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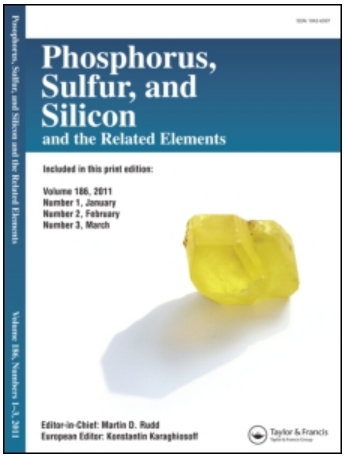

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A. A. Aly[a]
[a] Chemistry Department, Faculty of Science, Benha University, Benha, Egypt

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A Convenient Synthesis of Novel Functionalized Pyrimido[5′,4′:4,5]thieno[3,2-c]pyridazines and Related Fused Systems

A. A. Aly
Chemistry Department, Faculty of Science, Benha University, Benha, Egypt

*Possible approaches to the synthesis of functionalized, pyrimido[5′,4′:4,5]thieno[3,2-c]pyridazines **2-18**, pyridazino[3′,4′:4,5]thieno[2,3-d]triazines **19**, **20a,b** and pyrido[3′,2′:4,5]thieno[3,2-c]pyridazines **22a,b** are described. The sequence involves the heterocyclization of 6-amino-1,3-diphenyl-1,4-dihydrothieno[3,2-c]pyridazine-7-carboxamide (**1**) with appropriate reagents. The antimicrobial activity of some the newly synthesized compounds was examined. All tested compounds proved to be active as antibacterial and antifungal agents.*

Keywords Antimicrobial activities; pyrimidothienopyridazines; pyridazinothienotriazines; pyridothienopyridazines; thieno[3,2-c]pyridazine

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INTRODUCTION

Pyridazines and their annelated derivatives occupy a pivotal position in modern medicinal chemistry because the pyridazine ring is a prominent structural motif found in numerous natural and synthetic biologically active compounds. In addition to their powerful antioxidant and free radical scavenging properties.[1–6] The pyrimidine moiety is a frequent partner in many heterocyclic systems. It displays a wide range of pharmacological activities as fungicide, viricide, leishmanicide, phosphodiesterase inhibitor, besides the use as a component in photographic materials and agrochemical industries.[7–11] Encouraged by these assessment and continuing our interest in the chemistry and pharmacology of heterocyclic systems,[12,13] we report herein on efficient incorporation the latter heterocyclic moiety into pyridazine condensed

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Address correspondence to A. A. Aly, Chemistry Department, Faculty of Science, Benha University, Benha, Egypt. E-mail: alymaboud@yahoo.com

systems to develop a new synthetic strategy of functionalized biologically active derivatives, utilizing the readily available, 6-amino-1,3-diphenyl-1,4-dihydrothieno[3,2-c]pyridazine-7-carboxamide (1) as a key starting material.

RESULTS AND DISCUSSION

The required 6-amino-1,3-diphenyl-1,4-dihydrothieno[3,2-c]pyridazine -7-carboxamide (**1**) was prepared in a facile one-pot reaction *via* a three-component cyclocondensation of 2,6-diphenyl-2*H*-4,5-dihydropyridazin-3-one, cyanoacetamide and elemental sulfur in ethanolic triethylamine solution.[14] The structure of compound **1** was assigned by elemental analysis and spectroscopic data (IR, ^{1}H and ^{13}C NMR spectra) which agree with the assigned structure. The ^{1}H NMR ($CDCl_3$) of **1** showed signals at δ 3.99 as singlet for methylene protons, (5.95 and 6.30) two singlets for two amino groups and multiplet signals at 7.12−7.85 for aromatic protons. The reactivity of the conveniently accessible *o*-amino amide derivative **1** toward a variety of chemical reagents was investigated. It was found that the reaction of compound **1** with aromatic aldehyde *viz* benzaldehyde and 4-chlorobenzaldehyde in glacial acetic acid afforded 2-aryl-5,7-diphenyl-1*H*-2,3,5,8-tetrahydropyrimido[5′,4′:4,5]thieno[3,2-c]pyridazin-4-ones (**2a,b**) (Scheme 1).

The treatment of compound **1** with cyclopentanone and/or cyclohexanone in glacial acetic acid, yielded the tricyclic compounds **3a,b**. The reaction of compound **1** with triethyl orthoformate in the presence of acetic anhydride afforded pyrimidothienopyridazine derivative **4**. Moreover, the treatment of compound **1** with acetyl chloride and/or benzoyl chloride afforded the acyl derivatives **5a,b**. Compounds **5a,b** underwent cyclization upon refluxing in concentrated sulfuric acid at 160°C, to give 1,3-diphenyl-7-methyl/phenyl-8*H*-1,4-dihydropyrimido[5′,4′:4,5]thieno[3,2-c]pyridazin-9-ones (**6a,b**). A conclusive evidence for the structure of **6a** was achieved by independent synthesis *via* an alternative route through the reaction of compound **1** with excess of acetic anhydride, which gave a single product that was found to be identical in all respects (m.p., m.m.p., and spectroscopic data) with **6a**.

The work was further extended to shed more light on the reactivity of compound **1** as bifunctional reagent toward other electrophilic reagents. Thus, the reaction of **1** with carbon disulfide in boiling 1,4-dioxane solution gave the corresponding pyrimidothienopyridazine derivative **7**. The IR spectrum of **7** displayed absorption bands at

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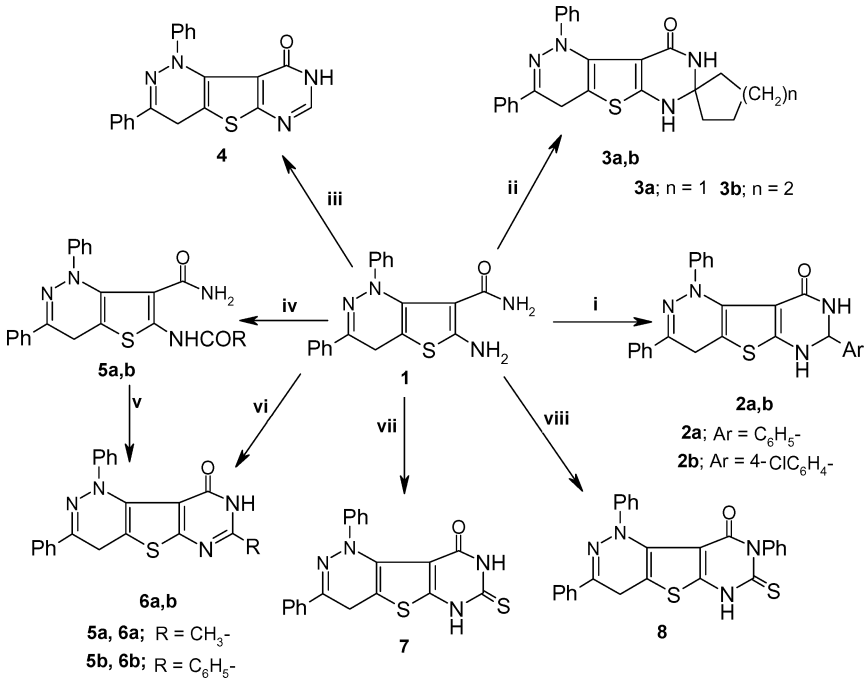

SCHEME 1 (i) ArCHO, AcOH; (ii) cyclopentanone or cyclohexanone, AcOH; (iii) $CH(OEt)_3$, Ac_2O; (iv) RCOCl; (v) H_2SO_4, 160°C; (vi) Ac_2O; (vii) CS_2, dioxane; (viii) PhNCS, EtOH, Et_3N.

