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# Pyrido[2,3-*d*]pyrimidine-2,7-dithiol in heterocyclic synthesis: Synthesis and characterization of several new fused pyridopyrimidine heterocycles

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Pyridine-2(1*H*)-thione **1** reacted with phenyl isothiocyanate to give pyrido[2,3-*d*]pyrimidine derivative **3**. Compound **3** reacted with halogen containing compounds **4a–d** and methyl iodide in dimethylformamide/potassium hydroxide solution at room temperature to give 2,7-bisalkylthiopyrido[2,3-*b*]pyrimidine derivatives **5a–d** and **9**, respectively. Compounds **5a–d** could be cyclized into thienopyrido[2,3-*d*]pyrimidine derivatives **6a–d** by boiling with ethanolic potassium hydroxide solution. Compound **6a** reacted with acetic anhydride or formic acid and gave the corresponding pyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido[2,3-*d*]pyrimidine derivatives **8a,b**. Compound **9** reacted with hydrazine hydrate to yield pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine derivative **11** which could be reacted with nitrous acid and dimethylformamide-dimethylacetal (DMF-DMA) and gave the final isolable products corresponding to the pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]tetrazolo-[5,1-*b*]pyrimidine and pyrimido[1″,2″:1′,5′]pyrazolo[4′,3′:5,6]pyrido[2,3-*d*][1,2,4]triazolo-[4,3-*b*] pyrimidine derivatives **13** and **17**, respectively. Compound **11** also reacted with some $\beta$-dicarbonyl compounds such as acetylacetone (**18**) and ethyl acetoacetate (**20**) to yield the corresponding pyrimido[1″,2″:1′,5′]pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine derivatives **19** and **21**, respectively. Finally, compound **11** reacted with chloroacetyl chloride (**22**) to give the corresponding imidazo[1‴,2‴:1″,5″]pyrazolo[4″,3″:5′,6′]pyrido[3′,2′:5,6]pyrimido[2,1-*c*][1,2,4]triazine derivative **23**.

*Keywords*: Pyridopyrimidine; Bisalkylthiopyrido[2,3-*d*]pyrimidine; Pyrazolopyrido[2,3-*d*]pyrimidine; Thienopyrido[2,3-*d*]pyrimidine; Pyrimidothienopyrido[2,3-*d*]pyrimidine; Pyrimidopyrazolopyridopyrimidine.

## 1. Introduction

As a continuation of previous work [1–12] on the synthesis and characterization of nitrogenous heterocyclic derivatives of our research group we report here the synthesis of novel heterocyclic compounds containing nitrogen and sulfur. From the numerous prepared heterocycles,

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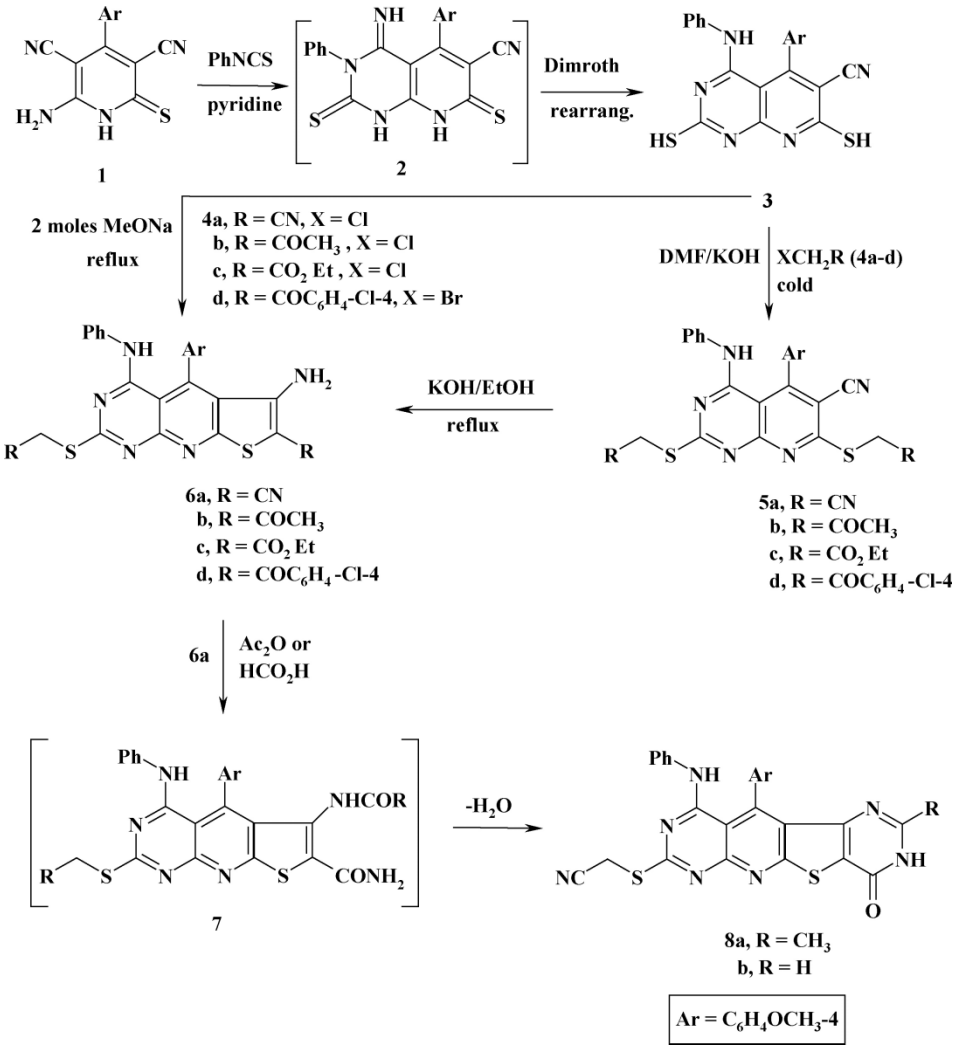
the pyridine and fused azolo-, azino- and thienopyridines constituted the main derivatives due to the diverse biological activities of such compounds. Pyridopyrimidines were reported to be used as cytotoxic agents and apoptosis inducers [13], adenosine kinase inhibitors [14, 15], inhibitors of pneumocystis carinii, toxoplasma gondii and mycobacterium dihydrofolate reductase [16], anti-tumor [17], antiviral [18] and antimicrobial [19] activities, in addition the arylaminopyridopyrimidines possess anti-proliferative properties [20]. Also pyrazolopyridopyrimidines were used as potent and selective PDE5 inhibitors [21] and antimicrobial agents [22].

