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НФаУ

У журналі розглянуто проблеми синтезу й аналізу органічних та елементоорганічних сполук, аналогів природних сполук і лікарських субстанцій, наведено результати фізико-хімічних досліджень у вищезазначених напрямах.

Для працівників науково-дослідних установ, вищих навчальних закладів та фахівців хімічного, фармацевтичного, біологічного, медичного і сільськогосподарського профілів.

«Журнал органічної та фармацевтичної хімії» внесено до затвердженого МОН України Переліку наукових фахових видань України (категорія «Б») для опублікування результатів дисертаційних робіт за спеціальністю 102 – Хімія та 226 – Фармація, промислова фармація (наказ МОН України від 28.12.2019 р. № 1643); індексовано в наукометричних базах даних: Chemical Abstracts (CAS), Index Copernicus; внесено до каталогів та пошукових систем: Directory of Open Access Journals (DOAJ), Bielefeld Academic Search Engine (BASE), Directory of Open Access scholarly Resources (ROAD), PKP Index, Ulrich's periodicals, Worldcat, НБУ ім. В. І. Вернадського і УРЖ «Джерело».

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A Universal Method for the Determination of Amlodipine in Industrial and Extemporaneous Pharmaceutical Preparations

Abstract

A universal UV spectrophotometric method for determining amlodipine besylate in industrially manufactured and extemporaneously prepared medicinal products in the form of tablets, powders, and oral solutions has been developed and validated. The methodological concept is based on the use of a single analytical model applicable to various dosage forms and dissolution media without modifying the analytical conditions. Spectral studies confirmed the presence of two absorption maxima at (238 ± 2) nm and (365 ± 2) nm, which corresponded to different chromophoric systems of the molecule and could be used to identify the compound; the wavelength of 365 nm was selected as the analytical wavelength, providing improved selectivity for the quantitative determination of the active pharmaceutical ingredient. The method was validated in accordance with pharmacopoeial requirements and ICH guidelines. The procedure is characterized by precision, accuracy, specificity, and linearity in the range of 0.04–0.06 μg mL^{-1} (80–120 % of the nominal concentration) ($r > 0.9981$) in all solvents proposed. The limits of detection (LOD) and quantification (LOQ) calculated were 0.59 % and 0.92 % for medicinal products in tablet and powder dosage forms, and 0.84 % and 1.09 % for the oral solution, respectively. The uncertainty of the method, including contributions from the sample preparation and the final analytical operation, was within acceptable limits for spectrophotometric assay procedures. The method proved to be applicable to industrial tablets, as well as extemporaneous powders and oral solutions, without interference from excipients in different dissolution media. Due to the minimal solvent consumption and the absence of requirements for chromatographic equipment, the approach proposed is an environmentally friendly, affordable and acceptable alternative from the point of view of regulatory requirements for the routine quality control of amlodipine medicinal products, particularly in small-scale production.

Keywords: amlodipine besylate; pharmaceutical market analysis; market availability of medicines; UV-spectrophotometry; standardization; quality; off-label; extemporaneous preparations

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Універсальний метод визначення амлодипіну в лікарських засобах промислового та екстемпорального виготовлення

Анотація

Розроблено та валідовано універсальну спектрофотометричну методику в ультрафіолетовому діапазоні визначення амлодипіну бесилату в лікарських засобах промислового та екстемпорального виготовлення у формі таблеток, порошку й розчину перорального. Методологічна концепція базується на використанні єдиної аналітичної моделі, застосованої до різних лікарських форм і середовищ розчинення без модифікації аналітичних умов. Спектральні дослідження підтвердили наявність двох максимумів поглинання за (238 ± 2) нм та (365 ± 2) нм, що відповідають різним хромофорним системам молекули і які можна використовувати для ідентифікації сполуки. Для кількісного визначення активного фармацевтичного інгредієнта за аналітичну довжину хвилі було обрано 365 нм, що забезпечує покращену селективність. Метод було валідовано відповідно до фармакопейних вимог та ICH. Методика характеризується точністю, правильністю, специфічністю та лінійністю в діапазоні 0.04–0.06 мкг $мл^{-1}$ (80–120 % від номінальної концентрації) ($r > 0,9981$) в усіх запропонованих розчинниках. Розраховані межі виявлення (LOD) та кількісного визначення (LOQ) становили 0,59 % і 0,92 % для лікарських засобів у формі таблеток і порошку, 0,84 % та 1,09 % для розчину перорального відповідно. Невизначеність методики, зокрема внески від пробопідготовки зразків та кінцевої аналітичної операції, була

в межах допускних значень для спектрофотометричних методик аналізу. Метод виявився застосовним до таблеток промислового виробництва, екстемпоральних порошку та розчину для перорального застосування, без впливу допоміжних речовин у різних середовищах розчинення. Завдяки мінімальному споживанню розчинника та відсутності вимог до хроматографічного обладнання запропонований підхід становить собою екологічну, доступну й прийнятну з погляду нормативних вимог альтернативу для рутинного контролю якості лікарських засобів амлодипіну, особливо малосерійного виробництва.

Ключові слова: амлодипіну бесилат; аналіз ринку лікарських засобів; доступність лікарських засобів на ринку; абсорбційна спектрофотометрія в ультрафіолетовій ділянці; стандартизація; якість; оф-лейбл; екстемпоральні лікарські засоби

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■ Introduction

Arterial hypertension (AH) and coronary heart disease remain leading causes of premature mortality in Ukraine and worldwide, which determines a high demand for modern antihypertensive medicines [1]. One of the key medicines used in the treatment of AH is amlodipine (amlodipine besylate, **Figure 1**), a long-acting dihydropyridine calcium channel antagonist characterized by a favorable efficacy and safety profile [2, 3].

As of the time of the study (October 2025), in Ukraine, according to the data of the State Register of Medicines of Ukraine, 244 tablet dosage forms containing amlodipine besylate (in terms of amlodipine – 2.5 mg, 5 mg and 10 mg) were registered in Ukraine and held by 36 marketing authorization holders. According to the ATC classification, 42 products (17.21%) of all positions were registered as monocomponent medicines (C08CA01), 202 products (82.79%) were fixed-dose combination medicines [4].

The share of medicines manufactured by Ukrainian companies was 29.92%, whereas 70.08% was accounted for by imported products, primarily from Slovenia, India, France, Poland, and Switzerland.

Such market saturation indicates a high level of competition, a wide range of options for physicians and patients, as well as a significant pharmacoeconomic potential due to the availability of medicines across both mid-priced and budget segments.

Although, according to the official prescribing information, the medicine is recommended for adults and children aged 6 years and older, available studies, including physiologically based pharmacokinetic (PBPK) modeling, clinical observations, and pharmacokinetic analyses, indicate the possibility of its use in newborns and children under 6 years of age, thereby confirming the off-label use in pediatric practice [5, 6]. At the same time, it should be considered that not all patient populations can be adequately provided with standard solid dosage forms due to swallowing difficulties. Such groups, in addition to newborns and young children, include elderly patients, patients with dysphagia, and bedridden patients. This creates a need for the preparation of medicines in pharmacies in the form of liquid or modified dosage forms adapted to the individual needs of specific patients.

However, ensuring the proper quality of such medicines is complicated by the fact that pharmacopoeial control methods [7, 8] recommended for industrial production, in particular liquid chromatography, have significant limitations for the routine use in pharmacy practice due to the requirement for complex equipment, reagents, reference standards, and highly qualified personnel. This makes the search for alternative, simpler, and technologically accessible analytical methods that ensure sufficient accuracy and reproducibility in the quality control of pharmacy-prepared medicines highly relevant.

The aim of the study was to select and develop a method for the quantitative determination of

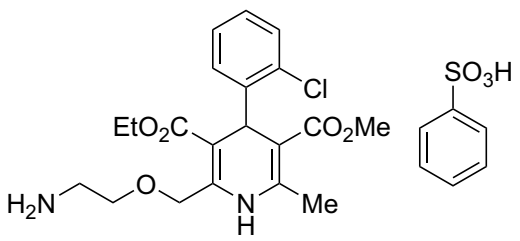

Figure 1. The chemical structure of amlodipine besylate (3-Ethyl 5-methyl (4*RS*)-2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate benzenesulfonate)

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amlodipine besylate suitable for the analysis of its dosage forms, particularly tablets and extemporaneous preparations in the form of powders and oral solutions.

■ Materials and methods

The study objects were medicinal products containing amlodipine besylate.

Industrial production:

– "Amlodipine-Astrapharm" (batch No. 010624, Astrapharm LLC, Ukraine), tablets containing 5 mg of amlodipine with an average tablet weight of 200 mg, formulated with calcium hydrogen phosphate, microcrystalline cellulose, magnesium stearate, and corn starch as excipients.

Extemporaneous production:

– "Amlodipine, 2.5 mg, powder for solution preparation", a powder dosage form with a unit weight of 100 mg containing mannitol as an excipient;

– "Amlodipine, 1 mg mL^{-1}", oral solution, in which 1 mL contains 1 mg of amlodipine in the form of 1.385 mg of amlodipine besylate, glycerin, maltitol, ethanol (96%), and peppermint flavoring.

Experimental batches of the dosage forms indicated were prepared at the Educational and Scientific Training Center for Chemical and Technological Research of the Educational and Scientific Institute of Applied Pharmacy of the National University of Pharmacy in accordance with the requirements of Order No. 812 of the Ministry of Health of Ukraine "On Approval of the Rules for the Preparation and Quality Control of Medicinal Products in Pharmacies", taking into account the requirements of the State Pharmacopoeia of Ukraine and the United States Pharmacopeia (USP) [9, 10, 11].

For the preparation of experimental samples and reference solutions, the following materials were used: amlodipine besylate (99.94%, batch No. AMV/016/01/19, Glochem Industries Limited, India); ethyl alcohol (96%, batch No. 120525, Biolik PJSC, Ukraine); glycerin (99.5%, batch No. 5602/432/1223, Agrohim Trading House, Ukraine); crystalline maltitol (99.1%, batch No. 2023050720, Shandong Lujian Biological Technology Co., Ltd., China); mannitol 200 SD (99.9%, batch No. 200SD2209003, Shijiazhuang Huaxu Pharmaceutical Co., Ltd., China); microcrystalline cellulose (batch No. 20240203, Huzhou City Lingha Xinwang Chemical Co., Ltd., China); anhydrous dicalcium phosphate (99.9%, batch No. 2428332, Prayon S.A., USA); potato starch (batch No. 29.10.2024, VYMAL PE, Ukraine) and magnesium stearate (batch No. MS-019, 0, Ukraine).

To develop a method for the quantitative determination of amlodipine besylate, absorption spectrophotometry in the ultraviolet and visible regions (SPhU 2.2.25N / Ph. Eur. 2.2.25) was employed [7, 12]. The study was performed using a SHIMADZU UV-2600 spectrophotometer equipped with UV-Probe software version 2.33.

The sample preparation was performed using AXIS analytical balances and Class A volumetric glassware. All reagents and titrated solutions used met the relevant pharmacopoeial requirements [7, 9].

Solvents: 0.1 M hydrochloric acid, 0.1 M sodium hydroxide or ethanol (96%).

Test solution. A mass (or volume) of the medicinal product equivalent to 2.5 mg of amlodipine (accurately weighed) is placed into a 50.0 mL volumetric flask, 30 mL of the solvent is added, the mixture is shaken for 10 min, diluted to the volume with the same solvent, and filtered if necessary.

Reference solution. An accurately weighed amount of amlodipine besylate equivalent to 50.0 mg of amlodipine is dissolved in 30 mL of the solvent, and the solution is diluted to 100.0 mL with the same solvent and mixed. Then, 5.0 mL of the resulting solution is transferred to a 50.0 mL volumetric flask and diluted to the volume with the same solvent.

Placebo solution. It is prepared using the same excipients in amounts corresponding to those used for *Test solution* without the addition of the active pharmaceutical ingredient.

Compensation solution. It is the solvent.

■ Results and discussion

According to published data, several liquid chromatography methods have been proposed for the determination of amlodipine besylate in pharmaceutical substances and medicinal products. In addition to the pharmacopoeial separation conditions on the octadecylsilyl silica gel column (250 × 4.0 mm, 5 µm) using the mobile phase of ammonium acetate (2.3 g L^{-1}) and methanol in the ratio of 30:70 (v/v) and detection at 237 nm [7, 8], the determination of the active pharmaceutical ingredient was also carried out using a C18 core-shell column (100 × 4.6 mm, 2.6 µm) and the mobile phase consisting of 0.4% ammonium

hydroxide solution in water and methanol in the gradient mode [13], as well as by liquid chromatography with the mass detection on a ZORBAX Eclipse Plus C18 column using the mobile phase of methanol–aqueous formic acid (5 mM) in the ratio of 95:5 (v/v) [14]. At the same time, a significant part of the research focused on alternative spectrophotometric methods for the determination of amlodipine besylate based on its intrinsic light absorption, particularly in methanolic media where analytical wavelengths in the range of 238–244 nm were commonly applied [15, 16], as well as in acidic media, such as 0.1 M hydrochloric acid, in which the determination was performed at 239 nm [17]. In addition, methods based on the formation of colored reaction products with dyes were described, including amido black with an absorption maximum at 592 nm [18] and sodium 1,2-naphthoquinone-4-sulfonate in the alkaline medium with an absorption maximum at 459 nm [19].

Considering current trends in the development of analytical chemistry, the concept of Green Analytical Chemistry is gaining increasing attention. It involves minimizing the use of toxic reagents and organic solvents, reducing waste generation, energy saving, and simplifying analytical procedures [20, 21]. To support the method selection, a preliminary assessment of the environmental friendliness of literature-reported methods used for the analysis of amlodipine besylate was carried out (**Figure 2**).

The results obtained (**Figure 2**) clearly demonstrate that spectrophotometric methods (**Figures 2B** and **2C**) have significant advantages over the pharmacopoeial chromatographic method (**Figure 2A**) as they do not require large volumes of organic solvents, complex high-cost and energy-consuming equipment, and are characterized by the shorter analysis time. These advantages make spectrophotometric methods suitable for the routine quality control of medicinal products, particularly under conditions of pharmacy compounding and industrial manufacturing.

The analysis of literature sources reveals the absence of the system approach to substantiating the choice of analytical wavelengths for the determination of amlodipine besylate, as well as the insufficient comprehensive validation of the corresponding methods. Therefore, the present study proposes an approach aimed at the scientifically justified selection of specific analytical wavelengths, their experimental confirmation, and full validation in accordance with current regulatory requirements [9].

At the first stage of the study, the spectral characteristics of amlodipine besylate were investigated in three different dissolution media: ethanol (96%), 0.1 M sodium hydroxide, and 0.1 M hydrochloric acid (**Figure 3**).

As shown in **Figure 3**, the absorption spectra of the test compound, regardless of the dissolution medium, are characterized by the presence of two absorption maxima at wavelengths of (238 ± 2) nm and (365 ± 2) nm.

It should be noted that the absorption maximum near 238 nm was used only for spectral characterization of the substance. This band is associated with the presence of aromatic and pyridine chromophores in the amlodipine molecule, as well as the benzenesulfonate moiety. In contrast, the absorption maximum at 365 nm is attributed predominantly to the amlodipine base. Therefore, it was selected as the analytical wavelength

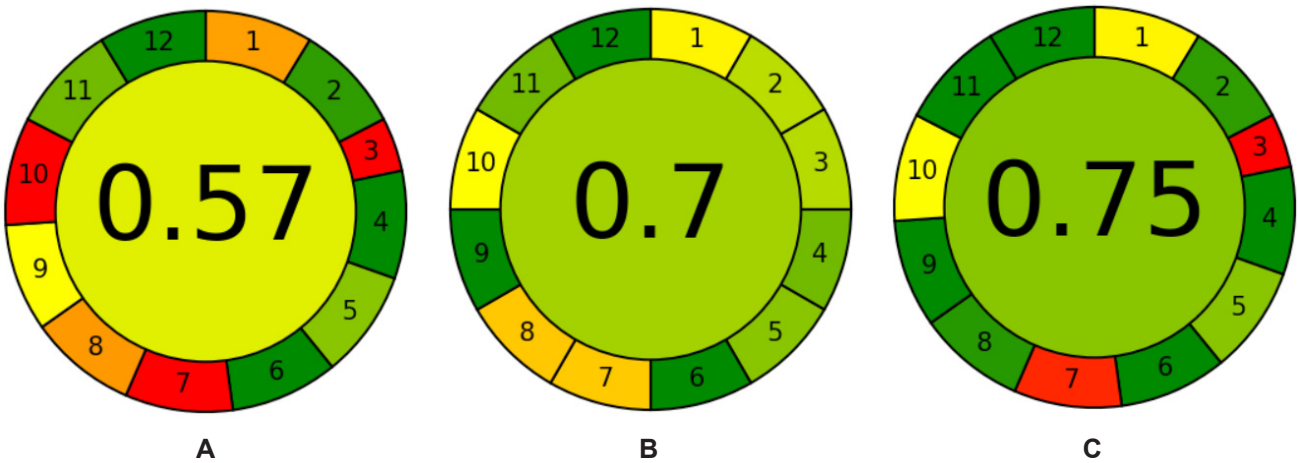

Figure 2. The AGREE analytical scale of amlodipine besylate studies: (A) by liquid chromatography according to the method described in the monograph of the European Pharmacopoeia [7]; (B) by Vis-spectrophotometry based on dye–reagent reactions [18, 19]; (C) by UV-spectrophotometry based on the intrinsic light absorption of the compound [15, 16, 17].

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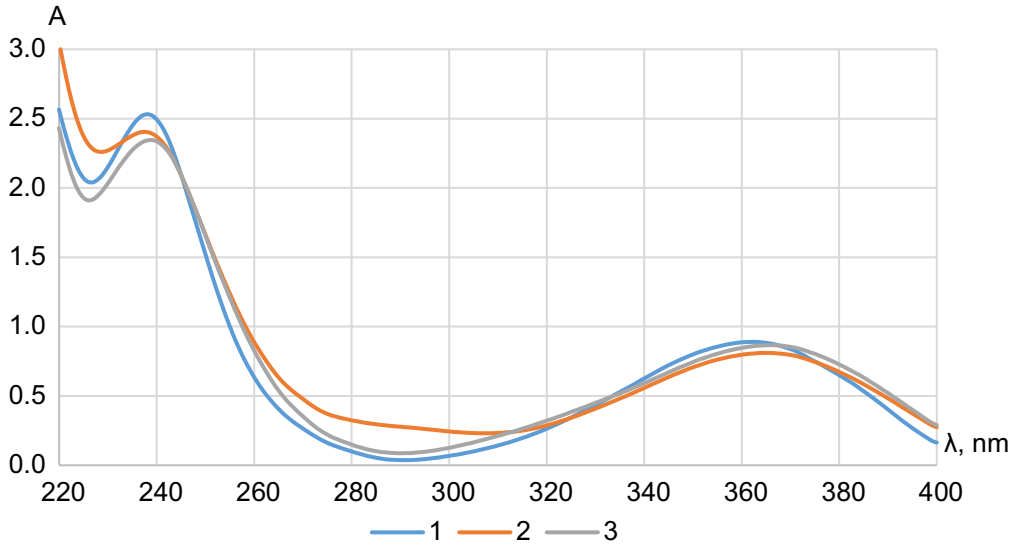

Figure 3. Absorption spectra of the amlodipine besylate reference solution (the amlodipine concentration – 0.05 μg mL^{-1}) in ethanol (96 %) (1), 0.1 M hydrochloric acid (2) and 0.1 M sodium hydroxide (3)

for the quantitative determination of the active pharmaceutical ingredient in medicinal products.

Quantitative measurements were performed at 365 nm where the absorbance values of working solutions were within the optimal instrumental range (A = 0.6–0.8), complying with Beer–Lambert law requirements.

The methodological distinction of the approach proposed from previously reported UV spectrophotometric procedures lies not only in the selection of the analytical wavelength, but in the concept of a unified assay model. The method was developed as a single analytical platform applicable to different dosage forms (industrial tablets, pharmacy-compounded powders and oral solutions) and different dissolution media without modifying the analytical conditions. In contrast, most published UV methods are optimized for one formulation type or one solvent system. The present study, therefore, demonstrates the transferability and robustness of a single spectrophotometric model across pharmaceutical matrices, which is essential for the routine quality control in pharmacy compounding practice.

However, it is worth noting that during the dissolution in 0.1 M sodium hydroxide, the substance clumps together, so for its dissolution it is necessary to use an ultrasonic device or dissolve with intensive stirring. In the medium of 0.1 M hydrochloric acid, the dissolution process lasts at least 10 minutes. But the methods have good convergence of results, so they can be transferred to determine the API in the composition of medicines, regardless of the form of release. The Beer–Lambert law is obeyed in all solvents within the concentration range of 0.02–0.7 μg mL^{-1}.

For further application of the method for the quantitative determination of API in the composition of the medicines studied, the characteristics of the spectra of drug solutions and placebo solutions in different dissolution media were studied (**Figures 4–6**).

As shown in **Figures 4–6**, the method is not affected by systematic error caused by excipients, indicating that the method is specific for the determination of amlodipine in the objects studied.

The method demonstrated linearity (**Table 1**) in the concentration range of 0.04–0.06 μg mL^{-1} (corresponding to 80–120% of the nominal concentration), with correlation coefficients r > 0.9981 in all media.

Although the determination of detection and quantification limits were not mandatory for assay methods intended for the quantitative determination of active substances in finished dosage forms, these parameters were additionally estimated to further characterize the analytical performance of the method proposed.

The detection limit (LOD) and quantification limit (LOQ) for amlodipine besylate were calculated using the standard ICH Q2 and the SPhU approach based on regression parameters (S_a and b): $LOD = 3.3 \cdot S_a \cdot b^{-1}$; $LOQ = 10 \cdot S_a \cdot b^{-1}$ (**Table 1**).

Both values are substantially lower than the lower limit of the validated concentration range, indicating that the working assay concentrations are well above the quantification limit. Therefore, the sensitivity characteristics of the method do not limit its accuracy or applicability for the quantitative determination.

As can be seen from **Table 2**, the analysis method is correct and is characterized by sufficient

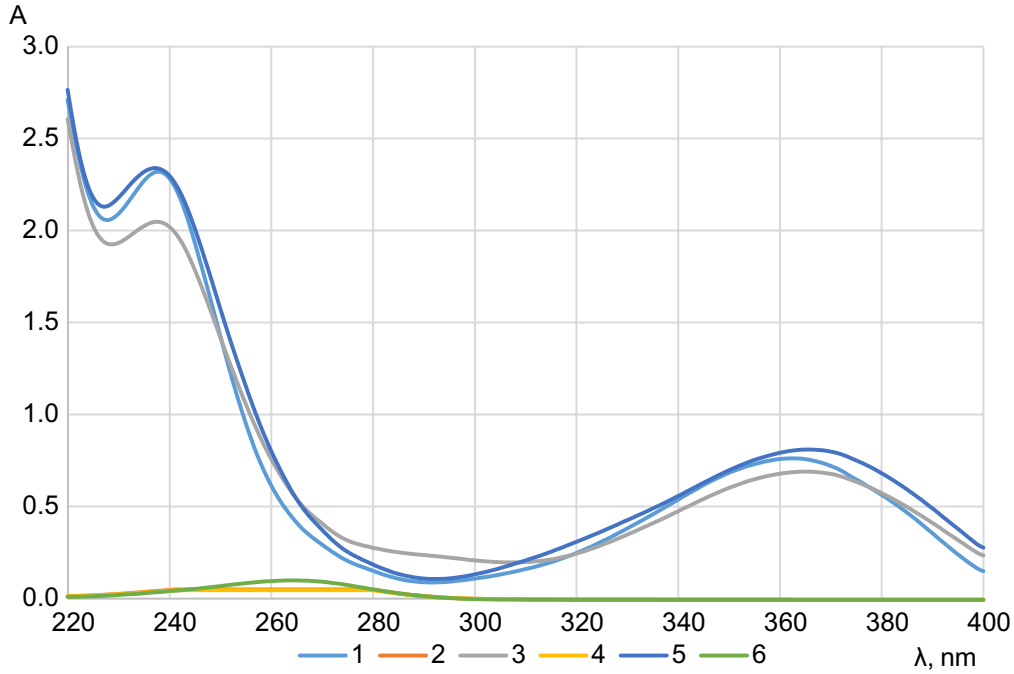

Figure 4. Absorption spectra of solutions of the drug "Amlodipine-Astrapharm" (the amlodipine concentration – 0.05 μg mL^{-1}) and placebo in ethanol (96 per cent) (1) and (2), 0.1 M hydrochloric acid (3) and (4), 0.1 M sodium hydroxide (5) and (6), respectively

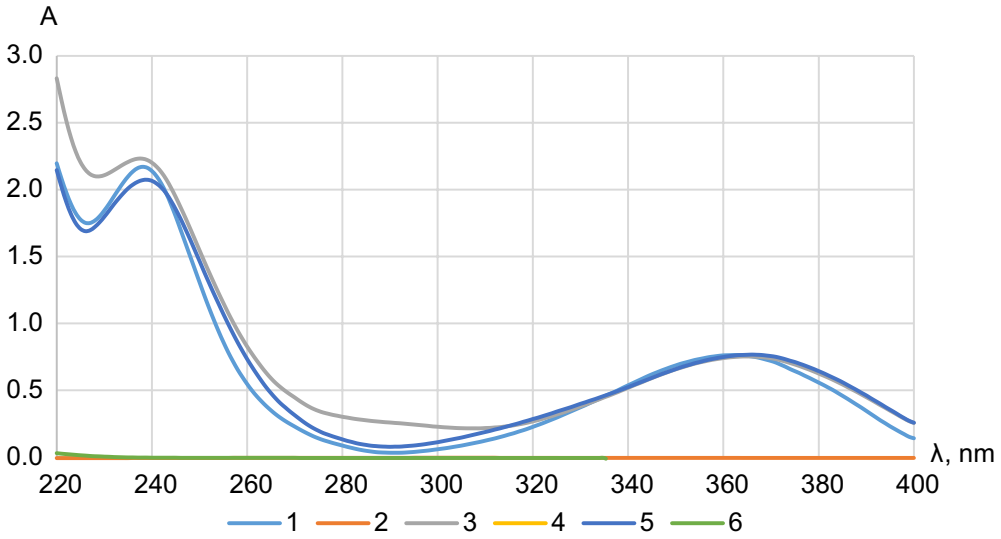

Figure 5. Absorption spectra of solutions of the drug "Amlodipine. 2.5 mg, powder for solution preparation" (the amlodipine concentration – 0.05 μg mL^{-1}) and placebo in ethanol (96 per cent) (1) and (2), 0.1 M hydrochloric acid (3) and (4), 0.1 M sodium hydroxide (5) and (6), respectively

convergence and accuracy in the entire concentration range of 80–120%.

