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Novel synthesis of new symmetrical bis-heterocyclic compounds: synthesis of bis-thiazolo, bis-pyrazolo-, bis-benzotriazolo, bis-indolo- and bis-pyrazolyl thiazolo-2,6-diamino pyridine derivatives

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The reaction of 2,6-diaminopyridine with chloroacetyl chloride yielded 2,6-bis-(2-chloroacetamido-N-yl) pyridine. The later reacted with KCN, KSCN, indole and benzotriazole separately to give 2,6-bis-(cyanoacetamido-N-yl)pyridine [which on coupling with benzenediazonium chloride yielded the bis-cyanophenyl hydrazone derivative and by refluxing the later compound with chloroacetonitrile afforded 2,6-diamido-bis-(4-amino-5-cyano-1-phenylpyrazol-3-yl)pyridine], 2,6-bis-(thiocyanate acetamido-N-yl)pyridine, 2,6-bis-[2-(1[H]-indol-3-yl)acetamido-N-yl] pyridine and 2,6-bis-[2-(1,2,3-benzotriazol-1-yl)acetamido-N-yl]pyridine, respectively. Acetylation of 2,6-diaminopyridine with acetic anhydride afforded 2,6-bis-(acetamido-N-yl) pyridine which on coupling with benzenediazonium chloride yielded the bis-phenyl-hydrazone derivative. By reacting the later with chloroacetonitrile afforded 2,6-diamino-bis-(5-cyano-1-phenylpyrazol-4-yl)pyridine. Under basic conditions the reaction of 2,6-diaminopyridine with CS_2 followed by ethyl-α-bromo-cyanoacetate and phenacyl bromide separately afforded 2,6-bis-(5-cyano-4-hydroxythiazol-3-yl-2-thione)pyridine and 2,6-bis-(4-phenyl thiazol-3-yl-2-thione)pyridine respectively. Condensation of the later compounds separately with malononitrile yielded the dicyanomethinothiazole derivatives. The reaction of either hydrazine hydrate or phenyl hydrazine with the thiazolyl thione derivatives or with the dicyanomethinothiazole derivatives afforded the hydrazono-thiazole and the pyrazole derivatives respectively.

Key words: 2,6-diaminopyridine; bis-(thiazolo)pyridine; bis-(pyrazolo)pyridine; bis-(hydrazonopyrazolo)pyridine.

INTRODUCTION

The incorporation of two moieties increases biological activity of both and thus it was of value to synthesize some new heterocyclic derivatives having two moieties in the same molecules. In continuation to our programme [1–10], this research has been devoted to the development of new classes of bis-heterocycle systems which incorporate the bis-thiazolo-, bis-pyrazolo-, bis-benzotriazolo-, bis-indolo-, bis-triazolo- and bis-pyrazolyl thiazolo- pyridine derivatives moiety. The importance of such compounds lies in their diverse pharmaceutical activities namely antibacterial [11, 12], antidiabetic [13], anti HIV [14], antiviral [15, 16] and analgesic activities.

RESULTS AND DISCUSSION

Mixing 2,6-diaminopyridine with chloroacetyl-chloride in dioxane afforded the 2,6-bis-(2-chloro-acetamido)pyridine **2** (Scheme 1). Compound **2** could be converted into **7** on treatment with potassium cyanide and into **8** on treatment with potassium thio-cyanate. Treatment of **2** with indole and with benzo-triazole separately in toluene/triethylamine afforded **9** and **10,** respectively. The ^{1}H NMR of **10** revealed non identity of all four benzotriazolyl protons.

Compound **11** is symmetrical and should have shown only two signals for these protons (Scheme 2). Compound **7** coupled readily with benzene diazonium chloride to yield the bis-aryl hydrazone derivative **12** which on refluxing in DMF with chloroacetonitrile afforded the bis-pyrazolyl diamidopyridine derivative **14** (Scheme 2). On the other hand acetylation of compound **1** yielded the 2,6-bis-(acetamido)pyridine **3** (Scheme 1). Coupling of **3** with benzene diazonium chloride afforded the bis-hydrazone derivative **15**. Thus, reacting **15** with chloroacetonitrile in a mixture of DMF and tri-ethylamine has afforded **17** in excellent yield. Inter-mediacy of **16** is most likely (Scheme 2). Further, the reaction of **1** with carbon disulphide under basic conditions in KOH/DMF solution affords the non isolable intermediate, the N-potassium thiocarba-mate salt **4** [17]. Thus, the reaction of **4** with ethyl-α-bromocyanoacetate and with phenacyl bromide separately afforded the thiazole derivatives **5** and **6** respectively (Scheme 1).

