# Synthesis of Some New [1,8]Naphthyridine, Pyrido[2,3-*d*]-Pyrimidine, and Other Annulated Pyridine Derivatives

Abu-Bakr A. A. M. El-Adasy, Ahmed A. Khames, and Mohamed A. M. Gad-Elkareem*

Department of Chemistry, Faculty of Science, Al-Azhar University, Assiut 71524, Egypt
*E-mail: m65gad@yahoo.com

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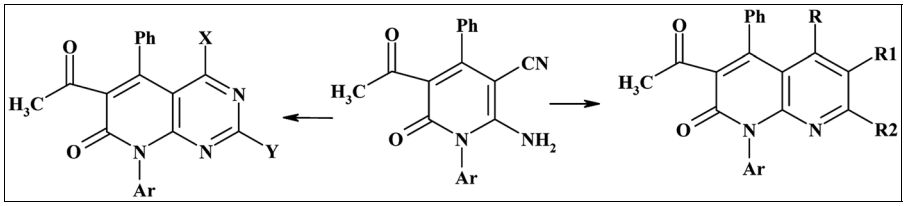


2-Aminopyridine-3-carbonitrile derivative **1** reacted with each of malononitrile, ethyl cyanacetate, benzylidenemalononitrile, diethyl malonate, and ethyl acetoacetate to give the corresponding [1,8] naphthyridine derivatives **3**, **5**, **8**, **11**, and **14**, respectively. Further annulations of **3**, **5**, and **8** gave the corresponding pyrido[2,3-*b*][1,8]naphthyridine-3-carbonitrile derivative **17**, pyrido[2,3-h][1,6]naphthyridine-3-carbonitrile derivatives **18** and **19**, respectively. The reaction of **1** with formic acid, formamide, acetic anhydride, urea or thiourea, and 4-isothiocyanatobenzenesulfonamide gave the pyridopyrimidine derivatives **20a**,**b**, **21**, **22a**,**b**, and **26**, respectively. Treatment of compound **1** with sulfuric acid afforded the amide derivative **27**. Compound **27** reacted with 4-chlorobenzaldehyde and 1*H*-indene-1,3(2*H*)-dione to give the pyridopyrimidine derivative **28** and spiro derivative **30**, respectively. In addition, compound **1** reacted with halo compounds afforded the pyrrolopyridine derivatives **32** and **34**. Finally, treatment of **1** with hydrazine hydrate gave the pyrazolopyridine derivative **35**. The structures of the newly synthesized compounds were established by elemental and spectral data.

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## INTRODUCTION

Naphthyridine systems are of great importance due to their chemical [1–3] and biological activities. The naphthyridine derivatives are used as potent acyl-CoA:cholesterol acyltransferase inhibitor [4], anticancer [5], anti-inflammatory [5], antiplatelet [6], for the treatment of Alzheimer's disease [7], HIV-1 integrase inhibitors [8], and antimicrobial [9] agents. Moreover, pyrido[2,3-*d*]-pyrimidine derivatives form a class of fused heterocyclic compounds, which have received considerable attention over the past years [10–13] due to their wide range of biological activities such as analgesic [14], ulcerogenic [14], antianexiety [15], antimicrobial [16], antioxidant [16], antitumor [17], antiviral [18], cytotoxic [18], anti-inflammatory [14], [19], antibacterial [20], antileishmanial [21] activities and used as cyclin-dependent kinase 4 (Cdk4) inhibitors [22]. In addition, pyrrolo[2,3-*b*]pyridine derivatives are of chemotherapeutic interest because they have been shown to act as antidiabetic [23], 5-$HT_6$ receptor agonists or antagonists, useful for the treatment of central nervous system disorders [24], antitumor [25], and antimicrobial [26] agents.

The above findings stimulated the interest for the synthesis of additional new number of these derivatives that are required in medicinal chemistry programs.

## RESULTS AND DISCUSSION

The key structure 5-acetyl-2-amino-1-(4-methylphenyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carbonitrile (**1**) used in our study was prepared from the reaction of benzylidene-malononitrile with *N*-(4-methylphenyl)-3-oxobutan-amide in ethanolic peperidine solution under reflux according to literature [27] procedure. The reactivity of the 2-aminopyridine-3-carbonitrile derivative **1** toward active methylene nitriles was investigated. Thus, treatment of compound **1** with malononitrile in refluxing *N*,*N*-dimethylformamide in presence of a catalytic amount of piperidine gave the [1,8] naphthyridine-3-carbonitrile derivative **3**. The structure of **3** was established based on elemental analyses and spectral data. Thus, the IR spectrum of compound **3** showed bands at 3433, 3323 (two $NH_2$), 2207 (CN), 1690, 1640 $cm^{-1}$(two C═O). Its $^1$H-NMR (DMSO-$d_6$) revealed singlet signals at $\delta$ = 2.35, 2.49 ppm assigned for $2CH_3$, singlet at $\delta$ = 4.98 ppm for $NH_2$, multiplet at $\delta$ = 7.29-7.46 ppm assigned for CH aromatic, and hump at $\delta$ = 8.60 ppm for $NH_2$. In a similar manner, treatment of compound **1** with ethyl cyanoacetate under reflux in acetic acid gave a colored crystalline product identified as [1,8]naphthyridine-3-carbonitrile derivative **5** rather than ethyl [1,8]naphthyridine-3-carboxylate derivative **4**. The structure **4** was ruled out on the basis of

