JOC The Journal of Organic Chemistry

Article

Photochemical in flow synthesis of 2,4-methanopyrrolidines: pyrrolidine analogues with improved water solubility and reduced lipophilicity

Vadym V. Levterov, Oleg Michurin, Petro O. Borysko, Sergey Zozulya, Iryna V. Sadkova, Andrey A. Tolmachev, and Pavel K. Mykhailiuk

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02071 • Publication Date (Web): 25 Oct 2018

ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

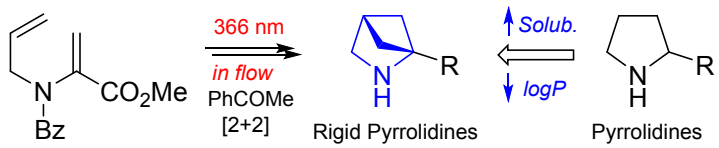
Photochemical *in flow* synthesis of 2,4-methanopyrrolidines: pyrrolidine analogues with improved water solubility and reduced lipophilicity

Vadym V. Levterov,[†] Oleg Michurin,[†] Petro O. Borysko,[††] Sergey Zozulya,[††] Iryna V. Sadkova,[†] Andrey A. Tolmachev,[†‡] and Pavel K. Mykhailiuk[†‡]*

[†] Enamine Ltd., Chervonotkatska 78, Kyiv 02094 (Ukraine), www.enamine.net,

[††] Bienta, Chervonotkatska 78, Kyiv 02094 (Ukraine), www.bienta.net,

[‡] Department of Chemistry, Taras Shevchenko National University of Kyiv, Volodymyrska 64, Kyiv 01601, Ukraine www.mykhailiukchem.org



ABSTRACT: A practical synthesis of 2,4-methanopyrrolidines was elaborated. The key synthetic step was an intramolecular photochemical [2+2]-cycloaddition of an acrylic acid derivative *in flow*. In spite of a higher molecular weight 2,4-methanopyrrolidines were shown to have higher solubility in water, and lower lipophilicity (logD) than pyrrolidines, - important characteristics of bioactive molecules in drug design.

INTRODUCTION

Recent trends in drug discovery - *Escape from Flatland*[1] and *Conformational restriction*[2] - significantly changed the structural requirements to bioactive compounds. In particular, medicinal chemists have been using now small saturated building blocks, rather than the bulky aromatic compounds.[3,4,5] On the other hand, at the early stages of drug discovery, scientists still pay much attention to lipophilicity and water solubility of bioactive compounds.[6] Tricks to fine-tune these characteristics during a *hit-to-lead* optimization become therefore important.[7] In particular, great progress in the area of bioisosteric replacements was achieved already.[8,9]

Pyrrolidine is among the most commonly used secondary amines in medicinal chemistry.[10] Moreover, its motif appears in more than 100 FDA-approved drugs.[11] Indeed, development of novel bioisosteres for pyrrolidine with the known physico-chemical characteristics is of interest to medicinal chemists. In this context, herein we report on the *in flow* photochemical synthesis of conformationally rigid pyrrolidine analogues – 2,4-methanopyrrolidines. We also demonstrate here experimentally, that in spite of a slightly higher molecular weight of 12 daltons compared to pyrrolidines, 2,4-methanopyrrolidines have higher solubility in water, and lower lipophilicity (logD) - important characteristics of bioactive molecules in drug design.

In 1980, 2,4-methanopyrrolidine was isolated from the seeds of *Ateleia Herbert smithii* Pittier, a tree commonly growing on the coast of Costa-Rica.[12,13] Due to a stabilization of the *N*-trans amide bond,[14] scientists used this conformationally restricted analogue of

L-Proline in the preparation of peptidomimetics.[15] Following these studies, diverse pharmaceutical companies employed 2,4-methanopyrrolidines as conformationally restricted surrogates of pyrrolidines (Figure 1). Moreover, in 2016, *Siu* and *Huestis* based on calculations, suggested that 2,4-methanopyrrolidines might be slightly less lipophilic than pyrrolidines.[16] The authors, however, did not validate this hypothesis experimentally.

In spite of a high potential, 2,4-methanopyrrolidines are still rare today in drug discovery programs – only 117 hits in the ChEMBL database (Figure 1).[17] Presumably, this is due to a lack of practical approaches to them.

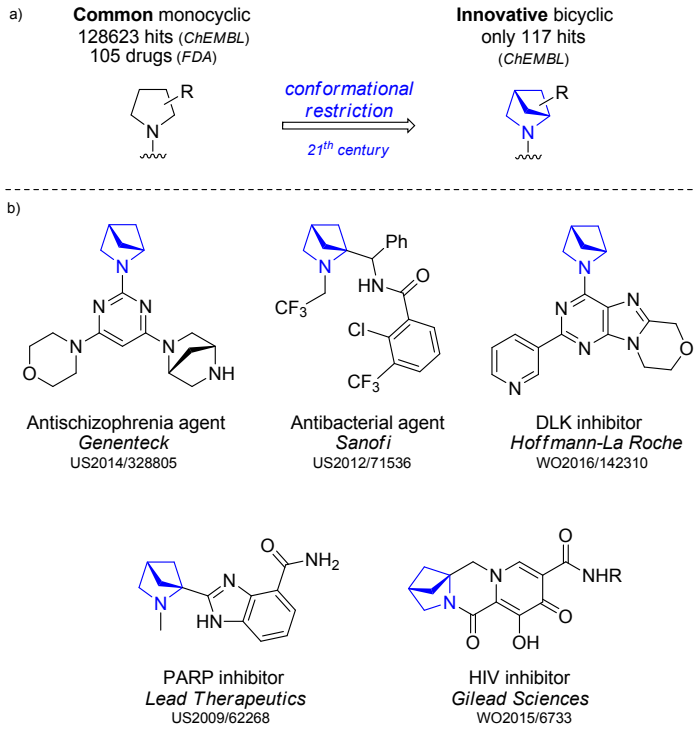


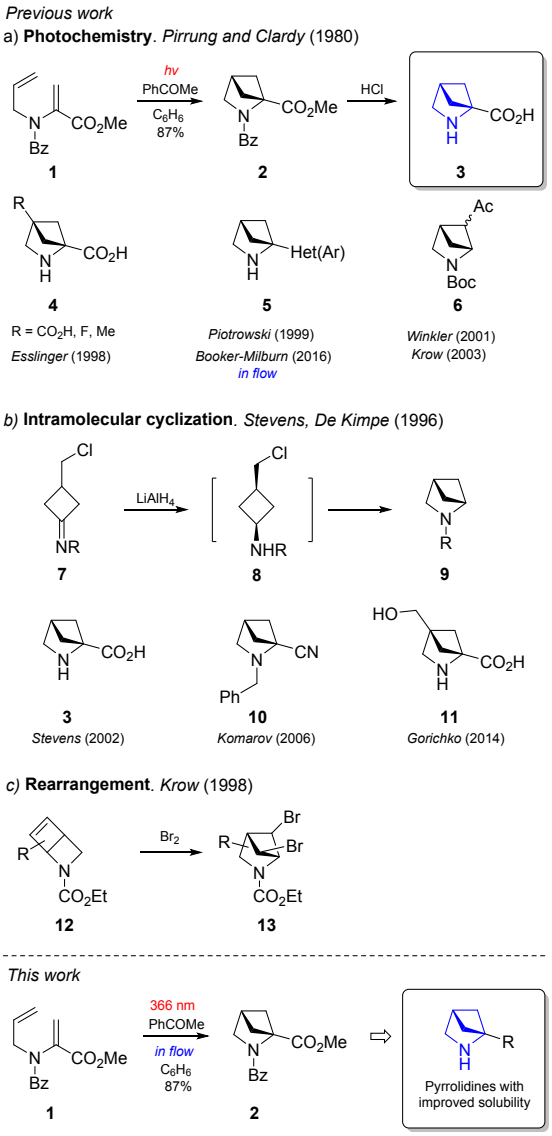
Figure 1. a) Pyrrolidines and 2,4-methanopyrrolidines in drug discovery; b) Bioactive derivatives of 2,4-methanopyrrolidine.

Three different approaches to 2,4-methanopyrrolidines were described in the literature. In 1980, *Pirrung*[18] and *Clardy*[19] independently cyclized diene **1** into the bicyclic amine **2** (Scheme 1a). The key step was an intramolecular photochemical [2+2]-cyclization.[20] In 2003, *Malpass* repeated the synthesis of amino acid **3**, and prepared conformationally restricted nicotinic acetylcholine ligands.[21] In 2010, *Varnes* and colleagues from *AstraZeneca* also used this strategy to obtain 20 g of amino acid **3**.[22] Subsequently, the photochemical approach was acquired by other groups to synthesize the substituted analogues of 2,4-methanopyrrolidine **4**. In particular, *Esslinger* synthesized GABA analogue **4** (R=CO_2H),[23] while our group reported on fluoro- and methyl-substituted analogues **4** (R=H, F; Figure 1a).[24] In 1999, *Piotrowski* synthesized aromatic and heteroaromatic 2,4-methanopyrrolidines **5** using intramolecular photochemical [2+2]-cyclization of acetophenone derivatives.[25] Following this method, *Elliott* and *Booker-Milburn* in 2016 performed the photochemical synthesis *in flow* of *N*-Bz product **5** (R=Ph) on a kilogram scale (Scheme 1a).[26] A photochemical approach was also used by *Winkler* in 2001 to synthesize the 2-acetyl 2,4-methanopyrrolidine **6**.[27] Later, *Krow* with coworkers followed this transformation and performed the subsequent transformations of compound **6**.[28]

The second strategy to 2,4-methanopyrrolidines relies on an intramolecular cyclization of the substituted aminocyclobutanes (Scheme 1b). In 1996, *Stevens* and *De Kimpe* reacted imine **7** with $LiAlH_4$, and the intermediate amine **8** immediately underwent rapid intramolecular cyclization into 2,4-methanopyrrolidine **9**.[29] Later, *Siu* and *Huestis* optimized this procedure to obtain 200 g of unsubstituted 2,4-methanopyrrolidine **9** (R=H).[16] *Stevens* used this tactic to develop an alternative synthesis of amino acid **3**.[30] *Grygorenko* and *Komarov* used the same approach to synthesize nitrile **10**[31] and *Gorichko* – to prepare the substituted amino acid **11**.[32] Slightly modified approaches to 2,4-methanopyrrolidine core by *Gaoni*[33]and *Huet*[34] are also worth mentioning.

The third approach to 2,4-methanopyrrolidines was elaborated in 1998 by *Krow* and co-workers: they reacted compound **12** with Br_2 to form the needed bicyclic molecule **13** (Scheme 1c).[35]

Although, several approaches to substituted 2,4-methanopyrrolidines already exist, only the synthesis of monofunctional compound **5** by *Elliott* and *Booker-Milburn* in collaboration with scientists from *GlaxoSmithKline* and *AstraZeneca* was performed on a large scale *in flow*.



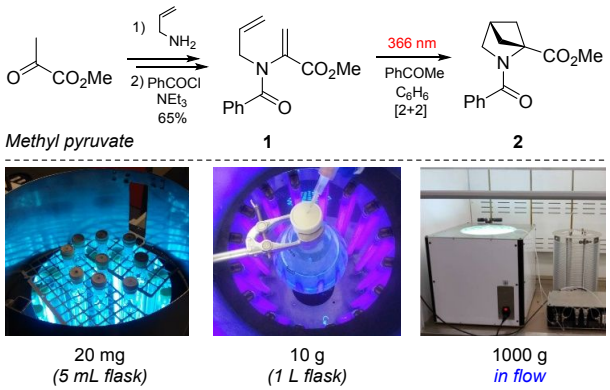
Scheme 1. Approaches to substituted 2,4-methanopyrrolidines.

In this work, we report on an in batch and *in flow* photochemical synthesis of a bifunctional compound **2**, and the subsequent synthesis of 2,4-methanopyrrolidine-containing pharmaceutically-related building blocks. We also demonstrate here, that in spite of a higher molecular weight, 2,4-methanopyrrolidines have slightly better solubility in water, and lower lipophilicity than pyrrolidines – important characteristics in drug design.

RESULTS AND DISCUSSION

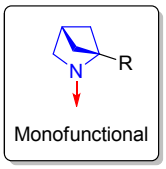
Optimization studies. Recently, we elaborated the photochemical synthesis of substituted analogues of 2,4-methanoproline, and studied the role of an electronic effect on the *cis-trans* amide bond population. Herein, we applied this method for the synthesis of

compound **2**. First, we synthesized the starting material **1** in two steps from methyl pyruvate.[21a] Next, the photochemical transformation of compound **1** into bicyclic compound **2** smoothly proceeded at room temperature, under irradiation at 366 nm with benzophenone as a triplet sensitizer. We performed the photochemical step on a milligram to gram scale using general 10 mL – 1 L glass flasks (Scheme 2). No special quartz glassware was required, as common glass transmits the light with the wavelength of 366 nm very efficiently.[5a,36] Subsequently, we performed the photochemical step *in flow* to obtain kilogram quantities of compound **2** in one run (Scheme 2).

