The Use of 2-Chloro-4*H*-4-oxo-pyrido[1,2-a]pyrimidine as a Building Block in the Synthesis of Some New Heterocyclic Compounds

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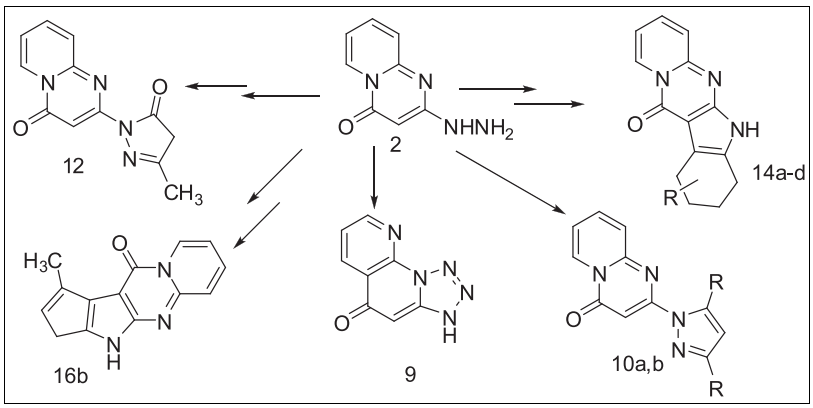

New approaches for the synthesis of some heterocyclic compounds, such as the pyridopyrimidodiazepine derivative **3,** pyrazolopyrido[1,2-a]pyrimidine derivative **4**, tetrazolo[1.5-a][1,8]naphthyridine derivative **9**, pyrazolylpyrido[1,2-a]pyrimidine derivatives **10a,b,12**, pyrrolopyrido[1,2-a]pyrimidine derivatives **14a-d**, and**16a,b,** starting from 2-chloro-4*H*-4-oxo-pyrido[1,2-a]pyrimidine (**1**), are described.

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INTRODUCTION

The pyridopyrimidines are the most important and investigated compounds among the family of the pyridodiazines. These compounds have found many applications due to their medicinal properties such as antibacterial [1], antiallergic [2], inhibitor of enzyme adenosine kinase [3], or dihydrofolate reductase [4], and irreversible inhibitor of epidermal growth factor receptor [5]. In addition, many hetero-fused pyrimidines exhibit attractive cancer chemotherapy properties as antitumor agents [6]. Risperidone, SSR6907, and ramastine are derivatives of pyrido[1,2-a]pyrimidin-4-one, which show antipsychotic activity [7–9]. Dominguez *et al.* [10] reported that some hetero-fused tricyclic systems exhibited significant antimalarial activity. It was cited that the biological reactivity of this category of these compounds is essentially due to presence of the pyrido[1,2-a]pyrimidinone moiety in their molecular structure [11]. Prompted with these investigations, our strategy aimed at developing new approaches for the synthesis of some new heterocyclic compounds of possible biological activity using 2-chloro-4*H*-4-oxo- pyrido[1,2-a] pyrimidine (**1**) as a building block.

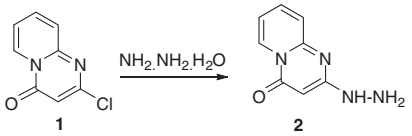
RESULTS AND DISCUSSION

The starting 2-chloro-4*H*-4-oxo-pyrido[1,2-a]pyrimidine (**1**) was prepared following the corresponding literature procedure [12]. It is well known that this type of α-haloheterocyclic compounds are susceptible to synthetically important nucleophilic substitution [13–16]. Thus, treatment of compound **1** with hydrazine hydrate in hot ethanol afforded 2-hydrazinyl-4*H*-pyrido[1,2-a] pyrimdin-4-one (**2**) [17,18] as shown in Scheme 1.

Treatment of **2** with excess of benzalmalononitrile, prepared by Knoevenagel condensation [19], in dry dimethylformamid at 125–130°C for 2 h gives access to the pyridopyrimidodiazepine derivative **3**, or pyrazoloprido [1,2-a]pyrimidine derivative **4** [20] (Scheme 2).

The elemental analysis and spectral data of the isolated product are in consistent with the pyridopyrimidodiazepene structure **3**. Its IR spectrum showed absorption bands at 3430, 3382, 3168 cm^{-1} for (NH_2, NH) groups, and 2217 cm^{-1} for (CN) group. The ^{1}H-NMR revealed signals at δ = 2.45, 3.25 ppm integrated for C4-H, C5-H, a singlet at 6.27 ppm attributed to NH_2, a multiplet at 7.08–8.13 ppm assigned to (Ar-H, NH), and a doublet at 9.11 ppm attributed to C-6 proton The mass spectrum showed a molecular ion peak [M^+] at *m*/*z* = 330 which was in agreement with its molecular weight. However, on heating the pyridopyrimidodiazepine derivative **3** with 1*N* HCl above 90°C for about 6 h, 3-phenylpyrazolo[3,4-d] pyrido[1,2-a]pyrimidin-4(1*H*)-one (**4**) was formed in low yield (30%). The IR spectrum showed absorption bands at 3257 for (NH) group, 1652 due to (C O) group, and

Scheme 1

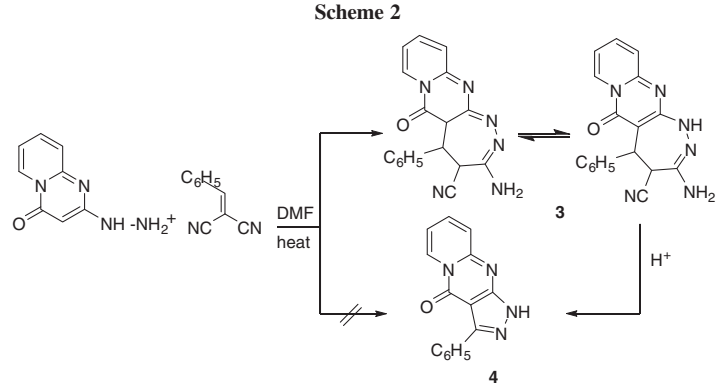


1627 cm^{-1} for (C N) group. The ^{1}H-NMR revealed signals at δ = 7.27–7.99 ppm assigned to (Ar-H, NH) and a doublet at 9.11 ppm attributed to C-6 proton. The mass spectrum showed a molecular ion peak [M^+] at *m*/*z* = 262 which was in agreement with its molecular weight.

