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Preparation of Partially Saturated Furo[3,2-*c*]- and Furo[2,3-*c*]annulated *N*-Heterocycles

Abstract

Practical multi-gram routes for obtaining three med-chem-relevant partially saturated furo[3,2-*c*]- and furo[2,3-*c*]annulated *N*-heterocycles that are significant for medical chemistry have been proposed. The key β-(furyl)ethylamine intermediates were accessed *via* the DPPA-mediated Curtius rearrangement, replacing the traditional Henry/LAH sequence and eliminating stoichiometric metal-hydride reductions. The tetrahydrofuropyridine cores were then assembled through the Pictet-Spengler cyclization, while the dihydrofuropyridinone previously unavailable was obtained *via* the Dieckmann/Feist-Benary annulation. All sequences proceed in ≤6 steps from commercial starting materials.

Keywords: furopyridine; Pictet-Spengler reaction; Curtius rearrangement; Feist-Benary reaction; tetrahydropyridine; heterocyclic building blocks

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Отримання частково насичених фуро[3,2-*c*]- та фуро[2,3-*c*]анельованих *N*-гетероциклів

Анотація

Запропоновано практичні мультиграмові методи одержання трьох значущих для медичної хімії частково насичених *N*-гетероциклів, анельованих за типом фуро[3,2-*c*]- та фуро[2,3-*c*]. Ключові проміжні β-(фурил)етиламіни було отримано за допомогою перегрупування Курціуса, під дією дифенілфосфорилазиду (DPPA), що дозволило замінити традиційну послідовність «реакція Анрі/відновлення алюмогідридом літію ($LiAlH_4$)» та уникнути використання стехіометричних кількостей металогідридних відновників. Основні тетрагідрофуропіридинові похідні було синтезовано шляхом циклізації Пікте-Шпенглера, тоді як раніше недоступний дигідрофуропіридинон було одержано за допомогою анелювання Дікмана/Фейста-Бенарі. Усі синтетичні послідовності реалізуються щонайбільше в шість стадій з використанням комерційно доступних реагентів.

Ключові слова: фуропіридин; реакція Пікте-Шпенглера; перегрупування Курціуса; реакція Файста-Бенарі; тетрагідропіридин; гетероциклічні будівельні блоки

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Introduction

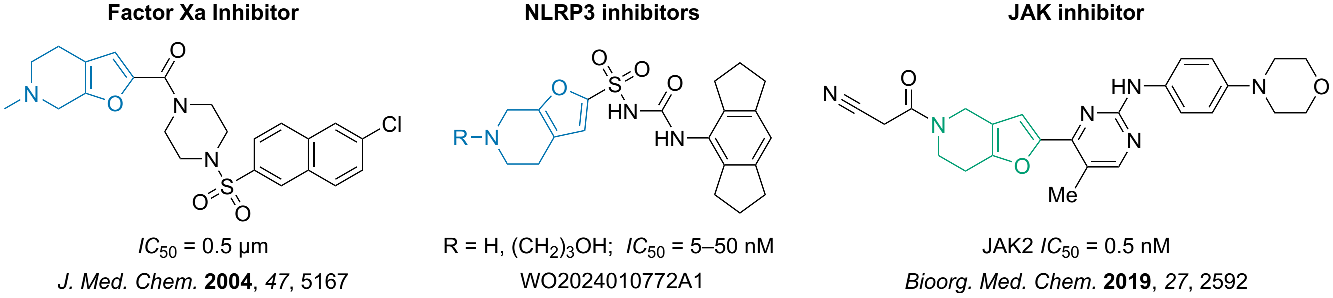
Partially saturated furo[3,2-*c*]- and furo[2,3-*c*]pyridines are involved in various medicinal chemistry programs. The 4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine core has been a key component in potent Janus kinase (JAK) inhibitors with the proven *in vivo* anti-inflammatory activity [1] and in agents that promote the cholesterol efflux via the reverse cholesterol transport [2]. Structurally related partially saturated [*c*]-fused bicyclics, including a tetrahydrofuropyridine-based Factor Xa inhibitor showing the submicromolar anti-fXa activity, have been investigated as binding components in this context [3], whereas the furo[2,3-*c*]pyridine motif and its variants appear in recent patent claims aimed at the NLRP3 inflammasome inhibition [4] (**Figure 1**). The fully aromatic counterparts of these ring systems have also been proven to be effective as pharmacophores for the PDE4 inhibition [5] and modulation of the α7 nicotinic acetylcholine receptor [6].

The established route to 4,5,6,7-tetrahydrofuropyridines depends on the Pictet-Spengler cyclization of a β-(2-furyl)ethylamine with formaldehyde [2], a reaction which success depends on easy access to the amine precursors. The main approach, the Henry reaction of furfural with nitromethane followed by the lithium aluminum hydride reduction, has been used in the intramolecular Diels–Alder [7], *N*-acyliminium ion cyclization [8], and alkaloid-targeted studies [8b], but it only gives yields of 30–54% [7, 8b] and requires stoichiometric lithium aluminum hydride (LAH), which limits scalability. For the [2,3-*c*] isomeric series and the dihydrofuropyridinone ring system, the situation is further complicated by the near-absence of reported routes. As part of a broader investigation into the fused-furan heterocyclic chemistry, including our recently reported tandem intramolecular Diels-Alder/retro-Diels-Alder cascade approach to 5,5-fused dihydrofuran heterobicycles [9], we became interested in developing practical methods to access the complementary 5,6-fused ring systems. Herein, we present routes to 4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine, 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine, and the previously unavailable 6,7-dihydrofuro[2,3-*c*]pyridin-4(5*H*)-one that employs hydrocinnamic acid (Meldrum's acid pathway) and cinnamate (Wittig pathway). For 6,7-dihydrofuro[2,3-*c*]pyridin-4(5*H*)-one, a unique approach using a custom aminoketone precursor has been developed. The resulting protocols produce the target compounds in multi-gram quantities, making them readily accessible as building blocks for further *N*-functionalization and furan ring derivatization.

