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THE USE OF 3-AMINO-4,6-DIMETHYL-PYRAZOLO[3,4-*b*]PYRIDINE IN THE SYNTHESIS OF NOVEL HETEROCYCLES OF PHARMACEUTICAL INTEREST

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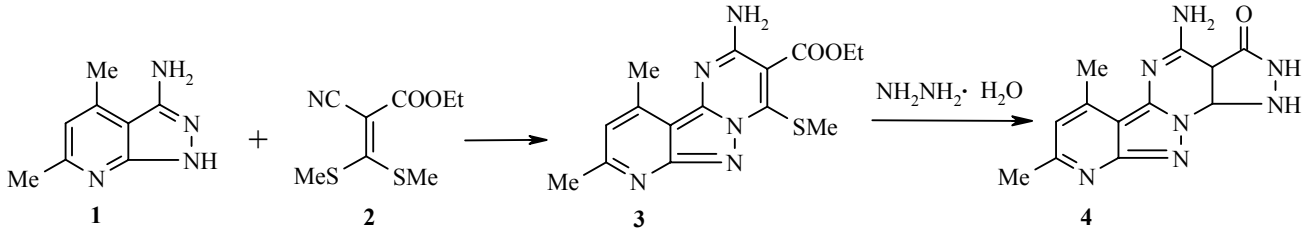
3-Amino-4,6-dimethylpyrazolo[3,4-b]pyridine was used for the preparation of some novel heterocycles of pharmaceutical interest. The starting material reacted with 2-cyano- 3,3-bis(methylthio)acrylate, chloroacetyl chloride, phenyl isothiocyanate, carbon disul- fide, and aromatic aldehydes to give the novel heterocycles. The structures of the hitherto unknown ring systems have been confirmed by analytical and spectral methods.

Keywords: pyrazolo[4,3-*e*]pyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidines, pyrido[2', 3':3,4]pyrazolo-[1,5-*a*]pyrimidines, substituted[3,4-*b*]pyridines.

In general, pyrazolopyridines represent a chemically unique class of non-sedative anxiolytic agents [1]. The treatment of 3-amino-4,6-dimethyl-pyrazolo[3,4-*b*]pyridine (**1**) with ethyl 2-cyano-3,3-bis(methylthio)-acrylate (**2**) [2] in DMF allowed the isolation of a compound which possessed elemental analysis and spectral data concordant with the formation of pyridopyrazolopyrimidine **3** (Scheme 1). The IR spectrum is characterized by the presence of strong absorption bands of NH_2 group at ν 3384 and 3247 cm^{-1} and carbonyl group at ν 1680 cm^{-1}. The ^1H NMR spectrum showed a triplet signal at δ 1.50 (CH_3 ester), a singlet at δ 2.70 (CH_3 pyridine), a singlet at δ 2.85 (CH_3 pyridine), a singlet at δ 3.10 (SCH_3), a quartet at δ 4.50 (ester CH_2), and a singlet at δ 7.00 (pyridine C-5 proton). The mass spectrum exhibited the molecular ion peak at *m/z* 332 [M^+ + H] (100%) corresponding to the formula [$C_{15}H_{17}N_5O_2S$ + H] in addition to other peaks at 189 (54%) and 163 (95%).

