DOI 10.1007/s10593-024-03315-1
Chemistry of Heterocyclic Compounds **2024**, *60*(3/4), 175–182

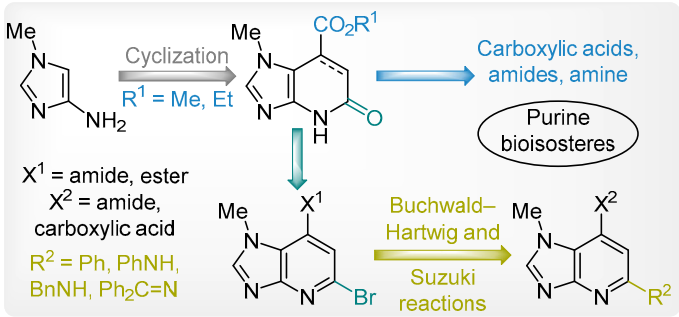
Synthesis and reactions of novel imidazo[4,5-*b*]pyridine building blocks

Tetiana F. Dubina[1], Anton V. Kosarevych[1,2], Olexandr V. Kucher[1,3], Bohdan S. Sosunovych[1], Oleg B. Smolii[3], Bohdan V. Vashchenko[1,2]*, Oleksandr O. Grygorenko[1,2]

[1] *Enamine Ltd., 78 Winston Churchill St., Kyiv 02094, Ukraine*
[2] *Taras Shevchenko National University of Kyiv, 60 Volodymyrska St., Kyiv 01601, Ukraine*
[3] *V. P. Kukhar Institute of Bioorganic Chemistry and Petrochemistry, National Academy of Sciences of Ukraine, 1 Akademika Kukhara St., Kyiv 02094, Ukraine; e-mail: vashchenko@knu.ua*

Published in Khimiya Geterotsiklicheskikh Soedinenii, 2024, *60*(3/4), 175–182

Submitted August 10, 2023
Accepted after revision October 10, 2023



The synthesis of a novel imidazo[4,5-*b*]pyridine and its partially saturated derivative relied on Michael addition of 1-methyl-1*H*-imidazol-4-amine to fumaric/maleic or acetylene dicarboxylates, followed by intramolecular cyclization into target compounds. The common transformations of the resulting pyridine carboxylate were performed to obtain a series of building blocks, i.e. carboxylic acids, amides, and amines. The pyridone fragment was transformed into the fused bromopyridine moiety which was used for Buchwald–Hartwig and Suzuki cross-coupling reactions providing a versatile access to an extended scope of imidazopyridines. All synthesized building blocks could be considered as promising purine bioisosteres for the synthetic and medicinal chemistry.

Keywords: imidazopyridines, purine bioisosteres, building blocks, coupling reactions, cyclization.

The design and synthesis of bioisosteres is an important part of medicinal chemistry and drug discovery.[1–5] Their application improves selectivity, pharmacokinetics, metabolic stability and reduces different side effects, including toxicity.[1] In recent years, special attention has been paid to the synthesis of fused pyridines[6–8] due to their biochemical activity and considering them as promising bioisosteres. Imidazopyridines are among the most promising purine bioisosteres for potential medical applications.[9–11] Special attention has been paid in recent years to imidazo[4,5-*b*]pyridine derivatives, which allowed for the design of compounds with valuable medicinal properties. The most successful examples are rimegepant (approved agent for the treatment of migraines),[12–14] telcagepant (investigational drug for the treatment of migraines),[15–18] ralimetinib (investigational agent for the treatment of cancer and Proteus syndrome),[19–21] and miransertib (investigational drug for the treatment of Proteus syndrome)[22–24] (Fig. 1).

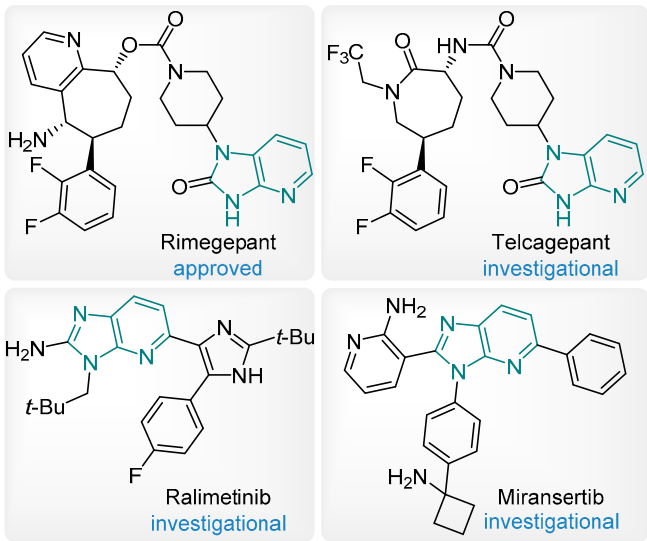
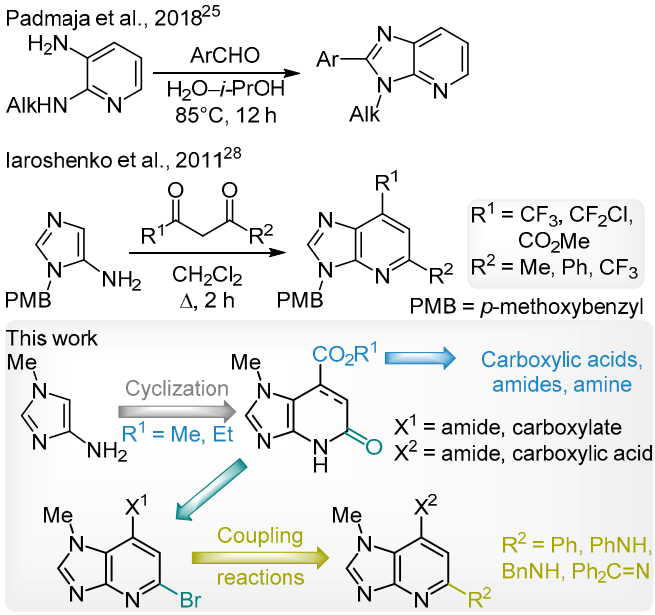


Figure 1. Biologically active imidazo[4,5-*b*]pyridines.

