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Novel approach to saturated amino acid derivatives with isolated (hetero)cyclic rings *via* the hydrogenation of dienes

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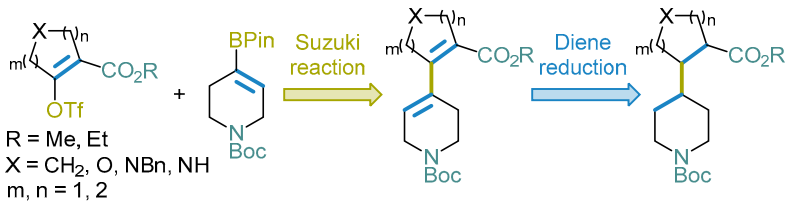


Synthesis of amino acids with isolated saturated (hetero)carbocyclic scaffold was disclosed. The method relied on Suzuki cross-coupling reaction of heteroacycloalkene triflates and *N*-Boc-tetrahydropyridine boron pinacolates followed by catalytic hydrogenation of the conjugated dienes thus obtained, which proceeded with good diastereoselectivity for scaffolds with two six-membered cycles and low diastereoselectivity for a five-membered analog. Several amino acid derivatives have also been obtained, i.e. amino esters, *N*H- and *N*-Boc-substituted amino acids – promising building blocks for medicinal and synthetic chemistry.

Keywords: amino acids, dienes, building blocks, diene reduction, isolated cycles, Suzuki coupling.

Synthetic amino acids,[1,2] especially cyclic derivatives,[3–6] play an important role in medicinal chemistry and drug discovery. Meanwhile, the high demand for new scaffolds is the driving force of modern chemistry design concepts and research programs. Latest promising three-dimensional scaffolds bear sp^3-enriched saturated isolated (hetero)-carbocycles (Fig. 1). The most prominent examples of compounds with the latter type of connectivity included rociverine,[7,8] dicyclomine (dicycloverine),[9] benzetimide,[10–12] or fosinopril (monopril).[13–15]

However, the synthetic accessibility of these scaffolds is limited because formal C(sp^3)–C(sp^3) coupling[16] is required to connect two cycles, which is a difficult task to achieve by most synthetic methods. Limited examples included the silyl-mediated photoredox Giese reaction (addition of nonactivated alkyl bromides to alkenes) in presence of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (Scheme 1*a*)[17] or Lewis acid promoted C(sp^3)–C(sp^3) coupling reaction of organozinc compounds[18] (Scheme 1*b*).

The construction of the target ring systems can be performed *via* the indirect approach involving a conventional C(sp^2)–C(sp^2) coupling followed by the reduction of both double bonds of dienes thus formed. Following this strategy, we have aimed at the synthesis of amino acid derivatives derived from isolated-ring scaffolds including cyclopentane and cyclohexane rings, as well as tetrahydro-

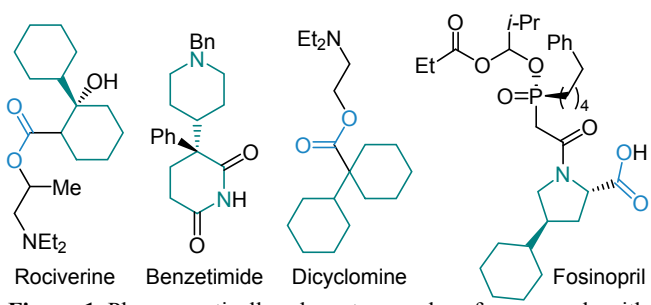
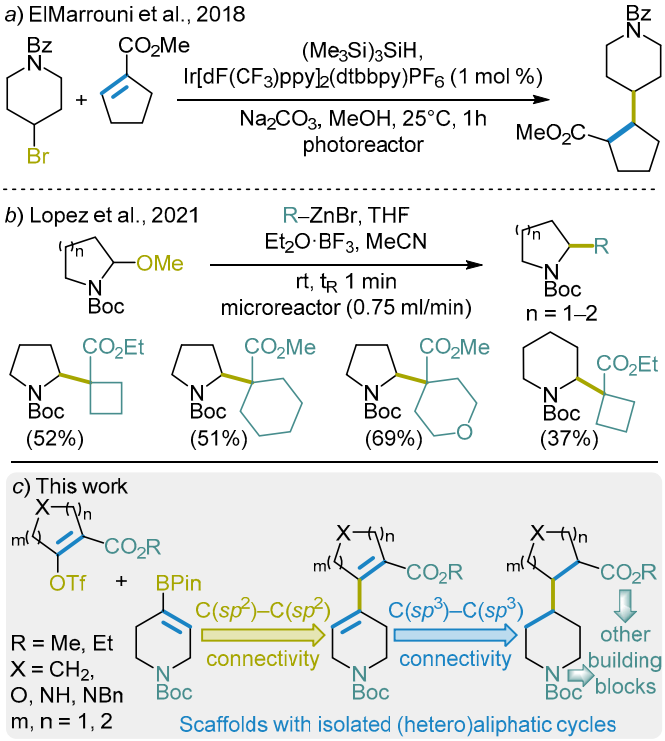


Figure 1. Pharmaceutically relevant examples of compounds with isolated (hetero)aliphatic rings scaffold.

Scheme 1. Synthetic approaches to amino esters with isolated (hetero)aliphatic rings

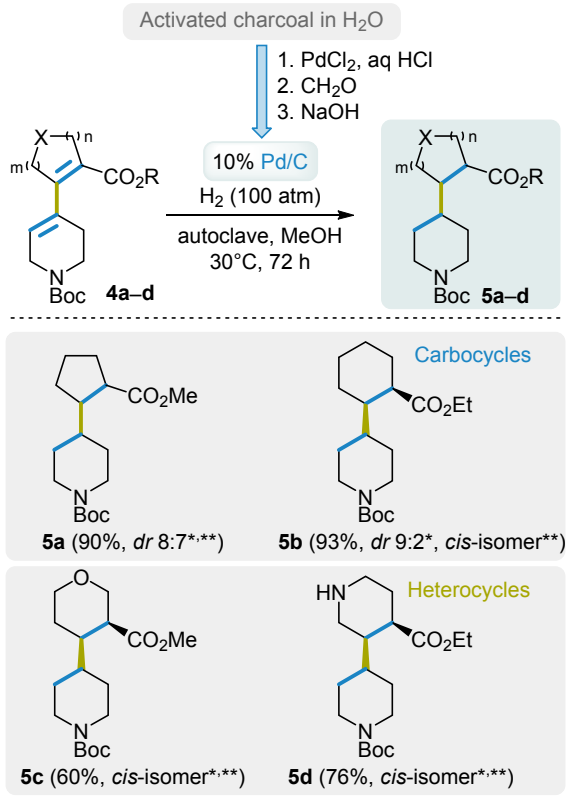


pyranyl and piperidinyl moieties *via* the cross-coupling reaction of (hetero)cycloalkenes followed by the catalytic hydrogenation (Scheme 1*c*). It was envisaged that the presence of two functional groups could be used to obtain various derivatives of mono- or deprotected amino acids.

