An Efficient Synthesis of Pyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridines from 5-Aminopyrazoles and Cyclic β-Keto Ester

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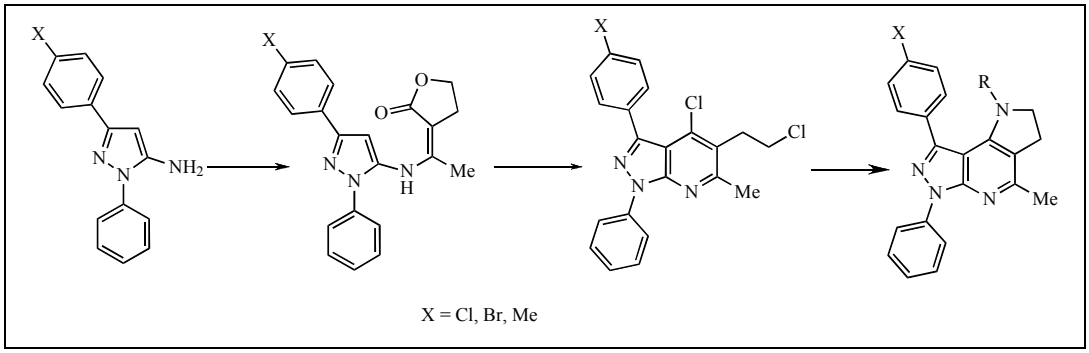

5-Chloroethylpyrazolo[3,4-*b*]pyridines were synthesized by condensation of 5-aminopyrazoles with α-acetyl γ-butyrolactone followed by cyclization treating with phosphorous oxychloride. 5-Chloroethyl-pyrazolo[3,4-*b*]pyridines, thus obtained, were then converted to the corresponded tricyclic pyrazolo[3,4-*b*]-pyrrolo[2,3-*d*]pyridines by treating with some primary amines.

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INTRODUCTION

Pyrazolo[3,4-*b*]pyridine system has shown many interesting biological and pharmacological applications such as antitubercular activity [1,2], against gram positive and negative bacteria [3] and ACTH (Adrenocorticotropic hormone) releasing factor (CRF: Corticotrophin-releasing factor) antagonist activity. CRF antagonists prove to be effective in the treatment of a wide variety of stress-related illnesses such as depression, gastrointestinal diseases, anorexia nervosa, haemorrhaged stress, drug and alcohol withdrawal symptom [4]. Pyrido[1,2-*a*]-pyrimidines having 3-chloroethyl side chain also showed interesting biological activities [5-8].

In our recent publication [9], some fused pyrimidines were synthesized by condensation of the corresponding 2-aminoheterocycles with α-formyl lactones. In our other previous papers [10-12], pyrazolo[3,4-*b*]pyridines were synthesized by *Friendlander* condensation of 5-amino-pyrazole-4-carbaldehyde with various reactive methylene compounds and the heterocyclic compounds with chloroethyl side chain [13]. In literature the pyrazolo[3,4-*b*]pyridines have been so far obtained by condensation of aminopyrazoles with α,β-unsaturated compounds [14-18], diethylethoxymethylenemalonate [19,20], active esters [21], cyclic ketones [11,12] and amides [12]. In the present paper, we have used the versatile cyclic β-ketoester *e.g.* α-acetyl-γ-butyrolactone [22] and 5-aminopyrazoles [23] for the synthesis of pyrazolo[3,4-*b*]pyridines having intractable substitutions such as 4-chloro and 5-(2-chloroethyl) side chain, which may increase the pharmacological activity and further facilitate the synthesis of new molecules. Thus, a new class of tricyclic heterocycles such as pyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridines were obtained due to these strategic substitution by condensation with amino/thio compounds.

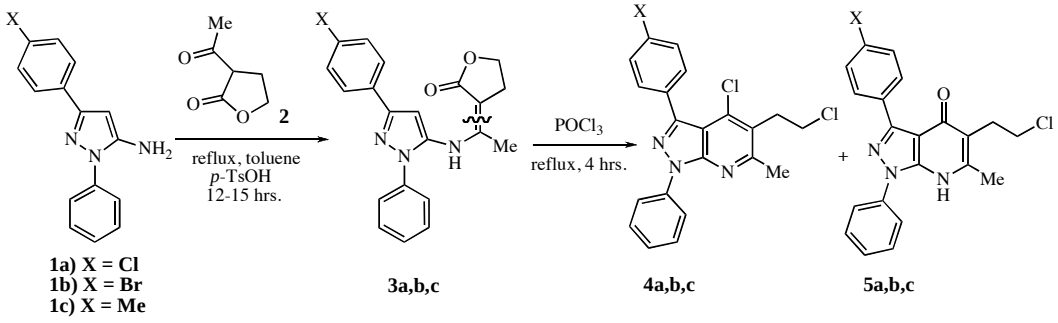
RESULTS AND DISCUSSION

The intermediates aminopyrazolodihydrofuranone **3**, (Scheme 1) were obtained by condensation reaction of 5-aminopyrazoles **1** with α-acetyl-γ-butyrolactone **2** in toluene at reflux temperature in presence of catalytic amount of *p*-toluene sulphonic acid using Dean Stark apparatus. Here, the *p*-toluenesulphonic acid used as a selective catalyst, protonates the oxygen of keto carbonyl of lactone and subsequent attack of amino function yield the enamine intermediates **3**. The use of other acids such as sulphuric acid, hydrochloric acid, acetic acid or ammonium acetate or neat reaction conditions leads to inseparable mixture of products. The compounds **3** were characterized by IR, ^{1}H nmr, mass spectroscopy and elemental analysis. For instance IR of **3a** showed lactone carbonyl stretching at 1689 cm^{-1}, NH at 3287 cm^{-1} and (C=C) at 1597 cm^{-1}. The ^{1}H nmr of this compound in $CDCl_3$ showed a singlet at δ 1.92, for methyl group, two

