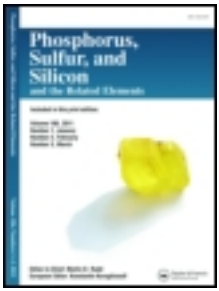

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Pyridazine Derivative and Related Compound, Part 18:[1] Pyridazino [3′,4′:3,4]pyrazolo [5,1-c]-1,2,4-triazine-3-carboxylic Acid: Synthesis, Reactions, and Antimicrobial Activity

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Pyridazine Derivative and Related Compound, Part 18:[1] Pyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine-3-carboxylic Acid: Synthesis, Reactions, and Antimicrobial Activity

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A series of 3-substituted pyridazino[3′,4′:3,4]pyrazolo[5,1-c]-1,2,4-triazens have been synthesized starting from the 3-carboxylic acid derivative ***2****. The reaction of the acid chloride* ***3*** *with amines gave the corresponding anilides* ***4****. The reaction of* ***2*** *with ethyl chloroformate and sodium azide in the presence of triethyl amine gave the carbonyl azide* ***5****, which underwent a Curtius rearrangement in boiling ethanol to afford the carbamate* ***6****, which converted to the 3-amino derivative* ***7*** *upon alkaline hydrolysis, and the reaction with acid chloride resulted in N-substituted products* ***9****. On other hand, the reaction of the carboxylic acid* ***2*** *with* $POCl_3$ *and thiosemicarbazide afforded 2-amino-1,3,4-thiadiazole derivative* ***13****. The condensation of* ***13*** *with aldehydes furnished* ***14*** *in a good yield. The products were screened for their antimicrobial activity against six microorganisms.*

Keywords Antimicrobial; 3-subsitituted pyridazinopyrazolotriazines

INTRODUCTION

Derivatives of pyridazines and heterocyclic annelated pyridazines are known to possess potent biological and pharmacological properties.[2–5] As a part of continuing study on the synthesis and antimicrobial activity of fused pyridazines.[6] During the biological screening of substituted pyridazino[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazines,[1]

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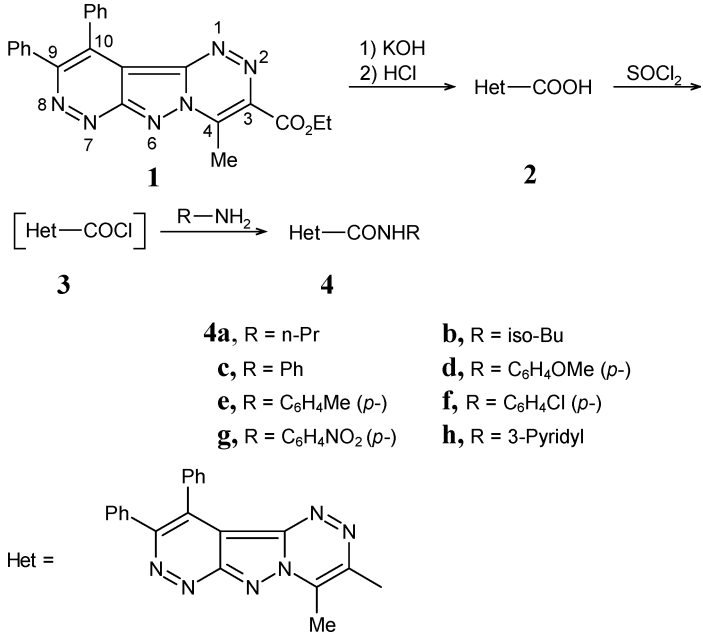
some showed significant activity. The most active of these was 4-amino-5-(4-methyl-9, 10-diphenyl-pyridazino[3′,4′:3, 4]pyrazolo [5,1-*c*]-1,2,4-triazin-3-yl)- 2,3-dihydro-1,2,4-triazole-3-thione which had anti *S. aureus* and *Ps. aeruginosa* activity. The work has now been extended further, and a number of related pyridazino[3′,4′:3, 4] pyrazolo[5,1-*c*]-1,2,4-triazines have been synthesized to exploit the lead.

