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ORIGINAL PAPER

Cyclopropyl boronic derivatives in parallel synthesis of sp^3-enriched compound libraries

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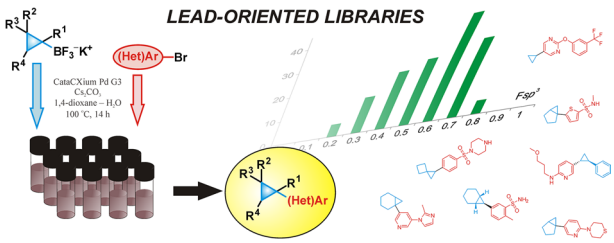
Abstract

The Suzuki–Miyaura coupling of cyclopropyl boronic derivatives with (het)aryl halides was evaluated as a method for parallel synthesis of sp^3-enriched compound libraries. The scope and limitation of the procedure were established. It was shown that the method was applicable to a wide range of cyclopropyl trifluoroborates and (het)aryl bromides. Limitations of the method included trifluoroborates bearing bulky substituents at the α position, as well as (het)aryl bromides with ester moieties. A 96-member library was prepared to illustrate the concept with 68% success rate and 30% average yield. Calculated physico-chemical properties of the products obtained (in particular, sp^3-hybrid carbon atom fraction $Fsp^3 = 0.16$-0.83 range, 0.52 on average), as well as neglectable "Log*P* drift" effect, observed experimentally (0.02 units) showed that the method is well-compatible with lead-oriented synthesis criteria.

Graphic abstract



Keywords Small rings · Combinatorial chemistry · Main group compounds · Trifluoroborates · Suzuki–Miyaura reaction · Lead-oriented synthesis

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Introduction

In the last two decades, medicinal chemistry witnessed increased interest in compound libraries enriched with more three-dimensional structures having higher sp^3 carbon atom fraction [1–3]. Together with the lead-likeness concept [4, 5], these "escape-from-flatland" ideas [3] became the background of the so-called "lead-oriented synthesis"—a catchphrase for all synthetic methods which provide low-molecular-weight, relatively hydrophilic, sp^3-enriched compounds in an efficient manner, preferably in combinatorial fashion [6, 7]. Although the precise definition of lead-oriented approaches is not clear, a number of examples have been reported in the literature based on multicomponent reactions

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[8–10] and other diversity-oriented approaches [11–15]. An alternative strategy to access sp^3-enriched lead-like compound libraries relies on the use of appropriate sp^3-enriched building blocks [16]. For (hetero)aliphatic building blocks, such methodologies were mostly based on the carbon–heteroatom bond formation [17–21], while the C–C couplings (e.g., Suzuki–Miyaura reaction) were more common for their aromatic counterparts. Although recent advances like Molander's photoredox chemistry seem to change this situation [22–25], many novel methods for the C–C bond formation are still difficult to implement into (semi)-automated parallel synthesis.

The design of compound libraries based on the C(sp^3)–C(sp^2) disconnection can be reliable if sufficiently reactive sp^3-enriched substrates are used. In this view, cyclopropane-derived organoboron derivatives are especially promising, which possess enhanced reactivity in the Suzuki–Miyaura reaction due to the partially unsaturated nature of the three-membered ring. Despite many literature precedents [26–36], the utility of cyclopropyl boronic derivatives for combinatorial chemistry, as well as the scope of the method was not demonstrated to a sufficient extent. This work is aimed to address this issue by design and parallel synthesis of a sp^3-enriched compound library based on the Suzuki–Miyaura reaction of various *C*-substituted cyclopropyl boronic derivatives.

As the main subject of this paper is related to combinatorial chemistry, a library member numbering system characteristic of this research area was followed (according to ACS standards). In particular, the reagent series used for the library synthesis were numbered with bold Arabic numbers (i.e., cyclopropyl trifluoroborates **1**, pinacolates **2**, or aromatic halides **3**), while each particular reagent was denoted by an additional number shown in curly brackets, e.g., **1**{*1*}, **1**{*2*}, **1**{*3*} etc. The product library was also designated by a bold Arabic number (**4**), while a particular library member prepared from the reagents **1**{*i*} and **3**{*j*} was denoted as **4**{*i*,*j*}.

Results and discussion

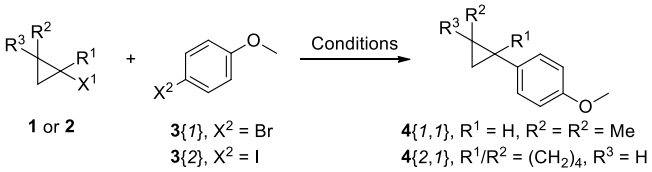
First of all, conditions for the Suzuki–Miyaura reaction described by Harris and co-workers for 1-substituted 3-azabicy-clo[3.1.0]hexane derivatives [35] were studied with model cyclopropyl boronic derivatives **1**{*1*}, **1**{*2*}, **2**{*1*}, and **2**{*2*}, as well as *p*-methoxyphenyl halides **3**{*1*} and **3**{*2*}. It was found that trifluoroborates **1**{*1*} and **1**{*2*} gave higher conversion into the target products **4**{*1*,*1*} or **4**{*2*,*1*} as compared to the corresponding pinacolates, and the difference was more significant for the sterically hindered substrates (Table 1, entries 1–8). This result is in good agreement with the literature data [35]. Although decreasing excess of aryl bromide **3**{*1*} from 2 eq to 1.1 eq slightly worsened the reaction outcome, the effect was not significant so that simplified purification of the products from the starting materials after the parallel synthesis might be beneficial. Variation of the reaction time showed that after 14 h, optimal results were obtained since after 5–7 h, the incomplete conversion was observed, whereas longer reaction time (24 h) did not improve the reaction outcome significantly (entries 9–11). It should be noted that under the standard conditions, trifluoroborate **1**{*2*} gave a moderate yield of the product in reaction with aryl iodide **3**{*2*}, while the corresponding pinacolate **2**{*2*} did not give the target compound at all (entries 12 and 13). Therefore (het)ar-aryl iodides were excluded from further study. Finally, since toluene might be not optimal solvent for the parallel synthesis as many (het) aryl halides bearing polar groups might have low solubility, a possibility to replace it with more polar 1,4-dioxane and DMF was evaluated. It was found that the first of these replacements worked well, and the observed conversion was even slightly improved (entries 14 and 15). Further optimizations including variation of the precatalyst (entries 16–18; Fig. 1) or its loading (entries 19 and 20), base (entries 21 and 22), and temperature (entries 23 and 24) did not result in increased conversion of the substrate (except using 10% mol of the Cataxium Pd G3 precatalyst, which is unreasonable due to its cost).

