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A CONVENIENT ROUTE FOR THE SYNTHESIS OF SOME NEW BI- AND TRIHETEROCONDENSED URACILS

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Some bifunctional heterocyclic systems having vicinal chlorocyano, chloroacetyl, and chloroethoxycarbonyl groups in their structures reacted with 6-amino-1,3-dimethyluracil to afford novel triheterocyclic systems having a pyrimidinedione moiety. Enaminones and α-cyanocinnamic acid derivatives in this reaction gave pyrido[2,3-d]pyrimidinediones. The antimicrobial activity of some new synthesized triheterocyclic systems was studied.

Keywords: bi-, triheterocycles, enaminones, uracil, antimicrobial activity.

Several bi- and oligocycles containing uracil rings were found to be an important class of compounds exhibiting biological and pharmacological activities. These compounds showed antitumor [1, 2], cardiotonic [3, 4], antifungal [5, 6], antibronchitic [7], antibacterial [6], and antifolate [8] activities. There are ample precedents for the synthesis of these fused heterocycles [9-14]. Most of these methods usually require rigorous conditions [15], long reaction times [16,17], and complex synthetic pathways [2]. As a part of our studies on diazines [18-22], the present investigation aims to search for simple and efficient routes for the synthesis of polynuclear heterocyclic systems having an uracil nucleus in their structure starting with 6-amino-1,3-dimethyluracil (**1**), which is considered as a versatile starting material of a typical synthon leading to the target polynuclear heterocyclic systems. The newly synthesized triheterocycles appear to be promising antimicrobial agents.

It was found that the reaction of compound **1** with some heterocyclic systems having vicinal chlorocyano groups is an interesting one. Thus, when compound **1** was subjected to reaction with 2-chloro-4,6-dimethylpyridine-3-carbonitrile (**2**) in boiling ethanol containing triethylamine as a base, three possible compounds **3-5** may be produced. The structure of compound **4** was ruled out on the basis of spectral data as IR spectrum of the product exhibited a peak at 2222 cm^{-1} attributed to the CN function and elemental analysis showed the absence of chlorine. The ^1H NMR spectrum (DMSO-d_6) excluded the formation of compound **3** as it displayed a signal at δ 4.70 ppm corresponding to the NH_2 group with the absence of the H-5 signal at δ 5.73 ppm. These confirmed the formation of 2-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4,6-dimethylpyridine-3-carbonitrile (**5**). Fusion of compound **5** above its melting point or increasing the reaction time between compounds **1** and **2** led to cycloaddition of the amino group of uracil to the cyano group of the other ring giving rise to 5-amino-2,4,7,9-tetramethylpyrimido[4,5-*h*][1,6]naphthyridine-8,10(7H,9H)-dione (**6**) (Scheme 1).

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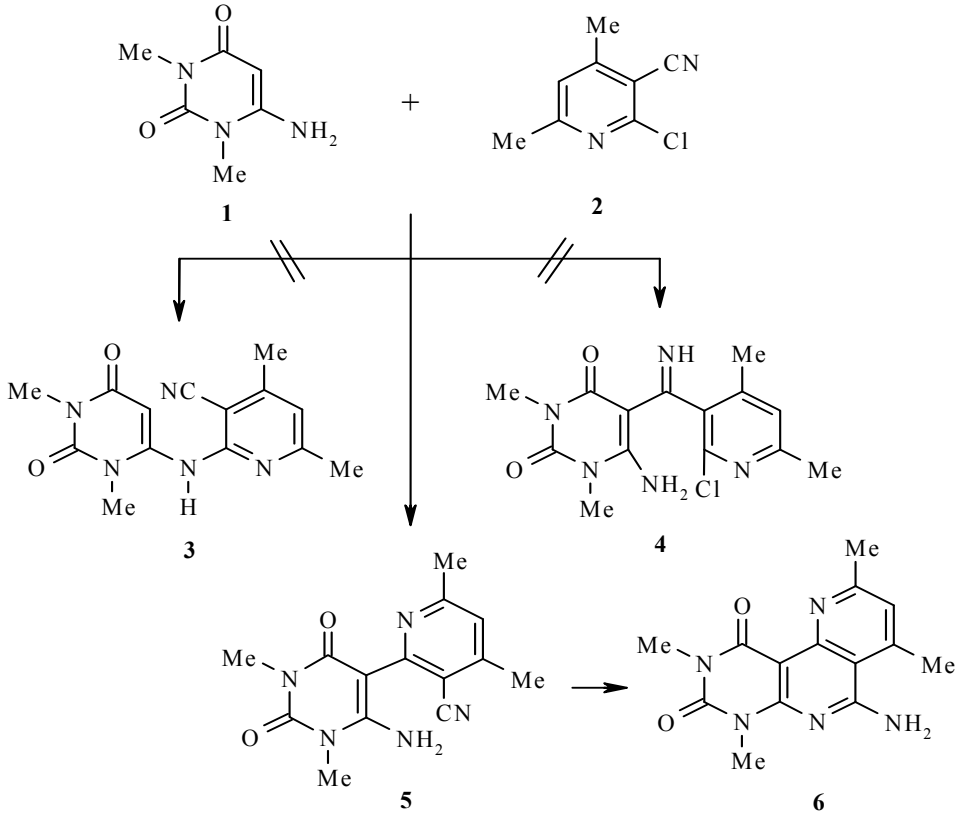
Scheme 1