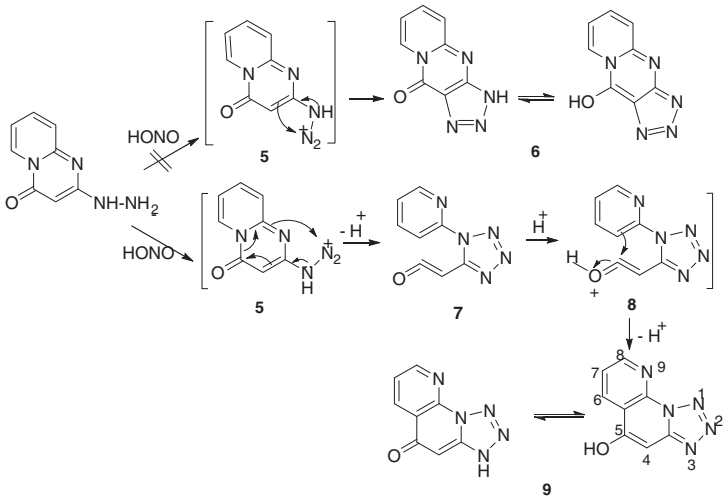
Interaction of **2** with sodium nitrite in acetic acid under cooling (0–5°C) afforded a single product (thin layer chromatography; TLC analysis) for which two possible structures has been assumed as shown in Scheme 3, wherein the initially formed intermediate **5** can undergo intramolecular cyclization *via* electrophilic attack either at C-3 to give the triazolopyrido[1,2-a]pyrimidine derivative **6** or at N-1 [21] followed by pyrimidine ring cleavage [22], which leads to the tetrazolo[1,8]naphthyridine derivative **9** *via* carbonyl ketene intermediates **7**,**8** [23]. The IR spectrum of the product displayed an intense absorption band at 3122 cm^{-1} for (NH) group and mass spectrum of the reaction product revealed a molecular ion peak [M^+] at *m*/*z* = 187 which was in consistent with the molecular weight of both 6 and 9. However, the ^{1}H-NMR spectrum which revealed a singlet at δ = 5.98 ppm assigned to olifenic proton at C-4 and ^{13}C-NMR spectrum which showed a signal at δ = 90.98 ppm assigned to (C-4), and a signal at δ = 159.63 ppm attributed to (C-5) attached to enolic OH of the naphthyridine derivative, supported structure **9**, and the other possible structure 6 was ruled out.

Then, we aimed to incorporate a fused pyrido[1,2-a] pyrimidine moiety into the 1-position of the pyrazole ring system to obtain new compounds which could be expected to possess notable biological activity. This could be readily achieved by the reaction of **2** with various 1,3-dicarbonyl compounds. Thus, compound **2** was reacted with acetylacetone in ethanol under reflux for 2 h to give 2-(3,5-dimethyl-1*H*-pyrazo-1-yl)-4*H*-pyrido[1,2-a]pyrimidin-4-one (**10a**) (Scheme 4).

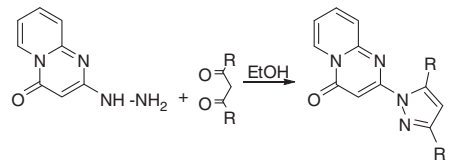
Scheme 2



Scheme 3

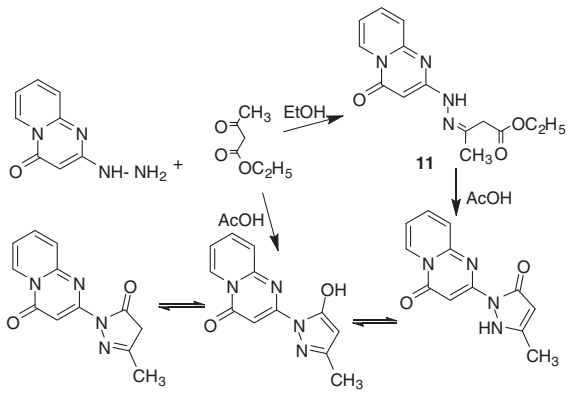


Scheme 4



10a, R = CH3
10b, R = ph

Scheme 5



The structure of **10a** was supported by elemental analysis and spectral data. The IR spectrum exhibited absorption bands at 3072 cm^{-1} for aromatic (CH), 2923 cm^{-1} for aliphatic (CH_3), 1676 cm^{-1} for (C O) group, and 1631 cm^{-1} for (C N) group. The ^{1}H-NMR spectrum revealed two signals at δ = 2.3 and 2.7 ppm integrated for the two methyl protons, two singlets at 6.01 and 6.98 ppm assigned to C3-H of the pyrido[1,2-a]pyrimidine moiety, C4-H of the pyrazole ring, other signals at 7.12–7.75 ppm attributed to three aromatic protons and a doublet at 9.04 ppm assigned to C6-H. The mass spectrum gave a molecular ion peak [M^+ + 1] at *m*/*z* = 241.