CHEMISTRY

The required 4-methyl-9,10-diphenypyridiazino[3′,4′:3,4]pyrazolo [5,1-*c*]-1,2,4-triazine-3-carboxylic acid **2** was prepared by the saponification of 3-carboxylate ester **1**[7] with potassium hydroxide followed by acidification (Scheme 1). The structure of compound **2** was assigned on the basis of analytical spectral data. The infrared spectrum revealed the presence of a broad band at 3200-2900 cm^{-1} (OH), and an absorption at 1725 cm^{-1} referred to the carbonyl of the carboxylic acid group. Treatment of **2** with thionyl chloride gave the acid chloride **3**, which was too unstable to be isolated.

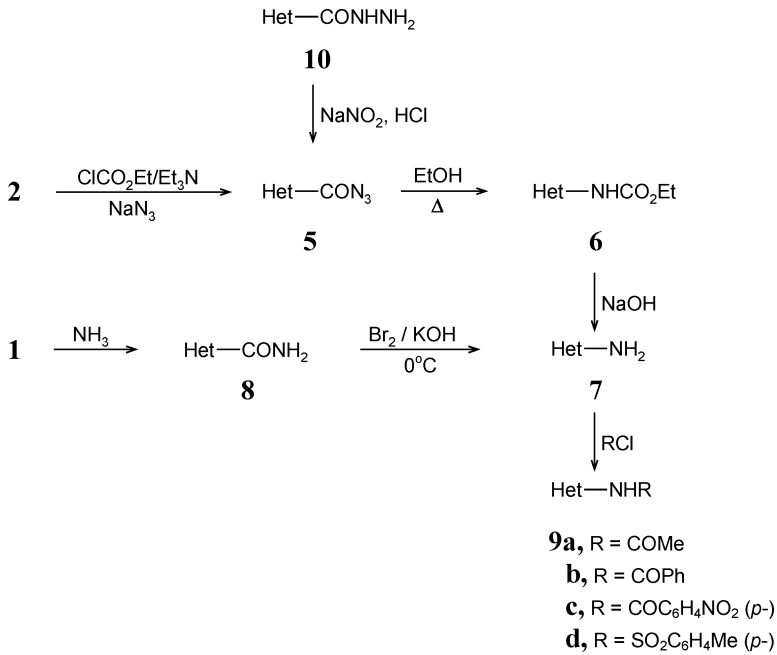


SCHEME 1

The reaction of **3** with aliphatic, aryl, and heteroarylamines such as n-propylamine, isobutylamine, aniline, *p*-anisidine, *p*-toluidine,

p-chloroaniline, *p*-nitroaniline, and 3-aminopyridine was carried out by heating under reflux in excess of amine and in benzene. The products that were identified as anilides **4a–h** (Scheme 1). The structural formulas were assigned considering the analytical and spectroscopic data.

In addition, the reaction of compound **2** with ethyl chloroformate and triethylamine in acetone gave a mixed acid anhydride, which was converted to the acid azide **5** using sodium azide in a one-pot synthesis. An IR analysis of this compound showed a strong azide absorption at 2146 cm^{-1}. The carbonyl azide **5** was also obtained by converting the ester **1** into the corresponding acid hydrazide **10**[6] followed by treatment with nitrous acid. The compound was sufficiently pure for further use in rearrangement reactions. It underwent a Curtius rearrangement in boiling ethanol to afford the carbamate **6**, which provided the expected 3-amino derivative **7** by alkaline hydrolysis (Scheme 2). Compound **7** was also obtained following another procedure by converting the ester **1** into the corresponding amide **8** followed by treatment with bromine and dilute aqueous potassium hydroxide at 0°C. The resulting Hofmann reaction product **7** was obtained in an 80% yield.