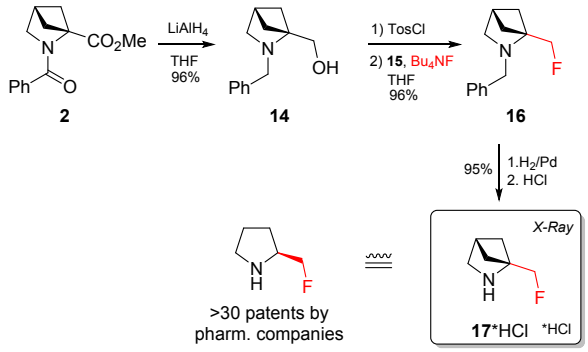


Scheme 2. [2+2]-Photochemical synthesis of compound **2** at different scale.

Synthesis of building blocks. Having synthesized intermediate **2** on a large scale, we next used it to obtain the appropriately substituted 2,4-methanopyrrolidines for the direct use in drug discovery projects.



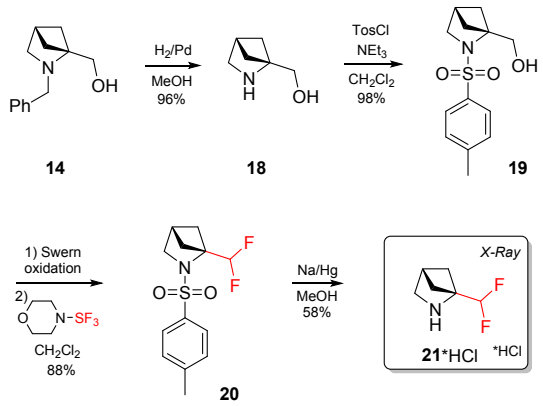
1. Fluorinated amines. Fluorinated amines play an important role in medicinal chemistry due to a unique impact of the fluorine atom on physico-chemical properties of organic molecules. In particular, placing fluorine atoms close to a nitrogen atom, makes amines less basic and more metabolically stable.[37,38] Therefore, we demonstrated the synthetic utility of compound **2** by synthesizing three fluorinated amines – monofluoromethyl, difluoromethyl and trifluoromethyl-substituted 2,4-methanopyrrolidines. In particular, simultaneous reduction of the ester and benzoyl groups in **2** with $LiAlH_4$, followed by a standard tosylation of alcohol **14**, and treatment of the intermediate tosylate **15** with Bu_4NF in THF at room temperature gave compound **16** in 92% yield. Hydrogenation of the *N*-Bn bond in **16** over Pd/C as a catalyst and acidic work-up provided the needed monofluoromethyl-pyrrolidine **17***HCl in 95% yield (Scheme 3). The structure of compound **17***HCl was confirmed by an *X-Ray* analysis (Figure 2). It is worth mentioning that the applications of analogous monofluoromethyl-substituted pyrrolidine is reported in more than 30 patents by diverse pharmaceutical companies.[39]



Scheme 3. Synthesis of monofluoromethyl-substituted amine **17***HCl.

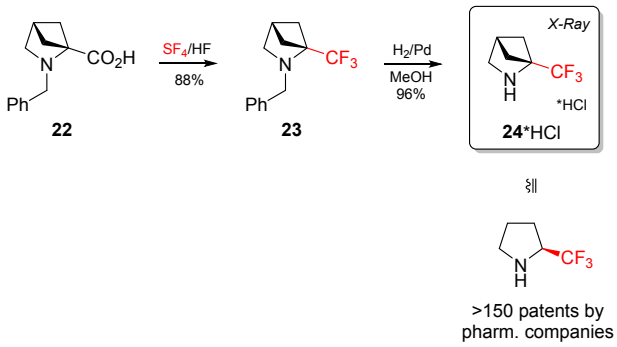
Hydrogenation of the *N*-Bn bond in compound **14** over Pd/C as a catalysis smoothly gave amino alcohol **18**. Treatment of compound **18** with TosCl in dichloromethane in the presence of triethylamine as a base afforded the *N*-Tos derivative of substituted alcohol **19**. Swern oxidation of the alcohol group and treatment of the intermediate aldehyde with Morpho-DAST gave difluoromethyl-

substituted compound **20** in 88% yield. Subsequent cleavage of *N*-Tos group in product **20** with sodium amalgam in methanol provided the needed difluoromethyl-substituted amine **21***HCl in 58% yield (Scheme 4). The structure of compound **21***HCl was confirmed by an *X-Ray* analysis (Figure 2). In the crystal structure of amine **17***HCl the F-C-C-N^+ gauche effect was present. It is also interesting to mention that in the crystal structure of amine **21***HCl only one fluorine atom was involved in the F-C-C-N^+ gauche effect.[40]



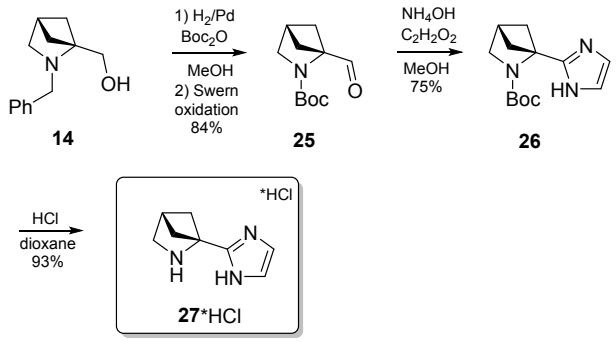
Scheme 4. Synthesis of difluoromethyl-substituted amine **21***HCl.

Reaction of amino acid derivative **22** with sulfur tetrafluoride in anhydrous liquid hydrogen fluoride resulted in the trifluoromethylated product **23** in 88% yield. Hydrogenation of compound **23** over Pd/C cleaved the *N*-Bn bond to give the target trifluoromethyl-substituted amine **24***HCl in 96% yield (Scheme 5). The structure of compound **24***HCl was also confirmed by an *X-Ray* analysis (Figure 2). It is also important to note that the application of trifluoromethyl-substituted pyrrolidine is mentioned in more than 150 patents by diverse pharmaceutical companies.[41]



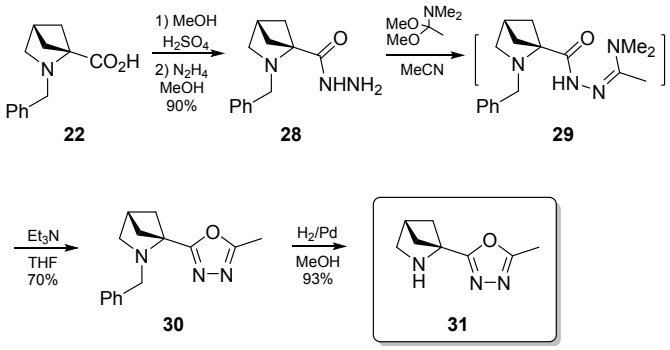
Scheme 5. Synthesis of trifluoromethyl-substituted amine **24***HCl.

2. Heterocycles. Hydrogenation of amino alcohol **14** using Pd/C as a catalyst in methanol in the presence of Boc_2O, followed by Swern oxidation of the intermediate *N*-Boc alcohol gave aldehyde **25**. Treatment of the latter with 10 M aqueous NH_4OH and an aqueous solution of 40% glyoxal at room temperature gave compound **26** in 75% yield. Acidic cleavage of the *N*-Boc protecting group finalized the synthesis of imidazole **27***HCl in 93% yield (Scheme 6).



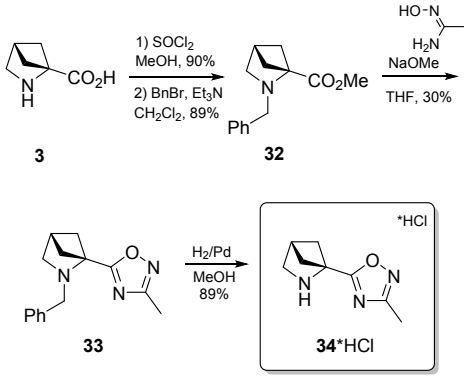
Scheme 6. Synthesis of substituted imidazole **27***HCl.

Next, the *N*-Bn protected amino acid **22** was treated first with sulfuric acid in methanol, and the formed methyl ester was reacted with hydrazine hydrate to give hydrazide **28** in 90% yield. Compound **28** was treated first with *N*,*N*-dimethylformamide dimethyl acetal under reflux in acetonitrile, and triethylamine was added. Under these conditions compound **29** underwent the cyclization into 1,2,4-oxadiazole **30**. Hydrogenation of the *N*-Bn bond in compound **30** over Pd/C as a catalyst in methanol furnished the synthesis of the heterocyclic compound **31** in 93% yield (Scheme 7).



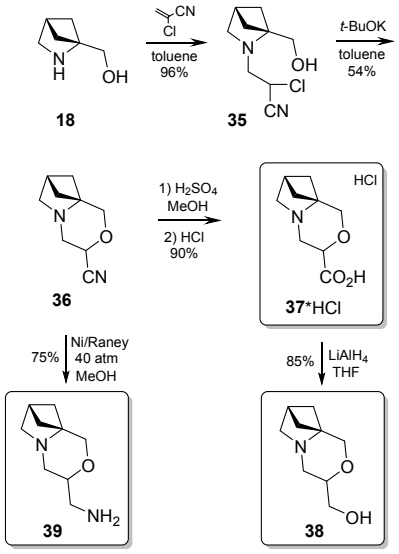
Scheme 7. Synthesis of substituted 1,2,4-oxadiazole **31**.

Treatment of compound **3** with $SOCl_2$ in MeOH under reflux resulted in the corresponding amino ester that was protected with BnBr to give **32**. The *N*-Bn protected ester **32** was treated with *N*-hydroxyacetimidamide in the presence of sodium methoxide as a base in THF gave the cyclized product **33** in 30% yield. Hydrogenation of the *N*-Bn bond in compound **33** over Pd/C as a catalyst in methanol led to the desired oxadiazole **34***HCl in 89% yield (Scheme 8).



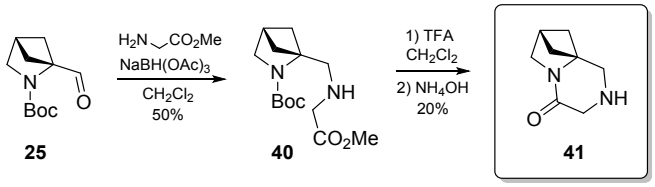
Scheme 8. Synthesis of substituted 1,3,4,-oxadiazole **34***HCl.

3.Tricyclic building blocks. Next, we synthesized several 2,4-methanopyrrolidine-containing building blocks. In particular, treatment of amino alcohol **18** with 2-chloroacrylonitrile in toluene at room temperature gave compound **35**. Addition of *t*-BuOK in toluene led to the cyclization of compound **35** into the tricyclic nitrile **36** in 54% yield. Hydrolysis of the nitrile **36** under the acidic conditions to acid **37***HCl followed by reduction with $LiAlH_4$ in THF at room temperature provided alcohol **38** in 85% yield. Finally, treatment of compound **36** with Ni-Raney alloy afforded amine **39** in 75% yield. (Scheme 9).



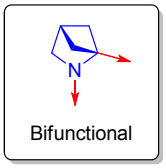
Scheme 9. Synthesis of tricyclic building blocks **37-39**.

Reductive amination of aldehyde **25** with methyl ester of glycine gave compound **40**. Acidic cleavage of *N*-Boc group, followed by an addition of aqueous ammonia as a base, gave piperazinone **41** in 20% yield (Scheme 10).

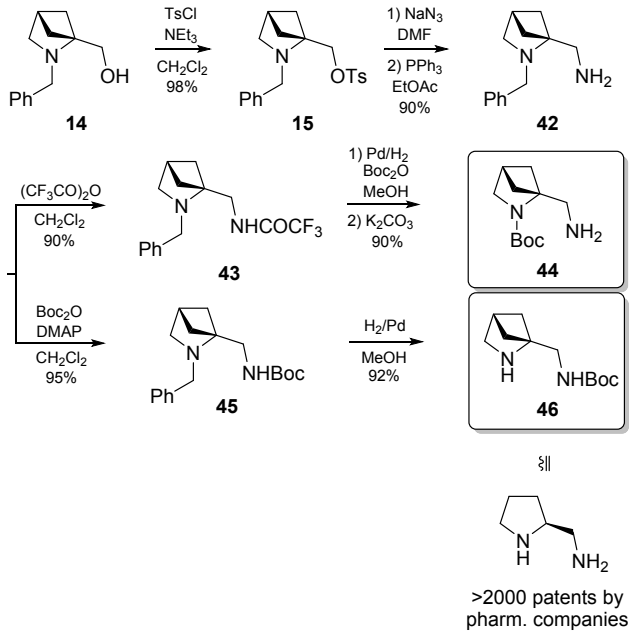


Scheme 10. Synthesis of the tricyclic compound **41**.

4. Functional building blocks. Next, we examined the synthesis of bifunctional 2,4-methanoproline-containing building blocks. In particular, alcohol **14** was reacted with TosCl in pyridine to form tosylate **15**. Reaction with NaN_3, followed by reduction of the intermediate azide with PPh_3 in ethyl acetate at room temperature gave *N*-Bn diamine **42** in 90% yield. Next, we synthesized two isomeric *N*-Boc substituted diamines. In particular, amine **42** was treated with $(CF_3CO_2)_2O$ in dichloromethane to give compound **43**. Hydrogenation of compound **43** over Pd/C as a catalyst in the presence of Boc_2O, followed by cleavage of *N*-TFA group with potassium carbonate gave the target *N*-Boc diamine **44**. Alternatively, *N*-Boc protection of compound **42**, followed by hydrogenative cleavage of *N*-Bn bond in intermediate **45**, gave an isomeric *N*-Boc diamine **46** in 92% yield (Scheme 11).

