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Incorporation of *gem*-Difluorocycloalkyl Substituents into Heterocycles *via* the Levin's "Nitrogen Deletion" Strategy

Abstract

A series of compounds containing heterocyclic cores and *gem*-difluorocycloalkyl substituents was obtained under conditions of the parallel synthesis (i.e., simultaneous performance of reaction procedures, treatment of the reaction mixture, and product isolation for a number of similar transformations) using the reductive amination – the "Nitrogen deletion" reaction sequence. The synthesis of the target compounds commenced from heteroaromatic aldehydes and the corresponding *gem*-difluorocycloalkyl or (*gem*-difluorocycloalkyl)methyl amines and included the $NaBH_3CN$-mediated reductive amination and "Nitrogen deletion" upon the action of Levin's anomeric amide. It has been shown that the method can be used to obtain compounds with the aforementioned structural fragments separated by one or two methylene units. The developed protocol allowed for the preparation of a 12-member compound library (67 % synthetic efficiency). Therefore, this novel synthetic methodology is suitable for decorating heterocyclic cores with sp^3-enriched substituents that are attractive for medicinal chemistry.

***Keywords**:* cycloalkanes; fluorine; Levin's anomeric amide; "Nitrogen deletion"; reductive amination

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Введення *гем*-дифлуороциклоалкільних замісників у гетероцикли через стратегію «видалення Нітрогену» Левіна

Анотація

В умовах паралельного синтезу (тобто одночасного виконання реакції, оброблення реакційної суміші та виділення продукту для низки споріднених перетворень) із застосуванням послідовності реакції відновного амінування та «видалення Нітрогену» було одержано серію сполук, що містять гетероциклічні фрагменти та *гем*-дифлуороциклоалкільні замісники. Синтез цільових сполук виходив з гетероароматичних альдегідів і відповідних *гем*-дифлуороциклоалкіл- або (*гем*-дифлуороциклоалкіл)метиламінів та передбачав відновне амінування за участі $NaBH_3CN$ і «видалення Нітрогену» під дією аномерного аміду Левіна. Доведено, що метод застосовний для одержання сполук із вищезгаданими структурними фрагментами, розділеними однією чи двома метиленовими ланками. Розроблений протокол дозволив одержати бібліотеку сполук із 12 представників (синтетична ефективність 67 %). Отже, ця новітня синтетична методологія є придатною для декорування гетероциклічних систем sp^3-збагаченими замісниками, що є привабливими для медичної хімії.

Ключові слова: циклоалкани; Флуор; аномерний амід Левіна; «видалення Нітрогену»; відновне амінування

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■ Introduction

The incorporation of fluorine-containing substituents into organic molecules of interest is a well-known approach to drug design, which can be illustrated by numerous success stories [1–5]. In particular, *gem*-difluorocycloalkyl groups have demonstrated their high relevance to modern drug discovery. For example, they have been incorporated into such marketed pharmaceuticals as Maraviroc, an anti-HIV medication, and Ivosidenib, an anticancer agent, as well as experimental drugs VU6001376, a mGluR4 positive allosteric modulator, IPN60090, a selective glutaminase-1 inhibitor, and RBx 343E48F0, a bronchodilator (**Figure 1**) [6].

To date, most methods for the incorporation of *gem*-difluorocycloalkyl substituents into the molecules of interest were based on the Carbon–heteroatom bond construction. Building blocks and synthetic methodologies for the C–C bond creation involving these moieties are rare and typically based on the multistep transformations. On the other hand, the Levin's "Nitrogen deletion" methodology provides a unique possibility to construct the C–C bond in an unusual manner [7]. Essentially, this approach involves the reaction of secondary amines with the so-called anomeric amides (e.g., **1**), which results in formal extrusion of the NH moiety and combining alkyl radicals attached to it (**Scheme**, *A*).

Recently, we have shown that in combination with reductive amination, this approach can be used for the synthesis of compound libraries by a formal coupling of (hetero)aromatic aldehydes and (het)arylmethylamines (**Scheme**, *B*) [8]. In this work, we sought to extend this methodology to primary amines containing the *gem*-difluorocycloalkyl moiety (**3**) in order to ensure the incorporation of these fluorinated substituents into heterocyclic cores **2** (**Scheme**, *C*).