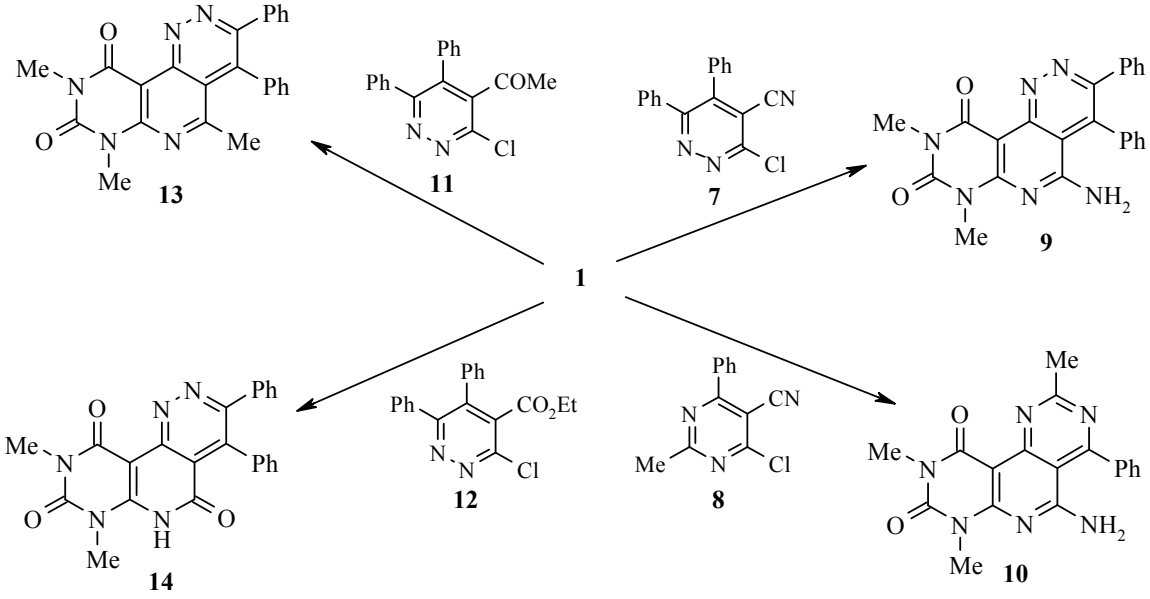


A similar reaction of aminouracil **1** with substituted chloropyridazine carbonitrile **7** or with chloropyrimidinecarbonitrile **8** under the same reaction conditions with increasing reaction time led to the formation of pyridazinopyridopyrimidine **9** and dipyrimidopyridine **10**, respectively.

Moreover, pyridazinopyridopyrimidine derivatives **13** and **14** were obtained on treatment of compound **1** with pyridazine having vicinal chloroacetyl groups like compound **11** or having vicinal chloroethoxycarbonyl groups like compound **12**, where 6-aminouracil is attacked at C-5 followed by cyclocondensation of the amino group with the acetyl or ethoxycarbonyl group with elimination of water and ethanol, respectively. The structure of the obtained triheterocyclic systems **6**, **9**, **10**, **13**, and **14** was deduced from their correct elemental analyses and spectral data (Scheme 2).

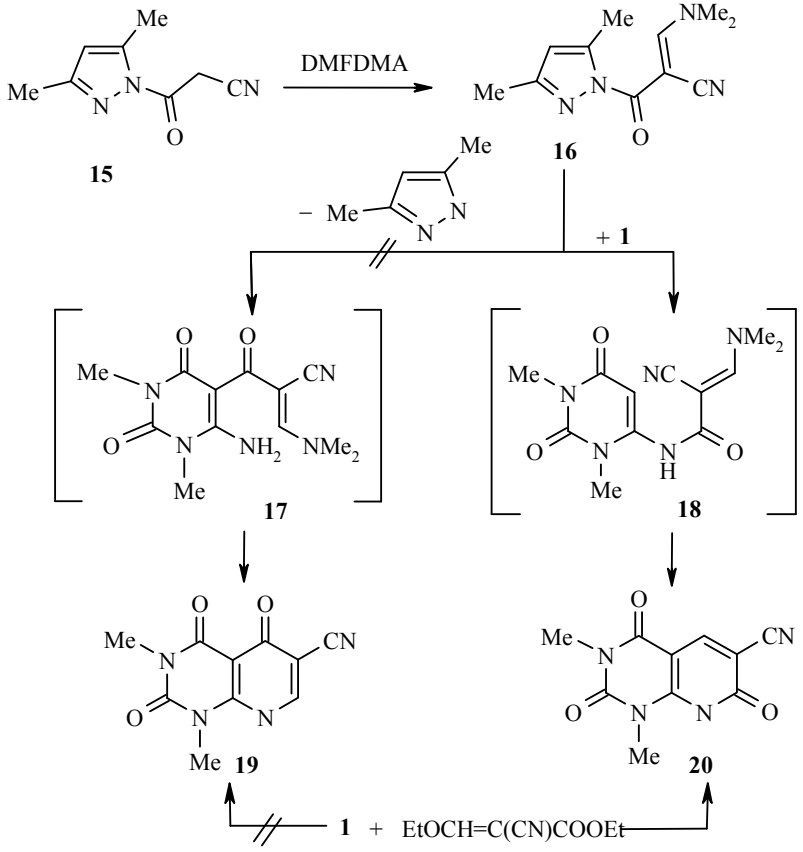
Recently an analogous method for the synthesis of pyrido[2,3-*d*]pyrimidines was proposed *via* the reaction of 6-amino-2-thiouracil with activated olefinic systems possessing a leaving group such as dimethylamino [23]. Motivated by this fact and as a part of our reaction on enaminones [24-27], we studied herein the effect of some enaminones of pyrazoles and simple enaminones on aminouracil **1**. For this purpose a novel enaminone, 3-(dimethylamino)-2-[(3,5-dimethyl-1H-pyrazol-1-yl)carbonyl]prop-2-enenitrile (**16**), was obtained from the reaction of 1-cyanoacetyl-3,5-dimethylpyrazole (**15**) with DMF/dimethylacetal (DMFDMA) in boiling xylene. The interaction of enaminone **16** with aminouracil **1** in boiling ethanol containing a few drops of triethylamine involves the removal of 3,5-dimethylpyrazole as a result of nucleophlic attack at the oxo group of the side chain by the electron-rich 5-position of the uracil or by its amino group. Formation of intermediate **17** was difficult due to a steric factor. Instead, intermediate **18** was formed and underwent ring closure to give compound **20** and not compound **19**.

