Synthesis of New Compounds Containing the Pyrazolo[3,4-*b*]pyridine-3-one Subunit

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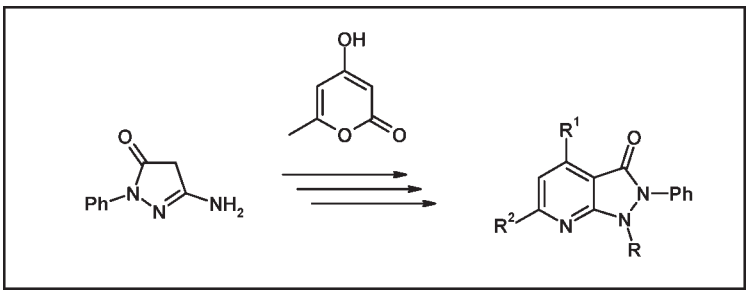

A convenient route for the synthesis of pyrazolo[3,4-*b*]pyridine-3-ones *via* condensation of 3-amino-1-phenylpyrazolin-5-one with 4-hydroxy-6-methylpyran-2-one is described. The pyrazolo[3,4-*b*]pyridine-3-one isomers obtained were functionalized at 1-, 4-, or 6- position by different pharmacophore entities allowing the synthesis of new compounds with promising biological activities.

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INTRODUCTION

The pyrazolo[3,4-*b*]pyridines are important compounds, particularly in pharmaceutical research because of their significant and versatile biological activities such as antimicrobial, antimalarial, antiviral, antiproliferative, anticoagulative, hypotensive, and antiarrythmic [1–5].

Because of the potential of pyrazolo[3,4-*b*]pyridines, much work has been done over the years. The most important synthetic method used to reach these derivatives the condensation of aminopyrazole with α,β-unsaturated compounds reported by Quiroga et al. [6,7].

We were interested in the synthesis of pyridine analogues of these systems involving the condensation of the aminopyrazolone **1** with 2-pyrone **2** [8]. The latter skeleton was proven to be valuable scaffold to obtain new heterocyclic compounds [9,10]. The pyrazolo[3,4-*b*]pyridines prepared will be functionalized at 1-, 4-, and 6-positions.

RESULTS AND DISCUSSION

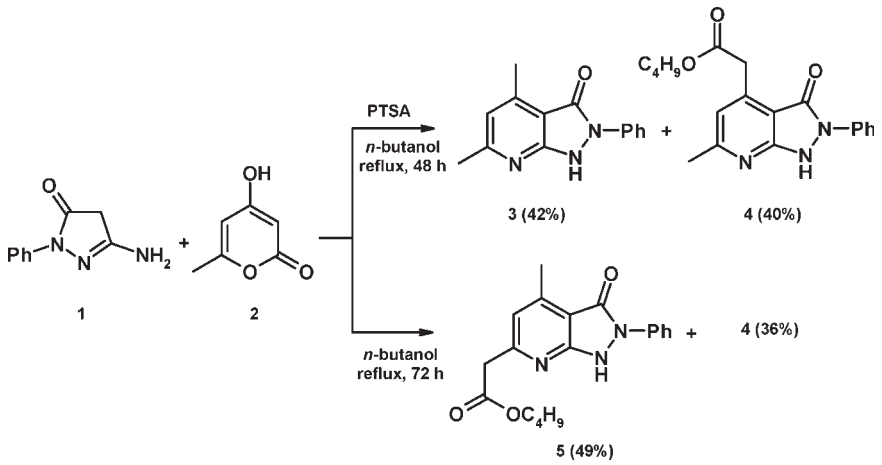
Synthesis of pyrazolo[3,4-*b*]pyridine-3-ones. The reaction of 3-amino-1-phenylpyrazolin-5-one **1** with 4-hydroxy-6-methylpyran-2-one **2** was carried out in butanol at reflux with or without PTSA as catalyst. Pyrazolo[3,4-*b*]pyridine-3-one **4** was isolated in both cases with moderate yields (36–40%). Depending on the reaction conditions used (presence or not of the catalyst), the product **4** was accompanied with pyrazolo[3,4-*b*]pyridine-3-ones **3** or **5** in comparable yields of 42 and 49%, respectively (Scheme 1) [8].

This sequence is of particular interest since it allows a rapid and easy functionalization of 1-, 4-, and 6-positions of the pyrazolo[3,4-*b*]pyridine-3-one scaffold. Thus, the development of synthesis of new molecules with potential biological and/or pharmacological properties appears attractive.

Synthesis of pyrazolo[3,4-*b*]pyridine-3-ones functionalized at 1- position. To widen the substitution of 1-position of pyrazolo[3,4-*b*]pyridine-3-ones, we decided to introduce a bromoethane linker in order to incorporate a bicyclic compound such as a saturated pyridodiazepine known to interact with 5-HT_7/5-HT_{1A} receptors [11].

For this purpose, Deprotonation of pyrazolo[3,4-b]pyridine-3-one 3 with sodium hydride and further nucleophilic substitution with dibromoethane allows the alkylation of position 1 and compound 7 was isolated in 60% yield (Scheme 2) [12].

Scheme 1



We then carried out the preparation of the decahydropyrido[1,2-*a*][1,4]diazepine **6**. This cyclic diamine was prepared in four steps from the piperidine-2-carboxylic acid ethyl ester according to the literature [13].

The final step of this synthetic route was the substitution of the bromine of derivative **7** with the saturated pyridodiazepine **6** in acetonitrile, in the presence of potassium carbonate and a catalytic amount of potassium iodide. The desired compound **8** was obtained in a good yield (78%) (Scheme 3).

Synthesis of pyrazolo[3,4-*b*]pyridine-3-ones functionalized at 4- or 6-position with an amine chain. In a second approach, we focused on the reactivity of the alkyl acetate group present at 4- or 6-position on pyrazolo[3,4-*b*]pyridine-3-ones. Functionalizations with amines and notably with aryl piperazines, often present in serotoninergic ligands, have been especially chosen.

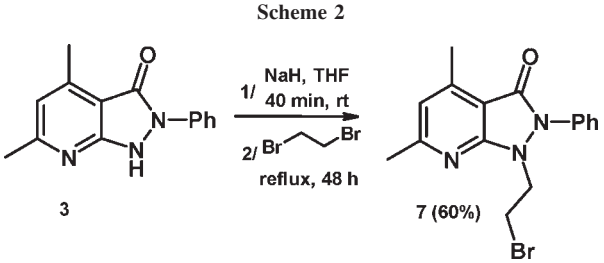
First, the protection of the amine present in compound **5** was necessary. To carry out this step, we choose the *para*-methoxybenzyl chloride (PMBCl) like protective agent. In a basic medium, reaction of pyrazolo[3,4-*b*]pyridine-3-one **5** with the PMBCl led to the amino protected derivative **9** in an excellent yield (97%). Reduction of the ester group with $LiAlH_4$ in THF at reflux led to the desired alcohol **10** in 40% yield. It is worth mentioning that a further reduction of the amide function occurred under these conditions to yield additional product **11** (29%).