## 2. Results and discussion

It has been found that 6-amino-4-(4-methoxyphenyl)-2-thioxo-1,2-dihydropyridine-3,5-dicarbonitrile (**1**) [23] reacted with phenyl isothiocyanate in pyridine to give a reaction product of molecular formula $C_{21}H_{15}N_5OS_2$ that corresponded to equimolecular addition of the reagent to **1**. The IR spectrum of this reaction product showed the absorption bands related to the presence of one NH, two SH and CN functions. Its $^1$H-NMR spectrum revealed signals of NH ($D_2O$ exchangeable), two SH ($D_2O$ exchangeable), ($CH_3-O-$) in addition to aromatic protons (cf. Experimental Part). Based on the above data, in addition to microanalysis, this reaction product could be formulated as the 2,7-dimercapto-5-(4-methoxyphenyl)-4-phenylaminopyrido[2,3-*d*]pyrimidine derivative **3** most likely formed *via* addition of the reagent to **1** to give **2** which underwent Dimroth rearrangement [24] to yield **3**. The reaction product was recovered completely unchanged when subjected to conditions leading to hydrolysis of the imino group to ring carbonyl function thus supporting the Dimroth rearrangement of **2** to **3** (cf. scheme 1).

Compound **3** was, in turn, taken as the starting material for several new heterocyclic derivatives. Thus, **3** reacted with chloroacetonitrile (**4a**) in DMF in the presence of potassium hydroxide on cold to give the corresponding 2,7-bis-*S*-cyanomethylpyrido[2,3-*d*]pyrimidine derivative **5a** whose IR spectrum showed the presence of one NH and CN groups. Similarly, compound **3** reacted with each of chloroacetone (**4b**), ethyl chloroacetate (**4c**) and *ω*-bromo-p-chloroacetophenone (**4d**) to yield the corresponding 2,7-bis-*S*-alkylpyrido[2,3-*d*] pyrimidine derivatives **5b–d**, respectively whose structure was established based on elemental analysis and spectral data studies (cf. Experimental Part). On the other hand, treatment of each of **5a–d** with boiling potassium hydroxide resulted in their cyclization *via* addition to the nitrile function to afford the corresponding thieno[3′,2′:5,6]pyrido[2,3-*d*] pyrimidine derivatives **6a–d**, respectively. Structure of **6a–d** was further established *via* their independent synthesis by performing the reaction of the corresponding **3** with **4a–d** in boiling sodium methoxide solutions. Compounds **6a–d** prepared *via* this route were found to be identical in all aspects (m.p., mixed m.p., analytical and spectral data) with **6a–d** previously synthesized as described before (cf. scheme 1 and Experimental Part). Furthermore, compound **6a** reacted with acetic anhydride to afford a reaction product, which showed the absorption bands of two NH, ring-CO and CN groups in its IR spectrum. Its $^1$H-NMR revealed only the signals of two NH ($D_2O$ exchangeable), $-OCH_3$, $-CH_2CN$ and a new singlet signal at $\delta = 3.64$ ppm which corresponded to the methyl group at the pyrimidine ring in addition to aromatic protons. Consequently, the reaction product could be formulated as the 2-methylpyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido[2,3-*d*] pyrimidine derivative **8a** most likely formed *via* the intermediacy of the corresponding carboxamidothieno[3′,2′:5,6]pyrido[2,3-*d*]pyrimidine derivative **7**, which on cyclization by the loss of the elements of water yielded **8a** (cf. scheme 1). Under practically the same reaction conditions, **6a** reacted with anhydrous formic acid to give also the




SCHEME 1

pyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido[2,3-*d*]pyrimidine derivative **8b**, which is most likely formed *via* first formylation of the amino group at position-3 in the thiophene ring in **6a** followed by hydrolysis and cyclization to **8b** *via* loss of water (cf. scheme 1 and Experimental Part).

The dithiol **3** could be alkylated using methyl iodide to give the corresponding bismethylthio derivative **9**. Compound **9** reacted with hydrazine hydrate to give the sulfur free non-isolable dihydrazino derivative **10** that cyclized under the applied reaction conditions *via* addition to the nitrile function to give the corresponding pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine derivative **11**. The IR spectrum of **11** showed the presence of $NH_2$ and NH groups. Its $^1$H-NMR revealed signals corresponding to the $D_2O$ exchangeable two $NH_2$ and three NH groups in addition to the $-OCH_3$ and aromatic protons (cf. Experimental Part).

Compound **11** could also be synthesized *via* the reaction of **3** with hydrazine hydrate. Compound **11** reacted with nitrous acid ($NaNO_2$/HCl) to give the corresponding diazonium salt that could be *in situ* cyclized *via* dehydrochlorination to afford the corresponding pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]tetrazolo[5,1-*b*]pyrimidine-7-diazonium chloride derivative

**12**. The IR spectrum of the reaction product showed the absorption bands of two NH groups and N≡N group (cf. scheme 2 and Experimental Part). Several attempts to couple **12** with active methylene reagents (such as ethyl acetoacetate and acetylacetone) in pyridine were unsuccessful and the formed 7-hydroxypyrazolo[4′,3′:5,6]pyrido[2,3-*d*]tetrazolo[5,1-*b*]pyrimidine derivative **13** was the sole reaction product. Compound **13** was most likely formed *via* loss of one molecule of nitrogen. The IR and $^1$H-NMR spectra were in accordance with the assigned structure and showed the characteristic absorption bands of the present functions. (cf. scheme 2 and Experimental Part).