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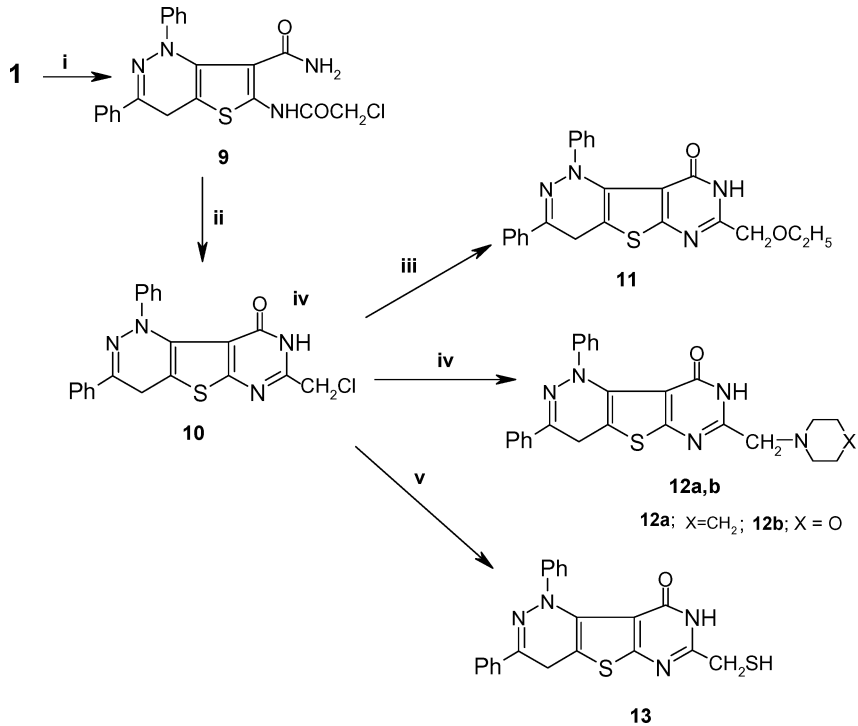
3250–3200 cm^{-1} (NH), 1670 cm^{-1} (CO) and 1280 cm^{-1} (CS). Its ^1H NMR spectrum ($CDCl_3$) showed singlet at δ 4.10 (CH_2), multiplet at (7.30–8.20) (ArH) and two singlets at 9.21, 9.32 for 2 NH which disappear on addition of D_2O to the NMR sample. The reaction of compound **1** with phenyl isothiocyanate in refluxing absolute ethanol containing a catalytic amount of triethylamine afforded 3,5,7-triphenyl-2-thioxo-1,3,5,8-tetrahydropyrimido[5′,4′:4,5]thieno[3,2-c]pyridazin-4- one (**8**) (Scheme 1).

The acetylation of **1** with chloroacetyl chloride resulted in the formation of thienopyridazine **9**, which in turn underwent cyclization to give 7-chloromethyl-1,3-diphenyl-8*H*-1,4-dihydropyrimido [5′,4′:4,5]thieno[3,2-c]pyridazin-9-one (**10**) (Scheme 2).

The assignment of structure **10** was based on analytical and spectroscopic data. The feasibility of the chlorine atom in compound **10** to undergo nucleophilic displacement was proved by reaction with sodium ethoxide, piperidine and/or morpholine which gave the pyridazine



SCHEME 2 (i) $ClCH_2COCl$; (ii) Ac_2O, AcOH; (iii) EtONa, EtOH; (iv) piperidine or morpholine; (v) thiourea, NaOH, AcOH.

derivatives **11** and **12a,b** respectively. The reaction of compound **10** with thiourea gave adduct which upon treatment with sodium hydroxide followed by acidification furnished the mercaptomethylpyridazine derivative **13**.

As an extension of this synthetic route, the behavior of compound **1** toward some cyanomethylene reagents was investigated. Thus, the reaction of equimolar amounts of compound **1** and malononitrile or ethyl cyanoacetate in refluxing absolute ethanol containing a catalytic amount of triethylamine yielded the corresponding pyrimidothienopyridazines **15a,b** respectively (Scheme 3).

The formation of compounds **15a,b** was assumed to proceed *via* the intermediacy of **14a,b**, which underwent cyclization *via* the elimination of ammonia yielding the final isolable products **15a,b**. The acetonitrile **15a** seemed to be suitable for the synthesis of interesting related systems as well as thiophene derivatives. Thus, the condensation of **1** with aromatic aldehyde in boiling absolute ethanol containing

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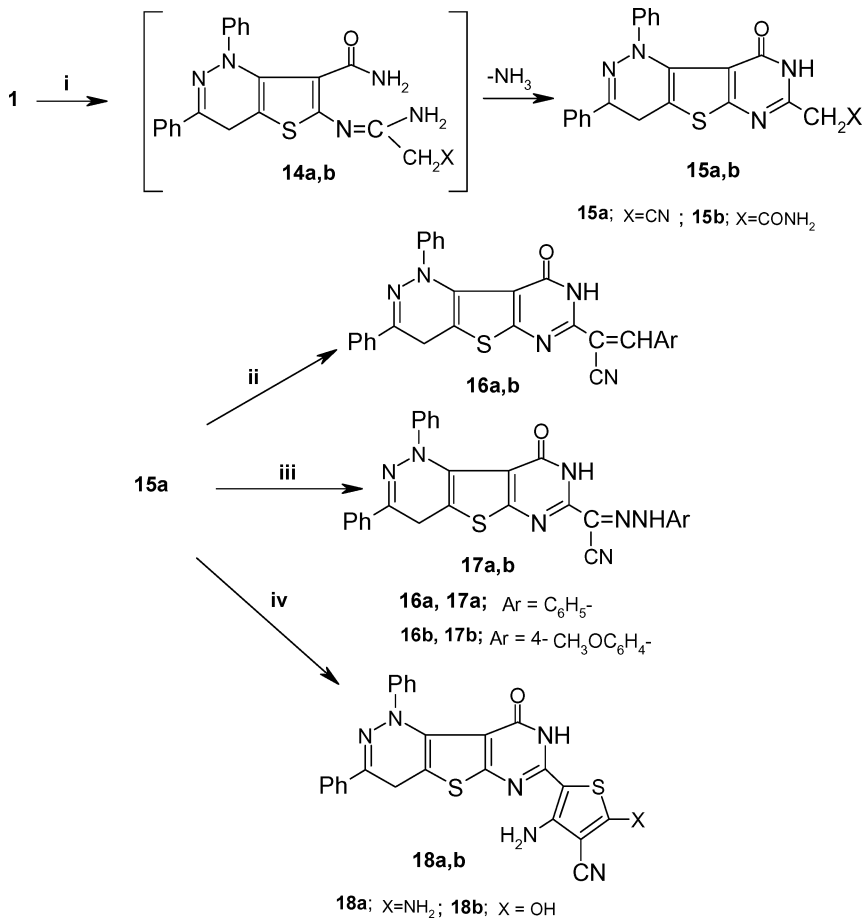