To increase the chemioselectivity of the reduction reaction, we performed the reaction in diethyl ether at 0°C. These conditions lead only to the reduction of the function ester making it possible to obtain compound **10** with an average yield (53%). Activation of the alcohol function with methylsulfonyl chloride in the presence of pyridine led to the mesylate derivative **12** in good yield. Substitution of the leaving group with *N*,*N*-dibutylamine and phenylpiperazine provided compounds **13** and **14** in 92 and 93% yields, respectively. The deprotection of the pyrazolic amine group of **13** and **14** was carried out in TFA at reflux leading to compounds **15** and **16** in very good yields (Scheme 4).

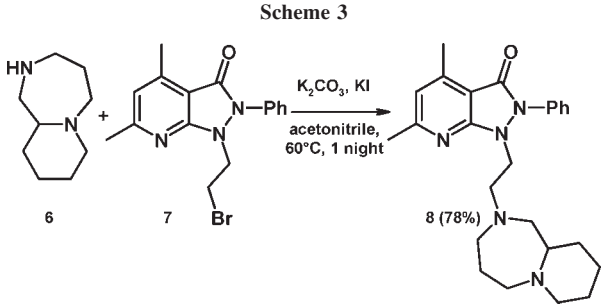
According to the procedure quoted earlier, we then prepared 4-aminoethylpyrazolo[3,4-*b*]pyridin-3-ones **22** and **23** from ester **4** with good yields (Scheme 5). The protection of the amine group of the pyrazoline ring with PMBCl was also realized in a quantitative yield.

The ester group of the resulting protected amine **17** was reduced by $LiAlH_4$ leading to alcohol **18** in 55% yield. The mesylation of the alcohol was carried out leading to the pyrazolo[3,4-*b*]pyridine-3-one **19** in 89% yield. Reaction of *N*,*N*-dibutylamine and phenylpiperazine provided

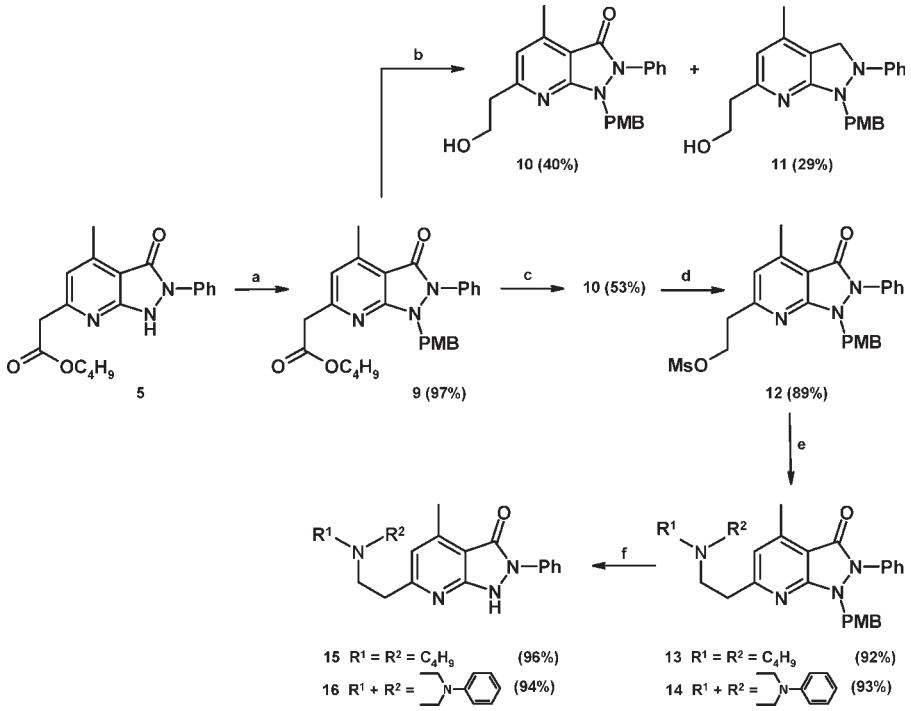
Scheme 2



Scheme 3



Scheme 4. (a) PMBCl, K_2CO_3, CH_2Cl_2, rt, 48 h; (b) $LiAlH_4$, THF, reflux, 3 h; (c) $LiAlH_4$, diethyl ether, 0°C, 24 h; (d) CH_3SO_2Cl, pyridine, 0°C to rt, 48 h; (e) *N*,*N*-dibutylamine or phenylpiperazine, DMF, 70°C, 1 night ; (f) TFA, reflux, 5 h.

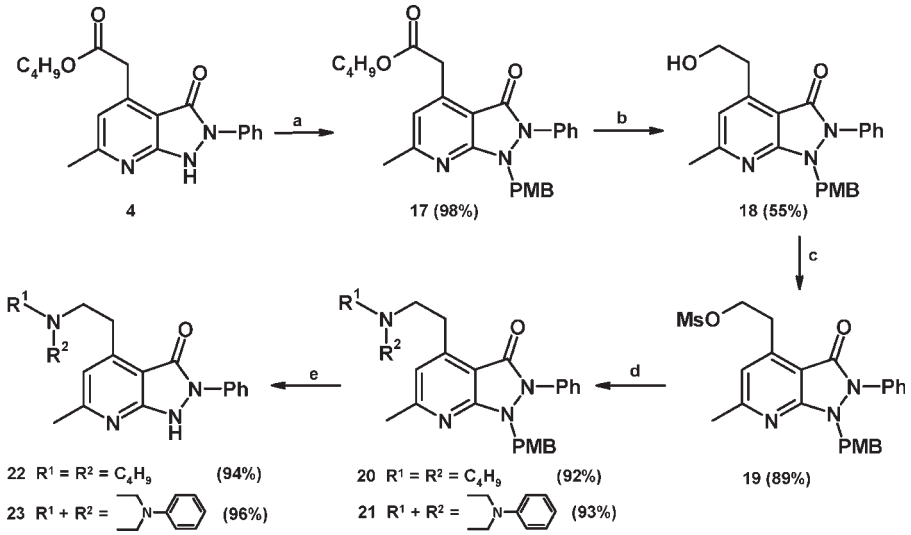


amino compounds **20** and **21** in 92 and 93% yields, respectively.