First, commercially available *α*-oxo esters **1a–d** were subjected to the reaction with $PhN(OTf)_2$ and NaH[19] (Scheme 2). This approach led to preparation of cycloalkenyl triflates **2a–d** in good to high yields (78–90%). These compounds were used in the subsequent Suzuki cross-coupling reaction[20] with *N*-Boc-tetrahydropyridinyl-4-boron pinacolate (**3**). All reactions were carried out using $Pd(dppf)Cl_2$ as a catalyst and K_2CO_3 as a base in 1,4-dioxane–H_2O at 100°C, which allowed for the preparation of diene carboxylates **4a–d** in 56–70% yield after chromatographic purification (Scheme 2).

The key step of the reaction sequence included the reduction of obtained dienes **4a–d** to the corresponding *N*-Boc-amino esters **5a–d** (Scheme 3). The hydrogenation of dienes to achieve formal $C(sp^3)$–$C(sp^3)$ coupling connectivity appeared to be a challenging task due to the stability of conjugated polysubstituted diene carboxylate fragments. Thus, catalytic hydrogenation of compounds **4a**,**b** was recently studied and optimized by our group by testing a series of Pd/C and $Pd(OH)_2$/C catalysts.[19] It was found that

Scheme 3. Reduction of dienes **4a–d** to saturated compounds **5a–d** (relative configurations are shown)



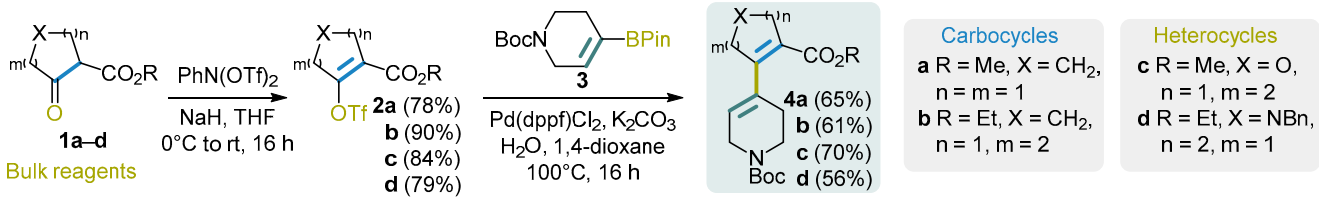
* *cis*/*trans* ratio of the crude product.
** *cis*/*trans* ratio after workup/chromatographic purification.

a Pd/C composite prepared by deposition of Pd nanoparticles (5–40 nm) *via* the reduction of Pd^{2+} with formaldehyde[20] demonstrated the best results in such transformations.

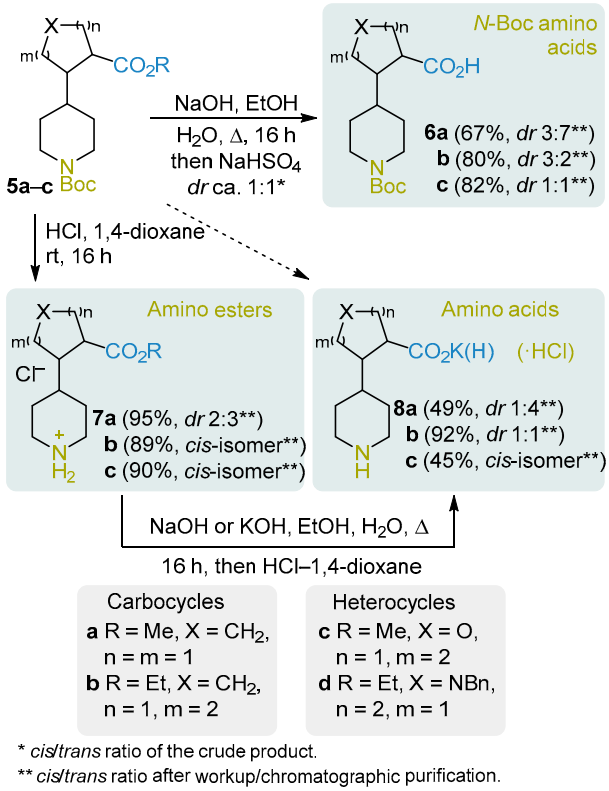
This catalyst was applied to a series of diene carboxylates **4a–d**. The hydrogenation proceeded in an autoclave under 100 atm of H_2 at 30°C for 72 h to ensure the complete conversion and reduction of both C=C double bonds. The reaction proceeded in a diastereoselective manner in the case of scaffolds containing two six-membered rings, i.e., for compounds **4b–d**. The corresponding saturated amino esters were obtained as a ca. 9:2 mixture of *cis*- and *trans*-diastereomers (for compound **5b**) or *cis*-isomers as sole products (for compounds **5c**,**d**). Cyclopentane carboxylate **5a** was obtained with *dr* 8:7 that retained after chromatographic purification.

N-Boc-amino esters **5a–c** could be easily transformed into other valuable amino acid-derived building blocks (Scheme 4). In particular, alkaline hydrolysis of the ester groups of derivatives **5a–c** was successfully achieved by refluxing with NaOH in EtOH–H_2O followed by acidi-

Scheme 2. Synthesis of dienes **4a–d** using Suzuki reaction of (hetero)cycloalkenyl triflates **2a–d** with tetrahydropyridine boronate **3**



Scheme 4. Synthesis of amino acids and their derivatives from compounds **5a–c** (relative configurations are shown)



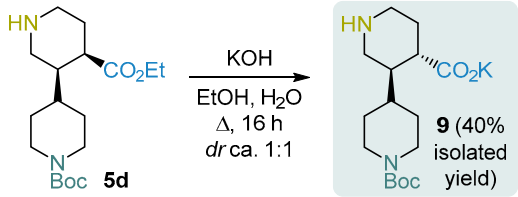
* *cis*/*trans* ratio of the crude product.
** *cis*/*trans* ratio after workup/chromatographic purification.

fication with aq $NaHSO_4$, leading to *N*-Boc-amino acids **6a–c**. Derivatives **6a–c** were obtained in good yields, however significant epimerization was observed, so that the products were obtained as ca. 1:1 mixture of *cis*- and *trans*-diastereomers. The *dr* ratio could be changed after the chromatographic purification used to obtain analytically pure samples according to 2D NMR experiments. Variation of the reaction conditions also resulted in epimerization, but in addition gave significantly lower yield of the target products **6a–c**. At the same time, *N*-Boc deprotection of the compounds **5a–c** in 1,4-dioxane–HCl at room temperature proceeded without epimerization and gave amino esters **7a–c** in high yield (89–95%).

Hydrolysis of ester group of esters **7a–c** proceeded in the way similar to the case of synthesis of compounds **6a–c** and provided title amino acids **8a–c** in 45–92% yield. The possibility of obtaining salt forms based on both the amino and the carboxyl groups was revealed. All final products were purified by HPLC. The structures and *dr* values of the products, as well as the relative configurations, were confirmed by a series of NMR experiments (see Supplementary information file for details). Attempted acidic hydrolysis of both ester and carbamate groups in molecules **5a–c** was inefficient and resulted in low yields of the target products **8a–c**. Finally, the KOH-mediated alkaline hydrolysis of bispiperidine derivative **5d** also proceeded with epimerization, and product **9** was isolated as a single diastereomer in 40% yield (Scheme 5).