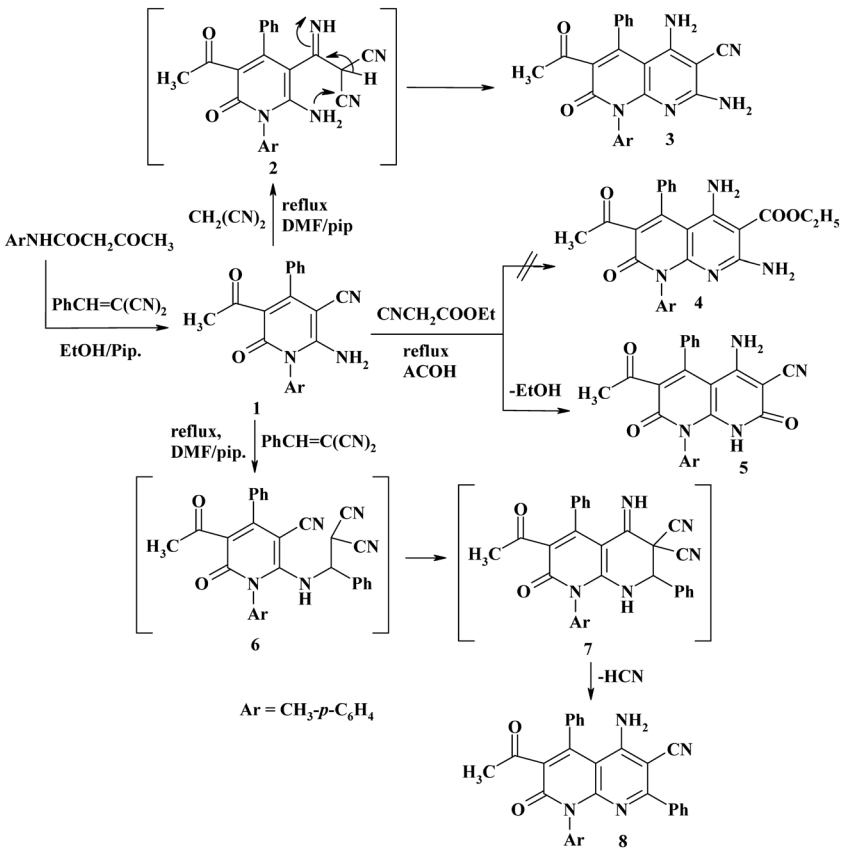
elemental analysis and spectral data. The IR spectrum of compound **5** revealed the presence of $NH_2$ and NH absorption bands at ν $cm^{-1}$ 3438, 3412, and 3261 $cm^{-1}$ and CN group at 2182 $cm^{-1}$ in addition to (three C═O) at 1722, 1710, and 1633 $cm^{-1}$ and its $^1$H-NMR spectrum revealed the signal of NH at δ = 10.2 ppm and absence of any signals due to $OCH_2CH_3$ protons (see Scheme 1 and Experimental section).

Treatment of compound **1** with benzylidenemalononitrile in DMF in the presence of a catalytic amount of piperidine under reflux afforded the [1,8]naphthyridine-3-carbonitrile derivative **8** in good yield. The structure of the latter compound was confirmed based on elemental analyses and spectral data. Compound **8** was formed via the addition of the amino group in compound **1** to the double bond in benzylidenemalononitrile to form the intermediate **6**, which cyclized via a nucleophilic addition of methyne hydrogen of arylidene to the cyano function of pyridine to form dihydropyridine intermediate **7**, the latter released hydrogen cyanide to form the final product **8** (Scheme 1 and Experimental section).

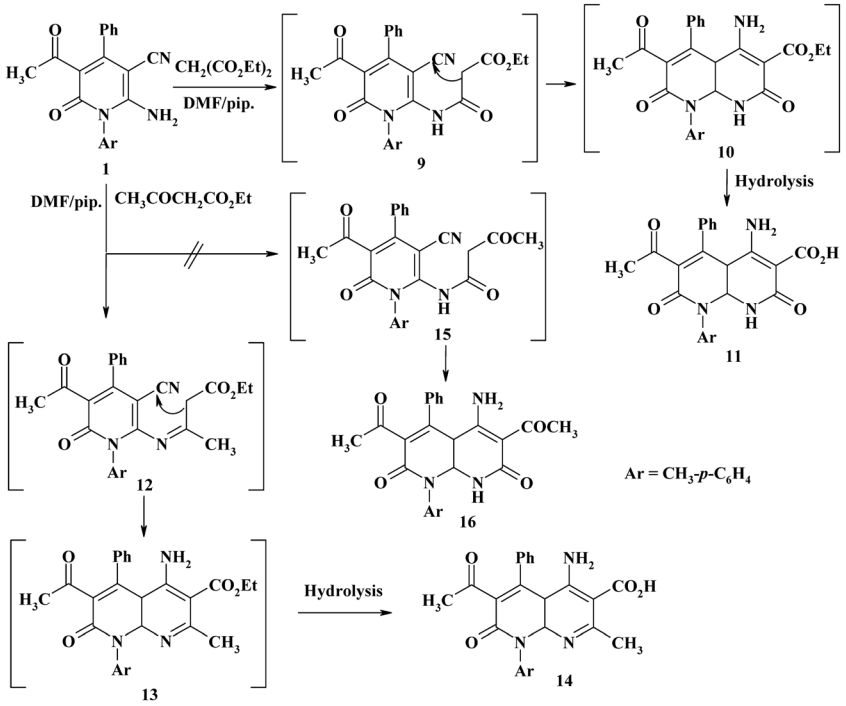
The reactivity of **1** toward ester compounds was studied, thus treatment of **1** with diethyl malonate under reflux in DMF/piperidine solution afford [1,8]naphthyridine-3-carboxylic acid derivative **11**. The IR spectrum of the reaction product indicated the presence of a broad band at ν = 3398–2382 $cm^{-1}$ due to acidic OH functional group. In addition, its $^1$H-NMR spectrum revealed the signal of acidic OH proton at δ = 14.33 ppm and absence of any signals may be attributed to $-CH_2CH_3$ protons. The formation of **11** in this reaction is assumed to proceed via the nonisolable intermediate analide **9**, which cyclized to the nonisolable ethyl carboxylate derivative **10** that underwent hydrolysis under the applied reaction conditions to give 6-acetyl-4-amino-8-(4-methylphenyl)-2,7-dioxo-5-phenyl-1,2,7,8-tetrahydro-1,8-naphthyridine-3-carboxylic acid (**11**) (see Scheme 2 and Experimental section).

