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Cyclization of 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles with β-dicarbonyl compounds

Andrei Yu. Potapov[1], Dmitriy Yu. Vandyshev[1], Yevgeniya A. Kosheleva[1], Vladimir A. Polikarchuk[1], Mikhail A. Potapov[1], Khidmet S. Shikhaliev[1]*

[1] *Voronezh State University,*
1 Universitetskaya Sq., Voronezh, 394006, Russia
e-mail: chocd261@chem.vsu.ru

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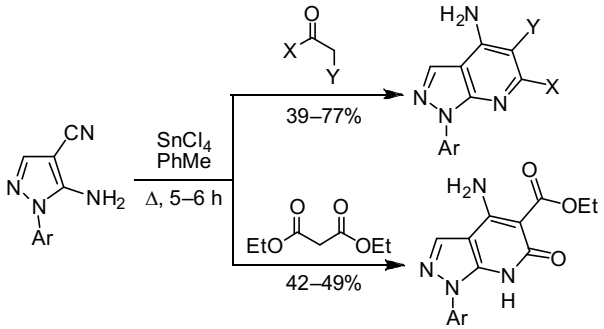


A method has been developed for the preparation of new pyrazolo[3,4-*b*]pyridines and tetrahydropyrazolo[3,4-*b*]quinolinones by the reactions of 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles with aliphatic and cyclic 1,3-dicarbonyl compounds in the presence of anhydrous tin(IV) chloride.

Keywords: acetylacetone, acetoacetic ester, 4-amino-1-aryl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridines, 4-amino-1-aryl-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridines, 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles, benzoylacetone, 1,3-cyclohexanediones, 1,6-diaryl-5-methanesulfonyl-1*H*-pyrazolo[3,4-*b*]pyridines, malonic ester, 1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolinones.

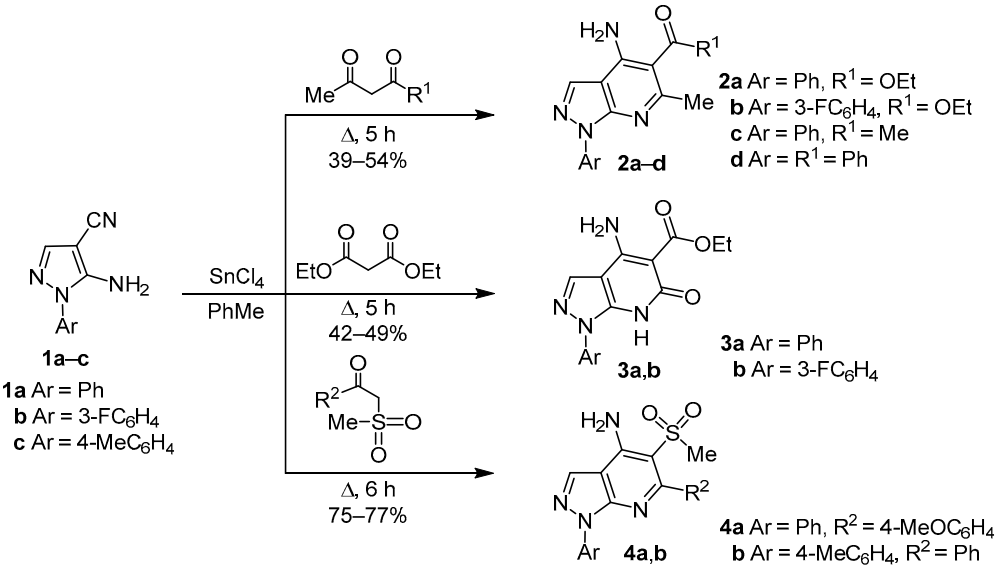
Compounds containing pyrazolopyrimidine or pyrazolopyridine frameworks are known to exhibit a wide range of physiological activity. Thus, such compounds are powerful selective inhibitors of phosphodiesterases PDE4 and PDE5, as well as inhibitors of adenosine A1 receptors.[1–7] Derivatives of pyrazolo[3,4-*b*]pyridine exhibit antiviral, antimalarial, antituberculosis, and antioxidative activity, have been used in the treatment of Alzheimer's disease, gastrointestinal conditions, and anorexia.[8–10] It should also be noted that nitrogen-containing heterocyclic compounds are employed as ligands for the preparation of active palladium catalysts for cross-coupling reactions in aqueous media.[11–16] For these reasons, the synthesis of heterocyclic systems containing pyrazolo[3,4-*b*]pyridine moiety represents an important task.

