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Full Paper

Synthesis of new pyrazolo[3,4-*b*]pyridines and related fused tricyclic systems with possible biological activities

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Abstract

The reaction of 5-acetyl-3-cyano-4-(*p*-methoxyphenyl)-6-methylpyridine-2(1*H*)-thione (**1**) with methyl iodide gave 2-methylthio derivative **2**. Heating of **2** with hydrazine hydrate produced the target 5-acetyl-3-amino-4-(*p*-methoxyphenyl)-6-methylpyrazolo[3,4-*b*]pyridine (**3**)**.** Reaction of **3** with some reagents, namely acetylacetone, ethyl acetoacetate, diethyl malonate and ethyl α-cyano-β-ethoxyacrylate were carried out and their products were identified. Diazotisation of aminopyrazole **3** gave the isolable diazonium salt, 5-acetyl-4-(*p*-methoxyphenyl)-6-methylpyrazolo [3,4-*b*]pyridine-3-diazonium chloride (**10**). The reactivity of **10** was checked by coupling with β-naphthol whereby the azo dye **11** was isolated. Also, coupling of **10** with active methylenes such as: barbituric acid, 3-methyl-1-phenyl-2-pyrazolin-5-one, 1,3-diphenyl-2-pyrazolin-5-one, malononitrile, ethyl cyanoacetate, cyanothioacet-amide and/ or phenacylcyanide furnished the corresponding hydrazono compounds **12**, **13a**,**b** and **14a-d**. Cyclization of **14a-d** into the corresponding 4-aminopyrido-pyrazolotriazines **15a-d** was achieved in boiling acetic acid. In contrast, reaction of **10** with acetyacetone or ethyl benzoylacetate furnished pyridopyrazolotriazines **17a** and **17b** directly.

Keywords: Pyrazolopyridines, hydrazono compounds, pyridopyrazolopyrimidines, barbituric acid, pyridopyrazolotriazines

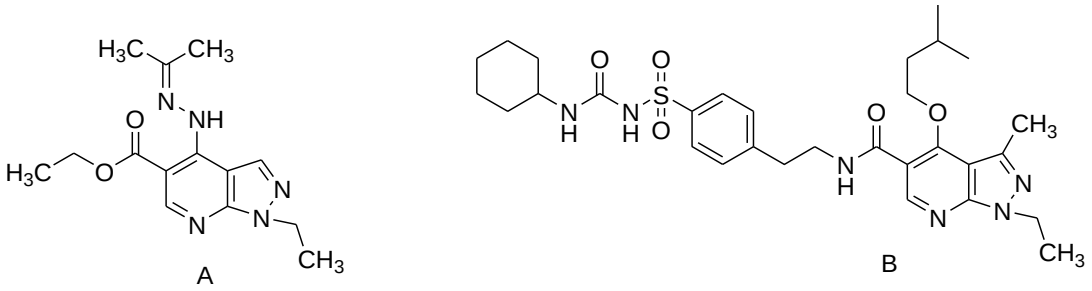
1. Introduction

Several pyrazolo[3,4-*b*]pyridine derivatives have been the subject of chemical and biological studies on account of their pharmacological properties [1-4]. Some derivatives have found applications as antimicrobial [5] antiviral [6], antiinflammatory [7], analgesic [8], and antitumor agents [9]. In addition, pyrazolo[3,4-*b*]pyridines represent the skeleton of pharmaceuticals possessing significant biological activities as represented by Etazolate EHT-0202 (**A**) and Glicaramide (**B**) (Scheme 1) [10,11]. Encouraged by the above facts and as a continuation of our program dealing with the development of bioactive heterocyclic derivatives [12-16], the present investigation was planned to synthesize new pyrazolo[3,4-*b*] pyridines, pyridopyrazolopyrimidines as well as pyridopyrazolo-triazines hoping to get compounds with good medicinal and biological importance.

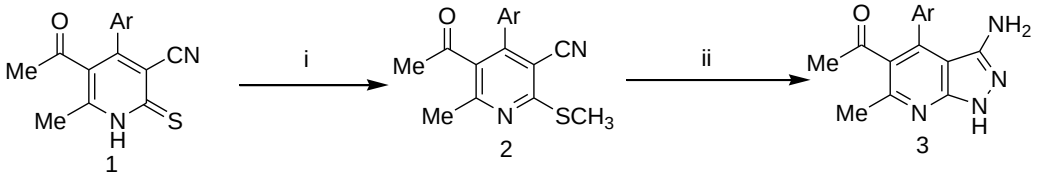
2. Results and Discussion

Our approach to the synthesis of the titled compounds started from 5-acetyl-3-amino-4-(p-methoxyphenyl) -6-methyl-1H-pyrazolo[3,4-b] pyridine (3) which was prepared according to scheme 2. Thus, the reaction of 5-acetyl-3-cyano-4-(p-methoxyphenyl) -6-methylpyridine-2(1H)-thione (**1**) with methyl iodide in the presence of sodium acetate gave 2-methylthio derivative **2**. Heating compound **2** with hydrazine hydrate under neat conditions led to the formation of the target 3-aminopyrazolopyridine **3**. When compound **3** was heated with acetylacetone in ethanol containing few drops of acetic acid, 9-acetyl-10-(p-methoxyphenyl)-2,4,8-trimethyl-pyrido[2',3':3,4]pyrazolo[1,5-a]pyrimi-dine (**4**) was obtained. Also, the reaction of **3** with ethyl acetoacetate under the same (above) conditions produced the corresponding pyrido-pyrazolopyrimidinone derivative **5** (Scheme 3). Refluxing compound **3** with diethyl malonate in acetic acid for one hour led to the formation of the ester **6.** When the reaction time was increased to 3 hours, the product was identified as 9-acetyl-10-(*p*-methoxyphenyl)-8-methylpyrido [2',3':3,4]pyrazolo[1,5-*a*]pyrimidine-2,4(1*H*,3*H*)-dione (**7**). Cyclization of **6** to **7** was achieved by boiling in acetic acid for 2 hours (Scheme 3). Similarly, heating compound **3** with ethyl α-cyano-β-ethoxyacrylate in ethanol produced the cyanoester **8**. Cyclization of the latter compound to ethyl 9-acetyl-4-amino-10-(*p*-methoxyphenyl) -8-methylpyrido[2',3':3,4]pyrazolo [1,5-*a*]pyrimidine-3-carboxylate (**9**) was achieved upon heating with acetic acid. Compound **9** was also obtained directly when the reaction of **3** with ethyl α-cyano-β-ethoxyacrylate was performed in boiling acetic acid (Scheme 3).