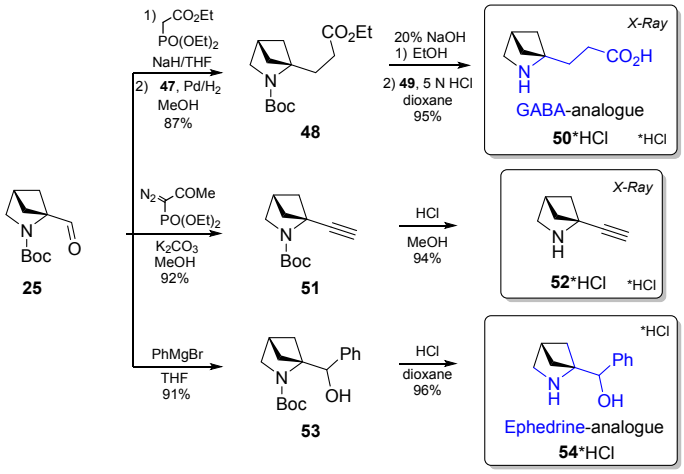


It is important to mention that proline analogues of diamines **44** and **46** are very common in drug design – they occur in more than 2000 patents by diverse pharmaceutical companies (Scheme 11).[41]



Scheme 11. Synthesis of isomeric *N*-Boc-protected diamines **44** and **46**.

The Horner–Wadsworth–Emmons reaction of aldehyde **25**, followed by hydrogenation of C=C double bond over Pd/C as a catalyst in the intermediate alkene **47** afforded ester **48** in 87% yield. Hydrolysis of the ester group **48** under the basic conditions resulted in **49**, followed by an acidic cleavage of the *N*-Boc group gave amino acid **50***HCl - a conformationally restricted analogue of γ-aminobutyric acid (GABA) - the chief inhibitory neurotransmitter in the mammalian central nervous system (Scheme 12). The structure of compound **50***HCl was confirmed by an *X-Ray* analysis (Figure 2). The Ohira-Bestmann reaction of aldehyde **25** gave alkyne **51** in 92% yield. Cleavage of *N*-Boc group under acidic conditions gave amino alkyne **52** – a small bifunctional linker useful for click-reactions with azides. Finally, an addition of PhMgBr followed by acidic cleavage of *N*-Boc group in **25** provided amino alcohol **54***HCl - a conformationally restricted analogue of Ephedrine – a medication used to prevent low blood pressure (Scheme 12).



Scheme 12. Synthesis of compounds **50***HCl, **52***HCl and **54***HCl.

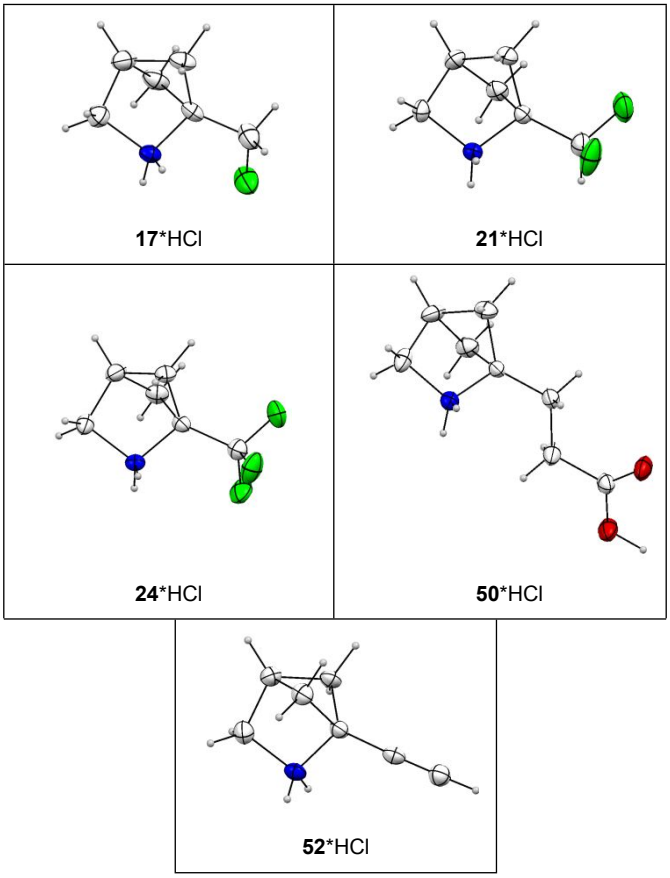


Figure 2. *X*-Ray crystal structure of compounds **17***HCl, **21***HCl, **24***HCl, **50***HCl, **52***HCl.[41] The *N*, *C*, *F*, *O*-atoms are shown at 30% thermal ellipsoid % probability.

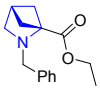
Physico-chemical properties. After the synthesis, we wanted to experimentally validate the hypothesis of *Siu* and *Huestis* that 2,4-methanopyrrolidines were less lipophilic than pyrrolidines. Therefore, we prepared first the *N*-Bn model compounds **55-58**, and measured experimentally their logD values. The measurement was performed in *n*-octanol / 100 mM sodium carbonate-sodium bicarbonate buffer at pH 10 to avoid the reversible protonation of the basic nitrogen atom (Table 1). Indeed, compound **56** was significantly less lipophilic than pyrrolidine **55** (logD = 2.4 *vs* 3.0; ΔlogD = -0.6) in spite of the higher molecular weight (187 *vs* 175). In larger compounds **57**, **58** this effect was less prominent (logD = 2.6 *vs* 2.5; ΔlogD = -0.1). Indeed, the higher the molecular weight, the smaller the input of intrinsic lipophilicity of 2,4-methanopyrrolidine/pyrrolidine units onto the overall lipophilicity.[42]

Next, we measured the thermodynamic solubility of molecules **55-58** in an aqueous buffer at pH = 10 (sodium carbonate - sodium bicarbonate buffer), again to avoid the partial protonation of the basic nitrogen atom. Incredibly, compound **56** had more than three times higher aqueous solubility than pyrrolidine **55** (Solubility = 25.1 *vs* 7.2)! As expected, in larger molecules **57**, **58** this effect was less profound (10.9 *vs* 8.4).

We think that the compact conformationally rigid structure of 2,4-methanopyrrolidines makes the lone pair of a nitrogen atom more accessible to the water solvent. This leads to reduced lipophilicity and better water solubility of compounds **56**, **58** compared to pyrrolidines **55**, **57**. Moreover, this effect is strong enough to override the higher molecular weight of 2,4-methanopyrrolidines compared to pyrrolidines.

It is important to mention, that both models **55** and **56** had similar metabolic stability, as measured by clearance rate in mouse liver microsomes. Compounds **57** and **58** were unstable metabolically due to a fast hydrolysis of the ester group.

Table 1. Experimental ADME-parameters.

Compound		LogD(10.0)[a]	Sol(10.0)[b]	CL_{int}[c]
55		3.0	7.2	3.9
56		2.4	25.1	2.6
57		2.6	8.4	*n.d.*[d]
58		2.5	10.9	*n.d.*[d]

[a]Experimental *n*-octanol/water (100 mM sodium carbonate - sodium bicarbonate buffer) distribution coefficient at pH 10.0 (log); [b]Thermodynamic aqueous solubility at pH = 10 in 100 mM sodium carbonate - sodium bicarbonate buffer (mM). [c]Intrinsic clearance rate CL_{int} (mg/(min·µL)) measured in mouse liver microsomes; [d] Very fast decomposition.

In short summary, 2,4-methanopyrrolidines possess an interesting ADME-profile for drug discovery. They have similar metabolic stability; possess lower lipophilicity, and higher water solubility than pyrrolidines.

CONCLUSIONS

Herein we developed a photochemical synthesis of compound **3** in batch on a milligram to gram scale, and *in flow* on a on kilogram scale. From compound **3**, several novel 2,4-methanopyrrolidine-containing building blocks were synthesized: amino acids, diamines, fluorinated amines, amino alcohols, amino alkynes, *etc*. We also showed experimentally that 2,4-methanopyrrolidines have similar metabolic stability to that of pyrrolidines. Importantly, in spite of a higher molecular weight of 12 daltons due to one additional carbon atom, 2,4-methanopyrrolidines they have better solubility in water and lower lipophilicity than pyrrolidines – important characteristics in drug design.

Given the rapid synthetic access to 2,4-methanopyrrolidines, and their interesting physico-chemical profile, we believe that medicinal chemists will soon start to use them as "water-soluble" bioisosteres of pyrrolidines in drug discovery projects.

EXPERIMENTAL SECTION

General methods

All chemicals were provided by Enamine Ltd (www.enamine.net). High pressure reactors were provided by UOSlab (en.uoslab.com). All solvents were treated according using standard methods. All reactions were monitored by thin-layer chromatography (TLC) and were visualized using UV light. Product purification was performed using silica gel column chromatography. TLC-characterization was performed with pre-coated silica gel GF254 (0.2 mm), while column chromatography characterization was performed with silica gel (100-200 mesh).^{1}H-NMR, ^{19}F-NMR, ^{13}C-NMR spectra were recorded with tetramethylsilane (TMS, δ = 0.00 ppm) as the internal standard. ^{1}H-NMR spectra were recorded at 400 or 500 MHz (Varian); ^{19}F-NMR spectra were recorded at 376 MHz (Varian), ^{13}C NMR spectra were recorded at 100 or 126 MHz (Varian). ^{1}H-NMR chemical shifts are reported downfield from $CDCl_3$ (δ = 7.26 ppm), D_2O (δ = 4.79 ppm) or DMSO-d_6 (δ = 2.50 ppm). ^{13}C-NMR chemical shifts for ^{13}C-NMR are reported relative to the central $CDCl_3$ (δ = 77.16 ppm) or DMSO-d_6 (δ = 39.52 ppm). Coupling constants are given in Hz. MS analysis was performed on an LCMS instrument with chemical ionization or GCMS with electrospray ionization. Melting points are reported for recrystallized and pure compounds.

Methyl 2-(*N*-allylbenzamido)acrylate (1)

To a solution of methyl pyruvate (1236.4 g, 12.19 mol, 1 equiv) in 8 L of toluene allylamine (695.2 g, 12.19 mol, 1 equiv) was added, and the mixture was stirred for 12 h at RT under argon. After stirring, the reaction mixture was poured into water and the organic layer was separated, washed with brine, dried over Na_2SO_4 and filtered. The filtrate was cooled to -10-0 ºC and triethylamine (1355.2 g, 13.42 mol, 1.1 equiv) was added followed by benzoyl chloride (1713.8 g, 12.19 mol, 1 equiv) maintaining the temperature. The resulting mixture was allowed to warm to RT and left overnight. The precipitate of triethyamine hydrochloride was filtered off and washed with toluene. The

filtrate was concentrated under reduced pressure and purified by flash chromatography (hexanes/ethyl acetate, 4:1) to afford the final compound as a yellow oil. Yield (1940.4 g, 7.92 mol, 65%). The product is relatively unstable and can be polymerized very quickly; therefore, it should be used immediately for the next step. All analytical data are consistent with the literature.[21]

Methyl (1*s*,4*s*)-2-benzoyl-2-azabicyclo[2.1.1]hexane-1-carboxylate (2)

The compound **1** (23.5 g, 0.096 mol) was dissolved in distilled acetonitrile (1 L) and acetophenone (2.5 g, 0.021 mol) was added. The reaction was irradiated at 366 nm, and reaction progress was monitored by NMR. After the reaction completeness, the mixture was concentrated under reduced pressure and the residue was purified by flash column chromatography using hexane/EtOAc = 3/2 as an eluent to give the desired product **2** as a white solid. Yield (20.5 g, 0.0837 mol, 87% yield), m. p. = 123-125 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.78-1.75 (2H, m), 2.11-2.28 (2H, m), 2.73-2.87 (1H, m), 3.55 (2H, s), 7.79-7.86 (5H, m). ^{13}C NMR (126 MHz, $CDC1_3$) δ: 35.2, 41.6, 51.9, 54.9, 69.9, 128.1, 128.3, 131.2, 134.2, 168.7, 173.6.

Methyl (1*s*,4*s*)-2-benzoyl-2-azabicyclo[2.1.1]hexane-1-carboxylate (2), 1 kg scale.

The compound **1** (1110 g, 4.53 mol) was dissolved in dry acetonitrile (5 L) and acetophenone (185 g, 1.54 mol) was added under argon. The reaction was irradiated at 366 nm for 1 d in a flow reactor (flow rate = 20 mL/min, tube diameter = 8 mm, material - fluorinated ethylene propylene, power = 4 × 600 W). After the reaction completeness, the mixture was concentrated under reduced pressure. The crude product was washed with a cold mixture of MTBE/EtOAc (1st portion). The resulted solution was concentrated under reduced pressure, and the solid residue washed again with a cold mixture of MTBE/EtOAc (2nd portion). Acetophenone was removed from the residue by distillation (1 mm Hg). The residue containing the desired product was washed with a cold mixture of MTBE/EtOAc (3rd portion). Yield (1000 g, 4.08 mol, 90%).

