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The Synthesis of Diverse Annulated Pyridines with 6-Membered Functionalized Saturated Cycles for Medical Chemistry Research

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Abstract
The article describes a set of pyridines annulated with functionalized 6-membered saturated rings, which are attractive building blocks for the synthesis of diversified compound libraries in medical chemistry. A certain array of compounds includes pyridines with condensed cyclohexane, piperidine and tetrahydropyran cycles containing keto-, amino-, carboxylic groups, as well as fluorinated fragments. The synthesis of the compounds using the procedure previously developed by us *via* $CuCl_2$-catalyzed condensation of propargylamine with ketones was performed. The limits of application of this reaction were further expanded and determined in this work compared to our previous results. Condensed pyridines, which proved problematic or impossible to obtain by this method, were synthesized using other synthetic pathways. Thus, the study offers a number of new building blocks for use in drug discovery.

Keywords: organic synthesis; heterocyclic compounds; pyridines; building blocks; organofluorines; "magic methyl"; scaffold hopping

Introduction

Pyridines annulated to saturated cycles (PASCs) are widely used in drug discovery. Among the compounds containing this fragment there are substances demonstrating anti-HIV [1], antiresorptive [2, 3], antibacterial [4] and antimigraine [5] activity (**Figure 1**).

Due to such a wide spectrum of the biological activity demonstrated, chemists need convenient and cost-effective methods for the synthesis of diverse functionalized PASCs in multigram and/oreven semi-industrial scales. In this research, wedemonstrate our strategy for solving this prob-lem and propose a synthetic strategy for produc- ing a set of bicyclic building blocks containing py- ridine and an annelated saturated core with va- rious substituents and functional groups. Accord- ing to the development of "magic methyl" and "ma- gic fluorine" concepts, along with classical func- tions, we included compounds bearing methyl- methylene (**2**), dimethylmethylene (**3**) and difluo-romethylene (**4**) moieties in our short-list. Isome- ric conformationally restricted ketones **6a–d**, car- boxylic acids **7a–d**, PASCs with exocyclic aminefunction **8a–d** and those featuring endocyclic one**9a–d** were also treated as utility building blocksfor modern combinatorial chemistry and drug dis-covery (**Figure 2**).

Reported approaches towards pyridines annu-lated with 6-membered saturated cycles include: (**A**) the partial reduction of the corresponding aromatic compounds, (**B**) the construction of the saturated 6-membered ring and (**C**) the construction of the pyridine ring. Viable routes to imple- ment the approaches are illustrated by a retrosynthetic analysis of compound **9c** (**Figure 3**).

Approach **C** can also be illustrated by the in- termolecular Diels-Alder reaction with an inver- se electron demand [6], intermolecular oxidative cyclization [7, 8] or [4+2]-cyclization. Examples of [4+2]-cyclization include reactions catalyzed by gold [9] and ruthenium [10–13]. Recently, our research group proposed a simple and scalable method *via* the condensation catalyzed by avail- able and cheap $CuCl_2$ [14] (**Figure 4**). Thanks to our research, this approach has become cost- effective and, along with good scalability and di- versity, very promising for obtaining such com- pounds.

In this light, we aimed to extend and deter- mine the scope of the method and perform the synthesis of the set of diverse PASCs. In addi-tion, in some cases of the method, we proposed other approaches for the synthesis of the target molecules.

In our previous work [9], we reported on the synthesis of the parent core **1**, ketones **6a** and **6b**, carboxylic acid **7b**, amines **8a**, **9a**, **9b** and dihy- dropyranopyridine **10b**. The scope of the methodwas successfully expanded to the synthesis of