Diazotisation of 3-aminopyrazolo-pyridine **3** using sodium nitrite and HCl at 0-5°C produced the diazonium chloride **10** which seems to be stable under normal conditions. The reactivity of the diazonium chloride **10** was firstly checked by coupling with β-naphthol, in a cold and stirred ethanol solution containing sodium acetate, wherein the expected azo dye **11** was obtained in a nearly quantitative yield (Scheme 4). According to DFT calculations for similar compounds, the hydrazono tautomer **11** is favored over **11'** [17] by 2.1 Kcal.mol^{-1}. The coupling between **10** and barbituric acid in the presence of sodium acetate produced compound **12** (Scheme 4). The **12**/ **12**'

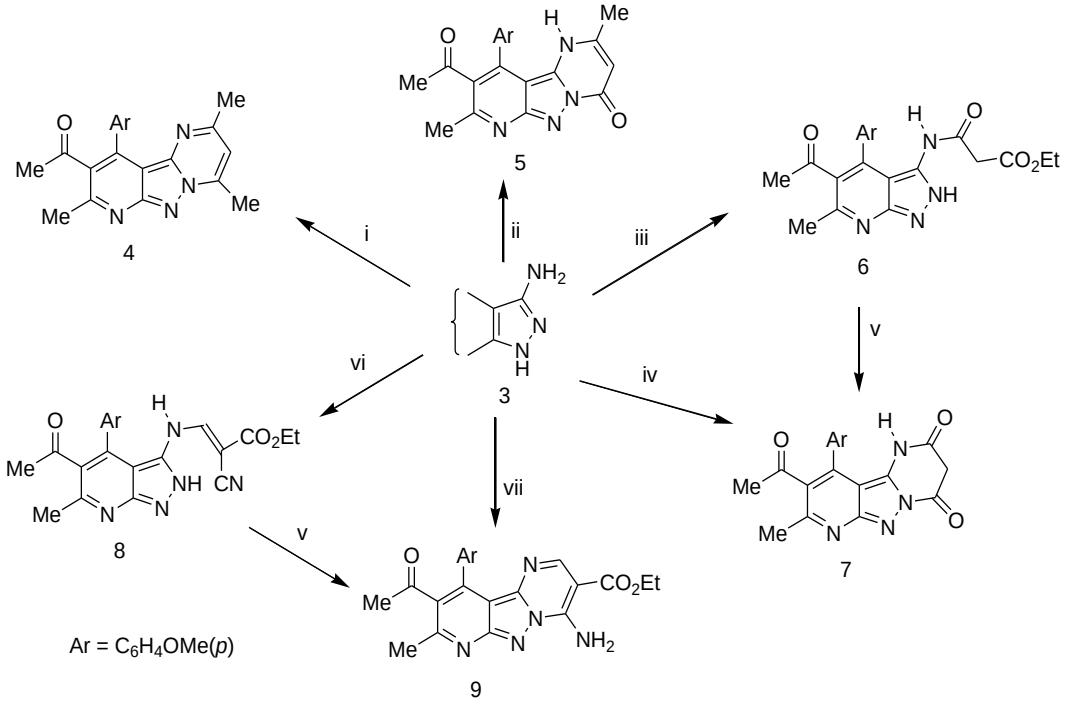


Scheme 1: Chemical structure of Etazolate (A) and Glicaramide (B).



i: MeI/ AcONa; ii: $NH_2NH_2.H_2O$/ EtOH

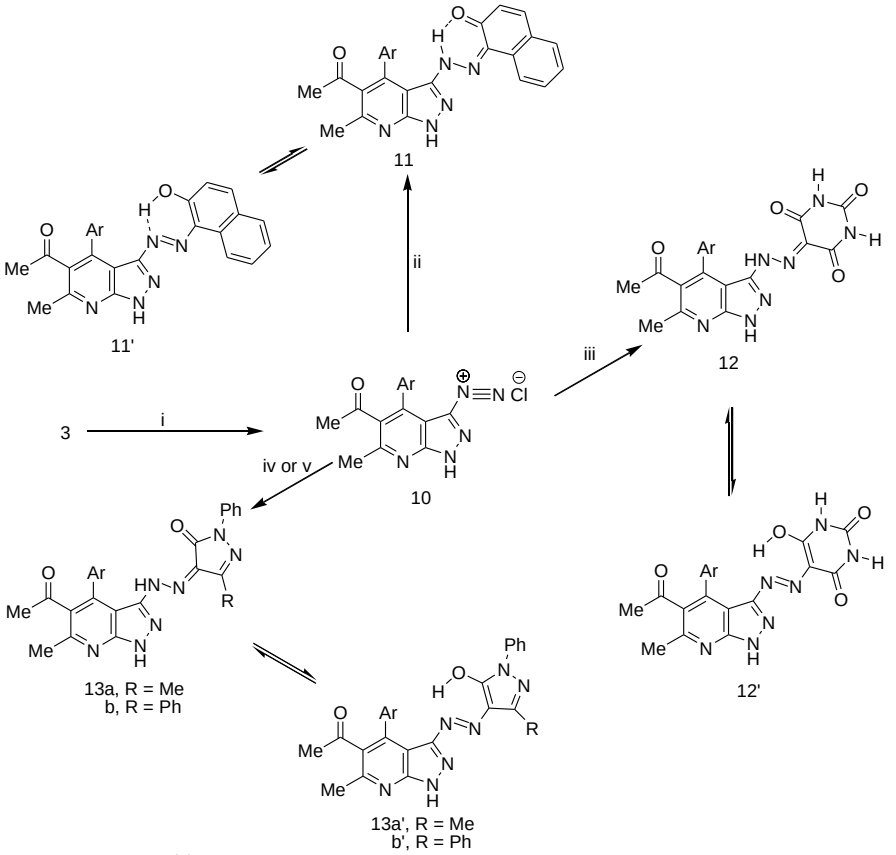
Scheme 2: Synthesis of compounds **2** and **3**.