SCHEME 2

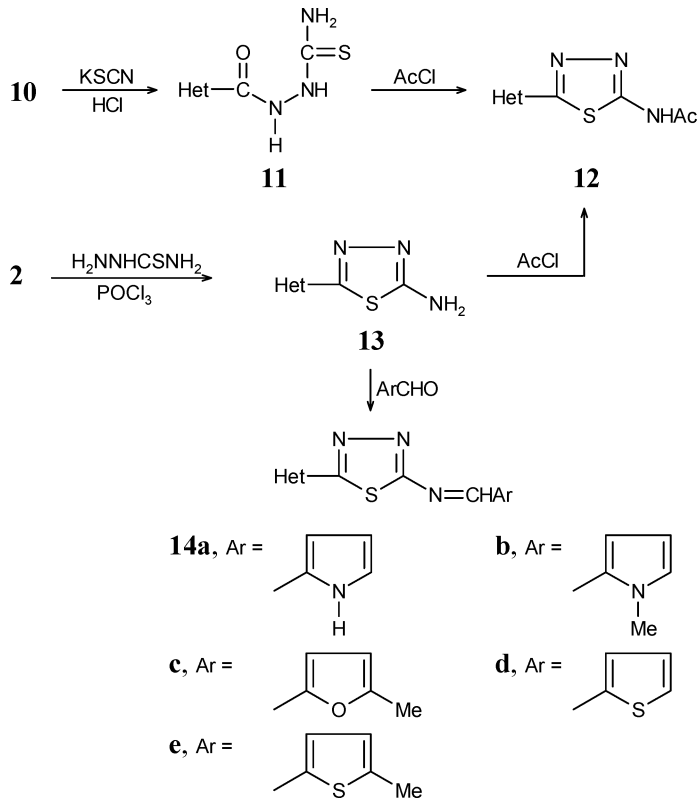
The structure of compound **7** was confirmed on the basis of analytical data and spectral evidence. The mass spectra showed the expected

molecular ion peak at $m/z = 353$, and the IR spectra exhibited characteristic bands of the amino group. Compound **7** with a free amino group at the 3-position reacted with acetyl chloride, benzoyl chloride, p-nitrobenzoyl chloride, or p-toluenesulfonyl chloride, by refluxing in acetonitrile and in dry pyridine to give N-substituted products **9a–d**. The structure of compound **9a–d** was established by spectral data and elemental analysis (*cf.* Experimental section).

On the other hand, the reaction of the carboxylic acid **2** with phosphourus oxychloride and thiosemicarbazide afforded 2-amino-1,3,4-thiadiazole derivative **13**. The structure of **13** was evident from its spectral data. The absence of a ν C=O band and the appearance of new bands in the region of 3475 and 3340 $cm^{-1}(NH_2)$ in the IR spectra and the mass spectral recorded molecular ion peak at m/z 437 corresponding to the molecular ion were particularly diagnostic. Additional evidence for the structure of **13** was provided by its reaction with acetyl chloride, which yielded 2-acetylamino **12** in an 88% yield. Compound **12** was also obtained following another procedure by converting the acid hydrazide **10** into 3-carbothiosemi-carbazide **11** followed by the cyclodehydration in the presence of acetyl chloride, which led to **12**[1]. The condensation of **13** with appropriate aldehyde in an ethanolic medium furnished **14a–e** in a good yields (Scheme 3). The structure of compounds **14a–e** were elucidated on the basis of their analytical and IR data. The IR absorption spectra showed the disappearance of the bands referred to the NH_2 group. The mass spectral of compounds **14a**, **14c,** and **14e** recorded molecular ion peaks at m/z 514, 529, and 545 corresponding to the molecular ions that were particularly diagnostic.

