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Towards chemical libraries based on heterocyclic scaffolds with monofluorinated and difluoroalkyl side chains

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ABSTRACT

The preparation of focused chemical libraries, based on five- and six-membered heteroaromatic systems with mono- and gemdifluoroalkyl side chains, is described. Four heterocyclic scaffolds with a *p*-bromophenyl group have been easily prepared from readily available propargylic fluorides. Starting from these scaffolds, palladium-catalyzed reactions have been performed, including by automated procedures, to prepare libraries of molecules designed for biological applications.

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1. Introduction

It is widely recognized that the introduction of fluorine in organic molecules modifies in depth their physical, chemical and biological properties and this has been already of much use in bioorganic as well as in medicinal chemistry [1]. It is also clear that heterocyclic molecules are very classically at the core of pharmaceutical products [2]. More recently, due to the development of high throughput screening methods in biochemistry and biology, medicinal chemists have introduced chemical libraries of molecules around so called priviledge scaffolds, which are often natural products and/or heterocyclic compounds [3]. Therefore it appears of much interest to develop new methodologies and novel synthetic strategies combining fluorine and heterocyclic chemistries which, further, can be applied to the preparation of chemical libraries of new fluorinated molecules.

Several years ago we started a programme dealing with new propargylic fluorides [4]. We have proposed a rationale for their easy synthesis, including in optically active series [5]. Then we have developed their use in the synthesis of various types of products such as fluorinated analogues of fatty acid metabolites [6], as well as carbocyclic systems [7]. More recently, we have also demonstrated that they can be of much interest for the preparation of various types of 5- and 6-membered heterocycles [8]. In continuation to these studies, the goal of this publication is to demonstrate that these approaches can be extended towards the preparation of focused chemical libraries for selected 5- or 6-membered heterocyclic systems with mono- or gemdifluoroalkyl side chains, using appropriate palladium-catalyzed coupling reactions (Scheme 1). We will also demonstrate that it is possible to prepare corresponding chemical libraries through automated procedures using an Automated Parallel Synthetiser [Chemspeed Accelerator®].

2. Results and discussion

The pyrimidine **2** was selected as a first example. It was easily prepared in excellent yield by reaction of propargylic fluoride **1** with acetamidine [8b]. Then, the aromatic bromide hence obtained, can be used for Suzuki-Miyaura type coupling reactions [9]. Model studies were performed first with phenyl boronic acid to optimize the reaction and to achieve the suitable conditions which will be compatible for automated processes. It was found that reaction of **2** with phenyl boronic acid (2 equiv.), sodium carbonate (2 equiv.) and palladiumdichlorobistriphenylphosphine (5 mol%) in a 5/1 (dioxane/water) mixture at 70 °C for 7 h furnished **3a** in 82% isolated yield. These reaction conditions were employed for the other boronic acids, using Automated Parallel Synthetiser, affording the desired pyrimidines **3a**–**3f** in 60–88% yields (Scheme 2 and Table 1).

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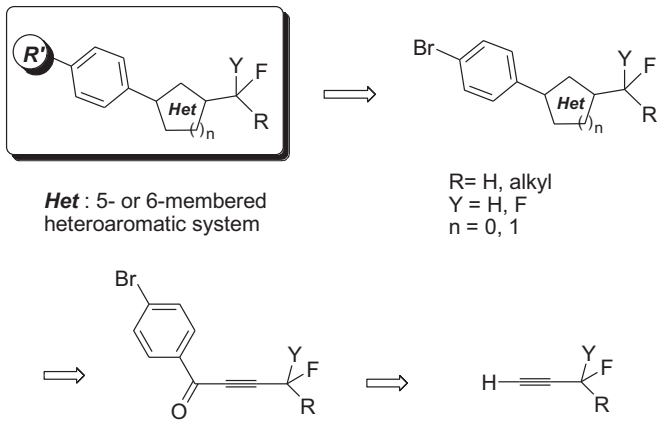
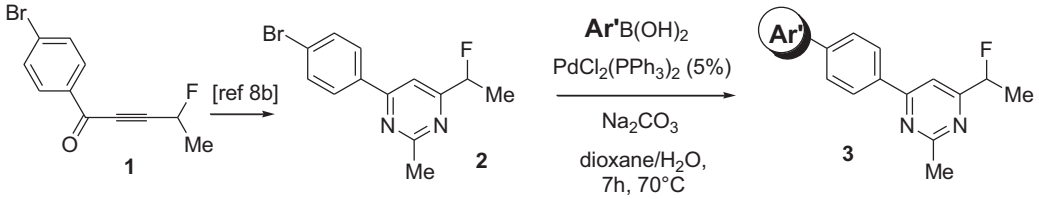


Scheme 1. Synthetic strategy towards targeted chemical libraries of heterocyclic systems with mono- and gemdifluoroalkyl side chains.

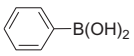
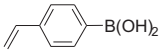
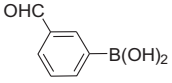
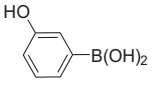
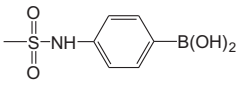
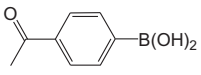
By this route, a first focused chemical library of pyrimidines fluorinated on the side chain could be easily obtained. Furthermore, it is worthy of note that most of the corresponding molecules of **3** series have still available functional groups (OH, carbonyl, vinyl and amine) which could be used for further transformations and extension to a second generation of pyrimidines fluorinated on side chain.

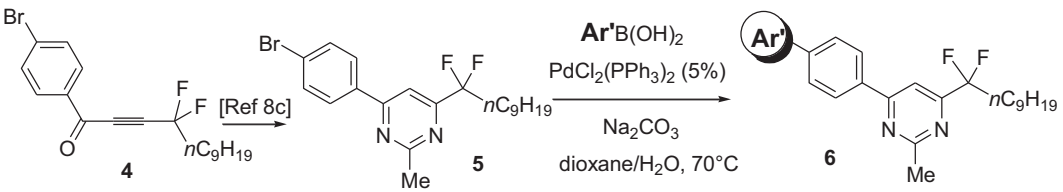
Then, pyrimidine **5** was selected as a first example for heterocycles with a gemdifluoroalkyl side chain. This scaffold was also easily prepared in excellent yield by the reaction of propargylic fluoride **4** with acetamidine [8c]. The aromatic bromide hence obtained can be used again for Suzuki-Miyaura type coupling reactions. Under the same reaction conditions as previously described, the pyrimidines **6a**–**6f** were obtained in 69–86% yields using the Automated Parallel Synthetizer (Scheme 3 and Table 1). Most molecules belonging to this second library of **6**-series still have the appropriate functionalities (double bond,



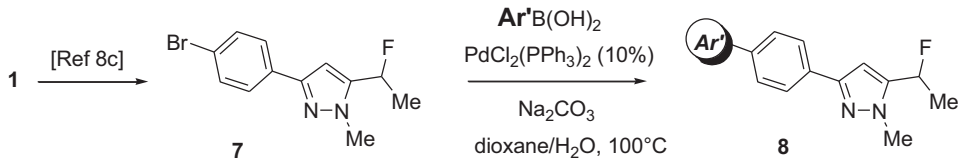
Scheme 2. Synthesis of the pyrimidine chemical library with a monofluorinated alkyl side chain.

Table 1
Pyrimidines **3** and **6** with fluorinated alkyl side chains.

Entry	**Ar'**B(OH)$_2$	Product **3** (yield %)	Product **6** (yield %)
1		**3a** (82%)	**6a** (84%)
2		**3b** (60%)	**6b** (70%)
3		**3c** (85%)	**6c** (86%)
4		**3d** (88%)	**6d** (81%)
5		**3e** (70%)	**6e** (82%)
6		**3f** (75%)	**6f** (69%)



Scheme 3. Synthesis of the pyrimidine chemical library with a gemdifluoroalkyl side chain.



Scheme 4. Synthesis of the pyrazole chemical library with a monofluorinated alkyl side chain.

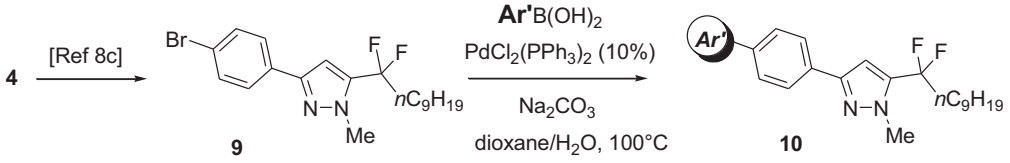
carbonyl group, phenol, amine) to prepare new derivatives and extend the scope of this chemical library.

