Organic & Biomolecular Chemistry

Accepted Manuscript

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Fluorinated hydroxypiperidines as selective β-glucosidase inhibitors

Cite this: DOI: 10.1039/xoxxoooooox

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Received ooth 2014,
Accepted ooth 2014

DOI: 10.1039/xoxxoooooox

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A new series of fluoroallylamines derived from hydroxypiperidines was prepared and evaluated against various glycosidases. The short synthesis of target molecules involved the modified Julia reaction between aldehydes and functionalized fluoroaminosulfones. Biological studies revealed good and selective β-glucosidase inhibition in the micromolar range for two compounds, while the non–fluorinated analogue of the most active compound was selective towards α-glucosidase.

Introduction

The conception of selective glycosidase inhibitors plays an important role in medicinal chemistry to design new drugs, targeting diseases such as viral infections,[1] cancers,[2] diabetes,[3] lysosomal storage disorders,[4] and tuberculosis.[5] Among the numerous glycomimetics already developed as potent inhibitors, iminosugars in which the endocyclic oxygen atom was replaced by a nitrogen atom represent the most promising class of carbohydrate-based therapeutic agents. Indeed, deoxynojirimycin (DNJ) **I**, *N*-butyl-deoxynojirimycin **II** (NB-DNJ, Zavesca™) and *N*-hydroxyethyl-deoxynojirimycin (Miglitol) **III** are glycoside inhibitors used for Gaucher disease as well as type II diabetes (Figure 1).[6]

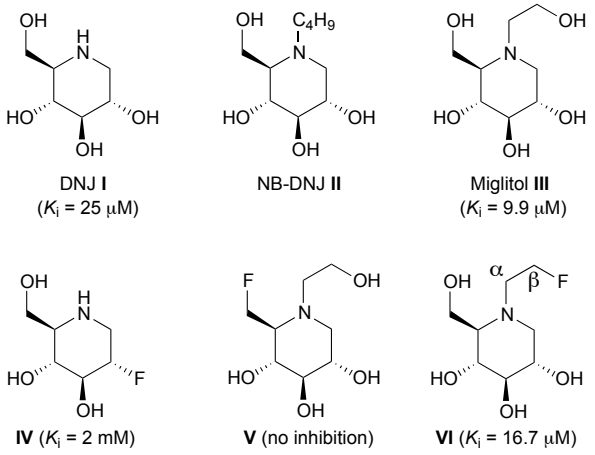


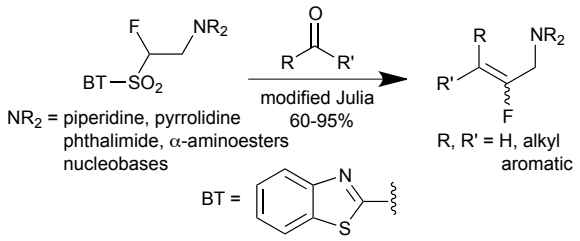
Figure 1. Chemical structures of DNJ derivatives

As known, in amine–containing drugs the protonation of the nitrogen atom in biological media could dramatically affect the bioavailability. To overcome this main limitation, decreasing the pKa value of the amine function can be realized by introduction of a fluorine atom onto the β-nitrogen position.[7] However, in the present case, the ammonium form should be necessary for inhibitory activity. Indeed, the ammonium group is supposed to mimic the oxonium ion of the transition state. For this reason the inhibitory properties were reduced when a fluorine atom was introduced as hydroxyl surrogate (Figure 1). As exemplified, compounds **IV** and **V** were not good inhibitors compared to Miglitol and DNJ. This negative effect of fluorine atoms was also noticed with polyhydroxylated pyrrolidines as glucosidase inhibitors. Substitution of a hydroxyl function by a fluorine atom in β position of the nitrogen atom shut down the inhibition of α-glucosidases.[7c] Nevertheless, a contrasted result was reported, in particular when the substitution of the hydroxyl function of the *exo*cyclic *N*–alkyl chain by a fluorine atom was realized. Indeed, compound **VI** presented an activity towards α glycosidases in the same range than Miglitol.[7b,8] These results already underscored the crucial importance of the carbohydrate hydroxyl functions for activity and prompted several research groups to explore the *N*-alkyl chain modification. For example, *N*-nonyl-DNJ was found to be a selective glycosidase inhibitor where selectivity was assigned to the correct orientation of the alkyl chain which facilitates the molecular recognition by the enzyme active site.[9] Only few articles describe the study of fluorinated piperidines such as DNJ analogues and up to date, only the fluorinated Miglitol analogue **VI** was reported as an efficient glycosidase inhibitor.

In this paper, the synthesis of fluorinated hydroxy-piperidines and their glucosidase inhibitory properties are reported. In addition, the influence of the fluorine atom was highlighted from the most potent inhibitor. Target molecules will all contain a hydroxylated piperidine

as potential sugar mimic, and a *N*-fluoroalkenyl chain. The introduction of a fluorovinylic moiety was motivated by our recent results in the field of glycosidase inhibitors where we showed the fluoroalkene residue in *exo*-glucal derivatives was necessary to observe potent selective β-glucosidase inhibitions and improve the molecular recognition.[10] In the present series, the presence of a fluorine atom and a carbon-carbon double bond are expected to influence the nitrogen protonation and to induce restriction of the alkyl chain conformation.[11]

The preparation of such compounds was based on our recent one-pot synthesis of fluorinated allylamines,[12] *via* the modified Julia reaction between carbonyl compounds and fluoroaminosulfones (Scheme 1).[12i] This approach, already efficient for the preparation of fluoroallylamines derived from primary and secondary amines as well as nucleic bases, was applied to the present study.



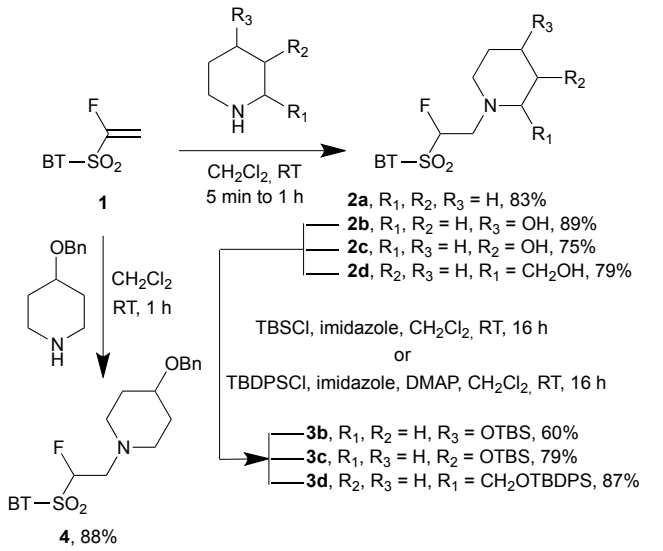
Scheme 1. Access to fluoroallylamines *via* the modified Julia reaction

Results and discussion

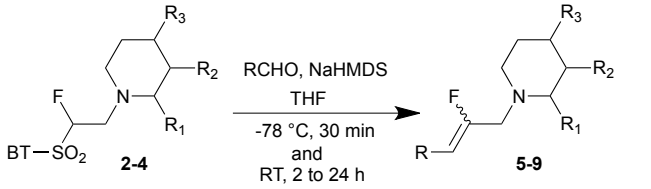
The synthesis of benzothiazolylfluoroaminosulfones **2**, **3** and **4** containing unprotected hydroxy- or hydroxymethyl- piperidine ring was first envisaged (Scheme 2). We reported the conjugated addition of secondary amines such as piperidine onto fluorovinylsulfone **1** was instantaneous and proceeded in excellent yields leading to sulfone **2a** when performed at 20 °C in dichloromethane.[12i,13] In the present study, from 4-hydroxy-, 3-hydroxy- and 2-hydroxymethyl-piperidine, the aza-Michael reaction was slower and reached completion after 1 h of stirring at 20 °C in dichloromethane. Corresponding fluoroaminosulfones **2b-d** were isolated in 75-89 % yields. From 3-hydroxy- and 2-hydroxymethyl-piperidine a non-separable mixture of diastereoisomers **2c** and **2d** was obtained.

To avoid competitive *ipso*-substitution during the fluoroolefination step, sulfones **2b-d** were treated with TBSCl or TBDPSCl in the presence of base to afford corresponding silylated hydroxy-piperidine derivatives **3b-d** in good yields. Direct benzylation of **2b-d** with benzyl bromide in the presence of NaH was not successful, and alternatively, compound **4** was obtained in 88 % yield *via* the conjugated addition of 4-benzyloxypiperidine onto vinylsulfone **1**.

Having in hands protected sulfones **3-4**, the study of their chemical behaviours in the modified Julia reaction was next investigated. To rapidly access to new *N*-alkyl iminosugar-type analogues containing aromatic, linear or bulky alkyl chain, the olefination reaction was carried out with aromatic as well as aliphatic aldehydes such as *p*-bromobenzaldehyde, heptanal and pivaldehyde (Scheme 3, Table 1).



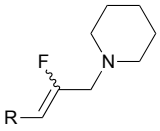
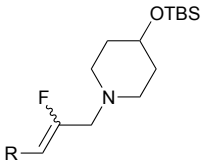
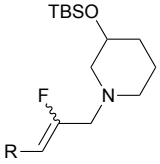
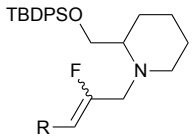
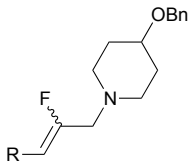
Scheme 2. Preparation of benzothiazolylfluoroaminosulfones derived from hydroxypiperidines by conjugated addition



Scheme 3. Synthesis of hydroxylated piperidines

The reactivity of piperidinyl sulfones **2a** was first evaluated and reacted with *p*-bromobenzaldehyde by adding slowly the base to a mixture of aldehyde and sulfone. After 30 min under stirring at -78 °C and 2 h at 20 °C, 3-piperidinyl-fluoroalkene **5** was isolated in 91% yields as a mixture of *E*/*Z* isomers (Table 1). The reaction was next realized with sulfones **3b-d** and **4**. From sulfone **3b** and aliphatic aldehydes such as heptanal and pivaldehyde, total conversion was observed after 4 h of stirring at 20 °C. In these cases, the corresponding fluoroolefins **6b-c** were isolated in 59-100% yields as a non-separable mixture of *E*/*Z* isomers (Table 1). The same pattern was observed with *p*-bromobenzaldehyde leading to alkene **6a** in excellent yield. In this series, we noticed the *E*/*Z* selectivity was better with aliphatic aldehydes than those observed with aromatic aldehydes. Similar results were obtained from sulfone **3c**, and fluoroalkylidenes **7a-c** were isolated in moderate to good yields. From sulfone **3d**, no deprotection product was detected in the crude mixture and silylated fluoroolefins **8a-c** were formed in 51-90 % yields. However, in these examples, *E*/*Z* selectivity was lower compared to the other series. We assume the bulky protecting group might interact within the reaction centre making more difficult the nucleophilic addition of the fluorinated carbanion onto aldehydes. The reactivity of sulfone **4** derived from 4-benzyloxypiperidine was also screened, and from aliphatic aldehydes and *p*-bromo-benzaldehyde, fluoroallylamines **9a-c** were obtained in good yields and again, a moderate selectivity was observed (Table 1).

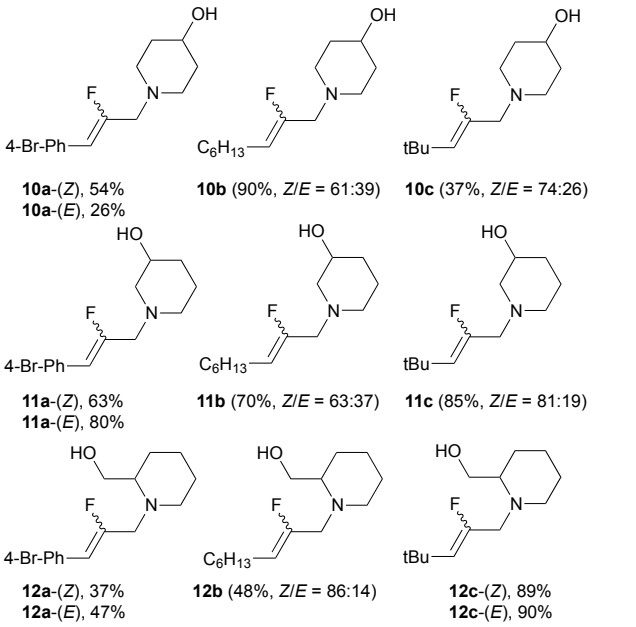
Table 1. Reactivity studies of sulfones **3-4** in the modified Julia reaction

Sulfone	Product	Number	Yield[a] (Z/E)[b]
2a		**5** (R=4-Br-Ph)	91% (55:45)
3b		**6a** (R=4-Br-Ph) **6b** (R=hexyl) **6c** (R=*t*Bu)	94% (52:48) 59% (64:36) 100% (73:27)
3c		**7a** (R=4-Br-Ph) **7b** (R=hexyl) **7c** (R=*t*Bu)	65% (40:60) 80% (53:47) 82% (78:22)
3d		**8a** (R=4-Br-Ph) **8b** (R=hexyl) **8c** (R=*t*Bu)	51% (44:56) 70% (60:40) 90% (46:54)
4		**9a** (R=4-Br-Ph) **9b** (R=hexyl) **9c** (R=*t*Bu)	80% (52:48) 75% (64:36) 65% (81:19)

[a] isolated yields. [b] *Z*/*E* ratio was determined by ^{19}F NMR.

To evaluate the inhibitory properties of the modified piperidines, deprotection of silylated fluoroallylamines was then realized under standard procedure. Fluorinated alkenes **6-8** were treated with TBAF (1.2 eq.) in THF at 20 °C. After 24 h to 48 h of stirring, full deprotection was observed. NMR analysis of the crude mixture showed no *E*/*Z* isomerization occurred during this step. Free hydroxypiperidine derivatives **10-12** were isolated in moderate to good yields (Figure 2). It is worthy of note that deprotection reactions were conducted from a *Z*/*E* isomers mixture of silylated fluoroalkenes excepted for compounds **6a**, **7a**, **8a** and **8c** where *Z* and *E* alkenes were separated prior to the deprotection step, affording pure isomers **10a**, **11a**, **12a**, **12c**. For compounds **9a-c**, both *Z* and *E* isomers were isolated after the deprotection step.

This new series of functionalized fluoroallylamines was evaluated towards several commercial glycosidases. No inhibition was observed against α-glucosidase (baker's yeast), α-galactosidase (green coffee), α-mannosidase (jack bean) and β-mannosidase (helix pomatia), while moderate to good activities were observed from β-glucosidase (almonds and bovine liver), naringinase (Penicilium decumbens) and β-galactosidase (*E. coli*).