triplets were observed at δ 2.83, (-CH_2-) and δ 4.35, (-CH_2O-) with J = 7 Hz. The broad singlet exchangeable with D_2O assigned for -NH appeared down field at δ 9.93, and the singlet at δ 6.41 corresponding to C_4H proton. The aromatic protons showed expected chemical shifts and splitting pattern. The mass spectra of **3a** showed M+ and M+2 at 379 and 381m/z due to presence of chlorine. The elemental analysis of this compound was also in agreement with the proposed structure. The obtained aminopyrazolodihydrofuranone **3** were cyclised by refluxing in $POCl_3$, which furnished a mixture of compounds **4** and **5** (TLC check). The reaction mixtures were separated readily by column eluting with toluene/ acetone (9:1) v/v to give about 75 % of **4** and 17 % of **5** as colorless solids. The structures of **4** and **5** were established by spectral and analytical data, the compound **4a** showed absence of carbonyl and –NH stretching frequency in IR, while compound **5a** showed pyridine carbonyl at 1629 cm^{-1} and –NH stretching frequency at 3433 cm^{-1}. The ^{1}H nmr of **5a** in $CDCl_3$ clearly showed the presence of -NH as broad exchangeable singlet at δ 11.50, whereas this peak was absent for **4a**. The mass spectrum of **4a** showed M+, M+2, M+4 and M+6 at 416, 418, 420 and 422 m/z respectively, due to presence of three chlorine atoms and **5a** showed M+, M+2 and M+4 at 398, 400 and 402 m/z due to presence of two chlorine atoms. Further, elemental analyses were in agreement with the proposed structures of **4a** and **5a**. On the basis of this spectral and analytical data structure **4a** was assigned to this compound *i.e*. 4-chloro-5-(2-chloroethyl)-3-(4-chlorophenyl)-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine and **5a** assigned to this compound *i.e.* 5-(2-Chloroethyl)-3-(4-chlorophenyl)-6-methyl-1-phenyl-1,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one. Analogously compounds **4b**, **4c** and **5b**, **5c** were characterized and assigned. The facile and well-documented nucleophilic substitutions [19,20] in the 4-halopyrdine systems **4** were also studied. The nucleophiles used in our study were namely $^-OC_2H_5$, β-hydrxoyethyl system and azide. With azide and ethylenegycol, only substitution at 4-position occurred to yield compounds **7** and **8** (Scheme 2). While with more basic solution using $^-$OEt/EtOH, substitution at 4-position as well as elimination of HCl from the β-chloroethyl moiety yielded **6**. These compounds were characterized by spectral and analytical methods. The band at 1591 cm^{-1} in IR spectrum of **6a** shows presence of C=C, and the signals at δ 3.71 (2H, quartet) and δ 1.12 (3H, triplet) with (J = 7 Hz) in ^{1}H NMR spectrum shows presence of O-CH_2CH_3. The doublet of doublet corresponding to =CH_2 protons at δ 5.57 and 5.76 ppm, (J = 5.3 Hz) and the multiplate corresponding to =CHR proton were observed at δ 6.70-6.84 ppm. The compound **4** on heating in DMF at 80-90 °C with sodium azide yielded azido derivatives **7**. This reaction was selective to replace chlorine on γ-position of pyridine ring [24], which is confirmed by ^{1}H nmr spectra of compound **4** and **7**, where there is no considerable difference in the signals of both compounds. The compound **7a** showed IR absorption peak at 2100 cm^{-1} for azide. The compound **4** when refluxed with ethylene glycol in presence of triethyl amine gives nucleophilic aromatic substitution reaction on pyridine ring to yield compound **8**. The pyrazolo[3,4-*b*]thieno[2,3-*d*]pyridine **9** were obtained in single step by the reaction of thiourea and **4** in acetic acid in 65-70 % yield.

The targeted new fused heterocyclic compounds pyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridines **10** were successfully synthesized in 75-85 % yield, from pyrazolo[3,4-*b*]-pyridines **4** by neat reaction with primary amines. The aliphatic and aromatic nucleophilic substitution reactions were facilitated due to presence of 4-chloro and 5-chloroethyl moieties on pyridine nucleus. The compounds **9** and **10** were characterized by IR, ^{1}H NMR, mass and elemental analysis given in experimental part. The compound **10** showed bathchromic shift in UV due to presence of substituted pyrrole as a donor and pyridine as acceptor [25]. It was observed that compound **4a** showed λ_{max} 362 nm, fluorescent at 394 nm while compound **10a** showed λ_{max} 374 nm, fluorescent at 404 nm and **10b** showed λ_{max} 392 nm, fluorescent at 417 nm (Scheme 2).

