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Gem-difluorination in superacid: The dramatic role of halonium ions

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ABSTRACT

In HF/SbF_5, in the presence of CCl_4 or NBS, unsaturated or hydroxylated piperidines yield difluoroanalogues in good yields. The ability to perform hydride abstraction on chloroderivatives, and the ability to form bridged bromonium ions from unsaturated substrates seem to completely influence the reaction course. Some aspects of the mechanism were clarified by DFT calculations.

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1. Introduction

The special properties of fluorine atom [1] can have considerable impact on the behavior of a molecule in a biological environment [2]. As a consequence numerous marketed fluorinated pharmaceuticals have been developed [3]. The advantages to the use of fluorine substitution in drug design have stimulated an enormous amount of research directed toward the discovery of novel fluorination reactions [4]. Based on superacid chemistry, Jacquesy et al. focused their efforts to develop novel methods of fluorination in HF/SbF_5 [5]. This extensive research led to the development of a novel reaction of *gem*-difluorination of nitrogen containing compounds and to the discovery of vinflunine, a novel difluorinated anticancer agent [6]. Then, this novel strategy has been applied to the synthesis of difluorinated analogues of Cinchona alkaloids [7] (Scheme 1). Starting from halogenated or unsaturated amines similar results were obtained using NBS instead of CCl_4 as coreactant [8].

The purpose of this paper is to evaluate the effects of halonium ions and substrate structure on the *gem*-difluorination reaction in superacid HF/SbF_5.

2. Results and discussion

2.1. Gem-difluorination in the presence of CCl_4

In their search for new bioactive compounds Jacquesy et al. investigated the reactivity of *Vinca* and *Cinchona* alkaloids in superacid. In the presence of CCl_4, precursor of activated CCl_3^+ and Cl^- ions in superacid [9], difluorinated analogues of vinorelbine and epiquinine could be selectively obtained (Scheme 1). It has to be pointed out that in both cases only unsaturated nitrogen containing core of the alkaloids (piperidine or quinuclidine) reacted in these conditions. This surprising stability was attributed to a protecting effect provided by polyprotonation of the alkaloids in superacid. Based on these results we decided to study with accuracy the influence of substrate structure on the reaction course.

2.1.1. Results

Firstly, analogously to the reacting part of vinorelbine, the reactivity of unsaturated piperidine was studied in the presence of CCl_4 (Fig. 1 and Table 1).

Starting from 3-ethyl or 4-ethyl derivatives (**1a** or **1b**), difluorinated product **2** was obtained in good yield. Surprisingly, the same result was obtained without external sources of oxidative agent, in the presence of NaCl (entry 3). This intriguing result seems to comfort previous hypothesis concerning the hydride abstracting power of superacid itself [10]. Indeed, it has been

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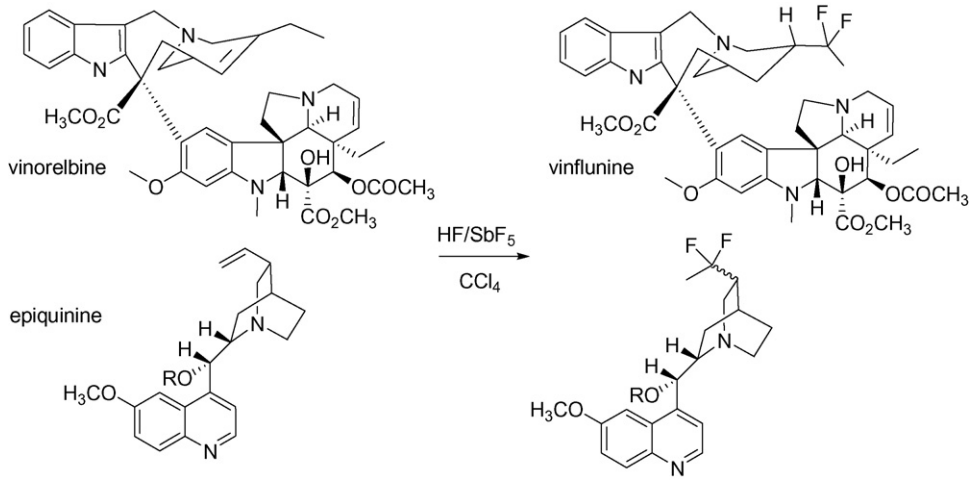


Scheme 1.