Scheme 2



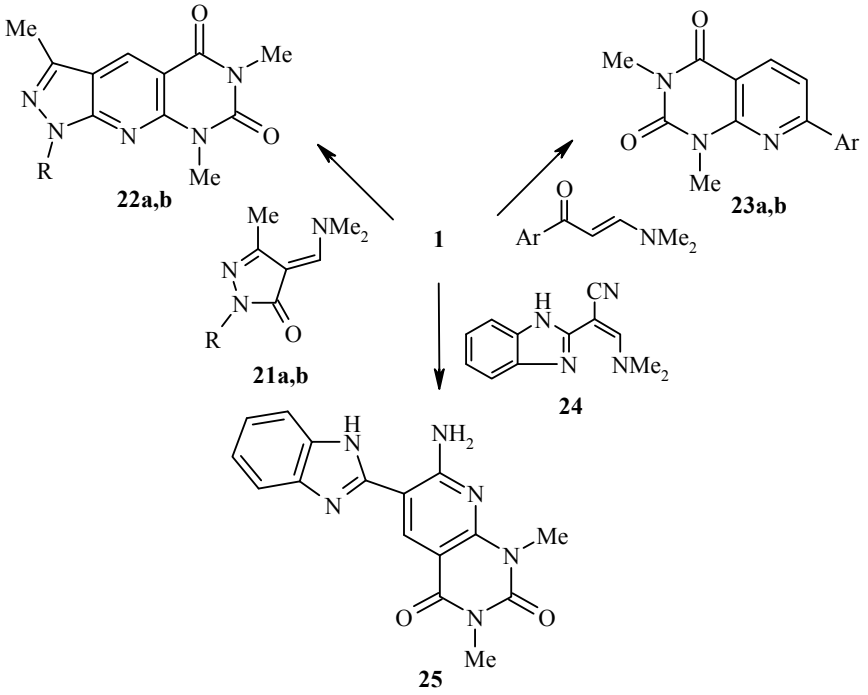
The structure of compound **19** was ruled out on the basis of the product being identical with an authentic sample of compound **20** previously prepared from compound **1** and ethyl ethoxymethylenecyanoacetate [28] (Scheme 3).

Scheme 3



Furthermore, pyrazolopyridopyrimidinediones **22a,b** were synthesized on treatment of compound **1** with 4-methylidenedimethylaminopyrazolones **21a,b**, while 5-arylpyrido[2,3-*d*]pyrimidinedione derivatives **23a,b** and 7-amino-6-(1H-benzimidazol-2-yl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (**25**) were obtained *via* interaction of compound **1** with 1-aryl-3-dimethylaminoprop-2-en-1-ones and enamine **24**, respectively (Scheme 4). The formation of compounds **22a,b** and **23a,b** is assumed to proceed by the Michael type addition of the most nucleophilic ring carbon, C-5 of uracil, to the activated double bond of the vinyl ketone, forming a Michael adduct as an intermediate, which undergoes cyclocondensation by water elimination.