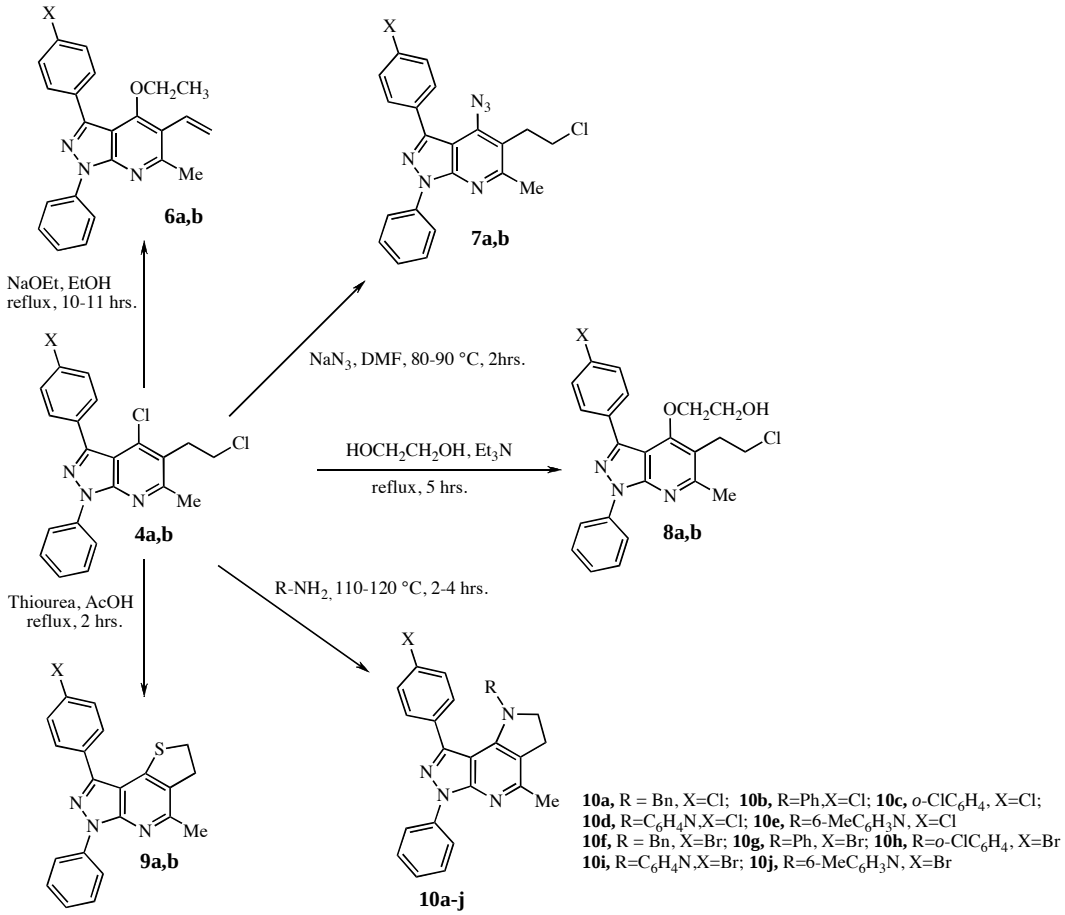
Scheme 1



1a) X = Cl
1b) X = Br
1c) X = Me

3a,b,c **4a,b,c** **5a,b,c**

Scheme 2



10a, R = Bn, X=Cl; **10b,** R=Ph,X=Cl; **10c,** *o*-ClC$_6$H$_4$, X=Cl; **10d,** R=C$_6$H$_4$N,X=Cl; **10e,** R=6-MeC$_6$H$_3$N, X=Cl **10f,** R = Bn, X=Br; **10g,** R=Ph, X=Br; **10h,** R=*o*-ClC$_6$H$_4$, X=Br **10i,** R=C$_6$H$_4$N,X=Br; **10j,** R=6-MeC$_6$H$_3$N, X=Br

The methods described the facile route towards the synthesis of new pyrazolo[3,4-*b*]pyridines having chloroethyl side chain by using cyclic β-ketoesters and 5-aminopyrazoles. The work was further elaborated on side chain and obtained new class of tricyclic heterocycles such as pyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridines.

EXPERIMENTAL

Melting points were determined on a Barnstead Electro Thermal melting point apparatus, Mod. No. IA-9200 in open capillary tubes and are uncorrected. ^{1}H nmr Spectra were recorded on Varian XL-300 spectrometer (300MHz). Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given δ-units. The solvents for NMR spectra was duterio-chloroform unless otherwise stated. Infrared spectra were taken on Shimadzu IR-408, instrument in potassium bromide pellets unless otherwise stated. Elemental analyses were performed on a Hosli CH-Analyzer and are within ± 0.3 of the theoretical percentage. High-resolution mass spectra were obtained with a Mat 112 Varian Mat Bremen (70 eV) mass spectrometer. Column chromatography was carried out on silica gel (SD Fine Chemicals, 60-80 mesh). Solutions were concentrated in a rotary evaporator under reduced pressure. All reactions were monitored by thin layer chromatography (TLC), carried out on 0.2 mm silica gel 60 F 254 (Merck) plates using UV light (254 and 366 nm) for detection. Common reagents-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

General procedure for the synthesis of 3-(1-{[3-(4-Aryl)–1-phenyl-1*H*-pyrazol-5-yl]amino}ethylidine)dihydrofuran-2(3*H*)-one (3). A mixture of 5-ami- nopyrazole **1** (0.01 mole) and α-acetyl-γ-butyrolactone **2** (1.282 g, 1.078 mL 0.01 mole) was refluxed in toluene (50 mL) in presence of catalytic amount of *p*-toluene sulphonic acid at for 12-15 hrs. by using Dean Stark apparatus (The reaction was monitored by separation of equivalent amount of water), toluene was removed under reduced pressure. The residue was dissolved in ethanol (20 mL), heated for 15 min. under reflux and then the mixture was cooled at rt. The solid that separated our was collected by suction filtration, washed with ethanol, dried and recrystallized from suitable solvent to furnished compound **3** in good yield.

3-(1-{[3-(4-Chlorophenyl)–1-phenyl-1*H*-pyrazol-5-yl]amino}-ethylidine)dihydrofuran-2(3*H*)-one (3a). This compound was obtained as light yellow prism (ethanol), 3.39 g (90 %), mp 171-172 °C; ir (potassium bromide): 3287s, 1689s, 1597m, 1444m, 1283w, 1230w, 956m, 834w cm^{-1}; ^{1}H nmr (CDCl$_3$): δ = 1.92 (s, 3H, CH$_3$), 2.83 (t, *J* = 7.5 Hz, 2H, CH$_2$), 4.31 (t, *J* = 7.1 Hz, 2H, CH$_2$), 6.41 (s, 1H, C$_4$-H), 7.36-7.50 (m, 5H, Ar-H), 7.55 (d, *J* = 7.8 Hz, 2H, Ar-H), 7.76 (d, *J* = 8.4 Hz, 2H, Ar-H), 9.90 (s, 1H, NH). MS: m/z (%) = 381 (30) [M+2], 379 (90) [M], 361 (40),

330 (10), 304 (15), 255 (07), 166 (10), 152 (13), 113 (50), 77 (100), 63 (10). *Anal*. Calcd. for $C_{21}H_{18}ClN_3O_2$: C, 66.40; H, 4.78; N, 11.06. found. C, 66.33; H, 4.49; N, 11.21.