A convenient synthetic approach to the construction of pyrazolo[3,4-*b*]pyridine systems is the annulation of pyridine ring to substituted pyrazoles. For example, pyrazolo[3,4-*b*]-pyridines have been obtained in a reaction of N^1-substituted 5-aminopyrazoles with 1,3-ketoesters in acetic acid or in ethanol in the presence of hydrochloric acid,[17,18] as well as with symmetrical 1,3-diketones upon heating in ethanol with the addition of zinc chloride and hydrochloric acid.[19]

A range of isomeric pyrazolo[4,3-*b*]pyridines were obtained as result of the reaction between 4-amino-3-methyl-1-phenyl-1*H*-pyrazole-5-carbonitrile and cyclopentanone or cyclohexanone in the presence of aluminum chloride.[20] However, the target products were isolated in low yields (40–45%). According to a published report,[21] the condensation of 5-amino-1-phenyl-1*H*-pyrazole-4-carbonitrile with ketones in the presence of anhydrous zinc chloride, depending on the structure of the ketones, led to the formation of either substituted pyrazolo[3,4-*b*]pyridines, or pyrazolo[3,4-*d*]-pyrimidin-4-ones, or a mixture of products.

In this work, we studied the reactions of 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles **1** in the presence of acidic initiators ($AlCl_3$, $ZnCl_2$, $SnCl_4$, TsOH) with dicarbonyl compounds containing activated methylene groups (acetoacetic ester, acetylacetone, benzoylacetone, malonic ester, β-ketosulfones). The optimum results were obtained in the presence of $SnCl_4$ (Scheme 1). The use of other catalysts led to either excessive resinification of the

Scheme 1



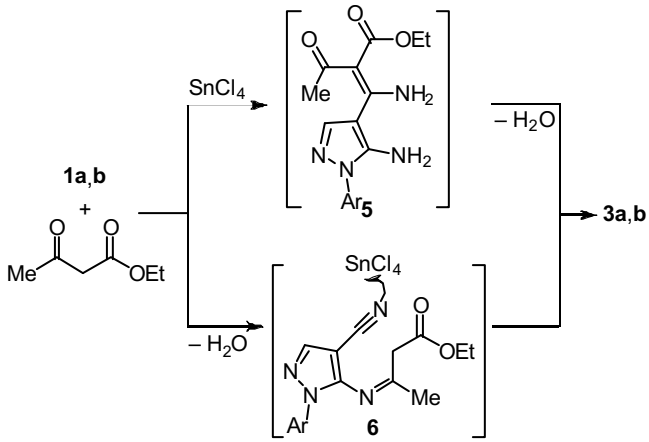
reaction mixtures, or resulted in a low degree of conversion of the starting materials. Besides that, it was experimentally observed that the maximum yields of the target products were achieved upon refluxing equimolar amounts of reagents in anhydrous toluene in a flask with Dean–Stark trap for 1 h, followed by the treatment of reaction mixture with a fourfold excess of $SnCl_4$ and continuing the refluxing for additional 5–6 h.

As a result, we obtained 4-amino-1-aryl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridines **2a**–**d**, 4-amino-1-aryl-5-carbethoxy-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridines **3a**,**b**, and 6-aryl-5-methanesulfonyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-amines **4a**,**b** in 39–77% yields. It should be noted that the reaction of aminonitrile **1a** with unsymmetrical benzoylacetone theoretically can lead to the formation of two isomers, 1-(4-amino-1,6-diphenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)ethanone and (4-amino-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-5-yl)phenylmethanone through cyclization at both carbonyl groups. We established on the basis of ^{1}H NMR spectral data that the product was the latter isomer **2d**, since the methyl group proton signals in its spectrum were observed as a singlet at 2.21 ppm, in a region characteristic for methyl pyridines, instead of acetylpyridines.[22]

The mechanism of the reactions between *o*-aminonitriles and carbonyl compounds containing activated methylene groups, performed in the presence of Lewis acids including tin(IV) chloride, is still under discussion. It is known from literature sources[23] that tin(IV) chloride acted as a catalyst activating the nitrile group of *o*-aminonitrile and a carbonyl group of 1,3-dicarbonyl compound, and the authors proposed that the reaction proceeded through the formation of enedione intermediates. On the basis of this, we can assume (Scheme 2, the example with acetoacetic ester) that the first stage of the reaction involves the formation of a carbon–carbon bond through the intermediate **5**, which further cyclizes to the final products, pyrazolo[3,4-*b*]-pyridines **3a**,**b**.

According to other literature sources,[24–26] the possible mechanism of the reaction between aminonitriles and 1,3-dicarbonyl compounds begins with the formation of carbon–nitrogen bond and subsequent formation of Schiff base, which undergo further cyclization at the nitrile group, providing the target products.

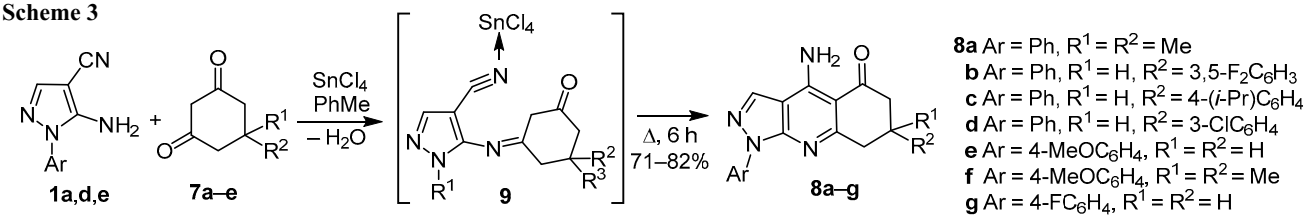
Scheme 2



The authors of another publication[23] performed a reaction of anthranyl nitriles and cyclohexane-1,3-dione (cyclopentane-1,3-dione) with *p*-TsOH as a relatively mild catalyst, and were able to isolate the intermediate, the structure of which was proved by methods of IR and ^{1}H NMR spectroscopy. Even though we were unable to isolate the intermediate compounds, we assume that the first stage of cascade process during refluxing of equimolar amounts of reagents in anhydrous toluene in a flask with a Dean–Stark trap in the absence of catalysts was the condensation of carbonyl and amine groups with the formation of Schiff base **6** (Scheme 2).