Similarly, **2** was reacted with 1,3-diphenylpropane-1,3-dione in ethanol to give 2-(3,5-diphenyl-1*H*-pyrazo-1-yl)-4*H*-pyrido[1,2-a]pyrimidin-4-one (**10b**). The IR spectrum of compound **10b** showed absorption bands at 1683 cm^{-1} characteristic for (C O) group and 1631 cm^{-1} characteristic for (C N) group. The ^{1}H-NMR spectrum revealed signals at δ = 6.19 (s, 1H, C3-H), 7.07–7.97 (m, 14 Ar-H), 8.94 ppm (d, 1H, *J* = 6 Hz, C6-H). The mass spectrum gave a molecular ion peak [M^+] at *m*/*z* = 364 which was in agreement with its molecular weight.

In the case of ethylacetoacetate, when the reaction was carried out in ethanol, ethyl 3-(2-(4-oxo-4*H*-pyrido[1,2a] pyrimidin-2-yl)hydrazonobutonoate (**11**) was obtained. The structure of **11** was established based on the elemental analysis and spectral data. The IR spectrum displayed absorption bands at 3119 cm^{-1} for (NH) group, 1711 cm^{-1} due to (C O ester) group, 1691 cm^{-1} for (C O) group. The ^{1}H-NMR revealed a triplet and a singlet at δ = 1.30 and 2.02 ppm assigned to the two methyl protons, a quartet at δ = 4.20 ppm integrated for the CH_2 protons, and a singlet at δ = 6.27 ppm attributed to the C-3 proton, and a broad doublet at δ = 8.20 ppm assigned to the NH proton. The mass spectrum gave a molecular ion peak [M^+ + 1] at *m*/*z* = 289.

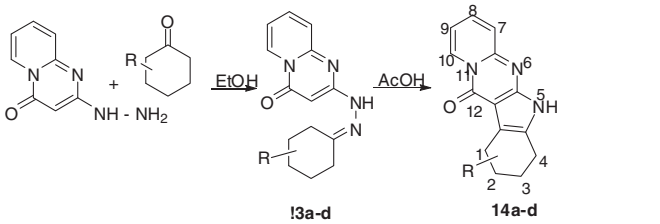
On the other hand, when the reaction was performed in acetic acid, 2-(3-methyl-5-oxo-2,5-dihydro-1*H*-pyrazol-1-yl)-4*H*-pyrido[1,2-a]pyrimidin-4-one (**12**) was produced. Compound **12** was also obtained on treatment of compound **11** with acetic acid as shown in Scheme 5.

The structure of **12** was fully characterized by spectral and elemental analyses. The IR spectrum exhibited absorption bands at 3434, 3122 cm^{-1} for (NH, enolic OH) groups, 2926, 2857 cm^{-1} for (CH_2, H_3) groups, and 1685 cm^{-1} for (C O) group. The ^{1}H-NMR revealed a singlet at δ = 2.26 ppm integrated for the methyl protons, a broad singlet at δ = 5.98 ppm assigned to the C-3 proton of the pyridopyrimidine moiety, a multiplet at 6.85–7.89 ppm integrated for (aromatic protons, NH), and a broad signal at δ = 9.12 ppm assigned to the C-6 proton. The mass spectrum showed a molecular ion peak [M^+] at *m*/*z* = 243.

In continuation of our investigation on the preparation of new pyrido[1,2-a]pyrimidines of potential biological interest, it was thought to be interesting to synthesize compounds containing the features namely, having pyrido [1,2-a]pyrimidine moiety fused with the pyrrole rings. Attempts to prepare pyrido[1,2-a] pyrrolopyrimidines by analogy to the Fisher indole synthesis [24] were explored by treating the hydrazones of **2**, prepared by condensation of **2** with various ketones, with acids such as polyphosphoric acid or acetic acid.

To obtain polyheterocyclic compounds, our investigation started from alicyclic ketones as precursors for the preparation of hydrazones. So, **2** was reacted with cyclohexanone, 4-methylcyclohexanone, 4-*tert*-butylcyclohexanone, or 4-cyclohexylcyclohexanone in refluxing ethanol to afford the corresponding hydrazones **13a–d**. The formed hydrazones **13a–d** were then treated with acetic acid at reflux for 4 h to provide the pyrido[1,2-a] pyrrolopyrimidine derivatives **14a–d** (Scheme 6). Their structures were assigned on the basis of elemental and spectral data. As an example, the IR spectrum showed absorption bands at 3217 (NH), 2933, 2857 (CH_2, aliphatic), 1658 (C O), and 1630 cm^{-1} (C N) groups, and the mass spectrum gave a molecular ion peak [M^+] at ms: *m*/*z* 256 (M^+) for compound **13a**, and absorption bands at 3217 cm^{-1} (NH) group, 2931, 2857 cm^{-1} for (CH_2) group, 1655 cm^{-1} due to (C O) group. ^{1}H-NMR revealed the disappearance of the signal assigned to C3-H of the pyridopyrimidine moiety, and the mass spectrum gave a molecular ion peak [M^{+1}] at *m*/*z* = 243 for compound **14a**.

Scheme 6



13a R = H
13b R = 4- CH3
13c R = t-butyl
13d R = 4-cyclohexyl

In a similar manner, cyclopentanone or 3-methyl-3-cyclopentenone reacted with **2** in ethanol under reflux to give the corresponding hydrazone derivatives **15a,b**, followed by treatment with acetic acid to give the pyrido [1,2-a] pyrrolo pyrimidine products **16a,b** (Scheme 7). The structures of the isolated products were fully characterized through their elemental analysis and spectral data.

