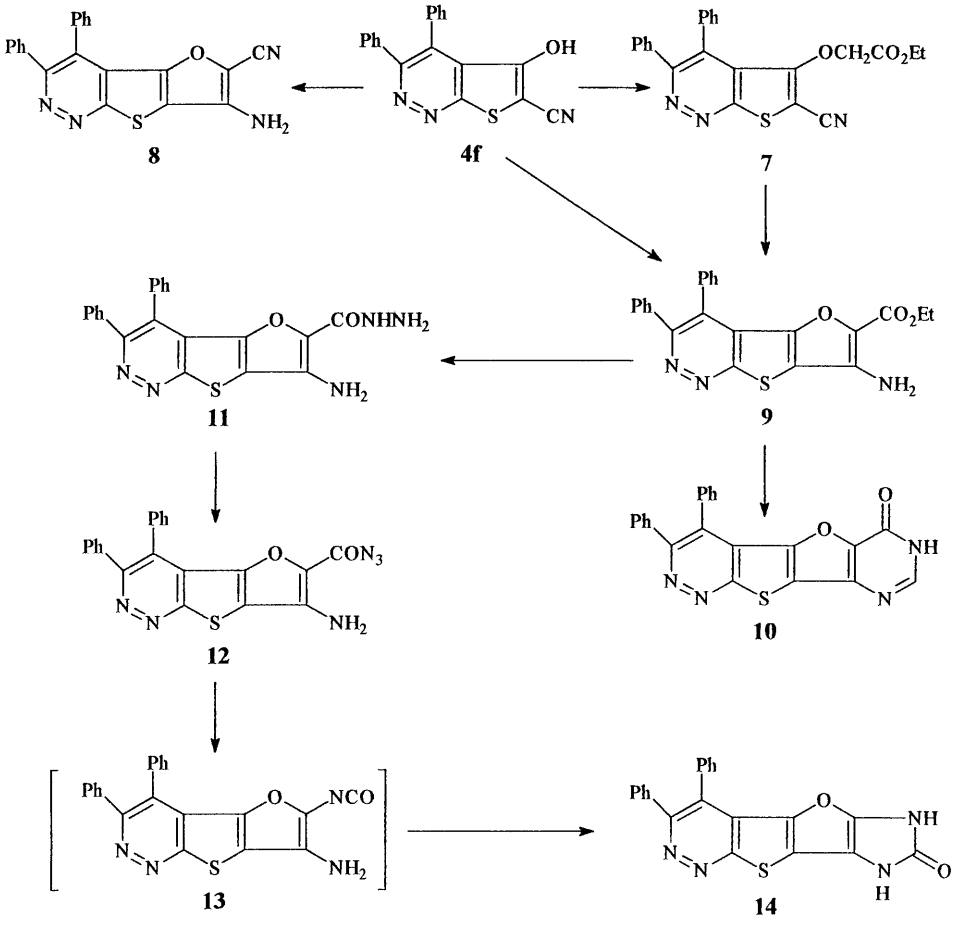


3, 4	*R*	3, 4	*R*
a	COPh	**e**	$CONHC_6H_4Cl(p)$
b	p-COC_6H_4Br	**f**	CN
c	CONHPh	**g**	CO_2Et
d	$CONHC_6H_4Me(p)$	**h**	COMe