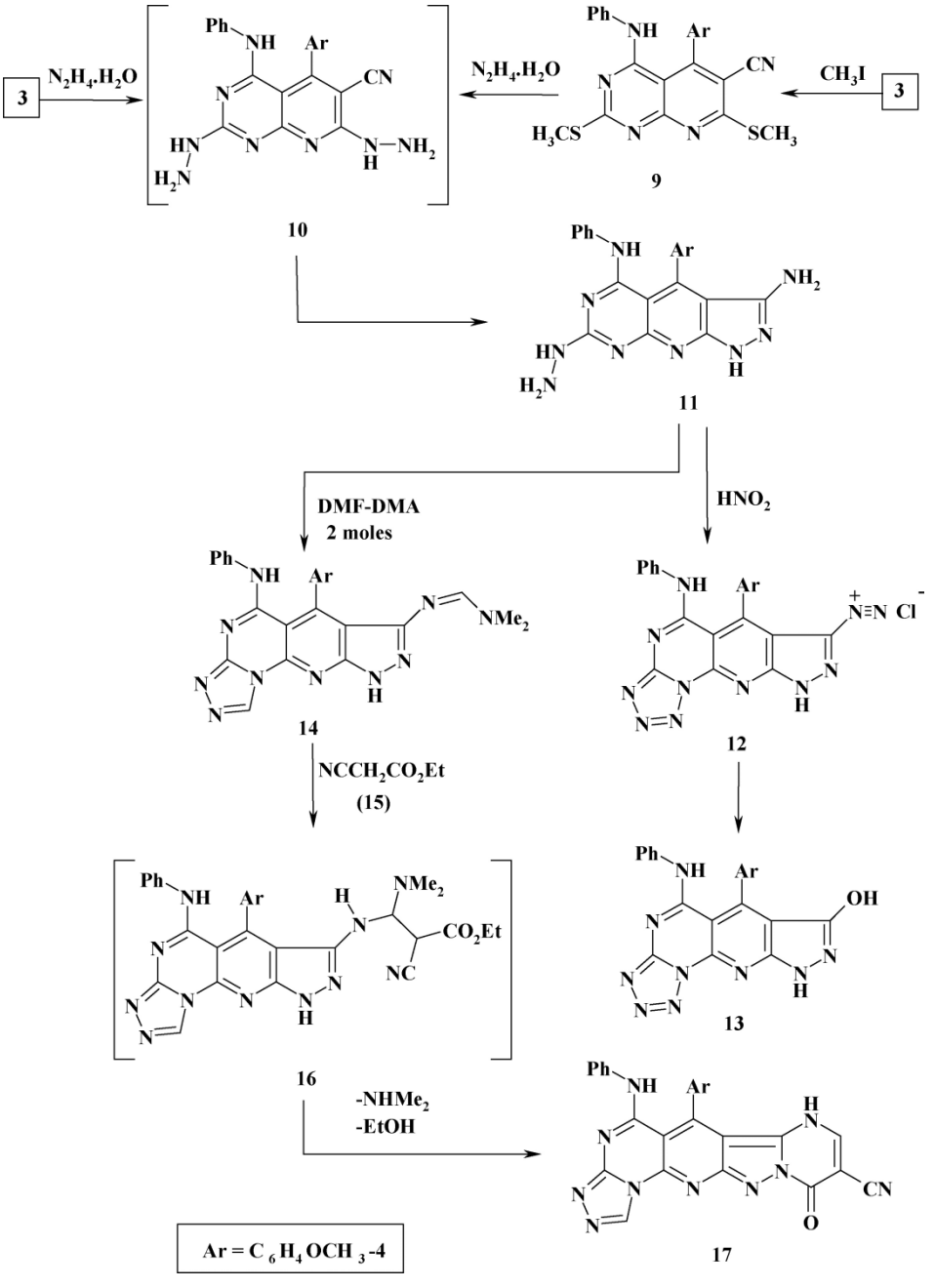
Additionally, compound **11** reacted with two molecules of DMF-DMA to yield the corresponding 7-{[(*N*,*N*-dimethylamino)methylene]amino}pyrazolo[4′,3′:5,6]pyrido[2,3-*d*][1,2,4]triazolo[3,4-*b*]-pyrimidine derivative **14** which is most likely formed *via* an *in situ* cyclization involving the hydrazino group of the pyrimidine ring. The reaction product showed in its IR spectrum the absorption bands of two NH groups while the bands related to the presence of $NH_2$ were entirely absent. Its $^1$H-NMR spectrum revealed a new singlet signal at $\delta = 3.25$ ppm corresponding to one $N(CH_3)_2$ group, a singlet signal corresponding to one N=CH at $\delta = 8.01$ ppm in addition to two NH groups ($D_2O$ exchangeable) $OCH_3$ and aromatic protons. (cf. scheme 2 and Experimental Part).

The reaction of **14** with ethyl cyanoacetate (**15**) afforded a reaction product that showed in its IR spectrum the absorption bands of two NH (3360, 3209 $cm^{-1}$), CN (2229 $cm^{-1}$), C=O (1702 $cm^{-1}$) functions only. Its $^1$H-NMR spectrum revealed only the signals of two NH ($D_2O$ exchangeable) at ($\delta = 3.37$, 9.49 ppm), 8H-pyrimidine, 1H-triazole in addition to the $OCH_3$ and aromatic protons [25]. Based on this finding and in addition to microanalytical data, this reaction product could be formulated as the 10-oxopyrimido[1″,2″:1′,5′]pyrazolo[4′,3′:5,6]pyrido[2,3-*d*][1,2,4]triazolo[3,4-*b*] pyrimidine derivative **17**. The formation of **17** in this reaction is assumed to proceed *via* the intermediacy of the non-isolable adduct **16**, which is then cyclized *via* loss of dimethylamine and ethanol to yield the final isolable **17** (cf. scheme 2).

Compound **11** underwent also a series of reactions with a variety of active methylene-containing ketones and esters. Thus, it has been found that **11** reacted with acetylacetone (**18**) to give 9-(pyrazol-1-yl)pyrimido[1″,2″:1′,5′]pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine derivative **19** which showed only the band of one NH group in its IR spectrum while its $^1$H-NMR spectrum was in a good agreement with the assigned structure (cf. scheme 3 and Experimental Part). In the same way, **11** reacted with each of ethyl acetoacetate (**20**) and chloroacetyl chloride (**22**) to give 9-(pyrazol-1-yl)pyrimido [1″,2″:1′,5′]pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine derivative **21** and the imidazo-[1‴,2‴:1″,5″]pyrazolo[4″,3″:5′,6′]pyrido[3′,2′:5,6]pyrimido-[2,1-*c*][1,2,4]triazine derivative **23**, respectively. Structure of both **21** and **23** was established on the basis of correct elemental analysis and spectral data studies which were in a good agreement with the proposed structure (cf. scheme 3 and Experimental Part).