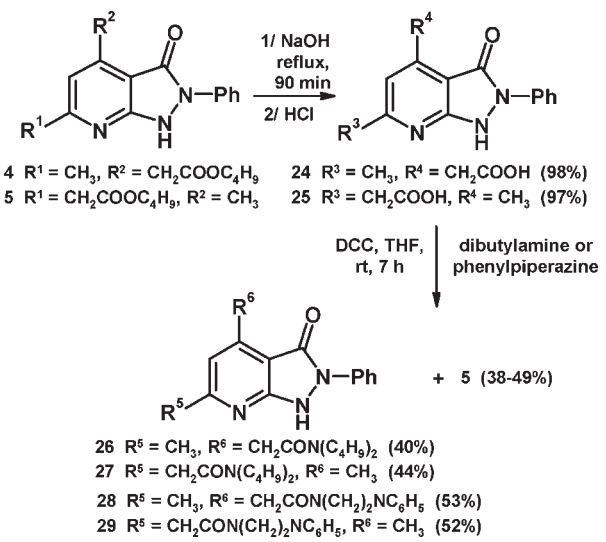
The final deprotection of the pyrazole amine systems was unrolled, like previously, in TFA at reflux affording 4-(2-(dibutylamino)ethyl)-6-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one **22** in a 94% yield and 6-methyl-2-phenyl-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one **23** in a 96% yield.

Synthesis of pyrazolo[3,4-*b*]pyridine-3-ones functionalized at 4- or 6-position with an amide chain. At last, we showed that the ester function at 4- or 6-position could be converted into amide. The preparation of

Scheme 5. (a) PMBCl, K_2CO_3, CH_2Cl_2, rt, 48 h; (b) $LiAlH_4$, diethyl ether, 0°C, 24 h; (c) CH_3SO_2Cl, pyridine, 0°C to rt, 48 h; (d) *N*,*N*-dibutylamine or phenylpiperazine, DMF, 70°C, 1 night ; (e) TFA, reflux, 5 h.



Scheme 6



amido-pyrazolopyridinones **26–29** was accomplished easily in two-step sequence by saponification of ester **4** and **5** followed by peptidic coupling with *N*,*N*-dibutylamine and phenylpiperazine using DCC as coupling agent (Scheme 6).

CONCLUSION

In summary, we have developed an efficient method for the synthesis of novel pyrazolo[3,4-*b*]pyridine-3-one derivatives. Thereafter, we have shown that 1-, 4-, and 6-positions of the pyrazolopyridine skeleton can be easily and rapidly functionalized in order to introduce new pharmacophore entities allowing the synthesis of potential biological molecules. One of the new molecules tested, is compound **26**, has shown pharmacological activities toward the serotoninergic receptors 5-HT_{1A} (Ki = 220 n*M*) and 5-HT_7 (Ki = 870 n*M*).

EXPERIMENTAL

All reagents were purchased either from Acros Organics or Aldrich. Thin layer chromatography was performed on 0.5 mm × 20 cm × 20 cm E. Merck silica gel plates (60 F-254). Infrared (IR) spectra were obtained on Perkin–Elmer Paragon 1000 PC FTIR. Infrared spectra were recorded using NaCl films or KBr pellets. ^{13}C and ^{1}H NMR spectra were recorded at room temperature using a Bruker Advance DXP250 at 62.9 and 250 MHz, respectively. Chemical shifts (δ) are given in parts per million downfield from tetramethylsilane as internal standard. Mass spectra were determined with a Perkin-Elmer SCIEX AOI 300 spectrometer. All chemicals were of reagent grade and used without further purification. THF was freshly distilled from Na/benzophenone, while CH_2Cl_2 was distilled over CaH_2. The biological characterization of the compounds was based on the screening protocol described by Zajdel et al. [14,15].

1-(2-Bromoethyl)-4,6-dimethyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one.(7). Sixty milligrams (1.51 mmol; 1.8 eq) of sodium hydride 60% were suspended in 8 mL of THF then 200 mg (0.84 mmol; 1 eq) of 4,6-dimethyl-2-phenyl-1,2-dihydro-pyrazolo[3,4-*b*]pyridin-3-one **3** were dissolved in 10 mL of THF and added slowly. The mixture was stirred for 40 min at room temperature. Then 0.216 mL (2.51 mmol; 5 eq) of dibromoethane in 3 mL of THF were added dropwise. The resulting mixture was heated at reflux for 30 h. The solution was hydrolyzed and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 6.5:3.5). Yield 60% (maroon solid); mp 84–86°C; IR (KBr) cm^{-1}: 1656 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.59 (s, 3H), 2.68 (s, 3H), 3.25 (t, 2H, *J* = 7.3 Hz), 4.25 (t, 2H, *J* = 7.3 Hz), 6.81 (s, 1H), 7.28–7.35 (m, 1H), 7.45–7.53 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.3 (CH_3), 25.1 (CH_3), 25.9 (CH_2), 49.2 (NCH_2), 107.7 (C), 120.6 (CH), 124.0 (2CH), 126.0 (CH), 129.4 (2CH), 135.0 (C), 149.6 (C), 160.7 (C), 162.3 (C), 163.8 (C); MS (m/z, %): 347 (M+1, 65), 348 (M+2, 82), 106 (100).

1-(2-(Hexanhydropyrido[1,2-*a*][1,4]diazepin-2(1*H*,3*H*,7*H*)-yl) ethyl)-4,6-dimethyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (8). Under inert atmosphere, 45 mg (0.29 mmol; 1 eq) of decahydropyrido[1,2-*a*][1,4]diazepine **6** were put in 8 mL of acetonitrile then 120 mg (0.87 mmol; 3 eq) of potassium carbonate, 7 mg (0.43 mmol; 0.15 eq) of potassium iodide and 100 mg (0.29 mmol;1 eq) of bromoethylpyrazolo[3,4-*b*]pyridin-3-one **7** were added. The resulting mixture was stirred overnight at 60°C. The solvent was evaporated and the residue was taken again with water and extracted with CH_2Cl_2. The organic phases were dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: CH_2Cl_2/MeOH/NH_4OH, 9:1:0.5). Yield 78% (maroon solid); mp 94–96°C; IR (KBr) cm^{-1}: 1683 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 1.02–1.32 (m, 4H), 1.48–1.68 (m, 5H), 1.81–1.94 (m, 2H), 2.04–2.10 (m, 1H), 2.23–2.32 (m, 1H), 2.35–2.40 (m, 4H), 2.57 (s, 3H), 2.60–2.71 (m, 5H), 4.02 (t, 2H, *J* = 6.0 Hz,), 6.75 (s, 1H), 7.24–7.30 (m, 1H), 7.44–7.58 (m, 4H); ^{13}C NMR (*CDCl*$_3$): δ (ppm) 17.3 (CH_3), 24.3 (CH_2), 25.1 (CH_3), 26.0 (CH_2), 27.4 (CH_2), 31.2 (CH_2), 46.0 (CH_2), 54.0 (CH_2), 55.6 (CH_2), 55.7 (CH_2), 57.3 (CH_2), 61.1 (CH_2), 65.6 (CH), 107.3 (C), 119.5 (CH), 123.4 (2CH), 126.2 (CH), 129.2 (2CH), 135.5 (C), 149.1 (C), 161.9 (C), 162.2 (C), 162.8 (C); MS (m/z, %): 420 (M+1, 100), 119 (25).