The uncertainty associated with the sample preparation for the quantitative determination was evaluated in accordance with the requirements of the State Pharmacopoeia of Ukraine [12].

The total uncertainty (ΔAs, r) of the analysis was calculated using the expression:

$$\Delta As,\ r = \sqrt{\Delta_{SP}^2 + \Delta_{FAO}^2} \leq max\Delta As = 1.6$$

where Δ_{SP} is the uncertainty contribution of the sample preparation operations, and Δ_{FAO} is the uncertainty contribution of the final analytical operation.

For medicinal products in the form of tablets and powders, the uncertainty of the sample preparation was:

$$\Delta_{SP,\,r} = \sqrt{(0.2^2 + 0.17^2) + (0.33^2 + 0.12^2 + 0.37^2 + 0.17^2)} = 0.59 < 1.6$$

For medicinal products in the form of the oral solution, the uncertainty of the sample preparation was:

$$\Delta_{SP,\,r} = \sqrt{(0.62^2 + 0.17^2) + (0.33^2 + 0.12^2 + 0.37^2 + 0.17^2)} = 0.84 < 1.6$$

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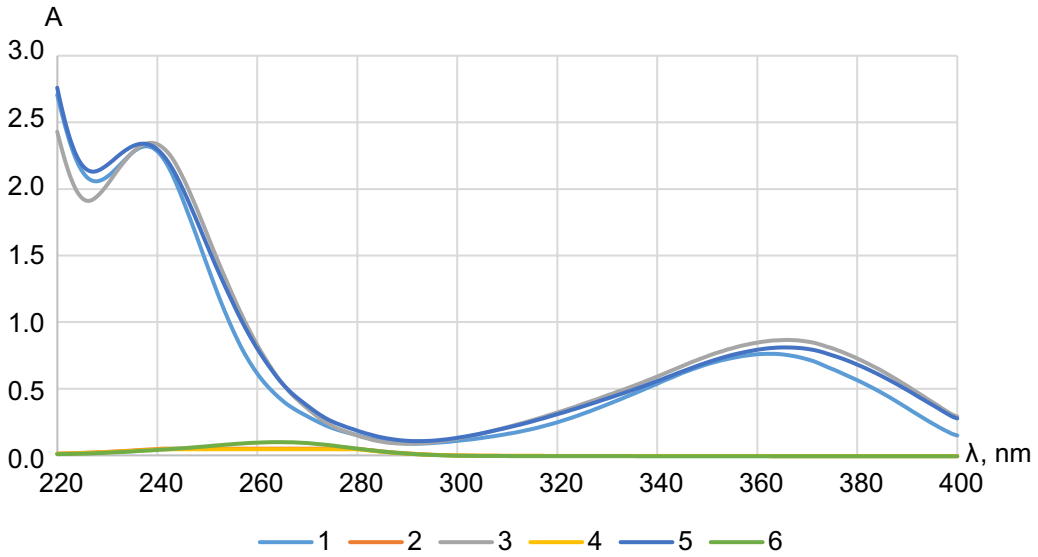

Figure 6. Absorption spectra of solutions of the drug "Amlodipine, 1 mg mL^{-1}, oral solution" (the amlodipine concentration – 0.05 μg mL^{-1}) and placebo in ethanol (96%) (1) and (2), 0.1 M hydrochloric acid (3) and (4), 0.1 M sodium hydroxide (5) and (6), respectively

Table 1. Metrological characteristics of the linear relationship between the measured concentration of amlodipine and its nominal concentration in normalized coordinates

Parameters	Value			Acceptance criteria	Conclusions
Dissolution medium	Ethanol (96%)	0.1 M hydrochloric acid	0.1 M sodium hydroxide		
"Amlodipine-Astrapharm", tablets					
b	0.9940	0.9950	1.0031		
S_b	0.0093	0.0103	0.0054		
a	0.8378	0.7033	0.4067	≤ 2.60	Meets acceptance criteria
S_a	0.9359	1.0373	0.5443		
S_0	0.3595	0.3984	0.2091	≤ 0.845	Meets acceptance criteria
r	0.9997	0.9996	0.9999	> 0.9981	Meets acceptance criteria
LOD	3.11	3.44	1.79	< 32%	Meets acceptance criteria
LOQ	9.42	10.43	5.43	< 32%	Meets acceptance criteria
"Amlodipine, 2.5 mg, powder for solution preparation"					
b	0.9873	0.9983	0.9966		
S_b	0.0144	0.0025	0.0044		
a	1.2511	0.2289	0.4633	≤ 2.60	Meets acceptance criteria
S_a	1.4478	0.2472	0.4426		
S_0	0.5561	0.0949	0.1700	≤ 0.845	Meets acceptance criteria
r	0.9992	1.0000	0.9999	> 0.9981	Meets acceptance criteria
LOD	4.83	0.82	1.47	< 32%	Meets acceptance criteria
LOQ	14.66	2.48	4.44	< 32%	Meets acceptance criteria
"Amlodipine, 1 mg mL^{-1}, oral solution"					
b	0.9968	0.9980	0.9971		
S_b	0.0054	0.0062	0.0031		
a	0.4444	0.3622	0.3944	≤ 2.60	Meets acceptance criteria
S_a	0.5425	0.6261	0.3078		
S_0	0.2084	0.2405	0.1182	≤ 0.8450	Meets acceptance criteria
r	0.9999	0.9998	1.0000	> 0.9981	Meets acceptance criteria
LOD	1.80	2.07	1.02	< 32%	Meets acceptance criteria
LOQ	5.44	6.27	3.09	< 32%	Meets acceptance criteria

Table 2. Results of the accuracy and precision assessment

Parameters	Value			Requirements for statistical non-significance	Requirements for practical significance	Conclusion
Dissolution medium	Ethanol (96 per cent)	0.1 M hydrochloric acid	0.1 M sodium hydroxide			
"Amlodipine-Astrapharm", tablets						
$\lvert\bar{Z} - 100\rvert$	0.25	0.22	0.12	≤ 0.35	≤ 0.51	Performed according to two criteria
Δintra	0.77	0.86	0.42	≤ 1.6	–	Conducted
"Amlodipine, 2.5 mg, powder for solution preparation"						
$\lvert\bar{Z} - 100\rvert$	0.00	0.06	0.13	≤ 0.35	≤ 0.51	Performed according to two criteria
Δintra	1.19	0.20	0.36	≤ 1.6	–	Conducted
"Amlodipine, 1 mg mL^{-1}, oral solution"						
$\lvert\bar{Z} - 100\rvert$	0.13	0.17	0.12	≤ 0.35	≤ 0.51	Performed according to two criteria
Δintra	0.42	0.50	0.27	≤ 1.6	–	Conducted

The values obtained are significantly lower than the maximum permissible uncertainty, confirming that the sample preparation does not introduce a critical contribution to the overall measurement uncertainty of the method.

According to the recommendations of the SPhU general chapter 5.3.N.2 "Validation of analytical procedures and tests" [12], the uncertainty of the final analytical operation for the spectrophotometric analysis using the standard method is 0.70%.

The total predicted uncertainty of the assay procedure was calculated according to equation:

for medicinal products in the form of tablets and powders:

$$\Delta As,\ r = \sqrt{(0.59^2 + 0.70^2)} = 0.92 \leq 1.6$$

for medicinal products in the form of the oral solution:

$$\Delta As,\ r = \sqrt{(0.84^2 + 0.70^2)} = 1.09 \leq 1.6$$

The values calculated demonstrate that the overall uncertainty of the spectrophotometric method developed for the quantitative determination of the finished medicinal product by the standard method complies with the recommendations of the general chapter 5.3.N.2 "Validation of analytical procedures and tests".

The validated method was transferred to the quantitative determination of API in the study objects (**Table 3**).

The results of the quantitative determination of the active pharmaceutical ingredient in the objects studied were independent of the dissolution medium, showed no significant systematic error, and were consistent with the declared content of the medicinal products.

The practical significance of the method lies in its applicability not only to the quality control of industrially manufactured medicinal products, but also for extemporaneous preparations. Compared with pharmacopoeial chromatographic

Table 3. Results of the quantitative determination of APIs in medicinal products

Dissolution media	Weight of the sample (volume) of the drug, g (mL)	A (average of 3 measurements)	Weight of amlodipine besylate	A_o	The quantitative content of amlodipine, mg
"Amlodipine-Astrapharm", tablets					
Ethanol (96%)	0.1025	0.762	0.0694	0.890	0.0052
0.1 M hydrochloric acid	0.1007	0.737	0.0632	0.810	0.0051
0.1 M sodium hydroxide	0.1004	0.740	0.0676	0.867	0.0051
"Amlodipine, 2.5 mg, powder for solution preparation"					
Ethanol (96%)	0.1017	0.659	0.0694	0.890	0.0025
0.1 M hydrochloric acid	0.1029	0.67	0.0632	0.810	0.0025
0.1 M sodium hydroxide	0.1008	0.655	0.0676	0.867	0.0025
"Amlodipine, 1 mg mL^{-1}", oral solution					
Ethanol (96%)	2.5	0.678	0.0694	0.890	0.0011
0.1 M hydrochloric acid	2.5	0.665	0.0632	0.810	0.0010
0.1 M sodium hydroxide	2.5	0.671	0.0676	0.867	0.0010

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methods, the approach proposed is simpler, more accessible, and less resource-intensive, making it suitable for implementation in pharmacy practice and small analytical laboratories.

Thus, it can be stated that the spectrophotometric method developed is a reliable, reproducible and cost-effective alternative for controlling the content of amlodipine besylate in medicinal products in various dissolution media by its own light absorption.

■ Conclusions

The features of the market of medicinal products containing amlodipine besylate have been identified, and the need for alternative control methods for pharmacy-compounded dosage forms has been determined due to the limited feasibility of full-scale application of pharmacopoeial chromatographic methods in routine practice.

It has been found that the absorption spectra of the test compound, regardless of the dissolution medium, are characterized by the presence of two absorption maxima at wavelengths (238 ± 2) nm and (365 ± 2) nm, which can be used for identification purposes. The wavelength of (365 ± 2) nm was selected as the analytical wavelength for the quantitative determination of amlodipine in the substance and medicinal products.

The spectrophotometric method proposed for the quantitative determination of amlodipine besylate has been validated; the procedure is characterized by precision, accuracy, specificity, and linearity in the range of 0.04–0.06 μg mL^{-1} (80–120% of the nominal concentration) ($r > 0.9981$) in all solvents proposed.

The limits of detection (LOD) and quantification (LOQ) calculated are 0.59% and 0.92% for medicinal products in tablet and powder dosage forms, and 0.84% and 1.09% for the oral solution, respectively.

The uncertainty of the method, including contributions from the sample preparation and the final analytical operation, was within acceptable limits for spectrophotometric assay procedures.

It has been determined that the results of the quantitative determination of amlodipine in tablets, powder and oral solution correspond to the declared content and are convergent, regardless of the dissolution medium.

The study demonstrates that UV spectrophotometry when methodologically optimized remains a scientifically justified and regulatory-acceptable alternative to chromatographic techniques for the routine assay of amlodipine in diverse pharmaceutical preparations.

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The improved synthesis of ROCKYPhos and its application for the asymmetric hydrogenation of dihydroisoquinoline derivatives

Abstract

An optimized approach to the multigram synthesis of [(1*R*,2*R*,3*S*)-(+)-1,2-dimethyl-2,3-bis(diphenylphosphinomethyl)cyclopentyl]methanol (ROCKYPhos, CatASium I®), a camphor-derived chiral diphosphine ligand, has been developed. The key improvement in the synthetic scheme involved the oxidative cleavage of 3,9-dibromocamphor with $V_2O_5 – HNO_3$ or $NH_4VO_3 – Cu(NO_3)_2 – HNO_3$ system, which gave the corresponding dicarboxylic acid in the yield of 28% and significantly reduced the reaction sequence. The NMR study of a diselenide derivative of ROCKYPhos showed that one of the PPh_2 groups had strong donor properties comparable to those of trialkylphosphines. The asymmetric hydrogenation of *N*-acetyl-1,2-dihydroisoquinoline-4-carboxylates in the presence of ROCKYPhos provided target tetrahydroisoquinolines with up to 52% *ee* – an outstanding result for this substrate class.

Keywords: asymmetric synthesis; phosphine ligands; nitrogen heterocycles; isoquinoline

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Удосконалений синтез ROCKYPhos та його застосування для асиметричного гідрування похідних дигідроізохіноліну

Анотація

Було розроблено оптимізований підхід до багатограмового синтезу [(1*R*,2*R*,3*S*)-(+)-1,2-диметил-2,3-біс(дифенілфосфінометил)циклопентил]метанолу (ROCKYPhos, CatASium I®) – хірального дифосфінового ліганду, похідної камфори. Ключове покращення синтетичної схеми полягало в окиснювальному розщепленні 3,9-дибромкамфори системою $V_2O_5 – HNO_3$ або $NH_4VO_3 – Cu(NO_3)_2 – HNO_3$, що дало відповідну дикарбонову кислоту з виходом 28% і суттєво скоротило послідовність реакцій. Дослідження методом ЯМР діселенідного похідного ROCKYPhos показало, що одна з груп PPh_2 має сильні донорні властивості, близькі до відповідних значень для триалкілфосфінів. Асиметричне гідрування *N*-ацетил-1,2-дигідроізохінолін-4-карбоксилатів у присутності ROCKYPhos забезпечило утворення цільових тетрагідроізохінолінів з енантіомерним надлишком до 52% *ee*, що є видатним результатом для цього класу субстратів.

Ключові слова: асиметричний синтез; фосфінові ліганди; азотовмісні гетероцикли; ізохінолін

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Introduction

Chiral diphosphines are widely used in various areas of organic synthesis, but became most famous for their Nobel prize-winning application in the asymmetric hydrogenation [1]. Ligands like BINAP, DIPAMP, or DuPhos (**Figure 1**) became classical in this area, and many others were synthesized and evaluated for the preparation of various enantioenriched products [2]. Nevertheless, most of them demonstrated a narrow substrate scope in the case of the asymmetric C=C bond hydrogenation, and despite numerous efforts and considerable achievements for specific substrate classes (e.g., α-dehydroamino acid derivatives), there is still no general method. Therefore, any new information on the possible extension of the asymmetric olefin hydrogenation scope remains valuable.

In 2001, Komarov, Börner, and co-authors reported the synthesis of camphor-derived hydroxydiphosphine ligand **1** (later named ROCKYPhos or CatASium I®) and illustrated its efficiency for the asymmetric hydrogenation of several α- and ß-dehydroamino acid derivatives [3]. The original synthetic approach to compound **1** proposed by authors was lengthy and the involved Bayer-Villiger oxidation of 9-bromocamphor (**4**) as one of the key steps (**Scheme 1**). This reaction provided modest yield of target lactone **5** (33%). An alternative approach included even more steps, i.e., the oxidation of ketone **4** with SeO_2, the Bayer-Villiger reaction, and the reduction of the resulting anhydride **9** (**Scheme 2**).

In this work, we report our efforts on further optimization of the synthesis of ligand **1**. In addition to that, we characterized its donor properties and evaluated it in the asymmetric

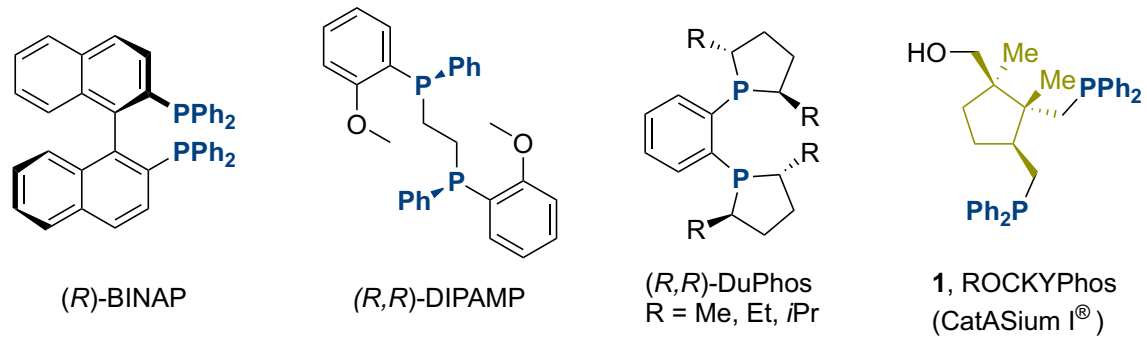
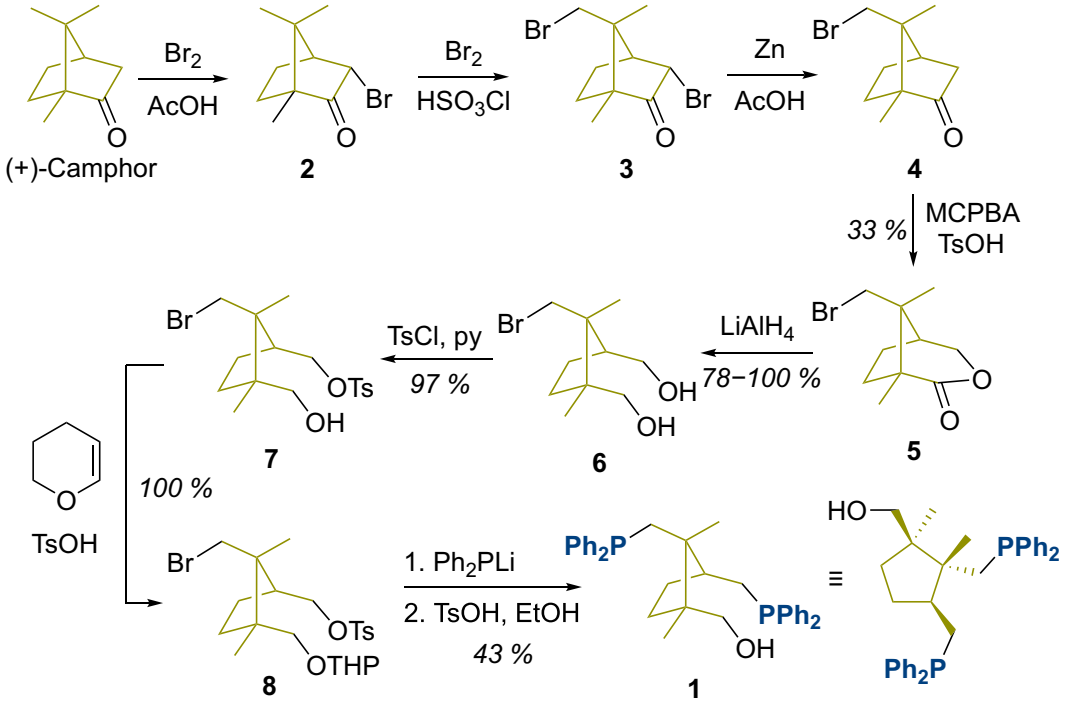


Figure 1. Diphosphine-based ligands used in the asymmetric hydrogenation



Scheme 1. The original synthetic approach to compound **1** proposed by Komarov, Börner, and co-authors in 2001

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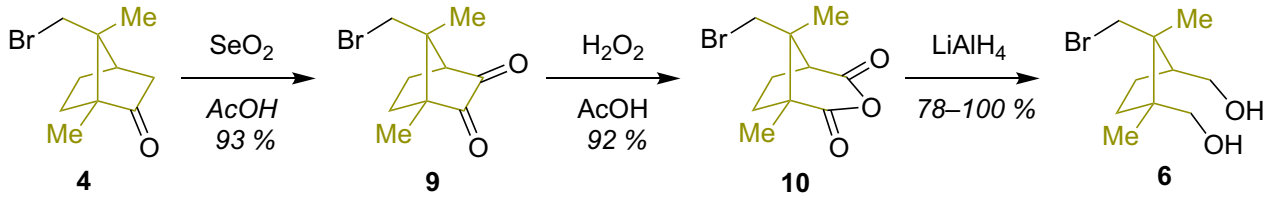


Scheme 2. An alternative approach to **6**

hydrogenation of *N*-acetyl-1,2-dihydroisoquinoline-4-carboxylates. It should be noted that while examples of the asymmetric hydrogenation of ß-dehydroamino acid derivatives were reported in the literature [4, 5], to the best of our knowledge, the method was never applied to the synthesis of enantioenriched tetrahydroisoquinoline derivatives.

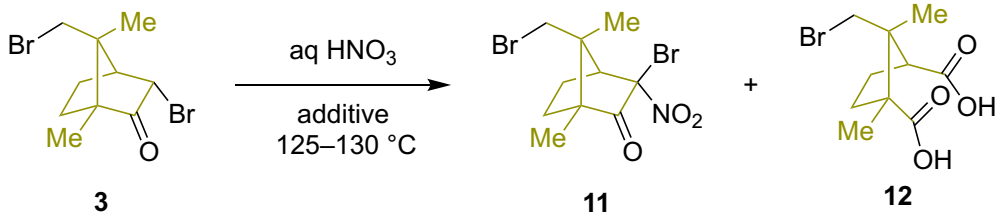
To further shorten the synthetic scheme used for the preparation of ligand **1**, we considered a direct oxidative cleavage of 3,9-dibromocamphor (**3**) as a possible alternative. We found that the reaction of compound **3** with 63% aq. HNO_3 at 130 °C, nitro derivative **11** was formed in an isolated yield of 68% (**Table 1**). The addition of V_2O_5 led to a mixture of compound **11** (65% yield) and target dicarboxylic acid **12** (15% yield). Decreasing the HNO_3 concentration to 53% improved the yield of **12** to 28%. Further dilution (to 30% HNO_3) was ineffective since the reaction became too slow. One more variation included the use of NH_4VO_3 – $Cu(NO_3)_2$ as additives (as reported by Whittaker and co-authors for the oxidation of cyclohexanol to adipic acid [6]). In this case, the yield of compound **12** was also 28%.

Unfortunately, a prolonged heating of compound **11** under the reaction conditions did not result in its transformation to target compound **12**.

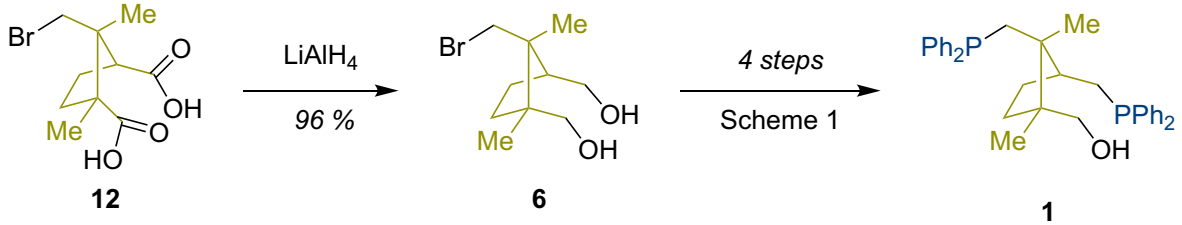
The reduction of dicarboxylic acid **12** with $LiAlH_4$ proceeded smoothly and gave target diol **6** in the yield of 96% (**Scheme 3**). Further transformation of compound **6** into ligand **1** followed the reaction sequence shown in **Scheme 1**.

To estimate the donor properties of diphosphine ligand **1**, we applied the method based on the analysis of $^1J(^{31}P–^{77}Se)$ coupling constants in the corresponding diselenides. The value of this constant correlated with electron-donating

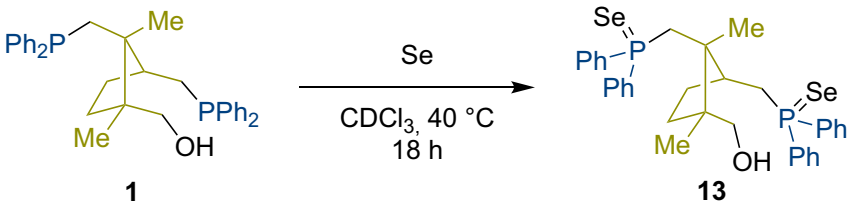
Table 1. The oxidative cleavage of 3,9-dibromocamphor (3) with HNO_3



No.	Reaction time, h	HNO_3 concentration	Additive	Yield, %		
				3	11	12
1	18	63	–	–	40	–
2	78	63	–	–	68	–
3	78	63	V_2O_5	–	65	15
4	78	53	V_2O_5	–	58	28
5	78	30	V_2O_5	35	12	13
6	78	30	NH_4VO_3 – $Cu(NO_3)_2$	traces	46	28



Scheme 3. Further access to **1** from **12**



1 **13**

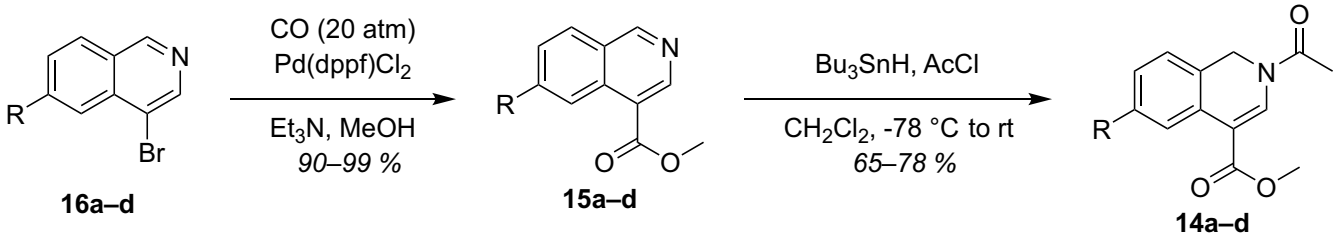
Scheme 4. The reaction of **1** with Se

properties of the substituents attached to the phosphorus atom [7]. The corresponding diselenide **13** was prepared by the reaction of compound **1** with Se (**Scheme 4**).