■ Results and discussion

In this study, a compound numbering system common for combinatorial chemistry was used: the reagents used in the parallel synthesis were denoted as **2**{*i*} and **3**{*j*}, whereas the resulting library members were obtained from **2**{*i*} and **3**{*j*}–**4**{*i*,*j*}.

To confirm the applicability of the *reductive amination – the "Nitrogen deletion"* sequence for the synthesis of compound library **4**, heteroaromatic aldehydes **2**{*1–6*} and primary amines **3**{*1–8*}

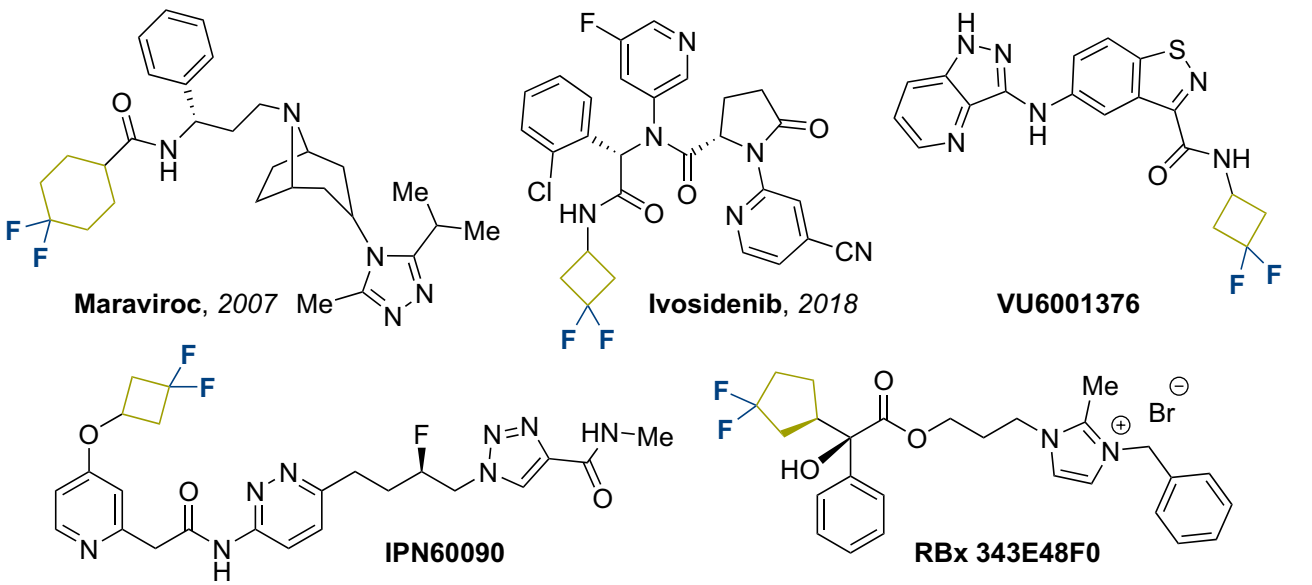

Figure 1. Marketed and experimental drug molecules containing *gem*-difluorocycloalkyl groups

