

**TETRAZOLO[1,5-*b*]PYRIDAZINE-8-CARBOHYDRAZIDE SYNTHESIS
AND SOME REACTIONS**

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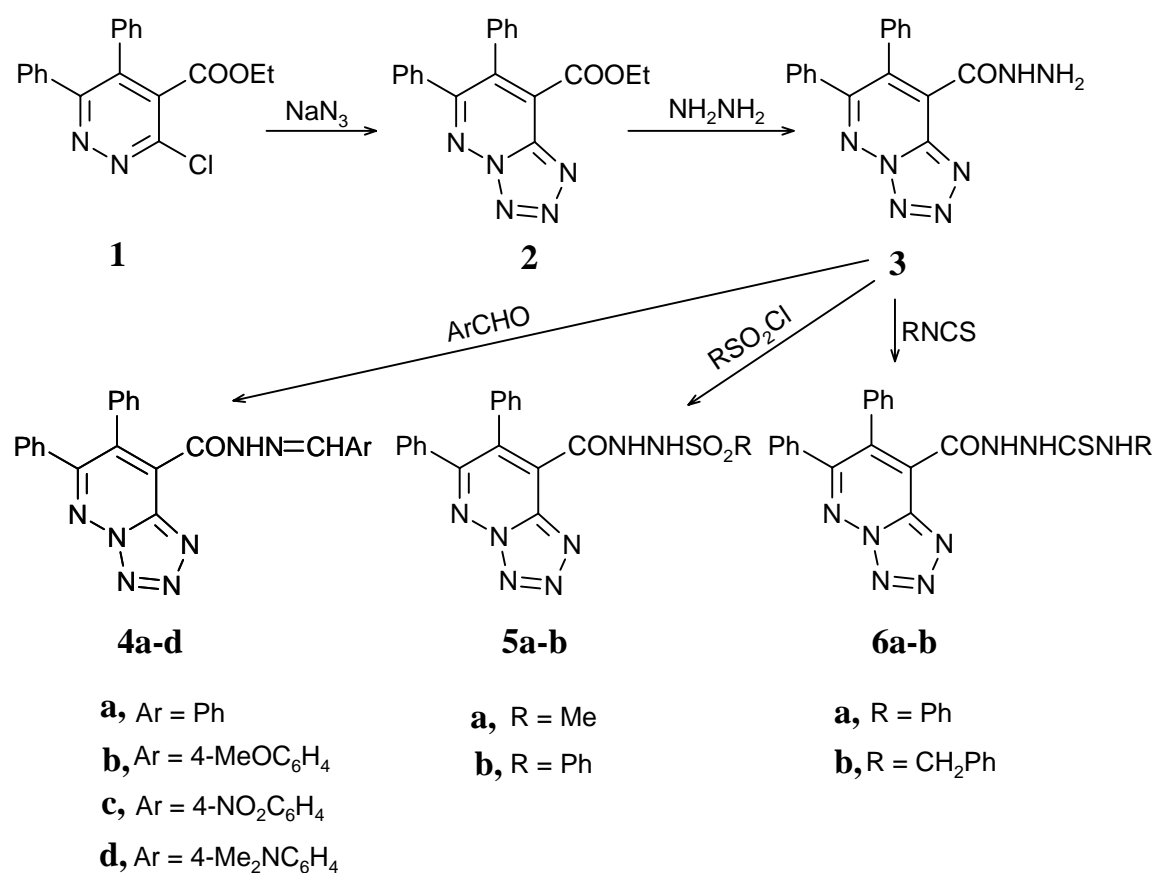
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Abstract-The reaction of the hydrazide of 6,7-diphenyltetrazolo[1,5-*b*]pyridazine-8-carboxylic acid (**3**) with aromatic aldehydes gave 8-arylidencarbohydrazide derivatives. The reaction of **3** with methanesulfonyl chloride, benzenesulfonyl chloride, phenyl and benzyl isothiocyanates afforded the corresponding *N*-substituted derivatives. The reaction of **3** with potassium ethylxanthate gave 5-(6,7-diphenyltetrazolo[1,5-*b*]pyridazin-8-yl)-1,3,4-oxadiazole-2-thione (**7**). The alkylation of this product in an alkaline medium proceeds at the sulfur atom, while the aminomethylation and acylation proceed at the nitrogen atom. Compound (**3**) also reacted with *N*-aminothiosemicarbazide to give 4-amino-5-(6,7-diphenyltetrazolo[1,5-*b*]pyridazin-8-yl)-1,2,4-triazole-3-thione (**11**).