i: Ac_2CH_2; ii: $MeCOCH_2CO_2Et$; iii: $CH_2(CO_2Et)$ AcOH/ 1 h; iv: $CH_2(CO_2Et)$ AcOH/ 3 h; v: AcOH/ 2 h
vi: $EtOCH=C(CN)CO_2Et$/ EtOH; vii: $EtOCH=C(CN)CO_2Et$/ AcOH

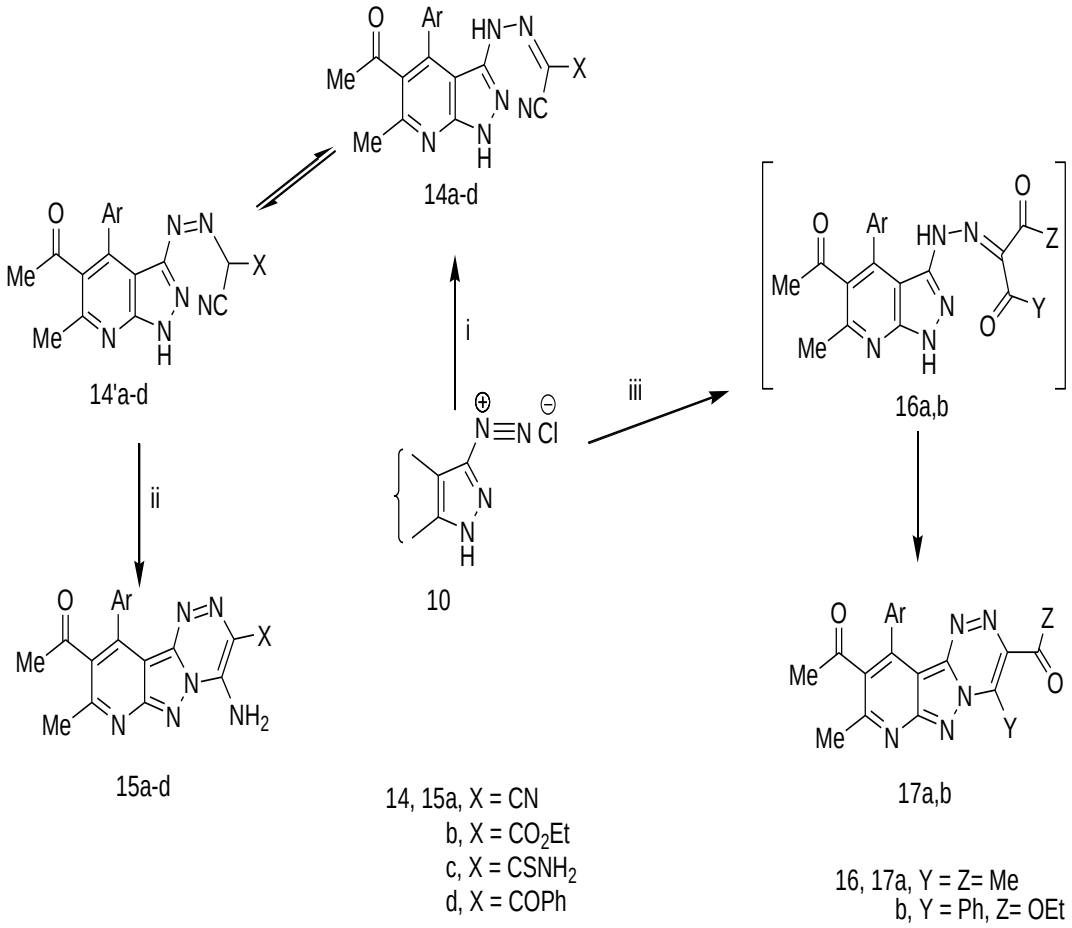
Scheme 3: Synthesis of compounds 4-9

tautomerism is clearly dominated by the barbituric acid moiety, and DFT calculations performed for related compounds [18] have the H-bridged hydrazone tautomer so much in favor over the azo form (>13 Kcal. mol^{-1}) that there cannot be any doubt that the molecular structure must be represented by **12** and not by **12'**. Similarly, coupling of the diazonium salt **10** with 3-methyl-1-phenyl-2-pyrazolin-4-one or 1,3-diphenyl-2-pyrazolin-4-one in a cooled and stirred ethanolic solution containing sodium acetate, produced the corresponding hydrazono compounds **13a,b** which may exist predominantly in hydrazono form rather than the azo one (Scheme 4). Moreover, coupling of **10** with other active methylene-containing reagents such as malononitrile, ethyl cyanoacetate, cyanothioacetamide or phenacylcyanide resulted in formation of the corresponding intermediates **14a-d**. Cyclization of the latter hydrazones **14a-d** into 3-substituted 9-acetyl-4-amino-10-(*p*-methoxyphenyl) -8-meth-ylpyrido[2',3':3,4]pyrazolo [5, 1-c][1,2,4]triazines (**15a-d**) was carried out by refluxing in glacial acetic acid (Scheme 5) .In contrast, coupling between **10** and each of the acetylacetone and ethyl benzoylacetate did not stop at the hydrazono intermediates **16a,b** but cyclized directly into the corresponding 4-methyl-pyrido[2',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazines **17a,b** (Scheme 5).