Scheme 1



Scheme 2



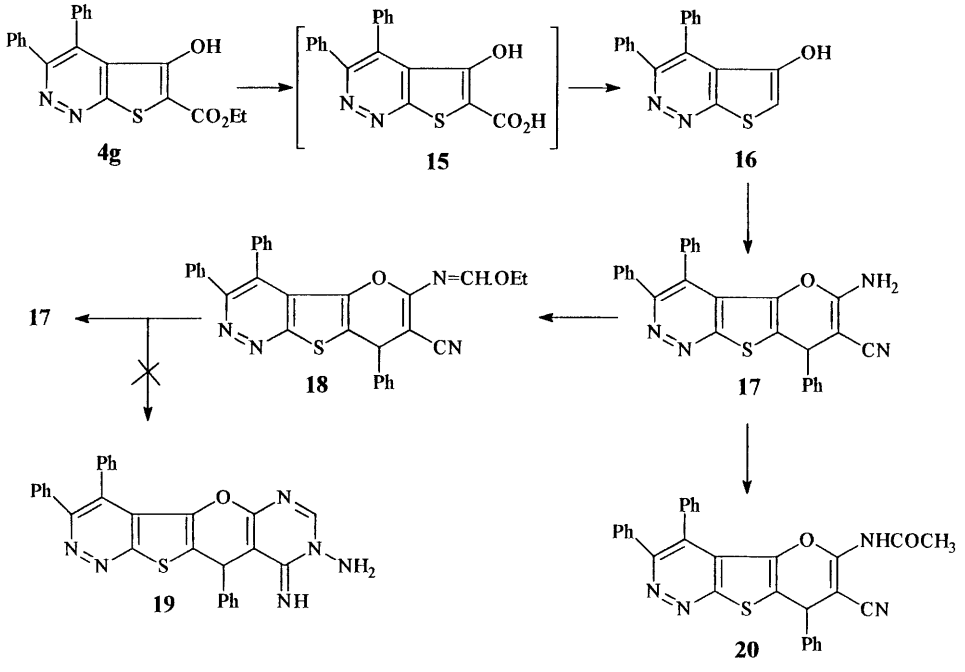
Scheme 3

with chloroacetonitrile under the same conditions afforded 3-amino-2-cyano-7,8-diphenylfuro[2′,3′:4,5]thieno[2,3-*c*]pyridazine (**8**). Upon treatment with sodium ethoxide in refluxing ethanol, **7** underwent *Thorpe-Ziegler* cyclization to furnish ethyl 3-amino-7,8-diphenylfuro[2′,3′:4,5]thieno[2,3-*c*]pyridazine-2-carboxylate (**9**)

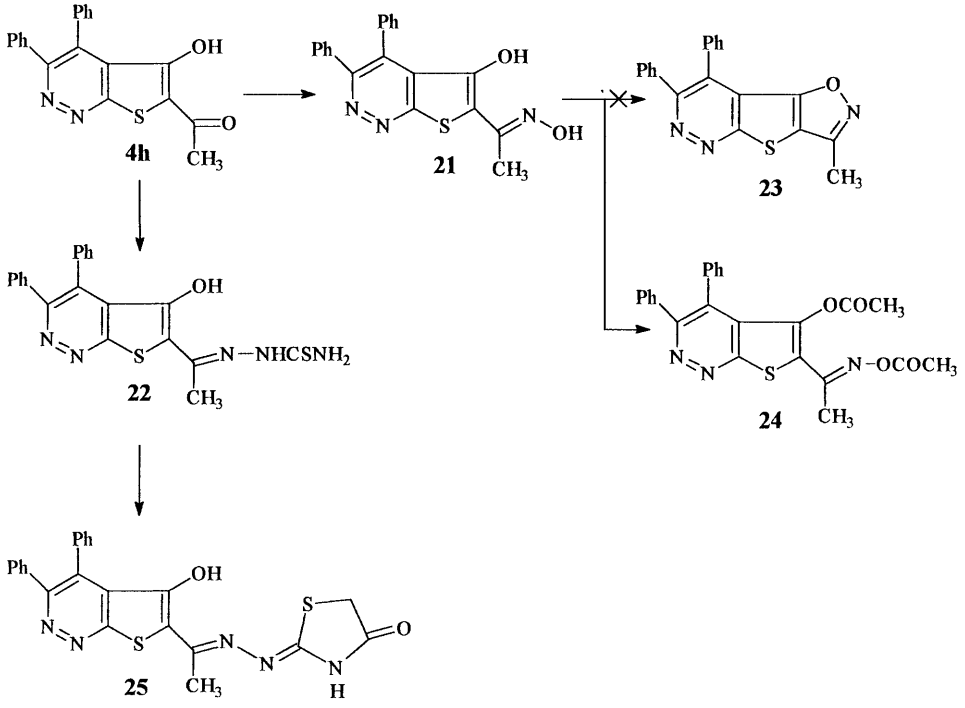
which could also be obtained by heating **4f** with ethyl chloroacetate in *DMF* at 100°C for 10 h in the presence of K_2CO_3. Heating of **9** with formamide resulted in the formation of the pyrimidofurothienopyridazine derivative **10**. The reaction of **9** with hydrazine hydrate gave the carbohydrazide **11**, which on treatment with sodium nitrite in glacial acetic acid yielded the corresponding carbonylazide **12**. On refluxing of **12** in dry toluene, *Curtius* rearrangement to imidazolo-[4,″5″:4,5]furo[2′,3′:4,5]thieno[2,3-*c*]pyridazine **14** occurred *via* the intermediate isocyanate derivative **13** (Scheme 3).