Now, pyrazole **7** was selected as a first example for 5-membered heteroaromatic derivatives. It was easily prepared by the reaction of propargylic fluoride **1** with *N*-methylhydrazine, following the literature procedure [8c] in excellent yield (Scheme 4). The aromatic bromide hence obtained was used for Suzuki-Miyaura type coupling reactions. These pyrazoles were found to be less reactive than previous pyrimidines and therefore higher catalyst loadings (10 mol%) and elevated temperatures were used. Under these conditions the pyrazoles **8a**–**8f** were obtained in 74–88% yields (Table 2).

Then, pyrazole **9** was selected as an example for five-membered heterocyclic scaffold with a gemdifluoroalkyl side chain. It was easily prepared in excellent yield by the reaction of propargylic fluoride **4** with *N*-methylhydrazine [8c]. The aromatic bromide hence obtained was also successfully used for representative Suzuki-Miyaura type coupling reactions affording the pyrazoles **10a**–**10f** in 76–89% yields (Scheme 5 and Table 2).

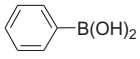
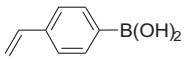
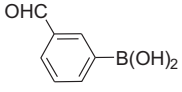
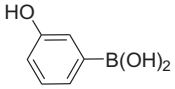
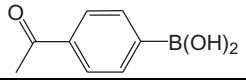
To extend the scope of these approaches it was of interest to demonstrate the possibility of using other Pd-catalyzed reactions and therefore we have selected the Stille cross coupling reaction [10]. Under appropriate reaction conditions [11], all four previous heterocycles with their mono- and gemdifluoroalkyl side chains (**2**, **5**, **7** and **9**) were reacted individually with tributylvinylstannane to afford the desired molecules **11**–**14** in fair to excellent yields (Scheme 6). However, as the pyrazoles were less reactive than the corresponding pyrimidines, hence required higher catalyst loading with longer reaction times. Here again it is important to make a note that these reactions afforded four scaffolds with vinyl groups, which can be used later towards various types of functionalization, including, in particular for cross metathesis reaction [12]. Therefore, these molecules open-up the route to new chemical libraries of heterocycles with fluorinated side chains.

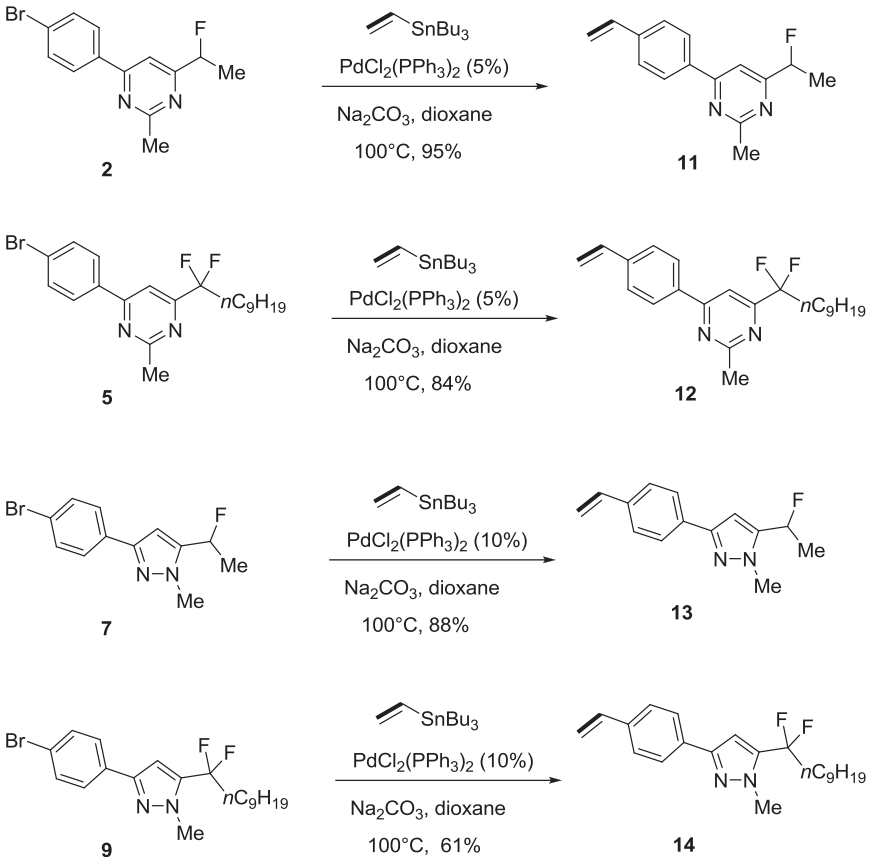
In conclusion, we have developed efficient procedures for the preparation of focused model chemical libraries of various heterocycles with mono- or gemdifluoroalkyl side chains. The heterocyclic scaffolds bearing an aromatic bromide are easily prepared through the chemistry previously developed, using propargylic fluorides as key intermediates. Palladium-catalyzed coupling reactions can be easily performed on these scaffolds, including automated procedures to access new chemical libraries. Taking into account the versatility of the propargylic systems in carbo- and heterocyclic chemistry and the number of possible transition metal-mediated coupling reactions, this strategy opens up the route to large libraries with a good molecular diversity. These chemical libraries would be of much interest for the preparation of fluorinated bioactive



Scheme 5. Synthesis of the pyrazole chemical library with a gemdifluoroalkyl side chain.

Table 2
Pyrazoles **8** and **10** with fluorinated alkyl side chains.

Entry	**Ar'**B(OH)$_2$	Product **8** (yield %)	Product **10** (yield %)
1		**8a** (76%)	**10a** (79%)
2		**8b** (88%)	**10b** (80%)
3		**8c** (82%)	**10c** (85%)
4		**8d** (74%)	**10d** (76%)
5		**8f** (79%)	**10f** (89%)



Scheme 6. Synthesis of styrene type derivatives through Stille cross coupling reactions.

molecules and corresponding studies are under development in our groups.

3. Experimental

3.1. General

All reagents were obtained commercially and used without further purification. All reactions were carried out under a nitrogen, or argon, atmosphere and anhydrous conditions. The solvents used were freshly distilled under anhydrous conditions, unless otherwise specified. The reaction mixtures were magnetically stirred with Teflon stirring bars, and the temperatures were measured externally. Reactions that require anhydrous conditions were carried out by using oven dried (120 °C, 24 h) glassware. Yields refer to chromatographically and spectroscopically (^{1}H and ^{13}C NMR) homogeneous materials, and the reactions were monitored by thin layer chromatography (TLC), carried out on 0.25 mm Merck silica gel plates (60 F254). The eluents used were mixtures of pentane (P) and ether (E), with detection by UV light, or a *p*-anisaldehyde staining solution. Acros silica gel (60, particle size 0.040–0.063 mm) was used for column chromatography. Nuclear magnetic resonance (NMR) spectra were recorded with Bruker Avance 500, 400 and 300 spectrometers. ^{1}H NMR spectra: δ (H) are given in ppm relative to tetramethylsilane (TMS) [TMS, δ (H) = 0.00 ppm] as internal reference. ^{13}C NMR spectra: δ (C) are given in ppm relative to TMS [**C**DCl$_3$, δ (**C**) = 77.0 ppm] as internal reference. ^{19}F NMR spectra: δ (F) are given in ppm relative to CFCl$_3$. Multiplicities were designated as singlet (s), doublet (d), triplet (t), quadruplet (q) or multiplet (m). Mass spectral analyses have been performed on a high resolution Micromass ZABSpecTOF mass spectrometer in electrospray mode or on a Bruker MicrO-Tof-Q 2 in APCI mode, at the "Centre Régional de Mesures Physiques" Rennes.