^{1}H NMR spectra of pyrazolo[3,4-*b*]pyridines **2a**–**d** and **3a**,**b** contained amino group signals in the range of 7.60–8.10 ppm, observed as broadened singlets. At the same time, in the case of pyrazolo[3,4-*b*]pyridine sulfonyl derivatives **4a**,**b**, these protons were observed as two broadened singlets in the range of 7.80–8.30 ppm. This can

Scheme 3



1 a Ar = Ph, **d** Ar = 4-$MeOC_6H_4$, **e** Ar = 4-FC_6H_4;
7 a $R^1 = R^2$ = Me; **b** R^1 = H, R^2 = 3,5-$F_2C_6H_3$; **c** R^1 = H, R^2 = 4-(*i*-Pr)C_6H_4;
d R^1 = H, R^2 = 3-ClC_6H_4; **e** $R^1 = R^2$ = H

be explained by the presence of an intramolecular hydrogen bond in compounds **4a**,**b** between one of the amino group protons and the oxygen atom of the sulfonyl group. The signals of methyl group protons in 4-amino-1-aryl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridines **2a**–**c** were observed at ~2.55 ppm as narrow singlets. Only in the case of compound **2d** the same signals were observed at 2.15 ppm. The signals due to the NH protons of the pyridinone ring in 4-amino-1-aryl-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridines **3a**,**b** appeared as broadened singlets at ~12.25–12.50 ppm. ^{1}H NMR spectra of compounds **3a**,**b** also contained the signals of ethoxy group protons at 1.37 and 4.32 ppm as a three-proton triplet and a two-proton multiplet, respectively. The spectra of 6-aryl-5-methanesulfonyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-amines **4a**,**b** featured signals of three methanesulfonyl group protons as narrow singlets at ~3.0 ppm. ^{13}C NMR spectra of 5-carbethoxypyrazolo[3,4-*b*]pyridines **2a**,**b** and **3a**,**b** contained signals due to the carbon atoms of carboxyl groups in the range of 168.1–170.3 ppm, while the characteristic signals of carbonyl carbon atoms in compounds **2c**,**d** were clearly observed at 203.6 and 197.6 ppm, respectively. IR spectra of compounds **2a**–**d** and **3a**,**b** contained absorption bands at ~3350 cm^{-1}, belonging to the stretching vibrations of amino groups, while the spectra of compounds **2c**,**d** contained also strong absorption bands of carbonyl group at 1645 cm^{-1}. In the case of the methanesulfonyl derivatives **4a**,**b**, strong absorption bands were observed at 3330 and 3420 cm^{-1}, which were characteristic for stretching vibrations of amino groups involved in intramolecular hydrogen bonds.

We also studied the reaction of 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles **1a**,**d**,**e** with cyclohexane-1,3-diones **7a**–**e**. The syntheses were accomplished under conditions that were analogous to the preparation of compounds **2**–**4**. As a result, 1-aryl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolinones **8a**–**g** were isolated in 71–82% yields (Scheme 3).

The proposed route of this reaction is analogous to the mechanism described above for the interaction of aminonitriles **1** with linear 1,3-dicarbonyl compounds. The process was initiated by the formation of a carbon–nitrogen bond giving rise to Schiff base **9**, which was cyclized at the nitrile group to the target 1,6,7,8-tetrahydro-5*H*-pyrazolo-[3,4-*b*]quinolinone **8** (Scheme 3).

^{1}H NMR spectra of 1,6,7,8-tetrahydro-5*H*-pyrazolo-[3,4-*b*]quinolinones **8**, in contrast to the spectra of the starting 5-amino-1-aryl-4-cyanopyrazoles **1**, contain the proton signals of two methylene groups of the hydrogenated quinolinone moiety as singlets at 2.48 and 2.88 ppm in the case of compounds **8a**–**g**, as well as four multiplets at the intervals of 2.36–2.77, 2.96–3.01, 3.07–3.30, and 3.22–3.37 ppm in the case of 7-aryl-substituted derivatives **8b**–**d**. The proton signals of three methylene groups in the molecular structures of tetrahydropyrazoloquinolines **8e**,**g** appeared at ~2.00, 2.60, and 2.99 ppm as a quintet and two triplets with spin-spin coupling constants of 6.6 and 6.0 Hz, respectively. The amino group protons were observed as two doublets at 8.45–8.51 and 9.47–9.51 ppm with a spin-spin coupling constant of 3.0–3.6 Hz, which can be explained by the formation of an intramolecular hydrogen bond between the amino group proton and the nearby oxygen atom of the carbonyl group in the quinolinone ring. The singlet signals of pyrazole ring CH protons were found in the range of 8.48–8.58 ppm. ^{13}C NMR spectra of compounds **8a**–**g** contained characteristic signals of carbonyl carbon atoms at 198.7–200.6 ppm. The spectrum of pyrazolo[3,4-*b*]quinolinone **8b**, similarly to the spectra of compounds **2b** and **3b**, featured additional carbon signals due to spin-spin interactions between the carbon and fluorine nuclei. IR spectra of compounds **8a**–**g** featured strong absorption bands at 3300 cm^{-1}, belonging to the stretching vibrations of N–H bonds in the amino group and additional strong absorption bands at 3400 cm^{-1}, characteristic for the stretching vibrations of N–H bonds in amino groups involved in intramolecular hydrogen bonds, as well as intensive absorption bands of the carbonyl group at 1620 cm^{-1}.