The optimized conditions (trifluoroborate **1** (1 eq), bromide **3** (1.1 eq), Cataxium Pd G3 catalyst (5% mol), Cs_2CO_3 (4 eq), 1,4-dioxane–H_2O (10:1), 100 °C, 14 h) were applied to the parallel synthesis of library **4** on 0.22–0.33 mmol scale, followed by reverse-phase HPLC purification. Cyclopropyl trifluoroborates **1**{*1-12*} (Fig. 2), as well as (het)aryl bromides **3**{*3-117*} randomly selected from our collection of building blocks with molecular weight limited by 180-350 (Fig. S1 in the Supporting information) were used as the reagents for the library synthesis.

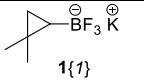
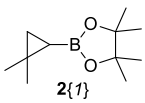
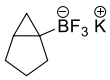
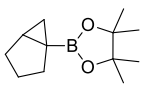
140 representative library members **4** were selected to evaluate the possibilities of the method (Fig. 3), and 96 of them were synthesized successfully (68% success rate, 30% average yield, see Table S1 in the Supporting information). It was found that the method did not work with protected α-aminoboronic derivative **1**{*12*}; the next lowest success rate (50%, 14 experiments) was observed for trifluoroborate **1**{*10*} bearing an α-phenyl substituent, which might be addressed to steric factors (Fig. 3). The corresponding library members could not be obtained (or were obtained with low yield) from (het)aryl bromides **3**{*51*}, **3**{*72*}, and **3**{*76*} bearing an ester function, obviously due to the hydrolysis at this moiety. No other meaningful regularities for the effects of the (het)aryl bromide structure on the reaction outcome could be found.

In the case of trifluoroborates **1**{*4*}, **1**{*5*}, and **1**{*8*} (where diastereoselectivity issues were possible), the

Table 1 Optimization of the Suzuki–Miyaura reaction conditions for model cyclopropyl boronic derivatives **1**{*1*}, **1**{*2*}, **2**{*1*}, **2**{*2*} and *p*-methoxyphenyl halides **3**{*1*}, **3**{*2*}



1 or **2** — **3**{*1*}, X^2 = Br; **3**{*2*}, X^2 = I — **4**{*1,1*}, R^1 = H, R^2 = R^2 = Me; **4**{*2,1*}, R^1/R^2 = $(CH_2)_4$, R^3 = H

#	Substrate	X^2	Time /h	Precatalyst	Base[a]	Solvent	*T* /°C	Excess of **3** /eq	Conversion /%[b]
1	 **1**{*1*}	Br	14	Cataxium Pd G3 (5% mol)	Cs_2CO_3	toluene - H_2O (10:1)	100	1.1	80
2								2	91
3	 **2**{*1*}	Br	14	Cataxium Pd G3 (5% mol)	Cs_2CO_3	toluene - H_2O (10:1)	100	1.1	57
4								2	59
5	 **1**{*2*}	Br	14	Cataxium Pd G3 (5% mol)	Cs_2CO_3	toluene - H_2O (10:1)	100	1.1	82
6								2	95
7	 **2**{*2*}	Br	14	Cataxium Pd G3 (5% mol)	Cs_2CO_3	toluene - H_2O (10:1)	100	1.1	22
8								2	44
9	**2**{*1*}	Br	5	Cataxium Pd G3 (5% mol)	Cs_2CO_3	toluene - H_2O (10:1)	100	1.1	73
10	**2**{*1*}	Br	7	Cataxium Pd G3 (5% mol)	Cs_2CO_3	toluene - H_2O (10:1)	100	1.1	75
11	**2**{*1*}	Br	24	Cataxium Pd G3 (5% mol)	Cs_2CO_3	toluene - H_2O (10:1)	100	1.1	84
12	**2**{*1*}	I	14	Cataxium Pd G3 (5% mol)	Cs_2CO_3	toluene - H_2O (10:1)	100	1.1	67
13	**2**{*2*}	I	14	Cataxium Pd G3 (5% mol)	Cs_2CO_3	toluene - H_2O (10:1)	100	1.1	0
14	**2**{*1*}	Br	14	Cataxium Pd G3 (5% mol)	Cs_2CO_3	1,4-dioxane - H_2O (10:1)	100	1.1	88
15	**2**{*2*}	Br	14	Cataxium Pd G3 (5% mol)	Cs_2CO_3	DMF	100	1.1	47
16	**2**{*2*}	Br	14	$Pd(PPh_3)_4$ (5% mol)	Cs_2CO_3	1,4-dioxane - H_2O (10:1)	100	1.1	58
17	**2**{*2*}	Br	14	$Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (5% mol)	Cs_2CO_3	1,4-dioxane - H_2O (10:1)	100	1.1	74
18	**2**{*2*}	Br	14	XPhos Pd G3 (5% mol)	Cs_2CO_3	1,4-dioxane - H_2O (10:1)	100	1.1	87
19	**2**{*2*}	Br	14	Cataxium Pd G3 (10% mol)	Cs_2CO_3	1,4-dioxane - H_2O (10:1)	100	1.1	90
20	**2**{*2*}	Br	14	Cataxium Pd G3 (2% mol)	Cs_2CO_3	1,4-dioxane - H_2O (10:1)	100	1.1	81
21	**2**{*2*}	Br	14	Cataxium Pd G3 (5% mol)	Na_2CO_3	1,4-dioxane - H_2O (10:1)	80	1.1	6
22	**2**{*2*}	Br	14	Cataxium Pd G3 (5% mol)	K_3PO_4	1,4-dioxane - H_2O (10:1)	120	1.1	27
23	**2**{*2*}	Br	14	Cataxium Pd G3 (5% mol)	Cs_2CO_3	1,4-dioxane - H_2O (10:1)	80	1.1	77
24	**2**{*2*}	Br	14	Cataxium Pd G3 (5% mol)	Cs_2CO_3	1,4-dioxane - H_2O (10:1)	120	1.1	80

[a]4 eq [b] Conversion of **1** or **2** into **4** calculated from **3**:**4** ratio after the reaction, in turn obtained from GS–MS data

method gave a single diastereomeric pair as the product. To establish the relative configuration of the corresponding library members, NOESY experiments were performed with