10a-(*Z*), 54% **10a**-(*E*), 26% **10b** (90%, *Z*/*E* = 61:39) **10c** (37%, *Z*/*E* = 74:26)

11a-(*Z*), 63% **11a**-(*E*), 80% **11b** (70%, *Z*/*E* = 63:37) **11c** (85%, *Z*/*E* = 81:19)

12a-(*Z*), 37% **12a**-(*E*), 47% **12b** (48%, *Z*/*E* = 86:14) **12c**-(*Z*), 89% **12c**-(*E*), 90%

Figure 2. Deprotected fluoroallylamines

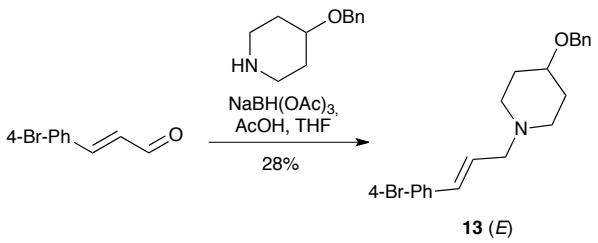
Table 2. Inhibitory activities (K_i in μM) for allylamines towards β-glucosidases[a,b]

Product	β-glucosidase (bovine liver)	β-glucosidase (almonds)	α-glucosidase (baker's yeast)
5-(*Z*)	720 ±53	n.i[c]	n.i
5-(*E*)	380 ±29	326 ±23	n.i
9a-(*Z*)	31 ±2	n.i	n.i
9a-(*E*)	162 ±13	n.i	n.i
9b-(*Z*)	214 ±19	n.i	n.i
9b-(*E*)	101 ±8	n.i	n.i
9c-(*Z*)	577 ±40	n.i	n.i
9c-(*E*)	n.i	n.i	n.i
10a-(*Z*)	411 ±39	n.i	n.i
10a-(*E*)	113 ±10	237 ±20	n.i
10b	55 ±4	n.i	n.i
10c	203 ±19	385 ±31	n.i
11a-(*Z*)	152 ±13	0	n.i
11a-(*E*)	143 ±11	164 ±12	n.i
11c	112 ±9	n.i	n.i
12a-(*Z*)	158 ±10	n.i	n.i
12a-(*E*)	93 ±8	92 ±7	n.i
12b	56 ±4	220 ±19	n.i
12c-(*E*)	244 ±20	n.i	n.i
13-(*E*)	277 ± 20	n.i	29 ± 3

[a] Inhibition percentage are reported in supporting information S2.2. [b] Inhibition was competitive in all case. [c]n.i: no inhibition observed at 2 mM.

Concerning naringinase and β-galactosidase inhibitions, only the fluoroallylamines **12a**, **12b** (naringinase K_i 320 μM and 933 μM), and **5**, **9b**-(*Z*) (β-galactosidase K_i 152 μM and 259 μM) presented moderate activities. Free hydroxyl derivatives were found completely inactive towards β-galactosidase. Interestingly, a 2-fold difference in the inhibitory potency was observed between *E* and *Z* isomers.

In contrast, the presence of at least one hydroxyl function seemed necessary for β-glucosidase inhibition (Table 2). Compound **5**-(*Z*) was found to be 2 to 5 fold less active than **10a**-(*Z*)-**12a**-(*Z*) towards bovine liver glucosidase and **5**-(*Z*) was totally inactive towards almonds glucosidase. The hydroxyl position also plays an important role. Compared to 3-hydroxy- and 2-hydroxymethyl-piperidines, the 4-hydroxy-piperidines had low effect on the β-glucosidase inhibition. In fact, **10a**-(*E*) showed lower activity than **11a**-(*E*) and **12a**-(*E*) towards almonds β-glucosidase. Similar results were obtained with bovine liver from **10a**-(*Z*)-**12a**-(*Z*). As previously discussed some differences regarding inhibitory potency and selectivity were observed between *E* and *Z* isomers. For example, against β-glucosidase (almonds) inhibition studies revealed that stereoisomer **12a**-(*E*) was active while **12a**-(*Z*) was completely inactive and **11a**-(*Z*) was more selective than **11a**-(*E*) towards β-glucosidase (bovine liver). As mentioned in the literature,[9b] these results comfort the idea that the activity is ascribed to the conformational restriction. Modification of the non-glycone part was also investigated in order to increase activity and/or selectivity. Substitution of the aromatic ring by a hexyl chain in the 4-hydroxypiperidine series allowed improvement of β-glucosidase inhibition and selectivity. In fact, compound **10b** containing a hexyl chain was 7 times more active than **10a**-(*Z*) containing an aryl group and much more selective than **10a**-(*E*). The same pattern was observed from **12b**, which acted as a better β-glucosidase inhibitor than **12a** (both isomers) with highest selectivity towards bovine liver β-glucosidase. For the 2-hydroxymethyl- and 3-hydroxy-piperidine series, high selectivity against β-glucosidase (bovine liver) was observed when the *tert*-butyl group was introduced. In these cases, the activity was higher than those obtained with 4-bromophenyl derivatives excepted for **12c**. Finally, 4-benzyloxypiperidine derivatives were evaluated.



Scheme 4. Synthesis of **13** (*E*)

While compounds **9b-c** (*Z* isomer) showed moderate activities, **9a**-(*Z*) was found to be the best β-glucosidase inhibitor of this study (K_i = 31 μM). In contrast, isomers *E* of this series presented moderate or no activity. The role of the fluorine atom was evaluated by testing the corresponding alkene **13**-(*E*), hydrocarbon analogue of **9a**-(*Z*). This latter was prepared in one step by reductive amination of (*E*)-4-bromo-cinnaldehyde with 4-benzyloxypiperidine (Scheme 4). Surprisingly, compound **13**-(*E*) is active towards glucosidases with a reverse selectivity. Best inhibition constant was observed with α-glucosidase (K_i = 29 μM, Table 2), while no inhibition or moderate activity was observed with β-glucosidases. The reverse selectivity observed in the presence of a fluorine atom can be directly associated with the catalytic enzymatic site of the both enzymes. In fact, it was shown that these two classes of this enzyme differ by the positioning of the catalytic nucleophile and the catalytic proton donor.[14] Based on the pKa value of fluoroamines and amines, this suggests that the less basic nitrogen (*ie* compound **9a**) could act as neutral inhibitor of β-glucosidases and interact with the active site through hydrogen bonding with the catalytic proton donor (Figure 3). In contrast, it is expected that compound **13** should be fully protonated to form a hydrogen-bonded ion pair with the catalytic nucleophile of α-glucosidase but not with β-glucosidases.

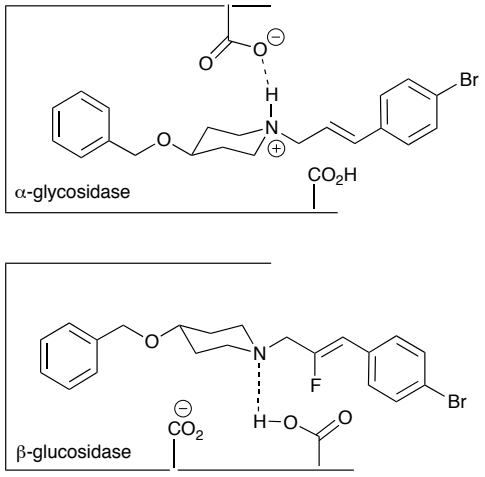


Figure 3. Hypothetic interaction between α- and β-glucosidases

Conclusions

We reported in this paper a short synthesis of new fluorinated analogues of hydroxypiperidines from aldehydes and functionalized fluoroaminosulfones. These piperidine derivatives have been tested against several glucosidases. The presence of a hydroxyl or hydroxybenzyl group onto the piperidine ring was found to be necessary for β-glucosidase inhibition. Replacement of the *N*-alkyl chain by an aryl group led in some cases to lower activity and selectivity. Best results were observed with 4-benzyloxypiperidine derivative **9a**-(*Z*) (K_i = 31 μM) and 4-hydroxypiperidine **10b** (K_i = 55 μM) that appeared as good selective β-glucosidase (bovine liver) inhibitors. In addition, selective inhibition of α-glucosidase was observed in the absence of a fluorine atom. Finally, since differences in terms of activity and selectivity were noticed between *Z* and *E* isomers, conformational restriction of the non-glycone chain appeared important and *Z* stereoisomer is usually preferred.

Experimental section

General

Unless otherwise specified, all reagents were obtained from commercial suppliers and were used without purification. For anhydrous conditions, the glassware was flamed under a continuous nitrogen flow and cooled to room temperature before performing the experiment. Anhydrous solvents (THF and CH_2Cl_2) were purified by passing the degassed solvents (N_2) through a column of activated alumina (solvent purification system purchased from Innovative Technologies Inc.). Flash column chromatography was performed on silica gel (Kieselgel 60, 40–63 µm, Merck) with air pressure. All thin layer chromatography was performed on aluminium backed plates pre-coated with silica gel (Merck, Silica Gel 60 F254). Compounds were visualised by exposure to UV light and/or by dipping the plates in solution of potassium permanganate followed by heating. ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Bruker Avance DPX 400 or 500 spectrometers in deuterated solvent and the observed signals are reported in parts per million (ppm) relative to the residual signal of the undeuturated solvent. All chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) in Hertz (Hz). The following abbreviations mean: s: singlet; d: doublet; t: triplet; q: quadruplet; quint: quintuplet; sext: sextet; sep: septet; m: multiplet. Mass spectra and high resolution mass spectra (HRMS) were obtained on a Waters-Micromass Q-Tof (Quadrupole time-of-flight) micro instrument with an electrospray source in the EI or ESI mode.

General procedure A for the synthesis of fluoroaminosulfones

To a solution of 1-benzothiazolylfluorovinylsulfone **1** (1.00 eq.) in CH_2Cl_2 (0.2 M) was added amine (1.30 eq.). The mixture was stirred at room temperature over a determined time, quenched with a saturated aqueous solution of NH_4Cl and extracted 3 times with CH_2Cl_2. Combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography to give corresponding fluoroaminosulfones **2a-d**.

General procedure B for the synthesis of silylated sulfones

To a solution of hydroxypiperidinylsulfone **2b-d** were added imidazole (1.50 to 1.80 eq.), DMAP (0 to 0.02 eq.), TBDPSCl or TBSCl (1.10 to 1.80 eq.) in CH_2Cl_2 (0.1 to 0.2 M). The mixture was stirred 16 h at room temperature, quenched with a saturated aqueous solution of $NaHCO_3$ and extracted 3 times with CH_2Cl_2. Combined organic layers were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography to give protected fluoroaminosulfone **3b-d**.

General procedure C for the synthesis of fluoroallylamines

To a solution of fluoroaminosulfone **2-4** (1.00 eq.) and aldehyde (1.05 eq.) in THF (0.1 M) cooled to –78 °C was added dropwise NaHMDS (1.0 M in THF, 1.50 eq.). After 30 min at –78 °C, the mixture was stirred at room temperature, quenched with a saturated aqueous solution of NH_4Cl and extracted 3 times with CH_2Cl_2. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography to give fluorinated allylamines **5-9**.

Genaral procedure D for deprotection of silylated derivatives

To a solution of fluorinated allylamine **5-8** (1.00 eq.) in THF (0.1 M) was added TBAF (1 M in THF, 1.20 eq.). The mixture was stirred at room temperature 24h to 48h, quenched with water and extracted 3 times with EtOAc. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography to give deprotected fluoroallylamines **10-12**.

N-[(2-Fluoro-2-benzothiazolylsulfonyl)-ethyl]-4-hydroxy-piperidine 2b

General procedure A was followed with vinylsulfone (**1)** (1.00 g, 4.11 mmol, 1.00 eq.), 4-hydroxypiperidine (0.54 g, 5.34 mmol, 1.30 eq.) and CH_2Cl_2 (20.60 mL). The mixture was stirred 1 h at room temperature. The purification by flash column chromatography (pentane/EtOAc, 40:60) afforded fluoroaminosulfone **2b** (1.26 g, 89%, white solid); mp 60-61 °C; δ_H (400 MHz, $CDCl_3$) 8.24 (1H, d, *J* 7.6), 8.03-8.01 (1H, m), 7.67-7.59 (2H, m), 5.83 (1H, ddd, *J* 48.4, 7.6, 2.4), 3.65 (1H, sep, *J* 4.4), 3.35 (1H, ddd, *J* 31.6, 14.8, 2.4), 3.15-3.05 (1H, m), 2.85-2.78 (2H, m), 2.38-2.33 (2H, m), 1.88 (1H, br s), 1.81-1.78 (m, 2H), 1.53-1.42 (m, 2H); δ_C (100 MHz, $CDCl_3$) 162.8, 152.8, 137.4, 128.5, 127.9, 125.8, 122.4, 100.9 (d, *J* 224.4), 67.1, 54.9 (d, *J* 19.4), 51.2, 51.1, 34.2, 34.1; δ_F (376 MHz, $CDCl_3$) –176.9 (1F, ddd, *J* 48.4, 31.6, 19.4); *m/z* (ESI$^+$) 345 ([M + H]$^+$, 54%), 327 (20), 273 (5), 244 (100), 146 (61), 128 (8), 114 (29); HRMS (ESI$^+$) $C_{14}H_{18}FN_2O_3S_2$ ([M + H]$^+$) requires 345.0743; found 345.0751.

N-[(2-Fluoro-2-benzothiazolylsulfonyl)-ethyl]-3-hydroxy-piperidine 2c

General procedure A was followed with vinylsulfone **1** (500 mg, 2.05 mmol, 1.00 eq.), 3-hydroxypiperidine (271 mg, 2.68 mmol, 1.30 eq.) and CH_2Cl_2 (10.30 mL). The mixture was stirred 30 min at room temperature. The purification by column chromatography (pentane/EtOAc, 40:60) afforded fluoroaminosulfone **2c** (546 mg, 75%, yellow oil) as a non-separable mixture of diastereoisomers (dr = 1:1); δ_H (400 MHz, $CDCl_3$) 8.22-8.20 (2H, m), 8.00-7.98 (2H, m), 7.64-7.55 (4H, m), 5.89-5.74 (2H, m), 3.73 (2H, br s), 3.36 (2H, ddd, *J* 28.5, 14.9, 3.1), 3.20-3.07 (2H, m), 2.81 (2H, br s), 2.71-2.65 (2H, m), 2.61-2.52 (4H, m), 2.49-2.42 (2H, m), 1.80-1.67 (2H, m), 1.58-1.36 (6H, m); δ_C (100 MHz, $CDCl_3$) 162.7, 162.6, 152.7, 137.4, 137.3, 128.5, 127.9 (4C), 125.7, 125.6, 122.4, 122.3, 101.9-99.5 (m), 66.0, 65.9, 60.6, 60.5, 55.2 (d, *J* 19.6), 55.1 (d, *J* 19.3), 53.9 (2C), 31.2, 31.1, 21.6 (2C); δ_F (376 MHz, $CDCl_3$) –177.2 (2F, m); *m/z* (ESI$^+$) 345 ([M + H]$^+$, 24%), 327 (17), 244 (100), 146 (42), 128 (8), 114 (21), 84 (6). HRMS (ESI$^+$) $C_{14}H_{18}FN_2O_3S_2$ ([M + H]$^+$) requires 345.0743; found 345.0736.

