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ORIGINAL PAPER

Use of sodium salt of cyclic β-formylester for synthesis of dihydro-2*H*-furo[2,3-*d*]pyrazolo[3,4-*b*]pyridines and pyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridines

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Abstract The chemoselective reaction of the sodium salt of α-formyl-γ-butyrolactone and 5-aminopyrazole furnished dihydrofuro[2,3-*d*]pyrazolo[3,4-*b*]pyridine at two different reaction conditions, i.e., with NH_4OAc or in refluxing AcOH. The same reactants when refluxed in MeOH and AcOH produced a pyrazolylamino dihydrofuranone derivative. A mixture of 2-chloroethyl-4-chloropyrazolopyridines and dihydrofuro[2,3-*d*]pyrazolo[3,4-*b*]pyridine derivatives was obtained on refluxing the intermediate dihydrofuranone in $POCl_3$. A one-step synthesis of tricyclic pyrazolopyrrolopyridines and thienopyrazolopyridines resulted from S_NAr reaction of 2-chloroethyl-4-chloropyrazolopyridines with primary aromatic amines and with thiourea.

Keywords α-Formyl-γ-butyrolactone · Pyrazolopyridines · Pyrazolopyrrolopyridines · Dihydrofuropyrazolopyridines

Introduction

Pyrazolo[3,4-*b*]pyridines have shown several interesting biological and pharmacological applications such as antitubercular action [1, 2], activity against Gram-positive and Gram-negative bacteria [3], and adrenocortropic hormone (ACTH)-releasing factor and corticotrophin-releasing factor (CRF) antagonist activity [4]. A literature survey reveals that pyrido[1,2-*a*]pyrimidines having an ethyl chain also showed interesting biological activity [5–8].

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To date, very few reactions involving use of α-formyl-γ-butyrolactone for synthesis of heterocyclic systems have been reported in literature. Several applications of the reaction of cyclic β-ketoesters with primary aromatic amines have been reported, such as the easy introduction of dihydrofuranones [9, 10], 2-chloroethyl/4-chloro functionality in pyridine derivatives, and one-step synthesis of fused tricyclic heteroaromatic systems [9]. The reactions of cyclic β-ketoesters are sensitive to temperature [11] and require mild reaction conditions.

In literature, pyrazolopyridines were obtained by condensation of 5-aminopyrazole with diethoxyethylene malonate [12], 1,3-diketone [13], and α,β-unsaturated ketone [14]. Previously we have used β-ketoesters for synthesis of pyrazolopyridine and obtained the required functionalities at the expected positions [15]. Here, we introduce β-formylester for synthesis of fused heterocycles. Instead of α-formyl-γ-butyrolactone, its sodium salt was used, being prepared by the reaction of γ-butyrolactone with ethyl formate and sodium hydride in dry ether [16]. Ethoxyethylenetetrahydrofuran-2-one also gave a similar reaction [17, 18], but for the preparation of the ethoxyethylenetetrahydrofuran-2-one, chloroethyl formate is required, which is lachrymatic and hence unhealthy for laboratory use. To avoid use of chloroethyl formate, we directly reacted the sodium salt of α-formyl-γ-butyrolactone with 5-aminopyrazole, which gave a facile reaction and better yields of the target molecules.

In this paper we report the chemoselective reactions of the sodium salt of α-formyl-γ-butyrolactone with 5-aminopyrazole under mild reaction conditions. The obtained pyrazolo[3,4-*b*]pyridines have reactive 4-chloro and 5-(2-chloroethyl) substituents which not only increase the pharmacological activity but also facilitate one-step synthesis of tricyclic heterocycles. The strategic substitutions

of pyrazolopyridines gave facile and neat reactions with amino and thio compounds to furnish a new class of tricyclic heterocycles such as pyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridine in good yield and high purity.

Results and discussion

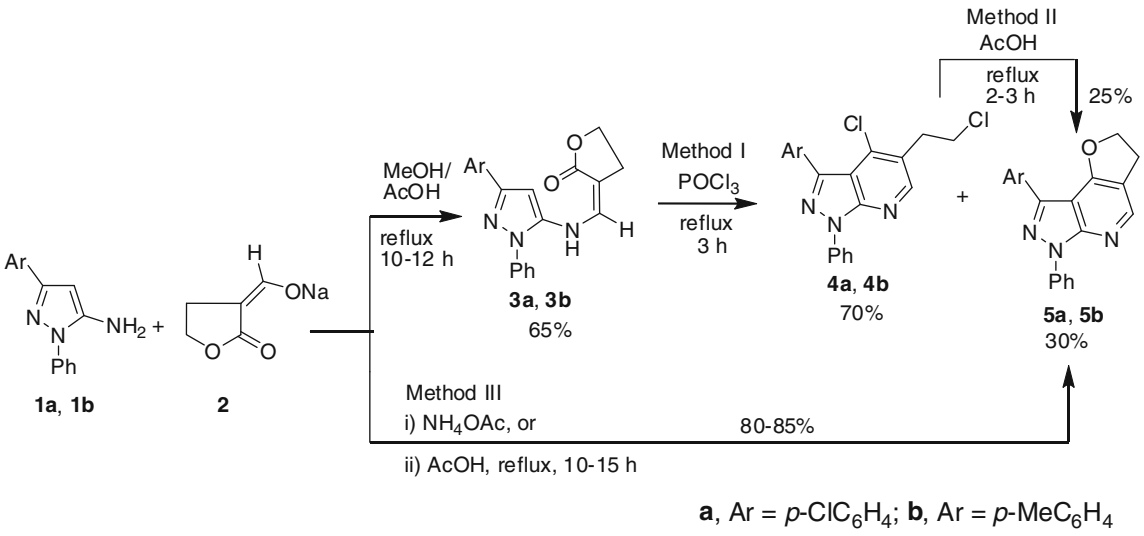
Intermediate pyrazolylamino dihydrofuranones **3** (Scheme 1) were obtained by condensation of 5-aminopyrazole **1** with the sodium salt of α-formyl-γ-butyrolactone (**2**) in AcOH and MeOH at reflux temperature. The in situ formed free formyl ester generated by the weak acid catalyst undergoes attack of the amino group, yielding the *Z*-enamine **3**. Use of mineral acid furnished a mixture of several products as seen by thin-layer chromatography (TLC). The *Z* stereochemistry of enamine **3** was proved on the basis of a decrease in lactone carbonyl stretching to 1,722–1,718 cm^{-1} due to hydrogen bonding between NH and lactone carbonyl. Also, the ^1H nuclear magnetic resonance (NMR) of compound **3b** showed a multiplet at $\delta = 2.81$ ppm for $= C–CH_2$ and a triplet at 4.21 ppm with $J = 8.4$ Hz for CH_2O, which is possible only in the *Z*-isomer.