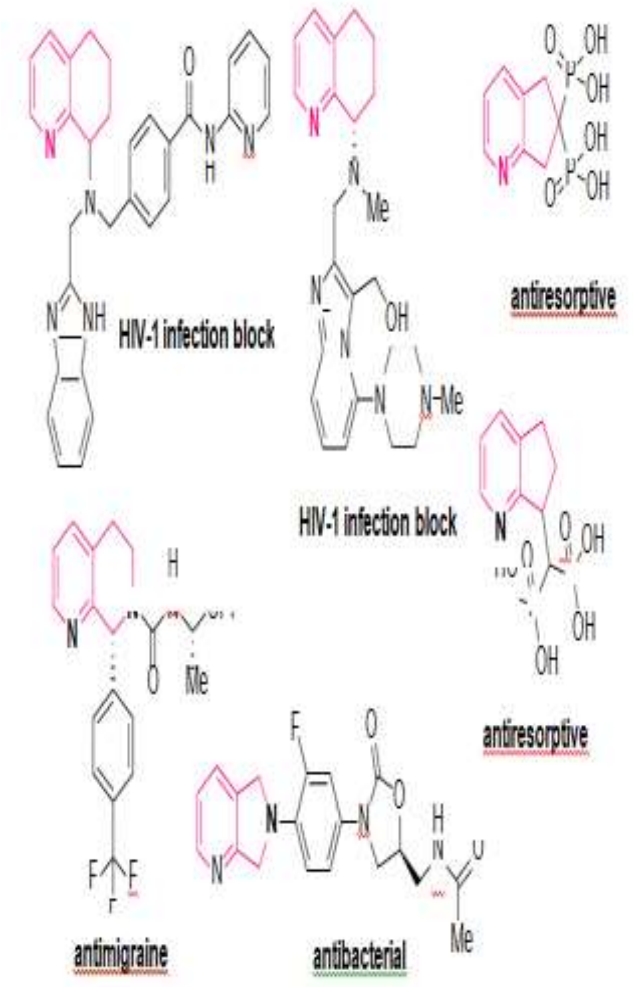


Figure 1. Examples of biologically active compounds containing a PASC moiety

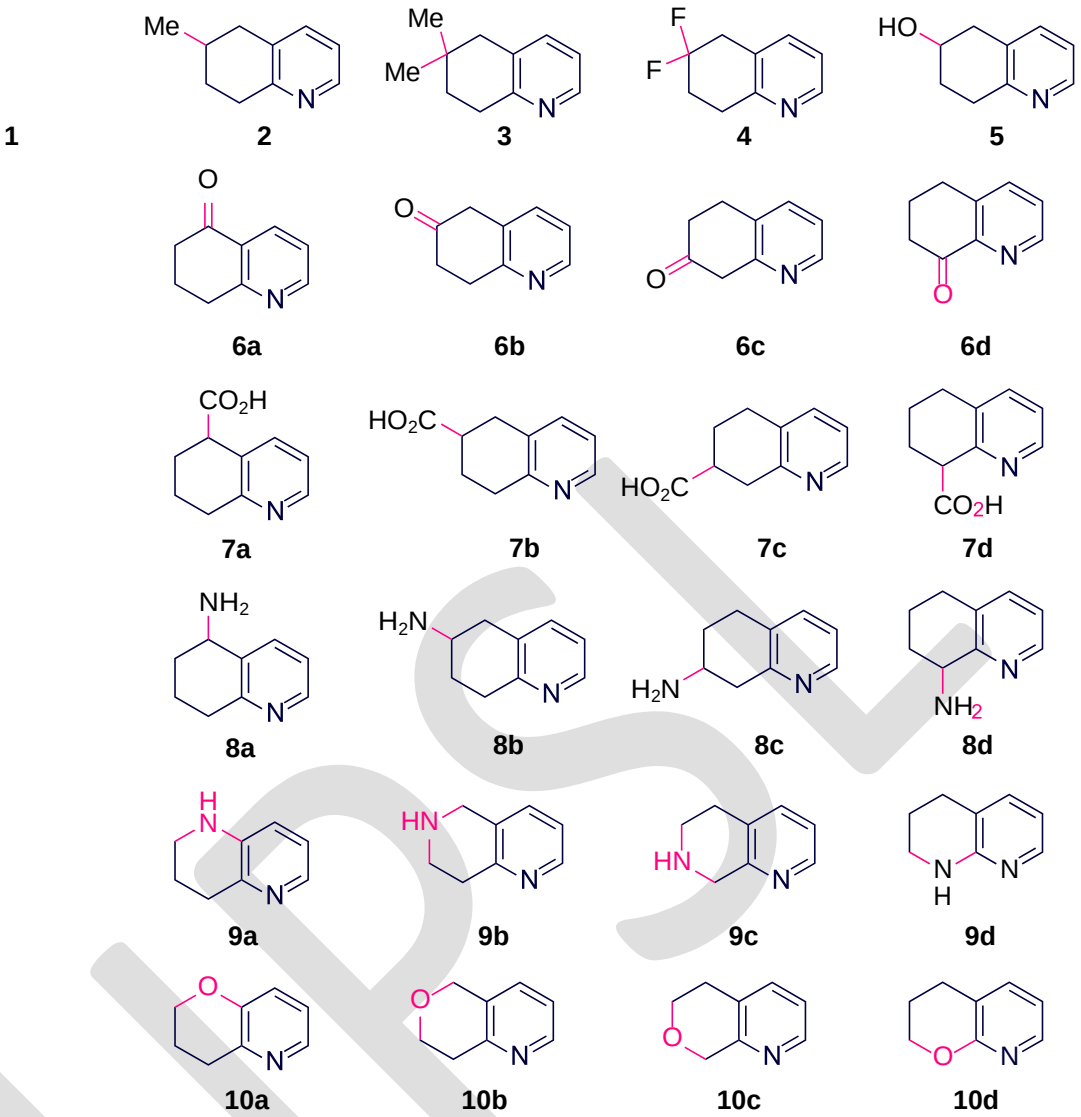


Figure 2. A representative set of PASC building blocks

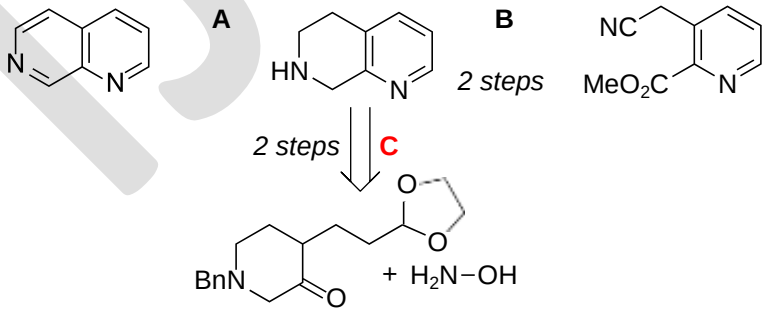


Figure 3. The retrosynthetic analysis of **9c**

pyridines fused with saturated rings bearing CHMe-, CMe_2-, CF_2-, CHOH-moieties. Propargylamine (**11**) was condensed with ketones **12**–**16** in the presence of anhydrous $CuCl_2$ to obtain the desired products (including compounds **3** and **4** previously unknown). Although alcohol **5** was reported previously, the yield was