Ar = $C_6H_4OMe(p)$
i: $NaNO_2$/ HCl/ 0-5C; ii: 2-naphthol/ AcONa; iii: barbituric acid/ AcONa; iv: 3-methyl-1-phenyl-2-pyrazolin-5-one/ AcOH;
v: 1,3-diphenyl-2-pyrazolin-5-one/ AcOH;

Scheme 4: Synthesis of compounds 10,11,12 and 13a,b.



Ar =$C_6H_4OMe(p)$
i: X CH_2CN (malononitrile, ethyl cyanoacetate, cyanothioacetamide or phenacyl cyanide) / AcONa; ii: AcOH;
iii: $YCOCH_2COZ$(acetylacetone or ethyl benzoylacetate/ AcONa.

Scheme 5: Synthesis of compounds 14a-c, 15a-c and 17a,b.

3. Experimental

Starting materials were obtained from commercial suppliers and used without further purification. Melting points were determined on a Gallan-Kamp apparatus and are uncorrected. The IR spectra were recorded on a Shimadzu 470 IR-spectrophotometer (KBr; ν_{max} in cm^{-1}). The ^1H NMR spectra were taken on a Varian EM-390, 90 MHz spectrometer or on a Jeol LA 400 MHz FT-NMR spectrometer using TMS as internal standard. Chemical shifts are given in δ ppm and coupling constants (*J*) are given in Hz. Electron impact (EI) MS spectra were carried out on a JEOL JMS-600 spectrometer. Elemental analyses (C, H, N and S) were performed on an Elemental Analyizer system GmbH VARIO EL $V_{2.3}$ 1998 CHNS Mode.

3.1. 5-Acetyl-3-cyano-4-(p-methoxy-phenyl)-6-methylpyridine-2(1H)-thione (1)

It was prepared according to the reported method [13].

3.2. 5-Acetyl-3-cyano-4-(p-methoxy-phenyl)-6-methyl-2-methylthio-pyridine (2)

A solution of **1** (2.98 g, 0.01 mol), methyl iodide (0.5 ml, 0.01 mol) and sodium acetate trihydrate (1.36 g, 0.01 mol) in ethanol (30 ml) was heated under reflux for 2 h. The precipitate that formed on cooling was collected and recrystallized from ethanol to give white needles of **2**. Yield: 3.0 g (96 %); m. p.: 153-154°C. IR: 2200 (C≡N), 1700 (C=O). ^{1}H NMR ($CDCl_3$) (400 MHz): δ = 7. 28-7.30 (d, *J* = 8.8 Hz, 2H, ArH's), 6.99-7.01 (d, *J* = 8.8 Hz, 2H, ArH's), 3.86 (s, 3H, OCH_3), 2.66 (s, 3H, SCH_3), δ 2.53 (s, 3H, $COCH_3$), δ 1.87 (s, 3H, CH_3 at C-6). Anal. Calcd. for $C_{17}H_{16}N_2O_2S$ (312.39): C, 65.36; H, 5.16; N, 8.97; S, 10.27 %. Found: C, 65.15; H, 5.12; N, 9.10; S, 10.02 %

3.3. 5-Acetyl-3-amino-4-(p-methoxy-phenyl)-6-methyl-1H-pyrazolo[3,4-b] pyridine (3).

A mixture of **2** (3.12 g, 0.01 mol) and hydrazine hydrate 99 % (15 ml) was heated under reflux for 6 h.. The reaction mixture was then left to cool and triturated with ethanol (20 ml). The solid product that formed was collected and recrystallized from ethanol to give yellow plates of **3**. Yield: 2.6 g (88 %); m. p.: 318-320°C. IR: 3450, 3300, 3200 (NH, NH_2), 1700 (C=O). ^{1}H NMR (DMSO-d_6) (400 MHz) : δ = 12.25 (s, 1H, pyrazole-NH), 7.27-7.29 (d, *J* = 8.5, Hz, 2H, ArH's), 7.08-7.11 (d, *J* = 8.5, 2H, ArH's), 4.36 (s, 2H, NH_2), 3.82 (s, 3H, OCH_3), 2.49 (s, 3H, $COCH_3$), 1.90 (s, 3H, CH_3 at C-6). Anal. Calcd. for $C_{16}H_{16}N_4O_2$ (296.32): C, 64.85; H, 5.44; N, 18.91; %. Found: C, 64.61; H, 5.39; N, 19.07 %.