When compounds **1** and **2** were refluxed in presence of AcOH or NH_4OAc, fused tricyclic dihydrofuropyrazolopyridines **5** were formed in 85% yield. Similar reactions with intermediate **3** in $POCl_3$ also yielded the same compound **5** (Fig. 1). The pyrazolyldihydrofuranones **3** on refluxing in $POCl_3$ furnished a mixture of compounds **4** and **5** (TLC check), which was separated on column by eluting with chloroform–methanol 9:1 to yield **4** and **5** in 70% and 25% yield, respectively. Analogously, compounds **4b** and **5b** were synthesized and assigned the structures shown in Scheme 1.

Compounds **4** on refluxing in sodium ethoxide/ethanol furnished a S_NAr reaction at C4 and E_2 elimination at the side-chain to yield substitution–elimination products **6**. The C4-Cl in pyrazolopyridine **4** was replaced by azide, when compound **4** was heated with sodium azide at 55 °C in dimethylformamide (DMF) and with ethylene glycol in presence of a catalytic amount of triethylamine to yield products **7** and **8**, respectively (Scheme 2).

Advantage of C4-Cl and C3-chloroethyl was also taken to annelate a tetrahydrofuran ring to the pyridine nucleus to yield compounds **5a**, **5b** (Scheme 1). Reaction of compounds **4a**, **4b** with thiourea in acetic acid under reflux condition furnished thienopyrazolopyridines **9a**, **9b** in good yields (Scheme 3). Boiling thiourea with AcOH in situ generates H_2S, which gave simultaneous S_NAr reaction at C4 and S_N2 at the chloroethyl side-chain to furnish tricyclic thienopyrazolopyridines. Similarly, compounds **4** on refluxing in AcOH or on heating in NH_4OAc furnished 3,6-dihydro-8-(4-chloro/4-methylphenyl)-6-phenyl-2*H*-furo[2,3-*d*]pyrazolo-[3,4-*b*]pyridines **5a**, **5b** (Scheme 3). Simultaneously, the targeted new fused pyrazolo[3,4-*b*]pyrrolo[2,3-*d*]pyridines **10** were successfully synthesized in 65-85% yield from pyrazolo[3,4-*b*]pyridines **4** by neat reaction with primary aromatic amines (Scheme 3).

We have also studied the effect of a neighboring electronegative element on chemical shifts observed on ^1H NMR of compounds **3**–**5** and **7**–**10**, which showed interesting chemical shifts for $–CH_2CH_2–X$ in functional groups such as furanone, tetrahydropyrane, 3-chloroethyl side-chain, and 4-hydroxyethyl ether as shown in Fig. 2, due to difference in electronegativity of the group or atom



Scheme 1

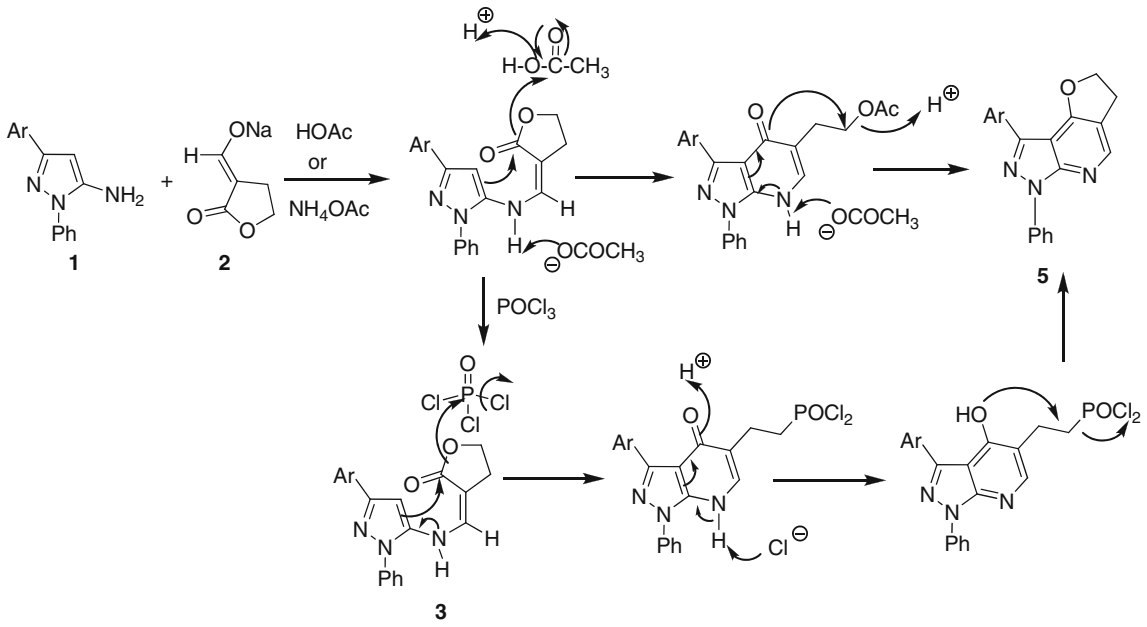
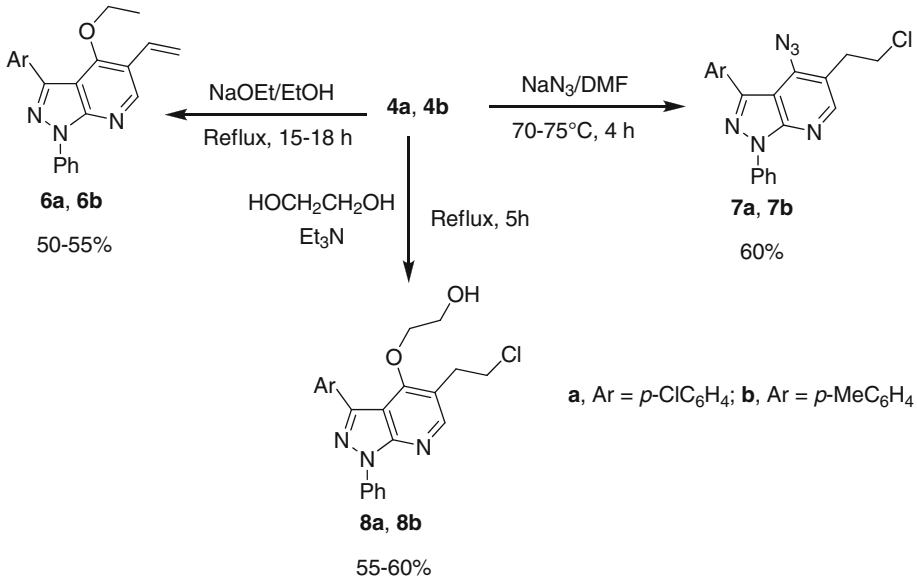


Fig. 1 Proposed mechanism for formation of tricyclic dihydrofuropyrazolopyridine in AcOH or in NH_4OAc and in $POCl_3$

Scheme 2



attached at the C4-position. The observed order of chemical shift is $OCH_2 > NCH_2 > SCH_2$.