Similarly to purines, many of the imidazo[4,5-*b*]pyridine derivatives were synthesized by the construction of imidazole fragments starting from readily available 2,3-diaminopyridines (Scheme 1).[25,26] In the case of formaldehyde as the carbonyl component for this transformation, an unsubstituted imidazole ring could be obtained, while iodine atom could be introduced in this ring *via* the metalation–halogenation sequence. Further, the obtained iodide can be used for the Suzuki reaction to introduce various aryl substituents.[27] Another common approach is based on the construction of pyridine ring starting from 4-aminoimidazole and 1,3-dicarbonyl compounds, which was used to obtain substituted imidazopyridines (Scheme 1).[28–30]

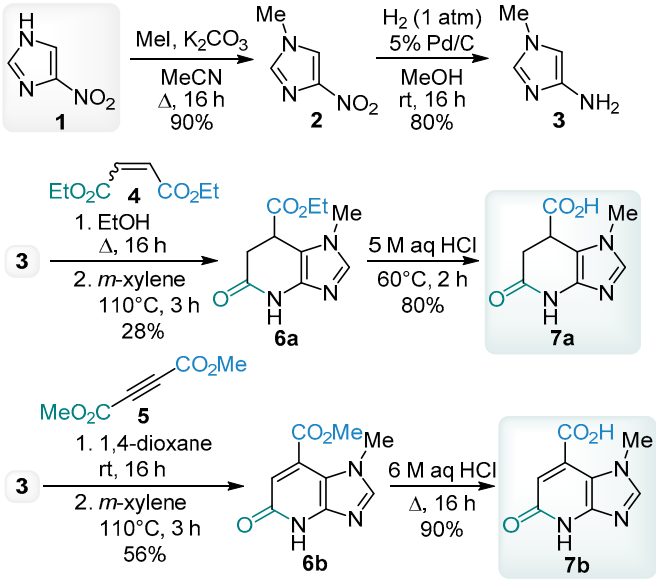
In this work, we have aimed at the synthesis of novel derivatives of (partially saturated) imidazopyridines. In particular, the preparation of various building blocks as purine bioisosteres for drug discovery was envisaged. In addition, we have aimed at the introduction of one or more halogen atoms into the pyridine ring for further cross-coupling reactions.

Scheme 1. Approaches to the synthesis of imidazo[4,5-*b*]pyridine building blocks



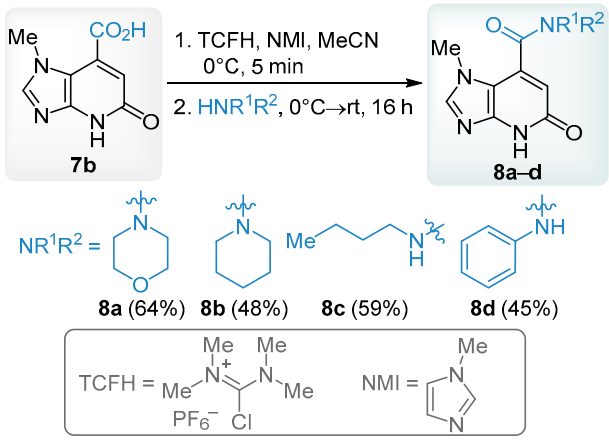
Imidazopyridine core and its saturated derivatives were constructed using Michael addition[31] followed by the intramolecular cyclization as the key step (Scheme 2). First, compound **3** was obtained according to the reported reaction sequence.[32] Alkylation of nitroimidazole **1** was accomplished using MeI and K_2CO_3 in MeCN followed by reduction of obtained product **2** with H_2 in the presence of 5% Pd/C in MeOH. Then, compound **3** was introduced into the Michael reactions with a mixture of fumarate/maleate **4** (reflux in EtOH for 16 h) and with acetylene dicarboxylate **5** (in 1,4-dioxane at room temperature for 16 h). The resulting Michael adducts were not isolated in pure form, but used in the intramolecular cyclization; the reaction was carried out in *m*-xylene at 110°C for 3 h (28% yield of compound **6a**, and 56% yield of compound **6b** over two steps).

Scheme 2. Synthesis of imidazopyridine-derived carboxylic acids **7a–b**



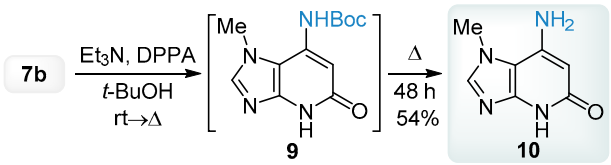
For the hydrolysis of compounds **6a**,**b**, it was found that 5 M aq HCl at 60°C was optimal to obtain carboxylic acid **7a** (80% yield), while the preparation of acid **7b** required refluxing in 6 M aq HCl (90% yield). Carboxylic acid **7b** was used for the synthesis of various amides using chloro-*N*,*N*,*N*',*N*'-tetramethylformamidinium hexafluorophosphate (TCFH) as a coupling agent and 1-methyl-1*H*-imidazole (NMI) as a base in MeCN (Scheme 3). To our delight, all model amines (i.e., morpholine, piperidine, *n*-butylamine, and aniline) were suitable for the preparation of amides **8a–d** (45–64% yields).

Scheme 3. Synthesis of amides **8a–d** from carboxylic acid **7b**



Another valuable building block, amine **10**, was obtained from carboxylic acid **7b** using the modified Curtius rearrangement. The reaction was carried out in the presence of Et_3N and diphenylphosphoryl azide (DPPA) in refluxing *t*-BuOH. While monitoring the reaction progress, we observed the formation of a mixture of *N*-Boc-amine **9** and *N*-Boc-deprotected amine **10** (likely through the thermal decomposition of amine **9**). Therefore, the reaction mixture was heated for 48 h until the complete conversion of

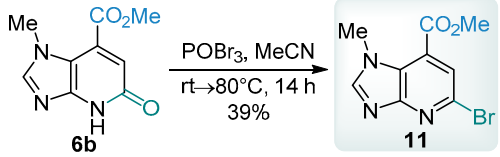
Scheme 4. Synthesis of amine **10** from carboxylic acid **7b**



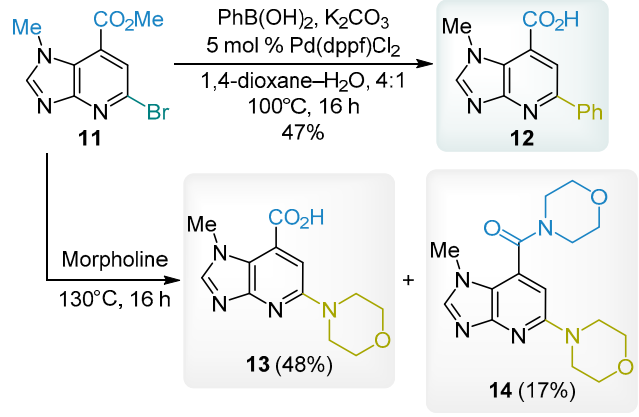
intermediate **9** was achieved, and solely the target amine **10** was obtained (Scheme 4).

Next, we have aimed at the synthesis of 5-haloimidazopyridine carboxylate **11** for its further study in the cross-coupling reactions. To this end, pyrimidone **6b** was subjected to the reaction with $POBr_3$ in MeCN to give target bromide **11** (39% yield, Scheme 5). Product **11** was then subjected to Suzuki reaction with phenylboronic acid in the presence of $Pd(dppf)Cl_2$ and K_2CO_3 in aqueous 1,4-dioxane at 100°C. The cross-coupling reaction proceeded successfully and was followed by K_2CO_3-mediated hydrolysis of the ester group to give carboxylic acid **12** in 47% yield (Scheme 6). The amination reaction at the C-5 position was carried out in morpholine at 130°C, which provided the expected S_NAr product **13** (48% yield), amide byproduct **14** (17% yield), as well as other unidentified products.