3.2. General procedure for Suzuki-Miyaura coupling reactions

Most of Suzuki-Miyaura coupling reactions were performed on a Chemspeed Accelerator SLT100 automated synthesizer. The robot was equipped with a four-needle head and an array of 16 parallel 13 mL glass reactors along with Solid Dosing Unit (SDU) for solid additions. All reactors were connected to a Huber Unistat (heating range: −70 to 300 °C) and were equipped with a coldfinger reflux condenser in which the temperature can be fixed from −5 to 40 °C. The inert atmosphere in the glass reactors of the Accelerator SLT100 was obtained by flushing with nitrogen for at least 30 min. Before the beginning of the coupling experiments, the reaction vessels were heated to 70 °C, evacuated for 15 min, and then filled with nitrogen. This procedure was repeated two times to perform the reactions under an inert atmosphere with 1.5 bar flowrate. Substrates and reagents were administrated using SDU unit and solvents were transferred from the stock solutions with water and dioxane into the reaction vessels. A mixture of pyrimidine **2** (or **5**) (1 mmol) in a (5/1 dioxane/water mixture, 7 mL), Dichlorobis(triphenylphosphine)-palladium(**II**) (5 mol%), sodium carbonate (2 mmol) and boronic acid (2 equiv.) was heated at 70 °C for 7 h with a 900 rpm vortex. After cooling to room temperature, $MgSO_4$ was added. The reaction mixture was filtered through a pad of celite, washed with CH_2Cl_2 and concentrated under vacuum. The product was purified by silica gel chromatography using pentane/ether (9/1) as eluent.

3.3. Spectral and analytical data for pyrimidines 3 and 6

3.3.1. Pyrimidines 3

3.3.1.1. Synthesis of 4-(biphenyl-4-yl)-6-(1-fluoroethyl)-2-methyl-pyrimidine 3a. The reaction was performed using pyrimidine **2**

according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrimidine **3a** as an oil (82% yield). *^{1}H NMR ($CDCl_3$, 300 MHz)*: δ (ppm) 8.27–8.14 (m, 2H); 7.80–7.69 (m, 3H); 7.69–7.59 (m, 2H); 7.54–7.33 (m, 3H); 5.64 (dq, J_{HF} = 48.1 Hz, J = 6.5 Hz, 1H); 2.80 (s, 3H); 1.76 (dd, J_{HF} = 24.5 Hz, J = 6.5 Hz, 3H). *^{13}C NMR ($CDCl_3$, 75 MHz)*: δ (ppm) 169.8 (d, J_{CF} = 24.7 Hz); 167.9 (d, J_{CF} = 2.9 Hz); 164.6 (d, J_{CF} = 1.5 Hz); 143.6; 140.2; 135.8; 128.9; 127.9; 127.8; 127.7; 127.6; 127.1; 108.3 (d, J_{CF} = 8.0 Hz); 90.5 (d, J_{CF} = 171.9 Hz); 26.2; 21.4 (d, J_{CF} = 22.5 Hz). *^{19}F NMR ($CDCl_3$, 376 MHz)*: δ (ppm) −183.41 (dq, J = 48.1 Hz, J = 24.5 Hz). *HRMS (ESI)* calcd for $C_{19}H_{17}N_2FNa$ [M+Na]+ m/z = 315.1273, found 315.1271.

3.3.1.2. Synthesis of 4-(1-fluoroethyl)-2-methyl-6-(4′-vinylbiphenyl-4-yl)pyrimidine 3b. The reaction was performed using pyrimidine **2** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrimidine **3b** as an oil (60% yield). *^{1}H NMR ($CDCl_3$, 300 MHz)*: δ (ppm) 8.26–8.15 (m, 2H); 7.80–7.69 (m, 3H); 7.67–7.58 (m, 2H); 7.57–7.45 (m, 2H); 6.77 (dd, J = 17.5 Hz, J = 11.0 Hz, 1H); 5.82 (dd, J = 17.5 Hz, J = 0.7 Hz, 1H); 5.64 (dq, J_{HF} = 48.1 Hz, J = 6.5 Hz, 1H); 5.31 (dd, J = 11.0 Hz, J = 0.7 Hz, 1H); 2.81 (s, 3H); 1.73 (dd, J_{HF} = 24.5 Hz, J = 6.5 Hz, 3H). *^{13}C NMR ($CDCl_3$, 75 MHz)*: δ (ppm) 169.8 (d, J_{CF} = 24.8 Hz); 167.9 (d, J_{CF} = 2.9 Hz); 164.6 (d, J_{CF} = 1.6 Hz); 143.1; 139;4; 137.2; 136.3; 135.8; 127.8; 127.4; 127.3; 127.2; 126.7; 114.3; 108.3 (J_{CF} = 8.0 Hz); 90.5 (J_{CF} = 171.8 Hz); 26.1; 21.4 (J_{CF} = 22.6 Hz). *^{19}F NMR ($CDCl_3$, 282 MHz)*: δ (ppm) −183.44 (dq, J = 48.1 Hz, J = 24.5 Hz). *HRMS (ESI)* calcd for $C_{21}H_{19}N_2FNa$ [M+Na]+ m/z = 341.1430, found 341.1431.

3.3.1.3. Synthesis of 4′-(6-(1-fluoroethyl)-2-methylpyrimidin-4-yl)biphenyl-3-carbaldehyde 3c. The reaction was performed using pyrimidine **2** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrimidine **3c** as an oil (85% yield). *^{1}H NMR ($CDCl_3$, 300 MHz)*: δ (ppm) 10.00 (s, 1H); 8.21–8.10 (m, 2H); 8.05 (broad s, 1H); 7.88–7.73 (m, 2H); 7.72–7.59 (m, 3H); 7.59–7.48 (m, 1H); 5.57 (dq, J_{HF} = 48.1 Hz, J = 6.5 Hz, 1H); 2.73 (s, 3H); 1.67 (dd, J_{HF} = 24.5 Hz, J = 6.5 Hz, 3H). *^{13}C NMR ($CDCl_3$, 75 MHz)*: δ (ppm) 192.1; 169.9 (d, J_{CF} = 24.7 Hz); 167.9 (d, J_{CF} = 2.9 Hz); 164.3 (d, J_{CF} = 1.6 Hz); 142.0; 141.1; 137.0; 136.5; 133.0; 129.6; 129.2; 128.0; 127.8; 127.6; 108.4 (d, J_{CF} = 8.1 Hz); 90.5 (d, J_{CF} = 171.9 Hz); 26.1; 21.4 (d, J_{CF} = 22.5 Hz). *^{19}F NMR ($CDCl_3$, 376 MHz)*: δ (ppm) −183.26 (dq, J = 48.1 Hz, J = 24.5 Hz). *HRMS (ESI)* calcd for $C_{20}H_{17}FN_2ONa$ [M+Na]+ m/z = 343.1217, found 343.1217.

3.3.1.4. Synthesis of 4′-(6-(1-fluoroethyl)-2-methylpyrimidin-4-yl)biphenyl-3-ol 3d. The reaction was performed using pyrimidine **2** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrimidine **3d** as an oil (88% yield). *^{1}H NMR ($CDCl_3$, 300 MHz)*: δ (ppm) 8.17–8.07 (m, 2H);7.73 (s, 1H);7.68–7.62 (m, 2H); 7.38 (broad s, 1H); 7.33–7.25 (m, 1H); 7.19–7.09 (m, 1H); 7.04–6.96 (m, 1H); 6.89–6.81 (m, 2H); 5.64 (dq, J_{HF} = 48.1 Hz, J = 6.5 Hz, 1H); 2.81 (s, 3H); 1.72 (dd, J_{HF} = 24.5 Hz, J = 6.6 Hz, 3H). *^{13}C NMR ($CDCl_3$, 75 MHz)*: δ (ppm) 169.9 (d, J_{CF} = 24.9 Hz); 167.9 (d, J_{CF} = 2.8 Hz); 165.1 (d, J_{CF} = 1.6 Hz); 153.3; 143.4; 141.7; 135.7; 130.1; 127.9; 127.7; 119.4; 115.0; 114.2; 108.9 (d, J_{CF} = 8.1 Hz); 90.3 (d, J_{CF} = 172.2 Hz); 25.8; 21.4 (d, J_{CF} = 22.7 Hz). *^{19}F NMR ($CDCl_3$, 282 MHz)*: δ (ppm) −183.30 (dq, J = 48.9 Hz, J = 24.5 Hz). *HRMS (ESI)* calcd for $C_{19}H_{17}N_2OFNa$ [M+Na]+ m/z = 331.1223, found 331.1224.