EXPERIMENTAL

Infrared (IR) spectra were recorded on MATSON 5000 FTIR spectrometer with only selected absorption being recorded, absorption maxima were recorded in cm^{-1}. Nuclear magnetic resonance (^{1}H-NMR) spectra were run at ^{1}H-NMR FX90Q Varian-Gemini 200 MHz spectrometer. Spectra were taken using $CDC1_3$ or DMSO-d_6 as solvent with chemical shift quoted in part per million (ppm) using TMS as internal standard. The mass spectra (ms) were recorded using Joel TMS-DX 303 (EL. GC245) mass spectrometer. The melting points were measured in an open capillary glass with Graffin melting apparatus and were uncorrected. The purity of the synthesized compounds was tested by TLC. Microanalyses were carried out by the Microanalytical Unit, National Research Center, Dokki, Giza, Cairo, Egypt, and Spectral Analysis Unit, Chemistry Department, Mansoura University, Mansoura, Egypt.

Synthesis of 2-hydrazinyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (2). A mixture of 1.82 g (0.01 mol) of 2-chloro-4*H*-pyrido [1,2-a]pyrimidin-4-one (**1**) and hydrazine hydrate (99%, 1.5 mL) in ethanol (20 mL) was refluxed for 1 h, then the reaction mixture was filtered while hot to give the title compound (**2**) as yellow needles, yield 1.14 g (65%), mp, 238–240°C.

IR (potassium bromide): 3244, 3146 (NH, NH_2), 3055 (Ar-CH),1686 (C O), 1636 (C N) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 4.30 (brs, 2H, NH_2), 5.57 (s, 1H, C3-H), 6.94 (m, 1H), 7.16 (d, 1H, J = 3 Hz), 7.69 (m, 1H), 8.13 (s, 1H, NH), 8.67 ppm (d, 1H, J = 6 Hz); ms: m/z 176 (M^+), Anal. Calcd. for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.52; H, 4.59; N, 31.81.

Synthesis of (*E*)-3-amino-6-oxo-5-phenyl-1,4,5,6-tetrahydro-pyrido[1′,2′:1,2]pyrimido[4,5-c][1,2]diazepine-4-carbonitrile (3). A solution of 1.76 g (10 mmol) of 2-hydrazinyl-4*H*-pyrido [1,2-a]pyrimidin-4-one (**2**) and 3.08 g (20 mmol) of benzalmalononitrile in 50 mL of dry DMF was heated at 125 – 130°C for 2 h. The solvent was removed from the reaction mixture *in vacuo*, treated with water (75 mL), filtered off, and recrystallized from ethanol to give the title compound as brown powder, yield 1.52 g (87%), mp 144–146°C.

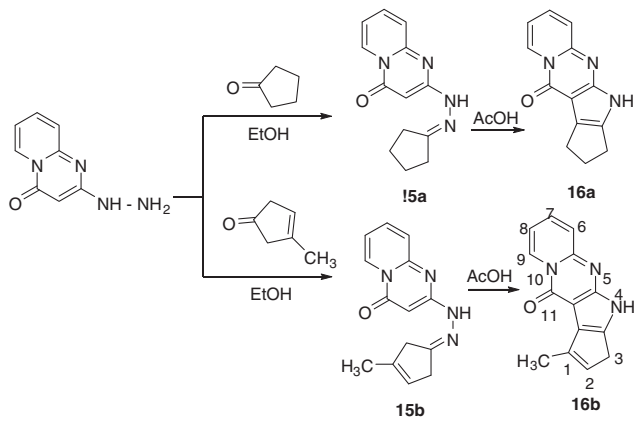
IR (potassium bromide): 3430, 3382 (NH_2), 3168 (NH), 3058 (Ar-H), 2217 (CN), 1658 (C O), 1633 (C N) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 2.45 (s, 1H, C4-H), 3.25 (s, 1H, C5-H), 6,27 (s, 2H, NH_2), 7.98–8.13 (m, 9H, Ar-H, NH), 8.82 (d, 1H, J = 6.0 Hz); ms: m/z = 330 (M^+). Anal. Calcd. for $C_{18}H_{14}N_6O$: C, 65.44; H, 4.27; N, 25.44. Found: C, 65.32; H, 4.22; N, 25.54.

Synthesis of 3-phenylpyrazolo[3,4 -d]pyrido[1,2-a]pyrimidin-4(1*H*)-one (4). A mixture of 3.30 g (0.01 mol) of compound **3** and 1*N* HCl (4 mL) in 20 mL ethanol was refluxed for 6 h. The reaction mixture was poured into crushed ice, and the formed solid was then filtered off, dried, and recrystallized from ethanol and benzene (1:1) to obtain compound **4** as yellow powder, yield 0.79 g (30%,); mp 220–223°C.

IR: (potassium bromide): 3257 (NH), 3059 (Ar-H), 1652 (C O), 1627 cm^{-1} (C N); ^{1}H-NMR (deuteriochloroform): δ 7.25–7.29 (m, 3H, Ar-H), 7.42 (br s, 2H, Ar-H), 7.71 (br d, 3H, Ar-H), 7.99 (s, 1H, NH), 9.11 (d, 1H, J = 4.2 Hz, C6-H); ms: m/z = 262 (M^+). Anal. Calcd. for $C_{15}H_{10}N_4O$: C 68.69; H, 3.84; N, 21.36; found: C, 68.64; H, 3.80, N, 21.31.