Conclusions

The sodium salt of α-formyl-γ-butyrolactone is a versatile, reactive, and selective reagent giving facile reactions with primary aromatic amines at mild reaction conditions to furnish new pyrazolopyridines, pyrazolopyrrolopyridines, dihydrofuropyrazolopyridines, and thienopyrazolopyridines in fair to good yields. Strategic substitutions of the pyrazolopyridines facilitate construction of new tricyclic fused heterocycles.

Experimental

Melting points were determined on a Gallenkamp melting point apparatus. The ^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded on a Varian XL-300 spectrometer. Chemical shifts are reported in ppm relative to tetramethylsilane (TMS) and multiplicities are given as s (singlet), bs (broad singlet), d (doublet), t (triplet), q

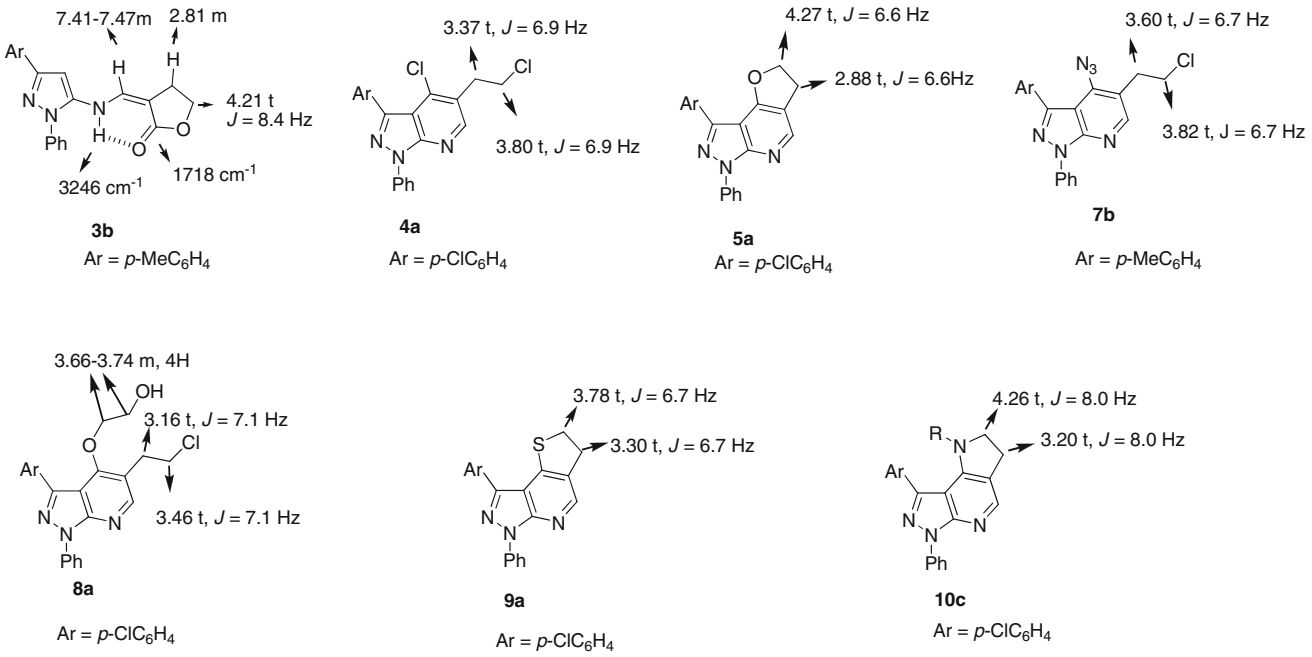


Fig. 2 Effect of electronegative atoms on chemical shifts

(quartet) or m (multiplet). The solvents for NMR spectra were dimethyl sulfoxide (DMSO)-d_6 and $CDCl_3$ unless otherwise stated. Infrared spectra were recorded as KBr pellets on a Shimadzu FTIR-408 spectrophotometer. Mass spectra were recorded on a Shimadzu GC–MS QP 2010A mass spectrometer with ionization potential of 70 eV. Elemental analyses were performed on a Thermo Quest Flash 1112 Series EA analyzer. The reactions were monitored by thin-layer chromatography, carried out on 0.2 mm silica gel 60 F_{254} (Merck) plates using ultraviolet (UV) light (254 and 366 nm) for detection. Common reagent-grade chemicals are either commercially available and were used without further purification or were prepared by standard literature procedures.

*General procedure for the synthesis of compounds **3a**, **3b***

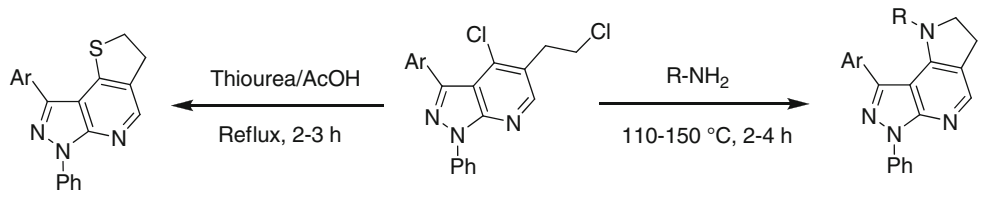
A mixture of the corresponding 5-aminopyrazole (0.1 mol) and 13.6 g of the sodium salt of α-formyl-γ-butyrolactone (0.1 mol) in 80 cm^3 MeOH and 70 cm^3 AcOH was refluxed in an oil bath for 10-12 h (TLC check, hexane–ethyl acetate 1:1). The reaction mixture was cooled to room temperature and poured into ice-cold water. The solid separated was isolated by filtration, dried, and recrystallized from toluene.