Thus, we have been able to develop a tin(IV) chloride-catalyzed method for the preparation of new potentially physiologically active 4-amino-1-aryl-6-methyl-1*H*-pyrazolo-[3,4-*b*]pyridines, 4-amino-1-aryl-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridines, 6-aryl-5-methanesulfonyl-1*H*-pyrazolo-[3,4-*b*]pyridin-4-amines and 1-aryl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolinones by a reaction of 5-amino-1-aryl-1*H*-pyrazole-4-carbonitriles with acyclic and cyclic CH-acidic carbonyl compounds.

Experimental

IR spectra were recorded on a Vertex-70 spectrophotometer. ^{1}H NMR spectra were acquired on Bruker DRX-500 (500 MHz) and Bruker DRX-400 (400 MHz) spectrometers in DMSO-d_6, with TMS as internal standard. ^{13}C NMR spectra were acquired on a Bruker DRX-500 (125 MHz) spectrometer in DMSO-d_6, with TMS as internal standard. Due to the long relaxation time of some ^{13}C nuclei, the signals of certain atoms were not practically

observable. High-resolution mass spectra were recorded on an Agilent Technologies LCMS6230B instrument, ionization method – dual electrospray under nitrogen atmosphere. Melting points were determined on a Stuart SMP30 apparatus. The individuality of reagents and the obtained compounds was controlled and qualitative analysis of reaction mixtures was performed by using TLC on Merck TLC Silica gel 60 F_{254} plates; the eluents were methanol, chloroform, and their mixtures in various proportions. The chromatograms were visualized under UV light and with iodine vapor.

The starting 5-amino-1-aryl-1*H*-pyrazolecarbonitriles **1a**–**e** were obtained according to a published procedure.[27] Cyclohexane-1,3-diones **7a**,**e** were purchased from Acros Organics, while 5-arylcyclohexane-1,3-diones 7**b**–**d** – from eMolecules.

Synthesis of 4-amino-1-aryl-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridines 3a,b (General method). A mixture of the appropriate amino nitrile **1a**,**b** (3 mmol) and malonic ester (3 mmol) in anhydrous toluene (12 ml) was refluxed for 1 h in a flask equipped with a Dean–Stark trap. Tin(IV) chloride (3 g, 11.5 mmol) was added to the reaction mixture, followed by refluxing for additional 5–6 h. A resinous precipitate was formed, and the colorless toluene layer was decanted. The residual solvent was removed on a rotary evaporator, the obtained glassy solids were dissolved in boiling dioxane, cooled, then the solution was poured into a solution of Na_2CO_3 (5.0 g) in water (100 ml) and left for 1 day. The precipitate that formed was filtered off, washed with water, dried, and recrystallized from 2-PrOH.

Ethyl 4-amino-6-oxo-1-phenyl-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (3a). Yield 0.38 g (42%). Mp 208–210°C. IR spectrum, ν, cm^{-1}: 3415 (NH pyridinone), 3367 (NH_2), 1647 (stretching vibrations of EtOC=O), 1589 (deformation vibrations of NH_2), 1502 (deformation vibrations of NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.36 (3H, t, *J* = 7.3, $OCH_2C\underline{H}_3$); 4.42 (2H, quin, *J* = 7.3, $OC\underline{H}_2CH_3$); 7.33–7.35 (1H, m, H Ph); 7.51–7.55 (2H, m, H Ph); 8.00–8.18 (4H, m, H Ph, NH_2); 8.46 (1H, s, H-3); 12.36 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 14.2 ($\underline{C}H_3CH_2O$); 61.2 ($CH_3\underline{C}H_2O$); 86.5 (C-5); 102.0 (C-3a); 120.9; 126.0; 129.0; 135.0; 138.8 (C-7a); 152.7 (C-6); 165.9 (C-4); 170.3 (COO). Found, *m*/*z*: 299.1143 $[M+H]^+$. $C_{15}H_{14}N_4O_3$. Calculated, *m*/*z*: 299.1139.