In conclusion, we have developed a straightforward and robust approach to amino acid derivatives based on

Scheme 5. Synthesis of potassium 1'-(*tert*-butoxycarbonyl)-[3,4'-bipiperidine]-4-carboxylate (**9**)
(relative configurations are shown)



scaffolds with two isolated saturated (hetero)carbocycles. The method relied on the C(sp^2)–C(sp^2) Suzuki cross-coupling reaction of heterocyclic alkenyl triflates and *N*-Boc-tetrahydropyridine-derived boronate.

We found suitable catalysts for the key step – catalytic hydrogenation of the conjugated dienes to achieve C(sp^3)–C(sp^3) connectivity, which proceeded with good diastereoselectivity for scaffolds with two six-membered cycles, and with *dr* ratio of ca. 1:1 for a five-membered counterpart. The resulting *N*-Boc-amino esters are convenient reagents for the preparation of free amino acids and their monoprotected derivatives. Notably, the alkaline hydrolysis reaction of the ester groups appeared to be somewhat challenging: while it gave good yields of the target products, it was accompanied by epimerization. Though we did not check applicability of the catalysts, proposed herein, for a wider range of dienes, we suppose that the reported procedure can be helpful for preparation of a series of similar compounds.

In our opinion, the proposed method to obtain scaffolds with saturated isolated cycles could be useful for synthetic chemists, while the synthesized compounds could be considered as promising building blocks[21] for the purposes of medicinal chemistry and drug discovery.

Experimental

^{1}H and ^{13}C NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (600 and 151 MHz, respectively), a Bruker 170 Avance 500 spectrometer (500 and 126 MHz, respectively), and a Varian Unity Plus 400 spectrometer (400 and 101 MHz, respectively). Internal standards: TMS and residual solvent signals at 7.26 and 77.2 ppm for ^{1}H and ^{13}C nuclei in $CDCl_3$, 2.50 and 39.5 ppm for ^{1}H and ^{13}C nuclei in DMSO-d_6. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and an Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. The reaction process was monitored by ^{1}H NMR and mass spectroscopy. Melting points were measured on a MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using silica gel (230–400 mesh) as the stationary phase.

The solvents were purified according to the standard procedures.[22] Compounds **1a–d** and **3** were available from Enamine Ltd.

Preparation of alkenyl triflates 2a–d[23–26] (General method). 0.2 M Solution of the corresponding α-keto ester (57.0 mmol) in THF (285 ml) was cooled to 0°C, and NaH (60% in mineral oil, 2.30 g, 57.5 mmol) was added in portions. The reaction mixture was stirred at 0°C for 30 min, then $PhN(OTf)_2$ (20.5 g, 57.5 mmol) was added. The resulting mixture was stirred at room temperature overnight, then poured into H_2O (500 ml) and extracted with EtOAc (2×300 ml). Combined organic layers were washed with brine (2×100 ml), dried over Na_2SO_4, filtered, and evaporated *in vacuo* to dryness. The crude product was purified by column chromatography on silica gel using hexanes–EtOAc, 20:1 as eluent.

Synthesis of diene carboxylates 4a–d by Suzuki cross-coupling reaction (General method). The corresponding triflate **2a–d** (3.65 mmol) was dissolved in 1,4-dioxane–H_2O (14 ml, 7:2), then K_2CO_3 (1.51 g, 10.9 mmol), $Pd(dppf)Cl_2$ (267 mg, 0.365 mmol), and *tert*-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydropyridine-1(2*H*)-carboxylate (**3**) (1.24 g, 4.01 mmol) were added. The reactor was degassed, purged with argon, and the reaction mixture was stirred at 100°C for 16 h. The resulting mixture was cooled to room temperature, EtOAc (40 ml) was added, the resulting solution was washed with H_2O (3×15 ml) and brine (3×15 ml), dried over Na_2SO_4, filtered, and evaporated *in vacuo* to dryness.

***tert*-Butyl 4-[2-(methoxycarbonyl)cyclopent-1-en-1-yl]-3,6-dihydropyridine-1(2*H*)-carboxylate (4a)**. The product was purified by column chromatography on silica gel using hexanes–*t*-BuOMe as eluent, gradient from 1:0 to 0:1. Yield 729 mg (65%), yellowish oil. The compound existed as a ca. 1:1 mixture of rotamers. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 5.91–5.38 (1H, m, H-4); 4.02–3.91 (2H, m, H-5); 3.68 (3H, s, CO_2CH_3); 3.48 (2H, t, *J* = 5.6, H-1); 2.67 (2H, t, *J* = 7.6, H-2); 2.59 (2H, td, *J* = 7.6, *J* = 2.3, H-12); 2.29–2.17 (2H, m, H-14); 1.85 (2H, quint, *J* = 7.6, H-13); 1.44 (9H, s, $C(CH_3)_3$). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm: 166.7; 154.3; 152.0; 132.8; 127.6; 122.9; 122.3; 79.1; 50.9; 43.2; 42.6; 40.5; 39.2; 37.7; 34.7; 28.0; 27.2; 21.2. Mass spectrum (ES-API), *m*/*z*: 208 $[M–CH=C(CH_3)_2–CO_2+H]^+$. Found, %: C 66.11; H 7.85; N 4.57. $C_{17}H_{25}NO_4$. Calculated, %: C 66.43; H 8.20; N 4.56.

***tert*-Butyl 4-[2-(ethoxycarbonyl)cyclohex-1-en-1-yl]-3,6-dihydropyridine-1(2*H*)-carboxylate (4b)**. The product was purified by column chromatography on silica gel using hexanes–*t*-BuOMe as eluent, gradient from 1:0 to 0:1. Yield 747 mg (61%), yellowish oil. The compound existed as a ca. 3:2 mixture of rotamers. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 5.38–5.19 (1H, m, H-4); 4.11 (2H, q, *J* = 7.1, H-19); 3.93–3.81 (2H, m, H-5); 3.53 (2H, t, *J* = 5.5, H-1); 2.29 (2H, dt, *J* = 6.6, *J* = 3.7, H-2); 2.24–2.16 (2H, m, H-12); 2.13 (2H, dd, *J* = 6.6, *J* = 3.7, H-15); 1.68–1.57 (4H, m, H-13,14); 1.47 (9H, s, $C(CH_3)_3$); 1.22 (3H, t, *J* = 7.1, H-20). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm: 169.2; 154.4; 154.3; 146.2; 146.0; 138.9; 138.7; 125.8; 118.2; 117.9; 79.0; 59.6; 42.9; 42.4; 40.4; 39.2; 29.6; 28.0; 27.3; 27.2; 25.7; 21.6; 21.5; 13.8. Mass spectrum (ES-API), *m*/*z*: 236 $[M–CH=C(CH_3)_2–CO_2+H]^+$. Found, %: C 68.16; H 9.06; N 4.51. $C_{19}H_{29}NO_4$. Calculated, %: C 68.03; H 8.71; N 4.18.

