JOC The Journal of Organic Chemistry

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b01678 • Publication Date (Web): 16 Aug 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Photochemical synthesis of 3-azabicyclo[3.2.0]heptanes: advanced building blocks for drug discovery

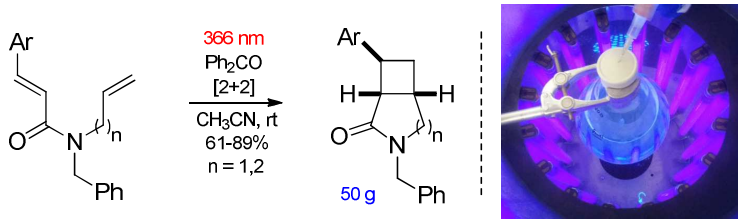
Aleksandr V. Denisenko,[a,b] Tetiana Druzhenko,[b,c] Yevhen Skalenko,[a,b] Maryna Samoilenko,[b] Oleksandr O. Grygorenko,[a] Sergey Zozulya,[b,d] and Pavel K. Mykhailiuk*[a]

[a]Department of Chemistry, National Taras Shevchenko University of Kyiv, Volodymyrska 64, Kyiv 01033 (Ukraine)

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

[c]Institute of High Technologies, Academician Glushkov av. 4G, Kyiv 03022 (Ukraine)

[d]ChemBioCenter, National Taras Shevchenko University of Kyiv, Volodymyrska 64, Kyiv 01601 (Ukraine)



ABSTRACT: We have developed a rapid two-step synthesis of substituted 3-azabicyclo[3.2.0]heptanes which are attractive building blocks for drug discovery. This new method utilizes very common chemicals - benzaldehyde, allylamine and cinnamic acid, - via intramolectular [2+2]-photochemical cyclization.

INTRODUCTION

Modern drug discovery has been changing rapidly with terms like *scaffold hopping*,[1] *escape flatland*[2] and *conformational restriction*[3] emerging which has gained great recognition in the scientific community. In this context chemists are currently looking for novel 3D-shaped F*sp*^{3}-rich building blocks.[4,5]

To this end substituted 3-azabicyclo[3.2.0]-heptanes were introduced as conformationally restricted surrogates for common piperidine motifs (Figure 1, a). This concept has already been validated by several bioactive compounds currently under clinical investigation (Figure 1, b).

Nevertheless, in spite of their significant potential, 3-azabicyclo[3.2.0]-heptanes remain quite rare in drug discovery (only 14 hits in ChEMBL database,[6] Figure 1a) due to the lack of a practical synthetic approach from available starting materials.[7]

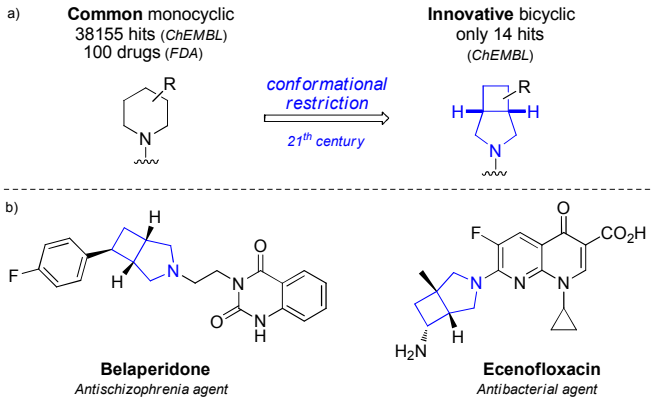
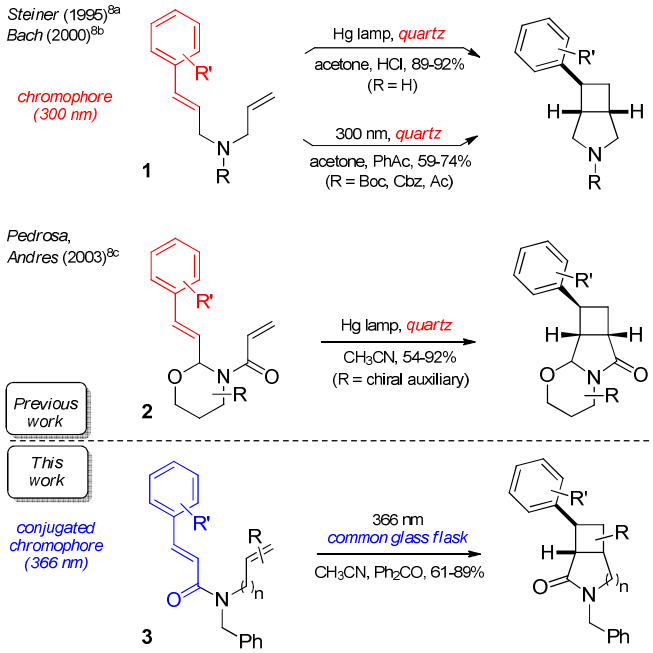


Figure 1. a) Motifs of piperidine and 3-azabicyclo[3.2.0]heptane in drug discovery; b) Bioactive 3-azabicyclo[3.2.0]heptanes.

There are only a few reports in the literature on 3-azabicyclo[3.2.0]heptanes with the a substituent on the cyclobutane ring (Scheme 1)[8] – the core of the antischizophrenia drug *Belaperidone* being an example (Figure 1, b).[9-12] In 1995, Steiner and colleagues[8a] performed [2+2]-intramolecular photocyclization of dienes **1** (R = H, Scheme 1) using a mercury quartz lamp apparatus to produce 3-azabicyclo[3.2.0]heptane skeletons. Later, in 2000, Bach and coworkers[8b] protected the *N*-atom (R = Boc, Cbz, Ac) which enabled them to perform the reaction at 300 nm in the presence of acetophenone as a sensitizer in a quartz apparatus. Finally, in 2003 Pedrosa and Andres[8c] synthesized the optically pure 3-azabicyclo[3.2.0]-heptanes by [2+2]-photocyclization of chiral substrate **2** using a medium pressure mercury quartz lamp apparatus.

Also worth mentioning the work of Yoon, who synthesized several 3-azabicyclo[3.2.0]heptanes with two substituents at the cyclobutane ring by [Ir]-catalyzed photoredox intramolecular [2+2]-cyclizations.[10]



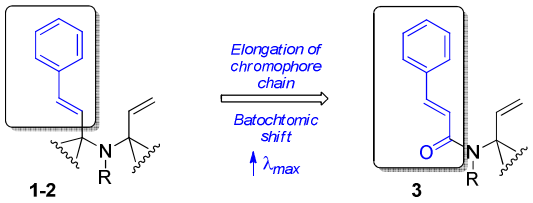
Scheme 1. Approaches to *mono*-substituted 3-azabicyclo[3.2.0]-heptanes.

In spite of the ongoing interest of medicinal chemists in 3-azabicyclo[3.2.0]heptanes, however, these methods have not found wide practical application to date, presumably due the low availability of the starting materials. Also, the need for a quartz photochemical apparatus might have to some extent inhibited the practical synthesis on a large scale.

In this work, we have developed a multigram two-step approach to monosubstituted 3-azabicyclo[3.2.0]-heptanes from very basic starting materials, - benzaldehyde, allylamine, cinnamic acids, and common chemical glassware available.

RESULTS AND DISCUSSION

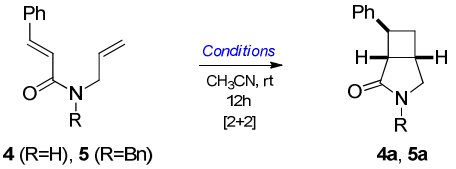
Design. Previous intramolecular [2+2] photocyclizations of substrates **1** and **2** (Scheme 1) were performed at 254-300 nm with (300 nm) or without (254 nm) sensitizer in a quartz apparatus. At the same time ordinary chemical flasks completely transmit the light at only above 350 nm.[13] Our aim was to find the conditions to force reaction to proceed at this or higher wavelength. Therefore, we added a carbonyl group to substrates **1**, **2** to elongate the conjugated chromophore chain (red-to-blue, Scheme 2). We envisioned that substrate **3** might absorb the light at a higher wavelength.



Scheme 2. Design of substrate **3** for [2+2]-photocyclization at $\lambda_{max} > 350$ nm.

Optimization of synthesis. We first tested the simplest amide **4**, synthesized from cinnamic acid and allylamine (Table 1). Unfortunately, all our attempts to perform [2+2]-photocyclization[14] at 366 nm failed. Only the starting material was remained. Next, to facilitate the reaction, we protected the *N*-atom in amide **4** with a benzyl group. Indeed, substrate **5** underwent [2+2]-photocyclization at 366 nm, however, after 12 h the conversion reached only *ca.* 20%. After some experimentation (Table 1), we found that adding benzophenone as a triplet sensitizer significantly facilitated the reaction, and the sole *trans*-isomer **5a** was easily formed. Also, we reduced the amount of sensitizer to 0.1 equiv, and increased the concentration up to 50 mM without any significant effect on the reaction outcome. At higher concentrations, formation of unidentified side products was observed.

Table 1. Optimization studies.



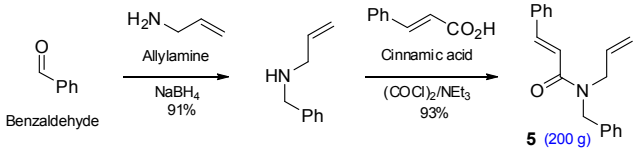
4 (R=H), **5** (R=Bn) **4a**, **5a**

Entry	λ_{max}	Concentration	Ph_2CO	Conversion[a]
1 (**4**)	366 nm	5 mM	–	0%
2 (**4**)	366 nm	5 mM	1.0 eq.	0%
3 (**5**)	366 nm	5 mM	–	20%
4 (**5**)	366 nm	5 mM	1.0 eq.	100%
5 (**5**)	366 nm	5 mM	0.5 eq.	100%
6 (**5**)	366 nm	5 mM	0.1 eq.	100%
7 (**5**)	366 nm	10 mM	0.1 eq.	100%
8 (**5**)	366 nm	20 mM	0.1 eq.	100%
9 (**5**)	366 nm	30 mM	0.1 eq.	100%

10 (**5**)	366 nm	50 mM	0.1 eq.	100%
11 (**5**)	366 nm	75 mM	0.1 eq.	100% *(ca. 10% side products*

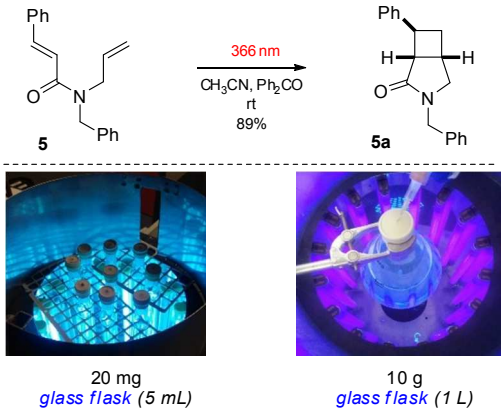
[a] Conversion of the reaction was determined by ^{1}H NMR of the reaction mixture.