SCHEME 3 (i) $NCCH_2CN$ or $NCCH_2COOEt$, EtOH, piperidine; (ii) ArCHO, EtOH, piperidine; (iii) ArN_2Cl, AcONa; (iv) $NCCH_2CN$ or $NCCH_2COOEt$, S, EtOH.

a catalytic amount of piperidine, afforded the corresponding arylidene derivatives **16a,b**. The coupling of **1** with aryl diazonium chlorides at 0−5°C in ethanolic sodium acetate solution gave the hydrazono derivatives **17a,b**. The reaction of equimolar amounts of **15a** with elemental sulfur and active methylene compounds in refluxing ethanol containing triethylamine afforded the thiophene derivatives **18a,b**, (Scheme 3).

Recently, there is a widespread interest in the design and synthesis of triazine derivatives as well as pyridine derivatives because of their potential biological activities associated with their

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skeletons.[15–17] Thus, the diazotization and self-coupling reaction[18] of amino amide derivative **1** with sodium nitrite and acetic acid afforded 5,7-diphenyl-5,8-dihydropyridazino[3′,4′:4,5]thieno[2,3-d]-1,2,3-triazin-4(3H)-one (**19**). The treatment of **19** with electrophilic reagents *viz* methyl iodide and 2-bromoacetophenone furnished 3-substituted triazine derivatives **20a,b** (Scheme 4).

Finally, the behavior of **1** toward β-addition was also investigated. It was treated with equimolar amounts of α-substituted cinnamonitrile derivatives in absolute ethanol containing a catalytic amount of piperidine, to afford the corresponding pyrido[3′,2′:4,5]thieno[3,2-c]pyridazine derivatives **22a,b** (Scheme 4). The reaction took place *via* the intermediacy of **21a,b** through a Michael-type addition, subsequent intramolecular cyclization *via* loss of ammonia, followed by elimination of hydrogen cyanide.[19] The structures of the synthesized derivatives were assigned on the basis of elemental analysis and spectroscopic data (*cf.* experimental).

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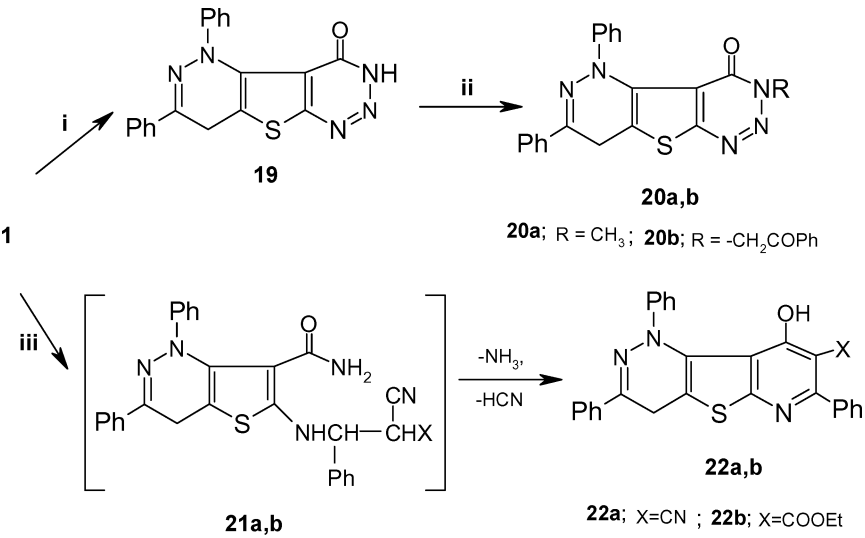
ANTIMICROBIAL ACTIVITY

The antimicrobial activity of some synthesized compounds against some pathogenic bacteria and fungi was tested *in vitro* using the hole plate and filter paper disc methods.[20] Chloramophenicol as an



SCHEME 4 (i) $NaNO_2$, AcOH; (ii) CH_3I, $PhCOCH_2Br$, acetone, KOH; (iii) PhCH=CXCN, EtOH, piperidine.

antibacterial agent and Terbinafin as an antifungal agent were used as references to evaluate the potency of the tested compounds under the same conditions. The results in Table I reveal that the tested compounds exhibited the highest or similar degree of inhibition area against the organisms relative to the standard antibacterial and antifungal agents.

EXPERIMENTAL

Melting points are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 298 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on Varian Gemini 200 MHz instrument using TMS as internal reference with chemical shifts expressed as δ ppm. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 instrument (70 eV El mode).

^{13}C NMR values of two phenyl groups attached to pyridazine moiety for compounds **2**–**22** are the same as in compound **1** with $\delta \pm 0.1$–0.4 ppm.