Scheme 5. Synthesis of bromide **11** as starting material for cross-coupling reactions



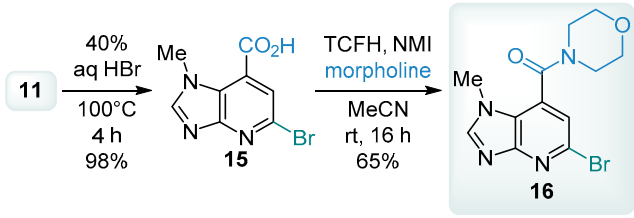
Scheme 6. Suzuki and S_NAr reactions of bromide **11**



In turn, selective preparation of amide **16** (Scheme 7) without additional arylation reaction could be achieved by hydrolysis of ester **11** with 40% aqueous HBr at 100°C. Carboxylic acid **15** thus obtained (98% yield) was treated with morpholine, TCFH, and NMI in MeCN at room temperature to give the target product **16** in 65% yield.

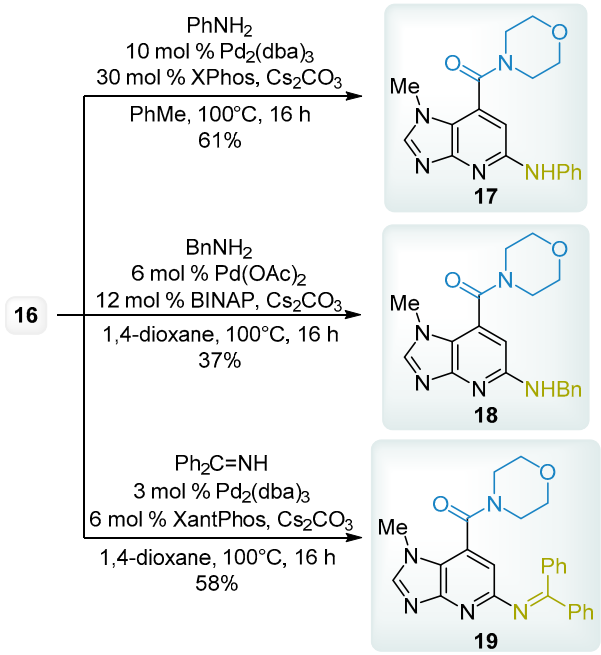
Next, aniline, benzylamine, and acetophenone imine (an NH_3 equivalent, see below) were chosen as model reagents for the study of the Buchwald–Hartwig reaction with amide **16** (Scheme 8). Aniline derivative **17** was easily synthesized in 61% yield. However, benzylamine derivative **18**

Scheme 7. Chemoselective synthesis of amide **16**



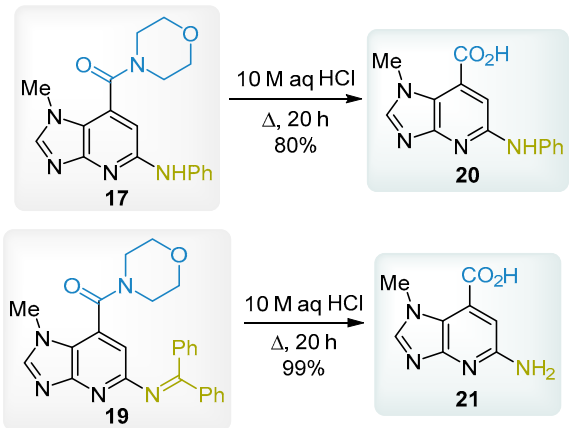
was obtained in only 37% yield. Diphenylmethylimine derivative **19** could be isolated in 58% yield. In all cases, the amide group remained intact.

Scheme 8. Buchwald–Hartwig reactions of amide **16**



Finally, amides **17** and **19** were hydrolyzed by refluxing in 10 M aqueous HCl to give target carboxylic acids **20** and **21** in 80 and 99% yields, respectively (Scheme 9). Therefore, Buchwald–Hartwig amination of bifunctional imidazo[4,5-*b*]pyridine derivatives could be performed selectively at the bromopyridine fragment using amides of type **16** instead of esters **11**. The amide fragment could be

Scheme 9. Hydrolysis of amides **17** and **19**



easily cleaved for the preparation of carboxylic acids after the Buchwald–Hartwig amination.

In conclusion, a series of novel imidazopyridine building blocks – promising purine bioisosteres for medicinal chemistry – were synthesized and introduced into common C–C and C–N couplings, i.e., amide synthesis, Suzuki cross coupling, and Buchwald–Hartwig reaction. The target 5-oxo-4,5-dihydro-1*H*-imidazo[4,5-*b*]pyridine-7-carboxylate framework or its partially hydrogenated derivative was constructed by Michael reaction of 1-methyl-1*H*-imidazol-4-amine with acetylene or fumarate/maleate dicarboxylates, respectively, followed by thermal intramolecular heterocyclization. The synthesized intermediate was successfully used for further functionalization at the pyridine ring.

In particular, synthesis of the corresponding carboxylic acids, amides, and amines at the C-7 position was performed through hydrolysis, amide coupling, and modified Curtius reaction, respectively. In addition to that, functionalization of the C-5 position was achieved through cross-coupling reactions. Thus, pyridone moiety of 5-oxo-4,5-dihydro-1*H*-imidazo[4,5-*b*]pyridine-7-carboxylate could be easily transformed into the corresponding fused bromopyridine, which in turn was successfully used in Suzuki reaction. It was also found that the selective C(5)-amination of fused 2-bromopyridine-4-carboxylic acid derivatives could be achieved by the initial transformation into morpholinamides (the direct use of esters was not possible due to the formation of amide byproducts). After the Buchwald–Hartwig reactions and further hydrolysis, 5-oxo-4,5-dihydro-1*H*-imidazo[4,5-*b*]-pyridine-7-carboxylic acids could be obtained.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (500 and 126 MHz, respectively), a Varian Unity Plus 400 spectrometer (400 and 101 MHz, respectively), or an Agilent ProPulse 600 spectrometer (^{13}C NMR spectra only, 151 MHz). NMR chemical shifts were referenced using residual NMR solvent peaks at 7.26 and 77.2 ppm for ^{1}H and ^{13}C nuclei, respectively, in $CDCl_3$ and 2.50 and 39.5 ppm for ^{1}H and ^{13}C nuclei, respectively, in DMSO-d_6, 4.79 ppm for ^{1}H nuclei in D_2O. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (electrospray atmospheric pressure ionization with quadrupole analyzer). High-resolution mass spectra were recorded on an Agilent 6224 Accurate-Mass TOF LC/MS instrument (electrospray ionization with time-of-flight analyzer). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv (Elementar vario MICRO cube CHNS/O analyzer). Melting points were determined on an MPA100 OptiMelt automated melting point system.

The solvents were purified according to the standard procedures.[33] Compounds **1**, **4**, and **5** were available from Enamine Ltd.

1-Methyl-4-nitro-1*H*-imidazole (2) was obtained according to the slightly modified literature procedure.[34] Imidazole **1** (50.0 g, 0.442 mol) was added to K_2CO_3 (122 g, 0.884 mol) and MeI (41.3 ml, 0.663 mol) in MeCN (500 ml), and the resulting mixture was refluxed for 16 h. Then, the reaction mixture was cooled to room temperature. The inorganic precipitate was filtered off, and then washed with MeCN (200 ml). The filtrate was evaporated under reduced pressure and the residue was dissolved in EtOAc (500 ml), washed with H_2O (100 ml), dried over Na_2SO_4, filtered, and evaporated under reduced pressure. Yield 50.5 g (90%). The spectral and physical data correspond to those reported in the literature.

