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3-((Hetera)cyclobutyl)azetidines – "stretched" analogues of piperidine, piperazine and morpholine: advanced building blocks for drug discovery

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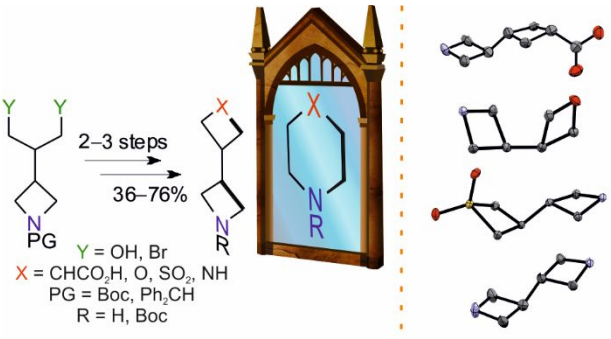


ABSTRACT. Four 3-((hetera)cyclobutyl)azetidine-based isosteres of piperidine, piperazine, and morpholine were designed and synthesized on up to gram scale. The key step of the synthetic sequence included cyclization of *N*-protected 2-(azetidin-3-yl)propane-1,3-diol or the corresponding 1,3-dibromide. X-ray diffraction studies of the products obtained, followed by exit vector plot analysis of their molecular geometry demonstrated their larger size and increased conformational flexibility as compared to the parent heterocycles, and confirmed their potential utility as building blocks for lead optimization programs.

INTRODUCTION

According to the recent extensive analysis of cyclic fragments in contemporary pharmaceuticals, piperidine, piperazine and morpholine occurred among top 20 heterocycles[1] and top 30 general ring systems[2] that were found in small molecule FDA approved drugs. Many efforts of current research have been put into design of structures that are topologically similar to the aforementioned scaffolds, whilst have slightly different geometrical and/or electronic parameters (*i.e.* bioiososteric replacements).[3] In many cases, such little structural alternation allowed to increase ligand selectivity and improve their pharmacokinetic properties.[4,5]

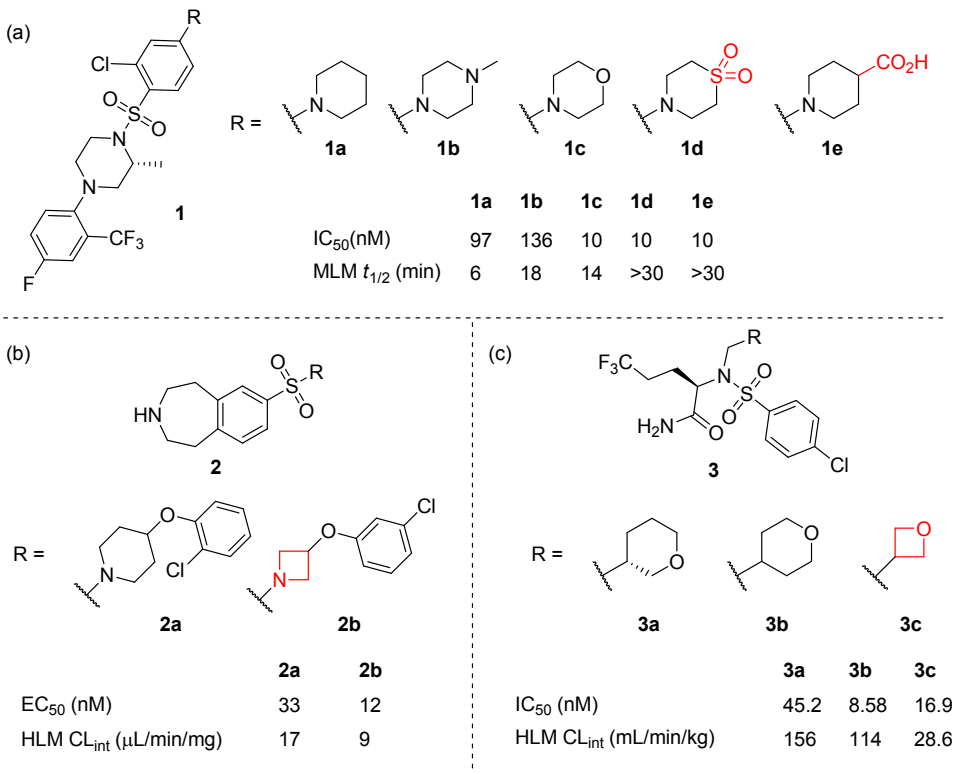


Figure 1. Some bioisosteric replacements of saturated six-membered heterocycles which resulted in improved potency and/or metabolic stability: (a) 11β-hydroxysteroid dehydrogenase type I inhibitors; (b) serotonin receptor subtype 2C agonists; (c) γ-secretase inhibitors

Among numerous possibilities available for design of piperidine, piperazine and morpholine bioisosteres, several approaches are worth mentioning here. In particular, extension of this heterocycle series with derivatives bearing sulfone or carboxylic functional groups can be suggested. Indeed, variation of the heteroaromatic side chain in a series of 11β-hydroxysteroid dehydrogenase type I (11β-HSD1) inhibitors **1** revealed that improved potency and metabolic stability in mouse liver microsomes (MLM) was observed for derivatives **1d** and **1e** as compared to the parent piperidine **1a**, piperazine **1b** and morpholine **1c** (Figure 1a).[6] Variation of the ring size is another possible option; in this view, four-membered carbo- and heterocycles have attracted much attention.[7–10] For example, replacement of the piperidine ring in the molecule of

serotonin receptor subtype 2C (5-HT2C) agonist **2a** with azetidine fragment resulted in improved human liver microsomal (HLM) stability and lowered EC_{50} value (Figure 1b).[11] Similar effect was observed when tetrahydropyran was replaced by oxetane in a course of optimization of *N*-arylsulfonamide-based γ-secretase inhibitors **3** (Figure 1c).[12]

Being inspired by these successful examples, we have designed four novel piperidine, piperazine and morpholine surrogates **4**–**7** which are based on the structural modifications mentioned above (*i.e.* the use of four-membered rings and/or incorporation of sulfone and carboxylic acid functionalities) (Figure 2). It should be noted that a number of fused, bridged and spirocyclic analogues of the parent saturated six-membered heterocycles were described in the literature.[13–16] These bicyclic ring systems have already proven their value for medicinal chemistry:[17–26] some of them can be found in the structures of marketed drugs, *e.g.* boceprevir[27], gliclazide[28], ledipasvir[27] *etc*. Nevertheless, all these surrogates were obtained by introducing additional conformational restriction to the piperidine, piperazine and morpholine rings; on the contrary, the molecules of **4**–**7** are more flexible as compared to the parent structures due to the presence of a rotatable bond.