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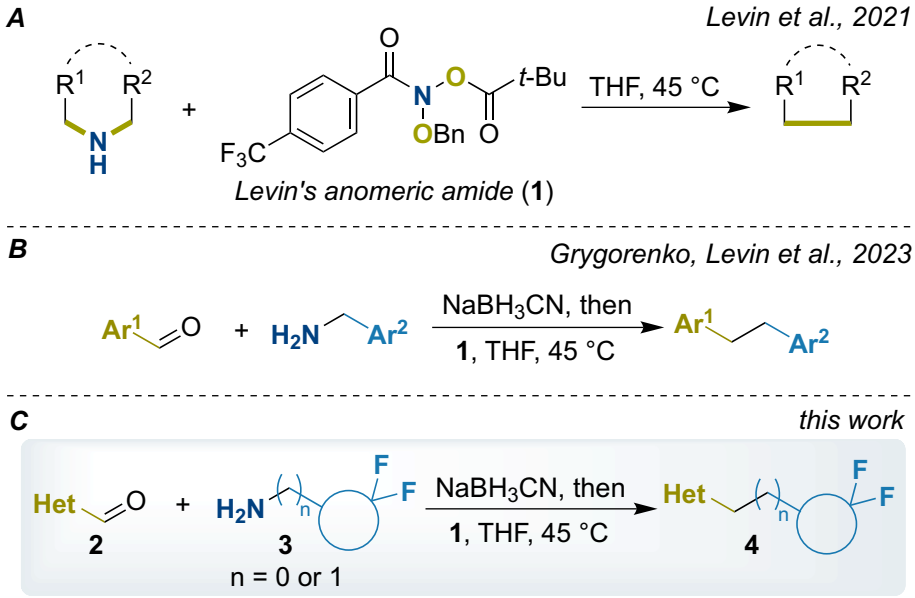

Scheme. Examples of the Levin's "Nitrogen deletion" methodology published before and the outline of the current work

were selected (**Figure 2**). Using the conditions described in our previous work [8], 18 parallel experiments were performed with different combinations of the starting materials, and in 12 of them, the target mini-library members **4**{*1–6,1–8*} were obtained (67% synthesis success rate, **Table 1**; see **Figure 3** for the examples of products obtained).

In general, amines with primary alkyl substituents (e.g., **3**{*8*}) gave somewhat higher yields of the products (17–33%) as compared to the α-branched ones (e.g., **3**{*1*}) (10–18%), which was in accordance with a high sensitivity of the "Nitrogen deletion" step towards steric factors [7]. As for the aldehyde component, compounds that demonstrated somewhat poorer results in our previous study (e.g., pyrimidine **2**{*3*} or pyrazole **2**{*5*} carbaldehydes) did not allow isolating the target products at all. According to LS-MS spectra of the crude reaction mixture, the products were formed, but their purification was not efficient.

■ Conclusions

Reductive amination – the Levin's "Nitrogen deletion" reaction sequence is an efficient approach

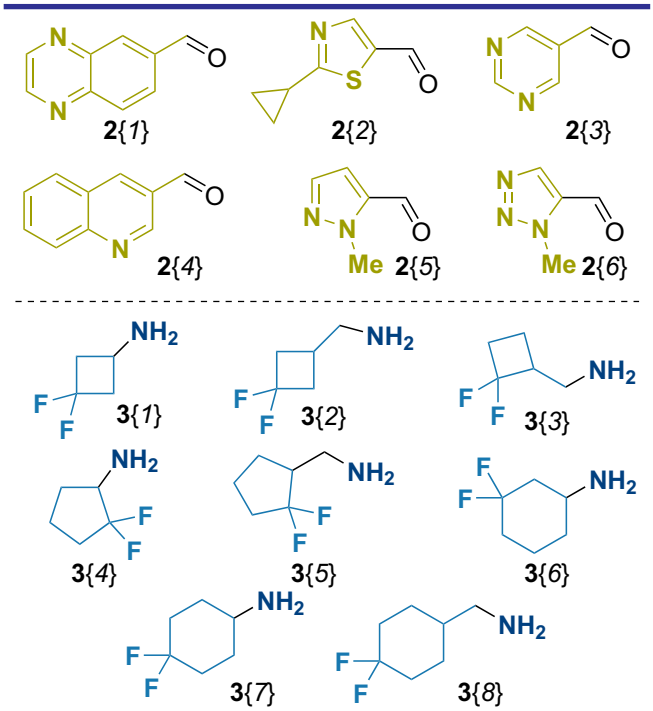

Figure 2. Selected representatives of starting aldehydes **2** and primary amines **3**

Table 1. The parallel synthesis of mini-library **4**{*1–6,1–8*} according to **Scheme** (*C*)