The present investigation was extended to the synthesis of novel pyrano-[2′,3′:4,5]thieno[2,3-*c*]pyridazines starting from the vicinal hydroxyester **4g**. Refluxing of **4g** in an ethanolic solution of sodium hydroxide resulted in hydrolysis followed by spontanous decarboxylation to give 4,5-diphenyl-3-hydroxy-thieno[2,3-*c*]pyridazine (**16**). The cycloaddition reaction of **16** with benzylidene-malononitrile afforded 2-amino-3-cyano-4,8,9-triphenyl-4*H*-pyrano[2′,3′:4,5]-thieno[2,3-*c*]pyridazine (**17**) in nearly quantitative yield. The condensation of **17** with triethyl orthoformate yielded methanimidate **18** which upon treatment with hydrazine hydrate according to literature [14] did not give the pyrimidopyr-anothienopyridazine **19**, most probably due to -N=C- fission, and compound **17** was recovered. Heating of **17** with acetic anhydride at reflux temperature led to the formation of the monoacetyl derivative **20** (Scheme 4).

2-Acetyl-4,5-diphenyl-3-hydroxythieno[2,3-*c*]pyridazine (**4h**) proved also to be a versatile synthon for the preparation of other new thienopyridazines. Thus, its condensation with hydroxylamine or thiosemicarbazide gave the corresponding oxime **21** and thiosemicarbazone **22**. An attempt to cyclize **21** to the isoxazolo-



Scheme 4



Scheme 5

thienopyridazine **23** by heating with acetic anhydride failed, and the biacetyl derivative **24** was isolated instead. The interaction of **22** with ethyl chloroacetate in refluxing ethanol in the presence of fused sodium acetate produced the thiazolidinone derivative **25** (Scheme 5).

The structural formulas of all newly synthesized compounds were confirmed by elemental and spectroscopic analyses (*cf.* Experimental). Moreover, the IR and ^{1}H NMR spectroscopic data revealed that compounds **4a–f** and **16** exist predominantly in their enol form. This fact was supported by the aforementioned behaviour of compounds **4c**, **4f**, and **16** towards some reagents, such as ethyl chloroformate, ethyl chloroacetate/chloroacetonitrile, or benzylidenemalononitrile.

Screening for antimicrobial activities

Compounds **3f**, **4a**, **4c**, **4g**, **7**, **9**, **14**, **16**, **17**, and **20** were tested *in vitro* for their antimicrobial activities against four straines of bacteria (*Staphylococcus aureus*, *Sarcina spp.*, *Pseudomonas aeruginosa*, *Bacillus cereus*) and four species of fungi (*Aspergillus fumigatus*, *Aspergillus niger*, *Aspergillus temcus*, *Fusarium solani*) using the filter paper disc method [15, 16]. The screening results given in Table 1 indicate that among the tested compounds only four (**3f**, **4a**, **4c**, and **16**) showed good growth inhibition against *Sarcina spp.* and *Bacillus cereus*. Compounds **3f** and **4c** are also active against *Staphylococcus aureus*. However, concerning the antifungal activities, only **4a** showed a considerable activity against *Aspergillus fumigatus* and *Aspergillus temcus*. The rest of the tested compounds showed no activity against bacterial and fungal species under investigation.

Experimental

All melting points are uncorrected and were measured on a Fisher-John apparatus. IR spectra: Shimadzu 470 IR-spectrophotometer (KBr; ν_{max} in cm^{-1}); ^1H NMR spectra: Varian EM-390, 90 MHz, *TMS* as internal standard (δ in ppm); MS: Jeol JMS-600; elemental analyses: Perkin-Elmer 240C elemental analyser. The results of the analyses were in good agreement with the calculated values.

Ethyl 2,3-dihydro-5,6-diphenyl-3-oxopyridazine-4-carboxylate (**1**)

1 was prepared according to Ref. [13].

Ethyl 2,3-dihydro-5,6-diphenyl-3-thioxopyridazine-4-carboxylate (**2**; $C_{19}H_{16}N_2O_2S$)

A mixture of 3.2 g **1** (0.01 mol) and 2.22 g P_2S_5 (0.01 mol) in 25 cm^3 dry pyridine was heated under reflux for 5 h. The reaction mixture was cooled, poured onto 50 cm^3 cold H_2O, and acidified with dil. HCl. The precipitated solid was collected and crystallized from ethanol to give **2** in the form of yellow needles.

Yield: 2.4 g (70%); m.p.: 230°C; IR: $\nu_{max} = 3100$ (NH), 2900–2750 (SH), 1720 (C=O)cm^{-1} ; ^1H NMR (*DMSO*-d_6): $\delta = 13.5$ (s, 1H, NH), 7.0–7.5 (m, 10H, ArH), 4.0–4.4 (q, 2H, CH_2), 1.2–1.5 (t, 3H, CH_3) ppm.

