Synthesis Characterization and Antibacterial Activities of Some New pyridazines and Thieno[2,3-c]pyridazines.

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Abstract - Novel ethyl 6-phenyltetrazolo[1,5-b]pyridazine-8-carboxylate **4** was synthesized from the reaction of 2-chloro-4-carbethoxy-6-phenylpyridazine **2** with sodium azide in DMF. Hydrazinolysis of compound **4** yielded the corresponding carbohydrazide, **5**. The reaction of 4-cyano-6-phenylpyridazine-3(2*H*)-thione **8** with bromoacetone and ethyl chloroacetate in the presence of sodium acetate afforded the novel thieno[2,3-c]pyridazine derivatives **9a,b.** The reaction of amino group in compounds **9a,b** with 2,5-dimethoxytetrahydrofuran in acetic acid afforded the corresponding pyrrolyl derivatives **10a, b**. Similarly, treatment of compound **9b** with succinc anhydride under reflux in acetic acid yielded the novel 3-(2,5-Dioxopyrrolidin-1-yl)- thienopyridazine **13**. Hydrazinolysis of compounds **10b** and **13** produced the novel carbohydrazides, **11** and **19,** respectively. Structure of the new obtained compounds were established by elemental analyses and spectral data. The new compounds were also screened for their antibacterial activity.