N-[(2-Fluoro-2-benzothiazolylsulfonyl)-ethyl]-2-(hydroxy-methyl)-piperidine 2d

General procedure A was followed with vinylsulfone **1** (1.00 g, 4.11 mmol, 1.00 eq.), 2-(hydroxymethyl)-piperidine (620 mg, 5.34 mmol,

1.30 eq.) and CH_2Cl_2 (20.60 mL). The mixture was stirred at room temperature for 1 h. The purification by column chromatography (pentane/EtOAc, 40:60) afforded fluoroamino-sulfone **2d** (1.16 g, 79%, yellow oil) as non-separable mixture of diastereoisomers (dr = 1:1); δ_H (400 MHz, $CDCl_3$) 8.15 (2H, d, *J* 8.8), 7.94 (2H, d, *J* 7.6), 7.58-7.51 (4H, m), 5.93-5.78 (2H, m), 3.76-3.15 (8H, m), 2.92-2.89 (2H, m), 2.79 (2H, br s), 2.51-2.39 (4H, m), 1.57-1.25 (12H, m); δ_C (100 MHz, $CDCl_3$) 162.7, 162.6, 152.7, 152.6, 137.3, 137.2, 128.4 (2C), 127.8 (2C), 125.6 (2C), 122.3 (2C), 100.8 (d, *J* 222.7), 100.4 (d, *J* 223.6), 62.8 (2C), 62.3, 61.4, 61.0 (2C), 52.1 (d, *J* 17.5), 50.9 (d, *J* 20.1), 26.9, 26.5, 24.1, 23.8, 22.8, 22.7; δ_F (376 MHz, $CDCl_3$) –176.8 (1F, ddd, *J* 48.9, 29.1, 19.9), –177.9 (1F, ddd, *J* 47.4, 29.1, 18.6); MS (ESI) *m/z* (ESI^+) 359 ($[M + H]^+$, 41%), 244 (83), 160 (72), 140 (33), 128 (100), 110 (10); HRMS (ESI^+) $C_{15}H_{20}FN_2O_3S_2$ 359.0899 ($[M + H]^+$) requires 359.0899; found 359.0900.

_N_-[(2-Fluoro-2-benzothiazolylsulfonyl)ethyl]-4-[(*tert*-butyldimethylsilyl)oxy]-piperidine 3b

General procedure B was followed with sulfone **2b** (1.00 g, 2.90 mmol, 1.00 eq.), imidazole (0.36 g, 5.22 mmol, 1.80 eq.), TBSCl (0.69 g, 4.60 mmol, 1.60 eq.) and CH_2Cl_2 (29.00 mL). The purification by flash column chromatography (pentane/EtOAc, 98:2) afforded protected fluoroaminosulfone **3b** (0.80 g, 60%, white solid); mp 97-98 °C; δ_H (400 MHz, $CDCl_3$) 8.27-8.25 (1H, m), 8.04-8.02 (1H, m), 7.68-7.59 (2H, m), 5.81 (1H, ddd, *J* 48.5, 7.3, 2.4), 3.67-3.66 (1H, m), 3.34 (1H, ddd, *J* 31.6, 15.0, 2.4), 3.13-3.03 (1H, m), 2.77-2.75 (2H, m), 2.40-2.38 (2H, m), 1.67-1.63 (2H, m), 1.48-1.43 (2H, m), 0.86 (9H, s), 0.01 (6H, s); δ_C (100 MHz, $CDCl_3$) 162.6, 152.6, 137.2, 128.1, 127.6, 125.5, 122.1, 100.7 (d, *J* 228.1), 66.4, 54.9 (d, *J* 19.4), 50.5, 50.4, 34.1, 34.0, 25.6 (3C), 17.8, –5.0 (2C); δ_F (376 MHz, $CDCl_3$) –177.0 (1F, ddd, *J* 48.5, 31.6, 18.8); *m/z* (ESI^+) 459 ($[M + H]^+$, 100%), 327 (36); HRMS (ESI^+) $C_{20}H_{32}FN_2O_3S_2Si$ ($[M + H]^+$) requires 459.1608; found 459.1618.

_N_-[(2-Fluoro-2-benzothiazolylsulfonyl)ethyl]-3-[(*tert*-butyldimethylsilyl)oxy]-piperidine 3c

General procedure B was followed with sulfone **2c** (1.50 g, 4.40 mmol, 1.00 eq.), imidazole (0.54 g, 7.92 mmol, 1.80 eq.) TBSCl (0.54 g, 7.92 mmol, 1.80 eq.) and CH_2Cl_2 (44.00 mL). The purification by flash column chromatography (pentane/EtOAc, 95:5) afforded protected fluoroaminosulfone **3c** (1.60 g, 79%, white solid) as a non-separable mixture of diastereoisomers (dr = 1:1); mp 72-73 °C; δ_H (400 MHz, $CDCl_3$) 8.27 (2H, d, *J* 7.6), 8.04 (2H, d, *J* 8.0), 7.69-7.61 (4H, m), 5.90-5.76 (2H, m), 3.61-3.53 (2H, m), 3.47-3.35 (2H, m), 3.21-3.10 (2H, m), 2.94-2.89 (2H, m), 2.81-2.74 (2H, m), 2.15-2.07 (4H, m), 1.82-1.80 (2H, m), 1.67-1.62 (2H, m), 1.46-1.32 (2H, m), 1.21-1.11 (2H, m), 0.87-0.85 (18H, m), 0.04 (6H, s), 0.03 (6H, s); δ_C (100 MHz, $CDCl_3$) 162.8 (2C), 152.9, 152.8, 137.5, 137.4, 128.5 (2C), 127.9 (2C), 125.9, 125.8, 122.4, 122.3, 100.9 (d, *J* 223.8), 100.7 (d, *J* 224.3), 68.1 (2C), 61.7, 61.5, 55.1 (d, *J* 19.1), 55.0 (d, *J* 19.2), 53.3, 53.2, 33.6, 33.5, 25.9 (6C), 23.6, 23.4, 18.2, 18.1, –4.5 (4C); δ_F (376 MHz, $CDCl_3$) –176.9 (2F, m); *m/z* (ESI^+) 459 ($[M + H]^+$, 100%), 327 (73), 244 (13); HRMS (ESI^+) $C_{20}H_{32}FN_2O_3S_2Si$ ($[M + H]^+$) requires 459.1608; found 459.1617.

_N_-[(2-Fluoro-2-benzothiazolylsulfonyl)-ethyl]-2-[(*tert*-butyldiphenyl)oxymethyl]piperdine 3d

General procedure B was followed with sulfone **2d** (500 mg, 1.39 mmol, 1.00 eq.), imidazole (142 mg, 2.09 mmol, 1.50 eq.), DMAP (4 mg, 0.03 mmol, 0.02 eq.), TBDPSCl (0.40 mL, 1.53 mmol, 1.10 eq.) and CH_2Cl_2 (6.95 mL). The purification by flash column chromatography (pentane/EtOAc, 92:8) afforded protected fluoroaminosulfone **3d** (722 mg, 87%, yellow oil) as a non-separable mixture of diastereoisomers (dr = 1:1); δ_H (400 MHz, $CDCl_3$) 8.23-8.21 (2H, m), 8.02 (2H, d, *J* 8.0), 7.70-7.59 (12H, m), 7.45-7.38 (12H, m), 5.92-5.75 (2H, m), 3.94-3.19 (8H, m), 2.90-2.83 (2H, m), 2.58 (2H, br s), 2.46-2.39 (2H, m), 1.55-1.23 (12H, m), 1.07-1.05 (18H, m); δ_C (100 MHz, $CDCl_3$) 163.1, 162.9, 152.7 (2C), 137.2, 137.1, 135.6 (2C), 135.5 (2C), 135.4 (4C), 133.3, 133.2 (2C), 133.1, 129.6, 129.5, 129.4 (2C), 128.1 (2C), 127.6 (2C), 127.5 (8C), 125.6, 125.5, 122.1 (2C), 101.5 (d, *J* 222.8), 101.0 (d, *J* 223.7), 65.7, 65.1, 62.4, 62.2, 52.9, 52.6, 51.9 (d, *J* 20.6), 51.7 (d, *J* 20.1), 28.4, 28.3, 26.7 (3C), 26.6 (3C), 25.2, 25.1, 22.5, 22.4, 19.0, 18.9; δ_F (376 MHz, $CDCl_3$) –177.2 (1F, ddd, *J* 48.1, 29.7, 18.4), –177.5 (1F, ddd, *J* 49.6, 31.6, 18.4); *m/z* (ESI^+) 597 ($[M + H]^+$, 100%), 499 (6), 341 (48), 244 (6); HRMS (ESI^+) $C_{31}H_{38}FN_2O_3S_2Si$ ($[M + H]^+$) requires 597.2077; found 597.2078.

_N_-[(2-Fluoro-2-benzothiazolylsulfonyl)-ethyl]-4-(benzyloxy)-piperidine 4

General procedure A was followed with vinylsulfone **1** (849 mg, 3.49 mmol, 1.00 eq.), 4-(benzyloxy)-piperidine (1.00 g, 5.23 mmol, 1.30 eq.) and CH_2Cl_2 (17.50 mL). The mixture was stirred at room temperature for 5 h. The purification by flash column chromatography (pentane/EtOAc, 80:20) afforded fluoro-aminosulfone **4** (1.34 g, 88%, white solid); mp 93-94 °C; δ_H (400 MHz, $CDCl_3$) 8.21-8.19 (1H, m), 7.98-7.96 (1H, m), 7.62-7.54 (2H, m), 7.27-7.20 (5H, m), 5.77 (1H, ddd, *J* 48.6, 7.6, 2.4), 4.44 (2H, s), 3.37-3.25 (2H, m), 3.10-3.04 (1H, m), 2.79-2.76 (2H, m), 2.35-2.30 (2H, m), 1.78-1.75 (2H, m), 1.58-1.52 (2H, m); δ_C (100 MHz, $CDCl_3$) 162.7, 152.7, 138.7, 137.3, 128.3 (2C), 128.2, 127.8, 127.4 (2C), 127.3, 125.7, 122.3, 100.8 (d, *J* 223.8), 73.2, 69.6, 54.9 (d, *J* 19.4), 51.1, 51.0, 31.0, 30.9; δ_F (376 MHz, $CDCl_3$) –176.9 (1F, ddd, *J* 48.6, 30.1, 18.8); *m/z* (ESI^+) 435 ($[M + H]^+$, 100%), 343 (3), 327 (55), 325 (19), 273 (3), 244 (20), 236 (9), 204 (3), 190 (2), 146 (13); HRMS (ESI^+) $C_{21}H_{24}FN_2O_3S_2$ 435.1212 ($[M + H]^+$) requires; found 435.1216.

1-[3-(4-Bromophenyl)-2-fluoroprop-2-enyl]-piperidine 5

General procedure C was followed with sulfone **2a** (300 mg, 0.61 mmol, 1.00 eq.), 4-bromobenzaldehyde (118 mg, 0.64 mmol, 1.05 eq.), NaHMDS (1.0 M in THF, 1 mL, 1.00 mmol, 1.50 eq.) and THF (6.10 mL). The mixture was stirred 30 min at –78 °C and 2 h at room temperature. The purification by flash column chromatography (pentane/EtOAc, 95:5 and 90:10) afforded pure alkenes **5**-(*Z*) and **5**-(*E*) (168 mg, 91%, yellow oil, *Z*/*E* = 55:45); **5**-(*Z*): δ_H (400 MHz, $CDCl_3$) 7.45-7.43 (2H, m), 7.38-7.35 (2H, m), 5.61 (1H, d, *J* 38.3), 3.17 (2H, d, *J* 17.6), 2.50 (4H, br s), 1.66-1.60 (4H, m), 1.48-1.44 (2H, m); δ_C (100 MHz, $CDCl_3$) 157.8 (d, *J* 268.9), 132.2 (d, *J* 2.6), 131.6 (2C), 130.1 (2C, d, *J* 7.7), 120.9 (d, *J* 3.5), 110.8 (d, *J* 7.2),

60.6 (d, *J* 26.4), 54.5 (2C), 26.0 (2C), 24.2; δ_F (376 MHz, $CDCl_3$) –101.9 (1F, dt, *J* 38.3, 17.6); *m/z* (ESI^+) 300 ([M($C_{14}H_{18}{}^{81}BrFN$) + H]$^+$, 59%), 298 [M($C_{14}H_{18}{}^{79}BrFN$) + H]$^+$, 59%), 215 (100), 134 (47); HRMS (ESI^+) $C_{14}H_{18}{}^{79}BrFN$ 298.0607 ([M + H]$^+$) requires; 298.0609; **5**-(*E*): δ_H (400 MHz, $CDCl_3$) 7.42 (2H, d, *J* 8.4), 7.16 (2H, d, *J* 8.4), 6.29 (1H, d, *J* 20.9), 3.19 (2H, d, *J* 22.5), 2.42 (4H, br s), 1.60-1.55 (4H, m), 1.43-1.40 (2H, m); δ_C (100 MHz, $CDCl_3$) 159.3 (d, *J* 255.8), 132.5 (d, *J* 13.3), 131.3 (2C), 130.3 (2C, d, *J* 2.7), 120.8 (d, *J* 0.9), 110.9 (d, *J* 28.2), 56.1 (d, *J* 25.7), 54.0 (2C), 25.7 (2C), 23.9; δ_F (376 MHz, $CDCl_3$) –94.8 (1F, dt, *J* 22.5, 20.9); *m/z* (ESI^+) 300 ([M($C_{14}H_{18}{}^{81}BrFN$) + H]$^+$, 100%), 298 ([M($C_{14}H_{18}{}^{79}BrFN$) + H]$^+$,100), 215 (51), 134 (39), 134 (39); HRMS (ESI^+) $C_{14}H_{18}{}^{79}BrFN$ ([M + H]$^+$) requires 298.0607; found 298.0613.