All procedures for **3**, **14**, **18**, **22**, **25**, **32** were taken from the literature.[21]

(2-Benzyl-2-azabicyclo[2.1.1]hexan-1-yl)methyl 4-methylbenzenesulfonate (15)

p-Toluenesulfonyl chloride (68.6 g, 0.36 mol, 1.2 equiv) was added to a solution of **14** (84.3 g, 0.3 mol, 1 equiv) and Et_3N (45.5 g, 0.45 mol, 1.5 equiv) in CH_2Cl_2 (1 L) dropwise at 0 °C. The mixture was stirred at RT overnight. Water was added, and the mixture was partitioned. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was used for the next step without further purification (126.1 g, 0.35 mol, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.58 – 1.49 (m, 2H), 1.73 – 1.62 (m, 2H), 2.41 (s, 3H), 2.63 (s, 3H), 3.54 (s, 2H), 4.17 (s, 2H), 7.36 – 7.19 (m, 7H), 7.75 (d, J = 8.2 Hz, 2H). *m/z* (APCI): 358.1 (M+H). Anal. calcd. for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.49; N, 3.92. Found: C, 67.45; H, 6.63; N, 3.70.

2-Benzyl-1-(fluoromethyl)-2-azabicyclo[2.1.1]hexane (16)

The tosylated compound **15** (20.0 g, 0.1 mol, 1 equiv) was dissolved in THF (300 mL), and Bu_4NF (41.2 g, 0.14 mol, 1.4 equiv) was added. The mixture was stirred at RT overnight. The reaction mixture was partially concentrated under reduced pressure, diluted with distilled water and CH_2Cl_2. The organic layer was separated, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The desired product was purified by column chromatography (gradient, hexanes/MTBE) to give a white solid. Yield (18.9 g, 0.09 mol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.75 – 1.71 (m, 2H), 1.67 – 1.62 (m, 2H), 2.73 – 2.67 (m, 3H), 3.73 (s, 2H), 4.53 (s, 1H), 4.65 (s, 1H), 7.24 (t, J = 7.1 Hz, 1H), 7.32 (t, J = 7.4 Hz, 2H), 7.41 (d, J = 7.3 Hz, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -225.0 (s). Anal. calcd. for $C_{13}H_{16}FN$: C, 76.06; H, 7.86; N, 6.82. Found: C, 75.93; H, 7.75; N, 6.99.

1-(Fluoromethyl)-2-azabicyclo[2.1.1]hexane hydrochloride (17)

The compound **16** (30.0 g, 0.147 mol) was dissolved in 300 mL of MeOH and 2 g of 10% Pd/C was added to the mixture. The mixture was hydrogenated at 10 atm at RT overnight. Pd/C was filtered out, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in a 5 M HCl solution in MeOH and concentrated under reduced pressure to afford the final compound as a white powder. Yield (21.1 g, 0.14 mol, 95%), mp 182-183 ºC.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.68 – 1.49 (m, 2H), 2.01 (s, 2H), 2.86 (s, 2H), 3.27 (s, 2H), 4.83 (d, J = 46.9 Hz, 2H), 9.83 (br s, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ: -227.2 (s). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 27.0 (d, J_{CF} = 7.5 Hz), 27.4 (d, J_{CF} = 18.0 Hz), 32.3 (d,

J_{CF} = 7.0 Hz), 37.5 (d, J_{CF} = 16.4 Hz), 50.2, 111.8 (d, $^{1}J_{CF}$ = 242.5 Hz). *m/z* (APCI): 116.2 (M+H). Anal. calcd. for $C_6H_{11}ClFN$: C, 47.53; H, 7.31; N, 9.24. Found: C, 47.23; H, 7.49; N, 9.41.

(2-Tosyl-2-azabicyclo[2.1.1]hexan-1-yl)methanol (19)

p-Toluenesulfonyl chloride (51.9 g, 0.27 mol, 1 equiv) was added in portions to a stirring solution of **18** (30.85 g, 0.27 mol, 1 equiv) and Et_3N (80 mL, 0.57 mol, 2.1 equiv) in CH_2Cl_2 (900 mL) to keep the temperature below 10 °C (water +ice bath). The reaction mixture was allowed to warm to RT and stirred for 12 h. The mixture was washed with a solution of 0.5 M HCl (2 × 500 mL) and brine (1 × 500 mL). The organic layer was separated, dried over Na_2SO_4, filtered and concentrated *in vacuo* to give the desired product as a white crystalline solid. Yield (71.2 g, 0.27 mol, 98 %), mp 134-136 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.28 (dd, 2H, *J* = 5.0, 1.9 Hz), 1.62 – 1.60 (m, 2H), 2.42 (s, 3H), 2.67 (t, 1H, *J* = 3.0 Hz), 3.14 (t, 1H, *J* = 6.9 Hz), 3.38 (s, 2H), 4.01 (d, 2H, *J* = 6.3 Hz), 7.32 (d, 2H, $^{3}J_{HH}$ = 8.1 Hz), 7.76 (d, 2H, $^{3}J_{HH}$ = 8.2 Hz). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 21.6, 35.0, 40.1, 54.0, 61.9, 128.1, 130.0, 135.2, 144.0. *m/z* (APCI): 268 (M+H). Anal. calcd. for $C_{13}H_{17}NO_3S$: C, 58.41; H, 6.41; N, 5.24; S, 11.99. Found: C, 58.25; H, 6.20; N, 5.45; S, 11.78.

1-(Difluoromethyl)-2-tosyl-2-azabicyclo[2.1.1]hexane (20)

To a stirred solution of oxalyl chloride (34.4 mL, 0.393 mol, 1.5 equiv) in dry CH_2Cl_2 (800 mL) was added DMSO (26 mL, 0.393 mol, 1.5 equiv) dropwise at -78 °C under argon atmosphere. The mixture was stirred 10 min at -78 °C, then a solution of compound **19** (70 g, 0.262 mol, 1 equiv) in CH_2Cl_2 (500 mL) was added dropwise. The resulting mixture was stirred for 30 min at -78 °C, and Et_3N (110 mL, 0.786 mol, 3 equiv) was added keeping the temperature below -60 °C. The mixture was allowed to warm to RT. The resulting solution was poured into water (700 mL), the organic layer was separated and washed with a solution of 0.5 M HCl (2 × 500 mL) and brine (500 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give crude aldehyde. The aldehyde was dissolved in dry CH_2Cl_2 (1000 mL) and morpholinosulfur trifluoride (137 g, 0.786 mol, 3 equiv) was added to the resulting solution over 20 min at temperature below 10 °C. The reaction was stirred overnight at RT, then poured onto ice and slowly neutralized with a 10% solution of K_2CO_3. The layers were separated, the organic layer was washed sequentially with a 0.5 M solution of HCl (2 × 500 mL) and brine (2 × 500 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (5% EtOAc in hexanes), affording **20** as a white solid. Yield (71.2 g, 0.25 mol, 98 %), mp 137-139 °C.

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.41 – 1.34 (m, 2H), 1.99 – 1.92 (m, 2H), 2.43 (s, 3H), 2.72 (t, 1H, *J* = 3.1 Hz), 3.45 (s, 2H), 6.53 (t, 1H, $^{2}J_{HF}$ = 55.1 Hz), 7.32 (d, 2H, $^{3}J_{HH}$ = 8.2 Hz), 7.76 (d, 2H, $^{3}J_{HH}$ = 8.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -122.3 (s).^{13}C NMR (101 MHz, $CDCl_3$) δ: 21.7, 34.1, 38.3 (t, $^{3}J_{CF}$= 3.5 Hz), 53.8, 74.8 (t, $^{2}J_{CF}$= 31.5 Hz), 111.7 (t, $^{1}J_{CF}$ = 237.6 Hz, *C*F_2), 128.3, 129.9, 135.4, 144.1. *m/z* (APCI): 288 (M+H). Anal. calcd. for $C_{13}H_{15}F_2NO_2S$: C, 54.34; H, 5.26; N, 4.87. Found: C, 54.14; H, 5.50; N, 4.99.

1-(Difluoromethyl)-2-azabicyclo[2.1.1]hexane hydrochloride (21)

Compound **20** (50 g, 6.96 mmol), solid sodium amalgam (2000 g) and CH_3OH (800 mL) were heated in 2 L round bottom flask at reflux for 12 h. The reaction mixture was allowed to cool to RT and decanted from the amalgam. pH of the mixture was adjusted to ~1 with 6 M HCl. The resulting mixture was concentrated under reduced pressure. The residue was dissolved in water (500 mL), and the resulting aqueous solution was extracted with EtOAc (5 × 400 mL). The aqueous layer was separated and basified to pH ~10 by a 10% solution of K_2CO_3. The resulting mixture was extracted with Et_2O (4 × 300 mL). The ethereal fractions were combined, dried over $MgSO_4$ and filtered. A solution of 2 M HCl in diethyl ether was added to the obtained organic solution, and then the precipitate was filtered, washed with diethyl ether and dried to give **21***HCl as a yellow crystalline solid. Yield (17 g, 58%), mp 181-182 ºC.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.66 (br s, 2H), 2.14 (br s, 2H), 2.89 (br s, 1H), 3.34 (br s, 2H), 6.55 (t, 1H, $^{2}J_{HF}$ = 54.1 Hz), 10.26 (br s, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ: -125.6 (s). ^{13}C NMR (101 MHz, DMSO-d_6) δ: 35.4, 36.4 (t, $^{3}J_{CF}$ = 2.8 Hz), 48.4, 69.8 (t, $^{2}J_{CF}$ = 27.7 Hz), 111.6 (t, $^{1}J_{CF}$ = 239.7 Hz). *m/z* (APCI): 134.2 (M+H). Anal. calcd. for $C_6H_{10}ClF_2N$: C, 42.49; H, 5.94; N, 8.26. Found: C, 42.61; H, 5.78; N, 8.11.

2-Benzyl-1-(trifluoromethyl)-2-azabicyclo[2.1.1]hexane (23)

Hydrogen fluoride (HF) and sulfur tetrafluoride SF_4 are toxic compounds! Special care must be taken when working with them.

The compound **22** (15.0 g, 0.069 mol, 1 equiv), anhydrous liquid HF (13.8 mL, 0.69 mol, 10 equiv) and SF_4 (0.207 mol, 3 equiv) were heated in a stainless steel autoclave at 70 °C for 12 h. After completion of the reaction, the gaseous products were vented off, the reaction mixture was poured onto ice and neutralized with a 10% aqueous solution of K_2CO_3. The product was extracted with MTBE (3 × 100 mL). Combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the pure **23** as a yellowish oil. Yield (14.6 g, 0.061 mol, 88%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.83 (dd, 2H, J = 4.5, 1.8 Hz), 1.99 (br s, 2H), 2.70 (br s, 3H), 3.81 (s, 2H), 7.27 (t, $^3J_{HH}$ = 7.2 Hz, 1H), 7.34 (t, 2H, $^3J_{HH}$ = 7.4 Hz), 7.43 (d, 2H, $^3J_{HH}$ = 7.3 Hz). ^{19}F NMR (376 MHz, $CDCl_3$) δ: -71.1 (s). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 36.2, 37.4 (d, J = 1.9 Hz), 56.9 (d, J = 1.3 Hz), 57.2, 70.7 (q, $^2J_{CF}$ = 32.5 Hz), 124.3 (q, $^1J_{CF}$ = 276.8 Hz), 127.1, 128.4, 128.9, 139.1. *m/z* (APCI): 242 (M+H). Anal. calcd. for $C_{13}H_{14}F_3N$: C, 64.72; H, 5.85; N, 5.81. Found: C, 64.47; H, 5.83; N, 5.84.

1-(Trifluoromethyl)-2-azabicyclo[2.1.1]hexane hydrochloride (24)

The compound **23** (14.0 g, 0.058 mol, 1 equiv) was dissolved in CH_3OH (500 mL) and 10% Pd/C (1.0 g) was added to the solution. The mixture was hydrogenated at RT under hydrogen pressure of 20 atm. for 10 h. The catalyst was filtered through a pad of Celite (ca. 1 cm), which was washed with CH_3OH (2 × 100 mL). A 2 M solution of HCl in CH_3OH (35 mL, 1.2 equiv) was added to the obtained solution, and the solvents were evaporated under reduced pressure to afford compound pure **24***HCl as a white powder. Yield (10.5 g, 0.056 mol, 96%), mp 176-177 ºC.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.89 – 1.77 (m, 2H), 2.33 (br s, 2H), 2.95 (br s, 1H), 3.43 (br s, 2H), 10.92 (br s, 2H). ^{19}F NMR (376 MHz, DMSO-d_6) δ: -71.3 (s). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 35.2, 37.1, 49.0, 67.9 (q, $^2J_{CF}$ = 37.0 Hz), 121.8 (q, $^1J_{CF}$ = 277.3 Hz). *m/z* (APCI): 152.2 (M+H). Anal. calcd. for $C_6H_9ClF_3N$: C, 38.42; H, 4.84; N, 7.47. Found: C, 38.12; H, 5.16; N, 7.31.

