Novel Syntheses of 5-Aminothieno[2,3-c]pyridazine, Pyrimido[4',5':4,5]thieno[2,3-c]pyridazine, Pyridazino[4',3':4,5]thieno-[3,2-d][1,2,3]triazine and Phthalazine Derivatives

Mohamed S. A. El-Gaby,[†] Adel M. Kamal El-Dean,[†] Abd El-Aal M. Gaber,[†] Hassan A. Eyada,[‡] and Ahmed S. N. Al-Kamali[†]

Chemistry Department, Faculty of Science, Al-Azhar University, at Assiut, 71524 Assiut, Egypt
[†]*Chemistry Department, Faculty of Science, Assiut University, Assiut 71516, Egypt*
[‡]*Chemistry Department, Faculty of Science, Al-Azhar University, Nasr City, Cairo, Egypt*
Received March 28, 2003

Condensation of 4-cyano-5,6-dimethyl-3-pyridazinone **1** with aromatic aldehydes gave the novel styryl derivatives **2a-c**. Refluxing of compound **2a** with phosphorus oxychloride furnished 3-chloropyridazine derivative **3**. Compound **3** was reacted with thiourea and produced pyridazine-3(2*H*)thione **4**. Thieno[2,3-c]-pyridazines **5a-e** were achieved by cycloalkylation of compound **4** with halocompounds in methanol under reflux and in the presence of sodium methoxide. Also, refluxing of compound **4** with *N*-substituted chloroacetamide in the presence of potassium carbonate afforded thienopyridazines **6a-e**. Cyclization of compound **6** with some electrophilic reagents as carbon disulfide and triethyl orthoformate furnished the novel pyrimido[4',5':4,5]thieno[2,3-c]pyridazines **12** and **13a-c**, respectively. Diazotisation of compound **6** with sodium nitrite in acetic acid produced the pyridazino[4',3':4,5]thieno[3,2-d][1,2,3]triazines **14a-c**. Ternary condensation of compound **1**, aromatic aldehydes and malononitrile in ethanol containing piperidine under reflux afforded the novel phthalazines **16a-c**. Compound **3** was subjected to some nucleophilic substitution reactions with amines and sodium azide and formed the aminopyridazines **17a**, **b** and tetrazolo[1,5-b]-pyridazine **19**, respectively. The structures of the synthesized compounds were established by elemental and spectral analyses.

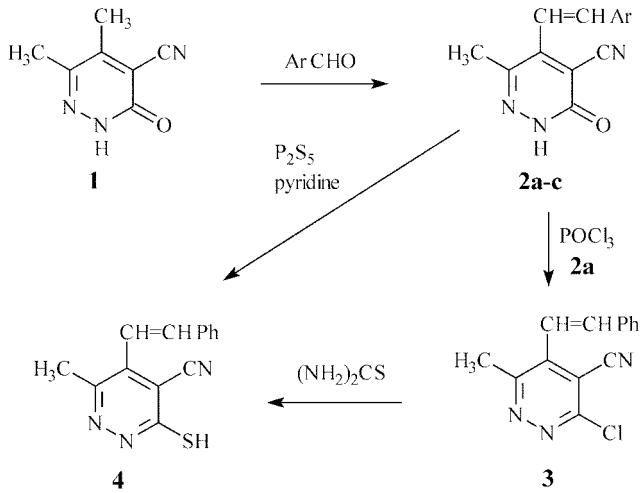
Key Words : Pyridazine, Thieno[2,3-c]pyridazine phthalazine and condensed pyridazines

Introduction

A considerable number of pyridazine derivatives were found to have antibacterial,[1] analgesic,[2] antiinflammatory,[3] anticonvulsant,[4] acetyl-cholinesterase inhibitors,[5] aldose reductase inhibitor and antioxidant[6] properties. Some thieno-pyridazines have been reported to possess considerable antiasthmatic[7] and fibrinolytic[8] activities. In addition, 1,2,3-triazine systems condensed with carbocycles or heterocycles are known to exhibit antiallergic activity.[9] On the basis of these reports and in continuation in the synthesis of novel condensed pyridazine derivatives,[10-14] we reported here the synthesis of 5-aminothieno[2,3-c]pyridazine, pyrimido[4',5':4,5]thieno[2,3-c]pyridazine, pyridazino[4',5':4,5]thieno[3,2-d]-[1,2,3]triazine and phthalazine from 4-cyano-3-mercapto-6-methyl-5-styryl-pyridazine **4** as starting material.

Results and Discussion

The starting material 4-cyano-5,6-dimethyl-3-pyridazinone **1** was readily obtained by treatment of diacetyl with hydrazine hydrate followed by cyclocondensation with ethyl cyanoacetate in the presence of sodium ethoxide.[15] Styryl derivatives **2a-c** were achieved by refluxing of pyridazinone **1** with aromatic aldehydes in ethanol and in the presence of piperidine. When compound **2a** was refluxed with phosphorus oxychloride gave the 3-chloropyridazine derivative **3** in 87% yield. Compound **3** was subjected to addition-elimination reaction with thiourea[16] in ethanol under reflux to afford 4-cyano-6-methyl-5-styryl-pyridazine-3(2*H*)thione **4** (Scheme 1). The structure of compound **4** was established by another



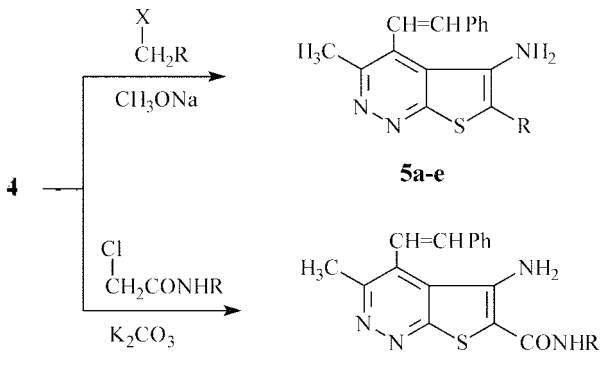
2a; Ar=C_6H_5
2b; Ar=$C_6H_4OCH_3$-p
2c; Ar=C_6H_4Cl-p

Scheme 1

synthetic route *via* thionation of compound **2a** with phosphorus pentasulfide under reflux in pyridine.