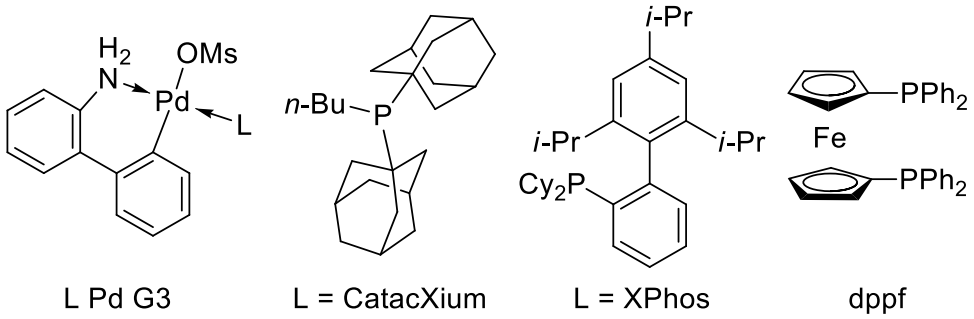


Fig. 1 Structures of palladium precatalysts and ligands used in this study

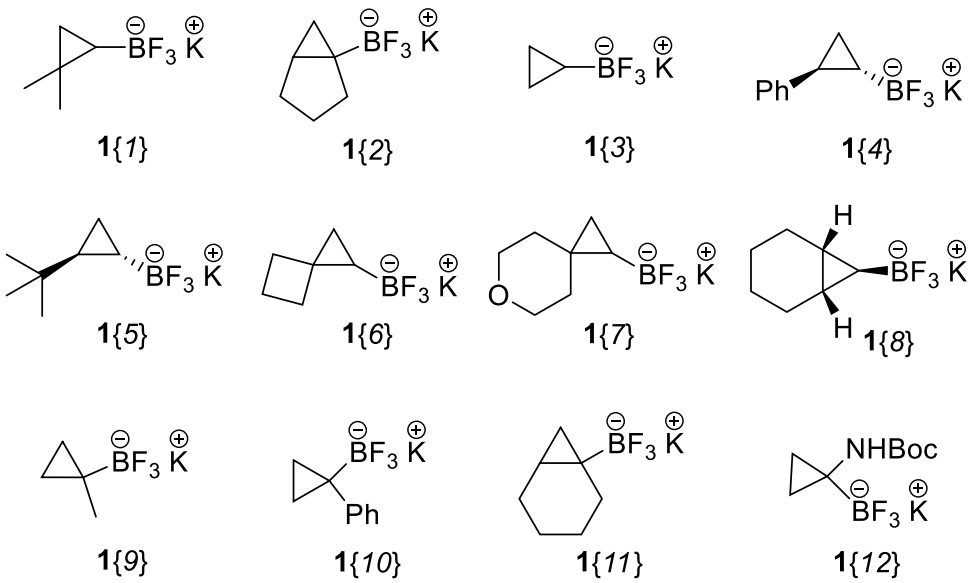


Fig. 2 Cyclopropyl boronic derivatives **1**{*1-12*} used for the synthesis of library **4** (relative configurations are shown)

library members **4**{*4,86*}, **4**{*5,26*}, and **4**{*8,115*}. Unfortunately, the configuration assignment could be achieved only for library member **4**{*5,26*} (Fig. 4) due to signal overlap observed for other compounds. Nevertheless, retention of the configuration was observed for this particular representative, which is in accordance with literature data [36]. Taking into account this result, we assume that the reaction occurred with retention of the configuration in other cases too. Obviously, for the cases, where aryl halide contained a chiral center and was a racemic material, mixtures of diastereomers were obtained.

All the synthesized library members were not described in the literature previously and had the following physicochemical properties: molecular weight (MW) 250.0-338.5 (273.2 on average), the calculated logarithm of partition coefficient in octanol–water system (cLog*P*) 1.01-5.97 (3.00 on average), hydrogen bond acceptor count (HAcc) 1-5 (2.4 on average), hydrogen bond donor count (HDon) 0-2 (0.8 on average), rotatable bond count (RotB) 1-9 (3.6 on average), and sp^3-hybrid carbon atom fraction (Fsp^3) 0.16-0.83 (0.52 on average) (Fig. 5) [37]. 88% of the resulting 96-member library was compliant with the so-called "rule of four" (proposed for lead-like compounds, i.e., MW < 400, Log*P* < 4, HAcc < 8, HDon < 4) [1], and 49% to the strictest criteria of lead-likeness introduced by Churcher and co-workers (MW = 200–350, Log*P* = -1-3) [7]. Notably, the method was very slightly susceptible to the so-called "Log*P* drift" effect (i.e., tendency to obtain more lipophilic part of the library with higher success rate [7])—average cLog*P* values for 140 planned and 96 synthesized library members were very close (2.98 and 3.00, respectively) (Figs. 6, 7).