***tert*-Butyl 4-[5-(methoxycarbonyl)-3,6-dihydro-2*H*-pyran-4-yl]-3,6-dihydropyridine-1(2*H*)-carboxylate (4c)**. The product was purified by flash column chromatography (5 bar, 80 g column) using $CHCl_3$–EtOAc as eluent, gradient from 1:0 to 0:1. Yield 826 mg (70%), colorless oil. The compound existed as a ca. 1:1 mixture of rotamers. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 5.48–5.30 (1H, m, H-4); 4.32 (2H, t, *J* = 2.5, H-14); 4.00–3.88 (2H, m, H-5); 3.78 (2H, t, *J* = 5.6, H-10); 3.68 (3H, s, CO_2CH_3); 3.57 (2H, t, *J* = 5.6, H-1); 2.35–2.26 (2H, m, H-11); 2.25–2.14 (2H, m, H-2); 1.48 (9H, s, $C(CH_3)_3$). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm: 166.2; 155.0; 148.3; 138.1; 124.4; 119.5; 79.8; 65.5; 64.0; 51.5; 43.6; 43.1; 41.3; 40.1; 31.0; 28.6; 27.9. Mass spectrum (ES-API), *m*/*z*: 224 $[M–CH=C(CH_3)_2–CO_2+H]^+$, 346 $[M+Na]^+$. Found, %: C 63.45; H 8.19; N 4.50. $C_{17}H_{25}NO_5$. Calculated, %: C 63.14; H 7.79; N 4.33.

1'-(*tert*-Butyl) 4-ethyl 1-benzyl-1,2,3',5,6,6'-hexahydro-[3,4'-bipyridine]-1',4(2'*H*)-dicarboxylate (4d). The product was purified by column chromatography on silica gel using hexanes–*t*-BuOMe as eluent, gradient from 1:0 to 0:1. Yield 874 mg (56%), yellowish oil. The compound existed as a ca. 11:9 mixture of rotamers. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 7.47–7.27 (5H, m, H Ph); 5.45–5.35 (1H, m, H-10); 5.15 (2H, s, CH_2Ph); 4.14 (2H, q, *J* = 7.1, H-26); 4.03–3.96 (2H, m, H-11); 3.94–3.87 (2H, m, H-1); 3.61–3.51 (4H, m, H-5,7); 2.48–2.39 (2H, m, H-4); 2.25–2.16 (2H, m, H-8); 1.47 (9H, s, $C(CH_3)_3$); 1.24 (3H, t, *J* = 7.1, H-27). ^{13}C NMR spectrum (151 MHz, $CDCl_3$, some signals are doubled due to the presence of rotamers), δ, ppm: 167.5; 155.2; 154.9; 136.7; 134.2; 128.7; 128.3; 128.2; 124.9; 124.5; 121.6; 121.1; 79.8; 67.4; 60.7; 47.2; 43.6; 43.0; 41.0; 40.5; 40.2; 39.8; 28.6; 28.3; 26.1; 25.7; 14.4. Mass spectrum (ES-API), *m*/*z*: 371 $[M–CH=C(CH_3)_2+H]^+$. Found, %: C 70.45; H 8.35; N 6.73. $C_{25}H_{34}N_2O_4$. Calculated, %: C 70.40; H 8.03; N 6.57.

Synthesis of *N*-Boc-amino esters 5a–d (General method). Compound **4a–d** (20.0 mmol), the optimal nanocomposite 10% Pd/C[20] (10 mol % counting per Pd), and MeOH (140 ml) were mixed directly in an autoclave, which was purged with argon. The autoclave was sealed, purged with hydrogen, and pressurized with hydrogen quickly after the mixing of the reagents. Hydrogenation was carried out under 100 atm of H_2 at 30°C for 72 h (*NOTE: as it was found, this time is required to achieve the complete hydrogenation in most cases*). Then, the catalyst was separated by centrifugation, the reaction mixture was evaporated, and the organic residue was analyzed by NMR and LC/MS.

***tert*-Butyl 4-[2-(methoxycarbonyl)cyclopentyl]piperidine-1-carboxylate (5a)**. The product was purified by column chromatography on silica gel using hexanes–*t*-BuOMe as eluent, gradient from 1:0 to 0:1. The compound was obtained as a ca. 8:7 mixture of diastereomers. Yield 5.59 g (90%), yellowish oil. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 4.05 (2H, t, *J* = 12.9, H-2,6); 3.64 (1.4H, s, CO_2CH_3); 3.62 (1.6H, s, CO_2CH_3); 2.90 (0.53H, t, *J* = 7.1, H-11); 2.51–2.36 (0.47H, m, H-11); 2.67–2.54 (2H, m, H-2,6); 2.08–1.99 (0.47H, m, CH, CH_2); 1.94–1.69 (4.53H, m, H-3–5,10,12–14); 1.68–1.45 (5H, m, H-3–5,10,12–14);

1.42 (9H, s, $C(CH_3)_3$); 1.39–1.17 (1.87H, m, CH, CH_2); 1.16–1.01 (2.13H, m, CH, CH_2). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm: 177.1; 175.8; 154.4; 154.3; 78.8; 78.7; 51.2; 50.3; 50.6; 47.0; 48.6; 45.2; 43.6; 43.5 (2C); 43.4; 40.4; 37.6; 31.3; 31.1; 30.9; 30.3; 29.8; 29.5; 29.1; 28.0; 24.9; 22.8. Mass spectrum (ES-API), *m*/*z*: 312 $[M+H]^+$. Found, %: C 65.40; H 9.53; N 4.10. $C_{17}H_{29}NO_4$. Calculated, %: C 65.57; H 9.39; N 4.50.

***cis-tert*-Butyl 4-[2-(ethoxycarbonyl)cyclohexyl]piperidine-1-carboxylate (5b)**. The product was purified by column chromatography on silica gel using hexanes–*t*-BuOMe as eluent, gradient from 1:0 to 0:1. The compound was obtained as a single *cis*-diastereomer. Yield 6.29 g (93%), yellowish oil. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 4.19–3.97 (4H, m, H-2,6,19); 2.83–2.72 (1H, m, H-11); 2.65–2.52 (2H, m, H-2,6); 2.02–1.90 (1H, m, H-12); 1.83–1.69 (3H, m, H-3,5,13); 1.67–1.55 (3H, m, H-12,14,15); 1.50–1.45 (3H, m, H-4,12,14); 1.42 (9H, s, $(C(CH_3)_3)$; 1.22 (3H, t, *J* = 7.1, H-20); 1.20–1.09 (2H, m, H-10,13); 1.04–0.90 (2H, m, H-3,5). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm: 174.1; 154.3; 78.7; 59.2; 43.9; 43.5; 40.6; 37.8; 29.9; 29.6; 28.8; 28.0; 25.5; 24.6; 21.5; 13.8. Mass spectrum (ES-API), *m*/*z*: 340 $[M+H]^+$. Found, %: C 66.88; H 10.09; N 4.28. $C_{19}H_{33}NO_4$. Calculated, %: C 67.22; H 9.80; N 4.13.

