Synthesis of Pyrazolo[3,4-*b*]pyridines and Attachment of Amino Acids and Carbohydrate as Linkers

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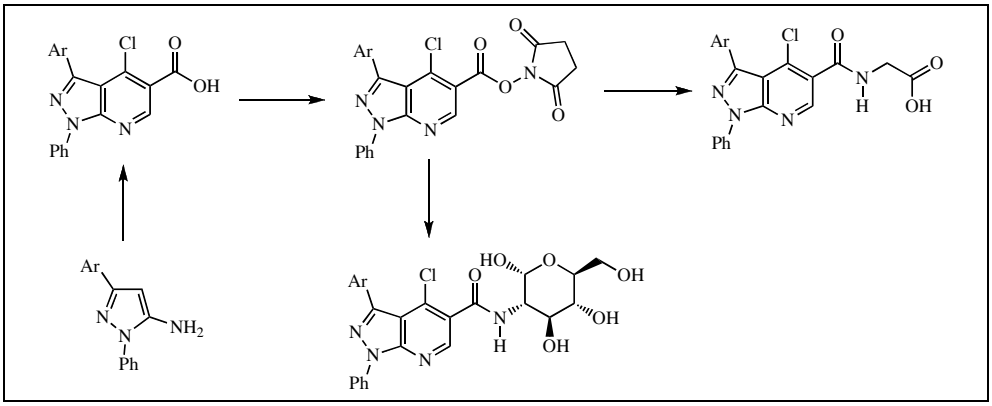

Synthesis of novel pyrazolo[3,4-*b*]pyridines has been achieved successfully by sequence of *Gould - Jacobs* reaction between 5-aminopyrazole and diethylethoxymethylenemalonate in good yield. Further the pyrazolo[3,4-*b*]pyridines were converted into succinimidoyl active esters which are then replaced by biological samples such as amino acids and carbohydrate in slightly aqueous medium.

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INTRODUCTION

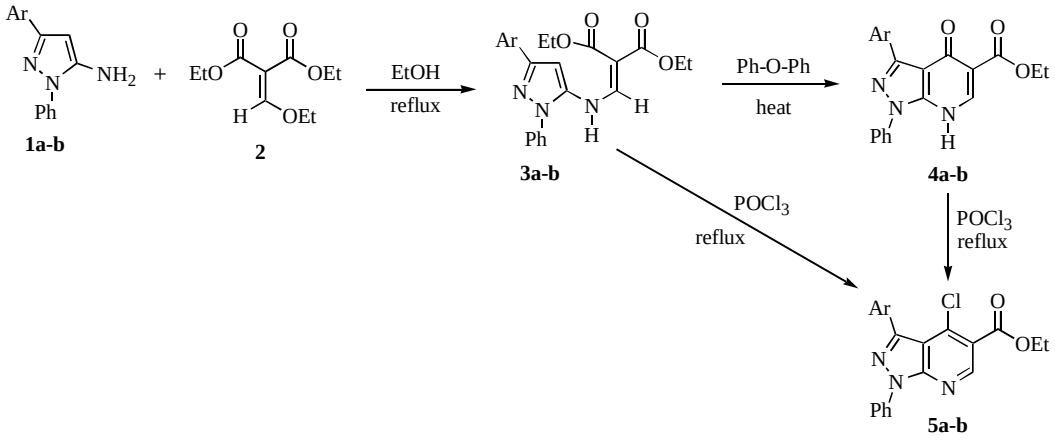
In recent years an increasing interest has been focused on the synthesis of biologically active compounds owing to their significant applications in the fields of synthetic organic chemistry and medicinal chemistry. The heterocyclic systems containing pyrazole ring are ranked among the most versatile bioactive compounds and a variety of procedures have been developed for their synthesis [1]. Pyrazolopyridines are examples of such fused systems, which are attractive targets in organic synthesis due to their significant biological and pharmacological activities, and are aza analogues of indazoles [2]. Pyrazolo[3,4-*b*]pyridine derivatives were first synthesized by *Ortoleva* [3]. They showed a number of interesting pharmacological activities such as hypotensive [4], hypoglycemic [5,6], psychotropic agents [7], as coronary vasodilators [8,9], cytotoxic [10] or antiviral activity [11]. These compounds are also found to be potential purine antagonists [12], anti-asthmatic [13], anti-allergic [14], anti-tumor [15] and antibacterial [16].