3.4. 9-Acetyl-2,4,8-trimethyl-10-(p-methoxyphenyl)pyrido[2́,3́:3,4] pyrazolo[1,5-a] pyrimidine (4)

A mixture of **3** (1.5 g, 0.005 mol), acetylacetone (0.6 ml, 0.006 mol) in ethanol (20 ml), a few drops of acetic acid were added. The reaction mixture was refluxed for 4 h. then concentrated and allowed to cool. The precipitate that formed was collected and recrystallized from ethanol to give yellow crystals of **4**. Yield: 1.1 g (61 %); m. p.: 227-228°C. IR: 1700 (C=O). ^{1}H NMR ($CDCl_3$) (90 MHz): δ7.6-7.8 (d, 2H, ArH's), 7.05-7.20 (d, 3H: pyrimidine-H and ArH's), 4.0 (s, 3H, OCH_3), 3.0 (s, 3H, CH_3 at C-4), 2.8 (s, 3H, CH_3 at C-2), 2.6 (s, 3H, $COCH_3$), 2.1 (s, 3H, CH_3 at C-8). Anal. Calcd. for $C_{21}H_{20}N_4O_2$ (360.41): C, 69.98; H, 5.59; N, 15.55. %. Found: C, 69.63; H, 5.62; N, 15.38 %.

3.5. 9-Acetyl-2,8-dimethyl-10-(p-methoxyphenyl)pyrido[2́,3́:3,4] pyrazolo[1,5-a]pyrimidine-4(1H)-one (5).

A mixture of **3** (1.78 g, 0.006 mol), ethyl acetoacetate (0.75 ml, 0.006 mol) and glacial acetic acid (15 ml) was reflux for 5 h. The solid product that formed after cooling was collected and recrystallized from ethanol to give yellow crystals of **5**. Yield: 1.5 g (70 %); m. p.: 337-338°C. IR: 3400 (NH), 1700 (2C=O). ^{1}H NMR in (CF_3CO_2D) (90 MHz): δ 7.0-7.8 (m, 5H: pyrimidinone-H and Ar'H), 4.0 (s, 3H, OCH_3), 3.0 (s, 3H, CH_3 at C-2), 2.6 (s, 3H, $COCH_3$), 2.1 (s, 3H, CH_3 at C-7). Anal. Calcd. for $C_{20}H_{18}N_4O_3$ (362.38): C, 66.29; H, 5.01; N, 15.46. %. Found:

C, 66.34; H, 4.88; N, 15.25 %.

3.6. Ethyl 3-{[5-acetyl-4-(p-methoxy-phenyl)-6-methyl-1H-pyrazolo[3,4-b] pyridin-3-yl]amino}-3-oxopropionate (6)

A mixture of **3** (0.59 g, 0.002 mol), diethylmalonate (0.31 ml, 0.002 mol) in glacial acetic acid (10 ml) was heated under fluxed for 1 h. The resulting mixture was poured onto water (10 ml) whereby a precipitate formed. It was collected and recrystallized from ethanol to give white crystals of **6**. Yield: 0.65 g (79 %); m. p.: 219-220°C. IR: 3400, 3200 (2NH), 1700 (3C=O). MS: m/z = 408 (M^+-2, 17 %), 294 (M+-$COCH_2CO_2Et$, 56 %), 279 (M^+-$COCH_2CO_2Et$-Me, 78 %), 28 (N_2^+, 100 %). Anal. Calcd. for $C_{21}H_{22}N_4O_5$(410.42): C, 61.46; H, 5.40; N, 13.65 %. Found: C, 61.25; H, 5.37; N, 13.38 %.

3.7. 9-Acetyl-10-(p-methoxyphenyl)-8-methylpyrido[2́,3́:3,4]pyrazolo[1,5-a] pyramid-ine-2,4(1H,3H)-dione (7)

3.7. 1. Method A)

A mixture of **3** (0.6 g, 0.002 mol), diethylmalonate (0.3 ml, 0.002 mol) in glacial acetic acid (10 ml) was heated under reflux for 3 h. The resulting mixture was poured onto water (10 ml). The precipitate was collected and crystallized from ethanol to give buff crystals of **7**. Yield: 0.6 g (82%); m. p.: 278-280°C. IR: 3380 (NH), 1700 (3C=O). ^{1}H NMR ($CDCl_3$) (90 MHz): δ 10.7 (1H, NH), 7.2-7.4 (d, 2H, ArH's), 6.8-7.0 (d, 2H, ArH's), 3.9 (s, 3H, OCH_3), 3.8 (s, 2H, CH_2), 2.6 (s, 3H, $COCH_3$), 1.9 (s, 3H, CH_3 at C-8). Anal. Calcd. for $C_{19}H_{16}N_4O_4$ (364.35): C, 62.63; H, 4.43; N, 15.38 %. Found: C, 62.48; H, 4.31; N, 15.53 %.

3.7. 2. Method B)

Compound **6** (0.85 g, 0.002 mol) in acetic acid (10 ml) was heated under reflux for 2 h. The resulting mixture was poured onto water (10 ml). The precipitate was collected and recrystallized from ethanol to give **7**. Yield: 0.6 g (73 %). This product was identical in all aspects to that described in method A.

3.8. Ethyl 3-[5-acetyl-4-(p-methoxy-phenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridin-yl]amino-2-cyanoacrylate (8)

A mixture of **3** (3.0 g, 0.01 mol) and ethyl α-cyano-β-ethoxyacrylate (1.7 g , 0.01 mol) in ethanol (25 ml) was heated under reflux for 4 h.. The reaction mixture was concentrated and allowed to cool. The separated solid was filtered off and recrystallized from ethanol to give pale yellow needles of **8**. Yield: 3.3 g (78 %); m. p.: 216-217°C. IR: 3400 (NH), 2200 (C≡N), 1710 (C=O, ester), 1700 (C=O, acetyl).^{1}H NMR ($CDCl_3$) (90 MHz): δ 6.9-7.3 (m, 5H: CH=C and ArH's), 4.0-4.2 (q, 2H, OCH_2), 3.85 (s, 3H, OCH_3), (s, 3H, $COCH_3$), 2.0 (3H, CH_3 at C-6), 1.2-1.4 (3H, CH_3). MS: m/z = 418 (M^+-1, 7 %), 403 (M^+-1-CH_3, 9 %), 28 (N_2^+, 100 %). Anal. Calcd. for $C_{22}H_{21}N_5O_4$ (419.43): C, 62.99; H, 5.05; N, 16.70 %. Found: C, 63.08; H, 5.11; N, 16.57 %.