Ethyl 4-amino-1-(3-fluorophenyl)-6-oxo-6,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (3b). Yield 0.46 g (49%). Mp 235–237°C. IR spectrum, ν, cm^{-1}: 3415 (NH pyridinone), 3360 (NH_2), 1645 (stretching vibrations of C=O), 1589 (deformation vibrations of NH_2), 1502 (deformation vibrations of NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.36 (3H, t, *J* = 7.3, $OCH_2C\underline{H}_3$); 4.43 (2H, q, *J* = 7.3, $OC\underline{H}_2CH_3$); 7.16 (1H, t, *J* = 8.3, H Ar); 7.56–7.58 (1H, m, H Ar); 8.00–8.17 (4H, m, H Ar, NH_2); 8.49 (1H, s, H-3); 12.37 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 14.2 ($\underline{C}H_3CH_2O$); 61.3 ($CH_3\underline{C}H_2O$); 86.7 (C-5); 102.4 (C-3a); 107.2; 107.4; 112.2; 112.3; 116.0; 130.7; 130.8; 135.5 (C-5); 140.3; 140.4; 152.5 (C-6); 161.1; 163.0; 166.3 (C-4); 170.2 (COO). Found, *m*/*z*: 317.1047 $[M+H]^+$. $C_{15}H_{13}FN_4O_3$. Calculated, *m*/*z*: 317.1045.

Synthesis of 4-amino-1-aryl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridines 2a–d, 5-methanesulfonyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-amines 4a,b, and 1,6,7,8-tetrahydropyrazolo[3,4-*b*]quinolin-5-ones 8a–g (General method). A mixture of the appropriate aminonitrile **1** (3.0 mmol) and 1,3-dicarbonyl compound (3.0 mmol) in anhydrous toluene (12 ml) was refluxed for 1 h in a flask equipped with a Dean–Stark trap. Tin(IV) chloride (3.0 g, 11.5 mmol) was added to the reaction mixture, and refluxing was continued for additional 5–6 h. A resinous precipitate was formed,and the colorless toluene layer was decanted. The residual solvent was removed on a rotary evaporator, the obtained glassy solids were dissolved in boiling dioxane, cooled, then poured into a solution of Na_2CO_3 (4.0 g) in water (70 ml). The precipitate that formed was filtered off, washed with water, dried, and recrystallized from a 5:1 mixture of 2-PrOH–DMF.

Ethyl 4-amino-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxylate (2a). Yield 0.36 g (41%). Mp 130–132°C. IR spectrum, ν, cm^{-1}: 3348 (NH_2), 1649 (stretching vibrations of C=O), 1587 (deformation vibrations of NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.34 (3H, t, *J* = 7.3, $OCH_2C\underline{H}_3$); 2.65 (3H, s, CH_3); 4.33 (2H, q, *J* = 7.3, $OC\underline{H}_2CH_3$); 7.29–7.32 (1H, m, H Ph); 7.51–7.55 (2H, m, H Ph); 7.83 (2H, br. s, NH_2); 8.25–8.27 (2H, m, H Ph); 8.52 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 14.1 ($\underline{C}H_3CH_2O$); 27.3 (CH_3); 60.5 ($CH_3\underline{C}H_2O$); 101.5 (C-3a); 104.9 (C-5); 120.6; 125.7; 129.0; 134.3; 139.4; 150.1 (C-4); 150.8 (C-6); 160.9 (C-7a); 168.1 (COO). Found, *m*/*z*: 297.1346 $[M+H]^+$. $C_{16}H_{16}N_4O_2$. Calculated, *m*/*z*: 297.1347.

Ethyl 4-amino-1-(3-fluorophenyl)-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylate (2b). Yield 0.51 g (54%). Mp 116–118°C. IR spectrum, ν, cm^{-1}: 3347 (NH_2), 1649 (stretching vibrations of C=O), 1587 (deformation vibrations of NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.32 (3H, t, *J* = 7.3, $OCH_2C\underline{H}_3$); 2.62 (3H, s, CH_3); 4.31 (2H, q, *J* = 7.3, $OC\underline{H}_2CH_3$); 7.10 (1H, t, *J* = 8.3, H Ar); 7.52–7.56 (1H, m, H Ar); 7.83 (2H, br. s, NH_2); 8.15–8.21 (2H, m, H Ar); 8.50 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 14.1 ($\underline{C}H_3CH_2O$); 27.2 (CH_3); 60.5 ($CH_3\underline{C}H_2O$); 101.8; 101.9; 105.1 (C-3a); 106.9; 107.1; 112.0; 112.1; 115.7; 130.8; 130.9; 134.8; 140.8; 140.9; 150.4 (C-9); 150.7 (C-6); 161.0; 161.2; 163.1 (C-7a); 170.0 (COO). Found, *m*/*z*: 315.1248 $[M+H]^+$. $C_{16}H_{15}FN_4O_2$. Calculated, *m*/*z*: 315.1253.

