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Fluoroalkene modification of mercaptoacetamide-based histone deacetylase inhibitors

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ABSTRACT

Inhibitors of histone deacetylases (HDAC) are emerging as a promising class of anti-cancer agents. The mercaptoacetoamide-based inhibitors are reported to be less toxic than hydroxamate and are worthy of further consideration. Therefore, we have designed a series of analogs as potential inhibitors of HDACs, in which the mercaptoacetamide group was replaced by (mercaptomethyl)fluoroalkene, and their HDAC inhibitory activity was evaluated. Subnanomolar inhibition was observed for all synthetic compounds.

1. Introduction

Epigenetic regulation of gene expression is mediated by several mechanisms, including DNA methylation, ATP-dependent chromatin remodeling, and post-translational modifications of histones.[1] Among several post-translational modification reactions, dynamic acetylation of ε-amino groups of lysine residues on histone tails is regulated by two opposing enzymes, histone acetyltransferase and histone deacetylase (HDAC).[2] Histone hyperacetylation by HDAC inhibition neutralizes the positive charge of the lysine side chain and is thought to be associated with change in the chromatin structure and the consequential transcriptional activation of several genes. One important outcome of histone hyperacetylation is induction of the cyclin-dependent kinase inhibitory protein $p21^{Waf1/Cip1}$, which causes cell cycle arrest.[3] Recently, HDAC inhibitors such as trichostatin A[4] and suberoylanilide hydroxamic acid (SAHA)[5] have been reported to inhibit proliferation of tumor cells by inducing terminal differentiation (Fig. 1). Thus, inhibitors of HDACs are emerging as a promising class of anti-cancer agents.[6,7]

The co-crystal structure of the histone deacetylase-like protein with SAHA reveals an active site consisting of a tubular pocket with a zinc ion at the bottom of the pocket.[8] While the hydroxamate head group of SAHA interacts with the zinc ion of the active site, the linker spans the tube-like portion of the binding pocket and the aromatic cap-group makes contact with the surface of the enzyme. Although hydroxamic acids are effective metal binding groups and are frequently employed as metalloprotease inhibitors, they have been found to exhibit unfavorable pharmacokinetic behavior including glucuronidation, sulfation, and metabolic hydrolysis.[9,10] Therefore, it is desirable to find replacement groups that strongly inhibit HDACs.

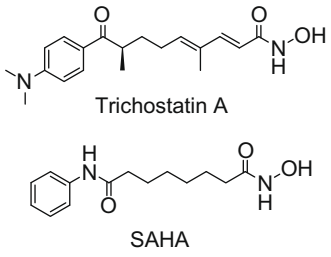

Figure 1. Structures of HDAC inhibitors.

Nonhydroxamate HDAC inhibitors such as *o*-aminoanilide,[11] trifluoromethyl ketones,[12] ketoamides,[13] phosphonates,[14] and *N*-formylhydroxylamine[15] have been reported; however, they are less potent than hydroxamates. The thiol group has been known to be a good chelator for zinc-dependent enzymes, and therefore, thiol-based SAHA analogs were recently developed.[16] Thiol-based SAHA analogs are reported to be potent HDAC inhibitors in spite of their monodentate zinc binding ability in comparison to SAHA's bidentate hydroxamic acid moiety. In searching for more effective units, three groups have independently designed mercaptoacetamide-based HDAC inhibitors that are supported by the ability of thiol and carbonyl groups to interact with zinc ion in a chelating manner.[17–19] Furthermore, a cortical neuron neuroprotection study

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revealed that the mercaptoacetoamide-based inhibitors are less toxic than hydroxamate.[20] Therefore, the thiol-based inhibitors are thought to be worthy of further consideration.