Results and discussion

The synthetic approach to 4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine (**4**) and 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine (**11**) is built around the Pictet-Spengler cyclization of an *N*-Boc-protected β-(2-furyl)ethylamine with paraformaldehyde, with the amine precursor accessed in each case through the modified Curtius rearrangement. For 6,7-dihydrofuro[2,3-*c*]pyridin-4(5*H*)-one (**18**), the order of the ring assembly is reversed: the piperidine-2,4-dione core is constructed first *via* the Dieckmann cyclization, and the furan ring is introduced subsequently through the Feist–Benary condensation.

The route to **4** begins with 3-(furan-2-yl)propanoic acid (**1**), which is available from furfural *via* the Meldrum's acid condensation (**Scheme 1**). The amine-forming step uses the Shioiri's modification of the Curtius rearrangement: treating **1** with diphenylphosphoryl azide (DPPA) in *tert*-butanol, with triethylamine, at 80 °C directly gives *N*-Boc amine **2** in the yield of 47%. This process avoids the need for the separate acid chloride formation, acyl azide isolation, or, most importantly, the stoichiometric LAH reduction typical of the traditional Henry/nitroalkene pathway. The Pictet-Spengler cyclization of **2** with paraformaldehyde under catalytic *p*-TsOH in refluxing toluene (Dean-Stark) provided *N*-Boc-tetrahydrofuropyridine **3**



Factor Xa Inhibitor

IC_{50} = 0.5 μm

J. Med. Chem. **2004**, *47*, 5167

NLRP3 inhibitors

R = H, (CH$_2$)$_3$OH; IC_{50} = 5–50 nM

WO2024010772A1

JAK inhibitor

JAK2 IC_{50} = 0.5 nM

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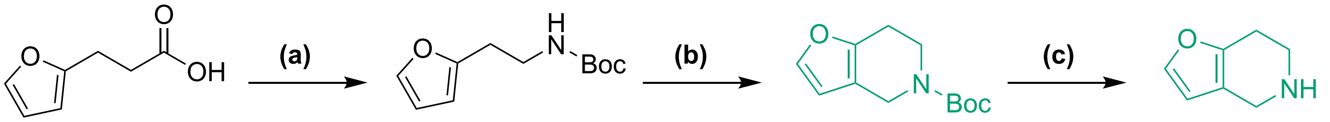
Figure 1. Furo[3,2-*c*]- and furo[2,3-*c*]pyridines as pharmacophore fragments in bioactive molecules



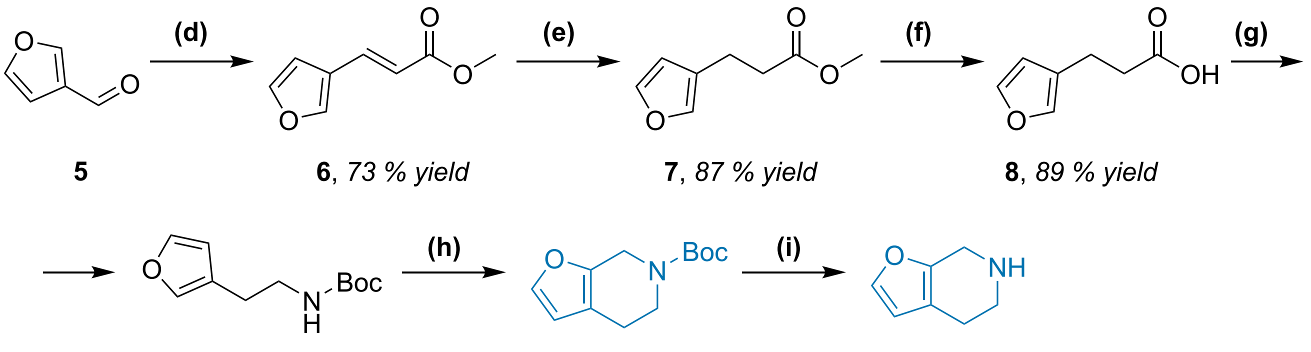
1 , *47 % yield* **2** **3**, *41 % yield* **4**, *97 % yield*

Experimental conditions: (a) DPPA, Et$_3$N, *t*BuOH, 80 °C, 16 h; **(b)** (CH$_2$O)$_n$, *p*TsOH·H$_2$O, PhMe, reflux, Dean–Stark, 16 h; **(c)** 4N HCl/dioxane, rt, 12 h

Scheme 1. The preparation of 4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine (**4**) *via* the Curtius/Pictet-Spengler route

in the yield of 41%. The moderate yield can be attributed to the well-documented sensitivity of the furan ring to Bronsted acids, further compounded by the vacant C-5 position of the furan ring in **2**, the most nucleophilic site of the heterocycle, which, under acidic conditions and in the presence of excess formaldehyde, is expected to undergo a competing hydroxymethylation, *bis*-aminomethylation, and acid-promoted oligomerization, accounting for the oligomeric/resinous polar by-products observed in the crude mixture; nonetheless, the reaction is operationally simple and proceeds smoothly on a multi-gram scale. The standard Boc cleavage (HCl/dioxane, rt) then gave **4** in the near-quantitative yield (97%).