It was found that the $^{1}J(^{31}P–^{77}Se)$ values for compound **13** were 702 Hz and 720 Hz, which was comparable to those for a bis(dimethylphosphino)-ethane derivative ($^{1}J(^{31}P–^{77}Se)$ = 706 Hz). This result suggests that ligand **1** is highly P-donating, which can be used as a rationale for its high efficiency potential.

As a further illustration of the promising properties of ligand **1** in the asymmetric catalysis (in addition to the previous work [3]), we evaluated the hydrogenation of *N*-acetyl-1,2-dihydroisoquinoline-4-carboxylates **14a–d**. Compounds **14a–d** were obtained from the corresponding esters **15a–d** (**Scheme 5**). For the first step, we used methoxycarbonylation of commercially available bromides **16a–d**, and the obtained esters **15a–d** were reduced with tributylstannane in the presence of acetyl chloride to form **14a–d**. It was found that the parent substrate underwent the hydrogenation smoothly: the conversion was complete after 18 h, and product **17a** was obtained with 52% *ee* (according to the chiral stationary phase HPLC) (**Table 2**). Substituted derivatives **14b–d** reacted much slower. Derivative **14b** with the electron-donating OMe group reached a 90% conversion after a week; the corresponding product **17b** was formed with 45% *ee*. The hydrogenation of substrates with electron-withdrawing substituents (**14c**, R = Cl, or **14d**, R = CF_3) was virtually inefficient.

To confirm the absolute configuration of the major enantiomer in product **17a**, it was transformed

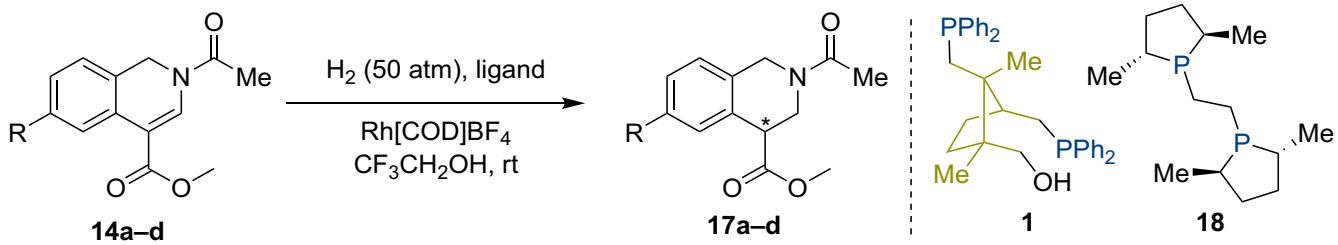


16a–d **15a–d** **14a–d**

a: R = H; **b:** R = OMe; **c:** R = Cl; **d:** R = CF_3

Scheme 5. Obtaining substrates for the hydrogenation

Table 2. The asymmetric hydrogenation of isoquinoline derivatives **14a–d**



14a–d **17a–d** **1** **18**

No.	Substrate	R	Ligand	Time, d	Conversion, %	*ee*, %
1	14a	H	1	0.75	100	52
2	14b	OMe	1	7	90	45
3	14c	Cl	1	7	67	7
4	14d	CF_3	1	7	6	–
5	14a	H	18	0.75	21	–
6	14a	H	18	3	100	0

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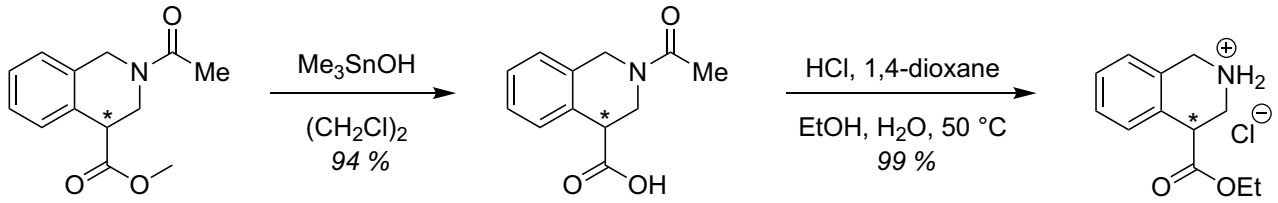

17a **19** **20**·HCl

Scheme 6. The confirmation of the absolute configuration of the major enantiomer in product **17a**

into the known ester **20**. The main challenge here was to avoid racemization at the hydrolysis/esterification steps. We achieved this by performing the ester hydrolysis with Me_3SnOH in 1,2-dichloroethane [8] and then, simultaneously, the amide hydrolysis and esterification of **19** with HCl in EtOH at 50 °C (**Scheme 6**). Product **20**×HCl had $[\alpha]_D$ = +19.7° (*c* 1.0, MeOH), which corresponded to (*S*) enantiomer (according to the literature data, $[\alpha]_D$ = –42.3° (*c* 1.0, MeOH) for (*R*) isomer [8]).

■ Conclusions

An improved and scalable route to the camphor-derived chiral diphosphine ligand ROCKYPhos has been developed and validated for the multigram synthesis. The key advancement of the updated strategy is an efficient oxidative cleavage of 3,9-dibromocamphor upon action of $V_2O_5 – HNO_3$ or NH_4VO_3–$Cu(NO_3)_2$–HNO_3, providing the corresponding dicarboxylic acid in the yield of 28% while significantly shortening the overall synthetic sequence.

The electronic properties of ROCKYPhos were investigated by the thNMR analysis of its diselenide derivative, revealing the pronounced donor ability of one of the PPh_2 fragment comparable to that of trialkylphosphines.

Finally, ROCKYPhos was successfully applied in the asymmetric hydrogenation of *N*-acetyl-1,2-dihydroisoquinoline-4-carboxylates, giving the corresponding tetrahydroisoquinolines with enantioselectivities of up to 52% *ee*. This level of stereocontrol represents a considerable advancement for this challenging substrate class and demonstrates the practical value of ROCKYPhos as a promising ligand for the asymmetric hydrogenation.

■ Experimental part

General part

The solvents were purified according to the standard procedures [9]. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($Pd(dppf)Cl_2$), (+)-3,9-dibromocamphor **3**, and other starting reagents were available commercially and obtained from Enamine Ltd. All operations with compounds **14a–d** were performed under the argon atmosphere in a glove box. Melting points were measured on the MPA100 OptiMelt automated melting point system. ^1H, $^{13}C\{^1H\}$, $^{19}F\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^1H NMR and 126 MHz for $^{13}C\{^1H\}$ NMR) or a Varian Unity Plus 400 spectrometer (at 400 MHz for ^1H NMR, 101 MHz for $^{13}C\{^1H\}$ NMR, and 376 MHz for $^{19}F\{^1H\}$ NMR), as well as using an Agilent ProPulse 600 spectrometer (at 600 MHz for ^1H, 151 MHz for $^{13}C\{^1H\}$ and 243 MHz for $^{31}P\{^1H\}$). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS or $CFCl_3$ (^{19}F) as an internal standard, and are referenced using residual NMR solvent peaks in $CDCl_3$ at 7.26 ppm for ^1H and 77.16 ppm for $^{13}C\{^1H\}$ respectively, in DMSO-d_6 at 2.50 ppm for ^1H and 39.52 ppm for $^{13}C\{^1H\}$, 4.78 and 3.31 ppm for ^1H or 49.15 ppm for $^{13}C\{^1H\}$ in CD_3OD. H_3PO_4 (85% in H_2O) used as an external $^{31}P\{^1H\}$ standard. Coupling constants (*J*) are given in Hz. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LC/MSD SL instrument (APCI atmospheric pressure chemical ionization). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer. Enantiomeric excess determinations were obtained by high-performance liquid chromatography (HPLC) with chiral columns Chiralpak IA-U (for **17a**), Chiralcel OJ-H (for **19**) and Chiralpak IC (for **20**·HCl). *ee* Values for **17a**, **19**, and **20**·HCl were not corrected for the chromatogram baseline and may include minor errors.

(1*S*,3*R*,4*S*,7*R*)-3-Bromo-7-(bromomethyl)-1,7-dimethyl-3-nitrobicyclo[2.2.1]heptan-2-one (11)

The mixture of 3,9-dibromocamphor **3** (0.76 g, 2.45 mmol) and the aq. nitric acid (13 M, 10 mL) was heated to reflux, and then stirred at this

temperature under the argon atmosphere for 78 h. The solvents were removed under reduced pressure, and distilled water (50 mL) was added to the residue. The mixture obtained was extracted with toluene (3×20 mL). The combined organic phases were dried over Na_2SO_4, and then concentrated under reduced pressure. The crude product was purified by crystallization from 2-propanol.

A colorless solid. Yield – 0.590 g (68%). M. p. 98–99 °C. $[\alpha]_D^{20}$ = +43.8 (*c* 0.5, MeOH). ^{1}H NMR (500 MHz, CD_3OD), δ, ppm: 1.08 (3H, s, CH_3), 1.31–1.40 (4H, m, CH_3 and CH_2), 1.64–1.74 (1H, m, CH_2), 1.90–2.00 (1H, m, CH_2), 2.08–2.20 (1H, m, CH_2), 3.15 (1H, d, *J* = 4.3 Hz, CH), 3.38 (1H, dd, *J* = 10.8, 1.5 Hz, CH_2), 3.82 (1H, d, *J* = 10.8 Hz, CH_2). ^{13}C{^{1}H} NMR (126 MHz, CD_3OD), δ, ppm: 10.3, 20.6, 24.8, 28.9, 39.7, 48.9, 55.8, 60.7, 92.3, 199.9. HRMS (ESI/QTOF), *m*/*z*: calculated for $C_{10}H_{14}Br_2NO_3^+$ 353.9335 $[M + H]^+$; found 353.9342.

1-(1*S*,2*R*,3*S*)-2-(Bromomethyl)-1,2-dimethylcyclopentane-1,3-dicarboxylic acid (12)

The mixture of 3,9-dibromocamphor **3** (5.00 g, 16.1 mmol) and vanadium (V) oxide (0.292 g, 1.60 mmol) in the aq. nitric acid (11.3 M, 80 mL, ca. 53% in water) was heated to reflux, and then stirred at the same temperature under the argon atmosphere for 78 h. Nitric acid was removed under reduced pressure, a fresh portion of distilled water (20 mL) was added to the residue, and the resulting mixture was re-evaporated under reduced pressure. The residue was mixed with water (100 mL) and extracted with EtOAc (3×200 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was triturated with benzene to give 1,3-dicarboxylic acid **12** (1.26 g, 4.5 mmol, 28% yield).

A colorless solid. Yield – 1.26 g (28 %). M. p. 199–201 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.04 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.40–1.49 (1H, m, CH_2), 1.80–1.99 (2H, m, CH_2), 2.38 (1H, td, *J* = 12.2, 7.6 Hz, CH_2), 3.00 (1H, t, *J* = 9.3 Hz, CH), 3.79 (1H, d, *J* = 10.5 Hz, CH_2), 3.89 (1H, d, *J* = 10.5 Hz, CH_2), 12.34 (2H, s, OH). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6), δ, ppm: 18.7, 21.3, 23.6, 33.7, 41.6, 48.7, 50.0, 55.8, 174.6, 176.3. HRMS (ESI/QTOF), *m*/*z*: calculated for $C_{10}H_{15}BrO_4Na^+$ 301.0046 $[M + Na]^+$; found 301.0039.

((1*S*,2*R*,3*S*)-2-(Bromomethyl)-1,2-dimethylcyclopentane-1,3-diyl)dimethanol (6)

To the stirred solution of dicarboxylic acid **12** (1.26 g, 4.52 mmol) in THF (50 mL), $LiAlH_4$ (0.690 g, 18.1 mmol) was added in portions under the gentle argon gas flow. The suspension obtained was heated at reflux for 5 h. Upon the completion, the mixture was cooled to 0 °C using an ice/water bath and quenched by the addition of water (1.5 mL) under vigorous stirring. Then EtOAc (300 mL) was added, the cooling bath was removed, and the resulting suspension was stirred for 2 h at r.t., then dried over Na_2SO_4 (50.0 g), filtered, and the filtrate was concentrated under reduced pressure. The residual viscous oil was dissolved in the CH_2Cl_2/MeOH mixture (300 mL, 9:1, v/v) and filtered through a small column packed with SiO_2 (approx. 100 g). The eluate containing the product was collected and concentrated under reduced pressure to give the title compound **6**, which was used further as obtained.

A colorless powder. Yield 1.08 g (96%). The spectral and physical data are consistent with those previously reported [3].

{[(1*R*,2*S*,3*S*)-2-{[diphenyl(selanylidene)-λ^5-phosphanyl]methyl}-3-(hydroxymethyl)-2,3-dimethylcyclopentyl]methyl}diphenyl-λ^5-phosphaneselone (13)

In an NMR vial, selenium (16.5 mg, 0.208 μmol) was added to the solution of diphosphine **1** (65 mg, 0.095 μmol) in $CDCl_3$ under the argon atmosphere. The reaction mixture was heated to 40 °C and shaken vigorously at that temperature overnight. The compound was characterized directly by the NMR analysis without further isolation or purification.

An orange solution. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.69–0.91 (1H, m), 1.07 (3H, s, CH_3), 1.14 (3H, s, CH_3), 1.17–1.36 (3H, m, CH_2), 2.32 (1H, dt, *J* = 14.2, 9.9 Hz), 2.56–2.73 (1H, m), 2.82 (1H, t, *J* = 14.8 Hz, CH), 3.11–3.23 (2H, m, CH_2), 3.45 (1H, t, *J* = 15.6 Hz, CH_2), 3.81 (1H, d, *J* = 11.9 Hz, CH_2), 7.22–7.33 (2H, m, Ph), 7.32–7.53 (10H, m, Ph), 7.70–7.81 (2H, m, Ph), 7.79–7.93 (2H, m, Ph), 7.92–8.07 (4H, m, Ph). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$), δ, ppm: 14.7 (d, J_{CP} = 10.5 Hz), 33.9 (d, J_{CP} = 46.2 Hz), 34.2, 35.4 (d, J_{CP} = 46.5 Hz), 44.9 (d, J_{CP} = 6.2 Hz), 48.8 (dd, J_{CP} = 12.5, 4.5 Hz), 48.9 (d, J_{CP} = 12.9 Hz), 49.9 (d, J_{CP} = 4.8 Hz), 67.6, 128.5 (d, J_{CP} = 12.2 Hz), 128.7 (d, J_{CP} = 12.0 Hz), 131.4 (dd, J_{CP} = 9.2, 3.0 Hz), 131.6 (d, J_{CP} = 14.3 Hz), 131.7 (d, J_{CP} = 14.6 Hz), 132.5 (t, J_{CP} = 11.4 Hz), 133.4 (dd, J_{CP} = 74.2, 5.76 Hz). ^{31}P{^{1}H} NMR (243 MHz, $CDCl_3$), δ, ppm: 28.0 (J_{PSe} = 702.8 Hz), 36.6 (J_{PSe} = 720.0 Hz).

The general procedure for the preparation of compounds 15a–d

In an autoclave, to the solution of the corresponding 4-bromoisoquinoline **16** (10.0 mmol) in MeOH (100 mL), $Pd(dppf)Cl_2$ (0.220 g, 0.3 mmol)

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and Et_3N (1.7 mL, 12.0 mmol, 1.22 g) were subsequently added at 25 °C. The reaction vessel was purged with argon for 5 min, then filled with CO from a gas cylinder. The reaction mixture was vigorously stirred at the temperatures indicated (80 °C for **15a**,**c**; 120 °C for **15b**; 110 °C for **15d**) under the CO atmosphere at 20 bar for 16 h (with the conversion monitored by the LC-MS analysis of the reaction aliquots). Upon the completion, the reaction mixture was concentrated under reduced pressure, and the residue was triturated with the anhydrous THF (10 mL) and filtered. The filtrate was evaporated under reduced pressure, and the residual crude product was used in the next step without further purification.

Methyl isoquinoline-4-carboxylate (**15a**)

The compound was synthesized according to the General Procedure from **16a** (3.00 g, 14.4 mmol). The reaction mixture was stirred at 80 °C for 16 h.

Beige crystals. Yield – 2.64 g (98%). M. p. 81–82 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.97 (3H, s, CH_3), 7.79 (1H, t, J = 7.6 Hz, Ar), 7.95 (1H, t, J = 7.7 Hz, Ar), 8.26 (1H, d, J = 8.2 Hz, Ar), 8.76 (1H, d, J = 8.7 Hz, Ar), 9.05 (1H, s, Ar), 9.53 (1H, s, Ar). LC-MS, *m*/*z* (APCI): 188 $[M+H]^+$. The analytical data are consistent with those previously reported [10].

Methyl 6-methoxyisoquinoline-4-carboxylate (**15b**)

The compound was synthesized according to the General Procedure from **16b** (2.50 g, 10.5 mmol). The reaction mixture was stirred at 120 °C overnight.

A colorless powder. Yield – 2.04 g (90 %). M. p. 122–124 °C. Anal. Calcd. for $C_{12}H_{11}NO_3$, %: C 66.35; H 5.10; N 6.45. Found, %: C 66.07; H 5.47; N 6.38. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 4.01 (3H, s, CH_3), 4.02 (3H, s, CH_3), 7.29 (1H, dd, J = 9.0, 2.5 Hz, Ar), 7.91 (1H, d, J = 9.0 Hz, Ar), 8.40 (1H, d, J = 2.5 Hz, Ar), 9.18 (1H, s, Ar), 9.22 (1H, s, Ar). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ, ppm: 52.2, 55.7, 103.1, 119.0, 120.9, 124.5, 130.1, 136.5, 148.0, 156.0, 162.8, 167.3. LC-MS, *m*/*z* (APCI): 218 $[M+H]^+$.

Methyl 6-chloroisoquinoline-4-carboxylate (**15c**)

The compound was synthesized according to the General Procedure from **16c** (2.44 g, 10.0 mmol). The reaction mixture was stirred at 80 °C for 18 h.

A light-brown powder. Yield – 2.03 g (92 %). M. p. 111–112 °C. Anal. Calcd. for $C_{11}H_8ClNO_2$, %: C 59.61; H 3.64; N 6.32; Cl 15.99. Found, %: C 59.93; H 3.82; N 6.60; Cl 16.11. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.96 (3H, s, CH_3), 7.83 (1H, dt, J = 8.8, 2.0 Hz, Ar), 8.31 (1H, dd, J = 8.8, 1.8 Hz, Ar), 8.82 (1H, s, Ar), 9.10 (1H, s, Ar), 9.55 (1H, s, Ar). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6), δ, ppm: 52.5, 118.8, 123.2, 126.4, 128.6, 130.9, 133.3, 137.7, 147.0, 157.1, 165.8. HRMS (ESI/QTOF), *m*/*z*: calculated for $C_{11}H_9ClNO_2^+$ 222.0316 $[M+H]^+$; found 222.0314.

Methyl 6-(trifluoromethyl)isoquinoline-4-carboxylate (**15d**)

The compound was synthesized according to the General Procedure from **16d** (2.80 g, 10.2 mmol). The reaction mixture was stirred at 110 °C overnight.

A brown powder. Yield – 2.57 g (99 %). M. p. 76–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 4.06 (3H, s, CH_3), 7.87 (1H, dd, J = 8.5, 1.7 Hz, Ar), 8.18 (1H, d, J = 8.5 Hz, Ar), 9.31 (1H, s, Ar), 9.37 (1H, s, Ar,), 9.47 (1H, s, Ar). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ, ppm: 52.7, 121.0, 123.4 (q, $^3J_{CF}$ = 4.7 Hz), 123.7 (q, $^3J_{CF}$ = 2.6 Hz), 123.8 (q, $^1J_{CF}$ = 272.9 Hz), 129.3, 129.5, 133.3, 133.8 (q, $^2J_{CF}$ = 32.5 Hz), 148.1, 157.1, 166.4. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6), δ, ppm: −62.2. HRMS (ESI/QTOF), *m*/*z*: calculated for $C_{12}H_9F_3NO_2^+$ 256.0580 $[M+H]^+$; found 256.0575.

The general procedure for the preparation of compounds 14a–d

To a pre-cooled to −78 °C solution of the corresponding ester **15a–d** (1 mmol) in CH_2Cl_2 (6 mL), Bu_3SnH (0.292 g, 1 mmol), and neat acetyl chloride (79.0 µL, 1.1 mmol, 87.0 mg) were sequentially added with stirring under the argon atmosphere. The reaction mixture was stirred, maintaining the same temperature for 2 h. The cooling bath was then removed, and the reaction mixture gradually warmed to rt with stirring. In case of the incomplete conversion (as determined by LC-MS of a small aliquot of the reaction mixture), the reaction mixture was treated with additional separate portions of Bu_3SnH and acetyl chloride at −40 °C, with stirring maintained at this temperature under the argon atmosphere for 2 h before warming to rt. Once the reaction was complete, a sat. aq. NH_4Cl solution was added, and the mixture was stirred overnight. The layers were separated, the organic layer was then dried over Na_2SO_4 and concentrated under reduced pressure. The residual crude product was purified by the trituration with hexane/*t*BuOMe mixture (5 mL, 4:1, v/v).

Methyl 2-acetyl-1,2-dihydroisoquinoline-4-carboxylate (**14a**)

The compound was synthesized according to the General Procedure from **15a** (0.750 g, 4.00 mmol).

A beige powder. Yield – 0.668 g (72 %). M.p. 88–91 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 2.34 (3H, s, CH_3), 3.86 (3H, s, CH_3), 4.88 (2H,

s, CH_2), 7.11 (1H, d, *J* = 7.5 Hz, Ar), 7.21 (1H, t, *J* = 7.4 Hz, Ar), 7.28 (1H, t, *J* = 7.7 Hz, Ar), 7.86 (1H, s, CH), 8.16 (1H, d, *J* = 8.0 Hz, Ar). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$), δ, ppm: 21.5, 44.9, 51.8, 110.4, 125.1, 126.1, 127.8, 128.1, 128.2, 128.9, 136.7, 166.1, 169.3. HRMS (ESI/QTOF), *m/z*: calculated for $C_{13}H_{14}NO_3^+$ 232.0968 $[M + H]^+$; found 232.0971.

Methyl 2-acetyl-6-methoxy-1,2-dihydroisoquinoline-4-carboxylate (**14b**)

The compound was synthesized according to the General Procedure from **15b** (0.560 g, 2.58 mmol).

A colorless powder. Yield – 0.522 g (78 %). M.p. 86–87 °C. Anal. Calcd. for $C_{14}H_{15}NO_4$, %: C 64.36; H 5.79; N 5.36. Found, %: C 64.43; H 5.83; N 5.06. ^1H NMR (500 MHz, $CDCl_3$), δ, ppm: 2.34 (3H, s, CH_3), 3.83 (3H, s, CH_3), 3.86 (3H, s), 4.83 (2H, s, CH_2), 6.77 (1H, dd, *J* = 8.8, 2.3 Hz, Ar), 7.02 (1H, d, *J* = 8.5 Hz, Ar), 7.83 (1H, s, Ar), 7.89 (1H, s, CH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 21.5, 44.5, 51.8, 55.5, 103.4, 110.6, 113.6, 121.0, 127.0, 129.3, 137.2, 159.5, 166.1, 169.3 (the compound demonstrated a significant decomposition rate in the solution). LC-MS, *m/z* (APCI): 262 $[M+H]^+$.

Methyl 2-acetyl-6-chloro-1,2-dihydroisoquinoline-4-carboxylate (**14c**)

The compound was synthesized according to the General Procedure from **15c** (0.325 g, 1.50 mmol).

A yellowish solid. Yield 0.260 g (67 %). M.p. 112–114 °C. Anal. Calcd. for $C_{13}H_{12}ClNO_3$, %: C 58.77; H 4.55; N 5.27; Cl 13.34. Found, %: C 58.81; H 4.68; N 5.40; Cl 13.22. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.35 (3H, s, CH_3), 3.87 (3H, s, CH_3), 4.85 (2H, s, CH_2), 7.03 (1H, d, *J* = 8.1 Hz, Ar), 7.18 (1H, dd, *J* = 8.1, 2.2 Hz, Ar), 7.91 (1H, s, CH), 8.23 (1H, s, Ar). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$), δ, ppm: 21.5, 44.5, 52.0, 109.1, 125.2, 127.0, 127.3, 127.6, 129.8, 134.1, 137.7, 165.7, 169.3. LC-MS, *m/z* (APCI): 266 $[M+H]^+$.

Methyl 2-acetyl-6-(trifluoromethyl)-1,2-dihydroisoquinoline-4-carboxylate (**14d**)

The compound was synthesized according to the General Procedure from **15d** (0.250 g, 1.00 mmol).

A beige powder. Yield – 0.192 g (65 %). M.p. 104–106 °C. Anal. Calcd. for $C_{14}H_{12}F_3NO_3$, %: C 56.19; H 4.04; N 4.68. Found, %: C 56.42; H 4.25; N 4.72. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: δ 2.37 (3H, s, CH_3), 3.89 (3H, s, CH_3), 4.95 (2H, s, CH_2), 7.22 (1H, d, *J* = 8.0 Hz, Ar), 7.47 (1H, d, *J* = 8.5 Hz, Ar), 7.96 (1H, s, CH), 8.54 (1H, s, Ar). $^{13}C\{^1H\}$ NMR, δ, ppm: the spectrum is uninformative due to the compound decomposition during NMR processing. LC-MS, *m/z* (APCI): 300 $[M+H]^+$.

