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Robust and Scalable Approach to 1,3-Disubstituted Pyridylcyclobutanes

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Abstract: An approach to all isomeric 3-pyridylcyclobutane-derived building blocks, *i.e.* ketones, alcohols and amines, is described. Synthesis of the title compounds relied on the five-step reaction sequence including alkylation of isomeric pyridyl acetonitriles with 1,3-dibromo-2,2-dimethoxypropane. Hydrolysis, decarboxylation and removal of the ketal moiety led to the key 3-pyridylcyclobutanones (obtained on up to 120 g scale in a single run), which were transformed into the corresponding alcohols and amines with high diastereosele-ctivity. The title cyclobutanone derivatives were used to synthesize three isomeric nicotine analogues, as well as for parallel synthesis of a small lead-like compound library *via* reductive amination.

Introduction

Pyridine is the top aromatic nitrogen heterocycle which is most often encountered in FDA-approved pharmaceuticals.[1] Prominent examples of pyridine-containing drugs are anticancer agent imatinib (**1**), and antiretroviral drug atazanavir (**2**) found in World Health Organization's list of essential medicines. Notably, both these molecules have the pyridyl moiety attached to an aromatic ring. Similar biaryl systems have become widespread in medicinal chemistry since ubiquitous implementation of the palladium-catalyzed C–C couplings.[2,3] Meanwhile, a concern has arisen that high abundance of drug candidates with low sp^3 atom fraction might increase attrition rate in clinical trials.[4] The «escape from flatland» concept was proposed which drew attention of organic and medicinal chemists to the molecules with higher degree of saturation.[5,6] Several pyridine derivatives bearing sp^3-enriched moieties can be found among FDA-approved drugs and/or natural compounds, *i.e.* pyridyl propylamine series represented by chlorpheniramine (**3**), brompheniramine (**4**), disopyramide (**5**), as well as alkaloids nicotine (**6**), epibatidine (**7**), and dianicline (**8**) (Figure 1).

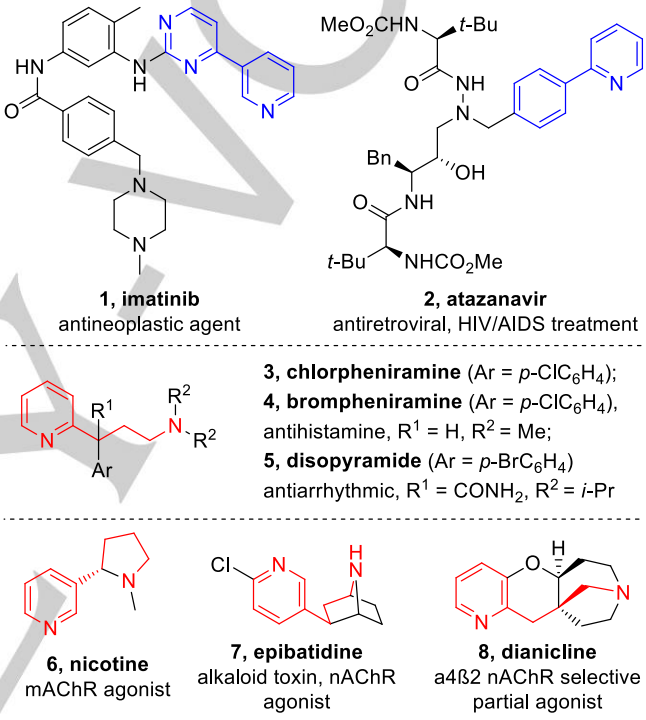

Figure 1. Some important pyridine derivatives

On the other hand, conformational restriction is a widely used design strategy in drug discovery which can potentially lead to enhanced potency, improved selectivity, and reduced metabolism rate of the compound due to minimization of entropic penalty upon binding to biological targets.[7] In this view, cyclobutane fragment seems to be especially promising as the conformational restriction tool since it is the smallest ring which does not lead to significant changes in chemical properties when introduced into the target molecules.[8–10]

Taking into account the aforementioned considerations, we have turned our attention to functionalized pyridylcyclobutanes as attractive chemotypes for design of biologically active compounds. The known approaches to the synthesis of pyridylcyclobutane derivatives include metal-catalyzed sp^2-sp^3 cross-couplings of halopyridines,[11–19] reactions of metallated pyridines,[20–23] the Minisci[17] or the Barton[24] radical reactions, transformations of pyridine *N*-oxides or their derivatives,[24–29] as well as other methods.[30–33] However, most literature examples relied on the [2+2] cycloadditions,[34] including photodimerization,[35–39] intra-[40–44] and intermolecular[45–49] reactions. Most of

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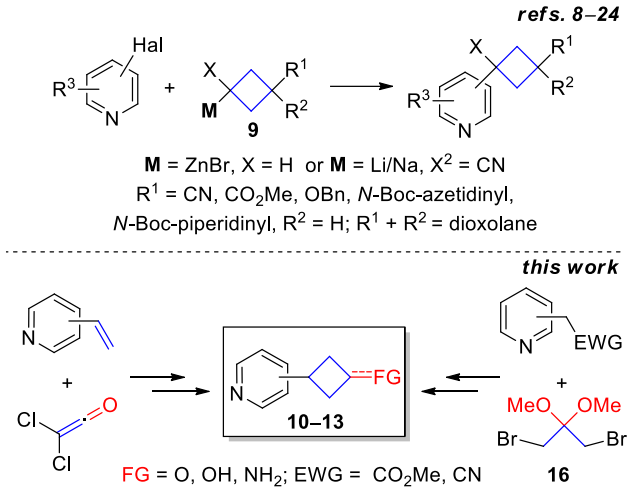
these methods were applied for the synthesis of derivatives lacking functional groups at the cyclobutane ring. Synthesis of functionalized pyridylcyclobutanes is less represented in the literature; in particular, 1,3-disubstituted cyclobutane derivatives were prepared *via* S_NAr or Negishi arylation of metallated cyclobutanes **9** with halopyridines (Scheme 1).[15,50–52]



Scheme 1. Syntheses of functionalized 1,3-disubstituted pyridylcyclobutanes

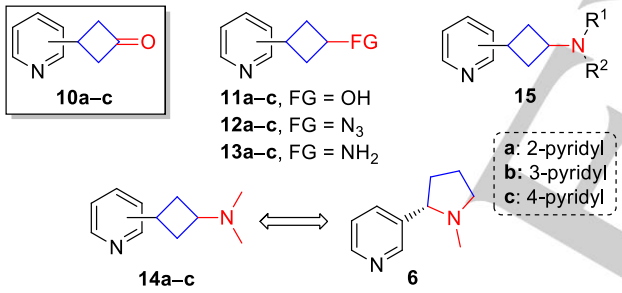
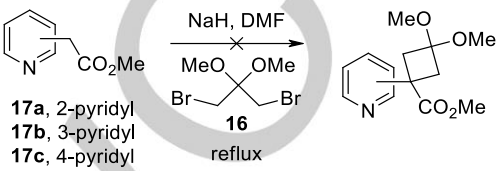


Figure 2. Building blocks **10**–**13** and other target compounds of this study

In this work, we have aimed at synthesis of all isomeric 3-pyridylcyclobutanones **10**, as well as other building blocks of these series, *i.e.* alcohols **11**, azides **12**, and amines **13** (Figure 2). To demonstrate utility of these products, their further modification to obtain nicotine analogues **14**, as well as a small lead-like compound library **15** under the parallel synthesis conditions was envisaged. Two synthetic strategies were considered for the preparation of the key intermediates **10**, *i.e.* [2+2] cycloaddition with ketenes, as well as double alkylation of pyridyl-substituted active methylene compounds with 1,3-dibromo-2,2-dimethoxypropane (**16**) (Scheme 1). It should be noted that neither approach has been used for the preparation of functionalized 1,3-disubstituted pyridylcyclobutanes to date, although the latter strategy was applied for the synthesis of cyclobutylpyridines lacking other substituents at the cyclobutane ring.[53–56]

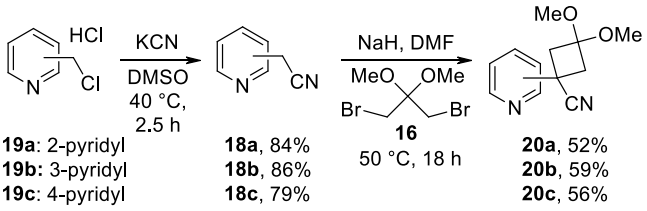
Results and Discussion

It was found that [2+2] cycloaddition of vinylpyridines with dichloroketene led to complex mixtures of products and was accompanied significant tar formation in all cases. Thus, we have switched to the second strategy and studied reaction of dibromide **16** with readily accessible pyridylacetates **17a–c** in the presence of NaH. Unfortunately, the reaction did not occur even in refluxing DMF (Scheme 2).



Scheme 2. Attempted double alkylation reaction of pyridylacetates **17a–c**

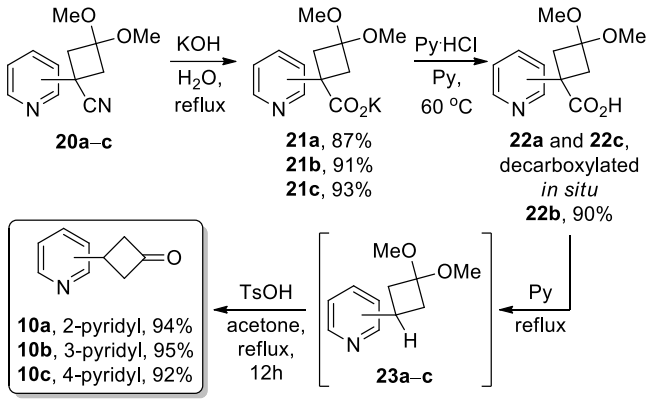
Therefore, (2-pyridyl)acetonitrile (**18a**) was synthesized from the commercially available 2-(chloromethyl)pyridine (**19a**) by reaction with KCN in DMSO at 40 °C in 84% yield (Scheme 3).[57,58] Subsequent alkylation of **18a** with **16** was fruitful when the reaction was performed in DMF at 50 °C for 18 h, which provided the target cyclobutane derivative **20a** in 52% yield. This result was successfully extended towards all other regioisomers. Thus, the starting chlorides **19b** and **19c** were transformed to pyridyl acetonitriles **18b** and **18c** (in 86% and 79% yield, respectively), which in turn were used in the reaction with **16** giving cyclobutanes **20b** and **20c** in 59% and 56% yield, respectively. It should be noted that applying higher temperatures to the highly exothermic double alkylation reaction did not result in better reaction outcome; partial decomposition of reagents as well as significant tar formation was observed. THF was not efficient as the solvent due to insufficient temperature; on the contrary, in the case of *N*-methylpyrrolidone, isolation and purification of the products **20** was complicated.



Scheme 3. Synthesis of the cyclobutane derivatives **23a–c**

Subsequent acidic hydrolysis of the nitriles **20a**–**c** led to complex mixtures of products. We believe that this result could be explained by the ketal moiety cleavage, followed by self-condensation of *in situ* generated ketones. Thus, the hydrolysis of **20a**–**c** was performed in the presence of alkali (aq KOH, reflux) tolerant to the ketal protecting group (Scheme 4). This protocol led to the formation of potassium carboxylates **21a**–**c** (87–93% yield), which were subjected to decarboxylation upon

action of an equimolar amount of Py·HCl in pyridine at 60 °C. It was found that carboxylic acids **22a** and **22c** thus formed were unstable under the reaction conditions, so that the corresponding ketals **23a** and **23c** were obtained (85% and 87% yield, respectively).



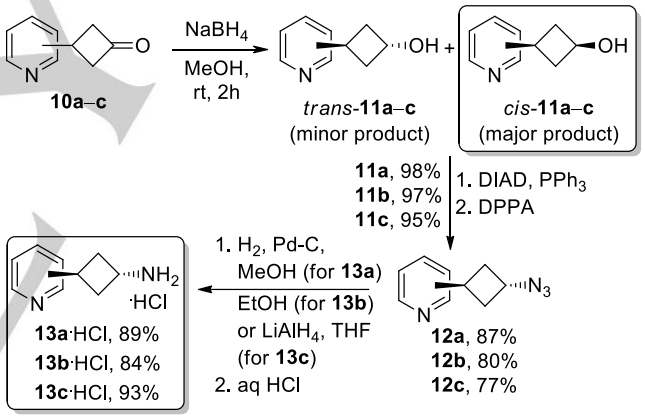
Scheme 4. Synthesis of the target ketones **10a–c**

Typically, the CO_2 evolution ceased after 2 h; however, the reaction mixture was stirred additionally overnight for the reaction completion. On the contrary, the corresponding carboxylic acid **22b** was stable under similar conditions and could be isolated in 90% yield. Further decarboxylation of **22b** required higher reaction temperature, *i.e.* refluxing in pyridine for 48 h, which resulted in the formation of **23b** (91% yield). Finally, TsOH-promoted removal of the dimethylketal moiety in **23a–c** led to the target cyclobutanones **10a–c** in excellent yield (92–95%). It should be noted that the title ketone **10a** was obtained on up to 120 g scale, while the preparation of β- and γ-isomers **10b** and **10c** was scaled up on to 50 g and 20 g, respectively.

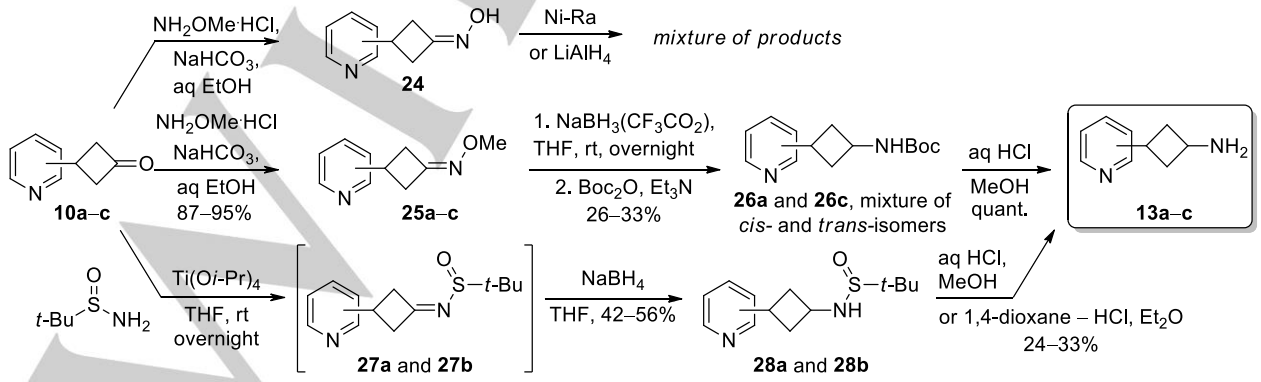
Next, we have aimed at synthesis of the amines **13a–c** from the ketones **10a–c** *via* corresponding oximes **24** or **25** (Scheme 5). Unfortunately, all the reduction conditions tested with **24** were unfruitful; in particular, catalytic hydrogenation in the presence of Raney nickel led to a complex mixture of products, while using $LiAlH_4$ resulted in predominant reduction of the pyridine ring. In turn, reaction of *O*-methyl derivatives **25** (obtained from **10a–c** in 87–95% yield) with generated *in situ* $NaBH_3(CF_3CO_2)$ in THF followed by quenching with Boc_2O gave the protected amines **26** in low yield (26–33%) after the purification step. Deprotection of **26** led to the formation of *cis*- and *trans*-**13a–c** mixtures**,** which were difficult to separate by common purification methods. As in the case of oximes **25**, using $LiAlH_4$ in THF in the case of **26** led to complex mixtures due to reduction of the pyridine ring.

