Journal of Organic and Pharmaceutical Chemistry

Original Research

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UDC 547.513+547.514+546.16

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Synthesis and Physicochemical Characteristics of 6,6-Difluorobicyclo[3.2.0]heptane Derivatives

Abstract

The gram-scale synthesis of 6,6-difluorobicyclo[3.2.0]heptane-derived building blocks (i.e., primary amine and carboxylic acid) was performed *via* the deoxofluorination of the corresponding bicyclic keto ester with diethylaminosulfur trifluride (DAST). Physicochemical properties of the compounds obtained (i.e., pK_a) or their model benzamide / anilide derivatives (i.e., Log*P*) were determined experimentally and compared to those of monocyclic and non-fluorinated bicyclic counterparts. It was found that *gem*-difluorination expectedly decreased the pK_a values by 0.3–0.5 units, whereas the Log*P* values were decreased by 0.54–0.55 units. Meanwhile, the bicyclic system itself had a negligible impact on the compounds' acidity and lipophilicity compared to the monocyclic counterparts.

***Keywords*:** fluorine; bicyclic compounds; acidity; lipophilicity; building blocks

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Синтез та фізико-хімічні характеристики похідних 6,6-дифлуоробіцикло[3.2.0]гептану

Анотація

Здійснено синтез будівельних блоків на основі 6,6-дифлуоробіцикло[3.2.0]гептану (а саме, первинного аміну та карбонової кислоти) у грамових кількостях шляхом деоксофлуорування відповідного кетоестеру. Експериментальним шляхом визначено фізико-хімічні властивості одержаних сполук (зокрема pK_a) або їх модельних бензамідних / анілідних похідних (зокрема Log*P*), а результати зіставлено з даними для моноциклічних та нефлуорованих біциклічних аналогів. Виявлено, що *гем*-дифлуорування очікувано зменшило значення pK_a на 0.3–0.5 одиниці, тоді як значення Log*P* зменшилось на 0.54–0.55 одиниці. Водночас власне біциклічна система мала незначний вплив на кислотні властивості та ліпофільність сполук, якщо порівнювати з моноциклічними аналогами.

***Ключові слова*:** Флуор; біциклічні сполуки; кислотність; ліпофільність; будівельні блоки

Citation: Moroz, B. L.; Holovach, S. M.; Melnykov, K. P.; Lesyk, D. S.; Filatov, A. A.; Grygorenko, O. O. Synthesis and physicochemical characteristics of 6,6-difluorobicyclo[3.2.0]heptane derivatives. *Journal of Organic and Pharmaceutical Chemistry* **2024**, *22* (3), 3–9
https://doi.org/10.24959/ophcj.24.314176
Supporting information: Copies of ^{1}H, ^{13}C and ^{19}F NMR spectra.
Received: *15 October 2024*; **Revised:** *3 November 2024*; **Accepted:** *5 November 2024*

Funding: The work was supported by Enamine Ltd., Ministry of Education and Science of Ukraine (grant No. 0122U001962 (22BF037-02)), and the National Academy of Sciences of Ukraine (grant No. 0119U102718).
Conflict of interests: The authors are employees or consulting scientists at Enamine Ltd. that offers the title compounds from the company's catalog.

■ Introduction

Fluorinated derivatives of saturated rings have attracted much attention recently, and several drug molecules of this class have entered the market over the last decade [1, 2]. On the other hand, conformational restriction through the introduction of a bicyclic ring system is a well-recognized design approach in medicinal chemistry, providing unique chemotypes with improved physicochemical and biological properties [3–5]. In this view, building blocks derived from fluorinated saturated bicyclic scaffolds can be considered advantageous to early drug discovery; however, only limited examples thereof can be found in the literature to date (**Figure 1**) [6–8].

In this work, we propose a novel fluorinated saturated bicyclic scaffold of potential interest to the drug discovery – 6,6-difluorobicyclo[3.2.0]heptane. We describe the synthesis of its functionalized derivatives – building blocks **1** and **2**, their physicochemical characteristics in terms of acid-base properties and lipophilicity, and comparison with non-fluorinated and monocyclic counterparts.