***tert*-Butyl 1-(1*H*-imidazol-2-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (26)**

Compound **25** (20.0 g, 0.1 mol, 1 equiv) was dissolved in a mixture of 50 mL of CH_3OH and 75 mL of 10 M NH_4OH (*Exothermic*!). The resulting mixture was stirred for 30 min; then an aqueous solution of 40% glyoxal (20.0 g, 0.13 mol, 1.3 equiv) was added, and the solution was stirred at RT overnight. The mixture was concentrated under reduced pressure; the residue was dissolved in water and extracted with CH_2Cl_2. The organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give a light brown solid. The crude product was washed with a mixture of MTBE with 5% of MeOH to afford the pure desired product. Yield (18.7 g, 0.075 mol, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.28 (s, 9H), 1.84 (d, J = 2.6 Hz, 2H), 2.26 (s, 2H), 2.75 (s, 1H), 3.50 (s, 2H), 6.95 (s, 2H), 10.62 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 28.4, 34.7, 44.7, 53.2, 68.8, 79.7, 121.8, 144.9, 157.2. *m/z* (APEI): 249 (M). Anal. calcd. $C_{13}H_{19}N_3O_2$: C, 62.63; H, 7.68; N, 16.85. Found: C, 62.44; H, 7.86; N, 16.67.

1-(1*H*-imidazol-2-yl)-2-azabicyclo[2.1.1]hexane dihydrochloride (27)

Compound **26** (15.7 g, 0.063 mol, 1 equiv) was dissolved in 100 mL of a solution of 5 M HCl in dioxane at RT. The mixture was stirred overnight. The resulting precipitate was filtered, dried to afford the desired product as a white solid. Yield (13.0 g, 0.059 mol, 93%), mp 208-210 ºC.

^{1}H NMR (400 MHz, D_2O) δ: 2.25 – 2.12 (m, 2H), 2.67 (br s, 2H), 3.20 (br s, 1H), 3.69 (br s, 2H) 3.74 (br s, 2H), 7.57 (s, 2H). ^{13}C NMR (126 MHz, D_2O) δ: 37.1, 40.8, 50.2, 63.3, 66.6, 120.9, 137.3. *m/z* (APCI): 150.2 (M+H). Anal. calcd. $C_8H_{13}Cl_2N_3$: C, 43.26; H, 5.90; N, 18.92. Found: C, 43.09; H, 6.12; N, 18.75.

2-Benzyl-2-azabicyclo[2.1.1]hexane-1-carbohydrazide (28)

To a solution of **22** (69.3 g, 0.3 mol, 1 equiv) in MeOH (500 mL) was added NH_2NH_2*H_2O (32.0 g, 0.6 mol, 2 equiv). The mixture was refluxed for 4 h, and then stirred for 16 h at RT. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1 L), washed with water, brine, dried over Na_2SO_4, and concentrated under reduced pressure. The highly pure product **27** obtained was analyzed without further purification. Yield (62.4 g, 0.27 mol, 90%), pale yellow oil.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.82 – 1.73 (m, 2H), 2.01 (br s, 2H), 2.68 (br s, 1H), 2.75 (s, 2H), 3.66 (s, 2H), 7.24 (t, 1H, ^3J = 6.5 Hz), 7.41 – 7.27 (m, 4H), 7.61 (br s, 1H). Anal. calcd. for $C_{13}H_{17}N_3O$: C, 67.51; H, 7.41; N, 18.17. Found: C, 67.41; H, 7.18; N, 18.43.

***N*'-(2-benzyl-2-azabicyclo[2.1.1]hexane-1-carbonyl)-*N,N*-dimethylacetohydrazonamide (29)**

To a solution of **28** (23.1 g, 0.1 mol, 1 equiv) in CH_3CN (150 mL) was added DMFDMA (52.4 g, 0.44 mol, 4.4 equiv). The mixture was refluxed for 6 h. The reaction mixture was allowed to cool to ambient temperature, and the resultant precipitate was filtered off, washed several times with Et_2O, and used for the next step without any purification.

2-(2-Benzyl-2-azabicyclo[2.1.1]hexan-1-yl)-5-methyl-1,3,4-oxadiazole (30)

To a stirred solution of **29** (18.0 g, 0.06 mmol, 1 equiv) in THF (200 mL) was added triethylamine (18.2 g, 0.18 mol, 3 equiv), and the reaction was stirred for 10 min at RT. *p*-Toluenesulfonyl chloride (17.2 g, 0.09 mol, 1.5 equiv) was added, and the stirring was continued for 15 h. The mixture was concentrated, diluted with CH_2Cl_2, washed with water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash chromatography to give the final product as a yellow viscous oil. Yield (10.7 g, 0.042 mol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.14 – 1.99 (m, 4H), 2.33 (s, 3H), 2.79 (br s, 1H), 2.87 (s, 2H), 3.65 (br s, 2H), 7.19 – 7.12 (m, 1H), 7.22 (t, *J* = 7.3 Hz, 2H), 7.27 (d, *J* = 7.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 10.9, 38.2, 40.8, 57.4, 57.8, 66.4, 126.9, 128.2, 128.8, 139.2, 164.1, 164.7. *m/z* (APEI): 255 (M). Anal. calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.80; H, 6.98; N, 16.21.

2-(2-Azabicyclo[2.1.1]hexan-1-yl)-5-methyl-1,3,4-oxadiazole (31)

Compound **30** (10.0 g, 0.04 mol, 1 equiv) was dissolved in 100 mL of MeOH and 1 g of 10%-Pd/C was added to the mixture. The mixture was hydrogenated at 10 atm at RT overnight. Then Pd/C was filtered out, and the reaction mixture was concentrated under reduced pressure to afford the desired compound as a pink oil. Yield (6.1 g, 0.024 mol, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.71 – 1.55 (m, 2H), 2.14 (br s, 2H), 2.18 (br s, 1H), 2.45 (s, 3H), 2.86 (br s, 1H), 3.08 (br s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 10.9, 38.5, 43.8, 48.5, 62.4, 163.8, 165.3. *m/z* (APCI): 166.2 (M+H). Anal. calcd. for $C_8H_{11}N_3O$: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.44; H, 6.84; N, 25.61.

5-(2-Benzyl-2-azabicyclo[2.1.1]hexan-1-yl)-3-methyl-1,2,4-oxadiazole (33)

Compound **32** (69.3 g, 0.3 mol, 1 equiv) was dissolved in 800 mL of THF and sodium methoxide (48.6 g, 0.9 mol, 3 equiv) was added. The resulting mixture was stirred for 30 min; then *N*-hydroxyacetimidamide (24.4 g, 0.33 mol, 1.1 equiv) was added, and the reaction was heated to 40 °C and stirred for 12 h. The mixture was cooled to RT and filtered; the filtrate was dissolved in water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure to give a brown solid. The crude product was washed with a mixture of MTBE with 5% of MeOH to afford the pure final product. Yield (23.2 g, 0.091 mol, 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.09 – 2.05 (m, 2H), 2.13 (s, 2H), 2.34 (s, 3H), 2.79 (s, 1H), 2.80 (s, 2H), 3.68 (s, 2H), 7.18 (t, *J* = 7.0 Hz, 1H), 7.27 (t, *J* = 7.2 Hz, 2H), 7.35 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 11.6, 38.1, 41.2, 56.8, 57.4, 67.1, 126.9, 128.2, 128.6, 139.0, 167.1, 176.8. *m/z* (APEI): 255 (M). Anal. calcd. for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.88; H, 6.95; N, 16.29.

5-(2-Azabicyclo[2.1.1]hexan-1-yl)-3-methyl-1,2,4-oxadiazole hydrochloride (34)

Compound **33** (20.8 g, 0.078 mol) was dissolved in 200 mL of MeOH and 2 g of 10%-Pd/C was added to the mixture. The mixture was hydrogenated at 10 atm at RT overnight. Then Pd/C was filtered out, and the reaction mixture was concentrated under reduced pressure to afford the desired compound as a white powder, mp 222-223 ºC. Yield (14.0 g, 0.07 mol, 89%).

^{1}H NMR (400 MHz, D_2O) δ: 2.15 – 1.99 (m, 2H), 2.46 (s, 3H), 2.72 (br s, 2H), 3.18 (br s, 1H), 3.68 (br s, 2H). ^{13}C NMR (126 MHz, D_2O) δ: 10.5, 37.1, 41.7, 49.8, 64.8, 168.1, 171.6. *m/z* (APEI): 165 (M). Anal. calcd. for $C_8H_{12}ClN_3O$: C, 47.65; H, 6.00; N, 20.84. Found: C, 47.49; H, 5.81; N, 20.99.

2-Chloro-3-(1-(hydroxymethyl)-2-azabicyclo[2.1.1]hexan-2-yl)propanenitrile (35)

To a solution of **18** (33.9 g, 0.3 mol, 1 equiv) in toluene (300 mL) was added 2-chloroacrylonitrile (29.0 g, 0.32 mol, 1.05 equiv) at RT. The reaction mixture was diluted with water, the organic layer was separated, and aqueous layer was additionally washed with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the desired product as a yellow oil. The compound is relatively unstable and should be immediately used for the next step. Yield (57.7 g, 0.29 mol, 96%).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.55 – 1.46 (m, 2H), 1.65 – 1.59 (m, 2H), 2.75 (s, 1H), 3.00 (s, 2H), 3.10 (dd, *J* = 13.1, 5.9 Hz, 1H), 3.19 (dd, *J* = 13.1, 8.4 Hz, 1H), 3.82 (d, *J* = 2.8 Hz, 2H), 4.49 (dd, *J* = 8.2, 6.0 Hz, 1H). *m/z* (APEI): 200 (M).

Tetrahydro-1*H*,6*H*-7,8a-methanopyrrolo[2,1-c][1,4]oxazine-3-carbonitrile (36)

To a solution of **35** (40.1 g, 0.2 mol, 1 equiv) in toluene (300 mL) was added potassium *tert*-butoxide (23.5 g, 0.21 mol, 1.05 equiv) at -30 °C. The reaction mixture was warmed to RT, and diluted with water, the organic layer was separated, and aqueous layer was additionally washed with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the desired product as a yellow solid. Yield (17.7 g, 0.1 mol, 54%), mp 43-44 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.54 (m, 4H), 2.61 – 2.26 (m, 1H), 2.70 (s, 1H), 2.93 (br s, 2H), 3.79 (d, *J* = 11.5 Hz, 1H), 4.01 (d, *J* = 12.0 Hz, 1H), 4.58 (br s, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ: 37.6, 53.2, 56.5, 64.7, 66.4, 68.1 (br s), 117.0. *m/z* (APEI): 164 (M). Anal. calcd. for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.61; H, 7.16; N, 17.31.

Tetrahydro-1*H*,6*H*-7,8a-methanopyrrolo[2,1-c][1,4]oxazine-3-carboxylic acid hydrochloride (37)

To a solution of **36** (32.8 g, 0.2 mol, 1 equiv) in MeOH (300 mL) was added H_2SO_4 (21.3 mL, 0.4 mol, 2 equiv). The mixture was brought to reflux for 2 d. The cold mixture was treated with a solution of $NaHCO_3$ to neutralize the solution, and then concentrated under reduced pressure. The residue was dissolved in water and extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give the desired product as a yellow oil. The crude product was treated with concd. HCl and brought to reflux for 2 h. The precipitate was filtered, washed with Et_2O, and dried to give the desired product as a beige solid (39.5 g, 90%), mp 206-208 °C.

^{1}H NMR (400 MHz, D_2O) δ: 1.62 (t, *J* = 9.9 Hz, 1H), 2.03 (t, *J* = 10.1 Hz, 1H), 2.12 (br s, 1H), 2.27 (d, *J* = 8.9 Hz, 1H), 3.03 (s, 1H), 3.27 (d, *J* = 9.8 Hz, 1H), 3.38 (t, *J* = 12.2 Hz, 1H), 3.82 (t, *J* = 9.0 Hz, 1H), 4.04 (dd, *J* = 13.0, 5.0 Hz, 2H), 4.37 (d, *J* = 13.5 Hz, 1H), 4.50 (d, *J* = 11.0 Hz, 1H). ^{13}C NMR (126 MHz, D_2O) δ: 35.7, 36.2, 37.7, 49.4, 57.8, 65.7, 71.2, 72.1, 169.8. *m/z* (APCI): 184.2 (M+H). Anal. calcd. for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.25; H, 7.32; N, 7.47.

(Tetrahydro-1*H*,6*H*-7,8a-methanopyrrolo[2,1-c][1,4]oxazin-3-yl)methanol (38)

$LiAlH_4$ (1.2 g, 0.03 mol, 0.65 equiv) was dissolved in dry THF and cooled to 0 °C. Compound **37**-CO_2Me (9.5 g, 0.048 mol, 1 equiv) was added in small portions. The mixture was stirred overnight at RT. The excess of $LiAlH_4$ was quenched with a 40% NaOH solution. Inorganic precipitates were filtered off, and the solution was concentrated under reduced pressure to afford the final compound as a white solid (6.9 g, 0.04 mol, 85%), mp 98-99 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.47 – 1.32 (m, 2H), 1.77 – 1.58 (m, 2H), 2.33 (d, *J* = 7.8 Hz, 1H), 2.43 (t, *J* = 10.4 Hz, 1H), 2.71 (s, 1H), 2.90 (d, *J* = 10.2 Hz, 1H), 3.18 (d, *J* = 7.3 Hz, 1H), 3.69 – 3.52 (m, 2H), 3.75 – 3.73 (m, 1H), 3.74 (d, *J* = 11.8 Hz, 1H), 3.97 (d, *J* = 11.8 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 35.0, 37.6, 40.5, 52.8, 57.1, 64.1, 67.2, 69.3. *m/z* (APEI): 169 (M). Anal. calcd. for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 64.08; H, 8.70; N, 8.54.