neither good (e.g., 28%) [15] nor even reported. Our approach works much better – a one-step scalable procedure provides 58%

yield of **5**. We also attempted to oxidize alcohol **5** to obtain known [16, 17] ketone **6b** *via* the Dess-Martin oxidation. However, the yields were low (10–15%), so this way needed further optimiza- tions. Notably, ketone **6b** can be involved in self- condensation reactions, and therefore, it should be stored in the freezer.

Ketone **6c** still remains a challenge for syn- thetic chemists (our attempts were unsuccessful

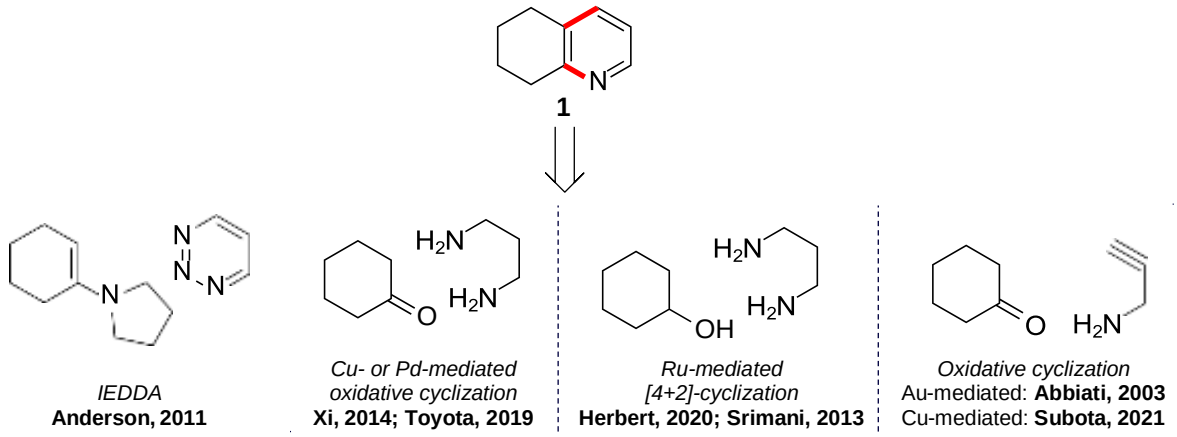
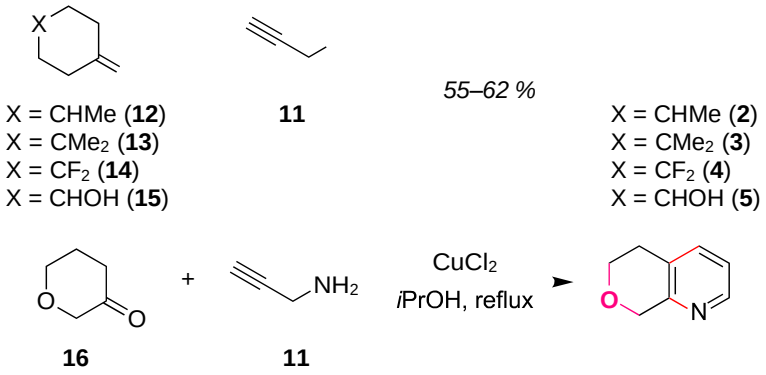