1-(4-Amino-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridin-5-yl)ethanone (2c). Yield 0.31 g (39%). Mp 166–168°C. IR spectrum, ν, cm^{-1}: 3350 (NH_2), 1643 (stretching vibrations of C=O), 1587 (deformation vibrations of NH_2). ^{1}H NMR spectrum, δ, ppm: 2.52 (3H, s, CH_3); 2.57 (3H, s, $COCH_3$); 7.30–7.32 (1H, m, H Ph); 7.54–7.56 (2H, m, H Ph); 7.64 (2H, br. s, NH_2); 8.26–8.28 (2H, m, H Ph); 8.49 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 25.8 (CH_3); 32.4 ($\underline{C}H_3CO$); 104.9 (C-3a); 113.1 (C-5); 120.3; 128.9; 134.1; 148.3 (C-4); 150.0; (C-7a); 158.0 (C-7); 203.3 (CO). Found, *m*/*z*: 267.1241 $[M+H]^+$. $C_{15}H_{14}N_4O$. Calculated, *m*/*z*: 267.1241.

(4-Amino-6-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]-pyridin-5-yl)(phenyl)methanone (2d). Yield 0.39 g (40 %). Mp 177–179°C. IR spectrum, ν, cm^{-1}: 3348 (NH_2), 1647 (stretching vibrations of C=O), 1566 (deformation

vibrations of NH_2). ^{1}H NMR spectrum, δ, ppm: 2.15 (3H, s, CH_3); 7.09 (2H, br. s, NH_2); 7.29–7.33 (1H, m, H Ph); 7.53–7.57 (4H, m, H Ph); 7.66–7.68 (1H, m, H Ph); 7.77–7.80 (2H, m, H Ph); 8.30–8.32 (2H, m, H Ph); 8.50 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 24.6 (CH_3); 104.7 (C-3a); 111.0 (C-5); 120.3; 125.4; 128.9 (2C Ph); 129.0; 134.0; 138.2; 139.5; 147.7 (C-9); 150.7 (C-6); 156.5 (C-7a); 197.6 (CO). Found, *m*/*z*: 329.1407 $[M+H]^+$. $C_{20}H_{16}N_4O$. Calculated, *m*/*z*: 329.1398.

5-Methanesulfonyl-6-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine (4a). Yield 0.89 g (75%). Mp 287–289°C. IR spectrum, ν, cm^{-1}: 3423, 3325 (NH_2), 1581 (deformation vibrations of NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.01 (3H, s, CH_3SO_2); 3.82 (3H, s, CH_3O); 6.96 (2H, d, *J* = 8.7, H Ar); 7.31–7.33 (1H, m, H Ph); 7.39 (2H, d, *J* = 8.7, H Ar); 7.50–7.52 (2H, m, H Ph); 7.8 (1H, br. s, NH_2); 8.12–8.14 (2H, m, H Ph); 8.3 (1H, br. s, NH_2); 8.69 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 44.9 (SO_2CH_3); 55.0 (CH_3O); 105.5 (C-3a); 110.2; 112.4; 120.8; 126.1; 129.0; 130.3; 133.6; 134.6; 138.8; 149.4 (C-4); 149.7 (C-7a); 159.0 ($\underline{C}OCH_3$); 160.6 (C-6). Found, *m*/*z*: 395.1171 $[M+H]^+$. $C_{20}H_{18}N_4O_3S$. Calculated, *m*/*z*: 395.1173.

5-Methanesulfonyl-1-(4-methylphenyl)-6-phenyl-1*H*-pyrazolo[3,4-*b*]pyridin-4-amine (4b). Yield 0.87 g (77%). Mp 254–256°C. IR spectrum, ν, cm^{-1}: 3416, 3348 (NH_2), 1587 (deformation vibrations of NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.32 (3H, s, CH_3); 3.04 (3H, s, CH_3SO_2); 7.30 (2H, d, *J* = 8.7, H Ar); 7.38–7.43 (5H, m, H Ph, H Ar); 7.8 (1H, br. s, NH_2); 7.93–7.95 (2H, d, *J* = 8.7, H Ar); 8.3 (1H, br. s, NH_2); 8.68 (1H, s, H-3). ^{13}C NMR spectrum, δ, ppm: 20.6 (CH_3); 45.0 (SO_2CH_3); 105.5 (C-3a); 110.0; 127.1; 127.8; 128.7; 129.5; 134.4; 135.7; 136.5; 141.6; 149.3 (C-4); 149.8 (C-7a); 160.9 (C-6). Found, *m*/*z*: 379.1219 $[M+H]^+$. $C_{20}H_{18}N_4O_2S$. Calculated, *m*/*z*: 379.1224.