***cis-tert*-Butyl 4-[3-(methoxycarbonyl)tetrahydro-2*H*-pyran-4-yl]piperidine-1-carboxylate (5c)**. The product was purified by column chromatography on silica gel using hexanes–*t*-BuOMe as eluent, gradient from 1:0 to 0:1. The compound was obtained as a single *cis*-diastereomer. Yield 3.92 g (60%), yellowish oil. ^1H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 4.25 (1H, d, *J* = 11.7, H-10,14); 4.19–3.96 (3H, m, H-2,6,10,14); 3.70 (3H, s, CO_2CH_3); 3.50 (1H, dd, *J* = 11.7, *J* = 3.1, H-10,14); 3.38 (1H, td, *J* = 12.0, *J* = 2.6, H-11); 2.74–2.49 (3H, m, H-2,6); 2.11–1.98 (1H, m, H-12); 1.87–1.76 (1H, m, H-3–5,13); 1.72–1.61 (2H, m, H-3–5,13); 1.59–1.53 (1H, m, H-3–5,13); 1.49–1.32 (10H, m, $C(CH_3)_3$, H-3-5,13); 1.15–0.83 (2H, m, H-3–5,13). ^{13}C NMR spectrum (101 MHz, $CDCl_3$), δ, ppm: 173.0; 154.9; 79.4; 70.5; 69.0; 51.7; 43.9; 42.6; 42.0; 37.7; 30.2; 29.7; 28.6; 26.0. Mass spectrum (ES-API), *m*/*z*: 228 $[M–H_2C=C(CH_3)_2–CO_2+H]^+$. Found, %: C 62.31; H 8.94; N 3.98. $C_{17}H_{29}NO_5$. Calculated, %: C 62.36; H 8.93; N 4.28.

***cis*-3-[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]-4-(ethoxycarbonyl)piperidin-1-ium chloride (5d)**. The product was purified by column chromatography on silica gel using hexanes–*t*-BuOMe as eluent, gradient from 1:0 to 0:1. After that, the amine (ca. 20.0 mmol) and *i*-Pr_2EtN (3.48 ml, 20.0 mmol) were dissolved in CH_2Cl_2 (200 ml) and benzyl chloroformate (2.85 ml, 20.0 mmol) was added at room temperature. After 1 h, saturated aq $NaHCO_3$ (500 ml) was added and the aqueous phase was extracted with EtOAc (3×100 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel using hexanes–*t*-BuOMe as eluent, gradient from 1:0 to 0:1.[23] The obtained *N*-Cbz-diamine (ca. 20.0 mmol) was dissolved in MeOH (75 ml). Pd/C (0.75 g) and $CHCl_3$ (1.60 ml, 20.0 mmol) were added. The mixture was hydrogenated under H_2 (1 bar) at 40°C for 16 h, then catalyst was filtered off, and filtrate was evaporated *in vacuo*. The residue was washed with EtOAc (3×25 ml) and dried in air.[5] The compound was obtained as a single *cis*-diastereomer. Overall yield 5.71 g (76%), colorless powder, mp 159–160°C. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 9.73 (1H, d, *J* = 9.9, NH_2^+); 9.46 (1H, d, *J* = 9.9, NH_2^+); 4.25–4.04 (4H, m, H-10,13,17); 3.40–3.16 (4H, m, H-2,6,13,17); 2.97–2.91 (1H, m, H-2,6); 2.65–2.52 (2H, m, H-2,4,6); 2.30–2.19 (1H, m, H-5); 2.09–2.02 (1H, m, H-5); 2.02–1.94 (1H, m, H-3); 1.78–1.71 (1H, m, H-14–16); 1.68–1.61 (1H, m, H-14–16); 1.52–1.32 (10H, m, $C(CH_3)_3$, H-14–16); 1.25 (3H, t, *J* = 7.1, H-11); 1.21–1.06 (2H, m, H-14–16). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm: 172.9; 154.7; 79.7; 61.0; 43.6; 42.6; 40.1; 39.8; 37.5; 36.5; 29.8; 29.3; 28.6; 25.3; 14.4. Mass spectrum (ES-API), *m*/*z*: 341 $[M–HCl+H]^+$. Found, %: C 57.46; H 8.62; N 7.08; Cl 9.14. $C_{18}H_{33}ClN_2O_4$. Calculated, %: C 57.36; H 8.83; N 7.43; Cl 9.41.

Synthesis of *N*-Boc-amino acids 6a–c (General method). Synthesized crude compound **5a–c** (5.00 mmol) was added to NaOH (400 mg, 10.0 mmol) in EtOH–H_2O (30 ml, 7:3), and the resulting mixture was refluxed for 16 h. Then, reaction mixture was cooled to room temperature, and byproducts were extracted with *t*-BuOMe (2×10 ml). Then, saturated aq $NaHSO_4$ was added until pH 5 was adjusted. After that, aqueous solution was extracted with *t*-BuOMe (3×10 ml). Combined organic layers were dried over Na_2SO_4 and evaporated *in vacuo*.

2-[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]cyclopentane-1-carboxylic acid (6a). The product was purified by column chromatography on silica gel using hexanes–*t*-BuOMe as eluent, gradient from 1:0 to 0:1. The compound was obtained as a 3:7 mixture of *cis*-/*trans*-diastereomers; existed as a mixture of rotamers. Yield 993 mg (67%), yellowish oil. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 8.81 (1H, br. s, CO_2H); 4.21–3.98 (2H, m, H-10,14); 3.56–3.48 (0.3H, m, H-1); 2.93 (0.3H, t, *J* = 6.8, H-1); 2.78–2.60 (2.4H, m, H-1,10,14); 2.56–2.46 (1H, m, H-2); 2.14–1.76 (4H, m, H-3,5,11,13); 1.75–1.49 (4H, m, H-3,5,11,13); 1.48–1.05 (12H, m, $C(CH_3)_3$, H-4,12). ^{13}C NMR spectrum (126 MHz, $CDCl_3$), δ, ppm: 182.8; 181.4; 171.0; 165.5; 155.0; 126.7; 79.6; 79.5 (2C); 51.0; 49.2; 47.5; 45.8; 44.1; 41.0; 38.0; 36.9; 34.8; 33.5; 31.9; 31.7; 31.6; 31.0; 30.5; 30.1; 30.0; 29.8; 28.6; 28.5; 25.7; 23.3; 21.5. Mass spectrum (ES-API), *m*/*z*: 242 $[M–CH=C(CH_3)_2+H]^+$, 320 $[M+Na]^+$. Found, %: C 64.69; H 9.11; N 4.36. $C_{16}H_{27}NO_4$. Calculated, %: C 64.62; H 9.15; N 4.71.