Methyl 2-acetyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (17a)

The mixture of isoquinoline methyl carboxylate **14a** (500.0 mg, 2.16 mmol), bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (43.9 mg, 108.1 μmol) and [(1*R*,2*R*,3*S*)-2,3-bis[(diphenylphosphanyl)methyl]-1,2-dimethylcyclopentyl]methanol **1** (56.7 mg, 108.1 μmol) was dissolved in degassed CF_3CH_2OH (5 mL). All operations with reagents for the asymmetric hydrogenation were performed in a glove box. The solution obtained was transferred to the autoclave. Subsequently, the autoclave was evacuated and backfilled with H_2 (50 bar) from a gas cylinder. The reaction mixture was vigorously stirred at 20 °C for 18 h. The solvent was evaporated under reduced pressure, and the residue was purified by the flash column chromatography (*t*BuOMe/MeOH = 1:0 to 5:1, v/v as an eluent) to give tetrahydroisoquinoline methyl carboxylate **17a**.

A viscous oil. Yield – 451.0 mg (1.94 mmol, 89%). ^1H NMR (400 MHz, $CDCl_3$), the compound exists as a mixture of rotamers (ca. 2:1) δ, ppm: 2.18 (0.36×3H, s, CH_3), 2.25 (0.64×3H, s, CH_3), 3.57 (0.64×1H, dd, *J* = 13.4, 4.1 Hz, CH_2), 3.64–3.69 (0.36×1H, m, CH_2), 3.71 (3H, m, CH_3), 3.87 (1H, dt, *J* = 12.7, 4.3 Hz, CH), 4.34 (0.64×1H, dd, *J* = 13.4, 3.6 Hz, CH_2), 4.42 (0.64×1H, d, *J* = 17.4 Hz, CH_2 AB system), 4.47 (0.36×1H, dd, *J* = 13.3, 5.1 Hz, CH_2), 4.60 (0.36×1H, d, *J* = 16.2 Hz, CH_2 AB system), 4.74 (0.36×1H, d, *J* = 16.2 Hz, CH_2 AB system), 5.06 (0.64×1H, d, *J* = 17.6 Hz, CH_2 AB system), 7.12–7.25 (2H, m, Ph), 7.28 (2H, t, *J* = 6.6 Hz, Ph). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$), the compound exists as a mixture of rotamers (ca. 2:1) δ, ppm: 21.5 and 21.9, 41.6 and 44.2, 44.3 and 45.0, 45.5 and 48.1, 52.5 and 52.6, 126.5 and 126.7, 127.0 and 127.3, 127.8 and 128.0, 129.2 and 129.7, 129.9 and 130.6, 133.3 and 133.8, 169.9 and 170.3, 172.0 and 172.5. HRMS (ESI/QTOF), *m/z*: calcd. for $C_{13}H_{15}NO_3Na^+$ 256.0944 $[M + Na]^+$; found 256.0951. *ee* = 52% (determined by chiral HPLC).

The general procedure for the synthesis of tetrahydroisoquinoline-4-carboxylates *rac*-17 (prepared for the *ee* determination)

In a high-pressure vessel to the solution of the corresponding dihydroisoquinoline-4-carboxylate **14a** (0.50 mol) in MeOH (5 mL), Pd/C (10% w/w, 50.0 mg) was added in one portion. The reaction vessel was evacuated and backfilled with H_2 from a gas cylinder (repeated twice), and the suspension was kept at rt with intensive stirring under the H_2 atmosphere at 50 bar for 24 h.

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The catalyst was filtered off, the filter cake was washed with MeOH (3×2 mL). The filtrate was concentrated under reduced pressure, the remained solid was dried under a high vacuum (1 mmHg) to give the title product **(±)-17a**.

2-Acetyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (19)

To the solution of tetrahydroisoquinoline methyl carboxylate (0.400 g, 1.72 mmol) in dichloroethane (50 mL), neat trimethylstannanol (0.936 g, 5.17 mmol) was added. The reaction mixture was heated to reflux and kept with stirring at that temperature for 18 h. After cooling to room temperature, the resulting solution was diluted with CH_2Cl_2 (100 mL), washed with the aq. 1 M solution of $NaHSO_4$ (2×50 mL), then a sat. aq. solution of NaCl (40 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude title compound, which was used in the next step without further purification. The analytical sample was obtained after the purification by the reverse-phase HPLC (performed on a puriFlash C18-HP column using CH_3CN–H_2O–0.1%HCOOH gradients).

A colorless powder. Yield – 0.353 g (94%). M. p. 155–157 °C. *ee* 53% (determined by HPLC). ^{1}H NMR (400 MHz, CD_3OD), the compound exists as a mixture of rotamers (ca. 2:1) δ, ppm: 2.18 (0.34×3H, s, CH_3), 2.24 (0.66×3H, s, CH_3), 3.50 (0.34×1H, dd, J = 13.2, 4.6 Hz, CH_2), 3.58 (0.64×1H, dd, J = 13.6, 4.1 Hz, CH_2), 3.88 (0.34×1H, t, J = 4.4 Hz, CH), 3.91 (0.64×1H, t, J = 3.6 Hz, CH), 4.34 (0.64×1H, d, J = 17.3 Hz, CH_2 AB system), 4.35–4.47 (0.66×1H, m, CH_2), 4.56 (0.34×1H, dd, J = 13.2, 4.2 Hz, CH_2), 4.65 (0.34×1H, d, J = 16.4 Hz, CH_2 AB system), 4.79 (0.34×1H, d, J = 16.4 Hz, CH_2 AB system), 5.01 (0.64×1H, d, J = 17.3 Hz, CH_2 AB system), 7.15–7.36 (4H, m, Ph). ^{13}C{^{1}H} NMR (101 MHz, CD_3OD), the compound exists as a mixture of rotamers (ca. 2:1) δ, ppm: 21.4 and 21.7, 42.8, 45.5 and 45.7, 45.1 and 46.7, 127.5 and 127.64, 127.60, 128.0 and 128.7, 130.1 and 130.8, 132.8 and 133.5, 134.0 and 134.1, 172.6 and 172.9, 175.1 and 175.6. HRMS (ESI/QTOF), *m/z*: calculated for $C_{12}H_{14}NO_3^+$ 220.0968 $[M + H]^+$; found 220.0964.

Ethyl 1,2,3,4-tetrahydroisoquinoline-4-carboxylate hydrochloride (20×HCl)

To the solution of tetrahydroisoquinoline carboxylic acid **19** (100.0 mg, 0.456 mol) in EtOH (5 mL), aq. HCl (0.2 mL, 10 M) was added. The resulting mixture was stirred at 50 °C for 9 days. After the completion of the reaction (by ^{1}H NMR spectra of the small aliquots of the reaction mixture) all volatiles were removed under reduced pressure. The residue was dissolved in a dry EtOH (4 mL), the solution was acidified with an anhydrous HCl (0.2 mL, *ca.* 3.6 M in 1,4-dioxane) and then stirred at 50 °C for 36 h. The reaction mixture was concentrated under reduced pressure to give tetrahydroisoquinoline hydrochloride **20** with a sufficient purity.

A colorless powder. Yield 109.6 mg (99 %). M. p. 124–126 °C. *ee* 57 % (determined by HPLC). $[\alpha]_D^{20}$ = +19.7 (*c* 1.0, MeOH) (lit. $[\alpha]_D$ = –42.3° (*c* 1.0, MeOH) [8]). Anal. Calcd. for $C_{12}H_{16}ClNO_2$: C 59.63; H 6.67; N 5.79; Cl 14.67. Found: C 60.02; H 6.39; N 5.62; Cl 14.59. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.23 (3H, t, J = 7.1 Hz, CH_3), 3.54 (2H, d, J = 6.2 Hz, CH_2), 4.18 (2H, q, J = 7.1 Hz, CH_2), 4.22–4.31 (3H, m, CH_2 and CH), 7.25–7.30 (1H, m, Ph), 7.32 (2H, dt, J = 7.2, 3.6 Hz, Ph), 7.35–7.39 (1H, m, Ph). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6), δ, ppm: 14.4, 40.9, 42.2, 43.8, 61.8, 127.6, 128.1, 128.2, 128.9, 129.6, 129.7, 171.2. LC-MS, *m/z* (APCI): 206 $[M+H]^+$. The spectral and physical data were consistent with those previously reported [8].

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Synthesis of (±)-(1R,6R,7R)-2-azabicyclo[4.2.0]octan-7-ol

Abstract

An approach to the synthesis of (±)-(1*R*,6*R*,7*R*)-2-azabicyclo[4.2.0]octan-7-ol, a promising amino alcohol building block for drug discovery, has been described. The method is based on [2+2] the cycloaddition of *tert*-butyl vinyl ether and a ketene generated *in situ* from a glutaric acid derivative, as well as the intramolecular lactam formation as the key steps. Although the [2+2] cycloaddition step and further transformations proceeded without any notable stereoselectivity, the title compound was synthesized in an amount greater than 30 g with a high diastereomeric purity. This was provided by the physical properties of the intermediate (±)-(1*R*,6*R*,7*R*)-7-(*tert*-butoxy)-2-azabicyclo[4.2.0]octan-3-one that was easily separated by crystallization.

Keywords: bicyclic compounds; [2+2] cycloaddition; lactams; building blocks

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Синтез (±)-(1*R*,6*R*,7*R*)-2-азабіцикло[4.2.0]октан-7-олу

Анотація

Описано підхід до синтезу (±)-(1*R*,6*R*,7*R*)-2-азабіцикло[4.2.0]октан-7-олу – перспективного будівельного блока класу аміноспиртів для пошуку лікарських засобів. Метод ґрунтується на [2+2] циклоприєднанні *трет*-бутилвінілового етеру та кетену, що було генеровано *in situ* з похідної глутарової кислоти, а також внутрішньомолекулярному утворенні лактаму як ключових стадіях. Хоча стадія [2+2] циклоприєднання та подальші перетворення відбувалися без помітної стереоселективності, цільову сполуку було одержано в кількості понад 30 г з високою діастереомерною чистотою, що забезпечили фізичні властивості проміжного (±)-(1*R*,6*R*,7*R*)-7-(*трет*-бутокси)-2-азабіцикло[4.2.0]октан-3-ону, який легко відділяли кристалізацією.

Ключові слова: біциклічні сполуки; [2+2] циклоприєднання; лактами; будівельні блоки

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■ Introduction

Saturated azabicyclic compounds have attracted much attention in organic and medicinal chemistry as promising three-dimensional chemotypes for drug discovery and other applications [1, 2]. They can be considered as conformationally restricted isosteres of piperidine, which is a top saturated heterocycle encountered in marketed drugs [3, 4]. 2-Azabicyclo[4.2.0]octane (**1**) is a representative of such bicyclic systems that can be found in a number of biologically active compounds (**Figure 1**). Notable examples include Bruton tyrosine kinase inhibitor **2** [5], acetylcholine esterase (AChE) inhibitor **3** [6], or chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTh2) antagonist **4** [7]. Despite these success stories, efficient synthetic approaches towards properly functionalized 2-azabicyclo[4.2.0]-octane derivatives are scarce. Thus, 7-functionalized derivative **5** was prepared by the Norrish type II reaction of *N*-tosyl piperidinyl ketone **6** (**Scheme 1**, *A*) [8]. 6-Substituted isomers **7** were synthesized by the intramolecular [2+2] cycloaddition involving keteniminium salt intermediates (**Scheme 1**, *B*) [9].

Recently, our group reported the synthesis of 6-functionalized 2-azabicyclo[3.2.0]heptane derivatives based on the [2+2] cycloaddition of *tert*-butyl vinyl ether and a ketene generated *in situ* from a cinnamic acid derivative, as well as the intramolecular lactam formation as the key steps [10]. In this work, we report an extension of this methodology to 7-substituted 2-azabicyclo[4.2.0]octane derivatives. We demonstrate the applicability of this approach by the preparation of (±)-(1*R*,6*R*,7*R*)-2-azabicyclo[4.2.0]octan-7-ol (**8**) – a promising amino alcohol building block for drug discovery (**Scheme 2**). Notably, none of the literature approaches described in **Scheme 1** is applicable to the synthesis of building block **8**. Meanwhile, favorable physicochemical properties of compound **8** (the molecular weight MW = 175, the calculated 1-octanol – the water partition coefficient logarithm for a model *N*-acetyl derivative cLog*P* = –0.75) and three-dimensional, sp^3-rich, conformationally restricted nature make it a promising building block for the compound library synthesis in drug discovery.

■ Results and discussion

Our synthesis of compound **8** started with the reaction of methyl 5-chloro-5-oxopentanoate (**11**) and *tert*-butyl vinyl ether (**12**) in the presence of Et_3N in toluene at 110 °C (**Scheme 3**). The ketene

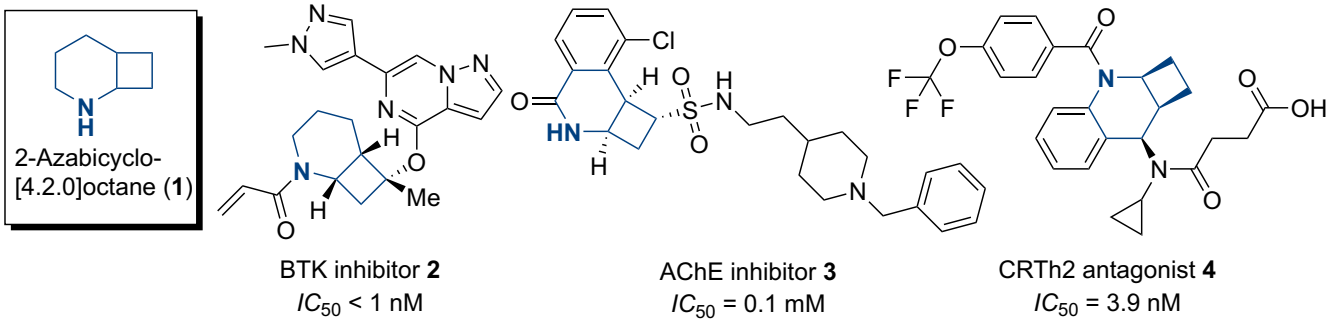
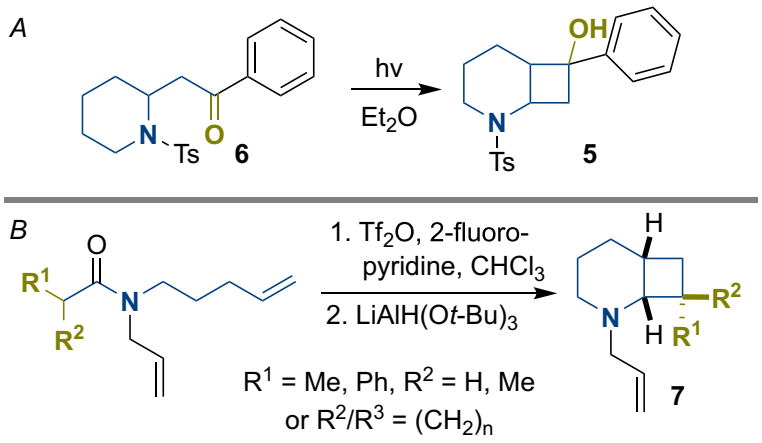


Figure 1. Biologically active 2-azabicyclo[4.2.0]octanes



Scheme 1. The known approaches to the synthesis of 2-azabicyclo[4.2.0]octanes

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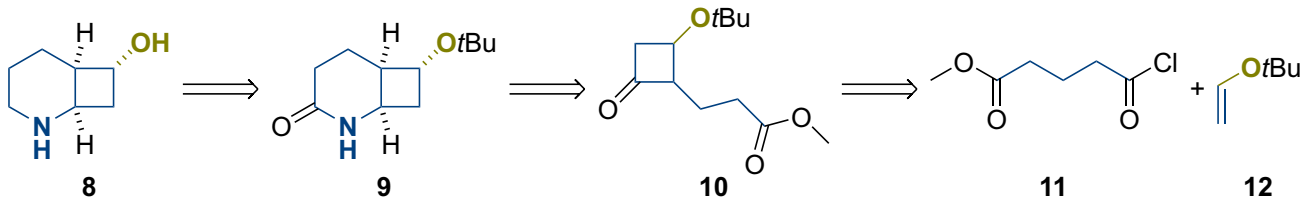
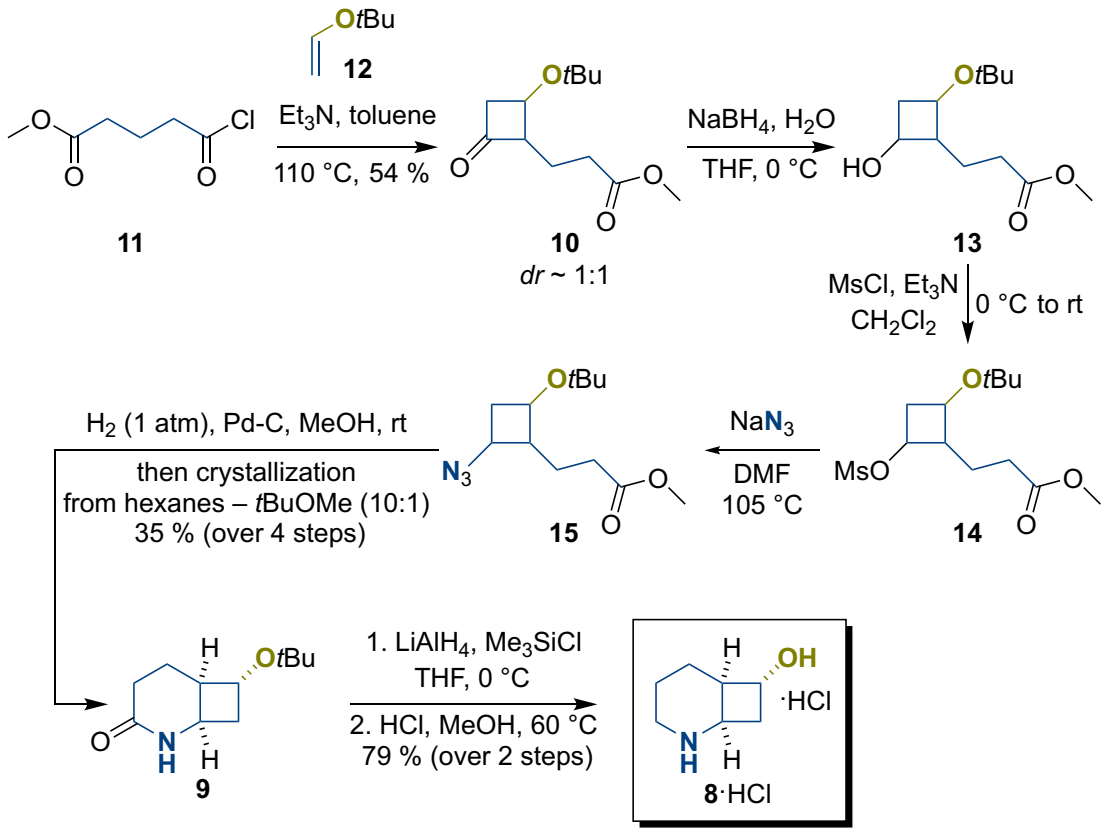


Scheme 2. The retrosynthetic analysis of amino alcohol **8**

intermediate generated from acyl chloride **11** upon the action of Et_3N reacted with electron-rich alkene **12**, which led to the formation of trisubstituted cyclobutane derivative **10** in the yield of 54%. Notably, this transformation required elevated temperature, unlike the case of the lower homolog that reacted at ambient temperature. Unfortunately, the cycloaddition step had a negligible diastereoselectivity (*dr* ~ 1:1), so that even after the chromatographic purification, compound **10** was obtained as a mixture of diastereomers used in further transformation.

We were not discouraged by the stereoselectivity issues and decided to proceed with further chemical transformation, i.e., the reduction with $NaBH_4$, the mesylation, reaction with NaN_3, and the catalytic hydrogenation. Intermediate alcohol **13**, mesylate **14**, and azide **15** were obtained as very complex mixtures of stereoisomers and other by-products and were therefore subjected to the next steps without characterization. To our delight, the catalytic hydrogenation of intermediate **15** was accompanied by the intramolecular lactam formation already at ambient temperature, and its main product **9** differed significantly by physical properties from all by-products obtained from any other possible stereoisomers. This fact enabled an easy separation of compound **9** upon the trituration with an appropriate solvent system, i.e., hexanes – *t*BuOMe (10:1). In this way, lactam **9** was obtained in the yield of 35% over four steps. The final steps of the synthetic sequence included the reduction of compound **9** with *in-situ* generated AlH_3 and removal of the *tert*-butyl protective group, which provided target amino alcohol **8** as hydrochloride (in the yield of 79% over two steps).

Notably, the synthetic scheme demonstrated good scalability: up to 32.7 g of compound **8**×HCl was obtained in a single run. The overall yield of the seven-step synthetic sequence was 15% (average 76% per step).



Scheme 3. The synthesis of amino alcohol **8**

The relative configuration of compound **8**×HCl was confirmed by the nuclear Overhauser effect (NOE) experiments. Thus, the significant NOEs were observed upon the irradiation of H-1 (at H-8a), H-6 (at H-8a), and H-7 (at H-4a and H-8b) protons (**Figure 2**).

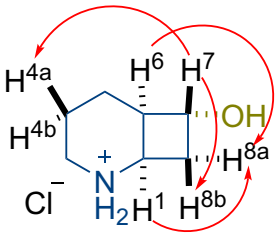


Figure 2. Significant NOEs observed for compound **8**×HCl

■ Conclusions

An efficient synthetic route to (±)-(1*R*,6*R*,7*R*)-2-azabicyclo[4.2.0]octan-7-ol has been developed based on the ketene-alkene [2+2] cycloaddition followed by the intramolecular lactam formation. Although the first stages of the reaction sequence proceeded without a noticeable stereoselectivity, the desired diastereomer could be obtained in high purity due to the favorable physical properties of a bicyclic lactam intermediate that allowed its straightforward separation by crystallization. The method has proven to be practical and scalable, enabling the preparation of multigram amounts of the target amino alcohol as a hydrochloride and providing a convenient entry to functionalized 2-azabicyclo[4.2.0]octane building blocks relevant for medicinal chemistry.

■ Experimental part

General

The solvents were purified according to the standard procedures [11]. Compound **11** and other starting reagents were available commercially and obtained from Enamine Ltd. Melting points were measured on the MPA100 OptiMelt automated melting point system. ^{1}H and ^{13}C{^{1}H} NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR and 126 MHz for ^{13}C{^{1}H} NMR) or a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR and 101 MHz for ^{13}C{^{1}H} NMR), or an Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR and 151 MHz for ^{13}C{^{1}H} NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as a standard, and are referenced using residual NMR solvent peaks in $CDCl_3$ at 7.26 ppm for ^{1}H and 77.16 ppm for ^{13}C{^{1}H} respectively, in DMSO-d_6 at 2.50 ppm for ^{1}H and 39.52 ppm for ^{13}C{^{1}H}. Coupling constants (*J*) are given in Hz. Mass spectra were recorded on an Agilent 1100 LC/MSD SL instrument (APCI atmospheric pressure chemical ionization). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

Methyl 3-(2-(*tert*-butoxy)-4-oxocyclobutyl)-propanoate (10)

In a two-necked reactor, equipped with a magnetic stir bar and a reflux condenser, the solution of *tert*-butyl vinyl ether **12** (138.6 g, 1.38 mol) in toluene (1 L) was prepared. Then Et_3N (133.6 g, 1.32 mol) was added in one portion, and the resulting mixture was gently heated to 110 °C. Methyl 5-chloro-5-oxopentanoate **11** (207 g, 1.26 mol) was added to the reaction mixture in a dropwise manner at the same temperature and then heated to reflux. Upon refluxing for 1 h, the mixture was cooled to room temperature, then diluted with water (600 mL) and concentrated under reduced pressure. The residue was diluted with water (500 mL) and extracted with *t*BuOMe (3×400 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a crude product purified by flash chromatography (hexanes – EtOAc (8:1) as an eluent, R_f = 0.53).

A colorless oil. Yield – 153 g (54%). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.21 (0.5×9H, s, $C(CH_3)_3$), 1.23 (0.5×9H, s, $C(CH_3)_3$), 1.86–1.99 (2H, m, CH_2), 2.37–2.54 (2H, m, CH_2), 2.89–3.02 (1H, m, CH), 3.04–3.09 (0.5×1H, m, CH), 3.21–3.24 (0.5×1H, m, CH) 3.25–3.31 (1H, m, CH), 3.66 (0.5×3H, s, CH_3), 3.67 (0.5×3H, s, CH_3), 3.99–4.03 (0.5×1H, m, CH), 4.42–4.46 (0.5×1H, m, CH). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ, ppm: 19.4, 22.3, 28.1, 28.2, 31.1, 31.5, 51.5, 51.6, 54.6, 55.5, 59.1, 62.7, 62.9, 66.2, 74.3, 74.4, 173.3, 173.7, 208.0, 210.1. HRMS (ESI/QTOF), *m/z*: calculated for $C_{12}H_{21}O_4^+$ 229.1440 $[M + H]^+$; found 229.1429.

(±)-(1*R*,6*R*,7*R*)-7-(*tert*-Butoxy)-2-azabicyclo[4.2.0]octan-3-one (9)

The mixture of THF (500 mL) and water (500 mL) was prepared, and 153 g (0.670 mol) of ketone **10** was dissolved in this biphasic system. The reaction mixture was cooled to 0 °C, and sodium borohydride (25.3 g, 0.670 mol, 1.0 equiv.) was added portionwise under stirring at the same temperature. The mixture was maintained at 0 °C for 1 h. Afterwards, the reaction was allowed to warm to room temperature, diluted with *t*BuOMe

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(600 mL), and water (400 mL) was added. The aqueous layer was extracted with *t*BuOMe (2 × 250 mL). The combined organic extracts were dried over the anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. Product **13** was obtained as a colorless oil (153 g) and used in the next step without characterization.