Reaction of thioxopyridazine **2** *with halocompounds; general procedure*

A mixture of 1.68 g **2** (0.005 mol), 0.68 g sodium acetate trihydrate (0.005 mol), and the respective halocompound (0.005 mol) in 30 cm^3 ethanol was refluxed for 2 h. The product which separated on cooling was collected and recrystallized from the proper solvent to give **3a–f**.

Ethyl 5,6-diphenyl-3-phenacylthiopyridazine-4-carboxylate (**3a**; $C_{27}H_{22}N_2O_3S$)

Prepared from **2** and phenacyl bromide; yield: 1.8 g (79%); m.p.: 124–126°C (methanol); IR: $\nu_{max} = 1720$ (C=O, ester), 1680 (C=O)cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 7.0$–8.3 (m, 15H, ArH), 5.1 (s, 2H, SCH_2), 4.0–4.3 (q, 2H, OCH_2), 0.9–1.2 (t, 3H, CH_3) ppm.

Ethyl 3-p-bromophenacylthio-5,6-diphenylpyridazine-4-carboxylate (**3b**; $C_{27}H_{21}BrN_2O_3S$)

Prepared from **2** and *p*-bromophenacyl bromide; yield: 2.35 g (85%); m.p.: 150–151°C (ethanol); IR: $\nu_{max} = 1720$ (C=O, ester), 1680 (C=O) cm^{-1}.

Ethyl 5,6-diphenyl-3-phenylcarbamoylmethylthiopyridazine-4-carboxylate (**3c**; $C_{27}H_{23}N_3O_3S$)

Prepared from **2** and chloro-*N*-phenylacetamide; yield: 2.0 g (85%); m.p.: 145–146°C (ethanol); IR: $\nu_{max} = 3300$ (NH), 1720 (C=O, ester), 1670 (C=O, amide) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 10.6$ (s, 1H, NH), 7.0–7.7 (m, 15H, ArH), 4.0 (s, 2H, SCH_2), 4.2–4.5 (q, 2H, OCH_2), 1.1–1.4 (t, 3H, CH_3) ppm.

Ethyl 5,6-diphenyl-3-p-tolylcarbamoylmethylthiopyridazine-4-carboxylate (**3d**; $C_{28}H_{25}N_3O_3S$)

Prepared from **2** and chloro-*N*-*p*-tolylacetamide; yield: 2.1 g (87%); m.p.: 160–161°C (ethanol); IR: $\nu_{max} = 3300$ (NH), 1720 (C=O, ester), 1670 (C=O, amide) cm^{-1}.

Ethyl 3-p-chlorophenylcarbamoylmethylthio-5,6-diphenylpyridazine-4-carboxylate (**3e**: $C_{27}H_{22}ClN_3O_3S$)

Prepared from **2** and chloro-*N*-*p*-chlorophenylacetamide; yield: 2.1 g (83%); m.p.: 150–152°C (ethanol); IR: $\nu_{max} = 3300$ (NH), 1720 (C=O, ester), 1670 (C=O, amide) cm^{-1}.

Ethyl 3-cyanomethylthio-5,6-diphenylpyridazine-4-carboxylate (**3f**; $C_{21}H_{17}N_3O_2S$)

Prepared from **2** and chloroacetonitrile; yield: 1.5 g (80%); m.p.: 202–203°C (benzene); IR: $\nu_{max} = 2210$ (C≡N), 1730 (C=O, ester)cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.0$–7.7 (m, 15H, ArH), 5.4 (s, 2H, SCH_2), 4.2–4.5 (q, 2H, OCH_2), 1.1–1.4 (t, 3H, CH_3) ppm.

4,5-Diphenyl-3-hydroxy-2-substituted-thieno[2,3-c]pyridazines **4a–f**; *general procedure*

A) To a suspension of **3a–f** (0.005 mol) in 30 cm^3 abs. ethanol, 1.65 g fused sodium acetate (0.02 mol) or sodium ethoxide solution (0.3 g sodium in 15 cm^3 abs. ethanol) was added. The resulting mixture was refluxed for 3 h, cooled, diluted with 50 cm^3 H_2O, and acidified with dil. HCl. The solid formed was collected and crystallized from ethanol to give **4a–f**.

B) A mixture of 1.68 g **2** (0.005 mol), 1.65 g fused sodium acetate (0.02 mol), and the respective halocompound (0.005 mol) in 35 cm^3 ethanol was refluxed for 10 h. The reaction mixture was diluted with 50 cm^3 H_2O and acidified with dil. HCl. The solid product formed was collected and crystallized from ethanol to give **4a–f**. The products obtained by the two synthetic routes are identical in all aspects.