## 3. Experimental

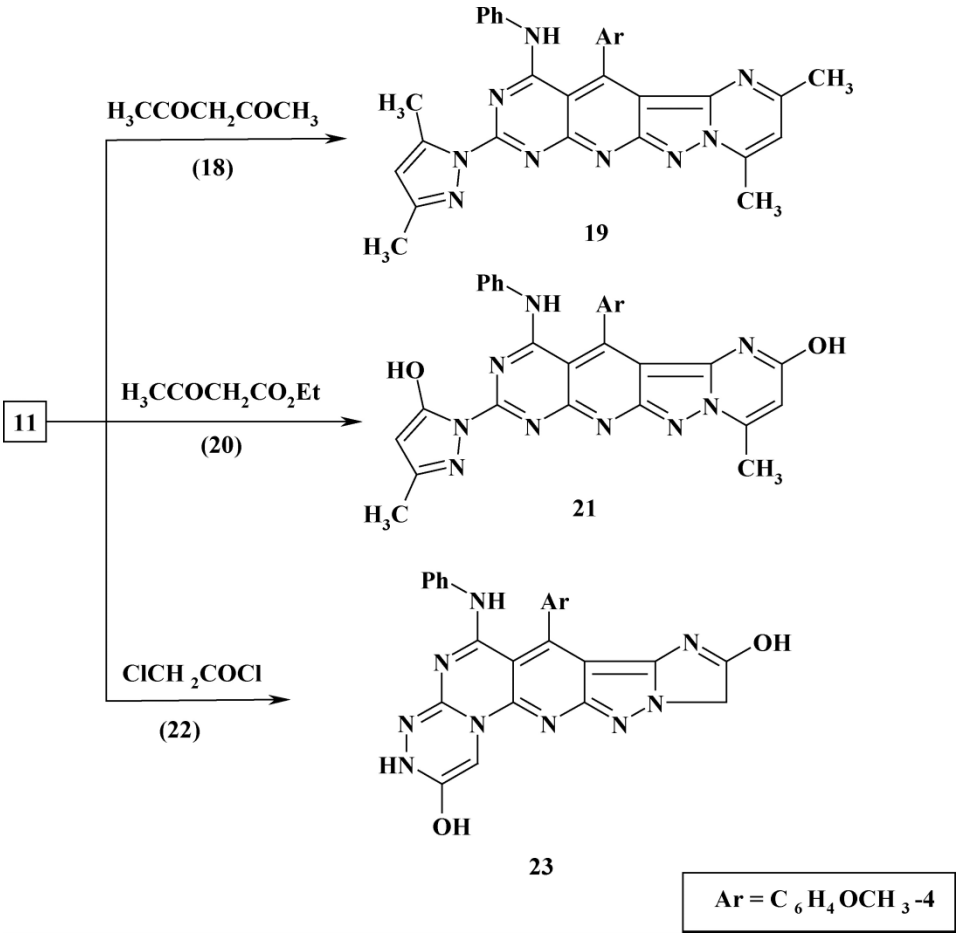
Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in potassium bromide disks on Bruker Vector 22 FTIR spectrophotometer. $^1$H-NMR spectra were determined in DMSO-$d_6$ and $CDCl_3$ at 300 MHz on Varian Mercury VX spectrometer using TMS as an internal standard. Chemical shifts are expressed as $\delta$ ppm units and coupling constant J as Hz. Elemental analyses were carried out at the Microanalytical Center of Cairo University. Compound **1** [23] was prepared according to literature procedures. In all the $^1$H-NMR spectra $*$ = Lost after $D_2O$ exchange.




SCHEME 2

### 3.1 *Reaction of 1 with phenyl isothiocyanate*

A solution of **1** (0.01 mole) in pyridine (20 ml) was treated with phenyl isothiocyanate (0.01 mole). The reaction mixture was heated under reflux for 8 hours then cooled, poured onto ice-cold water and acidified with dilute hydrochloric acid. The solid product obtained was filtered off, washed with water then crystallized from dioxan to yield the reaction product **3**.




SCHEME 3

**3.1.1 2,7-Dimercapto-5-(4-methoxyphenyl)-4-phenylaminopyrido[2,3-*d*]pyrimidine-6-carbonitrile (3).** Orange crystals from dioxanee (58%), m.p. 320–322 °C; IR ($cm^{-1}$) $\nu$ 3368 (NH), 2221 (CN), 1616 (N=C). $^1$H-NMR (DMSO-$d_6$) $\delta$ 3.91 (s, 3H, $OCH_3$), 7.12 (s, 1H, SH*), 7.16–7.65 (m, 9H, Ar−H), 10.05 (br, 1H, NH*), 14.04 (hump, 1H, SH*). Anal. For $C_{21}H_{15}N_5OS_2$ (417) Calcd.: C, 60.41; H, 3.62; N, 16.77; S, 15.36. Found: C, 60.10; H, 3.40; N, 17.00; S, 15.60%.

### 3.2 *Reactions with halogen-containing compounds in cold KOH/DMF solution*

**3.2.1 General procedure.** A solution of each of **3** (0.01 mole) and **4a–d** or methyl iodide (0.02 mole) were stirred in DMF (30 ml) containing 0.02 mole of KOH for 3 hours. The reaction mixture was then diluted with water, acidified with HCl and the precipitate that formed was collected by filtration and crystallized from dioxan to yield **5a–d** and **9**, respectively.

**3.2.2 2,7-bis[(Cyanomethyl)thio]-5-(4-methoxyphenyl)-4-phenylaminopyrido[2,3-*d*]-pyrimidine-6-carbonitrile (5a).** Orange crystals from dioxan (61%), m.p. 268–269°C; IR ($cm^{-1}$) $\nu$ 3310 (NH), 2251, 2220 (two CN), 1624 (N=C). $^1$H-NMR (DMSO-$d_6$) $\delta$ 3.90

(s, 3H, $OCH_3$), 4.46 (s, 4H, two $SCH_2$), 7.11–7.91 (m, 9H, Ar-H), 10.40 (br, 1H, NH*). Anal. For $C_{25}H_{17}N_7OS_2$ (495) Calcd.: C, 60.56; H, 3.46; N, 19.78; S, 12.94. Found: C, 60.80; H, 3.70; N, 20.00; S, 12.60%.