3.9. 9-Acetyl-4-amino-10-(p-methoxy phenyl)-8-methylpyrido[2́,3́:3,4] pyrazolo[1,5-a]pyrimidine-3-carboxylate (9).

3.9. 1. Method A

A mixture of **3** (3.0 g, 0.01 mol) and ethyl 2-cyano-3-ethoxyacrylate (1.7 g, 0.02 mol) in glacial acetic acid (15 ml) was refluxed for 4 h. The reaction mixture was poured onto water

(20 ml). The precipitate which formed was collected, washed with water, dried and recrystallized from ethanol to give orange needles of **9**. Yield: 3.2 g (76 %); m. p.: 284-285°C. IR: 3400, 3200 (NH_2), 1700 (2C=O).^{1}H NMR ($CDCl_3$) (90 MHz): δ 8.9 (br. s, 1H, NH), 8.8 (s, 1H, pyrimidine-H), 8.5 (br. s, 1H, NH), 7.3-7.6 (d, 2H, ArH's), 6.9-7.1 (d, 2H, ArH's), 4.2-4.5 (q, 2H, OCH_2), 3.8 (s, 3H, OCH_3), 2.6 (s, 3H, $COCH_3$), 1.9 (s, 3H, CH_3 at C-8), 1.2-1.4 (t, 3H, CH_3 of ester). MS: m/z = 418 (M^+-1, 2 %), 403 (M^+-1-Me, 8 %), 28 (N_2^+, 100 %). Anal. Calcd. for $C_{22}H_{21}N_5O_4$ (419.43): C, 62.99; H, 5.05; N, 16.70 %. Found: C, 62.75; H, 4.88; N, 16.92 %.

3.9. 2. Method B

To a sample of **8** (0.42 g, 0.001 mol), glacial acetic acid (10 ml) was added and the mixture was heated under reflux for 4 h. After cooling, the reaction mixture was poured onto water (10 mL). The precipitated solid was collected and crystallized from ethanol to give compound **9**. Yield: 0.4 g (95 %). This product was identical in all aspects to that described in method A.

3.10. 5-Acetyl-4-(p-methoxyphenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridine-3-diazonium chloride (10).

A solution of **3** (3.0 g, 0.01 mol) in conc. HCl (15 ml) was cooled to 0-5°C in an ice-bath and cooled sodium nitrite solution (1.5 g in 15 ml water) was added to it dropwise with stirring during 15 mins. The cooled reaction mixture was then stirred in an ice bath for 1 h. The solid product obtained was filtered off, washed with water and dried in air to give yellow crystals of 10. Yield: 2.9 g (84%); m. p.: 169-170°C (dec.). IR: 3420 (NH), 2130 (N≡N), 1690 (C=O). Anal. Calcd. for $C_{16}H_{14}ClN_5O_2$ (343.76): C, 55.90; H, 4.10; N, 20.37 %. Found: C, 56.11; H, 4.18; N, 20.29 %.

3. 11. Coupling of diazonium chloride 10 with β-naphthol and/ or active-methylene compounds; Synthesis of compounds 11, 12, 13a,b, 14a-d and 17a,b; General procedure.

To an ice-cooled mixture of β-naphthol or the appropriate active-methylene compound (0.005 mol) and sodium acetate trihydrate (4.1 g, 0.03 mol) in ethanol (40 ml), a freshly prepared diazonium chloride **10** (1.7 g, 0.005 mol) was added portion wise with stirring during 15 mins. The cooled reaction mixture was then stirred in an ice bath for additional one hour. The solid product was collected by filtration, dried in air and recrystallized from the proper solvent.

3. 11. 1. 1-[(5-Acetyl-4-(p-methoxy-phenyl)-6-methyl-1H-pyrazolo[3,4-b] pyridin-3-yl-diazo]-2-naphthol (11)

It is obtained by using β-naphthol as a coupler in the above general procedure, in the form of brown crystals (ethanol-chloroform). Yield: 1.5 g (67 %); m. p.: 224-225°C. IR: 1690 (C=O). Anal. Calcd. for $C_{26}H_{21}N_5O_3$ (451.48): C, 69.17; H, 4.69; N, 15.51 %. Found: C, 68.98; H, 4.47; N, 15.46 %.

3. 11. 2. 5-[(5-Acetyl-4-(p-methoxy-phenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)hydrazono] pyrimidine-2,4,6(1H,3H,5H)-trione (12)

It is obtained by using barbituric acid as coupler in the above general procedure, in the form of scarlet red crystals (ethanol-chloroform). Yield: 1.5 g (69 %); m. p.: 359-360°C. IR:

3410 (NH, pyrazole), 3200 (NH), 3120 (NH), 1720, 1700, 1680 (3C=O). Anal. Calcd. for $C_{20}H_{17}N_7O_5$ (435.39): C, 55.17; H, 3.94; N, 22.52 %. Found: C, 55.26; H, 4.08; N, 22.39 %.