Large-scale synthesis. When protecting the *N*-atom in amide **4** with benzyl group, we also kept in mind the availability of the corresponding starting materials. In fact, we easily synthesized 200 g of the needed substrate **5** in only two steps using very basic reagents (Scheme 3): benzaldehyde (20 *USD*/kg), allylamine (20 *USD*/kg) and cinnamic acid (25 *USD*/kg).



Scheme 3. Scaled up synthesis of diene **5a**.[5]

Finally, we studied this photochemical method in different scales. The synthesis in milligram scale was performed at 5 mM in 5 mL glass vials. The reaction in 10 g scale was efficiently performed at 50 mM in common 1L-glass flask (Scheme 4).[15]



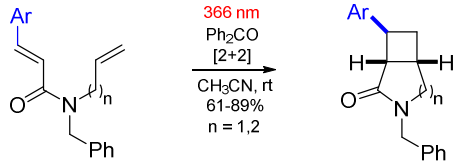
Scheme 4. Scaled up synthesis of compound **5a**.

Scope. Having a practical procedure in hands, we next studied its scope (Table 2). First, we varied substituents in cinnamic acids (alkenes **5-12**). The reaction was found to be effective with all – *ortho*-, *meta*- or *para*-substituents on the phenyl ring. Electron-donating (OMe), and withdrawing (F, CF_3) substituents on the benzene ring did not have a significant effect on the reaction outcome. The corresponding products **5a-11a** were isolated in 61-89% yield. Even the substitution at the C=C double bond did not influence the reaction, as the corresponding fluorinated bicycle **12a** was obtained in 62% yield.

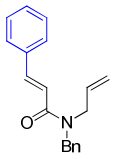
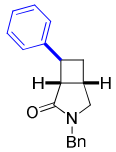
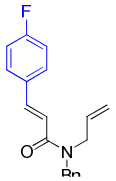
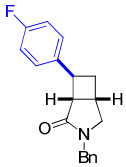
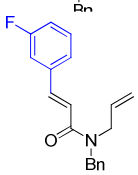
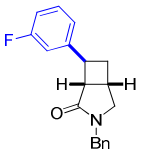
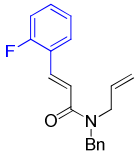
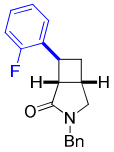
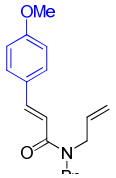
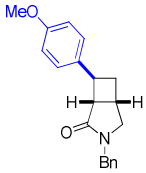
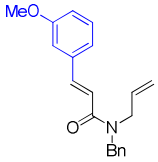
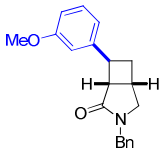
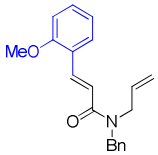
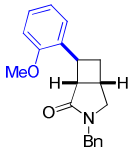
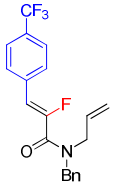
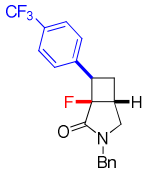
Next, we challenged the synthesis of optically active compounds. In fact, replacing Bn group with (*R*)-phenylethyl one (alkenes **13** and **14**) allowed to synthesize the individual optically pure diastereomers **13a**, **13b** and **14a**, **14b**. In each pair the stereoisomers were separated by column chromatography on silica gel. The stereoconfiguration of compounds **13a**, **14a** and **14b** was determined by an *X*-Ray analysis (please, see SI).[16]

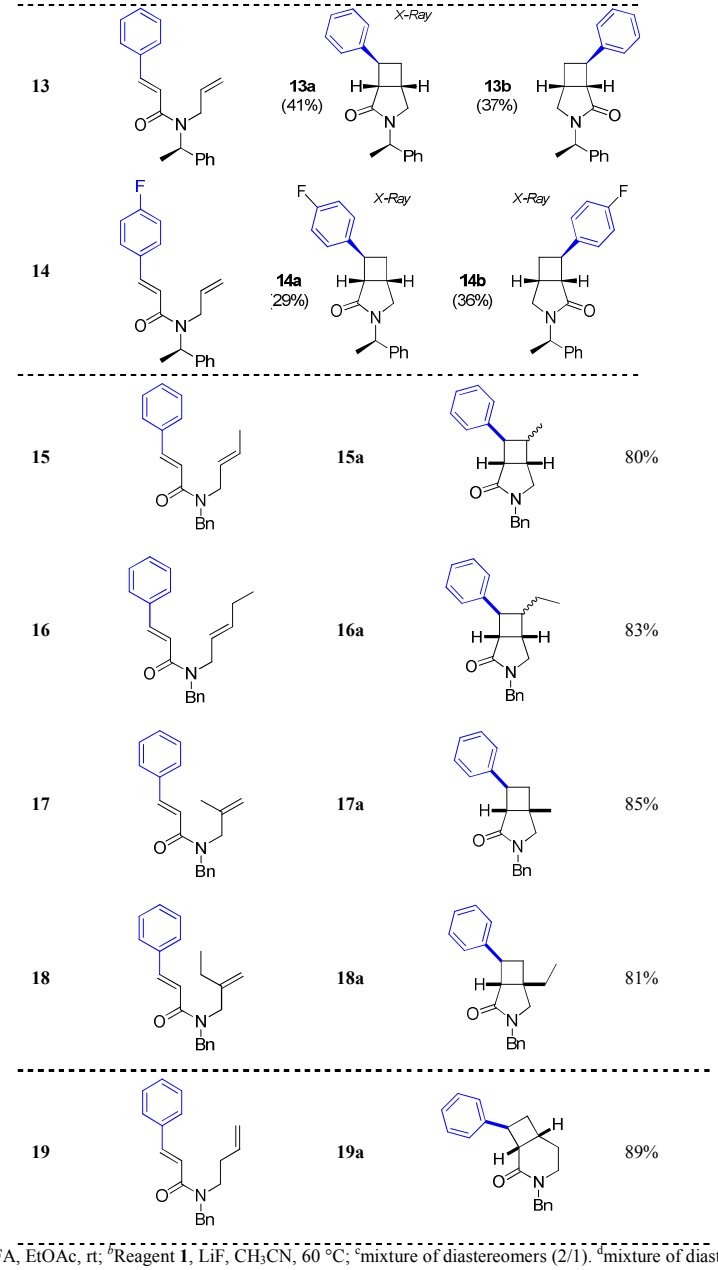
Variation of the structure of allylamine was next performed (alkenes **15-19**). Substrates with substituted allylamines **15-18** smoothly underwent the photocyclization to afford the products **15a-18a** in good yields of 80-85%. Alkene **19** with the fragment of homoallylamine selectively gave the piperidine derivative **19a**. Herein, we did not go further in elaboration of the scope of homoallylamines, but it seems that the current method can also be used towards preparation of diversely substituted bicyclic piperidines.

Table 2. Scope of the reaction.



5-19 **5a-19a**

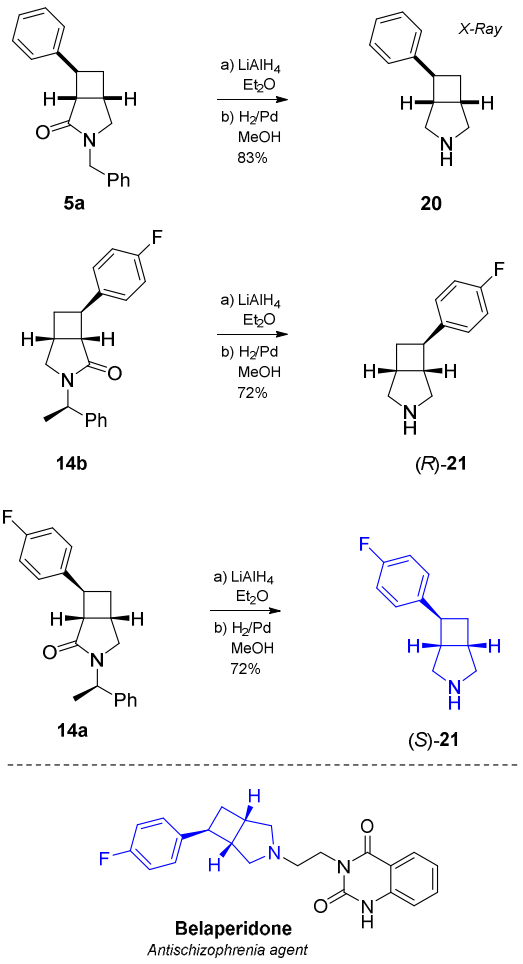
Alkene	Product	Yield
5 	**5a** 	89%
6 	**6a** 	80%
7 	**7a** 	61%
8 	**8a** 	85%
9 	**9a** 	82%
10 	**10a** 	61%
11 	**11a** 	74%
12 	**12a** 	62%



[a]Reagent **1**, TFA, EtOAc, rt; [b]Reagent **1**, LiF, CH_3CN, 60 °C; [c]mixture of diastereomers (2/1). [d]mixture of diastereomers (3/1).

Synthesis of building blocks. Next, we wanted to show that the obtained compounds could be easily transformed into the appropriate building blocks for drug discovery. In fact, reduction of the model compound **5a** with $LiAlH_4$ followed by cleavage of the *N*-benzyl protecting group with H_2/Pd gave the target amine **20** (*X-Ray*, please see SI)[16] in 25 g scale (Scheme 5).

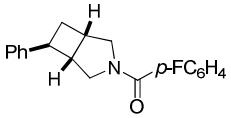
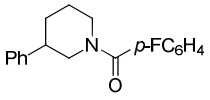
The individual diastereomers **14b** and **14a** were similarly transformed into the pure enantiomers (*R*)-**21** and (*S*)-**21**. It is important to mention that the current method represents a novel synthetic approach to amine (*S*)-**21**: the key component of *Belaperidone* drug.[17]



Scheme 5. Synthesis of racemic amine **20** *(X-Ray)* and the optically pure (*R*)-**21** and (*S*)-**21**: the key component of *Belaperidone*.