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TABLE I The Antimicrobial Activity of the Tested Compounds

Compd	Staphylococcus aureus		Pseudomon aeruginosa		Bacillus subtilis		Escherichia coli		Aspergillus fumigatus		Penicillium italicum		Penicillium notatum	
no.	A	MIC	A	MIC	A	MIC	A	MIC	A	MIC	A	MIC	A	MIC
1	+	250	++	500	+	250	+	125	–	–	–	–	–	–
2a	++	500	+	250	++	250	++	250	+	125	++	125	+	125
3b	++	250	++	125	+	125	++	125	+	250	+	125	+	125
4	+	125	+	250	+	250	+	250	+	125	+	250	–	–
6a	++	250	++	125	++	125	++	125	++	125	+	250	++	250
8	+	125	++	250	++	250	+	250	+	250	+	250	++	250
12a	+++	250	++	125	+++	125	++	125	+	125	+	125	+	250
13	+	125	+	250	++	250	++	125	++	500	+	250	+	125
15a	++	500	+	125	++	125	++	250	+	125	+	125	++	250
16b	+	125	+	250	+++	250	+	125	++	250	+	125	++	125
17b	++	250	+	125	++	125	++	250	+	125	–	–	–	–
18a	++	125	+	250	++	250	++	125	++	250	++	500	+	125
19	+	125	+	125	+++	125	++	250	+	125	–	–	–	–
22a	+	250	+	250	++	500	+	125	+	125	+	250	++	500
CH	++	250	+++	250	+++	250	++	250	–	–	–	–	–	–
TE	–	–	–	–	–	–	–	–	++	250	++	250	++	125

A = Antimicrobial activity of tested compounds; MIC = Minimum inhibitory concentration; –, inactive; + > 5mm, slightly active; ++ > 7 mm, moderately active; +++ > 9 mm, highly active; CH = chloramophenicol; TE = Terbinafin.

6-Amino-1,3-diphenyl-1,4-dihydrothieno[3,2-c]pyridazine-7-carboxamide (1)

A mixture of 2,6-diphenyl-2*H*-4,5-dihydropyridazin-3-one (5.00 g, 20 mmol), cyanoacetamide (1.68 g, 20 mmol) and elemental sulfur (0.64 g, 20 mmol) in absolute ethanol (30 mol) containing a catalytic amount of triethylamine (1 ml) was heated at reflux for 8h. The solvent was removed under reduced pressure and the residue was triturated with ice-cold water and neutralized with concentrated hydrochloric acid (3 ml). The solid product, so formed, was collected by filtration and recyrstallized from n-butanol to give **1**. Yield, 5.22 g (75%); m.p. 216–218°C; IR: $\nu = 3460–3325$ (NH_2), 1670 cm^{-1} (CO); ^1H NMR ($CDCl_3$): $\delta = 3.99$ (s, 2H, CH_2), 5.95 (s, 2H, NH_2), 6.30 (s, 2H, $CONH_2$), 7.12–7.85 (m, 10H, ArH); ^{13}C NMR: $\delta = 31.3$ (CH_2), 130.2 (C-7a), 140.2 (C-8), 145.3 (C-4a), 147.2 (C-7), 158.4 (C-3), 173.3 (CO), 112.1, 112.9, 119.2, 124.2, 124.8, 136.5 (C-phenyl attached to nitrogen atom), 125.2, 125.9, 131.2, 133.1, 133.9, 135.2 (C-phenyl at C-3); Anal. calcd. for $C_{19}H_{16}N_4OS$ (348.42): C, 65.50; H, 4.63; N, 16.08%. Found: C, 65.71; H, 4.85; N, 16.31%.

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2,5,7-Triphenyl-1H-2,3,5,8-tetrahydropyrimido[5′,4′:4,5]thieno-[3,2-c]pyridazin-4-one (2a) and 2-(4-chlorophenyl)- 5,7-diphenyl-1H-2,3,5,8-tetrahydropyrimido-[5′,4′:4,5]thieno[3,2-c]pyridazin-4-one (2b)

A mixture of compound **1** (1.04 g, 3 mmol) and benzaldehyde or 4-chlorobenzaldehyde (3 mmol) in glacial acetic acid (20 ml) was heated at reflux for 5 h. The reaction mixture was cooled, poured onto ice (20 g). The solid formed was collected by filtration and recrystallized to give **2a,b**.

2a; Yield, 0.92 g (71%) (1,4-dioxane); m.p. 231–233°C; IR:$\nu = 3320–3300$ (NH), 1675 cm^{-1} (CO); ^1H NMR (DMSO): $\delta = 3.97$ (s, 2H, CH_2), 5.31 (s, 1H, CH), 7.21–7.81 (m, 15H, ArH), 9.35, 9.61 (2s, 2H, 2NH, exchangeable); ^{13}C NMR: $\delta = 30.2$ (CH_2), 76.2 (C-2), 130.1 (C-4b), 139.2 (C-9a), 143.2 (C-8a), 146.1 (C-4a), 160.3 (C-7), 176.3 (CO), 126.7, 127.2, 129.3, 130.1, 132.3, 140.1 (C_6H_5); Anal. calcd. for $C_{26}H_{20}N_4OS$ (436.53): C, 71.54; H, 4.62; N, 12.83%. Found: C, 71.31; H, 4.29; N, 12.98%.

2b; Yield, 1.06 g (76%) (n-butanol); m.p. 243–245°C; IR:$\nu = 3340–3310$ (NH), 1670 cm^{-1} (CO); MS: m/z: 470 (M^+); Anal. calcd. for $C_{26}H_{19}ClN_4OS$ (470.97): C, 66.30; H, 4.07; N, 11.90%. Found: C, 66.65; H, 4.34; N, 11.70%.

General Procedure for the Preparation of Compounds 3a,b

A mixture of compound **1** (1.04 g, 3 mmol) and cyclopentanone or cyclohexanone (3 mmol) in glacial acetic acid (20 ml) was heated at reflux for 5h. The reaction mixture was cooled and poured onto ice (20 g). The resulting solid product was collected by filtration and recrystallized to give **3a,b**.

5,7-Diphenyl-2,2-tetramethylene-1H-2,3,5,8-tetrahydropyrimido[5′,4′:4,5]thieno[3,2-c]pyridazin-4-one (3a)

Yield, 0.86 g (69%) (DMF); m.p. 207–9°C; IR:ν = 3320-3290 (NH), 1673 cm^{-1} (CO); ^1H NMR (DMSO): δ = 1.53 (br s, 2H, CH_2 of cyclopentylidene ring), 1.85–2.30 (br s, 6H, $(CH_2)_3$ of cyclopentylidene ring), 4.11 (s, 2H, CH_2), 7.13-7.95 (m, 10H, ArH), 9.12, 9.21 (2s, 2H, 2NH, exchangeable); Anal. calcd. for $C_{24}H_{22}N_4OS$ (414.52): C, 69.54; H, 5.35; N, 13.52%. Found: C, 69.85; H, 5.61; N, 13.25%.

5,7-Diphenyl-2,2-pentamethylene-1H-2,3,5,8-tetrahydropyrimido[5′,4′:4,5]thieno[3,2-c]pyridazin-4-one (3b)

Yield, 0.81 g (63%) (1,4-dioxane); m.p. 236−238°C; IR:ν = 3340−3300 (NH), 1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 0.90−1.10 (m, 2H, CH_2 of cyclohexylidene ring), 1.50−2.0 (m, 4H, $(CH_2)_2$ of cyclohexylidene ring), 2.30−2.60 (m, 4H, $(CH_2)_2$ of cyclohexylidene), 3.95−4.11 (m, 4H, $(CH_2)_2$ of cyclohexylidene ring), 4.25 (s, 2H, CH_2), 7.51−8.21 (m, 10H, ArH), 9.41, 9.52 (2s, 2H, 2NH, exchangeable); Anal. calcd. for $C_{25}H_{24}N_4OS$ (428.55): C, 70.07; H, 5.64; N, 13.07%. Found: C, 70.40; H, 5.85; N, 13.42%.