Butyl.2-(1-(4-methoxybenzyl)-4-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)acetate (9). Ninety milligrams (0.65 mmol; 1.1 eq) of potassium carbonate were put in 8 mL of CH_2Cl_2 and 200 mg (0.59 mmol; 1 eq) of pyrazolo[3,4-*b*]pyridine-3-one **5** were added. After 20 min of stirring, 0.09 mL (0.65 mmol; 1.1 eq) of *para*-methoxybenzyl chloride in 4 mL of CH_2Cl_2 were added. The mixture was stirred for three days at room temperature. The solution was hydrolyzed and extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ then evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 7.5:2.5). Yield 97% (maroon clearly oil); IR (NaCl) cm^{-1}: 1650, 1723 (CO); ^{1}H NMR (*CDCl*$_3$): δ (ppm) 0.86 (t, 3H, *J* = 7.2 Hz), 1.19–1.36 (m, 2H), 1.48–1.59 (m, 2H), 2.67 (s, 3H), 3.68 (s, 3H), 4.04–4.12 (m, 4H), 5.01 (s, 2H), 6.62

(AB, 4H, J_{AB} = 8.8 Hz, Δν = 24.1 Hz), 6.90 (s, 1H), 7.25–7.33 (m, 1H), 7.53 (d, 4H, J = 3.1 Hz); ^{13}C NMR (*CDCl*$_3$): δ (ppm) 13.6 (CH_3), 19.0 (CH_2), 25.1 (CH_3), 30.4 (CH_2), 35.4 (CH_2), 51.3 (NCH_2), 55.0 (OCH_3), 65.0 (OCH_2), 108.1 (C), 113.4 (2CH), 119.7 (CH), 123.9 (2CH), 125.5 (C), 126.3 (CH), 129.1 (2CH), 130.3 (2CH), 135.0 (C), 143.9 (C), 159.3 (C), 160.7 (C), 161.2 (C), 163.6 (C), 169.9 (C); MS (m/z, %): 460 (M+1, 90), 119 (100).

1-(4-Methoxybenzyl)-6-(2-hydroxyethyl)-4-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (10). Under inert atmosphere, 440 mg (0.96 mmol; 1 eq) of compound **9** weredissolved in 8 mL of Et_2O and this mixture was added at 0°C to suspension of 36 mg (0.96 mmol; 1 eq) of $LiAlH_4$ in 10 mL of Et_2O. The resulting mixture was maintained at 0°C for 24 h. The medium was hydrolyzed and the salt was filtered off. The solution was extracted with CH_2Cl_2 and the organic phases were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 4.5:6.5). Yield 53% (white foam); IR (KBr) cm^{-1}: 1681 (CO), 3419 (OH); ^{1}H NMR (*CDCl*$_3$): δ (ppm) 2.67 (s, 3H), 3.21 (t, 2H, J = 6.0 Hz), 3.70 (s, 3H), 3.91 (t, 2H, J = 6.0 Hz), 5.03 (s, 2H), 6.62 (AB, 4H, J_{AB} = 8.8 Hz, Δν = 19.6 Hz), 6.83 (s, 1H), 7.29–7.35 (m, 1H), 7.44–7.49 (m, 4H); ^{13}C NMR (*CDCl*$_3$): δ (ppm) 25.3 (CH_3), 35.2 (CH_2), 51.4 (NCH_2), 55.2 (OCH_3), 63.0 (CH_2), 108.6 (C), 113.6 (2CH), 120.1 (CH), 124.4 (2CH), 125.6 (C), 126.8 (CH), 129.3 (2CH), 130.4 (2CH), 134.9 (C), 150.2 (C), 159.5 (C), 160.6 (C), 162.3 (C), 163.8 (C); MS (m/z, %): 390 (M+1, 60), 119 (100).

2-(1-(4-Methoxybenzyl)-4-methyl-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6yl)ethanol (11). This compound was obtained from **10** (eluent: petroleum ether/ethyl acetate, 6:4). Yield 29% (white foam); IR (KBr) cm^{-1}: 3416 (OH); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.46 (s, 3H), 2.56 (t, 2H, J = 6.6 Hz), 3.68–3.77 (m, 5H), 4.48 (s, 2H), 4.56 (s, 2H), 6.47 (s, 1H), 6.66 (d, 2H, J = 8.7 Hz), 6.90 (t, 1H, J = 7.3 Hz), 6.99 (d, 2H, J = 8.7 Hz), 7.07 (d, 2H, J = 8.5 Hz), 7.25–7.34 (m, 2H); ^{13}C NMR (*CDCl*$_3$): δ (ppm) 24.1 (CH_3), 36.3 (CH_2), 55.3 (OCH_3), 57.4 (CH_2), 57.5 (CH_2), 62.1 (CH_2), 115.2 (2CH), 118.9 (C), 120.1 (CH), 127.2 (CH), 127.8 (2CH), 129.2 (2CH), 129.3 (C), 130.1 (2CH), 136.7 (C), 143.1 (C), 152.2 (C), 157.2 (C), 162.2 (C); 376 (M+1, 100), 119 (23).