Pyrazolopyridines have been reported to be active compounds for phosphodiesterases (PDEs), adenosine, benzodiazepine receptors [17,18] and recently *H. Ochiai et.al.*, discovered chemical leads for phosphodiesterase 4 (PDE4) inhibitors [19]. Literature search reveals that pyrazolo[3,4-*b*]pyridine derivatives are GSK-3 inhibitors [20-24]. The remarkable applications of these compounds not only attracted many chemists to synthesize such type of compounds but also to become an active research area of continuing interest. Recently we have reported [25-30] the synthesis of pyrazolo[3,4-*b*]pyridines, pyrazolo[3,4-*b*]quinolines, pyrazolonapthridines, pyrazolopyridopyrimidines, fused pyrimidines and benzo[*h*]quinolines. These literature reports and our ongoing research in this area prompted us to extend our work towards the attachment of amino acids and carbohydrates to pyrazolo[3,4-*b*]pyridines.

RESULTS AND DISCUSSION

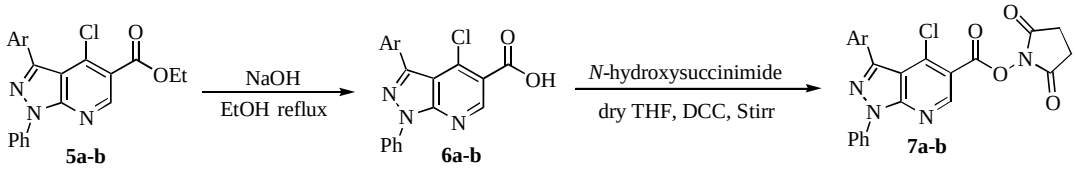
The linkage of fluorescent dyes with biopolymers such as proteins or polysaccharides is a method used for many purposes [31]. The starting material *i.e.* 5-aminopyrazoles **1** required for the synthesis of the title compounds were synthesized by the condensation of *p*-chloro or *p*-bromobenzoylacetonitrile with phenyl hydrazine according to the literature procedure [32]. Thus the reaction of 5-aminopyrazoles **1** with diethoxymethylenemalonate **2** in ethanol furnished the open chain enamine derivatives **3** in more than 70 % yield. The intermediate **3** were cyclized separately by using diphenyl ether or phosphorousoxychloride to give mainly the pyrazolo[3,4-*b*]pyridines **4** and **5** respectively in 70-80 % yield (Scheme 1). Compounds **5** contain bifunctional groups and were used as precursor for the linkage of

Scheme 1



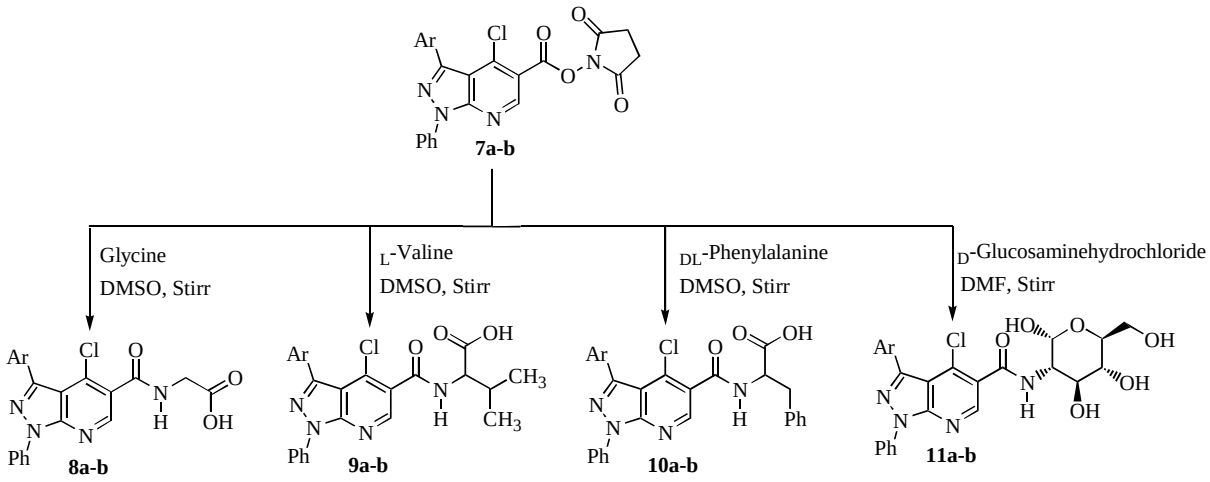
1,3,4,5	Ar
a	*p*-Cl-C_6H_4
b	*p*-Br-C_6H_4