1-Methyl-1*H*-imidazol-4-amine (3) was obtained according to the slightly modified literature procedure.[32] 5% Pd/C (4 g) was added to imidazole **2** (20.0 g, 0.157 mol) in MeOH (200 ml). The resulting mixture was stirred under H_2 atmosphere (1 atm) at room temperature for 16 h. The conversion was controlled by ^{1}H NMR. Afterward, Pd/C was filtered off, the filtrate was evaporated under reduced pressure, and the resulting crude compound **3** was used immediately in the next step due to its low stability. Yield 12.2 g (80%), brownish oil. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 7.15–6.95 (1H, m, CH); 6.08 (1H, d, *J* = 1.4, CH); 4.07 (2H, br. s, NH_2); 3.46 (3H, s, CH_3).

Ethyl 1-methyl-5-oxo-4,5,6,7-tetrahydro-1*H*-imidazo-[4,5-*b*]pyridine-7-carboxylate (6a). Diester **4** (33.3 ml, 0.206 mol) was added to imidazole derivative **3** (20.0 g, 0.206 mol) in EtOH (100 ml), and the resulting mixture was refluxed for 16 h. Then, the reaction mixture was cooled to room temperature and evaporated *in vacuo*. The residue was suspended in *m*-xylene (100 ml), and the resulting mixture was stirred at 110°C for 3 h. Then, the reaction mixture was cooled to room temperature and evaporated *in vacuo*. The resulting solid product was purified by crystallization from minimal amount of MeCN. Yield 12.9 g (28% over two steps), brownish solid, mp 182–183°C. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.86 (1H, s, NH); 7.22 (1H, s, H-2); 4.15 (2H, q, *J* = 7.1, C$\underline{H_2}$CH$_3$); 3.85 (1H, dd, *J* = 8.3, *J* = 2.2, 6-CH); 3.65 (3H, s, NCH_3); 3.06 (1H, dd, *J* = 16.5, *J* = 2.2) and 2.88 (1H, dd, *J* = 16.5, *J* = 8.3, 5-CH_2); 1.24 (3H, t, *J* = 7.1, $CH_2C\underline{H_3}$). ^{13}C NMR spectrum (151 MHz, $CDCl_3$), δ, ppm: 170.6; 167.8; 139.6; 135.3; 106.2; 62.0; 35.5; 34.2; 32.3; 14.2. Mass spectrum, *m*/*z* (I_{rel}, %): 224 $[M+H]^+$ (100). Found, %: C 54.20; H 6.16; N 18.74. $C_{10}H_{13}N_3O_3$. Calculated, %: C 53.81; H 5.87; N 18.82.

Methyl 1-methyl-5-oxo-4,5-dihydro-1*H*-imidazo[4,5-*b*]-pyridine-7-carboxylate (6b). Diester **5** (15.7 ml, 0.128 mol) was added to imidazole derivative **3** (12.4 g, 0.128 mol) in 1,4-dioxane (100 ml), and the resulting mixture was stirred at room temperature for 16 h. The precipitate was filtered off and washed with 1,4-dioxane (50 ml). The resulting product was suspended in *m*-xylene (100 ml), and the mixture was stirred at 110°C for 3 h. Then, the reaction mixture was cooled to room temperature. The resulting solid product was filtered off and washed with *n*-hexane (2×100 ml). Yield 14.8 g (56% over two steps), brownish solid, mp 205–207°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.66 (1H, br. s, NH); 8.15 (1H, s, CH); 6.68 (1H, s, CH); 3.92 (3H, s, CH_3); 3.84 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 164.6; 160.4;

151.8; 146.0; 128.9; 114.9; 110.1; 52.8; 34.8. Mass spectrum, *m*/*z* (I_{rel}, %): 208 $[M+H]^+$ (100). Found, %: C 51.89; H 4.62; N 20.42. $C_9H_9N_3O_3$. Calculated, %: C 52.17; H 4.38; N 20.28.

1-Methyl-5-oxo-4,5,6,7-tetrahydro-1*H*-imidazo[4,5-*b*]-pyridine-7-carboxylic acid (7a). Ester **6a** (10.0 g, 44.8 mmol) was dissolved in 5 M aqueous HCl (50 ml), and the resulting mixture was heated at 60°C for 2 h. After that, the reaction mixture was evaporated *in vacuo*. The resulting solid product was purified by crystallization from minimal amount of MeOH. Yield 6.99 g (80%), brownish powder, mp >300°C. ^{1}H NMR spectrum (400 MHz, D_2O), δ, ppm (*J*, Hz): 7.40 (1H, s, H-2); 3.81 (1H, dd, *J* = 8.7, *J* = 3.4, 6-CH); 3.63 (3H, s, CH_3); 3.06 (1H, dd, *J* = 16.9, *J* = 8.7) and 2.89 (1H, dd, *J* = 16.9, *J* = 3.4, 5-CH_2). ^{13}C NMR spectrum (151 MHz, D_2O), δ, ppm: 178.9; 172.4; 136.0; 135.0; 111.1; 37.4; 35.1; 31.6. Mass spectrum, *m*/*z* (I_{rel}, %): 196 $[M+H]^+$ (100). Found, *m*/*z*: 196.0719 $[M+H]^+$. $C_8H_{10}N_3O_3$. Calculated, *m*/*z*: 196.0717.

1-Methyl-5-oxo-4,5-dihydro-1*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid hydrochloride (7b). Ester **6b** (6.51 g, 31.4 mmol) was dissolved in 6 M aqueous HCl (50 ml), and the resulting mixture was refluxed for 16 h. After that, the reaction mixture was evaporated *in vacuo*. Yield 6.49 g (90%), brownish solid, mp 286–288°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 9.16 (1H, s, CH); 7.05 (1H, s, CH); 4.98 (3H, br. s, OH, NH, NH^+); 4.02 (3H, s, CH_3). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 164.5; 162.8; 144.9; 142.7; 131.8; 115.9; 110.0; 37.3. Mass spectrum, *m*/*z* (I_{rel}, %): 194 $[M–Cl]^+$. Found, *m*/*z*: 194.0561 $[M–Cl]^+$. $C_8H_8N_3O_3$. Calculated, *m*/*z*: 194.0560.

Synthesis of amides 8a–d (General method). TCFH (871 mg, 3.11 mmol) was added to carboxylic acid **7b** (500 mg, 2.59 mmol) in MeCN (10 ml) at 0°C, followed by adding of NMI (618 μl, 7.77 mmol). The resulting mixture was stirred at 0°C for 5 min, and then the respective amine (2.59 mmol) was added dropwise at 0°C. The resulting mixture was stirred at room temperature for 16 h. After that, reaction mixture was evaporated under reduced pressure. The obtained crude product was triturated with EtOAc–*i*-PrOH (1:1 v/v, 10 ml).

1-Methyl-7-(morpholine-4-carbonyl)-1,4-dihydro-5*H*-imidazo[4,5-*b*]pyridin-5-one (8a). Yield 433 mg (64%), greenish solid, mp 261–263°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.73 (1H, br. s, NH); 8.04 (1H, s, CH); 6.19 (1H, s, CH); 3.75–3.62 (7H, m), 3.59–3.49 (2H, m), and 3.39–3.33 (2H, m, 4CH_2, CH_3). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 163.8; 160.9; 149.3; 143.9; 133.4; 113.1; 107.7; 66.0; 65.8; 47.1; 41.5; 32.4. Mass spectrum, *m*/*z* (I_{rel}, %): 263 $[M+H]^+$ (100). Found, *m*/*z*: 263.1141 $[M+H]^+$. $C_{12}H_{15}N_4O_3$. Calculated, *m*/*z*: 263.1139.