■ Results and discussion

Our synthesis of compounds **1** and **2** was very straightforward and started from commercially available keto ester **3** that could also be prepared through [2+2] cycloaddition according the protocols [9] previously reported (**Scheme 1**). Deoxofluorination of compound **3** proceeded smoothly upon the action of DAST in refluxing CH_2Cl_2 and provided a target *gem*-difluorinated derivative **4** in the yield of 62%. A mild alkaline hydrolysis of ester **4** gave diastereopure carboxylic acid **1** in the yield of 86%. Its further DPPA-mediated Curtius reaction followed by the interception of the intermediate isocyanate with *t*BuOH and *N*-Boc deprotection gave amine **2** (59% yield, as hydrochloride).

Acid-base titrations of compounds **1** and **2**×HCl, as well as their non-fluorinated counterparts **5** and **6** were performed according to the protocol [10] previously reported. The results are summarized in **Figure 2** along with the data for the corresponding cyclohexane and cycloheptane derivatives **7**–**10** [10]. It was found that the *gem*-difluorination decreased acidity of the COOH and NH_3^+ functions by 0.3 and 0.5 pK_a units, respectively. Meanwhile, the impact of the bicyclic system on the compounds' acidity was negligible.

To evaluate the lipophilicity increment of the title scaffold, model benzamide or anilide derivatives were prepared from building blocks **1**, **2**×HCl, **5**, and **6** using chloro-*N*,*N*,*N*′,*N*′-tetramethylformamidinium hexafluorophosphate (TCFH) as an

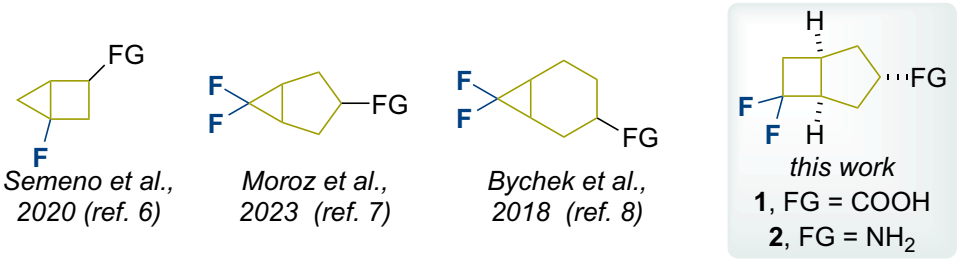
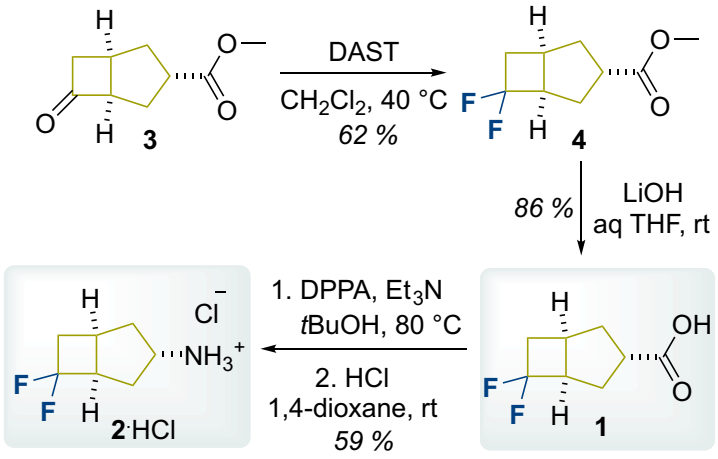


Figure 1. Selected examples of fluorinated fused bicyclic building blocks, including 6,6-difluorobicyclo[3.2.0]heptanes described in this work (FG = NH_2 or COOH)



Scheme 1. The synthesis of building blocks **1** and **2**×HCl

ISSN 2308-8303 (Print) / 2518-1548 (Online)