Scheme 2



5,6,7	Ar
a	*p*-Cl-C_6H_4
b	*p*-Br-C_6H_4

Scheme 3



7,8,9,10,11	Ar
a	*p*-Cl-C_6H_4
b	*p*-Br-C_6H_4

amino acids and carbohydrates. To attach a reactive linker group to the pyrazolopyridines **5** at the fifth position we followed the strategy of synthesizing the active esters **7**, which can be linked to the natural substrates such as amino acids, proteins, amino-carbohydrates or amino-polysaccharides. Thus the pyrazolopyridines **5** having the ester group at the five position were hydrolyzed in 10 % aqueous ethanolic sodium hydroxide and furnished the 3-aryl-4-chloro-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylic acids **6** in 70 % yield. In the next step we chose the preparation of the reactive succinimidoyl active esters **7**. This class of compounds are reported to have the advantage of both stability and high reactivity with amino groups in aqueous solution [33]. Thus the synthesis of active esters **7** were performed by the reaction of acids **6** and *N*-hydroxy-succinimide in dry tetrahydrofuran containing catalytic amount of dicyclohexylcarbodiimide as the water scavenger and afforded the succinimidoyl active esters **7** in 75 % yield (Scheme 2).

The reaction of active esters **7** with the free amino group of amino acid or carbohydrate should allow the labeling of such biocompounds under gentle conditions, whereas our attempts to conjugate the amino acid or carbohydrate to active ester at temperature between 15 to 35 °C were not successful. Thus the reaction of active esters **7** with glycine, L-valine and (D,L)-phenylalanine was performed at 45 to 55 °C in 10 % aq. Dimethyl-sulfoxide as the solvent and pH-7 buffer as basic catalyst. It afforded the compounds **8**, **9** and **10** respectively. The amino group of the sugar is further target for the linkage to the active esters **7**. Thus the reaction of D-glucosamine hydrochloride in 10 % aq. DMF with *N*-methyl morpholine as basic catalyst, yielded namely the 3-(4-aryl)-4-chloro-*N*-(2*R*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-2,4,5-tri-hydroxy-6-(hydroxymethyl)-2*H*-pyran-3-yl)-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxamides **11** in about 75 % yield. The reactions reported here represent the synthesis of novel pyrazolo[3,4-*b*]pyridines linked with amino acids and carbohydrate with simple workup and clean products with good yields. The attachment of such type of biological samples to the pyrazolo[3,4-*b*]pyridines has not been reported earlier.

In conclusion we have used a simple and convenient methodology for the synthesis of novel pyrazolo[3,4-*b*]-pyridines using a sequence of *Gould-Jacobs* reaction between 5-aminopyrazole and diethylethoxymethylene-malonate. Further the pyrazolopyridine were converted into succinimidoyl active esters, which are then easily replaced by linking the biological samples such as amino acids and carbohydrates in slightly aqueous medium.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus, Mod. MFB-595 in open capillary tubes and are uncorrected. The ^{1}H and ^{13}C nmr spectra were recorded on a Varian XL-300 spectrometer (300 MHz). Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given δ-units. The solvent for nmr spectra was deuteriochloro-form unless otherwise stated. Infrared spectra were taken on Shimadzu IR-408, a Shimadzu FTIR instrument in potassium bromide pellets unless otherwise stated. Elemental analyses were performed on a Hosli CH-Analyzer and are within ± 0.4 of the theoretical percentage. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merk) plates using UV light (254 and 366 nm) for detection.

3-Aryl-1-phenyl-1*H*-pyrazole-5-amine(1).This compound was prepared according to reference [32].

Diethyl 2-(ethoxymethylene) malonate (2). This compo-und is commercially available.