2-(1-(4-Methoxybenzyl)-4-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)ethyl methanesulfonate (12). 0.63 mL (7.71 mmol; 5 eq) of pyridine were added to 600 mg (1.54 mmol; 1 eq) of alcohol **10** in 15 mL of CH_2Cl_2 at 0°C. The solution was stirred 45 min at 0°C then 0.30 mL (3.86 mmol; 2.5 eq) of mesyl chloride in 2 mL of CH_2Cl_2 are run. The mixture was stirred for 48 h at room temperature. The medium was hydrolyzed then the solution was extracted with CH_2Cl_2. The organic phases were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 5:5). Yield 89% (yellow oil); IR (NaCl) cm^{-1}: (1678 (CO); ^{1}H NMR (*CDCl*$_3$): δ (ppm) 2.67 (s, 3H), 2.80 (s, 3H), 3.36 (t, 2H, J = 6.6 Hz), 3.68 (s, 3H), 4.54 (t, 2H, J = 6.6 Hz), 5.01 (s, 2H), 6.62 (AB, 4H, J_{AB} = 8.8 Hz, Δν = 23.1 Hz), 6.85 (s, 1H), 7.30–7.36 (m, 1H), 7.46–7.54 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) 25.1 (CH_3), 31.4 (CH_2), 36.8 (CH_3), 51.3 (CH_2), 55.0 (CH_3), 68.9 (CH_2), 107.7 (C), 113.4 (2CH), 120.1 (CH), 124.0 (2CH), 125.3 (C), 126.6 (CH), 129.2 (2CH), 130.3 (2CH), 134.7 (C), 146.5 (C), 159.3 (C), 160.8 (C), 161.0 (C), 163.9 (C); MS (m/z, %): 468 (M+1, 70), 119 (100).

1-(4-Methoxybenzyl)-6-(2-(dibutylamino)ethyl)-4-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (13). Two hundred milligrams (0.43 mmol; 1 eq) of sulphonate **12** were introduced into a sealed tube containing 2 mL of DMF then 1 mL (5.95 mmol; 13.9 eq) of *N*,*N*-dibutylamine. The mixture was heated with stirring at 70°C overnight. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 5:5). Yield 92% (yellow oil); IR (NaCl) cm^{-1}: 1672 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 0.86 (t, 6H, J = 7.2 Hz), 1.19–1.30 (m, 4H), 1.33–1.40 (m, 4H), 2.44 (t, 4H, J = 7.5 Hz), 2.65 (s, 3H), 2.75 (t, 2H, J = 7.5 Hz), 3.11 (t, 2H, J = 7.5 Hz), 3.68 (s, 3H), 4.99 (s, 2H), 6.62 (AB, 4H, J_{AB} = 8.8 Hz, Δν = 23.7 Hz), 6.81 (s, 1H), 7.28–7.34 (m, 1H), 7.50 (d, 4H, J = 4.1 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 14.2 ($2CH_3$), 20.7 ($2CH_2$), 25.2 (CH_3), 28.5 (CH_2), 29.7 ($2CH_2$), 51.6 (CH_2), 53.7 ($2CH_2$), 54.3 (CH_2), 55.2 (CH_3), 108.3 (C), 113.5 (2CH), 119.7 (CH), 124.1 (2CH), 125.8 (C), 126.3 (CH), 129.3 (2CH), 130.5 (2CH), 135.4 (C), 152.3 (C), 159.4 (C); 161.1 (C); 161.6 (C), 163.1 (C); MS (m/z, %): 501 (M+1, 100), 102 (10).

1-(4-Methoxybenzyl)-4-methyl-2-phenyl-6-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (14). This product was obtained using same procedure as for **13** (eluent: petroleum ether/ethyl acetate, 6:4). Yield 93% (yellow oil); IR (NaCl) cm^{-1}: 1686 (CO); ^{1}H NMR ($CDCl_3$): δ (ppm) 2.66–2.76 (m, 9H), 3.14–3.25 (m, 6H), 3.68 (s, 3H), 5.00 (s, 2H), 6.63 (AB, 4H, J_{AB} = 8.8 Hz, Δν = 24.8 Hz), 6.80–6.86 (m, 2H), 6.90 (d, 2H, J = 7.8 Hz), 7.21–7.33 (m, 3H), 7.51 (d, 4H, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 25.3 (CH_3), 28.5 (CH_2), 49.2 ($2CH_2$), 51.6 (CH_2), 52.9 ($2CH_2$), 55.2 (CH_3), 58.4 (CH_2), 108.3 (C), 113.5 (2CH), 116.1 (2CH), 119.6 (CH), 119.7 (CH), 124.2 (2CH), 125.7 (C), 126.5 (CH), 129.2 (2CH), 129.3 (2CH), 130.5 (2CH), 135.3 (C), 151.5 (2C), 159.5 (C), 161.1 (C), 161.5 (C), 163.4 (C); MS (m/z, %): 534 (M+1, 80), 102 (100).

6-(2-(Dibutylamino)ethyl)-4-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (15). One hundred and sixty milligrams (0.32 mmol; 1 eq) of compound **13** were dissolved in 5 mL of TFA then the solution was heated at reflux during 5 h. The solvent was evaporated under reduced pressure and the crude product was purified by column chromatography on silica gel (eluent: methanol/ethyl acetate, 1:9). Yield 96% (red solid); mp 114–116°C; IR (KBr) cm^{-1}: 1667 (CO), 3445 (NH); ^{1}H NMR ($CDCl_3$): δ (ppm) 0.85 (t, 6H, J = 7.2 Hz), 1.24–1.34 (m, 4H), 1.38–1.46 (m, 4H), 2.47 (s, 3H), 2.91–3.00 (m, 6H), 3.19 (t, 2H, J = 6.8 Hz), 6.61 (s, 1H), 7.16–7.23 (m, 1H), 7.41 (t, 2H, J = 7.8 Hz), 7.88 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 14.2 ($2CH_3$), 20.5 ($2CH_2$), 25.2 (CH_3), 29.2 (CH_2), 29.9 ($2CH_2$), 53.6 ($2CH_2$), 54.2 (CH_2), 108.9 (C), 118.5 (CH), 119.7 (2CH), 125.3 (CH), 129.2 (2CH), 137.3 (C), 151.8 (C), 156.4 (C), 159.6 (C), 159.9 (C); MS (m/z, %): 381 (M+1, 100), 102 (40).

4-Methyl-2-phenyl-6-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (16). This product was obtained in 94% yield from the pyrazolopyridine **14** (130 mg, 0.24 mmol) following the procedure described earlier for

compound **15** as a red solid; mp 116–118°C; IR (KBr) cm^{-1}: 1674 (CO), 3419 (NH); ^1H NMR ($CDCl_3$): δ (ppm) 2.35 (s, 3H), 3.03–3.18 (m, 6H), 3.32–3.45 (m, 6H), 6.70 (s, 1H), 6.92 (d, 3H, J = 8.2 Hz), 7.20–7.30 (m, 3H), 7.45 (t, 2H, J = 7.8 Hz), 7.87 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 23.0 (CH_3), 27.9 (CH_2), 48.5 ($2CH_2$), 52.6 ($2CH_2$), 57.5 (CH_2), 108.7 (C), 116.4 (C), 116.5 (2CH), 120.5 (CH), 120.6 (2CH), 125.8 (CH), 129.3 (4CH), 137.8 (C), 150.8 (C), 154.9 (C), 159.2 (C), 159.3 (C); MS (m/z, %): 414 (M+1, 100), 102 (30).