Cycloalkylation of compound **4** with chloroacetonitrile in the presence of an equimolar amount of sodium methoxide in methanol afforded 5-amino-3-methyl-4-styryl-thieno[2.3-c]-pyridazine-6-carbonitrile **5a** in high yield (Scheme 2). The structure of compound **5a** was established using microanalyses and spectroscopic data. The infrared spectrum of **5a** exhibited strong absorption at 2200 cm^{-1} due to the carbonitrile group in addition to amino functional group at 3450 and 3320 cm^{-1}. ^{1}HNMR spectrum of **5a** in DMSO-d_6 displayed a broad singlet because of amino protons at δ 6.10-6.20, singlet at δ 2.80 due to methyl protons and a multiplet at δ 6.60-7.42 which was assigned to aromatic and ethylene protons. In addition, the structure of compound **5a** was confirmed by its mass spectrum which showed a molecular ion peak at m/z 292 which is the base peak in the spectrum. In a similar manner when compound **4** was cyclocondensed with chloroacetone, ethyl chloroacetate and phenacyl bromide derivatives yielded the corresponding thienopyridazines **5b**, **5c**, **5d** and **5e**, respectively (Scheme 2). Cyclocondensation of compound **4** with *N*-substituted chloroacetamide in the presence of anhydrous potassium carbonate to form the novel carboxamide derivatives **6a-e** (Scheme 2). The infrared spectra of compounds **6a-e** showed the absence of nitrile functional group and the presence of NH/NH_2 as well as carbonyl groups. ^{1}HNMR spectrum of compound **6e** in DMSO-d_6 displayed the presence of acetyl, methyl, amino, aromatic, ethylene and NH protons. In the mass spectrum of compound **6c** a molecular ion peak was observed at m/z 416 which is the base peak in the spectrum.

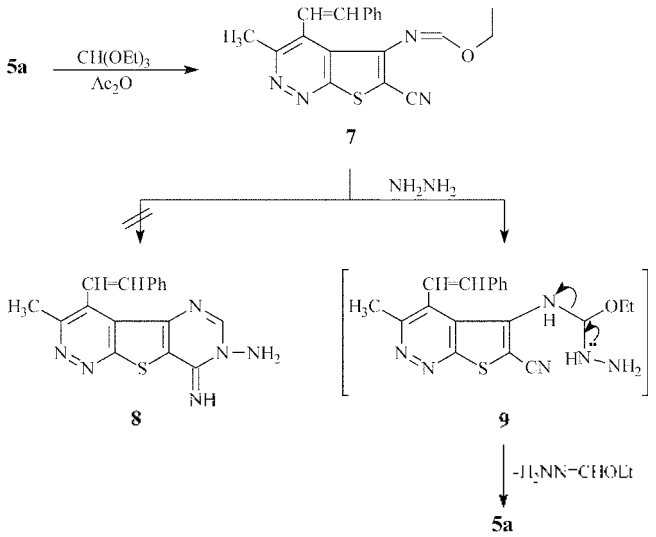
Ethoxymethyleneamino derivative **7** was obtained by treatment of enaminonitrile **5a** with triethyl orthoformate in the presence of acetic anhydride. When compound **7** was allowed to react with hydrazine hydrate in benzene at room temperature the starting material **5a** was produced (mp, mmp and TLC). The condensed pyrimidine **8** was ruled out on the basis of analytical and spectral data. The formation of compound **5a** from **7** was assumed to proceed *via* the addition of hydrazine at the imino functional group to form intermediate **9** followed by elimination of ethyl formate hydrazone[17] (Scheme 3).



5a: R= CN
5b: R= $COCH_3$
5c: R= $COOC_2H_5$
5d: R= COC_6H_5
5e: COC_6H_4Br-p

6a: R= H
6b: R= C_6H_5
6c: R= $C_6H_4OCH_3$-p
6d: R= $C_6H_4CH_3$-p
6e: R= $C_6H_4COCH_3$-p