2-Benzoyl-4,5-diphenyl-3-hydroxythieno[2,3-c]pyridazine (**4a**; $C_{25}H_{16}N_2O_2S$)

Obtained by cyclization of **3a** (yield: 90%) or by reaction of **2** with phenacyl bromide (yield: 75%); m.p.: 198–199°C; IR: $\nu_{max} = 3350$ (OH), 1620 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 13.2$ (br, 1H, OH), 7.3–8.3 (m, 15H, ArH) ppm.

2-p-Bromobenzoyl-4,5-diphenyl-3-hydroxythieno[2,3-c]pyridazine (**4b**; $C_{25}H_{15}BrN_2O_2S$)

Obtained by cyclization of **3b** (yield: 95%) or by reaction of **2** with *p*-bromophenacyl bromide (yield: 77%); m.p.: 253–255°C; IR: $\nu_{max} = 3350$ (OH), 1620 (C=O) cm^{-1}.

4,5-Diphenyl-3-hydroxy-2-phenylcarbamoylthieno[2,3-c]pyridazine (**4c**; $C_{25}H_{17}N_3O_2S$)

Obtained by cyclization of **3c** (yield: 84%) or by reaction of **2** with chloro-*N*-phenylacetamide (yield: 72%); m.p.: 266–267°C; IR: $\nu_{max} = 3300$–3100 (OH, NH), 1620 (C=O) cm^{-1}; ^{1}H NMR (*DMSO*): $\delta = 10.5$ (s, 1H, NH), 7.1–7.8 (m, 16H, ArH and OH) ppm.

4,5-Diphenyl-3-hydroxy-2-p-tolylcarbamoylthieno[2,3-c]pyridazine (**4d**; $C_{26}H_{19}N_3O_2S$)

Obtained by cyclization of **3d** (yield: 86%) or by reaction of **2** with chloro-*N*-*p*-tolylacetamide (yield: 77%); m.p.: > 300°C; IR: $\nu_{max} = 3300$–3100 (OH, NH), 1620 (C=O) cm^{-1}.

2-p-Chlorophenylcarbamoyl-4,5-diphenyl-3-hydroxythieno[2,3-c]pyridazine (**4e**; $C_{25}H_{16}ClN_3O_2S$)

Obtained by cyclization of **3e** (yield: 84%) or by reaction of **2** with chloro-*N*-*p*-chlorophenylacetamide (yield: 75%); m.p.: 282–284°C; IR: $\nu_{max} = 3300$–3100 (OH, NH), 1620 (C=O) cm^{-1}.

2-Cyano-4,5-diphenyl-3-hydroxythieno[2,3-c]pyridazine (**4f**; $C_{19}H_{11}N_3OS$)

Obtained by cyclization of **3f** (yield: 70%) or by reaction of **2** with chloroacetonitrile (yield: 67%); m.p.: 240–242°C; IR: $\nu_{max} = 3450$ (OH), 22000 (C≡N)cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 7.2$–7.5 (m, 11H, ArH and OH) ppm.

Reaction of thioxopyridazine **2** *with ethyl chloroacetate or chloroacetone: formation of thienopyridazines* **4g**, **h**; *general procedure*

A mixture of 3.36 g **2** (0.01 mol), 3.3 g fused sodium acetate (0.04 mol), and ethyl chloroacetate or chloroacetone (0.01 mol) in 45 cm^3 ethanol was heated under reflux for 6 h. The reaction mixture was diluted with 50 cm^3 H_2O and acidified with dil. HCl. The precipitate formed was collected and crystallized from ethanol to afford **4g** or **4f**, respectively.

4,5-Diphenyl-2-ethoxycarbonyl-3-hydroxythieno[2,3-c]pyridazine (**4g**; $C_{21}H_{16}N_2O_3S$)

Yield: 2.8 g (74%); m.p.: 190–191°C; IR: $\nu_{max} = 3200$ (OH), 1650 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 10.3$ (s, 1H, OH), 7.1–7.6 (m, 10H, ArH), 4.3–4.5 (q, 2H, OCH_2), 1.3–1.5 (t, 3H, CH_3) ppm; MS: *m/z* (%) = 376 (M^+, 58), 375 (M^+-H, 84), 346 (M^+-H-C_2H_5, 39), 300 (M^++H-C_6H_5, 100), 299 (M^+-C_6H_5, 17), 77 ($C_6H_5^+$, 12).

2-Acetyl-4,5-diphenyl-3-hydroxythieno[2,3-c]pyridazine (**4h**; $C_{20}H_{14}N_2O_2S$)

Yield: 2.4 g (69%); m.p.: 178–180°C; IR: $\nu_{max} = 3400$ (OH), 1620 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.1$–7.5 (m, 11H, ArH and OH), 2.6 (s, 3H, CH_3) ppm.