Scheme 4



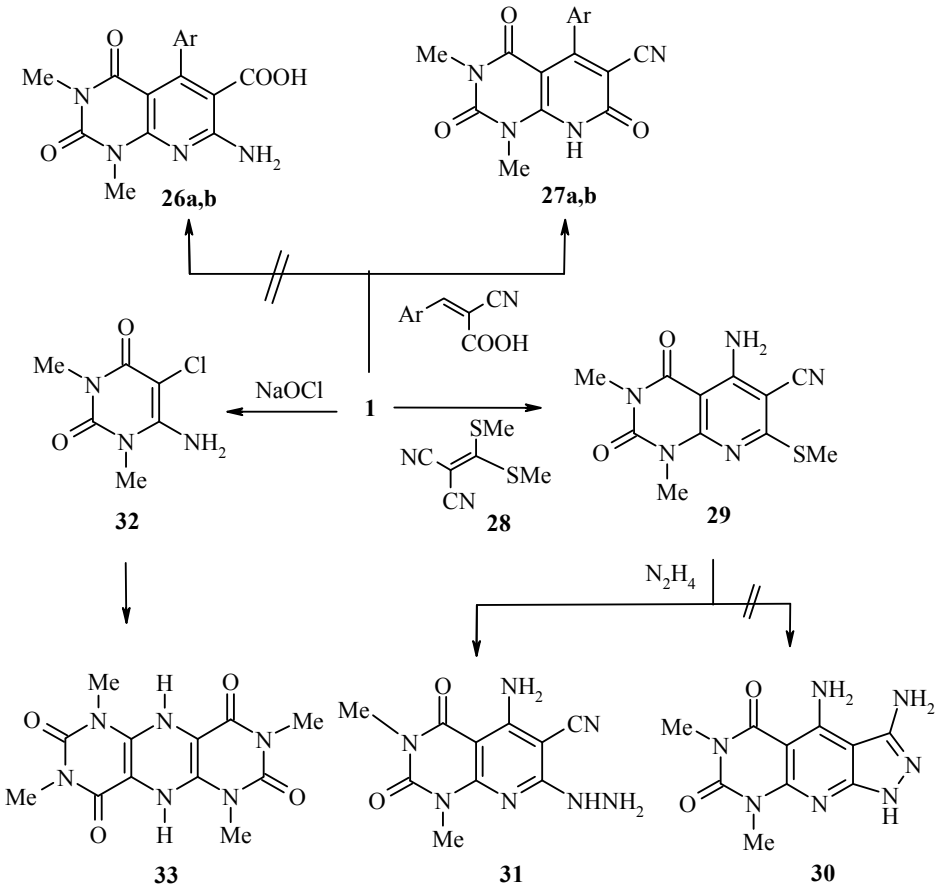
21, 22 a R = H, **b** R = Ph; **23 a** Ar = Ph, **b** Ar = CH═CHPh

Also, pyrido[2,3-*d*]pyrimidinetriones **27a,b** could be obtained on refluxing compound **1** with 3-aryl-2-cyanoprop-2-enoic acids in ethanol containing piperidine as a base. Compound **26** was not formed as the product did not give an acid reaction and the IR spectrum of the product showed CN at 2212 cm^{-1}. In addition, when compound **1** was subjected to reaction with 2-cyano-3,3-bis(methylthio)acrylonitrile (**28**), 5,6,7-trisubstituted pyrido[2,3-*d*]pyrimidinedione **29** was obtained [29], which reacted with hydrazine hydrate in boiling ethanol to yield the hydrazino derivative **31** but not the triheterocyclic system, pyrazolopyridopyrimidinedione **30,** as the IR spectrum of the product exhibited an absorption band at 2211cm^{-1} corresponding to the CN function.

On the other hand, when sodium hypochlorite reacted with compound **1**, 6-amino-5-chloro-1,3-dimethyluracil (**32**) was produced in a better yield than that obtained previously [30]. Boiling of compound **32** in DMF containing triethylamine afforded 1,3,6,8-tetramethyl-1,5,6,10-tetrahydropyrimido[4,5-*g*]pteridine-2,4,7,9(3H,8H)-tetrone (**33**), while its dehydrated form was previously obtained by photodecomposition of 6-azido-1,3-dimethyluracil [31] (Scheme 5).

The antimicrobial activity of the synthesized triheterocyclic systems against two Gram-positive bacteria (*Bacillus subtilis* and *Streptococcus faecalis*) and a Gram-negative bacteria (*Escherichia coli*) was investigated in comparison with ampicillin as an antibacterial standard agent. Also, the compounds were tested against fungus (*Candida albicans*) in comparison with nystatin as an antifungal standard agent using a filter paper disc method [32, 33]. The results are recorded in Table 1.

Scheme 5



26,27 a Ar = 3-$O_2NC_6H_4$, **b** Ar = 2,4-$Cl_2C_6H_3$

The results show that all the tested compounds are capable of inhibiting the growth of all the used microorganisms. Compounds **9** and **13** having a pyridazine moiety in their structure showed a higher antibacterial activity compared with those having pyrazole, pyridine, and pyrimidine in their structure, while compound **22a** exhibited antifungal activity greater than those having pyridine, pyridazine, and pyrimidine in their structure. Therefore, compounds **9** and **13** can be used as antibacterial agents and compound **22a** can be used as an antifungal agent.

TABLE 1. The Inhibition Zone Expressed in mm/mg Sample

Compound	Antibacterial activity			Antifungal activity
	B. subtilis	*S. faecalis*	*E. coli*	*Candida albicans*
6	12	12	12	12
9	16	18	15	11
10	10	12	10	11
13	15	16	15	10
14	11	10	11	15
22a	11	10	11	16
22b	12	11	12	14
31	10	11	10	12
Ampicillin	18	28	11	—
Nystatin	—	—	—	12

EXPERIMENTAL

All reported melting points are uncorrected. The IR spectra were recorded on a FTIR Bruker Vector 22 spectrometer using the KBr wafer technique. ^{1}H NMR spectra (DMSO-d_6) were measured on a Varian Gemini spectrophotometer 200 MHz using TMS as an internal standard. Mass spectra were obtained using a GCMS QP 1000 ex Shimadzu instrument (EI, 70 eV). Elemental analyses were carried out at the Micro Analytical Center, Cairo University.

2-Chloro-4,6-dimethylpyridine-3-carbonitrile (2) was prepared according to the reported method [18].