1,3-Diphenyl-8H-1,4-dihydropyrimido[5′,4′:4,5]thieno[3,2-c]pyridazin-4-one (4)

A mixture of compound **1** (1.04 g, 3 mmol) in acetic acid (20 ml) containing acetic anhydride (5 ml) and triethyl orthoformate (3 mmol) was heated at reflux for 4 h. The reaction mixture was cooled, poured onto ice-cold water and the solid product formed was collected by filtration and recrystallized from 1,4-dioxane to give **4**. Yield, 0.65 g (61%); m.p. 286−288°C; IR:ν = 3300 (NH), 1665 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 4.30 (s, 2H, CH_2), 7.31−8.10 (m, 11H, ArH), 9.20 (s, 1H,

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NH, exchangeable); Anal. calcd. for $C_{20}H_{14}N_4OS$ (358.42): C, 67.02; H, 3.94; N, 15.63%. Found: C, 67.40; H, 4.20; N, 15.36%.

6-Acetylamino-1,3-diphenyl-1,4-dihydrothieno[3,2-c]pyridazine-7-carboxamide (5a)

A mixture of compound **1** (1.04 g, 3 mmol) and acetyl chloride (3 mmol) in glacial acetic acid (10 ml) was heated at reflux for 4 h. The reaction mixture was cooled to room temperature and poured onto ice-cold water. The resulting solid product was collected by filtration and recrystallized from ethanol to give **5a**. Yield, 0.75 g (64%); m.p. 205–207°C; IR:ν = 3400–3210 (NH_2, NH), 1670–1665 cm^{-1} (CO); MS: m/z: 390 (M^+); Anal. calcd. for $C_{21}H_{18}N_4O_2S$ (390.46): C, 64.60; H, 4.65; N, 14.35%. Found: C, 64.30; H, 4.11; N, 14.55%.

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6-Benzoylamino-1,3-diphenyl-1,4-dihydrothieno[3,2-c]pyridazine-7-carboxamide (5b)

To a cold solution (0–5°C) of compound **1** (1.04 g, 3 mmol) in pyridine (15 ml), benzoyl chloride (3 mmol) was added dropwise with stirring for 1 h. The reaction mixture was heated, at reflux for 4 h and then evaporated in vacuo, the remaining product was triturated with ethanol and the formed solid product was filtered off and recrystallized from ethanol to give **5b**. Yield, 0.85 g (63%); m.p. 225–227°C; IR:ν = 3410–3300 (NH_2, NH), 1675–1670 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 4.10 (s, 2H, CH_2), 5.60 (br s, 2H, NH_2), 7.20–8.15 (m, 15H, ArH), 8.95 (s, 1H, NH, exchangeable); Anal. calcd. for $C_{26}H_{20}N_4O_2S$ (452.53): C, 69.01; H, 4.45; N, 12.38%. Found: C, 69.39; H, 4.73; N, 12.02%.

1,3-Diphenyl-7-(methyl/phenyl)-8H-1,4-dihydropyrimido[5′,4′:4,5]thieno[3,2-c]pyridazin-9-ones (6a,b)

Method A

A suspension of compound **5a** or **5b** (3 mmol) in concentrated sulfuric acid (10 ml) was heated in an oil bath (160°C) for 5 h, then left to cool. The reaction mixture was poured onto cold water (30 ml) and neutralized with sodium hydroxide (25%, 64 ml) and left overnight at room temperature. The formed solid product was collected by filtration and recrystallized from ethanol to give **6a,b**.

Method B

A solution of compound **1** (1.04 g, 3 mmol) in acetic anhydride (15 ml) was heated at reflux for 1 h. The reaction mixture was cooled, poured onto ice (30 g) and the separated solid was filtered off and recrystallized from ethanol to give **6a**. Yield, 0.84 g (76%).

6a; Yield, 0.81 g (72%); m.p. 193–195°C; IR:$\nu =$ 3260 (NH), 1670 cm^{-1} (CO); ^1H NMR ($CDCl_3$): $\delta = 1.95$ (s, 3H, CH_3), 4.15 (s, 2H, CH_2), 7.40–8.10 (m, 10H, ArH), 9.21 (s, 1H, NH, exchangeable); Anal. calcd. for $C_{21}H_{16}N_4OS$ (372.44): C, 67.72; H, 4.33; N, 15.04%. Found: C, 67.30; H, 4.10; N, 15.39%.

6b; Yield, 0.69 g (53%); m.p. 185–187°C; IR:$\nu =$ 3290 (NH), 1665 cm^{-1} (CO); MS: m/z: 434 (M^+); Anal. calcd. for $C_{26}H_{18}N_4OS$ (434.51): C, 71.87; H, 4.18; N, 12.89%. Found: C, 71.99; H, 4.46; N, 12.60%.

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5,7-Diphenyl-2-thioxo-1H-2,3,5,8-tetrahydropyrimido[5′,4′:4,5] thieno[3,2-c]pyridazin-4-one (7)

A suspension of compound **1** (1.04 g, 3 mmol) and carbon disulfide (3 ml) in 1,4-dioxane (20 ml) was heated at reflux for 10 h. The solid product which formed after cooling was filtered off and recrystallized from ethanol to give **7**. Yield, 0.60 g (61%); m.p. 251–253°C; IR:$\nu =$ 3250–3200 (NH), 1670 (CO), 1280 cm^{-1} (CS); ^1H NMR ($CDCl_3$): $\delta =$ 4.10 (s, 2H, CH_2), 7.30–8.20 (m, 10H, ArH), 9.21, 9.32 (2s, 2H, 2NH, exchangeable); ^{13}C NMR: $\delta = 30.5$ (CH_2), 130.1 (C-4b), 140.3 (C-9a), 145.2 (C-4a), 147.3 (C-8a), 159.1 (C-7), 176.3 (CO), 184.3 (CS); Anal. calcd. for $C_{20}H_{14}N_4OS_2$(390.48): C, 61.52; H, 3.61; N, 14.35%. Found: C, 61.23; H, 3.25; N, 14.62%.