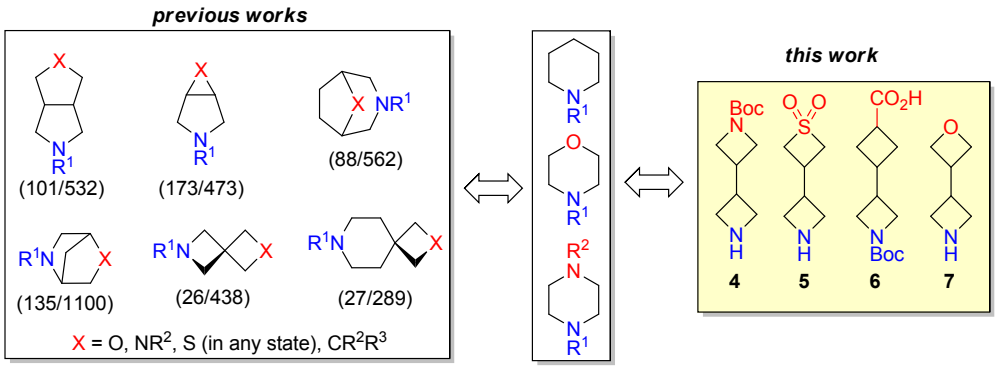
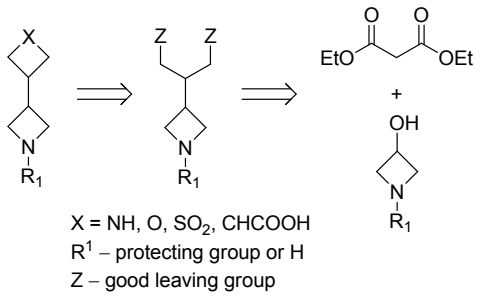


Figure 2. Surrogates of piperidine, piperazine and morpholine (values in brackets correspond to numbers of papers/patents reporting biological activity according to *Reaxys*® database[29])

In this work, we have developed an approach to the synthesis of all four building blocks **4**–**7** which allowed for their preparation on up to gram scale. In addition to that, structural characterization of these novel scaffolds was performed using an exit vector plot (EVP) tool, which was applied to the data of X-Ray diffraction studies.

RESULTS AND DISCUSSION

Synthesis. Previously, nucleophilic substitution of 1,3-dielectrophiles by electron-rich carbon- or heteroatom-containing reagents has proven itself as an efficient approach towards four-membered ring construction.[8,30,31] This method was successfully applied for similar spiro[3.3]heptane synthesis;[32–36] therefore, it was envisaged for the key retrosynthetic disconnection of **4**–**7** (Scheme 1). Since all our target structures contained azetidine fragment, *N*-protected azetidin-3-ol derivative **8** was used as a starting material. The choice of the benzhydryl protecting group was guided by its stability towards $LiAlH_4$ reduction implied by the developed synthetic strategy, as well as increase in lipophilicity of the intermediates involved into the synthetic scheme, which should facilitate their isolation and purification.

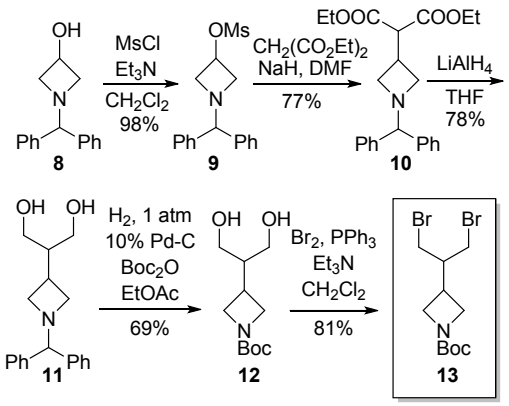


Scheme 1. Retrosynthetic analysis of the compounds **4**–**7**

The synthesis commenced with preparation of diester **10** using a slightly modified literature method,[37] *i.e.* mesylation of alcohol **8**, followed by nucleophilic substitution in the intermediate

mesylate **9** with diethyl malonate sodium salt (75% yield for two steps) (Scheme 2). The subsequent reduction of **10** with $LiAlH_4$ gave diol **11** (78% yield). The compound **11** was subjected to the protecting group replacement (*i.e.* benzhydryl to Boc), which was achieved by hydrogenolysis of **11** using 10% Pd-C as the catalyst in presence of Boc_2O and led to diol **12** (69% yield). Notably, hydrogenolysis of **11** using $Pd(OH)_2$ as the catalyst under similar conditions resulted in a mixture of the target compound **12** with unidentified by-products.

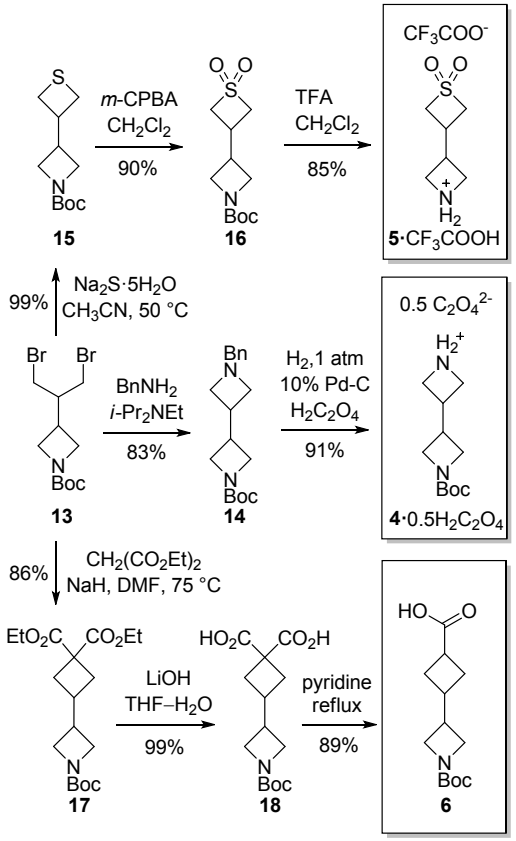
The next steps required transformation of the hydroxyl moieties in the molecule of the diol **12** into good nucleofuges. Our preliminary attempts relied on the use of sulfonates as the leaving groups; however, transformation of **12** into the corresponding 1,3-ditriflate or 1,3-dimesylate, followed by reaction with benzylamine or tosylamine appeared to be unfruitful. In the latter case, removal of the tosyl group could not be achieved with satisfactory yield using neither Na–Hg nor Mg in MeOH as the reducing reagents. Therefore, we have switched to 1,3-dibromide **13**, which appeared to be relatively stable and could be obtained by Appel reaction in 81% yield.