#	Library member	Aldehyde	Amine	Yield of the products	
				mg	%
1	**4**{*1,1*}	**2**{*1*}	**3**{*1*}	134	18
2	**4**{*1,2*}	**2**{*1*}	**3**{*2*}	165	19
3	**4**{*1,3*}	**2**{*1*}	**3**{*3*}	137	17
4	**4**{*1,4*}	**2**{*1*}	**3**{*4*}	–	0
5	**4**{*1,5*}	**2**{*1*}	**3**{*5*}	166	33
6	**4**{*1,6*}	**2**{*1*}	**3**{*6*}	179	28
7	**4**{*1,7*}	**2**{*1*}	**3**{*7*}	100	14
8	**4**{*1,8*}	**2**{*1*}	**3**{*8*}	192	32
9	**4**{*2,1*}	**2**{*2*}	**3**{*1*}	–	0
10	**4**{*2,8*}	**2**{*2*}	**3**{*8*}	115	13
11	**4**{*3,1*}	**2**{*3*}	**3**{*1*}	–	0
12	**4**{*3,8*}	**2**{*3*}	**3**{*8*}	–	0
13	**4**{*4,1*}	**2**{*4*}	**3**{*1*}	71	17
14	**4**{*4,8*}	**2**{*4*}	**3**{*8*}	222	27
15	**4**{*5,1*}	**2**{*5*}	**3**{*1*}	–	0
16	**4**{*5,8*}	**2**{*5*}	**3**{*8*}	–	0
17	**4**{*6,1*}	**2**{*6*}	**3**{*1*}	68	10
18	**4**{*6,8*}	**2**{*6*}	**3**{*8*}	105	21

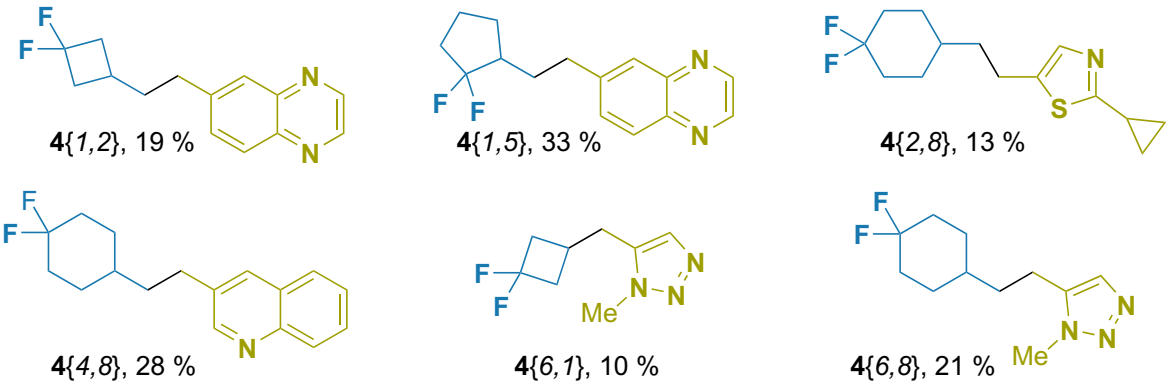

Figure 3. Examples of the products obtained

for introducing *gem*-difluorinated cycloalkyl substituents into heterocyclic systems under conditions of the parallel synthesis; the products having these moieties separated by one or two methylene units can be obtained. The use of α-branched primary amines as the starting materials results in somewhat lower yields of the corresponding library members. Limitations on the aldehyde component correlate with the results obtained in the previous study on (hetero)aromatic series: thus, pyrimidine and pyrazole derivatives were inefficient due to problems with the product isolation. The resulting lead-like fluorinated compound libraries are of special interest to medicinal chemistry; potentially, this method can also be extended to other applications in early drug discovery.

■ Experimental part

All starting materials were available from Enamine Ltd. and Ukrorgsyntez Ltd. Melting points were measured on a 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 and 151 MHz for ^{13}C{^{1}H} NMR). ^{19}F NMR spectra were recorded on a Varian Unity Plus 400 spectrometer at 376 MHz. NMR chemical shifts were reported in ppm (δ scale) downfield from TMS as an internal standard and were 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. For ^{19}F{^{1}H} NMR, $CFCl_3$ in $CHCl_3$ was used as an internal standard. Coupling constants (J) were given in Hz. Spectra were reported as follows: chemical shift (δ, ppm), integration, multiplicity, and coupling constants (Hz). LC-MS data were recorded on Agilent 1100 HPLC equipped with a diode-matrix and mass-selective detector Agilent LC/MSD SL instrument, the column: Zorbax SB-C18, 4.6 mm × 15 mm; eluent: (A) acetonitrile – water with 0.1% of TFA (95:5), (B) water with 0.1% of TFA; the flow rate: 1.8 mL min^{-1}. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (CI)).