General Procedure for Synthesis of Diethyl 2-((3-(4-aryl)-1-phenyl-1 *H*-pyrazole-5-ylamino) methylene) malonate (3). A solution of 5-aminopyrazoles **1** (10 mmol) and diethylethoxymethylenemalonate **2** (10 mmol) in absolute ethanol (20 mL) was refluxed for 12-15 h. The solid formed on cooling was filtered by suction, washed with ethanol (20 mL) and dried to afford **3** in 90 % yield.

General Procedure for Synthesis of Ethyl 3-(4-aryl)-4-oxo-1-phenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4a). A Solution of **3** (10 mmol) in diphenylether (20 mL) was heated at 230–240 °C for 1 h. Then the solution was allowed to cool to room temperature and the reaction mixture was poured into diethylether (50 mL) and stirred for 1 h. The solid that separated out was collected by suction filtration, washed with diethylether (250 mL), dried to afford **4** in 70 % yield.

General Procedure for Synthesis of Ethyl 4-chloro-3-(4-aryl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (5). A Solution of **3** or **4** (10 mmol) in phosphorous- oxychloride (20 mL) was refluxed at 110–130 °C for 5-8 h. Completion of reaction was checked by TLC. Then the solution was allowed to cool to room temperature and was dropwise poured into crushed ice with constant stirring. The obtained solid was collected by suction filtration, washed with cold water (250 mL), dried to afford **5** in 70-75 % yield.

General Procedure for Synthesis of 4-Chloro-3-(4-aryl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid(6). A solution of **5** (10 mmol) in ethanol (25 mL) and 10 % aq. NaOH (2 mL) was heated at reflux temperature for 7-8 h. Then the ethanol was removed under reduced pressure and the residue dissolved in water (50 mL). The mixture was acidified with conc. HCl and the resulting precipitate collected by suction filtration and washed with water, dried to afford **6** in 70 % yield.

General Procedure for Synthesis of 4-Chloro-3-(4-aryl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl]carbonyloxy)pyrrolidine-2,5-dione (7). A solution of **6** (10 mmol), *N*-hydroxy-succinimide (10 mmol) and dicyclohexylcarbodi-imide (10 mmol) as water scavenger in dry tetrahydrofuran (25 mL) was stirred at room temperature for 6-7 h. Then the solvent was removed under reduced pressure. The gummy mass obtained was stirred in ethanol, the solid that precipitated out was collected by suction filtration, washed with ethanol, dried to afford **7** in 70 % yield.

General Procedure for Synthesis of 4-Chloro-3-(4-aryl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamido)-acetic acid (8). A solution of succinimidoyl active esters **7** (5 mmol)

was dissolved in dimethylsulfoxide (10 mL) and drop wise added into the solution of glycine (5 mmol) in 10 % aq. dimethylsulfoxide (5 mL) at 20 °C with constant stirring. After this the buffer solution of pH-7 (0.5 mL) was added drop wise into above solution. Then the reaction mixture was stirred at 45-55 °C for 7 h and the solution was poured into cold water (20 mL) and neutralized by conc. HCl, the solid that separated out was collected by suction filtration, washed with water, dried to afford **8** in 50 % yield.

General Procedure for Synthesis of 4-Chloro-3-(4-aryl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamido)-3-methyl-butanoic acid (9). A solution of succinimidoyl active esters **7** (10 mmol) was dissolved in dimethylsulfoxide (10 mL) and drop wise added into the solution of L-valine (5 mmol) in 10 % aq. dimethylsulfoxide (7 mL) at 20 °C with constant stirring. Then the buffer solution of pH-7 (0.5 mL) was added drop wise into above solution and the reaction mixture was stirred at 45–55 °C for 7 h. The solution was poured into cold water (20 mL) and neutralized by conc. HCl. The solid that separated out was collected by suction filtration, washed with water, dried to afford **9** in 50 % yield.