Alternatively, reduction of Ellman's sulfinamides **27** (obtained from **10**) was performed with $NaBH_4$ in THF. It was found that purification of the products **28** was complicated, so that they were isolated in 42–56% yield. Moreover, subsequent deprotection of **28** upon action of aq HCl in MeOH or HCl in 1,4-dioxane - Et_2O was also unfruitful; low yields of the products **13a–c** (as hydrochlorides) were observed (less than 34% according to LCMS).

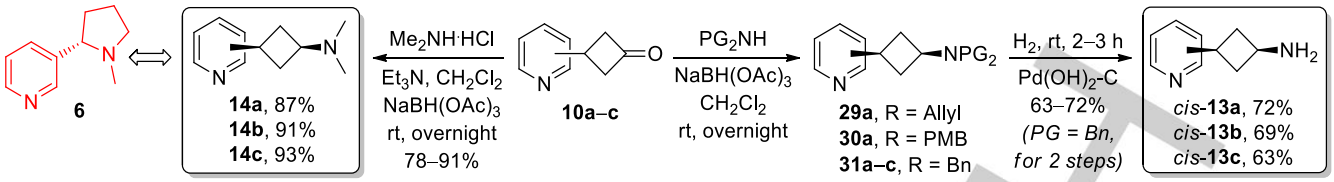
Therefore, an alternative approach to the synthesis of **13** was envisaged, including diastereoselective reduction of ketones **10** to the corresponding alcohols **11**, their transformation into azides **12** and subsequent reduction. It was found that reaction of ketones **10** with $NaBH_4$ in MeOH resulted in the predominant formation of *cis* alcohols **11a–c** (*dr* 9:1, 95–98% yield) (Scheme 6). Mesylation of *cis*-**11a–c** followed by nucleophilic substitution



Scheme 6. Synthesis of the target building blocks **11–13**



Scheme 5. Preliminary efforts towards preparation of amines **13**



Scheme 7. Synthesis of *cis* amines **13a**–**c** and nicotine analogues **14a–c**

with NaN_3 was not successful, possibly due to low stability of the corresponding mesylates (which were likely prone to elimination). Therefore, the Mitsunobu reaction was used (DIAD, PPh_3, DPPA), which proceeded smoothly and led to *trans* azides **12a**–**c**. It should be noted that *trans*-**12a** could be obtained in 87% yield as a single diastereomer after chromatographic purification, whereas *trans*-**12b** and *trans*-**12c** – with 4:1 *dr* (80% and 77% yield, respectively). It should be noted that attempted preparation of the corresponding *trans* alcohols **12** *via* the Mitsunobu reaction of their *cis* isomers and *p*-nitrobenzoic acid upon the aforementioned conditions was not successful: starting *cis*-**12** were recovered exclusively.

Catalytic hydrogenation of **12a** to *trans* isomer of the amine **13a** was performed in MeOH (1 atm of H_2, Pd-C, rt, 89% yield). In the case of **12b**, these conditions resulted in partial reduction of the pyridine ring. Interestingly, **12b** was smoothly hydrogenated in EtOH to give **13b** in 84% yield. In the case of **12c**, fruitful results were obtained only when $LiAlH_4$ was used as the reducing agent (93% yield), while the catalytic hydrogenation was successful in neither MeOH nor EtOH as the solvent.

For the preparation of *cis*-**13a**–**c**, reductive amination of ketones **10a**–**c** was considered. Reaction of **10** with $NaBH(OAc)_3$ and aq $NH_3·H_2O$ or NH_4Cl resulted in significant formation of the corresponding secondary amines. Therefore, reductive amination was performed with diallylamine, bis(4-methoxybenzyl)amine, and dibenzylamine to give tertiary amines **29**, **30**, and **31**, respectively, in up to 90% yield (Scheme 7). It was found that removal of allyl and *p*-methoxybenzyl protective groups (upon action of $Pd(PPh_3)_4$ and CAN, respectively) was not successful, whereas catalytic debenzyla-tion of **31** (H_2, $Pd(OH)_2$-C, rt, 2–3 h) led to the target *cis* amines **13a**–**c** in 63–72% yield (from **10**) with *dr* 4:1 (for **13b** and **13c**, Figure 3) to 9:1 (for **13a**).

Similar conditions were used to obtain nicotine analogues **14a–c** ($Me_2NH·HCl$, Et_3N, $NaBH(OAc)_3$, CH_2Cl_2, rt, 78–91% yield). The derivative **14a** was obtained as a single *cis* diastereomer, while regioisomers **14b** and **14c** were synthesized with moderate to good *cis* diastereoselectivity (*dr* 3:1 and 5.7:1, respectively, Figure 3).

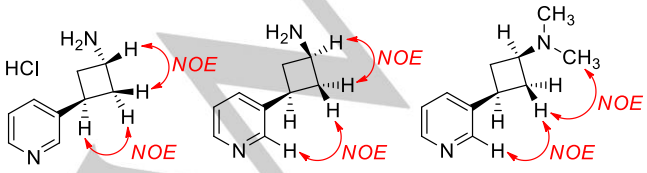
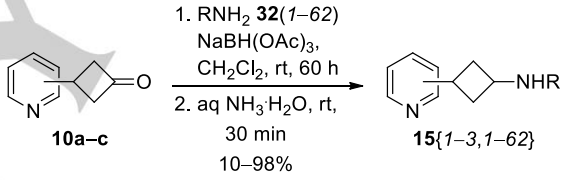


Figure 3. NOE correlations in the synthesized *cis* and *trans* isomers.

To further demonstrate utility of the building blocks obtained, a library of 62 compounds was generated by virtual coupling of building blocks **10a–c** and primary amines **32**(*1–62*) (see the SI). 60 of these library members **15**{*1–3*,*1–62*} were successfully obtained under parallel synthesis conditions with 47% average yield and 97% synthesis success rate (Scheme 8, Figure 4). Although common reaction conditions and work-up procedure were used, the corresponding *dr* values of derivatives **15** varied from low to moderate (*dr* 1:1 to 4:1). According to the previous results for **13** and **14**, formation of *cis* isomers as major ones might be suggested. Chromatographilc separation of the diastereomeric mixtures was not always successful, although could be achieved in some cases, *e.g.* **15**{*1*,*2*}, **15**{*3*,*3*}, **15**{*1*,*39*}, and **15**{*1*,*47*}.



Scheme 8. Parallel synthesis of library **15**

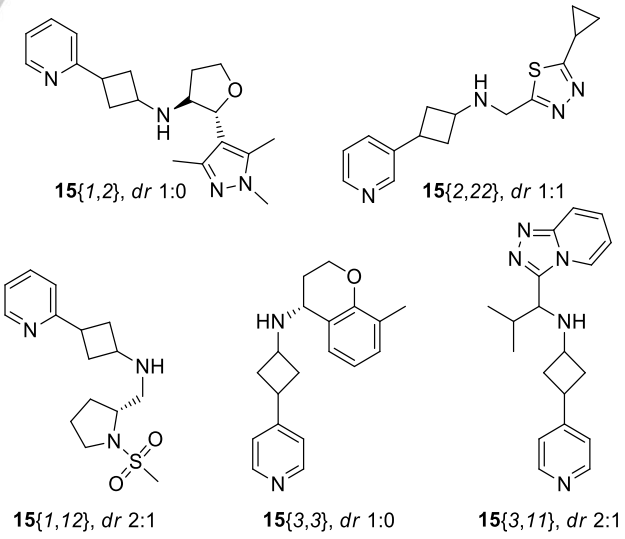


Figure 4. Representative library members **15** obtained *via* parallel reductive amination of **10a**–**c** (*dr*'s are reported for the products isolated after chromatographic purification)

Predicted physico-chemical of the synthesized library members show that the building blocks **10a–c** are perfectly suited for lead-oriented synthesis (that is, synthetic methodologies which allow preparation of lead-like compounds in robust and efficient manner, preferably under parallel synthesis conditions).[4,59] Indeed, the synthesis success rate was very high even when rather strict criteria of lead-likeness (MW = 200…350, cLogP = –1…4) were applied to the library design (Figure 5).

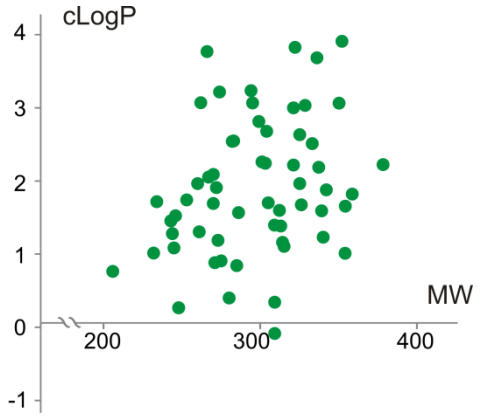


Figure 5. Predicted physico-chemical properties of 60 synthesized library members **15** shown in cLogP – MW plot[60]

Conclusions

Introduction of heteroaromatic substituents into organic molecules instead of their aryl counterparts often results in significant complications to the synthetic methodologies necessary for their preparation. This appeared to be the case for isomeric 3-pyridylcyclobutane-derived building blocks (ketones, alcohols, and amines). The interfering effects of the pyridyl substitutents were related to their strong acceptor properties (especially for 2- and 4-isomers), basicity of the nitrogen atom, as well as susceptibility to reduction. The optimized synthesis of the title cyclobutanones relied on a five-step reaction sequence including double alkylation of isomeric pyridylacetonitriles with 1,3-dibromo-2,2-dimethoxypropane as the key step. According to this scheme, the target ketones could be obtained on up to 120 g scale. Reduction of the resulting 3-(2-/3-/4-pyridyl)cyclo-butanones with $NaBH_4$ gave the corresponding *cis* alcohols with good diastereoselectivity (*dr* 9:1). Subsequent Mitsunobu reaction led to the corresponding *trans* azides, which were transformed into *trans*-3-(2-/3-/4-pyridyl)cyclobutanamines. *Cis* isomers of these amines were obtained *via* reductive amination of the title ketones with dibenzylamine, followed by catalytic hydrogenolysis (*dr* 4:1 to 9:1). A version of the latter method was also applied for the preparation of nicotine analogues and for parallel synthesis of lead-like compound libraries, which justifies utility of the building blocks obtained for medicinal chemistry.

Experimental Section

The solvents were purified according to the standard procedures.[61] Compounds **16**, **17a-c**, **19a-c**, and **32**(*1–62*) were available from Enamine Ltd. All other starting materials were purchased from commercial sources. Melting points were measured on MPA100 OptiMelt automated melting point system. Analytical TLC was performed using Polychrom SI F254 plates. Column chromatography was performed using Kieselgel Merck 60 (230–400 mesh) as the stationary phase. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^{1}H NMR, 126 MHz for ^{13}C NMR and 470 MHz for ^{19}F NMR) and Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H NMR, 101 MHz for ^{13}C NMR and 376 MHz for ^{19}F NMR). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS as an internal standard and are referenced using residual NMR solvent peaks at 7.26 and 77.16 ppm for ^{1}H and ^{13}C in $CDCl_3$, 2.50 and 39.52 ppm for ^{1}H and ^{13}C in DMSO-d_6. Coupling constants (*J*) are shown in Hz. Spectra are reported as follows: chemical shift (δ, ppm), multiplicity, integration, coupling constants (Hz). Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)) and Agilent 5890 Series II 5972 GCMS instrument (electron impact ionization (EI)).

General procedure for the preparation of pyridylacetonitriles 18a–c.[57] A solution of the corresponding chloromethylpyridine hydrochloride (40.0 g, 0.244 mol) in DMSO (120 mL) was added slowly to the suspension of NaCN (35.9 g, 0.732 mol) in DMSO (100 mL) at rt (NOTE: the temperature should not exceed 40 °C). The resulting mixture was stirred at 40 °C for 2.5 h, and solution of K_2CO_3 (101 g, 0.732 mol) and KOH (13.6 g, 0.240 mol) in H_2O (500 mL) was added. The mixture was extracted with EtOAc (3×300 mL), organic layer was separated, dried over Na_2SO_4 and evaporated in *vacuo*.

2-(Pyridin-2-yl)acetonitrile (18a).[57] The compound was purified by distillation in *vacuo*. Yield 24.2 g (84%); yellowish liquid; solidifies upon cooling below rt (mp 23–25 °C); bp 136–138 °C / 6 mmHg. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.56 (d, *J* = 4.2 Hz, 1H), 7.83 (td, *J* = 7.8, 1.9 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.37 – 7.33 (m, 1H), 4.21 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 151.3, 149.5, 137.4, 122.9, 122.7, 118.3, 25.6. LC/MS (CI): *m/z* = 119 $[M+H]^+$. Anal. Calcd. for $C_7H_6N_2$: C 71.17; H 5.12; N 23.71. Found: C 71.48; H 5.41; N 23.84.

2-(Pyridin-3-yl)acetonitrile (18b).[57] The compound was purified by distillation in *vacuo*. Yield 24.8 g (86%); yellowish liquid; bp 105–108 °C / 1.5 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 – 8.49 (m, 2H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.29 (dd, *J* = 7.6, 5.1 Hz, 1H), 3.74 (s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.5, 149.3, 136.3, 128.0, 124.4, 119.2, 20.5. LC/MS (CI): *m/z* = 119 $[M+H]^+$. Anal. Calcd. for $C_7H_6N_2$: C 71.17; H 5.12; N 23.71. Found: C 71.15; H 5.39; N 24.03.

2-(Pyridin-4-yl)acetonitrile (18c).[57,62] The compound was purified by distillation in *vacuo*. Yield 22.8 g (79%); orange solid; mp 42–44 °C; bp 141–142 °C / 16 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.9 Hz, 2H), 7.27 (d, *J* = 5.4 Hz, 2H), 3.76 (s, 2H). LC/MS (CI): *m/z* = 119 $[M+H]^+$. Anal. Calcd. for $C_7H_6N_2$: C 71.17; H 5.12; N 23.71. Found: C 71.53; H 4.86; N 23.96.

General procedure for the preparation of cyclobutyl ketales 20a–c. The corresponding pyridylacetonitrile **18** (44.7 g, 0.205 mol) was added dropwise to a suspension of NaH (60%, 20.5 g, 0.513 mol) in DMF (250 mL) at 0 °C under argon atmosphere. After completion of gas evolution, 1,3-dibromo-2,2-dimethoxypropane (64.5 g, 0.246 mol) was added in one portion. The resulting mixture was heated at 60 °C (for **20a** and **20c**) or 50 °C (for **20b**) for 18 h, then H_2O (500 mL) was added, and the mixture was evaporated in *vacuo*. The residue was diluted with H_2O (250 mL)

and extracted with EtOAc (3×200 mL), the organic layer was separated, dried over Na_2SO_4 and evaporated in *vacuo*.