Key words- *Pyridazines, Thieno[2,3-c]pyridazines*

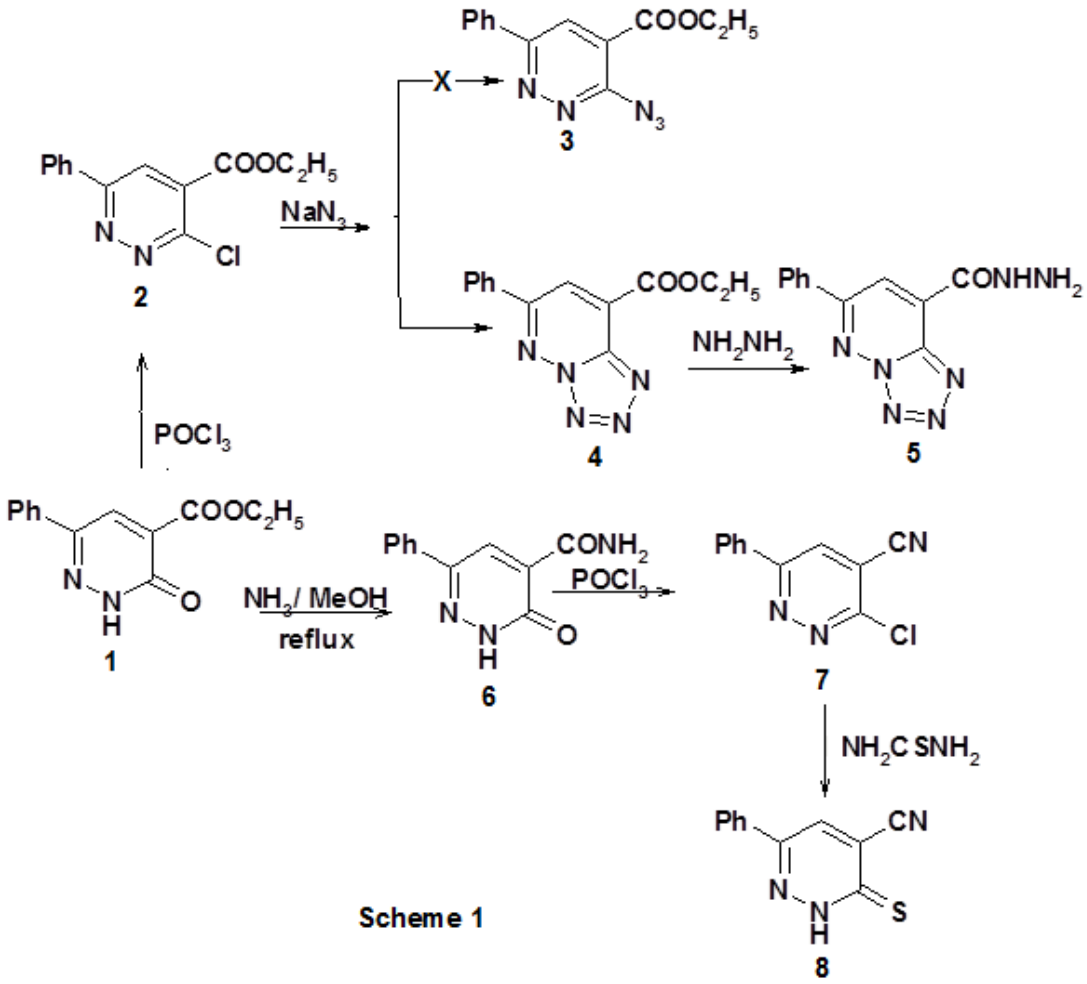
1. Introduction

Pyridazine ring is a part of the structures of a number of drugs available in the market [1] such as hydralazine, minaprine, pipofezine, and cefozopran. Pyridazine derivatives have been reported to possess various pharmacological activities including antimicrobial [2], anticancer [3], anti-tubercular [4], antihypertensive [5],and anticonvulsant [6]. On the other hand, the thienopyridazines skeleton has been reported as having interesting biological and pharmacological activities, such as were used for the treatment of inflammation, metabolic disorders and cancer [7], modules of protein tyrosine phosphatases (PT-Pases) [8], anticancer [9], antimicrobials [10], blood platelet

aggregation inhibitors [11], useful as NAD(P)H oxidase inhibitor [12], and identified as a new allosteric modulator of the adenosine A_1 receptor (A_1AR) [13]. Others are also useful as antitumor [14], and antibacterial activity [15].In view of the above and in continuation of our studies on the synthesis of heterocyclic compounds containing pyridazine moiety [16, 17] we report here, the synthesis of some novel tetrazolo[1,5-b]pyridazines and thieno[2,3-c]pyridazines using easily accessible 4-carbethoxy-6-phenylpyridazinone **1** as starting material**.