Scheme 2. Synthesis of the intermediate dibromide **13**

Reaction of the dibromide **13** with benzylamine gave the corresponding *N*-benzyl derivative **14** (83% yield), which was subjected to hydrogenolysis using 10% Pd-C as a catalyst. Unfortunately, the product **4** obtained as a free base decomposed slowly upon standing.

Therefore, isolation of the 3,3′-biazeditine derivative **4** as an oxalate salt[32] was envisaged to improve stability of this compound. Thus, hydrogenolysis of intermediate **14** using 10% Pd-C as the catalyst in the presence of oxalic acid gave oxalate **4**·0.5$H_2C_2O_4$ in good yield (91%) (Scheme 3).

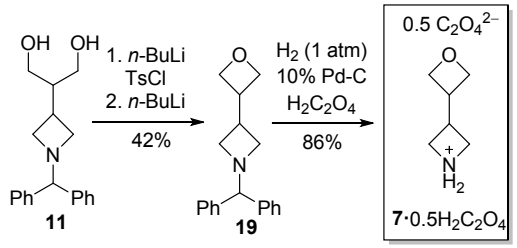


Scheme 3. Synthesis of the building blocks **4**–**6**

Synthesis of sulfone-containing building block **5** commenced with reaction of **13** and Na_2S, which gave thietane **15** in nearly quantitative yield. Subsequent oxidation of **15** with *m*-CPBA, followed by deprotection of **16** with TFA gave **5** as a trifluoroacetate salt (76% yield over two steps). Analogously, the amino acid **6** was synthesized in three steps including reaction of **13** with malonic ester sodium salt, alkaline hydrolysis of diester **17**, and decarboxylation of the

corresponding dicarboxylic acid **18** in pyridine (76% yield from **13**, *ca.* 1:1 mixture of diastereomers).

Initially, we tried to synthesize 3-(oxetan-3-yl)azetidine (**7**) by intramolecular cyclization of the diol **12**. However, the subsequent removal of the *N*-Boc protective group in acidic medium using either HCl – Et_2O or TFA – CH_2Cl_2 was accompanied by partial oxetane ring opening. In order to avoid the use of strong acids at the deprotection step, intramolecular cyclization with the benzhydryl protected compound **11** was performed. The oxetane-containing intermediate **19** was synthesized using the method of Moulines *et al.*,[38] namely, one-pot sequential treatment of a 1,3-diol with *n*-BuLi, TsCl, and another equivalent of *n*-BuLi. In the case of **11**, this reaction sequence gave the target product **19** in 42% yield (Scheme 4). Finally, hydrogenolysis of **19** in the presence of oxalic acid resulted in the formation of **7**, which was isolated as an oxalate salt in 86% yield.



Scheme 4. Synthesis of the building block **7**

EVP analysis. To validate the anticipated isosterism of **4**–**7** with saturated six-membered heterocycles, we have compared their three-dimensional structure using the exit vector plot (EVP) tool.[39,40] One of the main features of this method is visualization of the bifunctional scaffolds in the chemical space, which can be used to discuss the molecular geometry of diverse compounds classes. To generate the EVPs, exit vectors $\boldsymbol{n_1}$ and $\boldsymbol{n_2}$ are introduced simulating the functional groups (or any substituents) attached to the scaffold (Figure 3). The distance *r*

between the two variation points of the scaffold ($\mathbf{X^1}$ and $\mathbf{X^2}$) is used to assess the size of the scaffold, whereas two plane angles φ_1 (between vectors $\boldsymbol{n_1}$ and $\mathbf{X^1X^2}$) and φ_2 (between vectors $\boldsymbol{n_2}$ and $\mathbf{X^2X^1}$), as well as the dihedral angle θ defined by vectors $\boldsymbol{n_1}$, $\mathbf{X^1X^2}$, and $\boldsymbol{n_2}$ describe its three-dimensionality. Depiction of these parameters in $r - \theta$ and $\theta - \varphi_1/\varphi_2$ coordinates introduces the background for EVP-based chemical space analysis and provides a straightforward tool for rational scaffold replacement.

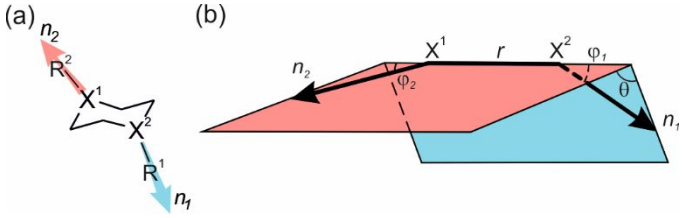


Figure 3. (a) Definition of exit vectors $\boldsymbol{n_1}$ and $\boldsymbol{n_2}$. (b) Definition of geometric parameters r, φ_1, φ_2 and θ.

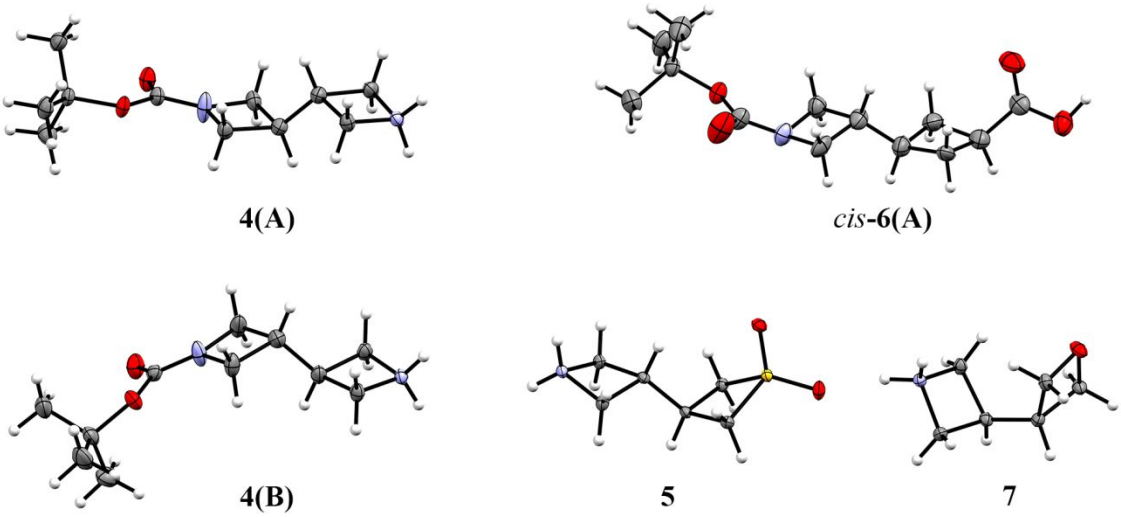


Figure 4. ORTEP diagram for compounds **4–7** (only cations are shown for the compounds **4**·0.5$H_2C_2O_4$ (two independent cations in the asymmetric unit), **5**·CF_3COOH and