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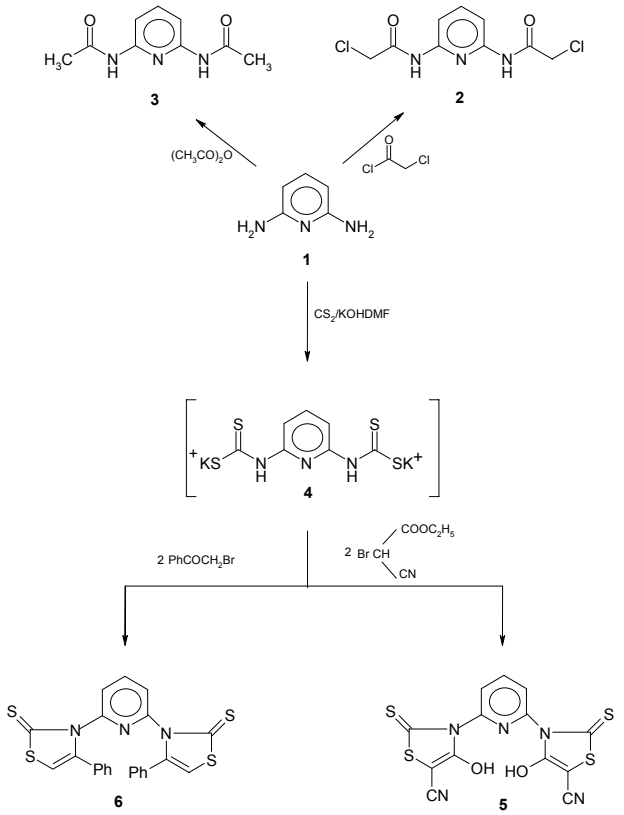


Scheme 1.

Confirmation of the structures of **5** and **6** were obtained through studying their reactivity towards chemical reagents. The reaction of compounds **5** or **6** with either hydrazine hydrate or phenyl hydrazine afforded the corresponding hydrazone derivatives **18a,b** and **22a,b** respectively (Scheme 3). Formation of the latter compounds took place through elimination of hydrogen sulphide. Their structures were confirmed by analytical and spectral data. The reaction of **5** and **6** with malononitrile gave the condensed products the dicyanomethino derivatives **19** and **23** respectively (Scheme 3); their formation took place *via* elimination of hydrogen sulphide. The reaction of **19** and **23** with either hydrazine hydrate or phenylhydrazine afforded the pyrazole derivatives **20**, **21**, **24** and **25** (Scheme 3). The structures of the latter compounds were confirmed by analytical and spectral data.

EXPERIMENTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on a Pye Unicam SP-100 spectrophotometer. ^{1}H and ^{13}C NMR spectra (DMSO-d_6 as a solvent) were obtained on a Varian Gemini 200 and on a Bruker AC200 and AC600 MHz spectrometers respectively, TMS as internal standard, chemical shifts in δ (ppm); mass spectra: AEI MS 30 mass spectrometer operating at 70 eV; elemental analysis were obtained from Microanalytical Data Unit at Cairo University, Egypt.

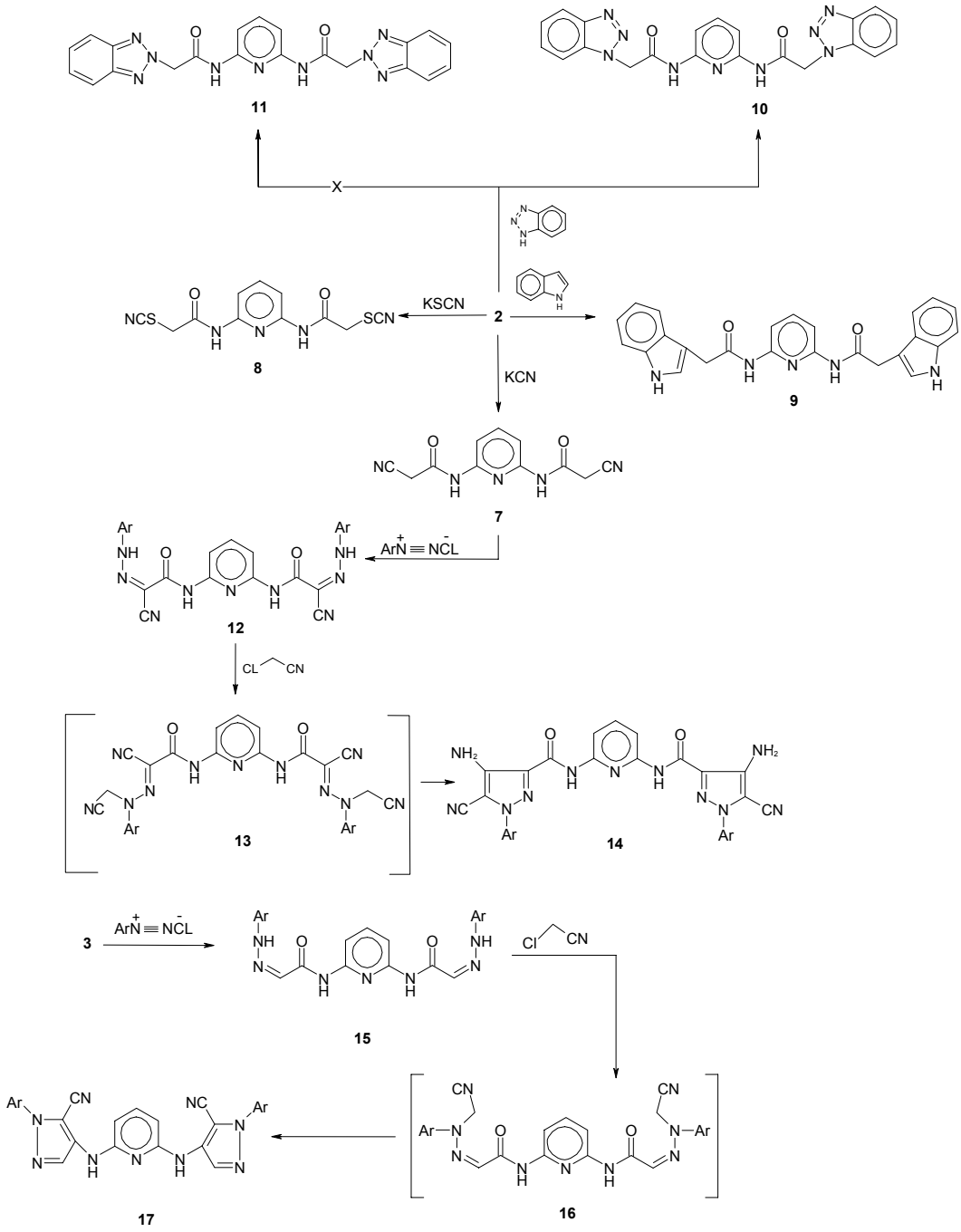
2,6-Bis-(2-chloroacetamido-N-yl) pyridine (**2**): A mixture of **1** (1.09 g, 10 mmol) and chloroacetyl-chloride (2.30 g, 20 mmol) in 20 ml of dioxane was refluxed for 45 min. The mixture was allowed to cool to room temperature then poured onto cold water. The obtained solid was collected by filtration and crystallized from methanol to give pale pink crystals (93% yield), m.p. 105°C; IR (KBr) ν (cm^{-1}): 3118 (NH) and 1700 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.58 (s, 4H, 2CH_2), 8.10–8.30 (m, 3H, pyr-H), 8.50 (s, 2H, 2NH); ^{13}C NMR (DMSO-d6) δ (ppm): 190.5 (2CO), 154.2 (C-2 and C-6 pyridine), 149.3 (C-3 and C-5 pyridine), 138.5 (C-4 pyridine), 53.23 (CH_2); MS: m/z = 262 [M$^+$]; Anal. Calcd. for $C_9H_9N_3Cl_2O_2$ (262.09): C, 41.24; H, 3.46; N, 16.03; Cl, 27.05. Found: C, 41.35; H, 3.47; N, 16.25; Cl, 27.35.