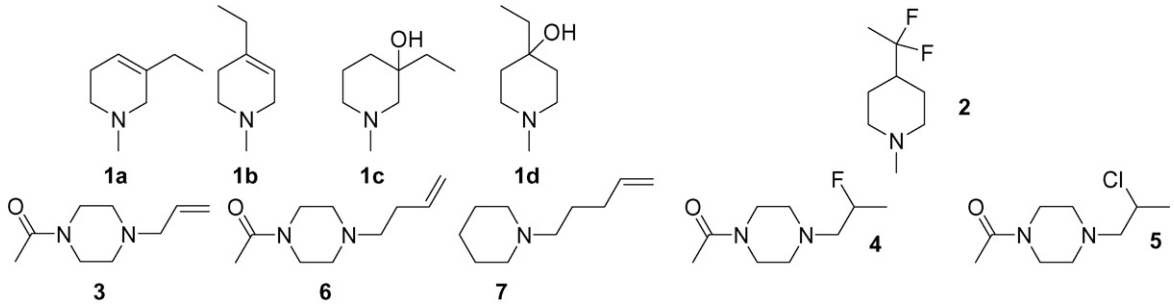


Fig. 1. Structures of compounds 1–7.

confirmed by submitting substrate **1b** in superacid without reactants (entry 4). After reaction in standard conditions (even in milder ones) difluorinated product was obtained in reasonable yield. Beside the confirmation of the hydride abstracting power of HF/SbF_5, this result showed that the same difluorination could be done without chlorine sources. To show an eventual influence of cyclic structure on the reaction course, acyclic starting material reactivity has also been studied, using piperazine **3** as model substrate. In usual conditions, monofluoroderivative **4** was formed in 60% yield, *via* hydrofluorination process [11]. In this case, like in the absence of CCl_4, the hydride abstraction did not occur and monofluoro derivative was obtained (entries 5 and 6). At higher temperature, in the presence of chlorine sources (CCl_4 or NaCl) chloro- and fluoroderivatives were obtained (entries 7 and 8). With longer reaction time (entry 8) the amount of chloroderivative increased at the expense of fluorinated one, demonstrating that fluoroderivative could be an intermediate in the reaction course. However starting from substrates **6** and **7**, where the distance between the double bond and the nitrogen atom increased, only a complex mixture of compounds was obtained and thus even in milder conditions. These results confirmed that the difluorination reaction in the presence of chloride sources strongly depends on the substrate structure. In addition, it appeared that depending on the ability to perform hydride abstraction, and so, on the stability of halonium ion intermediate, difluorination could occur or not. Based on this hypothesis we postulate the following mechanism (Scheme 2).

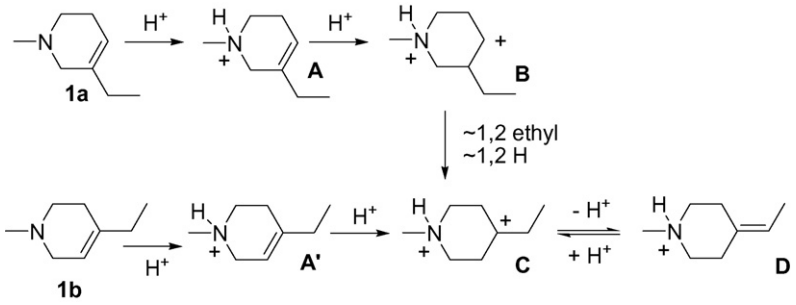
Table 1
Gem-difluorination in HF/SbF_5 in the presence of CCl_4

Entry	Substrate	Temperature (°C)	Time (min)	Product	Yield (%)
1	**1a**	−50	20	**2**	69
2	**1b**	−50	20	**2**	55
3[a]	**1b**	−50	20	**2**	52
4[b]	**1b**	−50	10	**2**	52
5	**3**	−50	10	**4**	60
6[b]	**3**	−20	10	**4**	69
7	**3**	0	10	**4**	45
				5	15
8	**3**	0	240	**4**	18
				5	33
9	**4**	0	240	**4**	12
				5	44
10	**6**	0	10	Complex mixture	
11	**7**	0	10	Complex mixture	

[a] Reaction performed in the presence of NaCl instead of CCl_4.
[b] Reaction performed without addition of CCl_4.