**3.2.3 2,7-bis[(Acetylmethyl)thio]-5-(4-methoxyphenyl)-4-phenylaminopyrido-[2,3-*d*] pyrimidine-6-carbonitrile (5b).** Orange crystals from dioxan (64%), m.p. 224–226 °C; IR ($cm^{-1}$) $\nu$ 3358 (NH), 2209 (CN), 1715 (C=O), 1604 (N=C). $^1$H-NMR (DMSO-$d_6$) $\delta$ 2.34 (s, 6H, two $COCH_3$), 3.86 (s, 3H, $OCH_3$), 4.21 (s, 4H, two $SCH_2$), 7.10–7.53 (m, 9H, Ar-H), 10.40 (br, 1H, NH*). Anal. For $C_{27}H_{23}N_5O_3S_2$ (529) Calcd.: C, 61.23; H, 4.38; N, 13.22; S, 12.11. Found: C, 61.50; H, 4.60; N, 12.90; S, 11.90%.

**3.2.4 2,7-bis[(Ethoxycarbonylmethyl)thio]-5-(4-methoxyphenyl)-4-phenyl-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5c).** Yellow crystals from dioxan (57%), m.p. 215 °C; IR ($cm^{-1}$) $\nu$ 3373 (NH), 2214 (CN), 1743 (C=O), 1606 (N=C). $^1$H-NMR (DMSO-$d_6$) $\delta$ 1.14 (t, 6H, two $CH_2\underline{CH_3}$), 3.84 (s, 3H, $OCH_3$), 4.12 (q, 4H, two $\underline{OCH_2}CH_3$), 4.23 (s, 4H, two $SCH_2$), 6.68–7.33 (m, 9H, Ar-H), 9.40 (br, 1H, NH*). Anal. For $C_{29}H_{27}N_5O_5S_2$ (589) Calcd.: C, 59.07; H, 4.62; N, 11.88; S, 10.88. Found: C, 59.30; H, 4.30; N, 12.10; S, 10.60%.

**3.2.5 2,7-bis{[(4-Chlorobenzoyl)methyl]thio}-5-(4-methoxyphenyl)-4-phenyl-aminopyrido[2,3-*d*]pyrimidine-6-carbonitrile (5d).** Orange crystals from dioxan (51%), m.p. 200–202 °C; IR ($cm^{-1}$) $\nu$ 3367 (NH), 2216 (CN), 1675(C=O), 1605 (N=C). $^1$H-NMR (DMSO-$d_6$) 3.82 (s, 3H, $OCH_3$), 4.19 (s, 4H, two $SCH_2$), 6.83–7.63 (m, 17H, Ar-H), 10.20 (br, 1H, NH*). Anal. For $C_{37}H_{25}N_5O_3S_2Cl_2$ (722) Calcd.: C, 61.49; H, 3.49; N, 9.69; S, 8.87; Cl, 9.81. Found: C, 61.80; H, 3.70; N, 9.90; S, 8.50; Cl, 9.60%.

**3.2.6 5-(4-Methoxyphenyl)-2,7-bis(methylthio)-4-phenylaminopyrido[2,3-*d*]-pyrimidine-6-carbonitrile (9).** White crystals from dioxan (62%), m.p. 300–301 °C; IR ($cm^{-1}$) $\nu$ 3367 (NH), 2220 (CN), 1614 (N=C). $^1$H-NMR (DMSO-$d_6$) $\delta$ 2.74 (s, 6H, two $SCH_3$), 3.81 (s, 3H, $OCH_3$), 6.90–7.31 (m, 9H, Ar-H), 9.92 (br, 1H, NH*). Anal. For $C_{23}H_{19}N_5OS_2$ (445) Calcd.: C, 62.00; H, 4.30; N, 15.72; S, 14.39. Found: C, 62.30; H, 4.10; N, 16.00; S, 14.20%.

**3.2.7 Cyclization of 4a–d in boiling MeOH/MeONa.** A solution of **3** (0.01 mole) and **4a–d** (0.02 mole) was heated under reflux in methanolic sodium methoxide (0.03 mole prepared from 0.03 atom of sodium metal in 30 ml of methanol) for 3 hours. The reaction mixture was then cooled, poured onto ice-cooled water and acidified with dilute HCl. The solid products so formed were filtered off and crystallized from dioxane to yield **6a,b** and from acetic acid to yield **6c,d**.

**3.2.8 Cyclization 5a–d in boiling ethanolic KOH.** A solution of **5a–d** (0.01 mole) was heated with ethanolic potassium hydroxide solution (0.01 mole KOH in 30 ml ethanol) under reflux for 3 hours. The reaction mixture was then cooled, poured onto ice-cooled water, acidified with dilute hydrochloric acid and the precipitated solid products were filtered off, washed with water then crystallized from dioxan to yield **6a,b** and from acetic acid to yield **6c,d**.

**3.2.9 6-Amino-2-[(cyanomethyl)thio]-5-(4-methoxyphenyl)-4-phenylaminothieno [3′,2′:5,6]pyrido[2,3-*d*]pyrimidine-7-carbonitrile (6a).** Orange crystals from dioxan (60%), m.p. 300–302 °C; IR ($cm^{-1}$) $\nu$ 3462, 3389, 3338 ($NH_2$, NH), 2247, 2194 (two CN), 1611 (N=C). $^1$H-NMR (DMSO-$d_6$) $\delta$ 3.35 (s, 2H, $SCH_2$), 3.96 (s, 3H, $OCH_3$), 5.26 (s, 2H, $NH_2^*$), 7.23–7.81 (m, 9H, Ar-H), 9.78 (br, 1H, NH*). Anal. For $C_{25}H_{17}N_7OS_2$ (495) Calcd.: C, 60.56; H, 3.46; N, 19.78; S, 12.94. Found: C, 60.80; H, 3.20; N, 20.10; S, 12.70%.