(Z)-3-[[3-(4-Chlorophenyl)-1-phenyl-1H-pyrazol-5-ylamino]methylene]dihydrofuran-2-(3H)-one
(**3a**, $C_{20}H_{16}ClN_3O_2$)
White crystalline solid; yield 23.7 g (65%); m.p.: 190–192 °C; $R_f = 0.41$ (hexane–ethyl acetate 1:1); IR (KBr): $\bar{\nu} = 3{,}246$ (NH), 2,959, 1,718, 1,647, 1,593, 1,564, 1,055, 1,026 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.72$ (dt, $J = 8.2$ Hz, 2H, CH_2), 4.19 (t, $J = 8.2$ Hz, 2H, CH_2), 5.56 (d, $J = 9.1$ Hz, 1H, NH), 6.16 (s, 1H, ArH), 7.15 (d, $J = 6.2$ Hz, 2H, ArH), 7.40 (m, 1H, ArH), 7.48–7.54 (m, 5H, ArH), 7.58–7.60 (d, $J = 6$ Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 33.5$, 43.1, 96.4, 99.2, 121.8, 125.7, 126.7, 128.2, 129.1, 131.9, 135.1, 137.4, 138.7, 144.0, 151.5, 168.9 ppm; MS (ESI): $m/z = 365$ (M^+), 367 ($[M + 2]^+$).

(Z)-Dihydro-3-[[3-(4-methylphenyl)-1-phenyl-1H-pyrazol-5-ylamino]methylene]furan-2-(3H)-one
(**3b**, $C_{21}H_{19}N_3O_2$)
White crystalline solid; yield 24.1 g (70%); m.p.: 178–180 °C; $R_f = 0.40$ (hexane–ethyl acetate 1:1); IR (KBr): $\bar{\nu} = 3{,}230$ (NH), 2,938, 2,723, 1,722, 1,640, 1,578, 1,048 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.41$ (s, 3H, CH_3), $\delta = 2.81$ (dt, $J = 8.4$ Hz, 2H, CH_2), 4.21 (t, $J = 8.4$ Hz, 2H, CH_2), 6.05 (d, $J = 9.3$ Hz, 1H, NH), 6.20 (s, 1H, ArH), 7.22 (d, $J = 6$ Hz, 2H, ArH), 7.39–7.42 (m, 1H, ArH), 7.44–7.53 (m, 5H, ArH), 7.73 (d, $J = 6$ Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 20.8$, 24.4, 64.8, 94.8, 97.2, 123.5, 125.1, 127.2, 129.2, 129.9, 137.3, 138.0, 138.7, 142.4, 150.4, 172.7 ppm; MS (ESI): $m/z = 345$ (M^+).

*General procedure for the synthesis of compounds **4** and **5** (method I)*

Aminopyrazolyldihydrofuranone **3** (0.01 mol) was stirred at room temperature in 20 cm^3 phosphorus oxychloride until the end of the exothermic reaction, which usually



9a, **9b**
80-90%

4a, **4b**

10a-10h
75-90%

a, Ar = *p*-ClC_6H_4; **b**, Ar = *p*-MeC_6H_4

10	Ar	R
a	*p*-ClC_6H_4	$C_6H_5CH_2$
b	*p*-ClC_6H_4	*p*-MeC_6H_4
c	*p*-ClC_6H_4	4-Cl-3-FC_6H_3
d	*p*-ClC_6H_4	C_6H_5
e	*p*-MeC_6H_4	$C_6H_5CH_2$
f	*p*-MeC_6H_4	*p*-MeC_6H_4
g	*p*-MeC_6H_4	4-Cl-3-FC_6H_3
h	*p*-MeC_6H_4	C_6H_5

Scheme 3

starts about 80–90 °C. The mixture was then refluxed further for 3–4 h. The excess $POCl_3$ was removed under reduced pressure. The residue obtained was stirred in ice-cold water for 2 h, and then the resulting solution was neutralized by addition of solid sodium carbonate (2–3 g). The solid separated was isolated by filtration and dried. The TLC analysis showed two products, which were separated by column chromatography using chloroform–methanol 9:1 as eluent, affording pyrazolo[3,4-*b*]pyridines **4** and 3,6-dihydro-2*H*-furo[2,3-*d*]pyrazolo[3,4-*b*]pyridines **5**.

General procedure for the synthesis of compounds ***5a***, ***5b*** *(method II)*

Compound **4** (0.001 mol) was refluxed in 5 cm^3 acetic acid for 2–3 h (TLC check, hexane–ethyl acetate 1:1). After completion of the reaction the mixture was cooled and poured into ice-cold water, upon which a solid separated. The solid was isolated by filtration, dried, and recrystallized from ethanol to furnish compound **5**.

General procedure for the synthesis of compounds ***5a***, ***5b*** *(method III)*

A mixture of 5-aminopyrazole **1** (0.001 mol) and 0.136 g of the sodium salt of α-formyl-γ-butyrolactone (0.001 mol) in 5 g NH_4OAc or 5 cm^3 AcOH was refluxed for 10–15 h (TLC check, hexane–ethyl acetate 1:1). The reaction mixture was cooled to room temperature and poured into ice-cold water. The solid separated was filtered, dried, and recrystallized from ethanol/DMF to furnish compound **5** in 80–85% yield.

4-Chloro-5-(2-chloroethyl)-3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**4a**, $C_{20}H_{14}Cl_3N_3$)
Colorless crystalline solid; yield 2.41 g (60%); m.p.: 185–187 °C; $R_f = 0.61$ (chloroform–methanol 9:1); IR (KBr): $\bar{\nu} = 2{,}930$, 1,601, 1,590, 1,290 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 3.37$ (t, $J = 6.9$ Hz, 2H, CH_2), 3.80 (t, $J = 6.9$ Hz, 2H, CH_2), 7.33–7.57 (m, 5H, ArH), 7.71 (d, $J = 8.4$ Hz, 2H, ArH), 8.24 (d, $J = 8.4$ Hz, 2H, ArH), 8.52 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 33.4$, 43.1, 121.8, 125.7, 126.1, 126.7, 128.2, 128.4, 129.0, 129.1, 130.7, 131.7, 135.0, 137.4, 138.7, 144.0, 151.0, 151.5 ppm; MS (ESI): $m/z = 403$ (M^+), 405 ($[M + 2]^+$), 407 ($[M + 4]^+$), 409 ($[M + 6]^+$).