Synthesis of tetrazolo[1,5-a][1,8]naphthyridin-5(3*H*)-one (9). An aqueous solution of sodium nitrite (20%, 4.2 mL) was slowly added in portions to a stirred mixture of 1.76 g (0.01 mol) of 2-hydrazinyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (**2**) in acetic acid (40 mL) at 0–5°C. The reaction mixture was then

Scheme 7



further stirred for 2 h at the same temperature, then it was diluted with cold water, and the solid obtained was filtered off, washed with water, dried, and recrystallized from ethanol to give compound (**4**) as white powder, yield 1.25 g (67%), mp 156–158°C.

IR (potassium bromide): 3122 (NH, or enolic OH), 2237, 2159, 2059, 1698 (C O), 1627 (C N), 1565, 1114, 1139 cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 5.92 (s, 1H, C4-H), 7.15 (m, 1H), 7.56 (d, 1H, *J* = 9 Hz), 7.82 (br, 1H, enolic OH), 9.03 ppm (d, 1H, *J* = 6,9 Hz); ^{13}C-NMR (dimethyl sulfoxide$_6$) δ 90.98 (C-4), 116.23, 125, 128.17, 139.80, 151.12, 157.95, 159.63 ppm, ms: *m/z* 187 (M^+). Anal. Calcd. for $C_8H_5N_5O$: C, 51.34; H, 2.69; N, 37.42. Found: C, 51.50; H, 2.79; N, 37.22.

General procedure for the synthesis of 1H-pyrazo-1-yl-4H-pyrido[1,2-a]pyrimidine-4-one (10a,b). A mixture of 2-hydrazinyl-4*H*-pyrido[1,2-a] pyrimidin-4-one (**2**) (0.01mol) and 1,3-dicarbonyl compounds (0.01 mol) in 30-mL absolute ethanol was refluxed for 2 h. The reaction mixture was poured into crushed ice, and the formed solid was then filtered off, dried, and recrystallized from a suitable solvent to give pure compound.

2-(3,5-Dimethyl-1H-pyrazol-1-yl)-4H-pyrido[1,2-a]pyrimidin-4-one (10a). Recrystallized from ethanol as white crystals, yield 1.60 g (67%). mp, 202–204°C. IR (potassium bromide): 3072 (Ar-H),2923 (CH_3), 1676 (C O), 1631 (C N) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 2.29 (s, 3H, CH_3), 2.71 (s, 3H, CH_3), 6.01 (s, 1H, C3-H, pyrido[1,2-a]pyrimidine moiety), 6.98 (s, 1H, C4-H, pyrazole ring), 7.12 (m, 1H), 7.55 (d, 1H, *J* = 8.8 Hz), 7.75 (m, 1H), 9.04 ppm (d, 1H, *J* = 7.4 Hz, C6-H). ms: *m/z* 241 (M^+ + 1). Anal. Calcd. for $C_{13}H_{12}N_4O$: C, 64.99; H, 5.03; N, 23.32. Found: C, 64.94; H, 5.10; N, 23.20

Synthesis of 2-(3,5 -diphenyl-1*H*-pyrazol-1-yl)-4*H*-pyrido [1,2-a]pyrimidin-4-one (10b). Recrystallized from ethanol as dark yellow needles, yield 2.80 g (77%), mp 136–138°C. IR (potassium bromide): 3099, 3052 (Ar-CH), 1683 (C O), 1631 (C N) cm^{-1}; 1H-NMR (deuteriochloroform): δ 6.19 (s, 1H, C3-H), 7.07–7.97 (m, 14 Ar-H), 8.94 ppm (d, 1H, *J* = 6 Hz, C6-H); ms: *m/z* 364 (M^+). Anal. Calcd. for $C_{23}H_{16}N_4O$: C, 75.81; H, 4.43; N, 15.38. Found C, 75.79, H, 4.40; N, 15.31.

Ethyl 3-(2-(4-oxo-4H-pyrido[1,2-a]pyrimidin-2-yl)hydrazono] butanoate (11). A mixture of 1.76 g (0.01 mol) of 2-hydrazinyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (**2**) and ethylacetoacetate (0.01 mol) in 50 mL ethanol was refluxed for 5 h. The reaction mixture was poured into crushed ice, and the formed solid was then filtered off, dried, and recrystallized from ethanol to give compound (**12**) as brown powder, yield 2.22 g (77%), mp 130–132°C.

IR (potassium bromide): 3375 (NH), 3072 (Ar-H), 2919, 2850 (CH_2, CH_3), 1711 (C O, ester), 1691 (C O), 1628 (C N) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.30 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 3.40 (s, 2H, CH_2), 4.20 (q, 2H, O$\underline{CH_2}CH_3$), 6.27 (s, 1H, C3-H), 6.95 (br s, 1H),7.30 (d, 1H, *J* = 8 Hz), 7.65 (br s, 1H), 7.88 (s, 1H, NH), 8.99 ppm (br s, 1H, C6-H); ms: *m/z* 289 (M^+ + 1). Anal. Calcd. for $C_{14}H_{16}N_4O_3$: C, 58.32; H, 5.59; N, 19.43. Found C, 58.33; H, 5.55; N, 19.40.