Supposing that the amide-bond in mercaptoacetamide located in the catalytic gorge of the HDACs may be sensitive to hydrolytic cleavage, we focused on replacing the amide functionality with a mimetic structure. For an amide-bond surrogate, (*Z*)-fluoroalkene (A) has been proposed to be equivalent to (*s*-*Z*)-amide (B) isostere (Fig. 2).[21] Since the first successful incorporation into a biologically active peptide (substance P),[22] the fluoroalkene unit has been applied to many peptidomimetics. Therefore, we have designed a series of SAHA analogs as potential inhibitors of HDACs, in which the hydroxamic acid was replaced by (mercaptomethyl)fluoroalkene moieties (Fig. 3). Based on results of SAR studies on HDAC inhibitors, the designed compounds focused on a 4-carbon or 5-carbon chain linker unit, capped with an aromatic ring at the terminal end.

2. Results and discussion

The synthesis of fluoroalkenes is outlined in Schemes 1 and 2, and the compounds prepared for this study are listed in Table 1.

Starting from commercially available diol **1a** or **1b**, one of the hydroxyl groups was selectively brominated by treating with aqueous HBr in toluene to afford ω-bromo alcohols **2**.[23] Then the other hydroxyl was converted to carboxylic acids **3** by the Anelli oxidation.[24] The acids **3** were converted to acid chlorides and were treated with aniline in the presence of *N*-methylmorpholine to obtain benzamides **4**. The benzamides **4** were reacted with sulfoxide anion, which is generated from ethyl phenylsulfinylfluoroacetate and NaH in anhydrous DMF, and then the adducts thus formed were heated to 95 °C to facilitate *syn* elimination, which results in the selective formation of thermodynamically stable *Z*-fluoroalkenes **5**. Obtained fluoroalkenes **5** were reduced to the allyl alcohols **6** using in situ formed $LiBH_4$, and these were converted to bromides **7** via the Appel reaction. The bromides **7** were treated with potassium thioacetate, and subsequent alkaline hydrolysis gave the desired thiols **9** accompanied by a small amount of disulfide forms **10**.

Recent inhibitor design has focused on the cap-group that is believed to be responsible for isozyme selectivity.[25] Although it becomes an inverse amide for synthetic reasons, construction of the fluoroalkene moiety prior to introduction of the capping group will be an efficient route for making isozyme-selective inhibitors. *N*-Boc-6-aminohexanoic acid methyl ester (**11**) was reduced by $LiAlH_4$ to yield alcohol **12**, which was transformed to bromide **13** via the Appel reaction. The bromide **13** was converted to *Z*-fluoroalkene **14** using a procedure similar to the one described for **5**, and the ester functionality was again reduced with $LiAlH_4$ to obtain allyl alcohol **15**. After acidic removal of the Boc group, condensation with benzoic acid derivatives gave benzamide derivatives **16**. The terminal alcohol was converted to a leaving group via the Appel reaction. However, conversion of **16b** to the corresponding bromide under the Appel condition was unsuccessful, presumably because of the formation of an insoluble salt caused by the presence of the dimethylamino group. In this case, the alcohol was activated as mesylate **17b**. Displacement of these leaving groups by potassium thioacetate followed by alkaline hydrolysis gave thiols **18**.

Synthetic thiols were tested with an in vitro assay using a HeLa nuclear extract. The HDAC inhibitory activity of these compounds

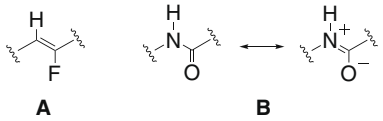


Figure 2. Fluoroalkene as an amide surrogate.

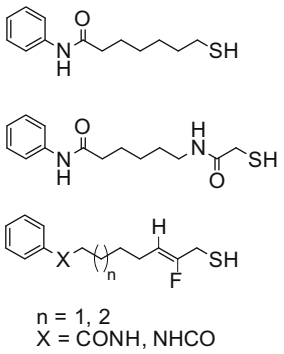


Figure 3. Thiol-based HDAC inhibitors and fluoroalkene-modified inhibitors.