3-(1-{[3-(4-Bromophenyl)-1-phenyl-1*H*-pyrazol-5-yl)amino}-ethylidine)dihydrofuran-2(3*H*)-one (3b). This compound was obtained as yellow needles (ethanol), 3.73 g (88 %), mp189-190 °C; ir (potassium bromide): 2993s, 1691s, 1641m, 1226w, 1230w, 1026m, 761w cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.89 (s, 3H, CH_3), 2.80 (t, *J* = 7.3 Hz, 2H, CH_2), 4.28 (t, *J* = 7.1 Hz, 2H, CH_2), 6.38 (s, 1H, C_4-H), 7.34-7.51 (m, 5H, Ar-H), 7.67 (d, J = 7.9 Hz, 2H, Ar-H), 7.70 (d, J = 8.5 Hz, 2H, Ar-H), 9.87 (s, 1H NH). MS: m/z (%) = 429 (40) [M+4], 427 (90) [M+2], 425 (90) [M], 404 (10), 378 (25), 362 (20), 338 (30), 313 (12), 259 (15), 197 (20), 157 (25), 117 (14), 91 (30), 77 (100). *Anal*. Calcd. for $C_{21}H_{18}BrN_3O_2$: C, 59.45; H, 4.28; N, 9.90. found. C, 59.24; H, 4.42; N 10.10.

3-(1-{[3-(4-Methylphenyl)-phenyl-1*H*-pyrazol-5-yl]amino}-ethylidine)dihydrofuran-(3*H*)-one (3c). This compound was obtained as yellow needles (ethanol), mp 160-161 °C; ir (potassium bromide): 2993s, 1695s, 1614m, 1126w, 1026w, 765w cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.89 (s, 3H, CH_3), 2.37 (s, 3H, Ar-CH_3), 2.81 (t, *J* = 7.5 Hz, 2H, CH_2), 4.29 (t, *J* = 7 Hz, 2H, CH_2), 6.40 (s, 1H, C_4-H), 7.22-7.42 (m, 5H, Ar-H), 7.56 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.71 (d, J = 8.1 Hz, 2H, Ar-H), 9.86 (s, 1H, NH). *Anal*. Calcd. for $C_{22}H_{21}N_3O_2$: C, 73.52; H, 5.89; N, 11.69. found. C, 73.39; H, 5.48; N, 11.10.

General procedure for the Synthesis of 4-Chloro-5-(2-chloroethyl)-3-(4-aryl)-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (4) and 5-(Chloroethyl)-3-(4-aryl)-6-methyl-1-phenyl-1,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4one (5). The aminopyrazolodihydrofuranone **3** (0.01mole) was refluxed in phosphorous oxychloride (20 mL) until the end of the exothermic reaction, which usually starts about 80–90 °C. The mixture was then refluxed for further 4 hrs. Excess $POCl_3$ was removed under vacuum and the oily residue was solidified upon treatment with ice-water neutralization with sodium carbonate and stirring overnight. The separated product was then collected by filtration and dried. TLC analysis showed two products in 95 % overall yield. These two solids were separated by column chromatography (Merck silica gel 60 H, 5-40μm). Using toluene and toluene / acetone (9:1) as eluent to afford pyrazolo[3,4-*b*]pyridine **4** in 80 % and pyrazolo[3,4-*b*]pyridin-4-one **5** in 15 % yields. Respectively.

4-Chloro-5-(2-chloroethyl)-3-(4-chlorophenyl)-6-*m*-ethyl-1-phenyl-*1H*-pyrazolo[3,4-*b*]pyridine (4a). This compound was obtained as colorless prisms (acetonitrile and ethanol), 3.24 g (78 %), mp163-164 ºC; ir (potassium bromide): 2918m, 1595m, 1500s, 1257m, 1147m, 1093w, 1018w, 906w, 756m, 686w cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.81 (s, 3H CH_3), 3.39 (t, *J* = 7.2 Hz, 2H, CH_2), 3.75 (t, *J* = 7.3 Hz, 2H, CH_2), 7.44-7.54 (m, 5H, Ar-H), 7.69 (d, *J* = 8.2,Hz, 2H, Ar-H), 8.26 (d, *J* = 7.8, Hz, 2H, Ar-H). MS: m/z (%) = 422 (20) [M+6], 420 (60) [M+4], 418 (92) [M+2], 416 (90) [M], 366 (10), 255 (10), 111 (15), 85 (40), 71(60), 57 (100), 55 (30). *Anal*. Calcd. for $C_{21}H_{16}Cl_3N_3$: C, 60.52; H, 3.87; N, 10.08. found. C, 61.02; H, 3.68; N, 10.18.

3-(4-Bromophenyl)-4-chloro-5-(2-chloroethyl)-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (4b). This compound was obtained as colorless needles (acetonitrile and ethanol), 3.55 g (77 %), mp 175-176 ºC; ir (potassium bromide): 2918m, 1595m, 1500s, 1255m, 1149m, 1093w, 1018w, 910w, 759m, 686w cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.82 (s, 3H, CH_3), 3.40 (t, J = 7.2 Hz, 2H, CH_2), 3.70 (t, J = 7.3 Hz, 2H, CH_2), 7.29-7.48 (m, 5H, Ar-H), 7.53 (d, J = 8.2 Hz, 2H, Ar-H), 8.14 (d, J = 7.8 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{21}H_{16}BrCl_2N_3$: C, 54.69; H, 3.50; N, 9.11. found. C, 54.98; H, 3.78; N, 9.21.

4-Chloro-5-(2-chloroethyl)-6-methyl-3-(4-methylphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (4c). This compound was obtained as colorless needles (acetonitrile and ethanol), 2.57 g (65 %), mp 145-146 ºC; ir (potassium bromide): 2919m, 1592m, 1500s, 1255m, 1149m, 1093w, 1020w, 915w, 760m, 688w cm^{-1}. ^1H nmr ($CDCl_3$): δ = 2.39 (s, 3H, ArCH_3), 2.80 (s, 3H, CH_3), 3.38 (t, *J* = 7.5 Hz, 2H, CH_2), 3.68 (t, *J* = 7.3 Hz, 2H, CH_2), 7.30-7.56 (m, 5H Ar-H), 7.60 (d, *J* = 8.3 Hz, 2H, Ar-H), 8.18 (d, *J* = 7.8 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{22}H_{19}Cl_2N_3$: C, 66.67; H, 4.83; N, 10.60. found. C, 66.90; H, 4.58; N, 10.83.