Access to the isomeric [2,3-*c*] system required the synthesis of 3-(furan-3-yl)propanoic acid (**8**), which, unlike its furan-2-yl analog, is not easily obtained through the Meldrum's acid chemistry due to the lower electrophilicity of furan-3-carbaldehyde in Knoevenagel-type condensations. Instead, a four-step sequence was developed (**Scheme 2**). The Horner-Wadsworth-Emmons olefination of 3-furaldehyde (**5**) with methyl 2-(diethoxyphosphoryl)acetate provided (*E*)-cinnamate ester **6** in the yield of 73%. The subsequent reduction of the double bond required a careful reagent selection: the catalytic hydrogenation was avoided owing to the risk of the furan ring reduction, and instead the CuCl/NaBH$_4$ system in the aqueous methanol at 0 °C was employed, delivering the saturated ester **7** in the yield of 87% with complete chemoselectivity. The saponification (LiOH, THF/H$_2$O) gave acid **8** in the yield of 89%, which was then subjected to the same DPPA-mediated Curtius protocol to give **9** (58%). The Pictet–Spengler cyclization of **9** to the *N*-Boc-protected product **10** proceeded in the yield of 30% – appreciably lower than for the [3,2-*c*] isomer (**3**, 41%). This difference is consistent with the reduced nucleophilic character of C-2 in the furan-3-yl tether relative to C-3 in the furan-2-yl series where the ring oxygen provides greater activation of the carbon undergoing electrophilic substitution [10]; additionally, the presence of two vacant α-positions (C-2 and C-5) in the furan ring of **9** – both available for competing the hydroxymethylation and oligomerization under the Bronsted-acid conditions – diverts a larger fraction of the substrate into higher-molecular-weight decomposition products relative to the furan-2-yl series. The Boc removal then gave **11** (96%). Notably, the HWE/CuCl-NaBH$_4$/saponification/Curtius sequence was equally applicable when furan-2-carbaldehyde was used as the starting material, providing an independent and fully



5 **6**, *73 % yield* **7**, *87 % yield* **8**, *89 % yield*

9, *58 % yield* **10**, *30 % yield* **11**, *96 % yield*

Experimental conditions: (**d**) (EtO)$_2$P(O)CH$_2$CO$_2$Me, NaH, THF, 0 °C → rt, 16 h; (**e**) CuCl, NaBH$_4$, MeOH/H$_2$O, 0 °C → rt, 16 h; (**f**) LiOH, THF/H$_2$O, rt, 16 h; (**g**) DPPA, Et$_3$N, *t*BuOH, 80 °C, 16 h; (**h**) (CH$_2$O)$_n$, *p*TsOH·H$_2$O, PhMe, reflux, Dean-Stark, 16 h; (**i**) 4 M HCl/dioxane, rt, 12 h

Scheme 2. The synthesis of 4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine (**11**) *via* the HWE/Curtius/Pictet-Spengler route chromatography-stage-compatible route to **4** and confirming the generality of this pathway across both regioisomeric aldehyde series.

The construction of 6,7-dihydrofuro[2,3-*c*]pyridin-4(5*H*)-one (**18**) demanded a fundamentally different approach (**Scheme 3**). The reaction sequence proceeds through the linear assembly of an *N*-functionalized diester, its Dieckmann cyclization to a 1,3-diketone, and the late-stage furan annulation. The *N*-alkylation of ethyl *N*-benzylglycinate (**12**) with chloroacetone provided **13** in the yield of 84%, installing the two-carbon ketone appendage required for the eventual Dieckmann ring closure. The chemoselective *N*-debenzylation (Pd/C, H_2, 1 atm) gave **14** (73%), which was protected as *N*-Boc derivative **15** (91%). The intramolecular Claisen condensation of **15** under the action of KO*t*Bu at 5 °C gave piperidine-2,4-dione **16** in the yield of 80%, generating the 1,3-dicarbonyl motif required for the subsequent furan ring formation. The exposure of **16** to chloroacetaldehyde under basic conditions (KOH, MeOH, 0 °C → rt) affected the Feist-Benary furan annulation, delivering *N*-Boc-furo[2,3-*c*]pyridinone **17** in the yield of 40%. The moderate yield is typical of Feist–Benary annulations involving chloroacetaldehyde, which is prone to the base-mediated self-condensation under the reaction conditions; nonetheless, the transformation proceeds cleanly on a preparative scale using a simple, commercially available C_2 electrophile. The standard Boc removal then provided **18**.

Across all three target compounds, the routes described operate on a scale of tens to hundreds of grams for the early-stage intermediates, delivering the final heterocycles in multi-gram quantities. The use of the DPPA-mediated Curtius rearrangement as the amine-forming step throughout **Schemes 1** and **2** eliminates the reliance on stoichiometric metal-hydride reductions and gives the *N*-Boc amines in a single operation from the respective carboxylic acids. These features combined with the modularity of the Feist-Benary approach to the dihydropyridinone ring system **18** provide a practical and operationally straightforward entry to a set of partially saturated furo-annulated *N*-heterocycles suitable for further derivatization.

