Substitution effect on the hydrofluorination reaction of unsaturated amines in superacid HF/SbF_5†

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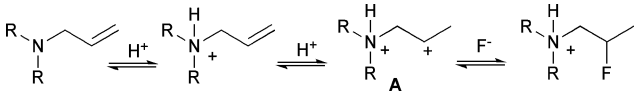
This paper describes the scope and limitations of the hydrofluorination reaction in superacid HF/SbF_5. On the basis of experimental studies of polyfunctional substrates' behaviour, the dramatic effect of substitution on the superelectrophilic character of ammonium–carbenium dications was emphasized. This reaction was applied to the synthesis of novel fluorinated key building blocks. Furthermore, the hydrofluorination reaction and the discovered homodimerization/fluorination reaction were applied to the synthesis of highly valued fluorinated diamines.

Introduction

Introducing fluorine atom(s) commonly alters the physical and/or chemical properties of a molecule,[1] with dramatic effects on its biological activity.[2] As a consequence, drug candidates with one or more fluorine atoms have became commonplace.[3] Among fluorine substitution's consequences, the strong inductive withdrawing effect of fluorine on the acidity or basicity of neighbouring functional groups is especially evident.[4] The changes in pKa can have effects on different parameters in lead optimization including physicochemical properties, binding, absorption, distribution, metabolism, excretion (ADME) and safety issues. Even if fluorine substitution's effects on oral bioavailability could not always be accurately predicted,[5] the incorporation of nitrogen-containing organofluorine cores in medicinal chemistry became very popular.[6] Despite the importance of (mono)fluorinated amines, few synthetic methods are reported in the literature for their preparation.[7] One common method is the ring opening of aziridines with nucleophilic fluoride sources,[8] but it lacks generality, substrate scope and requires starting materials that are not readily available. A widely used alternative is the nucleophilic substitution of aminoalcohol with DAST and derivatives,[9] but this method suffers from rearranged and dehydrated product formation.[10] Other routes *via* reductive amination of α-fluoroenones[11] or ketones[12] or *via* Grignard or organolithium reagents' addition to α-fluoroenimines have also recently been reported.[13] The simplest route to fluoroamines would appear to be the halofluorination or hydrofluorination of unsaturated amines using a combination of HF-base, Olah's reagents and an electrophilic source.[14] However, to the best of our knowledge, few successful examples are reported in the literature starting from either protected vinylimidazole[15] or from *N*-allylic imines.[16] The lack of regioselectivity and the poor reactivity of the double bond after protonation of the amino group[17] could explain the difficulty in performing such reactions with simple unsaturated amines. In our ongoing project toward the synthesis of fluorinated nitrogen containing compounds in superacid HF/SbF_5,[18] we recently developed a novel route to β-fluoroamines *via* a hydrofluorination reaction.[19] After successive protonations, the allylic amines gave dicationic ammonium–carbenium intermediates **A** in superacid HF/SbF_5. The dicationic intermediates then reacted in good yields to give β-fluoroamines after fluorination (Scheme 1).



Scheme 1 Hydrofluorination in superacid HF/SbF_5.

The ability to be fluorinated, even in the presence of a poor nucleophile such as solvated fluorine in the polymeric anion form $Sb_nF_{5n+1}^-$,[20] suggested that the dicationic intermediates **A** could be considered as superelectrophiles.

In the following report, we describe further studies to evaluate the scope and limitations of this original process. We report a dramatic effect of both nitrogen- and double bond-substitutions on the hydrofluorination reaction. We also show that the ammonium–carbenium dicationic intermediates can be involved in a homodimerization/fluorination process, which provides further advances toward the synthesis of fluorinated highly valued diamine building blocks.

Results and discussion

Nitrogen substitution effect on the hydrofluorination reaction

A series of *N*-allylic amines were subjected to reaction in superacid HF/SbF_5 (HF/SbF_5 molar ratio 7/1, –20 °C, 10 min). Starting from amines, hydrofluorination occurred to give the corresponding β-fluoroamines with reasonable yields (Table 1, entries 2–10). During the course of this preliminary study, we also assessed the difference in reactivity of allylic amines and amides toward the hydrofluorination reaction (Table 1, entries 1–3).[19] Whereas amines led to the desired fluorinated products, amide **1a** underwent

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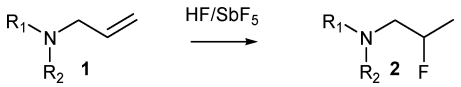
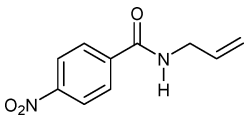
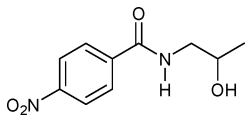
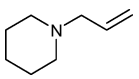
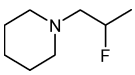
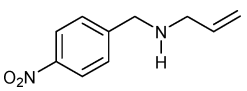
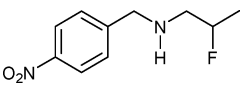
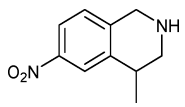
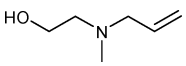
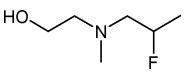
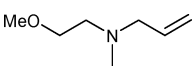
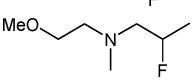
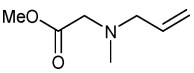
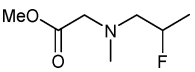
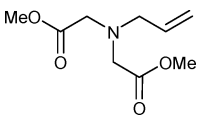
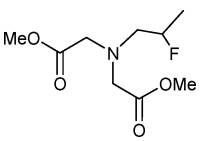
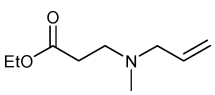
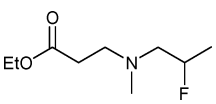
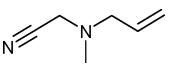
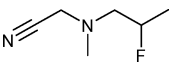
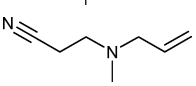
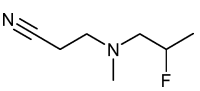
† Electronic supplementary information (ESI) available: Copies of NMR spectra. See DOI: 10.1039/b915077c

Table 1 Hydrofluorination of *N*-substituted allylic substrates[a]