4-Chloro-5-(2-chloroethyl)-3-(4-methylphenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**4b**, $C_{21}H_{17}Cl_2N_3$)
White crystalline solid; yield 2.48 g (65%); m.p.: 140–142 °C; $R_f = 0.60$ (chloroform–methanol 9:1); IR (KBr): $\bar{\nu} = 2{,}942$, 1,610, 1,599, 1,254 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.45$ (s, 3H, CH_3), 3.63 (t, $J = 5.4$ Hz, 2H, CH_2), 3.79 (t, $J = 5.4$ Hz, 2H, CH_2), 7.30–7.55 (m, 5H,

ArH), 7.60 (d, $J = 6$ Hz, 2H, ArH), 8.39 (d, $J = 6$ Hz, 2H, ArH), 8.52 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 20.9$, 33.3, 43.1, 121.1, 126.1, 126.5, 126.8, 128.2, 128.8, 129.0, 129.1, 130.7, 131.6, 135.3, 137.4, 140.1, 143.0, 150.9, 151.4 ppm; MS (ESI): $m/z = 381$ (M^+), 383 ($[M + 2]^+$), 385 ($[M + 4]^+$).

8-(4-Chlorophenyl)-3,6-dihydro-6-phenyl-2H-furo[2,3-d]pyrazolo[3,4-b]pyridine (**5a**, $C_{20}H_{14}ClN_3O$)
Crystalline cream colored solid; yields: method I: 0.104 g (30%), method II: 0.087 g (25%), method III: 0.277 g (80%); m.p.: 189–191 °C; $R_f = 0.52$ (chloroform–methanol 9:1); IR (KBr): $\bar{\nu} = 2{,}955$, 1,602, 1,593, 1,280 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.88$ (t, $J = 6.6$ Hz, 2H, CH_2), 4.27 (t, $J = 6.6$ Hz, 2H, CH_2), 7.39–7.57 (m, 5H, ArH), 7.20 (d, $J = 7.5$ Hz, 2H, ArH), 7.80 (d, $J = 7.5$ Hz, 2H, ArH), 7.89 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 27.3$, 70.8, 110.4, 116.6, 121.0, 125.7, 126.5, 128.2, 128.8, 128.9, 131.5, 134.2, 139.2, 142.8, 150.3, 168.5 ppm; MS (ESI): $m/z = 347$ (M^+), 349 (([M + 2]$^+$).

3,6-Dihydro-8-(4-methylphenyl)-6-phenyl-2H-furo[2,3-d]pyrazolo[3,4-b]pyridine (**5b**, $C_{21}H_{17}N_3O$)
Cream colored crystalline solid; yields: method I: 0.098 g (30%), method II: 0.081 g (25%), method III: 0.278 g (85%); m.p.: 197–199 °C; $R_f = 0.53$ (chloroform–methanol 9:1); IR (KBr): $\bar{\nu} = 2{,}955$, 1,602, 1,593, 1,280 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.39$ (s, 3H, CH_3), 2.78 (t, $J = 6.9$ Hz, 2H, CH_2), 4.32 (t, $J = 6.9$ Hz, 2H, CH_2), 7.09–7.46 (m, 5H, ArH), 7.29 (d, $J = 8.1$ Hz, 2H, ArH), 7.74 (d, $J = 8.1$ Hz, 2H, ArH), 8.01 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.1$, 27.3, 70.7, 110.4, 116.7, 120.9, 126.1, 126.5, 128.7, 128.9, 129.0, 131.5, 134.2, 141.4, 143.0, 150.2, 168.7 ppm; MS (ESI): $m/z = 327$ (M^+).

General procedure for the synthesis of compounds ***6a, 6b***

A solution of compound **4** (0.01 mol) and sodium ethoxide (prepared by reacting 0.27 g sodium with 50 cm^3 absolute ethanol) in 10 cm^3 ethanol was refluxed for about 9–10 h (monitored by TLC, toluene–acetone 8:2). The excess of solvent was removed under reduced pressure. The obtained solid was washed with ethanol, dried, and recrystallized from ethanol/DMF to furnish compounds **6** in good yield.

3-(4-Chlorophenyl)-5-ethenyl-4-ethoxy-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**6a**, $C_{22}H_{18}ClN_3O$)
Colorless crystalline solid; yield 1.88 g (50%); m.p.: 200–202 °C; $R_f = 0.29$ (toluene–acetone 8:2); IR (KBr): $\bar{\nu} = 2{,}954$, 2,720, 1,598, 1,580, 1,169 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.35$ (t, $J = 8.4$ Hz, 3H), 3.84 (q, $J = 8.4$ Hz, 2H), 5.38 (dd, 2H), 6.79–6.92 (m, 1H), 7.11–7.38 (m, 5H, ArH), 7.62 (d, $J = 7.7$ Hz, 2H, ArH), 8.02 (d, $J = 7.7$ Hz, 2H, ArH), 8.10 (s 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.7$, 56.4, 117.2, 118.3, 121.1, 125.3, 126.4, 127.3, 128.3, 128.8, 129.2, 130.5, 131.3, 131.5, 133.8, 134.1, 139.5, 143.2, 151.6, 158.2 ppm; MS (ESI): $m/z = 375$ (M^+), 377 ($[M + 2]^+$).

5-Ethenyl-4-ethoxy-3-(4-methylphenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**6b**, $C_{23}H_{21}N_3O$)
Colorless solid; yield 1.95 g (55%); m.p.: 218–220 °C; $R_f = 0.29$ (toluene–acetone 8:2); IR (KBr): $\bar{\nu} = 2{,}936$, 2,722, 1,609, 1,583 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 1.40$ (t, $J = 7.9$ Hz, 3H), 2.27 (s, 3H, CH_3) 3.78 (q, $J = 7.9$ Hz, 2H), 5.45 (dd, 2H), 6.68–6.84 (m, 1H), 7.07–7.30 (m, 5H, ArH), 7.38 (d, $J = 6.9$ Hz, 2H, ArH), 7.98 (d, $J = 6.9$ Hz, 2H, ArH), 8.04 (s 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 15.7$, 21.0, 56.5, 117.4, 118.3, 121.0, 125.4, 126.5, 127.4, 128.3, 128.9, 129.2, 130.3, 131.4, 132.0, 134.1, 136.4, 140.0, 143.7, 151.9, 157.9 ppm; MS (ESI): $m/z = 355$ (M^+).