7·0.5$H_2C_2O_4$; for *cis*-**6**, only position **A** with the main occupancy (60%) is presented). Thermal ellipsoids are shown at 50% probability level

X-Ray single crystal diffraction studies of the compounds **4**–**7** revealed that in the case of **4**, two crystallographically independent cations (**A** and **B**) with similar molecular geometry were found in the asymmetric unit (Figure 4). In the case of **6**, the crystals which were subjected to the X-Ray analysis contained only *cis*-isomer (*cis*-**6**); the two four-membered rings were disordered over two positions (**A** and **B**) with 60% and 40% occupancies, respectively (see the SI for more details).

Table 1. Geometric parameters r, φ_1, φ_2, and θ for **4**–**7**.

compound	r (Å)	φ_1 (°)	φ_2 (°)	$\lvert\theta\rvert$ (°)[a]
4·0.5$H_2C_2O_4$[b]				
cation **A**	5.301	25.1	17.0	169.2
cation **B**	5.317	27.4	6.4	171.7
5·CF_3COOH	5.371	47.4	7.0	4.8
cis-**6**[c]				
position **A**	5.459	49.6	20.6	166.7
position **B**	5.459	45.0	5.5	159.5
7·0.5$H_2C_2O_4$	4.229	56.7	54.5	40.9

[a] Since the signs of θ angle are opposite for different enantiomeric conformations, only absolute values of θ are considered. [b] Two independent cations in the asymmetric unit. [c] The two four-membered rings were disordered over two positions (**A** and **B**) with 60% and 40% occupancies, respectively

These data were used to calculate the values of the aforementioned geometrical parameters r, φ_1, φ_2 and θ for the compounds **4**, **5**, *cis*-**6**, and **7** were calculated from the X-ray diffraction data (Table 1). When assigning the plane angles φ_1 and φ_2, we let $\varphi_1 > \varphi_2$ (as it was done in the previous works[39,41]). The size of the scaffolds **4**–**7** is varied in a relatively wide range (r = 4.23–5.46 Å) depending on the conformation of the molecule (Figure 5). Expectedly, they are

significantly larger as compared to the 1,4-disubstituted six-membered saturated heterocycles (r = 2.43–3.22 Å[39,40]) and get close to 2,6-disubstituted (aza)spiro[3.3]heptanes ($r \sim 4.13$ Å[42]). The building blocks **4** and **6** adopt extended conformation which can be described as a "stretched chair", which correspond to larger values of r (5.30 Å (**4A**), 5.32 Å (**4B**), and 5.46 Å (**6**)). In the $\theta - \varphi_1/\varphi_2$ plot, these molecules are located in the γ region ($|\theta|$ = 160–172°, φ_1 = 25–50°, φ_2 = 6–21°), which is characteristic for the typical chair conformations of 1,4-disubstituted six-membered saturated heterocycles with equatorial position of the substitutent(s).

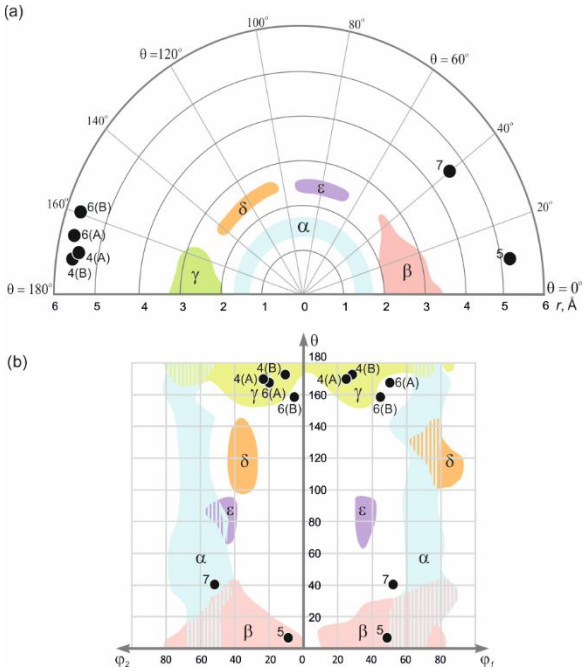


Figure 5. Geometric parameters of **4**·0.5$H_2C_2O_4$, **5**·CF_3COOH, *cis*-**6** and **7**·0.5$H_2C_2O_4$ shown in the (a) $r - \theta$ plot (polar coordinates), and (b) $\theta - \varphi_1/\varphi_2$ plot.

In the case of **5**, the corresponding data point is located in the β region of the $\theta - \varphi_1/\varphi_2$ plot ($|\theta|$ = 5°, φ_1 = 47°, φ_2 = 7°). The molecular conformation of **5** can be described as a "stretched boat", which is characterized by r = 5.37 Å, which is close to that of **4** and **6**. Such angle values are characteristic for *cis*-1,4-disubstituted cyclohexanes, and are encountered for less common

conformations of 1,4-disubstituted six-membered saturated heterocycles with axial position of one of the substituents. The molecule of **7** adopts a "stretched twist" conformation, which results in the lowest *r* value (4.23 Å) in a series studied. In the $\theta - \varphi_1/\varphi_2$ plot, the corresponding data point is shifted towards "three-dimensional" area which is remote from the θ = 0/180° and φ_1/φ_2 = 0° lines ($|\theta|$ = 41°, φ_1 = 57°, φ_2 = 54°).

These data show that the scaffolds of **4–7** can adopt a number of conformations, both similar to that of the parent six-membered saturated heterocycles (with $|\theta|$ close to 0° or 180°) and more "three-dimensional" (with $|\theta|$ being far from these boundary values). Therefore, the building blocks developed in this work can be used as "stretched" analogues of piperidine, piperazine and morpholine with slightly enhanced conformational flexibility.