Scheme 1



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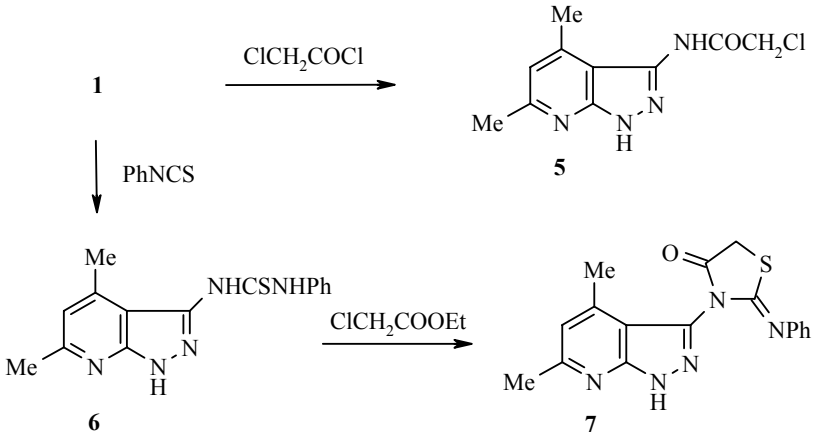
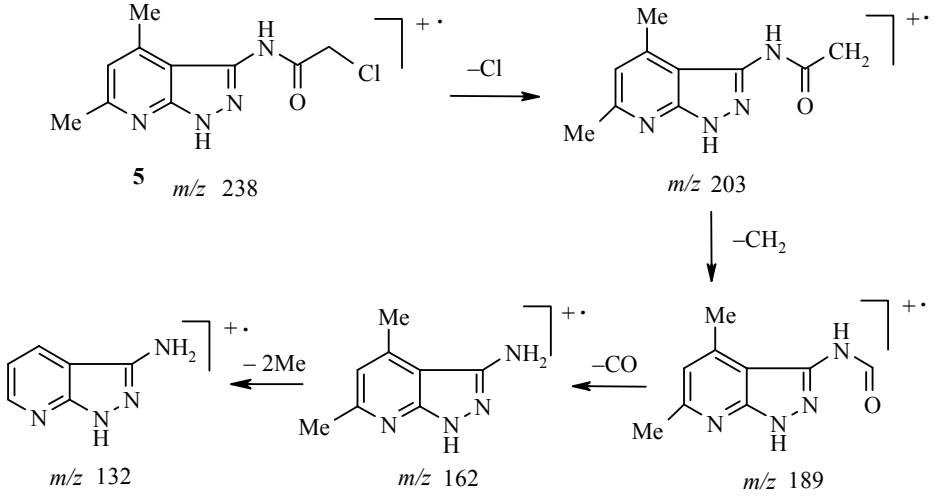
The treatment of compound **3** with hydrazine hydrate afforded the corresponding fused tetracyclic compound **4**. The formation of compound **4** is assumed to proceed *via* replacement of the SMe group by hydrazine followed by a loss of 1 mol of ethanol through the reaction with the ester group. The structure of compound **4** was confirmed by its spectral data and elemental analysis. The IR spectrum of compound **4** showed three absorption bands at 3422, 3365, and 3211 cm^{-1} assigned to the stretching vibrations of NH_2 and NH groups, in addition to the absorption band at 1654 cm^{-1} due to the amidic carbonyl group. The ^1H NMR spectrum revealed three singlet signals at δ 2.80, 2.90, and 7.10 due to the protons of two methyl groups and pyridine ring, respectively.

Scheme 2



The reaction of compound **1** with chloroacetyl chloride in DMF containing a few drops of triethylamine afforded the corresponding 3-(N-chloroacetyl- amino)pyrazolo[3,4-*b*]pyridine derivative **5** (Scheme 2). The IR spectrum of compound **5** showed three absorption bands at 3247, 3215, and 1669 cm^{-1} assigned to the stretching vibration of the two NH and CO groups, respectively. The ^1H NMR spectrum revealed two singlet signals at δ 2.40 and 2.50 ppm corresponding to the protons of two methyl groups, a singlet at δ 4.25 due to methylene protons, a singlet at δ 6.80 for the pyridine H-5 proton, in addition two singlet signals at δ 10.30 and 13.10 ppm due to the protons of two NH groups. The mass spectrum exhibited the molecular ion peak at *m/z* 238 [M^+] (95%) in addition to other peaks at 203 (16), 189 (40), 162 (100), 133 (20), 107 (22), 77 (18). The fragmentation pattern is shown in Scheme (3).