4-Amino-7,7-dimethyl-1-phenyl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolin-5-one (8a). Yield 0.66 g (72%). Mp 201–203°C. IR spectrum, ν, cm^{-1}: 3384, 3288 (NH_2), 1631 (stretching vibrations of C=O), 1622 (deformation vibrations of NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.03 (6H, s, $2CH_3$); 2.49 (2H, s, CH_2); 2.90 (2H, s, CH_2); 7.34 (1H, tt, *J* = 7.4, *J* = 1.1, *p*-H Ph); 7.52–7.56 (2H, m, *m*-H Ph); 8.23 (2H, dd, *J* = 8.6, *J* = 1.1, *o*-H Ph); 8.52 (1H, d, *J* = 3.3, NH_2); 8.54 (1H, s, H-3); 9.47 (1H, d, *J* = 3.6, NH_2). ^{13}C NMR spectrum, δ, ppm: 27.6 ($(\underline{C}H_3)_2$); 31.8 ($\underline{C}(CH_3)_2$); 47.7 (CH_2); 52.5 ($CO\underline{C}H_2$); 104.7 (C-3a); 105.2 (C-4a); 120.9; 126.0; 129.0; 135.0; 139.2; 150.8 (C-4); 151.6 (C-9a); 165.5 (C-8a); 199.9 (CO). Found, *m*/*z*: 307.1546 $[M+H]^+$. $C_{18}H_{18}N_4O$. Calculated, *m*/*z*: 307.1554.

4-Amino-7-(3,5-difluorophenyl)-1-phenyl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolin-5-one (8b). Yield 0.95 g (81%). Mp 246–248°C. IR spectrum, ν, cm^{-1}: 3488, 3299 (NH_2), 1633 (stretching vibrations of C=O), 1622 (deformation vibrations of NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.73–2.80 (1H, m, CH_2); 3.01 (1H, dd, *J* = 16.5, *J* = 12.5, CH_2); 3.13–3.17 (1H, m, CH_2); 3.30–3.37 (1H, m, CH_2); 3.55 (1H, tt, *J* = 12.2, *J* = 3.6, CH); 7.07–7.11 (1H, m, H Ph); 7.15–7.20 (2H, m, H Ar); 7.33 (1H, t, *J* = 7.4, H Ar); 7.52 (2H, t, *J* = 7.8, H Ar); 8.23 (2H, d, *J* = 7.9, *o*-H Ph); 8.56 (1H, s, H-3); 8.60 (1H, d, *J* = 3.0, NH_2); 9.50 (1H, d, *J* = 3.1, NH_2). ^{13}C NMR spectrum, δ, ppm: 38.0 (CH); 40.9 (CH_2); 45.3 ($CO\underline{C}H_2$); 101.8, 102.0 and 102.2 (C-4 Ar), 105.0 (C-3a); 105.1 (C-4a); 110.0, 110.1, 110.2 and 110.3 (C-2,6 Ar); 120.8; 125.9; 128.9; 135.0; 139.1; 148.0, 148.1 and 148.2 (C-1 Ar); 150.4; 151.8 (C-9a); 161.4 and 163.4 (2C CF); 165.3 (C-8a); 198.7 (CO). Found, *m*/*z*: 391.1360 $[M+H]^+$. $C_{22}H_{16}F_2N_4O$. Calculated, *m*/*z*: 391.1366.

4-Amino-7-(4-isopropylphenyl)-1-phenyl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolin-5-one (8c). Yield 0.88 g (74%). Mp 239–241°C. IR spectrum, ν, cm^{-1}: 3421, 3303 (NH_2), 1629 (stretching vibrations of C=O), 1612 (deformation vibrations of NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.19 (6H, d, *J* = 6.9, $CH(C\underline{H}_3)_2$); 2.74–2.80 (1H, m, CH_2); 2.83–2.90 (1H, m, $C\underline{H}(CH_3)_2$); 2.96 (1H, dd, *J* = 16.5, *J* = 11.8, CH_2); 3.15–3.20 (1H, m, CH_2); 3.30 (1H, dd, *J* = 16.2, *J* = 11.5, CH_2); 3.45 (1H, tt, *J* = 11.4, *J* = 3.9, CH); 7.20 (2H, d, *J* = 8.0, H Ar); 7.27–7.35 (3H, m, H Ar); 7.52 (2H, t, *J* = 7.8, H Ph); 8.23 (2H, d, *J* = 8.1, H Ph); 8.54–8.57 (2H, m, H-3, NH_2); 9.51 (1H, d, *J* = 3.2, NH_2). ^{13}C NMR spectrum, δ, ppm: 27.3 ($CH(\underline{C}H_3)_2$); 33.4 ($\underline{C}H(CH_3)_2$); 38.26 (CH); 42.0 (CH_2); 46.4 ($CO\underline{C}H_2$); 105.6 (C-3a); 105.7 (C-4a); 121.2; 126.3; 126.7; 127.1; 129.4; 135.4; 139.5; 141.2; 146.9; 150.9; 152.2 (C-9a); 166.2 (C-8a); 199.8 (CO). Found, *m*/*z*: 397.2019 $[M+H]^+$. $C_{25}H_{24}N_4O$. Calculated, *m*/*z*: 397.2024.