3.3.1.5. Synthesis of N-(4′-(6-(1-fluoroethyl)-2-methylpyrimidin-4-yl)biphenyl-4-yl)methanesulfonamide 3e. The reaction was performed using pyrimidine **2** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrimidine **3e** as an oil (70% yield). *^{1}H NMR ($CDCl_3$, 300 MHz)*: δ (ppm) 8.25–8.13 (m, 2H); 7.77–7.57 (m, 5H); 7.43–7.30 (m, 2H); 7.07 (broad s, 1H); 5.63 (dq, J_{HF} = 48.1 Hz, J = 6.5 Hz, 1H); 3.08 (s, 3H); 2.79 (s, 3H); 1.72 (dd, J_{HF} = 24.5 Hz, J = 6.5 Hz, 3H). *^{13}C NMR ($CDCl_3$, 75 MHz)*: δ (ppm) 169.8 (d, J_{CF} = 24.8 Hz); 167.8 (d, J_{CF} = 2.9 Hz); 164.5 (d, J_{CF} = 1.4 Hz); 142.4; 137.2; 136.6; 135.9; 128.4; 127.9; 127.3; 120.9; 108.4 (d, J_{CF} = 8.1 Hz); 90.5 (d, J_{CF} = 172.0 Hz); 39.5; 26.1; 21.4 (d, J_{CF} = 22.5 Hz). *^{19}F NMR ($CDCl_3$, 282 MHz)*: δ (ppm) −183.43 (dq, J = 48.1 Hz, J = 24.8 Hz). *HRMS (ESI)* calcd for $C_{20}H_{20}FN_3O_2SNa$ [M+Na]+ m/z = 408.1152, found 408.1151.

3.3.1.6. Synthesis of 1-(4′-(6-(1-fluoroethyl)-2-methylpyrimidin-4-yl)biphenyl-4-yl)ethanone 3f. The reaction was performed using pyrimidine **2** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrimidine **3f** as an oil (75% yield). *^{1}H NMR ($CDCl_3$, 400 MHz)*: δ (ppm) 8.18–8.03 (m, 2H); 7.97–7.85 (m, 3H); 7.69–7.53 (m, 4H); 5.53 (dq, J_{HF} = 48.1 Hz, J = 6.5 Hz, 1H); 2.70 (s, 3H); 2.51 (s, 3H); 1.63 (dd, J_{HF} = 24.5 Hz, J = 6.5 Hz, 1H). *^{13}C NMR ($CDCl_3$, 100 MHz)*: δ (ppm) 197.8; 169.9 (d, J_{CF} = 24.0 Hz); 167.9 (d, J_{CF} = 2.9 Hz); 164.4 (d, J_{CF} = 1.4 Hz); 144.7; 142.2; 136.7; 136.2; 129.0; 127.9; 127.7; 127.2; 108.5 (d, J_{CF} = 6.7 Hz); 90.4 (d, J_{CF} = 172.1 Hz); 26.7; 26.1; 21.4 (d, J_{CF} = 23.0 Hz). *^{19}F NMR ($CDCl_3$, 282 MHz)*: δ (ppm) −183.35 (dq, J = 48.1 Hz, J = 24.5 Hz). *HRMS (ESI)* calcd for $C_{21}H_{19}N_2OFNa$ [M+Na]+ m/z = 357.1379, found 357.1383.

3.3.2. Pyrimidines 6

3.3.2.1. Synthesis of 4-(biphenyl-4-yl)-6-(1,1-difluorodecyl)-2-methylpyrimidine 6a. The reaction was performed using pyrimidine **5** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrimidine **6a** as an oil (84% yield). *^{1}H NMR ($CDCl_3$, 300 MHz)*: δ (ppm) 8.29–8.17 (m, 2H); 7.85 (s, 1H); 7.81–7.71 (m, 2H); 7.71–7.61 (m, 2H); 7.55–7.45 (m, 2H); 7.45–7.35 (m, 1H); 3.11 (s, 3H); 2.47–2.22 (m, 2H); 1.60–1.45 (m, 2H); 1.44–1.26 (m, 12H); 0.90 (broad t, J = 7.0 Hz, 3H). *^{13}C NMR ($CDCl_3$, 75 MHz)*: δ (ppm) 168.8; 165.2; 163.4 (t, J_{CF} = 29.6 Hz); 144.0; 140.0; 135.3; 128.9; 128.0; 127.8; 127.6; 127.1; 121.1 (t, J_{CF} = 242.9 Hz); 119.3; 115.2; 114.2; 109.1 (t, J_{CF} = 4.6 Hz); 36.0 (t, J_{CF} = 24.6 Hz); 31.9; 29.4; 29.36; 29.30; 29.2; 26.3; 22.7; 21.9 (t, J_{CF} = 4.1 Hz); 14.1. *^{19}F NMR ($CDCl_3$, 282 MHz)*: δ (ppm) −101.84 (t, J = 17.2 Hz). *HRMS (ESI)* calcd for $C_{27}H_{32}N_2F_2Na$ [M+Na]+ m/z = 445.2431, found 445.2435.

3.3.2.2. Synthesis of 4-(1,1-difluorodecyl)-2-methyl-6-(4′-vinylbiphenyl-4-yl)pyrimidine 6b. The reaction was performed using pyrimidine **5** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrimidine **6b** (70% yield). *^{1}H NMR ($CDCl_3$, 300 MHz)*: δ (ppm) 8.26–8.18 (m, 2H); 7.82 (s, 1H); 7.80–7.72 (m, 2H); 7.68–7.60 (m, 2H); 7.57–7.49 (m, 2H); 6.78 (dd, J = 17.6 Hz, J = 10.9 Hz, 1H); 5.83 (dd, J = 17.6 Hz, J = 0.3 Hz, 1H); 5.32 (dd, J = 10.9 Hz, J = 0.3 Hz, 1H); 2.86 (s, 3H); 2.43–2.17 (m, 2H); 1.57–1.43 (m, 2H); 1.42–1.16 (m, 12H); 0.88 (t, J = 6.9 Hz, 3H). *^{13}C NMR ($CDCl_3$, 75 MHz)*: δ (ppm) 168.8; 165.2; 163.3 (t, J_{CF} = 29.4 Hz); 143.5; 139.3; 137.3; 136.2; 135.4; 127.8; 127.4; 127.2; 126.8; 121.1 (t, J_{CF} = 242.4 Hz); 114.4; 109.1 (t, J_{CF} = 4.5 Hz); 36.0 (t, J_{CF} = 24.5 Hz); 31.8; 29.4; 29.3; 29.27; 29.24; 26.3; 22.7; 21.9 (t, J_{CF} = 3.9 Hz); 14.1. *^{19}F NMR ($CDCl_3$, 282 MHz)*: δ (ppm) −102.01 (t, J = 17.1 Hz). *HRMS (ESI)* calcd for $C_{29}H_{34}F_2N_2Na$ [M+Na]+ m/z = 471.2582, found 471.2579.

3.3.2.3. Synthesis of 4′-(6-(1,1-difluorodecyl)-2-methylpyrimidin-4-yl)biphenyl-3-carbaldehyde 6c. The reaction was performed using pyrimidine **5** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded

pyrimidine **6c** (86% yield). *^{1}H NMR ($CDCl_3$, 400 MHz)*: δ (ppm) 10.09 (s, 1H); 8.26–8.11 (m, 2H); 8.17–8.12 (m, 1H); 7.93–7.84 (m, 2H); 7.81 (broad s, 1H); 7.79–7.72 (m, 2H); 7.66–7.59 (m, 1H); 2.84 (s, 3H); 2.42–2.20 (m, 2H); 1.53–1.41 (m, 2H); 1.39–1.13 (m, 12H); 0.86 (broad t, J = 7.0 Hz, 3H). *^{13}C NMR ($CDCl_3$, 100 MHz)*: δ (ppm) 192.03; 168.8; 164.9; 163.5 (t, J_{CF} = 29.7 Hz); 142.3; 141.0; 137.0; 136.1; 132.9; 129.6; 129.3; 128.0; 127.9; 127.6; 121.1 (t, J_{CF} = 242.6 Hz); 109.1 (t, J_{CF} = 4.5 Hz); 35.9 (t, J_{CF} = 35.8 Hz); 31.8; 29.4; 29.3; 29.25; 29.24; 26.2; 22.6; 21.9 (t, J_{CF} = 3.9 Hz); 14.1. *^{19}F NMR ($CDCl_3$, 376 MHz)*: δ (ppm) −101.73 (t, J = 17.1 Hz). *HRMS* (**ESI**) calcd for $C_{28}H_{32}F_2N_2ONa$ [M+Na]+ m/z = 473.2375, found 473.2375.