5-(2-Chloroethyl)-3-(4-chlorophenyl)-6-methyl-1-phenyl-1,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4one (5a). This compound was obtained as light yellow prism (acetonitrile), 0.676 g (17 %), mp 225-226 °C; ir (potassium bromide): 3433m, 3072m, 1629s, 1496s, 1409w, 1249m, 995w, 931w, 837w, 750m, 690m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.59 (s, 3H, CH_3), 3.28 (t, *J* = 7.2 Hz, 2H, CH_2), 4.87 (t, *J* = 7.3 Hz, 2H, CH_2), 7.42-7.53 (m, 5H, Ar-H), 8.21 (d, *J* = 8.3 Hz, 2H, ArH), 8.31 (d, *J* = 7.9Hz, 2H, ArH) 11.50 (s, 1H, -NH). MS: m/z (%) = 402 (20) [M+4], 400 (40) [M+2], 398 (90) [M], 363 (70), 361 (100), 359 (92), 344 (15), 325 (20), 280 (14), 172 (10). *Anal*. Calcd. for $C_{21}H_{17}Cl_2N_3O$: C, 63.33; H, 4.30; N, 10.55. found. C, 63.56; H, 4.63; N 10.96.

3-(4-Bromophenyl)-5-(2-chloroethyl)-6-methyl-1-phenyl-1,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one (5b). This compound was obtained as colorless needles (acetonitrile), 0.664 g (15 %) mp 240-241 °C; ir (potassium bromide): 3448m, 1629s, 1496s, 1298w, 1247m, 995w, 931w, 835w, 758m, 690m cm^{-1}.^1H nmr ($CDCl_3$): δ = 2.57 (s, 3H, CH_3), 3.25 (t, J = 7.2 Hz, 2H, CH_2), 4.84 (t, J = 7.2 Hz, 2H, CH_2), 7.41-7.59 (m, 5H, Ar-H), 8.13 (d, J = 8.4 Hz, 2H, Ar-H), 8.34 (d, J = 8.1 Hz, 2H, Ar-H) 11.54 (s, 1H, -NH). *Anal*. Calcd. For C_{21} H_{17} N_3BrClN_3O: C, 56.97; H, 3.87; N, 9.49. found. C, 57.10; H, 4.05; N, 9.25.

5-(2-Chloroethyl)-6-methyl-3-(4-methylphenyl)-1-phenyl-1,7-dihydro-4*H*-pyrazolo[3,4-*b*]pyridin-4-one (5c). This compound was obtained as light brown needles (acetonitrile), 0.453 g (12 %), mp 212-213 °C; ir (potassium bromide): 3448m, 1629s, 1496s, 1298w, 1247m, 995w, 935w, 837w, 758m, 692m. cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.38 (s, 3H, Ar-CH_3) 2.58 (s, 3H, CH_3), 3.30 (t, J = 7.1 Hz, 2H, CH_2), 4.85 (t, J = 7.2 Hz, 2H, CH_2), 7.41-7.56 (m, 5H, Ar-H), 8.10 (d, J = 8.3 Hz, 2H, Ar-H), 8.38 (d, J = 8.1Hz, 2H, Ar-H) 11.48 (s, 1H, -NH). *Anal*. Calcd. for $C_{22}H_{20}ClN_3O$: C, 69.93; H, 5.33; N, 11.12. found. C, 70.10; H, 5.57; N 10.97.

General procedure for the Synthesis of 3-(4-Aryl)-4-ethoxy-6-methyl-1-phenyl-5-vinyl-1*H*-pyrazolo[3,4-*b*]pyridine (6). To a stirred solution of **4** (0.01 mole), sodium ethoxide [prepared by reacting 0.27 g , 11.5 mg atom of sodium with 50 mL of absolute ethanol] in ethanol was added and refluxed for about 10-11 hrs. The reaction progress was monitored by TLC. Excess of solvent was removed under reduced pressure. Obtained solid was collected by filtration, washed with ethanol, dried and recrystallized from the proper solvent to furnished compound **6** in good yield.

3-(4-Chlorophenyl)-4-ethoxy-6-methyl-1-phenyl-5-vinyl-1*H*-pyrazolo[3,4-*b*]pyridine (6a). This compound was obtained as colorless needles (ethanol), 2.45 g (63 %) mp 101-102 °C; ir (potassium bromide): 1745w, 1591s, 1500s, 1342w, 1278w,

997m, 837m, 758w, 690m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.12 (t, *J* = 6.7 Hz, 3H, ethoxy CH_3) 2.72 (s, 3H, CH_3), 3.71 (q, *J* = 6.7 Hz, 2H, ethoxy OCH_2), 5.57 (dd, 2H, $=CH_2$), 6.70-6.84 (m, 1H, =CHR), 7.31-7.50 (m, 5H, Ar-H), 7.98 (d, *J* = 8.1 Hz, 2H, Ar-H), 8.31 (d, *J* = 7.8 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{23}H_{20}ClN_3O$: C, 70.85; H, 5.17; N, 10.78. found. C, 70.58; H, 5.49; N, 11.01.

3-(4-Bromophenyl)-4-ethoxy-6-methyl-1-phenyl-5-vinyl-1*H*-pyrazolo[3,4-*b*]pyridine (6b). This compound was obtained as colorless needles (ethanol), 2.51 g (58 %) mp 109-111 °C; ir (potassium bromide): 1746w, 1592s, 1504s, 1342w, 1278w, 997m, 838m, 758w, 692m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 1.11 (t, J = 6.2 Hz, 3H, ethoxy CH_3) 2.74 (s, 3H, CH_3), 3.74 (q, J = 6.1 Hz, 2H, ethoxy OCH_2), 5.59 (dd, 2H, $=CH_2$), 6.71-6.80 (m, 1H, =CHR), 7.33-7.53 (m, 5H, Ar-H), 7.96 (d, *J* = 8.3 Hz, 2H, Ar-H), 8.30 (d, *J* = 8 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{23}H_{20}BrN_3O$: C, 63.60; H, 4.64; N, 9.67. found. C, 63.33; H, 4.84; N, 9.39.

General procedure for the synthesis of 4-Azido-5-(2-chloroethyl)-3-(4-aryl)-6-methyl-1-phenyl-1*H*-pyrazo- lo[3,4-*b*]pyridine (7). To a stirred solution of **4** (0.01 mole) in DMF/H_2O (9:1) the sodium azide (2.60 g, 0.04 mole) was added and temperature was raised slowly to 80 °C. The mixture was kept at this temperature for about 2 hrs. until TLC showed no more starting material. The temperature was then raised to 110 °C for 1h. Then the solvent was removed under reduced pressure to give an oily residue that was poured in ice-cold water and stirred for 1h. The solid obtained was collected by filtration, washed with water, dried and recrystallized from the proper solvent to furnished compound **7** in 40-45 % yield.