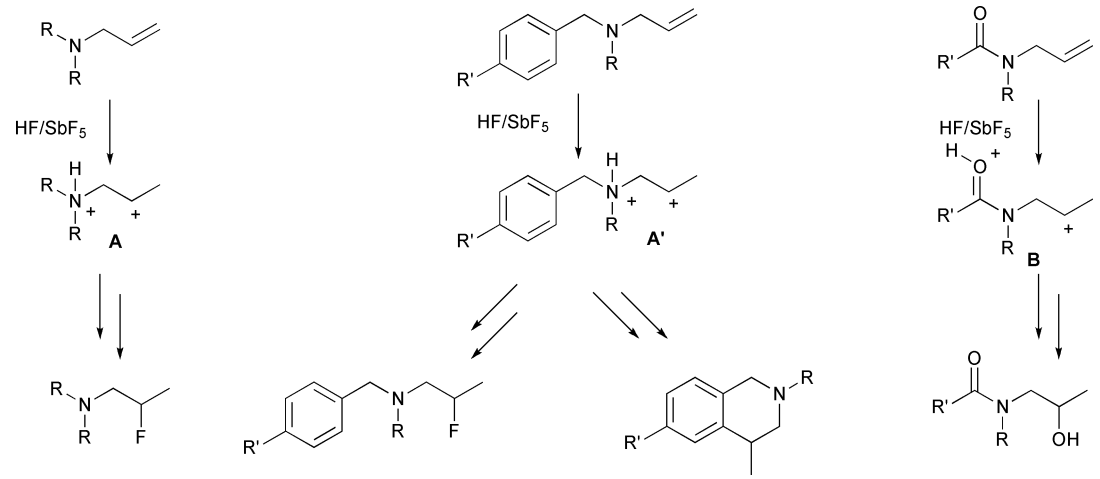


Entry	Substrate	Product	Yield (%)[b]
1	**1a** 	**2′a** 	69
2	**1b** 	**2b** 	72
3	**1c** 	**2c** 	45
		2′c 	24
4	**1d** 	**2d** 	31[c]
5	**1e** 	**2e** 	22[c]
6	**1f** 	**2f** 	35[d]
7	**1g** 	**2g** 	60[c]
8	**1h** 	**2h** 	55[c]
9	**1i** 	**2i** 	61[c]
10	**1j** 	**2j** 	46[d]

[a] Standard conditions: HF/SbF_5 molar ratio 7/1, −20 °C, 10 min. [b] Chemical yield after column chromatography. [c] 100% conversion. [d] Side product formation

hydration in the same conditions. Particularly noteworthy is also the formation of tetrahydroisoquinoline **2′c**, besides fluoroproduct **2c**, after reaction of *p*-NO_2-benzylamine **1c**. These results strengthen the hypothesis that the electrophilic character of the dicationic intermediates strongly influences the reaction course. The ammonium–carbenium dications **A** or **A′** (Scheme 2) obtained after protonation of allylic amines can be considered as superelectrophiles.[21] Indeed, the dications can be quenched by a poor nucleophile such as solvated fluorine in superacid,[20] or by a strongly deactivated aromatic ring in an intramolecular Friedel–Crafts process. However, the carboxonium–carbenium dication **B** formed after protonation of *N*-allylic amide was insufficiently electrophilic to react with fluoride ions of the media and led to the corresponding alcohol after hydrolysis.

In a previous study, we reported that ammonium–carbenium dications can be trapped by an intramolecular hydroxyl group. This behaviour of amino alcohols in superacid led to the synthesis of a novel chiral heterocyclic system starting from quinine in superacid.[22] No similar effect was observed on the hydrofluorination reaction. Amino alcohol **1d** and amino ether **1e** yielded corresponding fluoroamines (Table 1, entries 4 and 5), and no other products resulting from intramolecular nucleophilic attack were detected in the crude mixture. The low yields obtained after purification were probably due to the volatility of the fluorinated products. Amino esters and amino nitriles were also found to be compatible with the hydrofluorination reaction (Table 1, entries 6–10). However, the absence of selectivity starting from amino ester **1f** showed that the hydrofluorination reaction could present some limitations. As mentioned previously,[23] the intramolecular participation of the carbonyl group could be postulated. After formation of a six-membered ring carboxonium ion, the reactivity of the intermediate could be modified, leading to the formation



Scheme 2 Influence of dicationic superelectrophiles on the hydrofluorination reaction.

of undesired side products (entry 6). In a similar way, the formation of a seven-membered ring ammonium–nitrilium dication could explain why the formation of fluorinated product **2j** was not exclusive (entry 10). To conclude, the hydrofluorination of *N*-substituted allylic amines presents few limits and was applied to the synthesis of novel fluorinated key building blocks in moderate to good yields.

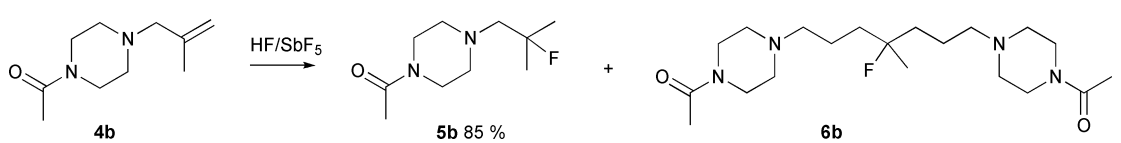
Double bond substitution effect on the hydrofluorination reaction

On the basis of these preliminary results, the superelectrophilic dicationic ammonium–carbenium intermediates were expected to be reactive toward fluoride ions and should allow, *via* the introduction of substituents on the double bond, the synthesis of various fluorinated amines. With *N*-acetyl piperazine **4a** as a model substrate,[19] substituted starting materials (**4b–i**) were subjected to superacid under standard conditions (Table 2).

Initially the reaction was attempted with methyl substituted substrate **4b**. Using an inductive donating methyl substituent, hydrofluorination still occurred and led to the formation of the fluorinated amine **5b** in 85% yield. Hydrofluorination was also compatible with phenyl substituted substrate, as shown by the formation of the fluorinated amine **5c** starting from amine **4c** (Table 2, entry 3). However, a large amount of side products could be detected in the crude mixture, products which could probably come from an intermolecular Friedel–Crafts reaction. Unfortunately, substitution with carbonyl containing groups, like an ester function, completely deactivated the substrate and no reaction occurred (Table 2, entries 4 and 9). To verify if a hydrofluorination process could be used to form fluorinated diamines, the reactivity of the diamine **4e** was tested. Unfortunately the reaction did not occur, even after a longer reaction time (1 day) at 0 °C (Table 2, entry 5). It appears that after protonation of the nitrogen atoms, the double bond is too deactivated by the proximal ammonium ions to be protonated, preventing the substrate from undergoing the hydrofluorination reaction. Based on this hypothesis, the amine function was protected by a *p*-NO_2-benzoyl group (substrate **4f**). In this case, the hydrofluorination reaction occurred after 10 min reaction at –20 °C with starting material remaining. Under optimized conditions (–20 °C, 4h), the desired product **5f** was obtained in 62% yield (Table 2, entry 6). The protonation on both functions, on the nitrogen atom of the amine and on the oxygen atom of the amide, let the double bond sufficiently reactive toward protonation (less withdrawing effects by increasing the distance) and hydrofluorination took place. In addition, methyl- and phenyl-substitution of the terminal position of the allylic chain in the substrates (compounds **4g** and **4h**) led to complex mixtures of compounds, even under milder conditions.