2,6-Bis-(acetamido-N-yl) pyridine (**3**): Reflux gently 1 g of **1** and 3 ml of acetic anhydride for 15 min. Pour in 20 ml of cold water then boil to destroy any excess of acetic anhydride. Filter the precipitate, wash with a little cold water and dry in air. Crystallization from ethanol afforded 0.18 g of a creamy crystals (95% yield), m.p. 95°C; IR (KBr) ν (cm^{-1}): 3225 (NH), 1700 (C=O); ^{1}H NMR (DMSO-d_6) δ ppm: 1.5 (s, 6H, 2CH_3), 8.10–8.30 (m, 3H, pyr-H), 8.55 (s, 2H, 2NH); ^{13}CNMR (DMSO-d6) δ (ppm): 184.5 (2CO), 153.5 (C-2 and C-6 pyridine), 148.4 (C-3 and C-5 pyridine), 138.7 (C-4 pyridine), 24.15 (CH_3); MS: m/z = 193 [M$^+$]; Anal. Calcd. for $C_9H_{11}N_3O_2$ (193.21): C, 55.95; H, 5.74; N, 21.75. Found: C, 55.90; H, 5.76; N, 21.90.

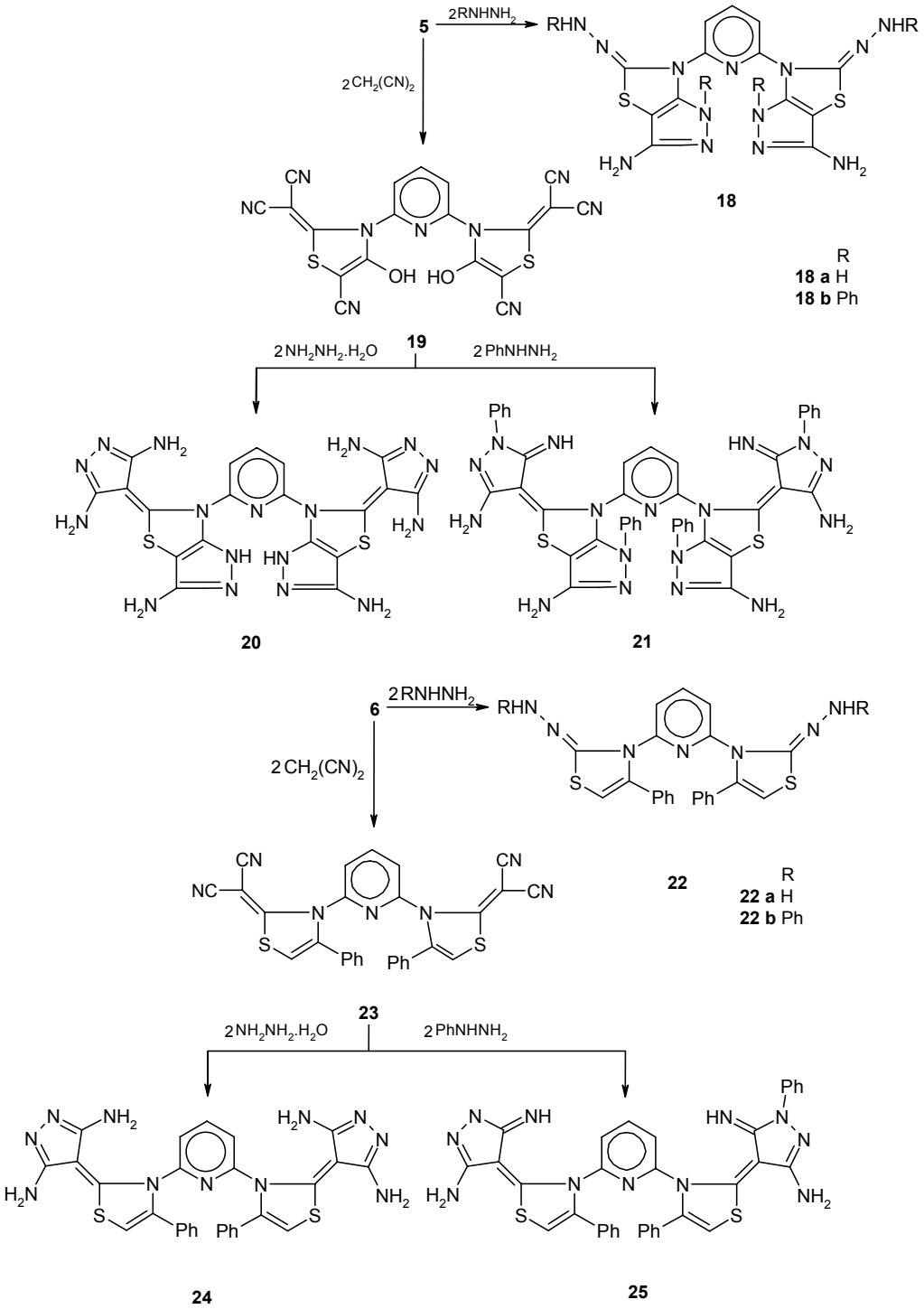
2,6-Bis (5-cyano-4-hydroxythiazol-3-yl-2-thione) pyridine (**5**): To a solution of **1** (1.09 g, 0.01 mol) in 30 ml of DMF, carbon disulphide (1.52 g, 0.02 mol) and potassium hydroxide (1.12 g, 0.02 mol) in 10 ml of water were added. The whole reaction mixture was heated in a boiling water bath for 1 h then left to cool till 20°C. To a cold solution of the reaction mixture (3.84 g, 0.02 mol) of ethyl α-bromocyano-acetate was added. The reaction mixture was stirred at room temperature for one night. The solid product, formed upon acidification with hydrochloric acid, was collected by filtration and crystallized from dioxane to give orange crystals (87% yield), m.p. 150°C; IR (KBr) ν (cm^{-1}): 3480–3340 (OH), 2225 (2 CN), 1210–1195 (2 C=S); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.90–8.25 (m, 3H, pyr-H), 10.33 (s, 2H, 2OH); ^{13}C NMR (DMSO-d6) δ (ppm): 164.5 (2C=S), 153.2 (C-2 and C-6 pyridine), 150.2 (C-4 and C-4' thiazole), 148.1 (C-3 and C-5 pyridine), 140.8 (C-5 and C-5' thiazole), 138.1 (C-4 pyridine), 119.7 (2CN); MS: m/z = 391 [M$^+$]; Anal. Calcd. for $C_{13}H_5N_5S_4O_2$

(391.47): C, 39.89; H, 1.29; N, 17.89; S, 32.76. Found: C, 39.95; H, 1.31; N, 18.01; S, 32.80.

2,6-Bis-(4-phenylthiazol-3-yl-2-thione)pyridine (**6**)**:** To a solution of **1** (1.09 g, 0.01 mol) in 30 ml of DMF, (1.52 g, 0.02 mol) of carbon disulphide and (1.12 g, 0.02 mol) of potassium hydroxide in 10 ml of water were added. The whole reaction mixture was heated in boiling water bath for 1 h then left to cool down to 20°C; (3.96 g, 0.02 mol) of phenacylbromide was added to this cold solution. The reaction mixture was stirred at room temperature for one night. The solid product formed upon acidification with hydrochloric acid was collected by filtration. Crystallization from dioxane gave red crystals (80% yield), m.p. 99°C; IR (KBr) ν (cm^{-1}): 3060 (CH aromatic), 1200–1190 (C=S); ^{1}H NMR (DMSO-d_6) δ (ppm): 6.95 (s, 2H, thiazole H-5), 7.32–7.55 (m, 10H, $2C_6H_5$), 7.95–8.30 (m, 3H, pyr-H); ^{13}C NMR (DMSO-d6) δ (ppm): 180.4 (C-5 and C-5' thiazole), 164.1 (2C=S), 153.4 (C-2 and C-6 pyridine), 148.8 (C-3 and C-5 pyridine), 146.5 (C-4 and C-4' thiazole), 138.5 (C-4 pyridine), 152.1, 143.2, 132.1, 129.5, 128.5, 126.2 (C-arom.); MS: m/z = 461 [$M^{+\cdot}$]; Anal. Calcd. for $C_{23}H_{15}N_3S_4$ (461.65): C, 59.84; H, 3.28; N, 9.10; S, 27.78. Found: C, 59.80; H, 3.27; N, 9.11; S, 27.82.