** The antibacterial activities were also investigated.

2. Results and Discussion

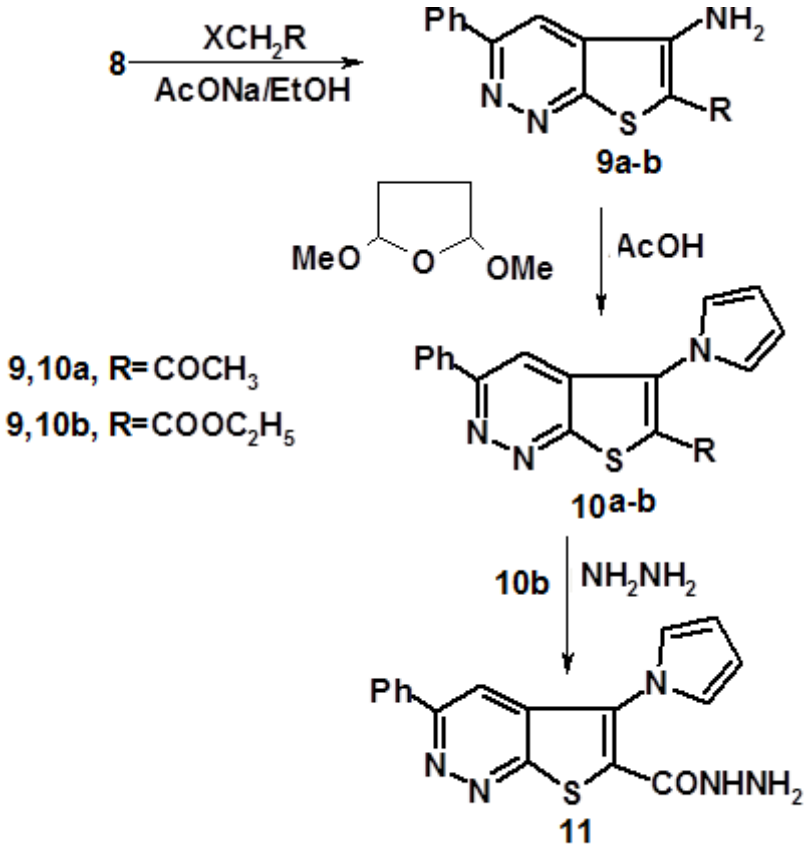
Treatment of 4-carbethoxy-6-phenylpyridazinone **1** with ammonia, in methanol afforded 4-carboxamide-6-phenylpyridazine-3(2*H*)-one **6** which was converted to the 3-chloro-4-cyano-6-phenylpyridazine **7** by heating with phosphorusoxychloride. Compound **7** was subjected to addition-elimination reaction with thiourea in ethanol under reflux to afford 4-cyano-6-phenylpyridazine-3(2*H*)-thione **8**. Compounds **1, 2, 6, 7** were obtained according to the reported method and the structures are in agreement with the reported data [18]. Sodium azide as nucleophile was reacted with chloropyridazine **2** in dimethylformamide at 90°C to form the novel tetrazolo[1,5-b]-pyridazine **4**. The azidopyridazine **3** was excluded on the basis of infrared spectrum which showed the absence of azide functional group. The carbohydrazide derivative **5** was obtained by refluxing of compound **4** with hydrazine hydrate in ethanol (Scheme 1).