Scheme 3

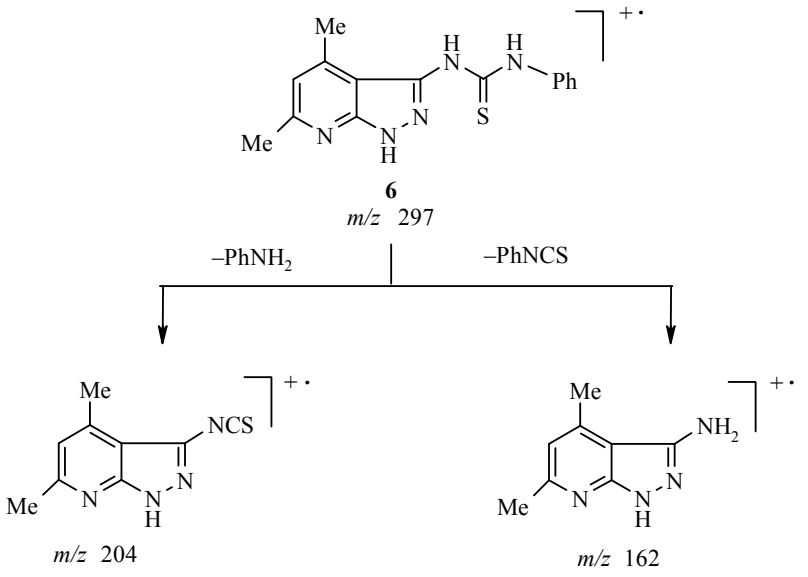


When compound **1** was allowed to react with phenyl isothiocyanate in boiling pyridine, the corresponding thiourea derivative **6** was produced, which underwent cyclization to thiazolidinone derivative **7** by reacting with ethyl chloroacetate in ethanol–pyridine mixture, 3:1. The structure of products **6** and **7** was secured by their elemental analyses and spectral data. For example, the IR spectrum of compound **7** showed the characteristic absorption bands of NH (3174) and CO (1720 cm^{-1}). The ^1H NMR displayed three singlet signals at δ 2.50, 2.80, and 4.25 corresponding to the protons of two Me and CH_2 groups, a singlet at δ 7.10 for pyridine H-5 proton, and a multiplet at δ 7.30–7.60 ppm for aromatic protons.

Moreover, the mass spectrum of compound **7** gave *m/z* 337 [M^+] (I_{rel} 100%) which corresponds to the molecular weight of the molecular formula $C_{17}H_{15}N_5OS$ of the assigned structure.

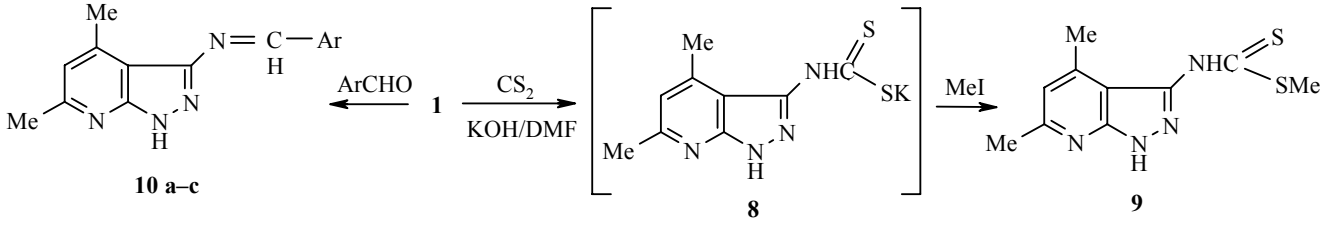
The mass spectrum of compound **6** gave *m/z* 297 [M^+] (I_{rel} 10%) corresponding to the molecular weight of the molecular formula $C_{15}H_{15}N_5S$ of the assigned structure (Scheme 4).