The parallel synthesis was performed in 20-mL vials or 100-mL flasks; loading of the reagents, as well as treatment of the reaction mixtures was performed manually in a parallel fashion. The reactions were performed in ultrasonic baths or laboratory ovens equipped with a shaker. Centrifugal evaporators were used to remove the solvents from the vials in a parallel fashion. Preparative HPLC was performed on Agilent 1260 Infinity systems equipped with DAD and a mass-detector using a Chromatorex 18 SNB100-5T 100 × 19 mm, 100 Å, 5-μm column with a SunFire C18 Prep Guard Cartridge, 100 Å, 10 μm, 19 mm × 10 mm, with H_2O – MeCN as a gradient, or H_2O – MeOH, or H_2O (with 0.2% HCO_2H) – MeOH as an eluent, with the flow of 30 mL min^{-1}.

For the library members **4**{*1–6,1–8*} synthesized, physical data and mass spectra (**Table 2**), ^{1}H NMR spectra (**Table 3**), ^{13}C NMR spectra (**Table 4**), and ^{19}F NMR spectra (**Table 5**) were given in a tabular format.

Table 2. Physical data and mass spectra for library members **4**{*1–6,1–8*} synthesized

Compound	Appearance	MS (*m/z*, APCI)
4{*1,1*}	Yellowish oil	235 $[M+H]^+$
4{*1,2*}	Yellowish oil	249 $[M+H]^+$
4{*1,3*}	Yellowish oil	249 $[M+H]^+$
4{*1,5*}	Yellowish oil	263 $[M+H]^+$
4{*1,6*}	Yellowish oil	263 $[M+H]^+$
4{*1,7*}	Brownish oil	263 $[M+H]^+$
4{*1,8*}	Yellowish oil	277 $[M+H]^+$
4{*2,8*}	Yellowish oil	272 $[M+H]^+$
4{*4,1*}	Yellowish oil	234 $[M+H]^+$
4{*4,8*}	Colorless oil	276 $[M+H]^+$
4{*6,1*}	Yellowish oil	188 $[M+H]^+$
4{*6,8*}	Brownish oil	230 $[M+H]^+$

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Table 3. ^{1}H NMR spectra data for library members **4**{*1–6,1–8*} synthesized