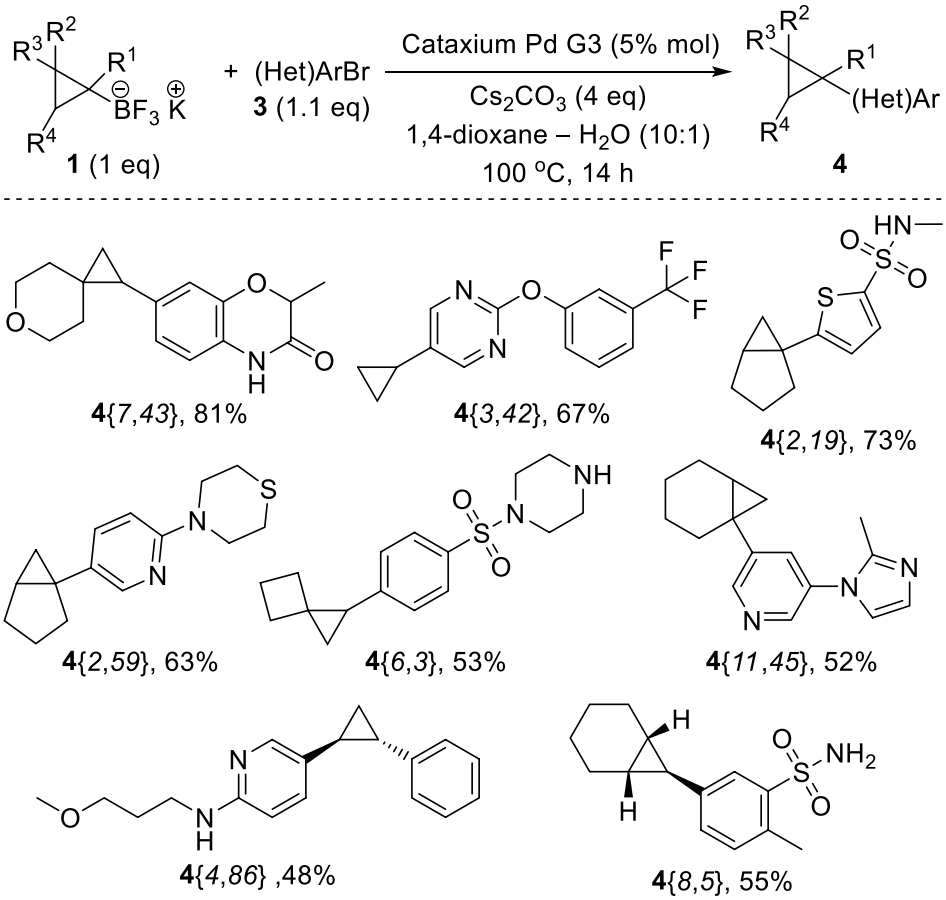


Fig. 3 Synthesis of library **4** and selected examples of the library members (relative configurations are shown)

Conclusions

The Suzuki–Miyaura coupling of cyclopropyl boronic derivatives with (het)aryl halides is a powerful method for parallel synthesis of sp^3-enriched compound libraries. Cyclopropyl trifluoroborates were confirmed to be much superior substrates over the corresponding pinacolates for that purpose; as for halide component, bromides were optimal. Using the optimized conditions (trifluoroborate (1 eq), (het)aryl bromide (1.1 eq), Cataxium Pd G3 catalyst (5% mol), Cs_2CO_3 (4 eq), 1,4-dioxane–H_2O (10:1), 100 °C, 14 h), a 96-member library was prepared to illustrate the concept (68% success rate, 30% average yield). Various mono-, di-, and trisubstituted trifluoroborates

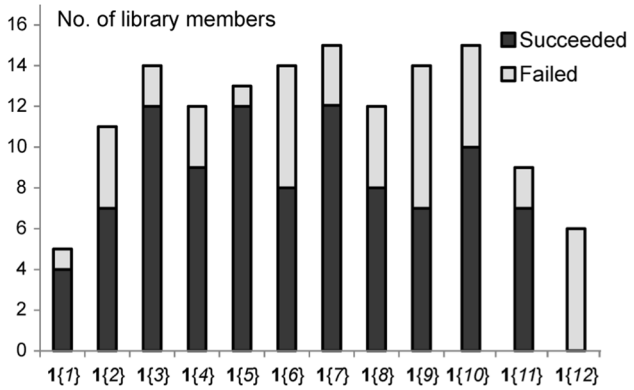


Fig. 4 Synthesis success rate for reagents **1**{*1-12*} in the preparation of library **4**

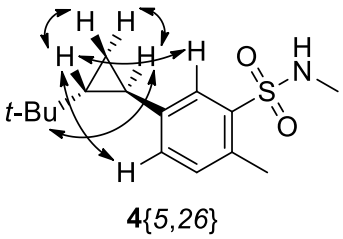


Fig. 5 Important NOESY correlations observed for compound **4**{*5,26*}

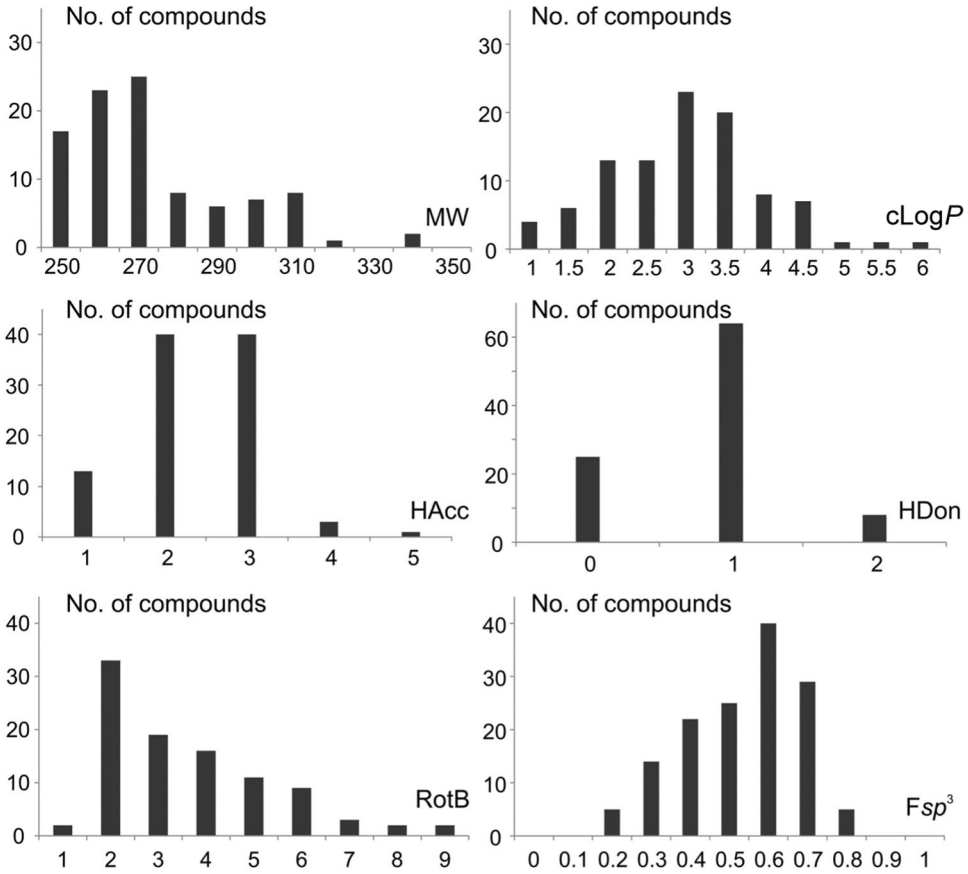


Fig. 6 Distribution of 96 synthesized library members **4** over selected physico-chemical parameters