1-Methyl-7-(piperidine-1-carbonyl)-1,4-dihydro-5*H*-imidazo[4,5-*b*]pyridin-5-one (8b). Yield 323 mg (48%), colorless solid, mp 260–261°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 11.67 (1H, br. s, NH); 8.03 (1H, s, CH); 6.12 (1H, s, CH); 3.75–3.55 (5H, m) and 3.32–3.28 (2H, m, 2CH_2, CH_3); 1.67–1.52 (4H, m) and 1.52–1.37 (2H, m, 3CH_2). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 163.4; 161.0; 149.1; 143.8; 134.2; 113.0; 107.3; 47.6; 41.7; 32.3; 25.8; 25.1; 23.8. Mass spectrum, *m*/*z*: (I_{rel}, %) 261 $[M+H]^+$ (100). Found, *m*/*z*: 261.1351 $[M+H]^+$. $C_{13}H_{17}N_4O_2$. Calculated, *m*/*z*: 261.1346.

***N*-Butyl-1-methyl-5-oxo-4,5-dihydro-1*H*-imidazo[4,5-*b*]-pyridine-7-carboxamide (8c)**. Yield 379 mg (59%), greenish solid, mp 244–246°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 11.71 (1H, br. s, NH); 8.77–8.70 (1H, m, NH); 8.02 (1H, s, CH); 6.25 (1H, s, CH); 3.72 (3H, s, CH_3); 3.27–3.23 (2H, m, CH_2); 1.52 (2H, quint, *J* = 7.2, CH_2); 1.35 (2H, sext, *J* = 7.2, CH_2); 0.91 (3H, t, *J* = 7.2, CH_3). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 164.6; 160.9; 149.3; 144.0; 135.5; 113.5; 109.2; 38.7; 33.4; 30.8; 19.6; 13.6. Mass spectrum, *m*/*z* (I_{rel}, %): 249 $[M+H]^+$ (100). Found, *m*/*z*: 249.1347 $[M+H]^+$. $C_{12}H_{17}N_4O_2$. Calculated, *m*/*z*: 249.1346.

1-Methyl-5-oxo-*N*-phenyl-4,5-dihydro-1*H*-imidazo-[4,5-*b*]pyridine-7-carboxamide (8d) was synthesized according to the general method except that the obtained crude product was triturated with MeOH (8 ml). Yield 312 mg (45%), colorless solid, mp 280–282°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 11.80 (1H, br. s, NH); 10.74 (1H, s, NH); 8.08 (1H, s, CH); 7.75 (2H, d, *J* = 7.8, H Ph); 7.38 (2H, t, *J* = 7.8, H Ph); 7.15 (1H, t, *J* = 7.8, H Ph); 6.47 (1H, s, CH); 3.74 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 163.2; 160.9; 149.7; 144.4; 138.4; 134.8; 128.8; 124.3; 120.1; 113.6; 109.3; 33.5. Mass spectrum, *m*/*z* (I_{rel}, %): 269 $[M+H]^+$ (100). Found, *m*/*z*: 269.1035 $[M+H]^+$. $C_{14}H_{13}N_4O_2$. Calculated, *m*/*z*: 269.1033.

7-Amino-1-methyl-1,4-dihydro-5*H*-imidazo[4,5-*b*]-pyridin-5-one (10). Et_3N (19.4 ml, 140 mmol) was added to the suspension of compound **7b** (10.0 g, 43.6 mmol) in *t*-BuOH (200 ml) followed by DPPA (10.3 ml, 48.0 mmol) being added dropwise at room temperature. The resulting mixture was refluxed for 48 h (control by ^{1}H NMR). After that, the formed precipitate was filtered off and washed with *t*-BuOMe (2×70 ml). Yield 3.86 g (54%), brownish solid, mp 293–295°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 11.13 (1H, br. s, NH); 7.69 (1H, s, H-2); 6.01 (2H, s, NH_2); 5.19 (1H, s, 6-CH); 3.89 (3H, s, CH_3). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 163.2; 147.0; 146.2; 140.9; 107.6; 91.0; 33.5. Mass spectrum, *m*/*z* (I_{rel}, %): 165 $[M+H]^+$ (100). Found, *m*/*z*: 165.0773 $[M+H]^+$. $C_7H_9N_4O$. Calculated, *m*/*z*: 165.0771.

Methyl 5-bromo-1-methyl-1*H*-imidazo[4,5-*b*]pyridine-7-carboxylate (11). $POBr_3$ (4.90 ml, 48.2 mmol) was added in one portion to compound **6b** (5.00 g, 24.1 mmol) in MeCN (30 ml) at room temperature, and the resulting mixture was stirred at 80°C for 14 h. Then, MeCN was evaporated under reduced pressure, and ice water (80 ml) was added to the residue. After that, saturated aqueous $NaHCO_3$ was added until the basic pH was reached (control using indicator paper), and then product **11** was extracted with CH_2Cl_2 (3×50 ml). Yield 2.54 g (39%), yellowish solid, mp 174–176°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 8.61 (1H, s, H-2); 7.73 (1H, s, H-6); 3.95 (6H, s, 2CH_3). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 163.5; 157.9; 150.8; 133.5; 126.3; 122.9; 121.0; 53.1; 35.3. Mass spectrum, *m*/*z* (I_{rel}, %): 272 $[M(^{81}Br)+H]^+$ (100), 270 $[M(^{79}Br)+H]^+$ (100). Found, *m*/*z*: 271.9853

$[M+H]^+$. $C_9H_9{}^{81}BrN_3O_2$. Calculated, *m/z*: 271.9852. Found, *m/z*: 269.9873 $[M+H]^+$. $C_9H_9{}^{79}BrN_3O_2$. Calculated, *m/z*: 269.9873.

1-Methyl-5-phenyl-1*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (12). $PhB(OH)_2$ (49.3 mg, 0.407 mmol) and K_2CO_3 (128 mg, 0.925 mmol) were added to ester **11** (100 mg, 0.370 mmol) in 1,4-dioxane–H_2O, 4:1 (5 ml). Then, Ar was bubbled through the resulting mixture for 5 min, and $Pd(dppf)Cl_2$ (13.5 mg, 18.5 μmol) was added. The reaction mixture was stirred at 100°C for 16 h and then evaporated under reduced pressure. The obtained product was purified by HPLC using a gradient mixture H_2O–MeCN as an eluent (column Chromatorex 18 SMB, flow rate 30 ml/min). Yield 44.3 mg (47%), yellowish solid, mp >300°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.31 (1H, s, H-2); 8.06 (2H, d, *J* = 7.4, H Ph); 7.71 (1H, s, H-6); 7.48 (2H, t, *J* = 7.4, H Ph); 7.37 (1H, t, *J* = 7.4, H Ph); 4.01 (3H, s); 3.40 (1H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 167.3; 157.1; 150.2; 147.8; 139.9; 138.4; 128.6; 127.9; 126.4; 122.3; 113.4; 33.7. Mass spectrum, *m/z* (I_{rel}, %): 254 $[M+H]^+$ (100). Found, *m/z*: 254.0926 $[M+H]^+$. $C_{14}H_{12}N_3O_2$. Calculated, *m/z*: 254.0924.