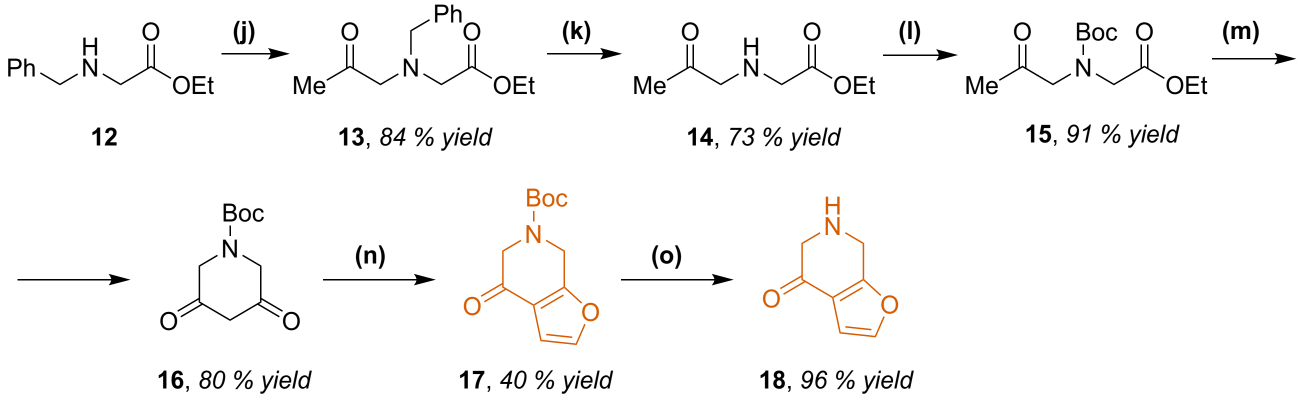
■ Conclusions

Three complementary partially saturated furopyridine scaffolds have been synthesized using concise, straightforward methods suitable for the multi-gram scale production. The main challenge tackled in this work – obtaining β-(furyl)ethylamine precursors reliably – was addressed through the DPPA-mediated Curtius rearrangement producing *N*-Boc-amines in a single step and overcoming the poor atom economy and scalability issues associated with the traditional Henry/LAH pathway. The Feist-Benary annulation enabled the synthesis of a dihydrofuropyridinone previously unreported, illustrating the orthogonal disconnection strategy that complements Pictet-Spengler approaches. These protocols provide essential building blocks – pharmacophore property-determining fragments of various bioactive heterocycles – in forms ready for the direct *N*-functionalization and the subsequent ring modifications.

■ Experimental part

General Information

The solvents were purified according to the standard procedures. All starting materials were



Experimental conditions: (**j**) $ClCH_2COCH_3$, $NaHCO_3$, THF/H_2O, 60 °C, 18 h; (**k**) H_2 (1 atm), 10 % Pd/C, MeOH, rt; (**l**) Boc_2O, Et_3N, THF, rt, 14 h; (**m**) KO*t*Bu, THF, 5 °C → rt, 12 h; (**n**) $ClCH_2CHO$ (aq.), KOH, MeOH, 0 °C → rt; (**o**) 4 M HCl/dioxane, rt, 12 h

Scheme 3. The synthesis of 6,7-dihydrofuro[2,3-*c*]pyridin-4(5*H*)-one (**18**) *via* the Dieckmann/Feist-Benary route obtained from Enamine Ltd. Melting points were measured on an automated melting point system. ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 MHz for protons and 126 MHz for Carbon-13) and a Varian Unity Plus 400 spectrometer (at 400 MHz for protons, 101 MHz for Carbon-13). Tetramethyl silane (^{1}H, ^{13}C) was used as a standard. HPLC analyses were done on an Agilent 1200 instrument. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)). The column chromatography was performed using silica gel (200–300 mesh). High-resolution mass spectrometric analyses (HRMS) were conducted using an Agilent instrument, specifically a hybrid system comprising the 6200 Series Time-of-Flight (TOF) and the 6500 Series Quadrupole Time-of-Flight (Q-TOF). This system was operated with the software version B.08.00 (B8058.0). Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine, their results were found to be in good agreement (±0.4%) with the calculated values.

tert-Butyl (2-(furan-2-yl)ethyl)carbamate (2)

Diphenylphosphoryl azide (245.5 g, 0.89 mol) was added to the solution of 3-(furan-2-yl)propanoic acid (**1**) (125.0 g, 0.89 mol) and triethylamine (108.3 g, 1.07 mol) in *tert*-butanol (2 L). The mixture was stirred at 80 °C for 16 h, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by the flash column chromatography (SiO_2; hexane/EtOAc, 80:20 → 50:50) to give **2** as a colorless oil.

A yellow oil. Yield – 90 g (47%). Anal. Calcd for $C_{11}H_{17}NO_3$, %: C 62.54, H 8.11, N 6.63. Found, %: C 62.23, H 8.20, N 7.02. ^{1}H NMR (400 MHz, Chloroform-*d*), δ, ppm: 1.43 (9H, s), 2.82 (2H, t, J = 6.63 Hz), 3.20–3.50 (2H, m), 4.67 (1H, br. s), 6.06 (1H, d, J = 3.12 Hz), 6.19–6.39 (1H, m), 7.32 (1H, s). ^{13}C NMR (151 MHz, Chloroform-*d*), δ, ppm: 27.6, 28.5, 28.8, 39.3, 79.4, 85.3, 106.3, 110.4, 141.6, 146.9, 153.4, 155.9. LC-MS, *m/z*: 112 $[M\text{-}C_4H_8\text{-}CO_2+H]^+$.

tert-Butyl 4,5,6,7-tetrahydrofuro[3,2-*c*]pyridine-5-carboxylate (3)

Paraformaldehyde (6.99 g, 0.233 mol) and *p*-toluenesulfonic acid monohydrate (554 mg, 2.91 mmol) were added to the solution of **2** (24.6 g, 0.116 mol) in toluene (3500 mL). The reaction mixture was heated to reflux for 16 h with azeotropic removal of water (Dean-Stark trap). After cooling to room temperature, the mixture was diluted with EtOAc (1000 mL) and washed with a saturated aqueous $NaHCO_3$ (500 mL) and brine (500 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The purification by the flash column chromatography (hexane/EtOAc, 10:1) gave **3** as a yellow oil.

A yellow oil. Yield – 10.2 g (41%). Anal. Calcd for $C_{12}H_{17}NO_3$, %: C 64.55, H 7.67, N 6.27. Found, %: C 64.44, H 7.32, N 6.05. ^{1}H NMR (400 MHz, Chloroform-*d*), δ, ppm: 1.06–1.20 (1H, m), 1.33 (9H, s), 2.50 (2H, t, J = 6.90 Hz), 3.07–3.29 (2H, m), 4.46 (1H, s), 6.17 (1H, s), 7.15 (1H, s). ^{13}C NMR (151 MHz, Chloroform-*d*), δ, ppm: 25.6, 28.6, 40.8, 111.0, 122.0, 139.7, 143.3, 156.0. LC-MS, *m/z*: 265.2 $[M+CH_3CN+H]^+$.

4,5,6,7-Tetrahydrofuro[3,2-*c*]pyridine hydrochloride (4·HCl)

The solution of **3** (10.2 g, 45.6 mmol) in 4 M HCl in dioxane (100 mL) was stirred at room temperature for 12 h (LC-MS control). The solvent was removed under reduced pressure, and the residue was dried under high vacuum to give **4·HCl** as a beige solid.