ANTIMICROBIAL ACTIVITY

Applying the agar plate diffusion technique,[7] some of the newly synthesized compounds were screened in vitro for antimicrobial activity against representative of gram positive bacteria (*Bacillus subtilis, Staphylococcus aureus*), gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*), yeast (*Candida albicans*), and fungi (*Asperggillus niger*). In this method, a standard 5-mm diameter sterilized filter paper disc impregnated with the compound (0.3 mg/0.1 mL of dimethylformamide) was placed on an agar plate seeded with the test organism. The plates were incubated for 24 h at 37°C. The zone of inhibition of bacterial growth around the disc was observed. The screening results given in Table I indicated that all the compounds exhibited antimicrobial activity against one or the other type of bacteria and fungi. Series **4** showed the highest inhibitory effect against all the test organisms. The N-substituted derivative **9** had activity against gram positive



SCHEME 3

B. Subtilis and *S. aureus*. Almost all the thiadiazole derivatives **14** showed low inhibition.

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. IR spectra of the compounds were recorded on a Perkin-Elmer spectrophotometer model 1430 as potassium bromide pellets and frequencies are reported in cm^{-1}. The ^1H NMR spectra were recorded on a Perkin-Elmer R12 B spectrometer, and chemical shifts (δ) are in ppm relative to internal TMS. Mass spectra were recorded on a Mass Spectrometer HP model MS 5988 E1 70 ev. Reactions were routinely followed by TLC on silica gel F_{254} aluminium sheets (Merck). The spots were detected by UV irradiation at 254–365 nm.

Compounds **1**, **2,** and **11** were synthesized as reported previously.[1,6]

TABLE I Antibacterial and Antifungal Activity

No.	*B. subtitils*	*S. aureus*	*E. coli*	*P. aeurgin.*	*C. albicans*	*A. niger*
4a	++	+++	++	++	++	−
4b	+++	+++	+++	+++	+++	−
4c	++	+++	++	++	++	++
4d	+++	+++	+++	+++	+++	+++
4e	++	++	++	++	++	++
4f	++	++	++	++	++	+
4g	++	++	++	++	++	−
4h	+++	+++	+++	+++	++	++
6	++	++	++	++	+	−
7	+	+	+	+	−	−
9a	+	++	−	−	−	−
9b	+	+	−	−	−	−
9c	+++	+++	−	−	−	−
9d	++	+++	−	−	−	−
11	+	+	−	−	−	−
13	+	+	−	−	−	−
14a	++	+	++	++	++	++
14b	+	+	−	−	−	−
14c	+	+	−	−	−	−
14d	+	+	−	−	−	−
14e	+	+	−	−	−	−

Zone of inhibition: + = 10–15 mm; ++ = 15–20 mm; +++ = 20–25 mm; − = no inhibition.

3-Chlorocarbonyl-4-methyl-9,10-diphenylpyridazino [3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine (3)

A mixture of **2** (0.5 g, 1.31 mmoles) and thionyl chloride (5 mL) was gently refluxed on a steam bath for 30 min. The excess of thionyl chloride was removed under reduced pressure to give 0.4 g, 76.3% of **3** which was used without purification.

3-Substituted carbamoyl-4-methyl-9,10-diphenylpyridazino [3′,4′:3,4]-pyrazolo[5,1-*c*]-1,2,4-triazine (4a–i)

General Procedures: For 4a,b

The acid chloride **3** (0.4 g, 0.99 mmoles) and a moderate excess of the corresponding n-propylamine and/or isobutylamine (molar ratio 1:3) were refluxed together for 1 h. After cooling to r.t. the precipitate that formed was filtered off and recrystallized from ethanol.

For 4c–i

Acid chloride **3** (0.4 g, 0.99 mmoles) and appropriate amine were refluxed in benzene (10 mL) for 1 h. The solvent was evaporated, and the residue was treated with diethylether to give crude products, which were recrystallized from ethanol.

4-Methyl-9,10-diphenyl-3-N-propylcarbamoylpyridazino [3′,4′:3,4]-pyrazolo[5,1-*c*]-1,2,4-triazine (4a)

The yield was 88%, m.p. 220–221°C; IR: 3423 (NH), 1660 cm^{-1} (C=O). Anal. calcd. for $C_{24}H_{21}N_4O$: C, 68.07; H, 4.99; N, 23.15. Found: C, 67.80; H, 4.70; N, 23.00.