Scheme 1

The thione derivative **8** was used a versatile compound for the synthesis of some new thieno[2,3-c]pyridazines. Thus, cyclocondensation of compound **8** with bromoacetone and ethyl chloroacetate was performed in ethanol in the presence of a catalytic amount of sodium acetate under reflux and yielded the novel thieno[2,3-c]pyridazine derivatives **9a,b** Scheme (2). The structures of the new compounds **9a, b** were proved on the bases of their elemental analyses and spectral data. The IR spectra of the amino group of compounds **9a, b** appears at 3430-3280 cm^{-1} in the form of two bands due to intramolecular association between the amino and the carbonyl group and disappearance of nitrile group. In addition, the structures were supported by the ^{1}H-NMR spectra, which showed that the presence of the expected protons signal in agreement with the proposed structures. The structure of compound **9a** was supported by its analytical and spectral data. The infrared spectrum of compound **9b** displayed absorption at 3440, 3330 cm^{-1} for NH_2 stretching at 1670 cm^{-1} for C=O stretching with lack of the characteristic absorption due to the C≡N stretching.

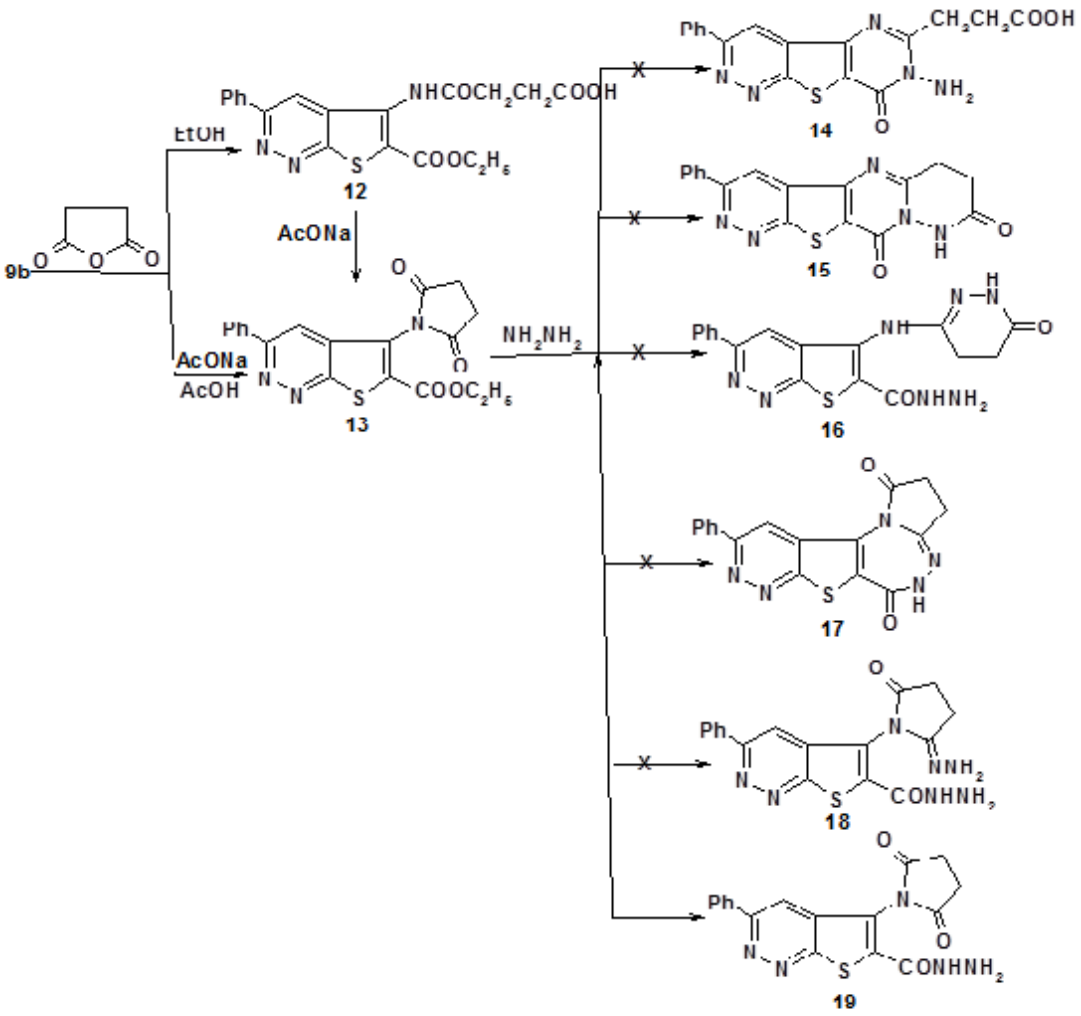
Its ^{1}H-NMR(DMSO-d_6) showed the appearance of the new signal for the amino group, and the appearance of ethoxycarbonyl moiety triplet at δ=1.3 ppm, and quartet at δ= 4.3 ppm assigned for in addition to amino group. The amino group in compounds **9a,b** readily reacted with 2,5-dimethoxytetrahydrofuran in acetic acid to give the pyrrolyl derivative **10a,b**. The infrared spectrum showed the presence of an absorption band at 1670 cm^{-1} (C=O) with lack the -NH_2 absorption for compound **10a**. The acid hydrazide **11** was prepared by the refluxing of the corresponding ester **10b** with hydrazine hydrate in ethanol, Scheme (2).