2-[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]cyclohexane-1-carboxylic acid (6b). The product was purified by column chromatography on silica gel using hexanes–*t*-BuOMe as eluent, gradient from 1:0 to 0:1. The compound was obtained as a 3:2 mixture of *cis*-/*trans*-diastereomers. Yield 1.24 g (80%), colorless solid, mp 134–135°C. ^1H NMR spectrum (600 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 11.95 (1H, s, CO_2H); 4.03–3.86 (2H, m, H-11,15); 2.75–2.49 (3H, m, H-1,11,15); 2.13 (0.4H, td, *J* = 11.3, *J* = 3.5, H-2); 1.91–1.86 (0.6H, m, H-2); 1.82–1.77 (0.4H, m, H-13); 1.77–1.73 (0.6H, m, H-13); 1.71–1.61 (2H, m, H-6); 1.58–1.21 (15H,

m, $C(CH_3)_3$, H-4,5,12,14); 1.21–1.11 (2H, m, H-4,5); 1.05–0.81 (2H, m, H-3). ^{13}C NMR spectrum (126 MHz, $CDCl_3$, some signals are doubled due to the presence of rotamers and diastereomers), δ, ppm: 181.5; 180.3; 155.0; 79.5 (2C); 47.0; 44.6; 44.5; 44.2; 43.6; 41.1; 39.2; 38.2; 30.6; 30.5; 30.4; 30.2; 29.5; 28.6; 26.3; 26.1; 25.9; 25.7; 25.6; 25.1; 22.2. Mass spectrum (ES-API), *m*/*z*: 212 $[M–CO_2–CH=C(CH_3)_2+H]^+$, 256 $[M–CH=C(CH_3)_2+H]^+$, 334 $[M+Na]^+$. Found, %: C 65.35; H 9.29; N 4.41. $C_{17}H_{29}NO_4$. Calculated, %: C 65.57; H 9.39; N 4.50.

4-[1-(*tert*-Butoxycarbonyl)piperidin-4-yl]tetrahydro-2*H*-pyran-3-carboxylic acid (6c). The product was purified by column chromatography on silica gel using hexanes–*t*-BuOMe as eluent, gradient from 1:0 to 0:1. The compound was obtained as a 1:1 mixture of *cis*-/*trans*-diastereomers. Yield 1.29 g (82%), beige powder, mp 138–139°C. ^1H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 9.87 (1H, br. s, CO_2H); 4.33 (0.5H, d, *J* = 11.8, H-1,5); 4.22–4.04 (3H, m, H-1,5,11,15); 4.02–3.97 (0.5H, m, H-1,5); 3.53 (0.5H, dd, *J* = 11.8, *J* = 3.0, H-1,5); 3.48–3.36 (1.5H, m, H-1,5); 2.73–2.55 (3H, m, H-2,11,15); 1.98–1.79 (2H, m, H-2,13); 1.70–1.55 (2H, m, H-12,14); 1.51–1.30 (11H, m, $C(CH_3)_3$, H-12,14); 1.25–0.93 (2H, m, H-4). ^{13}C NMR spectrum (126 MHz, $CDCl_3$, some signals are doubled due to the presence of rotamers and diastereomers), δ, ppm: 177.6; 177.0; 155.0; 79.7; 79.6; 70.3; 69.5; 69.1; 68.3; 46.1; 44.3; 44.0; 42.5; 42.0; 41.6; 38.8; 37.6; 30.1; 29.8; 29.7; 28.6; 26.6; 25.9; 25.7. Mass spectrum (ES-API), *m*/*z*: 214 $[M–CO_2–CH=C(CH_3)_2+H]^+$, 258 $[M–CH=C(CH_3)_2+H]^+$, 336 $[M+Na]^+$. Found, %: C 61.15; H 8.99; N 4.75. $C_{16}H_{27}NO_5$. Calculated, %: C 61.32; H 8.68; N 4.47.

Synthesis of amino esters 7a–c (General method). Synthesized compound **5a–c** (5.00 mmol) was dissolved in 2 M HCl solution in 1,4-dioxane (30 ml), and the resulting mixture was stirred at room temperature for 16 h. The formed solid product was filtered off and washed with *t*-BuOMe (2×10 ml).

4-[2-(Methoxycarbonyl)cyclopentyl]piperidin-1-ium chloride (7a) was obtained as a 2:3 mixture of *cis*-/*trans*-diastereomers. Yield 1.18 g (95%), beige powder, mp 100–101°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 9.15 (1H, br. s, NH_2^+); 8.95 (1H, br. s, NH_2^+); 3.59 (1.8H, s, CO_2CH_3); 3.58 (1.2H, s, CO_2CH_3); 3.23–3.14 (2H, m, H-2,6); 2.91–2.86 (0.4H, m, H-8); 2.81–2.68 (2H, m, H-2,6); 2.49–2.45 (0.6H, m, H-8); 1.98–1.91 (0.6H, m, H-7); 1.90–1.64 (6H, m, H-7, CH, CH_2); 1.61–1.52 (1.6H, m, CH, CH_2); 1.47–1.33 (3.2H, m, CH, CH_2); 1.29–1.21 (0.6H, m, CH, CH_2). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 176.4; 175.2; 51.5; 51.1; 49.5; 48.0; 46.5; 44.9; 44.0; 42.9; 42.8; 42.7; 37.7; 35.2; 30.9; 29.6; 28.9; 27.8; 27.8; 27.7; 27.0; 26.3; 24.9; 22.8. Mass spectrum (ES-API), *m*/*z*: 212 $[M–HCl+H]^+$. Found, %: C 57.97; H 8.58; N 5.27; Cl 14.43. $C_{12}H_{22}ClNO_2$. Calculated, %: C 58.17; H 8.95; N 5.65; Cl 14.31.

***cis*-4-[2-(Ethoxycarbonyl)cyclohexyl]piperidin-1-ium chloride (7b)** was obtained as a single *cis*-diastereomer. Yield 1.22 g (89%), colorless powder, mp 149–150°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 9.20–8.92 (2H, m, NH_2^+); 4.10–3.99 (2H, m, H-16); 3.20 (2H, t, *J* = 10.3, H-2,6); 2.82–2.62 (3H, m, H-2,6,8); 1.93–1.84 (2H, m, H-3–5,7,9–12); 1.83–1.76 (1H, m, H-3–5,9–12); 1.73–1.67 (1H, m, H-3–5,9–12); 1.63–1.57 (1H, m, H-3–5,9–12); 1.55–1.13 (12H, m, H-3–5,9–12,17). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 173.5; 59.3; 43.2; 43.0; 42.9; 40.2; 35.6; 28.5; 26.5; 26.2; 25.3; 24.4; 21.5; 14.1. Mass spectrum (ES-API), *m*/*z*: 240 $[M–HCl+H]^+$. Found, %: C 60.86; H 9.31; N 5.01; Cl 12.55. $C_{14}H_{26}ClNO_2$. Calculated, %: C 60.97; H 9.50; N 5.08; Cl 12.85.