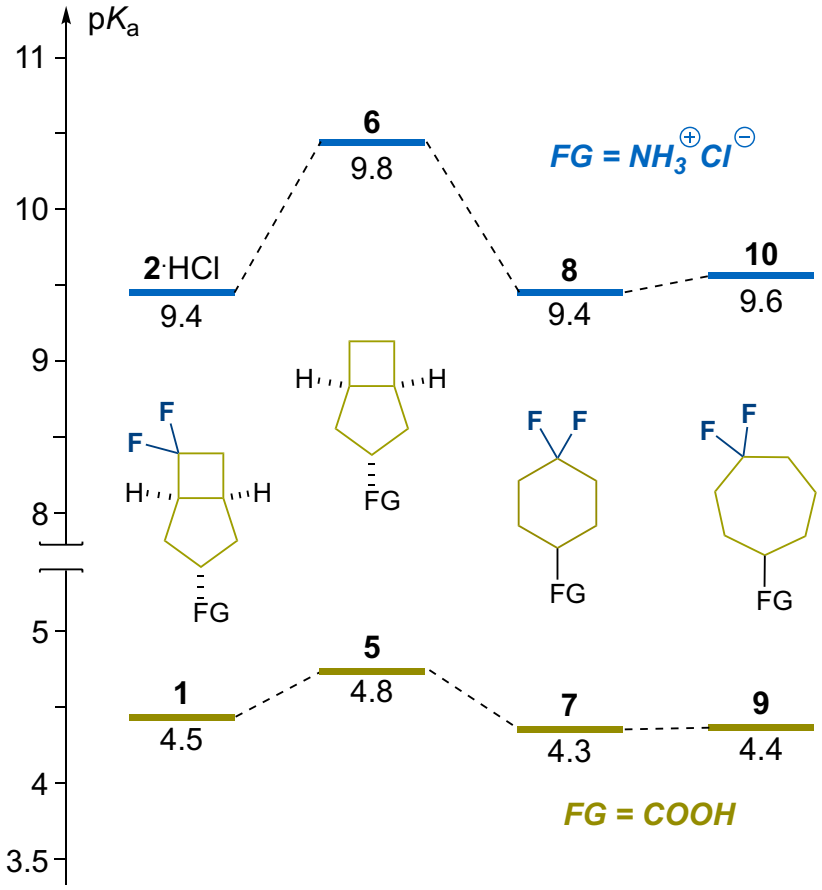
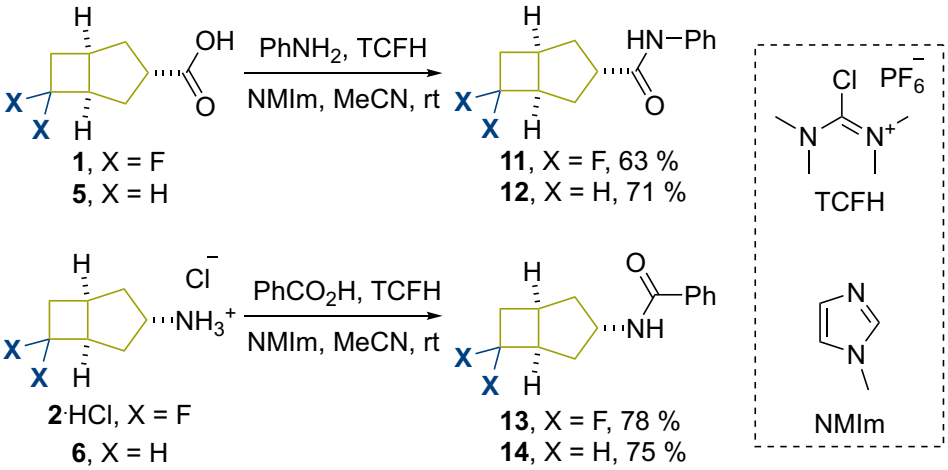


Figure 2. The pK_a values for compounds **1**, **2**×HCl, and **5**–**10**

activator (**Scheme 2**). The Log*P* values were determined using the shape-flask method [11]. The results are given in **Figure 3** along with the data previously reported for *gem*-difluorinated cycloalkanes **15**–**18**. It is apparent that *gem*-difluorination of the bicyclo[3.2.0]heptane system resulted in a decrease of the Log*P* values by 0.54–0.55 units, whereas the conformational restriction imposed by the bicyclic system did not have a considerable effect (compare **13**/**17** and **14**/**18** pairs). This is contrary to the previous results on the disubstituted bicyclic ring systems where diminished lipophilicity was noted compared to the monocyclic counterparts [12].