4-Amino-7-(3-chlorophenyl)-1-phenyl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolin-5-one (8d). Yield 0.93 g (80%). Mp 241–243°C. IR spectrum, ν, cm^{-1}: 3477, 3292 (NH_2), 1633 (stretching vibrations of C=O), 1593 (deformation vibrations of NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.73–2.79 (1H, m, CH_2); 3.01 (1H, dd, *J* = 16.5, *J* = 12.3, CH_2); 3.13–3.18 (1H, m, CH_2); 3.30–3.36 (1H, m, CH_2); 3.49–3.56 (1H, m, CH); 7.30–7.39 (4H, m, H Ar); 7.48–7.54 (3H, m, H Ar); 8.23 (2H, d, *J* = 7.6, H Ar); 8.56 (1H, s, H-3); 8.58 (1H, d, *J* = 3.0, NH_2); 9.50 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 38.1 (CH); 41.3 (CH_2); 45.7 ($CO\underline{C}H_2$); 105.2 (C-3a); 105.3 (C-4a); 120.9; 125.7; 126.0; 126.7; 127.0; 129.1; 130.4; 133.2; 135.1; 139.2; 146.1; 150.5; 151.9 (C-9a); 165.6 (C-8a); 199.1 (CO). Found, *m*/*z*: 389.1165 $[M+H]^+$. $C_{22}H_{17}ClN_4O$. Calculated, *m*/*z*: 389.1164.

4-Amino-1-(4-methoxyphenyl)-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolin-5-one (8e). Yield 0.76 g (82%). Mp 228–230°C. IR spectrum, ν, cm^{-1}: 3355, 3278 (NH_2), 1610 (stretching vibrations of C=O), 1606 (deformation vibrations of NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.00 (2H, quin, *J* = 6.6, $CH_2C\underline{H}_2CH_2$); 2.59 (2H, t, *J* = 6.0, CH_2); 2.97 (2H, t, *J* = 6.0, CH_2); 3.82 (3H, s, OCH_3); 7.10 (2H, d, *J* = 8.9, H Ar); 8.04 (2H, d, *J* = 8.9, H Ar); 8.45 (1H, d, *J* = 3.6, NH_2); 8.48 (1H, s, H-3); 9.51 (1H, d, *J* = 3.9, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.4 ($CH_2\underline{C}H_2CH_2$); 34.4 (CH_2); 39.2 ($CO\underline{C}H_2$); 55.4 (OCH_3); 104.8 (C-3a); 105.5 (C-4a); 114.2; 122.7; 132.4; 134.4; 150.0; 152.0 (C-9a); 157.4 ($\underline{C}OCH_3$); 166.6 (C-8a); 200.3 (CO). Found, *m*/*z*: 309.1346 $[M+H]^+$. $C_{17}H_{16}N_4O_2$. Calculated, *m*/*z*: 309.1346.

4-Amino-1-(4-methoxyphenyl)-7,7-dimethyl-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolin-5-one (8f). Yield

0.72 g (71%). Mp 187–189°C. IR spectrum, ν, cm^{-1}: 3425, 3305 (NH_2), 1616 (stretching vibrations of C=O), 1581 (deformation vibrations of NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.03 (6H, s, $2CH_3$); 2.48 (2H, s, CH_2); 2.87 (2H, s, CH_2); 3.82 (3H, s, OCH_3); 7.10 (2H, d, *J* = 8.9, H Ar); 8.05 (2H, d, *J* = 8.9, H Ar); 8.46 (1H, d, *J* = 3.3, NH_2); 8.48 (1H, s, H-3); 9.47 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 27.7 ($2CH_3$); 31.8 ($\underline{C}CH_3)_2$); 47.7 (CH_2); 52.6 ($CO\underline{C}H_2$); 55.4 (OCH_3); 104.5 (C-3a); 104.9 (C-4a); 114.1; 122.7; 132.4; 134.4; 150.3; 151.6 (C-9a); 157.4 ($\underline{C}OCH_3$ Ar); 165.4 (C-8a); 199.9 (CO). Found, *m*/*z*: 337.1658 $[M+H]^+$. $C_{19}H_{20}N_4O_2$. Calculated, *m*/*z*: 337.1660.

4-Amino-1-(4-fluorophenyl)-1,6,7,8-tetrahydro-5*H*-pyrazolo[3,4-*b*]quinolin-5-one (8g). Yield 0.69 g (78%). Mp 215–217°C. IR spectrum, ν, cm^{-1}: 3346, 3284 (NH_2), 1643 (stretching vibrations of C=O), 1614 (deformation vibrations of NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.00 (2H, quin, *J* = 6.6, $CH_2C\underline{H}_2CH_2$); 2.60 (2H, t, *J* = 6.0, CH_2); 2.99 (2H, t, *J* = 6.0, CH_2); 7.36–7.41 (2H, m, H Ar); 8.21–8.25 (2H, m, H Ar); 8.49 (1H, d, *J* = 3.0, NH_2); 8.52 (1H, s, H-3); 9.51 (1H, br. s, NH_2). ^{13}C NMR spectrum, δ, ppm: 21.7 ($CH_2\underline{C}H_2CH_2$); 34.7 (CH_2); 39.6 ($CO\underline{C}H_2$); 105.4 (C-3a); 106.0 (C-4a); 116.0; 116.2; 123.6 (C-3,5 Ar); 135.3; 136.0 (C-2,6 Ar); 150.6; 152.3; 159.3; 161.2; 167.2; 200.6 (CO). Found, *m*/*z*: 297.1153 $[M+H]^+$. $C_{16}H_{13}FN_4O$. Calculated, *m*/*z*: 297.1147.

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