{3-Oxa-6-azatricyclo[6.1.1.0,1,6]decan-4-yl}methanamine (39)

Compound **36** (14.7 g, 0.09 mol) was dissolved in 200 mL of CH_3OH followed by the addition of Raney nickel (3 g), filled with hydrogen two times and the resulting solution was stirred for 12 h, filtered. The filtrate was concentrated under reduced pressure to obtain as a colorless oil. Yield (11.3 g, 0.067 mol, 75%).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.55 – 0.96 (m, 6H), 2.08-1.96 (m, 2H), 2.48 – 2.20 (m, 3H), 2.71 (d, 1H, *J* = 10.6 Hz), 2.87 (d, 1H, *J* = 7.8 Hz), 3.29 – 3.13 (m, 1H), 3.35 (d, 1H, *J* = 11.4 Hz), 3.70 (d, 1H, *J* = 11.4 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 34.3, 37.0, 44.6, 54.0, 56.2, 66.7, 68.4, 78.3. *m/z* (APEI): 168.1 (M). Anal. calcd. for $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.03; H, 9.57; N, 16.67.

***tert*-Butyl 1-(((2-methoxy-2-oxoethyl)amino)methyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (40)**

The compound **25** (20.0 g, 0.1 mol, 1 equiv) was dissolved in CH_2Cl_2, and glycine methyl ester hydrochloride (18.8 g, 0.15 mol, 1.5 equiv) was added. The mixture was stirred for 30 min at RT, and sodium triacetoxyborohydride (42.4 g, 0.2 mol, 2 equiv) was added. The resulting mixture was stirred overnight. The precipitate was filtered out, and the filtrate was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by column chromatography (gradient, hexanes/EtOAc) to give a yellow oil. Yield (14.2 g, 0.05 mol, 50%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.40 (s, 9H), 1.54 – 1.44 (m, 2H), 1.77 (s, 2H), 2.21 (br s, 1H), 2.66 (s, 1H), 3.14 (s, 2H), 3.32 (s, 2H), 3.41 (s, 2H), 3.66 (s, 3H).

Tetrahydro-6*H*-7,8a-methanopyrrolo[1,2-a]pyrazin-4(1*H*)-one (41)

Compound **40** (10.0 g, 0.035 mol) was dissolved in 50 mL of CH_2Cl_2 and 10 mL of TFA. The resulting mixture was stirred for 2 h at RT, and then concentrated under reduced pressure. The residue was dissolved in 100 mL of CH_3OH and 50 mL of aq. NH_4OH. The mixture was concentrated under reduced pressure. The desired product was separated by extraction with CH_2Cl_2. Yield (1.0 g, 0.007 mol, 20%), yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.58 – 1.49 (m, 2H), 1.84 (br s, 2H), 2.85 (br s, 1H), 3.14 (br s, 2H), 3.38 (br s, 2H), 3.45 (br s, 2H), 5.44 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 34.3, 42.6, 46.7, 48.4, 49.9, 70.0, 168.1. *m/z* (APCI): 153.2 (M+H). Anal. calcd. for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41. Found: C, 62.87; H, 7.93; N, 18.45.

(2-Benzyl-2-azabicyclo[2.1.1]hexan-1-yl)methanamine (42)

A mixture of compound **15** (107.3 g, 0.30 mol, 1 equiv) and NaN_3 (29.3 g, 0.45 mol, 1.5 equiv) in DMF (1.5 L) was heated, and stirred at 40 °C for 10 h until TLC-analysis indicated the reaction to be complete. The reaction mixture was cooled to RT and poured into cold water (2 L). The mixture was extracted with EtOAc (3 × 700 mL). The organic extract was back-washed with water (3 × 500 mL), brine, dried over Na_2SO_4, and the solvent was partially evaporated under reduced pressure to give a solution of the desired compound. The solution of the azide approximately (68.4 g, 0.3 mol, 1 equiv) in EtOAc (1.5 L) was poured into a round bottomed flask equipped with magnetic stirring, mixed with PPh_3 (86.5 g, 0.33 mol, 1.1 equiv), and left for 14 h at RT. The reaction was monitored by TLC. Upon completion of the reaction, the reaction mixture was acidified with a 5 M HCl solution. The layers were separated, and the aqueous layer was additionally washed with EtOAc, then basified with K_2CO_3, extracted with CH_2Cl_2 several times. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The resulting oil was solidified in hexanes to give a yellow solid of the desired product. Yield (54.5 g, 0.27 mol, 90%).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.34 (br s, 2H), 1.49 (br s, 2H), 2.43 (br s, 1H), 2.46 (br s, 2H), 2.68 (s, 2H), 3.51 (s, 2H), 7.15 (t, 1H, $^3J_{HH}$ = 6.8 Hz), 7.23 (t, 2H, $^3J_{HH}$ = 6.8 Hz), 7.32 (d, 2H, $^3J_{HH}$ = 6.9 Hz). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 35.7, 36.9, 41.8, 55.0, 57.5, 74.8, 126.3, 128.0, 128.3, 140.5. *m/z* (APCI): 203.1 (M+H). Anal. calcd. for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.39; H, 9.09; N, 13.71.

***tert*-Butyl 1-(aminomethyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (44)**

Compound **42** (47.9 g, 0.258 mol, 1 equiv) was dissolved in a mixture of CH_2Cl_2 (1.5 L) and Et_3N (141.4 g, 1.4 mol, 5 equiv). The mixture was cooled to 0 °C, and TFAA (59.6 g, 0.28 mol, 1.1 equiv) was added. The ice-bath was removed after the addition was complete, and the reaction stirred for 16 h at RT. The mixture was poured into cold water and layers were separated. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford crude compound **43** as a yellow oil. The compound **43** (77.1 g, 0.259 mol, 1 equiv) was stirred in dry CH_3OH (1.5 L) with 10% Pd/C (8 g) and Boc_2O (39.5 g, 0.181 mol, 0.7 equiv) under 10 atm of H_2 at RT overnight. Then Pd/C was filtered out, and the reaction mixture was concentrated under reduced pressure. The residue was dissolved in water and extracted with CH_2Cl_2 several times. The combined layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH and K_2CO_3 (107.2 g, 0.78 mol, 3 equiv) was added at 0 °C. The mixture was sitter at RT for 4 h, then filtered and concentrated under reduced pressure. Finally, the product was purified by distillation to give a colorless oil. Yield (38.4 g, 0.18 mol, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.44 (s, 9H). 1.50 (d, 2H, *J* = 4.4 Hz), 1.68 (br s, 2H), 1.78 (br s, 2H), 2.69 (br s, 1H), 3.19 (br s, 2H), 3.34 (br s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 28.7, 33.8, 41.9, 43.6, 52.6, 75.3, 79.3, 155.2. *m/z* (APEI): 212.2 (M). Anal. calcd. for $C_{11}H_{20}N_2O_2$: C, 62.24; H, 9.50; N, 13.20. Found: C, 62.40; H, 9.77; N, 13.04.

***tert*-Butyl ((2-benzyl-2-azabicyclo[2.1.1]hexan-1-yl)methyl)carbamate (45)**

To a stirred solution of **42** (54.0 g, 0.267 mol, 1 equiv) in CH_2Cl_2 (1.5 L) at 0 °C were added Boc_2O (61.2 g, 0.28 mol, 1.05 equiv), DMAP (3.3 g, 0.1 equiv), and Et_3N (28.3 g, 0.28 mol, 1.05 equiv). After stirring at RT overnight, the mixture was diluted with EtOAc and poured into a saturated aqueous solution of NH_4Cl (30 mL). The aqueous layer was separated and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow oil. Yield (76.6 g, 0.25 mol, 95%). The crude product was sufficiently pure to be used for the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.86 – 0.71 (m, 2H), 1.18 (br s, 2H), 1.35 (s, 9H), 2.61 – 2.57 (m, 3H), 3.33 (br s, 2H), 3.54 (d, 2H, *J* = 3.8 Hz), 4.75 (br s, 1H), 7.16 (t, 1H, *J* = 6.6 Hz), 7.24 (t, 2H, *J* = 5.7 Hz), 7.31 (d, 2H, *J* = 5.8 Hz). Anal. calcd. for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.31; H, 8.89; N, 9.14.

***tert*-Butyl ((2-azabicyclo[2.1.1]hexan-1-yl)methyl)carbamate (46)**

Compound **45** (76.0 g, 0.25 mol) was dissolved in 500 mL of MeOH, and 7 g of 10%-Pd/C was added to the mixture. The mixture was hydrogenated at 10 atm at RT overnight. Then Pd/C was filtered out, and the reaction mixture was concentrated under reduced pressure to afford the final compound as a white powder. Yield (48.7 g, 0.23 mol, 92%), mp 65-67 ºC.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.06 (br s, 2H, CH_2). 1.37 (s, 9H), 1.49 (br s, 2H), 1.43 (br s, 1H), 2.59 (br s, 1H), 2.77 (br s, 2H), 3.13 (d, 2H, *J* = 5.3 Hz), 6.75 (br s, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 28.2, 36.4, 40.2, 42.3, 48.3, 69.5, 77.6, 155.7. Anal. calcd. for $C_{11}H_{20}N_2O_2$: C, 62.24; H, 9.50; N, 13.20. Found: C, 62.45; H, 9.74; N, 13.04.

***tert*-Butyl-1-(3-ethoxy-3-oxoprop-1-en-1-yl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (47)**

To a suspension of NaH (5.50 g, 0.125 mol, 1.2 equiv) in 150 mL of dry THF was added dropwise ethyl 2-(diethyl phosphono)acetate (27.0 g, 0.12 mol, 1.2 equiv) with rapid stirring under atmosphere of argon at RT. At the end of the addition, the mixture was stirred for 1 h at RT. The aldehyde **25** (20.0 g, 0.10 mol, 1 equiv) was dissolved in 50 mL of THF and added dropwise to the reaction. The reaction mixture was stirred at RT until TLC-analysis showed complete consumption of starting material (~ 1 h). The reaction was quenched with water, diluted with EtOAc, and washed with brine. The organic layer was separated and washed with 1 M HCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford the desired compound as a yellow oil. Yield (24 g, 0.09 mol, 90%). The crude compound was sufficiently pure to be used directly in the next step. All analytical data are consistent with the literature.[21]

***tert*-Butyl 1-(3-ethoxy-3-oxopropyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (48)**

Compound **47** (23.0 g, 0.086 mol, 1 equiv) was dissolved in 150 mL of MeOH and 4 g of 10%-Pd/C was added to the mixture. The mixture was hydrogenated at RT overnight. Then Pd/C was filtered out, and the reaction mixture was concentrated under reduced pressure to afford the final compound as a yellow oil. Yield (22.4 g, 0.083 mol, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.23 (t, *J* = 7.0 Hz, 3H), 1.44 (s, 11H), 1.68 (br s, 2H), 2.42 (br s, 4H), 2.67 (s, 1H), 3.35 (s, 2H), 4.10 (q, 6.7 Hz, 2H). Anal. calcd. for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.82; H, 8.69; N, 5.12.

3-(2-(*tert*-Butoxycarbonyl)-2-azabicyclo[2.1.1]hexan-1-yl)propanoic acid (49)

The crude compound **48** (20.0 g, 0.078 mol, 1 equiv) was dissolved in EtOH, and a 20% solution of NaOH (6.3 g, 0.157 mol, 2 equiv) was added at RT. The resulting mixture was stirred overnight, and then concentrated to dryness under reduced pressure. The residue was dissolved in cold water, acidified with 0.1 M HCl, diluted with $CHCl_3$ and partitioned. The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was solidified in pentane, filtered, dried to afford the final product as a white powder. Yield (18.9 g, 0.074 mol, 95%), mp 77-78 ºC.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.46 (s, 9H), 1.51-1.43 (m, 2H), 1.71 (br s, 2H), 2.53 – 2.40 (m, 4H), 2.71 (br s, 1H), 3.37 (br s, 2H), 10.98 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 27.3, 28.7, 30.8, 33.9, 43.2, 52.9, 73.3, 79.7, 155.9, 178.8. *m/z* (APCI): 256.0 (M+H). Anal. calcd. for $C_{13}H_{21}NO_4$: C, 61.16; H, 8.29; N, 5.49. Found: C, 61.29; H, 8.52; N, 5.32.

3-(2-Azabicyclo[2.1.1]hexan-1-yl)propanoic acid hydrochloride (50)

Compound **49** (18.5 g, 0.073 mol, 1 equiv) was dissolved in 50 mL of MeOH, and a solution of 5 M HCl in MeOH (150 mL) was added at RT. The mixture was stirred overnight, and then concentrated to dryness under reduced pressure. The crude product was washed with Et_2O, and dried to afford the desired product as a white solid. Yield (13.3 g, 0.07 mol, 96%), mp 189-190 ºC.