Derivatives of homo- and heterocyclic carbohydrazide display various types of biological activity,¹ the wide range of therapeutic properties reported for 1,3,4-oxadiazole² and 1,2,4-triazole³ derivatives. These and our interests in the synthetic potential of fused pyridazine derivatives⁴ prompted us to undertake a convenient synthesis of tetrazolo[1,5-*b*]pyridazine-8-carbohydrazide as well as its biheterocycles such as 1,3,4-oxadiazolyl and 1,2,4-triazolyltetrazolo[1,5-*b*]pyridazine derivatives. In the present study, some such biheterocycles were prepared from the readily accessible 4-carbomethoxy-5,6-diphenyl-3(2*H*)-pyridazinone.⁵

As starting substance we used ethyl 3-chloro-5,6-diphenylpyridazine-4-carboxylate (**1**) which reacted with sodium azide in ethanol to give ethyl 6,7-diphenyltetrazolo[1,5-*b*]pyridazine-8-carboxylate (**2**).⁶ This carboxylate (**2**) on refluxing with hydrazine hydrate gave the acid hydrazide (**3**) (Scheme 1). The IR spectrum displaying absorptions at 3450, 3257 (NH), 1660 (C=O) and 1592 (C=N) cm⁻¹.

Reaction of the hydrazide (**3**) with benzaldehyde, 4-methoxy, 4-nitro- and 4-*N,N*-dimethylaminobenzaldehyde in ethanol gave the corresponding 8-arylidencarbohydrazide derivatives (**4a-d**). Also the reactions of **3** with methanesulfonyl chloride and benzenesulfonyl chloride were carried out in refluxing toluene to yield sulfonylcarbohydrazide derivatives (**5a,b**), and with phenyl isothiocyanate and benzyl isothiocyanate in refluxing benzene gave arylthiocarbomoylcarbohydrazide derivatives (**6a,b**).



(Scheme 1)

5-(6,7-Diphenyltetrazolo[1,5-*b*]pyridazin-8-yl)-1,3,4-oxadiazole-2-thione (**7**) was obtained by two procedures: by the reaction of the hydrazide (**3**) with carbon disulfide in presence of KOH (method A, usually employed in the synthesis of 5-substituted 1,3,4-oxadiazole-2-thione⁷) and with potassium ethylxanthate (method B). Method B gives a higher yield than method A (87% vs. 64%). Furthermore, there is no need to work with dangerous carbon disulphide in method A.