■ Conclusions

A straightforward gram-scale synthesis of 6,6-difluorobicyclo[3.2.0]heptane-derived building blocks was described. The method is based on the deoxofluorination of the corresponding commercially available bicyclic ketoester with DAST. After the standard functional group transformations (i.e., ester hydrolysis and modified Curtius



Scheme 2. The synthesis of anilides / benzamides **11**–**14**

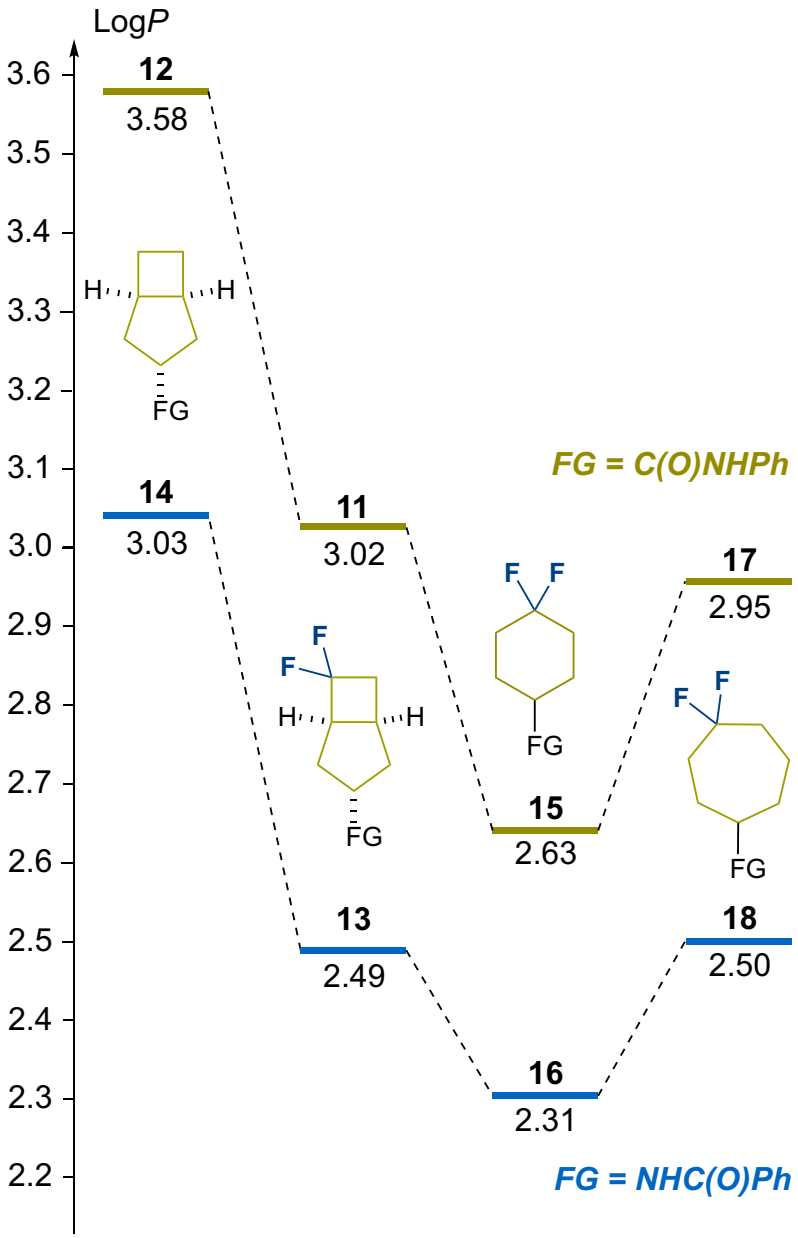


Figure 3. Log*P* values for compounds **11**–**18**

reaction), the corresponding carboxylic acid and primary amine hydrochloride were obtained in good overall yields. The acid-base titration of the products obtained, as well as their non-fluorinated and monocyclic counterparts showed that *gem*-difluorination expectedly decreased the compound's acidity (by 0.3–0.5 units). Lipophilicity was also decreased by 0.54–0.55 Log*P* units. Meanwhile, the bicyclic system itself did not have significant impact on either acidity or lipophilicity.