General Procedure for Synthesis of 2-(4-Chloro-3-(4-aryl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamido)-3-phenylpropanoic acid (10). A solution of succinimid-oyl active esters **7** (5 mmol) was dissolved in dimethyl- sulfoxide (10 mL) and drops wise added into the solution of (D,L)-phenylalanine (5 mmol) in 10 % aq. dimethylsulfoxide (8 mL) at 20 °C with constant stirring. After this the buffer solution of pH-7 (0.5 mL) was added drop wise into above solution and the reaction mixture was stirred at 50–55 °C for 12 h. Then the solution was poured into cold water (25 mL) and neutralized by conc. HCl, the solid that separated out was collected by suction filtration, washed with water, dried to afford **10** in 50 % yield.

General Procedure for Synthesis of 4-Chloro-3-(4-aryl)-*N*-(2*R*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-2,4,5-trihydroxy-6-(hydroxy-methyl)-2*H*-pyran-3-yl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (11). To a solution of D-glucosamine hydrochloride (5 mmol) in 10 % aq. DMF (10 mL) was drop wise added the solution of succinimidoyl active esters **7** (5 mmol) in DMF (8 mL) at 20 °C with constant stirring and the *N*-methylmorpholine (0.5 mL) was added, the mixture was stirred at 50-55 °C for 12-14 h and the solution was poured into cold water (20 mL) and neutralized by conc. HCl, the solid that separated out was collected by suction filtration, washed with water, dried to afford **11** in 75 % yield.

Diethyl 2-((3-(4-Chlorophenyl)-1-phenyl-1*H*-pyrazole-5-ylamino)methylene)malonate (3a). This compound was obtained as colorless prisms (ethanol), mp 115-116 °C; ir: (potassium bromide): 3145, 2983, 1691, 1643, 1552, 1444, 1384, 839 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 1.28 (m, 6H, $2CH_3$), 4.21 (m, 4H, $2CH_2$), 6.49 (s, 1H, C_4-H), 7.37 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.44 (m, 5H, Ar-H), 7.76 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.22 (d, *J* = 12.6 Hz, 1H, C_7-H), 11.03 (d, *J* = 12.6 Hz, 1H, NH). *Anal*. Calcd. for $C_{23}H_{22}ClN_3O_4$; C 62.80, H 5.03, N 9.54; found. C 62.90, H 5.02, N 9.41.

Diethyl 2-((3-(4-bromophenyl)-1-phenyl-1*H*-pyrazole-5-ylamino)methylene)malonate (3b). This compound was obtained as colorless prisms (ethanol), mp 122-124 °C; ir (potassium bromide): 3036, 2970, 1680, 1633, 1545, 1441, 1384, 954, 825 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 1.29 (m, 6H, 2-CH_3), 4.25 (m, 4H, 2-CH_2), 6.51 (s, 1H, C_4-H), 7.38 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.45 (m, 5H, Ar-H), 7.77 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.20 (d, *J* = 12.6 Hz, 1H, C_7-H), 11.01 (d, *J* = 12.6 Hz, 1H, NH). *Anal*. Calcd. for $C_{23}H_{22}BrN_3O_4$; C 57.04, H 4.57, N 8.67, found. C 57.00, H 4.44, N 8.51.

Ethyl 3-(4-chlorophenyl)-4-oxo-1-phenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate(4a). This com-pound was obtained as yellow prisms (ethanol), mp. 130-131 °C, yield 70 % , ir: (potassium bromide) : 2916, 2848, 1687, 1598, 1552, 1469, 1334, 1284, 1163, 935, 761 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 1.45 (t, 3H, CH_3), 4.46 (q, 2H, CH_2), 7.25 (m, 9H, Ar-H), 8.20 (d, 1H, C_6H), 8.97 (bs, 1H, NH); ^{13}C nmr: ($CDCl_3$) δ 14.5, 61.3, 115.9, 119.1, 123.3, 123, 124.2, 126, 127.3, 130.3, 134, 135.8, 144, 154.6, 156, 168, 177. *Anal*. Calcd. for $C_{21}H_{16}ClN_3O_3$; C: 64.14; H: 4.09; N: 10.68, Found. C: 64.00; H: 4.02; N: 10.55