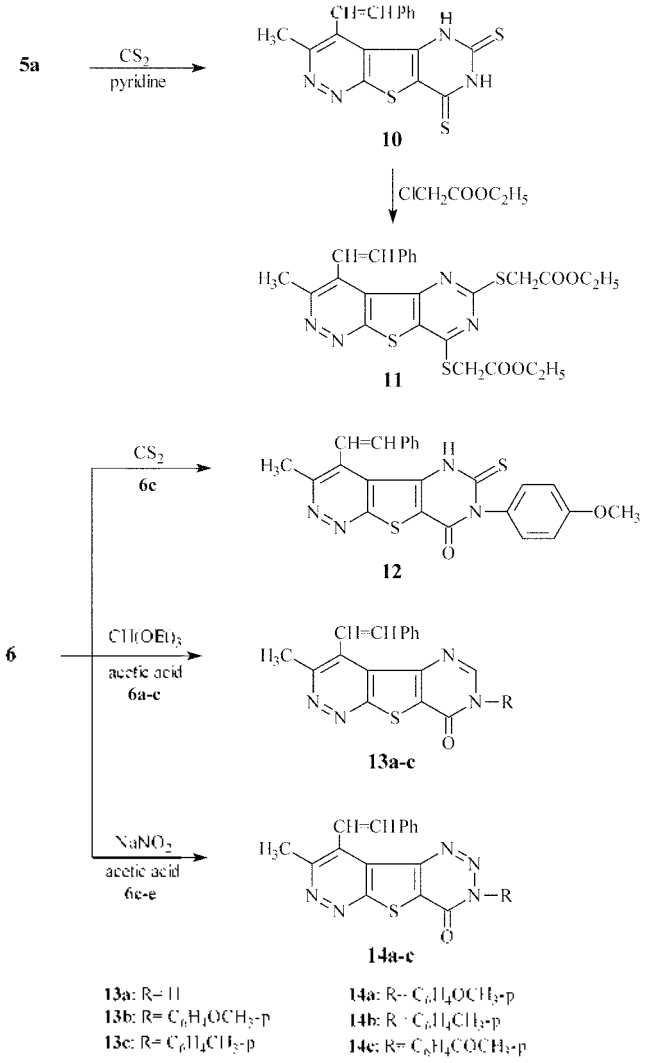
Scheme 2



Scheme 3

Refluxing of compound **5a** with carbon disulfide[18] in pyridine afforded the corresponding pyrimido[4',5':4.5]-thieno[2.3-c]pyridazine derivative **10**. The infrared spectrum of compound **10** was free of nitrile functional group and displayed the presence of two NH functional groups at 3460 and 3320 cm^{-1}. Compound **10** was subjected to react with two molecules of ethyl chloroacetate under reflux in the presence of fused sodium acetate and furnished the di(ethoxycarbonylthio) derivative **11**. Reaction of compound **6c** with carbon disulfide in pyridine gave the condensed pyrimidinethione derivative **12**. Cyclization of compounds **6a-c** with triethyl orthoformate in the presence of catalytic amounts of glacial acetic acid produced the pyrimidothieno-pyridazine derivatives **13a-c**. Pyridazino[4',3':4.5]thieno[3.2-d]-[1.2.3]triazine derivatives **14a-c** were obtained by diazotisation of compounds **6c-e** with sodium nitrite in glacial acetic acid at 0 °C (Scheme 4).

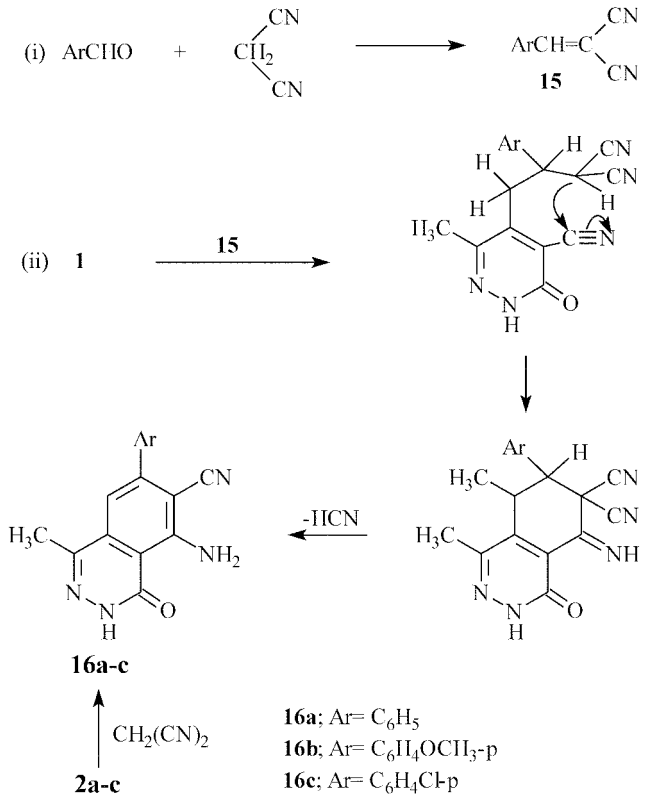
Ternary condensation of aromatic aldehyde, malononitrile and methyl carbonitrile **1** in the presence of a catalytic amount of piperidine afforded the novel derivatives of phthalazine **16a-c** in good yields (Scheme 5). Analytical and spectral data were consistent with this structure. The infrared spectra of compounds **16a-c** revealed the presence of amino, cyano and carbonyl functional groups whereas ^{1}H NMR spectrum of compound **16a** in DMSO-d_6 displayed the presence of signal at δ 2.4 (s, 3H, CH_3) in addition to amino and aromatic protons. A reaction mechanism[19] proposed for the formation of the phthalazines **16a-c** is illustrated in Scheme (5). The structure of phthalazine derivatives **16a-c** were confirmed by another synthetic route *via* refluxing of compound **1** with aromatic aldehydes in ethanol containing