3.3.2.4. Synthesis of 4′-(6-(1,1-difluorodecyl)-2-methylpyrimidin-4-yl)biphenyl-3-ol 6d. The reaction was performed using pyrimidine **5** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrimidine **6d** (81% yield). *^{1}H NMR ($CDCl_3$, 300 MHz)*: δ (ppm) 8.20–8.10 (m, 2H); 7.83 (s, 1H); 7.69–7.60 (m, 2H); 7.37–7.25 (m, 1H); 7.23–7.13 (m, 2H); 7.05–6.97 (m, 1H); 6.94–6.84 (m, 1H); 2.91 (s, 3H); 2.45–2.22 (m, 2H); 1.59–1.46 (m, 2H); 1.44–1.16 (m, 12H); 0.90 (broad t, J = 6.9 Hz, 3H). *^{13}C NMR ($CDCl_3$, 75 MHz)*: δ (ppm) 168.9; 165.7; 163.5 (t, J_{CF} = 29.5 Hz); 156.4; 143.8; 141.5; 135.2; 130.1; 128.7; 127.9; 127.7; 127.1; 121.0 (t, J_{CF} = 242.9 Hz); 119.3; 115.2; 114.2; 109.7 (t, J_{CF} = 4.9 Hz); 36.1 (t, J_{CF} = 24.5 Hz); 31.9; 29.4; 29.3; 29.28; 29.24; 26.0; 22.7; 21.9 (t, J_{CF} = 4.0 Hz); 14.1. *^{19}F NMR ($CDCl_3$, 282 MHz)*: δ (ppm) −101.71 (t, J = 17.2 Hz). *HRMS (ESI)* calcd for $C_{27}H_{32}F_2N_2ONa$ [M+Na]+ m/z = 461.2375, found 461.2373.

3.3.2.5. Synthesis of N-(4′-(6-(1,1-difluorodecyl)-2-methylpyrimidin-4-yl)biphenyl-4-yl)methanesulfonamide 6e. The reaction was performed using pyrimidine **5** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrimidine **6e** (82% yield). *^{1}H NMR ($CDCl_3$, 300 MHz)*: δ (ppm) 8.25–8.14 (m, 2H); 7.80 (s, 1H); 7.75–7.58 (m, 4H); 7.42–7.32 (m, 2H); 7.30 (broad s, 1H); 3.09 (s, 3H); 2.84 (s, 3H); 2.42–2.17 (m, 2H); 1.55–1.42 (m, 2H); 1.41–1.14 (m, 12H); 0.87 (broad t, J = 6.9 Hz, 3H). *^{13}C NMR ($CDCl_3$, 75 MHz)*: δ (ppm) 168.8; 165.1; 163.4 (t, J_{CF} = 29.9 Hz); 142.8; 137.0; 136.7; 135.5; 128.4; 127.9; 127.3; 121.1 (t, J_{CF} = 242.4 Hz); 120.9; 109.1 (t, J_{CF} = 4.9 Hz); 39.4; 36.0 (t, J_{CF} = 24.5 Hz); 31.8; 29.4; 29.3; 29.26; 29.23; 26.2; 22.6; 21.9 (t, J_{CF} = 3.9 Hz); 14.1. *^{19}F NMR ($CDCl_3$, 282 MHz)*: δ (ppm) −101.73 (t, J = 17.1 Hz). *HRMS (ESI)* calcd for $C_{28}H_{35}F_2N_2O_2SNa$ [M+Na]+ m/z = 538.2316, found 538.2316.

3.3.2.6. Synthesis of 1-(4′-(6-(1,1-difluorodecyl)-2-methylpyrimidin-4-yl)biphenyl-4-yl)ethanone 6f. The reaction was performed using pyrimidine **5** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrimidine **6f** (69% yield). *^{1}H NMR ($CDCl_3$, 300 MHz)*: δ (ppm) 8.28–8.12 (m, 2H); 8.06–7.93 (m, 2H); 7.78 (s, 1H); 7.74–7.58 (m, 4H); 2.80 (s, 3H); 2.57 (s, 3H); 2.42–2.15 (m, 2H); 1.54–1.41 (m, 2H); 1.40–1.10 (m, 12H); 0.83 (broad t, J = 6.8 Hz, 3H). *^{13}C NMR ($CDCl_3$, 75 MHz)*: δ (ppm) 197.6; 168.9; 164.9; 163.3 (t, J_{CF} = 29.7 Hz); 144.5; 142.5; 136.4; 136.3; 129.0; 127.9; 127.8; 127.3; 119.5 (t, J_{CF} = 242.5 Hz); 109.2 (t, J_{CF} = 4.5 Hz); 35.9 (t, J_{CF} = 24.6 Hz); 31.8; 29.4; 29.3; 29.26; 29.23; 26.7; 26.3; 22.6; 21.9 (t, J_{CF} = 4.0 Hz); 14.1. *^{19}F NMR ($CDCl_3$, 282 MHz)*: δ (ppm) −101.97 (t, J = 17.2 Hz). *HRMS (ESI)* calcd for $C_{29}H_{34}F_2N_2ONa$ [M+Na]+ m/z = 487.2531, found 487.2528.

3.4. Spectral and analytical data for pyrazoles 8 and 10

3.4.1. Pyrazole 7

A solution of **1** (157.0 mg, 0.41 mmol) and methylhydrazine (0.45 mmol, 1.1 equiv.) in EtOH (1 mL) was stirred under argon at room temperature for 1 h. The mixture was then concentrated under reduced pressure to obtain a solid, which was then purified by chromatography on silica gel (eluent: pentane/ether, 98/2) affording pyrazole **7** as a crystalline product *Mp*:74 °C (123.8 mg, 78%). *^{1}H NMR (300 MHz, $CDCl_3$)*: δ (ppm) 7.70–7.64 (m, 2H); 7.57–7.45 (m, 2H); 6.64 (d, J_{HF} = 2.7 Hz, 1H); 5.73 (dq, J_{HF} = 49.9 Hz, J = 6.5 Hz, 1H); 4.01 (d, J_{HF} = 1.0 Hz, 3H); 1.82 (dd, J_{HF} = 22.9, 6.5 Hz, 3H). *^{13}C NMR (75 MHz, $CDCl_3$)*: δ (ppm) 148.9 (d, J_{CF} = 2.0 Hz); 142.6 (d, J_{CF} = 20.5 Hz); 132.1; 131.7; 127.0; 121.5; 101.9 (d, J_{CF} = 3.5 Hz); 81.7 (d, J_{CF} = 164.7 Hz); 37.2 (d, J_{CF} = 2.0 Hz); 19.6 (d, J_{CF} = 23.6 Hz). *^{19}F NMR (282 MHz, $CDCl_3$)*: δ (ppm) −164.93 (dqd, J = 49.9 Hz, J = 22.9 Hz, J = 1.3 Hz). *HRMS (ESI)* calcd for $C_{12}H_{12}N_2F^{79}BrNa$ [M+Na]+ m/z = 305.0066, found 305.0066.

3.4.2. Pyrazoles 8

3.4.2.1. General procedure for Suzuki-Miyaura coupling reactions for pyrazoles. A mixture of pyrazole **7** or **9** (1.0 equiv.), Dichlorobis(-triphenylphosphine)-palladium(**II**) (10 mol%), sodium carbonate (2.0 equiv.) and boronic acid (2.0 equiv.) in a 5:1 mixture of dioxane and water was stirred at 100 °C for 24 h. After cooling to room temperature, the solution was diluted with CH_2Cl_2 and then dried over anhydrous $MgSO_4$. The reaction mixture was filtered through a pad of celite and concentrated under vacuum. The product was purified by silica gel chromatography using pentane/ether (9/1) as eluent.