A beige powder. M. p. 192–196 °C. Yield – 6.8 g (97%). Anal. Calcd for $C_7H_{10}ClNO$, %: C 52.68, H 6.32, N 8.78, Cl 22.21. Found, %: C 52.77, H 6.03, N 8.61, Cl 22.27. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 2.90 (3H, t, J = 6.12 Hz), 4.02 (3H, br. s), 6.44 (1H, d, J = 2.09 Hz), 7.61 (1H, d, J = 2.02 Hz), 9.60 (2H, br. s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 20.2, 40.5, 108.8, 111.3, 142.4, 146.2. LC-MS, *m/z*: 124.4 $[M+H]^+$ (compound as a hydrochloride salt).

Methyl (*E*)-3-(furan-3-yl)acrylate (6)

Methyl 2-(diethoxyphosphoryl)acetate (243 g, 1.16 mol) was added to the suspension of NaH (60% dispersion in mineral oil, 48.6 g, 1.16 mol) in THF (2500 mL) at 0 °C under the nitrogen atmosphere. After stirring for 1 h, 3-furaldehyde (**5**) (101 g, 1.05 mol) was added in one portion. The mixture was stirred at room temperature for 16 h, then poured into the saturated aqueous NH_4Cl (2 L). The organic layer was separated, washed with water (1 L), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give **6** as a yellow solid.

Yellow crystals. Yield –116 g (73%). M. p. 35–37 °C. Anal. Calcd for $C_8H_8O_3$, %: C 63.15, H 5.30. Found, %: C 62.85, H 5.21.^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.69 (3H, s), 6.36 (1H, d, J = 15.82 Hz), 6.96 (1H, d, J = 1.76 Hz), 7.58 (1H, d, J = 15.85 Hz), 7.74 (1H, s), 8.10 (1H, s). ^{13}C NMR spectrum is identical to that reported in literature [11].

Methyl 3-(furan-3-yl)propanoate (7)

Sodium borohydride (28.7 g, 0.759 mol) was added portionwise to the solution of **6** (116 g, 0.759 mol) and cuprous chloride (75.1 g, 0.759 mol) in methanol (1.6 L) and water (400 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was concentrated in vacuo, the residue was diluted with the saturated aqueous K_2CO_3 (500 mL), and extracted with EtOAc (2 L). The organic layer was washed with brine (500 mL), dried (Na_2SO_4), and concentrated in vacuo to give **7** as a yellow oil.

A yellow oil. Yield – 102 g (87%). Anal. Calcd for $C_8H_{10}O_3$, %: C 62.33, H 6.54. Found, %: C 61.93, H 6.81. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.54–2.60 (2H, m), 2.61–2.72 (2H, m), 3.59 (3H, s), 6.39 (1H, s), 7.44 (1H, s), 7.48–7.61 (1H, m). ^{13}C NMR spectrum is identical to that reported in literature [12].

3-(Furan-3-yl)propanoic acid (8)

The solution of **7** (102.0 g, 0.66 mol) and lithium hydroxide (55.7 g, 1.33 mol) in THF (1 L) and water (500 mL) was stirred at room temperature for 16 h (LC-MS control). The mixture was concentrated in vacuo. The residue was dissolved in water (400 mL), acidified to pH 2 with the 1 M aqueous HCl, and extracted with EtOAc (3 × 500 mL). The combined organic layers were washed with brine (500 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give **8** as a brown solid.

A brown crystalline powder. Yield – 83 g (89%). M. p. 67 °C. Anal. Calcd for $C_7H_8O_3$, %: C 60.00, H 5.75. Found, %: C 59.87, H 5.81. ^{1}H NMR (400 MHz, Chloroform-*d*), δ, ppm: 2.63 (2H, t, *J* = 7.41 Hz), 2.78 (2H, t, *J* = 7.40 Hz), 6.29 (1H, s), 7.26 (1H, d, *J* = 1.89 Hz), 7.36 (1H, s), 10.0 (1H, br. s, H-bond). ^{13}C NMR (126 MHz, Chloroform-*d*), δ, ppm: 20.0, 34.5, 110.7, 123.2, 139.1, 143.0, 179.0. LC-MS, *m*/*z*: 139.0 $[M-H]^-$.

***tert*-Butyl (2-(furan-3-yl)ethyl)carbamate (9)**

Diphenylphosphoryl azide (162.8 g, 0.59 mol) was added to the solution of **8** (83 g, 0.59 mol) and triethylamine (71.8 g, 0.71 mol) in *tert*-butanol (1 L). The mixture was stirred at 80 °C for 16 h, cooled to room temperature, and concentrated under reduced pressure. The residue was purified by the flash column chromatography (SiO_2; hexane/EtOAc, 80:20 → 50:50) to give **9**.

A colorless oil. Yield – 72.5 g (58%). Anal. Calcd for $C_{11}H_{17}NO_3$, %: C 62.54, H 8.11, N 6.63. Found, %: C 62.77, H 8.24, N 6.62. ^{1}H NMR (400 MHz, Chloroform-*d*), δ, ppm: 7.38 (1H, t, *J* = 1.7 Hz), 7.27 (1H, s), 6.30 (1H, s), 4.58 (1H, s), 3.32 (, *J* = 6.7 Hz), 2.62 (2H, t, *J* = 6.9 Hz), 1.45 (9H, s). ^{13}C NMR (151 MHz, Chloroform-*d*), δ, ppm: 155.8, 143.1, 139.5, 121.8, 110.8, 79.3, 40.6, 28.4, 25.4. LCMS, *m*/*z*: 157.2 $[M\text{-}t\text{Bu}+H]^+$.