Moreover, compound **1** reacted with ethyl acetoacetate under the above reaction conditions to give the [1,8] naphthyridine-3-carboxylic acid derivative **14** rather than the diacetyl derivative **16**. The structure **14** was established based on elemental analyses and spectral data studies. The IR spectrum of **14** indicated the presence of a broad band at ν = 3400–2500 $cm^{-1}$ due to acidic OH functional group. In addition its $^1$H-NMR spectrum revealed the signal of acidic OH proton at δ = 14.32 ppm and absence of any signals may be attributed to $-CH_2CH_3$ protons. The formation of compound **14** in this reaction is assumed to proceed via

**Scheme 1**



**Scheme 2**




the nonisolable condensation product **12**, which cyclized to the nonisolable ethyl carboxylate derivative **13** that underwent hydrolysis under the applied reaction conditions to give the 1,8-naphthyridine-3-carboxylic acid **14** (see Scheme 2 and Experimental section).

Further annulations of compounds **3**, **5** and **8** were also investigated. Thus, reaction of each of compounds **3**, **5**, and **8** with malononitrile in DMF/pepeidine solution under reflux yielded the corresponding pyrido[2,3*b*][1,8]-naphthyridine-3-carbonitrile derivative **17**, pyrido[2,3-*h*] [1,6]naphthyridine-3-carbonitrile derivatives **18** and **19**, respectively. The structures of **17**, **18**, and **19** were confirmed based on elemental analyses and spectral data (see Scheme 3 and Experimental section).

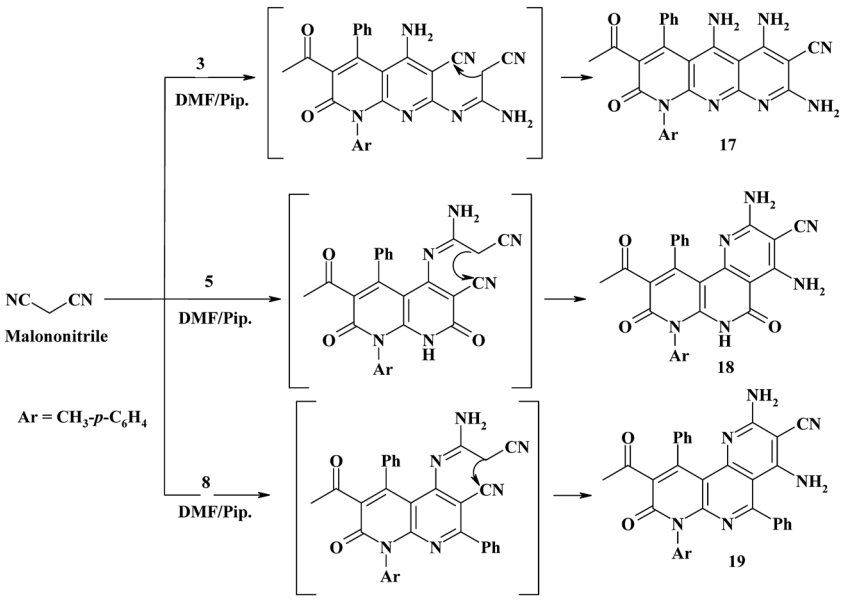
The key structure **1** was used to synthesize a new series of the biologically important pyridopyrimidine derivatives. Thus, the reaction of **1** with formic acid under reflux afforded the pyridopyrimidine derivative **20a** (Scheme 4). The IR spectrum of compound **20a** showed bands at 3210 (NH), 1711, 1670, 1630 $cm^{-1}$ (three C═O). The $^1$H-NMR spectrum showed signals at δ = 2.02, 2.36 ppm assigned for $2CH_3$, singlet at δ = 7.47 ppm assumed for $C_{(2)}$-H pyrimidine and the signal of NH at δ = 14.08 ppm. Similarly, compound **1** reacted with acetic anhydride to give the corresponding pyridopyrimidine derivative **20b** (Scheme 4), and also, compound **1** was condensed with formamide under reflux afforded the aminopyridopyrmidine derivative **21**. The structure of compound **21** was confirmed based on elemental analysis; IR and $^1$H-NMR spectra (see Scheme 4 and Experimental section).

When compound **1** was allowed to react with urea in the presence of sodium ethoxide in ethanol the pyridopyrimidine derivative **22a** or **23a** was isolated as a reaction product. The IR spectrum of the reaction product indicated the presence of the absorption band of CN function group at 2211 $cm^{-1}$ and absence of any bands may be attributed to the CO function groups. Also the $^1$H-NMR spectrum did not revealed any signals for the NH protons. From the above data, the reaction product was formulated as the pyrido[2,3-*d*]pyrimidine-6-carbonitrile derivative **22a**, and the 6-acetylpyrido[2,3-*d*]pyrimidine derivative **23a** was ruled out (see Scheme 4 and Experimental section). Analogously, compound **1** reacted with thiourea to yield the pyrido[2,3-*d*]pyrimidine-6-carbonitrile derivative **22b**, which established based on elemental analysis and spectral data (see Scheme 4 and Experimental section).