Scheme 2.



Scheme 3.

2,6-Bis-(cyanoacetamido-N-yl) pyridine (**7**)**:** To a warmed solution of **2** (1.31 g, 5 mmol) in 10 ml benzene, were added (0.78 g, 12 mmol) of potassium cyanide in 10 ml of water. The reaction mixture was stirred at 50°C (bath temperature) for 1 h, then the aqueous layer was separated and poured onto acidified cooled water. The product, so formed, was collected by filtration and dried. Crystallization from acetic acid gave creamy crystals (95% yield), m.p. 235°C; IR (KBr) ν (cm^{-1}): 2252 (CN), 3220 (NH), 1638 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.48 (s, 4H, 2 CH_2), 8.10–8.30 (m, 3H, pyr-H), 9.45 (s, 2H, 2NH); MS: m/z = 243 [M^{+}]; Anal. Calcd. for $C_{11}H_9N_5O_2$ (243.23): C, 54.32; H, 3.73; N, 28.79. Found: C, 54.37; H, 3.74; N, 28.84.

2,6-Bis-(thiocyanate acetamido-N-yl)pyridine (**8**): To a warmed solution of 2 (1.13 g, 5 mmol) in 10 ml acetonitrile, were added (0.92 g, 12 mmol) of potassium thiocyanate. The reaction mixture was stirred at 50°C (bath temperature) for 1 h, then

poured onto ice cold water. The product, so formed, was collected by filtration, crystallized from ethanol to give faint pink crystals (95% yield), m.p. 130°C; IR (KBr) ν (cm^{-1}): 3220 (NH), 2157 (SCN), 1696 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.48 (s, 4H, $2CH_2$), 8.10–8.30 (m, 3H, pyr-H), 9.20 (s, 2H, 2NH); MS: m/z = 307 [M^+]; Anal. Calcd. for $C_{11}H_9N_5S_2O_2$ (307.35): C, 42.99; H, 2.95; N, 22.79; S, 20.86. Found: C, 43.01; H, 2.98; N, 23.01; S, 20.88.

General procedure for the synthesis of compounds **9** *and* **10**

A mixture of **2** (2.62 g, 10 mmol), (2.34 g, 20 mmol) of indole or (2.38 g, 20 mmol) of benzotriazole and 2 ml triethylamine (20 mmol) in 15 ml of toluene was refluxed for 2 h. The solvent was removed in vacuum and the remaining residue was triturated with 5% sodium hydroxide. The solid product, so formed, was collected by filtration.

2,6-Bis-[2-(1[H]-indol-3-yl)acetamido-N-yl] pyridine (**9**): Crystallization from ethanol gave white crystals (78% yield), m.p. 162°C; IR (KBr) ν (cm^{-1}): 3225 (NH), 1700 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.60 (s, 4H, $2CH_2$), 7.38–7.75 (m, 8H, $2C_6H_4$), 8.10–8.30 (m, 3H, pyr-H), 8.44 (d, 2H, two indole H-2), 9.43 (s, 2H, 2NH), 11.92 (br s, 2H, two indole NH); MS: m/z = 423 [M^+]; Anal. Calcd. for $C_{25}H_{21}N_5O_2$ (423.48): C, 70.91; H, 4.99; N, 16.54. Found: C, 70.94; H, 4.98; N, 16.78.

2,6-Bis-[2-(1,2,3-benzotriazol-1-yl)acetamido-N-yl] pyridine (**10**): Crystallization from ethanol gave white solid (75% yield), m.p. 175°C; IR (KBr) ν (cm^{-1}): 3225 (NH), 1700 (C=O), ^{1}H NMR (DMSO-d_6) δ (ppm): 4.58 (s, 4H, $2CH_2$), 7.33–7.80 (m, 8H, $2C_6H_4$), 8.10–8.30 (m, 3H, pyr-H), 9.33 (s, 2H, 2NH); MS: m/z = 427 [M^+]; Anal. Calcd. for $C_{21}H_{17}N_9O_2$ (427.43): C, 59.01; H, 4.01; N, 29.49. Found: C, 59.05; H, 4.00; N, 29.55.

General procedure for the synthesis of compounds **12** *and* **15**

To a stirred solution of (0.01 mol) of 7 or 3 in 20 ml of dioxane containing 10 g of sodium acetate, was added benzene diazonium salt (prepared from 20 mmol of aniline and the appropriate quantities of sodium nitrite and hydrochloric acid). The solid product separated on standing was collected by filtration.