***tert*-Butyl 4,7-dihydrofuro[2,3-c]pyridine-6(5H)-carboxylate (10)**

Paraformaldehyde (6.99 g, 0.233 mol) and *p*-toluenesulfonic acid monohydrate (554 mg, 2.91 mmol) were added to the solution of **9** (24.6 g, 0.116 mol) in toluene (3500 mL). The reaction mixture was heated to reflux for 16 h with the azeotropic removal of water (Dean-Stark trap). After cooling to room temperature, the mixture was diluted with EtOAc and washed with the saturated aqueous $NaHCO_3$ and brine. The organic layer was dried (Na_2SO_4), filtered, and concentrated. The purification by the flash column chromatography (hexane/EtOAc, 10:1) gave **10** as light brown powder.

A light brown powder. M. p. 60–70 °C. Yield – 7.7 g (30%). Anal. Calcd for $C_{12}H_{17}NO_3$, %: C 64.55, H 7.67, N 6.27. Found, %: C 64.39, H 7.98, N 6.41. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 1.41 (9H, s), 2.62 (2H, s), 3.65 (2H, br.s), 4.27 (2H, s), 6.16 (1H, s), 7.21 (1H, d, *J* = 13.50 Hz). ^{13}C NMR (126 MHz, Chloroform-*d*), δ, ppm: 24.0, 27.6, 28.6, 80.1, 108.5, 141.5. LC-MS, *m*/*z*: 124.2 $[M\text{-}C_4H_8\text{-}CO_2+H]^+$.

4,5,6,7-Tetrahydrofuro[2,3-*c*]pyridine hydrochloride (11·HCl)

The solution of **10** (7.7 g, 34.4 mmol) in 4 M HCl in dioxane (70 mL) was stirred at room temperature for 12 h (LC-MS control). The solvent was removed under reduced pressure, and the residue was dried under high vacuum to give **11·HCl** as a beige solid.

A light beige powder. M. p. 193–196 °C. Yield – 5.2 g (96%). Anal. Calcd for $C_7H_{10}ClNO$, %: C 52.68, H 6.32, N 8.78, Cl 22.21. Found, %: C 52.89, H 6.72, N 9.12, Cl 22.05. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 2.70 (2H, t, *J* = 6.05 Hz), 3.29 (2H, t, *J* = 5.96 Hz), 4.18 (2H, s), 6.46 (1H, s), 7.65 (1H, s), 9.74 (2H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 19.3, 41.5, 110.8, 115.4, 142.6, 143.4 (one signal is obscured by the solvent signals). LC-MS, *m*/*z*: 124.0 $[M+H]^+$ (compound as a hydrochloride salt).

Ethyl *N*-benzyl-*N*-(2-oxopropyl)glycinate (13)

The solution of chloroacetone (251.3 g, 2.71 mol) in THF (500 mL) was added slowly to the mixture of ethyl *N*-benzylglycinate (**12**) (500 g, 2.59 mol) and sodium bicarbonate (260.8 g, 3.10 mol) in THF (4 L) and water (500 mL) at 60 °C. The reaction mixture was stirred at 60 °C for 18 h, cooled to room temperature, diluted with water (2 L), and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated on a rotary evaporator to give **13** as a yellow oil.

A yellow oil. Yield – 550 g (84%). B. p. 193–198 °C. Anal. Calcd for $C_{14}H_{19}NO_3$, %: C 67.45, H 7.68, N 5.62. Found, %: C 67.06, H 7.55, N 5.77. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 1.14–1.39 (3H, m), 2.12 (3H, s), 3.45 (2H, s), 3.51 (2H, s), 3.84 (2H, s), 4.05–4.26 (2H, m), 7.12–7.44 (5H, m). ^{13}C NMR (126 MHz, Chloroform-*d*), δ, ppm: 14.2, 27.5, 54.5, 58.5, 60.4, 63.2, 127.5, 128.4, 129.0, 138.2, 171.1, 207.9. LCMS, *m/z*: 250.2 $[M+H]^+$.

Ethyl *N*-(2-Oxopropyl)glycinate hydrochloride (14·HCl)

A 10% Pd/C (5 g) was added to the solution of **13·HCl** (630 g, 2.20 mol) in methanol (4 L). The mixture was hydrogenated under the atmosphere of hydrogen (1 atm) at room temperature until the reaction was complete (LC-MS control). The catalyst was removed by the filtration and washed with methanol. The combined filtrate was concentrated under reduced pressure to give **14·HCl** (314.6 g, 73%).

White crystals. M. p. 93 °C. Yield – 314.6 g (73%). Anal. Calcd for $C_7H_{14}ClNO_3$, %: C 42.98, H 7.21, N 7.16, Cl 18.12. Found, %: C 42.66, H 7.48, N 6.93, Cl 18.50. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.23 (3H, t, $J = 6.89$ Hz), 2.19 (3H, s), 3.90 (2H, s), 4.13 (2H, s), 4.20 (2H, q, $J = 6.79$ Hz), 9.76 (2H, s). The ^{13}C NMR spectrum is identical to that reported in the literature [13].

***tert*-Butyl *N*-(1-(ethoxycarbonyl)methyl)-*N*-(2-oxopropyl)carbamate (15)**

Di-*tert*-butyl dicarbonate (351 g, 1.61 mol) was added dropwise to a stirred solution of **14·HCl** (314.6 g, 1.60 mol) and triethylamine (211.5 g, 2.09 mol) in THF (3 L) at room temperature. The mixture was stirred for 14 h (LC-MS control), then diluted with CH_2Cl_2 (2 L) and washed with the saturated aqueous citric acid (1 L) and water (2 L). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give **15**.

A yellow oil. Yield – 417 g (91%). Anal. Calcd for $C_{12}H_{21}NO_5$, %: C 55.58, H 8.16, N 5.40. Found, %: C 55.32, H 8.11, N 5.35. ^{1}H NMR (400 MHz, Chloroform-*d*), δ, ppm: 1.26 (3H, q, $J = 6.96$ Hz), 1.42 (9H, d, $J = 1.80$ Hz), 3.93 (1H, s), 2.14 (3H, s), 4.03 (2H, d, $J = 16.11$ Hz), 4.13 (1H, s), 4.13–4.23 (2H, m). ^{13}C NMR spectrum is identical to that reported in literature [13].