3,3-Dimethoxy-1-(pyridin-2-yl)cyclobutanecarbonitrile (20a). The compound was purified by column chromatography on silica gel using gradient hexanes – EtOAc as eluent. Yield 23.3 g (52%); beige crystals; mp 35–38 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.5 Hz, 1H), 7.70 (td, *J* = 7.9, 1.6 Hz, 1H), 7.63 – 7.56 (m, 1H), 7.24 – 7.19 (m, 1H), 3.27 (s, 3H), 3.16 (s, 3H), 3.00 (d, *J* = 12.6 Hz, 2H), 2.94 (d, *J* = 12.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 156.7, 149.8, 137.1, 123.1, 122.9, 120.9, 98.1, 48.9, 48.7, 44.4, 33.5. LCMS (CI): *m/z* = 187 $[M-OMe]^+$. Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C 66.04; H 6.47; N 12.84. Found: C 65.83; H 6.48; N 12.61.

3,3-Dimethoxy-1-(pyridin-3-yl)cyclobutanecarbonitrile (20b). The compound was purified by column chromatography on silica gel using gradient hexanes – EtOAc as eluent. The reaction temperature was 50 °C. Yield 27.0 g (59%); beige crystals; mp 84–86 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.65 – 8.58 (m, 1H), 7.81 (d, *J* = 7.9 Hz, 1H), 7.35 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.28 (s, 3H), 3.19 (s, 3H), 3.15 (d, *J* = 12.1 Hz, 2H), 2.75 (d, *J* = 12.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 149.4, 147.5, 135.1, 133.5, 123.5, 122.6, 97.9, 48.9, 48.6, 45.7, 29.3. LCMS (CI): *m/z* = 219 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C 66.04; H 6.47; N 12.84. Found: C 65.93; H 6.41; N 12.50.

3,3-Dimethoxy-1-(pyridin-4-yl)cyclobutanecarbonitrile (20c). The compound was purified by column chromatography on silica gel using gradient hexanes – EtOAc as eluent. Yield 23.5 g (56%); red solid; decomposes upon heating. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 5.4 Hz, 2H), 7.43 (d, *J* = 5.4 Hz, 2H), 3.26 (s, 3H), 3.18 (s, 3H), 3.10 (d, *J* = 13.2 Hz, 2H), 2.70 (d, *J* = 13.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 148.1, 122.1, 120.7, 97.7, 48.9, 48.6, 45.5, 30.6. LCMS (CI): *m/z* = 219 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C 66.04; H 6.47; N 12.84. Found: C 65.68; H 6.24; N 13.08.

General procedure for the preparation of potassium carboxylates 21a–c. To a solution of the corresponding ketal **20** (27.0 g, 0.124 mol), a solution of KOH (20.8 g, 0.372 mol) in H_2O (250 mL) was added, and the resulting mixture was refluxed for 24 h (for **20a** and **20b**) or 48 h (for **20c**). Then, the reaction mixture was washed with CH_2Cl_2 (2×250 mL), aqueous layer was evaporated in *vacuo*. The residue was recrystallized from MeCN.

Potassium 3,3-dimethoxy-1-(pyridin-2-yl)cyclobutanecarboxylate (21a). Yield 25.5 g (87%); yellowish crystals; mp > 300 °C. ^{1}H NMR (400 MHz, D_2O) δ 8.33 (d, *J* = 4.7 Hz, 1H), 7.77 – 7.65 (m, 1H), 7.37 (d, *J* = 7.9 Hz, 1H), 7.20 (dd, *J* = 7.9, 5.3 Hz, 1H), 3.11 (s, 3H), 2.99 (s, 3H), 2.83 (d, *J* = 12.5 Hz, 2H), 2.68 (d, *J* = 12.5 Hz, 2H). ^{1}H NMR (DMSO-d_6) δ 8.35 (d, *J* = 4.7 Hz, 1H), 7.61 – 7.52 (m, 1H), 7.36 (d, *J* = 7.9 Hz, 1H), 7.04 (dd, *J* = 7.9, 4.7 Hz, 1H), 3.00 (s, 3H), 2.90 (s, 3H), 2.76 (d, *J* = 12.1 Hz, 2H), 2.52 (d, *J* = 12.1 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.3, 166.3, 147.7, 135.7, 122.2, 120.4, 99.5, 48.2, 48.0, 47.5, 42.4. LCMS (CI): *m/z* = 238 $[M-K+2H]^+$. Anal. Calcd. for $C_{12}H_{14}KNO_4$: C 52.35; H 5.13; N 5.09. Found: C 52.54; H 5.47; N 5.15.

Potassium 3,3-dimethoxy-1-(pyridin-3-yl)cyclobutanecarboxylate (21b). Yield 31.0 g (91%); yellowish powder; mp > 300 °C. ^{1}H NMR (400 MHz, D_2O) δ 8.41 (s, 1H), 8.28 (d, *J* = 3.9 Hz, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.31 (dd, *J* = 7.8, 3.9 Hz, 1H), 3.11 (s, 3H), 3.01 (s, 3H), 2.89 (d, *J* = 13.0 Hz, 2H), 2.55 (d, *J* = 13.0 Hz, 2H). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (s, 1H), 8.26 (d, *J* = 3.9 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.19 (dd, *J* = 7.9, 3.8 Hz, 1H), 3.01 (s, 3H), 2.93 (s, 3H), 2.88 (d, *J* = 12.2 Hz, 2H), 2.31 (d, *J* = 12.2 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.3, 148.4, 145.9, 143.9, 134.0, 122.8, 99.2, 48.2, 48.0, 43.6, 43.1. LCMS (CI): *m/z* = 238 $[M-K+2H]^+$. Anal. Calcd. for $C_{12}H_{14}KNO_4$: C 52.35; H 5.13; N 5.09. Found: C 52.26; H 4.97; N 4.97.

Potassium 3,3-dimethoxy-1-(pyridin-4-yl)cyclobutanecarboxylate (21c). Yield 27.6 g (93%); yellowish powder; mp > 300 °C. ^{1}H NMR (500 MHz, D_2O) δ 8.35 (d, *J* = 4.7 Hz, 2H), 7.32 (d, *J* = 4.7 Hz, 2H), 3.11 (s, 3H), 3.02 (s, 3H), 2.87 (d, *J* = 12.6 Hz, 2H), 2.55 (d, *J* = 12.6 Hz, 2H). ^{1}H NMR (DMSO-d_6) δ 8.34 (d, *J* = 4.7 Hz, 2H), 7.22 (d, *J* = 4.7 Hz, 2H), 3.01 (s, 3H), 2.92 (s, 3H), 2.85 (d, *J* = 12.5 Hz, 2H), 2.28 (d, *J* = 12.5 Hz, 2H). ^{13}C NMR (126 MHz, D_2O) δ 181.0, 154.8, 148.6, 122.0, 99.0, 48.5, 48.3, 45.9, 42.1. LCMS (CI): *m/z* = 238 $[M-K+2H]^+$. Anal. Calcd. for $C_{12}H_{14}KNO_4$: C 52.35; H 5.13; N 5.09. Found: C 52.72; H 5.09; N 4.82.

3,3-Dimethoxy-1-(pyridin-3-yl)cyclobutanecarboxylic acid (22b). To a solution of potassium carboxylate **21b** (31.0 g, 0.113 mol) in H_2O (250 mL) 6M aq HCl was added until pH = 5 was reached. The solution was extracted with EtOAc (3×200 mL), the organic layer was separated, dried over Na_2SO_4, and evaporated in *vacuo*. Yield 23.8 g (90%); yellowish crystals which decomposed upon heating above 90°C. ^{1}H NMR ($CDCl_3$) δ 8.56 (s, 1H), 8.47 (d, *J* = 2.6 Hz, 1H), 7.74 (d, *J* = 7.1 Hz, 1H), 7.37 (t, *J* = 2.6 Hz, 1H), 3.08 (s, 3H), 3.02 (d, *J* = 12.3 Hz, 2H), 3.00 (s, 3H), 2.58 (d, *J* = 12.3 Hz, 2H). ^{13}C NMR (DMSO-d_6) δ 175.8, 148.1, 148.0, 139.1, 134.8, 123.8, 98.9, 48.5, 48.5, 42.3, 42.3. LCMS (CI): *m/z* = 238 $[M+H]^+$. Anal. Calcd. for $C_{12}H_{15}NO_4$: C 60.75; H 6.37; N 5.9. Found: C 61.10; H 6.21; N 5.52.

General procedure for the preparation of pyridyl cyclobutanones 10a and 10c. The corresponding potassium carboxylate **21a** or **21c** (25.5 g, 92.6 mmol) was suspended in pyridine (250 mL), and Py·HCl (10.7 g, 92.6 mmol) was added. The resulting solution was warmed up to 60 °C for *ca.* 6 h (until a gas evolution ceased), then most of pyridine was evaporated in *vacuo*, the residue was diluted with H_2O (50 mL) and re-evaporated in *vacuo*. The residue was dissolved in EtOAc (150 mL), the precipitate was filtered off; the filtrates were dried over Na_2SO_4 and evaporated in *vacuo*. The residue was dissolved in acetone (150 mL), TsOH (*ca.* 50.0 mg) was added, and the resulting solution was refluxed for 12 h. Then, the reaction mixture was evaporated in *vacuo*, the residue was diluted with EtOAc (250 mL), washed with saturated aq $NaHCO_3$ (2×100 mL), the organic layer was separated, dried over Na_2SO_4 and evaporated in *vacuo*.

3-(Pyridin-2-yl)cyclobutanone (10a). The compound was purified by distillation in *vacuo*. Yield 10.9 g (94%, was scaled up to 120 g in a single run); yellowish oil; bp 75–76 °C / 0.22 mmHg. ^{1}H NMR ($CDCl_3$) δ 8.58 (d, *J* = 5.3 Hz, 1H), 7.66 – 7.57 (m, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 7.14 (dd, *J* = 6.7, 5.3 Hz, 1H), 3.76 – 3.65 (m, 1H), 3.51 (ddd, *J* = 12.3, 8.0, 5.4 Hz, 2H), 3.45 – 3.33 (ddd, *J* = 12.3, 8.0, 5.4 Hz, 2H). ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.07 (d, *J* = 4.9 Hz, 1H), 7.17 – 7.08 (m, 1H), 6.72 (d, *J* = 8.2 Hz, 1H), 6.68 – 6.60 (m, 1H), 3.25 – 3.15 (m, 1H), 3.05 – 2.96 (m, 2H), 2.94 – 2.85 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.5, 161.9, 149.7, 136.5, 122.2, 121.8, 54.0, 30.2. LCMS (CI): *m/z* = 148 $[M+H]^+$. Anal. Calcd. for C_9H_9NO: C 73.45; H 6.16; N 9.52. Found: C 73.74; H 5.83; N 9.28.

3-(Pyridin-4-yl)cyclobutanone (10c). The compound was purified by distillation in *vacuo*. Yield 11.8 g (92%, was scaled up to 20 g in a single run); yellowish liquid; bp 81–83 °C / 0.22 mmHg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 5.9 Hz, 2H), 7.23 (d, *J* = 5.4 Hz, 2H), 3.66 (q, *J* = 7.5 Hz, 1H), 3.58 – 3.49 (m, 2H), 3.30 – 3.22 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8, 152.4, 150.1, 121.9, 54.2, 27.9. LCMS (CI): *m/z* = 148 $[M+H]^+$. Anal. Calcd. for C_9H_9NO: C 73.45; H 6.16; N 9.52. Found: C 73.70; H 5.81; N 9.32.

3-(Pyridin-3-yl)cyclobutanone (10b). The corresponding potassium carboxylate **21a** or **21c** (23.7 g, 100 mmol) was dissolved in pyridine (250 mL), and Py·HCl (11.6 g, 100 mmol) was added. The resulting solution was refluxed for 48 h, then most of pyridine was evaporated in *vacuo*, the residue was diluted with H_2O (50 mL) and re-evaporated in *vacuo*. The residue was dissolved in EtOAc (150 mL), the precipitate was filtered off, the filtrates were dried over Na_2SO_4 and evaporated in *vacuo*. The product was purified by distillation in *vacuo*. Yield 12.6 g (95%, could be scaled up to 50 g in a single run); yellowish oil; bp 104–106 °C / 0.38 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.52 (d, *J* = 4.6 Hz,

1H), 7.64 (d, *J* = 6.4 Hz, 1H), 7.31 (dd, *J* = 6.4, 4.6 Hz, 1H), 3.71 (quint, *J* = 8.2 Hz, 1H), 3.60 – 3.53 (m, 2H), 3.30 – 3.24 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.2, 148.4, 147.9, 138.9, 133.9, 123.6, 54.6, 26.2. LCMS (CI): *m/z* = 148 $[M+H]^+$. Anal. Calcd. for C_9H_9NO: C 73.45; H 6.16; N 9.52. Found: C 73.27; H 6.41; N 9.38.

General procedure for the preparation of alcohols 11a–c. $NaBH_4$ (3.10 g, 81.9 mmol) was added in portions to a solution of the corresponding ketone (10.0 g, 67.9 mmol) in MeOH (100 mL) at 0 °C. Then, the reaction mixture was stirred at rt for 2 h, most of MeOH was evaporated in vacuo, the residue was diluted with H_2O (50 mL), and extracted with EtOAc (3×75 mL). Combined organic layers were dried over Na_2SO_4 and evaporated in *vacuo*.

***cis*-3-(Pyridin-2-yl)cyclobutanol (11a)**. The compound was obtained as *ca.* 9:1 mixture of diastereomers. Yield 9.31 g (92%); colorless liquid. ^{1}H NMR ($CDCl_3$) δ 8.51 (d, *J* = 4.9 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 1H), 7.13 – 7.05 (m, 1H), 4.66 – 4.63 (m, 0.1H) and 4.27 (quint, *J* = 6.8 Hz, 0.9H), 5.05 – 4.36 (m, 1H), 3.68 – 3.62 (m, 0.1H) and 3.11 (quint, *J* = 7.8 Hz, 0.9H), 2.81 – 2.73 (m, 1.8H) and 2.65 – 2.56 (m, 0.2H), 2.47 – 2.38 (m, 0.2H) and 2.27 – 2.17 (m, 1.8H). ^{13}C NMR ($CDCl_3$) δ 164.4 and 163.7, 149.2 and 149.0, 136.6 and 136.4, 121.9 and 121.5, 121.3 and 121.0, 65.5 and 63.8, 39.8 and 38.3, 34.8 and 33.1. LCMS (CI): *m/z* = 150 $[M+H]^+$. Anal. Calcd. for $C_9H_{11}NO$: C 72.46; H 7.43; N 9.39. Found: C 72.65; H 7.52; N 9.73.

***cis*-3-(Pyridin-3-yl)cyclobutanol (11b)**. The compound was obtained as *ca.* 9:1 mixture of diastereomers. Yield 8.61 g (85%); colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.59 (t, *J* = 6.8 Hz, 1H), 7.17 (d, *J* = 5.8 Hz, 1H), 7.12 (d, *J* = 6.8 Hz, 1H), 4.71 – 4.66 (m, 0.1H) and 4.31 (quint, *J* = 6.8 Hz, 0.9H), 3.99 (br s, 1H), 3.71 – 3.66 (m, 0.1H) and 3.20 (quint, *J* = 8.0 Hz, 0.9H), 2.86 – 2.81 (m, 1.8H) and 2.70 – 2.63 (m, 0.2H), 2.46 – 2.39 (m, 0.2H) and 2.25 – 2.20 (m, 1.8H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.4 and 148.3, 147.1 and 147.0, 140.8 and 140.0, 134.3 and 134.2, 134.2 and 123.4, 65.7 and 63.2, 40.7 and 38.9, 30.7 and 27.7. LCMS (CI): *m/z* = 150 $[M+H]^+$. Anal. Calcd. for $C_9H_{11}NO$: C 72.46; H 7.43; N 9.39. Found: C 72.77; H 7.14; N 9.21.