2.1.2. Mechanism

The selective formation of only one difluorinated product starting from either 3- or 4-ethyl tetrahydropyridines encouraged us to postulate the formation of the same key ammonium–carbenium intermediate **C** (Scheme 2). Starting from **1a**, after protonation of the nitrogen atom followed by double bond protonation, dication **B** undergoes successive 1,2-ethyl and hydride shifts and leads to the more stable intermediate **C** (inductive stabilization). After successive double protonation of **1b**, the same primordial intermediate could be obtained. Regarded to the isolation of an exo double bond intermediate after reaction of vinorelbine **1** in the same conditions [5,6] and regarded to the already demonstrated equilibrium between carbenium and double bond starting from unsaturated amines [11], a similar equilibrium



Scheme 2.

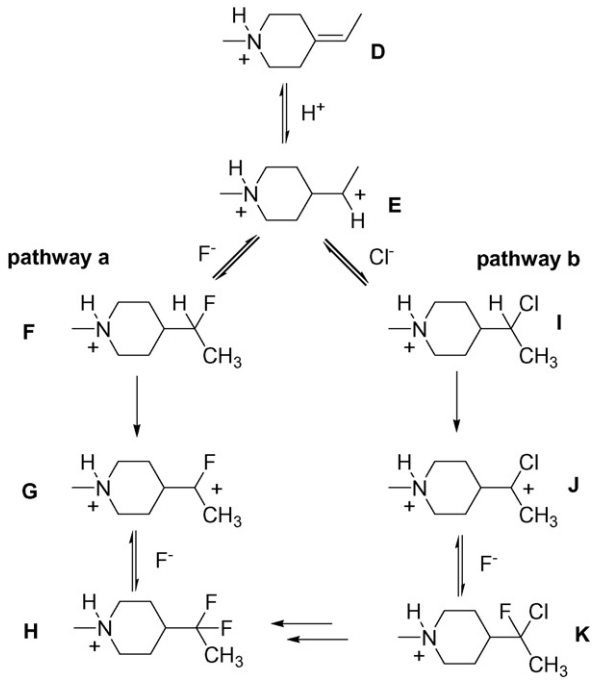
could be postulated between **C** and **D**. It has to be pointed out that starting from vinorelbine, no ethyl shifts occurred, as only vinorelbine isomer with exo double bond in the 3 position of the piperidine ring has been isolated. At this stage we could postulate that the spatial geometry of the polyprotonated vinorelbine could disfavor isomerisation of the piperidine scaffold.

The formation of difluoropiperidine **2** led to two postulated mechanistic pathways from intermediate **D** (Scheme 3). After protonation of **D**, ammonium–carbenium **E** can be trapped by fluoride ions of the media to give **F**, precursor of the fluoronium ion intermediate **G** [12], obtained after hydride abstraction with activated CCl_3^+ [13]. A second fluorination leads to ammonium ion **H** precursor of product **2**. Another possibility (pathway b), in the presence of chloride sources, is the chlorination of **E**, followed by hydride abstraction to give α-chloronium intermediate **J**, stabilized by back donation of the unbond electron pair of chlorine [12]. After fluorination and halogen exchange classical process, the ammonium ion **H** is formed.