Treatment of **1** with 4-isothiocyanatobenzenesulfonamide in refluxing pyridine afforded the pyrido[2,3-*d*]pyrimidine structure **26.** The formation of compound **26** was assumed to proceed via addition of the amino group of **1** to the isothiocyanato group to yield the nonisolable thiourea derivative **24**, which cyclized through the addition to the cyano function giving the intermediate pyridopyrimidine derivative **25** that underwent Dimroth rearrangement [13,20b], to give the final product **26** (Scheme 5).

The novel carboxamide derivative **27** was obtained via treatment of compound **1** with concentrated sulfuric acid at room temperature through partially hydrolysis of the cyano group. The IR spectrum of **27** showed the absence of cyano group absorption. The $^1$H-NMR showed signals

**Scheme 3**

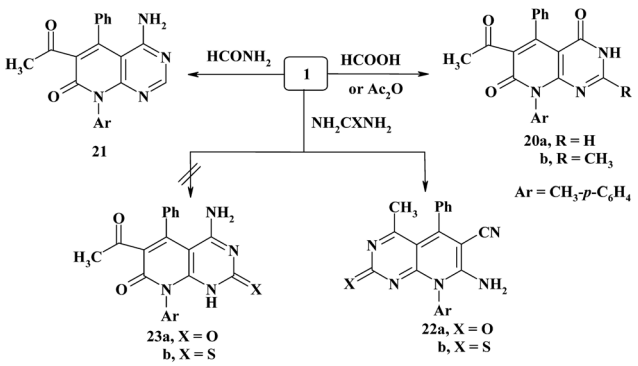



at δ 5.77, 10.91 ppm for two $NH_2$ protons. Furthermore, compound **27** also was used as starting compound for synthesizing other pyrido[2,3-*d*]pyrimidine derivative **28** and Spiro compound **30**. Thus, treatment of **27** with 4-chlorobenzaldehyde in acetic acid or in ethanol containing a few drops of concentrated hydrochloric acid [28], under reflux afforded the tetrahydropyridopyrimidine derivative **28**. Also refluxing of **27** with 1*H*-indene-1,3(2*H*)-dione under the same conditions afforded the corresponding spiro [28], compound **30** rather than the Schiff's base **29**. The $^1$H-NMR of the product revealed the signals of two NH protons at δ = 10, 10.4 ppm and absence of any signals may be attributed to the $NH_2$ protons (see Scheme 5 and Experimental section).

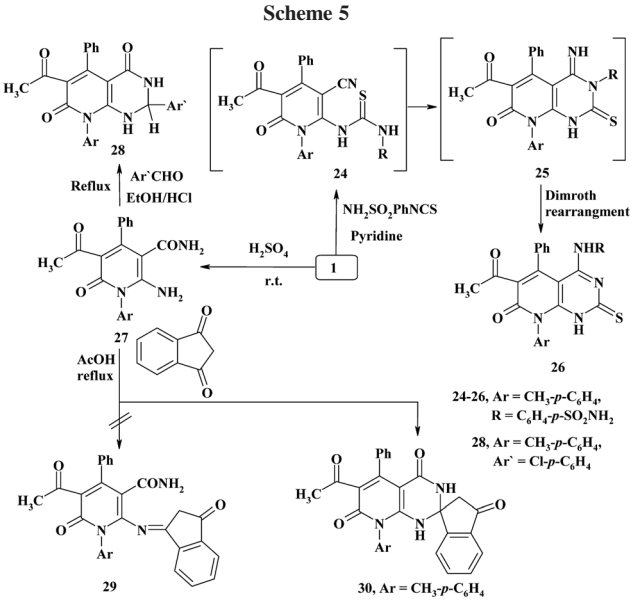
The reactivity of the aminonitrile derivative **1** toward the halogenated compounds was investigated. Thus, treatment of compound **1** with halogenated compounds such as chloroacetanilide and phenacylbromide derivatives using ethanolic sodium ethoxide afforded the corresponding pyrrolo[2,3-*b*]pyridine derivatives **32** and **34**, respectively, through the alkylation of the $NH_2$ group in **1** which leading to the N-alkylated intermediates **31** and **33**, respectively. The intermediates **31** and **33** were cyclized under the applied reaction condition to give the final reaction products **32** and **34**, respectively. The structural assignment is based on analytical and spectral data (see Scheme 6 and Experimental section).

Treatment of **1** with hydrazine hydrate under reflux resulted the formation of either the pyrazolopyridine structure **35** or **36**. The structure **35** was confirmed for

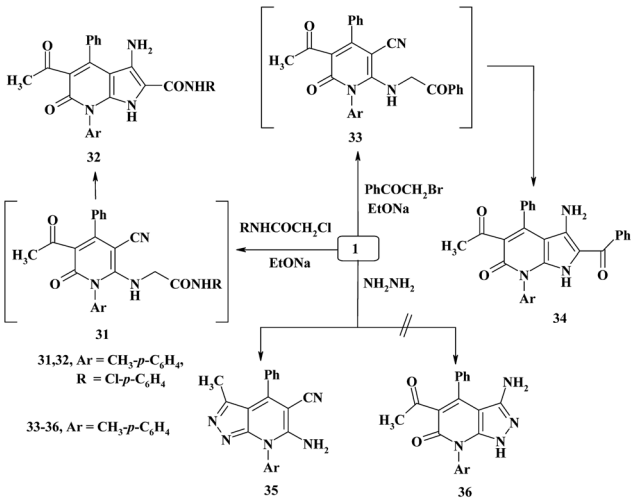
**Scheme 4**




**Scheme 5**



**Scheme 6**




the reaction product based on elemental analysis and spectral data. The IR spectrum of the reaction product revealed the absorption band of CN at 2208 $cm^{-1}$ and absence of any absorption bands may be attributed to the CO functions. Moreover, no signals were detected in the $^1$H-NMR spectrum that may be attributed to NH proton. Based on the above data, the structure **36** was ruled out (Scheme 6).