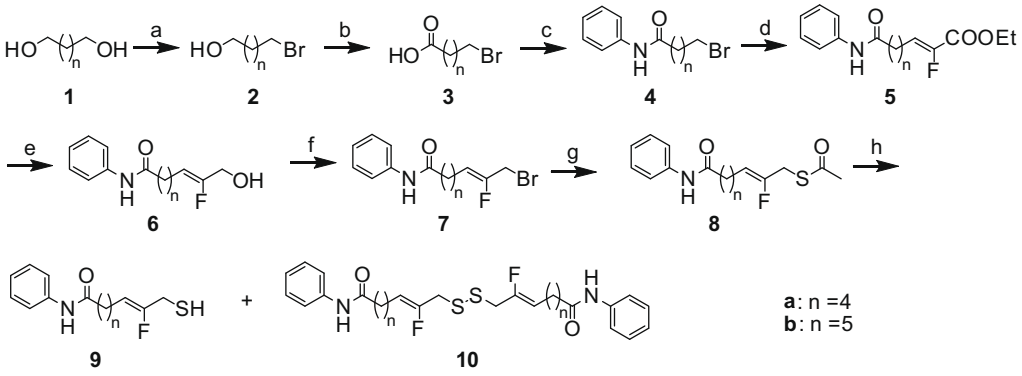
was determined using fluor-Lys as the substrate, and the result is a 50% inhibition of HDAC activity (see values in Table 1). SAHA was used as positive control, which had an IC_{50} value of 1.1 μM in our assays. According to the data, all synthetic compounds had superior inhibitory activity than SAHA. As in the preceding case, a five-carbon chain length proved better for the spacer unit. The reversal of the amide linkage and the introduction of *p*-dimethylaminophenyl moiety as found in trichostatin A did not influence the inhibition ability. In the case of the previously reported mercaptoacetamide analogs, significant activity drop was observed when the linker length was reduced from five- to four-carbon units.[17,18] However, the inhibitory activity of fluoroalkene-based inhibitors decreases less. In this context, the designed inhibitor unit is substantially superior than mercaptoacetamide. We assume that the chain-length dependency of mercaptoacetamide-based inhibitors may be because of the bidentate coordination, which may enforce to form an unfavorable conformation at the rim side of the catalytic gorge. According to calculations based on MP2 and B3LYP levels of theory, the charge distribution indicates that the fluoroalkene forms the proper polarity to mimic the polarity of an amide but the magnitude of the charge separation is less.[26] By nature, the fluoroalkene has a π-system that is able to interact with aromatic rings located in the channel of the HDAC catalytic pocket. Therefore, when the fluoroalkene inhibitor unit is obliged to penetrate shallowly into the channel, the hydrophobic environment of the channel tolerates the unit and accommodates it, and the unit is assumed to interact with zinc in a monodentate manner. As the fluoroalkene is known for nonhydrolyzable amide mimetic, it is stable with respect to hydrolytic cleavage. Cancellation of possibility of amide cleavage by the HDAC might be partly involved in the less chain-length dependency. Consequentially, we believe the fluoroalkene structure is a suitable mimic for delivering an amide-like structure to the catalytic center through the hydrophobic channel.

3. Conclusions

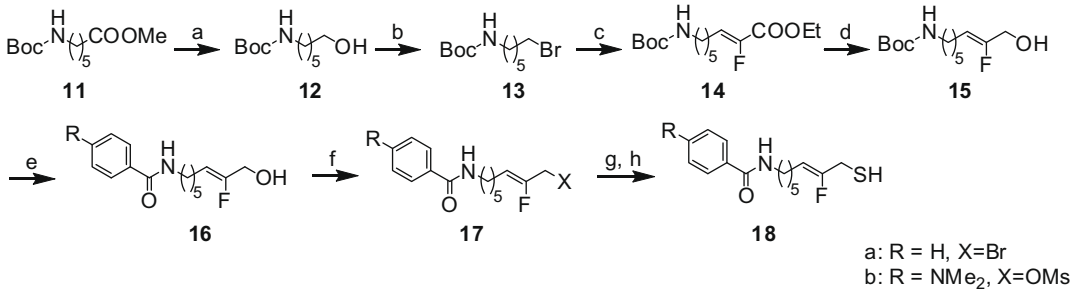
In conclusion, four fluoroalkene-containing analogs of mercaptoacetoamide-based inhibitors were synthesized and were assayed as inhibitors of HDAC. Potent inhibition activities of all four compounds suggest that the nonhydrolyzable fluoroalkenes can mimic substrates for HDACs. Further biological study of these compounds, such as isozyme selectivity, is underway.