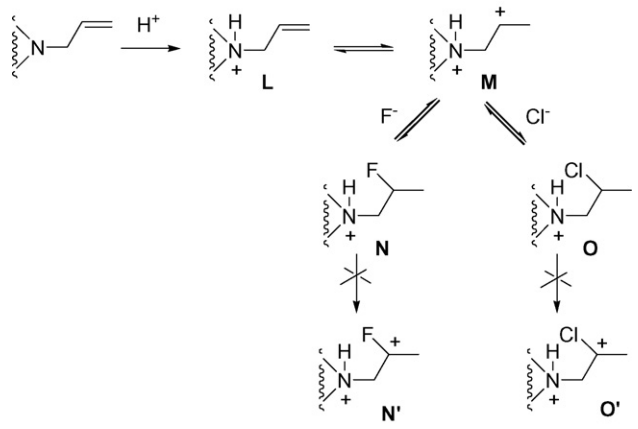
In summary, the obtained results starting from unsaturated piperidines emphasized different key points: firstly, the *gem*-difluorination process in the presence of CCl_4 is strongly dependant on the ability to perform oxidation with activated CCl_3^+ [13] or superacid itself [10]. Secondly, in the absence of chloride sources (entry 6), the reaction still took place, which is in accordance with pathway a. But, in the presence of chloride sources (CCl_4 or NaCl) pathway b could be an alternative route to difluorinated product. Indeed, chloroderivative of anhydrovinblastine has previously been isolated after reaction of anhydrovinblastine at low temperature in the presence of CCl_4 [6], and so the formation of chloride ion **I** can be postulated in our case. In order to evaluate this hypothesis, theoretical calculations at the density functional level have been performed [14]. The most energetic demanding step in the proposed mechanisms appeared to be the hydride abstraction from **F** to **G** and from **I** to **J**. For such an endothermic step, the Hammond's postulate states that the transition structure is very close to the intermediate, in energy and in geometry [17], and then allows comparing the relative energies of the intermediates instead of the transition structures. Consequently, we focused on the comparison of enthalpies of halonium ions **G** and **J**. Considering reactions with CCl_3^+ and neglecting solvent effects, the formation of **J** from **I** is slightly less favorable, by 0.3 kcal/mol, than the formation of **G** from **F** [18]. Consequently, in the presence of chloride sources, and thus even if no chlorofluoroderivatives have been isolated, pathway b can be considered as an alternative route to difluorinated product.

Starting from substrate **3**, depending on reaction conditions, monofluoro- and/or chloroderivatives can be formed. The absence of difluorination starting from substrate **3** confirmed the dramatic effect of the substrate shape on the reaction course and allowed us to propose the following mechanism (Scheme 4).

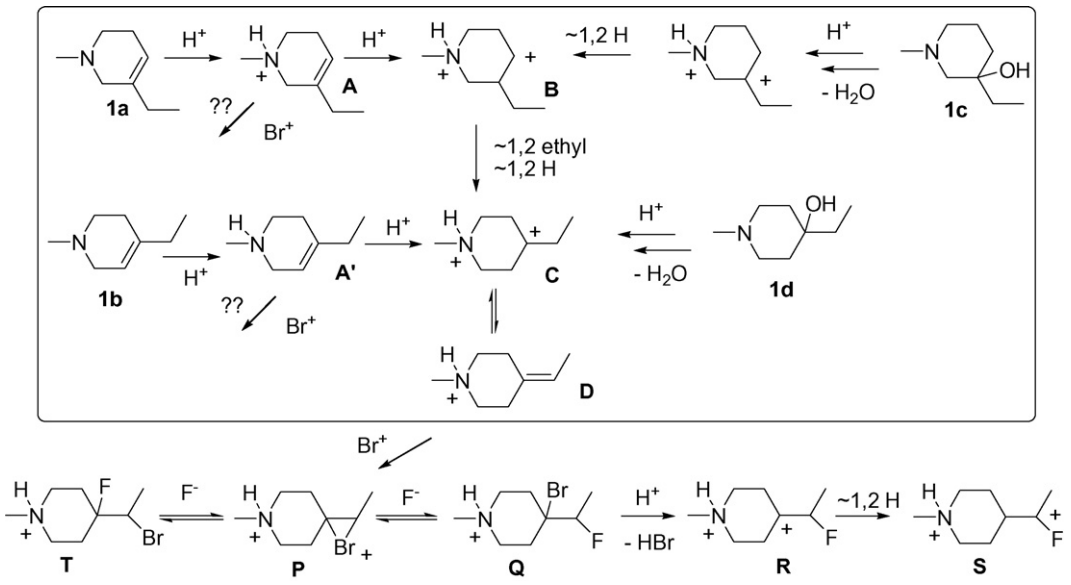
After N-protonation, the strong acidity of the media allows the formation of a superelectrophilic dication **M**. The activation of the electrophilic site, by the proximity of the ammonium ion allows fluorination to give ion **N**, or in the presence of chloride ion, ion **O** after chlorination. To confirm the postulated equilibriums between **N**, **M** and **O**, additional experiments have been performed. After 4 h at 0 °C, using fluorinated compound **4** as substrate, 44% of



Scheme 3.



Scheme 4.