***cis*-3-(Pyridin-4-yl)cyclobutanol (11c)**. The compound was obtained as *ca.* 9:1 mixture of diastereomers. Yield 9.53 g (94%); colorless crystals. ^{1}H NMR ($CDCl_3$) δ 8.41 (d, *J* = 4.7 Hz, 2H), 7.09 (d, *J* = 4.7 Hz, 2H), 4.58 – 4.39 (m, 0.1H) and 4.37 – 4.19 (m, 0.9H), 3.94 (br, 1H), 3.57 – 3.47 (m, 0.1H) and 2.97 – 2.82 (m, 0.9H), 2.73 (dd, *J* = 16.1, 9.4 Hz, 1.8H) and 2.43 (m, 0.4H) and 2.10 – 1.89 (m, 1.8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 153.7, 149.6 and 149.5, 122.1 and 122.1, 65.6 and 63.1, 40.1 and 38.6, 32.3 and 29.4. LCMS (CI): *m/z* = 150 $[M+H]^+$. Anal. Calcd. for $C_9H_{11}NO$: C 72.46; H 7.43; N 9.39. Found: C 72.68; H 7.21; N 9.49.

General procedure for the preparation of azides 12a–c. DIAD (4.54 g, 22.4 mmol) was added to a solution of PPh_3 (6.13 g, 23.4 mmol) in THF (50 mL) at 0 °C. After 15 min (the precipitate was formed), a mixture of DPPA (6.43 g, 23.4 mmol) and the corresponding alcohol **11a–c** (2.79 g, 18.7 mmol) (in the case of solid **11c**, a solution in THF (25 mL) was used) was added in portions (NOTE: the reaction is exothermic). The resulting mixture was stirred at rt overnight, then most of solvent was evaporated in *vacuo,* and the residue was purified by column chromatography.

***trans*-2-(3-Azidocyclobutyl)pyridine (12a)**. The compound was purified by column chromatography on silica gel using gradient MeCN – MeOH as eluent. Yield 2.83 g (87%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (dd, *J* = 3.7 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.13 – 7.11 (m, 1H), 7.09 (dd, *J* = 3.7, 1.2 Hz, 1H), 4.27 (quint, *J* = 6.9 Hz, 1H), 3.71 – 3.64 (m, 1H), 2.69 – 2.63 (m, 2H), 2.54 – 2.48 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.1, 149.5, 136.3, 121.7, 121.4, 54.0, 36.4, 34.5. LCMS (CI): *m/z* = 147 $[M-N_2+H]^+$, 175 $[M+H]^+$. Anal. Calcd. for $C_9H_{10}N_4$: C 62.05; H 5.79; N 32.16. Found: C 62.38; H 5.53; N 32.11.

***trans*-3-(3-Azidocyclobutyl)pyridine (12b)**. The compound was purified by column chromatography on silica gel using gradient $CHCl_3$ – MeCN as eluent; isolated as *ca.* 4:1 mixture of diastereomers. Yield 2.61 g (80%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.48 (d, *J* = 4.8 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.25 (m, 1H), 4.17 (quint, *J* = 5.1 Hz, 0.8H) and 3.91 (quint, *J* = 7.1 Hz, 0.2H), 3.73 (quint, *J* = 7.1 Hz, 0.8H) and 3.21 (quint, *J* = 8.7 Hz, 0.2H), 2.85 – 2.73 (m, 0.4H) and 2.63 – 2.57 (m, 1.6H), 2.56 – 2.49 (m, 1.6H) and 2.27 – 2.18 (m, 0.4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4 and 148.3, 147.8 and 147.7, 139.4 and 138.9, 133.8 and 129.3, 123.4 and 123.4, 53.9 and 51.1, 36.4 and 35.2, 32.6 and 29.9. LCMS (CI): *m/z* = 147 $[M-N_2+H]^+$, 175 $[M+H]^+$. Anal. Calcd. for $C_9H_{10}N_4$: C 62.05; H 5.79; N 32.16. Found: C 61.72; H 5.49; N 32.55.

***trans*-4-(3-Azidocyclobutyl)pyridine (12c)**. The compound was purified by column chromatography on silica gel using gradient CH_2Cl_2 – MeCN or gradient hexanes – EtOAc as eluent; isolated as *ca.* 4:1 mixture of diastereomers. Yield 2.51 g (77%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.5 Hz, 2H), 7.12 (d, *J* = 5.6 Hz, 2H), 4.11 (quint, *J* = 5.9 Hz, 0.8H) and 3.89 (quint, *J* = 7.4 Hz, 0.2H), 3.66 (quint, *J* = 7.4 Hz, 0.8H) and 3.16 (quint, *J* = 8.3 Hz, 0.2H), 2.81 – 2.69 (m, 0.4H) and 2.62 – 2.36 (m, 3.2H) and 2.22 – 2.14 (m, 0.4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 153.2, 149.9, 121.7, 53.8 and 51.0, 35.9 and 34.7, 34.1 and 31.5. LCMS (CI): *m/z* = 147 $[M-N_2+H]^+$, 175 $[M+H]^+$. Anal. Calcd. for $C_9H_{10}N_4$: C 62.05; H 5.79; N 32.16. Found: C 61.88; H 5.92; N 32.37.

***trans*-3-(Pyridin-2-yl)cyclobutanamine hydrochloride (13a)**. 10% Pd-C (*ca.* 250 mg). was added to a solution of azide **12a** (2.33 g, 13.4 mmol) in MeOH (25 mL). The resulting mixture was evacuated and backfilled with H_2 and stirred at rt for 2 h. Then, the catalyst was filtered off and filtrates was evaporated in *vacuo*. The crude amine was purified by HPLC (gradient 0 − 30% H_2O+HCl – MeCN, 30 mL / min flow rate; SunFire C18 Column, 100 Å, 3.5 µm, 4.6 mm×150 mm). Yield 2.20 g (89%); colorless crystals; mp 234–237 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.98 – 8.57 (m, 4H), 8.46 (q, *J* = 7.7 Hz, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.84 (t, *J* = 6.7 Hz, 1H), 4.28 (quint, *J* = 7.9 Hz, 1H), 3.93 – 3.83 (m, 1H), 2.77 – 2.67 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.9, 145.7, 142.6, 125.4, 125.0, 43.1, 33.1, 32.2. LCMS (CI): *m/z* = 149 $[M-HCl+H]^+$. Anal. Calcd. for $C_9H_{13}ClN_2$: C 58.54; H 7.10; N 15.17; Cl 19.20. Found: C 58.87; H 6.87; N 15.36; Cl 18.85.

***trans*-3-(Pyridin-3-yl)cyclobutanamine hydrochloride (13b)**. 10% Pd-C (*ca.* 250 mg). was added to a solution of azide **12a** (2.15 g, 12.3 mmol) in EtOH (25 mL). The resulting mixture was evacuated and backfilled with H_2 and stirred at rt for 2 h. Then, the catalyst was filtered off and filtrates was evaporated in *vacuo*. The crude amine was purified by HPLC (gradient 0 − 30% H_2O+HCl – MeCN, 30 mL / min flow rate; SunFire C18 Column, 100 Å, 3.5 µm, 4.6 mm×150 mm). The compound was obtained as *ca.* 5.7:1 mixture of diastereomers. Yield 1.91 g (84%); colorless crystals. ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.01 (s, 0.15H), 8.90 (s, 0.85H), 8.83 – 8.62 (m, 4H), 8.55 (d, *J* = 8.1 Hz, 1H), 8.01 (t, *J* = 6.9 Hz, 1H), 4.06 (quint, *J* = 8.6 Hz, 0.85H), 3.88 – 3.80 (m, 0.85H), 3.77 – 3.71 (m, 0.15H), 3.53 (quint, *J* = 8.5 Hz, 0.15H), 2.72 – 2.63 (m, 2H), 2.60 – 2.53 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 162.9, 144.8 and 144.4, 141.0 and 140.7, 140.3 and 140.1, 127.3, 43.3 and 43.2, 34.9 and 32.9, 32.9 and 31.9. LCMS (CI): *m/z* = 149 $[M-HCl+H]^+$. Anal. Calcd. for $C_9H_{13}ClN_2$: C 58.54; H 7.10; N 15.17; Cl 19.20. Found: C 58.55; H 7.20; N 15.42; Cl 18.98.

***trans*-3-(Pyridin-4-yl)cyclobutanamine hydrochloride (13c)**. The azide **12c** (2.45 g, 14.1 mmol) was added to a suspension of $LiAlH_4$ (587 mg, 15.5 mmol) in THF (25 mL) at 0 °C. When a gas evolution ceased, the reaction mixture was quenched with H_2O (279 µL,15.5 mmol), 15% aq NaOH (620 mg, 15.5 mmol in 4.13 mL of H_2O), and H_2O (837 µL, 46.5 mmol). The precipitate formed was filtered off, and filtrates were evaporated in *vacuo*. The residue was dissolved in Et_2O (25 mL), and 4M HCl − 1,4-dioxane (5 mL) was added dropwise. The precipitate was

filtered, washed with Et_2O (5 mL) and dried in *vacuo*. The compound was obtained as *ca.* 9:1 mixture of diastereomers. Yield 2.60 g (93%); colorless crystals. ^{1}H NMR (400 MHz, D_2O) δ 8.41 (d, *J* = 6.2 Hz, 2H), 7.54 (d, *J* = 5.7 Hz, 1.8H), 7.49 (d, *J* = 6.2 Hz, 0.2H), 3.99 – 3.67 (m, 1.8H), 3.55 – 3.35 (m, 0.2H), 2.80 – 2.68 (m, 0.4H), 2.64 – 2.51 (m, 3.2H), 2.41 – 2.07 (m, 0.4H). ^{13}C NMR (126 MHz, D_2O) δ 160.7 and 159.9, 144.1, 124.1 and 123.9, 43.6 and 41.4, 33.6 and 33.5, 32.2 and 31.8.LCMS (CI): *m/z* = 149 $[M-HCl+H]^+$. Anal. Calcd. for $C_9H_{13}ClN_2$: C 58.54; H 7.10 N 15.17; Cl 19.20. Found: C 58.56; H 6.81; N 14.87; Cl 19.30.

General procedure for the preparation of oximes 25a–c. To a solution of **10a–c** (2.50 g, 17.0 mmol) in EtOH - H_2O (25 mL, 3:1, v/v) was added $NaHCO_3$ (2.85 g, 34.0 mmol) and NH_2OMe·HCl (1.70 g, 20.4 mmol). The resulting mixture was refluxed for 6 h, then cooled to rt. Most of EtOH was evaporated in *vacuo*, the aqueous mixture was extracted with EtOAc (2×25 mL), dried over Na_2SO_4 and evaporated in *vacuo*.

3-(Pyridin-2-yl)cyclobutanone *O*-methyl oxime (25a). Yield 2.85 g (95%); yellowish liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 4.2 Hz, 1H), 7.58 (t, *J* = 8.2 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.13 – 7.06 (m, 1H), 3.81 (s, 3H), 3.64 (quint, *J* = 8.0 Hz, 1H), 3.52 – 2.92 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.3, 155.1, 149.6, 136.4, 121.7, 121.6, 61.6, 38.2, 37.5, 34.5. LCMS (CI): *m/z* = 177 $[M+H]^+$. Anal. Calcd. for $C_{10}H_{12}N_2O$: C 68.16; H 6.86; N 15.90. Found: C 68.46; H 6.94; N 15.99.

3-(Pyridin-3-yl)cyclobutanone *O*-methyl oxime (25b). Yield 2.91 g (87%); yellowish liquid.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1H), 8.44 (d, *J* = 4.8 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.23 (dd, *J* = 7.9, 4.8 Hz, 1H), 3.82 (s, 3H), 3.57 (quint, *J* = 8.2 Hz, 1H), 3.43 – 3.31 (m, 2H), 3.03 – 2.91 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.0, 148.5, 148.1, 139.2, 133.7, 123.5, 61.7, 39.3, 38.4, 30.5. LCMS (CI): *m/z* = 177 $[M+H]^+$. Anal. Calcd. for $C_{10}H_{12}N_2O$: C 68.16; H 6.86; N 15.90. Found: C 68.40; H 7.08; N 15.99.

3-(Pyridin-4-yl)cyclobutanone *O*-methyl oxime (25c). Yield 3.01 g (90%); yellowish liquid.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 5.3 Hz, 2H), 7.19 (d, *J* = 5.3 Hz, 2H), 3.82 (s, 3H), 3.56 (quint, *J* = 8.1 Hz, 1H), 3.45 – 3.31 (m, 2H), 3.04 – 2.92 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.1, 153.6 and 153.4, 149.2, 122.0, 61.7, 38.7, 37.9, 32.2. LCMS (CI): *m/z* = 177 $[M+H]^+$. Anal. Calcd. for $C_{10}H_{12}N_2O$: C 68.16; H 6.86; N 15.90. Found: C 68.22; H 7.21; N 16.06.

General procedure for the preparation of *N*-Boc amines 26a and 26c. TFA (809 mg, 543 µL, 7.10 mmol) was added to a solution of $NaBH_4$ (1.07 g, 28.4 mmol) in THF (25 mL) at 5 °C (NOTE: the temperature should not exceed 15 °C). Then, a solution of the corresponding oxime **25a** or **25c** (2.50 g, 14.2 mmol) in THF (10mL) was added at at 5 °C. The resulting mixture was stirred at rt overnight, then evaporated in *vacuo.* The residue was diluted with CH_2Cl_2 (50 mL) and washed with brine (25 mL), dried over $MgSO_4$. Et_3N (1.72 g, 2.37 mL, 17.0 mmol) and Boc_2O (3.41 g, 3.59 mL, 15.6 mmol) were added in portions to the resulting solution. When the gas evolution ceased, the reaction mixture was washed with H_2O (25 mL), brine (25 mL), dried over Na_2SO_4 and evaporated in *vacuo*.

***tert*-Butyl (3-(pyridin-2-yl)cyclobutyl)carbamate (26a)**. The compound was purified by column chromatography on silica gel using gradient $CHCl_3$ – MeCN as eluent; obtained as *ca.* 2:1 mixture of diastereomers. Yield 1.16 g (33%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 4.8 Hz, 1H), 7.59 – 7.50 (m, 1H), 7.22 – 7.09 (m, 0.67H) and 7.09 – 7.04 (m, 1.33H), 4.95 (s, 0.67H) and 4.87 (s, 0.33H), 4.32 (s, 0.33H) and 4.21 – 4.06 (m, 0.67H), 3.62 – 3.55 (m, 0.33H) and 3.21 (quint, *J* = 8.8 Hz, 0.67H), 2.72 (d, *J* = 8.5 Hz, 1.33H) and 2.64 (d, *J* = 4.5 Hz, 0.67H), 2.35 - 2.29 (m, 0.67H) and 2.20 – 2.09 (m, 1.33H), 1.41 (s, 3H) and 1.40 (s, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.8 and 163.0, 155.1 and 155.0, 149.3, 136.3 and 136.2, 121.8 and 121.3, 121.0, 79.2 and 79.1, 44.1 and 41.8, 37.5, 36.0 and 35.9, 34.7, 28.4. Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C 67.72; H 8.12; N 11.28. LCMS (CI): *m/z* = 193 $[M-H_2C=C(CH_3)_2+H]^+$, 249 $[M+H]^+$. Found: C 67.55; H 7.95; N 11.53.