4. Experimental

Melting points (uncorrected) were recorded on a Yanako MPS3 micro-melting point apparatus. All commercial reagents were used without further purification unless otherwise noted. ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra were obtained using a JEOL AL-300

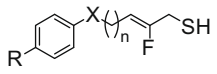


Scheme 1. Reagents and conditions: (a) HBr, toluene; (b) TEMPO, NaOCl, *n*-Bu_4NBr, AcOEt–water; (c) (i) $SOCl_2$, CH_2Cl_2, (ii) $PhNH_2$, NMM; (d) (i) NaH, PhSOCHFCOOEt, DMF, (ii) 95 °C; (e) $NaBH_4$, LiCl, THF–EtOH; (f) imidazole, Ph_3P, CBr_4, toluene; (g) AcSK, EtOH; (h) K_2CO_3, MeOH.



Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF; (b) imidazole, Ph_3P, CBr_4, toluene; (c) (i) NaH, PhSOCHFCOOEt, DMF, (ii) 95 °C; (d) $LiAlH_4$, THF; (e) (i) HCl–dioxane, (ii) PhCOOH, EDCI, HOBt, NMM, DMF; (f) imidazole, Ph_3P, CBr_4, toluene (for a) or MsCl, Et_3N (for b); (g) AcSK, EtOH; (h) K_2CO_3, MeOH.

Table 1
Synthesized HDAC inhibitors and inhibiting activities



Compd	*n*	R	X	IC_{50} (μM)
9a	4	–H	NHCO	0.51
9b	5	–H	NHCO	0.36
18a	5	–H	CONH	0.29
18b	5	$-NMe_2$	CONH	0.30

spectrometer (300 MHz, 75 MHz, and 283 MHz, respectively). All chemical shifts are reported in ppm as δ values relative to internal tetramethylsilane (^1H and ^{13}C) or benzotrifluoride (^{19}F) in $CDCl_3$ unless otherwise noted. Multiplicities are described using the abbreviations s, singlet; d, doublet, t, triplet; q, quartet; and m, multiplet. HRMS spectra were acquired using a JEOL GCmateII mass spectrometer or a JEOL JMS-700 mass spectrometer. Tetrahydrofuran was distilled from sodium benzophenone ketyl prior to use. All the manipulations with air-sensitive reagents were performed under a dry argon atmosphere. Analytical TLC was performed using Merck Silica Gel 60 F_{254} plates (0.25 mm on glass). Flash column chromatography was performed using either Wakogel C-300 (45–75 mm). Suberoylanilide hydroxamic acid was synthesized as previously described.[27] ω-Bromo alcohols **2a** and **2b** were prepared according to reported procedures.[23] ω-Bromo carboxybenzamides **4a** and **4b** were prepared in accordance with the method described in the literature.[28]

4.1. 6-Bromohexanoic acid (3a)

To a solution of 6-bromohexanol (2.0 g, 11 mmol) dissolved in EtOAc (30 mL) was added $NaHCO_3$ (5.0 g, 59 mmol), TEMPO (0.21 g, 1.3 mmol), and *n*-Bu_4NBr (0.68 g, 2.1 mmol), and this mixture was cooled to 0 °C. The mixture was stirred vigorously while slowly adding 0.35 M NaOCl aqueous solution (30 mL). Stirring was continued for 90 min, and then the reaction was quenched by adding aqueous $Na_2S_2O_3$. The aqueous phase was separated, washed with ether, acidified by adding 2 M HCl aqueous solution. The aqueous phase was extracted with ether and dried over Na_2SO_4. The solvent was removed in vacuo to give the acid **3a** as a heavy viscous liquid (1.7 g, 80%). The spectral data were identical to reported data.[29]

4.2. 7-Bromoheptanoic acid (3b)