Scheme 5.

chlorinated product **5** was formed beside 12% of fluorinated substrate **4** (entry 9), whereas in the same conditions, starting from chlorinated substrate **5**, only traces of fluorinated product **4** could be detected beside chlorinated substrate **5**. These results seem to comfort that at 0 °C, equilibriums between **N**, **M** and **O** are clearly displaced toward the formation of chlorinated product. In these conditions the equilibriums are favored by increasing the temperature, and in the presence of chloride ions, chlorinated product formation is clearly favored. The absence of difluorination starting from amine **3** could be explained by the difficulty to perform hydride abstraction. Indeed the formation of α-halonium ion in β position of ammonium ion is disfavored in comparison of similar α-halonium ion formation in δ position of ammonium ion, like observed in piperidine series. To evaluate this hypothesis, calculations at the density functional level have been performed. Using the Hammond's postulate as above, we compared the enthalpy of **G** from **F** (Scheme 3) to the enthalpy of **N′** from **N** (Scheme 4). The obtained results showed that the formation of **N′** is significantly disfavored by 31.2 kcal/mol than the formation of **G**. Not surprisingly the increase of the distance from ammonium ion favors the hydride abstraction, and further confirms the difficulty to perform difluorination on allylic amines in the presence of hydride abstracting agent. Starting from homoallylic substrate **6** or from **7** the reaction became not selective, probably due to unwanted isomerisation.

2.2. Gem-difluorination in the presence of N-bromosuccinimide (NBS)

Interestingly, Jacquesy et al. demonstrated that *gem*-difluorination of unsaturated amines can also be performed in superacid in the presence of *N*-bromosuccinimide (NBS) [8], whereas in similar conditions, vinorelbine led to difluorinated vinflunine in lower yield [5]. In order to evaluate the ability to perform such reaction on cyclic unsaturated amines we investigated the *gem*-difluorination reaction in the presence of NBS on piperidines.

Table 2
Gem-difluorination in HF/SbF_5 in the presence of NBS

Entry	Substrate	Temperature (°C)	Time (min)	Product	Yield (%)
1	**1a**	−45	20	**2**	89
2	**1b**	−45	20	**2**	95
3	**1c**	−45	20	**2**	70
4	**1d**	−45	20	**2**	70

2.2.1. Results

The obtained results are reported in Table 2.

We focused our attention on the behavior of unsaturated or hydroxylated piperidines **1a–d** as model substrates, analogously to the unsaturated piperidine scaffold of the bisindolic *Vinca* derivatives. In all cases difluorinated product **2** was selectively obtained in good yields. These results deserved several comments and allowed us to propose the following mechanism (Scheme 5).

2.2.2. Mechanism

The regioselectivity of the difluorination process was in accordance with the formation of the exo double bond ammonium intermediate **D**, which could be obtained analogously to previously postulated formation after reaction in the presence of CCl_4 (Scheme 2). For hydroxy analogues **1c** or **1d**, after nitrogen and oxygen atom protonation, elimination of H_2O followed by alkyl and hydride successive shifts, stabilized intermediate **C** could also be formed. In the presence of NBS, source of "Br^+" in superacid [19], electrophilic addition to the double bond could occur, leading to the bridged bromonium ion **P** [20]. Ring opening of bromonium ion **P** by solvated fluoride ion in polymeric anion form $Sb_nF_{5n+1}^-$ [21] can give bromofluoroderivatives **T** or **Q**. The irreversible elimination of HBr could displace the equilibrium toward the formation of **R** which could give the more stable α-fluoronium ion **S** precursor of product **2**. Taking into account the previously observed reactivity of diallylamine, and the identification of bromofluoroderivatives as intermediate in the reaction course [8], we supposed that the formation of bridged bromonium occured in cyclic series. Consequently the electrophilic attack of "Br^+" to the cyclic double bond of intermediates **A**, **A′** and **D**, leading to bridged bromonium ions cannot be ruled out, even if whatever reaction conditions, even milder ones, no bromofluoroderivatives have been isolated. In summary, in the presence of NBS, the outcome of the reaction clearly depends on the ability to perform electrophilic Br^+ attack. In piperidine cases **1a–d**, the favorable isomerisation (formation of the more stable carbocationic intermediate) allows the formation of an exo double bond in the 4 position of piperidine ring. With the