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.50 – 1.42 (m, 2H), 1.86 (br s, 2H), 2.07 (t, 2H, $^3J_{HH}$ = 7.7 Hz), 2.41 (t, 2H, $^3J_{HH}$ = 7.7 Hz), 2.73 (br s, 1H), 3.18 (br s, 2H), 9.43 (br s, 2H), 12.28 (br s, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 24.7, 29.5, 35.1, 38.6, 47.9, 72.9, 173.6. *m/z* (APCI): 156.2 (M+H). Anal. calcd. for $C_8H_{14}ClNO_2$: C, 50.14; H, 7.36; N, 7.31. Found: C, 50.31; H, 7.52; N, 7.05.

***tert*-Butyl 1-ethynyl-2-azabicyclo[2.1.1]hexane-2-carboxylate (51)**

To a solution of **25** (11.2 g, 0.053 mol, 1.0 equiv) and dimethyl-1-diazo-2-oxopropylphosphonate (15.3 g, 0.079 mol, 1.5 equiv) in MeOH (200 mL) was added K_2CO_3 (14.6 g, 0.106 mol, 2.0 equiv) in portions at 0 °C. After stirring for 1 h at 0 °C, then for 2 h at RT, the mixture was diluted with EtOAc, quenched with a saturated NH_4Cl solution. The aqueous layer was then extracted with EtOAc. The combined

organic layers were washed with brine, dried over Na_2SO_4, and concentrated in *vacuo*. Purification on silica gel column chromatography (hexane/EtOAc) afforded **51** as a colorless oil (10.1 g, 0.049 mol, 92%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.49 (s, 9H), 1.76 (br s, 2H), 2.11 (br s, 2H), 2.63 (br s, 1H), 2.68 (br s, 1H), 3.38 (br s, 2H). *m/z* (APEI): 207 (M). Anal. calcd. for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.82; H, 8.50; N, 6.49.

1-Ethynyl-2-azabicyclo[2.1.1]hexane hydrochloride (52)

The compound **51** (6.8 g, 0.033 mol) was dissolved in 100 mL of MeOH-HCl at RT. The mixture was stirred at RT overnight. The resulting precipitate was filtered, dried to afford the final compound as a beige powder, mp 194-195 ºC. Yield (4.4 g, 0.03 mol, 94%).

^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.93 – 1.66 (m, 2H), 2.21 (s, 2H), 2.75 (s, 1H), 3.22 (s, 3H), 4.03 (s, 1H), 10.14 (br s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ: 36.3, 42.3, 47.2, 59.0, 76.4, 80.6. *m/z* (APCI): 109.2 (M+H). Anal. calcd. for $C_7H_{10}ClN$: C, 58.54; H, 7.02; N, 9.75. Found: C, 58.78; H, 7.22; N, 9.51.

***tert*-Butyl 1-(hydroxy(phenyl)methyl)-2-azabicyclo[2.1.1]hexane-2-carboxylate (53)**

PhMgBr (1 M in THF, 95 mL, 0.095 mol, 1 equiv) was added to a solution of **25** (20.0 g, 0.095 mol, 1 equiv) in THF (200 mL). The resulting mixture was stirred at RT and the reaction was monitored by TLC. After complete conversion, saturated NH_4Cl solution (100 mL) was poured into the mixture. The mixture was extracted with EtOAc, and the organic layer was separated, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. Yield (17.9 g, 0.086 mol, 91%).

^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.34 – 1.16 (m, 1H), 1.54 – 1.40 (m, 2H), 1.49 (s, 9H), 1.70 – 1.58 (m, 1H), 2.56 (s, 1H), 3.37 (q, J = 8.7 Hz, 2H), 5.27 (s, 1H), 7.40 – 7.18 (m, 5H). *m/z* (APCI): 290.2 (M+H). Anal. calcd. for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.38; H, 8.32; N, 4.71.

(2-Azabicyclo[2.1.1]hexan-1-yl)(phenyl)methanol hydrochloride (54)

The compound **53** (7.8 g, 0.027 mol) was dissolved in 100 mL of a 4 M solution of dioxane-HCl at RT. The mixture was stirred at RT overnight. The resulting precipitate was filtered, dried to afford the final compound as a white powder, mp 224-225 ºC. Yield (5.4 g, 0.024 mol, 89%).

^{1}H NMR (500 MHz, D_2O) δ: 1.51 (t, J = 9.8 Hz, 1H), 1.64 (t, J = 9.8 Hz, 1H), 2.02 (d, J = 8.4 Hz, 1H), 2.13 (d, J = 8.3 Hz, 1H), 2.93 (s, 1H), 3.38 (q, J = 9.6 Hz, 2H), 5.19 (s, 1H), 7.70 – 7.30 (m, 5H). ^{13}C NMR (126 MHz, D_2O) δ: 34.9, 36.4, 37.2, 49.0, 70.1, 76.7, 125.8, 128.3, 128.5, 137.6. *m/z* (APCI): 190.2 (M+H). Anal. calcd. for $C_{12}H_{16}ClNO$: C, 63.86; H, 7.15; N, 6.21. Found: C, 63.99; H, 7.36; N, 6.01.

"ADME parameters of the compounds (aqueous solubility, logD, hepatic microsomal stability) were determined at Bienta (Enamine Biology Services) bioanalytical lab accordingly to the experimental protocols published elsewhere.[43]

ASSOCIATED CONTENT

Supporting Information

Experimental copies of NMR spectra and X-ray crystallography data. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

* E-mail: Pavel.Mykhailiuk@gmail.com

Homepage: www.mykhailiukchem.org

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

Authors are very grateful to Dr. E. Rusanov for X-Ray analysis of compounds **17***HCl, **21***HCl, **24***HCl, **50***HCl, **52***HCl.

REFERENCES

[1] (a) Lovering, F.; Bikker, J.; Humblet, C. Escape from flatland: increasing saturation as an approach to improving clinical success. *J. Med. Chem.* **2009**, *52*, 6752-6756. (b) Lovering, F. Escape from flatland 2: complexity and promiscuity. *Med. Chem. Comm.* **2013**, *4*, 515-519.

[2] Mann A. Conformational restriction and/or steric hindrance in medicinal chemistry. In *The Practice of Medicinal Chemistry*, 3rd ed.; Wermuth, C., Ed.; Academic Press/Elsevier: Amsterdam, **2008**; 363.

[3] (a) Goldberg F.W.; Kettle, J. G.; Kogej T.; Perry, M. W.; Tomkinson, N. P. Designing novel building blocks is an overlooked strategy to improve compound quality. *Drug Discov. Today* **2015**, *20*, 11-17. (b) Marson, C. M. New and unusual scaffolds in medicinal chemistry. *Chem. Soc. Rev.* **2011**, *40*, 5514-5533.

[4] (a) Ritchie, T. J.; Macdonald, S. J. F. The impact of aromatic ring count on compound developability – are too many aromatic rings a liability in drug design? *Drug Discov. Today* **2009**, *14*, 1011-1020. (b) Ritchie, T. J.; Macdonald, S. J. F.; Young, R. J.; Pickett, S. D. The impact of aromatic ring count on compound developability: further insights by examining carbo- and hetero-aromatic and -aliphatic ring types. *Drug Discov. Today* **2011**, *16*, 164-171.

[5] Our contribution to this area: (a) Kirichok, A. A.; Shton, I.; Kliachyna, M.; Pishel, I.; Mykhailiuk, P. K. 1-Substituted 2-azaspiro[3.3]heptanes: overlooked motifs for drug discovery. *Angew. Chem. Int. Ed.* **2017**, *56*, 8865-8869. (b) Denisenko, A. V.; Druzhenko, T.; Skalenko, Y.; Samoilenko, M.; Grygorenko, O. O.; Zozulya, S.; Mykhailiuk, P. K. Photochemical synthesis of 3-azabicyclo[3.2.0]heptanes: advanced building blocks for drug discovery. *J. Org. Chem.* **2017**, *82*, 9627-9636. (c) Druzhenko, T.; Skalenko, Y.; Samoilenko, M.; Denisenko, A.; Zozulya, S.; Borysko, P. O.; Sokolenko, M. I.; Tarasov, A.; Mykhailiuk, P. K. Photochemical synthesis of 2-azabicyclo[3.2.0]heptanes: advanced building blocks for drug discovery. Synthesis of 2,3-ethanoproline. *J. Org. Chem.* **2018**, *83*, 1394-1401.

[6] (a) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. Experimental and computational cpproaches to estimate solubility and permeability in drug discovery and development settings. *Adv. Drug Deliv. Rev.* **1997**, *23*, 3–25. (b) Nadin, A.; Hattotuwagama, C.; Churcher, I. Lead-oriented synthesis: a new opportunity for synthetic chemistry. *Angew. Chem. Int. Ed.* **2012**, *51*, 1114-1122. (c) Leeson, P. D.; Empfield, J. R. Chapter 24 - reducing the risk of drug attrition associated with physicochemical properties. *Annu. Rep. Med. Chem.* **2010**, *45*, 393-407.

[7] Ishikawa, M.; Hashimoto, Y. Improvement in aqueous solubility in small molecule drug discovery programs by disruption of molecular planarity and symmetry. *J. Med. Chem.* **2011**, *54*, 1539-1554.

[8] Some recent examples: (a) Stepan, A. F.; Subramanyam, C.; Efremov, I. V.; Dutra, J. K.; O'Sullivan, T. J.; DiRico, K. J.; McDonald, W. S.; Won, A.; Dorff, P. H.; Nolan, C. E.; Becker, S. L.; Pustilnik, L. R.; Riddell, D. R.; Kauffman, G. W.; Kormos, B. L.; Zhang, L.; Lu, Y.; Capetta, S. H.; Green, M. E.; Karki, K.; Sibley, E.; Atchison, K. P.; Hallgren, A. J.; Oborski, C. E.; Robshaw, A. E.; Sneed, B.; O'Donnell, C. J. Application of the bicyclo[1.1.1]pentane motif as a nonclassical phenyl ring bioisostere in the design of a potent and orally active γ-secretase inhibitor. *J. Med. Chem.* **2012**, *55*, 3414-3424 (bicyclo[1.1.1]pentanes); (b) Burkhard, J. A.; Wagner, B.; Fischer, H.; Schuler, F.; Müller, K.; Carreira, E. M. Synthesis of azaspirocycles and their evaluation in drug discovery. *Angew. Chem. Int. Ed.* **2010**, *49*, 3524-3527 (spirocycles).

[9] (a) Meanwell, N. A. Synopsis of some recent tactical application of bioisosteres in drug design. *J. Med. Chem.* **2011**, *54*, 2529-2591; (b) Meanwell, N. A. Improving drug design: an update on recent applications of efficiency metrics, strategies for replacing problematic elements, and compounds in nontraditional drug space. *Chem. Res. Toxicol.* **2016**, *29*, 564-616.

[10] Roughley, S. D.; Jordan, A. M. The medicinal chemist's toolbox: an analysis of reactions used in the pursuit of drug candidates. *J. Med. Chem.* **2011**, *54*, 3451-3479.

[11] The search was performed in August 2018 at www.drugbank.ca

[12] Bell, E. A.; Qureshi, M. Y.; Pryce, R. J.; Janzen, D. H.; Lemke, P.; Clardy, J. 2,4-Methanoproline (2-carboxy-2,4-methanopyrrolidine) and 2,4-methanoglutamic acid (1-amino-1,3-dicarboxycyclobutane) in seeds of Ateleia herbert smithii Pittier (Leguminosae). *J. Am. Chem. Soc.* **1980**, *102*, 1409-1412.

[13] Recently, **1** was also found in the legume *Bocoa alterna*: Kite, G. C.; Ireland, H. Non-protein amino acids of Bocoa (Leguminosae; Papilionoideae). *Phytochemistry* **2002**, *59*, 163-168.

[14] (a) Montelione, G. T.; Hughes, P.; Scheraga, H. A. Conformational properties of 2,4-methanoproline (2-carboxy-2,4-methanopyrrolidine) in peptides: determination of preferred peptide bond conformation in aqueous solution by proton Overhauser measurements . *J. Am. Chem. Soc.* **1986**, *108*, 6765-6773. (b) Talluri, S.; Montelione, G. T.; van Duyne, G.; Piela, L.; Chardy, J.; Scheraga, H. A. Conformational properties of 2,4-methanoproline (2-carboxy-2,4-methanopyrrolidine) in peptides: evidence for 2,4-methanopyrrolidine asymmetry based on solid-state x-ray crystallography, proton NMR in aqueous solution, and CNDO/2 conformational energy calculations. *J. Am. Chem. Soc.* **1987**, *109*, 4473-4477. (c) Piela, L.; Nemethy, G.; Scheraga, H. A. Conformational properties of 2,4-methanoproline (2-carboxy-2,4-methanopyrrolidine) in peptides: theoretical conformational energy analysis of restrictions of the polypeptide chain conformation. *J. Am. Chem. Soc.* **1987**, *109*, 4477-4485.