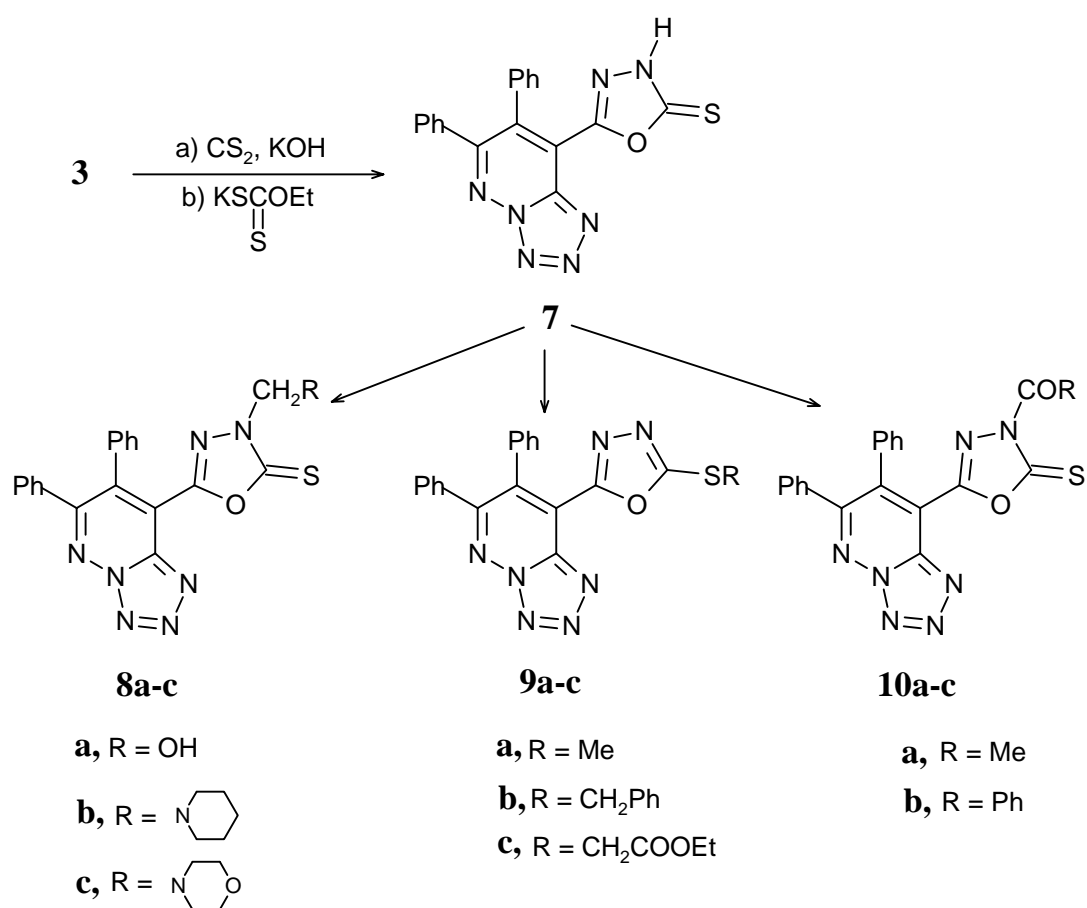
Product (**7**) in the solid state exists as the thione form as indicated by its IR spectrum, displaying bands for NH (3192) and C=S groups (1332), but lacking a band at 2600-2500 cm⁻¹ (SH stretching vibrations). The finding of these bands is in accord with the data of Ainwort⁷ for various 5-substituted 1,3,4-oxadiazole-2-thiones. Oxadiazolethione (**7**) undergoes hydroxymethylation and aminomethylation upon reaction with formaldehyde or formaldehyde with piperidine or morpholine in ethanol at reflux temperature. Afforded products (**8a-c**) (Scheme 2) N-derivatives, while the products of the alkylation of **7** by methyl iodide, benzyl chloride and ethyl bromoacetate in refluxed acetone with potassium carbonate were identified as S-derivatives (**9a-c**). The acylation of oxadiazolethione (**7**) by acetyl or benzoyl chloride in acetonitrile in the presence of triethylamine gave N-acetyl or N-benzoyl derivatives (**10a,b**).

When the IR spectra of **8** and **9** were compared, a strong band at 1324-1334 cm⁻¹ was observed in compound (**8**), which was assigned, in accord with starting 1,3,4-oxadiazole-2-thione (**7**), to C=S

stretching vibration which is characteristic for nitrogen substituted derivatives (**8**) and (**10**).

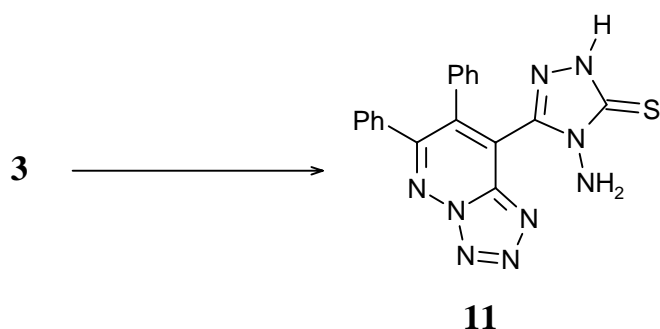
The chemical shifts of the methylene group are the most important in establishing the structure of **8** and **9** using PMR spectroscopy. The SCH₂ group signal for **9b** appears at 4.12 ppm, while the position of the NCH₂ group signal for **8c** is shifted somewhat down field. More detailed spectroscopy data will be mentioned in the experimental part.

Hence, the alkylation of 5-(6,7-diphenyltetrazolo[1,5-*b*]pyridazin-8-yl)-1,3,4-oxadiazole-2-thione (**7**) proceeds at the sulfur atom, while methylation, aminomethylation and acylation proceed at the nitrogen atom.



(Scheme 2)

These findings may be explained in the frame work of the theory of hard and soft acids and bases. The alkyl halide is a relatively soft (readily polarizable) electrophile and, thus, attacks the softer nucleophilic site, namely, the sulfur atom. On the other hand, formaldehyde and acylhalide are hard electrophiles than alkyl halide and attack the harder reaction site, namely, the nitrogen atom. Compound (**3**) also reacted with N-aminothiosemicarbazide to give 4-amino-5-(6,7-diphenyltetrazolo[1,5-*b*]pyridazin-8-yl)-1,2,4-triazole-3-thione (**11**).