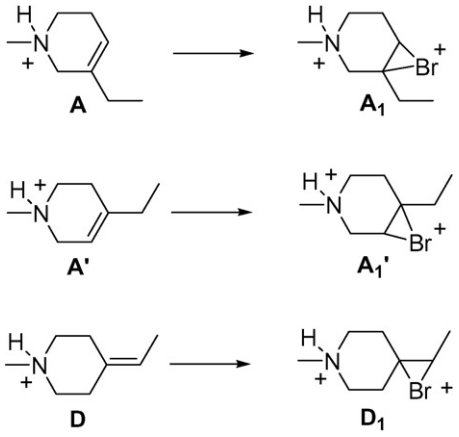


Fig. 2.

exo double bond in this position, electrophilic Br^+ attack appears to be possible allowing the formation of the *gem*-difluoroderivatives. At this stage, we could postulate that the difficulty to perform difluorination on vinorelbine using NBS as coreactant could be due to the difficulty to perform Br^+ electrophilic attack on the double bond in the 3 position of the piperidine ring and thus even after formation of an exo double bond in this position. Again the distance between the double bond reacting site and the protonated nitrogen atom and also the geometric structure of unsaturated amine have a real influence on the reaction course. In order to confirm this hypothesis, we decided to perform theoretical calculations on ammonium–bromonium intermediates (Fig. 2).

In calculations at the density functional level [14] we compared enthalpies of bridged bromonium ions $\mathbf{A_1}$, $\mathbf{A_1}'$ and $\mathbf{D_1}$. The formation of $\mathbf{A_1}$ and $\mathbf{A_1}'$ are, respectively 14.1 kcal/mol and 11.4 kcal/mol less favorable than the formation of $\mathbf{D_1}$ from ammonium **D**. In addition, the formation of corresponding opened bromonium ions is completely disfavored, result in accordance with previous studies [20]. In conclusion, the formation of exocyclic bridged bromonium ion $\mathbf{D_1}$ seems to be much more favorable, confirming the previously postulated mechanism.

3. Conclusion

In summary, we showed a real influence of substrate geometric shape on the *gem*-difluorination reaction in the presence of CCl_4 or NBS. Beside, the dramatic effect of halonium ion on reaction course has been showed, explaining the observed difference of selectivity depending on reactants. In addition, theoretical calculations confirmed a real impact of cyclic shape on halonium ion stability and so, on the reaction course. To conclude, the ability to perform hydride abstraction on chloroderivatives, and the ability to form bridged bromonium ions from unsaturated substrates seem to completely influence the reaction course and so the selectivity of the difluorination process. Further work is currently under progress in order to confirm halonium ions and substrate geometric structures influences.

4. Experimental

4.1. General methods

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 stirring. No further precautions have to be taken to prevent mixture from moisture (test reaction worked out in anhydrous conditions leads as expected to the same results).

Yields refer to isolated pure products. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR were recorded on a 300 MHz Bruker spectrometer using $CDCl_3$ as solvent and TMS (1H, 13C) as internal standard or C_6F_6 (^{19}F) as external standard.

Mass spectra were measured in the electron impact (EI) mode. High-resolution mass spectra were performed on a Micromass ZABSpec TOF by the Centre Régional de Mesures Physiques de l'Ouest, Université Rennes (France).

All separations were done under flash-chromatography conditions on silica gel (15–40 μm).

4.2. General procedure in superacidic media

To a mixture of SbF_5 (3 g, 0.014 mol) and HF (3 g, 0.15 mol) maintained at −45 °C in a Teflon® flask, was added substrate (1 mmol) with or without chloride source (CCl_4 (1.2 equiv.)) or NBS (1.2 equiv.). The reaction mixture was magnetically stirred at the same temperature for 20 min. The reaction mixture was then neutralized with water/ice (100 mL) and sodium carbonate (25 g) and worked-up by usual manner. The products were isolated by column chromatography over SiO_2.

4.3. Compound 2

After reaction of substrate **1a** (125 mg, 1 mmol), following the general procedure, 4-(1,1-difluoroethyl)-1-methylpiperidine **2** (112 mg, 69%) was eluted with the mixture CH_2Cl_2/MeOH/NH_3 aq. (97/2/1).