Physico-chemical properties. We measured the physicochemical characteristics of 3-azabicyclo[3.2.0]heptanes and compared them to the established piperidine scaffolds. In fact, all model compounds **22**–**24** (Table 3) had nearly identical lipophilicity (logD), water solubility (Sol.) and metabolic stability (CL_{int}): important characteristics in drug discovery. This data shows that monosubstituted 3-azabicyclo[3.2.0]heptanes are good conformationally restricted surrogates for piperidines needed in modern medicinal chemistry projects.

Table 3. Measured physico-chemical properties of models **22**–**24**.

Compound	LogD(10)[a]	Sol(7.4)[c]	CL_{int}[b]
22 	3.7	344	99
23 	3.6	370	100

24	3.5	365	88

[a]Experimental n-octanol/water distribution coefficient (log) at pH 10.0. [b]Intrinsic clearance rate CLint (mg/(min·μL)) measured in mouse liver microsomes. [c]Thermodynamic aqueous solubility (μM) in 50 mM phosphate buffer (pH 7.4).

Conformational properties. To compare spatial arrangement of the substitutents provided by 3-azabicyclo[3.2.0]heptane scaffold with that of piperidine derivatives, we used exit vector plots (EVP) tool.[18,19] In this approach, the substituents mounted onto the disubstituted scaffold were simulated by two exit vectors $\boldsymbol{n_1}$ and $\boldsymbol{n_2}$ (Figure 2). Relative spatial arrangement of these vectors can be described by four geometric parameters: the distance between the variation points **C** and **N** – r, the plane angles φ_1 (between vectors $\boldsymbol{n_1}$ and **CN**) and φ_2 (between $\boldsymbol{n_2}$ and **NC**), and the dihedral angle θ defined by vectors $\boldsymbol{n_1}$, **CN** and $\boldsymbol{n_2}$. Exit vector plots (EVP) were obtained by depicting the values of these parameters in $r - \theta$, $\theta - \varphi_1/\varphi_2$, and $\varphi_1 - \varphi_2$ coordinates.

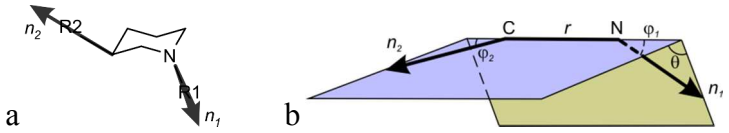


Figure 2. a) Definition of vectors n_1, n_2 (1,3-disubstituted piperidine scaffold is used as an example). b) Definition of geometric parameters r, φ_1, φ_2, and θ.

We calculated the values of r, φ_1, φ_2, and θ from the *X*-Ray data for the compounds **20**·HCl, **13a**, **14a** and **14b** (from this work), as well as piperidine derivatives **25-28** (described in the literature)[20-23] (Table 4). Analysis of the data obtained using EVP (Figure 3) showed that 3,6-disubstituted 3-azabicyclo[3.2.0]heptane scaffolds (3,6-ABH, r = 3.11–3.34 Å) were larger than both 1,3- and 1,4-disubstituted piperidines (r = 2.50–2.52 Å and 2.89–2.94 Å, respectively). 3,6-ABH scaffold appeared to have some flexibility related to the θ angle (θ = 106–156°). $\theta - \varphi_1/\varphi_2$ plot (Figure 3b) showed that the values of angles φ_1, φ_2, and θ for most conformations of 3,6-ABH could be considered as intermediate between those found for 1,3-disubstituted piperidines **25**, **26** and 1,4-disubstituted piperidone **27**. According to $\varphi_1 - \varphi_2$ plot (Figure 3c), the 3,6-ABH scaffolds provided more dissymmetry (which is characterized by the distance from $\varphi_1 = \varphi_2$ line) than piperidine-derived scaffolds.

All three EVPs demonstrated that 3,6-disubstituted 3-azabicyclo[3.2.0]heptanes occupy slightly different area of chemical space compared with piperidine derivatives. Therefore, 3-azabicyclo[3.2.0]heptanes must be considered as surrogates for piperidines, ideally featuring them in comprehensive structure-activiry relationship (SAR) studies in medicinal chemistry projects.

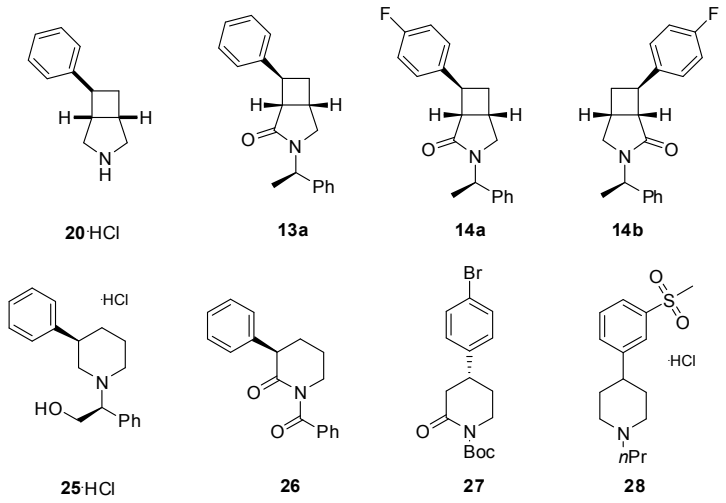


Table 4. The values of geometric parameters r, φ_1, φ_2, and θ for 3-azabicyclo[3.2.0]heptanes and piperidine derivatives.

Compound	r, Å	φ_1, deg	φ_2, deg	$\lvert\theta\rvert$, deg[a]	Ref.
20·HCl	3.113	51.9	20.8	106.1	This work
13a	3.326	33.7	25.9	132.7	This work
14a (I)[b]	3.288	32.1	23.7	113.7	This work
14a (II)[b]	3.318	35.8	24.6	149.9	This work
14b (I)[b]	3.335	33.0	24.1	142.5	This work
14b (I)[b]	3.333	34.2	24.5	156.3	This work
25	2.521	43.2	37.0	90.5	20
26	2.498	36.8	42.0	75.8	21
27	2.886	6.1	17.2	138.0	22
28 (I)[c]	2.942	25.5	28.4	4.2	23
28 (II)[c]	2.944	22.6	25.0	10.1	23

[a]Since the signs of θ angle are opposite for different enantiomers, only absolute values of θ were considered. [b]Two different molecules in the crystal cell. [c]Two polymorphs.

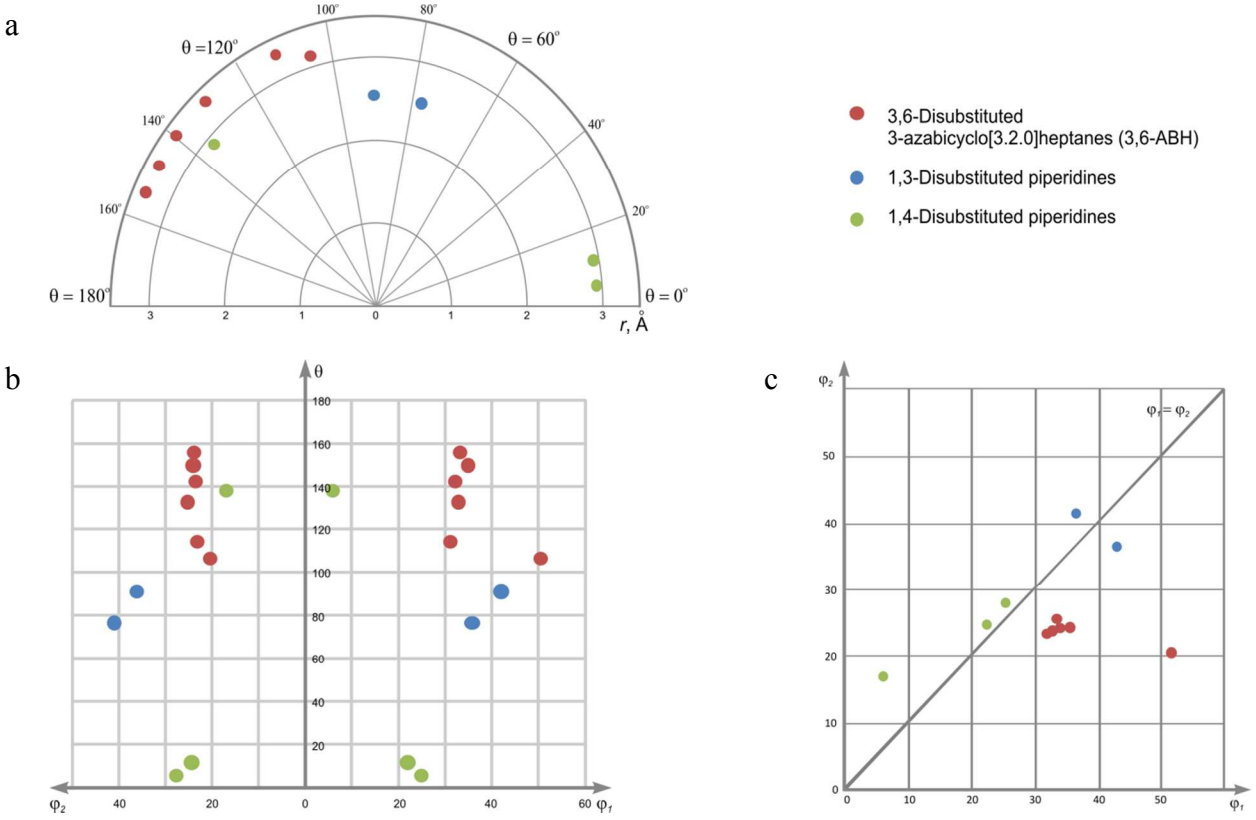


Figure 3. 3,6-Disubstituted 3-azabicyclo[3.2.0]heptanes and piperidine derivatives shown in a) $r - \theta$ plot (polar coordinates); b) $\theta - \varphi_1/\varphi_2$ plot; c) $\varphi_1 - \varphi_2$ plot

CONCLUSIONS

In summary, this work describes three important findings:

(1) We developed a multigram two-step approach to racemic and optically pure mono-substituted 3-azabicyclo[3.2.0]-heptanes from benzaldehyde, allylamine and cinnamic acid.

(2) The photochemical method was optimized to be performed at 366 nm in common none-quartz chemical glassware.