CONCLUSIONS

Cyclization of *N*-protected 2-(azetidin-3-yl)propane-1,3-diol or the corresponding 1,3-dibromide is a convenient method for the preparation of 3-((hetera)cyclobutyl)azetidines, in particular, 3-(oxetan-3-yl)- and 3-(thietan-3-yl)azetidine, 3,3'-biazetidine, as well as 3-(azetidin-3-yl)cyclobutanecarboxylic acid derivatives (compounds **4**–**7**). The target compounds were prepared in 5–8 steps from the commercially available materials in 21–25% overall yields on up to 24 g scale. Analysis of molecular geometry of the compounds described in this paper using exit vector plot (EVP) tool shows that their scaffolds can be considered "stretched" analogues of piperidine, piperazine and morpholine with diminished conformational restriction, which provides access not only to the molecular geometries covered by the parent heterocycles, but also to "three-dimensional" areas of chemical space. Therefore, the azetidine derivatives obtained in this work

are promising advanced building blocks for extensive application in drug discovery programs, in particular, for the isosteric replacement of saturated six-membered heteroaliphatic rings.

EXPERIMENTAL SECTION

General Methods. The solvents were purified according to the standard procedures.[43] All starting materials were purchased from commercial sources. Melting points were measured on automated melting point system. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded at 499.9 MHz or 400.4 MHz and 124.9 MHz or 100.7 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS as an internal standard. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, National Taras Shevchenko University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI), electrospray ionization (ESI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)). The X-Ray diffraction data sets were collected with a CMOS diffractometer for the compounds **4**·0.5$H_2C_2O_4$, *cis*-**6** and **7**·0.5$H_2C_2O_4$ and with a CCD diffractometer for the compound **5**·CF_3COOH**.** Single crystals were obtained by slow evaporation of the compound solutions in MeCN (**4**·0.5$H_2C_2O_4$ and **5**·CF_3COOH), hexane (*cis*-**6**) or MeOH (**7**·0.5$H_2C_2O_4$). Programs used in the X-Ray diffraction studies: data collection: APEX3 V2016.1-0;[44] cell refinement and data reduction: SAINT V8.37A;[45] absorption correction, SADABS V2014/7;[46] structure solution and structure refinement, SHELXT-2015.[47] *R*-values are given for observed reflections, and wR^2 values are given for all reflections. CCDC-1868836 (**4**·0.5$H_2C_2O_4$), CCDC-1868837 (**5**·CF_3COOH), CCDC-1868838 (*cis*-**6**) and CCDC-1868839 (**7**·0.5$H_2C_2O_4$) contain the supplementary

crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1-Benzhydrylazetidin-3-yl methanesulfonate (9).[48,49] Et_3N (13.1 mL, 94.0 mmol) was added to a solution of 1-benzhydrylazetidin-3-ol (**8**) (15.0 g, 62.7 mmol) in CH_2Cl_2 (150 mL) and reaction mixture was cooled to –20 °C. Methanesulfonyl chloride (8.61 g, 75.2 mmol) was added dropwise maintaining the temperature below –20 °C. When addition was completed the reaction mixture was allowed to warm to rt and then poured into H_2O (100 mL). The organic layer was separated, washed with 10% aq $NaHCO_3$ (3×50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the title compound. White solid, mp 114–116 °C (lit.[48] mp 115–116 °C); 98% yield (19.5 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40 (d, J = 7.4 Hz, 4H), 7.28 (t, J = 7.4 Hz, 4H), 7.20 (t, J = 7.2 Hz, 2H), 5.10 (quint, J = 5.8 Hz, 1H), 4.42 (s, 1H), 3.68 – 3.59 (m, 2H), 3.24 – 3.16 (m, 2H), 2.94 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 141.4, 128.7, 127.5, 127.4, 78.2, 68.0, 60.2, 38.1. LCMS (*m/z*): 318 ($M+H^+$). Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41; S, 10.10. Found: C, 64.42; H, 5.88; N, 4.21; S, 10.12.

Diethyl 2-(1-benzhydrylazetidin-3-yl)malonate (10).[37] Diethylmalonate (14.4 g, 89.9 mmol) was added dropwise to a suspension of NaH (60% in mineral oil, 3.27 g, 81.8 mmol) in DMF (90 mL) while the temperature of the reaction mixture was maintained below 25 °C. After stirring for additional 1 h, a solution of 1-benzhydrylazetidin-3-yl methanesulfonate (**9**) (13.0 g, 41.0 mmol) in DMF (20 mL) was added. The reaction mixture was stirred at 70 °C for 2 d, then cooled to rt, poured into H_2O (200 mL) and extracted with EtOAc (2×200 mL). The combined organic layers were washed with H_2O (3×150 mL), brine (100 mL), dried over Na_2SO_4 and concentrated under

reduced pressure. An excess of diethylmalonate was distilled off (1 mmHg, 50–60 °C), and the residue was purified by column chromatography on silica gel (hexanes – EtOAc – Et_3N (8:1:0.5) as eluent, $R_f = 0.4$) to afford the title product. White solid, mp 72–74 °C; 77% yield (12.0 g). ^1H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, $J = 7.3$ Hz, 4H), 7.25 (t, $J = 7.4$ Hz, 4H), 7.17 (t, $J = 7.2$ Hz, 2H), 4.32 (s, 1H), 4.21 – 4.09 (m, 4H), 3.64 (d, $J = 10.5$ Hz, 1H), 3.37 (t, $J = 7.1$ Hz, 2H), 3.07 – 2.96 (m, 1H), 2.90 (t, $J = 6.5$ Hz, 2H), 1.23 (t, $J = 7.1$ Hz, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 168.4, 142.1, 128.5, 127.5, 127.2, 78.1, 61.5, 57.8, 55.9, 29.5, 14.2. LCMS (*m/z*): 382 ($M+H^+$), 380 ($M–H^+$). Anal. Calcd for $C_{23}H_{27}NO_4$: C, 72.42; H, 7.13; N, 3.67. Found: C, 72.68; H, 6.98; N, 3.53.

2-(1-Benzhydrylazetidin-3-yl)propane-1,3-diol (11). To a suspension of $LiAlH_4$ (2.87 g, 75.5 mmol) in THF (150 mL), diethyl 2-(1-benzhydrylazetidin-3-yl)malonate (**10**) (12.0 g, 31.4 mmol) was added dropwise at rt, and the reaction mixture was stirred overnight. The reaction mixture was cooled to 0 °C and H_2O (3 mL) was added carefully, followed by 50% aq NaOH (3 mL) and H_2O (15 mL). The suspension was stirred for additional 30 min and then filtered. The solids were washed with THF (2×100 mL) and the combined filtrates were evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (200 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2 – MeOH – Et_3N (92:3:5) as eluent, $R_f = 0.35$) to give **11**. Amorphous white solid, mp 112–115 °C; 78% yield (7.27 g). ^1H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, $J = 7.4$ Hz, 4H), 7.27 (t, $J = 7.5$ Hz, 4H), 7.19 (t, $J = 7.3$ Hz, 2H), 4.37 (s, 1H), 3.92 (br s, 2H), 3.71 – 3.56 (m, 4H), 3.33 (t, $J = 7.6$ Hz, 2H), 2.98 (t, $J = 6.6$ Hz, 2H), 2.51 – 2.41 (m, 1H), 2.01 – 1.88 (m, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 141.5, 128.7, 127.5, 127.4, 78.2, 63.3, 58.0, 46.2,

29.1. LCMS (*m/z*): 298 ($M+H^+$). Anal. Calcd for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.65; H, 8.16; N, 4.34.