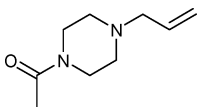
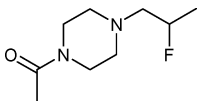
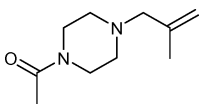
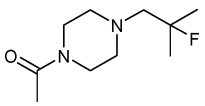
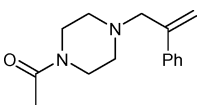
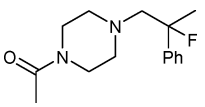
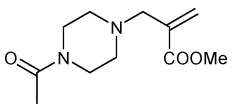
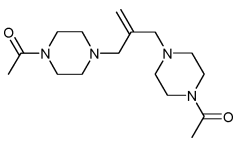
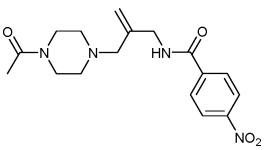
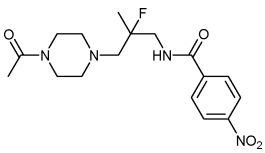
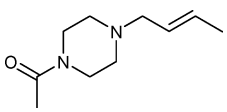
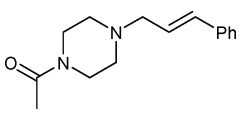
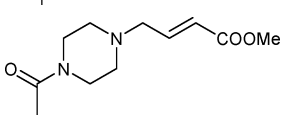
To summarize, it appears that the electronic deactivation of the double bond with inductive and/or mesomeric withdrawing groups such as an ester function (in neutral or protonated form) or an ammonium group, strongly deactivates the double bond toward the electrophilic addition and prevents substrates from undergoing the hydrofluorination reaction. An alternative toward the synthesis of fluorinated diamines has been found to be protection of one amino group as the amide form (formation of product **5f**). In addition, phenyl substitution allows substrates to react through the ammonium–carbenium dication, but a strong effect of aromatic substituent on the selectivity of the reaction is observed. Methyl substituted substrates seemed to be compatible with the reaction. Among the systems studied, compound **4b** was found to give product **5b** as a major product, along with an unidentified minor product (eqn 1).

Isolation and characterization of this minor product revealed its identity to be that of structure **6b**. This product could only arise from a homodimerization process. To the best of our knowledge, no similar process observed from unsaturated nitrogen derivatives has been reported yet in superacid. Despite the fact that superacid was known to catalyse polymerisation (styrene polymerisation for example),[24] Klumpp *et al.* had previously reported that no



(1)

Table 2 Hydrofluorination of double bond substituted substrates[a]

Entry	Substrate	Product	Yield (%)[b]
1	**4a** 	**5a** 	69
2	**4b** 	**5b** 	85
3	**4c** 	**5c** 	41[c]
4	**4d** 	/[d]	/[d]
5	**4e** 	/[d]	/[d]
6[e]	**4f** 	**5f** 	62
7	**4g** 	/[f]	/[f]
8	**4h** 	/[f]	/[f]
9	**4i** 	/[d]	/[d]

[a] Standard conditions: HF/SbF_5 molar ratio 7/1, –20 °C, 10 min. [b] Chemical yield after column chromatography. [c] Side product formation. [d] No reaction. [e] 4 h reaction time. [f] Complex mixture.

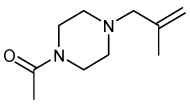
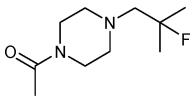
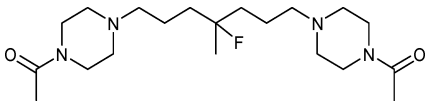
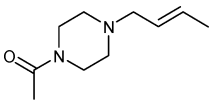
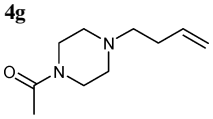
polymerisation or oligomerization of olefinic amines occurred in superacid.[25] This unusual homodimerization of unsaturated amines in superacid could open up novel alternatives for the synthesis of highly valued fluorinated diamines. For example, in the last few years, medicinal chemistry strategies largely used the concept of immolative linkers, applied toward the synthesis of biologically active compounds, such as anticancer agents.[26] Diamino linkers became interesting targets and got a primordial place in this strategy. As a fluorine substituent could modify the chemical and biological properties of diamines linkers by strongly changing the basicity of the proximal nitrogen functions, fluorinated diamine building blocks could become of great interest in SAR studies.[27] These considerations prompted us to examine this dimerization process, and the effect of the reaction parameters (HF/SbF_5 molar ratio, concentration,...) on the reaction course.

Homodimerization/fluorination reaction in superacid

The first attempt starting from amine **4b** using standard conditions confirmed the formation of the fluorinated dimer **6b** in very low yield beside fluoroamine **5b** (Table 3, entry 1). An isomerisation step was probably involved in the formation of **6b**, and thus the effect of the acidity on its formation was first evaluated. While strong acidic conditions were not appropriate for the dimerization process (Table 3, entry 2), using an HF/SbF_5 molar ratio of 2/1 value was found to improve the yield of desired dimer **6b** (Table 3, entry 3).

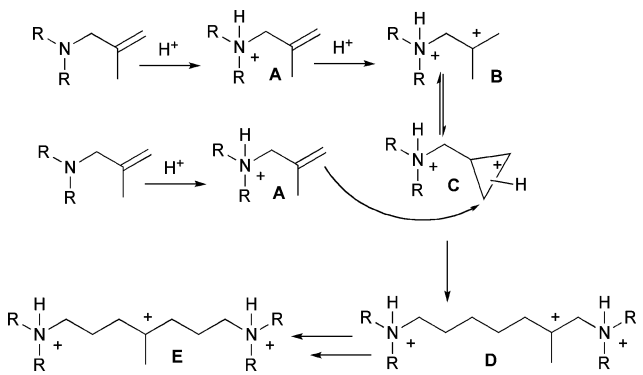
A dilution effect on oligomerization processes is well known and could also occur in this case. Thus, we therefore investigated the effect of substrate concentration in the superacid HF/SbF_5 medium, on the reaction course. With increasing dilution of the solution, product **6b** formation gradually increased until 36%.