1-[3-(4-Bromophenyl)-2-fluoroprop-2-enyl]-4-[(*tert*-butyl-dimethylsilyl)oxy]piperidine 6a

General procedure C was followed with sulfone **3b** (600 mg, 1.30 mmol, 1.00 eq.), 4-bromobenzaldehyde (260 mg, 1.40 mmol, 1.05 eq.), NaHMDS (1.0 M in THF, 1.95 mL, 1.95 mmol, 1.50 eq.) and THF (13.00 mL). The mixture was stirred 30 min at –78 °C and 4 h at room temperature. The purification by flash column chromatography (pentane/EtOAc, 95:5) afforded pure alkenes **6a**-(*Z*) and **6a**-(*E*) (527 mg, 94%, yellow oil, *Z*/*E* = 52:48); **6a**-(*Z*): δ_H (400 MHz, $CDCl_3$) 7.44-7.42 (2H, m), 7.38-7.34 (2H, m), 5.62 (1H, d, *J* 38.4), 3.76 (1H, br s), 3.19 (2H, d, *J* 17.2), 2.77-2.73 (2H, m), 2.40 (2H, br s), 1.83-1.78 (2H, m), 1.66-1.58 (2H, m), 0.88 (9H, s), 0.04 (6H, s); δ_C (100 MHz, $CDCl_3$) 157.8 (d, *J* 268.6), 132.1 (d, *J* 2.6), 131.6 (2C), 130.1 (2C, d, *J* 7.7), 120.9 (d, *J* 3.5), 107.8 (d, *J* 28.2), 67.3, 59.9 (d, *J* 26.8), 50.4 (2C), 34.5 (2C), 25.9 (3C), 18.1, –4.7 (2C); δ_F (376 MHz, $CDCl_3$) –102.3 (1F, dt, *J* 38.4, 17.2); *m/z* (ESI^+) 430 ([M($C_{20}H_{32}{}^{81}BrFNOSi$) + H]$^+$, 25%), 428 ([M($C_{20}H_{32}{}^{79}BrFNOSi$) + H]$^+$, 25%), 298 (16), 215 (100), 134 (85); HRMS (ESI^+) $C_{20}H_{32}{}^{79}BrFNOSi$ ([M + H]$^+$) requires 428.1421; found 428.1419; **6a**-(*E*): δ_H (400 MHz, $CDCl_3$) 7.44 (2H, d, *J* 8.4), 7.19 (2H, d, *J* 8.4), 6.31 (1H, d, *J* 20.8), 3.71-3.70 (1H, m), 3.23 (2H, d, *J* 22.4), 2.72 (2H, br s), 2.30-2.26 (2H, m), 1.80-1.75 (2H, m), 1.64-1.56 (2H, m), 0.88 (9H, s), 0.04 (6H, s); δ_C (100MHz, $CDCl_3$) 159.2 (d, *J* 255.6), 132.3 (d, *J* 13.2), 131.2 (2C), 130.2 (2C, d, *J* 2.7), 120.7, 110.8 (d, *J* 28.2), 67.1, 55.4 (d, *J* 26.0), 50.1 (2C), 34.3 (2C), 25.5 (3C), 17.8, –5.0 (2C); δ_F (376 MHz, $CDCl_3$) –94.9 (1F, dt, *J* 22.4, 20.8); *m/z* (ESI^+) 430 ([M($C_{20}H_{32}{}^{81}BrFNOSi$) + H]$^+$, 95%), 428 ([M($C_{20}H_{32}{}^{79}BrFNOSi$) + H]$^+$, 95%), 298 (36), 215 (81), 134 (100); HRMS (ESI^+) $C_{20}H_{32}{}^{79}BrFNOSi$ ([M + H]$^+$) requires 428.1421; found 428.1435.

1-(2-Fluorononon-2-enyl)-4-[(tert-butyldimethylsilyl)oxy]-piperidine 6b

General procedure C was followed with sulfone **3b** (400 mg, 0.87 mmol, 1.00 eq.), heptanal (13 µL, 0.91 mmol, 1.05 eq.), NaHMDS (1.0 M in THF, 1.30 mL, 1.30 mmol, 1.50 eq.) and THF (8.70 mL). The mixture was stirred 30 min at –78 °C and 3 h at room temperature. The purification by flash column chromatography (pentane/EtOAc, 96:4) afforded fluoroalkene **6b** (182 mg, 59%, colorless liquid) as a non-separable mixture of stereoisomers (*Z*/*E* = 64:36); **6b**-(*Z*): δ_H (400 MHz, $CDCl_3$) 4.64 (1H, dt, *J* 37.2, 7.6), 3.69 (1H, br s), 2.97 (2H, d, *J* 18.2), 2.62 (2H, br s), 2.26-2.25 (2H, m), 2.25-2.02 (2H, m), 1.76-171 (2H, m), 1.60-1.52 (2H, m), 1.28-1.24 (8H, m), 0.84 (12H, br s), 0.00 (6H, s); δ_C (100 MHz, $CDCl_3$) 155.4 (d, *J* 254.3), 109.2 (d, *J* 14.7), 67.2, 59.1 (d, *J* 27.3), 49.9 (2C), 34.3 (2C), 31.4, 29.1 (d, *J* 1.5), 28.6, 25.6 (3C), 23.3 (d, *J* 4.4), 22.4, 17.9, 13.8, –4.9 (2C); δ_F (376 MHz, $CDCl_3$) –112.1 (1F, t, *J* 37.2, 18.2); **6b**-(*E*): δ_H (400 MHz, $CDCl_3$) 5.18 (1H, dt, *J* 22.0, 8.0), 3.69 (1H, br s), 3.10 (2H, d, *J* 22.4), 2.62 (2H, br s), 2.26-2.25 (2H, m), 1.97-1.91 (2H, m), 1.76-171 (2H, m), 1.60-1.52 (2H, m), 1.28-1.24 (8H, m), 0.84 (12H, br s), 0.00 (6H, s); δ_C (100 MHz, $CDCl_3$) 155.6 (d, *J* 247.5), 110.0 (d, *J* 20.0), 67.2, 54.5 (d, *J* 27.2), 50.0 (2C), 34.2 (2C), 31.3, 29.6 (d, *J* 2.2), 28.5, 25.6 (3C), 25.2 (d, *J* 8.5), 22.3, 17.8, 13.8, –4.9 (2C); δ_F (376 MHz, $CDCl_3$) –104.1 (1F, dt, *J* 22.4, 22.0); *m/z* (ESI^+) 358 ([M + H]$^+$, 100%), 226 (21), 214 (5), 159 (4); HRMS (ESI^+) $C_{20}H_{41}FNOSi$ ([M + H]$^+$) requires 358.2941; found 358.2931.

1-(2-Fluoro-4,4-dimethylpent-2-en-1-yl)-4-[(*tert*-butyldimethyl-silyl)oxy]piperidine 6c

General procedure C was followed with sulfone **3b** (400 mg, 0.87 mmol, 1.00 eq.), pivaldehyde (0.10 mL, 0.92 mmol, 1.05 eq.), NaHMDS (1.0 M in THF, 1.31 mL, 1.31 mmol, 1.50 eq.) and THF (8.70 mL). The mixture was stirred 30 min at –78 °C and 2 h 30 at room temperature to afford without further purification fluoroalkene **6c** (287 mg, 100%, colorless oil) as a non-separable mixture of stereoisomers (*Z*/*E* = 73:27); **6c**-(*Z*): δ_H (400 MHz, $CDCl_3$) 4.59 (1H, d, *J* 42.4), 3.71 (1H, br s), 2.94 (2H, d, *J* 18.8), 2.64 (2H, br s), 2.26 (2H, br s), 1.78-1.73 (2H, m), 1.62-1.54 (2H, m), 1.11-1.10 (9H, m), 0.87 (9H, s), 0.02 (6H, s); δ_C (100 MHz, $CDCl_3$) 154.3 (d, *J* 258.5), 118.9 (d, *J* 9.7), 67.3, 60.0 (d, *J* 27.6), 50.0 (2C), 34.4 (2C), 31.3 (3C), 30.4 (d, *J* 3.2), 25.8 (3C), 18.1, –4.7 (2C); δ_F (376 MHz, $CDCl_3$) –109.2 (1F, dt, *J* 42.4, 18.8); **6c**-(*E*): δ_H (400 MHz, $CDCl_3$) 5.28 (1H, d, *J* 29.2), 3.71 (1H, br s), 3.20 (2H, d, *J* 23.2), 2.70 (2H, br s), 2.26 (2H, br s), 1.78-1.73 (2H, m), 1.62-1.54 (2H, m), 1.11-1.10 (9H, m), 0.87 (9H, s), 0.02 (6H, s); δ_C (100 MHz, $CDCl_3$) 155.0 (d, *J* 242.7), 120.7 (d, *J* 21.1), 67.3, 55.8 (d, *J* 28.0), 50.5 (2C), 34.7 (2C), 31.3 (3C), 30.4 (d, *J* 3.2), 25.7 (3C), 18.0, –4.7 (2C); δ_F (376 MHz, $CDCl_3$) –100.6 (1F, dt, *J* 29.2, 23.2); *m/z* (ESI^+) 330 ([M + H]$^+$, 100%), 198 (11); HRMS (ESI^+) $C_{18}H_{37}FNOSi$ ([M + H]$^+$) requires 330.2628; found 330.2636.

1-[3-(4-Bromophenyl)-2-fluoroprop-2-enyl]-3-[(*tert*-butyl-dimethylsilyl)oxy]piperidine 7a

General procedure C was followed with sulfone **3c** (400 mg, 0.87 mmol, 1.00 eq.), 4-bromobenzaldehyde (168 mg, 0.92 mmol, 1.05 eq.), NaHMDS (1.0 M in THF, 1.30 mL, 1.30 mmol, 1.50 eq.) and THF (8.70 mL). The mixture was stirred 30 min at –78 °C and 2 h 30 at room temperature. The purification by flash column chromatography (pentane/EtOAc, 98:2 and 95:5) afforded pure alkenes **7a**-(*Z*) and **7a**-(*E*) (272 mg, 65%, yellow oil, *Z*/*E* = 40:60); **7a**-(*Z*): δ_H (400 MHz, $CDCl_3$) 7.45 (2H, d, *J* 8.8), 7.37 (2H, d, *J* 8.4), 5.62 (1H, d, *J* 38.4), 3.78-3.73 (1H, m), 3.29-3.13 (2H, m), 2.98-2.94 (1H, m), 2.85-2.83 (1H, m), 2.04-1.96 (2H, m), 1.92-1.87 (1H, m), 1.74-1.69 (1H, m), 1.63-1.52 (1H, m), 1.27-1.17 (1H, m), 0.9 (9H, s), 0.06 (3H, s), 0.05 (3H, s); δ_C (100 MHz, $CDCl_3$) 157.7 (d, *J* 268.8), 132.1 (d, *J* 2.5), 131.6 (2C), 130.1 (2C, d, *J* 7.6 Hz), 121.0 (d, *J* 3.5), 108.0 (d, *J* 7.0), 68.5, 61.5, 59.8 (d, *J* 26.8), 53.0, 34.0, 25.9 (3C), 23.7, 18.2, –4.5, –4.6; δ_F (376 MHz, $CDCl_3$) –102.3 (1F,

dt, *J* 38.4, 17.3); *m/z* (ESI$^+$) 430 ([M($C_{20}H_{32}{}^{81}$BrFNOSi) + H]$^+$, 100%), 428 ([M($C_{20}H_{32}{}^{79}$BrFNOSi) + H]$^+$, 100%), 429 (4), 298 (64), 296 (4), 215 (50), 214 (4), 134 (17); HRMS (ESI$^+$) $C_{20}H_{32}{}^{79}$BrFNOSi ([M + H]$^+$) requires 428.1421; found 428.1417; **7a**-(*E*): δ_H (400 MHz, $CDCl_3$) 7.43 (2H, d, *J* 8.4), 7.17 (2H, d, *J* 8.4), 6.33 (1H, d, *J* 20.8), 3.75-3.67 (1H, m), 3.25 (2H, d, *J* 22.4), 2.91-2.87 (1H, m), 2.78-2.75 (1H, m), 1.98-1.84 (3H, m), 1.71-1.66 (1H, m), 1.59-1.47 (1H, m), 1.26-1.14 (1H, m), 0.88 (9H, s), 0.06 (3H, s), 0.05 (3H, s); δ_C (100 MHz, $CDCl_3$) 159.3 (d, *J* 256.0), 132.7 (d, *J* 13.3), 131.8 (2C), 130.5 (2C, d, *J* 2.7), 121.1, 111.3 (d, *J* 27.9), 68.4, 61.3, 55.6 (d, *J* 25.9), 52.9, 33.9, 25.9 (3C), 23.6, 18.2, –4.5, –4.6; δ_F (376 MHz, $CDCl_3$) –95.6 (1F, dt, *J* 22.4, 20.8); *m/z* (ESI$^+$) 430 ([M($C_{20}H_{32}{}^{81}$BrFNOSi) + H]$^+$, 100%), 428 ([M($C_{20}H_{32}{}^{79}$BrFNOSi) + H]$^+$, 100%), 429 (4), 298 (54), 296 (4), 215 (24), 214 (4), 134 (17); HRMS (ESI$^+$) $C_{20}H_{32}{}^{79}$BrFNOSi ([M + H]$^+$) requires 428.1421; found 428.1425.

1-(2-Fluorononon-2-enyl)-3-[(*tert*-butyldimethylsilyl)oxy]-piperidine 7b

General procedure C was followed with sulfone **3c** (400 mg, 0.81 mmol, 1.00 eq.), heptanal (130 µL, 0.92 mmol, 1.05 equiv), NaHMDS (1.0 M in THF, 1.32 mL, 1.32 mmol, 1.50 eq.) and THF (8.10 mL). The mixture was stirred 30 min at –78 °C and 3 h 30 at room temperature. The purification by flash column chromatography (pentane/EtOAc, 98:2) afforded fluoroalkene **7b** (233 mg, 80%, yellow oil) as a non-separable mixture of *Z*/*E* isomers (*Z*/*E* = 53:47); **7b**-(*Z*): δ_H (400 MHz, $CDCl_3$) 4.69 (1H, dt, *J* 37.0, 7.5), 3.76-3.69 (1H, m), 3.04 (2H, d, *J* 18.4), 2.95-2.91 (1H, m), 2.80-2.77 (1H, m), 2.10-2.05 (1H, m), 1.99-1.93 (3H, m), 1.70-1.64 (1H, m), 1.61-1.49 (1H, m), 1.35-1.13 (10H, m), 0.87 (12H, s), 0.05 (6H, s); δ_C (100 MHz, $CDCl_3$) 155.3 (d, *J* 254.2), 109.7 (d, *J* 14.6), 68.4, 61.0, 59.1 (d, *J* 27.3), 52.8, 34.0, 31.6, 29.3, 28.8, 25.9 (3C), 23.5, 23.4 (d, *J* 4.5), 22.5, 18.1, 14.0, –4.6 (2C); δ_F (376 MHz, $CDCl_3$) –112.2 (1F, dt, *J* 37.0, 18.4); **7b**-(*E*): δ_H (400 MHz, $CDCl_3$) 5.24 (1H, dt, *J* 22.2, 8.0), 3.76-3.69 (1H, m), 3.16 (2H, d, *J* 22.7), 2.95-2.91 (1H, m), 2.80-2.77 (1H, m), 2.10-2.05 (1H, m), 1.92-1.82 (3H, m,), 1.70-1.64 (1H, m), 1.61-1.49 (1H, m), 1.35-1.13 (10H, m), 0.87 (12H, s), 0.04 (6H, s); δ_C (100 MHz, $CDCl_3$) 155.5 (d, *J* 247.5), 110.4 (d, *J* 19.8), 68.3, 61.1, 54.5 (d, *J* 27.1), 52.7, 33.9, 31.5, 29.8 (d, *J* 2.1), 28.7, 25.8 (3C), 25.4 (d, *J* 8.4), 23.6, 22.5, 18.0, 14.0, –4.7 (2C); δ_F (376 MHz, $CDCl_3$) –104.4 (1F, dt, *J* 22.7, 22.2); *m/z* (ESI$^+$) 358 ([M + H]$^+$, 100%), 226 (57), 214 (2); HRMS (ESI$^+$) $C_{20}H_{41}FNOSi$ ([M + H]$^+$) requires 358.2941; found 358.2932.