3.4.2.2. Synthesis of 4-(biphenyl-4-yl)-5-(1-fluoroethyl)-1-methyl-1H-pyrazole 8a. The reaction was performed using pyrazole **7** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrazole **8a** (76% yield) *Mp*: 102 °C. *^{1}H NMR (300 MHz, $CDCl_3$)*: δ (ppm) 7.90–7.64 (m, 4H); 7.50–7.36 (m, 5H); 6.64 (d, J_{HF} = 2.4 Hz, 1H); 5.75 (dq, J_{HF} = 50.0, J = 6.5 Hz, 1H); 4.01 (d, J_{HF} = 1.0 Hz, 3H); 1.83 (dd, J_{HF} = 22.9, 6.5 Hz, 3H). *^{13}C NMR (75 MHz, $CDCl_3$)*: δ (ppm) 149.7 (d, J_{CF} = 2.2 Hz); 142.4 (d, J_{CF} = 20.4 Hz);140.8; 140.4; 132.2; 128.7; 127.3; 127.2; 126.9; 125.8; 102.0 (d, J_{CF} = 3.5 Hz); 81.8 (d, J_{CF} = 164.5 Hz); 37.1 (d, J_{CF} = 2.1 Hz); 19.6 (d, J_{CF} = 23.7 Hz). *^{19}F NMR (282 MHz, $CDCl_3$)*: δ (ppm) −164.68 (dqd, J = 50.0 Hz, J = 22.9 Hz, J = 1.6 Hz). *HRMS (ESI)* calcd for $C_{18}H_{17}N_2FNa$ [M+Na]+ m/z = 303.1273, found 303.1275.

3.4.2.3. Synthesis of 5-(1-fluoroethyl)-1-methyl-4-(4′-vinylbiphenyl-4-yl)-1H-pyrazole 8b. The reaction was performed using pyrazole **7** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrazole **8b** (88% yield) *Mp*: 104 °C. *^{1}H NMR (300 MHz, $CDCl_3$)*: δ (ppm) 7.90–7.40 (m, 8H); 6.78 (dd, J = 17.6, 10.9 Hz, 1H); 6.64 (d, J_{HF} = 2.5 Hz, 1H); 5.82 (dd, J = 17.6, 0.8 Hz, 1H); 5.76 (dq, J_{HF} = 50.0, 6.5 Hz, 1H); 5.28 (dd, J = 10.9, 0.8 Hz, 1H); 4.01 (d, J_{HF} = 0.9 Hz, 3H); 1.83 (dd, J_{HF} = 22.9, 6.5 Hz, 3H). *^{13}C NMR (75 MHz, $CDCl_3$)*: δ (ppm) 149.6 (d, J_{CF} = 2.0 Hz); 142.4 (d, J_{CF} = 20.4 Hz); 140.1, 139.9; 136.6; 136.4; 132.2; 127.1; 127.0; 126.6; 125.8; 113.9, 102.0 (d, J_{CF} = 3.5 Hz); 81.8 (d, J_{CF} = 164.4 Hz); 37.1 (d, J_{CF} = 2.1 Hz); 19.6 (d, J_{CF} = 23.7 Hz). *^{19}F NMR (282 MHz, $CDCl_3$)*: δ (ppm) −164.69 (dqd, J = 50.0 Hz, J = 22.9 Hz, J = 1.6 Hz). *HRMS (ESI)* calcd for $C_{20}H_{19}N_2FNa$ [M+Na]+ m/z = 329.1430, found 329.1430.

3.4.2.4. Synthesis of 4′-(5-(1-fluoroethyl)-1-methyl-1H-pyrazol-4-yl)biphenyl-3-carbaldehyde 8c. The reaction was performed using pyrazole **7** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrazole **8c** (82% yield) *Mp*: 88 °C. *^{1}H NMR (300 MHz, $CDCl_3$)*: δ (ppm) 10.10 (s, 1H); 8.20–7.60 (m, 8H); 6.65 (d, J_{HF} = 2.4 Hz, 1H); 5.74 (dq, J_{HF} = 49.9, 6.6 Hz, 1H); 4.00 (d, J_{HF} = 1.0 Hz, 3H); 1.83 (dd, J_{HF} = 22.9, 6.5 Hz, 3H). *^{13}C NMR (75 MHz, $CDCl_3$)*: δ (ppm) 192.4; 149.4 (d, J_{CF} = 2.1 Hz); 142.5 (d, J_{CF} = 20.5 Hz); 141.7; 138.7; 136.9; 132.9; 132.8; 129.5; 128.6; 127.9; 127.3; 126.0; 102.1 (d, J_{CF} = 3.4 Hz); 81.7 (d,

J_{CF} = 164.6 Hz); 37.1 (d, J_{CF} = 2.0 Hz); 19.6 (d, J_{CF} = 23.6 Hz). *^{19}F NMR (282 MHz, CDCl$_3$)*: δ (ppm) −164.70 (dqd, *J* = 50.0 Hz, *J* = 22.9 Hz, *J* = 1.5 Hz). *HRMS (ESI)* calcd for $C_{19}H_{17}N_2OFNa$ [M+Na]+ *m*/*z* = 331.1223, found 331.1224.

3.4.2.5. Synthesis of 4′-(5-(1-fluoroethyl)-1-methyl-1H-pyrazol-4-yl)biphenyl-3-ol 8d. The reaction was performed using pyrazole **7** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrazole **8d** as an oil (74% yield). *^{1}H NMR (300 MHz, CDCl$_3$)*: δ (ppm) 7.80–6.75 (m, 8H); 6.59 (d, J_{HF} = 2.5 Hz, 1H); 5.70 (dq, J_{HF} = 49.8, 6.5 Hz, 1H); 3.99 (d, J_{HF} = 0.8 Hz, 3H); 1.80 (dd, J_{HF} = 23.0, 6.5 Hz, 3H). *^{13}C NMR (75 MHz, CDCl$_3$)*: δ (ppm) 156.1; 150.1 (d, J_{CF} = 2.0 Hz); 142.9 (d, J_{CF} = 20.4 Hz); 142.4; 140.4; 131.5; 129.9; 127.4; 126.1; 119.4; 114.5; 114.1; 102.4 (d, J_{CF} = 3.3 Hz); 81.7 (d, J_{CF} = 164.9 Hz); 36.8 (d, J_{CF} = 2.1 Hz); 19.6 (d, J_{CF} = 23.5 Hz). *^{19}F NMR (282 MHz, CDCl$_3$)*: δ (ppm) −165.32 (dqd, *J* = 49.9 Hz, *J* = 23.0 Hz, *J* = 1.3 Hz).

3.4.2.6. Synthesis of 1-(4′-(5-(1-fluoroethyl)-1-methyl-1H-pyrazol-4-yl)biphenyl-4-yl)ethanone 8f. The reaction was performed using pyrazole **7** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrazole **8f** (79% yield) *Mp*: 142 °C. *^{1}H NMR (300 MHz, CDCl$_3$)*: δ (ppm) 8.10–7.60 (m, 8H); 6.65 (d, J_{HF} = 2.6 Hz, 1H); 5.75 (dq, J_{HF} = 49.9, 6.5 Hz, 1H); 4.00 (d, J_{HF} = 0.9 Hz, 3H); 2.66 (s, 3H); 1.83 (dd, J_{HF} = 22.9, 6.5 Hz, 3H). *^{13}C NMR (75 MHz, CDCl$_3$)*: δ (ppm) 197.8; 149.4 (d, J_{CF} = 2.0 Hz); 145.3; 142.6 (d, J_{CF} = 20.5 Hz); 138.9; 135.8; 133.1; 128.9; 127.5; 127.0; 125.9; 102.1 (d, J_{CF} = 3.4 Hz); 81.7 (d, J_{CF} = 164.7 Hz); 37.2 (d, J_{CF} = 2.1 Hz); 26.7, 19.6 (d, J_{CF} = 23.7 Hz). *^{19}F NMR (282 MHz, CDCl$_3$)*: δ (ppm) −164.80 (dqd, *J* = 49.9 Hz, *J* = 23.0 Hz, *J* = 1.3 Hz). *HRMS (ESI)* calcd for $C_{20}H_{19}N_2OFNa$ [M+Na]+ *m*/*z* = 345.1379, found 345.1377.

3.4.3. Pyrazoles 10

3.4.3.1. Synthesis of 3-(biphenyl-4-yl)-5-(1,1-difluorodecyl)-1-methyl-1H-pyrazole 10a. The reaction was performed using pyrazole **9** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrazole **10a** (79% yield) *Mp*: 52 °C. *^{1}H NMR (300 MHz, CDCl$_3$)*: δ (ppm) 7.90–7.84 (m, 2H); 7.67–7.62 (m, 4H); 7.50–7.29 (m, 3H); 6.70 (t, J_{HF} = 1.0 Hz, 1H); 4.06 (t, J_{HF} = 0.9 Hz, 3H); 2.40–2.15 (m, 2H), 1.80–1.45 (m, 2H); 1.40–1.15 (m, 12H); 0.90 (t, *J* = 6.9 Hz, 3H). *^{13}C NMR (75 MHz, CDCl$_3$)*: δ (ppm) 149.5; 140.7; 139.5 (t, J_{CF} = 30.6 Hz); 131.7; 128.8; 127.4; 127.3; 126.9; 125.8; 122.0; 116.4 (t, J_{CF} = 237.7 Hz); 103.5 (t, J_{CF} = 4.3 Hz); 38.6 (t, J_{CF} = 3.2 Hz); 37.2 (t, J_{CF} = 25.2 Hz); 31.8; 29.4; 29.3; 29.2; 22.6; 22.1 (t, J_{CF} = 3.8 Hz); 14.1. *^{19}F NMR (282 MHz, CDCl$_3$)*: δ (ppm) −92.82 (t, *J* = 16.5 Hz). *HRMS (ESI)* calcd for $C_{26}H_{32}N_2F_2Na$ [M+Na]+ *m*/*z* = 433.2431, found 433.2434.