■ Experimental part

The solvents were purified according to the standard procedures [13]. Diethyl(trifluoro-λ⁴-sulfanyl)amine (DAST), diphenyl phosphoryl azide (DPPA), tetramethylchloroformamidinium hexafluorophosphate (TCFH), starting compounds **3**, **5**, and **6** were obtained from Enamine stock; all other starting materials were available commercially. Melting points were measured on the MPA100 OptiMelt automated melting point system. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR), on an Agilent ProPulse 600 spectrometer (at 151 MHz for ^{13}C) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts were reported in ppm (δ scale) downfield from TMS as an internal standard and were referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. For ^{19}F NMR CCl_3F was

ISSN 2308-8303 (Print) / 2518-1548 (Online)

used as an internal standard. Coupling constants (*J*) were given in Hz. The column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. The reverse phase high-performance liquid chromatography (RP-HPLC) was performed on an Agilent 1260 Infinity instrument with an UV/VIS detection.

Methyl (1*R,3*S**,5*R**)-6,6-difluorobicyclo[3.2.0]heptane-3-carboxylate (4)**

To a solution of keto ester **3** (5.00 g, 29.7 mmol) in CH_2Cl_2 (150 mL), a neat DAST (39.3 mL, 0.297 mol) was added dropwise at 0 °C. The reaction mixture was warmed to rt and stirred at reflux (bath temperature 40 °C) overnight, then cooled and carefully poured onto ice-cold water. The biphasic solution was neutralized with saturated aq. $NaHCO_3$ to pH 6–7 and then extracted with CH_2Cl_2 (2×200 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and evaporated under reduced pressure. The product was purified by flash chromatography (gradient hexanes/*t*BuOMe 20:1 to 10:1 (*v*/*v*) as eluent) to give product **4**.

A yellowish oil. Yield – 3.50 g (62%). Anal. Calcd for $C_9H_{12}F_2O_2$, %: C 56.84, H 6.36. Found, %: C 57.05, H 6.31. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 1.77–1.88 (2H, m, CH_2), 1.95 (1H, dd, J_{HF} = 13.0 Hz, J_{HF} = 6.5 Hz, CH_2), 2.01–2.13 (1H, m, CH_2), 2.26 (1H, dd, J_{HF} = 13.6 Hz, J_{HF} = 6.7 Hz, CH), 2.64–2.80 (2H, m, CH_2), 3.02 (1H, hept, J_{HF} = 6.3 Hz, CH), 3.15–3.25 (1H, m, CH), 3.70 (3H, s, CH_3). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$), δ, ppm: 28.2 (dd, J_{CF} = 10.7 Hz, J_{CF} = 7.9 Hz), 29.7 (t, J_{CF} = 4.6 Hz), 36.3 (d, J_{CF} = 3.2 Hz), 39.5 (t, J_{CF} = 23.1 Hz), 43.0, 50.7 (dd, J_{CF} = 24.0 Hz, J_{CF} = 21.8 Hz), 52.0, 120.5 (dd, J_{CF} = 288.9 Hz, J_{CF} = 277.9 Hz), 175.4. ^{19}F{^{1}H} NMR (376 MHz, $CDCl_3$), δ, ppm: –90.7 (d, J_{FF} = 196.6 Hz, CF_2), –98.8 (d, J_{FF} = 196.6 Hz, CF_2).

(1*R,3*S**,5*R**)-6,6-Difluorobicyclo[3.2.0]heptane-3-carboxylic acid (1)**

To a solution of carboxylate **4** (2.50 g, 13.2 mmol) in THF (30 mL), a solution of LiOH·H_2O (1.11 g, 26.4 mmol) in water (8 mL) was added at rt, and the resulting mixture was stirred overnight. The volatiles were evaporated under reduced pressure (bath temperature below 40 °C), then the aqueous residue was acidified with aq. HCl (2 M, 35 mL) upon cooling in an ice water bath, and the product was extracted with CH_2Cl_2 (3×30 mL). The organic layer was washed with water (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure to give product **1**.