**3.2.10 7-Acetyl-6-amino-2-[(acetylmethyl)thio]-5-(4-methoxyphenyl)-4-phenylaminothieno[3′,2′:5,6]pyrido[2,3-*d*]pyrimidine (6b).** Yellow crystals from dioxan (62%), m.p. 304–305 °C; IR ($cm^{-1}$) $\nu$ 3466, 3387, 3339 ($NH_2$, NH), 1733 (C=O acetyl at S-alkyl), 1634 (C=O acetyl at thiophene), 1608 (N=C). $^1$H-NMR (DMSO-$d_6$) $\delta$ 2.24 (s, 3H, $COCH_3$), 2.30 (s, 3H, $COCH_3$), 3.37 (s, 4H, $NH_2^*$ & $SCH_2$), 3.87 (s, 3H, $OCH_3$), 7.05–7.82 (m, 9H, Ar-H), 9.76 (br, 1H, NH*). Anal. For $C_{27}H_{23}N_5O_3S_2$ (529) Calcd.: C, 61.23; H, 4.38; N, 13.22; S, 12.11. Found: C, 61.00; H, 4.70; N, 13.50; S, 12.40%.

**3.2.11 Ethyl-6-amino-2-[(ethoxycarbonylmethyl)thio]-5-(4-methoxyphenyl)-4-phenylaminothieno[3′,2′:5,6]pyrido[2,3-*d*]pyrimidine-7-carboxylate (6c).** Yellow crystals from AcOH (56%), m.p. 265–266 °C; IR ($cm^{-1}$) $\nu$ 3466, 3383, 3338 ($NH_2$, NH), 1720 (C=O ester at S-alkyl), 1675 (C=O ester at thiophene), 1610 (N=C). Anal. For $C_{29}H_{27}N_5O_5S_2$ (589) Calcd.: C, 59.07; H, 4.62; N, 11.88; S, 10.88. Found: C, 59.30; H, 4.30; N, 11.60; S, 11.10%.



**3.2.12 6-Amino-7-(4-chlorobenzoyl)-2-{[(4-chlorobenzoyl)methyl]thio}-5-(4-methoxyphenyl)-4-phenylaminothieno[3′,2′:5,6]pyrido[2,3-*d*]pyrimidine (6d).** Orange crystals from AcOH (50%), m.p. 290–293 °C; IR ($cm^{-1}$) $\nu$ 3474, 3378, 3273 ($NH_2$, NH), 2214 (CN), 1675 (C=O benzoyl at S-alkyl), 1630 (C=O benzoyl at thiophene) 1605 (N=C). Anal. For $C_{37}H_{25}N_5O_3S_2Cl_2$ (722) Calcd.: C, 61.49; H, 3.49; N, 9.69; S, 8.87; Cl, 9.81. Found: C, 61.80; H, 3.20; N, 10.00; S, 8.60; Cl, 10.10%.

### 3.3 *Reactions with acetic anhydride or anhydrous formic acid*

A solution of **6a** (0.01 mole) in acetic anhydride or formic acid (30 ml) was heated under reflux for 5 hours. The solid products obtained after cooling were filtered off and then crystallized from acetic acid to yield **8a** and from DMF to yield **8b**.

**3.3.1 8-[(Cyanomethyl)thio]-11-(4-methoxyphenyl)-2-methyl-4-oxo-10-phenylamino-3,4-dihydropyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido[2,3-*d*]pyrimidine (8a).** Brown crystals from AcOH (52%), m.p. 310–312 °C; IR ($cm^{-1}$) $\nu$ 3379, 3298 (two NH), 2217 (CN), 1657 (C=O), 1609 (N=C); $^1$H-NMR (DMSO-$d_6$) $\delta$ 3.64 (s, 3H, $CH_3$), 3.90 (s, 3H, $OCH_3$), 4.00 (s, 2H, $SCH_2$), 7.06–7.78 (m, 9H, Ar-H), 9.80 (br, 1H, NH*), 11.80 (br, 1H, NH*). Anal. For $C_{27}H_{19}N_7O_2S_2$ (537) Calcd.: C, 60.32; H, 3.56; N, 18.24; S, 11.93. Found: C, 60.60; H, 3.90; N, 18.00; S, 11.70%.

**3.3.2 8-[(Cyanomethyl)thio]-11-(4-methoxyphenyl)-4-oxo-10-phenylamino-3,4-dihydropyrimido[4″,5″:4′,5′]thieno[3′,2′:5,6]pyrido[2,3-*d*]-pyrimidine (8b).** Brown crystals from DMF (56%), m.p. >350 °C; IR ($cm^{-1}$) $\nu$ 3367, 3277 (two NH), 2214 (CN), 1663

(C=O), 1604 (N=C). Anal. For $C_{26}H_{17}N_7O_2S_2$ (523) Calcd.: C, 59.64; H, 3.27; N, 18.73; S, 12.25. Found: C, 59.30; H, 3.50; N, 19.00; S, 11.90%.

### 3.4 *Reactions with hydrazine hydrate*

A solution of **3** or **9** (0.01 mole) was treated with hydrazine hydrate (10 ml) and then heated under reflux for 6 hours. The solid product so obtained after cooling was collected by filtration and crystallized from dioxan to yield **11**.

**3.4.1 3-Amino-7-hydrazino-4-(4-methoxyphenyl)-5-phenylamino-1*H*-pyrazolo-[4′,3′:5,6]pyrido[2,3-*d*]-pyrimidine (11).** Orange crystals from dioxan (59%), m.p. 314–316 °C; IR ($cm^{-1}$) $\nu$ 3439, 3401, 3339, 3210, 3095 (two $NH_2$, three NH), 1609 (N=C); $^1$H-NMR (DMSO-$d_6$) $\delta$ 3.94 (s, 3H, $OCH_3$), 4.26 (s, 2H, $NH_2^*$), 6.99–8.00 (m, 12H, Ar-H, $NH_2^*$ & NH*), 9.50 (s, 1H, NH*), 12.04 (s, 1H, NH*). Anal. For $C_{21}H_{19}N_9O$ (413) Calcd.: C, 61.01; H, 4.63; N, 30.49. Found: C, 60.80; H, 4.80; N, 30.80%.



### 3.5 *Reactions with nitrous acid*

A cold solution of **11** (0.01 mole) in concentrated HCl (5 ml) and glacial acetic acid (5 ml) was treated with a cold saturated solution of sodium nitrite (0.025 mole) and then stirred in the ice chest for 30 minutes. The solid products obtained were filtered off, washed with water and then crystallized from ethanol to give **12**.