Compound **13** (153 g, ca. 0.670 mol) was dissolved in a dry dichloromethane (1 L) and cooled to 0 °C in an ice–water bath. Triethylamine (0.871 mol, 88 g, 122 mL, 1.3 equiv.) was added under stirring, followed by the dropwise addition of methanesulfonyl chloride (0.737 mol, 85 g, 1.1 equiv.) while maintaining the internal temperature below 10 °C. After the completion of the addition, the cooling bath was removed, and the mixture was stirred overnight at room temperature. The reaction mixture was quenched with water, the organic layer was separated and concentrated under reduced pressure. The residue was dissolved in *t*BuOMe (750 mL), extracted with water (2 × 350 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give crude mesylate **14** (159 g) as a reddish liquid used immediately in the next step.

Mesylate **14** was dissolved in DMF (1 L), and sodium azide (2.01 mol, 131 g, 3.0 equiv.) was added in portions. The suspension was heated to 105 °C and stirred for 40 h. Upon the reaction completion, the mixture was cooled to room temperature, poured onto water (1 L), and extracted with *t*BuOMe (4 × 400 mL). The combined organic extracts were washed with water (3 × 400 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure at 30–36 °C. (CAUTION! The concentration should be performed behind a protective shield due to the potential hazard of azide-containing residues). Product **15** was obtained as a yellowish liquid used in the next step without characterization.

The solution of crude azide **15** obtained in the previous step in MeOH (750 mL) was transferred into a high-pressure vessel. Pd/C (10% w/w, 11 g) was added in one portion, and the vessel was evacuated and backfilled with hydrogen from a balloon. The resulting suspension was stirred vigorously under a hydrogen atmosphere at 25 °C for 18–20 h. If the conversion was incomplete (as determined by the ^{1}H NMR analysis of small aliquots), the vessel was re-evacuated and recharged with fresh hydrogen. Upon the completion of the reduction, the catalyst was removed by the filtration through a silica gel pad and washed with MeOH (2 × 250 mL). The combined filtrates were concentrated under reduced pressure. The residue was triturated with hexanes – *t*BuOMe (10:1, 500 mL), and the resulting crystalline solid was collected by the filtration, washed with an additional portion of the same solvent system, and dried under high vacuum (0.075 mmHg) to give lactam **9**.

A brownish solid. Yield – 46.3 g (35 %). M. p. 99–102 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.18 (9H, s, $C(CH_3)_3$), 1.85–1.93 (2H, m, CH_2), 2.18–2.21 (2H, m, CH_2), 2.34–2.45 (2H, m, CH_2), 2.66–2.72 (1H, m, CH), 3.86–3.93 (1H, m, CH), 4.13–4.18 (1H, m, CH), 6.24 (1H, br. s, NH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 21.2, 28.4, 29.1, 40.5, 40.9, 44.5, 67.4, 73.7, 172.6. HRMS (ESI/QTOF), *m*/*z*: calculated for $C_{11}H_{20}NO_2^+$ 198.1494 $[M + H]^+$; found 198.1486.

(±)-(1*R*,6*R*,7*R*)-2-azabicyclo[4.2.0]octan-7-ol hydrochloride (8×HCl)

An oven-dried triple-necked reactor was flushed with argon, then THF (800 mL) was added, followed by the portionwise addition of $LiAlH_4$ (16.1 g, 0.423 mol, 1.8 equiv.) under a gentle gas flow. The suspension was cooled to 0 °C, and neat trimethylchlorosilane (45.7 g, 0.423 mol, 1.8 equiv.) was introduced dropwise. The solution of the lactam obtained in the previous step (46.3 g, 0.235 mol) in THF (200 mL) was then added dropwise at the same temperature. The cooling bath was replaced with an oil bath, and the mixture was warmed to 50 °C and stirred for 32 h. Upon the completion, the reaction was cooled to 0 °C in an ice/water bath and quenched by a careful addition of the THF/water mixture (50 mL, 1:1 v/v) followed by a dropwise addition of 7 M aqueous KOH (50 mL). The solids precipitated were filtered, and the filter cake was washed with *t*BuOMe (3 × 150 mL). The combined organic phases were concentrated under reduced pressure to give the corresponding intermediate as a brownish powder (40.3 g) used directly in the next step without further purification.

The solution of the previously obtained compound in MeOH (700 mL) was prepared, and the anhydrous HCl (ca. 4.0 M in 1,4-dioxane, 700 mL) was added in one portion at room temperature. The resulting mixture was stirred at 60 °C for 40 h. Upon the completion, the reaction mixture was concentrated under reduced pressure. The crude residue was purified by the recrystallization from CH_3CN – *i*PrOH (15:1, 100 mL), and the resulting solid was collected and dried under high vacuum to give product **8**×HCl.

A beige solid. Yield – 32.7 g (79 %). M. p. 179–181 °C (dec). ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.45–1.55 (1H, m, CH), 1.57–1.68 (2H, m, CH_2), 1.70–1.83 (1H, m, CH), 1.91–1.99 (1H, m, CH), 2.21–2.26 (1H, m, CH), 2.32–2.37 (1H, m, CH), 2.54–2.67 (1H, m, CH), 3.05–3.08 (1H, m, CH), 3.43–3.50 (1H, m, CH), 4.39–4.35 (1H, m, CH), 5.39 (1H, br s, OH), 8.82 (1H, br s, NH), 9.48 (1H, br s, NH). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6), δ, ppm: 18.4, 20.6, 34.9, 41.5, 42.2, 44.4, 65.5. HRMS (ESI/QTOF), *m*/*z*: calculated for $C_7H_{15}NO^+$ 128.1075 $[M + H]^+$; found 128.1069.

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The Synthetic Access to Fused 6,7,8,9-Tetrahydro-5*H*-pyridoazepines: Evaluation of Ring-Closure Strategies

Abstract

The synthetic accessibility of fused pyridoazepine frameworks was investigated by evaluating a series of strategies designed to construct differently fused azepine systems. Several precursor designs enabling alternative ring-closure topologies were considered. The "lactam" pathway proved to be synthetically inaccessible under various conditions due to chemoselectivity issues and competing intermolecular processes. In contrast, an efficient route to the 6,7,8,9-tetrahydro-5*H*-pyrido[3,2-*c*]azepine framework was achieved *via* the intramolecular cyclization strategy, in which the amine functionality was introduced prior to the ring assembly. The route developed proceeded under practical laboratory conditions using inexpensive reagents and was demonstrated on a gram scale. The results obtained provide insight into the structural factors governing the ring-closure efficiency in pyridoazepine systems and open up a practical access to a fused heterocyclic scaffold previously underexplored.

Keywords: pyridoazepine; fused heterocycles; ring-closure reactions; synthetic accessibility; organic synthesis

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Синтетичний доступ до конденсованих 6,7,8,9-тетрагідро-5*H*-піридоазепінів: оцінювання стратегій циклізації

Анотація

Синтетичну доступність конденсованих каркасів піридоазепіну було досліджено шляхом оцінювання серії стратегій, спрямованих на конструювання різних топологій конденсованих азепінових систем. Було розглянуто декілька варіантів синтетичних попередників, що дозволяють реалізувати альтернативні шляхи стадії циклізації. «Лактамний» шлях виявився синтетично непридатним за різних умов через проблеми хемоселективності та конкурентні міжмолекулярні процеси. Натомість ефективний шлях до каркаса 6,7,8,9-тетрагідро-5*H*-піридо[3,2-*c*]азепіну було реалізовано за допомогою стратегії внутрішньомолекулярної циклізації, коли аміногрупу вводили до стадії формування азепанового циклу. Розроблений синтетичний маршрут перебігає в практичних лабораторних умовах із використанням доступних недорогих реагентів. Його було продемонстровано у грамовому масштабі. Отримані результати дають уявлення про структурні чинники, що визначають ефективність замикання циклу в системах піридоазепіну, та відкривають практичний підхід до малодослідженого класу конденсованих гетероциклічних каркасів.

Ключові слова: піридоазепан; конденсовані гетероцикли; реакції циклізації; синтетична доступність; органічний синтез

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Introduction

Nitrogen-containing heterocyclic compounds constitute a fundamental structural motif in organic chemistry and play a central role in natural products, pharmaceuticals, agrochemicals, and functional materials. Consequently, the development of efficient synthetic methodologies for the preparation of nitrogen heterocycles remains a major focus of modern synthetic chemistry [1].

The importance of nitrogen heterocycles is particularly evident in medicinal chemistry. The analysis of FDA-approved small-molecule drugs showed that approximately 60% of them contained at least one nitrogen heterocycle as of 2014 [2a]. A subsequent analysis of ring systems presented in drug molecules conducted by *Taylor and co-workers* revealed that 63 of the Top 100 most frequently used ring systems found in drugs listed in the FDA Orange Book (as of January 2020) are nitrogen-containing heterocycles [3]. Notably, this represents a slight increase compared with their earlier 2014 study, where 61 nitrogen-containing heterocycles were identified among the top 100 ring systems [4]. A stronger trend is observed among clinical candidates. Among the Top 100 most frequently used ring systems in U.S. clinical trials (as of January 2020), 83 contain a nitrogen heterocycle [2a]. Recent analyses of the structural diversity of heterocycles in pharmaceuticals approved by the European Medicines Agency between 2014 and 2023 have confirmed the continuing dominance of N-heterocycles, both monocyclic and polycyclic, in the design of small-molecule drugs [2b].

One effective strategy for expanding the heterocyclic chemical space involves combining well-established ring fragments to form new bicyclic or polycyclic fused systems [5, 6]. In this context, and in line with the research direction of our group, we became interested in frameworks combining pyridine and azepane motifs [7–9]. This choice was motivated by two key considerations. First, pyridine is among the most frequently encountered heterocycles in pharmaceutical compounds and is widely recognized as a privileged scaffold in medicinal chemistry [10]. Second, azepane represents a member of the medium-sized ring family, which has attracted increasing attention in drug discovery [11]. Azepane, as a member of the saturated medium-sized rings family, provides a unique balance between conformational rigidity and three-dimensional spatial characteristics compared with small rings and macrocycles. These structural features can confer favorable physicochemical and biological properties, making medium-sized rings attractive motifs in medicinal chemistry. However, despite these advantages, medium-sized rings remain significantly underrepresented in screening libraries and marketed drugs, largely due to the intrinsic synthetic challenges associated with their preparation [12].

In the present study, we focused on fused pyridoazepane frameworks **A**–**D** differing in the relative position of the pyridine nitrogen atom with respect to the azepane ring (**Figure 1**a). From a medicinal chemistry perspective, such positional isomers are particularly attractive since they enable implementation of the *nitrogen walk* concept [13], allowing systematic tuning of electronic properties and interaction patterns while preserving the overall molecular framework.

A survey of the literature revealed that these frameworks remain largely unexplored. The unsubstituted topologies **A** and **D** have each been mentioned only once in the patent literature. In the case of compound **A**, the reported synthesis involved five steps and yielded only 5% [14], whereas for compound **D** [15], no synthetic route has been described. The topologies **B** and **C** have received somewhat greater attention. For example, 6,7,8,9-tetrahydro-5*H*-pyrido[3,4-*c*]azepine (**B**) has been investigated as a ligand for nicotinic acetylcholine receptors (nAChRs) [16]. Its synthesis relied on a Beckmann rearrangement of 5,6,7,8-tetrahydroisoquinolin-8-one followed by the reduction of the resulting lactam with lithium aluminum hydride. Meanwhile, 6,7,8,9-tetrahydro-5*H*-pyrido[4,3-*c*]azepine (**C**) has been studied in the development of matrix metalloproteinase-9 inhibitors [17] (**Figure 1**b). In that study, a substituted derivative of this scaffold displayed the highest inhibitory activity toward the target protease. However, the synthesis of the unsubstituted core was not described, and the reported substituted derivative required a nine-step sequence employing ring-closing metathesis as the key transformation.

Therefore, in contrast to benzannulated analogs, which synthesis has been extensively studied (19 documents in the Reaxys® database for 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine) [18], the preparation of pyridoazepane scaffolds remains poorly developed, with only a few isolated examples. As a result, their easy implementation in drug-discovery programs is complicated. Taking into account the potential of structures, such as

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three-dimensional nitrogen-rich scaffolds for medicinal chemistry, creating reliable routes to these systems represents an important synthetic challenge (**Figure 1**c).

In this work, we present an evaluation of ring-closure strategies toward fused pyridoazepane frameworks **A**–**D** (**Figure 1**d). By exploring the alternative cyclization approaches and comparing their efficiency and synthetic practicality, we aim to identify viable routes to these under-explored heterocyclic scaffolds and thereby expand the accessible chemical space of condensed medium-sized nitrogen heterocycles relevant to medicinal chemistry.

■ Results and discussion

The development of a practical synthetic route to the pyridoazepane frameworks required the evaluation of several strategic disconnections (**Schemes 1**–**3**). Particular attention was paid to the efficiency of the key ring-closure step and the chemoselectivity of the subsequent functional group interconversions within the electronically coupled pyridine-azepine system.

The first approach toward the target bicyclic compound **A** (**Scheme 1**) relied on the intramolecular cyclization of a suitably functionalized precursor **3** to furnish the fused seven-membered lactam **4**. Ester **3** was prepared in a high yield on a gram scale from commercially available aldehyde **1** *via* the Horner-Wadsworth-Emmons reaction (compound **2**), followed by the chemoselective catalytic hydrogenation of the alkene moiety. The cyclization **3**→**4** proceeded cleanly and reproducibly, delivering the desired bicyclic azepanone **4** core in a satisfactory yield. Structurally, this lactam intermediate appeared to be a promising platform for further transformation into the corresponding amine *via* well-established approaches for the lactam reduction. However, attempts to reduce the lactam carbonyl to the target amine revealed significant chemoselectivity challenges (**Scheme 1**). The mild sodium

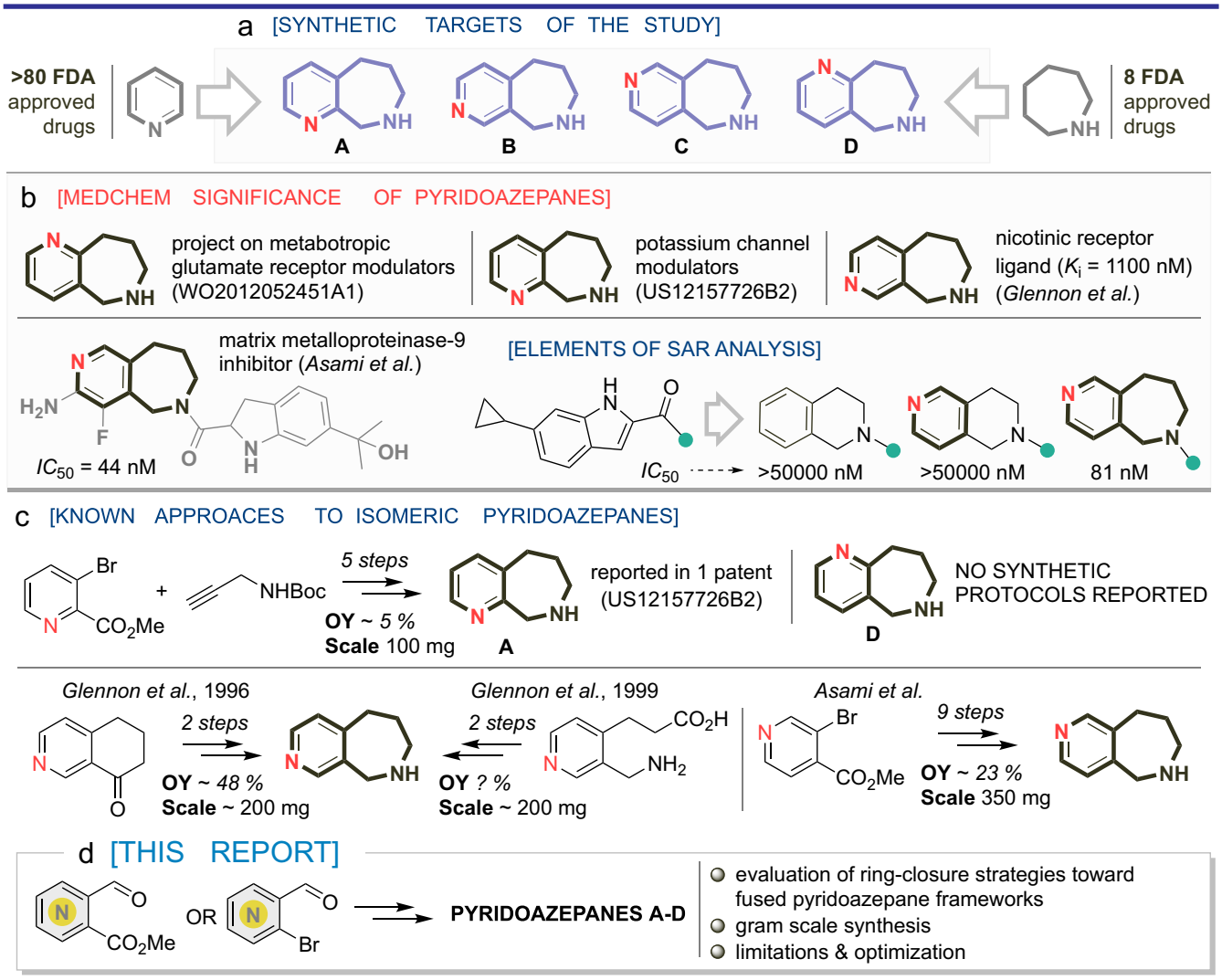
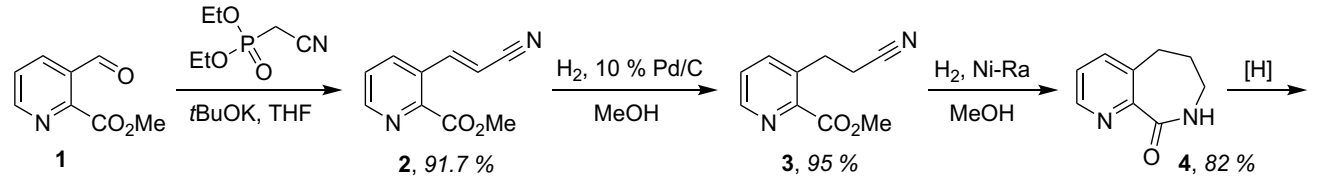
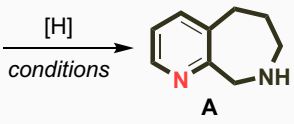


Figure 1. The status quo of the topic and the current work



[CONDITIONS FOR THE REDUCTION OF LACTAM 4]

Reducing agent	Conditions	Result
$NaBH_4$	MeOH, RT, 2 hours	complex mixture, amine **A** was not detected
BH_3 (DMS complex)	THF, reflux, 4 hours	40% lactam conversion, pyridine hydrogenation
BH_3 (generated *in situ*)	THF, reflux, 6 hours	mixture of partially reduced species
BH_3 (DMS complex)	THF, reflux, 12 hours	extensive over-reduction, decomposition products

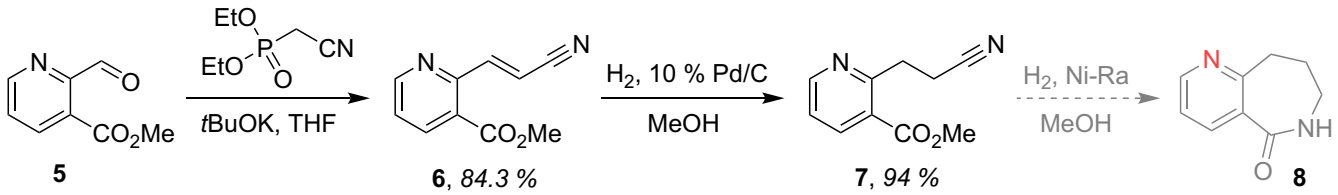


Scheme 1. The initial strategy toward **A** and lactam reduction studies

borohydride proved to be excessively reactive under the conditions studied. Instead of the selective reduction of the lactam carbonyl group, a rapid non-selective hydride transfer occurred, leading to complex product mixtures. The high intrinsic hydride reactivity likely promotes reduction at multiple electrophilic sites within the fused heterocyclic framework. Borane-based reducing systems commonly employed for the lactam reduction also failed to achieve the desired chemoselectivity. Although the partial conversion of the lactam functionality was observed, the simultaneous hydrogenation of the pyridine ring consistently occurred, producing mixtures of partially reduced intermediates. The lack of selectivity observed under borane conditions can be rationalized by competing coordination pathways. In addition to the activation of the lactam carbonyl group, borane can coordinate to the pyridine nitrogen atom. Such coordination increases the susceptibility of the heteroaromatic ring toward the hydride attack, thereby facilitating an undesired reduction of the pyridine fragment. Furthermore, the rigid fused architecture of the system likely enhances the electronic communication between the two heterocyclic subunits, altering the reduction behavior compared with simple monocyclic lactams. Consequently, in contrast to isolated lactams that are typically reduced smoothly under borane conditions, the presence of a fused electron-deficient pyridine ring significantly perturbs the reduction profile. Since competing reduction pathways could not be effectively suppressed, this synthetic direction was ultimately abandoned.

Faced with significant difficulties in reducing lactam **4** to obtain pyridoazepane **A**, we then attempted to apply an appropriate strategy to synthesize the alternative target framework **D**, using the isomeric aldehydoester **5** as the key precursor (**Scheme 2**). The starting nitrile **7** designed for the subsequent cyclization to the bicyclic lactam was obtained in two steps from the readily available precursor **5** in a high overall yield. However, the standard conditions for the nitrile reduction that proved to be effective in the previous system failed to deliver the expected transformation to intermediate **8**. Unexpectedly, instead of the anticipated intramolecular cyclization, the reaction predominantly proceeded through intermolecular pathways, leading to the formation of the insoluble polymeric material. No detectable formation of the desired bicyclic product was observed. This behavior suggests that, under the applied conditions, the uncontrolled intermolecular reactivity outcompeted the intended intramolecular ring closure. The formation of a polymeric material likely reflects the insufficient conformational preorganization of the substrate and/or the excessive intrinsic reactivity of the functional groups involved, both of which favor the chain propagation. As a result, the pathway discussed proved to be synthetically impractical, and further optimization of this approach was considered unjustified, as well as its implementation for the synthesis of isomeric compounds **B** and **C**.

These observations prompted us to reconsider the disconnection strategy and explore an



Scheme 2. Attempts to synthesize pyridoazepane **D**

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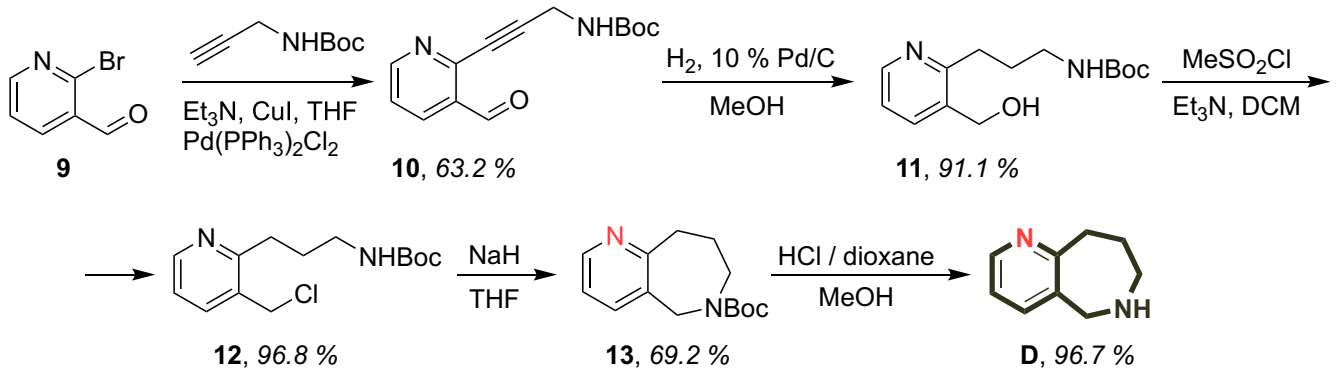

Scheme 3. The development of an optimized route toward isomer **D**

alternative approach to constructing the pyridoazepane core.

To circumvent the chemoselectivity issues associated with the post-cyclization lactam reduction and the intermolecular side reactions observed in the previous approaches, a redesigned synthetic strategy was implemented (**Scheme 3**). In this route, the amine functionality was introduced prior to the final ring-closure step, thereby eliminating the need for the fused lactam reductive transformation.

The optimized route proved to be operationally straightforward and relied on inexpensive, commercially available reagents. The synthesis commenced with bromoaldehyde **9**, which scalable preparation had previously been reported by our group [9]. The Sonogashira coupling of **9** with *N*-Boc-propargylamine enabled the installation of all carbon atoms required for the construction of the target pyridoazepane framework, giving aldehyde **10**. The subsequent catalytic hydrogenation reduced both the alkyne and aldehyde functionalities, delivering the corresponding amino alcohol **11**. The conversion of the hydroxyl group into the corresponding chloride, followed by the intramolecular nucleophilic substitution, provided the bicyclic intermediate **13**. Notably, in this case, the cyclization proceeded smoothly and in a practical yield on a gram scale without detectable intermolecular side reactions. The target building block **D** was obtained after removal of the Boc protecting group with the total yield of 37%. All transformations were carried out under practical laboratory conditions without the need for rigorously anhydrous techniques or specialized equipment. Intermediates were purified by the standard column chromatography or simple recrystallization. The scalability of the sequence further highlights its preparative robustness and synthetic utility.

The findings highlight the critical role of the precursor design in enabling the efficient formation of medium-ring systems within pyridine-containing fused systems. With an efficient route to pyridoazepane **D** in hand, future studies will focus on extending this strategy toward the scalable synthesis of the remaining isomeric pyridoazepane frameworks.