## EXPERIMENTAL

Melting points were measured with a Gallenkamp apparatus and are uncorrected. IR spectra in KBr discs were recorded on BRUKER Vector 22 FTIR spectrophotometer. $^1$H-NMR spectra were determined in DMSO-$d_6$ at 300 MHz on Varian Mercury VX spectrometer using TMS as an internal standard. Chemical shifts are expressed as δ ppm and *J* as Hz units. Elemental analyses were carried out at the Microanalytical Center of Cairo University.

**5-Acetyl-2-amino-1-(4-methylphenyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carbonitrile (1).** To a solution of *N*-(4-methylphenyl)-3-oxobutanamide (0.01 mol) in ethanol (40 mL) containing a catalytic amount of peperidine (0.5 mL), benzylidenemalononitrile (0.01 mol) was added. The reaction mixture was heated under reflux for 6 h. The solid product so formed on cooling was collected by filtration to give compound **1** as yellow crystals from ethanol (80%), m.p. 202°C, IR(KBr) ν $cm^{-1}$: 3230, 3210 ($NH_2$), 2190 (CN), 1696, 1648 (2 C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.20 (s, 3H, $CH_3$), 2.39 (s, 3H, $CH_3$), 5.98 (s, 2H, $NH_2$), 7.29–7.46 (m, 9H, Ar-H). Anal., for $C_{21}H_{17}N_3O_2$ (343.39), Calcd.: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.25; H, 4.73; N, 12.00%.

**6-Acetyl-2,4-diamino-8-(4-methylphenyl)-7-oxo-5-phenyl-7,8-dihydro-1,8-naphthyridine-3-carbonitrile (3).** A mixture of compound **1** (0.01 mol) and malononitrile (0.01 mol) in DMF (20 mL) containing piperidine (1.0 mL) was refluxed for 3 h. The reaction was left to cool at room temperature, and then poured onto ice-cold water. The solid product, so formed, was collected by filtration and recrystallization from ethanol to give **3** as yellow crystals (78%), m.p. 127°C, IR(KBr) ν $cm^{-1}$: 3433, 3223 (Two $NH_2$), 2207 (CN), 1690, 1640 (2 C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.35 (s, 3H, $CH_3$), 2.49 (s, 3H, $CH_3$), 4.98 (s, 2H, $NH_2$), 7.29–7.46 (m, 9H, Ar-H), 8.60 (br, 2H, $NH_2$). Anal., for $C_{24}H_{19}N_5O_2$ (409.45), calcd.: C, 70.40; H, 4.68; N, 17.10. Found: C, 70.62; H, 4.83; N, 17.30%.

**6-Acetyl-4-amino-8-(4-methylphenyl)-2,7-dioxo-5-phenyl-1,2,7,8-tetrahydro-1,8-naphthyridine-3-carbonitrile (5).** A solution of **1** (0.01 mol) and ethyl cyanoacetate (0.01 mol) in acetic acid (20 mL) was heated under reflux for 2 h. The solid formed during refluxing was collected by filtration, washed well with methanol, and recrystallized from ethanol to give **5** as brown crystals (62%), m.p. 132°C, IR(KBr) ν $cm^{-1}$: 3438, 3412 ($NH_2$), 3261 (NH), 2182 (CN), 1722, 1710, 1633 (3C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.21 (s, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$), 5.92 (s, 2H, $NH_2$), 7.08–7.44 (m, 9H, Ar-H) and 10.2 (s, 1H, NH). Anal., for $C_{24}H_{18}N_4O_3$ (410.42), calcd.: C, 70.23; H, 4.42; N, 13.65. Found: C, 70.34; H, 4.60; N, 13.88%.

**6-Acetyl-4-amino-8-(4-methylphenyl)-7-oxo-2,5-diphenyl-7,8-dihydro-1,8-naphthyridine-3-carbonitrile (8).** A mixture of compound **1** (0.01 mol) and benzylidenemalononitrile (0.01 mol) in DMF (20 mL) containing piperidine (1.0 mL) was refluxed for 5 h. The reaction was left to cool at room temperature, then poured onto cold water, the solid product, so formed, was collected by filtration and recrystallization from dioxan to give **8** as brown crystals (63%), m.p. 192°C, IR(KBr) ν $cm^{-1}$: 3426, 3320 ($NH_2$), 2186 (CN), 1712, 1629 (2 C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 1.90 (s, 3H, $CH_3$), 2.35(s, 3H, $CH_3$), 5.85 (s, 2H, $NH_2$), 7.09–7.50 (m, 14H, Ar-H). Anal., for $C_{30}H_{22}N_4O_2$ (470.52), calcd.: C, 76.58; H, 4.71; N, 11.91. Found: C, 76.70; H, 4.96; N, 11.75%.

**Synthesis of [1,8]naphthyridine-3-carboxylic acid derivatives 11 and 14.** A mixture of compound **1** (0.01 mol) and each of diethyl malonate and ethyl acetoacetate (0.01 mol) in DMF (20 mL) containing piperidine (1.0 mL) was heated under reflux for 5 h. The reaction was left to cool at room temperature, then poured onto cold water and acidified with dilute HCl, the solid product, so formed, was collected by filtration and recrystallization from ethanol to give **11** and **14**, respectively.