(3) 3-Azabicyclo[3.2.0]-heptanes may be considered as conformationally restricted piperidine surrogates for medicinal chemistry, which have very similar physicochemical properties, but occupy slightly different part of the chemical space according to the analysis of exit vectors.

The Ecenofloxacin and *Belaperidone* examples have demonstrated the potential of 3-azabicyclo[3.2.0]-heptanes in drug discovery. However, the lack of a practical synthetic approach to them from cheap starting materials has constrained their wide use. Given the high efficiency, simplicity, and low costs of our method, we believe that scientists will soon use it to prepare 3-azabicyclo[3.2.0]-heptanes, and they will soon become as popular in medicinal chemistry as piperidines.

EXPERIMENTAL SECTION

General methods

All starting materials were taken at Enamine. Column chromatography was performed using Kieselgel Merck 60 (230-400 mesh) as the stationary phase. Reverse phase column chromatography was performed using C_{18}-modified silica gel as a stationary phase, column: SunFire Waters, 5 µm, 19 mm × 100 mm. ^{1}H-, ^{19}F-, ^{13}C-NMR spectra were recorded on at 500 or 400 MHz, 376 MHz and 125 or 101 MHz respectively. Chemical shifts are reported in ppm downfield from TMS (^{1}H, ^{13}C) or $CFCl_3$ (^{19}F) as internal standards. Mass spectra were recorded on an LC-MS instrument with chemical ionization (CI). LC-MS data were acquired on Agilent 1200 HPLC system equipped with DAD/ELSD/LCMS-6120 diodematrix and mass-selective detector, column: Poroshell 120 SBC18, 4.6 mm × 30 mm. Eluent, A, acetonitrile–water with 0.1% of FA (99: 1); B, water with 0.1% of FA.

General procedure for synthesis of amides 5-19

DMF (0.02 equiv) was added to 1M solution of cinnamic acid (1.0 equiv) in CH_2Cl_2. Then, $(COCl)_2$ (2.0 equiv) was added dropwise. The resulted reaction mixture was stirred for 2 h. Solvent and volatile by-products were removed under reduced pressure. Formed acyl chloride was added dropwise to the previously cooled mixture of 1M solution of allylbenzylamine (0.8 equiv) in CH_2Cl_2 and triethylamine (1.0 equiv) at -20 °C. Reaction mixture was warmed to room temperature, stirred overnight and washed with 0.5 M aqueous solution of citric acid (approx. 1 equiv), saturated aqueous solution of $NaHCO_3$ (approx. 1 equiv) and water. The organic layer was separated, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The product was purified *via* filtration through silica gel using pure MTBE as an eluent.

(2*E*)-*N*-allyl-*N*-benzyl-3-phenylacrylamide (5)

Yellow oil. 201 g, 93% yield.

^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$) δ 7.79 (d, PhC*H*=CH, $^{3}J(H,H)$ = 15.3 Hz, 1H), 7.56 – 7.19 (m, 10H), 6.84 (d, PhCH=C*H*, $^{3}J(H,H)$ = 15.3 Hz, 1H), 5.83 (m, 1H), 5.21 (m, 2H), 4.71, 4.66 (2×s, 2H), 4.11, 3.99 (2×s, 2H). ^{13}C NMR of both amide rotamers (126 MHz, $CDCl_3$) δ 167.0, 166.8, 143.5, 143.1, 137.6, 137.0, 135.3, 135.2, 133.0, 129.6, 129.0, 128.8, 128.6,

128.3, 127.8, 127.7, 127.4, 126.5, 117.7, 117.6, 117.4, 117.0, 50.2, 49.3, 49.1, 48.6. MS (CI, m/z): 278 [M^++H]. Anal. calcd for $C_{19}H_{19}NO$: C, 82.28 H, 6.90 N, 5.05 Found: C, 82.61 H, 6.65 N, 5.20.

(2*E*)-*N*-allyl-*N*-benzyl-3-(4-fluorophenyl)acrylamide (6)

Yellow oil. 252 mg, 83% yield.

^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$) δ 7.74 (d, ArC*H*=CH, $^3J(H,H)$ = 15.4 Hz, 1H), 7.54 – 6.92 (m, Ph + Ar, 9H), 6.75 (d, PhCH=C*H*, $^3J(H,H)$ = 15.4 Hz, 1H), 5.80 (m, CH_2=C*H*, 1H), 5.18 (m, CH_2=CH, 2H), 4.68, 4.64 (2×s, CH_2Ph, 2H), 4.10, 3.96 (2×s, CH_2N, 2H). ^{13}C NMR of both amide rotamers (101 MHz, $CDCl_3$) δ 166.9, 166.7, 164.7, 162.3, 142.2, 142.0, 137.6, 137.0, 133.0, 131.6, 131.4, 129.7, 129.6, 129.0, 128.6, 128.3, 127.7, 127.4, 126.5, 117.7, 117.3, 117.2, 117.0, 115.99, 115.95, 115.8, 115.7, 50.2, 49.2, 49.1, 48.7. ^{19}F NMR of both amide rotamers (376 MHz, $CDCl_3$) δ -111.07, -111.12 (2×s). MS (CI, m/z): 296 [M^++H]. Anal. calcd for $C_{19}H_{18}FNO$: C, 77.27 H, 6.14 N, 4.74 Found: C, 77.05 H, 5.93 N, 5.03.

(2*E*)-*N*-allyl-*N*-benzyl-3-(3-fluorophenyl)acrylamide (7)

Yellow oil. 311 mg, 62% yield.

^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$) δ 7.72 (d, ArC*H*=CH, $^3J(H,H)$ = 15.4 Hz, 1H), 7.40 – 6.93 (m, Ar + Ph, 9H), 6.81 (d, ArCH=C*H*, $^3J(H,H)$ = 15.4 Hz, 1H), 5.81 (m, CH_2=C*H*, 1H), 5.19 (m, CH_2=CH, 2H), 4.69, 4.64 (2×s, PhCH_2, 2H), 4.09, 3.97 (2xs, CHCH_2N, 2H). ^{13}C NMR of both amide rotamers (126 MHz, $CDCl_3$) δ 166.6, 166.4, 163.0 (d, Ph, $^1J(C,F)$ = 246.4 Hz), 142.1, 141.9, 137.6, 137.6, 137.5, 137.5, 136.9, 132.9, 130.4, 130.3, 129.0, 128.6, 128.3, 127.7, 127.5, 126.5, 123.9, 118.9, 118.8, 117.8, 117.1, 116.5 (d, $^2J(C,F)$ = 21.4 Hz), 114.0 (d, $^2J(C,F)$ = 22.0 Hz), 114.0 (d, $^2J(C,F)$ = 21.8 Hz), 50.2, 49.3, 49.2, 48.7. ^{19}F NMR of both amide rotamers (376 MHz, $CDCl_3$) δ -113.3 (s). MS (CI, m/z): 296 [M^++H]. Anal. calcd for $C_{19}H_{18}FNO$: C, 77.27 H, 6.14 N, 4.74 Found: C, 77.58 H, 6.28 N, 4.56.

(2*E*)-*N*-allyl-*N*-benzyl-3-(2-fluorophenyl)acrylamide (8)

Yellow oil. 272 mg, 60% yield.

^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$) δ 7.85 (d, ArC*H*=CH, $^3J(H,H)$ = 15.6 Hz, 1H), 7.50 – 6.93 (m, Ar + Ph + ArCH=C*H*, 10H), 5.78 (m, CH_2=C*H*, 1H), 5.16 (s, CH_2=CH, 2H), 4.68, 4.62 (2xs, PhCH_2, 2H), 4.09, 3.94 (2×s, CHCH_2N, 2H). ^{13}C NMR of both amide rotamers (101 MHz, $CDCl_3$) δ 166.9, 166.7, 162.6, 162.5, 160.04, 159.99, 137.6, 137.0, 136.3, 136.1, 132.9, 131.0, 130.9, 129.64, 129.61, 129.51, 129.48, 128.9, 128.6, 128.3, 127.7, 127.4, 126.6, 124.42, 124.39, 123.3, 123.24, 123.21, 123.1, 120.6, 120.5, 120.4, 120.3, 117.8, 117.1, 116.22, 116.19, 116.00, 115.97, 50.2, 49.3, 49.2, 48.7. ^{19}F NMR of both amide rotamers (376 MHz, $CDCl_3$) δ -114.6 (s), -114.7 (s). MS (CI, m/z): 296 [M^++H]. Anal. calcd for $C_{19}H_{18}FNO$: C, 77.27 H, 6.14 N, 4.74. Found: C, 77.59 H, 6.01 N, 4.93.

(2*E*)-*N*-allyl-*N*-benzyl-3-(4-methoxyphenyl)acrylamide (9)

Yellow oil. 201 mg, 75% yield.

^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$) δ 7.74 (d, ArC*H*=CH, $^3J(H,H)$ = 15.3 Hz, 1H), 7.26 (m, Ar + Ph, 9H), 6.70 (d, ArCH=C*H*, $^3J(H,H)$ = 15.3 Hz, 1H), 5.78 (m, CH_2=C*H*, 1H), 5.16 (m, CH_2=CH, 2H), 4.67, 4.61 (2×s, PhCH_2, 2H), 4.08, 3.94 (2×s, CH-CH_2N, 2H), 3.73, 3.71 (2×s, CH_3O, 3H). ^{13}C NMR of both amide rotamers (126 MHz, $CDCl_3$) δ 167.2, 167.1, 137.8, 137.2, 133.2, 129.4, 128.9, 128.6, 128.3, 128.0, 127.9, 127.6, 127.3, 126.5, 117.6, 116.9, 115.0, 114.9, 114.2, 55.3, 50.2, 49.2, 49.1, 48.6. MS (CI, m/z): 308 [M^++H]. Anal. calcd for $C_{20}H_{21}NO_2$: C, 78.15 H, 6.89 N, 4.56. Found: C, 78.39 H, 6.74 N, 4.66.

(2*E*)-*N*-allyl-*N*-benzyl-3-(3-methoxyphenyl)acrylamide (10)

Yellow oil. 239 mg, 69% yield.