Compound	^{1}H NMR (600 MHz, DMSO-d_6), δ, ppm
4{*1,1*}	2.32–2.44 (2H, m); 2.52–2.58 (1H, m); 2.59–2.70 (2H, m); 3.05 (2H, d, *J* = 7.6 Hz); 7.75 (1H, dd, *J* = 8.6, 1.9 Hz); 7.92 (1H, s); 8.03 (1H, d, *J* = 8.6 Hz); 8.89 (1H, d, *J* = 1.8 Hz); 8.92 (1H, d, *J* = 1.8 Hz)
4{*1,2*}	1.88 (2H, q, *J* = 7.8 Hz); 2.04–2.14 (1H, m); 2.20–2.31 (2H, m); 2.60–2.70 (2H, m); 2.81 (2H, t, *J* = 7.8 Hz); 7.75 (1H, dd, *J* = 8.5, 1.9 Hz); 7.90 (1H, s); 8.02 (1H, d, *J* = 8.5 Hz); 8.88 (1H, d, *J* = 1.8 Hz); 8.91 (1H, d, *J* = 1.8 Hz)
4{*1,3*}	1.33–1.41 (1H, m); 1.75–1.91 (2H, m); 1.93–2.02 (1H, m); 2.35–2.46 (2H, m); 2.68–2.80 (1H, m); 2.83 (2H, t, *J* = 7.8 Hz); 7.73 (1H, dd, *J* = 8.6, 1.8 Hz); 7.88 (1H, s); 8.01 (1H, d, *J* = 8.6 Hz); 8.87 (1H, d, *J* = 1.8 Hz); 8.89 (1H, d, *J* = 1.8 Hz)
4{*1,5*}	1.36–1.46 (1H, m); 1.59–1.75 (3H, m); 1.88–2.17 (5H, m); 2.83–2.99 (2H, m); 7.76 (1H, dd, *J* = 8.5, 1.8 Hz); 7.90 (1H, s); 8.03 (1H, d, *J* = 8.5 Hz); 8.89 (1H, d, *J* = 1.8 Hz); 8.91 (1H, d, *J* = 1.8 Hz)
4{*1,6*}	1.03–1.11 (1H, m); 1.31–1.41 (1H, m); 1.49–1.75 (4H, m); 1.89–1.99 (3H, m); 2.78–2.89 (2H, m); 7.73 (1H, dd, *J* = 8.5, 1.8 Hz); 8.03 (1H, d, *J* = 8.5 Hz); 7.88 (1H, s); 8.89 (1H, d, *J* = 1.8 Hz); 8.92 (1H, d, *J* = 1.8 Hz)
4{*1,7*}	1.20–1.33 (2H, m); 1.64–1.88 (5H, m); 1.93–2.03 (2H, m); 2.80 (2H, d, *J* = 7.2 Hz); 7.72 (1H, dd, *J* = 8.5, 1.9 Hz); 7.89 (1H, d, *J* = 1.9 Hz); 8.02 (1H, d, *J* = 8.5 Hz); 8.89 (1H, d, *J* = 1.8 Hz); 8.91 (1H, d, *J* = 1.8 Hz)
4{*1,8*}	1.16–1.26 (2H, m); 1.37–1.46 (1H, m); 1.61–1.67 (2H, m); 1.69–1.87 (4H, m); 1.95–2.04 (2H, m); 2.83–2.89 (2H, m); 7.75 (1H, dd, *J* = 8.6, 1.8 Hz); 7.90 (1H, s); 8.01 (1H, d, *J* = 8.6 Hz); 8.88 (1H, d, *J* = 1.8 Hz); 8.90 (1H, d, *J* = 1.8 Hz)
4{*2,8*}	0.84–0.90 (2H, m); 1.01–1.07 (2H, m); 1.10–1.20 (2H, m); 1.34–1.43 (1H, m); 1.51 (2H, q, *J* = 7.5 Hz); 1.67–1.83 (4H, m); 1.92–2.02 (2H, m); 2.26–2.32 (1H, m); 2.76 (2H, t, *J* = 7.5 Hz); 7.28 (1H, s)
4{*4,1*}	2.32–2.44 (2H, m); 2.51–2.57 (1H, m); 2.61–2.72 (2H, m); 2.99 (2H, d, *J* = 7.7 Hz); 7.58 (1H, t, *J* = 7.6 Hz); 7.70 (1H, t, *J* = 7.6 Hz); 7.92 (1H, d, *J* = 8.3 Hz); 7.99 (1H, d, *J* = 8.3 Hz); 8.17 (1H, s); 8.80 (1H, d, *J* = 2.2 Hz)
4{*4,8*}	1.14–1.28 (2H, m); 1.37–1.47 (1H, m); 1.59–1.67 (2H, m); 1.68–1.89 (4H, m); 1.93–2.07 (2H, m); 2.76–2.84 (2H, m); 7.57 (1H, t, *J* = 7.2 Hz); 7.66–7.71 (1H, m); 7.91 (1H, d, *J* = 8.2 Hz); 7.98 (1H, d, *J* = 8.2 Hz); 8.14 (1H, s); 8.80 (1H, d, *J* = 2.2 Hz)
4{*6,1*}	2.26–2.37 (2H, m); 2.41–2.48 (1H, m); 2.68–2.78 (2H, m); 2.88 (2H, d, *J* = 7.7 Hz); 3.92 (3H, s); 7.53 (1H, s)
4{*6,8*}	1.15–1.23 (2H, m); 1.38–1.45 (1H, m); 1.55 (2H, q, *J* = 7.3 Hz); 1.71–1.84 (4H, m); 1.95–2.03 (2H, m); 2.64–2.69 (2H, m); 3.91 (3H, s); 7.50 (1H, s)