***tert*-Butyl (3-(pyridin-4-yl)cyclobutyl)carbamate (26c)**. The compound was purified by column chromatography on silica gel using gradient CH_2Cl_2 – MeCN as eluent; obtained as *ca.* 5.7:1 mixture of diastereomers. Yield 917 mg (26%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50 (d, *J* = 4.7 Hz, 2H), 7.17 (d, *J* = 4.7 Hz, 0.3H) and 7.10 (d, *J* = 4.7 Hz, 1.7H), 4.92 (s, 0.15H) and 4.80 (s, 0.85H), 4.31 – 4.25 (m, 0.15H) and 4.21 – 4.10 (m, 0.85H), 3.13 (quint, *J* = 9.2 Hz, 1H), 2.90 – 2.70 (m, 2H), 1.96 (q, *J* = 9.4 Hz, 2H), 1.45 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9, 153.3, 149.8 and 149.7, 121.9 and 121.8, 79.5 and 79.5, 42.0, 37.9 and 36.3, 33.4 and 31.9, 28.4. LCMS (CI): *m/z* = 193 $[M-H_2C=C(CH_3)_2+H]^+$, 249 [M+H Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C 67.72; H 8.12; N 11.28. Found: C 67.70; H 7.80; N 11.64.

General procedure for the preparation of sulfinamides 28a and 28b. Ti(O*i*-Pr)$_4$ (5.79 g, 6.04 mL, 20.4 mmol) was added to a solution of **10a** or **10b** (2.50 g, 17.0 mmol) and Ellman's sulfinamide $H_2NS(O)t$-Bu (2.16 g, 17.9 mmol) in THF (50 mL) at rt. The resulting mixture was stirred overnight, then quenched with brine (25 mL), and stirred for 1 h. The precipitate formed was filtered off, the filtrate was evaporated in *vacuo*. The intermediate obtained **27a** or **27b** was dissolved in THF (50 mL), and $NaBH_4$ (643 mg, 17.0 mmol) was added at rt. The resulting mixture was stirred for 4 h, then evaporated in *vacuo*, the residue was diluted with EtOAc (25mL) and water (25 mL). The organic phase was separated, washed with brine (25mL), dried over Na_2SO_4 and evaporated in *vacuo*.

2-Methyl-*N*-(3-(pyridin-2-yl)cyclobutyl)propane-2-sulfinamide (28a). The compound was purified by column chromatography on silica gel using gradient hexanes – EtOAc as eluent. Yield 2.40 g (56%); colorless solid; decomposed upon heating. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.9 Hz, 1H), 7.58 (td, *J* = 7.7, 1.9 Hz, 1H), 7.16 – 7.06 (m, 2H), 3.96 (d, *J* = 8.6 Hz, 1H), 3.88 (q, *J* = 7.8 Hz, 1H), 3.26 (quint, *J* = 8.6 Hz, 1H), 2.89 – 2.69 (m, 2H), 2.33 – 2.26 (m, 2H), 1.19 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.9, 149.3, 136.3, 121.8, 121.3, 55.5, 48.0, 39.1, 37.9, 35.1, 22.6. LCMS (CI): *m/z* = 253 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{20}N_2OS$: C 61.87; H 7.99; N 11.10; S 12.70. Found: C 61.78; H 7.61; N 11.30; S 12.45.

2-Methyl-*N*-(3-(pyridin-3-yl)cyclobutyl)propane-2-sulfinamide (28b). The compound was purified by column chromatography on silica gel using gradient hexanes – EtOAc as eluent. Yield 1.80 g (42%); colorless solid; decomposed upon heating. The compound existed as a mixture of ca. 5:1 of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 – 8.36 (m, 2H), 7.74 (d, *J* = 7.9 Hz, 1H), 7.42 (dd, *J* = 7.9, 5.7 Hz, 1H), 3.94 (q, *J* = 8.2 Hz, 1H), 3.53 (d, *J* = 7.6 Hz, 1H), 3.23 (quint, *J* = 9.7 Hz, 1H), 2.91 – 2.80 (m, 2H), 2.10 (quint, *J* = 10.7 Hz, 2H), 1.26 – 1.14 (m, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4 and147.5, 146.0 and 145.2, 137.2 and 133.9, 125.0 and 123.3, 55.6 and 55.5, 47.4 and 47.2, 39.6 and 39.3, 38.9 and 38.6, 30.6 and 30.4, 22.5. LCMS (CI): *m/z* = 253 $[M+H]^+$. Anal. Calcd. for $C_{13}H_{20}N_2OS$: C 61.87; H 7.99; N 11.10; S 12.70. Found: C 62.01; H 7.62; N 11.34; S 12.74.

General procedure for the preparation of 14 and 29–31. $NaBH(OAc)_3$ (10.8 g, 51.0 mmol) was added in portions to a solution of the corresponding ketone **10a–c** (2.50 g, 17.0 mmol) and amine (18.7 mmol) in CH_2Cl_2 (50 mL) at rt (NOTE: in the case of dimethylamine hydrochloride, Et_3N (1.89 g, 2.61 mL, 18.7 mmol) was also added). The resulting mixture was stirred overnight at rt; the completion of the reaction was monitored by LCMS. Then, the reaction mixture was quenched with saturated aq solution of $NaHCO_3$ (10 mL), diluted with brine (10 mL). The organic phase was separated, dried over Na_2SO_4 and evaporated in *vacuo*.

***cis*-*N*,*N*-Dimethyl-3-(pyridin-2-yl)cyclobutanamine hydrochloride (14a)**. The compound was purified by distillation in *vacuo*, then dissolved in Et_2O (20 mL) and transformed into hydrochloride with 2M HCl – Et_2O (10 mL), filtered, washed with Et_2O (5 mL) and dried on air. Yield 3.15 g

(87%); white crystals; mp 205–209 °C (the corresponding base: colorless liquid; bp 57–59 °C / 0.22 mmHg). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.73 (d, *J* = 6.4 Hz, 1H), 8.54 (d, *J* = 8.3 Hz, 1H), 8.37 (dd, *J* = 8.3, 2.7 Hz, 1H), 7.88 (d, *J* = 7.0 Hz, 1H), 3.89 – 3.72 (m, 2H), 2.90 – 2.67 (m, 4H), 2.65 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 158.0, 146.0, 141.8, 125.8, 125.5, 55.8, 39.2, 32.1, 28.8. LCMS (CI): *m/z* = 177 [M−HCl+H]$^+$. Anal. Calcd. for $C_{11}H_{17}ClN_2$: C 62.11; H 8.06; N 13.17; Cl 16.67. Found: C 62.47; H 8.03; N 12.86; Cl 16.63.

***cis*-*N*,*N*-Dimethyl-3-(pyridin-2-yl)cyclobutanamine (14b)**. The compound was purified by distillation in *vacuo*. The compound was obtained as *ca.* 3:1 mixture of diastereomers. Yield 2.73 g (91%); colorless liquid; bp 74–77 °C / 0.22 mmHg. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 0.25H) and 8.46 (s, 0.75H), 8.44 – 8.32 (m, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.26 – 7.14 (m, 1H), 3.48 – 3.45 (m, 0.25H) and 3.12 (tt, *J* = 10.2, 7.6 Hz, 0.75H), 2.85 (quint, *J* = 6.8 Hz, 0.25H) and 2.66 (tt, *J* = 8.7, 6.6 Hz, 0.75H), 2.60 – 2.49 (m, 1.5H) and 2.49 – 2.39 (m, 0.5H), 2.30 – 2.22 (m, 0.5H) and 2.17 (s, 1.5H), 2.16 (s, 4.5H) and 2.02 – 1.93 (m, 1.5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.7, 147.4 and 147.2, 140.0, 134.0, 123.2, 59.1 and 57.7, 41.9 and 41.7, 35.2 and 33.4, 30.7 and 29.5. LCMS (CI): *m/z* = 177 [M+H]$^+$. Anal. Calcd. for $C_{11}H_{16}N_2$: C 74.96; H 9.15; N 15.89. Found: C 74.63; H 9.17; N 15.75.

***cis*-*N*,*N*-Dimethyl-3-(pyridin-2-yl)cyclobutanamine (14c)**. The compound was purified by distillation in *vacuo*. The compound was obtained as *ca.* 5.7:1 mixture of diastereomers. Yield 2.79 g (93%); colorless crystals; mp 207–210 °C (the corresponding base: colorless liquid; bp 65–67 °C / 0.22 mmHg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (d, *J* = 4.8 Hz, 0.3H) and 8.47 (d, *J* = 4.8 Hz, 1.7H), 7.18 (d, *J* = 4.8 Hz, 0.3H) and 7.13 (d, *J* = 4.8 Hz, 1.7H), 3.44 (tt, *J* = 8.6, 4.2 Hz, 0.15H) and 3.08 (quint, *J* = 9.5 Hz, 0.85H), 2.84 – 2.80 (m, 0.15H) and 2.67 (quint, *J* = 7.4 Hz, 0.85H), 2.55 – 2.50 (m, 1.7H) and 2.46 – 2.43 (m, 0.3H), 2.27 – 2.23 (m, 0.3H) and 2.00 – 1.94 (m, 1.7H), 2.17 – 2.16 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0 and 153.7, 149.7 and 149.5, 122.1 and 122.0, 59.0 and 57.4, 41.8 and 41.5, 34.5 and 32.9, 32.3 and 31.1. LCMS (CI): *m/z* = 177 [M+H]$^+$. Anal. Calcd. for $C_{11}H_{16}N_2$: C 74.96; H 9.15; N 15.89. Found: C 75.19; H 8.97; N 16.20.

***cis*-*N*,*N*-Bis(4-methoxybenzyl)-3-(pyridin-2-yl)cyclobutanamine (29a)**. The compound was obtained as *ca.* 3:1 mixture of diastereomers which was used in the next step without additional purification. Yield 5.81 g (88%); yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 4.9 Hz, 0.25H) and 8.52 (d, *J* = 4.7 Hz, 0.75H), 7.61 (td, *J* = 7.7, 1.8 Hz, 0.25H) and 7.56 (td, *J* = 7.6, 1.9 Hz, 0.75H), 7.25 – 7.21 (m, 4H), 7.16 – 7.10 (m, 1H), 7.09 – 7.03 (m, 1H), 6.86 – 6.81 (m, 4H), 3.79 – 3.77 (m, 6H), 3.71 (s, 1H), 3.45 (s, 3H), 3.42 – 3.35 (m, 0.5H) and 3.22 – 3.10 (m, 1.5H), 2.51 – 2.41 (m, 1.5H) and 2.41 – 2.30 (m, 0.5H), 2.18 – 2.10 (m, 1.5H) and 2.08 – 1.79 (m, 0.5H). LCMS (CI): *m/z* = 389 [M+H]$^+$.

***cis*-*N*,*N*-Diallyl-3-(pyridin-2-yl)cyclobutanamine (30a)**. The compound was used in the next step without additional purification. Yield 3.49 g (90%); yellowish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (d, *J* = 4.7 Hz, 1H), 7.64 – 7.55 (m, 1H), 7.18 (d, *J* = 7.6 Hz, 1H), 7.08 (dd, *J* = 7.6, 4.7 Hz, 1H), 5.89 (ddt, *J* = 16.9, 10.1, 6.7 Hz, 2H), 5.17 (dd, *J* = 16.9, 1.9 Hz, 2H), 5.13 (dd, *J* = 10.1, 1.9 Hz, 2H), 3.30 – 3.21 (m, 1H), 3.21 – 3.15 (m, 1H), 3.13 (d, *J* = 6.7 Hz, 4H), 2.54 (qd, *J* = 7.4, 2.7 Hz, 2H), 2.18 (tdd, *J* = 11.1, 7.4, 2.7 Hz, 2H). LCMS (CI): *m/z* = 253 [M+H]$^+$.

General procedure for the preparation of *cis* amines 13a–c.

The corresponding amine **30** or **31** (20.0 mol) was dissolved in MeOH (50 mL), and 20% $Pd(OH)_2$–C (*ca.* 500 mg) was added. The resulting mixture was evacuated and refilled with H_2, then stirred at rt for 3 h. The catalyst was filtered off, and the filtrates were evaporated in vacuo.

***cis*-3-(Pyridin-2-yl)cyclobutanamine (13a)**. Yield 2.13 g (72%); colorless liquid. The compound was obtained as *ca.* 9:1 mixture of diastereomers. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 4.5 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.10 (d, *J* = 7.8 Hz, 1H), 7.08 – 7.05 (m, 1H), 3.83 – 3.69 (m, 0.1H) and 3.45 (quint, *J* = 8.2 Hz, 0.9H), 3.63 (quint, *J* = 7.4 Hz, 0.1H) and 3.17 (quint, *J* = 8.8 Hz, 0.9H), 2.74 – 2.68 (m, 1.8H) and 2.63 – 2.55 (m, 0.2H), 2.25 (s, 2H), 2.04 – 1.95 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.6, 149.2, 136.2, 121.5 and 121.4, 121.1 and 120.9, 45.8 and 44.5, 40.0 and 38.2, 35.6 and 34.1. LCMS (CI): *m/z* = 149 [M+H]$^+$. Anal. Calcd. for $C_9H_{12}N_2$: C 72.94; H 8.16; N 18.90. Found: C 73.33; H 8.14; N 18.75.

***cis*-3-(Pyridin-3-yl)cyclobutanamine (13b)**. The compound was purified by column chromatography on silica gel using gradient *t*-BuOMe – MeOH as eluent; obtained as *ca.* 4:1 mixture of diastereomers. Yield 2.05 g (69%); colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.43 – 8.38 (m, 1H), 7.56 (d, *J* = 7.4 Hz, 1H), 7.25 – 7.18 (m, 1H), 5.17 (s, 2H), 3.76 (quint, *J* = 6.1 Hz, 0.2H) and 3.55 (quint, *J* = 8.2 Hz, 0.8H), 3.68 (quint, *J* = 5.7 Hz, 0.2H) and 3.12 (quint, *J* = 8.7 Hz, 0.8H), 2.78 – 2.69 (m, 1.6H) and 2.51 – 2.45 (m, 0.4H), 2.44 – 2.39 (m, 0.4H) and 2.10 – 1.98 (m, 1.6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.3, 147.3 and 147.2, 140.3 and 139.6, 134.2 and 134.0, 123.4 and 123.3, 44.9 and 43.4, 38.9 and 36.9, 31.6 and 30.1. LCMS (CI): *m/z* = 149 [M+H]$^+$. Anal. Calcd. for $C_9H_{12}N_2$: C 72.94; H 8.16; N 18.90. Found: C 72.89; H 8.38; N 18.54.