***tert*-Butyl 3-(1,3-dihydroxypropan-2-yl)azetidine-1-carboxylate (12).** 10% Pd-C (1.50 g) was added to a solution of 2-(1-benzhydrylazetidin-3-yl)propane-1,3-diol (**11**) (15.0 g, 50.4 mmol) and Boc_2O (16.5 g, 75.6 mmol) in EtOAc (200 mL). The resulting mixture was hydrogenated at 1 atm and rt for 3 d. The catalyst was filtered off, the solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (CH_2Cl_2 – MeOH (10:1) as eluent, R_f= 0.36) to give the title product. Amorphous white solid, mp 79–81 °C; 69% yield (8.03 g). ^1H NMR (400 MHz, $CDCl_3$): δ 3.95 (t, *J* = 8.5 Hz, 2H), 3.72 – 3.63 (m, 4H), 3.56 (dd, *J* = 10.7, 6.5 Hz, 2H), 3.49 (s, 2H), 2.62 – 2.47 (m, 1H), 1.91 – 1.79 (m, 1H), 1.38 (s, 9H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 156.5, 79.7, 62.5, 52.8, 46.2, 28.4, 27.4. LCMS (*m/z*): 132 ($M+H^+–CO_2–C_4H_9$). Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.23; H, 8.85; N, 6.12.

***tert*-Butyl 3-(1,3-dibromopropan-2-yl)azetidine-1-carboxylate (13).** To a solution of PPh_3 (82.6 g, 315 mmol) in CH_2Cl_2 (450 mL), Br_2 (50.4 g, 315 mmol) was added dropwise at 0 °C, and the reaction mixture was stirred at the same temperature for 1 h. Then Et_3N (43.9 mL, 315 mmol) was added dropwise while the temperature was maintained below 5 °C, and the reaction mixture was stirred for additional 1 h. A solution of *tert*-butyl 3-(1,3-dihydroxypropan-2-yl)azetidine-1-carboxylate (**12**) (24.3 g, 105 mmol) in CH_2Cl_2 (100 mL) was added dropwise at 0 °C. When the addition was complete, the reaction mixture was allowed to warm to rt and stirred overnight. The resulting light brown suspension was poured into H_2O (500 mL), and the

organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2×250 mL), and the combined organic layers were washed with saturated aq $NaHCO_3$ (250 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was washed with petroleum ether (500 mL), the solids were filtered off, and the filtrate was evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexanes – EtOAc (7:1) as eluent, $R_f = 0.25$) to give the title product. White solid, mp 107–109 °C; 81% yield (30.4 g). ^{1}H NMR (500 MHz $CDCl_3$): δ 4.03 (t, J = 8.4 Hz, 2H), 3.79 – 3.64 (m, 2H), 3.57 (dd, J = 10.5, 3.0 Hz, 2H), 3.41 (dd, J = 10.4, 6.6 Hz, 2H), 2.71 – 2.59 (m, 1H), 2.27 – 2.18 (m, 1H), 1.43 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 156.2, 79.8, 52.8, 45.7, 32.9, 31.0, 28.5. LCMS (*m/z*): 258 ($M+H^+–CO_2–C_4H_9$). Anal. Calcd for $C_{11}H_{19}Br_2NO_2$: C, 37.00; H, 5.36; N, 3.92; Br, 44.75. Found: C, 36.66; H, 5.45; N, 3.57; Br, 44.59.

***tert*-Butyl 1'-benzyl-[3,3'-biazetidine]-1-carboxylate (14).** Benzylamine (15.0 g, 0.140 mol) and *i*-Pr_2NEt (61.1 mL, 0.350 mol) were added to a solution of *tert*-butyl 3-(1,3-dibromopropan-2-yl)azetidine-1-carboxylate (**13**) (25.0 g, 70.0 mmol) in CH_3CN (400 mL), and the reaction mixture was heated at reflux overnight. The solution was cooled to rt and concentrated to about 1/6 of the initial volume. The residue was dissolved in EtOAc (500 mL) and washed with H_2O (300 mL). The aqueous layer was separated and extracted with EtOAc (2×250 mL). The combined organic layers were washed with saturated aq $NaHCO_3$ (2×300 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexanes – EtOAc – Et_3N (2:1:0.2) as eluent, $R_f = 0.32$) to give the title compound. Light-yellow oil; 83% yield (17.6 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.27 (m, 2H), 7.27 – 7.19 (m, 3H), 3.98 (t, J = 8.3 Hz, 2H), 3.64 – 3.54 (m, 4H), 3.39 – 3.32 (m,

2H), 2.92 – 2.85 (m, 2H), 2.80 – 2.64 (m, 2H), 1.43 (s, 9H). $^{13}C\{^{1}H\}$ NMR (126 MHz, $CDCl_3$): δ 186.7, 156.2, 138.0, 128.3, 128.2, 126.9, 79.2, 63.4, 57.3, 33.5, 31.1, 28.3. LCMS (*m/z*): 303 ($M+H^+$). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.52; H, 8.94; N, 9.52.

***tert*-Butyl [3,3'-biazetidine]-1-carboxylate (4·0.5$H_2C_2O_4$).** To a solution of *tert*-butyl 1'-benzyl-[3,3'-biazetidine]-1-carboxylate (**14**) (17.0 g, 56.2 mmol) and $H_2C_2O_4$ (2.53 g, 28.1 mmol) in MeOH (300 mL), 10% Pd–C (2.00 g) was added, and the mixture was hydrogenated at 1 atm and rt for 4 d until full conversion of the starting material was observed by TLC. Then the catalyst was filtered off and washed with MeOH (100 mL), the filtrate was evaporated under reduced pressure to yield the title compound. White solid, mp = 169–171 °C; 91% yield (10.9 g). ^{1}H NMR (400 MHz, D_2O): δ 4.10 – 4.01 (m, 2H), 3.96 (t, *J* = 8.8 Hz, 2H), 3.81 – 3.71 (m, 2H), 3.50 (dd, *J* = 9.2, 5.2 Hz, 2H), 3.16 (sext, *J* = 8.4 Hz, 1H), 2.85 – 2.73 (m, 1H), 1.29 (s, 9H). $^{13}C\{^{1}H\}$ NMR (126 MHz, D_2O): δ 171.6, 157.9, 81.8, 51.6, 49.2, 34.0, 29.9, 27.6. GCMS (*m/z*): 212 (M^+). Anal. Calcd for $C_{24}H_{42}N_4O_8$: C, 56.01; H, 8.23; N, 10.89. Found: C, 55.76; H, 8.54; N, 11.20.