Scheme 4



Methyl dithiocarbamates are useful precursors in the synthesis of many important heterocyclic compounds, e.g., tetrahydroquinazolines or 3,1-benzoxazines [3]. It was found that the base-promoted nucleophilic addition of compound **1** to carbon disulfide in DMF containing potassium hydroxide afforded the corresponding non-isolable intermediate potassium salt **8.** Subsequent treatment of the latter with methyl iodide furnished the corresponding methyl-N-(pyrazolo[3,4-*b*]-3-pyridyl) dithiocarbamate **9** (Scheme 5). The IR

Scheme 5



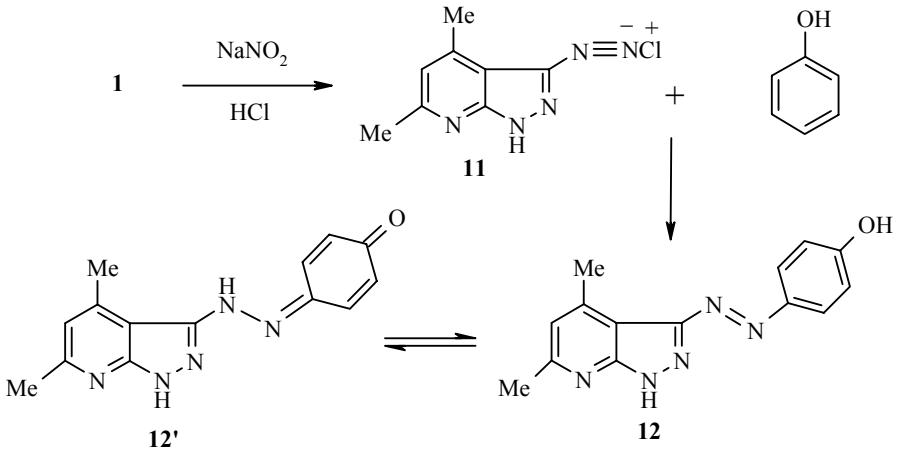
10 a Ar = 2-$O_2NC_6H_4$, **b** Ar = 3-$O_2NC_6H_4$, **c** Ar = 4-$O_2NC_6H_4$

spectrum of compound **9** showed absorption bands at 3391 (NH), 3160 (NH), and 1618 cm^{-1} (C=N). The ^1H NMR spectrum revealed two singlet signals at δ 2.40 and 2.60 due to six protons of methyl groups, a singlet at δ 6.80 for the pyridine proton, in addition to two singlet signals at δ 11.40, and 13.15 due to two NH protons. The mass spectrum gave the molecular ion peak at *m/z* 252 [M^+] (10%) and other fragmentation peaks at 204 (100), 170 (12), 84 (22), 78 (38).

Azomethines are important building blocks in enantioselective oxidations (chiral oxaziridines) [4], cycloadditions [5–8], and cyclizations [9]. Compound **1** undergoes condensation with 2-, 3-, and/or 4-nitrobenzaldehyde in refluxing ethanol containing a few drops of piperidine to give the corresponding Schiff's bases **10**.

The key starting material, 3-aminopyrazolo[3,4-*b*]pyridine **1**, can react with sodium nitrite to give pyrazolopyridinyldiazonium salt **11** (Scheme 6).