**3.5.1 6-(4-Methoxyphenyl)-5-phenylamino-9*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]-tetrazolo[5,1-*b*]pyrimidine-7-diazonium chloride (12).** Orange crystals from ethanol (48%), m.p. 270–272 °C; IR ($cm^{-1}$) $\nu$ 3353, 3204 (two NH), 2160 (N≡N), 1616 (N=C). Anal. For $C_{21}H_{14}N_{11}OCl$ (471.5) Calcd.: C, 53.45; H, 2.99; N, 32.65; Cl, 7.51. Found: C, 53.70; H, 2.70; N, 32.90; Cl, 7.80%.

### 3.6 *Synthesis of compound 13*

A solution of **12** (0.01 mole) and acetylacetone or ethyl acetoacetate (0.01 mole) in pyridine (30 ml) was heated under reflux for 3 hours. The reaction mixture was cooled, poured onto ice-cooled water and acidified with dilute HCl. The solid product so formed was filtered off and crystallized from ethanol to yield the reaction product **13**.

**3.6.1 7-Hydroxy-6-(4-methoxyphenyl)-5-phenylamino-9*H*-pyrazolo[4′,3′:5,6]-pyrido[2,3-*d*]tetrazolo[5,1-*b*]pyrimidine (13).** Red crystals from ethanol (61%), m.p. 308–310 °C; IR ($cm^{-1}$) $\nu$ 3383 (br, OH, two NH), 1604 (N=C); $^1$H-NMR (DMSO-$d_6$) $\delta$ 3.92 (s, 3H, $OCH_3$), 7.03–7.68 (m, 10H, Ar-H, & OH*), 9.65 (br, 1H, NH*), 13.67 (br, 1H, NH*). Anal. For $C_{21}H_{15}N_9O_2$ (425) Calcd.: C, 59.29; H, 3.55; N, 29.63. Found: C, 59.60; H, 3.80; N, 29.40%.

### 3.7 *Reactions with DMF-DMA in dry xylene*

A solution of **11** (0.01 mole) and DMF-DMA (0.02 mole) in dry xylene (30 ml) was heated under reflux for 3–5 hours. The solvent was then removed in *vacuo* and the solid so obtained

was triturated with petroleum ether, collected by filtration and crystallized from DMF to yield **14**.

**3.7.1 7-{[(*N*,*N*-Dimethylamino)methylene]amino}-6-(4-methoxyphenyl)-5-phenylamino-9*H*-pyrazolo[4′,3′:5,6]pyrido[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyrimidine (14).** Yellow crystals from DMF (54%), m.p. 285–286 °C; IR ($cm^{-1}$) $\nu$ 3384, 3212 (two NH), 1610 (N=C); $^1$H-NMR (DMSO-$d_6$) $\delta$ 3.25 (s, 6H, $N(CH_3)_2$), 3.89 (s, 3H, $OCH_3$), 7.02–7.66 (m, 9H, Ar-H), 7.86 (s, 1H, CH-triazole), 8.01 (s, 1H, N=CH), 9.50 (s, 1H, NH*), 12.40 (s, 1H, NH*). Anal. For $C_{25}H_{22}N_{10}O$ (478) Calcd.: C, 62.75; H, 4.63; N, 29.27. Found: C, 63.00; H, 4.40; N, 29.60%.

### 3.8 *Reactions with different reagents in glacial acetic acid*

**3.8.1 General procedure.** A solution of each of **14**, **11**, **11** (0.01 mole) and **15**, **18**, **20** (0.02 mole) in glacial acetic acid (30 ml) was heated under reflux for 4 hours. The solid products so obtained after cooling were collected by filtration and crystallized from acetic acid to yield the **17**, **19** and **21**, respectively.



**3.8.2 6-(4-Methoxyphenyl)-10-oxo-5-phenylamino-7,10-dihydropyrimido-[1″,2″:1′,5′]pyrazolo[4′,3′:5,6]pyrido[2,3-*d*][1,2,4]triazolo[4,3-*b*]pyrimidine-9-carbonitrile (17).** Orange crystals from AcOH (56%), m.p. 318–320 °C; IR ($cm^{-1}$) $\nu$ 3360, 3209 (two NH), 2229 (CN), 1702 (C=O), 1615 (N=C); $^1$H-NMR (DMSO-$d_6$) $\delta$ 3.37 (NH* & DMSO), 3.94 (s, 3H, $OCH_3$), 6.95 (s, 1H, C−H), 7.02 (s, 1H, C−H) 7.25–7.96 (m, 9H, Ar-H), 9.49 (s, 1H, NH*). Anal. For $C_{26}H_{16}N_{10}O_2$ (500) Calcd.: C, 62.40; H, 3.22; N, 27.99. Found: C, 62.10; H, 2.90; N, 28.30%.

**3.8.3 2,4-Dimethyl-12-(4-methoxyphenyl)-11-phenylamino-9-[(3,5-dimethyl)pyrazol-1-yl]pyrimido[1″,2″:1′,5′]pyrazolo[4′,3′:5,6]pyrido[2,3-*d*]pyrimidine (19).** Yellow crystals from AcOH (53%), m.p. 312–313 °C; IR ($cm^{-1}$) $\nu$ 3348 (NH), 1616 (N=C); $^1$H-NMR (DMSO-$d_6$) $\delta$ 2.28 (s, 6H, $2CH_3$), 2.68 (s, 6H, $2CH_3$), 3.94 (s, 3H, $OCH_3$), 6.99–7.55 (m, 9H, Ar-H,), 7.97 (s, 2H, 3H-pyrimidine & 4H-pyrazole), 9.40 (br, 1H, NH*). Anal. For $C_{31}H_{27}N_9O$ (541) Calcd.: C, 68.75; H, 5.02; N, 23.28. Found: C, 69.00; H, 4.80; N, 23.50%.

**3.8.4 2-Hydroxy-12-(4-methoxyphenyl)-4-methyl-11-phenylamino-9-[(3-hydroxy-5-methyl)pyrazol-1-yl]pyrimido[1″,2″:1′,5′]pyrazolo[4′,3′:5,6]pyrido[2,3-*d*] pyrimidine (21).** Red crystals from AcOH (55%), m.p. 295–297 °C; IR ($cm^{-1}$) $\nu$ 3362 (br, two OH, NH), 1614 (N=C); $^1$H-NMR (DMSO-$d_6$) $\delta$ 3.31 (s, 6H, $2CH_3$), 3.92 (s, 3H, $OCH_3$), 7.10–7.74 (m, 12H, Ar-H, 3H-pyrimidine, 4H-pyrazole & OH*), 11.05 (br, 1H, NH*), 15.09 (br, 1H, OH*). Anal. For $C_{29}H_{23}N_9O_3$ (545) Calcd.: C, 63.85; H, 4.25; N, 23.11. Found: C, 64.20; H, 4.00; N, 22.90%.