***tert*-Butyl 3,5-dioxopiperidine-1-carboxylate (16)**

The solution of **15** (380 g, 1.46 mol) in THF (4 L) was added over 3 h to a cooled (5 °C) suspension of potassium *tert*-butoxide (214 g, 1.46 mol) in THF. The resulting mixture was allowed to warm to room temperature, stirred for 12 h, and then concentrated in vacuo. The residue was dissolved in water (3 L) and acidified to pH 4 with the 1 M aqueous HCl. The precipitate was collected by the filtration, washed with water (2 × 1 L), and air-dried to give **16**.

A beige powder. M. p. 149 °C. Yield – 250 g (80%). Anal. Calcd for $C_{10}H_{15}NO_4$, %: C 56.33, H 7.09, N 6.57. Found, %: C 56.11, H 7.42, N 6.83. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.41 (9H, s), 3.97 (6H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 27.9, 80.0, 101.9, 153.4. LC-MS, *m/z*: 212.0 $[M-H]^-$.

***tert*-Butyl 4-oxo-4,7-dihydrofuro[2,3-c]pyridine-6(5H)-carboxylate (17)**

Under the argon atmosphere, **16** (50 g, 0.235 mol) was dissolved in methanol (700 mL) and cooled to 0 °C. Potassium hydroxide (13.2 g, 0.235 mol) was added, and the mixture was stirred at 0 °C for 30 min. A 50% aqueous solution of chloroacetaldehyde (66.2 mL, 0.29 mol) was then added. The reaction mixture was allowed to warm to room temperature and stirred overnight. The mixture was acidified with the 1 M aqueous HCl, extracted with EtOAc, and the organic layer was washed with water and brine, dried ($MgSO_4$), and concentrated to dryness to give a crude intermediate (41.4 g of a crude mixture). The purification by the flash column chromatography ($MeCN/CHCl_3$) gave **17**.

A yellow crystalline powder. M. p. 72 °C. Yield – 22 g (40%). Anal. Calcd for $C_{12}H_{15}NO_4$, %: C 60.75, H 6.37, N 5.90. Found: C 60.68, H 6.52, N 5.58. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.42 (9H, s), 4.12 (2H, s), 4.75 (2H, s), 6.80 (1H, d, $J = 2.04$ Hz), 7.86 (1H, d, $J = 2.01$ Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 27.8, 79.1, 80.5, 105.9, 119.0, 144.8, 153.6, 188.5. LC-MS, *m/z*: 260.0 $[M+Na]^+$.

6,7-Dihydrofuro[2,3-*c*]pyridin-4(5*H*)-one hydrochloride (18·HCl)

The solution of **17** (22 g, 93 mmol) in 4 M HCl in dioxane (200 mL) was stirred at room temperature for 12 h (LC-MS control). The solvent was removed under reduced pressure, and the residue was dried under high vacuum to give **18·HCl** (12.2 g, 96%).

A light brown crystalline powder. M. p. 154–170 °C. Yield – 12.2 g (96%). Anal. Calcd for $C_7H_8ClNO_2$, %: C 48.43, H 4.65, N 8.07, Cl 20.42. Found: C 48.15, H 4.45, N 8.01, Cl 20.63. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.91 (2H, s), 4.61 (2H, s), 6.88 (1H, d, J = 2.08 Hz), 7.97 (1H, d, J = 2.18 Hz), 10.73 (2H, s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 49.1, 66.3, 106.0, 119.6, 145.8, 159.5, 184.3. LC-MS, *m/z*: 138.2 [M+H]$^+$ (compound as a hydrochloride salt).