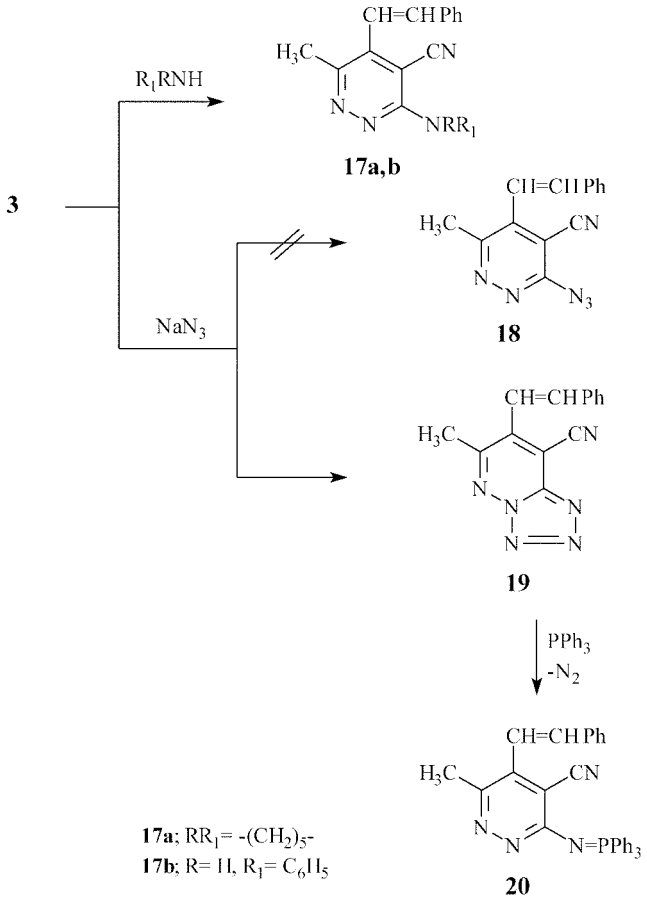
Scheme 4

piperidine to afford styryl derivatives **2a-c** which upon treatment with malononitrile in the presence of piperidine yielded the corresponding phthalazines **16a-c** (Scheme 5). Also, on refluxing compound **1** with arylidenemalononitriles **15** in ethanol in the presence of piperidine, the phthalazines **16a-c** were obtained.

This contribution was extended to study some nucleophilic substitution reactions with chloropyridazine **3**. Thus, compound **3** was reacted with piperidine and aniline in benzene under reflux to yield the novel aminopyridazine derivatives **17a** and **17b**, respectively. Sodium azide as nucleophile was reacted with chloropyridazine **3** in dimethylsulfoxide at 90 °C to form the novel tetrazolo[1,5-b]-pyridazine **19**. The azidopyridazine **18** was excluded on the basis of infrared spectrum which showed the absence of azide functional group. Treatment of compound **3** with triphenylphosphine under reflux to produce the (triphenylphosphoranilidene)-amino derivative **20**. The formation of **20** was assumed to proceed through triphenylphosphine attack the tetrazole moiety followed by elimination of nitrogen molecule[20] (Scheme 6).



Scheme 5



Scheme 6

Experimental Section

Melting points were determined on a Fisher-John melting points apparatus and are uncorrected. IR spectra were recorded on a Shimadzu 470 spectrophotometer using KBr pellets. ^{1}H-NMR spectra were measured on a Varian 390-90 MHz NMR spectrometer using TMS as internal standard. Elemental analyses were performed on a Perkin-Elmer 240 C microanalyzer. The mass spectra were recorded on Jeol-JMS-600 apparatus. The physical and spectral data are shown in Tables 1 and 2, respectively.

4-Cyano-6-methyl-5-styryl-3-pyridazinone derivatives (2a-c). To a solution of compound **1** (0.01 mole) in 50 mL of absolute ethanol, aromatic aldehyde (0.01 mole) and catalytic amount of piperidine were added. The reaction mixture was heated for 4 h, then poured into ice water/HCl mixture. The solid product was collected by filtration and recrystallized from the proper solvent to give **2a-c**.

3-Chloro-4-cyano-6-methyl-5-styrylpyridazine (3). Compound **2a** (0.01 mole) was refluxed with phosphorus oxychloride (15 mL) for 3 h. The cooled reaction mixture was slowly added into the crushed ice water. The resulting solid was filtered, dried and recrystallized from the proper solvent to give **3**.

4-Cyano-3-mercapto-6-methyl-5-styrylpyridazine (4).

Method A: A mixture of compound **3** (0.01 mole) and thiourea (0.012 mole) in dry ethanol (50 mL) was heated under reflux for 3 h. The obtained solid product was recrystallized from the proper solvent to give **4**.

Method B: A mixture of compound **2a** (0.01 mole) and phosphorus pentasulfide (0.012 mole) in pyridine (15 mL) was refluxed for 2 hr, then allowed to cool and poured into cold water (100 mL). The solid product was collected and recrystallized to give **4**.

5-Amino-3-methyl-4-styryl-6-substituted-thieno[2,3-c]-pyridazine derivatives (5a-e): General procedure. A mixture of compound **4** (0.01 mole), sodium methoxide (0.01 mole) and halocompound (0.01 mole) in 50 mL methanol was refluxed for 2 h. The separated product was collected on cooling and recrystallized from the proper solvent to give **5**.

5-Amino-3-methyl-4-styryl-6-(substituted carbamoyl)-thieno[2,3-c]-pyridazine derivatives (6a-e): General procedure. A mixture of compound **4** (0.01 mole), appropriate *N*-substituted chloroacetamide (0.01 mole) and anhydrous potassium carbonate (2 g) in absolute ethanol (40 mL) was heated under reflux for 2 h, then allowed to cool. The solid product was collected, washed with water and recrystallized from the proper solvent to give **6**. MS (**6a**): 310 (M^+; 2.1%), 312 (M+2; 0.4%), 308 (28%), 291 (61%), 264 (base peak; 100%), 215 (39%), 187 (7.9%), 164 (2.1%), 115 (1.4%) and 76 (1.1%).