2,6-Bis-(2-cyano-2-phenylhydrazonocetamido-N-yl)pyridine (**12**): Crystallization from dioxane gave yellow crystals (75% yield), m.p. 261°C; IR (KBr) ν (cm^{-1}): 3440, 3234 (NH), 2215 (CN), 1700 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.11–7.25 (m, 10H, $2C_6H_5$), 8.10–8.30 (m, 3H, pyr-H), 9.35 (s, 2H, 2NH), 12.04 (br, 2H, hydroazonyl NH); MS: m/z = 451 [M^+]; Anal. Calcd. for $C_{23}H_{17}N_9O_2$(451.451): C, 61.19; H, 3.79; N, 27.92. Found: C, 61.23, H, 3.77; N, 28.15.

2,6-Bis-(1-oxo-2-phenylhydrazonoethanoneamido-N-yl)pyridine (**15**): Crystallization from dioxane gave yellow crystals (78% yield), m.p. 255°C; IR (KBr) ν (cm^{-1}): 3440, 3230 (NH), 1700 (C=O); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.11–7.45 (m, 10H, $2C_6H_5$), 7.56 (s, 2H, olefinic CH), 8.10–8.30 (m, 3H, pyr-H), 9.30 (s, 2H, 2NH), 12.04 (br, 2H, two hydrazone NH); MS: m/z = 401 [M^+]; Anal. Calcd. for $C_{21}H_{19}N_7O_2$ (401.43): C, 62.83; H, 4.77; N, 24.42. Found: C, 62.85; H, 4.74; N, 24.46.

General procedure for the synthesis of compounds **14** *and* **17**

To a solution of (5 mmol) of **12** or **15** in a 2 ml of DMF and 10 ml of triethylamine, was added (1.3 ml, 20 mmol) of chloroacetonitrile. The reaction mixture was refluxed for 1 h and then left to cool to room temperature. The obtained residual product was triturated with ethanol to give a solid product that was collected by filtration, washed with water and crystallized from the proper solvent.

2,6-Diamido-bis-(4-amino-5-cyano-1-phenylpyrazol-3-yl) pyridine (**14**): Crystallization from ethanol gave faint brown crystals (75% yield), m.p. 268–270°C; IR (KBr) ν (cm^{-1}): 1700 (C=O), 3450 (NH_2), 3200 (NH), 2220 (CN), 1650 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 6.52(s, 4H, $2NH_2$), 7.31–7.65 (m, 10H, $2C_6H_5$), 8.10–8.30 (m, 3H, pyr-H), 8.90 (s, 2H, 2NH); MS: m/z = 529 [M^+]; Anal. Calcd. for $C_{27}H_{19}N_{11}O_2$ (529.53): C, 61.24; H, 3.62; N, 29.10. Found: C, 61.25; H, 3.61; N, 29.40.

2,6-Diamino-bis-(5-cyano-1-phenylpyrazol-4-yl) pyridine (**17**): Crystallization from ethanol gave faint brown crystals (85% yield), m.p. 230°C; IR (KBr) ν (cm^{-1}): 3200(NH), 2220 (CN), 1600 (C=C), 1650 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.30 (s, 2H, pyrazolyl H-3), 7.41–7.65 (m, 10H, $2C_6H_5$), 8.10–8.30 (m, 3H, pyr-H), 8.35 (s, 2H, 2NH); MS: m/z = 443 [M^+]; Anal. Calcd. for $C_{25}H_{17}N_9$ (443.48): C, 67.71; H, 3.86; N, 28.43. Found: C, 67.72; H, 3.84; N, 28.44.

2,6-Bis-(5-cyano-2-dicyanomethino-4-hydroxythiazol-N-yl)pyridine (**19**): A solution of **5** (3.91g, 0.01 mol) in 40 ml of DMF containing piperidine 0.5 ml, (1.32 ml, 0.02 mol) of malononitrile was added. The reaction mixture was heated under reflux for 10 h, then evaporated *in vacuo*. The remaining product was triturated with ethanol and the formed solid product was collected by filtration. Crystallization from dioxane gave brown crystals (75% yield), m.p. > 360°C; IR (KBr) ν (cm^{-1}): 3490 (OH), 2225, 2220, 2215 (CN), 1655 (C=C); ^{1}H NMR

(DMSO-d_6) δ (ppm): 8.10–8.30 (m, 3H, pyr-H), 10.44 (s, 2H, 2OH); MS: m/z = 455 [M^+]; Anal. Calcd. for $C_{19}H_5N_9S_2O_2$ (455.44): C, 50.11; H, 1.11; N, 27.68; S, 14.08.Found: C, 50.15; H, 1.09; N, 27.72; S, 14.12.

General procedure for the synthesis of compounds **18a**, **b**; **20**, **21** *and* **22a**, **b**

To a solution of **5**, **19** or **6** (0.01 mol) in 30 ml of DMF, hydrazine hydrate or phenylhydrazine (0.04 mol) or (0.02 mol) were added, respectively. The reaction mixture was heated under reflux for 6–8 h then poured into ice/water mixture containing few drops of hydrochloric acid and the formed solid product was collected by filtration.