4-Azido-5-(2-chloroethyl)-3-(4-chlorophenyl)-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (7a). This compound was obtained light brown prisms (acetonitrile), 1.69 g (40 %), mp 167-168°C; ir (potassium bromide): 3390w, 2916w, 2100 (N_3) s, 1595w, 1498w, 1452m, 1301w, 1145m, 1093w, 837s, 759w, 692m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.80 (s, 3H, CH_3), 3.23 (t, *J* = 7.2 Hz, 2H CH_2), 3.51 (t, *J* = 7.5 Hz, 2H, CH_2), 7.31-7.55 (m, 5H, Ar-H), 7.67 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.25 (d, *J* = 7.8 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{21}H_{16}Cl_2N_6$: C, 59.59; H, 3.81; N, 19.85. found. C, 59.91; H, 4.10; N, 19.61.

4-Azido-3-(4-bromophenyl)-5-(2-chloroethyl)-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine (7b). This compound was obtained as light brown needles (acetonitrile), 2.33 g (50 %), mp181-182 °C; ir (potassium bromide): 3390w, 2916w, 2100 (N_3) s, 1595w, 1498w, 1452m, 1301w, 1145m, 1093w, 837s, 759w, 692m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.79 (s, 3H, CH_3), 3.25 (t, *J* = 7.2 Hz, 2H, CH_2), 3.53 (t, *J* = 7.5 Hz, 2H, CH_2), 7.35-7.58 (m, 5H, Ar-H), 7.69 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.27 (d, *J* = 7.8 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{21}H_{16}BrClN_6$: C, 53.92; H, 3.45; N, 17.97. found. C, 53.65; H, 3.69; N, 18.10.

General procedure for the Synthesis of 2-{[5-(2-Chloroethyl)-3-(4-aryl)-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridin-4-yl]oxy}ethanol (8). A solution of compound **4** (0.01 mole) in ethylene glycol (10 mL) was refluxed in presence of triethyl amine (0.5 mL) as a catalyst for about 5 hrs, (the reaction was monitored by TLC). The excess of ethylene glycol was removed under reduced pressure. The solid obtained on adding ethanol was collected by filtration, washed with ethanol, dried and recrystallized from the proper solvent to afford **8** in good yield.

2-{[5-(2-Chloroethyl)-3-(4-chlorophenyl)-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl]oxy}ethanol (8a). This compound was obtained as colorless prisms (ethanol), 2.47 g (56 %), mp 147-148 °C; ir (potassium bromide): 3430s, 2950m, 3390w, 2916w, 1595w, 1498w, 1452m, 1301w, 1145m, 1093w, 837s, 759s, 692m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.81 (s, 3H, CH_3), 3.23 (t, *J* = 7.2 Hz, 2H, CH_2), 3.55 (t, *J* = 7.5 Hz, 2H, CH_2), 3.67-3.73 (m, 4H, -OCH_2-CH_2-OH), 7.28-7.53 (m, 5H, Ar-H), 7.67 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.26 (d, *J* = 7.8 Hz, 2H, Ar-H) *Anal*. Calcd. for $C_{23}H_{21}Cl_2N_3O_2$: C, 62.45; H, 4.79; N, 9.50. found. C, 62.64; H, 5.10; N, 9.95.

2-{[3-(Bromophenyl)-5-(2-chloroethyl)-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl]oxy}ethanol (8b). This compound was obtained as colorless prisms (ethanol), 3.06 g (63 %), mp 138-139 °C; ir (potassium bromide): 3430s, 2950m, 3390w, 2916w, 1595w, 1498w, 1452m, 1301w, 1145m, 1093w, 837s, 759s, 692m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.83 (s, 3H, CH_3), 3.22 (t, *J* = 7.2 Hz, 2H, CH_2), 3.54 (t, *J* = 7.5 Hz, 2H, CH_2), 3.65-3.71 (m, 4H, -OCH_2-CH_2-OH), 7.25-7.51 (m, 5H, Ar-H), 7.65 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.24 (d, *J* = 7.8 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{23}H_{21}BrClN_3O_2$: C, 56.75; H, 4.35; N, 8.63. found. C, 56.87; H, 4.10; N, 8.95.

General procedure for the Synthesis of 8-(4-Aryl)-4-methyl-6-phenyl-3,6-dihydro-2*H*-pyrazolo[3,4-*b*]thieno[2,3-*d*]-pyridine (9). A solution of **4** (0.01 mol) in acetic acid and thiourea (2.283 g, 0.01mole) was refluxed for about 2 hrs, (reaction was monitored by TLC). The excess of acetic acid was removed under reduced pressure. The obtained residue was dissolved in water (15 mL) under cooling. The resulting precipitate was collected by suction filtration, washed with water and dried and recrystallized from the suitable solvent to furnished compound **9** in good yield.

8-(4-Chlorophenyl)-4-methyl-6-phenyl-3,6-dihydro-2*H*-pyrazolo[3,4-*b*]thieno[2,3-*d*]pyridine (9a). This compound was obtained as colorless prisms (ethanol), 2.49 g (65 %), mp 213-214 °C; ir (potassium bromide): 2918m, 1595m, 1500s, 1257m, 1147m, 1093w, 1018w, 906w, 756m, 686w cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.83 (s, 3H, CH_3), 3.32 (t, *J* = 7.3 Hz, 2H, CH_2), 3.50 (t, *J* = 7.1 Hz, 2H, CH_2), 7.24-7.60 (m, 5H, Ar-H), 7.61 (d, *J* = 8.3 Hz, 2H, Ar-H), 8.34 (d, *J* = 8.1 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{21}H_{16}ClN_3S$: C, 66.75; H, 4.27; N, 11.12. found. C, 66.97; H, 4.05; N, 10.90.