Scheme 2

The reaction of compound **9b** with succinic anhydride in acetic acid furnished the new 3-(2,5-Dioxopyrrolidin-1-yl)-5-phenyl-2-

ethoxycarbonylthieno[2,3-c]pyridazine **13** which was reacted with hydrazine hydrate in ethanol, to give compound **19,** Scheme (3). The chemical structure of compounds **12, 13** and **19** were established based on its elemental analysis and spectral data. The chemical structure of compounds **9b, 10 a, b,** and **19** were also established based on its ^{13}C-NMR, (Figure 1).



Scheme 3

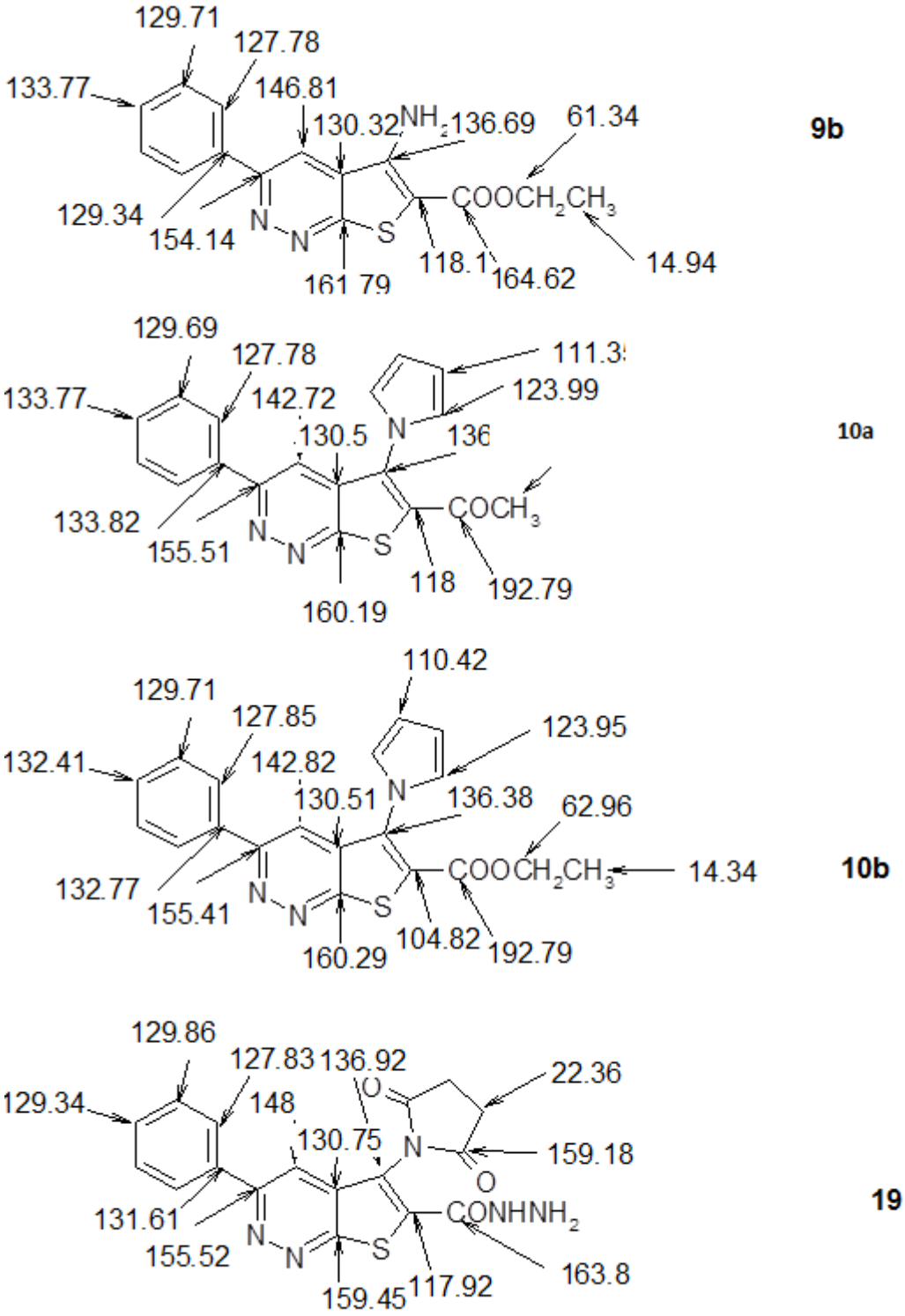


Figure (1) C^{13} –NMR assignments 9b,10a,b and 19.

3. Antibacterial Activity

Some of the newly synthesized compounds were screened for their antibacterial activity against Staphylococcus xylosus, Bacillus megaterium

(gram-positive bacteria) and Salmonella typhii **(**gram-negative bacteria) using the disc-diffusion method [19]. The tested compounds were dissolved in DMSO at 25, 50, 100 µg/mL concentrations in the nutrient agar media. The inhibition zones were measured in mm at the end of an incubation for 24 h at 37°C and the activity of each compound was compared with Ciprofloxacin as a positive control. All compounds under investigation were active against gram-positive bacteria. Most of the compounds showed slightly inhibition against *S. xylosus* and *B. megaterium*. Also, the results showed that most of the compounds are inactive against *S. typhii*, except compounds **5** and **11.** Particularly, the compounds named as **5, 11, 19,** exhibited more antibacterial potencies than other compounds against Gram-positive and Gram-negative bacteria. The results are summarized in Table**(1)**.

Table(1) : Results of antibacterial activity of the tested compounds.

Comp.	Concentration (µg /ml)	*S. xylosus.*	*B. meguterium.*	*S.typhii.*
4	25	-	-	-
	50	+	-	-
	100	++	+	-
5	25	-	-	-
	50	+	+	-
	100	++	+	+
8	25	-	-	-
	50	-	-	-
	100	-	+	-
9a	25	-	-	-
	50	+	+	-
	100	+	+	-
9b	25	-	-	-
	50	+	-	-

	100	++	+	-
10a	25	-	-	-
	50	+	+	-
	100	+	+	-
10b	25	-	-	-
	50	+	-	-
	100	++	+	-
11	25	+	+	+
	50	-	+	+
	100	++	+	+
12	25	-	-	-
	50	+	+	-
	100	+	+	-
13	25	-	-	-
	50	-	+	-
	100	+	+	-
19	25	+	+	-
	50	+	+	-
	100	+ +	+	-
Ciprofloxacin		+ + +	+ + +	+ + +

Key to symbols:

Highly active = + + + (inhibition zone > 27.9 mm)

Moderately active = + + (inhibition zone 18.7- 27.9 mm)

Slightly active = + (inhibition zone 9.3-18.6 mm)

Inactive = - (inhibition zone < 9.3 mm)

4. Experimental

Melting points were determined on an Electro thermal 9200 apparatus and are uncorrected. The reactions were monitored by thin layer chromatography (TLC) on a silica coated aluminum sheet. The eluent was a mixture of dichloromethane and methanol. IR spectra were recorded on a Shimadzu 470 IR spectrophotometer using KBr pellets. NMR spectra were measured on a JEOL 400 MHZ NMR spectrometer(400 MHz for ^{1}H, 100 MHz for ^{13}C) using TMS as internal standard (δ in ppm). The mass spectra were recorded on a Jeol-JMS-600 apparatus. The UV spectrum was recorded on a Shimadzu mini-1240 Spectrophotometer. Elemental analyses were performed on a Perkin-Elmer 240 C microanalyzer.
Compounds **1, 2** and **6-8** were prepared according to previous reported [17, 18]