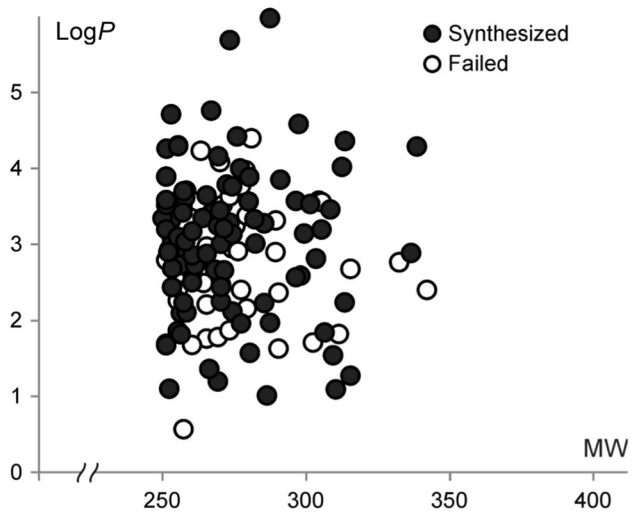


Fig. 7 140 library members **4** shown in MW - Log*P* plot

were more or less efficient substrates for the parallel synthesis; limitations of the method included the presence of bulky substituents (e.g., Ph on NHBoc) at the α position to the boron atom. As for the bromide (het)aryl bromide components, various functional groups present in their molecules were compatible with the procedure (except the ester moiety). Therefore, we recommend avoiding the use of such reagents into the library design or considering alternative retrosynthetic disconnections if such particular molecules are the synthetic targets. Analysis of physico-chemical properties of the products obtained showed that they were compatible with the lead-likeness criteria. Moreover, only a slight "Log*P*" drift was observed during the synthesis. Therefore, the proposed method can be considered as a convenient tool for lead-oriented synthesis.

Experimental

The solvents were purified according to the standard procedures [38]. Reagents **1**-**3** 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. ^{1}H and ^{13}C NMR spectra were recorded on an Agilent ProPulse 600 spectrometer (at 600 MHz for ^{1}H NMR, 151 MHz for ^{13}C NMR, and 564 MHz for ^{19}F NMR), 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, National Taras Shevchenko University of Kyiv, their results were found to be in good agreement ($\pm$0.4%) with the calculated values. 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)]. Synthesis of the library **4** was set up in vials for parallel synthesis, and the amounts of reagents for each substrate were calculated by in-house developed computational software. Silia*MetS*® DMT (dimercaptotriazine) was used for the filtration of the reaction mixtures.

General procedure for the parallel synthesis of library 4

Trifluoroborate **1** (0.3 mmol), (het)aryl bromide (0.33 mmol), Cs_2CO_3 (1.2 mmol), and Cataxium Pd G3 (16.5 μmol, 1 M in toluene) were mixed up. The reaction vessel was blown out with argon, and 0.5 cm^3 1,4-dioxane–H_2O (10:1) was added. The mixture was heated at 100 °C for 14 h, then cooled to rt and evaporated in vacuo. The residue was diluted with 0.3 cm^3 DMSO, and TFA was added until pH 5. The obtained mixture was filtered through 0.200 g dimercaptotriazine-functionalized silica gel and then subjected to preparative reverse-phase HPLC.

***N*,2-Dimethyl-5-(1-phenylcyclopropyl)benzenesulfonamide (4{*10,26*}, $C_{17}H_{19}NO_2S$)** Yield 60 mg (74%); colorless viscous oil; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.58 (d, J = 1.9 Hz, 1H), 7.42 (q, J = 4.9 Hz, 1H), 7.34 (dd, J = 7.9, 1.9 Hz, 1H), 7.28 (d, J = 7.9 Hz, 1H), 7.26 (d, J = 7.6 Hz, 1H), 7.24 (s, 1H), 7.19–7.14 (m, 3H), 2.48 (s, 3H), 2.35 (d, J = 4.9 Hz, 3H), 1.29-1.25 (m, 2H), 1.25–1.21 (m, 2H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6): δ = 145.1, 143.9, 137.9, 134.6, 133.1, 132.4, 128.9, 128.7, 128.5, 126.6, 29.8, 28.8, 19.8, 16.4 ppm; LC/MS (CI): m/z = 302 ([M + H]$^+$).

5-(Bicyclo[3.1.0]hexan-1-yl)-*N*-methylthiophene-2-sulfonamide (4{*2,19*}, $C_{11}H_{15}NO_2S_2$) Yield 55 mg (73%); colorless viscous oil; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.49 (s, 1H), 7.34 (d, J = 3.8 Hz, 1H), 6.84 (d, J = 3.8 Hz, 1H), 2.47 (dt, J = 3.8, 1.7 Hz, 1H), 2.44 (s, 3H), 2.02 (dd, J = 12.3, 8.0 Hz, 1H), 1.99-1.94 (m, 1H), 1.87–1.80 (m, 1H), 1.71 (dd, J = 12.3, 8.0 Hz, 1H), 1.66 (dd, J = 13.6, 8.0 Hz, 1H), 1.62 (dd, J = 8.5, 4.2 Hz, 1H), 1.36–1.25 (m, 1H), 1.06 (t, J = 5.0 Hz, 1H), 0.95 (dd, J = 8.5, 5.0 Hz, 1H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6): δ = 157.8, 135.4, 132.3, 122.6, 32.4, 31.0, 29.3, 29.2, 27.7, 21.0, 18.4 ppm; LC/MS (CI): m/z = 258 ([M + H]$^+$).