Thienopyridazine **6** ($C_{28}H_{21}N_3O_4S$)

A suspension of 0.42 g **4c** (0.001 mol) in 10 cm^3 ethyl chloroformate was heated under reflux for 2 h. The precipitate which formed after cooling was collected and recrystallized from ethanol to give colourless needles of **6**.

Yield: 0.42 g (74%); m.p.: 220–221°C; IR: $\nu_{max} = 3380$ (NH), 1760 (C=O, ester), 1660 (C=O, amide) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 10.6$ (s, 1H, NH), 7.0–7.8 (m, 15H, ArH), 3.6–4.0 (q, 2H, OCH_2), 0.8–1.2 (t, 3H, CH_3) ppm.

Ethyl-(2-cyano-4,5-diphenylthieno[2,3-c]pyridazine-3-yloxy)-acetate (**7**; $C_{23}H_{17}N_3O_3S$)

To a mixture of 3.3 g **4f** (0.01 mol) and 1.23 g ethyl chloroacetate (0.01 mol) in 20 cm^3 *DMF*, 2.76 g anhydrous K_2CO_3 (0.02 mol) were added. The reaction mixture was heated on a water bath for 2 h, cooled, and diluted with 30 cm^3 H_2O. The solid thus precipitated was collected and recrystallized from aqueous ethanol to give **7**.

Yield: 3.1 g (74%); m.p.: 150°C; IR: $\nu_{max} = 2200$ (CN), 1740 (C=O) cm^{-1}.

3-Amino-2-cyano-7,8-diphenylfuro[2′,3′:4,5]thieno[2,3-c]pyridazine (**8**; $C_{21}H_{12}N_4OS$)

8 was prepared by reaction of **4f** with chloroacetonitrile in analogy to the method described above. The product was crystallized from methanol and identified as **8**.

Yield: 2.0 g (54%); m.p.: 270°C; IR: $\nu_{max} = 3300$, 3200 (NH_2), 2200 (C≡N) cm^{-1}.

Ethyl 3-amino-7,8-diphenylfuro[2′,3′:4,5]thieno[2,3-c]pyridazine-2-caboxylate (**9**; $C_{23}H_{17}N_3O_3S$)

A) A suspension of 4.15 g **7** (0.01 mol) in sodium ethoxide solution (1.0 g sodium in 100 cm^3 abs. ethanol) was heated under reflux for 10 min. The solid product separating on cooling was collected and recrystallized from ethanol to give **9**.

Yield: 3.5 g (84%); m.p.: 252–254°C; IR: $\nu_{max} = 3450$, 3330 (NH_2), 1660 (C=O) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 7.1$–7.6 (m, 10H, ArH), 5.9 (s, 2H, NH_2), 4.1–4.4 (q, 2H, OCH_2), 1.2–1.5 (t, 3H, CH_3) ppm; MS: *m/z* (%) = 417 (M^++2, 13), 416 (M^++1, 37), 415 (M^+, 88), 414 (M^+-H, 84), 413 (M^+-2H, 100), 385 (M^+-H-C_2H_5, 17).

B) To a mixture of 3.3 g **4f** (0.01 mol) and 1.23 g ethyl chloroacetate (0.01 mol) in 20 cm^3 *DMF*, 2.76 g anhydrous K_2CO_3 (0.02 mol) was added. The reaction mixture was heated on a water bath for 10 h, cooled, and diluted with 15 cm^3 H_2O. The solid precipitated was collected and crystallized from ethanol to give **9** in 70% yield (2.9 g). The products obtained by the two synthetic routes are identical in all aspects.

3,4-Dihydro-6,7-diphenyl-4-oxopyrimido[4″,5″:4′,5′]furo[2′,3′:4,5]thieno[2,3-c]pyridazine (**10**; $C_{22}H_{12}N_4O_2S$)

A solution of 0.41 g **9** (0.001 mol) in 15 cm^3 formamide was heated under reflux for 4 h. The precipitate separating after cooling was collected and recrystallized from *DMF* to give **10**.

Yield: 0.3 g (70%); m.p.: >300°C; IR: $\nu_{max} = 3200$–2400 (br, NH), 1660 (C=O) cm^{-1}; MS: *m/z* (%) = 396 (M^+, 35), 394 (M^+-2H, 80), 481 (M^+-NH, 40), 380 (M^+-O, 100), 370 (M^+-CN, 85).

3-Amino-7,8-diphenylfuro[2′,3′:4,5]thieno[2,3-c]pyridazine-2-carbohydrazide (**11**; $C_{21}H_{15}N_5O_2S$)

A suspension of 4.15 g **9** (0.01 mol) in 10 cm^3 hydrazine hydrate 99% (0.2 mol) was heated under reflux for 3 h. The reaction mixture was titurated with 25 cm^3 ethanol and left to cool. The solid which formed was collected and recrystallized from dioxane to give **11**.