^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$) δ 7.74 (d, ArC*H*=CH, ^{3}*J(H,H)* = 15.4 Hz, 1H), 7.07 (m, Ar + Ph + ArCH=C*H*, 10H), 5.78 (m, CH_2=C*H*, 1H), 5.15 (m, CH_2=CH, 2H), 4.67, 4.62 (2×s, PhCH_2, 2H), 4.09, 3.94 (2×s, CH_2N, 2H), 3.74, 3.70 (s, OCH_3, 3H). ^{13}C NMR of both amide rotamers (126 MHz, $CDCl_3$) δ 166.9, 166.7, 159.9, 159.8, 143.3, 143.1, 137.6, 137.1, 136.7, 136.6, 133.1, 133.0, 129.82, 129.78, 128.9, 128.6, 128.3, 127.7, 127.4, 126.5, 120.4, 117.9, 117.8, 117.7, 117.0, 115.2, 115.1, 113.4, 113.2, 55.2, 50.2, 49.3, 49.1, 48.7. MS (CI, m/z): 308 [M^++H]. Anal. calcd for $C_{20}H_{21}NO_2$: C, 78.15 H, 6.89 N, 4.56. Found: C, 78.41 H, 7.10 N, 4.38.

(2*E*)-*N*-allyl-*N*-benzyl-3-(2-methoxyphenyl)acrylamide (11)

Yellow oil. 268 mg, 48% yield.

^{1}H NMR of both amide rotamers (500 MHz, $CDCl_3$) δ 8.07 (dd, ArC*H*=C*H,* 1H), 7.53 – 6.77 (m, Ph + Ar + ArCH=C*H*, 10H), 5.81 (m, CH_2=C*H*, 1H), 5.18 (m, CH_2=CH, 2H), 4.69, 4.62 (2xs, CH_2Ph, 2H), 4.12, 3.95 (2×s, NCH_2CH, 2H), 3.79, 3.70 (2xs, OCH_3, 3H). ^{13}C NMR of both amide rotamers (126 MHz, $CDCl_3$) δ 167.5, 167.4, 158.3, 139.0, 138.7, 137.8, 137.3, 133.23 (s), 133.18 (s), 130.8, 129.2, 129.0, 128.9, 128.6, 128.3, 127.5, 127.3, 126.6, 124.3, 124.2, 120.7, 118.6, 118.5, 117.5, 116.9, 111.2, 55.4, 55.3, 50.3, 49.3, 49.1, 48.7. MS (CI, m/z): 308 [M^++H]. Anal. calcd for $C_{20}H_{21}NO_2$: C, 78.15 H, 6.89 N, 4.56. Found: C, 77.84 H, 6.62 N, 4.72.

(2*Z*)-*N*-allyl-*N*-benzyl-2-fluoro-3-[4-(trifluoromethyl)phenyl]acrylamide (12)

Yellow oil. 273 mg, 61% yield.

^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$) δ 7.63 – 6.95 (m, 9H), 6.52, 6.49,(2xd, ^{3}*J(H,F)* = 20 Hz, ^{3}*J(H,F)* = 24 Hz, 1H), 5.63 (m, 1H), 5.15 (m, 2H), 4.61, 4.44 (2xs, 2H), 3.94, 3.79 (2×d, ^{3}*J*(H,H) = 6.0 Hz, ^{3}*J(H,H)* = 5.7 Hz, 2H). ^{13}C NMR of both amide rotamers (101 MHz, $CDCl_3$) δ 162.6, 162.5, 162.2, 162.1, 153.6, 153.5, 151.0, 150.9, 135.7, 135.1, 134.7, 134.6, 132.2, 131.0, 128.81, 128.75, 128.7, 128.59, 128.57, 128.48, 128.45, 128.0, 127.9, 127.6, 125.7, 125.63, 125.58, 125.55, 125.31, 125.28, 122.61, 122.57, 119.4, 119.1, 111.5, 111.3, 111.0, 51.1, 50.0, 46.8, 46.1. ^{19}F NMR of both amide rotamers (376 MHz, $CDCl_3$) δ -63.2, 63.3 (2×s, CF_3, 3F), -103.37, -104.44 (2×s, C*F*, F). MS (CI, m/z): 364 [M^++H]. Anal. calcd for $C_{20}H_{17}F_4NO$: C, 66.11 H, 4.72 N, 3.85. Found: C, 66.39 H, 4.50 N, 3.69.

Amides **13** (yellow oil, 311 mg, 84% yield, MS (CI, m/z): 292 [M^++H]) and **14** (yellow oil, 384 mg, 94% yield, MS (CI, m/z): 310 [M^++H]) were obtained in 90-95% purity and used for the next step without additional purification.

***N*-benzyl-*N*-((*E*)-but-2-en-1-yl)cinnamamide (15)**

Colorless oil. 229 mg, 91% yield.

^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$) δ 7.78 (d, PhC*H*=CH, ^{3}*J(H,H)* = 15.4 Hz, 1H), 7.57 – 7.21 (m, 10H), 6.88, 6.82 (2×d, PhCH=C*H*, ^{3}*J(H,H)* = 15.4 Hz, 1H), 5.72 – 5.55 (m, 1H), 5.55 – 5.34 (m, 1H), 4.69, 4.65 (2×s, 2H), 4.04 (d, *J* = 5.1 Hz, 1H), 3.92 (br s, 1H), 1.72 (d, CH_3, ^{3}*J(H,H)* = 6.7 Hz, 3H). ^{13}C NMR of both amide rotamers of both amide rotamers (101 MHz, $CDCl_3$) δ 166.8, 137.8, 137.2, 135.4, 135.3, 129.6, 129.4, 128.9, 128.82, 128.6, 128.3, 127.9, 127.6, 127.3, 126.5, 125.8, 117.7,

50.0, 48.8, 48.7, 47.9, 17.8. MS (CI, m/z): 292 [M^++H]. Anal. calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.74; H, 7.51; N, 4.68.

_N_-benzyl-_N_-((_E_)-pent-2-en-1-yl)cinnamamide (16)

Yellow oil. 238 mg, 81% yield.

^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$) δ 7.81 (d, PhC*H*=CH, $^3J(H,H)$ = 15.3 Hz, 1H), 7.56 – 7.22 (m, 10H), 6.88 (2×d, PhCH=C*H*, $^3J(H,H)$ = 14.2 Hz, 1H), 5.66 – 5.49 (m, 1H), 5.47 – 5.26 (m, 1H), 4.68 (2×s, 2H), 4.17 (d, J = 6.4 Hz, 1H), 4.00 (d, J = 5.6 Hz, 1H), 2.10 – 1.96 (m, 2H), 0.98, 0.96 (2×t, $^3J(H,H)$ = 7.3 Hz, 3H). ^{13}C NMR of both amide rotamers (101 MHz, $CDCl_3$) δ 166.8, 166.6, 143.2, 143.0, 137.5, 137.0, 135.7, 135.2, 135.1, 134.9, 129.5, 128.8, 128.70, 128.65, 128.5, 128.1, 127.7, 127.6, 127.3, 126.4, 124.4, 123.7, 117.53, 117.45, 50.1, 49.0, 44.2, 42.4, 20.7, 20.5, 14.1, 14.0. MS (CI, m/z): 306 [M^++H]. Anal. calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.74; H, 7.33; N, 4.72.

_N_-benzyl-_N_-(2-methylallyl)cinnamamide (17)

Colorless oil. 282 mg, 84% yield.

^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$) δ 7.80 (d, PhC*H*=CH, $^3J(H,H)$ = 15.4 Hz, 1H), 7.53 – 7.18 (m, 10H), 6.89, 6.81 (2×d, PhCH=C*H*, $^3J(H,H)$ = 15.3 Hz, 1H), 4.93 (d, $^2J(H,H)$ = 36.2 Hz, 1H), 4.85 (d, $^2J(H,H)$ = 54.8 Hz, 1H), 4.66 (2×s, 2H), 4.09 (s, 1H), 3.84 (s, 1H), 1.72 (s, 3H). ^{13}C NMR of both amide rotamers (101 MHz, $CDCl_3$) δ 167.1, 166.8, 143.5, 143.0, 140.5, 140.0, 137.5, 136.8, 135.2, 135.0, 129.5, 128.8, 128.7, 128.5, 128.1, 127.7, 127.5, 127.2, 126.4, 117.4, 117.1, 112.5, 111.9, 52.2, 50.9, 49.6, 49.0, 20.0. MS (CI, m/z): 293 [M^++H]. Anal. calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.20; H, 7.51; N, 4.98.

_N_-benzyl-_N_-(2-methylenebutyl)cinnamamide (18)

Yellow oil. 219 mg, 87% yield.

^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$) δ 7.81, 7.80 (2×d, PhC*H*=CH, $^3J(H,H)$ = 15.4 Hz, 1H), 7.51 – 7.20 (m, 10H), 6.89, 6.79 (2×d, PhCH=C*H*, $^3J(H,H)$ = 15.4 Hz, 1H), 4.96 (d, C*H*, $^2J(H,H)$ = 33.5 Hz, 1H), 4.87 (d, C*H*, $^2J(H,H)$ = 50.4 Hz, 1H), 4.70, 4.64 (2×s, 2H), 4.12, 3.89 (2×s, 2H), 2.08 – 1.97 (m, *2*H), 1.09, 1.08 (2×t, $^3J(H,H)$ = 7.3 Hz, 3H). ^{13}C NMR of both amide rotamers (101 MHz, $CDCl_3$) δ 167.3, 167.0, 146.2, 145.7, 143.7, 143.2, 137.7, 137.0, 135.4, 135.2, 129.69, 129.65, 129.0, 128.82, 128.78, 128.6, 128.3, 127.89, 127.85, 127.7, 127.4, 126.5, 117.6, 117.3, 110.5, 109.8, 51.3, 50.2, 49.8, 49.1, 26.6, 26.5, 12.3, 12.1. MS (CI, m/z): 306 [M^++H]. Anal. calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.41; H, 7.87; N, 4.26.

_N_-benzyl-_N_-(but-3-en-1-yl)cinnamamide (19)

Yellow oil. 213 mg, 95% yield.

^{1}H NMR of both amide rotamers (400 MHz, $CDCl_3$) δ 7.81, 7.76 (2×d, PhC*H*=CH, $^3J(H,H)$ = 15.6 Hz, 1H), 7.57 – 7.16 (m, 10H), 6.91, 6.81 (2×d, PhCH=C*H*, $^3J(H,H)$ = 15.4 Hz, 1H), 5.93 – 5.65 (m, 1H), 5.13 – 5.00 (m, 2H), 4.73, 4.67 (2×s, 2H), 3.55 (t, $^3J(H,H)$ = 7.2 Hz, 1H), 3.44 (t, $^3J(H,H)$ = 7.3 Hz, 1H), 2.43 – 2.28 (m, 2H). ^{13}C NMR of both amide rotamers (101 MHz, $CDCl_3$) δ 166.9, 166.5, 143.1, 143.0, 137.7, 137.1, 135.4, 135.2, 135.1, 134.2, 129.6, 129.5, 128.9, 128.8, 128.7, 128.5, 128.0, 127.8, 127.6, 127.3, 126.4, 117.6, 117.5, 117.3, 116.7, 51.5, 49.3, 46.7, 46.4, 33.6, 32.2. MS (CI, m/z): 292 [M^++H]. Anal. calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.69; H, 7.10; N, 4.70.