Starting from **2b** (1.66 g, 8.5 mmol), **3b** was obtained as a pale yellow viscous liquid (1.50 g, 84%) following a procedure similar to that described for **3a**. The spectral data were identical to reported data.[28]

4.3. (*Z*)-7-(*N*-Phenylcarbamoyl)-2-fluoro-2-heptenoic acid ethyl ester (5a)

Sodium hydride (60% in mineral oil, 1.36 g, 30 mmol), in which the oil was previously washed out with petroleum ether, was suspended in 23 mL of DMF under argon atmosphere. The suspension was cooled to 0 °C, and a solution of ethyl phenylsulfinylfluoroacetate (6.43 g, 28 mmol) in DMF (7.0 mL) was added in a dropwise manner. The mixture was stirred for 30 min at 0 °C, and then compound **4a** (8.37 g, 31 mmol), which was dissolved in 10 mL of DMF, was slowly added at 5 °C, and the reaction mixture was stirred for 12 h. The progress of adduct formation was monitored by TLC, and then the reaction mixture was warmed up to 95 °C and maintained for 3 h. After cooling to room temperature, the reaction was quenched with the NH_4Cl aqueous solution, and the solution was extracted with AcOEt. The organic extracts were successively washed with 1 M HCl, saturated $NaHCO_3$ solution, and brine. After

drying the organic phase over Na_2SO_4, the solvent was removed in vacuo and the residue was purified by flash chromatography (hexane/ethyl acetate = 1:1) yielding **5a** as colorless crystals (5.86 g, 72%). Mp 76–78 °C; ^{1}H NMR δ 7.45 (d, J = 8.1 Hz, 2H), 7.26 (t, J = 6.3 Hz, 2H), 7.17 (s, 1H), 7.03 (t, J = 7.4 Hz, 1H), 6.10 (dt, J = 33, 7.8 Hz, 1H), 4.21 (t, J = 6.9 Hz, 2H), 2.18–2.33 (m, 4H), 1.66–1.76 (m, 2H), 1.45–1.53 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 171.1, 160.5 (d, J = 36 Hz), 146.4 (d, J = 266 Hz), 137.9, 128.9, 124.1, 124.1, 119.9 (d, J = 13 Hz), 61.5, 37.0, 27.7, 24.9, 23.8, 14.1; ^{19}F NMR δ −131.7 (d, J = 32 Hz); HRMS (FAB) M^+ calculated for $C_{16}H_{20}NO_3F$ 293.1427, found 294.1488.

4.4. (*Z*)-8-(*N*-Phenylcarbamoyl)-2-fluoro-2-octenoic acid ethyl ester (5b)

Starting from **4b** (5.14 g, 22 mmol), **5b** was obtained as colorless crystals (5.44 g, 79%) following a procedure similar to that described above. Mp 66–68 °C; ^{1}H NMR δ 7.50 (d, J = 7.9 Hz, 2H), 7.46 (br s, 1H), 7.30 (t, J = 7.5 Hz, 2H), 7.09 (t, J = 7.2 Hz, 1H), 6.05 (dt, J = 33, 7.9 Hz, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.35 (t, J = 7.5 Hz, 2H), 2.20–2.30 (m, 2H), 1.73 (quin, J = 7.5 Hz, 2H), 1.26–1.53 (m, 4H), 1.33 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 171.2, 16.6 (d, J = 36 Hz), 146.4 (d, J = 256 Hz), 137.9, 128.9, 124.1, 120.3 (d, J = 12 Hz), 119.8, 61.5, 37.4, 28.7, 28.0, 25.2, 24.0, 14.1; ^{19}F NMR δ −132.0 (d, J = 34 Hz); HRMS (FAB) $(M+1)^+$ calculated for $C_{17}H_{23}FNO_3$ 308.1662, found 308.1658.