3-N-Isobutylcarbamoyl-4-methyl-9,10-diphenylpyridazino [3′,4′:3,4]-pyrazolo[5,1-*c*]-1,2,4-triazine (4b)

The yield was 90%, m.p. 160–161°C; IR: 3406 (NH), 1655 cm^{-1} (C=O). Anal. calcd. for $C_{25}H_{23}N_7O$: C, 68.63; H, 5.29; N, 22.41. Found: C, 68.40; H, 5.10; N, 22.20.

4-Methyl-9,10-diphenyl-3-N-phenylcarbamoylpyridazino [3′,4′:3,4]-pyrazolo[5,1-*c*]-1,2,4-triazine (4c)

The yield was 88%, m.p. 161–162°C; IR: 3388 (NH), 1650 cm^{-1} (C=O); ms (*m/z*, %), 443 (M^+-2, 2), 429 (3), 425 (5), 383 (13), 313 (10), 286 (100). Anal. calcd. for $C_{27}H_{19}N_7O$: C, 70.88; H, 4.18; N, 21.43. Found: C, 70.60; H, 4.00; N, 21,20.

4-Methyl-9,10-diphenyl-3-N-p-methoxyphenylcarbamoylpyridazino-[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine (4d)

The yield was 88%, m.p. 200–201°C; IR: 3405 (NH), 1650 cm^{-1} (C=O); ms (*m/z*, %), 486 (M^+-1, 3), 356 (38), 270 (26). Anal. calcd. for $C_{28}H_{21}N_7O_2$: C, 68.98; H, 4.34; N, 20.11. Found: C, 68.80; H, 4.20; N, 19.90.

4-Methyl-9,10-diphenyl-3-N-p-tolylcarbamoylpyridazino [3′,4′:3,4]-pyrazolo[5,1-*c*]-1,2,4-triazine (4e)

The yield was 80%, m.p. 240–241°C; IR: 3529 (NH), 1680 cm^{-1} (C=O); ms (*m/z*, %), 473 (M^+-2, 2), 305 (10), 287 (46), 286 (84). Anal. calcd. for

$C_{28}H_{21}N_7O$: C, 71.32; H, 4.48; N, 20.79. Found: C, 71.10; H, 4.30; N, 20.60.

3-N-p-Chlorophenylcarbamoyl-4-methyl-9,10-diphenylpyridazino-[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine (4f)

The yield was 75%, m.p. 230–231°C; IR: 3443 (NH), 1684 cm^{-1} (C=O). Anal. calcd. for $C_{27}H_{18}ClN_7O$: C, 65.92; H, 3.69; N, 19.93. Found: C, 65.80; H, 3.40; N, 19.70.

4-Methyl-3-N-p-nitrophenylcarbamoyl-9,10-diphenylpyridazino-[3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine (4g)

The yield was 50%, m.p. 288–290°C; IR: 3448 (NH), 1702 (C=O), 1570–1500 cm^{-1} (NO_2), ^{1}HNMR (DMSO-d_6): δ 11.3 (s, 1H, NH), 8.1 (m, 4H, Ph-3), 7.2 (m, 10H, 2Ph), 2.2 (s, 3H, CH_3). Anal. calcd. for $C_{27}H_{18}N_8O_3$: C, 64.53; H, 3.61; N, 22.30. Found: C, 64.40; H, 3.40; N, 22.10.

4-Methyl-9,10-diphenyl-3-N-3-pyridylcarbamoylpyridazino [3′,4′:3,4]-pyrazolo[5,1-*c*]-1,2,4-triazine (4h)

The yield was 75%, m.p. 188–190°C; IR: 3750 (NH), 1728 cm^{-1} (C=O); ^{1}HNMR ($CDCl_3$): δ 7.8–7.0 (m, 14H, aromatic protons), 2.05 (s, 3H, CH_3). Anal. calcd. for $C_{26}H_{18}N_8O$: C, 68.11; H, 3.95; N, 24.44. Found: C, 67.90; H, 3.70; N, 24.20.