Figure 4. The known approaches for the synthesis of the pyridine ring of PASCs



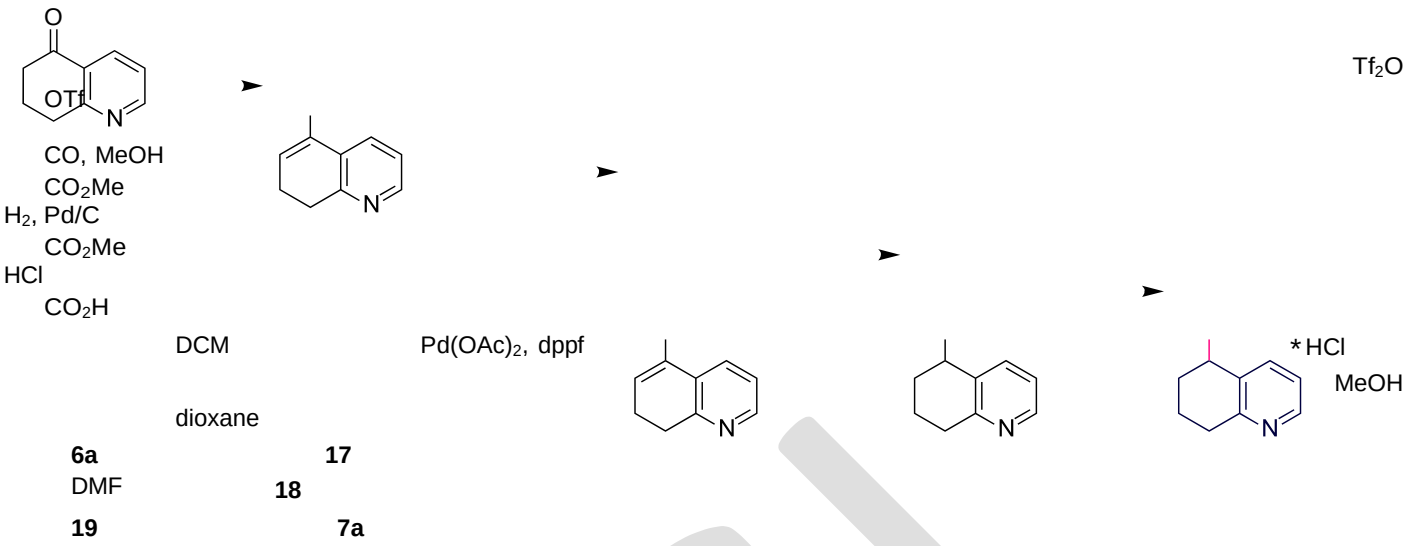
Scheme 1. The synthesis of pyridines **2-5** and **10c**

as well), while more than 20 different reactions for the synthesis of ketone **6d** were reported, even in a kilogram scale [18].

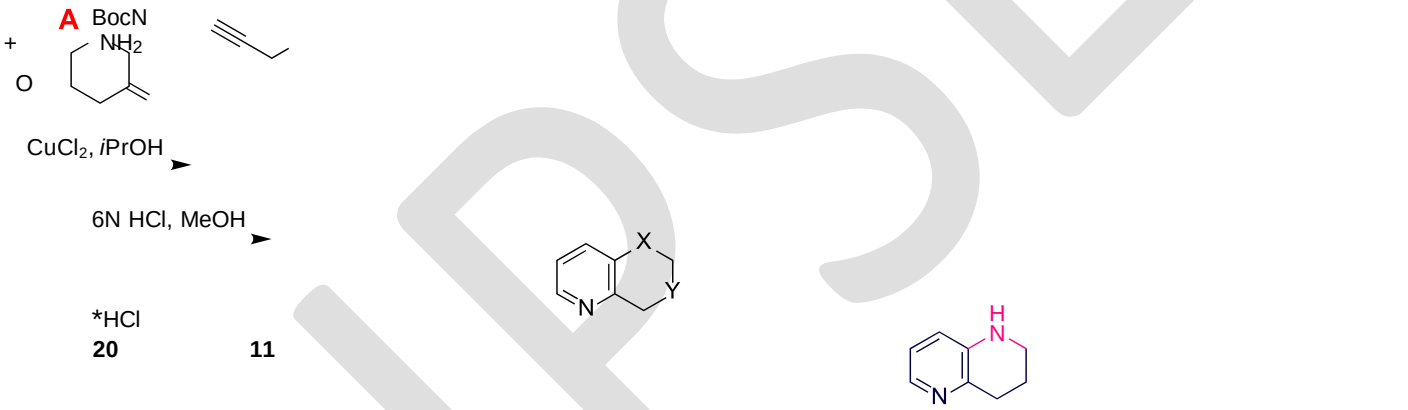
Previously, we obtained ethyl esters of car- boxylic acids **7a** and **7c** as an inseparable mix- ture. The synthesis of **7c** in 75% *via* the Wolff- Kishner reduction was reported in 1974 [19]. Carboxylic acids **7b** and **7d** [20] were also repor- ted. The synthesis of the previously unknown **7a** was carried out starting from ketone **6a**. At the first stage, the ketone was transformed to the enol triflate **17**, and the latter was further carbo- nylated with CO to form ester **18**. Compound **18** was successfully reduced to saturated acid **19**, the acidic hydrolysis of the latter led to the tar- get acid **7a** (**Scheme 2**).