EXPERIMENTAL

Melting points are uncorrected. $^1\text{H-NMR}$ spectra were recorded on a Varian EM-390-90 MHz spectrophotometer with TMS as an internal standard and chemical shifts are expressed as δ (ppm). IR spectra were obtained with a Perkin-Elmer 257 spectrometer (KBr).

Ethyl 5,6-diphenyl-3-chloropyridazine-4-carboxylate (**1**) was synthesized according to previous procedure.⁵

Ethyl 6,7-diphenyltetrazolo[1,5-*b*]pyridazine-8-carboxylate (**2**).

Sodium azide (0.65 g, 10 mmol) was added to a solution of ethyl 5,6-diphenyl-3-chloropyridazine-4-carboxylate (**1**) (3.338 g, 10 mmol) in dimethylformamide (20 mL). The suspension was stirred for 2 h at rt. Then, the mixture was diluted with H_2O (100 mL) and the precipitated product was isolated by suction; yield 2.51 g (73%); white needles, mp 145-147° (ethanol). Anal. Calcd for $\text{C}_{19}\text{H}_{15}\text{N}_5\text{O}_2$: C, 66.07; H, 4.38; N, 20.28. Found: C, 65.80; H, 4.10; N, 20.00.

6,7-Diphenyltetrazolo[1,5-*b*]pyridazine-8-carbohydrazide (**3**).

To a solution of **2** (3.45 g, 10 mmol) in ethanol (30 mL) was added hydrazine hydrate (4.0 mL, 68 mmol, 85%) and the mixture was heated under reflux on a water bath for 6 h. After most of ethanol removed under reduced pressure, the mixture was cooled and diluted with water. When a solid separated out, it was filtered and crystallized from benzene to give **3** (3 g, 91%); mp 160-161°. Anal. Calcd for $\text{C}_{17}\text{H}_{13}\text{N}_7\text{O}$: C, 61.62; H, 3.95; N, 29.59. Found: C, 61.50; H, 3.80; N, 29.40. IR: 3450, 3275, 1660 and 1560 cm^{-1} .

Preparation of 4a-d: General procedure

To a solution of **3** (3.30 g, 10 mmol) in hot ethanol (20 mL) was added an appropriate aldehyde (10 mmol) and the mixture was refluxed for 2 h and then cooled. The solid thus separated was filtered, dried and crystallized from ethanol to give crystalline needles of **4a-d** in 85-90% yields.

4a: (R = H); mp 207-208°. Anal. Calcd for $\text{C}_{24}\text{H}_{17}\text{N}_7\text{O}$: C, 68.72; H, 4.09; N, 23.38. Found: C, 68.60; H, 3.90; N, 23.10. IR: 3220, 1677 and 1611 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): $\delta = 7.2-8.3$ (m, 15H, arom.) and 8.40 (s, 1H, azomethine).

4b: (R = 4-OCH₃); mp 223-224°. Anal. Calcd for $\text{C}_{25}\text{H}_{19}\text{N}_7\text{O}_2$: C, 66.80; H, 4.26; N, 21.8. Found: C, 66.70; H, 4.00; N, 21.60. IR: 3320, 3280, 3230, 1680 and 1610 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3): $\delta = 3.85$ (s, 3H,

OCH₃), 7.0-8.4 (m, 14H, arom.) and 8.45 (s, 1H, azomethine).

4c: (R = 4-NO₂); mp 292-293°. Anal. Calcd for C₂₄H₁₆N₈O₃: C, 62.06; H, 3.47; N, 24.13. Found: C, 61.80; H, 3.20; N, 23.90. IR: 3310, 3290, 1670, 1610, 1570 and 1370 cm⁻¹.

4d: (R = 4-NMe₂); mp 274-275°. Anal. Calcd for C₂₆H₂₂N₈O: C, 67.51; H, 4.79; N, 24.23. Found: C, 67.30; H, 4.60; N, 24.00. IR: 3325, 3285, 3210, 1675, 1610 and 1320 cm⁻¹.

Preparation of 6,7-diphenyltetrazolo[1,5-*b*]pyridazine-8-sulfonylcarbohydrazide (5a,b).

To a solution of **3** (3.30 g, 10 mmol) in toluene (20 mL) was added methanesulfonyl chloride or benzenesulfonyl chloride (10 mmol) and the mixture was refluxed for 4 h, and then cooled. The solid thus separated was filtered, dried and crystallized from toluene to give crystalline needles of **5a,b** in (80-85%) yield.