2-(3-Methyl-5-oxo-2,5-dihydro-1H-pyrazol-1-yl)-4H-pyrido [1,2-a]pyrimidin-4-one (12). A mixture of 1.76 g (0.01 mol) of 2-hydrazinyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (**2**) and ethylacetoacetate (0.01 mol) or ethyl-3-[(4-oxo-4*H*-pyrido[1,2-a] pyrimidin-2-yl)hydrazono]butanoate (**11**) in 20 mL acetic acid was refluxed for 5 h. The reaction mixture was poured into crushed ice, and the formed solid was then filtered off, dried, and recrystallized from ethanol to give compound (**12**) as dark brown powder, yield 1.50 g (62%), mp 222–224°C; IR (potassium bromide): 3434, 3122 (NH, enolic OH) 3034 (Ar-H), 2926, 2857 (CH_2, CH_3),1685 (C O), 1622 (C N) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.61 (s, 2H, CH_3), 2.20 (s, 3H, CH_3), 5.45 (s, 1H, C3-H), 6.85–7.89 (m, 5H, Ar-H, NH), 9.12 ppm (br d, 1H, C6-H); ms: *m/z* 243 (M^+). Anal. Calcd. for $C_{12}H_{10}N_4O_2$: C, 59.50; H, 4.16; N, 23.13. Found: C, 59.7 8; H, 4.2 5; N, 23.27.

General procedure for the synthesis of Hydrazinyl-4H-pyrido [1,2-a]pyrimidin-4-one(13a–d), (15a,b). A mixture of 1.76 g (0.01 mol) of 2-hydrazinyl-4*H*-pyrido[1,2-a]pyrimidin-4-one (**2**) and ketone (0.01 mol) in 50 mL ethanol was refluxed for 4 h. The reaction mixture was poured into crushed ice, and the formed solid was then filtered off, dried, and recrystallized from the suitable solvent to obtain pure products, (**13a**–**d**) and (**15a**–**b**).

2-(2-Cyclohexylidenehydrazinyl)-4H-pyrido[1,2-a]pyrimidin-4-one(13a). Recrystallized from ethanol as white yellow powder, yield 1.89 g (74%), mp 178–180°C; IR (potassium bromide): 3217 (NH), 2933, 2857 (CH_2, aliphatic), 1658 (C O), 1630 (C N) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.68–1.85 (m, 6H, alicyclic-H), 2.32–2.37 (m, 4H, alicyclic-H), 6.24 (s, 1H, C3-H), 6.89 (d, 1H, *J* = 4.2), 7.24 (d, 1H, *J* = 4.8 Hz), 7.59 (m, 1H), 7.89 (s, 1H, NH), 8.94 ppm (d, 1H, *J* = 4.2 Hz, C6-H); ms: *m/z* =256 (M^+). Anal. Calcd. for $C_{14}H_{16}N_4O$: C, 65.61; H, 6.29; N, 21.86. Found: C, 65.55; H, 6.26; N, 21.79.

2-(2-(4-Methylcyclohexylidene)hydrazinyl)-4H-pyrido[1,2-a]pyrimidin-4-one(13b). Recrystallized from ethanol as yellow powder, yield 1.86 g (69%), mp 192–194°C; IR (potassium bromide): 3216 (NH), 2947, 2920, 2857 (CH_3, CH_2 aliphatic), 1657 (C O), 1633 (C N) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.95 (s, 3H, CH_3), 1.65–2.74 (m, 9H, alicyclic-H), 6.22 (s, 1H, C3-H), 6.89 (m, 1H),7.25 (m, 1H), 7.59 (d, 1H, *J* = 9 Hz), 7.88 (s, 1H, NH), 8.94 ppm (d, 1H, *J* = 4.2 Hz, C10-H); ms: *m/z* 270 (M^+). Anal. Calcd. for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73. Found: C, 66.55; H, 6.97; N, 20.70.

2-(2-(4-tert-Butylcyclohexylidene)hydrazinyl)-4H-pyrido [1,2-a]pyrimidin-4-one (13c). Recrystallized from ethanol as yellow powder, yield 1.68 g (54%), mp 188–190°C; IR (potassium bromide): 3239 (NH), 2949, 2863 (CH_3, CH_2-aliphatic), 1655 (C O), 1623 (C N) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.86 (s, 9H, $(CH_3)_3$), 1.24–2.83 (m, 9H, alicyclic-H) 6.25 (s, 1H, C3-H), 6.90 (m, 1H), 7.25 (d, 1H, *J* = 3.6 Hz), 7.60 (m, 1H), 7.88 (s, 1H, NH), 8.95 ppm (d, 1H, *J* = 4.2, C6-H); ms: *m/z* 312 (M^+). Anal. Calcd. for $C_{18}H_{24}N_4O$: C, 69.20; H, 7.74; N, 17.93. Found: C, 69.00; H, 7.64; N, 17.91.

2-(2-(Bi(cyclohexane)-2-ylidene)hydrazinyl)-4H-pyrido [1,2-a]pyrimidin-4-one(13d). Recrystallized from ethanol as yellow powder, yield 2.83 g (84%), mp 118–120°C; IR (potassium bromide): 3190 (NH), 2925, 2852 (CH_2-aliphatic), 1670 (C O), 1634 (C N) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.14–2.32 (m, 20H, alicyclic-H), 6.26 (s, 1H, C3-H), 6.91 (br s, 1H), 7.25 (br s, 1H) 7.50 (br s, 1H), 7.89 (s, 1H, NH), 8.95 ppm (br, s, 1H, C6-H); ms: *m/z* 338 (M^+). Anal. Calcd. for $C_{20}H_{26}N_4O$: C, 70.98; H, 7.74; N, 16.55. Found: 70.88; H, 7.61; N, 16.50.

2-(2-Cyclopentylidenehydrazinyl)-4H-pyrido[1,2-a]pyrimidin-4-one (15a). Recrystallized from ethanol as yellow powder, yield 2 g (83%), mp 250–252°C; IR (potassium bromide): 3246 (NH), 2958, 2924 (CH_2 aliphatic), 1688 (C O), 1636 (C N) cm^{-1}; ^{1}H-

NMR (deuteriochloroform): δ 1.24–2.50 (m, 8H, alicyclic-H), 6.22 (s, 1H, C3-H), 6.91 (br s, 1H), 7.25 (br s, 1H), 7.51 (br s, 1H), 7.75 (s, 1H, NH), 8.95 ppm (br s, 1H, C6-H); ms: *m/z* 242 (M^+). Anal. Calcd. for $C_{13}H_{14}N_4O$: C, 64.45; H, 5.82; N, 23.13. Found: C, 64.40; H, 5.80; N, 23.11.