2-(6-Amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4,6-dimethylpyridine-3-carbonitrile (5). Equimolar amounts of 6-amino-1,3-dimethyluracil (**1**) and 2-chloro-4,6-dimethylpyridine-3-carbonitrile (**2**) in ethanol (20 ml) containing triethylamine (5 drops) were refluxed for 1 h. The solid obtained after cooling the reaction mixture was filtered off and recrystallized from ethanol to give compound **5** as colorless crystals, yield 68%; mp 245-246°C. IR spectrum, ν, cm^{-1}: 3396, 3351, 3229 (NH_2), 2950 (aliphatic CH), 2222 (CN), 1656 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.23 (3H, s, 4-CH_3); 2.30 (3H, s, 6-CH_3); 3.08 (3H, s, NCH_3); 3.23 (3H, s, NCH_3); 4.70 (2H, s, NH_2); 6.14 (1H, s, H-5 pyridine). Mass spectrum, *m/z* (*I*, %): 268 [M-NH_3] (100), 118 (56.3), 101 (43.8). Found, %: C 59.00; H 5.39, N 24.80. $C_{14}H_{15}N_5O_2$. Calculated, %: C 58.94; H 5.26; N 24.65.

Triheterocondensed uracils 6,9,10,13,14 (General Method). A solution of compound **1** and an equimolar amount of the chloroheterocyclic compound in ethanol (20 ml) with triethylamine (5 drops) were refluxed for 4-8 h and allowed to cool overnight. The solid obtained was filtered off and crystallized from the proper solvent to afford the triheterocyclic systems.

5-Amino-2,4,7,9-tetramethylpyrimido[4,5-*h*][1,6]naphthyridine-8,10(7H,9H)-dione (6) was crystallized from DMF–H_2O and appeared as pale-yellow crystals, yield 75%; mp 283-285°C. IR spectrum, ν, cm^{-1}: 3450-3216 (NH_2), 2965 (aliphatic CH), 1654 (CO). Mass spectrum, *m/z* (*I*, %): 284 [M-1] (11.3). Found, %: C 58.60; H 5.40; N 24.86. $C_{14}H_{15}N_5O_2$. Calculated, %: C 58.94; H 5.26; N 24.56.

5-Amino-7,9-dimethyl-3,4-diphenylpyrimido[5',4':5,6]pyrido[4,3-*c*]pyridazine-8,10(7H,9H)-dione (9) was crystallized from ethanol and appears as yellow crystals, yield 66%; mp 261–262°C. IR spectrum, ν, cm^{-1}: 3410-3290 (NH_2), 2942 (CH aliphatic), 1655 (CO). ^{1}H NMR spectrum, δ, ppm: 3.01 (3H, s, NCH_3); 3.27 (3H, s, NCH_3); 4.8 (2H, br. s, NH_2); 6.77-7.42 (10H, m, H Ar). Mass spectrum, *m/z* (*I*, %): 408 [M-2] (11.4), 407 (16.2), 322 (29.5), 59 (100). Found, %: C 67.51; H 4.55; N 20.65. $C_{23}H_{18}N_6O_2$. Calculated, %: C 67.31; H 4.39; N 20.48.

5-Amino-2,7,9-trimethyl-4-phenylpyrimido[4',5':4,5]pyrido[2,3-*d*]pyrimidine-8,10(7H,9H)-dione (10) was crystallized from ethanol and appears as pale-yellow crystals, yield 82%; mp 210-212°C. IR spectrum, ν, cm^{-1}: 3397–3230 (NH_2), 2949 (CH aliphatic), 1657 (CO). Mass spectrum, *m/z* (*I*, %): 348 [M] (9.45), 332 [M-NH_2] (16.2), 318 [M-C_2H_6], 155 (100). Found, %: C 62.36; H 4.56; N 24.66. $C_{18}H_{16}N_6O_2$. Calculated, %: C 62.06; H 4.59; N 24.13.

5,7,9-Trimethyl-3,4-diphenylpyrimido[5',4':5,6]pyrido[4,3-*c*]pyridazine-8,10-(7H,9H)-dione (13) was crystallized from aqueous ethanol and appears as yellow crystals, yield 72%; mp 279-281°C. IR spectrum, ν, cm^{-1}: 3107 (aromatic CH), 2950 (aliphatic CH), 1656 (CO). ^{1}H NMR spectrum, δ, ppm: 3.07 (3H, s, 5-CH_3); 3.24 (3H, s, NCH_3); 3.34 (3H, s, NCH_3); 6.76-7.89 (10H, m, H Ar). Mass spectrum, *m/z* (*I*, %): 409 [M] (1.2), 311 (16.9), 208 (1.7), 155 (100). Found, %: C 70.30; H 4.55; N 17.34. $C_{24}H_{19}N_5O_2$. Calculated, %: C 70.14; H 4.64; N 17.11.

7,9-Dimethyl-3,4-diphenylpyrimido[5',4':5,6]pyrido[4,3-*c*]pyridazine-5,8,10-(6H,7H,9H)-trione (14) was crystallized from DMF–H_2O and appeared as pale-yellow crystals, yield 67%; mp 297-299°C. IR spectrum, ν, cm^{-1}: 3213 (NH_2), 3109 (aromatic CH), 2950 (aliphatic CH), 1657 (CO). ^{1}H NMR spectrum, δ, ppm: 3.06 (3H, s, NCH_3); 3.24 (3H, s, NCH_3); 6.76-7.34 (10H, m, H Ar); 8.01 (1H, s, NH). Found, %: C 67.45; H 4.35; N 17.36. $C_{23}H_{17}N_5O_3$. Calculated, %: C 67.15; H 4.13; N 17.03.