Ethyl 6-phenyltetrazolo[1,5-b]pyridazine-8-carboxylate **4**

A mixture of compound **(2)** (0.01 mole) and anhydrous sodium azide (0.012 mole) in dimethyl formamide (20 mL) was heated under reflux for 4 h. The solid product was collected and recrystallized from ethanol to give **(4)** as yellow crystals in 93% yield: m.p. 298 °C. IR (KBr): υ = 1740 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 1.3 (t, 3H, CH_3), 4.1 (q, 2H, OCH_2), 7.4-8.7 (m, 6H, Ar-H and Pyridazine-H), *Anal*.Calcd. for $C_{13}H_{11}N_5O_2$ (269.26); C, 57.99; H, 4.12; N, 26.01. Found: C, 57.69; H, 4.10; N, 25.90%.

6-Phenyltetrazolo[1,5-b]pyridazine-8-carbohydrazide **5**

A mixture of compound **(4)** (0.01mole) and hydrazine hydrate (0.012mole) in ethanol (50 mL) was refluxed for 3 h, and then allowed to cool. The solid product was collected and recrystallized from ethanol to give **(5)** as red crystals in 77% yield: m.p. 320 °C. IR: ύ = 3312, 3290, 3180 cm^{-1} (NH, NH_2), 1667 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 7.4-8.2 (m, 7H, Ar-H and NH_2), 8.76 (s, 1H, Pyridazine-H); 9.0 (s, 1H, NH); MS: m/z 255 ($M^{+\cdot}$,28.5%), 254 (100%), 199 (44.4%), 77 (1.70%), 51 (5%). *Anal*.Calcd. for $C_{11}H_9N_7O$ (255.23); C, 51.76; H, 3.55; N, 38.41. Found: C, 51.69; H, 3.50; N, 38.39%.

Synthesis of 4-Cyano-6-phenylpyridazine-3(2H)-thione **8**

A solution of compound **(7)** (0.01mole) and thiourea (0.012mole) in ethanol (20 mL) was heated under reflux for 4 h, the precipitate was boiled with 10% sodium hydroxide (5 mL) for 1 h. The solid salt was dissolved in water and acidified with 2N hydrochloric acid. The solid product was filtered off and recrystallized from ethanol to afford **(8)** as brown crystals in 89% yield; m.p. 206°C. IR: ύ = 3470 cm^{-1} (NH), 2222 cm^{-1} (C≡N), 1230 cm^{-1} (C=S); UV 324 nm (C=S); ^{1}H-NMR (DMSO-d_6) : δ 7.4-8.7 (m, 6H, Ar-H and Pyridazine-H), 11.10 (broad, 1H, NH). *Anal*.Calcd. for $C_{11}H_7N_3S$ (213.26); C, 61.95; H, 3.31; N, 19.70; S, 15.03. Found: C, 61.99; H, 3.27; N, 19.73; S, 15.01 %.

3-Amino-5-phenyl-2-substitutedthieno[2,3-c]pyridazine **9a,b**

A mixture of compound **(8)** (0.01mole), fused sodium acetate (0.012 mole) and *α*-halocarbonyl compound (0.01mole) in ethanol (50 mL) was refluxed for 4 h. The solid product was filtered off and recrystallized from ethanol to give **9a, b**.

3-Amino-5-phenyl-2-acetylthieno[2,3-c]pyridazine **9a**

9a: Orange crystals in 88% yield: m.p. 275°C. IR (KBr): υ = 3390, 3280 cm^{-1} (NH_2) , 1640 cm^{-1} (C=O); ^{1}H-NMR **(**DMSO-d_6**):** δ 2.4 (s, 3H, $COCH_3$), 7.5-8.1 (m, 6H, Ar-H and Pyridazine-H), 9.0 (s, 2H, NH_2). *Anal*.Calcd. for $C_{14}H_{11}N_3OS$ (269.32): C, 62.44; H, 4.12; N, 15.60; S, 11.90. Found: C, 62.47; H, 4.17; N, 15.57; S, 11.87 %.