1-Methyl-5-(morpholin-4-yl)-1*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (13). Ester **11** (100 mg, 0.370 mmol) was dissolved in morpholine (2 ml), and the resulting mixture was stirred at 130°C for 16 h, then evaporated under reduced pressure. The obtained mixture of products **13** and **14** was separated by HPLC using a gradient mixture H_2O–MeCN (with 0.1% HCO_2H) as an eluent (column Kinetex PFP, flow rate 30 ml/min). Yield 46.7 mg (48%), beige solid, mp 243–245°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 13.77 (1H, br. s, OH); 8.24 (1H, s, H-2); 7.09 (1H, s, H-6); 3.89 (3H, s, CH_3); 3.73 (4H, t, *J* = 4.7, $2CH_2$), 3.45 (4H, t, *J* = 4.7, $2CH_2$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 166.5; 156.6; 156.1; 147.6; 127.5; 117.1; 103.7; 66.0; 46.1; 34.8. Mass spectrum, *m/z* (I_{rel}, %): 263 $[M+H]^+$ (100). Found, *m/z*: 263.1141 $[M+H]^+$. $C_{12}H_{15}N_4O_3$. Calculated, *m/z*: 263.1139.

[1-Methyl-5-(morpholin-4-yl)-1*H*-imidazo[4,5-*b*]pyridin-7-yl](morpholin-4-yl)methanone (14). Yield 21.4 mg (17%), brownish glass. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 8.20 (1H, s, H-2); 6.77 (1H, s, H-6); 3.82–3.63 (11H, m) and 3.61–3.34 (8H, m, $8CH_2$, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 164.7; 156.3; 155.7; 146.3; 129.5; 116.0; 100.7; 66.0; 65.8; 47.3; 46.2; 41.6; 32.3. Mass spectrum, *m/z* (I_{rel}, %): 332 $[M+H]^+$ (100). Found, *m/z*: 332.1719 $[M+H]^+$. $C_{16}H_{22}N_5O_3$. Calculated, *m/z*: 332.1717.

5-Bromo-1-methyl-1*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid hydrobromide (15). Ester **11** (3.00 g, 11.1 mmol) was suspended in 40% aqueous HBr, and the resulting mixture was stirred at 100°C for 4 h. After that, the reaction mixture was evaporated under reduced pressure. Yield 3.67 g (98%), brownish solid, mp 225–227°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 8.86 (1H, s, H-2); 9.64–8.11 (2H, m, NH, OH); 7.77 (1H, s, H-6); 4.01 (3H, s, CH_3). ^{13}C NMR spectrum (151 MHz, DMSO-d_6), δ, ppm: 164.5; 155.7; 149.9; 134.5; 128.6; 122.8; 121.7; 35.8. Mass spectrum, *m/z* (I_{rel}, %): 258 $[M(^{81}Br)–Br]^+$ (100), 256 $[M(^{79}Br)–Br]^+$ (100). Found, *m/z*: 257.9798 $[M–Br]^+$. $C_8H_7{}^{81}BrN_3O_2$. Calculated, *m/z*: 257.9696. Found, *m/z*: 255.9718 $[M–Br]^+$. $C_8H_7{}^{79}BrN_3O_2$. Calculated, *m/z*: 255.9716.

(5-Bromo-1-methyl-1*H*-imidazo[4,5-*b*]pyridin-7-yl)-(morpholin-4-yl)methanone (16). NMI (2.27 ml, 28.5 mmol) and morpholine (736 μl, 8.54 mmol) were added to a suspension of compound **15** (2.40 g, 7.12 mmol) in MeCN (50 ml) upon cooling in water bath. After that, TCFH (3.00 g, 10.7 mmol) was added, and the resulting mixture was stirred at room temperature for 16 h. Then, the reaction mixture was evaporated under reduced pressure. The obtained product was purified by column chromatography on silica gel using *n*-hexane–THF (gradient from 1:0 to 0:1) as an eluent. Yield 1.51 r (65%), colorless solid, mp 251–253°C. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 8.09 (1H, s, H-2); 7.25–7.22 (1H, m, H-6); 3.96–3.75 (7H, m), 3.73–3.54 (2H, m), and 3.49–3.30 (2H, m, $4CH_2$, CH_3). ^{13}C NMR spectrum (101 MHz, DMSO-d_6), δ, ppm: 162.7; 156.9; 149.1; 133.9; 130.4; 121.9; 118.0; 65.9; 65.7; 47.2; 41.7; 32.6. Mass spectrum, *m/z* (I_{rel}, %): 327 $[M(^{81}Br)+H]^+$ (100), 325 $[M(^{79}Br)+H]^+$ (100). Found, *m/z*: 327.0275 $[M+H]^+$. $C_{12}H_{14}{}^{81}BrN_4O_2$. Calculated, *m/z*: 327.0274. Found, *m/z*: 325.0294 $[M+H]^+$. $C_{12}H_{14}{}^{79}BrN_4O_2$. Calculated, *m/z*: 325.0295.

[1-Methyl-5-(phenylamino)-1*H*-imidazo[4,5-*b*]pyridin-7-yl](morpholin-4-yl)methanone (17). Amide **16** (400 mg, 1.23 mmol) was added to a suspension of XPhos (176 mg, 369 μmol), Cs_2CO_3 (401 mg, 1.23 mmol), and $PhNH_2$ (0.135 ml, 1.48 mmol) in PhMe (7 ml). Then, Ar was bubbled through the resulting suspension for 5 min, and $Pd_2(dba)_3$ (113 mg, 123 μmol) was added. The resulting mixture was stirred at 100°C for 16 h. After that, the reaction mixture was cooled to room temperature. The inorganic precipitate was filtered off and washed with 1,4-dioxane (2×4 ml). The filtrate was evaporated under reduced pressure. The obtained product **17** was purified by HPLC using gradient H_2O–MeCN as an eluent (column Chromatorex 18 SMB, flow rate 30 ml/min). Yield 252 mg (61%), yellowish solid, mp 246–248°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 9.09 (1H, s, NH); 8.21 (1H, s, H-2); 7.78 (2H, d, *J* = 7.7, H Ph); 7.28 (2H, t, *J* = 7.7, H Ph); 6.88 (1H, t, *J* = 7.7, H Ph); 6.66 (1H, s, H-6); 3.76–3.69 (7H, m, $2CH_2$, CH_3); 3.55 (2H, t, *J* = 4.8) and 3.36–3.33 (2H, m, $2CH_2$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 164.4; 155.3; 152.0; 145.8; 141.9; 129.4; 128.5; 120.1; 117.4; 116.1; 104.0; 66.2; 65.9; 47.3; 41.6; 32.4. Mass spectrum, *m/z* (I_{rel}, %): 338 $[M+H]^+$ (100). Found, *m/z*: 338.1612 $[M+H]^+$. $C_{18}H_{20}N_5O_2$. Calculated, *m/z*: 338.1612.