***cis*-3-(Pyridin-4-yl)cyclobutanamine (13c)**. The compound was purified by column chromatography on silica gel using gradient *t*-BuOMe – MeOH as eluent; obtained as *ca.* 4:1 mixture of diastereomers. Yield 1.87 g (63%); colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 – 8.29 (m, 2H), 7.19 – 6.91 (m, 2H), 5.15 (s, 0.4H) and 5.07 (s, 1.6H), 3.72 (quint, *J* = 7.4 Hz, 0.2H) and 3.54 (quint, *J* = 7.2 Hz, 0.8H), 3.64 (quint, *J* = 8.3 Hz, 0.2H) and 3.10 (quint, *J* = 9.2 Hz, 0.8H), 2.78 – 2.67 (m, 1.6H) and 2.52 – 2.44 (m, 0.4H), 2.42 – 2.35 (m, 0.4H) and 2.04 – 1.94 (m, 1.6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.2 and 153.4, 149.6 and 149.5, 121.9, 44.8 and 43.4, 38.6 and 36.5, 33.2 and 31.7. LCMS (CI): *m/z* = 149 [M+H]$^+$. Anal. Calcd. for $C_9H_{12}N_2$: C 72.94; H 8.16; N 18.90. Found: C 72.61; H 8.50; N 18.94.

Parallel synthesis of the library 15. The corresponding ketone **10a–c** (0.5 mmol) and amine **32**(*1–62*) (0.5 mmol) were dissolved in CH_2Cl_2 (4 mL), and $NaBH(OAc)_3$ (1 mmol) was added (NOTE: in the case of amine hydrochlorides, Et_3N (0.55 mmol) was also added). The vial was sealed, shaken intensively, then slightly opened and left standing for 12 h; then sealed again, placed into a shaker, and stirred at rt for 48 h. Then, the vials were opened to remove the excessive pressure and placed in a cold ultrasonic bath for 4 h. 15% aq NH_3 (3 mL) was added to the reaction mixture (NOTE: extensive gas evolution may occur). The organic phase was separated, washed with H_2O (3×3 mL), dried over Na_2SO_4 and evaporated in *vacuo*.

2-(2,6-Difluorophenyl)-2-((3-(pyridin-2-yl)cyclobutyl)amino)ethanol (15{*1,1*}). The compound was obtained as *ca.* 4:1 mixture of diastereomers. Yield 96.3 mg (98%); brown oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60 – 8.52 (m, 0.2H) and 8.47 (s, 0.8H), 7.71 (t, *J* = 7.9 Hz, 0.2H) and 7.62 (t, *J* = 7.2 Hz, 0.8H), 7.46 – 7.36 (m, 0.2H) and 7.30 (quint, *J* = 7.2 Hz, 0.8H), 7.27 – 7.18 (m, 0.4H) and 7.18 – 7.05 (m, 1.6H), 7.00 (t, *J* = 9.1 Hz, 2H), 4.89 (br s, 1H), 4.12 (t, *J* = 7.8 Hz, 0.8H) and 4.10 – 4.01 (m, 0.2H), 3.93 – 3.83 (m, 0.2H) and 3.82 – 3.71 (m, 0.8H), 3.71 – 3.56 (m, 1H), 3.56 – 3.16 (m, 2H), 3.09 (h, *J* = 9.6 Hz, 1H), 2.49 – 2.25 (m, 1.4H) and 1.99 (q, *J* = 9.6 Hz, 0.8H) and 1.77 (q, *J* = 9.6 Hz, 0.8H), 2.25 – 2.07 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.8, 163.6, 162.9 (d, *J* = 9.3 Hz), 161.0 (d, *J* = 9.0 Hz), 149.4 and 149.3, 136.8 and 136.7, 129.6 (t, *J* = 10.7 Hz), 121.9 and 121.8, 121.6, 112.1 (d, *J* = 23.4 Hz), 63.7, 54.5 and 54.3, 50.3 and 49.4, 38.1 and 36.1, 37.6 and 35.9, 35.5 and 34.9. ^{19}F NMR (470 MHz, dmso) δ -113.0, -113.9. LCMS (CI): *m/z* = 305 [M+H]$^+$. Anal. Calcd. for $C_{17}H_{18}F_2N_2O$: C 67.09; H 5.96; N 9.20. Found: C 66.70; H 6.24; N 9.36.

(2*R*,3*R*)-*N*-(3-(Pyridin-2-yl)cyclobutyl)-2-(1,3,5-trimethyl-1*H*-pyrazol-4-yl)tetrahydrofuran-3-amine (15{*1,2*}). Yield 81.8 mg (84%); light brown oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.46 (d, *J* = 3.4 Hz, 1H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.6 Hz, 1H), 7.17 – 7.13 (m, 1H), 4.24 (dd,

J = 7.4, 2.2 Hz, 1H), 3.90 (q, *J* = 7.3 Hz, 1H), 3.79 (q, *J* = 7.3 Hz, 1H), 3.59 (s, 3H), 3.52 – 3.41 (m, 1H), 3.16 (qd, *J* = 7.2, 2.0 Hz, 1H), 3.12 – 3.03 (m, 2H), 2.40 (q, *J* = 9.9, 8.4 Hz, 2H), 2.15 (s, 3H), 2.07 (s, 3H), 2.04 – 1.96 (m, 1H), 1.92 (q, *J* = 9.6 Hz, 1H), 1.85 (q, *J* = 9.6 Hz, 1H), 1.77 – 1.71 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 163.9, 149.3, 144.4, 137.1, 136.7, 121.9, 121.6, 115.2, 79.3, 66.5, 62.2, 49.3, 38.7, 37.9, 35.9, 34.8, 34.2, 12.9, 9.9. LCMS (CI): *m/z* = 327 [M+H]$^+$. Anal. Calcd. for $C_{19}H_{26}N_4O$: C 69.91; H 8.03; N 17.16. Found: C 70.21; H 8.38; N 16.76.

(*R*)-8-Methyl-*N*-(3-(pyridin-4-yl)cyclobutyl)chroman-4-amine (15{*3*,*3*}). Yield 39.4 mg (79%); yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 – 8.41 (d, *J* = 3.1 Hz, 2H), 7.28 (d, *J* = 3.1 Hz, 2H), 7.09 (d, *J* = 6.7 Hz, 1H), 6.97 (d, *J* = 6.7 Hz, 1H), 6.73 (t, *J* = 7.3 Hz, 1H), 4.31 – 4.25 (m, 1H), 4.21 – 4.15 (m, 1H), 3.70 (s, 1H), 3.06 (quint, *J* = 8.6 Hz, 1H), 2.63 (quint, *J* = 7.4 Hz, 2H), 2.42 – 2.13 (m, 2H), 2.08 (s, 3H), 1.97 – 1.78 (m, 4H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.6, 152.9, 149.8, 129.5, 128.2, 125.0, 124.7, 122.7, 119.4, 62.7, 49.4, 47.8, 39.0, 32.2, 28.4, 16.4. LCMS (CI): *m/z* = 295 [M+H]$^+$. Anal. Calcd. for $C_{19}H_{22}N_2O$: C 77.52; H 7.53; N 9.52. Found: C 77.45; H 7.33; N 9.75.

1-(3-Chloropyridin-2-yl)-*N*-(3-(pyridin-3-yl)cyclobutyl)pyrrolidin-3-amine (15{*2*,*4*}). The compound was obtained as *ca.* 2:1 mixture of diastereomers. Yield 38.9 mg (78%); yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 0H), 8.46 (s, 0.33H) and 8.43 (d, *J* = 4.7Hz, 0.67H), 8.05 (d, *J* = 4.7 Hz, 1H), 7.59 (d, *J* = 7.9 Hz, 0.33H) and 7.55 (d, *J* = 7.9 Hz, 0.67H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.26 – 7.20 (m, 1H), 6.58 (dd, *J* = 7.7, 4.7 Hz, 1H), 3.88 – 3.83 (m, 1H), 3.81 – 3.71 (m, 2H), 3.65 – 3.58 (m, 0.67H) and 3.48 – 3.38 (m, 1.67H) and 3.21 – 3.14 (m, 0.67H), 3.55 – 3.49 (m, 1H), 2.84 – 2.75 (m, 1.33H) and 2.48 – 2.43 (m, 0.67H), 2.34 (tt, *J* = 9.5, 5.3 Hz, 1H), 2.20 – 2.03 (m, 2H), 1.91 – 1.86 (m, 1H), 1.83 – 1.75 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.2, 148.7 and 148.5, 147.4 and 147.3, 145.4, 140.8 and 139.4, 138.9, 133.9, 123.3 and 123.2, 116.7, 114.1, 55.8 and 55.8, 55.8 and 55.7, 50.1 and 49.2, 48.1, 39.1 and 39.1, 36.7, 32.3 and 32.2, 32.0 and 30.6. LCMS (CI): *m/z* = 329 [M+H]$^+$. Anal. Calcd. for $C_{18}H_{21}ClN_4$: C 65.75; H 6.44; N 17.04; Cl 10.78. Found: C 65.69; H 6.57; N 16.95; Cl 10.77.

2-((3-(Pyridin-2-yl)cyclobutyl)amino)-2-(2-(trifluoromethoxy)phenyl)-ethanol (15{*1*,*8*}). The compound was obtained as *ca.* 1:1 mixture of diastereomers. Yield 69.8 mg (69%); yellowish solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.49 (d, *J* = 4.8 Hz, 0.5H) and 8.44 (d, *J* = 4.8 Hz, 0.5H), 7.71 – 7.58 (m, 2H), 7.41 – 7.32 (m, 2H), 7.28 (t, *J* = 8.9 Hz, 1H), 7.21 – 7.10 (m, 2H), 5.02 (s, 1H), 4.06 (ddd, *J* = 13.8, 8.1, 4.2 Hz, 1H), 3.55 – 3.49 (m, 1H), 3.46 – 3.40 (m, 1H), 3.22 (quint, *J* = 7.1 Hz, 1H), 3.07 (quint, *J* = 9.1 Hz, 1H), 2.93 (quint, *J* = 8.1 Hz, 1H), 2.46 – 2.43 (m, 1H), 2.33 – 2.24 (m, 2H), 2.16 (q, *J* = 9.1 Hz, 1H), 2.08 (q, *J* = 9.1 Hz, 1H), 1.91 (q, *J* = 9.1 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.9, 163.7, 149.5 and 149.4, 147.4, 136.8 and 136.7, 135.1 and 135.0, 129.7 and 129.7, 128.9 and 128.9, 127.8, 121.9 and 121.9, 121.7 and 121.5, 120.7, 65.5, 55.4 and 55.4, 49.3 and 48.1, 38.0 and 37.5, 36.0 and 35.7, 35.7 and 34.6. ^{19}F NMR (470 MHz, dmso) δ -55.8, -55.9. LCMS (CI): *m/z* = 353 [M+H]$^+$. Anal. Calcd. for $C_{18}H_{19}F_3N_2O_2$: C 61.36; H 5.44; N 7.95. Found: C 61.51; H 5.35; N 7.69.

***N*-(1-([1,2,4]Triazolo[4,3-a]pyridin-3-yl)-2-methylpropyl)-3-(pyridin-4-yl)cyclobutanamine (15{*3*,*11*}).** The compound was obtained as *ca.* 2:1 mixture of diastereomers. Yield 31.5 mg (63%); yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.74 – 8.68 (m, 1H), 8.40 (d, *J* = 4.3 Hz, 2H), 7.72 (d, *J* = 9.3 Hz, 1H), 7.32 (dd, *J* = 9.3, 6.6 Hz, 1H), 7.15 (d, *J* = 4.3 Hz, 2H), 6.94 (t, *J* = 6.6 Hz, 1H), 4.10 – 4.01 (m, 1H), 3.13 – 3.04 (m, 0.33H) and 2.87 (quint, *J* = 7.6 Hz, 1.67H), 2.69 (s, 1H), 2.47 – 2.36 (m, 1H), 2.23 – 2.18 (m, 1H), 2.14 – 2.09 (m, 0.33H) and 1.74 (q, *J* = 9.9 Hz, 0.67H), 2.00 – 1.90 (m, 1H), 1.87 – 1.82 (m, 0.33H) and 1.57 (q, *J* = 9.9 Hz, 0.67H), 1.05 (d, *J* = 6.5 Hz, 3H), 0.72 (d, *J* = 6.9 Hz, 1H) and 0.69 (d, *J* = 6.9 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 154.2, 149.9 and 149.8, 149.0, 148.0, 127.7, 125.1 and 125.0, 122.5 and 122.4, 115.9, 113.5, 59.5 and 59.1, 50.0 and 48.8, 38.1 and 35.7, 38.0 and 35.9 33.5, 31.9 and 31.8, 20.4 and 20.3, 19.8. LCMS (CI): *m/z* = 322 [M+H]$^+$. Anal. Calcd. for $C_{19}H_{23}N_5$: C 71.00; H 7.21; N 21.79. Found: C 71.13; H 7.21; N 21.51.

(*R*)-*N*-((1-(Methylsulfonyl)pyrrolidin-2-yl)methyl)-3-(pyridin-2-yl)cyclobutanamine (15{*1*,*12*}). The compound was obtained as *ca.* 2:1 mixture of diastereomers. Yield 62.2 mg (62%); yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.51 (d, *J* = 2.5 Hz, 0.33H) and 8.48 (d, *J* = 2.5 Hz, 0.66H), 7.69 – 7.64 (m, 1H), 7.25 (d, *J* = 7.6 Hz, 1H), 7.17 (dd, *J* = 7.6, 4.7 Hz, 1H), 3.65 – 3.59 (m, 1H), 3.57 – 3.53 (m, 0.34H) and 3.43 – 3.38 (m, 0.66H), 3.26 – 3.20 (m, 2H), 3.20 – 3.09 (m, 2H), 2.88 (s, 2H) and 2.87 (s, 1H), 2.65 – 2.60 (m, 1H), 2.47 – 2.43 (m, 1H), 2.41 – 2.29 (m, 1H), 2.16 – 2.05 (m, 1H), 1.96 – 1.76 (m, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 165.0 and 163.9, 149.5 and 149.3, 136.8 and 136.7, 121.9 and 121.9, 121.6 and 121.5, 60.1 and 60.0, 51.7 and 51.5, 51.4 and 50.2, 49.2, 37.6 and 35.6, 37.4 and 35.5, 36.3 and 34.7, 34.1 and 34.0, 29.6 and 29.6, 24.3 and 24.3. LCMS (CI): *m/z* = 310 [M+H]$^+$. Anal. Calcd. for $C_{15}H_{23}N_3O_2S$: C 58.22; H 7.49; N 13.58; S 10.36. Found: C 58.53; H 7.67; N 13.49; S 10.37.

1,1,1-Trifluoro-2-(1-methyl-1*H*-imidazol-2-yl)-4-((3-(pyridin-2-yl)cyclobutyl)amino)butan-2-ol (15{*1*,*13*}). The compound existed as *ca.* 2:1 mixture of diastereomers. Yield 64.6 mg (59%); yellowish oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 – 8.47 (m, 1H), 7.67 (t, *J* = 7.2 Hz, 1H), 7.24 – 7.20 (m, 1H), 7.17 (dd, *J* = 7.5, 4.7 Hz, 1H), 7.13 (d, *J* = 6.4 Hz, 1H), 6.86 (d, *J* = 3.3 Hz, 1H), 3.83 (s, 1H), 3.80 (s, 2H), 3.58 – 3.53 (m, 0.33H), 3.49 – 3.40 (m, 0.67H), 3.23 – 3.05 (m, 2H), 2.85 – 2.78 (m, 1H), 2.63 – 2.54 (m, 2H), 2.48 – 2.38 (m, 1.67H), 2.38 – 2.32 (m, 0.33H), 2.31 – 2.25 (m, 0.33H), 2.17 – 1.97 (m, 1.67H), 1.99 – 1.74 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 164.4, 163.5, 149.5 and 149.3, 142.7, 136.8 and 136.8, 127.0 and 126.9, 125.0, 124.6, 121.8 (d, *J* = 13.7 Hz), 77.7 (q, *J* = 28.4 Hz), 50.4 and 48.8, 42.5 and 42.3, 36.5 and 36.4, 36.1 and 35.6, 34.6 and 34.3, 30.8 and 30.6. ^{19}F NMR (470 MHz, dmso) δ -79.1, -79.2. LCMS (CI): *m/z* = 355 [M+H]$^+$. Anal. Calcd. for $C_{17}H_{21}F_3N_4O$: C 57.62; H 5.97; N 15.81. Found: C 57.24; H 6.23; N 16.18.