Scheme 6

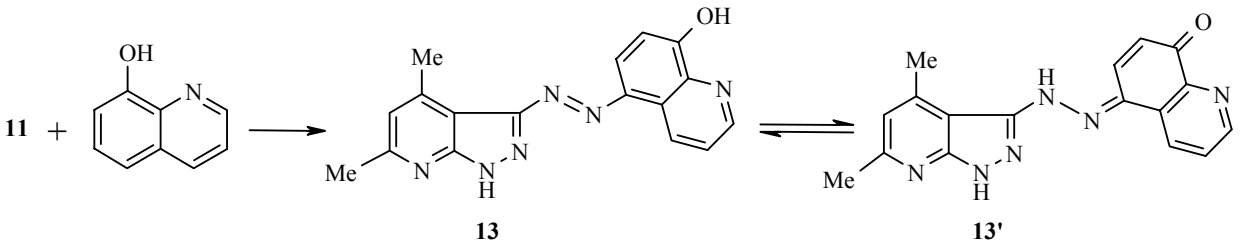


Azo coupling of the pyrazolopyridinyl diazonium salt **11** with phenol in the presence of sodium hydroxide afforded the corresponding azo derivative **12.** The chemical structure of compound **12** was proved by both analytical and spectral data. The IR spectrum showed stretching frequencies of NH at 3167 and C=N group at 1614 cm^{-1}. The ^1H NMR spectrum in CF_3COOD as a solvent revealed two singlet signals at δ 3.00 and 3.20 assigned to the two methyl groups, a singlet at δ 7.50 for pyridine H-5 proton, and two doublet signals at δ 7.70 and 8.20 ppm for the aromatic protons.

According to the previous DFT calculations at the B3LYP/6-31G* level [10], the azo tautomer **12** was found to be more stable by 3.6 kcal·mol^{-1} than the hydrazono tautomer **12'**.

Azo coupling of the pyrazolopyridinyldiazonium salt **11** with 8-hydroxy- quinoline afforded the corresponding azo derivative **13** (Scheme 7). The chemical structure of compound **13** was established on the basis of its analytical and spectral data.

Scheme 7



The IR spectrum showed stretching frequencies of NH at 3188, and C=N group at 1616 cm^{-1}. The ^1H NMR spectrum in CF_3COOD as a solvent revealed two singlet signals at δ 3.00 and 3.15 assigned to the two methyl groups, a singlet at δ 7.20 for pyridine H-5 proton, and a multiplet signal at δ 7.40-8.20 ppm for the aromatic protons.

EXPERIMENTAL

IR spectra were recorded on a SP-2000 Pye-Unicam Spectrometer. NMR spectra were obtained with Varian-Gemini 200 (200 MHz for ^1H) and Brucker 250 (250 MHz for ^1H and 62.5 MHz for ^{13}C) relative to TMS as an internal standard, δ 0 ppm. Mass spectra were recorded on a GCMS QP1000EX Schimadzu mass spectrometer at 70 eV. Melting points (uncorrected) were taken on a Fisher electric melting point apparatus. Elemental analyses were carried out in the Microanalytical Units, Faculties of Science, Mansoura and Cairo Universities.

Ethyl 2-amino-8,10-dimethyl-4-methylthiopyrido[2',3':3,4]pyrazolo[1,5-*a*]pyrimidine-3-carboxylate (**3**). A mixture of compound **1** (0.81 g, 0.005 mol) and ethyl 2-cyano-3,3-bis(methylthio)acrylate (**2**) (1.08 g, 0.005 mol) in 20 ml DMF was refluxed for 4 h, and then allowed to cool. The solid product that precipitated on cooling was filtered off, dried, and recrystallized from DMF as brown crystals. Yield 77%; mp 286–287°C. IR spectrum, ν, cm^{-1}: 3384, 3247 (NH_2), and 1680 (CO). ^1H NMR spectrum ($CDCl_3/CF_3COOD$), δ, ppm (*J*, Hz): 1.50 (3H, t, *J* = 7, CH_3); 2.70 (3H, s, CH_3); 2.85 (3H, s, CH_3); 3.10 (3H, s, CH_3); 4.50 (2H, q, *J* = 7, CH_2); 7.00 (1H, s, H-5 pyridine). Mass spectrum (M+H; CI *iso*-butane), *m/z* (I_{rel},%): 332 (100), 189 (54), 163 (95). Found, %: C 54.22; H 5.14; N 21.05. $C_{15}H_{17}N_5O_2S$ (331.39). Calculated, %: C 54.36; H 5.17; N 21.13.