5-Ethoxymethyleneamino-3-methyl-4-styryl-thieno[2,3c]-pyridazin-6-carbonitrile (7). A mixture of compound **5a** (0.01 mole), triethyl orthoformate (3 mL) and acetic anhydride (10 mL) was heated under reflux for 4 h, then allowed to cool. The product was collected and recrystallized from the proper solvent to give **7**.

Formation of 3-methyl-4-styryl-5,6,7,8-tetrahydro-6,8-dithioxo-pyrimido[4',5':4,5]thieno[2,3-c]pyridazine (10) and 3-methyl-4-styryl-7-(4-methoxyphenyl)-5,6,7,8-tetrahydro-6-thioxopyrimido[4',5':4,5]thieno[2,3-c]pyridazine (12). A mixture of compound **5a** or **6c** (0.01 mole) and carbon disulfide (10 mL) in dry pyridine (20 mL) was heated on a water bath for 10 h. The solid product was precipitated on cooling, then collected and recrystallized from the proper solvent to give **10** and **12** respectively.

3-Methyl-4-styryl-6,8-di(ethoxycarbonylmethylthio)-pyrimido-[4',5':4,5]thieno[2,3-c]pyridazine (11). A mixture of compound **10** (0.01 mole), ethyl chloroacetate (0.01 mole) and sodium acetate (2 g) in ethanol (30 mL) was refluxed for 1 h, then allowed to cool. The solid product was collected and recrystallized from the proper solvent to give **11**.

3-Methyl-4-styryl-7-(4-substituted phenyl)-7,8-dihydro-8-oxopyrimido [4',5':4,5]thieno[2,3-c]pyridazine derivatives (13a-c): General procedure. To a mixture of compound **6** (0.01 mole) and triethyl orthoformate (5 mL), drops of acetic acid was added. The reaction mixture was heated under reflux for 1 h. The solid product was collected and recrystallized from the proper solvent to give **13**. MS (**13a**): 320 (M^-; base peak), 322 (M+2; 6.7%), 291 (9.8%), 265 (1.3%), 242 (40%), 219 (1.5%) and 187 (1%). MS (**13b**): 426 (M^+; base peak), 396 (4%), 348 (17%), 291 (1.4%), 215 (7.9%) and 77 (0.22%).

3-Methyl-4-styryl-7-(4-substituted phenyl)-7,8-dihydro-8-oxopyridaz-ino[4',3':4,5]thieno[3,2-d][1,2,3]triazine (14a-c): General procedure. To a compound **6** (0.01 mole) dissolved in acetic acid (20 mL), sodium nitrite solution (0.5 g in 2 mL H_2O) was added drop by drop with stirring during 15 minutes. After the addition was finished, stirring was continued for additional one hour and then allowed to stand for 5 hours. The solid product was collected and recrystallized from the proper solvent to give **14**.

5-Amino-1-methyl-4-oxo-7-aryl-3,4-dihydrophthalazin-6-carbonitriles (16a-c): General procedure.

Method (A): A mixture of compound **1** (0.01 mole), aromatic aldehyde (0.01 mole) and malononitrile (0.01 mole) in ethanol (50 mL) in the presence of piperidine (0.5 mL) was heated under reflux for 4 h, then poured into ice/HCl mixture. The solid product was collected and recrystallized from the proper solvent to give **16**.

Method (B): To a solution of 4-styryl derivative **2** (0.01 mole) in 50 mL ethanol, malononitrile (0.01 mole) and catalytic amount of piperidine were added. The reaction mixture was heated under reflux for 4 h, then poured into ice/HCl mixture. The solid product was collected and recrystallized from the proper solvent to give **16**.

Method (C): To a solution of compound **1** (0.01 mole) in 50 mL of ethanol, benzylidenemalononitrile **15** (0.01 mole) and catalytic amount of piperidine were added. The reaction mixture was heated under reflux for 4 h, then poured into ice/HCl mixture. The solid product was collected and recrystallized from the proper solvnet to give **16**.