A brownish powder. Yield – 2.00 g (86%). M. p. 99–102 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.62–1.78 (2H, m, CH_2), 1.88 (1H, dd, J_{HF} = 12.8 Hz, J_{HF} = 6.4 Hz, CH_2), 2.06 (1H, dd, J_{HF} = 13.6 Hz, J_{HF} = 6.7 Hz, CH_2), 2.11–2.26 (1H, m, CH), 2.59–2.73 (2H, m, CH_2), 2.90 (1H, hept, J_{HF} = 6.6 Hz, CH), 3.09–3.21 (1H, m, CH). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6), δ, ppm: 27.5 (dd, J_{CF} = 11.3 Hz, J_{CF} = 7.6 Hz), 28.9 (t, J_{CF} = 4.7 Hz), 35.2 (d, J_{CF} = 3.3 Hz), 38.3 (t, J_{CF} = 22.4 Hz), 42.5, 49.9 (dd, J_{CF} = 23.5 Hz, J_{CF} = 21.4 Hz), 120.9 (dd, J_{CF} = 289.6 Hz, J = 276.7 Hz), 175.3. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6), δ, ppm: –96.8 (d, J_{FF}= 193.4 Hz, CF_2), –88.9 (d, J_{FF} = 193.4 Hz, CF_2). HRMS (ESI/QTOF), *m*/*z*: Calcd for $C_8H_9F_2O_2^-$ 175.0576 [M–H]$^-$. Found: 175.0579.

(1*R,3*S**,5*R**)-6,6-Difluorobicyclo[3.2.0]-heptan-3-amine hydrochloride (2×HCl)**

To a solution of carboxylic acid **1** (1.30 g, 7.38 mmol) in *t*BuOH (20.0 mL), Et_3N (1.13 mL, 8.12 mmol) and DPPA (1.91 mL, 8.85 mmol) were added sequentially at 80 °C. The reaction mixture was slowly heated to reflux and stirred at the same temperature overnight. Then, the solution was cooled, diluted with EtOAc (100 mL), and washed with brine (3×30 mL); the organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure. The residual crude *N*-Boc-protected amine was dissolved in anhydrous HCl (*ca.* 3.6 M in dioxane, 15 mL) and stirred at room temperature overnight. The resulting precipitate was filtered and washed with *t*BuOMe (4×10 mL) to give product **2**×HCl.

A brownish amorphous solid. Yield – 0.800 g (59%). ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.67–1.81 (2H, m, CH_2), 2.00 (1H, dd, J_{HF} = 12.7 Hz, J_{HF} = 6.3 Hz, 0.5×CH_2), 2.15–2.27 (2H, m, 0.5×CH_2+CH), 2.62–2.77 (2H, m, CH_2), 3.15–3.30 (1H, m, CH), 3.55–3.69 (1H, m, CH), 8.45 (3H, br. s, NH_3^+). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6), δ, ppm: 26.0 (t, J_{CF} = 9.3 Hz), 29.7, 35.4, 38.5 (t, J_{CF} = 22.4 Hz), 48.6 (m), 50.3, 120.7 (dd, J_{CF} = 288.1 Hz, J_{CF} = 277.8 Hz). ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6), δ, ppm: –96.3 (d, J_{FF} = 194.1 Hz, CF_2), –89.2 (d, J_{FF} = 194.3 Hz, CF_2). HRMS (ESI/QTOF), *m*/*z*: Calcd for $C_7H_{12}F_2N^+$ 148.0932 [M + H]$^+$. Found: 148.0928.

(1*R,3*S**,5*R**)-6,6-Difluoro-*N*-phenylbicyclo[3.2.0]heptane-3-carbox-amide (11)**

To a solution of compound **1** (0.200 g, 1.14 mmol) in CH_3CN (10.0 mL), aniline (110.0 μL, 1.25 mmol),

1-methyl-1*H*-imidazole (270.0 μL, 3.41 mmol, 0.280 g) and TCFH (0.351 g, 1.25 mmol) were sequentially added. The reaction mixture was stirred at room temperature overnight. The crude solution was then purified by RP-HPLC (column: CHROMATOREX C18 100×19 mm, 5 μm, 30 mL/min; 23–50% CH_3CN/H_2O gradient) to yield a pure product **11**.