Yield: 3.5 g (87%); m.p.: 295–297°C; IR: $\nu_{max} = 3420$, 3300, 3200, 3150 ($2NH_2$, NH), 1620 (C=O) cm^{-1}.

3-Amino-7,8-diphenylfuro[2′,3′:4,5]thieno[2,3-c]pyridazine-2-carbonylazide (**12**; $C_{21}H_{12}N_6O_2S$)

3.5 cm^3 chilled sodium nitrite solution (10%, 0.005 mol) was added dropwise to a solution of 2.0 g **11** (0.005 mol) in 10 cm^3 glacial acetic acid at 5–10°C during 5 min. with stirring. The reaction mixture was allowed to stand at room temperature for 1 h and then diluted with 25 cm^3 H_2O. The precipitate which formed was collected, dried in air, and used in the next step without purification.

Yield: 1.6 g (77%); m.p.: 230°C (dec.); IR: $\nu_{max} = 3450$, 3300 (NH_2), 2130 (N_3), 1660 (C=O) cm^{-1}.

5,6-Diphenyl-1H-imidazolo[4″,5″:4′,5′]furo[2′,3′:4,5]thieno[2,3-c]pyridazine-2(3H)-one (**14**; $C_{21}H_{12}N_4O_2S$)

A solution of 0.41 g **12** (0.001 mol) in 15 cm^3 dry toluene was heated under reflux for 3 h. The precipitate separating upon cooling was collected and recrystallized from *DMF* to give **14**.

Yield: 0.2 g (52%); m.p.: 293–295°C; IR: $\nu_{max} = 3300$–3100 (2NH), 1680 (C=O) cm^{-1}.

4,5-Diphenyl-3-hydroxythieno[2,3-c]pyridazine (**16**; $C_{18}H_{12}N_2OS$)

A solution of 3.8 g **4g** (0.01 mol) in 40 cm^3 ethanolic sodium hydroxide solution (7%) was heated under reflux for 5 h and left to cool. The reaction mixture was diluted with 40 cm^3 H_2O

and acidified with dil. HCl. The precipitated product was collected and crystallized from ethanol to give **16**.

Yield: 1.3 g (42%); m.p.: 230–231°C; IR: $\nu_{max} = 3500–2500$ (br, OH) cm^{-1}.

2-Amino-3-cyano-4,8,9-triphenyl-4H-pyrano[2′,3′:4,5]thieno[2,3-c]pyridazine (**17**; $C_{28}H_{18}N_4OS$)

To a mixture of 1.52 g **16** (0.005 mol) and 0.77 g benzylidenemalononitrile (0.005 mol) in 20 cm^3 ethanol, few drops of piperidine were added. The reaction mixture was heated under reflux for 1 h. The solid that precipitated while hot was filtered and recrystallized from dioxane to give white crystals of **17**.

Yield: 2.15 g (94%); m.p.: 281–282°C; IR: $\nu_{max} = 3480–3300$ (NH_2), 2200 (C≡N) cm^{-1}, ^{1}H NMR (*DMSO*-d_6: $\delta = 7.1–7.6$ (m, 15H, ArH), 6.8 (s, 2H, NH_2), 5.1 (s, 1H, CH pyran); MS: *m/z* (%) = 460 (M^++2, 17), 458 (M^+, 100), 457 (M^+-H, 83), 456 (M^+-2H, 40), 77 ($C_6H_5^+$, 27).

3-Cyano-4,8,9-triphenyl-4H-pyrano[2′,3′:4,5]thieno[2,3-c]pyridazine-2-methanimidate (**18**; $C_{31}H_{22}N_4O_2S$)

A suspension of 2.29 g **17** (0.005 mol) in 15 cm^3 triethyl orthoformate was heated under reflux for 3 h and allowed to cool. The precipitated solid was filtered and recrystallized from ethanol to give white crystals of **18**.

Yield: 2.1 g (82%); m.p.: 220–222°C; IR: $\nu_{max} = 2200$ (C≡N), 1600 (C=N) cm^{-1}; ^{1}H NMR (*DMSO*-d_6: $\delta = 7.1–7.6$ (m, 15H, ArH), 6.8 (s, 1H, N=CH), 5.2 (s, 1H, CH pyran), 4.1–4.5 (q, 2H, OCH_2), 1.2–1.5 (t, 3H, CH_3) ppm.