Table 1. Physical data for the synthesis compounds

Compd. No.	M.p. (°C)	Yield (%) (Color)	Solvent cryst.	Molecular formula	Elemental analysis (Calc./Found)			
					C%	H%	N%	S%
2a	298	94 (yellow)	Ethanol	$C_{14}H_{11}N_3O$ (237.25)	70.87 70.92	4.67 4.66	17.71 17.70	
2b	280	78 (yellow)	Ethanol	$C_{15}H_{13}N_3O_2$ (267.27)	67.40 67.50	4.90 4.89	15.72 15.75	
2c	312	50 (yellow)	Ethanol	$C_{14}H_{10}ClN_3O$ (271.69)	61.89 61.90	3.71 3.70	15.47 15.52	
3	200	87 (yellow)	Ethanol	$C_{14}H_{10}ClN_3$ (255.69)	65.76 65.80	3.94 3.94	16.43 16.50	
4	290	94 (red)	Ethanol	$C_{14}H_{11}N_3S$ (253.31)	66.40 66.45	4.35 4.42	16.60 16.71	12.65 12.68
5a	250	86 (yellow)	Ethanol	$C_{16}H_{12}N_4S$ (292.35)	65.73 65.77	4.14 4.01	19.16 19.10	10.97 10.89
5b	180	83 (yellow)	Ethanol	$C_{17}H_{15}N_3OS$ (309.37)	65.99 66.12	4.89 4.90	13.58 13.56	10.36 10.30
5c	160	48 (yellow)	Ethanol	$C_{18}H_{17}N_3O_2S$ (339.40)	63.69 63.77	5.05 5.02	12.38 12.30	9.45 9.50
5d	200	69 (red)	Ethanol	$C_{22}H_{17}N_3OS$ (371.44)	71.13 71.21	4.61 4.60	11.31 11.35	8.63 8.65
5e	176	82 (red)	Ethanol	$C_{22}H_{16}BrN_3OS$ (450.34)	58.67 58.72	3.58 3.60	9.33 9.40	7.12 7.13
6a	278	86 (red)	Ethanol	$C_{16}H_{14}N_4OS$ (310.36)	61.91 61.96	4.55 4.55	18.05 18.08	10.33 10.36
6b	280	80 (red)	Ethanol	$C_{22}H_{18}N_4OS$ (386.45)	68.37 68.42	4.69 4.70	14.50 14.48	8.29 8.30
6c	228	87 (red)	Ethanol	$C_{23}H_{20}N_4O_2S$ (416.48)	66.32 66.42	4.84 4.85	13.45 13.50	7.70 7.72
6d	270	81 (orange)	Ethanol	$C_{23}H_{20}N_4OS$ (400.48)	68.97 69.20	5.03 5.10	13.99 14.22	8.01 8.05
6e	250	88 (red)	Ethanol	$C_{24}H_{20}N_4O_2S$ (428.49)	67.27 67.25	4.70 4.66	13.07 13.12	7.48 7.51
7	170	91 (yellow)	Ethanol	$C_{19}H_{16}N_4OS$ (348.41)	65.49 65.63	4.63 4.62	16.08 16.19	9.20 9.15
10	220	73 (red)	Ethanol	$C_{17}H_{12}N_4S_3$ (368.49)	55.41 55.47	3.28 3.36	15.20 15.26	26.10 26.20
11	160	54 (brown)	Ethanol	$C_{25}H_{24}N_4O_4S_3$ (540.66)	55.53 55.62	4.47 4.50	10.36 10.47	17.79 17.87
12	250	80 (yellow)	Pyridine	$C_{24}H_{18}N_4O_2S_2$ (458.53)	62.86 62.92	3.96 3.97	12.22 12.20	13.98 14.10
13a	330	96 (yellow)	Acetic acid	$C_{17}H_{12}N_4OS$ (320.36)	63.73 63.82	3.77 3.82	17.49 17.56	10.00 10.20
13b	256	90 (yellow)	Acetic acid	$C_{24}H_{18}N_4O_2S$ (426.47)	67.59 67.66	4.25 4.18	13.14 13.11	7.52 7.48
13c	242	90 (yellow)	Acetic acid	$C_{24}H_{18}N_4OS$ (410.47)	70.22 70.32	4.42 4.35	13.65 13.50	7.81 7.88
14a	256	82 (yellow)	Ethanol	$C_{23}H_{17}N_5O_2S$ (427.47)	64.62 64.72	4.00 4.08	16.38 16.35	7.50 7.42
14b	300	87 (orange)	Ethanol /$CHCl_3$	$C_{23}H_{17}N_5OS$ (411.47)	67.13 67.12	4.16 4.16	17.02 17.15	7.79 7.82
14c	230	90 (yellow)	Ethanol	$C_{24}H_{17}N_5O_2S$ (439.48)	65.59 65.72	3.90 3.92	15.93 16.10	7.29 7.25
16a	300	50 (white)	Ethanol	$C_{16}H_{12}N_4O$ (276.29)	69.55 69.62	4.38 4.42	20.28 20.28	
16b	350	67 (yellow)	Ethanol	$C_{17}H_{14}N_4O_2$ (306.31)	66.65 66.75	4.61 4.60	18.29 18.40	
16c	334	40 (green)	Ethanol	$C_{16}H_{11}ClN_4O$ (310.73)	61.84 61.86	3.57 3.56	18.03 18.13	
17a	238	69 (yellow)	Pet. ether 60-80	$C_{19}H_{20}N_4$ (304.38)	74.97 75.12	6.62 6.60	18.41 18.45	
17b	130	73 (yellow)	Pet. ether 60-80	$C_{20}H_{16}N_4$ (312.36)	76.90 76.96	5.16 5.14	17.94 17.90	
19	244	91 (yellow)	Ethanol	$C_{14}H_{10}N_6$ (262.27)	64.11 64.15	3.84 3.85	32.04 32.16	
20	230	70 (yellow)	Ethanol	$C_{32}H_{25}N_4P$ (496.52)	77.40 77.40	5.07 5.08	11.28 11.21	