1-(2-Fluoro-4,4-dimethylpent-2-en-1-yl)-3-[(*tert*-butyldimethylsilyl)oxy]piperidine 7c

General procedure C was followed with sulfone **3c** (400 mg, 0.87 mmol, 1.00 eq.), pivaldehyde (0.10 mL, 0.92 mmol, 1.05 eq.), NaHMDS (1.0 M in THF, 1.31 mL, 1.31 mmol, 1.50 eq.) and THF (8.70 mL). The mixture was stirred 30 min at –78 °C and 3 h 30 at room temperature. The purification by flash column chromatography (pentane/EtOAc, 95:5) afforded pure fluoroalkenes **7c**-(*Z*) and **7c**-(*E*) (235 mg, 82%, yellow oil, *Z*/*E* = 78:22); **7c**-(*Z*): δ_H (400 MHz, $CDCl_3$) 4.61 (1H, d, *J* 42.4), 3.76-3.69 (1H, m), 3.04-2.89 (3H, m), 2.77-2.75 (1H, m), 1.92-1.79 (3H, m), 1.70-1.50 (2H, m), 1.25-1.16 (1H, m), 1.12 (9H, m), 0.90 (9H, s), 0.05 (6H, s); δ_C (100 MHz, $CDCl_3$) 154.1 (d, *J* 258.3), 119.2 (d, *J* 9.8), 68.5, 60.5, 60.0 (d, *J* 27.7), 53.0, 34.1, 31.5, 30.5 (3C, d, *J* 3.2), 25.9 (3C), 23.7, 18.3, –4.6, –4.7; δ_F (376 MHz, $CDCl_3$) –109.0 (1F, dt, *J* 42.4, 18.8); *m/z* (ESI$^+$) 330 ([M + H]$^+$, 100%), 198 (91); HRMS (ESI$^+$) $C_{18}H_{37}FNOSi$ ([M + H]$^+$) requires 330.2628; found 330.2629; **7c**-(*E*): δ_H (400 MHz, $CDCl_3$) 5.30 (1H, d, *J* 29.2), 3.73-3.68 (1H, m), 3.24 (2H, d, *J* 23.5), 2.96-2.92 (1H, m), 2.80-2.77 (1H, m), 1.96-1.85 (3H, m), 1.68-1.64 (1H, m), 1.58-1.51 (1H, m), 1.25-1.12 (1H, m), 1.09 (9H, m), 0.87 (9H, s), 0.03 (6H, s); δ_C (100 MHz, $CDCl_3$) 154.8 (d, *J* 243.0), 121.0 (d, *J* 21.1), 68.5, 61.5, 55.8 (d, *J* 27.8), 53.0, 34.0, 31.4 (3C, d, *J* 1.2), 30.1 (d, *J* 10.0), 25.9 (3C), 23.8, 18.2, –4.5, –4.6; δ_F (376 MHz, $CDCl_3$) –100.6 (1F, dt, *J* 29.2, 23.5); *m/z* (ESI$^+$) 330 ([M + H]$^+$, 100%), 198 (53); HRMS (ESI$^+$) $C_{18}H_{37}FNOSi$ ([M + H]$^+$) requires 330.2628; found 330.2643.

1-[3-(4-Bromophenyl)-2-fluoroallyl]-2-[(*tert*-butyldiphenyl)oxy-methyl]piperdine 8a

General procedure C was followed sulfone **3d** (611 mg, 1.02 mmol, 1.00 eq.), pivaldehyde (0.11 mL, 1.07 mmol, 1.05 eq.), NaHMDS (1.0 M in THF, 1.53 mL, 1.53 mmol, 1.50 eq.) and THF (10.20 mL). The mixture was stirred 30 min at –78 °C and 3 h at room temperature. The purification by flash column chromatography (pentane/EtOAc, 95:5) afforded pure alkenes **8a**-(*Z*) and **8a**-(*E*) (429 mg, 51%, brown oil, *Z*/*E* = 46/54); **8a**-(*Z*): δ_H (400 MHz, $CDCl_3$) 7.68 (4H, d, *J* 6.8), 7.45-7.31 (10H, m), 5.60 (1H, d, *J* 38.8), 3.90 (1H, dd, *J* 10.6, 5.2), 3.79-3.71 (1H, m), 3.61 (1H, dd, *J* 10.6, 5.0), 3.20-3.11 (1H, m), 2.96-2.93 (1H, m), 2.56-2.54 (1H, m), 2.33-2.28 (1H, m), 1.75-1.66 (2H, m), 1.62-1.56 (1H, m), 1.53-1.47 (1H, m), 1.39-1.27 (2H, m), 1.07 (9H, s); δ_C (100 MHz, $CDCl_3$) 159.1 (d, *J* 269.0), 135.6 (2C), 135.5 (2C), 133.4 (2C), 132.3 (d, *J* 2.3), 131.4 (2C), 130.0, 129.9, 129.6 (2C), 127.7 (4C), 120.6 (d, *J* 3.5), 106.9 (d, *J* 6.8), 66.5, 62.5, 55.9 (d, *J* 27.3), 52.8, 29.1, 26.8 (3C), 25.6, 23.3, 19.2; δ_F (376 MHz, $CDCl_3$) –101.8 (1F, dt, *J* 38.8, 14.0); *m/z* (ESI$^+$) 568 ([M($C_{31}H_{38}{}^{81}$BrFNOSi) + H]$^+$, 100%), 566 ([M($C_{31}H_{38}{}^{79}$BrFNOSi) + H]$^+$, 100%), 488 (28), 352 (4), 310 (70), 308 (8), 274 (26), 213 (32), 198 (3), 134 (12); HRMS (ESI$^+$) $C_{31}H_{38}{}^{79}$BrFNOSi ([M + H]$^+$) requires 566.1890; found 566.1902; **8a**-(*E*): δ_H (400 MHz, $CDCl_3$) 7.63-7.61 (4H, m), 7.43-7.36 (8H, m), 7.11 (2H, d, *J* 8.1), 6.27 (1H, d, *J* 21.2), 3.90-3.81 (2H, m), 3.53 (1H, dd, *J* 10.7, 5.1), 3.22 (1H, dd, *J* 23.6, 14.4), 2.87-2.84 (1H, m), 2.46-2.45 (1H, m), 2.20-2.15 (1H, m), 1.69-1.61 (2H, m), 1.57-1.54 (1H, m), 1.47-1.44 (1H, m), 1.34-1.25 (2H, m), 1.03 (9H, s); δ_C (100 MHz, $CDCl_3$) 160.2 (d, *J* 256.3), 135.6 (2C), 135.5 (2C), 133.5 (2C), 133.4 (2C), 131.4 (2C), 130.5 (d, *J* 2.6), 129.7 (2C), 127.7 (4C), 120.9, 110.8 (d, *J* 28.2), 66.3, 63.2, 52.3 (d, *J* 25.0), 52.2, 29.0, 26.8 (3C), 25.5, 23.2, 19.1; δ_F (376 MHz, $CDCl_3$) –95.8 (1F, dt, *J* 23.6, 21.2); *m/z* (ESI$^+$) 568 ([M($C_{31}H_{38}{}^{81}$BrFNOSi) + H]$^+$, 100%), 566 ([M($C_{31}H_{38}{}^{79}$BrFNOSi) + H]$^+$, 100%), 488 (28), 310 (78), 274 (5), 213 (8), 198 (4), 134 (4); HRMS (ESI$^+$) $C_{31}H_{38}{}^{79}$BrFNOSi ([M + H]$^+$) requires 566.1890; found 566.1895.

(2-Fluorononon-2-enyl)-2-[(*tert*-butyldiphenyl)oxy]-piperdine-methanol 8b

General procedure C was followed with sulfone **3d** (650 mg, 1.24 mmol, 1.00 eq.), heptanal (180 µL, 1.29 mmol, 1.05 eq.), NaHMDS (1.0 M in THF, 1.86 mL, 1.86 mmol, 1.50 eq.) and THF (12.40 mL).

The mixture was stirred 30 min at –78 °C and 2 h at room temperature. The purification by flash column chromatography (pentane/EtOAc, 95:5) afforded fluoroalkene **8b** (428 mg, 70%, yellow oil) as a non-separable mixture of *Z*/*E* isomers (*Z*/*E* = 60:40); **8b**-(*Z*): δ_H (400 MHz, $CDCl_3$) 7.73-7.71 (2H, m), 7.68-7.66 (2H, m), 7.42-7.36 (6H, m), 4.59 (1H, dt, *J* 36.0, 8.0), 3.93-3.87 (1H, m), 3.58-3.45 (2H, m), 3.02-2.93 (1H, m), 2.88-2.84 (1H, m), 2.47-2.46 (1H, m), 2.15-2.12 (1H, m), 2.06-2.03 (2H, m), 1.79-1.77 (1H, m), 1.68-1.65 (1H, m), 1.59-1.56 (1H, m), 1.52-1.47 (1H, m), 1.28-1.19 (10H, m), 1.07 (9H, s), 0.90-0.87 (3H, m); δ_C (100 MHz, $CDCl_3$) 156.0 (d, *J* 255.1), 135.6 (2C), 135.3 (2C), 134.9 (4C), 133.7, 133.6 (2C), 129.7, 127.7, 109.1 (d, *J* 14.5), 66.3, 62.4, 55.4 (d, *J* 27.2), 52.5, 31.6, 29.1 (d, *J* 1.4), 28.9, 26.9 (3C), 25.7, 23.6 (d, *J* 2.4), 23.5, 22.7, 19.3, 14.2; δ_F (376 MHz, $CDCl_3$) –111.4 (1F, dt, *J* 36.0, 20.7); **8b**-(*E*): δ_H (400 MHz, $CDCl_3$) 7.73-7.71 (2H, m), 7.68-7.66 (2H, m), 7.42-7.36 (6H, m), 5.25-5.12 (1H, m), 3.93-3.87 (1H, m), 3.66 (1H, dd, *J* 20.0, 16.0), 3.58-3.45 (1H, m), 3.10-3.00 (1H, m), 2.88-2.84 (1H, m), 2.15-2.12 (1H, m), 2.06-2.03 (2H, m), 1.79-1.77 (1H, m), 1.68-1.65 (1H, m), 1.59-1.56 (1H, m), 1.52-1.47 (1H, m), 1.28-1.19 (11H, m), 1.05 (9H, s), 0.90-0.87 (3H, m); δ_C (100 MHz, $CDCl_3$) 156.8 (d, *J* 247.9), 135.7 (2C), 135.3 (2C), 134.9 (4C), 133.7 (2C), 129.7, 127.8, 109.8 (d, *J* 20.0), 65.9, 63.3, 52.4, 51.2 (d, *J* 26.5), 31.7, 29.4 (d, *J* 1.4), 29.3, 28.9, 26.7 (3C), 25.7, 23.6 (d, *J* 2.4), 23.5, 22.6, 19.1, 14.2; δ_F (376 MHz, $CDCl_3$) –104.6 (1F, dt, *J* 22.6, 22.7); *m*/*z* (ESI^+) 496 ($[M + H]^+$, 93%), 418 (39), 308 (5), 274 (3), 240 (100), 220 (5); HRMS (ESI^+) $C_{31}H_{47}FNOSi$ ($[M + H]^+$) requires 496.3411; found 496.3419.

1-(2-Fluoro-4,4-dimethylpent-2-en-1-yl)-2-[(*tert*-butyldiphenyl)-oxy]piperdinemethanol 8c

General procedure C was followed with sulfone **3d** (611 mg, 1.02 mmol, 1.00 eq.), pivaldehyde (0.11 mL, 1.07 mmol, 1.05 eq.), NaHMDS (1.0 M in THF, 1.53 mL, 1.53, 1.50 eq.) and THF (10.20 mL). The mixture was stirred 30 min at –78°C and 3 h at room temperature. The purification by flash column chromatography (pentane/EtOAc, 95:5) afforded pure alkenes **8c**-(*Z*) and **8c**-(*E*) (429 mg, 90%, yellow oil, *Z*/*E* = 46:54); **8c**-(*Z*): δ_H (400 MHz, $CDCl_3$) 7.70-7.67 (4H, m), 7.44-7.38 (6H, m), 4.56 (1H, d, *J* 42.8), 3.90 (1H, dd, *J* 10.4, 4.9), 3.55 (1H, dd, *J* 10.4, 5.8), 3.44 (1H, dt, *J* 15.2, 15.3), 2.99-2.88 (2H, m), 2.49-2.48 (1H, m), 2.24-2.18 (1H, m), 1.82-1.80 (1H, m), 1.71-1.68 (1H, m), 1.62-1.58 (1H, m), 1.56-1.49 (1H, m), 1.45-1.24 (2H, m), 1.13 (9H, s), 1.08 (9H, s); δ_C (100 MHz, $CDCl_3$) 155.0 (d, *J* 260.0), 135.4 (2C), 135.3 (2C), 133.4, 133.3, 129.4 (2C), 127.5 (2C), 127.4 (2C), 118.0 (d, *J* 10.0), 66.1, 62.2, 55.8 (d, *J* 28.0), 52.2, 31.1, 30.3 (3C, d, *J* 3.0), 29.0, 26.7 (3C), 25.4, 23.3, 19.0; δ_F (376 MHz, $CDCl_3$) –108.4 (1F, dt, *J* 42.8, 18.8); *m*/*z* (ESI^+) 468 ($[M + H]^+$, 100%), 390 (14), 212 (51); HRMS (ESI^+) $C_{29}H_{43}FNOSi$ ($[M + H]^+$) requires 468.3098; found 468.3098; **8c**-(*E*): δ_H (400 MHz, $CDCl_3$) 7.67-7.65 (4H, m), 7.44-7.36 (6H, m), 5.27 (1H, d, *J* 29.2), 3.93-3.80 (2H, m), 3.56 (1H, dd, *J* 10.8, 4.8), 3.17 (1H, dd, *J* 26.4, 14.6), 2.95-2.93 (1H, m), 2.43 (1H, br s), 2.15 (1H, t, *J* 10.0), 1.64-1.56 (3H, m), 1.49-1.43 (1H, m), 1.33-1.20 (2H, m), 1.10 (9H, s), 1.05 (9H, s); δ_C (100 MHz, $CDCl_3$) 155.6 (d, *J* 245.0), 135.5 (2C), 135.4 (2C), 133.5 (2C), 129.6 (2C), 127.7 (2C), 127.6 (2C), 120.3 (d, *J* 21.0), 66.6, 63.7, 52.5 (d, *J* 26.0), 51.8, 31.4 (3C, d, *J* 1.0), 29.9 (d, *J* 10.0), 29.1, 26.7 (3C), 25.2, 23.4, 19.1; δ_F (376 MHz, $CDCl_3$) –101.3 (1F, dt, *J* 29.2, 26.4); *m*/*z* (ESI^+) 468 ($[M + H]^+$, 54%), 390 (20), 308 (7), 212 (49), 146 (61), 128 (8), 114 (29); HRMS (ESI^+) $C_{29}H_{43}FNOSi$ ($[M + H]^+$) requires 468.3098; found 468.3093.