Butyl.2-(1-(4-methoybenzyl)-6-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)acetate (17). This product was obtained in 98% yield from the pyrazolopyridine **4** (300 mg, 0.89 mmol) following the procedure described earlier for compound **9** as a maroon clearly oil; IR (NaCl) cm^{-1}: 1683, 1724 (CO); ^1H NMR ($CDCl_3$): δ (ppm) 0.93 (t, 3H, J = 7.2 Hz), 1.35–1.45 (m, 2H), 1.65–1.70 (m, 2H), 2.63 (s, 3H), 3.69 (s, 3H), 3.91 (s, 2H), 4.20 (t, 2H, J = 6.6 Hz), 4.99 (s, 2H), 6.63 (AB, 4H, J_{AB} = 8.8 Hz, Δν = 26.9 Hz), 6.68 (s, 1H), 7.32 (t, 1H, J = 4.4 Hz), 7.50 (d, 4H, J = 4.4 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 13.8 (CH_3), 17.3 (CH_3), 19.2 (CH_2), 30.8 (CH_2), 44.4 (CH_2), 51.6 (CH_2), 55.2 (CH_3), 65.2 (CH_2), 109.8 (C), 113.5 (2CH), 120.5 (CH), 124.1 (2CH), 125.5 (C), 126.5 (CH), 129.3 (2CH), 130.6 (2CH), 135.2 (C), 150.0 (C), 158.5 (C), 159.5 (C), 160.8 (C), 161.7 (C), 170.3 (C); MS (m/z, %): 460 (M+1, 100), 106 (26).

1-(4-Methoxybenzyl)-4-(2-hydroxyethyl)-6-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (18). This product was obtained in 55% yield from the pyrazolopyridine **17** (440 mg, 0.87 mmol) following the procedure described earlier for compound **10** as a white foam; IR (KBr) cm^{-1}: 1660 (CO), 3412 (OH); ^1H NMR ($CDCl_3$): δ (ppm) 2.61 (s, 3H), 3.10 (t, 2H, J = 5.7 Hz), 3.69 (s, 3H), 4.12 (dd, 2H, J = 11.3 Hz, J' = 5.3 Hz), 4.96 (s, 2H), 6.66 (AB, 4H, J_{AB} = 8.8 Hz, Δν = 31.4 Hz), 6.76 (s, 1H), 7.29–7.35 (m, 1H), 7.52 (d, 4H, J = 4.1 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.3 (CH_3), 39.8 (CH_2), 51.6 (CH_2), 55.2 (CH_3), 61.7 (CH_2), 109.3 (C), 113.6 (2CH), 120.2 (CH), 124.1 (2CH), 125.5 (C), 126.6 (CH), 129.3 (2CH), 130.4 (2CH), 135.1 (C), 149.7 (C), 159.5 (C), 160.4 (C), 161.8 (C), 164.7 (C); MS (m/z, %): 390 (M+1, 17), 102 (100).

2-(1-(4-Methoxybenzyl)-6-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)ethyl methanesulfonate (19). This product was obtained in 89% yield from the pyrazolopyridine **18** (500 mg, 1.29 mmol) and mesyl chloride (0.25 mL, 3.21mmol) following the procedure described earlier for compound **12** as a yellow oil; IR (NaCl) cm^{-1}: 1692 (CO); ^1H NMR ($CDCl_3$): δ (ppm) 2.61 (s, 3H), 2.94 (s, 3H), 3.29 (t, 2H, J = 6.6 Hz), 3.68 (s, 3H), 4.77 (t, 2H, J = 6.6 Hz), 4.99 (s, 2H), 6.64 (AB, 4H, J_{AB} = 8.8 Hz, Δν = 23.9), 6.79 (s, 1H), 7.29–7.35 (m, 1H), 7.50 (d, 4H, J = 4.1 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.2 (CH_3), 37.5 (CH_3), 37.7 (CH_2), 51.5 (CH_2), 55.2 (CH_3), 68.3 (CH_2), 109.7 (C), 113.6 (2CH), 120.4 (CH), 124.1 (2CH), 125.5 (C), 126.6 (CH), 129.3 (2CH), 130.4 (2CH), 135.1 (C), 149.9 (C), 159.5 (C), 160.7 (C), 160.8 (C), 161.6 (C); MS (m/z, %): 468 (M+1, 15), 97 (100).

1-(4-Methoxybenzyl)-4-(2-(dibutylamino)ethyl)-6-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (20). This product was obtained in 92% yield from the pyrazolopyridine **19** (200 mg, 0.43 mmol) and *N*,*N*-dibutylamine 1 mL (0.53 mL, 5.95 mmol) following the procedure described earlier for compound **13** as a yellow oil; IR (NaCl) cm^{-1}: 1697 (CO); ^1H NMR ($CDCl_3$): δ (ppm) 0.92 (t, 6H, J = 7.2 Hz), 1.24–1.42 (m, 4H), 1.44–1.54 (m, 4H), 2.53 (t, 4H, J = 7.5 Hz), 2.59 (s, 3H), 2.97 (s, 4H), 3.67 (s, 3H), 4.99 (s, 2H), 6.63 (AB, 4H, J_{AB} = 8.8 Hz, Δν = 32.9 Hz), 6.76 (s, 1H), 7.28–7.32 (m, 1H), 7.47–7.53 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) 14.2 ($2CH_3$), 17.2 (CH_3), 20.8 ($2CH_2$), 29.5 ($2CH_2$), 35.9 (CH_2), 51.5 (CH_2), 53.8 ($2CH_2$), 53.9 (CH_2), 55.1 (CH_3), 108.8 (C), 113.4 (2CH), 120.2 (CH), 123.9 (2CH), 125.7 (C), 126.2 (CH), 129.2 (2CH), 130.5 (2CH), 135.3 (C), 149.0 (C), 159.4 (C), 161.1 (C), 162.0 (C), 165.7 (C); MS (m/z, %): 501 (M+1, 41), 119 (100).