5a: (R = CH₃); mp 217-218°. Anal. Calcd for C₁₈H₁₅N₇O₃S: C, 52.80; H, 3.69; N, 23.94. Found: C, 52.60; H, 3.50; N, 23.70. IR: 3330, 3220, 1670, 1580, 1320 and 1150 cm⁻¹

5b: (R = C₆H₅); mp 241-242°. Anal. Calcd for C₂₃H₁₇N₇O₃S: C, 58.59; H, 3.63; N, 20.80. Found: C, 58.40; H, 3.50; N, 20.50. IR: 3325, 3210, 1670, 1575, 1315 and 1145 cm⁻¹

Preparation of 6,7-diphenyltetrazolo[1,5-*b*]pyridazine-8-carbothiosemicarbazide (6a,b).

A suspension of **3** (3.30 g, 10 mmol) in benzene (20 mL) was treated with phenyl isothiocyanate (1.35 g, 10 mmol). The reaction mixture was heated under reflux for 2 h and cooled. The separated solid was filtered, dried and crystallized from ethanol to give **6a,b** in (85-90 %) yield.

6a: (R=Ph); mp 210-212°. Anal. Calcd for C₂₄H₁₈N₈OS: C, 61.79; H, 3.89; N, 24.02. Found: C, 61.60; H, 3.70; N, 23.80. IR: 3350, 3200, 1660, and 1150 cm⁻¹.

6b: (R = CH₂Ph); mp 250-252°. Anal. Calcd for C₂₅H₂₀N₈OS: C, 62.48; H, 4.19; N, 23.32. Found: C, 62.10; H, 3.90; N, 23.00. IR: 3320, 3150, 1660, and 1140 cm⁻¹.

(6,7-Diphenyltetrazolo[1,5-*b*]pyridazine-8-yl)-1,3,4-oxadiazole-2-thione (7).

Method A: A solution of potassium hydroxide (1.17 g, 30 mmol) in 6 mL of water and carbon disulfide (2.66 g, 35 mmol) were added to a solution of **3** (9.90 g, 30 mmol) in 100 mL ethanol and the mixture was heated at reflux for 6 h. Then 50 mL of solvent was distilled off and 200 mL of water was added. The mixture was acidified to pH 4 by the addition of conc. HCl. The precipitate was filtered off, washed with water, dried, and crystallized from ethanol to give **7** (7.13 g, 64%); mp 220-222°. Anal. Calcd for C₁₈H₁₁N₇OS: C, 57.90; H, 2.97; N, 26.26. Found: C, 57.70; H, 2.80; N, 26.00. IR: 3220, 1677 and 1611 cm⁻¹. ¹H-NMR (DMSO-d₆): δ = 7.2-7.6 (s, 10H, arom).

Method B: A sample of potassium ethylxanthate (4.95g, 30 mmol) was added to a solution of hydrazide (**3**) (9.90 g, 30 mmol) in 100 mL ethanol and heated at reflux for 6 h. The product was isolated according to procedure A.

The yield of **7** was 3.37g (87 %), it was identical in every respect with that prepared by method A.

Preparation of 3-hydroxy(piperidino/morpholino)methyl-5-(6,7-diphenyltetrazolo[1,5-*b*]pyridazin-8-yl)-1,3,4-oxadiazole-2-thione (8a-c).

To a solution of **7** (3.72 g, 10 mmol) in ethanol (20 mL), was added formaline 40% (1.87 mL, 25 mmol) or/and piperidine (0.98 g, 10 mmol) or/and morpholine (0.87 g, 10 mmol), and the mixture was refluxed for 6 h, and then cooled. The solid thus separated was filtered dried and crystallized from ethanol to give compounds (**8a-c**) in (75-85%) yield.

8a: (R = OH); mp 245-247°. Anal. Calcd for C₁₉H₁₃N₇O₂S: C, 56.57; H, 3.25; N, 24.30. Found: C, 56.30; H, 3.00; N, 22.10. IR: 3500, 3220, 3150, 3040 and 1650 cm⁻¹

8b: (R = C₅H₁₀N); mp 220-222°. Anal. Calcd for C₂₄H₂₂N₈OS: C, 61.26; H, 4.71; N, 23.81. Found: C, 61.00; H, 4.60; N, 23.50. IR: 3200, 3100, 2890 and 1620 cm⁻¹.