4.5. (*Z*)-7-(*N*-Phenylcarbamoyl)-2-fluoro-2-heptenol (6a)

$NaBH_4$ (0.55 g, 14 mmol) was slowly added to a solution of LiCl (0.61 g, 14 mmol) dissolved in EtOH (9.2 mL). A solution of **5a** (1.05 g, 3.6 mmol) dissolved in THF (6.0 mL) was added to this suspension, and this mixture was stirred for 24 h at room temperature. The reaction was quenched with aqueous NH_4Cl and the solution was evaporated to remove EtOH. The residue was extracted with AcOEt, and the organic extracts were successively washed with saturated $NaHCO_3$ solution and brine. After drying the organic phase over Na_2SO_4, solvent was removed in vacuo and the residue was purified by flash chromatography (hexane/ethyl acetate = 1:1) yielding **6a** as colorless crystals (0.76 g, 84%). Mp 70–71 °C; ^{1}H NMR δ 7.48 (d, J = 7.8 Hz, 2H), 7.24–7.32 (m, 3H), 7.08 (t, J = 7.4 Hz, 1H), 4.76 (dt, J = 37 Hz, 7.5 Hz, 1H), 4.07 (dd, J = 16, 6.3 Hz, 2H), 2.34 (t, J = 7.2 Hz, 2H), 2.12 (t, J = 7.2 Hz, 2H), 1.96 (t, J = 6.6 Hz, 1H) 1.74 (quin, J = 7.5 Hz, 2H), 1.45 (quin, J = 7.2 Hz, 2H); ^{13}C NMR δ 172.2, 156.3 (d, J = 256 Hz), 137.9, 128.9, 124.2, 120.0, 107.0 (d, J = 14 Hz), 60.6 (d, J = 33 Hz), 37.1, 28.4, 24.9, 22.8; ^{19}F NMR δ −121.9 (dt, J = 37 Hz, 16 Hz); HRMS (FAB) $(M+H)^+$ calculated for $C_{14}H_{19}NO_2F$ 252.1400, found 252.1378.

4.6. (*Z*)-8-(*N*-Phenylcarbamoyl)-2-fluoro-2-octenol (6b)

Starting from **5b** (1.46 g, 4.7 mmol), **6b** was obtained as colorless crystals (0.88 g, 70%) following a procedure similar to that described for **6a**. Mp 71–73 °C; ^{1}H NMR δ 7.50 (d, J = 7.8 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 7.23 (br s, 1H), 7.10 (t, J = 7.4 Hz, 1H), 4.77 (dt, J = 37, 7.5 Hz, 1H), 4.07 (d, J = 17 Hz, 2H), 2.35 (t, J = 7.4 Hz, 2H), 2.11 (t, J = 6.6 Hz 2H), 1.96 (br s, 1H) 1.74 (quin, J = 7.4 Hz, 2H), 1.35–1.43 (m, 4H); ^{13}C NMR δ 172.0, 156.1 (d, J = 256 Hz), 137.9, 128.8, 124.1, 120.0, 107.4 (d, J = 14 Hz), 60.7 (d, J = 33 Hz), 37.4, 28.6, 28.5, 25.3, 23.0; ^{19}F NMR δ −122.3 (dt, J = 37 Hz, 17 Hz); HRMS (FAB) $(M+H)^+$ calculated for $C_{15}H_{21}NO_2F$ 266.1556, found 266.1536.

4.7. (*Z*)-8-Bromo-7-fluoro-*N*-phenyloct-6-enamide (7a)

To a solution of **6a** (0.76 g, 3.0 mmol) dissolved in toluene (30 mL) was added PPh_3 (1.02 g, 3.9 mmol), imidazole (0.27 g, 3.9 mmol), and CBr_4 (1.32 g, 3.9 mmol) at 0 °C, and this mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with AcOEt, washed with brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified by flash chromatography (hexane/ethyl acetate = 2:1), yielding **7a** as colorless crystals (0.66 g, 70%). Mp 84–85 °C; ^{1}H NMR δ 7.52 (d, J = 7.2 Hz, 2H), 7.29–7.34 (m,3H), 7.10 (t, J = 7.5 Hz, 1H), 4.93 (dt, J = 34, 7.7 Hz, 1H), 3.91 (d, J = 20 Hz, 2H), 2.37 (t, J = 7.4 Hz, 2H), 2.16 (q, J = 7.2 Hz, 2H), 1.76 (quin, J = 7.5 Hz, 2H), 1.49 (quin, J = 7.5 Hz, 2H); ^{13}C NMR δ 170.9, 152.8 (d, J = 252 Hz), 137.9, 129.0, 124.2, 119.8, 110.5 (d, J = 16 Hz), 37.3, 28.7 (d, J = 17 Hz), 28.2, 24.8, 23.4; ^{19}F NMR δ −116.0 (dt, J = 35, 20 Hz); HRMS (FAB) $(M+H)^+$ calculated for $C_{14}H_{18}NO^{79}BrF$ 314.0558, found 314.0552.