General procedure for [2+2] photocycloaddition (synthesis of amides 5a-19a, 13b, 14b)

Benzophenone (0.1 equiv) was added to 0.05 M solution of starting material (1.0 equiv) in dry acetonitrile. Reaction mixture was degassed by bubbling of argon for 15 minutes and irradiated at 365 nm. After the accomplishment (reaction was monitored by NMR, typically it was conducted for 36-72 h) reaction mixture was concentrated. The final product was purified *via* column chromatography.

(1*RS*,5*SR*,7*RS*)-3-benzyl-7-phenyl-3-aza-bicyclo[3.2.0]heptan-2-one (5a)

Colorless oil. 10.1 g, 89% yield. Was used as a crude material for further synthetic transformations. In order to characterize this compound, small amount was purified via a gradient reverse phase chromatography (H_2O/acetonitrile from 65/35 to 40/60).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.17 (m, 10H), 4.66 (d, $^2J(H,H)$ = 14.6 Hz, 1H), 4.42 (d, $^2J(H,H)$ = 14.6 Hz, 1H), 3.69 (m, 1H), 3.50 (m, 1H), 3.18 (d, $^3J(H,H)$ = 10.6 Hz, 2H), 2.99 (m, 1H), 2.49 (m, 1H), 2.32 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0 (s, *C*=O), 144.5 (s, Ph), 136.6 (s, Ph), 128.8 (s. Ph), 128.6 (s, Ph), 128.2 (s, Ph), 127.6 (s, Ph), 126.4 (s, Ph), 126.3 (s, Ph), 53.2, 48.4, 46.8, 42.8, 33.7, 27.4. MS (CI, m/z): 278 [M^++H]. Anal. calcd for $C_{19}H_{19}NO$: C, 82.28 H, 6.90 N, 5.05. Found: C, 82.08 H, 6.76 N, 5.27.

(1*RS*,5*SR*,7*SR*)-3-benzyl-7-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptan-2-one (6a)
Yellow oil. 139 mg, 80% yield. Purified via gradient reverse phase chromatography (H_2O/acetonitrile from 35/65 to 25/75).
^{1}H NMR (400 MHz, $CDCl_3$ 7.39 – 7.21 (m, Ar + Ph, 7H), 7.01 (t, ^3J = 8.6 Hz, 2H), 4.65 (d, CH_2Ph, $^2J(H,H)$ = 14.6 Hz, 1H), 4.41 (d, CH_2Ph, $^2J(H,H)$ = 14.6 Hz, 1H), 3.65 (m, 1H), 3.50 (m, 1H), 3.17 (m, 2H), 2.98 (m, 1H), 2.44 (m, 1H), 2.33 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8 (s, *C*=O), 161.5 (d, $^1J(C,F)$ = 244.6 Hz), 140.2 (d, $^4J(C,F)$ = 3.0 Hz), 136.5, 128.8, 128.2, 127.9 (d, $^3J(C,F)$ = 7.9 Hz), 127.6, 115.3 (d, $^2J(C,F)$ = 21.2 Hz), 53.2, 48.6, 46.8, 42.1, 33.9, 27.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.4 (s). MS (CI, m/z): 296 [M^++H]. Anal. calcd for $C_{19}H_{18}FNO$: C, 77.27 H, 6.14 N, 4.74. Found: C, 76.96 H, 6.30 N, 5.06.

(1*RS*,5*SR*,7*SR*)-3-benzyl-7-(3-fluorophenyl)-3-azabicyclo[3.2.0]heptan-2-one (7a)
Yellow oil. 182 mg, 61% yield. Purified via gradient reverse phase chromatography (H_2O/acetonitrile from 65/35 to 40/60).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.23 (m, Ar + Ph, 6H), 7.10 (d, Ar, ^3J = 7.6 Hz, 1H), 7.04 (d, Ar, ^3J = 9.8 Hz, 1H), 6.91 (t, Ar, ^3J = 7.6 Hz, 1H), 4.66 (d, CH_2Ph, $^2J(H,H)$ = 14.6 Hz, 1H), 4.42 (d, CH_2Ph, $^2J(H,H)$ = 14.6 Hz, 1H), 3.67 (m, 1H), 3.51 (m, 1H), 3.17 (m, 2H), 3.00 (m, 1H), 2.47 (m, 1H), 2.33 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.7 (s, *C*=O), 163.1 (d, Ar, $^1J(C,-F)$ = 245.8 Hz), 147.1 (d, Ar, $^3J(C,F)$ = 7.1 Hz), 136.5, 130.0 (d, Ar, $^3J(C-F)$ = 8.4 Hz), 128.8, 128.2, 127.7, 122.2 (d, Ar, $^4J(C,F)$ = 2.8 Hz), 113.3 (d, Ar, $^2J(C,F)$ = 21.4 Hz), 113.2 (d, Ar, $^2J(C,F)$ = 21.1 Hz), 53.1, 48.3, 46.8, 42.5 (d, ArCH, $^4J(C,F)$ = 1.7 Hz), 33.6, 27.4. ^{19}F NMR (376 MHz, $CDCl_3$) δ -113.7 (s). MS (CI, m/z): 296 [M^++H]. Anal. calcd for $C_{19}H_{18}FNO$: C, 77.27 H, 6.14 N, 4.74. Found: C, 77.65 H, 6.05 N, 4.87.

(1*RS*,5*SR*,7*SR*)-3-benzyl-7-(2-fluorophenyl)-3-azabicyclo[3.2.0]heptan-2-one (8a)
Yellow oil. 171 mg, 85% yield. Purified via gradient reverse phase chromatography (H_2O/acetonitrile from 35/65 to 30/70).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 6.97 (m, Ar + Ph, 9H), 4.66 (d, CH_2Ph, $^2J(H,H)$ = 14.5 Hz, 1H), 4.43 (d, CH_2Ph, $^2J(H,H)$ = 14.5 Hz, 1H), 3.84 (m, 1H), 3.50 (m, 1H), 3.32 (m, 1H), 3.05 (m, 1H), 2.46 (m, 1H), 2.36 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ

175.9 (s, C=O), 160.8 (d, $^{1}J(C,F)$ = 246.1 Hz), 136.6, 131.1 (d, $^{2}J(C,F)$ = 14.3 Hz), 128.8, 128.2, 128.1 (d, $^{3}J(C,F)$ = 8.3 Hz), 128.0 (d, $^{3}J(C,F)$ = 4.7 Hz), 127.6, 124.1 (d, $^{4}J(C,F)$ = 3.5 Hz), 115.6 (d, $^{2}J(C,F)$ = 22.0 Hz), 53.1, 46.8, 46.7, 37.6, 33.8, 27.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.2 (s). MS (CI, m/z): 296 [M^++H]. Anal. calcd for $C_{19}H_{18}FNO$: C, 77.27 H, 6.14 N, 4.74. Found: C, 76.96 H, 5.99 N, 4.94.

(1*RS*,5*SR*,7*SR*)-3-benzyl-7-(4-methoxyphenyl)-3-azabicyclo[3.2.0]heptan-2-one (9a)

Yellow oil. 151 mg, 82% yield. Purified via gradient reverse phase chromatography (H_2O/acetonitrile from 35/65 to 30/70).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.16 (m, Ph + Ar, 7H), 6.87 (d, Ar, $^{3}J(H,H)$ = 8.6 Hz, 2H), 4.65 (d, $^{2}J(H,H)$ = 14.6 Hz, 1H), 4.41 (d, $^{2}J(H,H)$ = 14.6 Hz, 1H), 3.79 (s, OCH_3, 3H), 3.62 (s, 1H), 3.48 (m, 1H), 3.15 (m, 2H), 2.97 (m, 1H), 2.44 (m, 1H), 2.29 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1(s, *C*=O), 158.1, 136.7, 128.7, 128.2, 127.6, 127.4, 113.9, 55.3, 53.2, 48.7, 46.8, 42.2, 33.9, 27.3. MS (CI, m/z): 308 [M^++H]. Anal. calcd for $C_{20}H_{21}NO_2$: C, 78.15 H, 6.89 N, 4.56. Found: C, 78.50 H, 7.15 N, 4.73.

(1*RS*,5*SR*,7*SR*)-3-benzyl-7-(3-methoxyphenyl)-3-azabicyclo[3.2.0]heptan-2-one (10a)

Yellow oil. 181 mg, 61% yield. Purified via gradient reverse phase chromatography (H_2O/acetonitrile from 35/65 to 30/70).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.20 (m, 6H), 6.93 (d, Ar, $^{3}J(H,H)$ = 7.6 Hz, 1H), 6.87 (s, Ar, 1H), 6.76 (d, Ar, $^{3}J(H,H)$ = 8.1 Hz, 1H), 4.65 (d, CH_2Ph, $^{2}J(H,H)$ = 14.6 Hz, 1H), 4.41 (d, CH_2Ph, $^{2}J(H,H)$ = 14.6 Hz, 1H), 3.80 (s, OCH_3, 3H), 3.65 (m, 1H), 3.48 (m, 1H), 3.17 (d, $^{3}J(H,H)$ = 10.2 Hz, 2H), 2.99 (m, 1H), 2.48 (m, 1H), 2.31 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0 (s, C=O), 159.8 (s, Ph), 146.2 (s, Ph), 136.6 (s, Ph), 129.5 (s, Ph), 128.7 (s, Ph), 128.2 (s, Ph), 127.6 (s, Ph), 118.7 (s, Ph), 112.3 (s, Ph), 111.6 (s, Ph), 55.2, 53.1, 48.4, 46.8, 42.8, 33.7, 27.4. MS (CI, m/z): 308 [M^++H]. Anal. calcd for $C_{20}H_{21}NO_2$: C, 78.15 H, 6.89 N, 4.56. Found: C, 77.87 H, 6.60 N, 4.44.