■ Conclusions

Thus, we evaluated several synthetic strategies for the construction of fused pyridoazepane frameworks. Initial approaches based on the post-cyclization reduction of fused lactam intermediates or nitrile-derived precursors proved to be synthetically impractical due to chemoselectivity issues and competing intermolecular processes. These observations highlight the challenges associated with the formation and functionalization of medium-sized nitrogen heterocycles embedded within electronically coupled pyridine systems.

The redesigned strategy, in which the amine functionality was introduced prior to the ring closure, made it possible to effectively construct the pyrido[3,2-*c*]azepine framework. The route developed proceeds under practical laboratory conditions, employs inexpensive and readily available reagents, and has proven its reliability on a gram scale. With an efficient entry to pyridoazepane **D** established (5-step synthetic sequence, 37% total yield), ongoing studies are directed toward extending this strategy to the scalable synthesis of the remaining positional isomers. The access to these frameworks will expand the available chemical space of pyridine-containing medium-sized heterocycles and facilitate their further study as nitrogen-rich building blocks for medicinal chemistry.

■ Experimental part

All solvents were purified according to the standard procedures. The starting materials were obtained from Enamine Ltd. NMR spectra were

recorded on a Bruker Avance 500 spectrometer (at 500 MHz for ^{1}H and 126 MHz for ^{13}C) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H, 101 MHz for ^{13}C). Tetramethylsilane (^{1}H, ^{13}C) was used as an internal standard. The column chromatography was performed with silica gel (200–300 mesh). The elemental analysis was performed at the Analytical Laboratory of the Institute of Organic Chemistry, NAS of Ukraine.

Methyl-3-(2-cyanovinyl)picolinate (2)

Potassium *tert*-butoxide (8.5 g, 75.8 mmol) was added to the solution of diethyl (cyanomethyl)phosphonate (15.0 g, 84.8 mmol) in the anhydrous THF (150 mL) at 0 °C. The mixture was stirred for 30 min at room temperature, after which methyl 3-formylpicolinate (**1**) (10.0 g, 60.6 mmol) was added. The reaction mixture was stirred overnight at room temperature, diluted with water, and extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with water (1 × 100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give compound **2**, which was used in the next step without further purification.

A pale yellow amorphous solid. Yield – 11.0 g (91.7%). Anal. Calcd. for $C_{10}H_8N_2O_2$, %: C 63.83; H 4.29; N 14.89. Found, %: C 64.09; H 4.10; N 14.59. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 3.87 (3H, s), 6.10 (1H, d, J = 11.8 Hz), 7.77 (1H, dd, J = 7.8, 4.8 Hz), 7.83 (1H, d, J = 11.8 Hz), 8.21 (1H, d, J = 8.0 Hz), 8.73 (1H, d, J = 4.4 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 52.40, 101.97, 117.50, 124.32, 130.11, 136.08, 144.90, 145.45, 146.56, 166.78. LC–MS, m/z (ES–API): 189.1 $[M+H]^+$.

Methyl-3-(2-cyanoethyl)picolinate (3)

To the solution of compound **2** (11.0 g, 58.5 mmol) in MeOH (150 mL), Pd/C (10%) (1 g) was added. The mixture was hydrogenated at 1 atm and room temperature until the LC–MS analysis indicated the complete consumption of the starting material. The catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure to give compound **3**.

A colorless oil. Yield – 11.0 g (95%). Anal. Calcd. for $C_{10}H_{10}N_2O_2$, %: C 63.15; H 5.30; N 14.73. Found, %: C 63.53; H 4.81; N 14.83. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 2.84 (2H, t, J = 7.3 Hz), 3.11 (2H, t, J = 7.1 Hz), 3.86 (3H, s), 7.58 (1H, dd, J = 8.0, 4.7 Hz), 7.90 (1H, d, J = 7.7 Hz), 8.53–8.56 (1H, m). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 16.68, 28.08, 52.40, 119.11, 125.18, 134.46, 136.22, 146.67, 148.27, 165.99. LC–MS, m/z (ES–API): 191.1 $[M+H]^+$.

5,6,7,8-Tetrahydro-9*H*-pyrido[2,3-*c*]azepin-9-one (4)

To the solution of compound **3** (11.0 g, 57.9 mmol) in MeOH (200 mL), Raney nickel was added. The mixture was hydrogenated at 70 atm and 70 °C in a 500 mL autoclave until the LC–MS analysis indicated the reaction was complete (typically within 16 h). The catalyst was filtered off, and the solvent was removed under reduced pressure to give compound **4**.

An off-white solid. Yield – 9.3 g (82%). Anal. Calcd. for $C_9H_{10}N_2O$, %: C 66.65; H 6.21; N 17.27. Found: C 66.83; H 6.49; N 17.62. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.87 (2H, t, J = 6.8 Hz), 2.73 (2H, t, J = 7.1 Hz), 2.89 (2H, q, J = 6.3 Hz), 7.41 (1H, dd, J = 7.6, 4.6 Hz), 7.71 (1H, d, J = 7.8 Hz), 8.23 (1H, s), 8.48–8.58 (1H, m). ^{13}C NMR (101 MHz, DMSO-d_6), δ, ppm: 29.52, 31.17, 41.74, 125.01, 138.26, 139.69, 148.10, 153.80, 166.68. LC–MS, m/z (ES–API): 163.1 $[M+H]^+$.

Methyl-2-(2-cyanovinyl)nicotinate (11)

Potassium *tert*-butoxide (8.5 g, 75.8 mmol) was added to the solution of diethyl (cyanomethyl)phosphonate (15 g, 84.8 mmol) in the anhydrous THF (150 mL) at 0 °C. The mixture was stirred for 30 min at room temperature, and methyl 2-formylnicotinate (**10**) (10 g, 60.6 mmol) was added. The reaction mixture was stirred overnight at room temperature, diluted with water, and extracted with ethyl acetate (3 × 100 mL). The organic layer was washed with water (1 × 100 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give compound **11**.

A pale yellow amorphous solid. Yield – 10.1 g (84.3%). Anal. Calcd. for $C_{10}H_8N_2O_2$, %: C 63.83; H 4.29; N 14.89. Found, %: C 63.61; H 3.93; N 15.09. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 3.89 (3H, s), 6.12 (1H, d, J = 11.8 Hz), 7.56–7.66 (1H, m), 7.98 (1H, d, J = 11.8 Hz), 8.27–8.36 (1H, m), 8.73–8.90 (1H, m). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 52.32, 104.51, 117.83, 121.06, 122.04, 137.02, 138.28, 148.91, 152.75, 167.48. LC–MS, m/z (ES–API): 189.1 $[M+H]^+$.

Methyl-2-(2-cyanoethyl)nicotinate (12)

To the solution of compound **11** (10.1 g, 53.7 mmol) in MeOH (150 mL), Pd/C (10%) (1 g) was added. The mixture was hydrogenated at ambient pressure and room temperature until the LC–MS analysis indicated the reaction was complete. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to give compound **12**.

A colorless oil. Yield – 10.0 g (94%). Anal. Calcd. for $C_{10}H_{10}N_2O_2$, %: C, 63.15; H, 5.30; N, 14.73.

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Found, %: C, 63.31; H, 5.49; N, 14.26. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 2.91 (2H, t, J = 7.2 Hz), 3.41 (2H, t, J = 7.2 Hz), 3.86 (3H, s), 7.45 (1H, dd, J = 7.6, 4.9 Hz), 8.23 (1H, d, J = 7.9 Hz), 8.68–8.76 (1H, m). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 15.39, 31.49, 52.31, 119.22, 121.50, 126.27, 137.81, 151.67, 159.73, 167.92. LC–MS, m/z (ES–API): 191.1 $[M+H]^+$.

***tert*-Butyl (3-(3-formylpyridin-2-yl)prop-2-yn-1-yl)carbamate (15)**

A mixture of 2-bromonicotinaldehyde (**14**) (10.0 g, 54.0 mmol), *tert*-butyl prop-2-yn-1-ylcarbamate (10.0 g, 64.8 mmol), CuI (0.6 g, 3.2 mmol), $Pd(PPh_3)_2Cl_2$·DCM (1.3 g, 1.6 mmol) and Et_3N (16.4 g, 162.2 mmol) in a dry THF (120 mL) was stirred under argon at 60 °C for 16 h. After the completion (TLC monitoring), the mixture was cooled, diluted with ethyl acetate (150 mL) and washed with water (100 mL) and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The purification by column chromatography (hexane/ethyl acetate) gave compound **15**.

A pale yellow amorphous solid. Yield – 8.9 g (63.2%). Anal. Calcd. for $C_{14}H_{16}N_2O_3$, %: C, 64.60; H, 6.20; N, 10.76. Found, %: C, 64.75; H, 5.94; N, 10.70. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.40 (9H, s), 4.08 (2H, d, J = 5.5 Hz), 7.57 (1H, dd, J = 7.7, 4.9 Hz), 8.14 (1H, dd, J = 7.9, 1.4 Hz), 8.74–8.85 (1H, m), 10.41 (1H, s). ^{13}C NMR (101 MHz, DMSO-d_6), δ, ppm: 28.31, 32.02, 79.69, 79.73, 82.57, 123.55, 131.62, 134.00, 146.19, 151.09, 155.30, 189.99. LC–MS, m/z (ES–API): 261.1 $[M+H]^+$.

***tert*-Butyl (3-(3-(hydroxymethyl)pyridin-2-yl)propyl)carbamate (16)**

Compound **15** (8.9 g, 34.2 mmol) was dissolved in MeOH and hydrogenated over Pd/C (10%) (1 g) at ambient pressure and room temperature until the LC–MS analysis indicated the completion of the reaction. The catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure to give compound **16**.

A colorless oil. Yield – 8.3 g (91.1%). Anal. Calcd. for $C_{14}H_{22}N_2O_3$, %: C, 63.13; H, 8.33; N, 10.52. Found, %: C, 63.38; H, 8.18; N, 10.12. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.41 (9H, s), 1.81–1.90 (2H, m), 2.98 (2H, t, J = 6.4 Hz), 3.22 (2H, td, J = 6.3, 4.4 Hz), 4.62 (1H, dd, J = 7.8, 5.9 Hz), 4.65–4.74 (2H, m), 6.68 (1H, t, J = 4.4 Hz), 7.33 (1H, dd, J = 7.7, 3.5 Hz), 7.71 (1H, dd, J = 7.9, 2.2 Hz), 8.42–8.57 (1H, m). ^{13}C NMR (101 MHz, DMSO-d_6), δ, ppm: 26.89, 28.32, 32.64, 39.54, 61.28, 79.56, 121.64, 133.83, 134.05, 147.39, 156.55, 157.25. LC–MS, m/z (ES–API): 267.2 $[M+H]^+$.

***tert*-Butyl (3-(3-(chloromethyl)pyridin-2-yl)propyl)carbamate (17)**

Methanesulfonyl chloride (4.2 g, 37.4 mmol) was added to a stirred solution of alcohol **16** (8.3 g, 31.1 mmol) and triethylamine (9.4 g, 93.5 mmol) in a dry dichloromethane at 0 °C. The reaction mixture was stirred for 3 h while warming to room temperature. The mixture was quenched with water and extracted with dichloromethane (3 × 80 mL). The organic layer was washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give compound **17**, which was used in the next step without further purification.

A light-yellow oil. Yield – 8.6 g (96.8%). Anal. Calcd. for $C_{14}H_{21}ClN_2O_2$, %: C, 59.05; H, 7.43; N, 9.84. Found, %: C, 59.07; H, 7.07; N, 9.88. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.40 (9H, s), 1.83–1.91 (2H, m), 2.98 (2H, t, J = 6.4 Hz), 3.17–3.26 (2H, m), 4.78 (2H, s), 6.57 (1H, t, J = 4.4 Hz), 7.24 (1H, dd, J = 7.8, 3.5 Hz), 7.46 (1H, dd, J = 7.8, 2.2 Hz), 8.40–8.48 (1H, m). ^{13}C NMR (101 MHz, DMSO-d_6), δ, ppm: 26.91, 28.32, 32.69, 39.27, 41.93, 79.50, 122.15, 129.00, 135.56, 147.52, 155.71, 156.55. LC–MS, m/z (ES–API): 285.1 $[M+H]^+$.

***tert*-Butyl 5,7,8,9-tetrahydro-6H-pyrido-[3,2-c]azepine-6-carboxylate (18)**

Compound **17** (8.6 g, 30.2 mmol) was dissolved in a dry THF and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 1.4 g, 36.3 mmol) was added portionwise under argon. The mixture was stirred for 1 h at 0 °C and then for 16 h at room temperature. The reaction was quenched with water and extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The purification by column chromatography gave compound **18**.

A white amorphous solid. Yield – 5.2 g (69.2%). Anal. Calcd. for $C_{14}H_{20}N_2O_2$, %: C, 67.72; H, 8.12; N, 11.28. Found, %: C, 67.49; H, 7.68; N, 10.98. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.44 (9H, s), 1.98–2.05 (2H, m), 2.94–3.01 (2H, m), 3.35–3.43 (1H, m), 3.44–3.53 (1H, m), 4.25–4.33 (1H, m), 4.46 (1H, d, J = 13.5 Hz), 7.16 (1H, dd, J = 7.8, 3.5 Hz), 7.54 (1H, dd, J = 7.9, 2.2 Hz), 8.39 (1H, dd, J = 3.5, 2.2 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 25.91, 28.35, 32.73, 47.97, 50.19,

79.50, 121.50, 130.75, 135.21, 147.48, 154.78, 158.37. LC–MS, *m/z* (ES–API): 249.2 $[M+H]^+$.

6,7,8,9-Tetrahydro-5H-pyrido[3,2-c]azepine (19)

Compound **18** (5.2 g, 20.9 mmol) was dissolved in methanol (100 mL) and treated with hydrochloric acid (100 mL) (4 M in dioxane). The reaction mixture was stirred for 2 h at room temperature. The solvent was removed under reduced pressure, and the residue was neutralized with a saturated $NaHCO_3$ solution. The extraction with dichloromethane (3 × 80 mL) followed by drying (Na_2SO_4) and the concentration gave compound **19**.

A colorless oil. Yield – 3.0 g (96.7%). Anal. Calcd. for $C_9H_{12}N_2$, %: C, 72.94; H, 8.16; N, 18.90. Found, %: C, 72.97; H, 8.33; N, 18.43. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.73–1.82 (2H, m), 3.15–3.21 (2H, m), 3.21–3.27 (2H, m), 3.93 (2H, s), 7.04 (1H, dd, J = 7.3, 4.9 Hz), 7.38 (1H, dd, J = 7.5, 1.4 Hz), 8.33 (1H, dd, J = 4.9, 1.5 Hz). ^{13}C NMR (126 MHz, $CDCl_3$), δ, ppm: 28.55, 35.10, 50.17, 53.78, 121.42, 134.57, 135.86, 147.42, 161.35. LC–MS, *m/z* (ES–API): 149.1 $[M+H]^+$.

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An Efficient Method for the Synthesis of Benzofused Five-Membered Cyclic Sulfamates

Abstract

An efficient and scalable method for the synthesis of 1,2,3-benzoxathiazole 2,2-dioxides and related five-membered cyclic sulfamates employing gaseous sulfuryl fluoride (SO_2F_2) in the presence of Et_3N is described. The one-pot cyclization of 2-aminophenol derivatives proceeds at rt and tolerates a variety of substituents on the aromatic ring, including electron-withdrawing groups, as well as *N*-substituted substrates. The method provides the target heterocycles in improved yields compared to classical SO_2Cl_2-based protocols and is readily scalable to 50 g without the loss of efficiency. A virtual library of 49 cyclic sulfamate derivatives was generated and evaluated using the LLAMA approach. The library members demonstrate favorable lead-like physicochemical profiles with 100% compliance with the Lipinski, Veber, Muegge, and GSK 4/400 filters, supporting the utility of the chemotypes proposed for medicinal chemistry applications.

***Keywords*:** heterocycles; organosulfur compounds; sulfamates; building blocks

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Ефективний метод синтезу бензоконденсованих п’ятичленних циклічних сульфаматів

Анотація

Описано ефективний і масштабований метод синтезу 1,2,3-бензоксатіазол-2,2-діоксидів та споріднених п’ятичленних циклічних сульфаматів з використанням газоподібного сульфурилфториду (SO_2F_2) у присутності Et_3N. Одностадійна циклізація похідних 2-амінофенолу з різноманітними замісниками на ароматичному кільці, разом із електроноакцепторними групами, а також *N*-заміщеними субстратами, відбувається за кімнатної температури. Метод забезпечує одержання цільових гетероциклів з покращеними виходами, якщо порівнювати з класичними методами, які полягали у використанні SO_2Cl_2, і, на відміну від останніх, дозволяє масштабувати спосіб синтезу цільових сульфаматів. Було створено віртуальну бібліотеку з 49 циклічних похідних сульфаматів та оцінено її за допомогою підходу LLAMA. Представники бібліотеки демонструють сприятливі лідер-подібні фізико-хімічні характеристики зі 100% відповідністю фільтрам Ліпінського, Вебера, Мюгге та GSK 4/400, що підтверджує корисність запропонованих хемотипів для застосування в медичній хімії.

***Ключові слова*:** гетероцикли; сульфурорганічні сполуки; сульфамати; будівельні блоки

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Introduction

The pioneering synthesis of 1,2,3-benzoxathiazole 2,2-dioxides was reported by *Andersen et al.* in 1991 [1] by the treatment of *N*-(2-hydroxyphenyl)-*p*-toluenesulfonamides (the parent heterocycle and a NO_2-substituted derivative) with sulfuryl chloride and triethylamine. The *N*-unsubstituted (NH) cyclic sulfamates were subsequently obtained by the removal of the *N*-tosyl group using potassium fluoride or sodium azide [2]. An alternative approach to five-membered cyclic sulfamidates from 1,2-amino alcohols was developed through the sequential treatment with thionyl chloride followed by the ruthenium-catalyzed oxidation ($RuCl_3/NaIO_4$) [3–6]. Another synthetic strategy involves the use of the Burgess reagent (*N*-(triethylammoniumsulfonyl)-carbamates) for the construction of spiro-sulfamidate glycosides from *exo*-glycals [7].

Cyclic sulfamates have found significant applications as enzyme inhibitors in medicinal chemistry. Hanson, Whalen, and Wong evaluated five-membered cyclic sulfamates (CySAs) as mechanism-based inhibitors of sulfatases [8] (**Figure 1**). In the context of the steroid sulfatase (STS) inhibition, Lawrence Woo et al. prepared cyclic sulfamate derivatives of estrone (EMATE) by fusing the 1,2,3-benzoxathiazole 2,2-dioxide ring in 2,3- or 3,4-positions of the steroidal A-ring [9]. *Kok et al.* reported that a 1,6-*epi*-cyclophellitol cyclosulfamidate acts as a selective, reversible α-glucosidase inhibitor that mimics the $^4C_1$ Michaelis complex conformation [6]. Critically, this cyclosulfamidate stabilized recombinant human GAA *in vitro*, *in cellulo* (Pompe disease fibroblasts), and *in vivo* (zebrafish), outperforming *N*-butyldeoxynojirimycin (Miglustat) as a pharmacological chaperone for Pompe disease. *Benltifa et al.* demonstrated that deprotected spiro-sulfamidate glycosides act as selective, competitive inhibitors of α-glucosidase from yeast (K_i = 190 μM) and amyloglucosidase from *Aspergillus niger* (K_i = 258 μM) [7].

Kim et al. incorporated five-membered cyclic sulfamidate motifs into the side chains of 1ß-methylcarbapenems [3] and oxazolidinones [4]. In the carbapenem series, derivatives bearing cyclic sulfonamide moieties demonstrated the broad-spectrum antibacterial activity comparable to or superior to meropenem and imipenem against a panel of Gram-positive and Gram-negative bacteria.

Clarke et al. described BACE-1 hydroxyethylamine inhibitors, in which a cyclic sulfamate-containing fragment was evaluated as part of the non-prime side substituent interacting with Arg-296 via an edge-to-face aromatic interaction [10]. Yan et al. designed a 1,2,3-benzoxathiazole 2,2-dioxide derivative as a phosphotyrosine mimetic for the inhibition of protein tyrosine phosphatases [11]. In the area of GPCR ligands, Saitoh et al. constructed a cyclic sulfamate by bridging the 14-hydroxyl and 17-amino groups

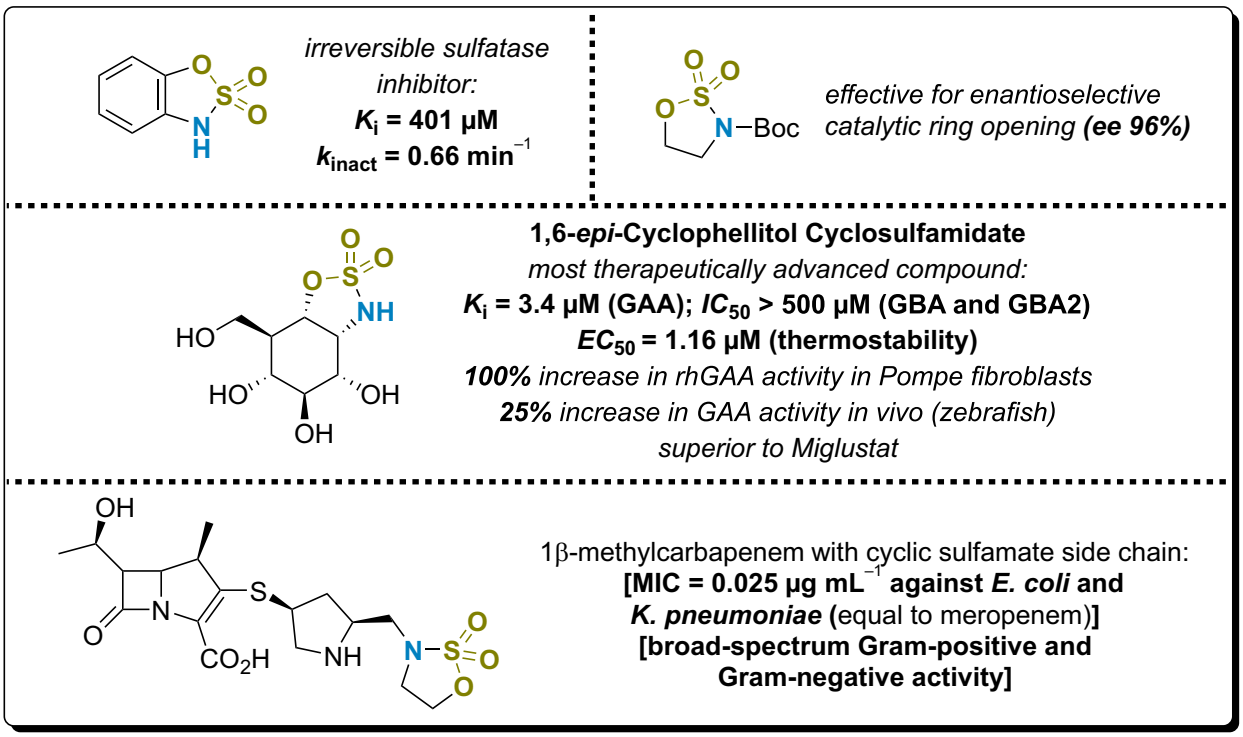


Figure 1. Important examples of cyclic 5-membered sulfamates in organic and medicinal chemistry

of a simplified morphinan scaffold as part of the structure–activity relationship studies toward orexin 1 receptor antagonists [12].

Herein, we report an improved, scalable synthesis of five-membered cyclic sulfamates using gaseous sulfuryl fluoride (SO_2F_2) in the presence of a base as a readily available, bench-stable alternative to sulfuryl chloride (**Figure 2**). This approach affords the target heterocycles in higher yields than classical methods and is readily amenable to scale-up, as demonstrated by the preparation of up to 50 g of the final product. Furthermore, to evaluate the drug discovery potential of the resulting cyclic sulfamate scaffolds, a virtual compound library was generated from the compounds synthesized. It was analyzed using the Lead-Likeness and Molecular Analysis (LLAMA) approach. Key physicochemical descriptors were calculated, and a set of established molecular property filters was applied to assess the lead-likeness of the library members.

Results and discussion

The synthesis of five-membered cyclic sulfamates is outlined in **Scheme 1**. The treatment of 2-amino-4-substituted phenols **1a–e** with SO_2F_2 in the presence of triethylamine in acetonitrile at rt and 1 atm for 16 h afforded the corresponding 1,2,3-benzoxathiazole 2,2-dioxides **3a–e** in a one-pot fashion. The reaction is presumed to proceed *via* the intermediacy of *O*-sulfamoyl fluorides **2a–c**, which undergo the spontaneous intramolecular cyclization through the nucleophilic substitution of fluoride. This protocol proved applicable to substrates bearing electron-withdrawing substituents on the aromatic ring, including bromo (**3a–c**), nitro (**3d**), and methyl carboxylate (**3e**) groups (**Scheme 1**).