***6-Acetyl-4-amino-8-(4-methylphenyl)-2,7-dioxo-5-phenyl-1,2,7,8-tetra-hydro-1,8-naphthyridine-3-carboxylic acid (11).*** Yellow crystals from ethanol (58%), m.p. 140°C, IR(KBr) ν $cm^{-1}$: 3441, 3284 ($NH_2$), 3210 (NH), 3398–2382 (br. OH), 1710, 1699, 1661, and 1633 (4 C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.15 (s, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 5.92 (s, 2H, $NH_2$), 6.75–7.37 (m, 9H, Ar-H), 10.43 (s, 1H, NH) and 14.33 (s, 1H, OH). Anal., for $C_{24}H_{19}N_3O_5$ (429.42) calcd.: C, 67.13; H, 4.46; N, 9.79. Found: C, 67.34; H, 4.70; N, 9.50%.

***6-Acetyl-4-amino-2,methyl-8-(4-methylphenyl)-7-oxo-5-phenyl-7,8-dihydro-1,8-naphthyridine-3-carboxylic acid (14).*** Yellow crystals from ethanol (53%), m.p.160°C, IR(KBr) ν $cm^{-1}$: 3441, 3284 ($NH_2$), 3400–2500 (br. OH), 1705, 1698, and 1632 (3 C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.27 (s, 3H, $CH_3$), 2.35 (s, 3H, $CH_3$), 5.91 (s, 2H, $NH_2$), 6.80-7.55 (m, 9H, Ar-H) and 14.42 (s, 1H, OH). Anal., for $C_{25}H_{21}N_3O_4$ (427.45) calcd.: C, 70.25; H, 4.95; N, 9.83. Found: C, 70.53; H, 4.70; N, 9.66%.

**Synthesis of pyridonaphthyridine derivatives 17, 18, and 19.** A mixture of each of compounds **3**, **5**, or **8** (0.01 mol) and malononitrile (0.01 mol) in DMF (20 mL) containing piperidine (1.0 mL) was refluxed for 5 h. The reaction was left to cool at room temperature, then poured onto cold water, the solid product, so formed, was collected by filtration and recrystallization from benzene to give **17**, **18**, and **19**, respectively.

***7-Acetyl-2,4,5-triamino-9-(4-methylphenyl)-8-oxo-6-phenyl-8,9-dihydropyrido[2,3-b][1,8]naphthyridine-3-carbonitrile (17).*** Yellow crystals from benzene (50%), m.p.110°C, IR(KBr) ν $cm^{-1}$:

3441, 3406, 3330 ($3NH_2$), 2208 (CN), 1698, and 1654 (2 C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.22 (s, 3H, $CH_3$), 2.38 (s, 3H, $CH_3$), 4.11 (s, 2H, $NH_2$), 4.25 (s, 2H, $NH_2$), 6.70 (s, 2H, $NH_2$) and 7.03–7.62 (m, 9H, Ar-H). Anal., for $C_{27}H_{21}N_7O_2$ (475.50) calcd.: C, 68.20; H, 4.45; N, 20.62. Found: C, 68.30; H, 4.70; N, 20.35%.

***9-Acetyl-2,4-diamino-7-(4-methylphenyl)-5,8-dioxo-10-phenyl-5,6,7,8-tetrahydropyrido[2,3-h][1,6]naphthyridine-3-carbonitrile (18).*** Yellow crystals from benzene (55%), m.p.121°C, IR(KBr) ν cm$^{-1}$: 3441, 3352, 3289 ($2NH_2$), 3205 (NH), 2209 (CN), 1694, 1658 (2 C=O), and 1632 (C=O with H-bonded). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.27 (s, 3H, $CH_3$), 2.33 (s, 3H, $CH_3$), 4.25 (s, 2H, $NH_2$), 4.65 (s, 2H, $NH_2$), 6.90–7.57 (m, 9H, Ar-H) and 10.43 (s, 1H, NH). Anal., for $C_{27}H_{20}N_6O_3$ (476.48) calcd.: C, 68.06; H, 4.23; N, 17.64. Found: C, 68.30; H, 4.60; N,17.40%.

***9-Acetyl-2,4-diamino-7-(4-methylphenyl)-5-phenyl-8-oxo-10-phenyl-7,8-dihydropyrido[2,3-h][1,6]naphthyridine-3-carbonitrile (19).*** Yellow crystals from benzene (59%), m.p. 100°C, IR(KBr) ν cm$^{-1}$: 3450, 3381, 3343 ($2NH_2$), 2205 (CN) and 1685, 1661 (2 C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.23 (s, 3H, $CH_3$), 2.37 (s, 3H, $CH_3$), 4.26 (s, 2H, $NH_2$), 4.43 (s, 2H, $NH_2$) and 6.75-7.69 (m, 14H, Ar-H). Anal., for $C_{33}H_{24}N_6O_2$ (536.58) calcd.: C, 73.87; H, 4.51; N, 15.66. Found: C, 73.60; H, 4.80; N, 15.40%.

**Reaction of 1 with formic acid or acetic anhydride.** A mixture of compound **1** (0.01 mol) and each of formic acid or acetic anhydride (20 mL) was heated under reflux for 6 h and then cooled. The solid products thus formed were collected and recrystallized from ethanol to give **20a**,**b**, respectively.

***6-Acetyl-8-(4-methylphenyl)-5-phenylpyrido[2,3-d]pyrimidine-4,7(3H,8H)-dione (20a).*** Yellow crystals from ethanol (66%), m.p. 200–202°C, IR(KBr) ν cm$^{-1}$: 3210 (NH), 1711, 1670, 1630 (3 C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.02 (s, 3H, $CH_3$), 2.36 (s, 3H, $CH_3$), 7.11–7.43 (m, 9H, Ar-H), 7.47 (s, 1H, CH-pyrimidine) and 14.08 (s, 1H, NH). Anal., for $C_{22}H_{17}N_3O_3$ (371.38) calcd.: C, 71.15; H, 4.61; N, 11.31. Found: C, 71.40; H, 4.80; N, 11.50%.