3.4.3.2. Synthesis of 5-(1,1-difluorodecyl)-1-methyl-3-(4′-vinylbiphenyl-4-yl)-1H-pyrazole 10b. The reaction was performed using pyrazole **9** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrazole **10b** (80% yield) *Mp*: 84 °C. *^{1}H NMR (300 MHz, CDCl$_3$)*: δ (ppm) 7.90–7.45 (m, 8H); 6.78 (dd, *J* = 17.6, 10.9 Hz, 1H); 6.70 (t, J_{HF} = 1.0 Hz, 1H); 5.82 (dd, *J* = 17.6, 0.9 Hz, 1H); 5.29 (dd, *J* = 10.9, 0.9 Hz, 1H); 4.06 (t, J_{HF} = 0.9 Hz, 3H); 2.45–2.19 (m, 2H); 1.80–1.45 (m, 2H); 1.40–1.15 (m, 12H); 0.90 (t, *J* = 6.9 Hz, 3H). *^{13}C NMR (75 MHz, CDCl$_3$)*: δ (ppm) 149.2; 140.1; 140.0; 139.1 (t, J_{CF} = 30.5 Hz); 136.7; 136.4; 131.8; 127.1; 127.0; 126.7; 125.9; 118.8 (t, J_{CF} = 237.7 Hz); 113.9; 103.5 (t, J_{CF} = 4.5 Hz); 38.6 (t, J_{CF} = 3.1 Hz); 37.2 (t, J_{CF} = 25.2 Hz); 31.9; 29.4; 29.3; 29.2; 29.1; 22.6; 22.1 (t, J_{CF} = 3.7 Hz); 14.1. *^{19}F NMR (282 MHz, CDCl$_3$)*: δ (ppm) −92.83 (t, *J* = 16.6 Hz). *HRMS* (*m*/*z*): [M+H]+ calculated for $C_{28}H_{35}N_2F_2$ *m*/*z* = 437.2768, found 437.2771.

3.4.3.3. Synthesis of 4′-(5-(1,1-difluorodecyl)-1-methyl-1H-pyrazol-3-yl)biphenyl-3-carbaldehyde 10c. The reaction was performed using pyrazole **9** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrazole **10c** (85% yield) *Mp*: 58 °C. *^{1}H NMR (300 MHz, CDCl$_3$)*: δ (ppm) 10.12 (s, 1H); 8.16–7.60 (m, 8H); 6.72 (t, J_{HF} = 1.0 Hz, 1H); 4.07 (t, J_{HF} = 0.9 Hz, 3H); 2.45–2.18 (m, 2H); 1.80–1.45 (m, 2H); 1.40–1.15 (m, 12H); 0.90 (t, *J* = 6.9 Hz, 3H). *^{13}C NMR (75 MHz, CDCl$_3$)*: δ (ppm) 192.3; 149.2; 141.7; 139.2 (t, J_{CF} = 30.5 Hz); 139.0; 136.9; 132.8; 132.5; 129.5; 128.7; 127.9; 127.4; 126.0; 118.8 (t, J_{CF} = 237.8 Hz); 103.6 (t, J_{CF} = 4.4 Hz); 38.7 (t, J_{CF} = 3.2 Hz); 37.2 (t, J_{CF} = 25.2 Hz); 31.8; 29.4; 29.3; 29.2; 22.6; 22.1 (t, J_{CF} = 3.8 Hz); 14.1. *^{19}F NMR (282 MHz, CDCl$_3$)*: δ (ppm) −92.88 (t, *J* = 16.6 Hz). *HRMS (ESI)* calcd for $C_{27}H_{32}N_2OF_2Na$ [M+Na]+ *m*/*z* = 461.2380, found 461.2380.

3.4.3.4. Synthesis of 4′-(5-(1,1-difluorodecyl)-1-methyl-1H-pyrazol-3-yl)biphenyl-3-ol 10d. The reaction was performed using pyrazole **9** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrazole **10d** as an oil (76% yield). *^{1}H NMR (300 MHz, CDCl$_3$)*: δ (ppm) 7.80–6.80 (m, 8H); 6.68 (t, J_{HF} = 1.0 Hz, 1H); 4.07 (t, J_{HF} = 0.8 Hz, 3H); 2.40–2.05 (m, 2H); 1.80–1.45 (m, 2H); 1.40–1.15 (m, 12H); 0.90 (t, *J* = 6.9 Hz, 3H). *^{13}C NMR (75 MHz, CDCl$_3$)*: δ (ppm) 156.3; 149.7; 142.2; 140.5; 139.4 (t, J_{CF} = 30.7 Hz); 131.5; 129.9; 127.4; 126.1; 119.2; 118.8 (t, J_{CF} = 237.7 Hz); 114.5; 114.1; 103.7 (t, J_{CF} = 4.4 Hz); 38.5 (t, J_{CF} = 3.2 Hz); 37.2 (t, J_{CF} = 25.1 Hz); 31.9; 29.4; 29.3; 29.2; 29.1; 22.6; 22.1 (t, J_{CF} = 3.8 Hz,); 14.1. *^{19}F NMR (282 MHz, CDCl$_3$)*: δ (ppm) −92.96 (t, *J* = 16.6 Hz). *HRMS (APCI)* calcd for $C_{26}H_{32}N_2OF_2$[M]+ *m*/*z* = 426.2477, found 426.2478.

3.4.3.5. Synthesis of 1-(4′-(5-(1,1-difluorodecyl)-1-methyl-1H-pyrazol-3-yl)biphenyl-4-yl)ethanone 10f. The reaction was performed using pyrazole **9** according to the general procedure. A purification on silica gel (eluent: pentane/ether, 9/1) afforded pyrazole **10f** (89% yield) *Mp*: 126 °C. *^{1}H NMR (300 MHz, CDCl$_3$)*: δ (ppm) 8.10–7.60 (m, 8H); 6.72 (t, J_{HF} = 1.0 Hz, 1H); 4.07 (t, J_{HF} = 0.9 Hz, 3H); 2.66 (s, 3H); 2.45–2.19 (m, 2H); 1.80–1.45 (m, 2H); 1.40–1.15 (m 12H); 0.90 (t, *J* = 6.9 Hz, 3H). *^{13}C NMR (75 MHz, CDCl$_3$)*: δ (ppm) 197.7; 149.2; 145.3; 139.3 (t, J_{CF} = 30.5 Hz); 139.2; 135.9; 132.7; 128.9; 127.5; 127.0; 127.9; 126.0; 118.8 (t, J_{CF} = 237.8 Hz); 103.6 (t, J_{CF} = 4.4 Hz); 38.7 (t, J_{CF} = 3.2 Hz); 37.2 (t, J_{CF} = 25.2 Hz); 31.8; 29.4; 29.3; 29.2; 29.1; 26.6; 22.6; 22.1 (t, J_{CF} = 3.8 Hz); 14.1. *^{19}F NMR (282 MHz, CDCl$_3$)*: δ (ppm) −92.88 (t, *J* = 16.6 Hz). *HRMS (ESI)* calcd for $C_{28}H_{34}N_2OF_2Na$ [M+Na]+ *m*/*z* = 475.2537, found 475.2535.