Ketone **20** reacts with propargylamine yield- ing pyridine **Boc-9a**, as it was described in our previous work, and isomer **Boc-9c** were detect- ed (**Scheme 3**, A). Therefore, the condensation of ketone **20** with propargylamine is not a suit- able method for the synthesis of **9c**. Multistep preparations of **9c** were reported earlier [8, 9]. Alternatively, 1,7-naphtyridine partial reduction gave mixtures of isomers [7]. Hereby, we proposed an alternative 4-step way starting from nitrile **21** (**Scheme 3**, B).

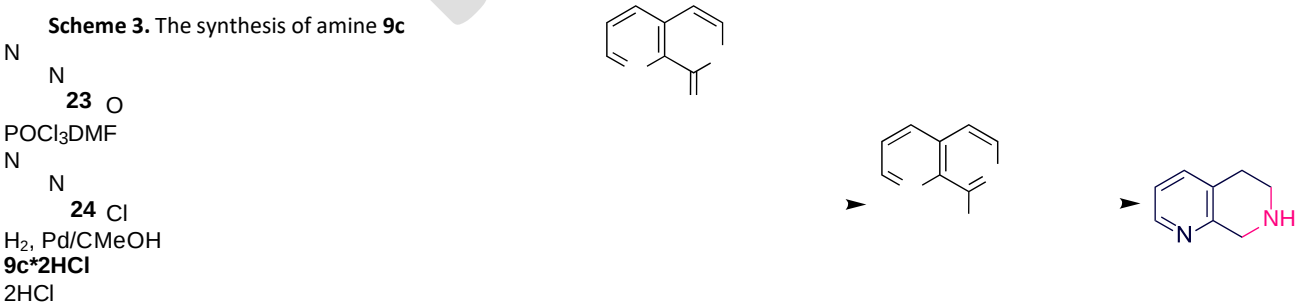
The scalable synthesis of amine **9d** from pyridine **25** was performed through an elegant route based on the construction of the piperi- dine ring on the b-bond of pyridine in 2-fluoro- 4-chloropyridine (**25**) (**Scheme 4**). In contrast to the procedures previously reported [21–23], the proposed reaction sequence leads to a single iso- mer, consists of common organic procedures and uses available starting materials.

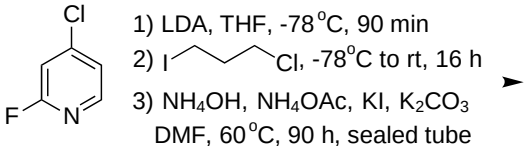


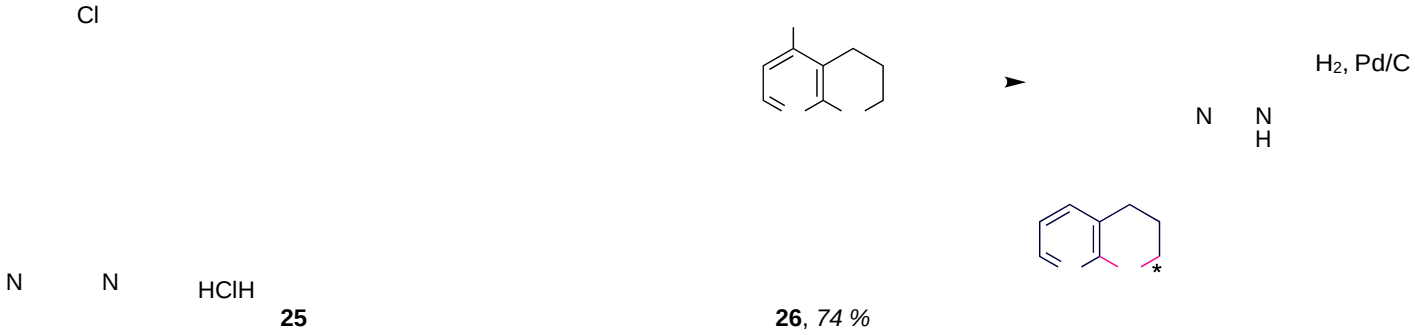
Scheme 2. The synthesis of carboxylic acid **7a**



Scheme 3. The synthesis of amine **9c**







Scheme 4. The synthesis of amine **9d**
9d*HCl, *85 %*

Conclusions

A representative set of pyridines annelated with 6-membered functionalized saturated rings has been synthesized. The scope of $CuCl_2$-cata- lyzed condensation of propargylamine with ke- tones has been extended. Other synthetic meth- ods have been proposed for pyridines that cannot be obtained using this procedure. A set of novel building blocks related to medical chemistry has been created for drug development.