General procedure for the synthesis of compounds ***7a, 7b***

To a stirred solution of **4** (0.01 mol) in DMF-H_2O (9:1), 2.60 g sodium azide (0.04 mol) was added and temperature was raised slowly to 80 °C. The mixture was kept at this temperature for about 2–2.5 h until TLC showed no more starting material. The temperature was then raised to 110 °C for 1 h. Then the solvent was removed reduced under pressure, and the oily residue was poured into ice-cold water and stirred for 1 h. The solid separated was isolated by filtration, washed with water, dried, and recrystallized from ethanol to furnish compounds **7** in good yield.

4-Azido-5-(2-chloroethyl)-3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**7a**, $C_{20}H_{14}Cl_2N_6$)
Yellow crystalline solid; yield 2.45 g (60%); m.p.: 90–92 °C; $R_f = 0.37$ (chloroform–methanol 9:1); IR (KBr): $\bar{\nu} = 2{,}927$, 2,150, 1,620, 1,582, 1,205 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.62$ (t, $J = 6.9$ Hz, 2H), 3.80 (t, $J = 6.9$ Hz, 2H), 7.25–7.52 (m, 5H, ArH), 7.18 (d, $J = 7.4$ Hz, 2H, ArH), 7.78 (d, $J = 7.4$ Hz, 2H, ArH), 7.90 (s 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 32.9$, 42.3, 121.5, 125.3, 126.3, 127.9, 128.3, 128.9, 129.0, 129.2, 130.5, 131.7, 136.1, 136.8, 137.4, 144.2, 150.1, 152.3 ppm; MS (ESI): $m/z = 408$ (M^+), 410 ($[M + 2]^+$), 412 ($[M + 4]^+$).

4-Azido-5-(2-chloroethyl)-3-(4-methylphenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridine (**7b**, $C_{21}H_{17}ClN_6$)
Yellow crystalline solid; yield 2.72 g (60%); m.p.: 110–112 °C; $R_f = 0.38$ (chloroform–methanol 9:1); IR (KBr): $\bar{\nu} = 2{,}945$, 2,167, 1,607, 1,564, 1,227 cm^{-1}; ^{1}H

NMR ($CDCl_3$): $\delta = 2.32$ (s, 3H, CH_3), 3.60 (t, $J = 6.7$ Hz, 2H), 3.82 (t, $J = 6.7$ Hz, 2H), 7.20–7.60 (m, 5H, ArH), 7.45 (d, $J = 6.1$ Hz, 2H, ArH), 8.00 (d, $J = 6.1$ Hz, 2H, ArH), 8.10 (s 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.1$, 33.0, 42.5, 121.6, 125.9, 126.5, 127.9, 128.5, 129.0, 129.1, 130.6, 131.7, 135.4, 136.3, 137.2, 138.9, 144.0, 149.9, 152.0 ppm; MS (ESI): $m/z = 388$ (M^+), 390 ($[M + 2]^+$).

General procedure for the synthesis of compounds ***8a, 8b***

A solution of compound **4** (0.01 mol) in 10 cm^3 ethylene glycol was refluxed in presence of 0.5 cm^3 triethylamine for about 5 h (TLC check, chloroform–methanol 9:1). The excess of ethylene glycol was removed under reduced pressure. The solid obtained on addition of ethanol was isolated by filtration, washed with ethanol, dried, and recrystallized from ethanol/DMF to afford **8** in good yield.

2-[5-(2-Chloroethyl)-3-(4-chlorophenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-4-yloxy]ethanol
(**8a**, $C_{21}H_{17}Cl_2N_3O_2$)
Off-white solid; yield 2.35 g (55%); m.p.: 212–214 °C; $R_f = 0.76$ (chloroform–methanol 9:1); IR (KBr): $\bar{\nu} = 3{,}400$, 2,926, 1,593, 1,500, 1,290 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.16$ (t, $J = 7.1$ Hz, 2H), 3.46 (t, $J = 7.1$ Hz, 2H), 3.66–3.74 (m, 4H), 7.20–7.55 (m, 5H, ArH), 7.62 (d, $J = 8.1$ Hz, 2H, ArH), 8.34 (d, $J = 8.1$ Hz, 2H, ArH), 8.41 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 28.8$, 43.4, 60.4, 69.9, 112.1, 116.5, 121.0, 125.4, 126.5, 127.6, 128.1, 128.8, 129.0, 130.8, 131.5, 134.1, 139.2, 143.0, 150.9, 167.4 ppm; MS (ESI): $m/z = 413$ (M^+), 415 ($[M + 2]^+$), 417 ($[M + 4]^+$).

2-[5-(2-Chloroethyl)-3-(4-methylphenyl)-1-phenyl-1H-pyrazolo[3,4-b]pyridin-4-yloxy]ethanol
(**8b**, $C_{22}H_{20}ClN_3O_2$)
Colorless solid; yield 2.45 g (60%); m.p.: 233-235 °C; $R_f = 0.77$ (chloroform–methanol 9:1); IR (KBr): $\bar{\nu} = 3{,}388$, 2,902, 2,718, 1,610, 1,515, 1,278 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.49$ (s, 3H, CH_3), 3.13 (t, $J = 7.4$ Hz, 2H), 3.52 (t, $J = 7.4$ Hz, 2H), 3.60–3.76 (m, 4H), 7.26–7.48 (m, 5H, ArH), 7.70 (d, $J = 8.2$ Hz, 2H, ArH), 8.27 (d, $J = 8.2$ Hz, 2H, ArH), 8.37 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.1$, 28.7, 43.4, 60.3, 70.0, 112.3, 116.5, 121.5, 125.3, 126.5, 127.5, 127.9, 128.8, 130.1, 130.6, 131.5, 134.3, 139.0, 143.3, 150.7, 167.8 ppm; MS (ESI): $m/z = 393$ (M^+), 395 ($[M + 2]^+$).

General procedure for the synthesis of compounds ***9a, 9b***

A solution of **4** (0.01 mol) and 2.28 g thiourea (0.01 mol) in 10 cm^3 acetic acid was refluxed for about 2–3 h (TLC check, chloroform–methanol 9:1). The excess of acetic acid was removed under pressure. The obtained residue was stirred in 15 cm^3 cold water. The resulting precipitated solid was isolated by filtration, washed with water, and dried to get analytically pure solid **9** in good yield. This solid product did not need further purification.