3-Azidocarbonyl-4-methyl-9,10-diphenylpyridazino [3′,4′:3,4]pyrazolo-[5,1-*c*]-1,2,4-triazine (5)

Method A

Compound **2** (3.82 g, 10 mmoles) was suspended in 35 mL of acetone and cooled to 0°C, and triethylamine (5 mL) was added under stirring. Then the solution of ethyl chloroformate (1.08 g, 10 mmoles) in 5 mL of acetone was added dropwise keeping the temperature below 0°C. The mixture was stirred for 30 min, then sodium azide (0.65 g, 10 mmoles) in 12 mL of water was added. The mixture was stirred for an additional hour and then poured into ice water (140 mL). The yellow precipitate was filtered off, washed with water, and air dried. Yield 9.86 g, 93%, m.p. 160°C (dec) (dichloromethane/hexane); IR: 2146 (N_3), 1682 cm^{-1} (C=O). Anal. calcd. for $C_{21}H_{13}N_9O$: C, 61.91; H, 3.21; N, 30.95. Found: C, 61.70; H, 3.00; N, 30.80.

Method B

To a cold suspension of compound **10** (0.39 g, 10 mmoles) in 3 M hydrochloric acid (3 mL), a solution of sodium nitrite (0.14 g, 20 mmoles) in water (1 mL) was added dropwise with stirring. After 30 min, a small amount of urea was added; then the yellow solid **5** was filtered and washed with water, 0.36 g (90%). The products obtained by the two synthetic routes are identical in all aspects.

3-Ethoxycarbonylamino-4-methyl-9,10-diphenylpyridazino [3′,4′:3,4]-pyrazolo[5,1-*c*]-1,2,4-triazine (6)

A solution of the azide **5** (1.19 g, 2.94 mmoles) in absolute ethanol (10 mL) was refluxed for 24 h. The title compound precipitated by cooling as a white solid, which was recrystallized from ethanol to give 0.83 g, 67%, m.p. 135°C (dec.); IR: 3374 (NH), 1754 cm^{-1} (C=O). Anal. calcd. for $C_{23}H_{19}N_7O_2$: C, 64.92; H, 4.50; N, 23.04. Found: C, 64.70; H, 4.20; N, 22.80.

3-Carboxamido-4-methyl-9,10-diphenylpyridazino [3′,4′:3,4]pyrazolo-[5,1-*c*]-1,2,4-triazine (8)

Ammonia gas was bubbled for 2 h in a solution of compound **1** (0.8 g, 1.94 mmoles) in dry methanol (20 mL) at r.t. When the solution was concentrated to a small volume, the crystalline solid precipitated and was collected by filtration, yield 0.63 g, 85%. An analytical sample was recrystallized from methanol, m.p. 240–241°C; IR: 3381, 3197 (NH_2), 1683 cm^{-1} (C=O). Anal. calcd. for $C_{21}H_{15}N_7O$: C, 66.13; H, 3.96; N, 25.71. Found : C, 65.90; H, 3.80; N, 25.50.

3-Amino-4-methyl-9,10-diphenylpyridazino [3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine (7)

Method A: From 3-Ethoxycarbonylamino Derivative 6

A solution of 3-ethoxycarbonylamino derivative **6** (0.4 g, 0.94 mmoles) in ethanol (6 mL) and 2 M sodium hydroxide (10 mL) was gently refluxed for 5 h. After cooling, the solution was extracted with dichloromethane, and the organic layer was evaporated to give the title compound, 0.1 g, 30%, m.p. 214–215°C (ethanol); IR; 3420 cm^{-1} (NH_2); ms (*m/z*, %): (M^+-1, 7), 351 (18), 349 (13), 270 (13). Anal. calcd. for $C_{20}H_{15}N_7$: C, 67.97; H, 4.28; N, 27.75. Found: C, 67.80; H, 4.00; N, 27.50.