1-[6-(6-Oxaspiro[2.5]octan-1-yl)pyridin-2-yl]-1*H*-benzo[*d*]-imidazole (4{*7,47*}, $C_{19}H_{19}N_3O$) Yield 53 mg (71%); colorless viscous oil; the compound was obtained as ca. 1:1 mixture of diastereomers; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.97 (s, 1H) and 8.91 (s, 1H), 8.25 (d, J = 3.3 Hz, 1H), 8.24 (d, J = 3.4 Hz, 1H), 8.01–7.95 (m, 1H), 7.89 (t, J = 7.8 Hz, 1H) and 7.75 (t, J = 7.8 Hz, 1H), 7.67 (d, J = 8.0 Hz, 1H) and 7.63 (dd, J = 7.0, 1.2 Hz, 1H), 7.41 (d, J = 7.5 Hz, 1H) and 7.39 (d, J = 7.5 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.33 (t, J = 7.6 Hz, 1H) and 7.30 (t, J = 7.6 Hz, 1H), 3.69-3.64 (m, 2H), 3.43 (ddd, J = 10.4, 6.5, 3.6 Hz, 1H), 3.25-3.19 (m, 1H), 2.24 (dd, J = 8.1, 5.6 Hz, 1H), 1.61–1.52 (m, 2H), 1.51–1.44 (m, 2H), 1.33 (ddd, J = 13.6, 6.5, 3.3 Hz, 1H), 1.00 (dd, J = 8.1, 4.4 Hz, 1H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6): δ = 159.7, 150.1, 149.2, 144.7, 144.6, 142.8, 142.7, 142.5, 139.6, 132.3, 132.0, 125.9, 124.7, 124.3, 123.9, 123.4, 122.2, 120.4, 120.4, 114.4, 114.2, 113.7, 111.3, 67.1, 66.9, 37.6, 29.9, 29.4, 27.7, 18.2 ppm; LC/MS (CI): m/z = 306 ([M + H]$^+$).

5-Cyclopropyl-2-[3-(trifluoromethyl)phenoxy]pyrimidine (4{*3,42*}, $C_{14}H_{11}F_3N_2O$) Yield 50 mg (67%); colorless viscous oil; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.41 (s, 2H), 7.64 (t, J = 8.1 Hz, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.57 (s, 1H), 7.49 (d, J = 8.1 Hz, 1H), 1.89 (tt, J = 8.4, 5.2 Hz, 1H), 0.97–0.93 (m, 2H), 0.76–0.73 (m, 2H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6): δ = 163.3, 157.7, 153.8, 132.7, 131.3, 130.8 (q, J = 32.3 Hz), 126.4, 124.2 (q, J = 272.4 Hz), 122.2 (q, J = 3.7 Hz), 119.1 (q, J = 3.5 Hz), 10.2, 8.9 ppm; ^{19}F NMR (376 MHz, DMSO-d_6): δ = − 61.6 ppm; LC/MS (CI): m/z = 281 ([M + H]$^+$).

4-[5-(Bicyclo[3.1.0]hexan-1-yl)pyridin-2-yl]thiomorpholine (4{*2,59*}, $C_{15}H_{20}N_2S$) Yield 47 mg (63%); colorless viscous oil; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.98 (d, J = 2.6 Hz, 1H), 7.32 (dd, J = 8.8, 2.6 Hz, 1H), 6.74 (d, J = 8.8 Hz, 1H), 3.85–3.80 (m, 4H), 2.57–2.53 (m, 4H), 1.98 (dd, J = 12.1, 7.8 Hz, 1H), 1.91–1.77 (m, 2H), 1.73 (dd, J = 12.2, 7.9 Hz, 1H), 1.63 (dt, J = 13.1, 7.9 Hz, 1H), 1.52 (dt, J = 7.9, 4.2 Hz, 1H), 1.33-1.20 (m, 1H), 0.78 (t, J = 4.6 Hz, 1H), 0.65 (dd, J = 8.2, 4.6 Hz, 1H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 156.7, 145.9, 136.3, 129.4, 107.5, 47.9, 32.3, 29.3, 27.8, 25.5, 21.1, 15.2 ppm; LC/MS (CI): m/z = 261 ([M + H]$^+$).

5-[(1*R*,2*R*)-2-(*tert*-Butyl)cyclopropyl]-*N*,2-dimethylbenzenesulfonamide (4{*5,26*}, $C_{15}H_{23}NO_2S$) Yield 47 mg (63%); colorless viscous oil; ^{1}H NMR (600 MHz, DMSO-d_6):

δ = 7.46 (d, J = 1.9 Hz, 1H), 7.38 (s, 1H), 7.22 (d, J = 7.9 Hz, 1H), 7.18 (dd, J = 7.9, 1.9 Hz, 1H), 2.47 (p, J = 1.8 Hz, 2H), 2.46 (s, 3H), 2.38 (s, 3H), 1.85 (dt, J = 8.1, 4.8 Hz, 1H), 0.94–0.88 (m, 2H), 0.85 (s, 9H), 0.73 (dd, J = 13.2, 4.8 Hz, 1H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6): δ = 142.6, 137.7, 133.4, 132.9, 129.7, 126.1, 36.0, 30.3, 28.8, 28.5, 19.8, 18.3, 12.2 ppm; LC/MS (CI): m/z = 282 ([M + H]$^+$).

4-[3-(6-Oxaspiro[2.5]octan-1-yl)phenyl]thiazole (4{*7,34*}, $C_{16}H_{17}NOS$) Yield 47 mg (62%); colorless viscous oil; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 9.16 (d, J = 1.8 Hz, 1H), 8.16 (d, J = 1.8 Hz, 1H), 7.81 (t, J = 1.8 Hz, 1H), 7.76 (dt, J = 7.6, 1.8 Hz, 1H), 7.32 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 7.6 Hz, 1H), 3.72-3.66 (m, 1H), 3.65–3.58 (m, 1H), 3.42–3.36 (m, 1H), 3.35-3.30 (m, 1H), 2.03 (dd, J = 8.3, 5.4 Hz, 1H), 1.57-1.44 (m, 2H), 1.21–1.13 (m, 1H), 1.12–1.08 (m, 1H), 1.06 (d, J = 5.4 Hz, 1H), 0.82 (dd, J = 8.3, 5.4 Hz, 1H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6): δ = 155.6, 154.8, 139.8, 134.1, 128.8, 126.6, 124.0, 114.6, 67.1, 66.7, 37.5, 30.6, 28.7, 24.7, 16.3 ppm; LC/MS (CI): m/z = 272 ([M + H]$^+$).

1-[2-[(1*R*,6*S*,7*R*)-Bicyclo[4.1.0]heptan-7-yl]pyridin-3-yl]-piperidin-2-one (4{*8,115*}, $C_{17}H_{22}N_2O$) Yield 49 mg (60%); colorless viscous oil; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 8.28 (dd, J = 4.7, 1.6 Hz, 1H), 7.48 (dd, J = 7.8, 1.6 Hz, 1H), 7.11 (dd, J = 7.8, 4.7 Hz, 1H), 3.55-3.49 (m, 1H), 3.41–3.36 (m, 1H), 2.45–2.34 (m, 2H), 1.95–1.79 (m, 6H), 1.70–1.64 (m, 1H), 1.64-1.55 (m, 3H), 1.38 (q, J = 6.1 Hz, 1H), 1.31–1.17 (m, 4H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 169.4, 159.3, 148.1, 138.1, 135.6, 121.0, 51.6, 32.7, 25.5, 23.8, 23.5, 23.4, 23.0, 21.5, 21.4, 21.4 ppm; LC/MS (CI): m/z = 271 ([M + H]$^+$).