1-(4-Methoxybenzyl)-6-methyl-2-phenyl-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (21). This product was obtained in 93% yield from the pyrazolopyridine **19** (150 mg, 0.24 mmol) and phenylpiperazine (0.53 mL, 4.50 mmol) following the procedure described earlier for compound **14** as a yellow oil; IR (NaCl) cm^{-1}: 1683 (CO); ^1H NMR ($CDCl_3$): δ (ppm) 2.62 (s, 3H), 2.77 (t, 4H, J = 5.0 Hz), 2.97 (dd, 2H, J = 8.1 Hz, J' = 6.3 Hz), 3.12 (dd, 2H, J = 8.1 Hz, J' = 6.3 Hz), 3.27 (t, 4H, J = 5.0 Hz), 3.68 (s, 3H), 5.02 (s, 2H), 6.65 (AB, 4H, J_{AB} = 8.8 Hz, Δν = 32.0 Hz), 6.80 (s, 1H), 6.87 (t, 1H, J = 7.8 Hz), 6.96 (d, 2H, J = 7.8 Hz), 7.25–7.32 (m, 3H), 7.50–7.54 (m, 4H); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.2 (CH_3), 36.1 (CH_2), 49.3 ($2CH_2$), 51.6 (CH_2), 53.3 ($2CH_2$), 55.2 (CH_3), 60.5 (CH_2), 109.1 (C), 113.5 (2CH), 116.2 (2CH), 119.8 (CH), 120.1 (CH), 124.0 (2CH), 125.7 (C), 126.3 (CH), 129.2 (4CH), 130.5 (2CH), 135.3 (C), 149.3 (C), 151.4 (C), 159.4 (C), 161.0 (C), 162.0 (C), 164.9 (C); MS (m/z, %): 534 (M+1, 42), 102 (100).

4-(2-(Dibutylamino)ethyl)-6-methyl-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (22). This product was obtained in 94% yield from the pyrazolopyridine **20** (150 mg, 0.30 mmol) following the procedure described earlier for compound **15** as a red solid; mp 118–120°C; IR (KBr) cm^{-1}: 1697 (CO), 3440 (NH); ^1H NMR ($CDCl_3$): δ (ppm) 0.94 (t, 6H, J = 7.2 Hz), 1.30–1.40 (m, 4H), 1.61–1.68 (m, 4H), 2.66 (s, 3H), 3.03–3.08 (m, 6H), 3.40 (t, 2H, J = 6.6 Hz), 6.60 (s, 1H), 7.14–7.21 (m, 1H), 7.40 (t, 2H, J = 7.8 Hz), 7.91 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 13.7 ($2CH_3$), 17.3 (CH_3), 20.1 ($2CH_2$), 25.1 ($2CH_2$), 30.6 (CH_2), 50.5 (CH_2), 52.7 ($2CH_2$), 109.1 (C), 118.3 (CH), 119.7 (2CH), 125.4 (CH), 129.1 (2CH), 137.4 (C), 150.8 (C), 156.8 (C), 159.5 (C), 159.8 (C); MS (m/z, %): 381 (M+1, 100), 102 (44).

6-Methyl-2-phenyl-4-(2-(4-phenylpiperazin-1-yl)ethyl)-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (23). This product was obtained in 96% yield from the pyrazolopyridine **21** (120 mg, 0.23 mmol) following the procedure described earlier for compound **15** as a red solid; mp 122–124°C; IR (KBr) cm^{-1}: 1669 (CO), 3422 (NH); ^1H NMR ($CDCl_3$): δ (ppm) 2.63 (s, 3H), 3.10–3.42 (m, 12H), 6.59 (s, 1H), 6.86–6.98 (m, 3H), 7.17 (t, 1H, J = 7.6 Hz), 7.25–7.32 (m, 2H), 7.39 (t, 2H, J = 7.8 Hz), 7.90 (d, 2H, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.1 (CH_3), 31.1 (CH_2), 47.0 ($2CH_2$), 52.0 ($2CH_2$), 55.3 (CH_2), 109.7 (C), 117.0 (2CH), 119.5 (2CH), 121.6 (CH), 125.4 (CH), 129.1 (2CH), 129.4 (2CH), 137.4 (C), 149.4 (C), 151.0 (C), 159.2 (C), 159.8 (C); MS (m/z, %): 414 (M+1, 100), 102 (32).

2-(6-Methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl) acetic acid (24). Three hundred milligrams (0.88 mmol; 1 eq) of pyrazolo[3,4-*b*]pyridine **4** were

introduced under magnetic agitation into 15 mL of NaOH solution 10%. The solution was heated at reflux during 90 min. After cooling, the solution was neutralized until pH = 2 with concentrated HCl. The precipitate thus formed was filtered and washed with water and then with diethyl ether (no purification was necessary). Yield 98% (yellow solid); mp 122–124°C; IR (KBr) cm^{-1}: 1706 (CO), 3070 (OH); ^1H NMR (CD_3OD): δ (ppm) 2.73 (s, 3H), 3.85 (s, 2H), 6.83 (s, 1H), 7.29 (m, 1H), 7.49 (t, 2H, J = 7.9 Hz), 7.91 (d, 2H, J = 7.9 Hz); ^{13}C NMR (CD_3OD): δ (ppm) 17.2 (CH_3), 42.3 (CH_2), 111.9 (C), 119.8 (2CH), 122.6 (CH), 125.2 (CH), 129.9 (2CH), 140.5 (C), 151.9 (C), 155.5 (C), 157.2 (C), 160.5 (C), 178.0 (C); MS (m/z, %): 284 (M+1, 100), 181 (65).

2-(4-Methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)-acetic acid (25). Three hundred milligrams (0.88 mmol; 1 eq) of pyrazolo[3,4-*b*]pyridine **5** were introduced under magnetic agitation into 15 mL of NaOH solution 10%. The solution was heated at reflux during 90 min. After cooling, the solution was neutralized until pH = 2 with concentrated HCl. The precipitate thus formed was filtered and washed with water and then with diethyl ether (no purification was necessary). Yield 97% (yellow solid); mp 172–174°C; IR (KBr) cm^{-1}: 1700 (CO), 3061 (OH); ^1H NMR (CD_3OD): δ (ppm) 2.50 (s, 3H), 4.04 (s, 2H), 6.93 (s, 1H), 7.26 (m, 1H), 7.46 (t, 2H, J = 7.9 Hz), 7.85 (d, 2H, J = 7.9 Hz); ^{13}C NMR (CD_3OD): δ (ppm) 15.7 (CH_3), 48.4 (CH_2), 111.3 (C), 120.1 (2CH), 122.5 (CH), 126.2 (CH), 130.8 (2CH), 141.2 (C), 151.5 (C), 155.3 (C), 157.1 (C), 160.9 (C), 178.3 (C); MS (m/z, %): 284 (M+1, 53), 181 (100).