(1*RS*,5*SR*,7*SR*)-3-benzyl-7-(2-methoxyphenyl)-3-azabicyclo[3.2.0]heptan-2-one (11a)

Yellow oil. 159 mg, 74% yield. Purified via gradient reverse phase chromatography (H_2O/acetonitrile from 40/60 to 25/75).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 6.80 (m, Ar + Ph, 9H), 4.65 (d, CH_2Ph, $^{2}J(H,H)$ = 14.7 Hz, 1H), 4.44 (d, CH_2Ph, $^{2}J(H,H)$ = 14.4 Hz, 1H), 3.90 (m, 1H), 3.83 (s, OCH_3, 3H), 3.48 (m, 1H), 3.28 (m, 1H), 3.18 (d, J = 10.3 Hz, 1H), 2.96 (m, 1H), 2.42 (m, 1H), 2.30 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5 (s, *C*=O), 157.1, 136.8, 132.3, 128.7, 128.2, 127.54, 127.51, 126.6, 120.4, 110.5, 55.4, 53.2, 46.8, 46.6, 38.3, 33.6, 27.3. MS (CI, m/z): 308 [M^++H]. Anal. calcd for $C_{20}H_{21}NO_2$: C, 78.15 H, 6.89 N, 4.56. Found: C, 77.93 H, 6.65 N, 4.34.

(1*SR*,5*RS*,7*RS*)-3-benzyl-1-fluoro-7-(4-fluorophenyl)-3-azabicyclo[3.2.0]heptan-2-one (12a)

Yellow oil. 174 mg, 62% yield. Purified via gradient reverse phase chromatography (H_2O/acetonitrile from 35/65 to 25/75).
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.12 (m, Ph, Ar, 9H), 4.71 (d, CH_2Ph, $^{2}J(H,H)$ = 14.6 Hz, 1H), 4.47 (d, CH_2Ph, $^{2}J(H,H)$ = 14.6 Hz, 1H), 3.99 (m, 1H, H-7), 3.58 (m, 1H, H-4), 3.25 (m, 1H, H-5), 3.10 (m, 1H, H-4), 2.53 (m, 1H, H-6), 1.79 (m, 1H, H-6). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.3 (d, $^{2}J(C,F)$ = 24.6 Hz, *C*O), 141.3 (C_{ar}), 135.5 (C_{ar}), 129.4 (q, $^{2}J(C,F)$ = 32.6 Hz, C_{ar}), 129.0 (*C*H$_{ar}$), 128.6 (*C*H$_{ar}$), 128.3 (*C*H$_{ar}$), 128.1 (*C*H$_{ar}$), 125.5 (q, $^{3}J(C,F)$ = 3.7 Hz, *C*H$_{ar}$), 124.2 (q, $^{1}J(C,F)$ = 272.0 Hz, *C*F$_3$), 92.8 (d, $^{1}J(C,F)$ = 252.7 Hz, *C*F), 50.2 (s, C-4), 47.2 (s, *C*H$_2$Ph), 45.5 (d, $^{2}J(C,F)$ = 23.9 Hz, C-7), 36.3 (d, $^{2}J(C,F)$ = 19.5 Hz, C-5), 25.5 (d, $^{3}J(C,F)$ = 11.8 Hz, C-6). ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.0 (s, CF_3, 3F), -159.4 (s, C*F*, F). MS (CI, m/z): 364 [M^++H]. Anal. calcd for $C_{20}H_{17}F_4NO$: C, 66.11 H, 4.72 N, 3.85. Found: C, 65.98 H, 4.58 N, 3.55.

(1*R*,5*S*,7*S*)-7-phenyl-3-((*R*)-1-phenylethyl)-3-aza-bicyclo[3.2.0]heptan-2-one (13a)

Mp = 100-102 °C. White crystals. 144 mg, 37% yield. Purified *via* column chromatography (hexanes/ethyl acetate = 80/20). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.26 (m, 10H), 5.63 (q, *J* = 7.1 Hz, 1H), 3.64 (s, 1H), 3.56 (m, 1H), 3.19 (m, 1H), 3.01 (m, 1H), 2.91 (m, 1H), 2.40 (m, 1H), 2.14 (m, 1H), 1.59 (d, $^{3}J(H,H)$ = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5 (s, *C*=O), 144.6 (s, Ph), 140.6 (s, Ph), 128.6 (s, Ph), 128.5 (s, Ph), 127.5 (s, Ph), 127.0 (s, Ph), 126.4 (s, Ph), 126.3 (s, Ph), 48.89, 48.86, 48.5, 42.8, 33.4, 27.4, 15.7. MS (CI, m/z): 292 [M^++H]. Anal. calcd for $C_{20}H_{21}NO$: C, 82.44 H, 7.26 N, 4.81. Found: C, 82.12 H, 7.54 N, 4.63.

(1*S*,5*R*,7*R*)-7-phenyl-3-[(1*R*)-1-phenylethyl]-3-azabicyclo[3.2.0]heptan-2-one (13b)

Mp = 101-103 °C. White crystals. 123 mg, 41% yield. Purified via column chromatography (hexanes/ethyl acetate = 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.13 (m, Ph, 10H), 5.59 (m, PhC*H*N, 1H), 3.67 (m, 1H), 3.19 (m, 3H), 2.92 (m, 1H), 2.50 (m, 1H), 2.37 (m, 1H), 1.62 (d, $^{3}J(H,H)$ = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5 (s, *C*=O), 144.5, 139.8, 128.6, 127.5, 127.3, 126.4, 126.3, 49.2, 48.91, 48.86, 42.7, 33.8, 27.4, 16.3. MS (CI, m/z): 292 [M^++H]. Anal. calcd for $C_{20}H_{21}NO$: C, 82.44 H, 7.26 N, 4.81. Found: C, 82.82 H, 7.03 N, 4.66.

(1*R*,5*S*,7*S*)-7-(4-fluorophenyl)-3-[(1*R*)-1-phenylethyl]-3-azabicyclo[3.2.0]heptan-2-one (14a)

Mp = 112-114 °C. White crystals. 109 mg, 29% yield. Purified via column chromatography (hexanes/ethyl acetate = 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (m, Ar + Ph, 7H), 6.99 (t, Ar, *J* = 8.5 Hz, 2H), 5.60 (q, PhC*H*CH_3, $^{3}J(H,H)$ = 7.0 Hz, 1H), 3.54 (m, 2H), 3.10 (m, 1H), 2.96 (m, 1H), 2.87 (d, $^{3}J(H,H)$ = 10.1 Hz, 1H), 2.31 (m, 1H), 2.10 (m, 1H), 1.55 (d, PhCHC*H*$_3$, ^{3}J(H,H) = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3 (s, *C*=O), 161.4 (d, Ar, $^{1}J(C,F)$ = 244.3 Hz), 140.5 (s, Ph), 140.3 (d, Ar, $^{4}J(C,F)$ = 3.0 Hz), 128.6 (s, Ph), 127.9 (d, Ar, $^{3}J(C,F)$ = 7.9 Hz), 127.5 (s, Ph), 127.0 (s, Ph), 115.3 (d, Ar, $^{2}J(C,F)$ = 21.2 Hz), 49.0, 48.9, 48.5, 42.2, 33.5, 27.3, 15.7. ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.4. MS (CI, m/z): 310 [M^++H]. Anal. calcd for $C_{20}H_{20}FNO$: C, 77.64 H, 6.52 N, 4.53. Found: C, 77.33 H, 6.73 N, 4.34.

(1*S*,5*R*,7*R*)-7-(4-fluorophenyl)-3-[(1*R*)-1-phenylethyl]-3-azabicyclo[3.2.0]heptan-2-one (14b)

Mp = 113-114 °C. White crystals. 131 mg, 36% yield. Purified via column chromatography (hexanes/ethyl acetate = 80/20). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, Ph + Ar, 7H), 7.00 (t, *J* = 8.6 Hz, 2H), 5.59 (q, PhC*H*CH_3, $^{3}J(H,H)$ = 7.0 Hz, 1H), 3.64 (m, 1H), 3.19 (m, 2H), 3.08 (m, 1H), 2.91 (m, 1H), 2.40 (m, 2H), 1.61 (d, PhCHC*H*$_3$, $^{3}J(H,H)$ = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3 (s, *C*=O), 161.4 (d, Ar, $^{1}J(C,F)$ = 244.3 Hz), 140.2 (d, Ar, $^{4}J(C,F)$ = 3.1 Hz), 139.8 (s, Ph), 128.6 (s, Ph), 127.9 (d, Ar, $^{3}J(C,F)$ = 7.9 Hz), 127.6 (s, Ph), 127.3 (s, Ph), 115.3 (d, Ar, $^{2}J(C,F)$ = 21.2 Hz), 49.2, 49.0, 48.9, 42.1, 33.9, 27.2, 16.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -117.4 (s). MS (CI, m/z): 310 [M^++H]. Anal. calcd for $C_{20}H_{20}FNO$: C, 77.64 H, 6.52 N, 4.53. Found: C, 77.76 H, 6.77 N, 4.24.

(1*R*,5*S*,7*S*)-3-benzyl-6-methyl-7-phenyl-3-azabicyclo[3.2.0]heptan-2-one (15a)

Colorless oil. 162 mg, 80% yield. ^{1}H NMR (400 MHz, $CDCl_3$) Mixture of diastereomers : δ 7.56 – 6.72 (m, 10H), 4.68, 4.61 (d, $^{2}J(H,H)$ = 14.6 Hz, 1H), 4.44, 4.40 (2×d, $^{2}J(H,H)$ = 3.5 Hz, 1H), 3.80 – 3.72 (m, 1H), 3.52 – 3.41 (m, 1H), 3.40 – 3.28 (m, 1H), 3.20 – 3.10 (m, 1H), 3.03 – 2.89, 2.81

– 2.69 (m, 1H), 2.63 – 2.53 (m, 1H), 1.05, 0.64 (d, $^2J(H,H)$ = 7.1, 6.5 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 176.5 (C=O), 140.4, 136.71, 128.9, 128.8, 128.6, 128.5, 128.32, 128.27, 128.2, 127.8, 127.7, 126.5, 126.4, 52.2, 51.3, 47.0, 46.9, 46.5, 45.8, 43.7, 39.1, 37.7, 36.8, 29.3, 16.3, 15.8. MS (CI, m/z): 292 [M^++H]. Anal. calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.20; H, 7.54; N, 4.93.