Table 3 Homodimerization/fluorination in superacid[a]

Entry	Substrate	Concentration (mol L^{-1})[b]	HF/SbF_5 molar ratio	Products (Yield %)[c]	
					
1	**4b**	0.3	7/1	**5b** (85)	**6b** (<5%)
2	**4b**	0.3	1/1		/[d]
3	**4b**	0.3	2/1	**5b** (44)	**6b** (12)
4	**4b**	0.6	2/1	**5b** (36)	**6b** (<5%)
5	**4b**	0.17	2/1	**5b** (39)	**6b** (20)
6	**4b**	0.06	2/1	**5b** (10)	**6b** (36)
					
7	**4g**	0.3	7/1		**6b** (38)
8	**4g**	0.17	2/1		**6b** (66)
					
9	**4j**	0.3	2/1		**6b** (42)

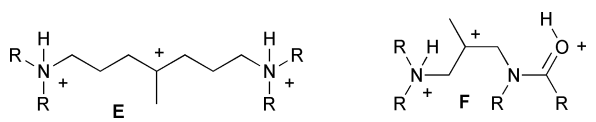
[a] Standard conditions : –20 °C, 10 min. [b] Molar concentration of substrate in HF/SbF_5 media. [c] Chemical yield after column chromatography. [d] Complex mixture.

It has to be noted that even under these conditions, the usual hydrofluorination process still occurred in 10% yield (Table 3, entries 4–6). Based on these promising results, a mechanism was postulated (Scheme 3).



Scheme 3 Postulated mechanism for the homodimerization/fluorination reaction in superacid.

Starting from methyl substituted substrate, *N*-protonation (formation of **A**), followed by double bond protonation allows the formation of the superelectrophilic ammonium–carbenium dication **B**. Based on the carbenium ion's behaviour in superacid, an equilibrium between **B** and protonated cyclopropane **C** can be postulated.[28] The intermolecular attack of **A** on intermediate **C** could be the key step for the dimerization process, allowing the formation of trication **D**. By repulsion of charges, **D** could isomerize toward the formation of the more stable intermediate **E** (less repulsion of charges, inductive stabilizing effect), precursor of the fluorinated dimer **6b**. The postulated mechanism emphasizes two points. First, as already reported for an intramolecular way by our group,[29] despite the strong deactivation of the double bond, due to the inductive withdrawing effect of the proximal ammonium ion, the intermediate **A** can play the role of nucleophilic partner. Then, repulsive electrostatic effects, usually mentioned to explain the absence of polymerisation of polycationic species, do not occur during the process. Since the formation of the intermediate **E**, precursor of the desired fluorinated product **6b**, seems to be fully dependant on the inter-molecular trapping of intermediate **C**, we postulated that the methyl substituted substrate **4g** or the homoallylic substrate **4j** could undergo a similar process. As predicted, the desired fluorinated dimer could be formed in 66% yield using optimized conditions starting from substrate **4g** (Table 3, entries 7 and 8) and in 42% yield from substrate **4j** (Table 3, entry 9). Increasing dilution had no positive effect in the latter case, and the yield could not be improved. The ability to form tricationic species (Scheme 4) such as intermediates **F** (by protonation of substrate **4f**) or **E** (precursor of product **6b**), further advances HF/SbF_5 superacid chemistry, toward the synthesis of highly valued fluorinated diamines, *via* both hydrofluorination and dimerization/fluorination reactions.



Scheme 4 Tricationic species in superacid.

Conclusion

In summary, we have showed that the hydrofluorination reaction in superacid HF/SbF_5 can be extended to polyfunctional substrates to form novel fluorinated key building blocks. In addition, the dramatic effect of substitution on the superelectrophilic character of the ammonium–carbenium dications, and thus on the hydrofluorination reaction, has been emphasized. Interestingly, an original homodimerization/fluorination reaction occurred starting from methyl substituted unsaturated substrates, leading to fluorinated symmetrical diamine synthesis. Similar intermolecular reactions between polycationic superelectrophiles and unsaturated partners could be exploited in synthetic methodologies to access to fluorinated highly valued products.

Experimental details

General method

The authors draw the reader's attention to the dangerous features of superacidic chemistry. Handling of hydrogen fluoride and antimony pentafluoride must be done by experienced chemists with all the necessary safety arrangements in place.

Reactions performed in superacid were carried out in a sealed Teflon® flask with a magnetic stirrer. No further precautions have to be taken to prevent the mixture from moisture (test reaction worked out in anhydrous conditions leads to the same results as expected). Yields refer to isolated pure products. ^{1}H, ^{13}C and ^{19}F NMR were recorded on a 300 MHz Brüker spectrometer using $CDCl_3$ as solvent. Melting points were determined in a capillary tube and are uncorrected. High-resolution mass spectra were performed on a Micromass ZABSpec TOF by the Centre Regional de Mesures Physiques de l'Ouest, Université Rennes (France). All separations were done under flash-chromatography conditions on silica gel (15–40 μm).

Optimized procedure in superacidic media

To a mixture of HF/SbF_5 (3 or 6 mL, 7/1 molar ratio) maintained at −20 °C was added the nitrogen derivative (1 or 2 mmol). The mixture was magnetically stirred at the same temperature for the reaction time. The reaction mixture was then neutralized with water–ice–Na_2CO_3, and extracted with dichloromethane (×3). The combined organic phases were dried ($MgSO_4$) and concentrated *in vacuo*. Products were isolated by column chromatography over silica gel.

Compound 2′a: *N*-(2-hydroxypropyl)-4-nitrobenzamide. Optimized procedure (10 min reaction time) was followed, starting from 412 mg of **1a** (2 mmol). Purification by flash column chromatography (99/1, dichloromethane/methanol) afforded 310 mg of the title compound as a white solid (69%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.46 (3H, d, J=6.3 Hz, CH_3CHOH), 3.67 (1H, dd, J=14.9 Hz, J=7.5 Hz, CH_aH$_b$CHOH), 4.21 (1H, dd, J=14.9 Hz, J=9.5 Hz, CH$_a$$H_b$CHOH), 4.94 (1H, m, C$H$OH), 8.10 (2H, d, J=9.0 Hz, CH_{arom}), 8.27 (2H, d, J=9.0 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 21.5 (*C*H_3CHOH), 62.2 (*C*H_2CHOH), 77.4 (*C*HOH), 123.8 (*C*H_{arom}), 129.5 (*C*H_{arom}), 134.2 (*C*$_{arom}$), 149.8 (*C*$_{arom}$), 162.5 (*CO*). MS (GCT, CI$^+$): *m/z* (relative intensity%) 206 [M]$^+$ (100). HRMS (ESI): Calc for $C_{10}H_{10}N_2O_3$: 206.06914, found 206.0692. Mp: 136 °C (CH_2Cl_2/hexane (20/80, v/v)).