Experimental part

All solvents were purified according to the standard procedures. Absolute ethanol and iso- propanol were used. All starting materials were obtained from Enamine Ltd. Melting points were measured on an automated melting point sys- tem. ^1H and ^{13}C NMR spectra were measured on a Bruker Avance 500 spectrometer (at 500 MHzfor ^1H and 126 MHz for ^{13}C nuclei) and a VarianUnity Plus 400 spectrometer (at 400 MHz for $^1H$and 101 MHz for ^{13}C nuclei). Tetramethylsilane (^1H, ^{13}C) was used as an internal standard. Mass spectra were recorded on an Agilent 5890 Series II5972 GCMS instrument (atmospheric pressureelectrospray ionization (ESI)).

The general procedure for the synthesis of pyridines 2–5 and 10c

Pyridines **2–5** and **10c** were obtained accord-ing to the procedure previously developed [9].

6-Methyl-5,6,7,8-tetrahydroquinoline (2)

A brownish oil. Yield – 28 g (62%). Anal. Calcdfor $C_{10}H_{13}N$, %: C 81.58; H 8.90; N 9.51. Found, %: C 81.38; H 9.01; N 9.59. ^1H NMR (400 MHz, Chloroform-*d*), δ, ppm: 1.09 (3H, d, J = 6.5 Hz); 1.43–1.62 (1H, m); 1.86–2.02 (2H, m); 2.43 (1H, dd, J = 16.6, 10.5 Hz); 2.81 (1H, dd, J = 16.5, 5.0 Hz); 2.90–3.04 (2H, m); 7.02 (1H, dd, J = 7.7, 4.8 Hz); 7.34 (1H, d, J = 7.7 Hz); 8.35 (1H, d, J = 4.8 Hz). LC-MS (ESI, positive mode), *m/z*: 148$[M+H]^+$.

6,6-Dimethyl-5,6,7,8-tetrahydroquinoli- ne (3)

A yellowish oil. Yield – 38 g (57%). Anal. Calcdfor $C_{11}H_{15}N$, %: C 81.94; H 9.38; N 8.69. Found, %: C 81.88; H 9.47; N 8.62. ^1H NMR (400 MHz, Chloroform-*d*), δ, ppm: 1.02 (6H, s); 1.69 (2H, t, J = 6.9 Hz); 2.56 (2H, s); 2.96 (2H, t, J = 6.9 Hz); 7.03 (1H, dd, J = 7.6, 4.8 Hz); 7.33 (1H, d, J = 7.6 Hz); 8.38 (1H, d, J = 4.8 Hz). LC-MS (ESI, positivemode), *m/z*: 162 $[M+H]^+$.

6,6-Difluoro-5,6,7,8-tetrahydroquinoli- ne (4)

A yellowish oil. Yield – 42 g (55%). Anal. Calcd for $C_9H_9F_2N$, %: C 63.90; H 5.36; F 22.46; N8.28. Found, %: C 63.82; H 5.45; F 22.54; N 8.17.

^1H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.26–2.41(1H, m); 3.04 (3H, t, J = 7.1 Hz); 3.29–3.43 (3H, m); 7.22 (1H, dd, J = 7.8, 4.7 Hz); 7.55 (1H, d, J = 7.8 Hz); 8.39 (1H, d, J = 4.7 Hz). ^{19}F NMR (376 MHz, DMSO-d_6) δ, ppm: -95.84. LC-MS (ESI, positive mode), *m/z*: 170 $[M+H]^+$.

5,6,7,8-Tetrahydroquinolin-6-ol (5)

A brown solid. Yield – 35 g (58%). M. p. 114°C. ^{1}H NMR corresponds to the reported previously [15]. LC-MS (ESI, positive mode), *m/z*: 150 $[M+H]^+$.

5,8-Dihydro-6H-pyrano[3,4-b]pyridine (10c)

A yellowish oil. Yield – 18 g (34%). Anal. Calcd for C_8H_9NO, %: C 71.09; H 6.71; N 10.36. Found, %: C 70.97; H 6.83; N 10.29. ^{1}H NMR (400 MHz, Chloroform-*d*), δ, ppm: 2.90 (2H, t, *J* = 5.7 Hz); 4.00 (2H, t, *J* = 5.7 Hz); 4.82 (2H, s); 7.12 (1H, dd, *J* = 7.7, 4.9 Hz); 7.45 (1H, d, *J* = 7.7 Hz); 8.41 (1H, d, *J* = 4.8 Hz). LC-MS (ESI, positive mode), *m/z*: 136 $[M+H]^+$.