2-(2-(3-Methylcyclopent-2-enylidene)hydrazinyl)-4H-pyrido [1,2-a]pyrimidin-4-one (15b). Recrystallized from ethanol as yellow powder, yield 1.88 g (74%), mp 232–234°C; IR (potassium bromide): 3202 (NH), 2968, 2902 (CH_3, CH_2 aliphatic), 1656 (C O), 1629 (C N) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.25–2.00 (m, 4H, $2CH_2$), 2.59 (s, 3H, CH_3), 6.07 (s, 1H, CH C), 6.21 (s, 1H, C3-H), 6.91–7.61 (m, 4H, Ar-H, NH), 8.96 ppm (brs, 1H, C-6H); ms: *m/z* 254 (M^+), Anal. Calcd. for $C_{14}H_{14}N_4O$: C, 66.13; H, 5.55; N, 22.03. Found: C, 66.11; H, 5.53; N, 22.00.

General procedure for the synthesis of pyrido[1,2-a] pyrrolopyrimidines. A mixture of (0.01 mol) of hydrazinylpyrido [1.2-a]pyrimidine derivative **13a–d** and **15a**,**b**, and aliphatic ketone (0.01 mol) in 20 mL acetic acid was refluxed for 4 h. The reaction mixture was poured into crushed ice, and the formed solid was then filtered off, dried, and recrystallized from the suitable solvent to obtain pure products, (**14a–d**) and (**16a,b**).

1,2,3,4-Tetrahydro- pyrido[1′,2′: 1,2]pyrimido[4,5-b]indol-12(5H)-one(14a). Recrystallized, from ethanol as dark brown powder, yield 1.29 g (53%), mp 270–272°C; IR (potassium bromide): 3217 (NH), 1638 (C O) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.68–2.35 (m, 8H), 6.94–7.65 (m, 4H, Ar-H, NH), 8.89 (d, 1H); ms: *m/z* 243 (M^+). Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.48; N, 17.56. Found: C, 69.75; H, 5.20; N, 17.71.

2-Methyl-1,2,3,4-tetrahydro-pyrido[1′,2′: 1,2]pyrimido[4,5-b]indol-12(5H)-one (14b). Recrystallized from ethanol as yellow powder. yield 1.87 g (74%), mp 242–244°C, IR (potassium bromide):3220 (NH), 2925 (CH_3), 1660 (C O) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.95 (s, 3H, CH_3), 1.64–2.68 (m, 7H, alicyclic-H), 6.93 (m, 1H),7.23 (m, 1H), 7.55 (brd, 1H), 7.83 (s, 1H, NH), 8.91 ppm (d, 1H); ms: *m/z* 253 (M^+). Anal. Calcd. for $C_{15}H_{15}N_3O$: C, 71.13; H, 5.97; N, 16.59. Found: C, 70.93; H, 5.87; N, 16.66%.

2-tert-Butyl-1,2,3,4-tetrahydro-pyrido[1′,2′:1,2]pyrimido [4,5-b]indol-12(5H)-one (14c). Recrystallized from ethanol as a yellow powder, yield 1.53 g (52%), mp 252–254°C; IR (potassium bromide): 3336 (NH), 2955 (CH_3), 1660 (C O) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.91 (s, 9H, $(CH_3)_3$), 1.44–2.85 (m, 7H, alicyclic-H), 7.25 (m, 1H), 7.42 (d, 1H), 7.60 (m, 1H), 7.88 (s, 1H, NH), 8.95 ppm (brd, 1H);ms: *m/z* 295 (M^+). Anal. Calcd. for $C_{18}H_{21}N_3O$: C, 73.19; H, 7.17; N, 14.23. Found: C, 73.22; H, 7.14; N, 14.13.

2-Cyclohexyl-1,2,3,4-tetrahydro-pyrido[1′,2′: 1,2]pyrimido [4,5-b]indol-12(5H)-one (14d). Recrystallized from ethanol as yellow powder, yield 1.96 g (61%) mp 222–224°C; IR (potassium bromide): 3197 (NH), 1638 (C O) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 1.24–2.62 (m, 18H, alicyclic-H), 6.98 (brs, 1H), 7.25 (brs, 1H) 7.54 (brs, 1H), 7.89 (s, 1H, NH), 8.97 ppm (brs, 1H); ms: *m/z* 321 (M^+). Anal. Calcd. for $C_{20}H_{23}N_3O$: C, 74.74; H, 7.21; N, 13.07. Found: C, 74.24; H, 7.11; N, 13.46.

1,2,3,4-Tetrahydro-11H-[1]cyclopentapyrrolo[2′,3′:4,5] pyrido[1,2-a]pyrimidin-11-one (16a). Recrystallized from ethanol as yellow powder, yield 1.73 g (77%), mp 220–222°C; IR (potassium bromide): 3218 (NH), 1661 (C O) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 0.84–1.83 (m, 6H), 6.94–7.65 (m, 4H, Ar-H, NH), 8.89 (d, 1H); ms: *m/z* 225 (M^+). Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.34; H, 4.90; N, 18.66.