3. 11. 3. 4-[(5-Acetyl-4-(p-methoxy-phenyl)-6-methyl-1H-pyrazolo[3,4-b] pyridin-3-yl) hydrazino]-1-methyl-3-phenyl-2-pyrazolin-5-one (13a)

It is obtained by using 3-methyl-1-phenyl-2-pyrazolin-5-one as a coupler in the above general procedure, in the form of orange needles (ethanol). Yield: 1.87 g(78%) m. p.: 244-245°C . IR: 3420 (NH), 1690 (C=O, acetyl) 1660 (C=O, pyrazolinone).^{1}H NMR (DMSO-d_6) (90 MHz): δ 10.9 (s, 1H, NH), 7.0-8.0 (m, 9H, ArH's), 3.8 (s, 3H, OCH_3), 2.6 (3H, $COCH_3$), 2.2 (3H, CH_3), 2.0 (3H, CH_3). Anal. Calcd. for $C_{26}H_{23}N_7O_3$ (481.51): C, 64.85; H, 4.81; N, 20.36 %. Found: C, 64.73; H, 4.67; N, 20.09 %.

3. 11. 4. 4-[(5-Acetyl-4-(p-methoxy-phenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl) hydrazino]-1,3-diphenyl-2-pyrazolin-5-one (13b)

It is obtained by using 1,3-diphenyl-2-pyrazolin-5-one as a coupler in the above general procedure, in the form of orange needles (ethanol). Yield: 2.0 g (74%) m. p.: 299-300°C. IR: 3420 (NH), 1690 (C=O, acetyl) 1660 (C=O, pyrazolinone). 1H NMR (CF3CO2D) (90 MHz): δ 7.2-8.3 (m, 14H, ArH's), 4.0 (s, 3H, OCH3), 3.0 (s, 3H, $COCH_3$), 2.2 (s, 3H, CH_3). Anal. Calcd. for $C_{31}H_{25}N_7O_3$ (543.58): C, 68.50; H, 4.64; N, 18.04 %. Found: C, 68.77; H, 4.58; N, 18.32 %.

3. 11. 5. 2-{2-[5-Acetyl-4-(p-methoxyphenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl] hydrazono}malononitrile (14a)

It is obtained by using malononitrile as a coupler in the above general procedure, in the form of pale yellow needles (ethanol). Yield: 1.5 g (80 %); m. p.:221-222°C. IR: 3400, 3200 (2 NH), 2210 (2 C≡N), 1690 (C=O), 1630 (C=N). Anal. Calcd. for $C_{19}H_{15}N_7O_2$ (373.37): C, 61.12; H, 4.05; N, 26.26 %. Found: C, 60.92; H, 4.16; N, 26.11 %.

3 . 11. 6. Ethyl 2-{2-[5-acetyl-4-(p-methoxyphenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl] hydrazono}-2-cyanoacetate (14b)

It is obtained by using ethyl cyanoacetate as a coupler in the above general procedure, in the form of pale yellow needles (ethanol). Yield: 1.6 g (76 %); m. p.:148-150°C. IR 3400, 3200 (2NH), 2220 (C≡N), 1690 (2 C=O), 1620 (C=N). ^{1}H NMR ($CDCl_3$) (90 MHz): δ 9.3 (s, 1H, NH), 6.9-7.3 (m, 4H, ArH's), 4.0-4.2 (q, 2H, OCH_2), 3.9 (s, 3H, OCH_3), 2.7 (s, 3H, $COCH_3$), 2.0 (s, 3H, CH_3 at C-6), 1.2-1.4 (t, 3H, CH_3 of ester). MS: m/z = 420.22 (M^+, 6 %). Anal. Calcd. for $C_{21}H_{20}N_6O_4$ (420.42): C, 59.99; H, 4.79; N, 19.99 %. Found: C, 60.12; H, 4.64; N, 19.75 %.

3. 11. 7. 2-{2-[5-Acetyl-4-(p-methoxy phenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl]hydrazono}-2-cyanothioacetamide (14c)

It is obtained by using cyanothioacetamide as a coupler in the above general procedure, in the form of pale 1680 (C=O). Anal. Calcd. for $C_{19}H_{17}N_7O_2S$ (407.45): C, 56.01; H, 4.21; N, 24.06; S, 7.87 %. Found: C, 56.12; H, 4.35; N, 23.90; S, 7.71%.

3 . 11. 8. 1-{2-[5-Acetyl-4-(p-methoxyphenyl)-6-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl] hydrazono}-2-oxo-2-phenyl-ethylcyanide (14d)

It is obtained by using phenacyl-cyanide as a coupler in the above general procedure, in the form of pale yellow needles (ethanol). Yield: 1.9 g (84 %); m. p.: 198-199 °C. IR: 3400, 3200 (2NH), 2220 (C≡N), 1690 (2 C=O), 1620 (C=N). Anal. Calcd. for $C_{25}H_{20}N_6O_3$ (452.47): C, 66.36; H, 4.46; N, 18.57 %. Found: C, 66.28; H, 4.54; N, 18.39 %.

3. 11. 9. 3,9-Diacetyl-4,8-dimethyl-10-(p-methoxyphenyl)pyrido[2́,3́:3,4] pyrazolo [5,1-c][1,2,4]triazine (17a)

It is obtained by using acetylacetone in the above general procedure as brown crystals (ethanol). Yield: 1.65 g (85%); m. p.: 249-250°C. IR: 1680 (2C=O).^{1}H NMR ($CDCl_3$) (90 MHz): δ 7.7-7.8 (d, 2H, ArH's), 7.1-7.2 (d, 2H, ArH's), 4.0 (s, 3H, OCH_3), 3.4 (s, 3H, $COCH_3$ at C-3), 3.0 (s, 3H, $COCH_3$ at C-9), 2.8 (s, 3H, CH_3 at C-4), 2.1 (s, 3H, CH_3 at C-8). MS: m/z = 388 (M^+-1, 57 %), 373 (M+-1-Me, 100 %), 43 ($COCH_3^+$, 93%), 28 (N_2^+, 25 %). Anal. Calcd. for $C_{21}H_{19}N_5O_3$ (389.41): C, 64.77; H, 4.92; N, 17.98 %. Found: C, 64.51; H, 4.82; N, 18.02 %.