^{1}H NMR (300 MHz, $CDCl_3$): 1.47 (t, $^3J_{HF}$ = 18.9 Hz, 3H, $H_{2'}$); 1.62 (m, 5H, H_3, H_4 and H_5); 1.83 (t, ^3J = 11.7 Hz, 2H, H_{2ax} and H_{6ax}); 2.26 (s, 3H, N–CH_3); 2.92 (d, ^3J = 10.0 Hz, 2H, H_{2eq} and H_{6eq}).

^{13}C NMR (75 MHz, $CDCl_3$): 21.0 (t, $^2J_{CF}$ = 28 Hz, CH_3, $C_{2'}$); 26.1 (t, $^3J_{CF}$ = 4 Hz, $2CH_2$, C_3 and C_5); 43.3 (t, $^2J_{CF}$ = 24 Hz, 1CH, C_4); 46.6 (s, $1CH_3$, N–CH_3); 55.6 (s, $2CH_2$, C_2 and C_6); 125.5 (t, $^1J_{CF}$ = 238 Hz, $C_{1'}$). ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$, ppm): −96.5. MS (70 eV), *m*/*z* (%): 163(40), 162(100), 141(32). HRMS: Calc. for $C_8H_{14}NF_2$: 162.10943, found 162.1089.

4.4. Compound 4

After reaction of substrate **3** (168 mg, 1 mmol), following the general procedure, 1-(4-(2-fluoropropyl)piperazin-1-yl)ethanone **4** (130 mg, 69%) was eluted with the mixture CH_2Cl_2/MeOH/NH_3 aq. (97/2/1).

^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.34 (3H, dd, $^3J_{HF}$ = 23.7 Hz, ^3J = 6.4 Hz, $H_{3''}$), 2.09 (3H, s, H_2), 2.53 (6H, m, $H_{3'}$ $H_{5'}$ and $H_{1''}$), 3.48 (2H, t, ^3J = 5.1 Hz, $H_{2'ax}$ and $H_{6'ax}$), 3.64 (2H, m, $H_{2'eq}$ and $H_{6'eq}$), 4.87 (1H, dm, $^2J_{HF}$ = 49.6 Hz, $H_{2''}$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 19.3 (CH_3, d, $^2J_{CF}$ = 22 Hz, $C_{3''}$), 21.3 (CH_3, C_2), 41.4 (CH_2, $C_{2'}$ or $C_{6'}$), 46.2 (CH_2, $C_{2'}$ or $C_{6'}$), 53.3 (CH_2, $C_{3'}$ or $C_{5'}$), 53.7 (CH_2, $C_{3'}$ or $C_{5'}$), 63.5 (CH_2, d, $^2J_{CF}$ = 20 Hz, $C_{1''}$), 88.9 (CH, d, $^1J_{CF}$ = 167 Hz, $C_{2''}$), 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.

4.5. Compound 5

After reaction of substrate **3** (400 mg, 2.38 mmol), following the general procedure, 1-(4-(2-fluoropropyl)piperazin-1-yl)ethanone **4** (203 mg, 45%) was eluted with the mixture CH_2Cl_2/MeOH/NH_3

aq. (97/2/1) and then 1-(4-(2-chloropropyl)piperazin-1-yl)ethanone **5** (72 mg, 15%) was eluted with the same mixture.

^{1}H NMR (300 MHz, $CDCl_3$, ppm): 1.49 (3H, d, ^3J = 6.5 Hz, $H_{3''}$), 2.05 (3H, s, H_2), 2.46 (5H, m, $H_{3'}$ $H_{5'}$ and $H_{1''}$), 2.62 (1H, dd, ^2J = 13.2 Hz, ^3J = 7.1 Hz, $H_{1''}$), 3.44 and 3.59 (4H, 2t, ^3J = 5.2 Hz, $H_{2'}$ and $H_{6'}$), 4.05 (1H, m, $H_{2''}$). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): 21.7 (CH_3, C_2), 23.7 (CH_3, $C_{3''}$), 41.7 and 46.6 (2 CH_2, $C_{2'}$ and $C_{6'}$), 53.4 and 54.0 (2 CH_2, $C_{3'}$ and $C_{5'}$), 54.7 (CH, $C_{2''}$), 66.6 (CH_2, $C_{1''}$), 169.3 (CO). MS (EI, 70 ev): *m*/*z* (relative intensity %): 204 (12), 168 (40), 141 (100) HRMS (ESI): Calc. for $C_7H_{13}N_2O$: 141.10279, found 141.1026.

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