***tert*-Butyl 3-(thietan-3-yl)azetidine-1-carboxylate (15).** To a solution of *tert*-butyl 3-(1,3-dibromopropan-2-yl)azetidine-1-carboxylate (**13**) (41.1 g, 115 mmol) in a mixture of CH_3CN (1 L) and H_2O (100 mL), $Na_2S·5H_2O$ (38.6 g, 230 mmol) was added and the reaction mixture was stirred at 50 °C for 12 h. Then it was allowed to cool to rt and was concentrated under vacuum. The residue was diluted with EtOAc (1 L) and washed with H_2O (2×500 mL). The aqueous phase was extracted with EtOAc (2×500 mL). The combined organic layers were washed with

brine (500 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give the title compound. Crystalline white solid, mp = 76–78 °C; 99% yield (26.2 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.96 (t, *J* = 8.5 Hz, 2H), 3.60 – 3.51 (m, 2H), 3.48 – 3.36 (m, 1H), 3.19 (t, *J* = 8.9 Hz, 2H), 2.95 – 2.87 (m, 2H), 2.82 – 2.69 (m, 1H), 1.40 (s, 9H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 156.3, 79.5, 51.7, 42.3, 33.1, 28.4, 28.1. LCMS (*m/z*): 130 ($M+H^+–CO_2–C_4H_9$) Anal. Calcd for $C_{11}H_{19}NO_2S$: C, 57.61; H, 8.35; N, 6.11; S, 13.98. Found: C, 57.51; H, 8.66; N, 6.17; S, 13.74.

***tert*-Butyl 3-(1,1-dioxidothietan-3-yl)azetidine-1-carboxylate (16).** A solution of *tert*-butyl 3-(thietan-3-yl)azetidine-1-carboxylate (**15**) (26.2 g, 114 mmol) in CH_2Cl_2 (250 mL) was treated with m-chloroperoxybenzoic acid (85%, 70.0 g, 239 mmol) in CH_2Cl_2 (700 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred overnight, then the solids were filtered off and filtrate was washed with saturated aq. $Na_2S_2O_3$ (400 mL), 10% aq. Na_2CO_3 (400 mL) and H_2O (400 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the title compound. Amorphous beige solid, mp = 177–179 °C dec.; 90% yield (26.8 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.24 (dd, *J* = 14.2, 9.1 Hz, 2H), 4.07 (t, *J* = 8.3 Hz, 2H), 3.79 (dd, *J* = 13.7, 5.1 Hz, 2H), 3.57 (dd, *J* = 8.6, 3.8 Hz, 2H), 2.93 – 2.76 (m, 2H), 1.42 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 156.0, 79.9, 67.5, 52.1, 31.8, 28.2, 22.3. LCMS (*m/z*): 162 ($M+H^+–CO_2–C_4H_9$). Anal. Calcd for $C_{11}H_{19}NO_4S$: C, 50.56; H, 7.33; N, 5.36; S, 12.27. Found: C, 50.29; H, 7.16; N, 5.38; S, 11.88.

3-(1,1-Dioxidothietan-3-yl)azetidin-1-ium 2,2,2-trifluoroacetate (5·CF_3COOH). To a solution of *tert*-butyl 3-(1,1-dioxidothietan-3-yl)azetidine-1-carboxylate (**16**) (26.8 g, 103 mmol)

in CH_2Cl_2 (270 mL), TFA (135 mL) was added dropwise at 0 °C. The resulting solution was slowly warmed to rt and left to stir overnight. CH_2Cl_2 and TFA were distilled off under vacuum, the residue was dissolved in H_2O, solids were filtered off and filtrate was evaporated under reduced pressure. Drying over P_2O_5 in desiccator gave the title product. White solid, mp = 110–112 °C; 85% yield (24.3 g). ^{1}H NMR (500 MHz, D_2O): δ 4.41 – 4.30 (m, 2H), 4.17 (t, *J* = 10.0 Hz, 2H), 3.98 – 3.90 (m, 2H), 3.90 – 3.81 (m, 2H), 3.36 – 3.20 (m, 1H), 3.07 – 2.91 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO): δ 158.6 (q, *J* = 32.1 Hz), 117.00 (q, *J* = 298.0 Hz), 67.1, 48.8, 34.7, 21.3. LCMS (*m/z*): 162 ($M+H^+$) Anal. Calcd for $C_8H_{12}F_3NO_4S$: C, 34.91; H, 4.39; N, 5.09; S, 11.65. Found: C, 34.89; H, 4.37; N, 4.90; S, 11.95.

Diethyl 3-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)cyclobutane-1,1-dicarboxylate (17). To a suspension of NaH (6.05 g of 60% dispersion in mineral oil, 151 mmol) in DMF (270 mL), diethylmalonate (26.7 g, 166 mmol) was added dropwise maintaining the temperature below 25 °C, and the resulting mixture was stirred for additional hour. A solution of *tert*-butyl 3-(1,3-dibromopropan-2-yl)azetidine-1-carboxylate (**13**) (27.0 g, 75.6 mmol) in DMF (50 mL) was added and the reaction mixture was stirred at 70 °C overnight**,** then cooled to rt, poured into H_2O (450 mL) and extracted with EtOAc (2×400 mL). The combined organic layers were washed with H_2O (3×250 mL), brine (250 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuum. The residue was purified by column chromatography (hexanes – EtOAc (3:1), R_f = 0.33) to give the title product. Colorless oil; 86% yield (23.3 g). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.20 – 4.05 (m, 4H), 3.86 (t, *J* = 8.2 Hz, 2H), 3.45 (dd, *J* = 8.2, 5.1 Hz, 2H), 2.63 – 2.39 (m, 4H), 2.25 – 2.06 (m, 2H), 1.35 (s, 9H), 1.21 – 1.16 (m, 6H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 171.6, 171.3, 156.3, 79.2, 61.5, 61.4, 52.0, 48.8, 32.6, 32.0, 31.6, 28.3, 14.0. LCMS

(*m/z*): 256 ($M+H^+–CO_2–C_4H_9$). Anal. Calcd for $C_{18}H_{29}NO_6$: C, 60.83; H, 8.22; N, 3.94. Found: C, 61.01; H, 7.89; N, 4.03.