2,6-Bis-(3-amino-1[H]-5-hydrazonopyrazolo[4,5-d]thiazol-N-yl) pyridine (**18a**): Crystallization from ethanol gave pale yellow crystals (68% yield), m.p.> 360°C; IR (KBr) ν (cm^{-1}): 3465–3365 (NH, NH_2), 1660 (exocyclic C=N), 1645 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.46, 5.35 (2s, 8H, $4NH_2$), 8.10–8.30 (m, 3H, pyr-H), 8.44 (s, 2H, 2NH); MS: m/z = 415 [M^+]; Anal. Calcd. for $C_{13}H_{13}N_{13}S_2$ (415.46): C, 37.58; H, 3.15;N, 43.83; S, 15.44. Found: C, 37.56; H, 3.16; N, 43.85; S, 15.43.

2,6-Bis-(3-amino-1-phenyl-5-phenylhydrazono-pyrazolo[4,5-d]thiazol-N-yl)pyridine (**18b**): Crystallization from dioxane gave yellow crystals (70% yield), m.p. > 360°C; IR (KBr) ν (cm^{-1}): 3450–3370 (NH_2, NH), 1665 (exocyclic C=N), 1650 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 5.32 (s, 4H, $2NH_2$), 7.36–7.48 (m, 20H, $4C_6H_5$), 8.10–8.30 (m, 3H, pyr-H), 8.45 (s, 2H, 2NH); MS: m/z =719 [M^+]; Anal. Calcd. for $C_{37}H_{29}N_{13}S_2$ (719.86): C, 61.74; H, 4.06; N, 25.29; S, 8.91. Found: C, 61.75, H, 4.04; N, 25.3; S, 8.90.

2,6-Bis[3-amino-1[H]-5-(3',5'-diaminopyrazol-4'-ylidino) pyrazolo [4,5-d]thiazol-N-yl] pyridine (**20**): Crystallization from ethanol gave white crystals (68% yield), m.p. > 360°C; IR (KBr) ν (cm^{-1}): 3460–3370 (NH_2, NH), 1660 (C=N), 1655 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 5.31, 5.36, 7.42 (3s, 12H, $6NH_2$), 8.10–8.30 (m, 3H, pyr-H), 8.41 (s, 2H, 2NH); MS: m/z = 547 [M^+]; Anal. Calcd. for $C_{19}H_{17}N_{17}S_2$ (547.59): C, 41.68; H, 3.13; N, 43.48; S, 11.71. Found: C, 41.65; H, 3.14; N, 43.52; S, 11.69.

2,6-Bis-[3-amino-1-phenyl-5-(3'-amino-5'-imino-1'-phenylpyrazolo-4'-ylidino) pyrazolo[4,5-d] thiazol-N-yl] pyridine (**21**): Crystallization from dioxane gave pale brown crystals (74% yield), m.p. > 360°C; IR (KBr) ν (cm^{-1}): 3460–3365 (NH_2, NH), 1670 (exocyclic C=N), 1660 (C=N), 1645 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.82, 5.45 (2s, 8H, $4NH_2$), 7.30–7.46 (m, 20H, $4C_6H_5$), 8.10–8.30 (m, 3H, pyr-H), 8.33 (s, 2H, 2NH); MS: m/z = 851 [M^+]; Anal. Calcd. for $C_{43}H_{33}N_{17}S_2$ (851.94): C, 60.62; H, 3.90; N, 27.95; S, 7.53. Found: C, 60.60; H, 3.91; N, 27.99; S, 7.50.

2,6-Bis-(2-hydrazono-4-phenylthiazol-N-yl)pyridine (**22a**): Crystallization from dioxane gave buff crystals (75% yield), m.p. 125°C; IR (KBr) ν (cm^{-1}): 3460 (NH_2), 1665 (exocyclic C=N), 1650 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 6.35 (s, 4H, $2NH_2$), 6.37 (s, 2H, thiazolyl H-5), 7.32–7.37 (m, 10H, $2C_6H_5$), 8.10–8.30 (m, 3H, pyr-H); MS: m/z = 457 [M^+]; Anal. Calcd. for $C_{23}H_{19}N_7S_2$ (457.59): C, 60.37; H, 4.19; N, 21.43; S, 14.01. Found: C, 60.39; H, 4.17; N, 21.55; S, 13.89.

2,6-Bis-(2-phenylhydrazono-4-phenylthiazol-N-yl) pyridine (**22b**): Crytallization from dioxane gave pale yellow crystals (73% yield), m.p. 120°C; IR (KBr) ν (cm^{-1}): 3460–3375°C (NH), 1665 (exocyclic C=N), 1650 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 6.37 (s, 2H, thiazolyl H-5), 7.32–7.48 (m, 20H, $4C_6H_5$), 8.10–8.30 (m, 3H, pyr-H), 8.33 (s, 2H, 2NH); MS: m/z = 609 [M^+]; Anal. Calcd. for $C_{35}H_{27}N_7S_2$ (609.78): C, 68.94; H, 4.46; N, 16.08; S, 10.52. Found: C, 68.97; H, 4.44; N, 16.10, S, 10.49.

