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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

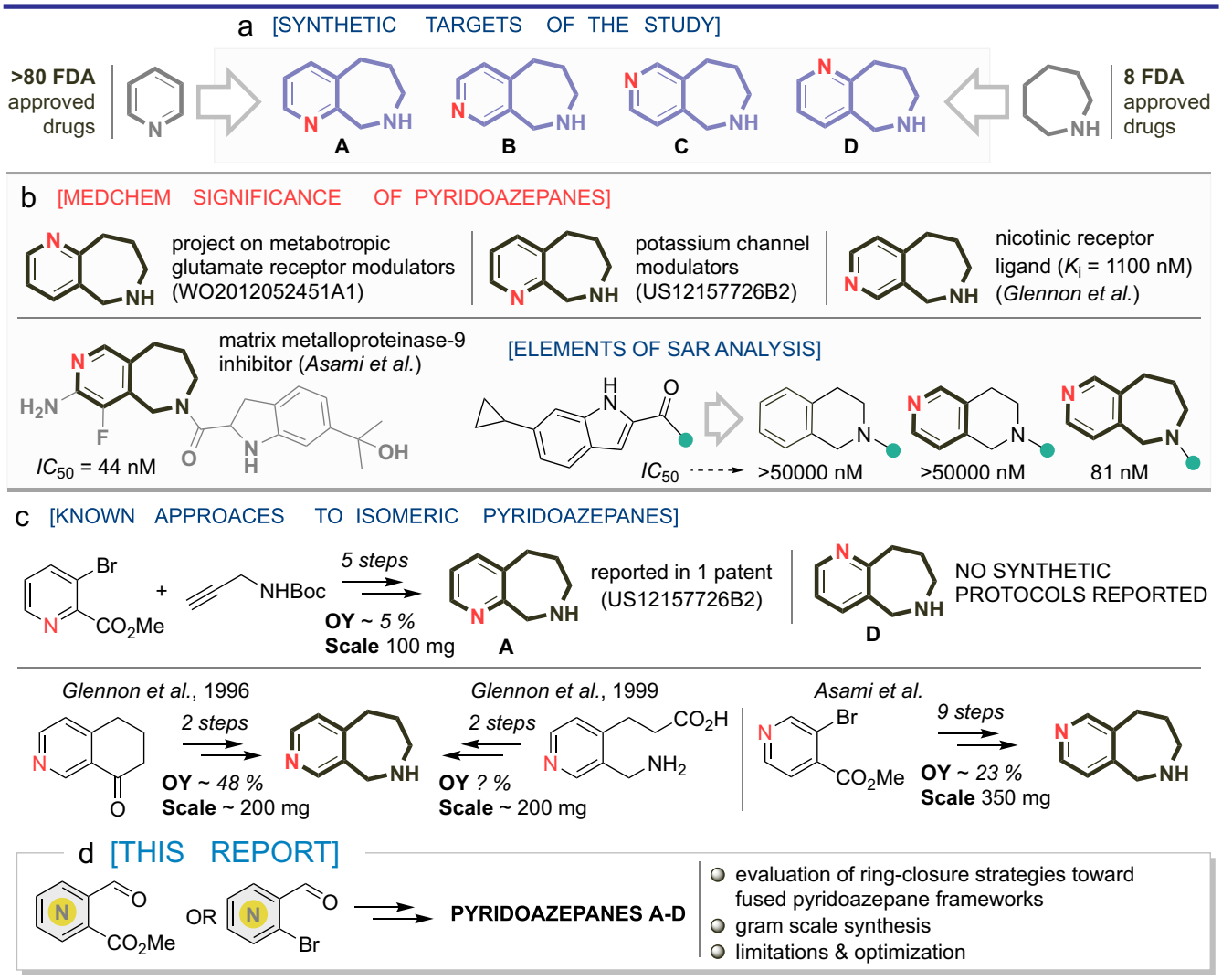
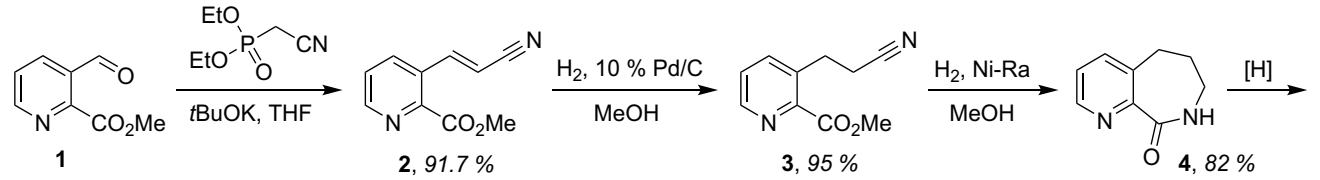
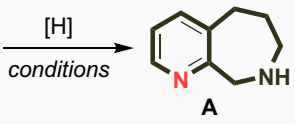


Figure 1. The status quo of the topic and the current work



[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

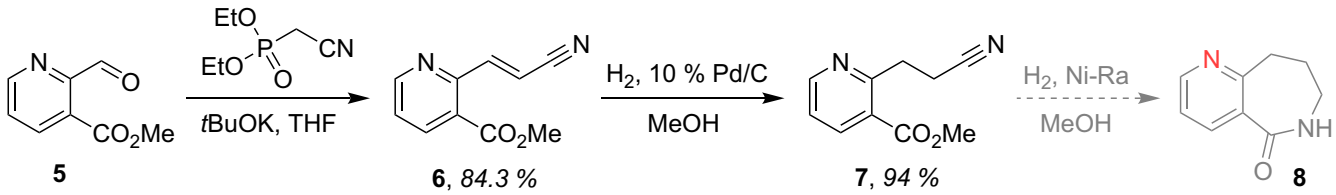


Scheme 1. The initial strategy toward **A** and lactam reduction studies

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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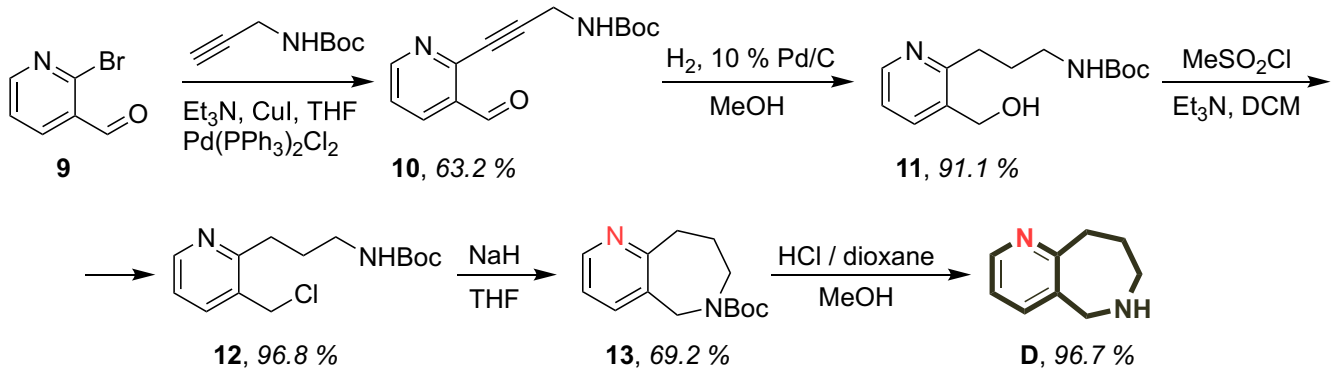

Scheme 3. The development of an optimized route toward isomer **D**

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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