Enaminones 16 and 21a,b (General Method). A mixture of the active methylene compound (10 mmol) and DMF/dimethylacetal (1.5 ml, 12 mmol) in xylene (20 ml) was refluxed for 6 h, and the solid obtained on evaporating the excess solvent was collected and crystallized from the proper solvent.

3-(Dimethylamino)-2-[(3,5-dimethyl-1H-pyrazol-1-yl)carbonyl]prop-2-enenitrile (16) was crystallized from ethanol and appears as yellow crystals, yield 86%; mp 210–212°C. IR spectrum, ν, cm^{-1}: 2956 (aliphatic CH), 1668 (CO), 2218 (CN). Mass spectrum, *m/z* (*I*, %): 218 [M] (23.15). Found, %: C 60.98; H 6.31; N 26.01. $C_{11}H_{14}N_4O$. Calculated, %: C 60.55; H 6.42; N 25.68.

3-Methyl-4-methylidenedimethylamino-1H-pyrazol-5-one (21a) was crystallized from methanol and appears as pale-yellow crystals, yield 78%; mp 158-159°C. IR spectrum, ν, cm^{-1}: 3215 (NH), 2964 (aliphatic CH), 1665 (CO). Mass spectrum, *m/z* (*I*, %): 154 [M+1] (1.13), 153 [M] (12.13). Found, %: C 55.15; H 7.32; N 27.56. $C_7H_{11}N_3O$. Calculated, %: C 54.90; H 7.18; N 27.45.

3-Methyl-4-methylidenedimethylamino-1-phenylpyrazol-5-one (21b) was crystallized from ethanol and appears as orange crystals, yield 86%; mp 187-188°C. IR spectrum, ν, cm^{-1}: 3095 (aromatic CH), 2965 (aliphatic CH), 1668 (CO). ^{1}H NMR spectrum, δ, ppm: 2.21 (3H, s, CH_3); 2.95 (3H, s, NCH_3); 3.22 (3H, s, NCH_3); 6.11 (1H, s, olefinic H); 7.43-7.91 (5H, m, H Ar). Mass spectrum, *m/z* (*I*, %): 229 [M] (6.09), 77 (100). Found, %: C 68.36; H 6.50; N 18.58. $C_{13}H_{15}N_3O$. Calculated, %: C 68.12; H 6.55; N 18.34.

Reaction of Compound 1 with Enaminones and with Enamines 24 (General Method). A mixture of compound **1** (10 mmol), enaminone (12 mmol) in absolute ethanol (20 ml), and triethylamine (5 drops) was refluxed for 4-8 h and left to cool overnight. The solid obtained was collected and crystallized from the proper solvent.

3,6,8-Trimethyl-1H-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6H,8H)-dione (22a) was crystallized from DMF–H_2O and appeared as yellow crystals, yield 78%; mp 242-244° C. IR spectrum, ν, cm^{-1}: 3341 (NH_2), 2953 (aliphatic CH), 1712, 1642 (2CO). Mass spectrum, *m/z* (*I*, %): 245 [M] (1.25), 191 (100). Found, %: C 53.66; H 4.56; N 28.82. $C_{11}H_{11}N_5O_2$. Calculated, %: C 53.87; H 4.48; N 28.57.

3,6,8-Trimethyl-1-phenyl-1H-pyrazolo[4',3':5,6]pyrido[2,3-*d*]pyrimidine-5,7(6H,8H)-dione (22b) was crystallized from ethanol and appeared as orange crystals, yield 55%; mp 239-241°C. IR spectrum, ν, cm^{-1}: 3052 (aromatic CH), 2950 (aliphatic CH), 1710-1645 (2CO). ^{1}H NMR spectrum, δ, ppm: 2.26 (3H, s, CH_3); 3.22 (3H, s, NCH_3); 3.35 (3H, s, NCH_3); 7.19-8.06 (5H, m, H Ar); 8.97 (1H, s, H-4). Mass spectrum, *m/z* (*I*, %): 322 [M+1] (2.2), 191 (100), 136 (26.6), 84 (22.4). Found, %: C 63.75; H 4.55; N 21.66. $C_{17}H_{15}N_5O_2$. Calculated, %: C 63.55; H 4.67; N 21.80.

1,3-Dimethyl-7-phenylpyrido[2,3-*d*]pyrimidine-2,4-dione (23a) was crystallized from isopropanol and appeared as yellow crystals, yield 62%; mp 190-192°C. IR spectrum, ν, cm^{-1}: 3055 (aromatic CH), 2944 (aliphatic CH), 1705, 1658 (2CO). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.21 (3H, s, NCH_3); 3.54 (3H, s, NCH_3); 7.47-7.76 (5H, m, H Ar); 7.80 (1H, d, *J* = 6.4, H-5,); 8.21 (1H, d, *J* = 6.5, H-6). Mass spectrum, *m/z* (*I*, %): 267 [M] (89), 268 [M+] (1.30), 239 (80.6), 191(100). Found, %: C 67.45; H 4.67; N 15.85. $C_{15}H_{13}N_3O_2$. Calculated, %: C 67.41; H 4.86; N 15.73.