Table 4. ^{13}C NMR spectra data for library members **4**{*1–6,1–8*} synthesized

Compound	^{13}C{^{1}H} NMR (151 MHz, DMSO-d_6),δ, ppm
4{*1,1*}	23.7 (dd, *J* = 13.1, 5.9 Hz); 39.7 (dd, *J* = 22.3, 20.9 Hz); 40.4 (dd, *J* = 3.2, 1.4 Hz); 120.7 (dd, *J* = 284, 273 Hz); 127.7; 129.0; 131.6; 141.1; 142.3; 142.4; 145.1; 145.7
4{*1,2*}	22.3 (dd, *J* = 12.7, 6.0 Hz); 33.0; 36.5 (d, *J* = 2.9 Hz); 39.9 (t, *J* = 22.0 Hz); 120.9 (dd, *J* = 284, 274Hz); 127.4; 128.9; 131.6; 141.0; 142.3; 144.3; 144.9; 145.6
4{*1,3*}	16.6 (dd, *J* = 16.5, 3.8 Hz); 29.4 (d, *J* = 4.8 Hz); 32.3 (t, *J* = 22.0 Hz); 32.9; 45.8 (t, *J* = 21.0 Hz); 123.4 (dd, *J* = 288, 277 Hz); 127.9; 129.4; 131.9; 141.5; 142.8; 144.5; 145.4; 146.1
4{*1,5*}	19.5 (dd, *J* = 5.7, 3.3 Hz); 28.7 (dd, *J* = 22.3, 6.6 Hz); 33.0; 34.5 (t, *J* = 24.6 Hz); 39.2; 44.7 (t, *J* = 22.5 Hz); 127.3; 129.0; 131.5; 132.8 (t, *J* = 251 Hz); 141.0; 142.3; 144.4; 145.0; 145.6
4{*1,6*}	21.5 (d, *J* = 9.8 Hz); 29.9; 33.1 (dd, *J* = 24.8, 21.5 Hz); 36.2 (d, *J* = 9.1 Hz); 39.1 (dd, *J* = 24.8, 21.0 Hz); 41.4; 124.4 (dd, *J* = 242, 239 Hz); 128.3; 128.9; 131.9; 141.0; 142.2; 142.4; 145.0; 145.7
4{*1,7*}	28.7 (d, *J* = 9.5 Hz); 33.1 (dd, *J* = 24.8, 22.3 Hz); 36.9; 41.5 (d, *J* = 2.5 Hz); 124.8 (dd, *J* = 241, 239 Hz); 128.7; 129.2; 132.5; 141.5; 142.7; 143.6; 145.4; 146.1
4{*1,8*}	28.4 (d, *J* = 9.4 Hz); 32.6; 32.7 (dd, *J* = 24.8, 22.0 Hz); 34.3 (d, *J* = 1.4 Hz); 36.5 (d, *J* = 2.5 Hz); 124.4 (dd, *J* = 241, 239 Hz); 127.2; 128.9; 131.6; 140.9; 142.4; 144.85; 144.94; 145.6
4{*2,8*}	10.4; 13.9; 23.8; 28.3 (d, *J* = 9.5 Hz); 32.7 (dd, *J* = 24.9, 22.1 Hz); 34.0 (d, *J* = 1.4 Hz); 37.0 (d, *J* = 2.4 Hz); 124.3 (dd, *J* = 241, 239 Hz); 136.7; 138.6; 170.6
4{*4,1*}	23.6 (dd, *J* = 13.0, 6.1 Hz); 37.8 (dd, *J* = 3.2, 1.4 Hz); 39.7; 120.7 (dd, *J* = 284, 273 Hz); 126.6; 127.68; 127.73; 128.6; 128.8; 132.8; 134.2; 146.4; 151.9
4{*4,8*}	28.4 (d, *J* = 9.3 Hz); 29.8; 32.7 (dd, *J* = 24.8, 22.1 Hz); 34.3 (d, *J* = 1.4 Hz); 36.5 (d, *J* = 2.4 Hz); 124.4 (dd, *J* = 241, 239 Hz); 126.5; 127.5; 127.8; 128.5; 128.6; 133.7; 135.1; 146.2; 151.9
4{*6,1*}	21.1 (dd, *J* = 13.6, 6.0 Hz); 28.0 (dd, *J* = 3.3, 1.3 Hz); 34.0; 39.8 (t, *J* = 20.8 Hz); 120.5 (dd, *J* = 284, 273 Hz); 131.6; 135.5
4{*6,8*}	19.9; 28.3 (d, *J* = 9.4 Hz); 32.7 (dd, *J* = 24.9, 22.1 Hz); 33.0 (d, *J* = 2.5 Hz); 33.9; 34.2 (d, *J* = 1.5 Hz); 124.3 (dd, *J* = 241, 239 Hz); 131.4; 137.4