4.8. (*Z*)-9-Bromo-8-fluoro-*N*-phenylnon-7-enamide (7b)

Starting from **6b** (0.72 g, 2.7 mmol), **7b** was obtained as colorless crystals (0.66 g, 74%) following a procedure similar to that described for **7a**. Mp 96–98 °C; ^{1}H NMR δ 7.48 (d, J = 7.8 Hz, 2H), 7.24–7.32 (m, 3H), 7.08 (t, J = 7.2 Hz, 1H), 4.88 (dt, J = 35, 7.5 Hz, 1H), 3.87 (d, J = 20 Hz, 2H), 2.33 (t, J = 7.5 Hz, 2H), 2.09 (t, J = 6.3 Hz 2H), 1.71 (quin, J = 7.2 Hz, 2H), 1.37–1.39 (m, 4H); ^{13}C NMR δ 171.2, 152.6 (d, J = 252 Hz), 137.9, 129.0, 124.2, 119.8, 110.8 (d, J = 16 Hz), 37.6, 28.6 (d, J = 17 Hz), 28.5, 28.4, 25.2, 23.7; ^{19}F NMR δ −116.4 (dt, J = 35, 19 Hz); HRMS (FAB) $(M+H)^+$ calculated for $C_{15}H_{20}NO^{79}BrF$ 328.0712, found 328.0720.

4.9. (*Z*)-7-(Phenylcarbamoyl)-2-fluorohept-2-enyl acetylsulfane (8a)

To a solution of **7a** (0.53 g, 1.6 mmol) dissolved in EtOH (5.6 mL) was added AcSK (0.70 g, 5.8 mmol), and the mixture was stirred for 19 h at room temperature. To this mixture was added THF–AcOEt, washed with water and brine. After drying the organic phase over Na_2SO_4, solvent was removed in vacuo and the residue purified by flash chromatography (hexane/ethyl acetate = 3:2), yielding **8a** as colorless crystals (0.42 g, 84%). Mp 68–70 °C; ^{1}H NMR δ 7.50 (d, J = 7.8 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 7.18 (br s, 1H), 7.10 (t, J = 7.5 Hz, 1H), 4.76 (dt, J = 36, 7.8 Hz, 1H), 3.61 (d, J = 19 Hz, 2H), 2.32–2.37 (m, 5H), 2.11 (q, J = 7.5 Hz, 2H), 1.73 (quin, J = 7.5 Hz, 2H), 1.45 (quin, J = 7.5 Hz, 2H); ^{13}C NMR δ 194.5, 171.2, 152.7 (d, J = 253 Hz), 137.9, 128.9, 124.1, 119.7, 108.2 (d, J = 15 Hz), 37.3, 30.4, 30.0, 28.4, 24.9, 23.3: ^{19}F NMR δ −113.5 (dt, J = 35, 19 Hz); HRMS (FAB) $(M+H)^+$ calculated for $C_{16}H_{21}NO_2FS$ 310.1277, found 310.1248.