Ethyl 3-(4-bromophenyl)-4-oxo-1-phenyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (4b). This com-pound was obtained as yellow prisms (ethanol), mp. 141-142 °C, yield 75 % , ir: (potassium bromide) : 2926, 2855, 1674, 1578, 1447, 1355, 1281, 1161, 945, 753 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 1.47 (t, 3H, CH_3), 4.43 (q, 2H, CH_2), 7.24 (m, 9H, Ar-H), 8.18 (d, 1H, C_6H), 8.94 (bs, 1H, NH); ^{13}C nmr: ($CDCl_3$) δ 14.6, 61.8, 113.9, 118.2, 122, 123, 124.8, 125.3, 129, 130, 134.7, 137, 144.2, 155.5, 156, 169.1, 179.3. *Anal*. Calcd for $C_{21}H_{16}BrN_3O_3$; C: 57.62; H: 3.68; N: 9.59 Found. C: 57.50; H: 3.45; N: 9.44

Ethyl 4-chloro-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate (5a). This compound was obtained as colorless prisms (ethanol), mp 170-172 °C; ir (potassium bromide): 1733, 1581, 1552, 1458, 1363, 1288, 937, 844 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 1.43 (t, 3H, CH_3), 4.43 (q, 2H, CH_2), 7.38 (m, 5H, Ar-H), 7.68 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.19 (d, *J* = 8.4 Hz, 2H, Ar-H), 9.05 (s, 1H, C_6-H); ^{13}C nmr: ($CDCl_3$) δ 14.8, 58.7, 107.2, 120.5, 125.2, 126.8, 128.9, 129.4, 129.8, 131.5, 134.4, 139.8, 140.3, 145.8, 150.7, 151.3, 168.9. ^{13}C nmr: ($CDCl_3$) δ 14.9, 61.2, 111.2, 119.3, 124.1, 125.1, 127, 127.4, 129.5, 130.2, 134, 137.6, 147.2, 153.8, 156.1, 167.3, 177.4. *Anal*. Calcd. for $C_{21}H_{15}Cl_2N_3O_2$; C 58.91, H 3.50 N, 9.81 found. C 58.80, H 3.35, N 9.75

Ethyl 3-(4-bromophenyl)-4-chloro-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxylate (5b). This compound was obtained as colorless prisms (ethanol), mp 180-182 °C; ir: (potassium bromide): 1725, 1563, 1435, 1343, 1285, 1235, 935, 834 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 1.44 (t, 3H, CH_3), 4.46 (q, 2H, CH_2), 7.33 (m, 5H, Ar-H), 7.67 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.20 (d, *J* = 8.4 Hz, 2H, Ar-H), 9.02 (s, 1H, C_6-H); ^{13}C nmr: ($CDCl_3$) δ 14.7, 58.8, 108.2, 119.4, 125.3, 126.9, 127.8, 129.5, 129.7, 131.4, 134.9, 138.5, 140.6, 144.8, 151.4, 152.2, 169.2. *Anal*. Calcd. For $C_{21}H_{15}BrClN_3O_2$; C 55.24, H 3.28, N 9.19, found. C 55.15, H 3.15, N 9.05.

4-Chloro-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxylic acid (6a). This compound was obtained as colorless prisms (ethanol), mp 205-207 °C; ir: (potassium bromide): 1733, 1533, 1415, 1320, 1245, 925, 814 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 7.24 (m, 5H, Ar-H), 7.91 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.20 (d, *J* = 8.4 Hz, 2H, Ar-H) 9.26 (s, 1H, C_6-H). *Anal*. Calcd. for $C_{19}H_{11}Cl_2N_3O_2$; C 59.39, H 2.89, N 10.94, found. C 59.25, H 2.65, N 10.77.

3-(4-Bromophenyl)-4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxylic acid (6b). This compound was obtained as colorless prisms (ethanol), mp 215-217 °C; ir: (potassium bromode): 1721, 1545, 1405, 1330, 1233, 925, 844 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 7.22 (m, 5H, Ar-H), 7.90 (d, *J* = 8.4 Hz, 2H, Ar-

H), 8.21 (d, *J* = 8.4 Hz, 2H, Ar-H), 9.25 (s, 1H, C_6-H). *Anal*. Calcd. for $C_{19}H_{11}BrClN_3O_2$; C 53.24, H 2.59, N 9.80, found. C 53.20, H 2.66, N 9.98.