Table 5. ^{19}F NMR spectra data for library members **4**{*1*–*6*,*1*–*8*} synthesized

Compound	$^{19}F\{^1H\}$ NMR (376 MHz, DMSO-d_6), δ, ppm
4{*1*,*1*}	–94.1 (d, *J* = 190 Hz); –81.0 (d, *J* = 190 Hz)
4{*1*,*2*}	–110.7 (d, *J* = 189 Hz); –81.8 (d, *J* = 189Hz)
4{*1*,*3*}	–104.5 (d, *J* = 225 Hz); –96.5 (d, *J* = 224 Hz)
4{*1*,*5*}	–98.4 (d, *J* = 234 Hz); –86.7 (d, *J* = 234 Hz)
4{*1*,*6*}	–99.9 (d, *J* = 232 Hz); –90.1 (d, *J* = 233 Hz)
4{*1*,*7*}	–100.0 (d, *J* = 232 Hz); –89.9 (d, *J* = 232 Hz)
4{*1*,*8*}	–100.1 (d, *J* = 232Hz); –89.9 (d, *J* = 232Hz)
4{*2*,*8*}	–94.0 (d, *J* = 190 Hz); –81.0 (d, *J* = 190 Hz)
4{*4*,*1*}	–94.0 (d, *J* = 190 Hz); –81.0 (d, *J* = 190 Hz)
4{*4*,*8*}	–100.0 (d, *J* = 232 Hz); –89.9 (d, *J* = 232 Hz)
4{*6*,*1*}	–94.2 (d, *J* = 191 Hz); –81.0 (d, *J* = 191 Hz)
4{*6*,*8*}	–100.0 (d, *J* = 232 Hz); –90.0 (d, *J* = 232 Hz)

The general procedure for the synthesis of compound library 4

The procedure from our previous work [8] was followed. Amine **3** (3 mmol) was placed into a 20-mL vial, and MeOH (6 mL), aldehyde **2** (3 mmol), and AcOH (3.6 mmol) were added. The reaction mixture was sonicated at rt for 12 h. Then $NaBH_3CN$ (6 mmol) was added, and the reaction mixture was sonicated at rt for additional 12 h. Volatiles were removed *in vacuo*; the residue was treated with 10% aq Na_2CO_3 (6 mL) and extracted with CH_2Cl_2 (2 × 6 mL). The combined organic layers were placed into a 100-mL flask and concentrated *in vacuo*. The residue was dried thoroughly *in vacuo* and used in the next step without purification. The flask with the crude reductive amination product was filled with argon, and a degassed solution of anomeric amide **1** (0.3 M in dry THF, 15 mL, 4.5 mmol) was added under an argon flow (CAUTION! Compound **1** can be potentially mutagenic). The mixture was shaken in an oven at 45 °C for 16 h (CAUTION! N_2 evolution is observed), then cooled to rt, saturated aq $NaHCO_3$ (30 mL) was added, and the mixture was extracted with Et_2O (2 × 15 mL). The combined extracts were evaporated *in vacuo*, and the residue was subjected to the reverse-phase HPLC purification.

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