The methodology was also extended to *N*-substituted 2-aminophenol derivatives **4a** and **4b**, which furnished the *N*-substituted cyclic sulfamates **5a** and **5b** under the same conditions, demonstrating that secondary amines and amides

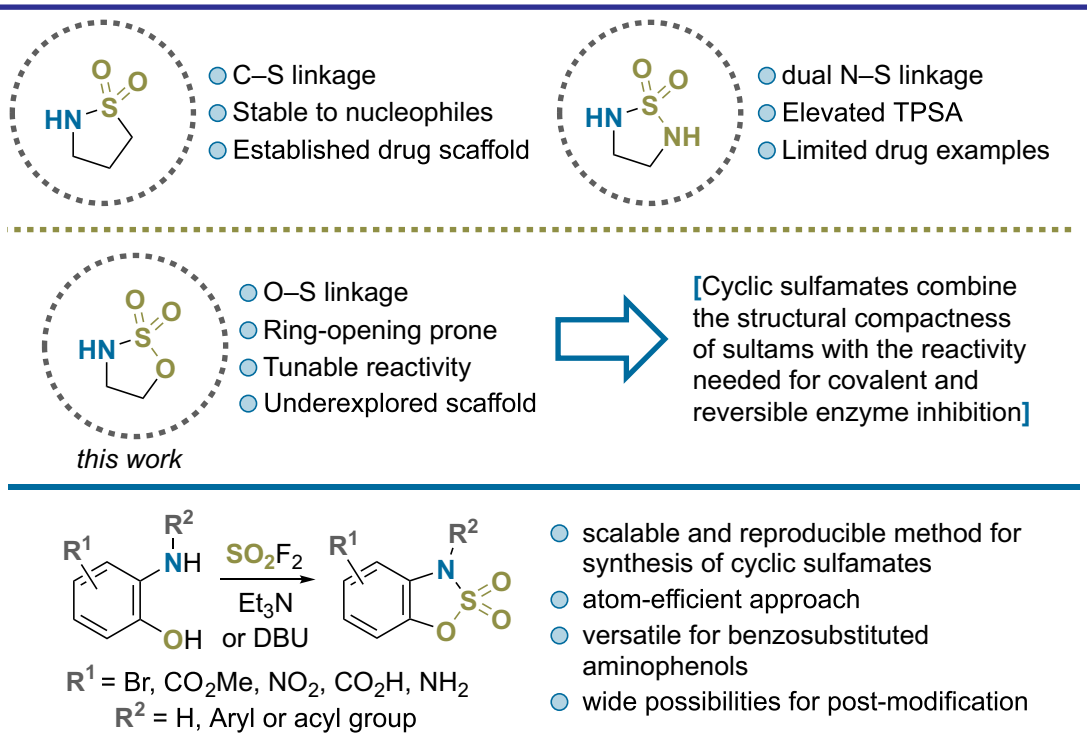
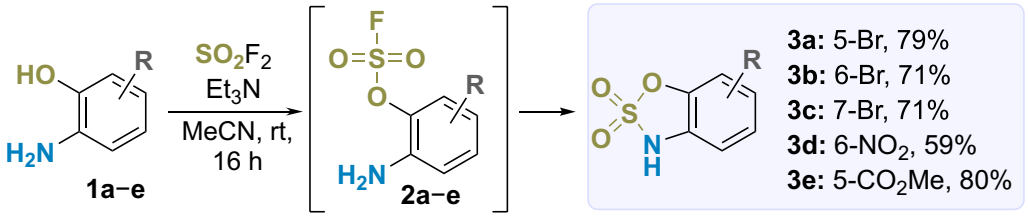


Figure 2. Five-membered cyclic sulfamates as a reactive and underexplored class of S–N heterocycles: the scaffold comparison and a scalable synthetic approach



Scheme 1. The synthesis of substituted cyclic sulfamates **3a–e**

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were competent nucleophiles for the ring closure (**Scheme 2**). It is worth noting that steric hindrance from the second *N*-substituent led to a mixture of closed- and open-ring products, resulting in a lower reaction yield. The target compounds were isolated from the mixtures by flash chromatography.

The versatility of the products was further demonstrated by straightforward functional group interconversions: the nitro group reduction in **3d** gave amine **3f**, while the hydrolysis of ester **3e** provided carboxylic acid **3g**, both of which offered handles for further diversification (**Scheme 3**).

To evaluate the drug discovery potential of the cyclic sulfamate building blocks synthesized, a virtual compound library of 49 derivatives was generated and analyzed using the Lead-Likeness and Molecular Analysis (LLAMA) approach, as previously described by Nelson and co-workers [13] (**Figure 3**). Key physicochemical descriptors were computed for each library member. The molecular weight (MW) of the compounds ranged from 228.3 to 343.4 Da (mean 290.6 ± 28.2), with cLog*P* values spanning from –1.85 to 1.99 (mean 0.45 ± 0.93), indicating that the library occupied a predominantly hydrophilic chemical space. The topological polar surface area (TPSA) ranged from 67.4 to 127.6 Å^2 (mean 93.7 ± 15.8), and the number of hydrogen-bond acceptors (estimated as the sum of nitrogen and oxygen atoms) was between 5 and 9, reflecting the polar character of the cyclic sulfamate moiety.

The library was then subjected to a series of established molecular property filters (**Figure 4**). All 49 compounds (100%) satisfied Lipinski Ro5, the Veber filter (rotatable bonds ≤ 10, TPSA ≤ 140 Å^2), and the Muegge filter, confirming an excellent overall drug-likeness of the scaffold. The GSK 4/400 rule (MW ≤ 400, cLog*P* ≤ 4) was also met by all 49 members (100%), consistent with the cyclic sulfamate core compact, polar nature. The Ghose filter was satisfied by 41 out of 49 compounds (84%); the eight failures were attributed exclusively to cLog*P* values falling below the lower Ghose threshold (cLog*P* ≥ –0.4), highlighting the high polarity imparted by the sulfamate ring (**Figure 4**).

More stringent lead-likeness criteria yielded predictably lower pass rates. The Oprea lead-like filter (150 < MW ≤ 350, –1 ≤ cLog*P* ≤ 3) was satisfied by 46 compounds (94%), with the three failures caused by cLog*P* values below –1.0. Churcher's criteria (MW < 350, cLog*P* < 3, 60 ≤ TPSA ≤ 100 Å^2) were met by 32 compounds (65%); here, the sole limiting parameter was TPSA, with 17 compounds exceeding the upper bound of 100 Å^2 due to the cumulative contribution of sulfonyl oxygens and additional heteroatoms. All compounds satisfied the MW and cLog*P* requirements of the Churcher's filter individually (49/49, 100%) (**Figure 4**).

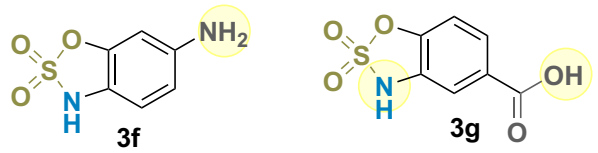
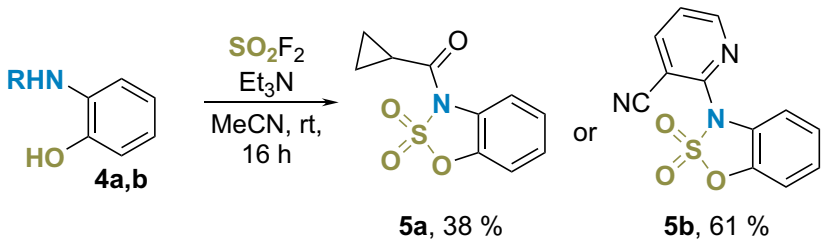
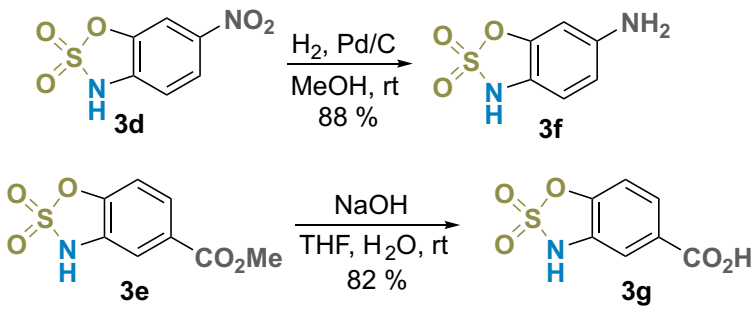


Figure 3. Building blocks used as scaffolds to generate the virtual library



Scheme 2. The synthesis of *N*-substituted cyclic sulfamates **5a** and **5b**



Scheme 3. The synthesis of sulfamates **3f** and **3g** via the functional group transformations of **3d** and **3e**

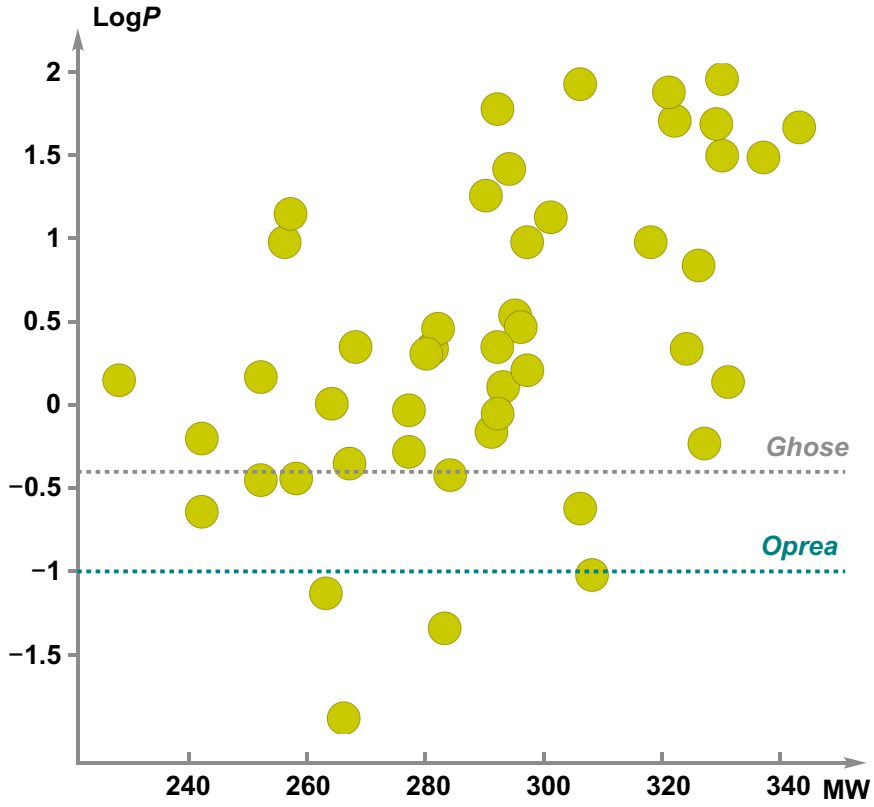


Figure 4. The log*P*–MW plot for the generated compound library

These results demonstrate that five-membered cyclic sulfamate derivatives occupy a favorable lead-like physicochemical space characterized by the low molecular weight, moderate-to-low lipophilicity, and adequate polar surface area. The principal limitation, e.g., elevated TPSA in a subset of compounds, is an inherent consequence of the sulfamate pharmacophore and the nitrogen-rich heterocyclic substituents, but it does not preclude oral bioavailability as TPSA values remain well below the 140 Å^2 threshold commonly associated with poor absorption. The high pass rates across multiple orthogonal drug-likeness filters support the utility of this scaffold class as starting points for lead optimization campaigns.

■ Conclusions

We have developed an expedient synthesis of five-membered cyclic sulfamates using sulfuryl fluoride at atmospheric pressure as a readily available, bench-stable, and less aggressive alternative to the classically employed sulfuryl chloride. The key advantages of the present method include high yields, mild reaction conditions (rt, 16 h), and the straightforward scalability, as demonstrated by the preparation of up to 50 g of the final product. The generality of the approach was determined across substrates bearing diverse ring substituents and *N*-acyl/aryl groups, with further diversification achievable through post-cyclization functional group manipulations, such as the nitro group reduction and the ester hydrolysis.

The lead-likeness assessment of a 49-member virtual library conducted using the LLAMA platform revealed an exceptionally favorable physicochemical profile for the cyclic sulfamate scaffold. All library members satisfied the Lipinski Rule of Five, Veber, Muegge, and GSK 4/400 filters (100%), while the Ghose filter was passed by 41 compounds (84%), and the Oprea lead-like criteria by 46 (94%). The more stringent Churcher's criteria were met by 32 compounds (65%), with the sole limiting factor being elevated TPSA values (>100 Å^2) in a subset of derivatives – an inherent feature of the polar sulfamate pharmacophore that nonetheless remained well within the acceptable range for oral bioavailability. The library is characterized by low molecular weights (mean MW 290.6 Da), moderate lipophilicity (mean cLog*P* 0.45), and the high polar surface area (mean TPSA 93.7 Å^2), collectively positioning these compounds in a physicochemical space that is well-suited for the lead optimization.

■ Experimental part

The solvents were purified according to the standard procedures.[14] All starting compounds

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were available from Enamine Ltd. or purchased from other commercial sources. Operations with SO_2F_2 were performed at atmospheric pressure using a balloon. Melting points were measured on the MPA100 OptiMelt automated melting point system. ^{1}H and ^{13}C{H} spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, and 126 MHz for ^{13}C{H} NMR) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, and 101 MHz for ^{13}C{H} NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 2.50 and 39.52 ppm for ^{1}H and ^{13}C{^{1}H}, respectively. Coupling constants (*J*) are given in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, and coupling constants (Hz). Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer.

The general procedure for the synthesis of 3a–e, 5a, and 5b

5-Bromo-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (3a)

Compound **1a** (30.0 g, 0.159 mol) was dissolved in MeCN (500 mL), and Et_3N (48.4 g, 0.479 mol, 66.7 mL) was added. The reaction mixture was then cooled to 0–5 °C and was degassed three times with SO_2F_2. The mixture was stirred at rt and 1 atm of SO_2F_2 (in a balloon) for 16 h. After the completion, the solvent was evaporated in *vacuo*, and the residue was dissolved in a saturated aq. $NaHSO_4$ solution and extracted three times with EtOAc (3 × 300 mL). The ethyl acetate solution was washed with a saturated aq. $NaHSO_4$ solution and brine, dried over Na_2SO_4, and evaporated in *vacuo*.

A pink powder. Yield – 31.7 g (79%). M. p. 153–155°C. ^{1}H NMR (500 MHz, DMSO-d_6), *δ*, ppm: 6.89 (1H, s), 7.06 (1H, dd, *J* = 8.5, 2.2 Hz), 7.09–7.21 (2H, m). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 112.6, 114.8, 116.5, 124.4, 133.4, 142.2. LC-MS, *m*/*z* (ESI): 248/250 [M–H]$^-$.

6-Bromo-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (3b)

A brownish powder. Yield – 47.3 g (71%) from 50.0 g, 0.266 mol of **1b**. M. p. 174–175°C (lit. [2] 178–181°C). ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 6.58 (1H, br. s), 6.91 (1H, d, *J* = 8.4 Hz), 7.24 (1H, dd, *J* = 8.4, 2.1 Hz), 7.51 (1H, d, *J* = 2.1 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 112.7, 113.9, 114.2, 127.8, 131.3, 143.5. HRMS, *m*/*z* (ESI–TOF): [M–H]$^-$ calcd. for $C_6H_3BrNO_3S$ 247.9022/249.9002, found 247.9029/249.9007.

7-Bromo-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (3c)

A brownish powder. Yield – 38.0 g (71%) from 40.0 g, 0.213 mol of **1c**. M. p. 125–127°C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 5.91 (1H, br. s), 6.88 (1H, d, *J* = 8.0 Hz), 6.96 (1H, t, *J* = 8.0 Hz), 7.06 (1H, d, *J* = 8.0 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 102.3, 111.5, 124.4, 126.1, 133.4, 141.1. LC-MS, *m*/*z* (ESI): 248/250 [M–H]$^-$.

6-Nitro-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (3d)

A yellow solid. Yield – 2.49 g (59%) from 3.00 g, 19.5 mmol of **1d**. M. p. 194–196°C (lit. [2] 200–202°C). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 6.59 (1H, d, *J* = 8.8 Hz), 7.63 (1H, d, *J* = 2.5 Hz), 7.82 (1H, dd, *J* = 8.8, 2.5 Hz). ^{13}C NMR (101 MHz, DMSO-d_6), δ, ppm: 102.9, 108.3, 122.1, 135.1, 144.3, 149.9. HRMS, *m*/*z* (ESI–TOF): [M–H]$^-$ calcd. for $C_6H_3N_2O_5S$ 214.9768, found 213.9777.

Methyl 3*H*-benzo[*d*][1,2,3]oxathiazole-5-carboxylate 2,2-dioxide (3e)

A colorless solid. Yield – 21.9 g (80%) from 20.0 g, 0.120 mol of **1e**. M. p. 53–56°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.76 (3H, s), 6.79 (1H, d, *J* = 8.0 Hz), 6.99 (1H, d, *J* = 2.0 Hz), 7.08 (1H, dd, *J* = 8.0, 2.0 Hz). LC-MS, *m*/*z* (ESI): 228 [M–H]$^-$.

Cyclopropyl(2,2-dioxido-3*H*-benzo[*d*]-[1,2,3]oxathiazol-3-yl)methanone (5a)

A colorless powder. Yield – 0.102 g (38%) from 200 mg, 1.13 mmol of **4a**. The compound was purified by flash chromatography (gradient: $CHCl_3$ – MeCN, 95:5 to 85:15). M. p. 75–76°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.17–1.31 (4H, m), 2.31 (1H, tt, *J* = 7.5, 4.4 Hz), 7.36 (2H, dd, *J* = 6.4, 3.3 Hz), 7.54 (1H, dd, *J* = 6.4, 3.3 Hz), 7.88 (1H, dd, *J* = 6.4, 3.3 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 8.1, 11.5, 15.0, 112.4, 116.7, 126.4, 126.4, 126.6, 139.8, 169.7. HRMS, *m*/*z* (ESI–TOF): [M+H]$^+$ calcd. for $C_{10}H_{10}NO_4S$ 240.0331, found 240.0323.

2-(2,2-Dioxido-3*H*-benzo[*d*][1,2,3]oxathiazol-3-yl)nicotinonitrile (5b)

A yellow crystalline powder. Yield – 0.235 g (61%) from 300 mg, 1.42 mmol of **4a**. The compound was purified by flash chromatography (gradient: hexanes – EtOAc, 80:20 to 0:100). M. p. 175–176°C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 7.29–7.43 (3H, m), 7.57–7.66 (1H, m), 7.79 (1H, dd, *J* = 7.9, 4.9 Hz), 8.68 (1H, dd, *J* = 7.9, 1.9 Hz),

8.83 (1H, dd, J = 4.9, 1.9 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 106.8, 112.7, 114.8, 117.4, 125.2, 126.3, 126.8, 129.5, 142.8, 145.2, 149.6, 154.1. HRMS, m/z (ESI–TOF): $[M+H]^+$ calcd. for $C_{12}H_8N_3O_3S$ 274.0286, found 274.0281.

6-Amino-3*H*-benzo[*d*][1,2,3]oxathiazole 2,2-dioxide (3f)

10% Pd/C (50.0 mg) was added to the solution of **3d** (*ca.* 2.50 g) in MeOH (25 mL). The solution was carefully degassed and vigorously stirred under 50 atm of H_2 at rt. Upon the completion of the reaction, the catalyst was filtered off, and the mixture was concentrated in *vacuo*.

A purple solid. Yield – 1.89 g (88%). M. p. 185–188°C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 6.48–6.62 (2H, m), 6.67 (1H, s), 9.00 (3H, br. s). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 101.4, 110.5, 115.2, 145.8. LC-MS, m/z (ESI): 187 $[M+H]^+$.

3*H*-Benzo[*d*][1,2,3]oxathiazole-5-carboxylic acid 2,2-dioxide (3g)

Compound **3e** (*ca.* 22.0 g, 96.0 mmol) was dissolved in THF (300 mL) and cooled to 0–5 °C. An aqueous solution of NaOH (9.60 g, 240 mmol) in water (100 mL) was added to the reaction mixture. The mixture was stirred at rt for 16 h. After the completion, the solvent was evaporated to leave an aqueous residue. The aqueous solution was washed with EtOAc (100 mL) and acidified to pH = 2–3 with 6 M aq. HCl. The mixture was then extracted with EtOAc (3 × 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated in *vacuo*.

A beige powder. Yield 17.0 g (82%). M. p. 144–145°C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 7.28 (1H, d, J = 8.4 Hz), 7.41 (1H, s), 7.56 (1H, d, J = 8.4 Hz). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 110.9, 112.7, 124.2, 127.7, 131.9, 145.9, 166.8. HRMS, m/z (ESI–TOF): $[M–H]^-$ calcd. for $C_7H_4NO_5S$ 213.9816, found 213.9823.

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The Multigram-Scale Access to 2-Oxaadamantan-1-amine and 2-Oxaadamantan-1-ol *via* the Optimized Synthesis of Bicyclo[3.3.1]nonane-3,7-dione

Abstract

The practical tens-of-grams-scale access to 2-oxaadamantan-1-amine and 2-oxaadamantan-1-ol – two overlooked heteroadamantane building blocks of interest for medicinal chemistry – has been achieved through the optimization and scale-up of existing literature protocols. The key precursor – bicyclo[3.3.1]nonane-3,7-dione– and both target compounds can be obtained in good overall yields using straightforward procedures and standard reagents. It is noteworthy that 2-oxaadamantan-1-amine is an exceptionally stable *N*,*O*-acetal, in stark contrast to the high hydrolytic lability usually seen in this compound class.

Keywords: oxaadamantane; bicyclo[3.3.1]nonane-3,7-dione; *N*,*O*-acetal; hemiaminal; cage compounds; scale-up synthesis; heteroadamantane; building blocks

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Отримання 2-оксаадамантан-1-аміну та 2-оксаадамантан-1-олу в мультиграмових кількостях через оптимізований синтез біцикло[3.3.1]нонан-3,7-діону

Анотація

Завдяки оптимізації та масштабуванню вже відомих методик вдалося розробити практичний спосіб синтезу 2-оксаадамантан-1-аміну та 2-оксаадамантан-1-олу в кількостях, вимірюваних десятками грамів. Ці два структурні блоки, які раніше лишалися поза увагою дослідників, становлять особливий інтерес для медичної хімії. Ключовий прекурсор – біцикло-[3.3.1]нонан-3,7-діон – та обидві цільові сполуки можна отримати з високим загальним виходом, використовуючи нескладні процедури й стандартні реагенти. Показово, що 2-оксаадамантан-1-амін виявляє виняткову стабільність як *N*,*O*-ацеталь, що яскраво контрастує з високою гідролітичною лабільністю, зазвичай властивою сполукам цього класу.

Ключові слова: оксаадамантан; біцикло[3.3.1]нонан-3,7-діон; *N*,*O*-ацеталь; геміаміналь; каркасні сполуки; масштабований синтез; гетерадамантан; будівельні блоки

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■ Introduction

The 2-oxaadamantane motif appears in several biologically important natural products. Tetrodotoxin (TTX), a powerful neurotoxin from pufferfish, has a densely functionalized dioxaadamantane core that enables its highly selective blockage of voltage-gated Na^+ ion channels [1]. Other naturally occurring (poly)oxaadamantanes, including the trioxaadamantanes muamvatin and caloundrin B, the sedative daigremontianin, and bersaldegenin orthoacetate, further demonstrate the recurrence of this cage scaffold in nature [1]. In synthetic chemistry, despite the difficulties in constructing and functionalizing the heteroadamantane skeleton, several oxaadamantane-containing compounds show a significant biological activity across various targets, such as NMDA receptor antagonists and trypanocidal agents [2], heteroadamantyl cannabinoids with the nanomolar CB_1/CB_2 affinity [3], σ-receptor ligands [4], reversed-chloroquine antimalarial conjugates [5] (**Figure 1**), rigid acetylcholine-like pharmacophore models [6], and the highly efficient AZADO family of nitroxyl-radical oxidation catalysts [7]. Additionally, the constrained geometry of (oxa) adamantane systems has been used to explore the fundamental chemical reactivity, including the transition-state geometry in aldol condensations [8].

The simplest way to synthesize 1-heteroatom-substituted 2-oxaadamantanes involves bicyclo-[3.3.1]nonane-3,7-dione, which acts as a common precursor for both the amine and the alcohol through the transannular cyclization. Several synthetic approaches to this diketone have been reported: the condensation of dicarboxylic acid derivatives [9], the fragmentation–ozonolysis of 1,3-dibromoadamantane [10], the double-condensation of dimethyl 3-oxoglutarate with malondialdehyde [11], routes *via* bicyclo[3.3.1]nonanone intermediates [12], and a three-step sequence from adamantan-2-one through a lactone and diol [13]. Of these, the latter route is arguably the most practical, employing inexpensive, commercially available adamantan-2-one and involving the Baeyer-Villiger oxidation, the $LiAlH_4$ reduction, and the chromium-based oxidation of the resulting diol – a versatile intermediate that has also been used in related skeletal transformations [14]. However, all reported procedures for the diketone have been developed and validated only on a small scale (typically ≤ 10 g), and reliable upscale methods have not been documented. This limitation has thus restricted practical access to the downstream target compounds – 2-oxaadamantan-1-amine and 2-oxaadamantan-1-ol – which remain underexplored as building blocks despite their potential. The amine itself has been prepared *via* reductive amination of the diketone [2, 10], but the reported protocols operate on a few-gram scale and require a high-pressure hydrogenation for the final deprotection step. Herein, we report modifications to existing protocols that enable a reliable, the tens-of-grams-scale access to the diketone in three steps with a good overall yield, thereby enabling the access to both the amine and the alcohol in multigram quantities – determining these compounds as practical building blocks for further research.