Method B: From 3-Carboxamide Derivative (8)

A mixture of 3-carboxamide derivative **8** (0.78 g, 2.04 mmoles) and 1 N KOH (20 mL) was stirred at 0°C. To the fine suspension was quickly added with rapid stirring a mixture of bromine (0.5 mL) and 1 N KOH

(5 mL). After brief stirring at 0°C, the mixture was heated up immediately in a boiling water bath for 1 h. The reaction mixture was then cooled to 0°Cand was acidified with a dropwise addition of 2N HCl (10 mL). After 1 h stirring, the solid product was collected by filtration and washed with cold water. It was purified by recrystallization from ethanol to give 0.57 g, 80%; it was identical in all aspects with the product prepared by Method A.

3-Acetamido-4-methyl-9,10-diphenylpyridazino [3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine (9a)

A mixture of 3-amino derivative **7** (0.76 g, 2.15 mmoles) and acetyl chloride (5 mL) was warmed on a water-bath for 20 minutes and then decomposed in ice-water (20 mL). The insoluble material was collected, washed several times with water, and recrystallized from ethanol 0.7 g, 90%, m.p. 200-201°C; IR: 3230 (NH), 1670 cm^{-1} (C=O); ms (*m/z* %): 395 (M^+, 0.7), 352 (2.3), 351 (4.5). Anal. calcd. for $C_{22}H_{17}N_7O$: C, 66.82; H, 4.33; N, 24.80. Found: C, 66.60; H, 4.10; N, 24.60.

3-Benzamido-4-methyl-9,10-diphenylpyridazino [3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine (9b)

To a boiling solution of 3-amino derivative **7** (0.76 g, 2.15 mmoles) in acetonitrile (10 mL), benzoyl chloride (5 mL) was slowly dropped. Then, the mixture was boiled for 3 h and cooled. The precipitate was collected and recrystallized from ethanol to give 0.74 g, 90%, m.p. 290–291°C; IR: 3320 (NH), 1690 cm^{-1} (C=O). Anal. calcd. for $C_{27}H_{19}N_7O$: C, 70.88; H, 4.19; N, 21.43. Found: C, 70.60; H, 4.00; N, 21.20.

4-Methyl-3-p-nitrobenzoylamino-9,10-diphenylpyridazino[3′,4′:3,4]-pyrazolo[5,1-*c*]-1,2,4-triazine (9c)

Preparation of **9c** from **7** (0.76 g, 2.15 mmoles) and *p*-nitrobenzoyl chloride (5 mL) was carried out in a similar manner to that described for **9b**, yield 0.7 g, 80%, m.p. 210–211°C (ethanol); IR: 3144 (NH), 1696 (C=O), 1543 and 1349 cm^{-1} (NO_2). Anal. calcd. for $C_{27}H_{18}N_8O_3$: C, 64.54; H, 3.61; N, 22.30. Found: C, 64.30; H, 3.40; N, 22.20.

4-Methyl-3-tosylamino-9,10-diphenylpyridazino [3′,4′:3,4]pyrazolo[5,1-*c*]-1,2,4-triazine (9d)

A solution of **7** (0.76 g, 2.15 mmoles) and *p*-toluenesulfonyl chloride (0.4 g, 2.15 mmoles) in dry pyridine (10 mL) was refluxed for 3 h and

TABLE II 5-Heteroarylideneamino-2-(4-Methyl-9,10-Diphenylpyridazino[3′, 4′ : 3, 4]pyrazolo[5,1-*c*]-1,2,4-Triazin-3-Yl)-1,3,4-Thiadiazole (14a–e)