4-Amino-3-(bicyclo[3.1.0]hexan-1-yl)benzenesulfonamide (4{*2,14*}, $C_{12}H_{16}N_2O_2S$) Yield 41 mg (55%); colorless viscous oil; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.43 (d, J = 2.3 Hz, 1H), 7.32 (dd, J = 8.4, 2.3 Hz, 1H), 6.86 (s, 2H), 6.63 (d, J = 8.4 Hz, 1H), 5.40 (s, 2H), 2.04–1.93 (m, 2H), 1.75 (dd, J = 12.2, 7.8 Hz, 1H), 1.67–1.60 (m, 1H), 1.58 (dd, J = 12.2, 8.2 Hz, 1H), 1.42 (dt, J = 8.2, 4.4 Hz, 1H), 1.31-1.21 (m, 1H), 0.86 (t, J = 4.4 Hz, 1H), 0.45 (dd, J = 8.2, 4.4 Hz, 1H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6): δ = 151.0, 130.7, 128.2, 126.4, 125.7, 113.3, 31.8, 30.0, 27.7, 23.8, 21.5, 12.9 ppm; LC/MS (CI): m/z = 251 ([M-H]$^-$).

5-[(1*R*,6*S*,7*R*)-Bicyclo[4.1.0]heptan-7-yl]-2-methylbenzenesulfonamide (4{*8,5*}, $C_{14}H_{19}NO_2S$) Yield 41 mg (55%); colorless solid; m.p.: 131–133 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.49 (d, J = 2.1 Hz, 1H), 7.27 (s, 2H), 7.19 (d, J = 7.8 Hz, 1H), 7.08 (dd, J = 7.8, 2.1 Hz, 1H), 2.49 (s, 3H), 1.97–1.86 (m, 2H), 1.76–1.66 (m, 3H), 1.31–1.19 (m, 6H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 142.6, 142.3, 132.5, 132.4, 128.4, 124.2, 27.7, 23.5, 22.8, 21.3, 19.8 ppm; LC/MS (CI): m/z = 264 ([M-H]$^-$).

1-[[4-(Spiro[2.3]hexan-1-yl)phenyl]sulfonyl]piperazine (4{*6,3*}, $C_{16}H_{22}N_2O_2S$) Yield 39 mg (53%); colorless solid; m.p.: 98–101 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.57 (d, J = 8.0 Hz, 2H), 7.20 (d, J = 8.0 Hz, 2H), 3.32 (s, 1H), 2.76–2.72 (m, 4H), 2.71–2.67 (m, 4H), 2.28-2.22 (m, 1H), 2.18-1.99 (m, 4H), 1.91–1.83 (m, 1H), 1.83-1.75 (m, 1H), 1.19 (dd, J = 8.8, 5.4 Hz, 1H), 1.04 (t, J = 5.4 Hz, 1H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$): δ = 147.7, 131.6, 127.8, 127.3, 47.3, 45.2, 31.2, 30.2, 28.0, 26.3, 21.8, 16.4 ppm; LC/MS (CI): m/z = 307 ([M + H]$^+$).

3-(Bicyclo[4.1.0]heptan-1-yl)-5-(2-methyl-1*H*-imidazol-1-yl)-pyridine (4{*11,45*}, $C_{16}H_{19}N_3$) Yield 39 mg (51%); colorless viscous oil; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.55 (d, J = 2.3 Hz, 1H), 8.48 (d, J = 2.3 Hz, 1H), 7.69 (t, J = 2.3 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 6.93 (d, J = 1.5 Hz, 1H), 2.29 (s, 3H), 2.11–2.02 (m, 2H), 2.02–1.94 (m, 1H), 1.67–1.57 (m, 1H), 1.53–1.44 (m, 1H), 1.40-1.30 (m, 2H), 1.30-1.19 (m, 2H), 1.06 (dd, J = 9.5, 5.0 Hz, 1H), 0.78 (t, J = 5.0 Hz, 1H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 148.1, 145.4, 144.4, 143.2, 134.4, 131.3, 128.0, 121.5, 30.2, 23.6, 21.9, 21.3, 21.2, 19.7, 19.0, 14.0 ppm; LC/MS (CI): m/z = 254 ([M + H]$^+$).

3-[4-(Bicyclo[3.1.0]hexan-1-yl)phenyl]piperazin-2-one (4{*2,61*}, $C_{16}H_{20}N_2O$) Yield 37 mg (49%); colorless solid; m.p.: 199–202 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.70 (s, 1H), 7.24 (d, J = 7.8 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 4.24 (s, 1H), 3.30-3.21 (m, 1H), 3.19–3.11 (m, 1H), 2.94-2.84 (m, 2H), 2.84–2.76 (m, 1H), 2.08–1.99 (m, 1H), 1.93 (q, J = 11.6 Hz, 1H), 1.88–1.79 (m, 1H), 1.75 (dd, J = 12.1, 7.8 Hz, 1H), 1.66 (dt, J = 12.1, 7.8 Hz, 1H), 1.60 (dt, J = 8.3, 4.5 Hz, 1H), 1.37–1.24 (m, 1H), 0.87 (t, J = 4.5 Hz, 1H), 0.70 (dd, J = 8.3, 4.5 Hz, 1H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): δ = 170.1, 144.3, 138.1, 128.7, 125.7, 63.3, 42.8, 41.1, 31.9, 31.7, 27.8, 26.6, 21.1, 16.8 ppm; LC/MS (CI): m/z = 257 ([M + H]$^+$).