2,6-Bis-(2-dicyanomethino-4-phenylthiazol-N-yl) pyridine (**23**): To a solution of 6 (4.61 g, 0.01 mol) in 30 ml of DMF, (1.32 ml, 0.02 mol) of malononitrile was added. The mixture was heated under reflux for 6 h (till the evolution of H_2S was ceased). The solid product formed upon pouring into water was collected by filtration. Crystallization from dioxane gave brown crystals (80% yield), mp 145°C; IR (KBr) ν (cm^{-1}): 2225–2220 (CN), 1655 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 6.34 (s, 2H, thiazolyl H-5), 7.34–7.45 (m, 10H, $2C_6H_5$), 8.10–8.30 (m, 3H, pyr-H); MS: m/z = 525 [M^+]; Anal. Calcd. for $C_{29}H_{15}N_7S_2$ (525.62): C, 66.27; H, 2.88; N, 18.65; S, 12.20. Found: C, 66.28; H, 2.87; N, 18.66; S, 12.19.

General procedure for the synthesis of compounds **24** *and* **25**

To a solution of **23** (5.01 g, 0.01 mol) in 40 ml of dioxane, hydrazine hydrate or phenyl hydrazine (0.02 mol) was added. The reaction mixture was heated under reflux for 3–4 h, then left to cool. The solid product formed upon standing was collected by filtration.

2,6-Bis-[2-(3',5'-diaminopyrazolo-4'-ylidino)-4-phenyl thiazol-N-yl] pyridine (**24**): Crystallization from DMF gave white crystals (70% yield), m.p. 323°C; IR (KBr) ν (cm^{-1}): 3465 (NH_2), 1645 (C=C), 1660 (C=N); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.44, 5.03 (2s, 8H, $4NH_2$), 6.42 (s, 2H, thiazolyl H-5), 7.35–7.58 (m, 10H, $2C_6H_5$), 8.10–8.30 (m, 3H, pyr-H); MS: m/z = 589 [M^+]; Anal. Calcd. for

$C_{29}H_{23}N_{11}S_2$ (589.71): C, 59.07; H, 3.93; N, 26.13; S, 10.87. Found: C, 59.05; H, 3.94; N, 26.17; S, 10.84.

2,6-Bis-[2-(3'-amino-5'-imino-1'-phenylpyrazolo-4'-ylidino)-4-phenylthiazol-N-yl] pyridine (**25**): Crystallization from ethanol afforded pale yellow crystals (65% yield), m.p. > 360°C; IR (KBr) ν (cm^{-1}): 3465, 3390 (NH_2, NH), 1660 (C=N), 1645 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 4.43 (s, 4H, $2NH_2$), 6.43 (s, 2H, thiazolyl H-5), 7.30–7.64 (m, 20H, $4C_6H_5$), 8.10–8.30 (m, 3H, pyr-H), 8.37 (s, 2H, 2NH); MS: m/z = 741 [M^+]; Anal. Calcd. for $C_{41}H_{31}N_{11}S_2$ (741.91): C, 66.38; H, 4.21; N, 20.77; S, 8.64. Found: C, 66.40; H, 4.20; N, 20.80; S, 8.60.

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НОВИ СИНТЕЗИ НА НОВИ СИМЕТРИЧНИ БИС-ХЕТЕРОЦИКЛЕНИ СЪЕДИНЕНИЯ: СИНТЕЗ НА БИС-ТИАЗОЛ-, БИС-ПИРАЗОЛ-, БИС-БЕНЗОТРИАЗОЛ-, БИС-ИНДОЛ- И БИС-ПИРАЗОЛИЛТИАЗОЛ-2,6-ДИАМИНПИРИДИНОВИ ПРОИЗВОДНИ

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При реакция на 2,6-диаминопиридин с хлорацетилхлорид се получава 2,6-бис-(2-хлорацетамид-N-ил)пиридин. Реакцията на продукта поотделно с KCl, KSCN, индол и бензотриазол води съответно до 2,6-бис-(цианацетамид-N-ил)пиридин (продуктът при купелуване с бензендиазониев хлорид дава бис-цианфенил-хидразоновото производно и чрез дестилация на последното съединение с обратен хладник и хлорацетонитрил се получава 2,6-диамин-5-циан-1-фенилпиразол-3-ил)пиридин), 2,6-бис-(тиоцианат ацетамид-N-ил)пиридин, 2,6-бис-[2-(1[H]-индол-3-ил)ацетамид-N-ил]пиридин и 2,6-бис-[2-(1,2,3-бензотриазол-1-ил)ацетамид-N-ил)пиридин. Ацетилиране на 2,6-диаминопиридин с оцетен анхидрид води до 2,6-бис-(ацетамид-N-ил)пиридин, който при купелуване с бензендиазониев хлорид дава бис-фенилхидразоново производно. При реакцията на последното с хлорацетонитрил се получава 2,6-диамино-бис-(5-циан-1-фенил-пиразол-N-ил)пиридин. В алкална среда реакцията на 2,6-диаминопиридин с CS_2 последвана поотделно с етил-α-бромцианоацетат и фенацил-бромид дава съответно 2,6-бис-(5-циан-4-хидрокси-тиазол-3-ил-2-тионил)пиридин и 2,6-бис-(4-фенил-тиазол-3-ил-2-тионил)пиридин. При кондензация на получените съединения поотделно с малононитрил се получават дицианметинтиазолови производни. При реакция на хидразинхидрат или фенилхидразин с тиазолилтионови производни или с дицианметинтиазолови производни води съответно до хидразонтиазолови и пиразолови производни.