Compound 2b: 1-(2-fluoropropyl)piperidine. Optimized procedure (60 min reaction time) was followed, starting from 250 mg of **1b** (2 mmol). Purification by flash column chromatography (97/2/1: dichloromethane/methanol/NH_3 aq.) afforded 209 mg of the title compound as a colourless oil (72%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.23 (3H, dd, $^3J_{HF}$ = 23.6 Hz, J=6.4 Hz, CH_3CHF), 1.36 (2H, m, $CH_2CH_2CH_2$), 1.52 (4H, m, $CH_2CH_2CH_2$), 2.29 (1H, ddd, $^3J_{HF}$ = 31.2 Hz, J=13.9 Hz, J=3.0 Hz, CH_aH$_b$CHF), 2.37 (4H, m, CH_2NCH_2), 2.50 (1H, ddd, $^3J_{HF}$ = 21.6 Hz, J=13.9 Hz, J=7.7 Hz, CH$_a$$H_b$CHF), 4.77 (1H, m incl. app. d, $^2J_{HF}$ = 49.8 Hz, CH$_3$CHF). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 19.9 (d, $^2J_{C\text{-}F}$ = 22 Hz, *C*H_3CHF), 24.5 ($CH_2CH_2CH_2$), 26.3 ($CH_2CH_2CH_2$), 55.4 (CH_2NCH_2), 65.0 (d, $^2J_{C\text{-}F}$ = 21 Hz, *C*H_2CHF), 89.2 (d, $^1J_{C\text{-}F}$ = 167 Hz, CH$_3$*C*HF). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, ppm): δ −173.7. MS (EI, 70 ev): *m/z* (relative intensity%) 146 [M + H]$^+$ (100). HRMS (ESI): Calc for $C_8H_{16}NF$: 145.12668, found 145.1269.

Compound 2c and 2′c. Optimized procedure (10 min reaction time) was followed, starting from 324 mg of **1c** (1.68 mmol). Purification by flash column chromatography (99/1: dichloromethane/methanol) afforded 160 mg of the title compound as a colourless oil (45%). The second compound 1,2,3,4-tetrahydro-4-methyl-6-nitroisoquinoline **2′c** (80 mg, 24%) was then eluted (95/4/1: dichloromethane/methanol/NH_3 aq.). **Compound 2c**: ***N*-(4-nitrobenzyl)-2-fluoropropan-1-amine** ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.27 (3H, dd, $^3J_{HF}$ = 23.9 Hz, J=6.4 Hz, CH_3CHF), 1.66 (1H, broad s, N*H*), 2.70 (2H, m, CH_2CHF), 3.87 (2H, s, Ph-CH_2-NH), 4.75 (1H, m incl. app. d, $^2J_{HF}$ = 49.3 Hz, CH$_3$CHF), 7.45 (2H, d, J=8.8 Hz, CH_{arom}), 8.11 (2H, d, J=8.8 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 17.7 (d, $^2J_{C\text{-}F}$ = 22 Hz, *C*H_3CHF), 51.8 (Ph-*C*H_2-NH), 53.5 (d, $^2J_{C\text{-}F}$ = 20 Hz, *C*H_2CHF), 89.3 (d, $^1J_{C\text{-}F}$ = 165 Hz, CH$_3$*C*HF), 122.6 (*C*H_{arom}), 127.5 (*C*H_{arom}), 146.0 (*C*$_{arom}$), 146.9 (*C*$_{arom}$).^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, ppm): δ −179.6. MS (GCT, CI$^+$): *m/z* (relative intensity%) 212 [M]$^+$ (100). HRMS (ESI): Calc for $C_{10}H_{13}N_2O_2F$: 212.09611, found 212.0967. **Compound 2′c: 1,2,3,4-tetrahydro-4-methyl-6-nitroisoquinoline** ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 1.27 (3H, d, J=7.0 Hz, CH_3CH), 1.97 (1H, broad s, N*H*), 2.76 (1H, dd, J=12.6 Hz, J=6.3 Hz, NHCH_aH$_b$CH), 2.89 (1H, m, NHCH$_2$CH), 3.16 (1H, dd, J=12.6 Hz, J=5.0 Hz, NHCH$_a$$H_b$CH), 4.01 (2H, s, Ph-C$H_2$-NH), 7.08 (1H, d, J=8.5 Hz, CH_{arom}), 7.88 (1H, dd, J=8.4 Hz, J=2.3 Hz, CH_{arom}), 8.02 (1H, d, J=2.3 Hz, CH_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 19.2 (*C*H_3CH), 31.4 (NHCH$_2$*C*H), 48.4 (Ph-*C*H_2-NH), 50.1 (NH*C*H_2CH), 120.3 (*C*H_{arom}), 122.8 (*C*H_{arom}), 126.6 (*C*H_{arom}), 141.4 (*C*$_{arom}$), 142.8 (*C*$_{arom}$), 146.2 (*C*$_{arom}$). MS (GCT, CI$^+$): *m/z* (relative intensity%) 192 [M]$^+$ (100). HRMS (ESI): Calc for $C_{10}H_{12}N_2O_2$: 192.08988, found 192.0907.

Compound 2d: 2-(*N*-(2-fluoropropyl)-*N*-methylamino)ethanol. Optimized procedure (10 min reaction time) was followed, starting from 115 mg of **1d** (1 mmol). Purification by flash column chromatography (94/6: dichloromethane/methanol) afforded 43 mg of the title compound as a colourless oil (31%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.31 (3H, dd, $^3J_{HF}$= 23.6 Hz, J=6.3Hz, CH_3CHF), 2.35 (3H, s, NCH_3), 2.59 (5H, m, HOCH$_2$CH_2N, NCH_2CHF and

O*H*), 3.58 (2H, t, *J*=5.3Hz, HOCH_2CH$_2$N), 4.82 (1H, m incl. app. d, $^2J_{HF}$= 48.9 Hz, CH$_3$C*H*F). ^{13}C NMR (75 MHz, CDCl$_3$, ppm): 18.2 (d, ^{2}J$_{C\text{-}F}$ = 22 Hz, *C*H$_3$CHF), 41.5 (d, ^{4}J$_{C\text{-}F}$ = 1 Hz, N*C*H$_3$), 57.4 (HOCH$_2$*C*H$_2$N), 58.3 (HO*C*H$_2$CH$_2$N), 61.7 (d, ^{2}J$_{C\text{-}F}$ = 21 Hz, N*C*H$_2$CHF), 88.0 (d, ^{1}J$_{C\text{-}F}$ = 166 Hz, CH$_3$*C*HF). ^{19}F {^{1}H} NMR (282 MHz, CDCl$_3$, ppm): –175.7. MS (GCT, CI$^+$): *m*/*z* (relative intensity%) 106(100). HRMS (ESI): Calc for $C_5H_{11}NF$: 104.08755, found 104.0873.