***cis*-4-[3-(Methoxycarbonyl)tetrahydro-2*H*-pyran-4-yl]-piperidin-1-ium chloride (7c)** was obtained as a single *cis*-diastereomer. Yield 1.19 g (90%), beige powder, mp 206–207°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 9.09 (2H, br. s, NH_2^+); 4.06 (1H, d, *J* = 11.5, H-7,11); 3.89 (1H, dd, *J* = 11.5, *J* = 4.6, H-7,11); 3.60 (3H, s, CO_2CH_3); 3.46 (1H, dd, *J* = 11.5, *J* = 3.0, H-7,11); 3.33–3.26 (1H, m, H-7,11); 3.23–3.18 (2H, m, H-2,6); 2.83–2.67 (3H, m, H-2,6,8); 1.94–1.86 (1H, m, H-9); 1.82–1.64 (3H, m, H-3–5,10); 1.52–1.46 (1H, m, H-3–5,10); 1.44–1.23 (3H, m, H-3–5,10). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 172.2; 69.5; 67.7; 51.2; 42.9; 42.8; 41.0; 40.9; 34.9; 26.2; 25.7; 25.2. Mass spectrum (ES-API), *m*/*z*: 228 $[M–HCl+H]^+$. Found, %: C 54.86; H 8.03; N 5.27; Cl 13.35. $C_{12}H_{22}ClNO_3$. Calculated, %: C 54.65; H 8.41; N 5.31; Cl 13.44.

Synthesis of amino acids 8a–c (General method). Synthesized crude compound **7a–c** (3.00 mmol) was added to NaOH (240 mg, 6.00 mmol for compounds **7a**,**b**) or KOH (336 mg, 6.00 mmol for compound **7c**) in EtOH–H_2O (18 ml, 7:3), and the resulting mixture was refluxed for 16 h. Then, reaction mixture was cooled to room temperature, and evaporated to dryness.

4-(2-Carboxycyclopentyl)piperidin-1-ium chloride (8a). Then 2 M HCl–1,4-dioxane (10 ml) was added to the obtained compound, and the resulting mixture was stirred at room temperature for 15 min. After that, the precipitate was filtered off, and the target product was purified by HPLC using H_2O–MeCN as eluent, gradient from 1:0 to 0:1 (30 ml/min flow, XBridge BEH C18 column). The compound was obtained as a 1:4 mixture of *cis*- and *trans*-diastereomers. Yield 342 mg (49%), brownish powder, mp 183–184°C. ^1H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 12.09 (1H, br. s, CO_2H); 9.24–9.03 (1H, m, NH_2^+); 8.98–8.81 (1H, m, NH_2^+); 3.25–3.13 (2H, m, H-2,6); 2.84–2.67 (2H, m, H-2,6); 2.38 (1H, q, *J* = 7.9, H-8); 1.99–1.89 (1H, m, H-7); 1.88–1.62 (5H, m, H-3,5,9,10,11); 1.60–1.32 (5H, m, H-3–5,10,11); 1.28–1.18 (1H, m, H-3,5,10,11). ^{13}C NMR spectrum (126 MHz, DMSO-d_6, some signals are doubled due to the presence of diastereomers), δ, ppm: 177.6; 176.4; 49.4; 47.7; 46.9; 45.1; 43.0; 43.0; 42.9; 42.8; 37.9; 35.2; 31.0; 29.7; 29.1; 27.9; 27.8 (2C); 27.1; 26.4; 25.1; 22.8. Mass spectrum (ES-API), *m*/*z*: 198 $[M–HCl+H]^+$. Found, %: C 56.76; H 8.89; N 6.12; Cl 15.39. $C_{11}H_{20}ClNO_2$. Calculated, %: C 56.52; H 8.62; N 5.99; Cl 15.17.

4-(2-Carboxycyclohexyl)piperidin-1-ium chloride (8b). 2 M HCl–1,4-dioxane (10 ml) was added to the obtained compound, and the resulting mixture was stirred at room temperature for 15 min. After that, the precipitate was

filtered off, and the target product was purified by HPLC using H_2O–MeCN as eluent, gradient from 1:0 to 0:1 (30 ml/min flow, XBridge BEH C18 column). The compound was obtained as a 1:1 mixture of *cis*- and *trans*-diastereomers. Yield 684 mg (92%), yellowish powder, mp 184–185°C. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 12.08 (1H, br. s, CO_2H); 9.19–8.80 (2H, m, NH_2^+); 3.28–3.16 (2H, m, H-2,6); 2.86–2.74 (1H, m, H-2,6); 2.74–2.59 (1.5H, m, H-2,6,8); 2.16 (0.5H, td, *J* = 11.1, *J* = 3.5, H-8); 1.97–1.86 (1H, m, CH, CH_2); 1.85–1.79 (1H, m, CH, CH_2); 1.72–1.14 (11.5H, m, CH, CH_2); 1.01–0.93 (0.5H, m, CH, CH_2). ^{13}C NMR spectrum (126 MHz, DMSO-d_6, some signals are doubled due to the presence of diastereomers), δ, ppm: 176.5; 175.3; 46.2; 43.5; 43.3; 43.1; 43.0; 42.6; 40.2; 36.1; 35.4; 29.9; 28.8; 26.7; 26.4; 26.3; 25.4; 25.3; 24.9; 24.5; 22.8; 21.8. Mass spectrum (ES-API), *m*/*z*: 212 $[M–HCl+H]^+$. Found, %: C 58.21; H 9.08; N 5.55; Cl 14.63. $C_{12}H_{22}ClNO_2$. Calculated, %: C 58.17; H 8.95; N 5.65; Cl 14.31.

Potassium *cis*-4-(piperidin-4-yl)tetrahydro-2*H*-pyran-3-carboxylate (8c) was obtained as a single *cis*-diastereomer by crystallization. Yield 339 mg (45%), yellowish solid, mp >300°C. ^{1}H NMR spectrum (500 MHz, D_2O), δ, ppm (*J*, Hz): 3.99 (1H, d, *J* = 11.6, H-5); 3.86 (1H, d, *J* = 11.6, H-1); 3.46 (1H, dd, *J* = 11.6, *J* = 3.0, H-5); 3.32 (1H, td, *J* = 11.6, *J* = 2.5, H-1); 3.19–3.04 (2H, m, H-11,15); 2.71–2.57 (2H, m, H-11,15); 2.44–2.34 (1H, m, H-2); 1.93–1.74 (3H, m, H-4,12,14); 1.61–1.53 (1H, m, H-13); 1.47–1.41 (1H, m, H-4); 1.40–1.31 (1H, m, H-3); 1.16–1.00 (2H, m, H-12,14); NH signal is not visible due to the exchange with D_2O. ^{13}C NMR spectrum (151 MHz, D_2O), δ, ppm: 181.6; 70.3; 68.0; 44.7; 44.6; 40.8; 36.3; 28.1; 28.0; 25.1. Mass spectrum (ES-API), *m*/*z*: 212 $[M–K]^-$. Found, %: C 52.29; H 7.59; N 5.44. $C_{11}H_{18}KNO_3$. Calculated, %: C 52.56; H 7.22; N 5.57.