4-Chloro-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridin-5-yl]carbonyl-oxy) pyrrolidine-2,5-dione (7a). This compound was obtained as colorless prisms (ethanol), mp 226-227 °C; ir (potassium bromide): 1741, 1665, 1524, 1439, 1301, 1230, 905, 814 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 2.93 (s, 4H, $2CH_2$), 7.24 (m, 5H, Ar-H), 7.87 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.19 (d, *J* = 8.4 Hz, 2H, Ar-H) 9.13 (s, 1H, C_6-H). *Anal*. Calcd. for $C_{23}H_{14}Cl_2N_4O_4$; C 57.40, H 2.93, N 11.64, found. C 57.31, H 2.86, N 11.78.

3-(4-Bromophenyl)-4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridin-5-yl]carbonyl-oxy) pyrrolidine-2,5-dione (7b). This compound was obtained as colorless prisms (ethanol), mp 235-236 °C; ir: (potassium bromide): 1740, 1661, 1520, 1432, 1300, 1235, 902, 854 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 2.94 (s, 4H, $2CH_2$), 7.23 (m, 5H, Ar-H), 7.86 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.18 (d, *J* = 8.4 Hz, 2H, Ar-H) 9.14 (s, 1H, C_6-H). *Anal*. Calcd. for $C_{23}H_{14}BrClN_4O_4$; C 52.54, H 2.68, N 10.66, found. C 52.41, H 2.56, N 10.48.

4-Chloro-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxamido) acetic acid (8a). This compound was obtained as colorless prisms (ethanol), mp 256-257 °C; ir: (potassium bromide): 1724, 1651, 1552, 1422, 1231, 922, 851 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 3.90 (d, *J* = 6.6 Hz, 2H, NCH_2), 7.31 (m, 5H, Ar-H), 7.84 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.19 (d, *J* = 8.4 Hz, 2H, Ar-H) 8.37 (bs, 1H, NH), 9.28 (s, 1H, C_6-H). *Anal*. Calcd. for $C_{21}H_{14}Cl_2N_4O_3$; C 57.16, H 3.20, N 12.70, found. C 57.21, H 3.26, N 12.68.

3-(4-Bromophenyl)-4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxamido) acetic acid (8b). This compound was obtained as colorless prisms (ethanol), mp 265-267 °C; ir: (potassium bromide): 1734, 1641, 1522, 1412, 1221, 922 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 3.91 (d, *J* = 6.6 Hz, 2H, NCH_2), 7.33 (m, 5H, Ar-H), 7.85 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.20 (d, *J* = 8.4 Hz, 2H, Ar-H) 8.38 (bs, 1H, NH), 9.27 (s, 1H, C_6-H). *Anal*. Calcd. for $C_{21}H_{14}ClBrN_4O_3$; C 51.93, H 2.91, N 11.53, found. C 51.71, H 2.86, N 11.68.

4-Chloro-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxamido)-3-methylbutanoic acid (9a). This compound was obtained as colorless prisms (ethanol), mp 255-257 °C; ir: (potassium bromide): 1727, 1648, 1521, 1434, 1211, 928 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 1.09 (m, 6H, $2CH_3$), 3.91 (m, 1H, CH), 4.85 (t, 1H, CH), 7.24 (m, 5H, Ar-H), 7.84 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.20 (d, *J* = 8.4 Hz, 2H, Ar-H) 8.22 (d, *J* = 7.9 Hz, 1H, NH), 9.33 (s, 1H, Ar-H). *Anal*. Calcd. for $C_{24}H_{20}Cl_2N_4O_3$; C 59.64, H 4.17, N 11.59, found. C 59.50, H 4.06, N 11.63.

3-(4-Bromophenyl)-4-chloro-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxamido)-3-methylbutanoic acid (9b). This compound was obtained as colorless prisms (ethanol), mp 266-267 °C; ir: (potassium bromide): 1723, 1638, 1531, 1444, 1251, 958 cm^{-1}; ^1H nmr: (CDCl3) δ 1.10 (m, 6H, $2CH_3$), 3.92 (m, 1H, CH), 4.86 (t, 1H, CH), 7.26 (m, 5H, Ar-H), 7.85 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.22 (d, *J* = 8.4 Hz, 2H, Ar-H) 8.26 (d, *J* = 7.9 Hz, 1H, NH), 9.35 (s, 1H, Ar-H). *Anal*. Calcd. for $C_{24}H_{20}BrClN_4O_3$; C 54.62, H 3.82, N 10.62, found. C 54.52, H 3.76, N 10.68.