3-Amino-5-phenyl-2-ethoxycarbonylthieno[2,3-c]pyridazine **9b**

9b: Yellow crystals in 91% yield: m.p. 225 °C. IR (KBr): υ = 3430, 3300 cm^{-1} (NH_2) , 1670 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 1.3 (t, 3H, CH_3), 4.3 (q, 2H, OCH_2), 7.4-8.2 (m, 6H, Ar-H and Pyridazine-H), 9.0 (s, 2H, NH_2); ^{13}C-NMR(DMSO-d_6): δ 14.94 (CH_3), 61.34 (CH_2), 118.1, 127.31(2C),129.34, 129.71(2C), 130.32, 133.77, 136.69, 146.81, 154.14, 161.79, 164.62 ; MS: m/z 299 ($M^{+\cdot}$,100 %) , 271 (7.61%), 253 (69.80 %), 226(6.00%), 77(15.83%), 51(13.6%). *Anal*.Calcd. for $C_{15}H_{13}N_3O_2S$ (299.35): C, 60.19; H, 4.38; N, 14.04; S, 10.71. Found: C, 59.90; H, 4.50; N, 14.25; S, 10.67 %.

5-Phenyl-3-(1-pyrryl)-2-substitutedthieno[2,3-*c*] pyridazine **10a, b**
General procedure :

A mixture of compound **9a,b** (0.01 mol) and 2,5-dimethoxytetrahydrofuran(0.01 mol) in glacial acetic acid (30 ml) was heated under reflux for 2 h. The solid product was collected and recrystallized from acetic acid to give**10a, b**.

2-Acetyl-5-phenyl-3-(1-pyrryl)thieno[2,3-*c*] pyridazine **10a**
10a: Yellow crystals in 78% yield, m.p. 288°C. IR (KBr): υ = 1670 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 2.13, (s,3H, CO CH_3) 6.46, 6.47 (2d, 4H, pyrrol-H), 7.32-8.32 (m, 6H, Ar-H and Pyridazine-H), ^{13}C-NMR(DMSO-d_6): δ 27.70 (CH_3), 111.35(2C), 118, 123.99(2C), 127.78(2C), 129.69(2C), 130.50,133.77,133.82, 136.29, 142.72, 155.51, 160.19, 192.79; MS: m/z 319 ($M^{+\cdot}$, 100%), 318(53. 6%), 289 (8%), 247 (6%), 42(29. 5%). *Anal*.Calcd. for $C_{18}H_{13}N_3OS$ (319.38); C, 67.69; H, 4.10; N, 13.16; S, 10.04. Found: C, 67.59; H, 4.11; N, 13.15; S, 10.01%.

Ethyl 5-phenyl-3-(1-pyrryl)thieno[2,3-*c*] pyridazine-2-carboxylate **10b**

10b Yellow crystals in 83% yield: m.p. 276 °C. IR (KBr): υ = 1720 cm^{-1} (C=O); ^{1}H-NMR (DMSO-d_6): δ 1.3 (t, 3H, CH_3), 4.1 (q, 2H, OCH_2), 6.45, 6.46 (2d, 4H, pyrrol-H), 7.4-8.7 (m, 6H, Ar-H and Pyridazine-H), ^{13}C-NMR(DMSO-d_6): δ 13.92, 14.34 (CH_3), 62.96 (CH_2),104.82,110.42(2C) 123.95(2C), 127.85(2C), 129.71(2C), 130.51, 132.41,132.77, 136.38, 142.82, 155.41, 160.29, 192.79. *Anal*.Calcd. for $C_{19}H_{15}N_3O_2S$ (349.41); C, 65.31; H, 4.33; N, 12.03; S, 9.18 . Found: C, 65.29; H, 4.35; N, 12.06; S, 9.17 %.

Synthesis of 5-Phenyl-3-(1-pyrryl)thieno[2,3-c]pyridazine-2-carbohydrazide **11**

A mixture of compound **(10b)** (0.01mole) and hydrazine hydrate (0.01mole) in ethanol (50 mL) was refluxed for 6 h, and then allowed to cool. The solid product was collected and recrystallized from ethanol to give **(11)** as yellow crystals in 93% yield: m.p. 321 °C. IR: ύ = 3306, 3290, 3180 cm^{-1} (NH, NH_2), 1663 cm^{-1} (C=O)**;** MS: m/z 335 ($M^{+\cdot}$, 78.1%) 334 (98.9%), 304 (100%) 247 (20.2%), 204 (25.6%), 51(2.5%).
Anal.Calcd. for $C_{17}H_{13}N_5OS$ (335.36); C, 60.88; H, 3.91; N, 20.87; S, 9.56 . Found: C, 60.85; H, 3.89; N, 20.75; S, 9.46 %.