(*S*)-2-((3-(Pyridin-4-yl)cyclobutyl)amino)propan-1-ol (15{*3*,*14*}). The compound was obtained as *ca.* 2:1 mixture of diastereomers. Yield 29.4 mg (59%); yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.59 – 8.30 (m, 2H), 7.28 (d, *J* = 3.9 Hz, 1H), 7.26 – 7.13 (m, 1H), 4.38 (s, 1H), 3.51 – 3.39 (m, 1H), 3.31 – 3.13 (m, 4H), 3.11 – 2.99 (m, 1H), 2.67 – 2.61 (m, 0.67H) and 2.33 – 2.12 (m, 1.33H), 2.59 – 2.56 (m, 0.67H) and 1.83 – 1.65 (m, 1.33H), 1.09 – 0.68 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.4 and 154.5, 150.0 and 149.8, 122.6, 66.2 and 66.0, 53.2 and 53.1, 49.2 and 48.0, 39.0 and 36.6, 38.9 and 36.9, 33.5 and 32.1, 18.1 and 18.0. LCMS (CI): *m/z* = 207 [M+H]$^+$. Anal. Calcd. for $C_{12}H_{18}N_2O$: C 69.87; H 8.80; N 13.58. Found: C 70.27; H 8.74; N 13.70.

1-Methyl-*N*-(3-(pyridin-4-yl)cyclobutyl)piperidin-4-amine (15{*3*,*16*}). The compound was obtained as *ca.* 3:2 mixture of diastereomers. Yield 28.0 mg (56%); yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 – 8.42 (m, 2H), 7.27 (d, *J* = 5.1 Hz, 0.8H) and 7.24 (d, *J* = 5.1 Hz, 1.2H), 3.46 – 3.42 (m, 1H), 3.20 (quint, *J* = 7.6 Hz, 1H), 3.14 (s, 1H), 3.07 – 2.96 (m, 1H), 2.65 (d, *J* = 10.7 Hz, 2H), 2.55 (qd, *J* = 7.6, 2.8 Hz, 2H), 2.37 – 2.31 (m, 1H), 2.29 – 2.22 (m, 1H), 2.21 – 2.14 (m, 1H), 1.82 (t, *J* = 11.6 Hz, 2H), 1.75 (q, *J* = 10.7 Hz, 2H), 1.68 (d, *J* = 11.6 Hz, 2H), 1.28 – 1.17 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.4 and 154.6, 150.0 and 149.8, 122.6 and 122.6, 54.7 and 54.6, 52.8, 49.0 and 47.9, 46.5, 39.3, 36.9, 33.6 and 33.1, 33.1 and 32.3. LCMS (CI): *m/z* = 246 [M+H]$^+$. Anal. Calcd. for $C_{15}H_{23}N_3$: C 73.43; H 9.45; N 17.13. Found: C 73.05; H 9.57; N 17.37.

***N*-(3-(Pyridin-4-yl)cyclobutyl)-1-((tetrahydrofuran-3-yl)methyl)-piperidin-4-amine (15{*3*,*18*}).** The compound was obtained as *ca.* 3:2 mixture of diastereomers. Yield 27.8 mg (56%); yellow oil. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.44 (s, 2H), 7.28 (d, *J* = 3.2 Hz, 0.8H), 7.24 (d, *J* = 3.2 Hz, 1.2H), 3.71 – 3.65 (m, 2H), 3.58 (q, *J* = 6.8 Hz, 1H), 3.47 – 3.42 (m, 1H), 3.26 – 3.15 (m, 2H), 3.03 (quint, *J* = 9.1 Hz, 1H), 2.79 (d, *J* = 11.0 Hz, 1H), 2.73 (d, *J* = 11.2 Hz, 1H), 2.55 (q, *J* = 8.2 Hz, 1H), 2.40 – 2.33 (m, 2H), 2.30 – 2.23 (m, 1.2H), 2.21 – 2.12 (m, 2.8H), 1.91 – 1.82

(m, 2.8H), 1.76 (q, *J* = 10.2 Hz, 1.2H), 1.69 (d, *J* = 11.4 Hz, 2H), 1.47 (dq, *J* = 13.9, 7.2 Hz, 1H), 1.26 – 1.14 (m, 2H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 155.4 and 154.6, 150.0 and 149.8, 122.6 and 122.6, 71.9, 67.2, 62.0, 53.3 and 53.1, 53.1 and 53.0, 52.6 and 52.5, 49.0 and 47.9, 39.2, 36.9 and 36.8, 33.6, 33.2 and 33.1, 32.3, 30.7. LCMS (CI): *m/z* = 316 $[M+H]^+$. Anal. Calcd. for $C_{19}H_{29}N_3O$: C 72.34; H 9.27; N 13.32. Found: C 72.57; H 9.24; N 13.72.

1-(3-(((3-(Pyridin-4-yl)cyclobutyl)amino)methyl)benzyl)piperidine-3-carboxamide (15{*3,21*}). The compound was obtained as *ca.* 2:1 mixture of diastereomers. Yield 27.3 mg (55%); yellow oil. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.44 (d, *J* = 4.3 Hz, 2H), 7.26 – 7.15 (m, 5H), 7.15 – 7.10 (m, 1H), 6.75 (s, 1H), 3.63 (s, 2H), 3.56 – 3.44 (m, 1H), 3.41 (d, *J* = 4.4 Hz, 2H), 3.39 – 3.33 (m, 2H), 3.15 (quint, *J* = 7.6 Hz, 1H), 3.03 (quint, *J* = 8.7 Hz, 1H), 2.76 (d, *J* = 10.1 Hz, 1H), 2.68 (d, *J* = 9.6 Hz, 1H), 2.57 – 2.51 (m, 1H), 2.32 – 2.26 (m, 1H), 2.22 (t, *J* = 7.1 Hz, 1H), 1.97 (t, *J* = 10.8 Hz, 1H), 1.88 (t, *J* = 10.1 Hz, 1H), 1.80 (q, *J* = 9.3 Hz, 1H), 1.74 – 1.69 (m, 1H), 1.62 – 1.55 (m, 1H), 1.42 (q, *J* = 11.3 Hz, 1H), 1.30 (q, *J* = 11.3 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 176.1, 155.3 and 154.6, 150.0 and 149.8, 141.2, 138.6, 129.0, 128.3, 127.6, 127.1, 122.6 and 122.5, 63.1, 56.3, 53.7, 50.9 and 50.9, 50.7, 49.7, 42.8, 38.0 and 35.7, 34.0 and 32.1, 27.7, 24.8. LCMS (CI): *m/z* = 379 $[M+H]^+$. Anal. Calcd. for $C_{23}H_{30}N_4O$: C 72.98; H 7.99; N 14.8. Found: C 73.25; H 7.71; N 15.12.

***N*-((5-Cyclopropyl-1,3,4-thiadiazol-2-yl)methyl)-3-(pyridin-3-yl)cyclobutanamine (15{*2,22*})**. The compound existed as a mixture of *ca.* 1:1 of diastereomers. Yield 27.3 mg (55%); yellow oil. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.45 (s, 1H), 8.38 (d, *J* = 4.6 Hz, 1H), 7.69 (d, *J* = 6.7 Hz, 1H), 7.33 – 7.29 (m, 1H), 3.96 (s, 2H), 3.58 – 3.54 (m, 0.5H) and 3.43 – 3.40 (m, 0.5H), 3.18 (quint, *J* = 8.0 Hz, 1H), 3.05 (quint, *J* = 9.2 Hz, 1H), 2.58 – 2.53 (m, 1H), 2.47 – 2.42 (m, 1H), 2.28 – 2.20 (m, 2H), 1.82 (q, *J* = 9.8 Hz, 1H), 1.19 – 1.15 (m, 2H), 0.97 – 0.93 (m, 2H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 173.6, 171.7 and 171.6, 148.8 and 148.7, 147.6 and 147.4, 141.4 and 140.8, 134.6 and 134.4, 123.9 and 123.8, 51.0 and 49.7, 45.6 and 45.4, 38.3 and 35.9, 32.1, 30.0, 11.5. LCMS (CI): *m/z* = 287 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{18}N_4S$: C 62.91; H 6.34; N 19.56; S 11.19. Found: C 63.09; H 6.37; N 19.73; S 11.18.

1-(2-(((3-(Pyridin-2-yl)cyclobutyl)amino)methyl)benzyl)pyrrolidin-3-ol (15{*1,24*}). The compound was obtained as *ca.* 2:1 mixture of diastereomers. Yield 59.9 mg (54%); brownish oil. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.52 (d, *J* = 4.8 Hz, 0.33H) and 8.48 (d, *J* = 4.7 Hz, 0.67H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.41 – 7.33 (m, 1H), 7.33 – 7.28 (m, 1H), 7.28 – 7.20 (m, 3H), 7.19 – 7.13 (m, 1H), 4.82 (s, 1H), 4.21 (s, 2H), 3.80 (dd, *J* = 20.5, 9.8 Hz, 3H), 3.64 (t, *J* = 11.4 Hz, 2H), 3.51 – 3.38 (m, 1H), 3.32 (quint, *J* = 8.2 Hz, 1H), 3.22 (quint, *J* = 9.0 Hz, 1H), 2.72 (q, *J* = 7.8 Hz, 1H), 2.63 – 2.55 (m, 1H), 2.44 – 2.37 (m, 2H), 2.36 – 2.28 (m, 1H), 2.09 – 1.95 (m, 2H), 1.62 – 1.52 (m, 1H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 164.5 and 163.4, 149.6 and 149.3, 138.1 and 138.0, 136.9 and 136.9, 131.0, 130.5, 128.0 and 127.9, 122.1, 122.0, 121.8, 121.7, 69.6, 62.4 and 62.4, 57.9, 52.4 and 52.3, 50.7, 49.1 and 48.4, 36.4 and 36.1, 34.9 and 34.6, 34.5 and 34.3. LCMS (CI): *m/z* = 338 $[M+H]^+$. Anal. Calcd. for $C_{21}H_{27}N_3O$: C 74.74; H 8.06; N 12.45. Found: C 74.91; H 8.22; N 12.73.

1-Isopropyl-3-((3-(pyridin-2-yl)cyclobutyl)amino)pyrrolidin-2-one (15{*1,25*}). The compound was obtained as *ca.* 3:2 mixture of diastereomers. Yield 49.6 mg (51%); brownish oil. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.52 (d, *J* = 4.8 Hz, 0.4H) and 8.49 (d, *J* = 4.8 Hz, 0.6H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 0.6H) and 7.25 (d, *J* = 7.8 Hz, 0.4H), 7.21 – 7.14 (m, 1H), 4.11 (quint, *J* = 7.0 Hz, 1H), 3.71 – 3.46 (m, 3H), 3.30 – 3.11 (m, 3H), 2.66 – 2.51 (m, 1H), 2.44 – 2.34 (m, 1H), 2.33 – 2.12 (m, 2H), 2.04 (q, *J* = 9.7 Hz, 1H), 1.94 (q, *J* = 9.7 Hz, 1H), 1.69 – 1.49 (m, 1H, 1.06 (d, *J* = 7.0 Hz, 2.4H), 1.04 (d, *J* = 7.0 Hz, 3.6H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 172.8, 164.8 and 163.7, 149.5 and 149.3, 136.9 and 136.8, 122.1 and 121.9, 121.7 and 121.6, 57.2 and 57.0, 49.9 and 48.2, 42.6, 39.0, 37.4 and 35.6, 37.2 and 35.3, 35.7 and 34.8, 27.3 and 27.1, 19.9. LCMS (CI): *m/z* = 274 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{23}N_3O$: C 70.30; H 8.48; N 15.37. Found: C 69.94; H 8.49; N 15.71.

3-((3-(Pyridin-2-yl)cyclobutyl)amino)-1-(2,2,2-trifluoroethyl)-pyrrolidin-2-one (15{*1,27*}). The compound was obtained as *ca.* 2:1 mixture of diastereomers. Yield 60.8 mg (50%); brownish oil. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.52 (d, *J* = 5.2 Hz, 0.33H) and 8.51 – 8.44 (m, 0.67H), 7.68 (t, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 0.67H) and 7.25 (d, *J* = 9.5 Hz, 0.33H), 7.20 – 7.14 (m, 1H), 4.11 – 3.99 (m, 2H), 3.74 – 3.59 (m, 1H), 3.58 – 3.46 (m, 2H), 3.35 (quint, *J* = 8.1 Hz, 2H), 3.18 (quint, *J* = 8.1 Hz, 1H), 2.44 – 2.35 (m, 1H), 2.32 – 2.15 (m, 2H), 2.03 (q, *J* = 9.3 Hz, 1H), 1.96 (q, *J* = 9.3 Hz, 1H), 1.73 (quint, *J* = 8.7 Hz, 1H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 175.2, 164.8 and 163.7, 149.5 and 149.3, 136.8 and 136.8, 125.1 (q, *J* = 280.6 Hz), 122.0 and 121.9, 121.7 and 121.6, 55.9 and 55.8, 49.8 and 48.2, 45.3, 43.9 (q, *J* = 33.3 Hz), 37.5 and 35.7, 37.3 and 35.4, 35.7 and 34.8, 27.6 and 27.4. ^{19}F NMR (470 MHz, DMSO-*d*$_6$) δ -68.7 (t, *J* = 9.6 Hz). LCMS (CI): *m/z* = 314 $[M+H]^+$. Anal. Calcd. for $C_{15}H_{18}F_3N_3O$: C 57.50; H 5.79; N 13.41. Found: C 57.19; H 5.45; N 13.22.

1-Cyclopropyl-3-((3-(pyridin-2-yl)cyclobutyl)amino)pyrrolidin-2-one (15{*1,34*}). The compound was obtained as *ca.* 4:1 mixture of diastereomers. Yield 43.9 mg (43%); yellow oil. ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ 8.51 (d, *J* = 4.8 Hz, 0.2H) and 8.48 (d, *J* = 4.7 Hz, 0.8H), 7.67 (t, *J* = 7.1 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.19 – 7.15 (m, 1H), 3.51 – 3.42 (m, 1H), 3.29 – 3.24 (m, 2H), 3.19 – 3.13 (m, 2H), 2.93 (dd, *J* = 9.5, 4.4 Hz, 1H), 2.60 (quint, *J* = 5.9 Hz, 1H), 2.39 (dd, *J* = 16.5, 7.5 Hz, 2H), 2.12 (q, *J* = 9.1 Hz, 1H), 2.02 (dd, *J* = 16.6, 5.4 Hz, 1H), 1.93 (q, *J* = 9.9 Hz, 2H), 0.62 – 0.58 (m, 4H). ^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ 173.9, 164.9 and 163.8, 149.5 and 149.3, 136.8, 122.0 and 121.9, 121.7 and 121.5, 53.5, 49.6 and 49.4, 49.2 and 48.3, 38.1 and 36.0, 38.1 and 36.2, 35.0, 25.4, 4.9, 4.6. LCMS (CI): *m/z* = 272 $[M+H]^+$. Anal. Calcd. for $C_{16}H_{21}N_3O$: C 70.82; H 7.80; N 15.49. Found: C 70.43; H 8.13; N 15.48.