4-Amino-6,8-dimethyl-1,2-dihydro-3H-pyrazolo[4,3-*e*]pyrido[2',3':3,4]pyrazolo-[1,5-*a*]pyrimidin-3-one (**4**). A mixture of compound **3** (1.65 g, 0.005 mol) and hydrazine hydrate (0.50 ml, 0.01 mol) in 20 ml DMF was refluxed for 4 h, and then allowed to cool. The reaction mixture was poured into ice-cooled water, and the precipitate was filtered off, dried, and recrystallized from ethanol–DMF mixture (1:1) as red crystals. Yield 44%; mp 265–266°C. IR spectrum, ν, cm^{-1}: 3422, 3365, 3211 (NH_2, NH), and 1654 (CO). ^1H NMR spectrum ($CDCl_3/CF_3COOD$), δ, ppm: 2.80 (3H, s, CH_3); 2.90 (3H, s, CH_3); 7.10 (1H, s, H-5 pyridine). Found, %: C 53.43; H 4.18; N 36.37. $C_{12}H_{11}N_7O$ (269.26). Calculated, %: C 53.53; H 4.12; N 36.41.

2-Chloro-N-(4,6-dimethyl-1H-pyrazolo[3,4-*b*]pyridin-3-yl)acetamide (**5**). To a solution of compound **1** (0.81 g, 0.005 mol) in DMF (15 ml) containing anhydrous sodium carbonate (0.70 g), chloroacetyl chloride (0.8 ml, 0.01 mol) was added dropwise with stirring at room temperature. Stirring was continued for 4 h, and the reaction mixture was poured into ice-cooled water. The precipitate was collected by filtration, dried, and recrystallized from ethanol–DMF mixture (1:1). Yield 84%; mp > 300°C. IR spectrum, ν, cm^{-1}: 3247, 3215 (NH), and 1669 (CO). ^1H NMR spectrum (DMSO), δ, ppm: 2.40 (3H, s, CH_3); 2.50 (3H, s, CH_3); 4.25 (2H, s, CH_2); 6.80 (1H, s, H-5 pyridine); 10.30 (1H, s, NH); 13.10 (1H, s, NH). ^{13}C NMR spectrum (DMSO), δ, ppm: 15.96; 22.50; 40.76; 106.98; 116.47; 135.36; 139.99; 150.64; 156.59; 165.35. Mass spectrum (EI), *m/z* (I_{rel},%): 238 (95), 203 (16), 189 (40), 162 (100), 133 (20), 107 (22), 77 (18). Found, %: C 50.40; H 4.60; N 23.52. $C_{10}H_{11}ClN_4O$ (238.67). Calculated, %: C 50.32; H 4.65; N 23.47.

1-(4,6-Dimethyl-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-3-phenylthiourea (**6**). A mixture of compound **1** (1.62 g, 0.01 mol) and phenyl isothiocyanate (1.20 ml, 0.01 mol) in pyridine was refluxed for 5 h and then allowed to cool. The solid product **6** was collected and recrystallized from DMF as white crystals. Yield 75%; mp > 300°C. IR spectrum, ν, cm^{-1}: 3436, 3208, 3168 (NH), and 1641 (C=N). ^1H NMR spectrum ($CDCl_3/CF_3COOD$), δ, ppm: 2.80 (3H, s, CH_3); 2.90 (3H, s, CH_3); 7.10 (1H, s, H-5 pyridine); 7.20-7.50 (5H, m, Ar-H). Mass spectrum (EI), *m/z* (I_{rel},%): 297 (10), 263 (18), 204 (100), 162 (95), 135 (15), 93 (30), 78 (68), 63 (68). Found, %: C 60.63; H 5.26; N 23.45. $C_{15}H_{15}N_5S$ (297.38). Calculated, %: C 60.58; H 5.08; N 23.55.