A yellow powder. Yield – 0.180 g (63%). M. p. 158–160 °C. Anal. Calcd for $C_{14}H_{15}F_2NO$, %: C 66.92, H 6.02, N 5.57. Found, %: C 67.28, H 6.21, N 5.71. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.72–1.94 (3H, m, CH_2+CH), 2.04–2.15 (2H, m, CH_2), 2.65–2.80 (2H, m, CH_2), 3.08 (1H, m, CH), 3.17–3.27 (1H, br. m, CH_2), 7.03 (1H, t, J_{HH} = 7.6 Hz, PhH), 7.29 (2H, m, PhH), 7.62 (2H, d, J_{HH} = 8.0 Hz, PhH), 10.05 (1H, s, NH). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6), δ, ppm: 27.8 (dd, J_{CF} = 11.2 Hz, J_{CF} = 7.6 Hz), 29.4 (t, J_{CF} = 4.5 Hz), 36.1 (d, J_{CF} = 3.1 Hz), 38.6 (t, J_{CF} = 22.4 Hz), 44.2, 50.2 (t, J_{CF} = 22.3 Hz), 119.1, 121.1 (dd, J_{CF} = 289.8 Hz, J_{CF} = 276.5 Hz), 123.0, 128.6, 139.2, 172.0. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6), δ, ppm: –96.1 (d, J_{FF} = 193.1 Hz, CF_2), –88.9 (d, J_{FF} = 192.9 Hz, CF_2).

***N*-[(1*R**,3*S**,5*R**)-6,6-Difluorobicyclo[3.2.0]-heptan-3-yl]benzamide (12)**

To a solution of compound **2**×HCl (0.307 g, 1.67 mmol) in CH_3CN (10.0 mL), benzoic acid (0.225 g, 1.84 mmol), 1-methyl-1*H*-imidazole (530.0 μL, 6.69 mmol, 0.549 g) and TCFH (0.515 g, 1.84 mmol) were sequentially added. The reaction mixture was stirred at room temperature overnight. The crude solution was then purified by RP-HPLC (column: XBridge BEH C18 100×19 mm, 5 μm, 30 mL/min; 18–40% CH_3CN/H_2O gradient) to yield a pure product **12**.

A yellowish powder. Yield – 0.300 g (71%). M. p. 155–157 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.71–1.86 (2H, m, CH_2), 1.90 (1H, dd, J_{HF} = 12.9 Hz, J_{HF} = 6.6 Hz, CH_2), 2.03–2.19 (2H, m, 0.5×CH_2+CH), 2.65–2.82 (2H, m, CH_2), 3.07 (1H, hept, J_{HF} = 6.5 Hz, CH), 3.20–3.25 (1H, m, CH), 7.03 (1H, t, J_{HH} = 7.4 Hz, PhH), 7.29 (2H, t, J_{HH} = 7.7 Hz, PhH), 7.62 (2H, d, J_{HH} = 8.0 Hz, PhH), 10.04 (1H, s, PhH). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6), δ, ppm: 25.8 (dd, J_{CF} = 10.9 Hz, J_{CF} = 7.5 Hz), 31.0 (t, J_{CF} = 4.2 Hz), 36.7 (d, J_{CF} = 3.0 Hz), 38.9 (t, J_{CF} = 22.7 Hz, overlapped with the solvent residual peak), 48.5 (t, J_{CF} = 22.5 Hz), 49.5, 121.2 (dd, J_{CF} = 289.3 Hz, J_{CF} = 277.3 Hz), 127.2, 128.1, 131.0, 134.5, 166.0. $^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6), δ, ppm: –96.3 (d, J_{FF} = 193.3 Hz, CF_2), –88.6 (d, J_{FF} = 193.3 Hz, CF_2). HRMS (ESI/QTOF), *m*/*z*: Calcd for $C_{14}H_{16}F_2NO^+$ 252.1194 $[M + H]^+$. Found 252.1189.