[15] (a) Salahuddin, A. Proline peptide isomerization and protein folding. *J. Biosci.* **1984**, *6*, 349-355. (b) Mapelli, C.; Van Halbeek, H.; Stammer, C. H. Synthesis and conformational studies by ^{1}H and ^{13}C nmr spectroscopy of a novel, sterically constrained analogue of thyrotropin-releasing hormone. *Biopolymers* **1990**, *29*, 407-422. (c) Juvvadi, P.; Dooley, D. J.; Humblet, C. C.; Lu, G. H.; Lunney, E. A.; Panek, R. L.; Skeean, R.; Marshall, G. R. Bradykinin and angiotensin II analogs containing a conformationally constrained proline analog. *Int. J. Pept. Protein Res* **1992**, *40*, 163-170.

[16] Liao, H.; Li, A.; Chen, X.; Liang, K.; Shen, Y.; Liang, Q.; Xu, K.; Shore, D. G. M.; Villemure, E.; Siu, M.; Huestis, M. P. Preparation of 2-azabicyclo[2.1.1]hexane hydrochloride. *Synlett* **2016**, *27*, 2251-2253.

[17] The search was performed in August 2018 at www.ebi.ac.uk/chembl

[18] Pirrung, M. C. Total synthesis of 2,4-methanoproline. *Tetrahedron Lett.* **1980**, *21*, 4577-4578.

[19] (a) Hughes, P.; Martin, M.; Clardy, J. Synthesis of 2,4-methanoproline. *Tetrahedron Lett.* **1980**, *21*, 4579-4580. (b) Hughes, P.; Clardy, J. Total synthesis of cyclobutane amino acids from Atelia herbert smithii. *J. Org. Chem.* **1988**, *53*, 4793-4796.

[20] (a) Petz, S.; Wanner, K. T. Synthesis of 3-abicyclo[3.2.0]heptane derivatives as γ-aminobutyric acid analogues through intermolecular [2+2] photo-cycloaddition. *Eur. J. Org. Chem.* **2013**, *19*, 4017-4025. (b) Kriis, K.; Ausmees, K.; Pehk, T.; Lopp, M.; Kanger, T. A novel diastereoselective multicomponent cascade reaction. *Org. Lett.* **2010**, *12*, 2230-2233. (c) Reinart-Okugbeni, R.; Ausmees, K.; Kriis, K.; Werner, F.; Rinken, A.; Kanger, T. Chemoenzymatic synthesis and evaluation of 3-azabicyclo[3.2.0]heptane derivatives as dopaminergic ligands. *Eur. J. Med. Chem.* **2012**, *55*, 255-261.

[21] (a) Malpass, J. R.; Patel, A. B.; Davies, J. W.; Fulford, S. Y. Modification of 1-substituents in the 2-azabicyclo[2.1.1]hexane ring system; approaches to potential nicotinic acetylcholine receptor ligands from 2,4-methanoproline derivatives. *J. Org. Chem.* **2003**, *68*, 9348-9355. (b) Patel, A. B.; Malpass, J. R. Potential nicotinic acetylcholine receptor ligands from 2,4-methanoproline derivatives. *J. Med. Chem.* **2008**, *51*, 7005-7009.

[22] Varnes, J. G.; Lehr, G. S.; Moore, G. L.; Hulsizer, J. M; Albert, J. S. Efficient preparation of 2,4-methanoproline. *Tetrahedron Lett.* **2010**, *51*, 3756-3758.

[23] Esslinger, C. S.; Koch, H. P.; Kavanaugh, M. P.; Philips, D. P.; Chamberlin, A. R.; Thompson, C. M.; Bridges, R. J. Structural determinants of substrates and inhibitors: probing glutamate transporters with 2,4-methanopyrroldidine-2,4-dicarboxylate. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3101-3106.

[24] (a) Tkachenko, A. N.; Radchenko, D. S.; Mykhailiuk, P. K.; Grygorenko, O. O.; Komarov, I. V. 4-Fluoro-2,4-methanoproline. *Org. Lett.* **2009**, *11*, 5674-5676; (b) Mykhailiuk, P. K.; Kubyshkin, V.; Bach, T.; Budisa, N. Peptidyl-prolyl model study: how does the electronic effect influence the amide bond conformation? *J. Org. Chem.* **2017**, *82*, 8831-8841.

[25] Piotrowski, D. W. A Concise route to novel 1-aryl and 1-pyridyl-2-azabicyclo[2.1.1]hexanes. *Synlett* **1999**, 1091-1093.

[26] (a) Elliott L. D.; Berry, M.; Harji, B.; Klauber, D.; Leonard, J. Booker-Milburn K. I. A Small-footprint, high-capacity flow reactor for uv photochemical synthesis on the kilogram scale. *Org. Process. Res. Dev.* **2016**, *20*, 1806-1811.

[27] Kwak Y.-S.; Winkler J. D. Synthesis of 6-aza-bicyclo[3.2.1]octan-3-ones via vinylogous imide photochemistry: an approach to the synthesis of the hetisine alkaloids. *J. Am. Chem. Soc.* **2001**, 7429-7430.

[28] (a) Krow, G. R.; Lin, G.; Herzon, S. B.; Thomas, A. M.; Moore, K. P.; Huang, Q.; Carroll, P. J. Convenient preparations of 2,4-methanopyrrolidine and 5-carboxy-2,4-methanopyrrolidines. *J. Org. Chem.* **2003**, *68*, 7562-7564. (b) Krow, G. R.; Huang, Q.; Lin, G.; Centafont, R. A.; Thomas, A. M.; Gandla, D.; DeBrosse, C.; Carroll, P. J. 5-Carboxy-2-azabicyclo[2.1.1]hexanes as precursors of 5-halo, amino, phenyl, and 2-methoxycarbonylethyl methanopyrrolidines. *J. Org. Chem.* **2006**, *71*, 2090-2098.

[29] Stevens, C.; De Kimpe, N. A new entry into 2-azabicyclo[2.1.1]hexanes via 3-(chloromethyl)cyclobutanone. *J. Org. Chem.* **1996**, *61*, 2174-2178.

[30] (a) Rammeloo, T.; Stevens, C. V. A new and short method for the synthesis of 2,4-methanoproline. *Chem. Comm.* **2002**, 250-251. (b) Rammeloo, T.; Stevens, C. V.; De Kimpe, N. Synthesis of 2,4-methanoproline analogues via an addition−intramolecular substitution sequence. *J. Org. Chem.* **2002**, *67*, 6509-6513. (c) Stevens, C. V.; Smagghe, G.; Rammeloo, T.; De Kimpe, N. Insect repellent/antifeedant activity of 2,4-methanoproline and derivatives against a leaf- and seed-feeding pest insect. *J. Agric. Food Chem.* **2005**, *53*, 1945-1948. (d) Heugebaert, T.; Van Hevele, J.; Couck, W.; Bruggeman, V.; Van der Jeught, S.; Masschelein, K.; Stevens, C. V. A Straightforward entry to 7-azabicyclo[2.2.1]heptanes-1-carbonitriles in the synthesis of novel epibatidine analogues. *Eur. J. Org. Chem.* **2010**, 1017-1020. (e) Wauters, I.; De Blieck, A.; Muylaert, K.; Heugebaert, T. S. A.; Stevens, C. V. Synthesis of epibatidine analogues having a 2-substituted 2-azabicyclo[2.2.2]octane skeleton. *Eur. J. Org. Chem.* **2014**, 1296-1304.

[31] Grygorenko, O. O.; Artamonov, O. S.; Palamarchuk, G. V.; Zubatyuk, R. I.; Shishkin O. V.; Komarov, I. V. Stereoselective synthesis of 2, 4-methanoproline homologues. *Tetrahedron: Asymm.* **2006**, *17*, 252-258.

[32] Vasiuta, R. I.; Gorichko, M. V. Synthesis of 4-hydroxymethyl-2,4-methanoproline. *Tetrahedron Lett.* **2014**, 466-468.

[33] Gaoni, Y. Synthesis of aminocyclobutane mono- and dicarboxylic acids and derivatives thereof from (phenylsulfonyl)bicyclobutanes. *Org. Prep. Proced. Int.* **1995**, *27*, 185-212.

[34] Lescop, C.; Mevellec, L.; Huet, F. A new synthesis of 2-azabicyclo[2.1.1]hexanes. *J. Org. Chem.* **2001**, *66*, 4187-4193.

[35] (a) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Christian, H.; Shaw, D. A.; Yuan, J. A novel synthesis of 2-azabicyclo[2.1.1]hexane from pyridine. *J. Org. Chem.* **1998**, *63*, 8558-8560. (b) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Liu, N.; Yuan, J.; Duo, J.; Herzon, S. B.; Nguyen, Y.; Zacharias, D. 2-Azabicyclo[2.1.1]hexanes. 2. Substituent effects on the bromine-mediated rearrangement of 2-azabicyclo[2.2.0]hex-5-enes. *J. Org. Chem.* **2001**, *66*, 1805-1810. (c) Krow, G. R.; Herzon, S. B.; Lin, G.; Qiu, F.; Sonnet, P. E. Complex-induced proximity effects. Temperature-dependent regiochemical diversity in lithiation−electrophilic substitution reactions of N-BOC-2-azabicyclo[2.1.1]hexane. 2,4- and 3,5-Methanoprolines. *Org. Lett.* **2002**, *4*, 3151-3154. (d) Krow, G. R.; Edupuganti, R.; Gandla, D.; Yu, F.; Sender, M.; Zdilla, M. J.; DeBrosse, C.; Cannon, K. C.; Ross, C. W. III.; Choudhary, A.; Shoulders, M. D.; Raines, R. T. Synthesis of

conformationally constrained 5-fluoro- and 5-hydroxymethanopyrrolidines. Ring-puckered mimics of gauche- and anti-3-fluoro- and 3-hydroxypyrrolidines. *J. Org. Chem.* **2011**, *76*, 3626-3634.

[36] Wang, H.; Fang, W.-H.; Chen, X. Mechanism of the enantioselective intramolecular [2 + 2] photocycloaddition reaction of coumarin catalyzed by a chiral Lewis acid: comparison with enone substrates. *J. Org. Chem.* **2017**, *8,* 7093–7101.

[37] (a) Bioorganic and Medicinal Chemistry of Fluorine (Eds.: Bégué, J.-P.; Bonnet-Delpon, D.), John Wiley & Sons, New Jersey, 2008. (b) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: Ojima, I.), Blackwell Publishing, **2009**. (c) *Fluorine in Pharmaceutical and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications* (Eds.: Gouverneur, V.; Müller, K.), Imperial College Press, London, **2012**. (d) Munemori, D.; Narita, K.; Nokami, T.; Itoh, T. Synthesis of gem-difluoromethylene building blocks through regioselective allylation of gem-difluorocyclopropanes. *Org. Lett.* **2014**, *16*, 2638-2641.

[38] Our previous interest in fluorinated alicyclic amines: (a) Kubyshkin, V. S.; Afonin, S.; Kara, S.; Budisa, N.; Mykhailiuk, P. K.; Ulrich, A. S. γ-(S)-Trifluoromethyl proline: evaluation as a structural substitute of proline for solid state ^{19}F-NMR peptide studies. *Org. Biomol. Chem.* **2015**, *13*, 3171-3181. (b) Mykhailiuk, P. K.; Voievoda, N. M.; Afonin, S.; Ulrich, A. S.; Komarov, I. V. An optimized protocol for the multigram synthesis of 3-(trifluoromethyl)bicyclo[1.1.1]pent-1-ylglycine (CF_3-Bpg). *J. Fluorine Chem.* **2010**, *131*, 217-220. (c) Bychek, R. M.; Levterov, V. V.; Sadkova, I. V.; Tolmachev, A. A.; Mykhailiuk, P. K. Synthesis of functionalized difluorocyclopropanes: unique building blocks for drug discovery. *Chem. Eur. J.* **2018**, *24,* 12291-12297.

[39] The search was performed in August 2018 on Reaxys DB database.

[40] Briggs, C. R. S.; Allen, M. J.; O'Hagan, D.; Tozer, D. J.; Slawin, A. M. Z.; Goet, A. E.; Howard, J. A. K. The observation of a large gauche preference when 2-fluoroethylamine and 2-fluoroethanol become protonated. *Org. Biomol. Chem.* **2004**, *2*, 732-740.

[41] CCDC numbers: 1859863 (**17***HCl), 1859075 (**21***HCl), 1859076 (**24***HCl), 1859077 (**50***HCl), 1859078 (**52***HCl).

[42] While this manuscript was under revision, a related effect on morpholine and piperazine derivatives was observed: Degorce, S. L.; Bodnarchuk, M. S.; Cumming, I. A.; Scott, J. S. Lowering lipophilicity by adding carbon: one-carbon bridges of morpholines and piperazines. *J. Med. Chem.* **2018**, *in press* (DOI: 10.1021/acs.jmedchem.8b01148).

[43] Krasavin, M.; Lukin, A.; Zhurilo, N.; Kovalenko, A.; Zahanich, I.; Zozulya, S. Novel agonists of free fatty acid receptor 1 (GPR40) based on 3-(1,3,4-thiadiazol-2yl) propanoic acid scaffold. *J. Enzyme Inhib. Med. Chem.* **2016**, *24*, 2954–2963.