1-[3-(4-Bromophenyl)-2-fluoroallyl]-4-(benzyloxy)piperidine 9a

General procedure C was followed with sulfone **4** (200 mg, 0.46 mmol, 1.00 eq.), 4-bromobenzaldehyde (89 mg, 0.48 mmol, 1.05 eq.), NaHMDS (1.0 M in THF, 0.69 mL, 0.69 mmol, 1.50 eq.) and THF (4.60 mL). The mixture was stirred 30 min at –78 °C and 3 h 30 at room temperature. The purification by flash column chromatography (pentane/EtOAc, 90:10 and 80:20) afforded pure alkenes **9a**-(*Z*) and **9a**-(*E*) (155 mg, 80%, yellow oil, *Z*/*E* = 52:48); **9a**-(*Z*): δ_H (400 MHz, $CDCl_3$) 7.34 (2H, d, *J* 8.8), 7.27-7.21 (6H, m), 7.20-7.45 (1H, m), 5.51 (1H, d, *J* 38.4), 4.45 (2H, s), 3.38-3.34 (1H, m), 3.08 (2H, d, *J* 17.2), 2.75-2.72 (2H, m), 2.24-2.19 (2H, m), 1.95-1.84 (2H, m), 1.70-1.61 (2H, m); δ_C (100 MHz, $CDCl_3$) 157.6 (d, *J* 268.4), 138.8, 132.0, 131.5 (2C), 130.0 (2C, d, *J* 7.7), 128.3 (2C), 127.4 (3C), 120.8, 107.7 (d, *J* 6.8), 73.7, 69.6, 59.7 (d, *J* 26.9), 50.8 (2C), 31.1 (2C); δ_F (376 MHz, $CDCl_3$) –102.3 (1F, dt, *J* 38.4, 17.2); *m*/*z* (ESI^+) 406 ($[M(C_{21}H_{24}{}^{81}BrFNO) + H]^+$, 85%), 404 ($[M(C_{21}H_{24}{}^{79}BrFNO) + H]^+$, 85%), 312 (4), 296 (16), 213 (100), 190 (11), 134 (42); HRMS (ESI^+) $C_{21}H_{24}{}^{79}BrFNO$ ($[M + H]^+$) requires 404.1025; found 404.1010; **9a**-(*E*): δ_H (400 MHz, $CDCl_3$) 7.36 (2H, d, *J* 8.3), 7.28-7.27 (4H, m), 7.24-7.19 (1H, m), 7.11 (2H, d, *J* 8.3), 6.26 (1H, d, *J* 20.8), 4.47 (2H, s), 3.39-3.35 (1H, m), 3.18 (2H, d, *J* 22.4), 2.73-2.71 (2H, m), 2.21-2.17 (2H, m), 1.88-1.85 (2H, m), 1.70-1.62 (2H, m); δ_C (100 MHz, $CDCl_3$) 159.1 (d, *J* 255.5), 138.7, 132.4 (d, *J* 13.2), 131.4 (2C), 130.3 (2C, d, *J* 2.7), 128.2 (2C), 127.3 (2C), 127.2, 120.9, 111.1 (d, *J* 28.0), 73.6, 69.5, 55.3 (d, *J* 25.9), 50.6 (2C), 30.9 (2C); δ_F (376 MHz, $CDCl_3$) –95.6 (1F, dt, *J* 22.4, 20.8); *m*/*z* (ESI^+) 406 ($[M(C_{21}H_{24}{}^{81}BrFNO) + H]^+$, 100%), 404 ($[M(C_{21}H_{24}{}^{79}BrFNO) + H]^+$, 100%), 312 (5), 296 (21), 213 (32), 190 (5), 134 (21); HRMS (ESI^+) $C_{21}H_{24}{}^{79}BrFNO$ ($[M + H]^+$) requires 404.1025; found 404.1009.

1-(2-Fluorononon-2-en-1-yl)-4-(benzyloxy)piperidine 9b

General procedure C was followed with sulfone **4** (200 mg, 0.46 mmol, 1.00 eq.), heptanal (70 µL, 0.48 mmol, 1.05 eq.), NaHMDS (1.0 M in THF, 0.69 mL, 0.69 mmol, 1.50 eq.) and THF (4.60 mL). The mixture was stirred 30 min at –78 °C and 5 h 30 at room temperature. The purification by flash column chromatography (pentane/EtOAc, 90:10) afforded pure alkenes **9b**-(*Z*) and **9b**-(*E*) (114 mg, 75%, colorless liquid, *Z*/*E* = 64:36); **9b**-(*Z*): δ_H (400 MHz, $CDCl_3$) 7.36-7.33 (4H, m), 7.30-7.26 (1H, m), 4.68 (1H, dt, *J* 37.1, 7.5), 4.54 (2H, s), 3.46-3.40 (1H, m), 3.03 (2H, d, *J* 18.8), 2.78-2.75 (2H, m), 2.22 (2H, t, *J* 9.3), 2.09 (2H, q, *J* 6.9), 1.96-1.92 (2H, m), 1.77-1.68 (2H, m), 1.36-1.25 (8H, m), 0.88 (3H, t, *J* 6.9); δ_C (100 MHz, $CDCl_3$) 155.5 (d, *J* 254.1), 139.0, 128.3 (2C), 127.5 (2C), 127.4, 109.6 (d, *J* 14.7), 74.1, 69.6, 59.2 (d, *J* 27.2), 50.7 (2C), 31.6 (2C), 31.1, 29.3 (d, *J* 1.6), 28.8, 23.5 (d, *J* 4.4), 22.6, 14.0; δ_F (376 MHz, $CDCl_3$) –112.3 (1F, dt, *J* 37.1, 18.8); *m*/*z* (ESI^+) 334 ($[M + H]^+$, 100%), 242 (6), 226 (36), 190 (10); HRMS (ESI^+) $C_{21}H_{33}FNO$ ($[M + H]^+$) requires 334.2546; found 334.2539; **9b**-(*E*): δ_H (400 MHz, $CDCl_3$) 7.36-7.34 (4H, m), 7.30-7.27 (1H, m), 5.25 (1H, dt, *J* 22.2, 8.0), 4.55 (2H, s), 3.47-3.43 (1H, m), 3.17 (2H, d, *J* 22.6), 2.80-2.77 (2H, m), 2.29 (2H, t, *J* 9.2), 2.01-1.93 (4H, m), 1.79-

1.70 (2H, m), 1.35-1.28 (8H, m), 0.91-0.88 (3H, m); δ_C (100 MHz, $CDCl_3$) 155.4 (d, *J* 247.0), 138.8, 128.2 (2C), 127.3 (2C), 127.2, 110.3 (d, *J* 19.7), 73.6, 69.5, 54.4 (d, *J* 27.1), 50.5 (2C), 31.5 (2C), 30.9, 29.7 (d, *J* 2.1), 28.6, 25.3 (d, *J* 8.4), 22.5, 13.9; δ_F (376 MHz, $CDCl_3$) –104.4 (1F, dt, *J* 22.6, 22.2); *m*/*z* (ESI^+) 334 ($[M + H]^+$, 100%), 242 (5), 226 (27), 190 (5); HRMS (ESI^+) $C_{21}H_{33}FNO$ ($[M + H]^+$) requires 334.2546; found 334.2557.

1-(2-Fluoro-4,4-dimethylpent-2-en-1-yl)-4-(benzyloxy)-piperidine 9c

General procedure C was followed with sulfone **4** (200 mg, 0.46 mmol, 1.00 eq.), pivaldehyde (52 µL, 0.48 mmol, 1.05 eq.), NaHMDS (1.0 M in THF, 0.69 mL, 0.69 mmol, 1.50 eq.) and THF (4.60 mL). The mixture was stirred 30 min at –78 °C and 2 h 30 at room temperature. The purification by flash column chromatography (pentane/EtOAc, 80:20) afforded pure alkenes **9c**-(*Z*) and **9c**-(*E*) (91 mg, 65%, colorless liquid, *Z*/*E* = 81:19); **9c**-(*Z*): δ_H (400 MHz, $CDCl_3$) 7.35-7.34 (4H, m), 7.27 (1H, s), 4.62 (1H, d, *J* 42.4), 4.55 (2H, s), 3.48-3.42 (1H, m), 2.98 (2H, d, *J* 18.8), 2.79-2.76 (2H, m), 2.26-2.22 (2H, m), 1.97-1.93 (2H, m), 1.78-1.70 (2H, m), 1.13 (9H, s); δ_C (100 MHz, $CDCl_3$) 154.2 (d, *J* 258.5), 139.1, 128.4 (2C), 127.5 (2C), 127.4, 119.2 (d, *J* 9.7), 74.1, 69.7, 60.0 (d, *J* 27.7), 50.6 (2C), 31.5 (2C), 31.1 (3C), 30.5 (d, *J* 3.2); δ_F (376 MHz, $CDCl_3$) –109.0 (1F, dt, *J* 42.4, 18.8); *m*/*z* (ESI^+) 306 ($[M + H]^+$, 100%), 214 (7), 198 (40), 190 (10), 115 (3); HRMS (ESI^+) $C_{19}H_{29}FNO$ ($[M + H]^+$) requires 306.2233; found 306.2230; **9c**-(*E*): δ_H (400 MHz, $CDCl_3$) 7.36-7.35 (4H, m), 7.27 (1H, s), 5.33 (1H, d, *J* 29.2), 4.56 (2H, s), 3.48-3.44 (1H, m), 3.27 (2H, d, *J* 22.8), 2.84-2.82 (2H, m), 2.33-2.28 (2H, m), 1.95 (2H, br s), 1.79-1.70 (2H, m), 1.13 (9H, s); δ_C (100 MHz, $CDCl_3$) 154.6 (d, *J* 242.8), 138.9, 128.3 (2C), 127.4 (2C), 127.3, 121.1 (d, *J* 21.0), 73.8, 69.6, 55.6 (d, *J* 27.9), 50.7 (2C), 31.3 (3C, d, *J* 1.2), 31.1 (2C), 30.1 (d, *J* 10.0); δ_F (376 MHz, $CDCl_3$) –100.5 (1F, dt, *J* 29.2, 22.8); *m*/*z* (ESI^+) 306 ($[M + H]^+$, 100%), 214 (4), 198 (23), 190 (3), 91 (3), 84 (5); HRMS (ESI^+) $C_{19}H_{29}FNO$ ($[M + H]^+$) requires 306.2233; found 306.2234.

(*Z*)-1-(3-(4-Bromophenyl)-2-fluoroallyl)-4-hydroxypiperidine 10a-(*Z*)

General procedure D was followed with fluoroalkene **6a**-(*Z*) (120 mg, 0.26 mmol, 1.00 eq.), TBAF (1.0 M in THF, 0.31 mL, 0.31 mmol, 1.20 eq.) and THF (2.60 mL). The mixture was stirred 24 h at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 98:2) afforded compound **10a**-(*Z*) (44 mg, 54%, yellow oil); δ_H (400 MHz, $CDCl_3$) 7.44 (2H, d, *J* 8.8), 7.35 (2H, d, *J* 8.4), 5.61 (1H, d, *J* 38.4), 3.76-3.71 (1H, m), 3.19 (2H, d, *J* 17.6), 2.86-2.83 (2H, m), 2.33-2.28 (2H, m), 1.95-1.91 (2H, m), 1.71-1.60 (3H, m); δ_C (100 MHz, $CDCl_3$) 157.4 (d, *J* 268.5), 131.9 (d, *J* 2.7), 131.5 (2C), 130.0 (2C, d, *J* 7.7), 120.9 (d, *J* 3.5), 108.0 (d, *J* 7.2), 67.5, 59.6 (d, *J* 26.7), 50.7 (2C), 34.2 (2C); δ_F (376 MHz, $CDCl_3$) –102.4 (1F, dt, *J* 38.4, 17.6); *m*/*z* (ESI^+) 316 ($[M(C_{14}H_{18}{}^{81}BrFNO) + H]^+$, 67%), 314 ($[M(C_{14}H_{18}{}^{79}BrFNO) + H]^+$, 67%), 213 (100), 134 (36); HRMS (ESI^+) $C_{14}H_{18}{}^{79}BrFNO$ ($[M + H]^+$) requires 314.0556; found 314.0558.

(*E*)-1-(3-(4-Bromophenyl)-2-fluoroallyl)-4-hydroxypiperidine 10a-(*E*)

General procedure D was followed with fluoroalkene **6a**-(*E*) (50 mg, 0.12 mmol, 1.00 eq.), TBAF (1.0 M in THF, 0.14 mL, 0.14 mmol, 1.17 eq.) and THF (1.20 mL). The mixture was stirred 24 h at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 98:2) afforded compound **10a**-(*E*) (10 mg, 26%, yellow oil); δ_H (400 MHz, $CDCl_3$) 7.45 (2H, d, *J* 8.4) 7.17 (2H, d, *J* 8.4), 6.33 (1H, d, *J* 20.8), 3.74-3.67 (1H, m), 3.25 (2H, d, *J* 22.4), 2.80-2.77 (2H, m), 2.27-2.22 (2H, m), 1.92-1.88 (2H, m), 1.65-1.57 (3H, m); δ_C (100.61 MHz, $CDCl_3$) 159.1 (d, *J* 255.5), 132.5 (d, *J* 13.2), 131.6 (2C), 130.4 (2C, d, *J* 2.7), 121.1, 111.4 (d, *J* 28.0), 67.5, 55.4 (d, *J* 25.9), 50.7 (2C), 34.3 (2C); δ_F (376 MHz, $CDCl_3$) –95.9 (1F, dt, *J* 22.4, 20.8); *m*/*z* (ESI^+) 316 ($[M(C_{14}H_{18}{}^{81}BrFNO) + H]^+$, 100%), 314 ($[M(C_{14}H_{18}{}^{79}BrFNO) + H]^+$, 100%), 296 (3), 213 (54), 134 (43), 100 (3); HRMS (ESI^+) $C_{14}H_{18}{}^{79}BrFNO$ ($[M + H]^+$) requires 314.0556; found 314.0560.