***N*-(3-Methoxypropyl)-5-[(1*R*,2*R*)-2-phenylcyclopropyl]pyridin-2-amine (4{*4,86*}, $C_{18}H_{22}N_2O$)** Yield 40 mg (48%); colorless viscous oil; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.83 (d, J = 2.5 Hz, 1H), 7.23 (t, J = 7.7 Hz, 2H), 7.14–7.08 (m, 4H), 6.37 (d, J = 8.6 Hz, 1H), 6.26 (t, J = 5.7 Hz, 1H), 3.35 (t, J = 6.5 Hz, 2H), 3.24–3.15 (m, 2H), 3.20 (s, 3H), 2.03–1.94 (m, 2H), 1.70 (quint, J = 6.5 Hz, 2H), 1.29 (dd, J = 8.1, 6.5 Hz, 2H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6): δ = 157.9, 145.8, 143.1, 134.3, 128.7, 125.8, 124.9, 108.2, 70.4, 58.3, 38.5, 29.6, 26.6, 25.3, 17.6 ppm; LC/MS (CI): m/z = 283 ([M + H]$^+$).

1-[4-(Bicyclo[4.1.0]heptan-1-yl)phenyl]pyrrolidin-2-one (4{*11,9*}, $C_{17}H_{21}NO$) Yield 35 mg (47%); yellowish solid; m.p.: 60–62 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 7.52$ (d, $J = 8.6$ Hz, 2H), 7.21 (d, $J = 8.6$ Hz, 2H), 3.78 (t, $J = 6.9$ Hz, 2H), 2.46 (t, $J = 8.0$ Hz, 2H), 2.07–1.96 (m, 4H), 1.91–1.83 (m, 1H), 1.64–1.56 (m, 1H), 1.48–1.39 (m, 1H), 1.38-1.30 (m, 1H), 1.29–1.19 (m, 2H), 1.18–1.11 (m, 1H), 0.87 (dd, $J = 9.4$, 4.7 Hz, 1H), 0.64 (t, $J = 4.7$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): $\delta = 173.9$, 144.9, 137.5, 127.4, 119.9, 48.6, 32.7, 31.2, 23.9, 23.8, 21.6, 21.5, 19.2, 18.6, 17.9 ppm; LC/MS (CI): $m/z = 256$ ($[M + H]^+$).

6-[3-(Bicyclo[4.1.0]heptan-1-yl)phenyl]pyrimidin-4-amine (4{*11,37*}, $C_{17}H_{19}N_3$) Yield 35 mg (47%); yellowish solid; m.p.: 164–167 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 8.44$ (s, 1H), 7.86 (s, 1H), 7.74 (d, $J = 7.6$ Hz, 1H), 7.38 (t, $J = 7.6$ Hz, 1H), 7.33 (d, $J = 7.6$ Hz, 1H), 6.90 (s, 1H), 6.87 (s, 2H), 2.11–2.00 (m, 2H), 1.95–1.87 (m, 1H), 1.67–1.58 (m, 1H), 1.50-1.41 (m, 1H), 1.40–1.32 (m, 1H), 1.30–1.19 (m, 3H), 0.93 (dd, $J = 9.4$, 4.8 Hz, 1H), 0.70 (t, $J = 4.8$ Hz, 1H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): $\delta = 164.9$, 161.4, 159.0, 149.8, 137.7, 129.2, 129.2, 125.4, 124.0, 100.2, 31.4, 24.5, 23.9, 21.6, 21.6, 19.2, 18.6 ppm; LC/MS (CI): $m/z = 266$ ($[M + H]^+$).

4-[[5-(1-Methylcyclopropyl)thiophen-2-yl]sulfonyl]morpholine (4{*9,7*}, $C_{12}H_{17}NO_3S_2$) Yield 35 mg (47%); yellowish solid; m.p.: 117–119 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 7.45$ (d, $J = 3.8$ Hz, 1H), 6.98 (d, $J = 3.8$ Hz, 1H), 3.66 (t, $J = 4.7$ Hz, 4H), 2.89 (t, $J = 4.7$ Hz, 4H), 1.47 (s, 3H), 1.06–0.96 (m, 4H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): $\delta = 161.7$, 134.2, 129.7, 123.5, 65.7, 46.3, 24.4, 19.8, 17.7 ppm; LC/MS (CI): $m/z = 288$ ($[M + H]^+$).

1-[4-(Methylsulfonyl)phenyl]-6-oxaspiro[2.5]octane (4{*7,8*}, $C_{14}H_{18}O_3S$) Yield 33 mg (44%); yellowish solid; m.p.: 97-100 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 7.80$ (d, $J = 8.3$ Hz, 2H), 7.49 (d, $J = 8.3$ Hz, 2H), 3.74–3.67 (m, 1H), 3.67–3.60 (m, 1H), 3.46–3.39 (m, 1H), 3.32-3.27 (m, 1H), 2.50 (s, 3H), 2.12 (dd, $J = 8.3$, 6.0 Hz, 1H), 1.61–1.46 (m, 2H), 1.24–1.16 (m, 2H), 1.12–1.04 (m, 1H), 0.93 (dd, $J = 8.3$, 5.1 Hz, 1H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): $\delta = 146.0$, 138.5, 129.7, 127.0, 67.1, 66.6, 44.1, 37.5, 30.3, 28.7, 26.1, 17.1 ppm; LC/MS (CI): $m/z = 284$ ($[M + H_2O + H]^+$).

3-[3-[(1*R*,6*S*,7*R*)-Bicyclo[4.1.0]heptan-7-yl]phenyl]piperazin-2-one (4{*8,60*}, $C_{17}H_{22}N_2O$) Yield 30 mg (40%); colorless solid; m.p.: 145–147 °C; ^{1}H NMR (500 MHz, DMSO-d_6): $\delta = 7.69$ (s, 1H), 7.13 (t, $J = 7.7$ Hz, 1H), 7.06 (d, $J = 7.7$ Hz, 1H), 7.02 (s, 1H), 6.83 (d, $J = 7.7$ Hz, 1H), 4.23 (s, 1H), 3.30-3.23 (m, 1H), 3.19-3.11 (m, 1H), 2.94–2.85 (m, 2H), 2.84–2.76 (m, 1H), 1.96–1.88 (m, 2H), 1.75–1.68 (m, 2H), 1.60 (t, $J = 4.8$ Hz, 1H), 1.28–1.25 (m, 4H), 1.22–1.17 (m, 2H) ppm; ^{13}C NMR (126 MHz, DMSO-d_6): $\delta = 170.0$, 144.0, 141.0, 128.0, 126.0, 125.6, 123.5, 63.7, 42.8, 41.2, 28.3, 23.6, 22.62, 22.58, 21.4 ppm; LC/MS (CI): $m/z = 271$ ($[M + H]^+$).

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