Table 2. Spectral data of the synthesized compounds

Compd. No.	IR / ν_{max} (cm^{-1})	^1H NMR (δ/ppm)
2a	3100 (NH), 2220 (C≡N).	CF_3COOD; 2.7 (s, 3H, CH_3), 7.10-7.90 (m, 7H, Ar-H and ethylene protons), 8.00 (s, 1H, NH).
2b	3350 (NH), 2210 (C≡N).	DMSO-d_6; 2.5 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 6.90-7.80 (m, 7H, Ar-H, ethylene-H and NH).
2c	3120 (NH), 2220 (C≡N).	CF_3COOD; 2.80 (s, 3H, CH_3), 6.89-7.80 (m, 6H, Ar-H and ethylene protons), 8.41 (s, 1H, NH)
3	2210 (C≡N).	DMSO-d_6; 2.80 (s, 3H, CH_3), 7.10-7.70 (m, 7H, Ar-H and ethylene-H).
4	3380 (NH), 2220 (C≡N).	DMSO-d_6; 2.7 (s, 3H, CH_3), 7.20-7.70 (m, 7H, Ar-H and ethylene-H), 8.70 (s, 1H, NH).
5a	3450, 3320 (NH_2), 2200 (C≡N).	DMSO-d_6; 2.80 (s, 3H, CH_3), 6.20 (broad, 2H, NH_2), 6.60-7.42 (m, 7H, Ar-H and ethylene-H).
5b	3460, 3340 (NH_2), 1660 (C=O).	$CDCl_3$; 2.65 (s, 3H, $COCH_3$), 2.95 (s, 3H, CH_3), 7.15 (s, 2H, NH_2), 7.30-7.80 (m, 7H, Ar-H and ethylene-H).
5c	3480, 3350 (NH_2), 1680 (C=O).	
5d	3400, 3330 (NH_2), 1620 (C=O).	$CDCl_3$; 2.85 (s, 3H, CH_3), 4.95 (s, 2H, NH_2), 7.70-7.90 (m, 12H, Ar-H and ethylene-H).
5e	3400, 3280 (NH_2), 1670 (C=O).	
6a	3400, 3280, 3100 (NH, NH_2), 1670 (C=O).	DMSO; 2.71 (s, 3H, CH_3), 5.01 (s, 2H, NH_2), 7.20-7.50 (s, 9H, Ar-H, ethylene protons and NH_2)
6b	3450, 3400 (NH_2), 1620 (C=O).	DMSO-d_6; 2.70 (s, 3H, CH_3), 7.05 (s, 2H, NH_2), 7.30-7.60 (m, 12H, Ar-H and ethylene-H), 8.85 (s, 1H, NH).
6c	3480, 3320 (NH_2), 1630 (C=O).	$CDCl_3$; 3.00 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.05-7.60 (m, 13H, Ar-H, ethylene-H and NH_2), 8.70 (s, 1H, NH).
6d	3480, 3210 (NH_2), 1640 (C=O).	DMSO; 2.31, 2.73 (2s, 6H, $2CH_3$), 5.41 (s, 2H, NH_2), 7.20-7.52 (m, 11H, Ar-H and ethylene protons), 8.40 (s, 1H, NH)
6e	3450, 3320 (NH_2), 1670 (C=O).	CF_3COOD; 2.75 (s, 3H, $COCH_3$), 3.10 (s, 3H, CH_3), 7.30-8.30 (m, 11H, Ar-H and ethylene-H), 10.0 (s, 1H, NH).
7	2980 (CH-aliph), 2200 (C≡N), 1620 (C=N).	DMSO-d_6; 0.90 (t, 3H, CH_3), 2.70 (s, 3H, CH_3), 4.00 (q, 2H, OCH_2), 7.30-7.60 (m, 7H, Ar-H and ethylene-H), 8.10 (s, 1H, CH=N).
10	3460, 3320 (NH).	
11	2980 (CH-aliph), 1730 (C=O).	CF_3COOD; 1.50 (t, 6H, $2CH_3$), 3.28 (s, 3H, CH_3), 4.10 (s, 4H, two SCH_2), 4.40 (q, 4H, two OCH_2), 7.30-7.80 (m, 7H, Ar-H and ethylene-H).
12	3400 (NH), 1690 (C=O).	$CDCl_3$; 2.80 (s, 3H, CH_3), 3.90 (s, 3H, OCH_3), 7.10-7.40 (m, 11H, Ar-H and ethylene-H), 8.10 (s, 1H, NH).
13a	3400 (NH), 1640 (C=O).	DMSO; 2.76 (s, 3H, CH_3), 7.10-7.60 (m, 7H, Ar-H and ethylene protons), 8.03 (s, 1H, pyrimidine-H), 8.70 (s, 1H, NH)
13b	1680 (C=O).	CF_3COOD; 3.18 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 7.20-7.70 (m, 11H, Ar-H and ethylene-H), 8.70 (s, 1H, pyrimidine-H).
13c	1680 (C=O).	CF_3COOD; 2.50, 3.40 (2s, 6H, $2CH_3$), 7.30-7.73 (m, 11H, Ar-H and ethylene-H), 8.65 (s, 1H, pyrimidine-H).
14a	1660 (C=O).	CF_3COOD; 2.35 (s, 1H, CH_3), 3.70 (s, 3H, OCH_3), 7.10-7.80 (m, 11H, Ar-H and ethylene-H).
14b	1675 (C=O).	CF_3COOD; 2.35, 2.98 (2s, 6H, $2CH_3$), 7.25-7.38 (m, 11H, Ar-H and ethylene-H).
14c	1680 (C=O; broad)	DMSO-d_6; 2.60 (s, 3H, $COCH_3$), 2.70 (s, 3H, CH_3), 7.20-7.60 (m, 11H, Ar-H and ethylene protons)
16a	3330, 3200 (NH_2), 2200 (C≡N), 1630 (C=O).	DMSO-d_6; 2.40 (s, 3H, CH_3), 6.80 (s, 2H, NH_2), 7.40-7.80 (m, 6H, Ar-H), 8.30 (hump, 1H, NH).
16b	3450, 3190 (NH_2), 2200 (C≡N), 1650 (C=O).	DMSO-d_6; 2.40 (s, 3H, CH_3), 3.80 (s, 3H, OCH_3), 6.7 (s, 2H, NH_2), 6.90-7.60 (m, 5H, Ar-H), 8.10 (hump, 1H, NH).
16c	3450, 3400 (NH_2), 2200 (C≡N), 1660 (C=O).	
17a	2950, 2800 (CH-aliph), 2180 (C≡N).	$CDCl_3$; 1.60 (s, 6H, $3CH_2$), 2.75 (s, 3H, CH_3), 3.10 (s, 4H, $N(CH_2)_2$), 6.90-7.34 (m, 7H, Ar-H and ethylene protons)
17b	3200 (NH), 2200 (C≡N).	DMSO-d_6; 2.78 (s, 3H, CH_3), 6.90-7.80 (m, 12H, Ar-H and ethylene-H), 8.40 (hump, 1H, NH).
19	2200 (C≡N).	
20	2200 (C≡N).	DMSO-d_6; 2.5 (s, 3H, CH_3), 6.9-8.2 (m, 22H, Ar-H and ethylene-H).