■ Results and discussion

Our approach follows the general strategy outlined by *Zalikowski et al.* [13], with modifications at each step to ensure reproducibility and enhanced yields during scale-up (**Scheme 1**). The Baeyer-Villiger oxidation of adamantan-2-one (**1**) with *m*CPBA in CH_2Cl_2 proceeded smoothly, delivering lactone **2** quantitatively on a 77 g scale –

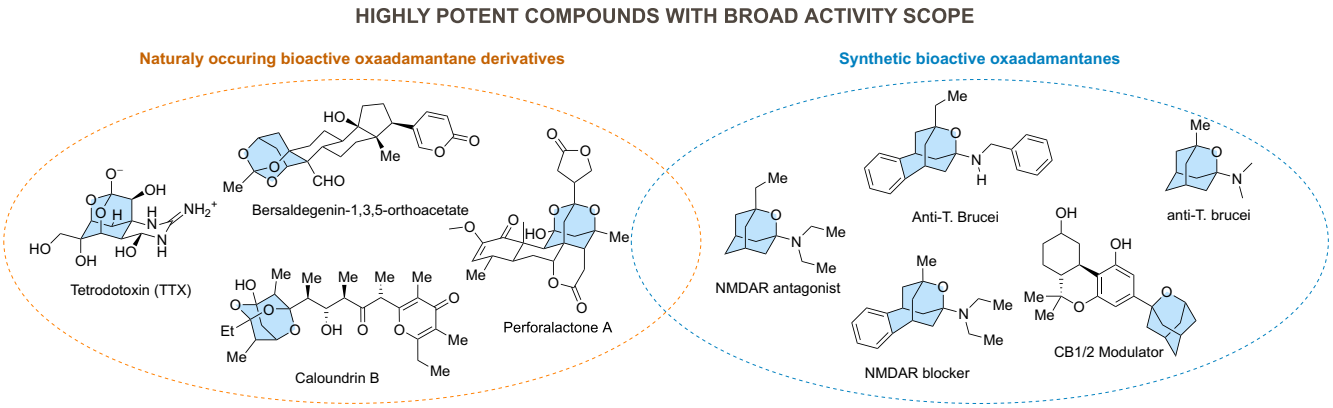
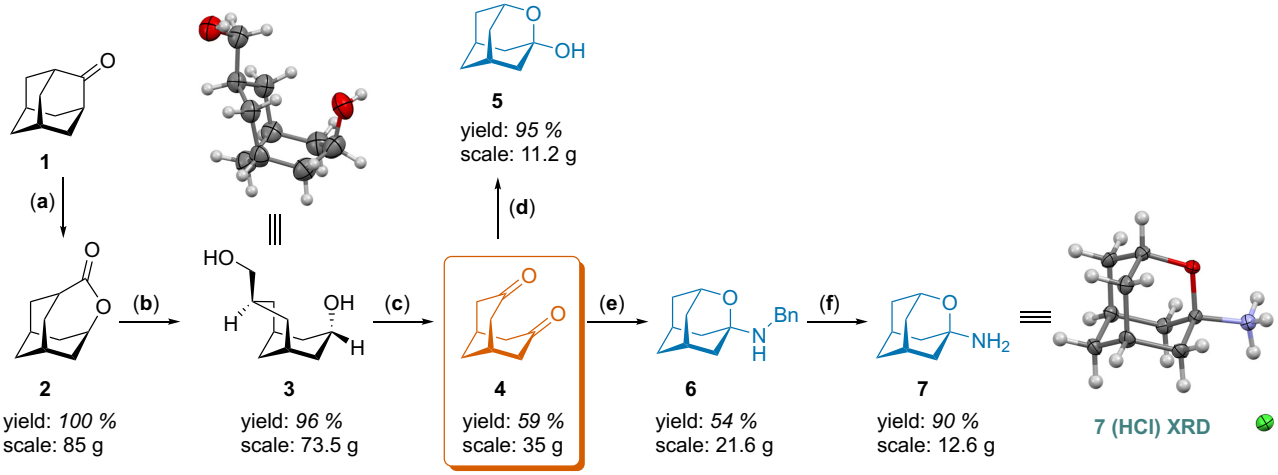


Figure 1. Selected natural products and synthetic bioactive compounds incorporating oxaadamantane and related (poly)oxaadamantane scaffolds

approximately fifteen-fold larger than the batch size reported in the previous work [13]. The single aqueous NaOH wash of the original protocol was replaced by sequential Na_2CO_3/$Na_2S_2O_3$ washes followed by the MTBE trituration; both were necessary to achieve complete removal of *m*CPBA and residual CH_2Cl_2 at this scale, which otherwise interfered with the subsequent reduction with $LiAlH_4$ in THF – substituted for the less practical diethyl ether used in the original protocol [13] – gave diol **3** in 96% yield (73.5 g). As previously noted [13], diol **3** is poorly soluble in common organic solvents; therefore, the inorganic residue from the $LiAlH_4$ quench must be washed repeatedly with a hot THF to ensure complete recovery of the product. The oxidation of diol **3** to diketone **4** was the main bottleneck in the sequence. While the literature protocol uses pyridinium dichromate (PDC) and reports a 75% yield on about 5 g [13], we could not replicate this result on larger scales. Testing alternatives, including PDC at higher temperatures and Dess-Martin periodinane, produced inferior or inconsistent results. Ultimately, 7 equiv. of pyridinium chlorochromate (PCC), on silica in CH_2Cl_2 at room temperature over three days delivered diketone **4** reproducibly in the yield of 59% (35 g from 66 g of **3**) – modestly below the 75% reported previously [13] on a ~5 g batch, but, crucially, reliably reproducible at the tens-of-grams scale, with lactone **2** (from over-oxidation) as the main by-product. The overall three-step yield of diketone from adamantan-2-one is 57%, and the entire sequence requires no chromatography, which is a key advantage for the routine preparation.

With a sustainable supply of diketone **4**, the target oxaadamantanes were synthesized *via* two different routes. 2-Oxaadamantan-1-ol (**5**) was obtained simply through the $NaBH_4$ reduction of **4** in methanol (95% yield, 11.2 g). The amine was synthesized through the two-step process adapted from *Duque et al.* [2] work: the one-pot condensation of **4** with benzylamine followed by the *in situ* $LiAlH_4$ reduction produced *N*-benzyl-2-oxaadamantan-1-amine (**6**) as its hydrochloride salt (54%, 21.6 g), and the subsequent hydrogenolysis over Pd/C at atmospheric pressure in methanol yielded the primary 2-oxaadamantan-1-amine as its hydrochloride **7** (90%, 12.6 g). Both the yield and operational simplicity of this debenzylation significantly improve upon the literature methods, which involve the high-pressure hydrogenation (40 atm, 100 °C), followed by the base extraction and sublimation, yielding only 70% on an around 1 g scale [2].

Compound **7** is a bridgehead hemiaminal: the amine nitrogen is directly attached to the carbon that also forms part of the oxaadamantane ether linkage, making it a cyclic *N*,*O*-acetal. This functional motif – a cyclic α-amino ether – belongs to a notoriously unstable compound class: most known representatives decompose upon the attempted isolation, and even the comparatively stabilized 1-aminoisochroman can only be handled *in situ* in solution and must be reacted immediately to avoid decomposition [15]. In contrast, **7** remains stable after the prolonged exposure to both acidic and basic aqueous conditions at high temperatures. This notable stability results from the geometric constraints of the Bredt's rule, which prevents the formation of



Experimental conditions: (**a**) *m*CPBA, DCM, 25 °C, 24 h; (**b**) LAH, THF, 0 °C → r.t., overnight; (**c**) PCC, SiO_2, DCM, r.t., 3 d; (**d**) $NaBH_4$, MeOH, 0 °C → r.t., 1 d; (**e**) $BnNH_2$, THF, 65 °C, 0.5 h; then LAH, THF, 0 °C → r.t., overnight; then HCl, MeAc; (**f**) H_2, Pd/C (10%), MeOH, r.t., 1 d

Scheme 1. The synthesis of 2-oxaadamantan-1-ol (**5**) and 2-oxaadamantan-1-amine (**7**) from adamantan-2-one (**1**). Thermal ellipsoid plots from the single-crystal X-ray diffraction of **7·(HCl)** and **5** are given with the 50% probability (*see* SI File)

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the bridgehead iminium ion needed for the hydrolytic cleavage – a stabilization first noted by Stetter for the related 1-hydroxy-2-oxaadamantane [9]. The structures of **5** and **7** (hydrochloride) were confirmed by the single-crystal X-ray diffraction (**Scheme 1**).

Since 2-oxaadamantane-derived 1-amines have already withstood the conditions of biological assays without the apparent breakdown of the *N*,*O*-acetal linkage (see Introduction), the question is whether this robustness extends to both amine **7** and alcohol **5** derivatives in more challenging environments, such as extended metabolic exposure and *in vivo* testing. With multigram quantities now available, we plan to undertake a systematic ADMET profiling as the next logical step.

■ Conclusions

We have shown that two previously overlooked heteroadamantane building blocks – 2-oxaadamantan-1-amine and 2-oxaadamantan-1-ol – can be reliably prepared on the tens-of-grams scale from commercially available adamantan-2-one by optimizing existing literature protocols. All steps use standard reagents, do not require chromatographic purification, and yield good overall results. The exceptional hydrolytic stability of 2-oxaadamantan-1-amine – a rare trait for an *N*,*O*-acetal – is a unique feature that, along with the increased practical accessibility of both compounds, may promote their wider study as rigid, heteroatom-containing scaffolds in medicinal chemistry and drug discovery.

■ Experimental part

General Information

The solvents were purified according to the standard procedures. All starting materials were 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 ^{1}H, 101 MHz for ^{13}C). 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). The 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.

All crystallographic measurements for this publication were performed at 173K on a Bruker Smart Apex II diffractometer operating in the φ and w scans mode. The intensity data were collected using the Mo-K_a radiation (l = 0.71078 Å). The crystals were mounted on a glass fiber and mounted on the diffractometer. The structures were solved by direct methods and refined by the full-matrix least-squares technique using the Bruker SHELXTL program package [16].

Non-hydrogen atoms were refined anisotropically. All CH hydrogen atoms were placed at calculated positions and refined as 'riding' model, with U_{iso}(H)=1.2U_{eq}(CH_2) and U_{iso}(H)=1.5U_{eq}(CH_3).

The NH hydrogen atoms in structures **5** and **7 (HCl)** were found in difference Fourier syntheses and refined isotropically. The absolute configuration of **8** is not determined because no heavy atoms are present in the molecule. The X-ray crystallographic data for all compounds are listed in the SI File.

Crystallographic data for the structures in this paper were deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 2543739 (compound **3**) and 2543738 (compound **7**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

4-Oxatricyclo[4.3.1.1^{3,8}]undecan-5-one (2)

The solution of adamantan-2-one (**1**; 77.2 g, 0.514 mol, 1.0 equiv.) in CH_2Cl_2 (2400 mL) was stirred at room temperature (25 °C) with a magnetic stirrer (400 rpm). *m*CPBA (177.4 g, 90% purity, 1.028 mol, 2.0 equiv.) was added portionwise over 5 min. The reaction mixture was stirred at room temperature for 24 h, then washed with a 10% aqueous Na_2CO_3 (2 × 1400 mL) and a 10% aqueous $Na_2S_2O_3$ (2 × 1400 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, MTBE (600 mL) was added, and the mixture was evaporated again to remove residual CH_2Cl_2. The product was obtained as white crystals.

Yield – 85 g (100%). M. p. 238–248 °C (dec.). Anal. Calcd for $C_{10}H_{14}O_2$, %: C 72.26, H 8.49. Found, %: C 72.38, H 8.28. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 1.73 (1H, s), 1.79–1.88 (2H, m), 1.89–1.98 (2H, m), 1.98–2.07 (3H, m), 2.10 (1H, br.s), 2.98–3.13 (4H, m), 4.47 (1H, s). ^{13}C NMR (126 MHz, Chloroform-*d*), δ, ppm: 26.0, 31.1, 33.9, 35.9, 41.4, 73.3, 179.0. ^{13}C NMR_APT (126 MHz, Chloroform-*d*), δ, ppm: 25.7, 30.9, 33.7, 35.7, 41.1, 73.0. GC-MS, *m/z* (EI): 166 $[M]^+$.

7-(Hydroxymethyl)bicyclo[3.3.1]nonan-3-ol (3)

To an ice-cooled dry THF (1100 mL), $LiAlH_4$ (20.55 g, 0.542 mol, 1.2 equiv.) was added portionwise. The suspension was stirred at 0 °C for 10 min, then lactone **2** (75.0 g, 0.451 mol, 1.0 equiv.) was added portionwise over 5 min at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the dropwise addition of water (75 mL) at 0 °C, followed by stirring at 0 °C for 15 min. Na_2SO_4 (150 g) was added, and the inorganic solids were collected by the filtration and washed thoroughly with a hot THF. The combined filtrates were concentrated under reduced pressure, and the residue was triturated with CH_2Cl_2 (300 mL).

Note: The product is insoluble in $CHCl_3$; NMR spectra were recorded in DMSO-d_6.

A white-yellow solid. Yield – 73.5 g (96%). M. p. 175 °C. Anal. Calcd for $C_{10}H_{18}O_2$, %: C 70.55, H 10.66. Found, %: C 70.67, H 10.54. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.04 (1H, d, J = 12.39 Hz), 1.48–1.84 (8H, m), 1.97 (2H, s), 2.54 (1H, s), 3.14 (2H, t, J = 5.51 Hz), 3.32 (2H, br.s), 3.93 (1H, s), 4.09–4.24 (1H, m). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 23.7, 28.2, 29.6, 32.9, 65.3, 67.4. ^{13}C NMR_APT (126 MHz, DMSO-d_6), δ, ppm: 23.6, 28.1, 29.5, 32.7, 65.1, 67.2, 108.8, 109.2, 159.2. GC-MS, *m/z* (EI): 152 $[M\text{-}H_2O]^+$.

Bicyclo[3.3.1]nonane-3,7-dione (4)

To the solution of diol **3** (66.0 g, 0.388 mol, 1.0 equiv.) in CH_2Cl_2 (3000 mL), SiO_2 (600 g) and PCC (585 g, 2.71 mol, 7.0 equiv.) were added. The resulting mixture was stirred at room temperature for 3 days. EtOAc (600 mL) was added, and the mixture was filtered through a silica pad, which was washed with EtOAc (2000 mL), and the combined filtrates were concentrated under reduced pressure. The residue was dissolved in MTBE (2000 mL) and heated to reflux; the mixture was filtered while hot, and the filtrate was partially concentrated to approximately one-quarter of its original volume, cooled with ice, and the precipitate was collected by the filtration and air-dried for 1 h.

A white-yellow solid. Yield – 35.0 g (59%). M. p. 214–223 °C. Anal. Calcd for $C_9H_{12}O_2$, %: C 71.03, H 7.95. Found, %: C 70.89, H 8.05. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 2.20 (2H, s), 2.41 (4H, d, J = 15.42 Hz), 2.58 (4H, dd, J = 15.46, 5.41 Hz), 2.86 (2H, br.s). ^{13}C NMR (126 MHz, Chloroform-*d*), δ, ppm: 31.7, 32.8, 48.0, 208.4. ^{13}C NMR_APT (126 MHz, Chloroform-*d*), δ, ppm: 31.7, 32.8, 48.0. GC-MS, *m/z* (EI): 152 $[M]^+$.

2-Oxaadamantan-1-ol (5)

To an ice-cooled solution of diketone **4** (11.69 g, 76.8 mmol, 1.0 equiv.) in a dry MeOH (210 mL), $NaBH_4$ (3.49 g, 92.2 mmol, 1.2 equiv.) was added portionwise. The reaction mixture was stirred at room temperature for 24 h, then concentrated under reduced pressure. The residue was quenched with a saturated aqueous Na_2CO_3 (350 mL) and stirred for 10 min. The aqueous layer was extracted with $CHCl_3$/MeOH (6:1, 3 × 400 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

A white solid. Yield – 11.2 g (95%). M. p. 195–238 (dec.). Anal. Calcd for $C_9H_{14}O_2$, %: C 70.10, H 9.15. Found, %: C 70.26, H 9.03. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 1.55 (2H, d, J = 12.35 Hz), 1.72 (1H, d, J = 11.90 Hz), 1.76–1.87 (5H, m), 1.92 (2H, d, J = 11.59 Hz), 2.30 (2H, s), 2.96 (1H, br. s, H-bond), 4.28 (1H, s). ^{13}C NMR (101 MHz, Chloroform-*d*), δ, ppm: 29.3, 34.7, 42.0, 72.2, 93.8. ^{13}C NMR_APT (101 MHz, Chloroform-*d*), δ, ppm: 29.3, 34.7 42.0, 72.2, 93.8. EIMS, *m/z* (EI): 154 $[M]^+$.

***N*-Benzyl-2-oxaadamantan-1-amine hydrochloride (6)**

To the solution of diketone **4** (22.0 g, 0.144 mol, 1.0 equiv.) in a dry THF (800 mL), benzylamine (17.6 mL, 0.159 mol, 1.1 equiv.) was added. The mixture was stirred at 65 °C for 30 min, then cooled to room temperature to form the solution of the corresponding imine. Separately, to an ice-cooled dry THF (280 mL), $LiAlH_4$ (10.8 g, 0.289 mol, 2.0 equiv.) was added portionwise and stirred at 0 °C for 10 min. The solution of the imine was then added dropwise to the $LiAlH_4$ suspension at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the dropwise addition of the solution of NaOH (5.6 g, 0.144 mol, 1.0 equiv.) in H_2O (40 mL) at 0 °C, stirred for 15 min, and Na_2SO_4 (400 g) was added. The inorganic solids

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were removed by the filtration and washed with EtOAc. The combined filtrates were concentrated under reduced pressure. The residue was taken up in methyl acetate (440 mL), treated with 10 M HCl (22 mL), and stirred at 0 °C for 10 min. The precipitate was collected by the filtration and air-dried.

A white-yellow solid (HCl salt). Yield – 21.6 g (54%). M. p. 218–227 °C (dec.). Anal. Calcd for $C_{16}H_{21}NO$, %: C 78.97, H 8.70, N 5.76. Found, %: C 78.81, H 8.55, N 5.66. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 1.55 (2H, d, *J* = 12.84 Hz), 1.74 (3H, s), 1.83–2.04 (5H, m,), 2.11–2.24 (2H, m), 4.06 (1H, t, *J* = 5.44 Hz), 4.19–4.37 (1H, m), 7.20–7.34 (3H, m), 7.61 (2H, d, *J* = 7.47 Hz), 9.83 (2H, s). ^{13}C NMR (126 MHz, Chloroform-*d*), δ, ppm: 28.0, 34.0, 34.4, 37.0, 44.1, 72.0, 85.7, 128.8, 131.5. ^{13}C NMR_APT (126 MHz, Chloroform-*d*), δ, ppm: 27.7, 33.9, 36.7, 43.9, 71.7, 85.5, 128.5, 131.3, 159.8. LC-MS, *m*/*z* (CI): 244.2 $[M+H]^+$.

2-Oxaadamantan-1-amine Hydrochloride (7)

To the solution of **6** (21.0 g, 74.9 mmol, 1.0 equiv.) in MeOH (630 mL), 10% Pd/C (7.0 g) was added. The flask was evacuated and backfilled with hydrogen five times, then stirred under the hydrogen atmosphere (1 atm, balloon) at room temperature for 24 h. The reaction mixture was filtered through a thin pad of SiO_2, and the filtrate was concentrated under reduced pressure. The residue was triturated with a dry MeCN (350 mL) and concentrated under reduced pressure.

A beige powder (HCl salt). Yield – 12.6 g (90%). M. p. >200 °C (gradual dec.). Anal. Calcd for $C_9H_{15}NO$, %: C 70.55, H 9.87, N 9.14. Found, %: C 70.39, H 9.97, N 9.25. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.63 (2H, d, *J* = 12.47 Hz), 1.71 (1H, d, *J* = 12.42 Hz), 1.75–1.99 (8H, m), 2.24 (2H, s), 4.21 (1H, s), 8.60 (2H, s). ^{13}C NMR_APT (126 MHz, DMSO-d_6), δ, ppm: 27.1, 33.5, 38.3, 39.9, 70.3, 80.6. GC-MS, *m*/*z* (EI): 153 $[M]^+$.

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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

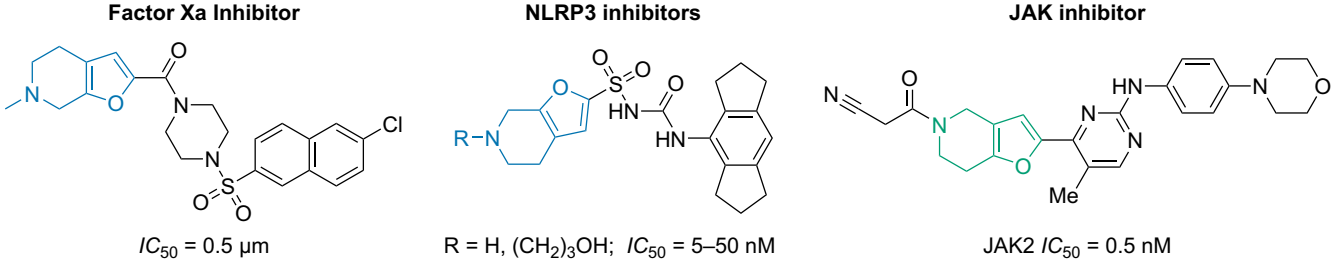
Partially saturated furo[3,2-*c*]- and furo[2,3-*c*]-pyridines are involved in various medicinal chemistry programs. The 4,5,6,7-tetrahydrofuro-[3,2-*c*]pyridine core has been a key component in potent Janus kinase (JAK) inhibitors with the proven *in vivo* anti-inflammatory activity [1] and in agents 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 ß-(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(*5H*)-one that employs hydrocinnamic acid (Meldrum's acid pathway) and cinnamate (Wittig pathway). For 6,7-dihydrofuro[2,3-*c*]-pyridin-4(*5H*)-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 ß-(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**



IC_{50} = 0.5 μm — *J. Med. Chem.* **2004**, *47*, 5167

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

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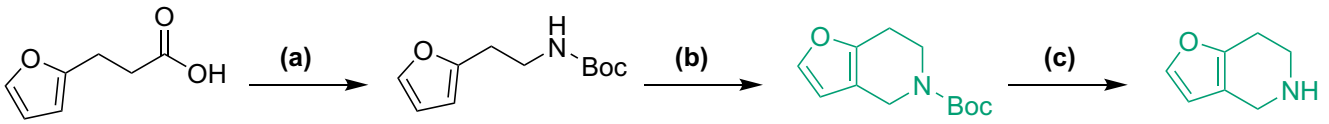


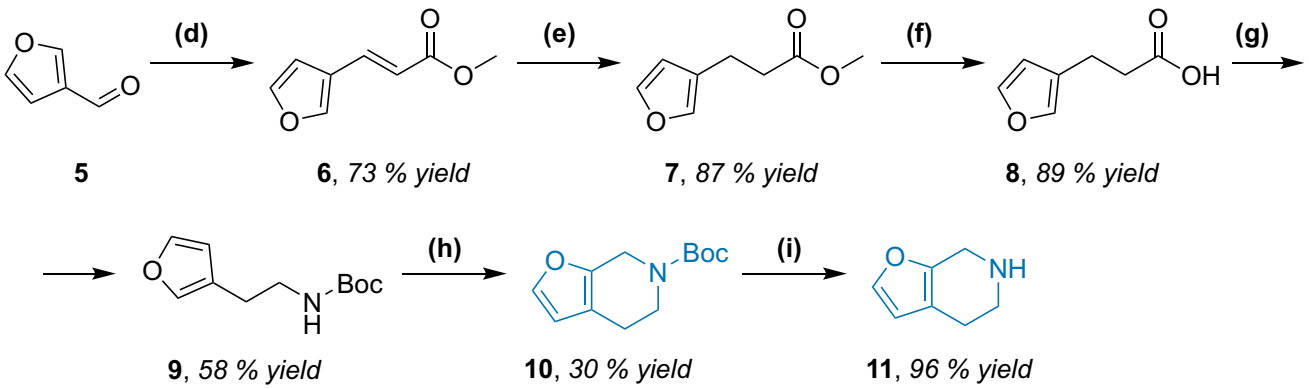
1 , *47 % yield* **2** **3**, *41 % yield* **4**, *97 % yield*

Experimental conditions: (a) DPPA, Et_3N, *t*BuOH, 80 °C, 16 h; **(b)** $(CH_2O)_n$, *p*TsOH·H_2O, 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_2O) 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**) $(EtO)_2P(O)CH_2CO_2Me$, NaH, THF, 0 °C → rt, 16 h; (**e**) CuCl, $NaBH_4$, MeOH/H_2O, 0 °C → rt, 16 h; (**f**) LiOH, THF/H_2O, rt, 16 h; (**g**) DPPA, Et_3N, *t*BuOH, 80 °C, 16 h; (**h**) $(CH_2O)_n$, *p*TsOH·H_2O, 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.

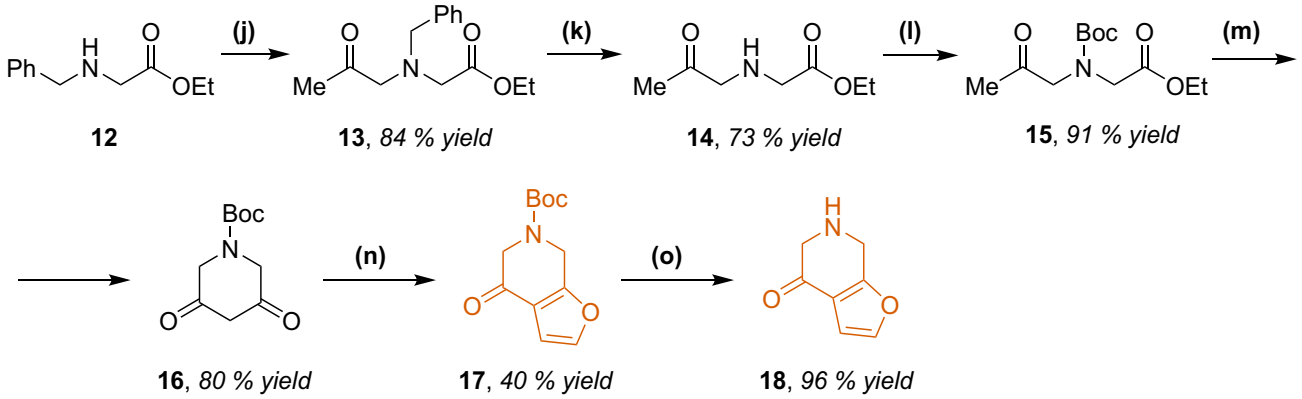
■ Conclusions

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 ß-(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



12 **13**, *84 % yield* **14**, *73 % yield* **15**, *91 % yield*

16, *80 % yield* **17**, *40 % yield* **18**, *96 % yield*

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

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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-C_4H_8-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-*t*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-C_4H_8-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)

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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).

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