■ References

1. (a) Wang, Y.; Huang, W.; Xin, M.; Chen, P.; Gui, L.; Zhao, X.; Zhu, X.; Luo, H.; Cong, X.; Wang, J.; Liu, F. Discovery of Potent Anti-Inflammatory 4-(4,5,6,7-Tetrahydrofuro[3,2-c]Pyridin-2-Yl) Pyrimidin-2-Amines for Use as Janus Kinase Inhibitors. *Bioorg. Med. Chem.* **2019**, *27* (12), 2592–2597. https://doi.org/10.1016/j.bmc.2019.03.048. (b) Yamazaki, S.; Morio, H.; Inami, M.; Ito, M.; Fujii, Y.; Hanaoka, K.; Yamagami, K.; Okuma, K.; Morita, Y.; Shirakami, S.; Inoue, T.; Miyata, S.; Higashi, Y.; Seki, N. THU0101 ASP015K: A Novel Jak Inhibitor Demonstrated Potent Efficacy in Adjuvant-Induced Arthritis Model in Rats. *Ann. Rheum. Dis.* **2013**, *72*, A197. https://doi.org/10.1136/annrheumdis-2013-eular.629.
2. Oniciu, D. C.; Dasseux, J.-L. H.; Barbaras, R.; Kochubey, V.; Kovalsky, D.; Rodin, O. G.; Geoffroy, O.; Rzepiela, A. (Abionyx Pharma SA). Compounds, compositions and methods useful for cholesterol mobilisation. WO2012054535A2, 2012.
3. Haginoya, N.; Kobayashi, S.; Komoriya, S.; Yoshino, T.; Suzuki, M.; Shimada, T.; Watanabe, K.; Hirokawa, Y.; Furugori, T.; Nagahara, T. Synthesis and Conformational Analysis of a Non-Amidine Factor Xa Inhibitor That Incorporates 5-Methyl-4,5,6,7-Tetrahydrothiazolo[5,4-*c*]Pyridine as S4 Binding Element. *J. Med. Chem.* **2004**, *47* (21), 5167–5182. https://doi.org/10.1021/jm049884d.
4. Chao, J.; Bishop, M. J.; Perlroth, D. V. (Kodiak Sciences Inc.). Nlrp3 inhibitors. WO2024010772A1, 2024.
5. Buckley, G. M.; Cooper, N.; Davenport, R. J.; Dyke, H. J.; Galleway, F. P.; Gowers, L.; Haughan, A. F.; Kendall, H. J.; Lowe, C.; Montana, J. G.; Oxford, J.; Peake, J. C.; Picken, C. L.; Richard, M. D.; Sabin, V.; Sharpe, A.; Warneck, J. B. H. 7-Methoxyfuro[2,3-c]Pyridine-4-Carboxamides as PDE4 Inhibitors: A Potential Treatment for Asthma. *Bioorg. Med. Chem. Lett.* **2002**, *12* (3), 509–512. https://doi.org/10.1016/S0960-894X(01)00786-7.
6. Wishka, D. G.; Walker, D. P.; Yates, K. M.; Reitz, S. C.; Jia, S.; Myers, J. K.; Olson, K. L.; Jacobsen, E. J.; Wolfe, M. L.; Groppi, V. E.; Hanchar, A. J.; Thornburgh, B. A.; Cortes-Burgos, L. A.; Wong, E. H. F.; Staton, B. A.; Raub, T. J.; Higdon, N. R.; Wall, T. M.; Hurst, R. S.; Walters, R. R.; Hoffmann, W. E.; Hajos, M.; Franklin, S.; Carey, G.; Gold, L. H.; Cook, K. K.; Sands, S. B.; Zhao, S. X.; Soglia, J. R.; Kalgutkar, A. S.; Arneric, S. P.; Rogers, B. N. Discovery of *N*-[(3*R*)-1-Azabicyclo[2.2.2]Oct-3-Yl]Furo[2,3-*c*]Pyridine-5-Carboxamide, an Agonist of the A7 Nicotinic Acetylcholine Receptor, for the Potential Treatment of Cognitive Deficits in Schizophrenia: Synthesis and Structure–Activity Relationship. *J. Med. Chem.* **2006**, *49* (14), 4425–4436. https://doi.org/10.1021/jm0602413.
7. Demircan, A.; Kandemir, M.; Colak, M.; Karaarslan, M. One-Pot Cascade Synthesis of Fused Nitrogen-Containing Heterocycles in Aqueous Media – Utility of N-Protective Groups in Intramolecular Diels–Alder Reaction of Furan. *Synthesis* **2016**, *48* (17), 2873–2880. https://doi.org/10.1055/s-0035-1562458.
8. (a) Shengule, S. R.; Ryder, G.; Willis, A. C.; Pyne, S. G. Highly Diastereoselective N-Acyliminium Ion Cyclization Reactions of a Tethered Furan. *Tetrahedron* **2012**, *68* (50), 10280–10285. https://doi.org/10.1016/j.tet.2012.10.014. (b) Gao, S.; Tu, Y. Q.; Hu, X.; Wang, S.; Hua, R.; Jiang, Y.; Zhao, Y.; Fan, X.; Zhang, S. General and Efficient Strategy for Erythrinan and Homoerythrinan Alkaloids: Syntheses of (±)-3-Demethoxyerythratidinone and (±)-Erysotramidine. *Org. Lett.* **2006**, *8* (11), 2373–2376. https://doi.org/10.1021/ol0607185.
9. Kishko, I. S.; Kotsiubchyk, R. I.; Ostapchuk, E. N.; Rozhenko, A. B.; Vaskevych, A. I.; Pashenko, Y.; Vovk, M. V.; Volochnyuk, D. M.; Ryabukhin, S. V. Tandem Intramolecular Diels-Alder/Retro-Diels-Alder Approach to Dihydrofuro[2,3-c]Pyrroles and Related Fused Dihydrofurans: Reaction Scope and Computational Insight. March 12, 2026. https://doi.org/10.26434/chemrxiv.15000836/v1.
10. (a) Herrlich, M.; Hampel, N.; Mayr, H. Electrophilic aromatic substitutions of silylated furans and thiophenes with retention of the organosilyl group. *Org. Lett.* **2001**, 3 (11), 1629–1632. https://doi.org/10.1021/ol015810+. (b) Belen’kii, L. I.; Suslov, I. A.; Chuvylkin, N. D. Substrate and Positional Selectivity in Electrophilic Substitution Reactions of Pyrrole, Furan, Thiophene, and Selenophene Derivatives. *Chem. Heterocycl. Compd.* **2003**, 39 (1), 36–48. DOI: 10.1023/a:1023060406534. (c) Ghomri, A.; Mekelleche, S. M. Reactivity and regioselectivity of five-membered heterocycles in electrophilic aromatic substitution: A theoretical investigation. *J. Mol. Struct.: THEOCHEM* **2010**, 941 (1–3), 36–40. https://doi.org/10.1016/j.theochem.2009.10.035.
11. Parsons, R. L.; Berk, J. D.; Kuehne, M. E. Total synthesis of strychnan- and aspidospermatan-type alkaloids. 2. Generation of 15-(3-furanyl) ABCE tetracyclic intermediates. *J. Org. Chem.* **1993**, *58* (26), 7482–7489. https://doi.org/10.1021/jo00078a029.
12. Schelkun, R. M.; Yuen, P. W.; Wustrow, D. J.; Kinsora, J.; Su, T. Z.; Vartanian, M. G. Heteroaromatic side-chain analogs of pregabalin. *Bioorg. Med. Chem. Lett.* **2006**, *16* (9), 2329–2332. https://doi.org/10.1016/j.bmcl.2005.06.090.
13. Pérez-Martín, C.; Rebolledo, F.; Brieva, R. Amine Transaminase Mediated Synthesis of Optically Pure Piperazinones and 1,4-Diazepanones. *Adv. Synth. Catal.* **2022**, *364* (7), 1326–1336. https://doi.org/10.1002/adsc.202101510.

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