Compound 2e: 2-fluoro-*N*-(2-methoxyethyl)-*N*-methylpropan-1-amine. Optimized procedure (10 min reaction time) was followed, starting from 129 mg of **1e** (1 mmol). Purification by flash column chromatography (96/4: dichloromethane/methanol) afforded 33 mg of the title compound as a colourless oil (22%). ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 1.27 (3H, dd, $^3J_{HF}$=23,6Hz, *J*=6,3Hz, C*H*$_3$CHF), 2.32 (3H, s, NC*H*$_3$), 2.55 (2H, m, NC*H*$_2$CHF), 2.62 (2H, t, *J*=5.6Hz, MeOCH$_2$C*H*$_2$N), 3.31 (3H, s, OC*H*$_3$), 3.44 (2H, t, *J*=5.6Hz, MeOC*H*$_2$CH$_2$N), 4.79 (1H, m incl. app. d, $^2J_{HF}$= 49.7 Hz, CH$_3$C*H*F). ^{13}C NMR (75 MHz, CDCl$_3$, ppm): 19.7 (d, ^{2}J$_{C\text{-}F}$ = 22 Hz, *C*H$_3$CHF), 43.8 (d, ^{4}J$_{C\text{-}F}$ = 1 Hz, N*C*H$_3$), 57.6 (MeOCH$_2$*C*H$_2$N), 59.2 (O*C*H$_3$), 63.5 (d, ^{2}J$_{C\text{-}F}$ = 21 Hz, NC*H*$_2$CHF), 71.1 (MeO*C*H$_2$CH$_2$N), 89.6 (d, ^{1}J$_{C\text{-}F}$ = 166 Hz, CH$_3$*C*HF). ^{19}F {^{1}H} NMR (282 MHz, CDCl$_3$, ppm): –174.9. MS (GCT, CI$^+$): *m*/*z* (relative intensity%) HRMS (ESI): Calc for $C_7H_{17}NOF$: 150.1294, found 150.1287.

Compound 2f: methyl 2-(*N*-(2-fluoropropyl)-*N*-methylamino)-acetate

Optimized procedure (10 min reaction time) was followed, starting from 143 mg of **1f** (1 mmol). Purification by flash column chromatography (99/1: dichloromethane/methanol) afforded 57 mg of the title compound as a colourless oil (35%). ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 1.25 (3H, dd, $^3J_{HF}$= 23.6 Hz, *J*=6.3Hz, C*H*$_3$CHF), 2.41 (3H, s, NC*H*$_3$), 2.64 (2H, m, C*H*$_2$CHF), 3.33 (2H, broad s, MeOOCC*H*$_2$N), 3.64 (3H, s, COOC*H*$_3$), 4.77 (1H, m incl. app. d, $^2J_{HF}$= 49.7 Hz, CH$_3$C*H*F). ^{13}C NMR (75 MHz, CDCl$_3$, ppm): 19.5 (d, ^{2}J$_{C\text{-}F}$ = 22 Hz, C*H*$_3$CHF), 43.3 (d, ^{4}J$_{C\text{-}F}$ = 1 Hz, N*C*H$_3$), 51.8 (COO*C*H$_3$), 58.8 (d, ^{4}J$_{C\text{-}F}$ = 2 Hz, MeOOC*C*H$_2$N), 62.1 (d, ^{2}J$_{C\text{-}F}$ = 20 Hz, *C*H$_2$CHF), 89.9 (d, ^{1}J$_{C\text{-}F}$ = 166 Hz, CH$_3$*C*HF), 171.8 (*CO*). ^{19}F {^{1}H} NMR (282 MHz, CDCl$_3$, ppm): –175.7. MS (GCT, CI$^+$): *m*/*z* (relative intensity%) 165(20), 106(100).

Compound 2g: methyl 2-(*N*-(2-fluoropropyl)-*N*-methylacetate)-acetate. Optimized procedure (10 min reaction time) was followed, starting from 201 mg of **1g** (1 mmol). Purification by flash column chromatography (dichloromethane) afforded 132 mg of the title compound as a colourless oil (60%). ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 1.21 (3H, dd, ^{3}J$_{HF}$= 23.7 Hz, *J*=6.2 Hz, C*H*$_3$CHF), 2.85 (2H, m, C*H*$_2$CHF), 3.56 (4H, d, *J*=4.2 Hz, MeOOCC*H*$_2$N), 3.63 (6H, s, COOC*H*$_3$), 4.79 (1H, m incl. app. d, ^{2}J$_{HF}$= 49.6 Hz, CH$_3$C*H*F). ^{13}C NMR (75 MHz, CDCl$_3$, ppm): 19.1 (d, ^{2}J$_{CF}$= 23 Hz, C*H*$_3$CHF), 51.9 (COO*C*H$_3$), 56.2 (MeOOC*C*H$_2$N), 59.8 (d, ^{2}J$_{CF}$= 20 Hz, *C*H$_2$CHF), 91.1 (d,^{1}J$_{CF}$= 165 Hz, CH$_3$*C*HF), 172.0 (*CO*). ^{19}F {^{1}H} NMR (282 MHz, CDCl$_3$, ppm): –176.0. MS (GCT, CI$^+$): *m*/*z* (relative intensity%) 221(15), 201(15), 174(50), 162(100). HRMS (ESI): Calc for $C_{20}H_{38}N_4O_2F$: 385.29788, found 385.2975.

Compound 2h: ethyl 3-(*N*-(2-fluoropropyl)-*N*-methylamino) propanoate. Optimized procedure (10 min reaction time) was followed, starting from 171 mg of **1h** (1 mmol). Purification by flash column chromatography (99/1: dichloromethane/methanol) afforded 105 mg of the title compound as a colourless oil (55%). ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 1.23 (3H, t, *J*=6.9Hz, C*H*$_3$CH$_2$O), 1.27 (3H, dd, $^3J_{HF}$= 22.9 Hz, *J*=6.3Hz, C*H*$_3$CHF), 2.29 (3H, s, NC*H*$_3$), 2.44 (2H, t, *J*=7.1Hz, NCH$_2$C*H*$_2$COOEt), 2.51 (2H, m, C*H*$_2$CHF), 2.75 (2H, t, *J*=7.3Hz, NC*H*$_2$CH$_2$COOEt), 4.11 (2H, q, *J*=7.1Hz, CH$_3$C*H*$_2$O), 4.77 (1H, m incl. app. d, $^2J_{HF}$= 50.9 Hz, CH$_3$C*H*F). ^{13}C NMR (75 MHz, CDCl$_3$, ppm): 14.5 (*C*H$_3$CH$_2$O), 19.6 (d, ^{2}J$_{C\text{-}F}$ = 22 Hz, *C*H$_3$CHF), 33.1 (NCH$_2$*C*H$_2$COOEt), 43.1 (d, ^{4}J$_{C\text{-}F}$ = 1 Hz, N*C*H$_3$), 53.8 (N*C*H$_2$CH$_2$COOEt), 60.7 (CH$_3$*C*H$_2$O), 62.9 (d, ^{2}J$_{C\text{-}F}$ = 21.2 Hz, *C*H$_2$CHF), 89.5 (d, ^{1}J$_{C\text{-}F}$ = 165 Hz, CH$_3$*C*HF), 172.9 (s, *CO*). ^{19}F {^{1}H} NMR (282 MHz, CDCl$_3$, ppm): –175.6. MS (GCT, CI$^+$): *m*/*z* (relative intensity%) 193(15), 146(100). HRMS (ESI): Calc for $C_9H_{19}NO_2F$: 192.1400, found 192.1398.