(1*R,3*S**,5*S**)-N-Phenylbicyclo[3.2.0]heptane-3-carboxamide (13)**

To a solution of carboxylic acid **5** (0.200 g, 1.43 mmol) in CH_3CN (10.0 ml), aniline (140.0 μL, 1.57 mmol), 1-methyl-1*H*-imidazole (340.0 μL, 28 mmol, 3.0 equiv) and TCFH (0.439 g, 1.57 mmol) were sequentially added. The reaction mixture was then stirred at room temperature overnight. The crude solution was purified by RP-HPLC (column: CHROMATOREX C18 SMB100–5T 100×19 mm, 5 μm, 30 mL/min; 23–50% CH_3CN/H_2O gradient) to yield product **13**.

A beige powder. Yield – 0.240 g (78%). M. p. 175–178 °C. ^{1}H NMR (500 MHz, $CDCl_3$), the compound exists as *ca.* 3:1 mixture of rotamers, δ, ppm: 1.42–1.55 (0.75×2H, br. m, CH_2), 1.70–1.79 (0.25×2H, m, CH_2), 1.82 (0.75×2H, dd, J_{HH} = 12.7 Hz, J_{HH} = 6.4 Hz, CH_2), 1.86–2.04 (0.75×2H and 0.25×2H, m, CH_2), 2.15–2.29 (0.75×2H and 0.25×4H, m, CH_2), 2.68–2.78 (0.25×3H, m, 3×CH), 2.91 (0.75×2H, br. s, 2×CH), 3.18 (0.75×1H, hept, J_{HH} = 6.4 Hz, CH), 7.10 (1H, t, J_{HH} = 7.5 Hz, PhH), 7.32 (2H, t, J_{HH} = 7.8 Hz, PhH), 7.43 (1H, br. s, NH), 7.56 (2H, d, J_{HH} = 7.8 Hz, PhH). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$), the compound exists as a mixture of rotamers, δ, ppm: 24.4 and 25.6, 38.1 and 38.2, 38.6 and 39.2, 46.2 and 51.3, 119.9, 124.2, 129.1, 138.3, 173.7. HRMS (ESI/QTOF), m/z: Calcd for $C_{14}H_{18}NO^+$ 216.1383 $[M + H]^+$. Found 216.1378.

***N*-[(1*R**,3*S**,5*S**)-bicyclo[3.2.0]heptan-3-yl]-benzamide (14)**

To a solution of hydrochloride **6** (0.200 g, 1.36 mmol) in CH_3CN (10.0 mL), benzoic acid (0.183 g, 1.50 mmol), 1-methyl-1*H*-imidazole (430.0 μL, 5.44 mmol, 0.447 g) and TCFH (0.419 g, 1.50 mmol) were sequentially added. The reaction mixture was stirred at room temperature overnight. The crude solution was then purified by RP-HPLC (column: XSelect FluoroPhenyl 100×19 mm, 5 μm, 30 mL/min; 8–35% H_2O/CH_3CN gradient) to yield a pure product **14**.

A colorless powder. Yield – 0.220 g (75%). M. p. 160–162 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.48–1.60 (4H, m, CH_2), 1.77 (2H, dd, J_{HH} = 12.2 Hz, J_{HH} = 6.3 Hz, CH_2), 2.15 (2H, dq, J_{HH} = 11.9 Hz, J_{HH} = 6.6 Hz, CH_2), 2.76 (2H, br.

ISSN 2308-8303 (Print) / 2518-1548 (Online)

s, CH), 4.75–4.87 (1H, m, CH), 7.43 (2H, t, J_{HH} = 7.5 Hz, PhH), 7.46–7.53 (1H, m, PhH), 7.83 (2H, d, J_{HH} = 7.5 Hz, PhH), 8.28 (1H, d, J_{HH} = 7.9 Hz, NH). $^{13}C\{^1H\}$ NMR (151 MHz, DMSO-d_6), δ, ppm: 23.9, 35.6, 38.8, 49.7, 127.2, 128.1, 130.9, 134.8, 166.0. HRMS (ESI/QTOF), *m/z*: Calcd for $C_{14}H_{18}NO^+$ 216.1383 $[M + H]^+$. Found 216.1381.

Acknowledgments

The authors express their gratitude to Olga Kovalenko and Margaryta Bolgova for pK_a titrations, Prof. Andriy O. Tolmachov for his encouragement and support, and all the brave defenders of Ukraine who made this publication possible.

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