[5-(Benzylamino)-1-methyl-1*H*-imidazo[4,5-*b*]pyridin-7-yl](morpholin-4-yl)methanone (18). Amide **16** (400 mg, 1.23 mmol) was added to a suspension of BINAP (92.0 mg, 148 μmol), Cs_2CO_3 (401 mg, 1.23 mmol), and $BnNH_2$ (0.161 ml, 1.48 mmol) in 1,4-dioxane (7 ml). Then, Ar was bubbled through the resulting suspension for 5 min, and $Pd(OAc)_2$ (16.6 mg, 73.8 μmol) was added. The resulting mixture was stirred at 100°C for 16 h. After that, the reaction mixture was cooled to room temperature. The inorganic precipitate was filtered off and washed with 1,4-dioxane (2×4 ml). The filtrate was evaporated under reduced pressure The obtained product **18** was purified by

HPLC using a gradient mixture H_2O–MeCN (with 0.1% $NH_3 \cdot H_2O$) as an eluent (column XBridge C18, flow rate 30 ml/min). Yield 158 mg (37%), yellowish glass. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.05 (1H, s, H-2); 7.36 (2H, d, *J* = 7.5, H Ph); 7.30 (2H, t, *J* = 7.5, H Ph); 7.21 (1H, t, *J* = 7.5, H Ph); 7.03 (1H, t, *J* = 5.9, NH); 6.38 (1H, s, H-6); 4.52 (2H, d, *J* = 5.9, NHC$\underline{H}_2$); 3.72–3.66 (4H, m, $2CH_2$); 3.65 (3H, s, CH_3); 3.50 (2H, t, *J* = 4.7) and 3.27 (2H, t, *J* = 4.7, $2CH_2$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 164.8; 156.0; 155.4; 144.8; 140.6; 129.1; 128.1; 127.3; 126.4; 114.9; 101.8; 66.0; 65.9; 47.2; 41.5; 44.4; 32.3. Mass spectrum, *m*/*z* (I_{rel}, %): 352 $[M+H]^+$ (100). Found, *m*/*z*: 352.1768 $[M+H]^+$. $C_{19}H_{22}N_5O_2$. Calculated, *m*/*z*: 352.1768.

{5-[(Diphenylmethylidene)amino]-1-methyl-1*H*-imidazo-[4,5-*b*]pyridin-7-yl}(morpholin-4-yl)methanone (19). Amide **16** (400 mg, 1.23 mmol) was added to a suspension of XantPhos (42.7 mg, 73.8 μmol), Cs_2CO_3 (401 mg, 1.23 mmol), and Ph_2C=NH (335 mg, 1.85 mmol) in 1,4-dioxane (7 ml). Then, Ar was bubbled through the resulting suspension for 5 min, and $Pd_2(dba)_3$ (33.8 mg, 36.9 μmol) was added. The resulting mixture was stirred at 100°C for 16 h. After that, the reaction mixture was cooled to room temperature. The inorganic precipitate was filtered off and washed with 1,4-dioxane (2×4 ml). The filtrate was evaporated under reduced pressure. Obtained product **19** was purified by HPLC using gradient H_2O–MeCN as an eluent (column XBridge C18, flow rate 60 ml/min). Yield 304 mg (58%), greenish solid, mp 148–150°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 8.32 (1H, s, H-2); 7.71 (2H, d, *J* = 7.4, H Ph); 7.58 (1H, t, *J* = 7.4, H Ph); 7.51 (2H, t, *J* = 7.4, H Ph); 7.31–7.25 (3H, m, H Ph); 7.19–7.11 (2H, m, H Ph); 6.45 (1H, s, H-6); 3.67 (3H, s, CH_3); 3.65–3.59 (4H, m, $2CH_2$); 3.42–3.33 (2H, m) and 2.81–2.69 (2H, m, $2CH_2$). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 169.6; 163.8; 158.6; 156.0; 147.5; 138.2; 135.9; 131.4; 129.0; 128.7; 128.4; 128.0; 118.7; 107.2; 65.7; 46.8; 41.5; 32.5. Mass spectrum, *m*/*z* (I_{rel}, %): 426 $[M+H]^+$ (100). Found, *m*/*z*: 426.1921 $[M+H]^+$. $C_{25}H_{24}N_5O_2$. Calculated, *m*/*z*: 426.1925.

1-Methyl-5-(phenylamino)-1*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (20). Compound **17** (189 mg, 0.559 mmol) was dissolved in 10 M aqueous HCl (3 ml), and the resulting mixture was refluxed for 20 h. Then, the reaction mixture was cooled to room temperature. The formed solid product was filtered off and washed with H_2O (2×3 ml). The obtained product was triturated in boiling *i*-PrOH (3 ml). Yield 120 mg (80%), greenish solid, mp 218–220°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 9.74 (1H, s, NH); 8.93 (1H, s, H-2); 7.81 (2H, d, *J* = 7.5, H Ph); 7.42 (1H, s, H-6); 7.32 (2H, t, *J* = 7.5, H Ph); 6.96 (1H, t, *J* = 7.5, H Ph); 4.02 (1H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 165.3; 153.4; 150.0; 143.7; 141.0; 128.7; 128.6; 121.2; 118.1; 115.8; 110.4; 36.5. Mass spectrum, *m*/*z* (I_{rel}, %): 269 $[M+H]^+$ (100). Found, *m*/*z*: 269.1034 $[M+H]^+$. $C_{14}H_{13}N_4O_2$. Calculated, *m*/*z*: 269.1033.

5-Amino-1-methyl-1*H*-imidazo[4,5-*b*]pyridine-7-carboxylic acid (21) was synthesized analogously to compound **20** from compound **19** (235 mg, 0.553 mmol). Yield 105 mg (99%), yellowish solid, mp 277–278°C. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 8.55 (1H, s, H-2); 6.94 (1H, s, H-6); 3.93 (3H, s, CH_3). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 165.7; 156.8; 144.1; 135.7; 129.1; 115.2; 107.1; 35.9. Mass spectrum, *m*/*z* (I_{rel}, %): 193 $[M+H]^+$ (100). Found, *m*/*z*: 193.0721 $[M+H]^+$. $C_8H_9N_4O_2$. Calculated, *m*/*z*: 193.0720.

Supplementary information file, containing NMR and mass spectra of the synthesized compounds, is available at the journal website http://link.springer.com/journal/10593.

The work was funded by Enamine Ltd. An additional funding was received from Ministry of Education and Sciences of Ukraine, grants No. 0121U100387 (21BF037-01M) and 0122U001962 (22BF037-02). The authors thank Prof. Andrey A. Tolmachev for his encouragement and support and the people of Ukraine who made finalizing this publication possible.