3,5,7-Triphenyl-2-thioxo-1,3,5,8-tetrahydropyrimido[5′,4′:4,5] thieno[3,2-c]pyridazin-4-one (8)

A mixture of compound **1** (1.04 g, 3 mmol) and phenyl isothiocyanate (3 mmol) in absolute ethanol (25 ml) containing a catalytic amount of triethylamine (0.5 ml) was heated at reflux for 7 h. The reaction mixture was poured onto ice-cold water and neutralized with dilute hydrochloric acid (5 ml). The solid product which formed was recrystallized from 1,4-dioxane to give **8**. Yield, 1.01 g (73%); m.p. 243–245°C; IR:$\nu = 3310$ (NH), 1670 (CO), 1275 cm^{-1} (CS); ^1H NMR ($CDCl_3$): $\delta = 3.99$ (s, 2H, CH_2), 7.50–8.41 (m, 15H, ArH), 9.13 (s, 1H, NH, exchangeable); Anal. calcd. for $C_{26}H_{18}N_4OS_2$(466.58): C, 66.93; H, 3.89; N, 12.01%. Found: C, 66.60; H, 3.51; N, 12.36%.

6-(2-Chloroacetylamino)-1,3-diphenyl-1,4-dihydrothieno[3,2-c]pyridazine-7-carboxamide (9)

A mixture of compound **1** (2.78 g, 8 mmol) and chloroacetyl chloride (10 mmol) in dimethylformamide (25 ml) was stirred at room temperature for 2 h. The reaction mixture was poured onto ice-cold water. The formed solid product was filtered off and recrystallized from n-butanol to give **9**. Yield, 2.24 g (66%); m.p. 237–239°C; IR:ν = 3410–3340 (NH_2, NH), 1675–1670 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 3.65 (s, 2H, CH_2Cl), 4.12 (s, 2H, CH_2), 5.85 (br s, 2H, NH_2), 7.25–8.15 (m, 10H, ArH), 9.35 (s, 1H, NH, exchangeable); Anal. calcd. for $C_{21}H_{17}ClN_4O_2S$ (424.90): C, 59.36; H, 4.03; N, 13.19%. Found: C, 59.67; H, 4.39; N, 13.41%.

7-Chloromethyl-1,3-diphenyl-8H-1,4-dihydropyrimido[5′,4′:4,5]thieno[3,2-c]pyridazin-9-one (10)

A solution of compound **9** (1.27 g, 3 mmol) in glacial acetic acid (20 ml) containing acetic anhydride (5 ml) was heated at reflux for 5h. The reaction mixture was cooled, poured onto crushed ice (30 g), and the formed solid product was collected by filtration and recrystallized from benzene to give **10**. Yield, 0.66 g (54%); m.p. 177–179°C; IR:ν = 3290 (NH), 1675 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 3.85 (s, 2H, CH_2Cl), 4.23 (s, 2H, CH_2), 7.15–8.20 (m, 10H, ArH), 9.20 (s, 1H, NH, exchangeable); ^{13}C NMR: δ = 30.2 (CH_2), 52.1 (CH_2Cl), 129.2 (C-9b), 141.1 (C-5a), 146.2 (C-9a), 147.3 (C-4a), 160.5 (C-3), 168.4 (C-7), 177.2 (CO); Anal. calcd. for $C_{21}H_{15}ClN_4OS$ (406.89): C, 61.99; H, 3.72; N, 13.77%. Found: C, 61.60; H, 3.32; N, 13.98%.

7-Ethoxymethyl-1,3-diphenyl-8H-1,4-dihydropyrimido[5′,4′:4,5]thieno[3,2-c]pyridazin-9-one (11)

A solution of compound **10** (1.22 g, 3 mmol) in sodium ethoxide solution (0.46 g of sodium in 30 ml of absolute ethanol) was heated at reflux for 1 h. The precipitate that formed on cooling was collected and recrystallized from toluene to give **11**. Yield, 0.91 g (73%); m.p. 202–204°C; IR:ν = 3260 (NH), 1670 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 1.40 (t, 3H, CH_3), 3.75 (q, 2H, $\underline{CH_2}CH_3$), 3.95 (s, 2H, CH_2O), 4.10 (s, 2H, CH_2), 7.13–8.15 (m, 10H, $\overline{ArH}$), 9.31 (s, 1H, NH, exchangeable); Anal. calcd. for $C_{23}H_{20}N_4O_2S$ (416.50): C, 66.33; H, 4.84; N, 13.45%. Found: C, 66.70; H,4.98; N, 13.10%.

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1,3-Diphenyl-7-(piperidin-1-ylmethyl/morpholin-4-ylmethyl)-8H-1,4-dihydropyrimido[5′,4′:4,5]thieno[3,2-c]pyridazin-9-ones (12a,b)

Compound **10** (1.22 g, 3 mmol) in piperidine or morpholine (10 ml) was heated on a water bath for 4 h. The reaction mixture was then triturated with ethanol (20 ml) and left to cool. The precipitate was collected and recrystallized from ethanol to give **12a,b**.

12a; Yield, 1.04 g (76%); m.p. 183–185°C; IR:ν = 3260 (NH), 1672 cm^{-1} (CO); MS: m/z: 455 (M^+); Anal. calcd. for $C_{26}H_{25}N_5OS$ (455.58):C, 68.55; H, 5.53; N, 15.37%. Found: C, 68.81; H, 5.84; N, 15.10%.

12b; Yield, 0.99 g (72%); m.p. 196–198°C; IR:ν = 3290 (NH), 1670 cm^{-1} (CO); ^{1}H NMR (DMSO): δ = 2.40–2.60 (m, 4H, CH_2NCH_2), 3.20–3.50 (m, 4H, CH_2OCH_2), 3.77 (s, 2H, CH_2N), 4.10 (s, 2H, CH_2), 7.30–8.21 (m, 10H, ArH); 9.11 (s, 1H, NH, exchangeable); Anal. calcd. for $C_{25}H_{23}N_5O_2S$ (457.55): C, 65.63; H, 5.07; N, 15.31%. Found: C, 65.95; H, 5.30; N, 15.05%.

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1,3-Diphenyl-7-mercaptomethyl-8H-1,4-dihydropyrimido-[5′,4′:4,5]thieno[3,2-c]pyridazin-9-one (13)

A mixture of compound **10** (1.22 g, 3 mmol) and thiourea (0.23 g, 3 mmol) in absolute ethanol (25 ml) was refluxed for 4 h. The product that formed while hot was collected and dissolved in aqueous sodium hydroxide (10%, 10 ml), then heated on a water bath for 1 h. The reaction mixture was filtered off and the clear filtrate was acidified with acetic acid. The formed yellow precipitate was collected and recrystallized from ethanol to give **13**. Yield, 1.00 g (83%); m.p. 281–283°C; IR:ν = 3290 (NH), 2585 (SH), 1670 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 2.40 (s, 1H, SH), 3.75 (s, 2H, CH_2S), 4.20 (s, 2H, CH_2), 7.13–8.12 (m, 10H, ArH); ^{13}C NMR: δ = 30.1 (CH_2), 33.5 (CH_2SH), 128.3 (C-9b), 130.3 (C-5a), 136.8 (C-9a), 143.4 (C-4a), 152.3 (C-3), 156.7 (C-7), 176.5 (CO); Anal. calcd. for $C_{21}H_{16}N_4OS_2$ (404.51): C, 62.35; H, 3.99; N, 13.85%. Found: C, 62.10; H, 3.65; N, 13.51%.