1,3-Dimethyl-7-styrylpyrido[2,3-*d*]pyrimidine-2,4-dione (23b) was crystallized from ethanol and appeared as yellow crystals, yield 78%; mp 296-298°C. IR spectrum, ν, cm^{-1}: 3065 (aromatic CH), 2946 (CH aliphatic), 1701, 1646 (2CO). Mass spectrum, *m/z* (*I*, %): 293 [M] (11.2), 191 (100). Found, %: C 69.89; H 5.36; N 14.49. $C_{17}H_{15}N_3O_2$. Calculated, %: C 69.62; H 5.11; N 14.33.

7-Amino-6-(1H-benzimidazol-2-yl)-1,3-dimethylpyrido[2,3-*d*]pyrimidine-2,4(1H,3H)-dione (25) was crystallized from DMF–H_2O and appeared as pale-yellow crystals, yield 65%; mp 297-299°C. IR spectrum, ν, cm^{-1}: 3396, 3351, 3228 (NH_2, NH); 3108 (aromatic CH); 2948 (aliphatic CH); 1700, 1656 (2CO). ^{1}H NMR spectrum, δ, ppm: 3.08 (3H, s, NCH_3); 3.24 (3H s, NCH_3); 4.7 (2H, s, NH_2); 6.71-7.33 (6H, m, H Ar, H-5 and NH). Mass spectrum, *m/z* (*I*, %): 322 [M] (1.2), 155 (100), 82 (64.2), 68 (19.4). Found %: C 59.56; H 4.55; N 25.96. $C_{16}H_{14}N_6O_2$. Calculated, %: C 59.62; H 4.34; N 26.08.

1,3-Dimethyl-5-(3-nitrophenyl)-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (27a). A mixture of compound **1** (1.55 g, 10 mmol) and 3-nitrobenzylidene cyanoacetic acid (2.12 g, 12 mmol) in absolute ethanol (20 ml) containing a few drops of piperidine was refluxed for 6 h. The solid obtained on cooling was filtered off and crystallized from absolute ethanol, yield 82%; mp 297-298°C. IR spectrum, ν, cm^{-1}: 3399 (NH), 2950 (aliphatic CH), 2212 (CN), 1716-1675 (2CO). ^{1}H NMR spectrum, δ, ppm: 3.15 (3H, s, NCH_3); 3.65 (3H, s, NCH_3); 7.35-8.22 (4H, m, H Ar); 8.26 (1H, s, NH). Found %: C 54.83; H 3.32; N 19.78. $C_{16}H_{11}N_5O_5$. Calculated, %: C 54.39; H 3.11; N 19.83.

5-(2,4-Dichlorophenyl)-1,3-dimethyl-2,4,7-trioxo-1,2,3,4,7,8-hexahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (27b) was obtained applying the same method used for compound **27a** and crystallized from ethanol as yellow crystals, yield 62%; mp 286-288°C. IR spectrum, ν, cm^{-1}: 3314 (NH); 3055 (CH aromatic), 2965 (CH aliphatic), 2222 (CN), 1706, 1745 (2CO). Mass spectrum, *m/z* (*I*, %): 378 [M] (12.8), 306 [M-Cl_2] (1.7), 154 (100). Found, %: C 50.66; H 2.66; N 15.01. $C_{16}H_{10}Cl_2N_4O_3$. Calculated, %: C 0.79; H 2.64; N 14.18.

4-Amino-3-cyano-6,8-dimethyl-2-methylthiopyrido[2,3-*d*]pyrimidine-5,7-dione (29) was prepared according to the reported method [29].

5-Amino-7-hydrazinyl-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-*d*]pyrimidine-6-carbonitrile (31). A mixture of compound **29** (2.66 g, 10 mmol) and hydrazine hydrate (5 ml) in ethanol (20 ml) was refluxed for 3 h. The solid was obtained upon evaporating, and the excess solvent was collect. Crystallized from ethanol to give compound **31** as yellow crystals, yield 72%; mp 149–150°C. IR spectrum, ν, cm^{-1}: 3429, 3314, 3230, 3144 (NH_2, NH); 2978 (aliphatic CH); 2211 (CN); 1700, 1656 (2CO). ^{1}H NMR spectrum, δ, ppm: 3.11 (3H, s, NCH_3); 3.16 (3H, s, NCH_3); 3.52 (1H, s, NH); 6.02 (2H, br. s, NH_2); 10.96 (2H, br. s, NH_2). Mass spectrum, *m/z* (*I*, %): 261 [M] (1.9), 191 (100), 135 (22.5), 68 (19.4). Found, %: C 50.11; H 4.36; N 37.25. $C_{10}H_{11}N_7O_2$. Calculated, %: C 49.97; H 4.21; N 37.54.

6-Amino-5-chloro-1,3-dimethyluracil (32). To a solution of compound **1** (1.55 g, 10 mmol) in ethanol (10 ml) sodium hypochlorite (5 ml) was added dropwise and the reaction mixture was stirred for 2 h. The solid obtained was filtered off and crystallized from ethanol to give yellow crystals, yield 92%; mp 155–156°C [30].