3-(4,6-Dimethyl-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-2-(phenylimino)thiazolidin-4-one (**7**). A mixture of compound **6** (1.48 g, 0.005 mol) and ethyl chloroacetate (0.55 ml, 0.005 mol) in ethanol–pyridine mixture (10:10, ml) was refluxed for 4 h, and then allowed to cool. The solid product **7** was collected and recrystallized from dioxane as yellow crystals. Yield 68%; mp > 300°C. IR spectrum, ν, cm^{-1}: 3174 (NH) and 1720 (CO). ^1H NMR spectrum ($CDCl_3/CF_3COOD$), δ, ppm: 2.50 (3H, s, CH_3); 2.80 (3H, s, CH_3); 4.25 (3H, s, CH_3); 7.10 (1H, s, H-5 pyridine); 7.30–7.60 (5H, m, Ar-H). Mass spectrum (EI), *m/z* (I_{rel},%): 337 (100), 290 (30), 264 (52), 189 (16), 160 (32), 149 (30), 104 (40), 77 (37). Found, %: C 60.48; H 4.56; N 20.67. $C_{17}H_{15}N_5OS$ (337.40). Calculated, %: C 60.52; H 4.48; N 20.76.

M**ethyl N-(pyrazolo[3,4-*b*]pyridin-3-yl)dithiocarbamate** (**9**). To a well stirred solution of compound **1** (1.62 g, 0.01mol) in DMF (20 ml) in an ice-bath were added dropwise and successively aqueous potassium hydroxide (0.56 g in 5 ml H_2O), carbon disulfide (0.6 ml), and methyl iodide (0.65 ml). Stirring was continued for 3 h, and the mixture was then poured into water. The solid thus obtained was filtered off, washed with water, and recrystallized from ethanol. Yield 62%; mp 246-247°C. IR spectrum, ν, cm^{-1}: 3391, 3160 (NH), and 1618 (C=N). ^1H NMR spectrum (DMSO), δ, ppm: 2.40 (3H, s, CH_3); 2.60 (6H, s, $2CH_3$); 6.80 (1H, s, H-5 pyridine), 11.40 (1H, s, NH); 13.15 (1H, s, NH). Mass spectrum (EI), *m/z* (I_{rel},%): 252 (10), 204 (100), 170 (12), 84 (22), 78 (38). Found, %: C 47.40; H 4.85; N 22.13. $C_{10}H_{12}N_4S_2$ (252.36). Calculated, %: C 47.59; H 4.79; N 22.20.

N-(Nitrobenzylidene)-1H-pyrazolo[3,4-*b*]-pyridin-3-amines (**10**) (General procedure). A mixture of compound **1** (0.81 g, 0.005 mol) and nitrobenzaldehyde (0.75 g, 0.005 mol) in ethanol containing of piperidine (0.5 ml) was refluxed for 2 h. The solid product precipitated on cooling was filtered off and recrystallized from ethanol.

N-(2-Nitrobenzylidene)-4,6-dimethyl-1H-pyrazolo[3,4-*b*]pyridin-3-amine (**10a**). Yield 80%; mp 246-247°C. IR spectrum, ν, cm^{-1}: 3096 (NH) and 1603 (C=N). ^1H NMR spectrum ($CDCl_3/CF_3COOD$), δ, ppm: 2.90 (3H, s, CH_3); 3.00 (3H, s, CH_3); 7.30 (1H, s, H-5 pyridine); 7.60–8.20 (4H, m, Ar-H); 10.00 (1H, s, N=CH). Mass spectrum (EI), *m/z* (I_{rel},%): 295 (18), 249 (15), 162 (31), 133 (15), 77 (16), 40 (100). Found, %: C 61.13; H 4.60; N 23.65. $C_{15}H_{13}N_5O_2$ (295.30). Calculated, %: C 61.01; H 4.44; N 23.72.