***N*,*N*-Dibutyl-2-(6-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-4-yl)acetamide (26).** One hundred and nine milligrams (0.53 mmol; 1.5 eq) of DCC were put in 10 mL of THF then 100 mg (0.35 mmol; 1 eq) of acid **24** were added. After stirring at room temperature for 20 min, 65 μL (0.39 mmol; 1.1 eq) of *N*,*N*-dibutylamine in 2 ml of THF were cast. The mixture was stirred for 7 h at room temperature. The solution was hydrolyzed with a saturated solution of NH_4Cl and extracted with AcOEt. The organic phases were dried over $MgSO_4$ and evaporated in vacuo. The crude reaction was purified by column chromatography on silica gel (eluent: petroleum ether/ethyl acetate, 5:5). Yield 40% (yellow clearly solid); mp 134–136°C; IR (KBr) cm^{-1}: 1591, 1637 (CO), 3414 (NH); ^1H NMR ($CDCl_3$): δ (ppm) 0.87–0.94 (m, 6H), 1.25–1.32 (m, 4H), 1.43–1.49 (m, 4H), 2.69 (s, 3H), 3.16 (t, 2H, J = 7.6 Hz), 3.29 (t, 2H, J = 7.6 Hz), 3.70 (s, 2H), 6.67 (s, 1H), 7.18 (t, 1H, J = 7.9 Hz), 7.41 (t, 2H, J = 7.9 Hz), 7.93 (d, 2H, J = 7.9 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 13.6 ($2CH_3$), 17.2 (CH_3), 19.9 (CH_2), 20.0 (CH_2), 29.5 (CH_2), 29.6 (CH_2), 41.9 (CH_2), 45.9 (CH_2), 47.9 (CH_2), 109.6 (C), 118.6 (CH), 118.7 (2CH), 125.1 (CH), 129.0 (2CH), 137.6 (C), 150.8 (C), 156.2 (C), 157.7 (C), 159.9 (C), 168.6 (C); MS (m/z, %): 395 (M+1, 26), 119 (100).

***N*,*N*-Dibutyl-2-(4-methyl-3-oxo-2-phenyl-2,3-dihydro-1*H*-pyrazolo[3,4-*b*]pyridin-6-yl)acetamide (27).** This product was obtained in 44% yield from acid **25** (100 mg, 0.35 mmol) and *N*,*N*-dibutylamine (65 μL, 0.39 mmol) following the procedure described earlier for compound **29** as a orange solid; mp 128–130°C; IR (KBr) cm^{-1}: 1612, 1683 (CO), 3424 (NH); ^1H NMR ($CDCl_3$): δ (ppm) 0.82–0.91 (m, 6H), 1.21–1.29 (m, 4H), 1.40–1.48 (m, 4H), 2.36 (s, 3H), 3.04 (t, 2H, J = 7.6 Hz), 3.23 (t, 2H, J = 7.6 Hz), 3.77 (s, 2H), 6.69 (s, 1H), 7.21 (t, 1H, J = 7.7 Hz), 7.41 (t, 2H, J = 7.7 Hz), 7.89 (d, 2H, J = 7.7 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 13.9 ($2CH_3$), 20.0 (CH_2), 20.1 (CH_2), 23.2 (CH_3), 29.7 (CH_2), 29.8 (CH_2), 42.1 (CH_2), 46.2 (CH_2), 48.0 (CH_2), 109.1 (C), 118.1 (CH), 119.0 (2CH), 125.4 (CH), 129.1 (2CH), 137.5 (C), 148.8 (C), 155.6 (C), 158.7 (C), 159.8 (C), 168.7 (C); MS (m/z, %): 395 (M+1, 44), 119 (100).

6-Methyl-4-(2-oxo-2-(4-phenylpiperazin-1-yl)ethyl)-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridine-3-one (28). This product was obtained in 56% yield from acid **24** (100 mg, 0.35 mmol) and phenylpiperazine (46 μL, 0.39 mmol) following the procedure described earlier for compound **26** as a yellow clearly solid; mp 142–144°C; IR (KBr) cm^{-1}: 1591, 1651 (CO), 3440 (NH); ^1H NMR ($CDCl_3$): δ (ppm) 2.69 (s, 3H), 3.03–3.12 (m, 4H), 3.53 (t, 2H, J = 4.9 Hz), 3.69–3.74 (m, 4H), 6.78 (s, 1H), 6.86–6.93 (m, 3H), 7.19–7.30 (m, 3H), 7.41 (t, 2H, J = 8.0 Hz), 7.90 (d, 2H, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 17.4 (CH_3), 41.9 (CH_2), 42.6 (CH_2), 45.9 (CH_2), 49.2 (CH_2), 49.6 (CH_2), 109.5 (C), 116.7 (2CH), 119.4 (2CH), 119.7(CH), 120.7 (CH), 125.3 (CH), 129.2 (2CH), 129.3 (2CH), 137.5 (C), 150.7 (C), 150.8 (C), 157.4 (C), 158.4 (C), 160.0 (C), 167.8 (C); MS (m/z, %): 428 (M+1, 60), 119 (100).

4-Methyl-6-(2-oxo-2-(4-phenylpiperazin-1-yl)ethyl)-2-phenyl-1,2-dihydropyrazolo[3,4-*b*]pyridin-3-one (29). This product was obtained in 52% yield from acid **25** (130 mg, 0.46 mmol) and phenylpiperazine (60 μL, 0.51 mmol) following the procedure described earlier for compound **26** as a orange solid; mp 136–138°C; IR (KBr) cm^{-1}: 1618, 1690 (CO), 3454 (NH); ^1H NMR ($CDCl_3$): δ (ppm) 2.35 (s, 3H), 3.01–3.11 (m, 4H), 3.51 (t, 2H, J = 4.9 Hz), 3.64–3.70 (m, 2H), 4.19 (s, 2H), 6.75 (s, 1H), 6.84–6.92 (m, 3H), 7.18–7.28 (m, 3H), 7.40 (t, 2H, J = 8.2 Hz), 7.88 (d, 2H, J = 8.2 Hz); ^{13}C NMR ($CDCl_3$): δ (ppm) 19.4 (CH_3), 40.7 (CH_2), 43.6 (CH_2), 46.0 (CH_2), 49.2 (CH_2), 49.7 (CH_2), 110.5 (C), 115.9 (2CH), 118.8 (2CH), 119.0 (CH), 120.1 (CH), 125.1 (CH), 129.2 (2CH), 129.5 (2CH), 137.7 (C), 149.4 (C), 150.1 (C), 156.8 (C), 159.1 (C), 160.1 (C), 168.8 (C); MS (m/z, %): 428 (M+1, 65), 119 (100).

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