References

1. Brown, N. *Mol. Inform.* **2014**, *33*, 458.
2. Kułaga, D.; Drabczyk, A. K.; Satała, G.; Latacz, G.; Boguszewska-Czubara, A.; Plażuk, D.; Jaśkowska, J. *Int. J. Mol. Sci.* **2022**, *23*, 13308.
3. Patani, G. A.; LaVoie, E. J. *Chem. Rev.* **1996**, *96*, 3147.
4. Dick, A.; Cocklin, S. *Pharmaceuticals* **2020**, *13*, 36.
5. Subbaiah, M. A. M.; Meanwell, N. A. *J. Med. Chem.* **2021**, *64*, 14046.
6. Stepaniuk, O. O.; Rudenko, T. V.; Vashchenko, B. V.; Matvienko, V. O.; Kondratov, I. S.; Tolmachev, A. A.; Grygorenko, O. O. *Synthesis* **2020**, *52*, 1915.
7. Stepaniuk, O. O.; Vashchenko, B. V.; Matvienko, V. O.; Kondratov, I. S.; Tolmachev, A. A.; Grygorenko, O. O. *Chem. Heterocycl. Compd.* **2020**, *56*, 377.
8. Vashchenko, B.; Grygorenko, O.; Stepaniuk, O. *Ukr. Bioorganica Acta* **2022**, *17*(1), 56.
9. Khatun, S.; Singh, A.; Bader, G. N.; Sofi, F. A. *J. Biomol. Struct. Dyn.* **2022**, *40*, 14279.
10. Vanda, D.; Zajdel, P.; Soural, M. *Eur. J. Med. Chem.* **2019**, *181*, 111569.
11. Krause, M.; Foks, H.; Gobis, K. *Molecules* **2017**, *22*, 399.
12. Luo, G.; Chen, L.; Conway, C. M.; Kostich, W.; Macor, J. E.; Dubowchik, G. M. *Org. Lett.* **2015**, *17*, 5982.
13. Lipton, R. B.; Croop, R.; Stock, E. G.; Stock, D. A.; Morris, B. A.; Frost, M.; Dubowchik, G. M.; Conway, C. M.; Coric, V.; Goadsby, P. J. *N. Engl. J. Med.* **2019**, *381*, 142.
14. Negro, A.; Martelletti, P. *Expert Opin. Invest. Drugs* **2019**, *28*, 555.
15. Salvatore, C. A.; Hershey, J. C.; Corcoran, H. A.; Fay, J. F.; Johnston, V. K.; Moore, E. L.; Mosser, S. D.; Burgey, C. S.; Paone, D. V.; Shaw, A. W.; Graham, S. L.; Vacca, J. P.; Williams, T. M.; Koblan, K. S.; Kane, S. A. *J. Pharmacol. Exp. Ther.* **2008**, *324*, 416.
16. Paone, D. V.; Shaw, A. W.; Nguyen, D. N.; Burgey, C. S.; Deng, J. Z.; Kane, S. A.; Koblan, K. S.; Salvatore, C. A.; Mosser, S. D.; Johnston, V. K.; Wong, B. K.; Miller-Stein, C. M.; Hershey, J. C.; Graham, S. L.; Vacca, J. P.; Williams, T. M. *J. Med. Chem.* **2007**, *50*, 5564.
17. Ho, T. W.; Mannix, L. K.; Fan, X.; Assaid, C.; Furtek, C.; Jones, C. J.; Lines, C. R.; Rapoport, A. M. *Neurology* **2008**, *70*, 1304.
18. Link, A. S.; Kuris, A.; Edvinsson, L. *J. Headache Pain* **2008**, *9*, 5.

19. Patnaik, A.; Haluska, P.; Tolcher, A. W.; Erlichman, C.; Papadopoulos, K. P.; Lensing, J. L.; Beeram, M.; Molina, J. R.; Rasco, D. W.; Arcos, R. R.; Kelly, C. S.; Wijayawardana, S. R.; Zhang, X.; Stancato, L. F.; Bell, R.; Shi, P.; Kulanthaivel, P.; Pitou, C.; Mulle, L. B.; Farrington, D. L.; Chan, E. M.; Goetz, M. P. *Clin. Cancer Res.* **2016**, *22*, 1095.
20. Vergote, I.; Heitz, F.; Buderath, P.; Powell, M.; Sehouli, J.; Lee, C. M.; Hamilton, A.; Fiorica, J.; Moore, K. N.; Teneriello, M.; Golden, L.; Zhang, W.; Pitou, C.; Bell, R.; Campbell, R.; Farrington, D. L.; Bell-McGuinn, K.; Wenham, R. M. *Gynecol. Oncol.* **2020**, *156*, 23.
21. Biau, J.; Thivat, E.; Chautard, E.; Stefan, D.; Boone, M.; Chauffert, B.; Bourgne, C.; Richard, D.; Molnar, I.; Levesque, S.; Bellini, R.; Kwiatkowski, F.; Karayan-Tapon, L.; Verrelle, P.; Godfraind, C.; Durando, X. *Radiother. Oncol.* **2021**, *154*, 227.
22. Keppler-Noreuil, K. M.; Sapp, J. C.; Lindhurst, M. J.; Darling, T. N.; Burton-Akright, J.; Bagheri, M.; Dombi, E.; Gruber, A.; Jarosinski, P. F.; Martin, S.; Nathan, N.; Paul, S. M.; Savage, R. E.; Wolters, P. L.; Schwartz, B.; Widemann, B. C.; Biesecker, L. G. *Am. J. Hum. Genet.* **2019**, *104*, 484.
23. Leoni, C.; Gullo, G.; Resta, N.; Fagotti, A.; Onesimo, R.; Schwartz, B.; Kazakin, J.; Abbadessa, G.; Crown, J.; Collins, C. D.; Ranieri, C.; Scambia, G.; Zampino, G. *Am. J. Med. Genet.*, *Part A* **2019**, *179*, 1319.
24. Forde, K.; Resta, N.; Ranieri, C.; Rea, D.; Kubassova, O.; Hinton, M.; Andrews, K. A.; Semple, R.; Irvine, A. D.; Dvorakova, V. *Orphanet J. Rare Dis.* **2021**, *16*, 109.
25. Padmaja, R. D.; Devi, V. C.; Mukku, N.; Chanda, K.; Maiti, B. *ACS Omega* **2018**, *3*, 4583.
26. Doganc, F.; Alp, M.; Karabay, A.; Koç, A.; Eren, G.; Göker, H. *ChemistrySelect* **2021**, *6*, 1519.
27. Sajith, A. M.; Muralidharan, A. *Tetrahedron Lett.* **2012**, *53*, 1036.
28. Iaroshenko, V. O.; Ostrovskyi, D.; Petrosyan, A.; Mkrtchyan, S.; Villinger, A.; Langer, P. *J. Org. Chem.* **2011**, *76*, 2899.
29. Iaroshenko, V. O.; Sevenard, D. V.; Volochnyuk, D. M.; Wang, Y.; Martiloga, A.; Tolmachev, A. O. *Synthesis* **2009**, 1865.
30. Wu, J.; Xing, X.; Cuny, G. *Lett. Org. Chem.* **2009**, *6*, 203.
31. Al-Shaar, A. H. M.; Gilmour, D. W.; Lythgoe, D. J.; McClenaghan, I.; Ramsden, C. A. *J. Chem. Soc.*, *Perkin Trans. 1* **1992**, 2779.
32. Takubo, C.; Kimura, S.; Ichinomiya, M.; Hayakawa, A.; Murata, M.; Urushibara, K.; Masu, H.; Katagiri, K.; Kawahata, M.; Kudo, M.; Azumaya, I.; Kagechika, H.; Tanatani, A. *J. Org. Chem.* **2022**, *88*, 16707,.
33. Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*; Elsevier: Oxford, 2003, 5th ed.
34. Morais, E. M.; Grillo, I. B.; Stassen, H. K.; Seferin, M.; Scholten, J. D. *New J. Chem.* **2018**, *42*, 10774.