N-(3-Nitrobenzylidene)-4,6-dimethyl-1H-pyrazolo[3,4-*b*]pyridin-3-amine (**10b**). Yield 84%; mp 231-242°C. IR spectrum, ν, cm^{-1}: 3093 (NH) and 1608 (C=N). ^1H NMR spectrum ($CDCl_3/CF_3COOD$), δ, ppm: 2.90 (3H, s, CH_3); 3.00 (3H, s, CH_3); 7.30 (1H, s, H-5 pyridine); 7.70–8.55 (3H, m, Ar-H); 8.80 (1H, m, Ar-H); 10.00 (1H, s, N=CH). Mass spectrum (EI), *m/z* (I_{rel},%): 295 (100), 249 (40), 173 (44), 147 (45). Found, %: C 61.16; H 4.33; N 23.81. $C_{15}H_{13}N_5O_2$ (295.30). Calculated, %: C 61.01; H 4.44; N 23.72.

N-(4-Nitrobenzylidene)-4,6-dimethyl-1H-pyrazolo[3,4-*b*]pyridin-3-amine (**10c**). Yield 84%; mp >300°C. IR spectrum, ν, cm^{-1}: 3089 (NH) and 1597 (C=N). ^1H NMR spectrum ($CDCl_3/CF_3COOD$), δ, ppm (*J*, Hz): 2.90 (3H, s, CH_3), 3.00 (3H, s, CH_3); 7.30 (1H, s, H-5 pyridine); 8.25 (2H, d, *J* = 8, Ar-H); 8.50 (2H, d, *J* = 8, Ar-H); 10.10 (1H, s, N=CH). Mass spectrum (EI), *m/z* (I_{rel},%): 295 (100), 249 (48), 162 (30), 173 (12), 147 (40), 51 (18). Found, %: C 61.12; H 4.46; N 23.80. $C_{15}H_{13}N_5O_2$ (295.30). Calculated, %: C 61.01; H 4.44; N 23.72.

Synthesis of dyes 12 and 13 (General Method). The solution of diazonium salt **11** (0.01 mol) was added with continuous stirring to a cold solution (0-5ºC) of phenol (0.01 mol) or 8-hydroxyquinoline in 10% sodium hydroxide (25 ml). The reaction mixture was stirred at 0-5ºC for 2 h, and then neutralized with diluted HCl. The solid product was collected by filtration, dried, and recrystallized from ethanol-DMF mixture (3:1).

4-(4,6-Dimethylpyrazolo[3,4-*b*]pyridin-3-ylazo)phenol (**12**). Yield 82%; mp 267-268°C. IR spectrum, ν, cm^{-1}: 3167 (NH) and 1614 (C=N). ^1H NMR spectrum (CF_3COOD), δ, ppm (*J*, Hz): 3.00 (3H, s, CH_3); 3.20 (3H, s, CH_3); 7.50 (1H, s, H-5 pyridine); 7.70 (2H, d, *J* = 8, Ar-H); 8.20 (1H, d, *J* = 8, Ar-H). Found, %: C 62.78; H 4.81; N 26.13. $C_{14}H_{13}N_5O$ (267.29). Calculated, %: C 62.91; H 4.90; N 26.20.

5-(4,6-Dimethylpyrazolo[3,4-*b*]pyridin-3-ylazo)-8-hydroxyquinoline (**13**). Yield 88%; mp > 300°C. IR spectrum, ν, cm^{-1}: 3188 (NH) and 1616 (C=N). ^1H NMR spectrum (CF_3COOD), δ, ppm: 3.00 (3H, s, CH_3);

3.15 (3H, s, CH_3); 7.20 (1H, s, H-5 pyridine); 7.40–8.20 (5H, m, Ar-H). Found, %: C 64.33; H 4.52; N 26.48. $C_{17}H_{14}N_6O$ (318.33). Calculated, %: C 64.14; H 4.43; N 26.40.

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