Compound no.	m.p. (°C)	Yield (%)	Molecular formula	Analysis (Calcd./ Found, %) C	H	N	IR	MS: *m/z*, %	^{1}HNMR (DMSO-d_6)
14a	230–232	88	$C_{27}H_{18}N_{10}S$	63.03 62.80	3.53 3.30	27.22 27.00	3163, 3059, 1606, 1562	514 (M^+, 0.6, 452 (1.1), 362 (3.6, 142 (17), 55 (100)	—
14b	220–221	83	$C_{28}H_{20}N_{10}S$	63.62 63.40	3.81 3.60	26.50 26.20	3057, 1602, 1565	—	—
14c	278–280	78	$C_{28}H_{19}N_9OS$	63.50 63.30	3.62 3.40	23.81 23.70	3060, 2987, 1617, 1563	529 (M^+, 0.5), 420 (2), 340 (10), 225 (17)	—
14d	130–131	83	$C_{27}H_{17}N_9S_2$	61.00 60.90	3.22 3.00	23.71 23.50	3060, 2924, 1610, 1562	—	—
14e	260–262	66	$C_{28}H_{19}N_9S_2$	61.63 61.40	3.51 3.40	23.10 23.00	3057, 2921, 1563, 1490	545 (M^+, 1), 540 (2), 425 (6), 340 (16)	8.5 (s, 1H, N=CH), 7.2–7.6 (m, 12H, arom. H), 2.45 (s, 3H, CH_3-4), 2.5 (s, 3H, CH_3-thiolphene-5)

then poured into water (50 mL). The resulting suspension was filtered with suction; the remaining solid was washed several times with water and recrystallized from ethanol to give 0.7 g, 70%, m.p. 207–208°C; IR: 3423 (NH), 1382 and 1187 cm^{-1} (SO_2). Anal. calcd. for $C_{27}H_{21}N_7O_2S$: C, 63.89; H, 4.17; N, 19.32. Found: C, 63.70; H, 4.00; N, 19.10.

5-Amino-2-(4-methyl-9,10-diphenylpyridazino[3′,4′:3,4] pyrazolo[5,1-c]-1,2,4-triazine-3-yl)-1,3,4-thiadiazole (13)

A mixture of compound **2**[6] (0.76 g, 1.98 mmoles), thiosemicarbazide (0.18 g, 2.0 mmoles), and phosphorus oxychloride (1.0 mL) was refluxed gently for half an hour. After cooling, water (2.6 mL) was added. The mixture was refluxed for 4 h and filtered. The solution was neutralized with potassium hydroxide. The precipitate was filtered and recrystallized from ethanol to give 0.69 g, 80% of **13**, m.p. 237–239°C; IR: 3475, 3340 (NH_2), 1610 cm^{-1} (C=N); ms (*m/z*%): 437 (M^+, 0.07), 435 (0.06), 423 (0.1), 286 (100). Anal. calcd. for $C_{22}H_{15}N_9S$: C, 60.40; H, 3.46; N, 28.82. Found: C, 60.20; H, 3.20; N, 28.70.

5-Acetylamino-2-(4-methyl-9,10-diphenylpyridazino [3′,4′:3,4]pyr-azolo[5,1-*c*]-1,2,4-triazin-3-yl)-1,3,4-thiadiazole (12)

A mixture of 5-amino derivative **13** (0.87 g, 1.98 mmoles) and acetyl chloride (20 mL) was warmed on a water-bath for 30 min and then decomposed in ice-water (100 mL). The insoluble material was collected, washed several times with water, and recrystallized from ethanol afforded 0.85 g, 85% of acetylamino derivative **12**, m.p. 270–272°C (ref.,[1] 268–270°C).

Reaction of 13 with Heteroaromatic Aldehydes: The Formation of 14a–e

General Procedure

A mixture of 5-amino derivative **13** (0.87 g, 1.98 mmoles) and heteroaromatic aldehydes (2.0 mmoles) in ethanol (20 mL) was refluxed for 3 h and then allowed to cool. The solid product was collected and recrystallized from ethanol. The results are summarized in Table II.

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