2-(4-Chloro-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxamido)-3-phenylpropanoic acid (10a). This compound was obtained as colorless prisms (ethanol), mp 264-265 °C; ir: (potassium bromide): 1720, 1650, 1555, 1420, 1211, 908, 859 cm^{-1}; ^1H nmr ($CDCl_3$) δ 3.35 (m, 2H, CH_2), 5.12 (q, 1H, CH), 7.23 (m, 10H, Ar-H), 7.78 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.18 (d, *J* = 8.4 Hz, 2H, Ar-H) 8.30 (d, *J* = 7.9 Hz, 1H, NH), 9.32 (s, 1H, Ar-H). *Anal*. Calcd. for $C_{28}H_{20}Cl_2N_4O_3$; C 63.29, H 3.79, N 10.54, found. C 63.21, H 3.66, N 10.68.

2-(3-(4-Bromophenyl)-4-chloro-1-phenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxamido)-3-phenylpropanoic acid (10b). This compound was obtained as colorless prisms (ethanol), mp 269-271 °C; ir: (potassium bromide): 1726, 1658, 1553, 1219, 988, 879 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 3.36 (m, 2H, CH_2), 5.13 (q, 1H, CH), 7.25 (m, 10H, Ar-H), 7.79 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.19 (d, *J* = 8.4 Hz, 2H, Ar-H) 8.31 (d, *J* = 7.9 Hz, 1H, NH), 9.32 (s, 1H, Ar-H). *Anal*. Calcd. for $C_{28}H_{20}BrClN_4O_3$; C 58.40, H 3.50, N 9.73, found. C 58.36, H 3.56, N 9.68.

4-Chloro-3-(4-chlorophenyl)-*N*-(2*R*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-2,4,5-trihydroxy-6-(hydroxymethyl)-2*H*-pyran-3-yl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (11a). This compound was obtained as colorless prisms (ethanol), mp 277-278 °C; ir: (potassium bromide): 3544, 3325, 1627, 1598, 1551, 1427, 948 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 3.58 (d, *J* = 4.7 Hz, 2H, 7-CH_2), 3.88 (t, *J* = 7.2 Hz, 1H, C_5-H), 4.07 (t, *J* = 7.2 Hz, 1H, C_4-H), 4.48 (m, 1H, C_6-H), 4.68 (m, 1H, C_3-H), 6.48 (d, *J* = 3.2 Hz, 1H, α-H), 7.38 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.41 (m, 5H, Ar-H), 7.78 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.78 (d, *J* = 7.9 Hz, 1H, NH), 9.18 (s, 1H, Ar-H). *Anal*. Calcd. for $C_{25}H_{22}Cl_2N_4O_6$; C 55.06, H 4.07, N 10.27, found. C 55.11, H 4.06, N 10.38.

3-(4-Bromophenyl)-4-chloro-*N*-(2*R*,3*S*,4*S*,5*R*,6*S*)-tetrahydro-2,4,5-trihydroxy-6-(hydroxymethyl)-2*H*-pyran-3-yl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (11b). This compound was obtained as colorless prisms (ethanol), mp 284-285 °C; ir: (potassium bromide): 3549, 3222, 1647, 1595, 1553, 1417, 948 cm^{-1}; ^1H nmr: ($CDCl_3$) δ 3.55 (d, *J* = 4.7 Hz, 2H, 7-CH_2), 3.89 (t, *J* = 7.2 Hz, 1H, C_5-H), 4.05 (t, *J* = 7.2 Hz, 1H, C_4-H), 4.47 (m, 1H, C_6-H), 4.67 (m, 1H, 3-CH), 6.48 (d, *J* = 3.2 Hz, 1H, α-H), 7.37 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.42 (m, 5H, Ar-H), 7.78 (d, *J* = 8.4 Hz, 2H, Ar-H), 8.79 (d, *J* = 7.9 Hz, 1H, NH), 9.19 (s, 1H, Ar-H). *Anal*. Calcd. for $C_{25}H_{22}BrClN_4O_6$; C 50.91, H 3.76, N 9.50, found. C 50.78, H 3.66, N 9.38.

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