3-Amino-5-phenyl-2-ethoxycarbonylthieno[2,3-c]pyridazine-3-succinamic acid **12**

A suspension of compound **9a** (0.01 mol) and succinic anhydride (0.01 mol) in ethanol (50 mL) was heated under reflux for 2 h. The solid product was filtered off and recrystallized from ethanol to give **12** as pale yellow crystals in 86% yield: m.p. 135 °C. IR (KBr): υ = 3438 cm^{-1} (OH), 3301 cm^{-1} (NH), 1712 cm^{-1}, 1679 cm^{-1} (2C=O); ^{1}H-NMR (DMSO-d_6): δ 1.32 (t, 3H, CH_3), 2.5, 2.7(2s,4H, 2 CH_2) 4.31 (q, 2H, OCH_2), 6.51 (broad, 1H, NH amide), 7.50-7.62 (m, 3H, Ar-H), 8.16 (d, 2H, Ar-H), 9.04 (s, 1H, Pyridazine-H), 10.30 (s, 1H, OH); *Anal*.Calcd. for $C_{19}H_{17}N_3O_5S$ (399.42); C, 57.13; H, 4.29; N, 10.52; S, 8.03. Found: C, 57.03; H, 4.30; N, 10.50; S, 8.00%.

3-(2,5-Dioxopyrrolidin-1-yl)-5-phenyl-2-ethoxycarbonylthieno[2,3-c]pyridazine **13**

Method A:

A suspension of compound **9a** (0.01 mol) and succinic anhydride (0.01 mol) in the presence of acetic acid/ sodium acetate (2 gm) was heated under reflux for 2 h. The solid product was filtered off and recrystallized from acetic acid to give **13** as white crystals in 78% yield: m.p. 191°C.

Method B:

A suspension of compound **12** (0.01 mol) and sodium acetate (2 gm) (0.01 mol) in acetic acid (30 mL) was heated under reflux for 2 h. The solid product was filtered off and recrystallized from acetic acid to give **13** as white crystals in 78% yield: m.p. 191°C. IR (KBr): υ = 1712, 1679 cm^{-1} (2C=O); ^{1}H-NMR (DMSO-d_6): δ 1.32 (t, 3H, CH_3),2.5, 2.7(2s,4H, 2 CH_2) 4.31 (q, 2H, OCH_2), 7.49-7.60 (m, 3H, Ar-H), 8.18 (d, 2H, Ar-H), 9.06 (s, 1H, Pyridazine-H); ^{13}C-NMR(DMSO-d_6):δ 14.94 (CH_3),22.32, (2CH2), 61.34 (CH_2), 118.1, 127.31(2C),129.34, 129.71(2C), 130.32, 133.77, 136.69, 146.81, 154.14, 159.16 160, 164.62; MS: m/z 381 ($M^{+\cdot}$, 0.2%), 340 (68. 6%), 298 (100%), 253 (40.4%), 42(27.8%). *Anal*.Calcd. for $C_{19}H_{15}N_3O_4S$ (381.41); C, 59.83; H, 3.96; N, 11.02; S, 8.41. Found: C, 59.83; H, 3.96; N, 11.02; S, 8.41%.

3-(2,5-Dioxopyrrolidin-1-yl)-5-phenylthieno[2,3-c]pyridazine-2-carbohydrazide **19**

A mixture of derivative **13** (0.01 mol) and hydrazine hydrate (0.014 mol) in ethanol (50 mL) was refluxed for 2 h. The solid product was collected and recrystallized from ethanol to produce **19** as yellow crystals in 86% yield: m.p. 275°C. IR (KBr): υ= 3416, 3273 (NH,

NH_2), 1675, 1617 (2C=O); ^{1}H-NMR (DMSO-d_6): δ 2.5, 2.72(2s,4H, 2 CH_2), 6.18 (s, 2H, NH_2), 7.55-7.59 (m, 4H, Ar-H and Pyridazine-H), 8.19, 8.31(d, 2H, Ar-H), 8.78 (s, 1H, NH); ^{13}C-NMR(DMSO-d_6):δ 22.36 (2 CH_2), 117.92, 127.83(2C),129.34,129.86(2C), 130.75,131.61, 136.92, 148, 155.52,159.18, 159.45, 163.80; MS: m/z 368 ($M^{+\cdot}$, +1, 0.7%), 298 (100%), 253(90%), 77 (1.1%), 52(1.4%). *Anal.*Calcd. for $C_{17}H_{13}N_5O_3S$ (367.38); C, 55.58; H, 3.57; N, 19.06; S, 8.73. Found: C, 55.51; H, 3.46; N, 19.02; S, 8.69%. 123.12,

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