3.5. Syntheses of styrene type derivatives through Stille cross coupling reactions

3.5.1. Pyrimidine 11

3.5.1.1. Synthesis of 4-(1-fluoroethyl)-2-methyl-6-(4-vinylphenyl)-pyrimidine 11. A mixture of pyrimidine **2** (0.67 mmol, 1 equiv.), vinyl tributyltin (1.35 mmol, 2 equiv.) and $PdCl_2(PPh_3)_3$ (5 mol%) in dioxane (10 mL) was stirred at 100 °C overnight under argon. The mixture was concentrated under reduced pressure and the crude product was purified by chromatography on silica gel (eluent Pentane/Et_2O, 95/5, then 9/1) affording **11** as a yellow oil (156.0 mg, 95% yield). *^{1}H NMR (CDCl$_3$, 300 MHz)*: δ (ppm) 8.13–8.05 (m, 2H); 7.67 (s, 1H); 7.57–7.47 (m, 2H); 6.76 (dd, *J* = 17.6 Hz, *J* = 10.9 Hz, 1H); 5.86 (dd, *J* = 17.6 Hz, *J* = 0.6 Hz, 1H); 5.61 (dq, J_{HF} = 48.1 Hz, *J* = 6.5 Hz, 1H); 5.35 (dd, *J* = 10.9 Hz, *J* = 0.6 Hz, 1H); 2.77 (s, 3H); 1.70 (dd, J_{HF} = 24.5 Hz, *J* = 6.5 Hz, 3H). *^{13}C NMR (CDCl$_3$, 75 MHz)*: δ (ppm) 169.7 (d, J_{CF} = 24.7 Hz); 167.8 (d, J_{CF} = 2.9 Hz); 164.5 (d, J_{CF} = 1.6 Hz); 140.1; 136.2; 136.1; 127.5; 126.7; 115.5;

108.2 (d, J_{CF} = 8.0 Hz); 90.5 (d, J_{CF} = 171.8 Hz); 26.2; 21.4 (d, J_{CF} = 22.5 Hz). *^{19}F NMR (CDCl$_3$, 282 MHz)*: δ (ppm) −183.61 (dq, J = 48.1 Hz, J = 24.5 Hz). *HRMS (ESI)* calcd for $C_{15}H_{15}FN_2Na$ [M+Na]+ m/z = 265.11170, found 265.1119.

3.5.2. Pyrimidine 12

3.5.2.1. Synthesis of 4-(1,1-difluorodecyl)-2-methyl-6-(4-vinylphenyl)pyrimidine 12. A mixture of pyrimidine **5** (0.20 mmol, 1 equiv.), vinyl tributyltin (0.31 mmol, 1.5 equiv.) and $PdCl_2(PPh_3)_2$ (5 mol%) in dioxane (3 mL) was stirred at 100 °C for 20 h under argon. The mixture was concentrated under reduced pressure and the crude product was purified by chromatography on silica gel (eluent pentane/Et_2O, 98/2) affording **12** as a pale yellow oil (62.6 mg, 84% yield). *^{1}H NMR (CDCl$_3$, 300 MHz)*: δ (ppm) 8.18–8.03 (m, 2H); 7.77 (s, 1H); 7.60–7.46 (m, 2H); 6.77 (dd, J = 17.6 Hz, J = 10.9 Hz, 1H); 5.87 (d, J = 17.6 Hz, 1H); 5.37 (d, J = 10.9 Hz, 1H); 2.83 (s, 3H); 2.42–2.16 (m, 2H); 1.55–1.40 (m, 2H); 1.37–1.18 (m, 12H); 0.87 (t, J = 6.8 Hz, 3H). *^{13}C NMR (CDCl$_3$, 75 MHz)*: δ (ppm) 168.7; 165.1; 163.3 (t, J_{CF} = 29.6 Hz); 140.4; 136.0; 135.7; 127.5; 126.8; 121.1 (t, J_{CF} = 242.6 Hz); 115.7; 109.0 (t, J_{CF} = 4.7 Hz); 35.9 (t, J_{CF} = 24.6 Hz); 31.8; 29.4; 29.3; 29.26; 29.23; 26.2; 22.6; 21.9 (t, J_{CF} = 3.9 Hz); 14.1. *^{19}F NMR (CDCl$_3$, 282 MHz)*: δ (ppm) −101.93 (t, J = 17.1 Hz). *HRMS (ESI)* calcd for $C_{23}H_{30}F_2N_2Na$ [M+Na]+ m/z = 395.22748, found 395.2277.

3.5.3. Pyrazole 13

3.5.3.1. Synthesis of 5-(1-fluoroethyl)-1-methyl-3-(4-vinylphenyl)-1H-pyrazole 13. A mixture of pyrazole **7** (0.67 mmol, 1 equiv.), vinyl tributyltin (1.35 mmol, 2 equiv.) and $PdCl_2(PPh_3)_3$ (10 mol%) in dioxane (10 mL) was stirred at 100 °C during 24 h under argon. The mixture was concentrated under reduced pressure and the crude product was purified by chromatography on silica gel (eluent Pentane/ether 95/5, then 9/1) affording **13** as a yellow oil (136 mg, 88% yield). *^{1}H NMR (300 MHz, CDCl$_3$)*: δ (ppm) 7.90–7.40 (m, 4H), 6.78 (dd, J = 17.6, 10.9 Hz, 1H), 6.64 (d, J_{HF} = 2.5 Hz, 1H), 5.82 (dd, J = 17.6, 0.8 Hz, 1H) 5.76 (dq, J_{HF} = 50.0 Hz, J = 6.5 Hz, 1H), 5.28 (dd, J = 10.9, J = 0.8 Hz, 1H) 4.01 (d, J = 0.9 Hz, 3H), 1.83 (dd, J_{HF} = 22.9, J = 6.5 Hz, 3H). *^{13}C NMR (75 MHz, CDCl$_3$)*: δ (ppm) 149.6 (d, J_{CF} = 2.0 Hz), 142.4 (d, J_{CF} = 20.4 Hz), 140.1, 139.9, 136.6, 136.4, 132.2, 127.1, 127.0, 126.6, 125.8, 113.9, 102.0 (d, J_{CF} = 3.5 Hz), 81.8 (d, J_{CF} = 164.4 Hz), 37.1 (d, J_{CF} = 2.1 Hz), 19.6 (d, J_{CF} = 23.7 Hz). *^{19}F NMR (282 MHz, CDCl$_3$)*: δ (ppm) −164.69 (dqd, J = 50.0 Hz, J = 22.9 Hz, J = 1.6 Hz). *HRMS (ESI)* calcd for $C_{14}H_{15}N_2FNa$ [M+Na]+ m/z = 253.1117, found 253.1116.

3.5.4. Pyrazole 14

3.5.4.1. Synthesis of 5-(1,1-difluorodecyl)-1-methyl-3-(4-vinylphenyl)-1H-pyrazole 14. A mixture of pyrazole **9** (0.67 mmol, 1 equiv.), vinyl tributyltin (1.35 mmol, 2 equiv.) and $PdCl_2(PPh_3)_3$ (10 mol%) in dioxane (10 mL) was stirred at 100 °C during 24 h under argon. The mixture was concentrated under reduced pressure and the crude product was purified by chromatography on silica gel (eluent pentane/ether, 95/5, then 9/1) affording **14** as a yellow oil (146 mg, 61% yield). *^{1}H NMR (300 MHz, CDCl$_3$)*: δ (ppm) 7.80–7.40 (m, 4H), 6.68 (dd, J = 17.6, 10.9 Hz, 1H), 6.64 (t, J_{HF} = 1.1 Hz, 1H), 5.78 (dd, J = 17.6, 0.9 Hz, 1H), 5.27 (dd, J = 10.9, 0.9 Hz, 1H) 4.03 (t, J_{HF} = 1.0 Hz, 3H), 2.45–2.19 (m, 2H), 1.80–1.45 (m, 2H,), 1.40–1.15 (m, 12H), 0.92 (t, J = 6.9 Hz, 3H). *^{13}C NMR (75 MHz, CDCl$_3$)*: δ (ppm) 149.5, 139.1 (t, J_{CF} = 30.5 Hz), 137.1, 136.5, 132.2, 126.5, 125.6, 118.8 (t, J_{CF} = 237.7 Hz), 113.8, 103.5 (t, J_{CF} = 4.5 Hz), 38.6 (t, J_{CF} = 3.1 Hz), 37.2 (t, J_{CF} = 25.2 Hz), 31.9, 29.4, 29.3, 29.2, 29.1, 22.7, 22.1 (t, J_{CF} = 3.6 Hz), 14.1. *^{19}F NMR (282 MHz, CDCl$_3$)*: δ (ppm) −92.87 (t, J = 16.6 Hz). *HRMS (APCI)* calcd for $C_{22}H_{30}N_2F_2$[M]+ m/z = 360.2372, found 360.2379.

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