***6-Acetyl-2-methyl-8-(4-methylphenyl)-5-phenylpyrido[2,3d]-pyrimidine-4,7(3H,8H)-dione (20b).*** White crystals from ethanol (55%), m.p. 230–232°C, IR(KBr) ν cm$^{-1}$: 3360 (NH), 1740, 1680, 1635 (3 C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.18 (s, 3H, $CH_3$), 2.22 (s, 3H, $CH_3$), 2.31 (s, 3H, $CH_3$), 6.99–7.36 (m, 9H, Ar-H), 12.47 (s, 1H, NH). Anal., for $C_{23}H_{19}N_3O_3$ (385.43) calcd.: C, 71.68; H, 4.97; N, 10.90. Found: C, 71.90; H, 4.75; N, 10.70%.

***6-Acetyl-4-amino-8-(4-methylphenyl)-5-phenylpyrido[2,3-d]-pyrimidin-7(8H)-one (21).*** Compound **1** (0.01 mol) in formamide (10 mL) was heated under reflux for 6 h and left to cool. The crystalline product thus formed was filtered, washed with ether, and recrystallized from dioxane to give **21** as white crystals (59%), m.p. 122°C, IR(KBr) ν cm$^{-1}$: 3300, 3185 ($NH_2$), 1700, 1625 (2 C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 1.28 (s, 3H, $CH_3$), 2.24 (s, 3H, $CH_3$), 5.00 (s, 2H, $NH_2$), 7.09–7.44 (m, 9H, Ar-H) and 8.39 (s, 1H, CH-pyrimidine). Anal., for $C_{22}H_{18}N_4O_2$ (370.40) calcd.: C, 71.34; H, 4.90; N, 15.13. Found: C, 71.60; H, 4.68; N, 15.30%.

**Reaction of 1 with urea and thiourea.** To a solution of sodium ethoxide (prepared from 0.5 gm of sodium and 50 mL of absolute ethanol), compound **1** (0.01 mol) and urea or thiourea (0.01 mol) were added. The reaction mixture was refluxed for 6 h and then cooled and neutralizing with HCl, a solid formed, which was collected by filtration, washed with water, and recrystallized from ethanol to give **22a**,**b**, respectively.

***7-Amino-4-methyl-8-(4-methylphenyl)-2-oxo-5-phenyl-2,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile (22a).*** Brown crystals from ethanol (65%), m.p. 142°C, IR(KBr) ν cm$^{-1}$: 3390, 3270 ($NH_2$), 2211 (CN), 1680 (C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.38 (s, 3H, $CH_3$), 2.49 (s, 3H, $CH_3$), 7.07–7.39 (m, 9H, Ar-H), 10.0 (s, 2H, $NH_2$). Anal., for $C_{22}H_{17}N_5O$ (367.40) calcd.: C, 71.92; H, 4.66; N, 19.06. Found: C, 71.70; H, 4.80; N, 19.30%.

***7-Amino-4-methyl-8-(4-methylphenyl)-5-phenyl-2-thioxo-2,8-dihydropyrido[2,3-d]pyrimidine-6-carbonitrile (22b).*** Brown crystals from ethanol (60%), m.p. 170°C, IR(KBr) ν cm$^{-1}$: 3326, 3229 ($NH_2$), 2209 (CN). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.19 (s, 3H, $CH_3$), 2.23 (s, 3H, $CH_3$), 6.98 (s, 2H, $NH_2$), 7.16–7.57 (m, 9H, Ar-H). Anal., for $C_{22}H_{17}N_5S$ (383.64) calcd.: C, 68.61; H, 4.47; N, 18.26; S, 8.36. Found: C, 68.70; H, 4.63; N, 18.49; S, 8.61%.

***4-[(6-Acetyl-8-(4-methylphenyl)-7-oxo-5-phenyl-2-thioxo-1,2,7,8-tetrahydropyrido[2,3-d]pyrimidin-4-yl)amino]benzene-sulfonamide (26).*** A mixture of compound **1** (0.01 mol) and isothiocyanatosulfonamide (0.01 mol) in pyridine (15 mL) was refluxed for 8 h. The reaction mixture was cooled, poured onto water, and neutralized with diluted HCl. The resulting solid was recrystallized from ethanol to give **26** as yellow crystals (60%), m.p. 134°C, IR(KBr) ν cm$^{-1}$: 3410, 3314 ($NH_2$), 3210, 3130 (2NH), 1721, 1696 (2C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.06 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$), 4.09 (s, 2H, $NH_2$), 7.01–7.46 (m, 13H, Ar-H), 12.47 (s, 1H, NH), 14.42 (s, 1H, NH). Anal., for $C_{28}H_{23}N_5O_4S_2$ (557.64) calcd.: C, 60.31; H, 4.16; N, 12.56; S, 11.50. Found: C, 60.50; H, 4.40; N, 12.80; S, 11.25%.

***5-Acetyl-2-amino-1-(4-methylphenyl)-6-oxo-4-phenyl-1,6-dihydropyridine-3-carboxamide (27).*** Compound **1** (0.01 mol) in concentrated $H_2SO_4$ (15 mL) was stirred at room temperature for 1 h and then diluted by water (100 mL). The solid product thus formed was collected and recrystallized from ethanol to give **27** as white crystals (58%), m.p. 220–222°C, IR(KBr) ν cm$^{-1}$: 3382, 3222 (broad, $2NH_2$), 1752, 1716, 1654 (3C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.33 (s, 3H, $CH_3$), 2.49 (s, 3H, $CH_3$), 5.77 (s, 2H, $NH_2$), 6.91–7.54 (m, 9H, Ar-H), 10.91 (s, 2H, $NH_2$). Anal., for $C_{21}H_{19}N_3O_3$ (369.31) calcd.: C, 69.79; H, 5.30; N, 11.63 Found: C, 69.58; H, 5.51; N, 11.90%.