8-(4-Chlorophenyl)-3,6-dihydro-6-phenyl-2H-pyrazolo-[3,4-b]thieno[2,3-d]pyridine (**9a**, $C_{20}H_{14}ClN_3S$)
White amorphous solid; yield 2.91 g (80%); m.p.: 268–270 °C; $R_f = 0.72$ (chloroform–methanol 9:1); IR (KBr): $\bar{\nu} = 2{,}921$, 1,616, 1,545, 1,210 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.30$ (t, $J = 6.7$ Hz, 2H), 3.78 (t, $J = 6.7$ Hz, 2H), 7.20–7.54 (m, 5H, ArH), 7.80 (d, $J = 8.5$ Hz, 2H, ArH), 8.24 (d, $J = 8.5$ Hz, 2H, ArH), 8.30 (s, 1H, Py-H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 29.6$, 34.4, 121.6, 126.7, 128.7, 129.0, 130.1, 130.3, 134.9, 139.3, 143.4 ppm; MS (ESI): $m/z = 363$ (M^+), 365 ($[M + 2]^+$).

3,6-Dihydro-8-(4-methylphenyl)-6-phenyl-2H-pyrazolo-[3,4-b]thieno[2,3-d]pyridine (**9b**, $C_{21}H_{17}N_3S$)
White amorphous solid; yield 3.10 g (90%); m.p.: 177–180 °C; $R_f = 0.73$ (chloroform–methanol 9:1); IR (KBr): $\bar{\nu} = 2{,}934$, 2,730, 1,599, 1,545, 1,234 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 2.45$ (s, 3H, CH_3), 3.34 (t, $J = 6.8$ Hz, 2H), 3.86 (t, $J = 6.8$ Hz, 2H), 7.29–7.38 (m, 3H, ArH), 7.50–7.57 (m, 2H, ArH), 7.89 (d, $J = 8.3$ Hz, 2H, ArH), 8.26 (s, 1H, Py-H), 8.30 (d, $J = 8.3$ Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 21.0$, 29.6, 34.3, 121.6, 126.7, 128.6, 130.2, 130.3, 131.1, 135.0, 139.4, 143.4 ppm; MS (ESI): $m/z = 343$ (M^+).

General procedure for the synthesis of compounds ***10a–10 h***

A mixture of **4** (0.01 mol) and primary aliphatic or aromatic amines (0.04 mol) was heated at 110–120 °C for about 2–3 h, until TLC showed no more starting material. Then the mixture was cooled to 20 °C and 20 cm^3 cold methanol (5 °C) was added. The resulting solid was filtered by suction, washed with methanol, dried, and recrystallized from ethanol/DMF to furnish compounds **10** in good yield.

1-Benzyl-8-(4-chlorophenyl)-1,2,3,6-tetrahydro-6-phenylpyrazolo[3,4-b]pyrrolo[2,3-d]pyridine
(**10a**, $C_{28}H_{25}ClN_4$)
White amorphous solid; yield 4.07 g (90%); m.p.: 179–181 °C; $R_f = 0.47$ (chloroform–methanol 9:1); IR (KBr): $\bar{\nu} = 2{,}908$, 1,605, 1,596, 1,313, 1,090 cm^{-1}; ^{1}H NMR ($CDCl_3$): $\delta = 3.14$ (t, $J = 8.7$ Hz, 2H), 3.49 (t, $J = 8.7$ Hz, 2H), 4.13 (s, 2H, CH_2), 7.04 (d, $J = 7.8$ Hz, 2H, ArH), 7.18 (d, $J = 8.4$ Hz, 2H, ArH), 7.23–7.31 (m, 4H, ArH), 7.49–7.57 (m, 4H, ArH), 8.14 (s, 1H, ArH), 8.29 (d, $J = 7.8$ Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$):

δ = 31.4, 43.6, 51.2, 120.1, 120.7, 121.2, 122.4, 126.2, 126.5, 127.3, 127.5, 128.2, 128.5, 129.1, 129.8, 130.1, 131.1, 133.1, 144.4, 153.1 ppm; MS (ESI): *m/z* = 452 (M^+), 454 ($[M + 2]^+$).

8-(4-Chlorophenyl)-1,2,3,6-tetrahydro-1-(4-methylphenyl)-6-phenylpyrazolo[3,4-b]pyrrolo[2,3-d]pyridine (**10b**, $C_{27}H_{21}ClN_4$)

Off-white solid; yield 3.05 g (70%); m.p.: 192–194 °C; R_f = 0.49 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 2,950, 2,717, 1,610, 1,202 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.23 (s, 3H, CH_3), 3.33 (t, *J* = 9 Hz, 2H), 4.18 (t, *J* = 9 Hz, 2H), 6.50 (d, *J* = 8.1 Hz, 2H, ArH), 6.80 (d, *J* = 8.4 Hz, 2H, ArH), 6.92 (d, *J* = 8.4 Hz, 2H, ArH), 7.26 (m, 2H, ArH), 7.30 (d, *J* = 7.5 Hz, 2H, ArH), 7.51 (t, *J* = 7.5 Hz, 2H, ArH), 8.22 (d, *J* = 8.1 Hz, 2H), 8.24 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 21.1, 31.2, 43.6, 120.1, 120.8, 121.9, 126.5, 126.7, 127.5, 128.2, 128.3, 128.7, 129.0, 129.5, 130.1, 132.5, 134.3, 140.3, 143.7, 150.8 ppm; MS (ESI): *m/z* = 434 (M^+), 436 ($[M+2]^+$).

1-(3-Chloro-4-fluorophenyl)-8-(4-chlorophenyl)-1,2,3,6-tetrahydro-6-phenylpyrazolo[3,4-b]pyrrolo[2,3-d]pyridine (**10c**, $C_{26}H_{17}Cl_2FN_4$)

Orange amorphous solid; yield 3.56 g (75%); m.p.: 158–160 °C; R_f = 0.49 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 2,900, 1,616, 1,585, 1,240 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.20 (t, *J* = 8 Hz, 2H), 4.26 (t, *J* = 8 Hz, 2H), 6.72 (s, 1H, Ar–H), 6.80–6.82 (m, 2H, ArH), 7.01 (d, *J* = 6 Hz, 2H, ArH), 7.26-7.45 (m, 5H, ArH), 7.89 (d, *J* = 6 Hz, 2H, ArH), 8.02 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 31.2, 43.4, 118.4, 120.8, 122.0, 125.8, 126.7, 127.5, 128.3, 128.7, 129.2, 129.5, 129.8, 130.2, 130.9, 131.8, 132.3, 143.4, 144.6, 151.1, 157.0 ppm.