1-(2-Fluorononon-2-en-1-yl)-4-hydroxypiperidine 10b

General procedure D was followed with fluoroalkene **6b** (120 mg, 0.35 mmol, 1.00 eq.), TBAF (1.0 M in THF, 0.42 mL, 0.42 mmol, 1.20 eq.) and THF (3.50 mL). The mixture was stirred 48 h at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 95:5) afforded **10b** (77 mg, 90%, yellow oil) as a non-separable mixture of isomers (*Z*/*E* = 61:39); **10b**-(*Z*): δ_H (400 MHz, $CDCl_3$) 4.64 (1H, dt, *J* 36.0, 8.0), 3.64-3.60 (1H, m), 2.99 (2H, d, *J* 20.0), 2.75-2.72 (2H, m), 2.55 (1H, br s), 2.21-2.12 (2H, m), 2.06-1.99 (2H, m), 1.86-1.82 (2H, m), 1.61-1.53 (2H, m), 1.29-1.22 (8H, m), 0.84-0.81 (3H, m); δ_C (100 MHz, $CDCl_3$) 155.1 (d, *J* 255.0), 109.8 (d, *J* 15.0), 67.5, 58.9 (d, *J* 27.0), 50.5 (2C), 34.1 (2C), 31.4, 29.1 (d, *J* 2.0), 28.6, 23.3 (d, *J* 4.0), 22.4, 13.9; δ_F (376 MHz, $CDCl_3$) –112.1 (1F, dt, *J* 36.0, 20.0); **10b**-(*E*): δ_H (400 MHz, $CDCl_3$) 5.19 (1H, dt, *J* 24.0, 8.0), 3.64-3.60 (1H, m), 3.10 (2H, d, *J* 24.0), 2.75-2.72 (2H, m), 2.55 (1H, br s), 2.21-2.12 (2H, m), 1.92 (2H, q, *J* 8.0), 1.86-1.82 (2H, m), 1.61-1.53 (2H, m), 1.29-1.22 (8H, m), 0.84-0.81 (3H, m); δ_C (125 MHz, $CDCl_3$) 155.3 (d, *J* 247.0), 110.4 (d, *J* 20.0), 67.5, 54.2 (d, *J* 28.0), 50.5 (2C), 34.1 (2C), 31.4, 29.6 (d, *J* 3.0), 28.5, 25.2 (d, *J* 8.0), 22.4, 13.7; δ_F (376 MHz, $CDCl_3$) –104.3 (1F, dt, *J* 24.0, 23.9); *m*/*z* (ESI^+) 244 ($[M + H]^+$, 100%), 226 (48), 100 (19), 84 (15); HRMS (ESI^+) $C_{14}H_{27}FNO$ ($[M + H]^+$) requires 244.2077; found 244.2065.

1-(2-Fluoro-4,4-dimethylpent-2-en-1-yl)-4-hydroxypiperidine 10c

General procedure D was followed with fluoroalkene **6c** (260 mg, 0.79 mmol, 1.00 eq.), TBAF (1.0 M in THF, 0.90 mL, 0.90 mmol, 1.14 eq.) and THF (7.90 mL). The mixture was stirred 48 h at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 95:5) afforded **10c** (63 mg, 37%, yellow oil) as a non-separable mixture of isomers (*Z*/*E* = 74:26); **10c**-(*Z*): δ_H (400 MHz, $CDCl_3$) 4.60 (1H, d, *J* 42.4), 3.72-3.67 (1H, m), 2.96 (2H, d, *J* 18.8), 2.82-2.75 (2H, m), 2.28-2.16 (2H, m), 1.93-1.88 (2H, m), 1.66-1.57 (3H, m), 1.12 (9H, s); δ_C (100 MHz, $CDCl_3$) 154.2 (d, *J* 258.4), 119.1 (d, *J* 9.8), 67.8, 59.9 (d, *J* 27.6), 50.6 (2C), 34.4 (2C), 30.5 (3C, d, *J* 3.3), 30.0; δ_F (376 MHz, $CDCl_3$) –109.2 (1F, dt, *J* 42.4, 18.8); **10c**-(*E*): δ_H (400 MHz, $CDCl_3$) 5.31 (1H, d, *J* 29.2), 3.72-3.67 (1H, m), 3.24 (2H, d, *J* 23.2), 2.82-2.75 (2H, m), 2.28-2.16 (2H, m), 1.93-1.88 (2H, m), 1.66-1.57 (3H, m), 1.11 (9H, s); δ_C (100

MHz, $CDCl_3$) 154.8 (d, *J* 242.6), 121.0 (d, *J* 20.9), 67.8, 55.7 (d, *J* 27.9), 50.8 (2C), 34.5 (2C), 31.4 (3C, d, *J* 1.3), 30.1; δ_F (376 MHz, $CDCl_3$) –100.6 (1F, dt, *J* 29.2, 23.2); *m*/*z* (ESI^+) 216 ($[M + H]^+$, 100%), 198 (21), 115 (5), 100 (10), 84 (14); HRMS (ESI^+) $C_{12}H_{23}FNO$ ($[M + H]^+$) requires 216.1764; found 216.1774.

(*Z*)-1-[3-(4-Bromophenyl)-2-fluoroallyl]-3-hydroxypiperidine 11a-(*Z*)

General procedure D was followed with fluoroalkene **7a**-(*Z*) (87 mg, 0.20 mmol, 1.00 eq.), TBAF (1.0 M in THF, 0.24 mL, 0.24 mmol, 1.20 eq.) and THF (2.00 mL). The mixture was stirred 24 h at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 98:2) afforded fluoroalkene **11a**-(*Z*) (40 mg, 63%, yellow oil); δ_H (400 MHz, $CDCl_3$) 7.43 (2H, d, *J* 8.5), 7.34 (2H, d, *J* 8.5), 5.58 (1H, d, *J* 38.4), 3.85-3.83 (1H, m), 3.20 (2H, d, *J* 18.0), 2.67-2.65 (1H, m), 2.59 (1H, br s), 2.50-2.45 (3H, m), 1.85-1.78 (1H, m), 1.66-1.63 (1H, m), 1.60-1.51 (2H, m); δ_C (100 MHz, $CDCl_3$) 157.1 (d, *J* 269.0), 131.6 (d, *J* 2.6), 131.4 (2C), 129.9 (2C, d, *J* 7.6), 120.8 (d, *J* 3.5), 108.0 (d, *J* 7.1), 66.1, 59.8, 59.5 (d, *J* 26.6), 53.0, 31.4, 21.6; δ_F (376 MHz, $CDCl_3$) –102.4 (1F, dt, *J* 38.4, 18.0); *m*/*z* (ESI^+) 316 ($[M(C_{14}H_{18}{}^{81}BrFNO) + H]^+$, 100%), 314 ($[M(C_{14}H_{18}{}^{79}BrFNO) + H]^+$, 100%), 213 (66), 134 (18); HRMS (ESI^+) $C_{14}H_{18}{}^{79}BrFNO$ ($[M + H]^+$) requires 314.0556; found 314.0552.

(*E*)-1-[3-(4-Bromophenyl)-2-fluoroallyl]-3-hydroxypiperidine 11a-(*E*)

General procedure D was followed with fluoroalkene **7a**-(*E*) (170 mg, 0.40 mmol, 1.00 eq.), TBAF (1.0 M in THF, 0.48 mL, 0.48 mmol, 1.20 eq.) and THF (4.00 mL). The mixture was stirred 24 h at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 98:2) afforded compound **11a**-(*E*) (101 mg, 80%, yellow oil); δ_H (400 MHz, $CDCl_3$) 7.43 (2H, d, *J* 8.0), 7.11 (2H, d, *J* 8.0), 6.31 (1H, d, *J* 20.8), 3.82-3.78 (1H, m), 3.26 (2H, d, *J* 22.0), 2.64-2.57 (2H, m), 2.42-2.40 (3H, m), 1.78-1.73 (1H, m), 1.64-1.60 (1H, m), 1.56-1.47 (2H, m); δ_C (100 MHz, $CDCl_3$) 158.8 (d, *J* 255.8), 132.3 (d, *J* 13.1), 131.5 (2C), 130.3 (2C, d, *J* 2.7), 121.3 (d, *J* 0.8), 111.3 (d, *J* 27.8), 66.1, 59.9, 55.4 (d, *J* 25.9), 53.1, 31.5, 21.6; δ_F (376 MHz, $CDCl_3$) –95.8 (1F, dt, *J* 22.0, 20.8); *m*/*z* (ESI^+) 316 ($[M(C_{14}H_{18}{}^{81}BrFNO) + H]^+$, 100%), 314 ($[M(C_{14}H_{18}{}^{79}BrFNO) + H]^+$, 100%), 296 (3), 213 (43), 134 (21); HRMS (ESI^+) $C_{14}H_{18}{}^{79}BrFNO$ ($[M + H]^+$) requires 314.0556; found 314.0549.

***N*-(2-Fluorononen-2-enyl)-3-hydroxypiperidine 11b**

General procedure D was followed with fluoroalkene **7b** (130 mg, 0.36 mmol, 1.00 eq.), TBAF (1.0 M in THF, 0.44 mL, 0.44 mmol, 1.22 eq.) and THF (3.60 mL). The mixture was stirred 24 h at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 98:2) afforded **11b** (62 mg, 70%, yellow oil) as a non-separable mixture of isomers (*Z*/*E* = 63:37); **11b**-(*Z*): δ_H (400 MHz, $CDCl_3$) 4.66 (1H, dt, *J* 37.0, 7.5), 3.83-3.79 (1H, m), 3.03 (2H, d, *J* 18.8), 2.57 (2H, br s), 2.40-2.39 (3H, m), 2.07 (2H, q, *J* 6.5), 1.82-1.75 (1H, m), 1.63-1.61 (1H, m), 1.57-1.50 (2H, m), 1.34-1.25 (8H, m), 0.88-0.85 (3H, m); δ_C (100 MHz, $CDCl_3$) 155.3 (d, *J* 254.5), 109.9 (d, *J* 14.6), 66.4, 59.9, 59.3 (d, *J* 27.3), 53.1, 31.9, 31.7, 29.3 (d, *J* 1.6), 28.9, 23.6 (d, *J* 4.5), 22.7, 21.8, 14.1; δ_F (376 MHz, $CDCl_3$) –112.0 (1F, dt, *J* 37.0, 18.8); **11b**-(*E*): δ_H (400 MHz, $CDCl_3$) 5.22 (1H, dt, *J* 22.1, 8.0), 3.83-3.79 (1H, m), 3.15 (2H, d, *J* 22.6), 2.57 (2H, br s), 2.40-2.39 (3H, m), 1.95 (2H, q, *J* 7.3), 1.82-1.75 (1H, m), 1.63-1.61 (1H, m), 1.57-1.50 (2H, m), 1.34-1.25 (8H, m), 0.88-0.85 (3H, m); δ_C (100 MHz, $CDCl_3$) 155.6 (d, *J* 247.7), 110.6 (d, *J* 19.7), 66.3, 60.0, 54.6 (d, *J* 27.1), 53.2, 31.7, 31.6, 29.9 (d, *J* 2.2), 28.8, 25.5 (d, *J* 8.4), 22.6, 21.8, 14.1; δ_F (376 MHz, $CDCl_3$) –103.9 (1F, dt, *J* 22.6, 22.1); *m*/*z* (ESI^+) 244 ($[M + H]^+$, 91%), 226 (100), 102 (2), 100 (13); HRMS (ESI^+) $C_{14}H_{27}FNO$ ($[M + H]^+$) requires 244.2077; found 244.2077.

1-(2-Fluoro-4,4-dimethylpent-2-en-1-yl)-3-hydroxypiperidine 11c

General procedure D was followed with fluoroalkene **7c** (80 mg, 0.24 mmol, 1.00 eq.), TBAF (1.0 M in THF, 0.30 mL, 0.30 mmol, 1.25 eq.) and THF (2.40 mL). The mixture was stirred 48 h at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 98:2) afforded **11c** (44 mg, 85%, yellow oil) as a non-separable mixture of isomers (*Z*/*E* = 81:19); **11c**-(*Z*): δ_H (400 MHz, $CDCl_3$) 4.56 (1H, d, *J* 42.4), 3.83-3.79 (1H, m), 2.96 (2H, d, *J* 18.8), 2.61-2.48 (2H, m), 2.34 (1H, br s), 1.80-1.74 (2H, m), 1.64-1.61 (1H, m), 1.57-1.10 (3H, m), 1.10 (9H, s); δ_C (100 MHz, $CDCl_3$) 153.9 (d, *J* 258.4), 119.1 (d, *J* 9.7), 66.2, 59.9 (d, *J* 23.5), 59.7, 52.9, 31.7, 31.4, 30.4 (3C, d, *J* 3.2), 21.7; δ_F (376 MHz, $CDCl_3$) –109.1 (1F, dt, *J* 42.4, 18.8); **11c**-(*E*): δ_H (400 MHz, $CDCl_3$) 5.30 (1H, d, *J* 28.8), 3.82-3.79 (1H, m), 3.23 (2H, d, *J* 24.0), 2.61-2.57 (2H, m), 2.34 (1H, br s), 1.80-1.74 (2H, m), 1.64-1.61 (1H, m), 1.57-1.10 (3H, m), 1.10 (9H, s); δ_C (100 MHz, $CDCl_3$) 154.6 (d, *J* 242.9), 121.1 (d, *J* 20.9), 66.1, 60.0, 55.6 (d, *J* 27.9), 53.3, 31.5, 31.3 (3C, d, *J* 1.2), 30.0 (d, *J* 3.2), 21.7; δ_F (376 MHz, $CDCl_3$) –100.0 (1F, dt, *J* 28.8, 24.0); *m*/*z* (ESI^+) 216 ($[M + H]^+$, 100%), 198 (44), 115 (7), 102 (12), 95 (18), 87 (5), 84 (30); HRMS (ESI^+) $C_{12}H_{23}FNO$ ($[M + H]^+$) requires 216.1764; found 216.1774.