3. 11. 10. Ethyl 9-acetyl-10-(p-methoxyphenyl)-8-methyl-4-phenyl-pyrido[2́,3́:3,4] pyrazolo[5,1-c][1,2,4]triazine-3-carboxylate (17b)

It is obtained by using ethyl benzoyl-acetate as yellow crystals (ethanol). Yield: 1.9 g (79 %); m. p.: 199-200°C. IR: 1740 (C=O, ester), 1690 (C=O, acetyl).^{1}H NMR (CDCl3) (90 MHz): δ 7.0-7.9 (m, 9H, ArH's), 4.2-4.5 (q, 2H, OCH_2), 3.9 (s, 3H, OCH_3), 2.7 (s, 3H, $COCH_3$), 2.1 (s,3H, CH_3 at C-8), 1.0-1.3 (t, 3H, CH_3 of ester). Anal. Calcd. for $C_{27}H_{23}N_5O_4$ (481.50): C, 67.35; H, 4.81; N, 14.54 %. Found: C, 67.29; H, 4.77; N, 14.59 %.

3.12. Cyclization of compounds 14a-d; Formation of 3-functionalized 9-acetyl-4-amino-10-(p-methoxy-phenyl)-8-methylpyrido[2́,3́:3,4] pyrazolo[5,1-c][1,2,4]triazines 15a-d; General procedure

A solution of **14a-d** (0.002 mol) in glacial acetic acid (10 ml) was heated under reflux for 30 min. and then left to cool. The precipitate was collected and recrystallized from acetic acid to give yellow crystals of **15a-d**.

3.12.1. 9-Acetyl-4-amino-10-(p-methoxyphenyl)-8-methylpyrido [2́,3́:3,4]pyrazolo [5,1-c] [1,2,4] triazine-3-carbonitrile (15a)

It is prepared by using compound **14a** in the above general procedure. Yield: 0.6 (80%); m. p.: 309-310°C. IR: 3500, 3400 (NH_2), 2200 (C≡N), 1700 (C=O). MS: m/z = 372 (M^+-1, 22 %), 357 (M^+-NH_2, 37 %), 28(N_2^+ 100 %). Anal. Calcd. for $C_{19}H_{15}N_7O_2$ (373.37): C, 61.12; H, 4.05; N, 26.26 %. Found: C, 61.19; H, 3.92; N, 26.39 %.

3.12.2. Ethyl 9-acetyl-4-amino-10-(p-methoxyphenyl)-8-methylpyrido[2́,3́:3,4]pyrazolo[5,1-c][1,2,4]triazine-3-carboxylate (15b)

It is prepared by using compound **14b**. Yield: 0.7(83%); m. p.: 268-270°C. IR: 3380, 3280 (NH_2), 1680 (2 C=O). ^{1}H NMR ($CDCl_3$) (90 MHz): δ 8.9 (s, 1H, NH), 8.4 (br. s, 1H, NH), 7.5-7.7 (d, 2H, ArH's), 7.0-7.2 (d, 2H, ArH's), 4.3-4.6 (q, 2H, OCH_2), 3.9 (s, 3H, OCH_3), 2.7 (s, 3H, $COCH_3$), 2.0 (3H, CH_3 at C-8), 1.3-1.6 (t, 3H, CH_3 of ester). MS: m/z = 420 (M^+, 12%), 405 (M^+-Me, 2 %), 347 (M^+-CO_2Et, 5 %), 18 (H_2O^+). Anal. Calcd. for $C_{21}H_{20}N_6O_4$ (420.42): C, 59.99; H, 4.79; N, 19.99 %. Found: C, 59.78; H, 4.71; N, 20.02 %.

3.12.3. 9-Acetyl-4-amino-10-(p-methoxyphenyl)-8-methylpyrido [2́,3́:3,4]pyrazolo [5,1-c][1,2,4] triazine-3-carbothioamide (15c)

It is prepared by using compound **14c** in the above general procedure. Yield: 0.65 (80 %); m. p.: >360°C. IR: 3430, 3300, 3150 (2 NH_2), 1690 (C=O). Anal. Calcd. for $C_{19}H_{17}N_7O_2S$ (407.45): C, 56.01; H, 4.21; N, 24.06; S, 7.87 %. Found: C, 56.16; H, 4.08; N, 24.00; S, 7.77 %.

3.12.4. 9-Acetyl-4-amino-3-benzoyl-10-(p-methoxyphenyl)-8-methyl-pyrido[2́,3́:3,4] pyrazolo[5,1-c] [1,2,4]triazine (15d)

It is prepared by using compound **14d** in the above general procedure. Yield: 0.7 g (77 %); m. p.: 288-290°C. IR: 3500, 3400 (NH_2), 1700 (C=O). ^{1}H NMR ($CDCl_3$): δ 7.1-8.4 (m, 11H: NH_2 and ArH's), 4.0 (s, 3H, OCH_3), 2.8 (s, 3H, $COCH_3$), 2.1 (3H, CH_3 at C-8). Anal. Calcd. for $C_{25}H_{20}N_6O_3$ (452.47): C, 66.36; H, 4.46; N, 18.57 %. Found: C, 66.30; H, 4.45; N, 18.45 %.

4. Conclusion

In this paper we have successfully prepared the starting compound, 5-acetyl-3-amino-4-(*p*-methoxyphenyl)-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine (**3**) and converted it into the corresponding diazonium chloride **10**. Also, the synthetic utility of both **3** and **10** for preparation of new pyrazolopyridines, pyridopyrazolo-pyrimidines and pyridopyrazolo-triazines with anticipated biological activities was evaluated.

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