8-(4-Chlorophenyl)-1,2,3,6-tetrahydro-1,6-diphenylpyrazolo[3,4-b]pyrrolo[2,3-d]pyridine (**10d**, $C_{26}H_{19}ClN_4$)

White amorphous solid; yield 3.29 g (78%); m.p.: 207–209 °C; R_f = 0.47 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 2,908, 1,616, 1,598, 1,238 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 3.34 (t, *J* = 6.9 Hz, 2H), 4.23 (t, *J* = 6.9 Hz, 2H), 6.78–6.84 (m, 2H, ArH), 6.88–6.92 (m, 5H, ArH), 7.32–7.34 (m, 3H, ArH), 7.52 (d, *J* = 8.7 Hz, 2H, ArH), 8.25 (d, *J* = 8.7 Hz, 2H, ArH), 8.25 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 31.3, 43.9, 119.8, 120.6, 121.0, 122.2, 126.4, 126.7, 127.1, 128.1, 128.5, 129.1, 129.5, 130.1, 131.1, 138.5, 143.2, 144.4, 151.3 ppm; MS (ESI): *m/z* = 422 (M^+), 424 ($[M+2]^+$).

1-Benzyl-1,2,3,6-tetrahydro-8-(4-methylphenyl)-6-phenylpyrazolo[3,4-b]pyrrolo[2,3-d]pyridine (**10e**, $C_{28}H_{24}N_4$)

Faint brown crystalline solid; yield 3.41 g (82%); m.p.: 227–229 °C; R_f = 0.45 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 2,934, 2,727, 1,599, 1,580, 1,338 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.24 (s, 3H, CH_3), 3.18 (t, *J* = 8.3 Hz, 2H), 3.52 (t, *J* = 8.3 Hz, 2H), 4.16 (s, 2H, CH_2), 6.95–7.06 (m, 4H, ArH), 7.21–7.23 (m, 1H, ArH), 7.31–7.36 (m, 2H, ArH), 7.43–7.56 (m, 5H, ArH), 8.15 (s, 1H, ArH), 8.26 (d, *J* = 7.6 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 21.1, 31.3, 43.5, 51.4, 120.0, 120.6, 121.2, 122.2, 126.5, 126.9, 127.3, 127.8, 128.0, 129.1, 129.4, 130.3, 131.1, 132.3, 133.5, 145.2, 152.8 ppm; MS (ESI): *m/z* = 416 (M^+).

1,2,3,6-Tetrahydro-1,8-bis(4-methylphenyl)-6-phenylpyrazolo[3,4-b]pyrrolo[2,3-d] pyridine (**10f**, $C_{28}H_{24}ClN_4$)

Yellow solid; yield 3.33 g (80%); m.p.: 203–205 °C; R_f = 0.48 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 3,065, 2,918, 2,864, 1,593, 1,494 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.27 (t, *J* = 8.3 Hz, 2H), 4.20 (t, *J* = 8.3 Hz, 2H), 6.49 (d, *J* = 7.3 Hz, 2H, ArH), 6.89–7.04 (m, 4H, ArH), 7.29 (t, *J* = 6.9 Hz, 2H, ArH), 7.37–7.40 (m, 3H, ArH), 8.14 (d, *J* = 8.7 Hz, 2H, ArH), 8.20 (s, 1H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 21.1, 21.3, 31.3, 43.3, 119.9, 120.7, 121.8, 126.4, 126.9, 127.4, 128.1, 128.5, 128.7, 129.3, 129.8, 130.4, 134.8, 136.2, 139.9, 143.9, 151.1 ppm.

1-(4-Chloro-3-fluorophenyl)-1,2,3,6-tetrahydro-8-(4-methylphenyl)-6-phenylpyrazolo[3,4-b]pyrrolo[2,3-d]-pyridine (**10g**, $C_{27}H_{20}ClFN_4$)

Colorless solid; yield 3.41 g (75%); m.p.: 160–162 °C; R_f = 0.48 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 2,949, 2,716, 1,608, 1,588 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.32 (s, 3H, CH_3), 3.28 (t, *J* = 8.8 Hz, 2H), 4.17 (t, *J* = 8.8 Hz, 2H), 6.62 (s, 1H, ArH), 6.78 (d, *J* = 7.2 Hz, 1H, ArH), 6.83 (d, *J* = 7.2 Hz, 1H, ArH), 7.02 (d, *J* = 6.9 Hz, 2H, ArH), 7.08-7.34 (m, 5H, ArH), 8.02 (s, 1H, ArH), 8.12 (d, *J* = 6.9 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 21.1, 31.2, 43.5, 118.5, 121.6, 121.9, 125.9, 126.3, 127.7, 128.3, 128.9, 129.3, 129.4, 129.8, 130.5, 131.1, 132.4, 134.9, 143.3, 144.4, 151.6, 156.8 ppm; MS (ESI): *m/z* = 455 (M^+), 457 ($[M+2]^+$).

1,2,3,6-Tetrahydro-8-(4-methylphenyl)-1,6-diphenylpyrazolo[3,4-b]pyrrolo[2,3-d]pyridine (**10h**, $C_{27}H_{22}N_4$)

Off-white crystalline solid; yield 3.17 g (79%); m.p.: 174–176 °C; R_f = 0.46 (chloroform–methanol 9:1); IR (KBr): $\bar{\nu}$ = 2,920, 2,736, 1,596, 1,580 cm^{-1}; ^1H NMR ($CDCl_3$): δ = 2.34 (s, 3H, CH_3), 3.28 (t, *J* = 8.0 Hz, 2H), 4.22 (t, *J* = 8.0 Hz, 2H), 6.60–6.64 (m, 3H, ArH), 6.70 (d, *J* = 7.8 Hz, 2H, ArH), 7.05–7.27 (m, 5H, ArH), 7.30–7.38 (m, 2H, ArH), 8.08 (s, 1H, ArH), 8.12 (d, *J* = 7.1 Hz, 2H, ArH) ppm; ^{13}C NMR ($CDCl_3$): δ = 21.2, 31.4, 43.8, 120.1, 120.8, 121.0, 122.4, 126.3, 126.5, 127.0, 128.3, 128.9, 129.3, 129.5, 130.1, 134.5, 138.5, 143.6, 144.4, 151.0 ppm.

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