(*Z*)-1-[3-(4-Bromophenyl)-2-fluoroprop-2-enyl]-2-(hydroxymethyl)piperidine 12a-(*Z*)

General procedure D was followed with fluoroalkene **8a**-(*Z*) (110 mg, 0.19 mmol, 1.00 eq.), TBAF (1.0 M in THF, 0.23 mL, 0.23 mmol, 1.20 eq.) and THF (1.90 mL). The mixture was stirred 24 h at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 98:2) afforded compound **12a**-(*Z*) (23 mg, 37%, brown oil); δ_H (400 MHz, $CDCl_3$) 7.44 (2H, d, *J* 7.8), 7.36 (2H, d, *J* 7.9), 5.65 (1H, d, *J* 36.1), 3.86 (1H, dd, *J* 10.6, 3.5), 3.65 (1H, dd, *J* 15.0, 15.1), 3.55 (1H, dd, *J* 10.6, 3.5), 3.30 (1H, dd, *J* 20.7, 15.1), 3.10-3.07 (1H, m), 2.86 (1H, br s), 2.56-2.54 (1H, m), 2.46-2.40 (1H, m), 1.76-1.72 (1H, m), 1.68-1.62 (3H, m), 1.56-1.48 (1H, m), 1.41-1.35 (1H, m); δ_C (100 MHz, $CDCl_3$) 157.4 (d, *J* 269.0), 131.7 (d, *J* 2.5), 131.5 (2C), 130.0 (2C, d, *J* 7.7), 120.9 (d, *J* 3.4), 108.4 (d, *J* 7.0), 62.4, 60.6, 54.5 (d, *J* 26.3), 51.6, 27.5, 24.2, 23.2; δ_F (376 MHz, $CDCl_3$) –102.3 (1F, dt, *J* 36.1, 20.7); *m*/*z* (ESI^+) 330 ($[M(C_{14}H_{18}{}^{81}BrFNO) + H]^+$, 87%), 328 ($[M(C_{14}H_{18}{}^{79}BrFNO) + H]^+$, 87%), 213 (100), 134 (29), 114 (4); HRMS (ESI^+) $C_{15}H_{20}{}^{79}BrFNO$ ($[M + H]^+$) requires 328.0712; found 328.0722.

(*E*)-1-[3-(4-Bromophenyl)-2-fluoroprop-2-enyl]-2-(hydroxymethyl)piperidine 12a-(*E*)

General procedure D was followed with fluoroalkene **8a**-(*E*) (164 mg, 0.29 mmol, 1.00 eq.), TBAF (1.0 M in THF, 0.35 mL, 0.35 mmol, 1.20 eq.) and THF (2.90 mL). The mixture was stirred 3 h 30 at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 98:2) afforded compound **12a**-(*E*) (45 mg, 47%, brown oil); δ_H (400 MHz, $CDCl_3$) 7.47 (2H, d, *J* 8.3), 7.11 (2H, d, *J* 8.3), 6.35 (1H, d, *J* 21.0), 3.73-3.65 (2H, m), 3.46 (1H, dd, *J* 11.8, 4.0), 3.37 (1H, dd, *J* 23.4, 14.4), 2.95-2.91 (1H, m), 2.63 (1H, br s), 2.46-2.43 (1H, m), 2.32-2.26 (1H, m), 1.71-1.65 (1H, m), 1.64-1.52 (3H, m), 1.46-1.39 (1H, m), 1.38-1.25 (1H, m); δ_C (100 MHz, $CDCl_3$) 159.3 (d, *J* 255.8), 132.3 (d, *J* 13.5), 131.7 (2C), 130.4 (2C, d, *J* 2.7), 121.2, 111.3 (d, *J* 27.8), 62.4, 60.9, 51.3, 50.2 (d, *J* 24.7), 27.4, 24.3, 23.3; δ_F (376 MHz, $CDCl_3$) –98.4 (1F, dt, *J* 23.4, 21.0); *m*/*z* (ESI^+) 330 ([M($C_{14}H_{18}{}^{81}BrFNO$) + H]$^+$, 100%), 328 ([M($C_{14}H_{18}{}^{79}BrFNO$) + H]$^+$, 100%), 213 (41), 134 (21), 114 (3); HRMS (ESI^+) $C_{15}H_{20}{}^{79}BrFNO$ ([M + H]$^+$) requires 328.0712; found 328.0709.

1-(2-Fluorononon-2-enyl)-2-(hydroymethyl)piperdine 12b

General procedure D was followed with fluoroalkene **8b** (262 mg, 0.54 mmol, 1.00 eq.), TBAF (1.0 M in THF, 0.65 mL, 0.65 mmol, 1.20 eq.) and THF (5.40 mL). The mixture was stirred 24 h at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 98:2) afforded **12b** (64 mg, 48%, yellow oil) as a non-separable mixture of isomers (*Z*/*E* = 86:14); **12b**-(*Z*): δ_H (400 MHz, $CDCl_3$) 4.68 (1H, dt, *J* 37.2, 7.5), 3.80 (1H, dd, *J* 11.1, 4.0), 3.47-3.38 (2H, m), 3.08 (1H, dd, *J* 22.1, 14.7), 3.01-2.94 (1H, m), 2.72 (1H, br s), 2.43-2.41 (1H, m), 2.34-2.26 (1H, m), 2.07 (2H, q, *J* 6.9), 1.73-1.67 (1H, m), 1.62-1.55 (3H, m), 1.49-1.39 (1H, m), 1.35-1.26 (9H, m), 0.87 (3H, t, *J* 6.7); δ_C (100 MHz, $CDCl_3$) 155.6 (d, *J* 254.8), 109.7 (d, *J* 14.7), 62.3, 60.2, 53.8 (d, *J* 27.0), 51.4, 31.5, 29.2 (d, *J* 1.5), 28.7, 27.6, 24.4 (d, *J* 7.2), 24.3, 23.4 (2C), 14.0; δ_F (376 MHz, $CDCl_3$) –111.9 (1F, dt, *J* 37.2, 22.1); **12b**-(*E*): δ_H (400 MHz, $CDCl_3$) 5.22 (1H, dt, *J* 22.3, 5.2), 3.80 (1H, dd, *J* 11.1, 4.0), 3.55-3.48 (1H, m), 3.47-3.38 (1H, m), 3.18 (1H, dd, *J* 24.1, 14.4), 3.01-2.94 (1H, m), 2.72 (1H, br s), 2.43-2.41 (1H, m), 2.34-2.26 (1H, m), 1.97 (2H, q, *J* 7.1), 1.73-1.67 (1H, m), 1.62-1.55 (3H, m), 1.49-1.39 (1H, m), 1.35-1.26 (9H, m), 0.87 (3H, t, *J* 6.7); δ_C (100 MHz, $CDCl_3$) 156.0 (d, *J* 247.2), 110.3 (d, *J* 20.0), 62.3, 60.5, 51.2, 49.4 (d, *J* 26.6), 31.5, 29.8 (d, *J* 2.1), 28.7, 27.6, 25.4 (d, *J* 8.5), 24.4, 22.5 (2C), 14.0; δ_F (376 MHz, $CDCl_3$) –105.0 (1F, dt, *J* 24.1, 22.3); *m*/*z* (ESI^+) 258 ([M + H]$^+$, 100%), 240 (4), 238 (7), 116 (10), 114 (39); HRMS (ESI^+) $C_{15}H_{29}FNO$ ([M + H]$^+$) requires 258.2233; found 258.2231.

(*Z*)-[1-(2-Fluoro-4,4-dimethylpent-2-en-1-yl)]-2(hydroxymethyl)-piperidine 12c-(*Z*)

General procedure D was followed with fluoroalkene **8c**-(*Z*) (61 mg, 0.13 mmol, 1.00 eq.), TBAF (1.00 M in THF, 0.16 mL, 0.16 mmol, 1.20 eq.) and THF (1.30 mL). The mixture was stirred 24 h at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 98:2) afforded compound **12c**-(*Z*) (26 mg, 89%, yellow oil); δ_H (400 MHz, $CDCl_3$) 4.63 (1H, d, *J* 42.6), 3.82 (1H, dd, *J* 11.3, 3.9), 3.44 (1H, dd, *J* 11.3, 3.5), 3.37 (1H, dd, *J* 14.9, 15.0), 3.09-2.96 (3H, m), 2.45-2.42 (1H, m), 2.36-2.29 (1H, m), 1.74-1.69 (1H, m), 1.65-1.58 (3H, m), 1.53-1.40 (1H, m), 1.37-1.24 (1H, m), 1.11 (9H, s); δ_C (100 MHz, $CDCl_3$) 154.0 (d, *J* 258.6), 119.5 (d, *J* 9.8), 62.2, 60.4, 54.4 (d, *J* 27.3), 51.3, 31.4, 30.3 (d, *J* 3.2), 27.5 (3C), 24.3, 23.4; δ_F (376 MHz, $CDCl_3$) –109.0 (1F, dt, *J* 42.6, 21.1); *m*/*z* (ESI^+) 230 ([M + H]$^+$, 100%), 116.1 (21), 114 (16); HRMS $C_{13}H_{25}FNO$ ([M + H]$^+$) requires 230.1920; found 230.1930.

(*E*)-[1-(2-Fluoro-4,4-dimethylpent-2-en-1-yl]-2(hydroxymethyl)-piperidine 12c-(*E*)

General procedure D was followed with fluoroalkene **8c**-(*E*) (193 mg, 0.41 mmol, 1.00 eq.), TBAF (1.0 M in THF, 0.50 mL, 0.50 mmol, 1.22 eq.) and THF (4.10 mL). The mixture was stirred 24 h at room temperature. The purification by flash column chromatography (CH_2Cl_2/MeOH, 95:5) afforded compound **12c**-(*E*) (84 mg, 90%, yellow oil); δ_H (400 MHz, $CDCl_3$) 5.33 (1H, d, *J* 29.5), 3.80 (1H, dd, *J* 11.1, 4.1), 3.66 (1H, dd, *J* 19.1, 14.4), 3.50 (1H, dd, *J* 11.1, 4.1), 3.29 (1H, dd, *J* 25.2, 14.4), 3.09-3.04 (1H, m), 2.50-2.47 (2H, m), 2.36-2.30 (1H, m), 1.74-1.68 (1H, m), 1.67-1.56 (3H, m), 1.52-1.44 (1H, m), 1.43-1.32 (1H, m), 1.13 (9H, s); δ_C (100 MHz, $CDCl_3$) 154.9 (d, *J* 242.2), 121.0 (d, *J* 21.2), 62.3, 60.8, 50.9, 50.6 (d, *J* 26.9), 31.5 (3C, d, *J* 1.1), 30.2 (d, *J* 10.1), 27.4, 24.4, 23.4; δ_F (376 MHz, $CDCl_3$) –102.3 (1F, ddd, *J* 29.5, 25.2, 19.1); *m*/*z* (ESI^+) 230 ([M + H]$^+$, 100%), 212 (4), 210 (3), 116 (24), 114 (24); HRMS (ESI^+) $C_{13}H_{25}FNO$ ([M + H]$^+$) requires 230.1920; found 230.1930.

***(E)*-4-(Benzyloxy)-1-[3-(4-bromophenyl)allyl]piperidine 13**

To a solution of 4-(benzyloxy)-piperidine (50 mg, 0.26 mmol, 1.00 eq) and *trans*-4-bromocinnamaldehyde (55 mg, 0.26 mmol, 1.00 eq) in THF (1.00 mL) was added $NaBH(OAc)_3$ (78 mg, 0.37 mmol, 1.40 eq) and acetic acid (15 µL, 0.26 mmol, 1.00 eq. The mixture was stirred at 20 °C for 24 h, quenched with an aqueous solution of 1 N NaOH and extracted 3 times with Et_2O. Combined organic layers were washed with a saturated aqueous solution of NaCl, dried over $MgSO_4$, filtered and evaporated under reduced pressure. The purification by flash column chromatography (CH_2Cl_2/MeOH, 95:5) afforded alkene **13** (28 mg, 28%, yellow oil). δ_H (400 MHz, $CDCl_3$) 7.33 (d, *J* 8.4, 2H), 7.26-7.25 (m, 3H), 7.20-7.13 (m, 4H), 6.36 (d, *J* 15.8, 1H), 6.20 (d, *J* 15.8, 6.6, 1H), 4.46 (s, 2H), 3.34 (br s, 1H), 3.06 (d, *J* 6.6, 2H), 2.73 (br s, 2H), 2.18-2.16 (m, 2H), 1.87 (br s, 2H), 1.68-1.64 (m, 2H); δ_C (100 MHz, $CDCl_3$) 138.8, 135.8, 131.6 (3C), 128.3 (3C), 127.8 (2C), 127.4 (3C), 121.2, 73.8, 69.7, 60.8, 50.9 (2C), 31.0, 30.3; *m*/*z* (ESI^+) 388 ([M($C_{21}H_{25}{}^{81}BrFNO$)+H]$^+$, 71%), 386 ([M($C_{21}H_{25}{}^{79}BrFNO$)+H]$^+$, 71%), 195 (100), 190 (6), 116 (9); HRMS (ESI^+) $C_{21}H_{25}{}^{79}BrNO$ ([M + H]$^+$) requires 386.1120, found 386.1121.

Enzyme measurements

Inhibition constant (K_i) values were determined by spectrophotometrically measuring the residual hydrolytic activities of the glycosidases against the respective *p*-nitrophenyl α- or β-D-glycopyranoside (*o*-nitrophenyl-β-D-galactopyranoside for β-galactosidases), in the presence of potential inhibitors. Each assay was performed in phosphate buffer or phosphate-citrate buffer (for α - or β-mannosidase) at the optimal pH of each enzyme. The reactions were initiated by addition of an enzyme to a solution of the substrate in the absence or presence of various concentrations of the inhibitor.

The mixture was incubated for 10–30 min at 37 °C (for amyloglucosidase), and the reaction was quenched by addition of 1 M Na_2CO_3. Reaction times were appropriate to obtain 10–20% conversion of the substrate in order to achieve linear rates. The absorbance of the resulting mixture was determined at 405 nm using an ELISA Multiskan Plus reader (Menarini) in microtiter plates Nunc-NunclonTM of 96 wells. Approximate values of K_i were determined using a fixed concentration of the substrate (around the K_m value for the different glycosidases) and various concentrations of the inhibitor. Full K_i determinations and enzyme inhibition mode were determined from the slope of Dixon plots (*see* supporting information S2.3 to S2.5).

Acknowledgements

The authors thank the Ministère de l'Enseignement Supérieur et de la Recherche for a research fellowship to C. Le Guen and AI-CHEM program for financial support and the Spanish Ministerio de Economía y Competitividad (contract number SAF2013-44021R).

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† Electronic supplementary information (ESI) available: A copy of NMR spectra (^1H, ^{13}C) and HRMS is available for all new compounds. See DOI: 10.1039/b000000x/

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