Compound 2i: 2-(*N*-(2-fluoropropyl)-*N*-methylamino)acetonitrile. Optimized procedure (10 min reaction time) was followed, starting from 111 mg of **1i** (1 mmol). Purification by flash column chromatography (100%: dichloromethane) afforded 81 mg of the title compound as a colourless oil (61%). ^{1}H NMR (300 MHz, CDCl$_3$, ppm) : 1.26 (3H, dd, $^3J_{HF}$= 23.7 Hz, *J*=6.3Hz, C*H*$_3$CHF), 2.36 (3H, s, NC*H*$_3$), 2.53 (2H, m, C*H*$_2$CHF), 3.53 (2H, broad s, NCC*H*$_2$N), 4.76 (1H, m incl. app. d, $^2J_{HF}$= 50.2 Hz, CH$_3$C*H*F). ^{13}C NMR (75 MHz, CDCl$_3$, ppm): 19.2 (d, ^{2}J$_{C\text{-}F}$ = 22 Hz, *C*H$_3$CHF), 43.3 (N*C*H$_3$), 46.2 (d, ^{4}J$_{C\text{-}F}$ = 2.7 Hz, NCC*H*$_2$N), 60.9 (d, ^{2}J$_{C\text{-}F}$ = 20 Hz, *C*H$_2$CHF), 89.6 (d, ^{1}J$_{C\text{-}F}$ = 166 Hz, CH$_3$*C*HF), 115.2 (*CN*). ^{19}F {^{1}H} NMR (282 MHz, CDCl$_3$, ppm): –176.5. MS (GCT, CI$^+$): *m*/*z* (relative intensity%) 132(20), 85(100). HRMS (ESI): Calc for $C_6H_{11}N_2F$: 130.09063, found 130.0905.

Compound 2j: 3-(*N*-(2-fluoropropyl)-*N*-methylamino)propanitrile. Optimized procedure (10 min reaction time) was followed, starting from 124 mg of **1j** (1 mmol). Purification by flash column chromatography (100%: dichloromethane) afforded 67 mg of the title compound as a colourless oil (46%). ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 1.28 (3H, dd, $^3J_{HF}$= 23.8 Hz, *J*=6.3Hz, C*H*$_3$CHF), 2.33 (3H, s, NC*H*$_3$), 2.44 (2H, t, *J*=6.9Hz, NCC*H*$_2$CH$_2$N), 2.61 (2H, m, *C*H$_2$CHF), 2.77 (2H, t, *J*=6.9Hz, NCCH$_2$C*H*$_2$N), 4.76 (1H, m incl. app. d, $^2J_{HF}$= 49.4 Hz, CH$_3$C*H*F). ^{13}C NMR (75 MHz, CDCl$_3$, ppm): 16.7 (NC*C*H$_2$CH$_2$N), 19.4 (d, ^{2}J$_{C\text{-}F}$ = 22 Hz, *C*H$_3$CHF), 42.8 (N*C*H$_3$), 53.6 (NCCH$_2$*C*H$_2$N), 62.5 (d, ^{2}J$_{C\text{-}F}$ = 21 Hz, *C*H$_2$CHF), 89.7 (d, ^{1}J$_{C\text{-}F}$ = 166 Hz, CH$_3$*C*HF), 119.2 (*CN*). ^{19}F {^{1}H} NMR (282 MHz, CDCl$_3$, ppm): –175.5. MS (GCT, CI$^+$): *m*/*z* (relative intensity%) 106(38), 99(100). HRMS (ESI): Calc for $C_7H_{13}N_2F$: 145.1141, found 145.1135.

Compound 5a: 1-(4-(2-fluoropropyl)piperazin-1-yl)ethanone. Optimized procedure (10 min reaction time) was followed, starting from 168 mg of **4a** (1 mmol). Purification by flash column chromatography (97/2/1: dichloromethane/methanol/NH$_3$ aq.) afforded 130 mg of the title compound as a colourless oil (69%). ^{1}H NMR (300 MHz, CDCl$_3$, ppm): 1.34 (3H, dd, $^3J_{HF}$ = 23.7 Hz, *J*=6.4 Hz, C*H*$_3$CHF), 2.09 (3H, s, C*H*$_3$CO), 2.53 (6H, m, C*H*$_2$NC*H*$_2$ and C*H*$_2$CHF), 3.48 (2H, t, *J*=5.1 Hz, C*H*$_a$H$_b$NC*H*$_a$H$_b$), 3.64 (2H, m, CH$_a$*H*$_b$NCH$_a$*H*$_b$), 4.87 (1H, m incl. app. d, $^2J_{HF}$ = 49.6 Hz, CH$_3$C*H*F). ^{13}C NMR (75 MHz,

$CDCl_3$, ppm): 19.3 (d, J = 22 Hz, CH_3CHF), 21.3 (CH_3CO), 41.4 (CH_2NCH_2), 46.2 (CH_2NCH_2), 53.3 (CH_2NCH_2), 53.7 (CH_2NCH_2), 63.5 (d, J = 20 Hz, CH_2CHF), 88.9 (d, J = 167 Hz, CH_3CHF), 168.9 (*CO*). ^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$, ppm): −174.3. MS (EI, 70 ev): *m/z* (relative intensity%) 189 [M + H^+]$^+$ (20). HRMS (ESI): Calc for $C_9H_{16}N_2O$: 168.12626, found 168.1263.