(1*R*,5*S*,7*S*)-3-benzyl-6-ethyl-7-phenyl-3-azabicyclo[3.2.0]heptan-2-one (16a)

Colorless oil. 151 mg, 83% yield. Purified via column chromatography (hexanes/ethyl acetate = 80/20).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 – 7.04 (m, 10), 4.64, 4.57 (2×d, *J* = 14.5 Hz, 1H), 4.52 – 4.44 (m, 1H), 3.82 – 3.76 (m, 1H), 3.54 –3.35 (m, 1H), 3.29-3.12 (m, 1H), 3.12 – 2.96 (m, 1H), 2.71 – 2.53 (m, 1H), 2.42 – 2.28 (m, 1H), 1.11 – 0.92 (m, 2H), 0.78, 0.59 (2×t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.5, 140.7, 136.7, 128.9, 128.8, 128.7, 128.6, 128.5, 128.3, 128.2, 127.8, 127.7, 127.4, 127.1, 126.7, 126.4, 52.6, 50.0, 47.1, 46.9, 46.49, 46.47, 46.2, 45.9, 44.4, 44.0, 35.6, 28.5, 24.1, 11.6, 11.1. MS (CI, m/z): 306 [M^++H]. Anal. calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.20; H, 7.91; N, 4.38.

(1*R*,5*S*,7*S*)-3-benzyl-5-methyl-7-phenyl-3-azabicyclo[3.2.0]heptan-2-one (17a)

Colorless oil. 176 mg, 85% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.17 (m, 10H), 4.67 (d, $^2J(H,H)$ = 14.8 Hz, 1H), 4.41 (d, $^2J(H,H)$ = 14.7 Hz, 1H), 3.67 – 3.53 (m, 1H), 3.35 (d, $^3J(H,H)$ = 10.1 Hz, 1H), 3.11 (d, $^3J(H,H)$ = 10.1 Hz, 1H), 2.92 (d, *J* = 4.4 Hz, 1H), 2.52 – 2.43 (m, 1H), 2.28 – 2.20 (m, 1H), 1.24 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.1, 144.0, 136.8, 128.9, 128.6, 128.2, 127.7, 126.6, 126.4, 60.1, 53.9, 46.8, 39.6, 33.9, 33.6, 25.7. MS (CI, m/z): 292 [M^++H]. Anal. calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.60; H, 7.12; N, 4.98.

(1*R*,5*S*,7*S*)-3-benzyl-5-ethyl-7-phenyl-3-azabicyclo[3.2.0]heptan-2-one (18a)

Colorless oil. 182 mg, 81% yield. Purified via column chromatography (hexanes/ethyl acetate = 80/20).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 – 7.14 (m, 10H), 4.64 (d, $^2J(H,H)$ = 14.6 Hz, 1H), 4.43 (d, $^2J(H,H)$ = 14.7 Hz, 1H), 3.62 (m, 1H), 3.30 (d, $^2J(H,H)$ = 10.1 Hz, 1H), 3.19 (d, $^2J(H,H)$ = 10.1 Hz, 1H), 2.94 (d, $^3J(H,H)$ = 5.1 Hz, 1H), 2.43-2.37 (m, 1H), 2.29-2.24 (m, 1H), 1.64 – 1.40 (m, 2H), 0.76 (t, $^3J(H,H)$ = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.2 (s, C=O), 144.0, 136.7, 128.9, 128.6, 128.2, 127.7, 126.6, 126.3, 57.8, 52.2, 46.8, 39.7, 37.7, 31.5, 8.0. MS (CI, m/z): 306 [M^++H]. Anal. calcd for $C_{21}H_{23}NO$: C, 82.58; H, 7.59; N, 4.59. Found: C, 82.25; H, 7.97; N, 4.41.

(1*S*,6*R*,8*S*)-3-benzyl-8-phenyl-3-azabicyclo[4.2.0]octan-2-one (19a)

Colorless oil. 171 mg, 89% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 – 7.14 (m, 10H), 4.70 (d, $^2J(H,H)$ = 14.6 Hz, 1H), 4.62 (d, $^2J(H,H$ = 14.6 Hz, 1H), 3.80 (q, *J* = 8.8 Hz, 1H), 3.44 – 3.32 (m, 1H), 3.32 – 3.19 (m, 2H), 2.75 – 2.62 (m, 1H), 2.45 – 2.34 (m, 1H), 2.24 – 2.11 (m, 1H), 2.04 – 1.93 (m, 1H), 1.93 – 1.73 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.9, 144.5, 137.5, 128.7, 128.4, 128.2, 127.5, 126.7, 126.2, 50.4, 45.9, 44.8, 42.7, 30.8, 29.9, 28.6. MS (CI, m/z): 292 [M^++H]. Anal. calcd for $C_{20}H_{21}NO$: C, 82.44; H, 7.26; N, 4.81. Found: C, 82.21; H, 7.54; N, 4.98.

General procedure for synthesis of amines 20 and 21

1M solution of product of [2+2] cycloaddition (1.0 equiv) was added dropwise to 2M suspension of $LiAlH_4$ in THF (2.0 equiv) at room temperature. The reaction mixture was heated at reflux for 5 h, cooled to -20 °C and treated dropwise with 40% aqueous KOH solution (approx. 5 equiv). Formed suspension was filtered through Na_2SO_4. The solution was concentrated. The obtained product was distilled (0.1 mm Hg) and dissolved in methanol to get 1M solution. 10% Palladium on charcoal (0.1 equiv) and 2M aqueous HCl (1.5 equiv) were added. The resulted reaction mixture was stirred under hydrogen atmosphere (50 atm.) overnight at 50 ^{0}C, then filtered, evaporated and dried *in vacuo* to give the desired product.

(1*SR*,5*RS*,6*SR*)-6-phenyl-3-azoniabicyclo[3.2.0]heptane hydrochloride (20)

Mp = 154-155 °C. White crystals. 25.2 g, 83% yield.

^{1}H NMR (400 MHz, D_2O) δ 7.32 – 7.11 (m, Ph, 5H), 3.40 (m, 2H), 3.13 (m, 5H), 2.27 (m, 1H), 2.10 (m, 1H). ^{13}C NMR (101 MHz, D_2O) δ 144.6 (s, Ph), 128.9 (s, Ph), 126.6 (s, Ph), 126.4 (s, Ph), 51.7, 51.7, 44.6, 40.8, 33.3, 30.1. MS (CI, m/z): 174 [M$^+$-Cl]. Anal. calcd for $C_{12}H_{16}ClN$: C, 68.73 H, 7.69 N, 6.68. Found: C, 68.40 H, 7.97 N, 6.47.

(1*S*,5*R*,6*S*)-6-(4-fluorophenyl)-3-azoniabicyclo[3.2.0]heptane chloride ((*S*)-21)

Mp = 147-148 °C. White crystals. 89 mg, 72% yield.

^{1}H NMR (400 MHz, MeOD) δ 7.29 (dd, *J* = 8.5, 5.4 Hz, 2H), 7.02 (t, *J* = 8.7 Hz, 2H), 3.51 (m, 2H), 3.26 (m, 5H), 2.32 (m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 161.5 (d, Ar, $^1J(C,F)$ = 243.1 Hz), 140.2 (d, Ar, $^4J(C,F)$ = 3.1 Hz), 127.8 (d, Ar, $^3J(C,F)$ = 8.0 Hz), 114.8 (d, Ar, $^2J(C,F)$ = 21.5 Hz), 51.39, 51.37, 45.4, 40.3, 33.4, 30.4. ^{19}F NMR (376 MHz, MeOD) δ -119.3 (s). MS (CI, m/z): 192 [M$^+$+H]. Anal. calcd for $C_{12}H_{15}ClFN$: C, 63.30 H, 6.64 N, 6.15. Found: C, 63.61 H, 6.42 N, 6.32.

(1*R*,5*S*,6*R*)-6-(4-fluorophenyl)-3-azoniabicyclo[3.2.0]heptane chloride ((*R*)-21)

Mp = 147-148 °C. 92 mg, 86% yield.

^{1}H NMR (400 MHz, MeOD) δ 7.29 (dd, *J* = 8.6, 5.4 Hz, 2H), 7.03 (t, *J* = 8.6 Hz, 2H) 3.54 (m, 2H), 3.26 (m, 5H), 2.33(m, 2H). ^{13}C NMR (101 MHz, MeOD) δ 161.6 (d, Ar, $^1J(C,F)$ = 243.2 Hz), 140.2 (d, Ar, $^4J(C,F)$ = 3.1 Hz), 127.8 (d, Ar, $^3J(C,F)$ = 8.0 Hz), 114.8 (d, Ar, $^2J(C,F)$ = 21.5 Hz), 51.41, 51.39, 45.3, 40.3, 33.4, 30.4. ^{19}F NMR (376 MHz, MeOD) δ -119.4 (s). MS (CI, m/z): 192 [M$^+$+H]. Anal. calcd for $C_{12}H_{15}ClFN$: C, 63.30 H, 6.64 N, 6.15. Found: C, 63.01 H, 6.80 N, 6.39.

General procedure for synthesis of amides 22-24 for biophysical studies

DMF (0.02 equiv) was added to 1 M solution of 4-fluorobenzoic acid (1.0 equiv) in CH_2Cl_2. Then, $SOCl_2$ (3.0 equiv) was added dropwise at room temperature and reaction mixture was heated at reflux for 2 h. Solvent and volatile by-products were removed under reduced pressure; 4-fluorobenzoyl chloride was distilled (44-46 °C at 3 mm Hg) and added dropwise to 1M solution of the corresponding amine (0.8 equiv) with triethylamine (1.1 equiv) at -20 °C. Reaction mixture was warmed to room temperature, stirred overnight and washed with 0.5 M aqueous solution of citric acid (approx. 1 equiv), saturated aqueous solution of $NaHCO_3$ (approx. 1 equiv) and water. Organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure to afford pure product (87-92% yield).

Measurement of lipophilicity, aqueous solubility and metabolic stability of compounds 22-24

Metabolic stability is defined as the percentage of parent compound lost over time in the presence of a metabolically active test system.

ASSOCIATED CONTENT

Supporting Information

Measurement of lipophilicity, aqueous solubility and metabolic stability of compounds **22**-**24**. X-ray crystallography information. Copies of NMR spectra. 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

ACKNOWLEDGMENT

Authors are very grateful to Dr. S. Shishkina for *X*-Ray studies, to Prof. A. Tolmachev for financial support. P.M. is very grateful to Prof. T. Bach for the inspiration in photochemistry, and to Dr. Bill Heilman and Mrs. I. Sadkova for the helpful suggestions on the manuscript.

Keywords: • drug discovery, • building blocks, • photochemistry, • conformational restriction, • amines

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