General Procedure for the Preparation of Compounds 15a,b

A mixture of compound **1** (1.04 g, 3 mmol) and malononitrile or ethyl cyanoacetate (3 mmol) in ethanol (30 ml) containing a catalytic amount of triethylamine (0.6 ml), was heated at reflux for 8 h. The reaction mixture was cooled, poured onto cold water (25 ml), neutralized with

dilute HCl. The formed solid product was collected by filtration and recrystallized to give **15a,b**.

(5,7-Diphenyl-4-oxo-3,4,5,8-tetrahydropyrimido[5′,4′:4,5]-thieno[3,2-c]pyridazin-2-yl)acetonitrile (15a)

Yield, 0.61 g (51%) (ethanol); m.p. 192–194°C; IR:ν = 3260 (NH), 2225 (C≡N), 1670 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 4.12 (s, 2H, CH_2), 4.50 (s, 2H, CH_2CN), 7.15–8.10 (m, 10H, ArH), 9.15 (s, 1H, NH, exchangeable); ^{13}C NMR: δ = 29.3, 30.2 ($2CH_2$), 120.1 (CN), 127.3 (C-4b), 130.2 (C-9a), 136.4 (C-4a), 145.2 (C-8a), 153.4 (C-2), 156.3 (C-7), 176.5 (CO); Anal. calcd. for $C_{22}H_{15}N_5OS$ (397.45): C, 66.48; H, 3.80; N, 17.62%. Found: C, 66.75; H, 3.98; N, 17.30%.

2-(5,7-Diphenyl-4-oxo-3,4,5,8-tetrahydropyrimido[5′,4′:4,5]-thieno[3,2-c]pyridazin-2-yl)acetamide (15b)

Yield, 0.66 g (53%) (ethanol); m.p. 205–207°C; IR:ν = 3410–3240 (NH_2, NH), 1670–1665 cm^{-1} (CO); ^{1}H NMR (DMSO): δ = 3.50 (s, 2H, CH_2CO), 4.20 (s, 2H, CH_2), 5.95 (br s, 2H, NH_2), 7.30–8.20 (m, 10H, ArH), 9.20 (s, 1H, NH, exchangeable); Anal. calcd. for $C_{22}H_{17}N_5O_2S$ (415.47): C, 63.60; H, 4.12; N, 16.86%. Found: C, 63.95; H, 4.41; N, 16.52%.

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2-(5,7-Diphenyl-4-oxo-3,4,5,8-tetrahydropyrimido[5′,4′:4,5]-thieno[3,2-c]pyridazin-2-yl)-3-[phenyl/(4-methoxyphenyl)] acrylonitriles (16a,b)

A mixture of compound **15a** (1.19 g, 3 mmol) and the aromatic aldehyde (3 mmol) in absolute ethanol (40 ml) containing a catalytic amount of piperidine (0.4 ml), was heated at reflux for 6 h. The reaction mixture was poured onto ice (30 g) and neutralized with dilute HCl. The formed solid product was filtered off and recrystallized to give **16a,b**.

16a; Yield, 1.02 g (70%) (DMF-H_2O); m.p. 212–214°C; IR:ν = 3290 (NH), 2215 (C≡N), 1665 cm^{-1} (CO); MS: m/z: 485 (M^+); Anal. calcd. for $C_{29}H_{19}N_5OS$ (485.56): C, 71.73; H, 3.94; N, 14.42%. Found: C, 71.40; H, 3.61; N, 14.75%.

16b; Yield, 0.97 g (63%) (1,4-dioxane); m.p. 202–204°C; IR:ν = 3280 (NH), 2224 (C≡N), 1675 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$): δ = 3.95 (s, 3H, OCH_3), 4.20 (s, 2H, CH_2), 7.30–8.25 (m, 15H, ArH and benzylic proton); 9.20 (s, 1H, NH, exchangeable); Anal. calcd. for $C_{30}H_{21}N_5O_2S$ (515.59): C, 69.89; H, 4.11; N, 13.58%. Found: C, 69.95; H, 4.31; N, 13.22%.

(5,7-Diphenyl-4-oxo-3,4,5,8-tetrahydropyrimido[5′,4′:4,5] thieno[3,2-c]pyridazin-2-yl)phenylhydrazono/(4-methoxyphenylhydrazono)acetonitriles (17a,b)

To a cold solution (0−5°C) of compound **15a** (1.19 g, 3 mmol) in absolute ethanol (40 ml) containing sodium acetate (1.80 g), a cold solution of aryl diazonium chlorides [prepared from the corresponding aryl amine (3 mmol) and appropriate quantities of concentrated HCl (10 ml) and $NaNO_2$ (2.00 g)] were added dropwise with stirring for 30 min. After the complete addition, the reaction mixture was stirred at room temperature for additional 1 h. The precipitated product was filtered off, washed with water (3 × 40 ml) and recrystallized to give **17a,b**.

17a; Yield, 1.01 g (67%) (1,4-dioxane); m.p. 190−192°C; IR:ν = 3290−3200 (NH), 2215 (C≡N), 1673 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 4.11 (s, 2H, CH_2), 7.40−8.13 (m, 15H, ArH), 9.10, 9.23 (2s, 2H, 2NH, exchangeable); Anal. calcd. for $C_{28}H_{19}N_7OS$ (501.56): C, 67.05; H, 3.82; N, 19.55%. Found: C, 67.38; H, 3.99; N, 19.21%.

17b; Yield, 0.95 g (60%) (n-butanol); m.p. 201−203°C; IR:ν = 3310−3250 (NH), 2220 (C≡N), 1670 cm^{-1} (CO); Anal. calcd. for $C_{29}H_{21}N_7O_2S$ (531.59): C, 65.52; H, 3.98; N, 18.44%. Found: C, 65.21; H, 3.59; N, 18.77%.