(3-((3-(Pyridin-2-yl)cyclobutyl)amino)tetrahydrofuran-3-yl)methanol (15{*1,39*}). Yield 44.9 mg (40%); colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 5.0 Hz, 1H), 7.58 (t, *J* = 7.5 Hz, 1H), 7.18 – 7.08 (m, 2H), 3.95 (q, *J* = 7.9 Hz, 1H), 3.86 (q, *J* = 8.2 Hz, 1H), 3.70 – 3.64 (m, 1H), 3.61 – 3.55 (m, 2H), 3.52 – 3.45 (m, 1H), 3.35 (quint, *J* = 7.9 Hz, 1H), 3.24 (quint, *J* = 8.9 Hz, 1H), 2.79 – 2.66 (m, 2H), 2.38 (s, 1H), 2.29 (quint, *J* = 10.0 Hz, 1H), 2.14 (q, *J* = 9.9 Hz, 2H), 1.90 (dt, *J* = 13.4, 6.7 Hz, 1H), 1.80 (dt, *J* = 13.4, 7.5 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.2, 149.3, 136.3, 121.6, 121.2, 75.6, 67.5, 66.4, 64.8, 45.2, 39.9, 39.6, 35.2, 34.6. LCMS (CI): *m/z* = 249 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C 67.72; H 8.12; N 11.28. Found: C 67.81; H 7.98; N 11.51.

3-(((3-(Pyridin-2-yl)cyclobutyl)amino)methyl)tetrahydrofuran-3-ol (15{*1,47*}). Yield 31.2 mg (28%); brownish oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.9 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.19 – 7.08 (m, 2H), 4.01 (q, *J* = 8.1 Hz, 1H), 3.91 (td, *J* = 8.5, 3.6 Hz, 1H), 3.75 (d, *J* = 9.2 Hz, 1H), 3.63 (d, *J* = 9.1 Hz, 1H), 3.42 – 3.19 (m, 2H), 2.82 – 2.70 (m, 3H), 2.68 – 2.18 (m, 4H), 2.08 (q, *J* = 9.5 Hz, 1H), 2.02 – 1.95 (m, 1H), 1.91 – 1.82 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 149.3, 136.4, 121.8, 121.3, 79.4, 77.6, 67.7, 53.2, 50.5, 38.8, 36.8, 36.8, 34.8. LCMS (CI): *m/z* = 249 $[M+H]^+$. Anal. Calcd. for $C_{14}H_{20}N_2O_2$: C 67.72; H 8.12; N 11.28. Found: C 67.67; H 8.19; N 11.65.

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References

[1] E. Vitaku, D. T. Smith, J. T. Njardarson, *J. Med. Chem.* **2014**, *57*, 10257–10274.

[2] P. R. Parry, C. Wang, A. S. Batsanov, M. R. Bryce, B. Tarbit, *J. Org. Chem.* **2002**, *67*, 7541–7543.

[3] A. Y. Cherepakha, K. O. Stepannikova, B. V. Vashchenko, M. V Gorichko, A. A. Tolmachev, O. O. Grygorenko, *Eur. J. Org. Chem.* **2018**, *2018*, 6682–6692.

[4] A. Nadin, C. Hattotuwagama, I. Churcher, *Angew. Chem. Int. Ed.* **2012**, *51*, 1114–1122.

[5] F. Lovering, J. Bikker, C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752–6756.

[6] M. Aldeghi, S. Malhotra, D. L. Selwood, A. W. E. Chan, *Chem. Biol. Drug Des.* **2014**, *83*, 450–461.

[7] Z. Fang, Y. Song, P. Zhan, Q. Zhang, X. Liu, *Future Med. Chem.* **2014**, *6*, 885–901.

[8] J. C. Namyslo, D. E. Kaufmann, *Chem. Rev.* **2003**, *103*, 1485–1538.

[9] A. Sergeiko, V. V. Poroikov, L. O. Hanus, V. M. Dembitsky, *Open Med. Chem. J.* **2008**, *2*, 26–37.

[10] V. M. Dembitsky, *Bioactive Cyclobutane-Containing Alkaloids*, **2008**.

[11] G. A. Molander, V. Colombel, V. A. Braz, *Org. Lett.* **2011**, *13*, 1852–1855.

[12] R. Murakami, K. Tsunoda, T. Iwai, M. Sawamura, *Chem. Eur. J.* **2014**, *20*, 13127–13131.

[13] M. H. Bolli, C. Lescop, M. Birker, R. de Kanter, P. Hess, C. Kohl, O. Nayler, M. Rey, P. Sieber, J. Velker, T. Weller, B. Steiner, *Eur. J. Med. Chem.* **2016**, *115*, 326–341.

[14] I. Abdiaj, A. Fontana, M. V. Gomez, A. de la Hoz, J. Alcázar, *Angew. Chem. Int. Ed.* **2018**, *57*, 8473–8477.

[15] M. Tissot, N. Body, S. Petit, J. Claessens, C. Genicot, P. Pasau, *Org. Lett.* **2018**, *20*, 8022–8025.

[16] J. M. McCabe Dunn, J. T. Kuethe, R. K. Orr, M. Tudge, L.-C. Campeau, *Org. Lett.* **2014**, *16*, 6314–6317.

[17] J. D. Galloway, D. N. Mai, R. D. Baxter, *Org. Lett.* **2017**, *19*, 5772–5775.

[18] I. B. Perry, T. F. Brewer, P. J. Sarver, D. M. Schultz, D. A. DiRocco, D. W. C. MacMillan, *Nature* **2018**, *560*, 70–75.

[19] S. Chang, M. Holmes, J. Mowat, M. Meanwell, R. Britton, *Angew. Chem. Int. Ed.* **2017**, *56*, 748–752.

[20] T. Meyer, Z. Yin, X. F. Wu, *Tetrahedron Lett.* **2019**, *60*, 864–867.

[21] T. J. Kohn, X. Du, S. Lai, Y. Xiong, R. Komorowski, M. Veniant, Z. Fu, X. Jiao, V. Pattaropong, D. Chow, M. Cardozo, L. Jin, M. Conn, W. E. DeWolf, C. F. Kraser, R. J. Hinklin, M. L. Boys, J. C. Medina, J. Houze, P. Dransfield, P. Coward, *ACS Med. Chem. Lett.* **2016**, *7*, 666–670.

[22] A. I. Subota, O. O. Grygorenko, Y. B. Valter, M. A. Tairov, O. S. Artamonov, D. M. Volochnyuk, S. V. Ryabukhin, *Synlett* **2015**, *26*, 408–411.

[23] A. I. Subota, A. O. Lutsenko, B. V. Vashchenko, D. M. Volochnyuk, V. Levchenko, Y. V. Dmytriv, E. B. Rusanov, A. O. Gorlova, S. V. Ryabukhin, O. O. Grygorenko, *Eur. J. Org. Chem.* **2019**, in press.

[24] A. C. Sun, E. J. McClain, J. W. Beatty, C. R. J. Stephenson, *Org. Lett.* **2018**, *20*, 3487–3490.

[25] S. Han, P. Chakrasali, J. Park, H. Oh, S. Kim, K. Kim, A. K. Pandey, S. H. Han, S. B. Han, I. S. Kim, *Angew. Chem. Int. Ed.* **2018**, *57*, 12737–12740.

[26] B. Xiao, Z. J. Liu, L. Liu, Y. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 616–619.

[27] X. Ma, S. B. Herzon, *J. Am. Chem. Soc.* **2016**, *138*, 8718–8721.

[28] X. Ma, H. Dang, J. A. Rose, P. Rablen, S. B. Herzon, *J. Am. Chem. Soc.* **2017**, *139*, 5998–6007.

[29] I. Kim, B. Park, G. Kang, J. Kim, H. Jung, H. Lee, M. H. Baik, S. Hong, *Angew. Chem. Int. Ed.* **2018**, *57*, 15517–15522.

[30] P. L. Johnson, J. M. Renga, C. V. Galliford, G. T. Whiteker, N. C. Giampietro, *Org. Lett.* **2015**, *17*, 2905–2907.

[31] Y. Wang, Z. Fu, M. Schmitt, X. Wang, W. Shen, E. Rickel, T. Martin, A. Budelsky, D. Marshall, T. Collins, H. L. Tang, J. C. Medina, J. Liu, *Bioorg. Med. Chem. Lett.* **2012**, *22*, 367–370.

[32] L. Debien, S. Z. Zard, *J. Am. Chem. Soc.* **2013**, *135*, 3808–3811.

[33] R. Y. Zhu, L. Y. Liu, H. S. Park, K. Hong, Y. Wu, C. H. Senanayake, J. Q. Yu, *J. Am. Chem. Soc.* **2017**, *139*, 16080–16083.

[34] S. Poplata, A. Tröster, Y. Q. Zou, T. Bach, *Chem. Rev.* **2016**, *116*, 9748–9815.

[35] G. Ortega, A. Briceño, *CrystEngComm* **2018**, *20*, 2932–2939.

[36] K. Singh, W. Trinh, J. D. Weaver, *Org. Biomol. Chem.* **2019**, *17*, 1854–1861.

[37] D. Schmidt, T. Rodat, L. Heintze, J. Weber, R. Horbert, U. Girreser, T. Raeker, L. Bußmann, M. Kriegs, B. Hartke, C. Peifer, *ChemMedChem* **2018**, *13*, 2415–2426.

[38] G. K. Kole, U. Sambasivam, G. K. Tan, J. J. Vittal, *Cryst. Growth Des.* **2017**, *17*, 2694–2699.

[39] F. L. Hu, Y. Mi, C. Zhu, B. F. Abrahams, P. Braunstein, J. P. Lang, *Angew. Chem. Int. Ed.* **2018**, *57*, 12696–12701.

[40] Z. Lu, T. P. Yoon, *Angew. Chem. Int. Ed.* **2012**, *51*, 10329–10332.

[41] S. Yamada, Y. Azuma, K. Aya, *Tetrahedron Lett.* **2014**, *55*, 2801–2804.

[42] M. V. S. N. Maddipatla, M. Pattabiraman, A. Natarajan, K. Srivastav, J. T. Mague, V. Ramamurthy, *Org. Biomol. Chem.* **2012**, *10*, 9219–9222.

[43] W. J. Gong, Z. G. Ren, H. X. Li, J. G. Zhang, J. P. Lang, *Cryst. Growth Des.* **2017**, *17*, 870–881.

[44] X. Gao, T. Friščić, L. R. MacGillivray, *Angew. Chem. Int. Ed.* **2003**, *43*, 232–236.

[45] H. Senboku, M. Takashima, M. Suzuki, K. Kobayashi, H. Suginome, *Tetrahedron* **1996**, *52*, 6125–6138.

[46] A. D. Volodin, A. A. Korlyukov, E. N. Zorina-Tikhonova, A. S. Chistyakov, A. A. Sidorov, I. L. Eremenko, A. V. Vologzhanina, *Chem. Commun.* **2018**, *54*, 13861–13864.

[47] R. A. Marcus, *J. Phys. Chem.* **1992**, *96*, 1753–1757.

[48] C. Reddy, N. Bisht, R. Parella, S. A. Babu, *J. Org. Chem.* **2016**, *81*, 12143–12168.

[49] S. Inokuma, H. Ide, T. Yonekura, T. Funaki, S. I. Kondo, S. Shiobara, T. Yoshihara, S. Tobita, J. Nishimura, *J. Org. Chem.* **2005**, *70*, 1698–1703.

[50] A. D. Thompson, M. P. Huestis, *J. Org. Chem.* **2013**, *78*, 762–769.

[51] E. A. Voight, J. F. Daanen, R. G. Schmidt, A. Gomtsyan, M. J. Dart, P. R. Kym, *J. Org. Chem.* **2016**, *81*, 12060–12064.

[52] A. Gomtsyan, R. G. Schmidt, E. K. Bayburt, G. A. Gfesser, E. A. Voight, J. F. Daanen, D. L. Schmidt, M. D. Cowart, H. Liu, R. J. Altenbach, M. E. Kort, B. Clapham, P. B. Cox, A. Shrestha, R. Henry, D. N. Whittern, R. M. Reilly, P. S. Puttfarcken, J. D. Brederson, P. Song, B. Li, S. M. Huang, H. A. McDonald, T. R. Neelands, S. P. McGaraughty, D. M. Gauvin, S. K. Joshi, P. N. Banfor, J. A. Segreti, M. Shebley, C. R. Faltynek, M. J. Dart, P. R. Kym, *J. Med. Chem.* **2016**, *59*, 4926–4947.

[53] S. Kosiński, K. Wojciechowski, *Eur. J. Org. Chem.* **2000**, 1263–1270.

[54] D. Zhang, H. Zheng, X. Wang, *Tetrahedron* **2016**, *72*, 1941–1953.

[55] M. C. Viaud, P. Jamoneau, G. Guillaumet, *Synth. Commun.* **1997**, *27*, 3861–3870.

[56] D. Sun, Z. Wang, M. Cardozo, R. Choi, M. DeGraffenreid, Y. Di, X. He, J. C. Jaen, M. Labelle, J. Liu, J. Ma, S. Miao, A. Sudom, L. Tang, H. Tu, S. Ursu, N. Walker, X. Yan, Q. Ye, J. P. Powers, *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1522–1527.

[57] N. Rüger, M. Roatsch, T. Emmrich, H. Franz, R. Schüle, M. Jung, A. Link, *ChemMedChem* **2015**, *10*, 1875–1883.

[58] J. Hung, L. M. Werbel, *J. Heterocycl. Chem.* **1984**, *21*, 741–744.

[59] C. A. Lipinski, F. Lombardo, B. W. Dominy, P. J. Feeney, *Adv. Drug Deliv. Rev.* **1997**, *23*, 3–25.

[60] Instant JChem, version 15.3.16.0, ChemAxon (http://www.chemaxon.com).

[61] W. L. F. Armarego, C. Chai, *Purification of Laboratory Chemicals*, Elsevier: Oxford, **2003**.

[62] R. F. Borne, H. Y. Aboul-Enein, *J. Heterocycl. Chem.* **1980**, *17*, 1609–1611.

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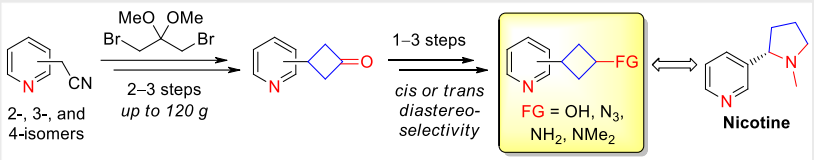

Robust and scalable synthesis of functionalized 1,3-disubstituted pyridylcyclobutanes (including nicotine analogues) is developed, which relies on double alkylation of pyridylacetonitriles.

Cyclobutanes

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Robust and Scalable Approach to 1,3-Disubstituted Pyridylcyclobutanes