8-(4-Bromophenyl)-4-methyl-6-phenyl-3,6-dihydro-2*H*-pyrazolo[3,4-*b*]thieno[2,3-*d*]pyridine (9b). This compound was obtained as colorless prisms (ethanol), 2.44 g (70 %), mp 225-226 °C; ir (potassium bromide): 2918m, 1595m, 1500s, 1257m, 1147m, 1093w, 1018w, 906w, 756m, 686w cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.84 (s, 3H, CH_3), 3.31 (t, *J* = 7.3 Hz, 2H, CH_2), 3.48 (t, *J* = 7.1 Hz, 2H, CH_2), 7.25-7.62 (m, 5H, Ar-H), 7.59 (d, *J* = 8.3 Hz, 2H, Ar-H), 8.32 (d, *J* = 8.1 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{21}H_{16}BrN_3S$: C, 59.72; H, 3.82; N, 9.95. found. C, 59.41; H, 4.05; N, 10.11.

General procedure for the Synthesis of 1-Phenyl-8-(4-aryl)-4-methyl-6-phenyl-1,2,3,6-tetrahydropyrazolo[3,4-*b*]-pyrrolo[2,3-*d*]pyridine (10). A mixture of **4** (0.01 mole) and primary aliphatic or aromatic amines (0.04 mole) was heated at 110-120 °C. for about 2 h, until TLC showed no more starting material. Then the mixture was cooled at 20 °C, after cooling methanol (20 mL) was added and the resulting solid was collected by suction filtration, washed with methanol, dried and recrystallized from the suitable solvent to furnished compound **10** in good yield.

1-Benzyl-8-(4-chlorophenyl)-4-methyl-6-phenyl-1,2,3,6-tetrahydropyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridine (10a). This compound was obtained as colorless prisms (ethanol), 4.01 g (89

%) mp150-151 °C; ir (potassium bromide): 2918m, 1743m, 1595s, 1500s, 1257m, 1147, 1093m, 1018m, 906m, 756w, 686m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.50 (s, 3H, CH_3), 3.06 (t, *J* = 7.3 Hz, 2H, CH_2), 3.50 (t, *J* = 7.1 Hz, 2H, CH_2), 4.14(s, 2H, Ar-CH_2), 6.98-7.06 (m, 5H, Ar-H), 7.24 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.43-7.49 (m, 5H, Ar-H), 8.29 (d, *J* = 8.3 Hz, 2H, Ar-H). MS: m/z (%) = 452 (90) [M+2], 450 (100) [M], 447 (20), 359 (25), 324 (35), 186 (20), 167 (20), 139 (10), 123 (30), 111 (15), 91 (90), 77 (80), 65 (60). *Anal*. Calcd. for $C_{28}H_{23}ClN_4$: C, 74.57; H, 5.14; N, 12.42. found. C, 74.67; H, 4.88; N, 12.69.

8-(4-Chlorophenyl)-4-methyl-1,6-diphenyl-1,2,3,6-tetrahydropyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridine (10b). This compound was obtained as light green prisms (ethanol and DMF), 3.58 g (82 %), mp 212-213 °C; ir (potassium bromide): 2918m, 1743m, 1595s, 1500s, 1257m, 1147, 1093m, 1018m, 906m, 756w, 686m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.56 (s, 3H, CH_3), 3.21 (t, *J* = 7.1 Hz, 2H, CH_2), 4.20 (t, *J* = 7.3 Hz, 2H, CH_2), 6.74-6.90 (m, 5H, Ar-H), 7.24-7.45 (m, 5H, Ar-H), 7.48 (d, *J* = 7.5 Hz, 2H, Ar-H), 8.31 (d, *J* = 7.5 Hz, 2H, Ar-H). MS: m/z (%) = 438 (80) [M+2], 436 (100) [M], 419 (20), 399 (25), 361 (35), 298 (20), 255 (20), 218 (10), 200 (30), 192 (15), 179 (30), 152 (35), 111 (10), 91 (10), 77 (60), 65 (15). *Anal*. Calcd. for $C_{27}H_{21}ClN_4$: C, 74.22; H, 4.84; N, 12.82. found. C, 74.49; H, 5.05; N, 12.68.

1-(2-Chlorophenyl)-8-(4-chlorophenyl)-4-methyl-6-phenyl-1,2,3,6-tetrahydropyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridine (10c). This compound was obtained as light green prisms (ethanol and DMF), 3.67 g (78 %), mp 223-224 °C; ir (potassium bromide): 2918m, 1743m, 1595s, 1500s, 1257m, 1147, 1093m, 1018m, 906m, 756w, 686m cm^{-1}. ^1H nmr ($CDCl_3$): δ = 2.57 (s, 3H, CH_3), 3.26 (t, *J* = 8.4 Hz, 2H, CH_2), 4.86 (t, *J* = 8.4 Hz, 2H, CH_2), 6.23-7.51 (m, 9H Ar-H), 8.20 (d, *J* = 7.8 Hz, 2H, Ar-H), 8.34 (d, *J* = 7.8 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{27}H_{20}Cl_2N_4$: C, 68.80; H, 4.28; N, 11.89. found. C, 69.09; H, 4.41; N, 12.10.

8-(4-Chlorophenyl)-4-methyl-6-phenyl-1-pyridin-2-yl-1,2,3,6-tetrahydropyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridine (10d). This compound was obtained as light green prisms (ethanol and DMF), 3.24 g (74 %) mp.182-183 °C; ir (potassium bromide): 2918m, 1743m, 1595s, 1500s, 1257m, 1147, 1093m, 1018m, 906m, 756w, 686m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.57 (s, 3H, CH_3), 3.26 (t, *J* = 8.4 Hz, 2H, CH_2), 4.86 (t, *J* = 8.4 Hz, 2H, CH_2), 6.23-7.51 (m, 9H, Ar-H), 8.20 (d, *J* = 7.8 Hz, 2H, Ar-H), 8.34 (d, *J* = 7.8 Hz, 2H, Ar-H). MS: m/z (%) = 439 (80) [M+2], 437 (100) [M+], 422 (10), 410 (25), 395 (20), 359 (30), 283 (12), 258 (15), 220 (20), 201 (65), 193 (14), 111 (30), 91 (10), 77 (60) 65 (10), 44 (90). *Anal*. Calcd. for $C_{26}H_{20}ClN_5$: C, 71.31; H, 4.60; N, 15.99. found. C, 71.62; H, 4.31; N, 16.16.