4-Cyano-3-substituted amino-6-methyl-4-styryl-pyridazine derivatives (17a, b): General procedure

A mixture of compound **3** (0.01 mole) and amino compound (0.012 mole) in dry benzene (30 mL) was heated under reflux for 0.5 h. The solid product was collected and recrystallized from the proper solvent to give **17**.

6-Methyl-7-styryl-tetrazolo[1,5-b]pyridazin-8-carbonitrile (19). A mixture of compound **3** (0.01 mole) and sodium azide (0.01 mole) in dimethylsulfoxide (10 mL) was heated under reflux for 1 h, then poured into ice water. The

solid product was collected and recrystallized from the proper solvent to give **19**.

4-Cyano-6-methyl-5-styryl-3-[(triphenylphosphoraniliden)-amino]pyridazine (20). A mixture of compound **19** (0.01 mole) and triphenylphosphine (0.01 mole) in dry benzene (50 mL) was heated under reflux for 1 h. After cooling, the precipitate product was obtained, then filtered off and recrystallized from the proper solvent to give **20**.

References

1. Purohit, D. M.; Shah, V. H. *Indian J. Chem.* **1998**, *37B*(9), 956. [Chem. Abstr. **1999**, *130*(9): 110223k].
2. Rohet, F.; Rubat, C.; Coudert, P.; Albuisson, E.; Couquelet, J. *Chem. Pharm. Bull.* **1996**, *44*, 980.
3. Takaya, M.; Sato, M. *Yakugaki Zassha* **1994**, *114*, 94.
4. Kornet, M. J.; Chu, J. *J. Heterocycl. Chem.* **1981**, *18*, 293.
5. Contreras, J.; Rival, Y. M.; Chayer, S.; Bourguignon, J.; Wermuth, C. G. *J. Med. Chem.* **1999**, *42*, 730.
6. Coudert, P.; Albuisson, E.; Boire, J. Y.; Duroux, E.; Bastide, P.; Conquelet, J. *Eur. J. Med. Chem.* **1994**, *29*, 471.
7. Yamaguchi, M.; Maruyama, N.; Koga, T.; Akima, K.; Kuroki, T.; Hamana, M.; Ohi, N. *Chem. Pharm. Bull.* **1995**, *43*, 236.
8. Vartanyan, R. S.; Kazaryan, Zh. V.; Sheiranyan, M. A.; Agaronyan, A. S.; Stepanyan, N. O. *Khim. Farm. Zh.* **1996**, *30*, 29.
9. Ferrand, G.; Dumas, H.; Depin, J. C.; Chouvernac, G. *Eur. J. Med. Chem.* **1987**, *22*, 337.
10. Kamal El-Dean, A. M.; Radwan, Sh. M. *Pharmazie* **1998**, *53*, 839.
11. Kamal El-Dean, A. M.; Radwan, Sh. M.; Abdel-Moneam, M. I. *Afinidad LIII* **1996**, *466*, 387.
12. Radwan, Sh. M.; Kamal El-Dean, A. M. *Phosphorus, Sulfur and Silicon* **2000**, *164*, 299.
13. Hussein, A. M.; Atalla, A. A.; Kamal El-Dean, A. M. *Pharmazie* **1995**, *50*(H12), 788.
14. Radwan, Sh. M.; Kamal El-Dean, A. M. *Pharmazie* **1997**, *52*(H6), 483.
15. Druey, J.; Schmidt, P. *Swiss 320* **1957**, *131*, Apr. 30. [Chem. Abstr. **1958**, *52*, 6416d].
16. Ho, Y. W.; Wang, I. J. *J. Heterocycl. Chem.* **1995**, *32*, 819.
17. Hassan, S. M.; Emam, H. A.; Abdelall, M. M. *J. Chem. Research (S)* **2000**, 544; *J. Chem. Research (M)* **2000**, 1301.
18. Kamal El-Dean, A. M. *Monatshefte für Chemie* **1998**, *129*, 523.
19. El-Gaby, M. S. A.; Zahran, M. A.; Ismail, M. M. F.; Ammar, Y. A. *IL-Farmaco* **2000**, *55*, 227.
20. Kappe, T. *J. Heterocycl. Chem.* **1998**, *35*, 1111.