**Reactions of compound 27 with carbonyl compounds.** A mixture of compound **27** (0.01 mol) and each of 4-chlorobenzaldehyde or 1*H*-indene-1,3(2*H*)-dione (0.01 mol) in glacial acetic acid (20 mL) or in ethanol (20 mL) containing a few drops of concentrated hydrochloric acid was heated at reflux for 3 h. The products were collected and recrystallized from ethanol to give **28** and **30**, respectively.

***6-Acetyl-2-(4-chlorophenyl)-8-(4-methylphenyl)-5-phenyl-2,3-dihydropyrido[2,3-d]pyrimidine-4,7(1H,8H)-dione (28).*** Yellow crystals from ethanol (64%), m.p. 131°C, IR(KBr) ν cm$^{-1}$: 3390, 3200 (2NH), 1703, 1680, 1650 (3C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.10 (s, 3H, $CH_3$), 2.34 (s, 3H, $CH_3$), 6.80 (s, 1H, CH-pyrimidine), 7.02–7.46 (m, 13H, Ar-H) 10.0 (s, 1H, NH), 10.40 (s, 1H, NH). Anal., for $C_{28}H_{22}N_3O_3Cl$ (483.94) calcd.: C, 69.49; H, 4.58; N, 8.68; Cl, 7.33. Found: C, 69.70; H, 4.41; N, 8.97; Cl, 7.56%.

***6-Acetyl-8-(4-methylphenyl)-5-phenyl-2,3-dihydrospiro[indan-1′-one-4,3′-pyrido[2,3-d]pyrimidine-4,7(1H,8H)-dione] (30).*** Yellow crystals from ethanol (67%), m.p. 167°C, IR(KBr) ν cm$^{-1}$: 3230, 3120 (2NH), 1710, 1685 (4C=O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.33 (s, 3H, $CH_3$), 2.49 (s, 3H, $CH_3$), 4.20 (s, 2H, $CH_2$), 6.91 (s, 1H, NH), 7.08–7.40 (m, 13H, Ar-H)

7.93 (s, 1H, NH). Anal., for $C_{30}H_{23}N_3O_4$ (489.54); calcd.: C, 73.61; H, 4.74; N, 8.58. Found: C, 73.95; H, 4.52; N, 8.78%.

**Synthesis of the pyrrolo[2,3-*b*]pyridine derivatives 32 and 34.** A mixture of compound **1** (0.01 mol), and each of 2-chloro-*N*-(4-chlorophenyl)acetamide or 2-bromo-1-phenylethanone (0.01 mol), and sodium ethoxide (0.01 mL) in absolute ethanol (30 mL) was heated under reflux for 6 h and then allowed to cool, poured into cold water, and neutralized with diluted HCl. The resulting solid products were collected and recrystallized from ethanol to give **32** and **34**, respectively.

***5-Acetyl-3-amino-N-(4-chlorophenyl)-7-(4-methylphenyl)-6-oxo-4-phenyl-6,7-dihydro-1H-pyrrolo[2,3-b]pyridine-2-carboxamide (32).*** Brown crystals from ethanol (66%), m.p. 195°C, IR(KBr) ν $cm^{-1}$: 3354, 3320, 3217 ($NH_2$, 2NH), 1692, 1646 (2C═O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.24 (s, 3H, $CH_3$), 2.49 (s, 3H, $CH_3$), 3.90 (s, 2H, $NH_2$), 7.07–7.39 (m, 13H, Ar-H), 8.60 (s, 1H, NH), 9.98 (s, 1H, NH). Anal., for $C_{29}H_{23}N_4O_3Cl$ (510.97); calcd.: C, 68.17; H, 4.54; N, 10.96; Cl, 6.94. Found: C, 68.40; H, 4.80; N, 10.70; Cl, 6.73%.

***5-Acetyl-3-amino-2-benzoyl-7-(4-methylphenyl)-4-phenyl-1,7-di-hydro-6H-pyrrolo[2,3-b]pyridin-6-one (34).*** Brown crystals from ethanol (66%), m.p. 145°C, IR(KBr) ν $cm^{-1}$: 3373, 3323, 3215 ($NH_2$ and NH), 1710, 1701, 1635 (3C═O). $^1$H-NMR (DMSO-$d_6$) δ ppm: 1.90 (s, 3H, $CH_3$), 2.25 (s, 3H, $CH_3$), 5.85 (s, 2H, $NH_2$), 7.01–7.69 (m, 14H, Ar-H), 9.58 (s, 1H, NH). Anal., for $C_{29}H_{23}N_3O_3$ (461.51) calcd.: C, 75.47; H, 5.02; N, 9.10. Found: C, 75.65; H, 5.28; N, 9.32%.

***6-Amino-3-methyl-7-(4-methylphenyl)-4-phenyl-7H-pyrazolo-[3,4-b]-pyridine-5-carbonitrile (35).*** A solution of **1** (0.01 mol) in hydrazine hydrate (20 mL) was heated under reflux for 7 h. The reaction mixture was evaporated under vacuum. The solid product thus formed was collected and recrystallized from ethanol to give **35** as yellow crystals (58%), m.p. 200–202°C, IR(KBr) ν $cm^{-1}$: 3340, 3235 ($NH_2$), 2208 (CN). $^1$H-NMR (DMSO-$d_6$) δ ppm: 2.02 (s, 3H, $CH_3$), 2.20 (s, 3H, $CH_3$), 6.90 (s, 2H, $NH_2$), 7.01–7.48 (m, 9H, Ar-H). Anal., for $C_{21}H_{17}N_5$ (339.39) calcd.: C, 74.32; H, 5.05; N, 20.63 Found: C, 74.55; H, 5.26; N, 20.40%.

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