8-(4-Chlorophenyl)-4-methyl-1-(6-methylpyridin-2-yl)-6-phenyl-[3,4-*b*]pyrrolo[2,3-*d*] pyridine (10e). This compound was obtained as light green prisms (DMF), 3.79 g (88 %), mp.198-199 °C; ir (potassium bromide): 2918m, 1743m, 1595s, 1500s, 1257m, 1147, 1093m, 1018m, 906m, 756w, 686m cm^{-1}. ^1H nmr ($CDCl_3$): δ = 2.30 (s, 3H, Ar-CH_3), 2.60 (s, 3H, CH_3), 3.25 (t, *J* = 7.2 Hz, 2H, CH_2), 4.22 (t, *J* = 7.5 Hz, 2H, CH_2), 7.24-7.45 (m, 8H, Ar-H), 7.45 (d, *J* = 7.8 Hz, 2H, Ar-H), 8.35 (d, *J* = 7.8 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{27}H_{22}ClN_5$: C 71.75, H 4.91, N 15.50; found. C 71.96, H 5.12, N 15.68.

1-Benzyl-8-(4-bromophenyl)-4-methyl-6-phenyl-1,2,3,6-tetrahydropyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridine (10f). This compound was obtained as colorless prisms (ethanol), 4.30 g (87 %), m.p.172-173 °C; ir (potassium bromide): 2918m, 1743m, 1595s, 1500s, 1257m, 1147, 1093m, 1018m, 906m, 756w, 686m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.49 (s, 3H, CH_3), 3.04 (t, *J* = 7.3 Hz, 2H, CH_2), 3.48 (t, *J* = 7.1 Hz, 2H, CH_2), 4.13(s, 2H, Ar-CH_2), 6.95-7.08 (m, 5H, Ar-H), 7.25 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.42-7.50 (m, 5H, Ar-H), 8.28 (d, *J* = 8.3 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{28}H_{23}BrN_4$: C 67.88, H 4.68, N 11.31; found. C 67.58, H 4.47, N 11.03.

8-(4-Bromophenyl)-4-methyl-1,6-diphenyl-1,2,3,6-tetrahydropyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridine (10g). This compound was obtained as light green prisms (ethanol and DMF) 3.70 g (77 %), mp 216-217 °C; ir (potassium bromide): 2918m, 1743m, 1595s, 1500s, 1257m, 1147, 1093m, 1018m, 906m, 756w, 686m cm^{-1}.^1H nmr ($CDCl_3$): δ = 2.57 (s, 3H, CH_3), 3.22 (t, *J* = 7.1 Hz, 2H, CH_2), 4.21 (t, *J* = 7.3 Hz, 2H, CH_2), 6.76-6.92 (m, 5H, Ar-H), 7.26-7.47 (m, 5H, Ar-H), 7.47 (d, *J* = 7.5 Hz, 2H, Ar-H), 8.32 (d, *J* = 7.5 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{27}H_{21}BrN_4$: C, 67.37; H, 4.40; N, 11.64. found. C, 67.61; H, 4.63; N, 11.36.

8-(4-Bromophenyl)-1-(2-chlorophenyl)-4-methyl-6-phenyl-1,2,3,6-tetrahydropyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridine (10f). This compound was obtained as light green prisms (DMF), 4.07 g (79 %), mp 212-213 °C; ir (potassium bromide): 2918m, 1743m, 1595s, 1500s, 1257m, 1147, 1093m, 1018m, 906m, 756w, 686m cm^{-1}; ^1H nmr ($CDCl_3$): δ = 2.58 (s, 3H CH_3), 3.28 (t, *J* = 8.4 Hz, 2H, CH_2), 4.87 (t, *J* = 8.4 Hz, 2H, CH_2), 6.22-7.55 (m, 9H Ar-H), 8.20 (d, *J* = 7.8 Hz, 2H, Ar-H), 8.33 (d, *J* = 7.8 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{27}H_{20}BrClN_4$: C, 62.87; H, 3.91; N, 10.86. found. C, 62.63; H, 4.16; N, 11.09.

8-(4-Bromophenyl)-4-methyl-6-phenyl-1-pyridin-2-yl-1,2,3,6-tetrahydropyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridine (10i). This compound was obtained as light green prisms (ethanol and DMF), 3.47 g (72 %), mp. 189-190 °C; ir (potassium bromide): 2918m, 1743m, 1595s, 1500s, 1257m, 1147, 1093m, 1018m, 906m, 756w, 686m cm^{-1}. ^1H nmr ($CDCl_3$): δ = 2.60 (s, 3H, CH_3), 3.26 (t, *J* = 7.5 Hz, 2H, CH_2), 4.88 (t, *J* = 7.3 Hz, 2H, CH_2), 7.26-7.55 (m, 9H, Ar-H), 8.23 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.36 (d, *J* = 8.1 Hz, 2H, Ar-H). *Anal*. Calcd. for $C_{26}H_{20}BrN_5$: C 64.74, H 4.18, N 14.52; found. C 64.35, H 3.89, N 14.74.

8-(4-Bromophenyl)-4-methyl-1-(6-methylpyridin-2-yl)-6-phenyl-[3,4-*b*]pyrrolo[2,3-*d*]pyridine (10j). This compound was obtained as light green prisms (ethanol and DMF) mp. 205-206 °C; ir (potassium bromide): 2918m, 1743m, 1595s, 1500s, 1257m, 1147, 1093m, 1018m, 906m, 756w, 686m cm^{-1}. ^1H nmr ($CDCl_3$): δ = 2.32 (s, 3H, $ArCH_3$), 2.61 (s, 3H, CH_3), 3.23 (t, *J* = 7.2 Hz, 2H, CH_2), 4.24 (t, J = 7.5 Hz, 2H, CH_2), 7.25-7.46 (m, 8H, Ar-H), 7.46 (d, *J* = 7.8 Hz, 2H, Ar-H), 8.36 (d, *J* = 7.8 Hz, 2H, ArH). *Anal*. Calcd. for $C_{27}H_{22}BrN_5$: C, 65.33; H, 4.47; N, 14.11. found. C, 65.56; H, 4.74; N, 13.96.

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