1,3,6,8-Tetramethyl-1,5,6,10-tetrahydropyrimido[4,5-*g*]pteridine-2,4,7,9(3H,8H)-tetrone (33). A solution of compound **32** (1.9 g, 10 mmol) in DMF (10 ml) containing triethyl amine (5 ml) was refluxed for 3 h, then cooled and poured into cold water. The solid obtained was filtered off and crystallized from DMF–water to give compound **33** as colorless crystals, yield 92%; mp 274-276°C. IR spectrum, ν, cm^{-1}: 3230, 3144 (2NH); 2958 (aliphatic CH); 1700, 1656 (CO). Mass spectrum, *m/z* (*I*, %): 306 [M] (11.9), 276(12), 191 (100). Found, %: C 47.11; H 4.36; N 27.25. $C_{12}H_{14}N_6O_4$. Calculated, %: C 47.05; H 4.57; N 27.45.

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REFERENCES

1. A. Gangjee, O. Aldair, and S. F.Queener, *J. Med. Chem.*, **42**, 2447 (1999).
2. Michael D. Varney, Cynthial L. Palmer, and Williams H. Romines, PCT Int. Appl. WO 94 17076, US Pat. Appl. 1086129 (1993); *Chem*. *Abstr.*, **121**, 205385 (1994).
3. S. Furuya and T. Ohtaki, Eur. Pat. Appl. EP 608565 (1994); *Chem*. *Abstr*., **121**, 205395 (1994).
4. D. Haber, C. Heers, and U. Ravens, *Pharmazie*, **48**, 537 (1993).
5. G. Singh, A. K. Yadav, and K. Mishraa, *Indian J. Chem.*, **41**, 430 (2002).
6. N. R. Mohamed, M. T. Elsaidi, Y. M. Ali, and M. H. Elnagdi, *Bioorg*., *Med*. *Chem.*, **41**, 430 (2002).
7. Y. Sakuma, M. Hasegawa, K. Kataoka, K. Hoshina, N. Yamazaki, T. Kadota, and H. Yamaguchi, PCT Int. Appl. WO 91 05785; *Chem*. *Abstr*., **115**, 71646 (1991).

8. J. I. De-Graw, P. H. Christie, W. T. Clowell, and F. Sirotnak, *J. Med. Chem*., **35**, 320 (1992).
9. E. Lunt, C. C. Newton, in: R. Katritzky, C. W. Rees (editors), *Comprehensive Heterocyclic Chemistry*, Pergamon Press, Oxford, 1984, Vol. 3, p. 199.
10. H. Wamhoff, J. Dzenis, and K. Hirota, *Adv. Heterocycl. Chem.*, **55**, 129 (1992).
11. J. Qurroga, J.Garcia, B. Insuasty, N. L. Mendoza, M. Pungo, and H. Meier, H. *Ann. Quim.*, **90**, 300 (1994).
12. J. Qurroga, J. Garcia, B. Insuasty, M. Nogueras, and H. Mier, *J. Heterocycl. Chem.*, **29**, 1045 (1992).
13. J. Qurroga, A. Hormaza, B. Insuasty, M. Nogueras, A. Sanchez, N. Hanold, and H. Mier, *J. Heterocycl. Chem.*, **34**, 521 (1997).
14. J. Bulic, *Bioorg. Med. Chem*., **14**, 2837 (2006).
15. K. Hirota, H. Kuki, and Y. Maki, *Heterocycles*, **37**, 163 (1994).
16. P. Srivastava, A. S. Saxena, and V. J. Ram, *Synthesis*, 541 (2000).
17. A. D. Room, J. I. Shim, and G. L. Anderson*, J. Org. Chem.*, **41**, 1095 (1976).
18. M. Abdel-Megid, *Pharmazie*, **55**, 263 (2006).
19. M. Abdel-Megid, *Synth. Commmun*., **37**, 3211 (2007).
20. M. Abdel-Megid, *Int. J. Chem.*, **16**, 149 (2006).
21. M. Abdel-Megid, *Heterocycl. Commmun*., **4**, 235 (1998).
22. M. Seada, M. Fawazy, H. Jahine, M. Abdel-Megid, and R. R Saad, *J. Chin. Chem. Soc.*, **36**, 241 (1989).
23. J. Quiroga, B. Insusaty, H. Insusty, and R. Absenes, *J. Heterocycl. Chem.*, **38**, 339 (2001).
24. M. Abdel-Megid, M. H. Elnagdi, and A. M. Negm, *J. Heterocycl. Chem*., **39**, 105 (2003).
25. M. Abdel-Megid, *Synth. Commmun.*, **33**, 153 (2003).
26. M. Abdel-Megid, M. Abass, and M. H. Hassan, *J. Heterocycl. Chem.*, **44**, 315 (2007).
27. M. Abdel-Megid, *Int. J. Chem*., **16**, 149 (2006*)*.
28. K. Hirota, Y. Kitade, and S. Senda*, J. Heterocycl. Chem*., **22**, 345 (1985).
29. Y. Tominaga, H. Oknda, Y. Mitsutomi, Y. Mastuda, G. Kobayashi, and K. Sakemi, *Heterocycles*, **12**, 503 (1979).
30. E. F.Schoeder and R. M. Dadsom, *J. Am. Chem. Soc*., **84**, 1904 (1962).
31. W. Pfleiderer, K. H. Schundehutte, and H. Ferch, *Liebigs Ann. Chem*., **615**, 57 (1958).
32. J. C. Vincent and H. W. Vincent, *Proc. Soc. Exp. Biol. Med*., **55**, 162 (1964).
33. M. Seada, M. Abdel-Megid, and I. M. El-Deen, *Ind. J. Heterocycl. Chem*., **3**, 81 (1993).