Monoacetyl derivative **20** ($C_{30}H_{20}N_4O_2S$)

A solution of 2.29 g **17** (0.005 mol) in 25 cm^3 acetic anhydride was heated under reflux for 4 h. The reaction mixture was cooled, diluted with 20 cm^3 H_2O, and allowed to stand at room temperature for 2 h. The solid formed was collected and crystallized from acetic acid to give yellow crystals of **20**.

Yield: 1.5 g (60%); m.p.: > 300°C; IR: $\nu_{max} = 3200$ (NH), 2200 (C≡N), 1710 (C=O) cm^{-1}; MS: *m/z* (%) = 500 (M^+, 31), 458 (M^+-$COCH_3$, 47), 381 (M^+-$COCH_3$-C_6H_5, 100), 77 ($C_6H_5^+$, 15).

Oxime derivative **21** ($C_{20}H_{15}N_3O_2S$)

A mixture of 1.73 g **4h** (0.005 mol), 0.35 g hydroxylamine · HCl (0.005 mol), and 1.36 g sodium acetate trihydrate (0.01 mol) in 30 cm^3 ethanol was heated under reflux for 3 h. The solid formed after cooling was collected and recrystallized from methanol to give **21**.

Yield: 1.5 g (81%); m.p.: 298–299°C; IR: $\nu_{max} = 3450$ (OH), 3250 (OH), 1600 (C=N) cm^{-1}.

Diacetyl derivative **24** ($C_{24}H_{19}N_3O_4S$)

A solution of 0.72 g **21** (0.002 mol) in 10 cm^3 acetic anhydride was heated under reflux for 4 h and then diluted with 15 cm^3 H_2O. The solid precipitated was collected and recrystallized from methanol to give **24** as pale yellow needles.

Yield: 0.65 g (73%); m.p.: 217–218°C; IR: $\nu_{max} = 1770$ (C=O), 1600 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 7.1–7.5$ (m, 10H, ArH), 2.4 (s, 3H, CH_3), 2.2 (s, 3H, CH_3), 1.5 (s, 3H, CH_3) ppm.

Thiosemicarbazone derivative **22** ($C_{21}H_{17}N_5OS_2$)

To a mixture of 3.46 g **4h** (0.01 mol) and 0.91 g thiosemicarbazide (0.01 mol) in 30 cm^3 ethanol, few drops of acetic acid were added. The reaction mixture was heated under reflux for 3 h and left to

Table 1. Antibacterial and antifungal activities; -: no inhibition zone

	Staph. aureus	*Sarcina spp.*	*Pseud. aeurgin.*	*Bacillus cereus*	*Asp. fumigatus*	*Asp. niger*	*Asp. temc.*	*Fusa. solani*
3f	12	11	–	17	–	–	–	–
4a	–	16	–	24	9	–	8	–
4c	16	14	–	12	–	–	–	–
4g	–	–	–	–	–	–	–	–
7	–	–	–	–	–	–	–	–
9	–	–	–	–	–	–	–	–
14	–	–	–	–	–	–	–	–
16	–	10	–	14	–	–	–	–
17	–	–	–	–	–	–	–	–
20	–	–	–	–	–	–	–	–
Trosyd	7	22	–	21	16	14	22	12

cool. The product that precipitated was filtered and recrystallized from methanol to give yellow needles of **22**.

Yield: 3.5 g (83%); m.p.: 235–237°C; IR: $\nu_{max} = 3500$–3100 (OH, NH_2, NH), 1600 (C=N) cm^{-1}.

Thiazolidinone derivative **25** ($C_{23}H_{17}N_5O_2S_2$)

To a suspension of 2.20 g **22** (0.005 mol) and 0.62 g ethyl chloroacetate (0.005 mol) in 30 cm^3 ethanol, 1.64 g fused sodium acetate (0.02 mol) were added. The resulting mixture was heated under reflux for 4 h. The precipitate which formed on cooling was filtered and recrystallized from dioxane to give **25** as orange needles.

Yield: 2.0 g (71%); m.p.: >300°C; IR: $\nu_{max} = 3450$ (OH), 3100 (NH), 1700 (C=O) cm^{-1}; ^1H NMR (*TFA*): $\delta = 7.2$–7.7 (m, 11H, ArH+OH), 4.2 (s, 2H, SCH_2), 2.8 (s, 3H, CH_3) ppm.

Biological screening

The filter paper disc method [15, 16] was employed in nutrient agar for bacteria and dox agar for fungi. The eagar 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/1 ml of *DMSO*) were placed on the indicated agar media. The incubation time was 48 h at 28°C. Discs saturated with *DMSO* were used as control. Trosyd was used as a reference substance. The diameters of inhibition zones (mm) were measured and are recorded in Table 1.

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