8c: (R = C₄H₈NO): mp 180-182°. Anal. Calcd for C₂₃H₂₀N₈O₂S: C, 58.46; H, 4.27; N, 23.71. Found: C, 58.30; H, 4.00; N, 23.50. IR: 3210, 3130, 3150, 2890 and 1640 cm⁻¹. ¹H-NMR (DMSO-d₆): δ = 2.5 (t, 4H, 2CH₂); 3.6 (br, 4H, 2CH₂); 5.0 (s, 2H, CH₂) and 7.2-7.6 (s, 10H, arom.).

Alkylation of compound (7)

To a solution of **7** (3.72 g, 10 mmol) in dry acetone (30 mL), were added anhydrous K₂CO₃ (1.38 g, 10 mmol) and methyl iodide, benzyl chloride or ethyl bromoacetate (10 mmol) and the mixture was heated under reflux on a water bath for 15 h. The reaction mixture poured onto ice-water and neutralized to pH 6 with conc. HCl. The solid formed was filtered and crystallized from benzene to give **9a-c** (65-75 %) yield.

9a: (R = CH₃) mp 198-200°. Anal. Calcd for C₁₉H₁₃N₇OS: C, 58.90; H, 3.38; N, 25.31. Found: C, 58.70; H, 3.10; N, 25.00. IR: 3250, 3150 and 1140 cm⁻¹. ¹H-NMR (CDCl₃): δ = 2.7 (s, 3H, CH₃) and 7.2-7.6 (s, 10H, arom.)

9b: (R = CH₂Ph): mp 245-247°. Anal. Calcd for C₂₅H₁₇N₇OS: C, 64.78; H, 3.70; N, 21.15. Found: C, 64.60; H, 3.50; N, 20.90. IR: 3332, 3171 and 1150 cm⁻¹. ¹H-NMR (CDCl₃): δ = 4.1 (s, 2H, CH₂) and 6.6-7.6 (m, 15H, arom.).

9c: (R = CH=COOEt): mp 230-232°. Anal. Calcd for C₂₂H₁₇N₇O₂S: C, 57.50; H, 3.73; N, 22.34. Found: C, 57.30; H, 3.50; N, 22.00. IR: 3748, 2982, 1793 and 1145 cm⁻¹.

Preparation of 3-acetyl(benzoyl)-5-(6,7-diphenyltetrazolo[1,5-*b*]pyridazin-8-yl)-1,3,4-oxadiazole-2-thione (10a-b).

To a solution of **7** (3.72 g, 10 mmol) in ethanol (20 mL) was added acetyl chloride or benzoyl chloride (10 mmol) and the reaction mixture was refluxed for 1 h in presence of triethyl amine (1 mL, 9.9 mmol). The reaction mixture poured onto ice-water and neutralized to pH 6 with conc. HCl, and the solid formed was filtered and crystallized from acetone to give **10a-b** (70-78 %) yield.

10a: (R =CH₃): mp 218-219°. Anal. Calcd for C₂₀H₁₃N₇O₂S: C, 57.82; H, 3.15; N, 23.60. Found: C, 57.60; H, 3.00; N, 23.30. IR: 3210, 3130, 1670 and 1580 cm⁻¹. ¹H-NMR (CDCl₃): δ =1.8 (s, 3H, CH₃)and 7.1-7.7 (s, 10H, arom.).

10b: (R = C₆H₅): mp 145-147°. Anal. Calcd for C₂₅H₁₅N₇O₂S: C, 62.88; H, 3.17; N, 20.53. Found: C, 62.70; H, 2.90; N, 20.30. IR: 3300, 3053. 1720 and 1147 cm⁻¹. ¹H-NMR (CDCl₃): δ = 7.2-8.05 (m, 15H, arom.).

Preparation of 4-amino-5-(6,7-diphenyltetrazolo[1,5-*b*]pyridazin-8-yl)-1,2,4-triazole-3-thione (11).

To a solution of **3** (3.30 g, 10 mmol) in ethanol (30 mL) was added thiocarbohydrazide (1.06 g, 10 mmol) and the mixture was refluxed for 6 h, and then cooled. The solid thus separated was filtered, dried and crystallized from benzene to give compound (**11**) (3.29 g, 85%), mp 183-185°. Anal. Calcd for C₁₈H₁₃N₉S: C, 55.80; H, 3.38; N, 32.54. Found: C, 55.60; H, 3.10; N, 32.20. IR: 3434, 1570 and 1150 cm⁻¹.

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