### 3.9 *Reaction of 11 with chloroacetyl chloride*

A solution of **11** (0.01 mole) and chloroacetyl chloride (**22**) (0.025 mole) in DMF (20 ml) was stirred at room temperature for 1 hour. After then the reaction mixture was heated under reflux for 4 hours then cooled and poured onto ice-cold water. The solid product obtained was filtered off and crystallized from ethanol to yield the reaction product **23**.

**3.9.1 2,9-Dihydroxy-7-(4-methoxyphenyl)-6-phenylamino-3,10-dihydroimidazo [1‴,2‴:1″,5″]pyrazolo[4″,3″:5′,6′]pyrido[3′,2′:5,6]-pyrimido[2,1-*c*] [1,2,4]triazine (23).** Dark brown crystals from ethanol (51%), m.p. 240–242 °C; IR ($cm^{-1}$) $\nu$ 3417, 3366, 3204 (two OH, two NH), 1600 (N=C); $^1$H-NMR (DMSO-$d_6$) $\delta$ 3.90 (s, 2H, $CH_2$), 3.93 (s, 3H, $OCH_3$), 7.13–7.73 (m, 13H, Ar−H, two OH*, NH* & CH-triazine), 10.45 (br, 1H, NH*). Anal. For $C_{25}H_{19}N_9O_3$ (493) Calcd.: C, 60.85; H, 3.38; N, 25.55. Found: C, 61.20; H, 3.60; N, 25.80%.

## References


[1] A.A. Abbas, M.A.A. Elneairy, Y.N. Mabkhot. *J. Chem. Res.(S)*, **4**, 124 (2001).
[2] B.Y. Riad, A.M. Negem, S.E. Abdou, H.A. Daboun. *Heterocycles*, **26**, 205 (1987).
[3] F.A. Attaby, S.M. Eldin, M.A.A. Elneairy, A.K.K. El-Louh. *Phosphorus, Sulfur and Silicon*, **179**, 2205 (2004).
[4] M.A.M. Gad-Elkareem, A.O. Abedelhamid. *Afinidad*, **61**(513), 427 (2004).
[5] F.A. Attaby, S.M. Eldin, M.A.A. Elneairy. *Heteroat. Chem.*, **9**(6), 571 (1998).
[6] M.A.M. Gad-Elkareem, A.M. Abdel-Fattah, M.A.A. Elneairy. *Phosphorus, Sulfur and Silicon*, in press (2005).
[7] M.A.A. Elneairy, M.A.M. Gad-Elkareem, A.M. Abdel-Fattah. *Phosphorus, Sulfur and Silicon*, in press (2005).
[8] M.A.A. Elneairy, F.A. Attaby, M.S. Elsayed. *Phosphorus, Sulfur and Silicon*, **167**, 161 (2000).
[9] F.A. Attaby, M.A.A. Elneairy, M.S. Elsayed. *Arch. Pharm. Res.*, **22**(2), 194 (1999).
[10] M.A.A. Elneairy. *Phosphorus, Sulfur and Silicon*, **178**, 2201 (2003).
[11] F.A. Attaby, S.M. Eldin, M.A.A. Elneairy. *J. Chem. Res. (S)*, **10**, 632 (1998).
[12] M.A.A. Elneairy, T.M. Abdel-Rahman, A.M. Hammad. *J. Chem. Res. (S)*, **11**, 684 (1998).
[13] C. Sanmartin, M. Echeverria, B. Mendivil, L. Cordeu, E. Cubedo, J. Garcia-Foncillas, M. Font, J.A. Palop. *Bioorg. Med. Chem.*, **13**, 2031 (2005).
[14] R.J. Perner, C. Lee, M. Jiang, Y. Gu, S. DiDomenico, E.K. Bayburt, K.M. Alexander, K.L. Kohlhaas, M.F. Jarvis, E.L. Kowaluk, S.S. Bhagwat. *Bioorg. Med. Chem. Lett.*, **15**, 2803 (2005).
[15] G.Z. Zheng, Y. Mao, C. Lee, J.K. Pratt, J.R. Koenig, R.J. Perner, M.D. Cowart, G.A. Gfesser, S. McGaraughty, K.L. Chu, C. Zhu, H. Yu, K. Kohlhaas, K.M. Alexander, C.T. Wismer, J. Mikusa, M.F. Jarvis, E.A. Kowaluk, A.O. Stewart. *Bioorg. Med. Chem. Lett.*, **13**, 3041 (2003).
[16] A. Rosowsky, H. Chen, H. Fu, S.F. Queener. *Bioorg. Med. Chem.*, **11**, 59 (2003).
[17] F. Pochat, F. Lavelle, C. Fizames, A. Zerial. *Eur. J. Med. Chem.*, **22**, 135 (1987).
[18] M. N. Nasr, M.M. Gineinah. *Arch. Pharm.*, **335**, 289 (2002).
[19] N. Kumar, G. Singh, A.K. Yadav. *Heteroat. Chem.*, **12**, 52 (2001).
[20] D.W. Fry, J.M. Nelson, V. Slintak, P.R. Keller, G.W. Rewcastle, W.A. Denny, H. Zhou, A.J. Bridges. *Biochem. Pharmaco.*, **54**, 877 (1997).
[21] Y. Bi, P. Stoy, L. Adam, B. He, J. Krupinski, D. Normandin, R. Pongrac, L. Seliger, A. Watson, J.E. Macor. *Bioorg. Med. Chem. Lett.*, **11**, 2461(2001).
[22] S.A. Et-Assiery, G.H. Sayed, A. Fouda. *Acta Pharm.*, **54**, 143 (2004).
[23] A.M. El-Torgoman, S.M. El-Kousy, Z.E. Kandeel. *Z. Naturforsch.*, **42b**(1), 107 (1987); *C.A.*, **107**, 198039p (1987).
[24] M.S.A. El-Gaby. *Phosphorus, Sulfur and Silicon*, **156**, 157 (2000).
[25] S.M. Al-Mousawi, M.A. Mohammed, M.H. Elnagdi. *J. Heterocycl. Chem.*, **38**, 989 (2001).