Compound 5b: 1-(4-(2-fluoro-2-methyl-propyl)-piperazin-1-yl)-ethanone. Optimized procedure (10 min reaction time) was followed, starting from 182 mg of **4b** (1 mmol). Purification by flash column chromatography (98.5/1/0.5: dichloromethane/methanol/NH_3 aq) afforded 171 mg of the title compound as a colourless oil (85%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.34 (6H, d, $^3J_{HF}$=21.4 Hz, CH_3CFCH_3), 2.05 (3H, s, CH_3CO), 2.42 (2H, d, $^3J_{HF}$=22.8 Hz, CH_2CF), 2.52 (2H, 2t, *J*=5.1 Hz, CH_2NCH_2), 2.56 (2H, 2t, *J*=5.1 Hz, CH_2NCH_2), 3.45 (2H, t, *J*=5.1 Hz, CH_2NCH_2), 3.61 (2H, t, *J*=5.1 Hz, CH_2NCH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 21.7 (s, CH_3, *CH3*CO), 25.5 (d,$^2J_{C\text{-}F}$ = 24 Hz, CH_3CFCH_3), 41.9 (CH_2NCH_2), 46.8 (CH_2NCH_2), 54.6 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, CH_2NCH_2), 54.8 (d, $^4J_{C\text{-}F}$ = 3.1 Hz, CH_2NCH_2), 66.5 (d, $^2J_{C\text{-}F}$ = 21 Hz, CH_2CF), 96.9 (d,$^1J_{C\text{-}F}$= 240 Hz, CH_3CFCH_3), 169.3 (*CO*). ^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$, ppm): −139.6. MS (GCT, CI^+): *m/z* (relative intensity%) 202(50), 182(60), 141(100). HRMS (ESI): Calc for $C_{10}H_{19}N_2OF$: 202.14814, found 202.1461.

Compound 5c: 1-(4-(2-fluoro-2-phenyl-propyl)-piperazin-1-yl)-ethanone. Optimized procedure (10 min reaction time) was followed, starting from 244 mg of **4c** (1 mmol). Purification by flash column chromatography (96.5/3/0.5: dichloromethane/methanol/NH_3 aq) afforded 108 mg of the title compound as a colourless oil (41%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.72 (3H, d, $^3J_{HF}$=22.7 Hz, CH_3CFPh), 2.05 (3H, s, CH_3CO), 2.57 (6H, m, CH_2NCH_2 and CH_2CFPh), 3.37 (2H, m, CH_2NCH_2), 3.55 (2H, m, CH_2NCH_2), 7.32 (5H, m, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 19.8 (CH_3CO), 23.0 (d,$^2J_{C\text{-}F}$ = 24 Hz, CH_3CFPh), 40.0 (CH_2NCH_2), 44.8 (CH_2NCH_2), 52.6 (CH_2NCH_2), 52.8 (CH_2NCH_2), 65.7 (d, $^2J_{C\text{-}F}$ = 23 Hz, CH_2, CH_2CFPh), 96.8 (d,$^1J_{C\text{-}F}$= 173 Hz, CH_2CFPh), 122.8 (CH_{arom}), 122.9 (CH_{arom}), 125.9 (CH_{arom}), 126.5 (CH_{arom}), 142.0 (d,$^2J_{C\text{-}F}$= 22 Hz, C_{arom}), 167.3 (*CO*). ^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$, ppm): −148.5. MS (GCT, CI^+): *m/z* (relative intensity%) 244 (25), 172(40), 141(100). HRMS (ESI): Calc for $C_{15}H_{21}N_2OF$: 264.16379, found 264.1656.

Compound 5f: *N*-(3-(4-acetylpiperazin-1-yl)-2-fluoro-2-methyl-propyl)-4-nitrobenzamide. Optimized procedure (10 min reaction time) was followed, starting from 374 mg of **4f** (1 mmol). Purification by flash column chromatography (98/2: dichloromethane/methanol) afforded 226 mg of the title compound as a colourless oil (62%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.34 (3H, d, $^3J_{HF}$=21.8 Hz, CH_3CF), 2.01 (3H, s, CH_3CO); 2,60 (6H, m, CH_2NCH_2 and CH_2CF), 3.39 (2H, t, *J* =4.7 Hz, $CH_aH_bNCH_aH_b$), 3.70 (4H, m, $CH_aH_bNCH_aH_b$ and CH_2CF), 7.63 (1H, t, *J* =4.9 Hz; N*H*), 7.96 (2H, d, *J* =8.6 Hz; H_{arom}), 8.23 (2H, d, *J*=8.6 Hz; H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 21.7 (CH_3CO), 22.4 (d,$^2J_{C\text{-}F}$ = 23 Hz, CH_3CF), 41.9 (CH_2NCH_2), 46.7 (CH_2NCH_2), 47.3 (d, $^2J_{C\text{-}F}$ = 22 Hz, CH_2CF), 54.8 (CH_2NCH_2), 55.2 (CH_2NCH_2), 64.7 (d, $^2J_{C\text{-}F}$ = 20 Hz, CH_2CF), 97.2 (d,$^1J_{C\text{-}F}$= 172 Hz, *CF*), 124.3 (CH_{arom}), 128.6 (CH_{arom}), 140.3 (C_{arom}), 150.1 (C_{arom}), 166.1 (*CO*), 169.3 (*CO*). ^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$, ppm): −154.2. HRMS (ESI): Calc for [M − HF]$^+$ ($C_{17}H_{22}N_4O_4$) : 346.16411, found 346.1625.

Compound 6b: 1-(4-(7-(4-acetyl-piperazin-1-yl)-4-fluoro-4-methyl-heptyl)-piperazin-1-yl)ethanone. Optimized procedure (10 min reaction time) was followed, starting from 182 mg of **4g** (1 mmol). Purification by flash column chromatography (89.5/10/0.5: dichloromethane/methanol/NH_3 aq) afforded 126 mg of the title compound as a colourless oil (66%). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.28 (3H, d, $^3J_{HF}$=21.7 Hz, CH_3CF), 1.59 (8H, m, $NCH_2CH_2CH_2$), 2.05 (6H, s, CH_3CO), 2.32 (12H, m, CH_2NCH_2); 3,43 (4H, t, *J*=4.8 Hz, CH_2NCH_2), 3,58 (4H, t, *J*=4.8 Hz, CH_2NCH_2). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 21.4 (d,$^3J_{C\text{-}F}$=5 Hz, $NCH_2CH_2CH_2CF$), 21.7 (CH_3CO), 24.5 (d,$^2J_{C\text{-}F}$ = 25 Hz, CH_3CF), 37.5 (d,$^2J_{C\text{-}F}$ = 23 Hz, $NCH_2CH_2CH_2CF$), 41.7 (CH_2NCH_2), 46.6 (CH_2NCH_2), 53.1 (CH_2NCH_2), 53.7 (CH_2NCH_2), 58.8 ($NCH_2CH_2CH_2CF$), 97.3 (d,$^1J_{C\text{-}F}$= 166 Hz, $NCH_2CH_2CH_2CF$), 169.3 (*CO*). ^{19}F {^{1}H} NMR (282 MHz, $CDCl_3$, ppm): −145.5. HRMS (ESI): Calc for $C_{20}H_{38}N_4O_2F$: 385.29788, found 385.2975.

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