1-Methyl-3,4-dihydro-11H-[1]cyclopentapyrrolo[2′,3′,4,5] pyrido[1,2-a]pyrimidin-11-one (16b). Recrystallized from ethanol as brown powder, yield 1.35 g (57%) mp 266–268°C; IR (potassium bromide): 3200 (NH), 2902 (CH_3), 1650 (C O) cm^{-1}; ^{1}H-NMR (deuteriochloroform): δ 2.01 (s, 3H, CH_3), 3.25 (s, 2H, CH_2), 6.74–7.94 (m, 5H, Ar-H, NH), 8.91 (d, 1H); ms: *m/z* 237 (M^+). Anal. Calcd. for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C 70.85; H, 4.61; N, 17.66.

REFERENCES AND NOTES

[1] Hiber, B. S.; Valenti, B. F. J Med Chem 1968, 11, 708.

[2] (a) Althins, T. H.; Moore, P. E.; Hess, H. J. J Med Chem 1979, 22, 44; (b) Althins, T. H.; Kadin, S. B.; Czuba, I. J.; Moore, P. F.; Hess, H. J Med Chem 1980, 23, 262.

[3] (a) Cowart, M.; Lee, C. -H.; Gfesser, G. A.; Baybutt, E. K.; Bhagwat, S. S.; Stewart, A. O.; Yu, H.; Kohlhass, K. L.; McGaraughty, S.; Wismer, C. T.; MIkusa, J.; Zhu, C.; Alexander, K. M.; Jarvis, M. F.; Kowaluk, E. A. Bioorg Med Chem Lett 2001, 11, 83; (b) Glesser, G. A.; Baybutt, E. K.; Cowart, M.; DiDomenico, S.; Gomtsyan, A.; Lee, C. -H.; Stewart, A. O.; Jarvis, M. F.; Kowaluk, E. A.; Bhagwat, S. S. Eur J Med Chem 2003, 38, 245.

[4] Smaill, J. B.; Palmer, B. D.; Rewcastle, G. W.; Denny, W. A.; McNamar Dobrusin, E. M.; Bridges, A. J.; Zhou, H.; Showalter, H. D. H.; Winters, R. T.; Leapold, W. P.; Fry, D. W.; Nelson, J. M.; Slintak, V.; Elliot, W. L.; Roberts, B. J.; Vincent, P. W.; Patmore, S. J Med Chem 1999, 42, 1803.

[5] Wang, S.; Folkes, A.; Chuckowree, I.; Cockcroft, X.; Sohal, S.; Miller, W.; Milton, J.; Wren, S. P.; Vicker, N.; Depledge, P.; Scott, J.; Smith, L.; Jones, H.; Mistry, P.; Faint, R.; Thompson, D.; Cocks, S. J Med Chem 2004, 47, 1329.

[6] Bruno, O.; Brullo, C.; Schenone, S.; Bondavalli, F.; Ranise, A.; Tognolini, M.; Impicciatore, M.; Ballabeni, V.; Barocelli, E. Bioorg Med Chem 2006, 14, 121.

[7] (a) Josephine, K. L. E.; Aloysius, P. S. M.; Paul, B. F. PCT Int Appl WO2000020422 A120000413, 2000; (b) Josephine, K. L. E.; Aloysius, P. S. M.; Paul, B. F. Chem Abstr 265 188t.

[8] (a) Josephine, K. L. E.; Keybus, V. D.; Alfons, F. M.; Carolus, M. J. PCT Int Appl WO2000020421 A2 20000413, 2000; (b) Josephine, K. L. E.; Keybus, V. D.; Alfons, F. M.; Carolus, M. J. Chem Abstr 265187c.

[9] Dominguez, J.; Charris, J.; Iarrusso, L.; Lopez, S.; Lobo, G.; Riggione F. Farmaco 1996, 51, 781.

[10] Katritzky, A. R.; Rogers, J. W.; Witek, R. M.; Nair S. K. ARKIVOC 2004, 8, 52.

[11] Snyder, H. R.; Robison, M. M. J Am Chem Soc 1952, 74, 4910.

[12] Katritzky, A. R.; Waring, A. J. J Chem Soc 1962, 1544.

[13] di Braccio, M.; Roma, G.; Mazzei, M.; Balbi, A.; Schiantarelli, P.; Cadel, S.; Bongrani, S. Farmaco 1988, 43, 705.

[14] Plug, C.; Frank, W.; Wentrup, C. J Chem Soc Perkin Trans 1999, 2, 1087.

[15] Snyder, H. R.; Robison, M. M. J Am Soc 1952, 74, 4910.

[16] Oakes, V.; Rydon, H. N. J Chem Soc 1958, 209.

[17] Ingalls, E. A.; Popp, F. D. J Heteocyclic Chem 1967, 4, 523.

[18] (a) Emerson, W. S.; Patric. T. M. J Org Chem 1949, 14, 795; (b) Popp, F. D.; Catala, A. J Org Chem 1961, 26, 2738.

[19] Dipak, P.; Partha, P. B.; Balkuntha, J. G.; Jaglir, S. S. Beilstein J Org Chem 2006, 2, 5.

[20] Chaitanya, G. D.; Rina, D. S. Molecules 2002, 7, 554.

[21] Snyder, H. R.; Robison, M. M. J Am Soc 1952, 74, 5945.

[22] Fiksdahl, A.; Plug, C.; Wentrup, C. J Chem Soc Perkin Trans 2002, 2000, 1841.

[23] Robinson, B. The Fisher Indole Synthesis; Wiley: Chichester, 1982.

[24] (a) Rosowsky, A.; Chen, H.; Fu, H. J Org Chem 2001, 66, 7522; (b) Rosowsky, A.; Chen, H.; Fu, H.; Queener, S. F. Bioorg Med Chem 2003, 11, 59.