2,4-Diamino-5-(5,7-diphenyl-4-oxo-3,4,5,8-tetrahydropyrimido-[5′,4′:4,5]thieno[3,2-c]pyridazin-2-yl)thiophene-3-carbonitrile (18a) and 4-amino-2-hydroxy-5-(5,7-diphenyl-4-oxo-3,4,5,8-tetrahydropyrimido[5′,4′:4,5]thieno[3,2-c]pyridazin-2-yl)-thiophene-3-carbonitrile (18b)

A mixture of compound **15a** (1.19 g, 3 mmol), elemental sulfur (0.096 g, 3 mmol) and malononitrile or ethyl cyanoacetate (3 mmol) in absolute ethanol (25 ml) containing a catalytic amount of triethylamine (0.5 ml) was heated at reflux for 6 h. The reaction mixture was cooled, poured onto ice (20 g) and neutralized with dilute hydrochloric acid. The formed solid product was collected by filtration and recrystallized to give **18a,b**.

18a; Yield, 0.87 g (59%) (1,4-dioxane); m.p. 230−232°C; IR:ν = 3480−3310 (NH_2, NH), 2215 (C≡N), 1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 4.10 (s, 2H, CH_2), 5.85, 5.95 (2br s, 4H, $2NH_2$), 7.20−8.12 (m, 10H, ArH); 9.21 (s, 1H, NH, exchangeable); ^{13}C NMR: δ = 30.3 (CH_2), 108.2 (C-3 of thiophene), 110.2 (CN), 120.1 (C-4 of thiophene), 123.3 (C-5 of thiophene), 128.3 (C-2 of thiophene), 119.3 (C-4b), 132.1 (C-9a), 135.2 (C-8a), 136.3 (C-4a), 150.2 (C-2), 151.3 (C-7), 176.4 (CO); Anal. calcd. for $C_{25}H_{17}N_7OS_2$ (495.58): C, 60.59; H, 3.46; N, 19.78%. Found: C, 60.21; H, 3.12; N, 19.96%.

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18b; Yield, 0.86 g (58%) (DMF-H_2O); m.p. 260–262°C; IR:ν = 3495–3300 (OH, NH_2, NH), 2217 (C≡N), 1670 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 4.11 (s, 2H, CH_2), 5.85 (br s, 2H, NH_2), 7.30–8.20 (m, 10H, ArH), 9.12 (s, 1H, NH, exchangeable); Anal. calcd. for $C_{25}H_{16}N_6O_2S_2$ (496.57): C, 60.47; H, 3.25; N, 16.92%. Found: C, 60.81; H, 3.57; N, 16.61%.

5,7-Diphenyl-5,8-dihydropyridazino[3′,4′:4,5]thieno[2,3-d]-1,2,3-triazin-4(3H)-one (19)

To a cold solution of compound **1** (1.04 g, 3 mmol) in acetic acid (25 ml), a cold solution of sodium nitrite (1.20 g in 3 ml H_2O) was added dropwise with stirring. The stirring was continued for 1 h and left to stand at room temperature for 2 h. The solid product formed was collected by filtration and recrystallized from n-butanol to give **19**. Yield, 0.57 g (53%); m.p. 221–223°C; IR:ν = 3325 (NH), 1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 4.13 (s, 2H, CH_2), 7.12–8.20 (m, 10H, ArH), 9.10 (s, 1H, NH, exchangeable); ^{13}C NMR: δ = 30.9 (CH_2), 118.3 (C-4b), 138.3 (C-9a), 144.3 (C-8a), 148.3 (C-4a), 157.4 (C-7), 177.3 (CO); Anal. calcd. for $C_{19}H_{13}N_5OS$ (359.41): C, 63.49; H, 3.65; N, 19.49%. Found: C, 63.20; H, 3.25; N, 19.76%.

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5,7-Diphenyl-3-(methyl/phenacyl)-5,8-dihydropyridazino-[3′,4′:4,5]thieno[2,3-d]-1,2,3-triazin-4(3H)-ones (20a,b)

A solution of compound **19** (0.72 g, 2 mmol), potassium hydroxide (15%, 2 ml) and methyl iodide or phenacyl bromide (4 mmol) in acetone (20 ml) was refluxed for 5 h. The solvent was removed under reduced pressure, cold water (25 ml) was added. The mixture was neutralized with 2N HCl (18 ml). The solid formed was collected by filtration and recrystallized to give **20a,b**.

20a; Yield, 0.44 g (59%) (DMF); m.p. 231–233°C; IR:ν = 1670 cm^{-1} (CO); MS: m/z: 373 (M^+); Anal. calcd. for $C_{20}H_{15}N_5OS$ (373.43): C, 64.33; H, 4.05; N, 18.75%. Found: C, 64.67; H, 4.38; N, 18.40%.

20b; Yield, 0.48 g (50%) (1,4-dioxane); m.p. 217–219°C; IR:ν = 1680–1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 4.13 (s, 2H, CH_2), 4.85 (s, 2H, CH_2CO), 7.13–8.15 (m, 15H, ArH); Anal. calcd. for $C_{27}H_{19}N_5O_2S$ (477.54): C, 67.91; H, 4.01; N, 14.67%. Found: C, 67.55; H, 3.84; N, 14.92%.

General Procedure for the Preparation of Compounds 22a,b

To a suspension of **1** (1.04 g, 3 mmol) in absolute ethanol (25 ml) containing a catalytic amount of piperidine (0.4 ml), the appropriate α-substituted cinnamonitrile derivatives (3 mmol) were added. The reaction mixture was refluxed for 8 h. The reaction mixture was cooled and triturated with cold water (20 ml), then neutralized with HCl. The resulting solid product was collected by filtration and recrystallized to give **22a,b**.

9-Hydroxy-1,3,7-triphenyl-1,4-dihydropyrido[3′,2′:4,5]-thieno[3,2-c]pyridazine-8-carbonitrile (22a)

Yield, 0.86 g (63%) (ethanol); m.p. 251−253°C; IR:$\nu = 3495-3200$ (OH), 2215 cm^{-1} (C≡N); MS: m/z: 458 (M^+); Anal. calcd. for $C_{28}H_{18}N_4OS$ (458.53): C, 73.34; H, 3.96; N, 12.22%. Found: C, 73.10; H, 3.79; N, 12.01%.

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Ethyl 9-Hydroxy-1,3,7-triphenyl-1,4-dihydropyrido[3′,2′:4,5]-thieno[3,2-c]pyridazine-8-carboxylate (22b)

Yield, 1.07 g (71%) (n-butanol); m.p. 273−275°C; IR:$\nu = 3490-3210$ (OH), 1725 cm^{-1} (CO); ^1H NMR ($CDCl_3$): $\delta = 1.75$ (t, 3H, CH_3), 4.10 (s, 2H, CH_2), 4.50 (q, 2H, CH_2), 7.15−8.20 (m, 15H, ArH), 10.50 (br s, 1H, OH, exchangeable); Anal. calcd. for $C_{30}H_{23}N_3O_3S$ (505.59): C, 71.27; H, 4.59; N, 8.31%. Found: C, 71.53; H, 4.85; N, 8.67%.

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