3-(1-(*tert*-Butoxycarbonyl)azetidin-3-yl)cyclobutane-1,1-dicarboxylic acid (18). To a solution of diethyl 3-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)cyclobutane-1,1-dicarboxylate (**17**) (22.0 g, 61.9 mmol) in THF (120 mL), a solution of $LiOH·H_2O$ (13.0 g, 310 mmol) in H_2O (360 mL) was added. The resulting solution was stirred overnight, diluted with H_2O (200 mL), washed with *t*-BuOMe (250 mL), and acidified to pH = 3 using 10% aq $NaHSO_4$. The mixture was extracted with EtOAc (2×300 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the title product. White solid, mp 160–163 °C dec.; 99% yield (18.5 g). ^1H NMR (500 MHz, $CDCl_3$): δ 10.94 – 10.75 (br s, 2H), 3.95 (t, *J* = 8.3 Hz, 2H), 3.55 (dd, *J* = 8.2, 5.2 Hz, 2H), 2.77 – 2.62 (m, 3H), 2.62 – 2.52 (m, 1H), 2.35 – 2.25 (m, 2H), 1.40 (s, 9H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 175.9, 175.4, 157.0, 80.4, 52.34 – 51.27 (br s), 48.6, 32.6, 31.9(2C), 28.3. LCMS (*m/z*): 200 ($M+H^+–CO_2–C_4H_9$), 298 ($M–H^+$). Anal. Calcd for $C_{14}H_{21}NO_6$: C, 56.18; H, 7.07; N, 4.68. Found: C, 56.36; H, 6.80; N, 4.53.

3-(1-(*tert*-Butoxycarbonyl)azetidin-3-yl)cyclobutanecarboxylic acid (6). A solution of 3-(1-(*tert*-butoxycarbonyl)azetidin-3-yl)cyclobutane-1,1-dicarboxylic acid (**18**) (18.2 g, 60.1 mmol) in pyridine (200 mL) was heated to reflux overnight. After cooling to rt, pyridine was evaporated under reduced pressure. The residue was diluted with H_2O (250 mL), acidified with aq. $NaHSO_4$ to pH~3 and extracted with EtOAc (2×250 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuum. The product was obtained by crystallization from hexanes – EtOAc (5:1). White solid, mp 103–105 °C; 89% yield (13.6 g). The compound

was obtained as *ca*. 1:1 mixture of stereoisomers. ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.31 – 10.67 (br s, 1H), 3.96 (t, *J* = 8.4 Hz, 1H) , 3.92 (t, *J* = 8.2 Hz, 1H), 3.61 – 3.46 (m, 2H), 3.12 – 3.05 (m, 0.5H), 3.01 (quint, *J* = 9.0 Hz, 0.5H), 2.71 – 2.63 (m, 0.5H), 2.63 – 2.56 (m, 0.5H), 2.56 – 2.45 (m, 1H), 2.44 – 2.35 (m, 1H), 2.35 – 2.24 (m, 1H), 2.02 – 1.88 (m, 2H), 1.41 (s, 9H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 181.1 and 180.2, 156.49 and 156.46, 79.51 and 79.48, 52.1 (2C), 34.8 and 34.2, 33.8 and 33.6, 32.8 and 32.7, 28.4, 28.0, 27.5. LCMS (*m/z*): 254 ($M–H^+$). Anal. Calcd for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 60.95; H, 8.60; N, 5.44.

1-Benzhydryl-3-(oxetan-3-yl)azetidine (19). To a solution of 2-(1-benzhydrylazetidin-3-yl)propane-1,3-diol (**11**) (3.54 g, 11.9 mmol) in THF (70 mL), *n*-BuLi (2.5 M in hexanes, 4.76 mL, 11.9 mmol) was added slowly at –30 °C and stirred for 15 min. Then *p*-toluenesulfonyl chloride (2.27 g, 11.9 mmol) was added and reaction mixture was warmed to rt and stirred for additional 1 hour. Then reaction mixture was cooled to –30 °C and *n*-BuLi (2.5 M in hexanes, 4.76 mL, 11.9 mmol) was added and the resulting solution was left to stir at rt for 12 h. The solution was diluted with H_2O (120 mL) and extracted with EtOAc (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (EtOAc:hexanes:Et_3N = 1:3:0.5, Rf= 0.53) to give the title product. Colorless oil; 42% yield (1.39 g). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.7 Hz, 4H), 7.30 (t, *J* = 7.0 Hz, 4H), 7.21 (t, *J* = 6.8 Hz, 2H), 4.84 (t, *J* = 6.3 Hz, 2H), 4.50 (t, *J* = 5.4 Hz, 2H), 4.38 (s, 1H), 3.33 (t, *J* = 7.2 Hz, 2H), 3.30 – 3.22 (m, 1H), 2.93 (t, *J* = 6.2 Hz, 2H), 2.84 – 2.74 (m, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 142.2, 128.3, 127.4, 127.0, 77.9, 75.4, 56.4, 37.6, 31.7. LCMS (*m/z*): 280 ($M+H^+$) Anal. Calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.53; H, 7.37; N, 4.85.

3-(Oxetan-3-yl)azetidin-1-ium oxalate (7·0.5$H_2C_2O_4$). To a solution of 1-benzhydryl-3-(oxetan-3-yl)azetidine (**19**) (1.20 g, 4.29 mmol) and oxalic acid (195 mg, 2.16 mmol) in mixture EtOAc–THF (3:1) (120 mL), Pd–C (200 mg, 10% on activated coal) was added and the mixture was stirred under H_2 atmosphere (1 atm) for 48 h. Then Pd–C was filtered off and washed with THF (50 mL), the filtrate was evaporated under reduced pressure to yield the title compound. Crystalline white solid, mp 148–150 °C dec.; 86% yield (420 mg). ^{1}H NMR (500 MHz, D_2O): δ 4.81 (t, *J* = 7.2 Hz, 2H), 4.35 (t, *J* = 6.2 Hz, 2H), 4.12 (t, *J* = 10.0 Hz, 2H), 3.88 – 3.77 (m, 2H), 3.41 – 3.22 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, D_2O): δ 173.4, 75.1, 49.3, 36.1, 33.4. GCMS (*m/z*): 113 (M^+). Anal. Calcd for $C_{14}H_{24}N_2O_6$: C, 53.15; H, 7.65; N, 8.86. Found: C, 53.45; H, 7.75; N, 8.59.

ASSOCIATED CONTENT

Supporting Information. The following files are available free of charge:

copies of NMR spectra and results of X-Ray diffraction studies (PDF)

crystallographic information files (CIF)

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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