The procedure for the synthesis of 5,6,7,8- tetrahydroquinoline-5-carboxylic acid hydrochloride (7a*HCl) To 6 L round-bottomed flask dried in the oven,

7,8-dihydroquinolin-5(6*H*)-one (**6a**) (147.2 g, 1 mol, 1.0 equiv) was added. The flask was sealed and purged with argon before the addition of CH_2Cl_2 (2.8 L) and Et_3N (208 mL, 1.5 mol, 1.5 equiv). The reaction mixture was cooled to 0°C, and trifluoromethanesulfonic anhydride (242 mL, 6.2 mmol, 1.5 equiv) was added dropwise under argon atmosphere before heating to 40°C and kept at this temperature while stirring for 24 h. Upon completion of the reaction, the solution was washed with water (2×20 mL), and the organic substances were passed through a hydrophobic frit, and concentrated under reduced pressure to give compound **17** quantitatively (~279 g) as a brown oil (85–90% purity), which was used in the next step without purification.

A solution of **17** (279 g, 1 mol) in DMF (2.2 L) was treated with methanol (1.1 L) and N,N-diisopropylethylamine (526 mL, 3 mol), and bubbled with argon for 30 min. The resulting mixture was treated with DPPF (4.5 g, 8 mmol) and palladium (II) acetate (1.8 g, 8 mmol). The resulting solution was bubbled with carbon monoxide for 30 min, and then stirred under a carbon monoxide balloon at 60°C for 6 h. After that, the mixture was cooled to room temperature and diluted with ethyl acetate. The resulting mixture was washed with 1 M aqueous HCl, twice with water, once with the saturated aqueous sodium carbonate, dried over sodium sulfate and then concentrated under vacuum to yield 147.6 g of a residue (78%, ~90% purity) as a yellowish powder. The product was used in the next step without purification.

A solution of **18** (147.6 g, 0.78 mol) in MeOH (2 L) was heated at 50°C under atmospheric pressure and bubbled with H_2 for 2 h in the presence of 10% Pd on charcoal (10 g). After completing the reaction, Pd/C was filtered off, and the residue was evaporated under reduced pressure. The yellowish powder (~149 g, ~90% purity) obtained was used in the next step without purification.

The product **19** (95.6 g, 0.5 mol) was dissolved in the saturated solution of HCl in dioxane (1 L) and boiled until the end of the precipitate formation. Then the solid was filtered off and dried on air. The final product **7a** was obtained as a white powder in 84% yield as hydrochloride (89.8 g).

A white powder. M. p. 164°C. Anal. Calcd for $C_{10}H_{12}ClNO_2$, %: C 62.67; H 4.94; Cl 11.10; N 14.62. Found, %: C 62.60; H 5.03; Cl 10.97; N 14.55. ^{1}H NMR (DMSO-d_6, 500 MHz), δ, ppm: 1.55–1.86(1H, m); 1.86–2.07 (2H, m); 2.07–2.35 (1H, m); 2.92–3.27 (2H, m); 4.06 (1H, t, *J* = 5.0 Hz); 7.81 (1H, dd, *J* = 7.8, 5.6 Hz); 8.37 (1H, d, *J* = 7.8 Hz); 8.69 (1H, d, *J* = 5.6 Hz). LC-MS (ESI, positive mode), *m/z*: 178 $[M-Cl]^+$.

The procedure for the synthesis of 1,7- naphthyridin-8(7*H*)-one (23)

3-Methylpicolinonitrile (**21**) (23.62 g, 0.2 mol) and the Bredereck's reagent (69.6 g, 0.2 mmol) were dissolved in DMF (250 mL). The reaction mixture was heated at 75°C under argon for 72 h. After that, the solvent was removed *in vacuo*. Trituration with MTBE gave a brown oil **21** (~35 g, ~0.2 mol, a quantitative yield, ~85% purity). Further all 35 g of the product was used without additional purification.

The oil from the previous step was dissolved in the saturated solution of HCl in dioxane (200

mL). The reaction mixture was warmed at45–50°C for 24 h. The reaction solution was fil-tered, and the filtrate was collected and dried. The light brown solid **23** (24.2 g, 83% yield) ob- tained was directly used in the next reaction.

A brown solid. M. p. 227°C. Anal. Calcd for $C_8H_6N_2O$, %: C 65.75; H 4.14; N 19.17. Found, %: C 65.64; H 4.19; N 19.28. ^{1}H NMR (DMSO-d_6, 400 MHz), δ, ppm: 6.53 (1H, d, J = 7.1 Hz); 7.25 (1H, d, J = 7.0 Hz); 7.67 (1H, dd, J = 8.1, 4.4 Hz); 8.10 (1H, dd, J = 8.1, 1.7 Hz); 8.75 (1H, dd, J = 4.3, 1.7 Hz); 11.50 (1H, s). LC-MS (ESI, positive mode), m/z: 147 $[M+H]^+$.