Potassium 1'-(*tert*-butoxycarbonyl)[3,4'-bipiperidine]-4-carboxylate (9) was synthesized according to general method for the synthesis of amino acids **8a–c** from compound **5d** (0.500 mmol). The compound was obtained as a single *trans*-diastereomer by crystallization. Yield 70.1 mg (40%), yellowish solid, mp >300°C. ^{1}H NMR spectrum (600 MHz, D_2O), δ, ppm (*J*, Hz): 4.03–3.91 (2H, m, H-8,12); 3.32 (1H, d, *J* = 12.8, H-6); 3.28 (1H, dd, *J* = 12.8, *J* = 3.8, H-2); 2.84 (1H, td, *J* = 13.1, *J* = 3.3, H-6); 2.73–2.56 (3H, m, H-2,8,12); 2.37 (1H, td, *J* = 11.7, *J* = 3.7, H-4); 2.02–1.97 (1H, m, H-5); 1.87–1.82 (1H, m, H-3); 1.76–1.69 (1H, m, H-5); 1.60–1.51 (2H, m, H-10,11); 1.46–1.41 (1H, m, H-9); 1.37–1.14 (10H, m, $C(CH_3)_3$, H-9); 1.03–0.97 (1H, m, H-11); NH signal is not visible due to the exchange with D_2O. ^{13}C NMR spectrum (151 MHz, D_2O), δ, ppm: 181.0; 156.4; 81.6; 45.8; 44.0; 43.2; 39.9; 37.0; 29.3; 27.6; 26.3; 26.0. Mass spectrum (ES-API), *m*/*z*: 311 $[M–K]^-$. Found, %: C 55.04; H 7.49; N 8.28. $C_{16}H_{27}KN_2O_4$. Calculated, %: C 54.83; H 7.76; N 7.99.

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of the synthesized compounds is available at the journal website http://link.springer.com/journal/10593.

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References

1. Han, J.; Konno, H.; Sato, T.; Soloshonok, V. A.; Izawa, K. *Eur. J. Med. Chem.* **2021**, *220*, 113448.
2. Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 230.
3. Liu, J.; Han, J.; Izawa, K.; Sato, T.; White, S.; Meanwell, N. A.; Soloshonok, V. A. *Eur. J. Med. Chem.* **2020**, *208*, 112736.
4. Kiss, L.; Mándity, I. M.; Fülöp, F. *Amino Acids* **2017**, *49*, 1441.
5. Feskov, I. O.; Golub, B. O.; Vashchenko, B. V.; Levterov, V. V.; Kondratov, I. S.; Grygorenko, O. O.; Haufe, G. *Eur. J. Org. Chem.* **2020**, 4755.
6. Hys, V. Y.; Shevchuk, O. I.; Vashchenko, B. V.; Karpenko, O. V.; Gorlova, A. O.; Grygorenko, O. O. *Eur. J. Org. Chem.* **2020**, 3896.
7. Barbier, P.; Renzetti, A. R.; Turbanti, L.; Di Bugno, C.; Fornai, F.; Vaglini, F.; Maggio, R.; Corsini, G. U. *Eur. J. Pharmacol. Mol. Pharmacol.* **1995**, *290*, 125.
8. Subissi, A.; Alberto Maggi, C.; Meli, A. *Jpn. J. Pharmacol.* **1986**, *42*, 153.
9. Ali, A.; Jadhav, A.; Jangid, P.; Patil, R.; Shelar, A.; Karuppayil, S. M. *J. Antibiot.* (*Tokyo*) **2018**, *71*, 456.
10. Dom, R.; Lommel, R.; Baro, F. *Acta Psychiatr. Scand.* **1971**, *47*, 399.
11. van Wijngaarden, I.; Soudijn, W. *Life Sci.* **1968**, *7*, 225.
12. van Wijngaarden, I. *Life Sci.* **1969**, *8*, 517.
13. DeForrest, J. M.; Waldron, T. L.; Harvey, C.; Scalese, B.; Rubin, B.; Powell, J. R.; Petrillo, E. W.; Cushman, D. W. *J. Cardiovasc. Pharmacol.* **1989**, *14*, 730.
14. Murdoch, D.; McTavish, D. *Drugs* **1992**, *43*, 123.
15. Pilote, L.; Abrahamowicz, M.; Eisenberg, M.; Humphries, K.; Behlouli, H.; Tu, J. V. *Can. Med. Assoc. J.* **2008**, *178*, 1303.
16. Subota, A. I.; Lutsenko, A. O.; Vashchenko, B. V.; Volochnyuk, D. M.; Levchenko, V.; Dmytriv, Y. V.; Rusanov, E. B.; Gorlova, A. O.; Ryabukhin, S. V.; Grygorenko, O. O. *Eur. J. Org. Chem.* **2019**, 3636.
17. ElMarrouni, A.; Ritts, C. B.; Balsells, J. *Chem. Sci.* **2018**, *9*, 6639.
18. López, E.; Melis, C.; Martín, R.; Petti, A.; Hoz, A.; Díaz-Ortíz, Á.; Dobbs, A. P.; Lam, K.; Alcázar, J. *Adv. Synth. Catal.* **2021**, *363*, 4521.
19. Subotin, V. V.; Vashchenko, B. V.; Asaula, V. M.; Verner, E. V.; Ivanytsya, M. O.; Shvets, O.; Ostapchuk, E. N.; Grygorenko, O. O.; Ryabukhin, S. V.; Volochnyuk, D. M.; Kolotilov, S. V. *Molecules* **2023**, *28*, 1201.
20. Cai, C.-Y.; Wu, Z.-J.; Liu, J.-Y.; Chen, M.; Song, J.; Xu, H.-C. *Nat. Commun.* **2021**, *12*, 3745.
21. Mozingo, R. *Org. Synth.* **1946**, *26*, 77.
22. Grygorenko, O. O.; Volochnyuk, D. M.; Vashchenko, B. V. *Eur. J. Org. Chem.* **2021**, 6478.
23. Armarego, W. L. F.; Chai, C. *Purification of Laboratory Chemicals*; Elsevier: Oxford, 2003.
24. Hsu, D.-S.; Liang, S.-P. *J. Org. Chem.* **2020**, *85*, 1270.
25. Peil, S.; Fürstner, A. *Angew. Chem., Int. Ed.* **2019**, *58*, 18476.
26. Su, N.; Theorell, J. A.; Wink, D. J.; Driver, T. G. *Angew. Chem., Int. Ed.* **2015**, *54*, 12942.
27. Whelligan, D. K.; Solanki, S.; Taylor, D.; Thomson, D. W.; Cheung, K.-M. J.; Boxall, K.; Mas-Droux, C.; Barillari, C.; Burns, S.; Grummitt, C. G.; Collins, I.; van Montfort, R. L. M.; Aherne, G. W.; Bayliss, R.; Hoelder, S. *J. Med. Chem.* **2010**, *53*, 7682.
23. Binanzer, M.; Hsieh, S.-Y.; Bode, J. W. *J. Am. Chem. Soc.* **2011**, *133*, 19698.