The procedure for the synthesis of 8-chlo-ro-1,7-naphthyridine (24)

1,7-Naphthyridin-8(7*H*)-one (**23**) (19.1 g, 0.15 mol) was dissolved in 200 mL of toluene. $POCl_3$ (31 g, 0.2 mol) and DIPEA (72 g, 4 mol) were added to the reaction mixture, and then it was refluxed for 6 h. After cooling down, the mixture was diluted with EtOAc (15 mL) and washed with ice-cold water, the saturated $NaHCO_3$, brine. The organic layer was dried over Na_2SO_4. The sol-vent was removed under reduced pressure, and the residue was purified by washing with *i*PrOH to give 20.2 g of a yellow solid in 82% yield.

A yellow solid. M. p. 89°C. Anal. Calcd for $C_8H_5ClN_2$, %: C 58.38; H 3.06; Cl 21.54; N 17.02. Found, %: C 58.27; H 3.11; Cl 21.47; N 16.95. ^{1}H NMR (Chloroform-*d*, 400 MHz), δ, ppm: 7.65(1H, d, J = 5.6 Hz); 7.71 (1H, dd, J = 8.4, 4.2 Hz); 8.23 (1H, dd, J = 8.4, 1.7 Hz); 8.41 (1H, d, J = 5.6 Hz); 9.16 (1H, dd, J = 4.2, 1.7 Hz). LC-MS (ESI, positive mode), m/z: 165 $[M+H]^+$.

The procedure for the synthesis of 5,6,7,8-Tetrahydro-1,7-naphthyridine dihydrochlo-ride (9c*2HCl)

A solution of 8-chloro-1,7-naphthyridine (**24**) (16.5 g, 0.1 mol) in MeOH (300 mL) was placed into the autoclave and heated at 50°C under 10 atm pressure of H_2 for 6 h in the presence of 10% Pd on charcoal (5 g). After completing the reac- tion, Pd/C was filtered off, and the residue was evaporated under reduced pressure. Then the crude substrate was dissolved in the saturated solution of HCl in dioxane. The yellowish pow- der (~12.3 g, 87% yield) was obtained as a dihy- drochloride after simple filtration.

A yellow solid. M. p. 210°C (decomp.). Anal. Calcd for $C_8H_{12}Cl_2N_2$, %: C 46.40; H 5.84; Cl 34.23; N 13.53. Found, %: C 46.34; H 5.93; Cl 34.18; N 13.44. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.12(1H, t, J = 6.2 Hz); 3.40 (1H, q, J = 6.4 Hz); 4.38(1H, t, J = 4.5 Hz); 7.55 (1H, dd, J = 7.8, 5.1 Hz); 8.58 (1H, d, J = 5.1 Hz); 10.02 (1H, s). LC-MS (ESI, positive mode), m/z: 135 $[M-HCl-Cl]^+$.

References

5-Chloro-1,2,3,4-tetrahydro-1,8-naphthy- ridine (26)

The synthesis was performed from 4-chloro- 2-fluoropyridine (**25**) according to the procedure reported [24].

A yellow solid. Yield – 21 g (74%). M. p. 97°C. Anal. Calcd for $C_8H_9ClN_2$, %: C 56.98; H 5.38; Cl 21.02; N 16.61. Found, %: C 57.05; H 5.33; Cl 20.94; N 16.66. ^{1}H NMR (400 MHz, Chloroform-*d*), δ, ppm: 1.94 (3H, pent, J = 6.2 Hz); 2.78 (3H, t, J = 6.5 Hz); 3.32–3.43 (3H, m); 6.56 (1H, d, J = 5.5 Hz); 7.74 (1H, d, J = 5.5 Hz). LC-MS (ESI, positive mode), m/z: 169 $[M+H]^+$.

The procedure for the synthesis of 1,2,3,4-tetrahydro-1,8-naphthyridine (9d*HCl)

The reduction of 5-chloro-1,2,3,4-tetrahydro- 1,8-naphthyridine (**26**) was performed by the se-minal procedure used for preparation of amine **9c**. Amine **9d** was obtained in 85% yield as a yellow powder in a hydrochloride form (28 g).

A yellow solid. M. p. 71°C. Anal. Calcd for $C_8H_9ClN_2$, %: C 56.98; H 5.38; Cl 21.02; N 16.61. Found, %: C 57.08; H 5.24; Cl 20.93; N 16.66.

^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 1.94–1.87 (2H, pent, *J* = 6.2 Hz); 2.71 (2H, t, *J* = 6.3 Hz); 3.29–3.64 (2H, m); 6.47 (1H, dd, *J* = 7.1, 5.0 Hz); 7.12 (1H, d, *J* = 7.1 Hz); 7.84 (1H, d, *J* = 4.4 Hz). LC-MS (ESI, positive mode), *m/z*:135 $[M+H]^+$.

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