4.10. (*Z*)-8-(Phenylcarbamoyl)-2-fluorooct-2-enyl acetylsulfane (8b)

Starting from **7b** (0.26 g, 0.80 mmol), **8b** was obtained as colorless crystals (0.25 g, 97%) by a similar procedure described for **8a**. Mp 53–54 °C; ^{1}H NMR δ 7.48 (d, J = 7.8 Hz, 2H), 7.29 (t, J = 7.8 Hz, 2H), 7.25 (br s, 1H), 7.07 (t, J = 7.9 Hz, 1H), 4.71 (dt, J = 36, 7.5 Hz, 1H), 3.58 (d, J = 19 Hz, 2H), 2.29–2.34 (m, 5H), 2.04–2.05 (m, 2H), 1.71 (quin, J = 7.2 Hz, 2H), 1.34–1.36 (m, 4H); ^{13}C NMR δ 194.3, 171.2, 152.6 (d, J = 252 Hz), 137.9, 129.0, 124.2, 119.8, 108.5 (d, J = 15 Hz), 36.7, 30.4, 30.1, 28.6, 25.3, 23.5; ^{19}F NMR δ −113.2 (dt, J = 37 Hz, 18 Hz); HRMS (FAB) $(M+H)^+$ calculated for $C_{17}H_{23}NO_2FS$ 324.1234, found 324.1427.

4.11. (*Z*)-7-Fluoro-8-mercapto-*N*-phenyloct-6-enamide (9a) and its dimer (10a)

To a solution of compound **8a** (0.40 g, 1.3 mmol) dissolved in MeOH (12 mL) was added K_2CO_3 (0.10 g, 2.5 mmol), and this mixture was stirred for 2 h at room temperature. The mixture was di-

luted with AcOEt, washed with water and brine, and dried over Na_2SO_4. Solvent was removed in vacuo and the residue was purified by flash chromatography (hexane/ethyl acetate = 3:2), yielding **9a** (0.27 g, 78%) as a white solid. Disulfide dimer **10a** (0.06 g, 0.11 mmol, 17%) was also obtained as a white solid. **9a**; mp 53–55 °C; ^{1}H NMR δ 7.50 (d, J = 8.1 Hz, 2H), 7.32 (t, J = 8.0 Hz, 2H), 7.19 (br s, 1H), 7.10 (t, J = 7.4 Hz, 1H), 4.70 (dt, J = 36, 7.5 Hz, 1H), 3.20 (dd, J = 17, 8.1 Hz, 2H), 2.36 (t, J = 7.5 Hz, 2H), 2.12 (q, J = 7.2 Hz, 2H), 1.70–1.82 (m, 3H), 1.46 (q, J = 7.4 Hz, 2H); ^{13}C NMR δ 171.3, 155.6 (d, J = 252 Hz), 137.9, 128.9, 124.2, 119.8, 106.2 (d, J = 16 Hz), 37.3, 28.5 (d, J = 1.9 Hz), 25.6, 24.9, 23.2; ^{19}F NMR δ −115.0 (dt, J_{HF} = 37 Hz, 18 Hz); HRMS (FAB) (M+H)$^+$ calculated for $C_{14}H_{19}NOFS$ 268.1171, found 268.1168. Compound **10a**; mp 98–100 °C; ^{1}H NMR δ 7.47–7.50 (m, 6H), 7.27 (t, J = 7.4 Hz, 4H), 7.07 (t, J = 7.2 Hz, 2H), 4.68 (dt, J = 36, 7.5 Hz, 2H), 3.29 (d, J = 20 Hz, 4H), 2.34 (t, J = 7.4 Hz, 4H), 2.12 (q, J = 7.1 Hz, 4H), 1.74 (quin, J = 7.5 Hz, 4H) 1.45 (quin, J = 7.7 Hz, 4H); ^{13}C NMR δ 171.3, 152.2 (d, J = 253 Hz), 137.9, 128.9, 124.2, 119.9, 109.6 (d, J = 15 Hz), 40.3 (d, J = 31 Hz), 37.3, 28.6, 24.9, 23.5; ^{19}F NMR δ −115.2 (dt, J_{HF} = 35 Hz, 18 Hz); HRMS (FAB) (M+H)$^+$ calculated for $C_{28}H_{35}N_2O_2F_2S_2$ 533.2108, found 533.2109.

4.12. (*Z*)-8-Fluoro-9-mercapto-*N*-phenylnon-7-enamide (9b) and its dimer (10b)

By a treatment similar to that described for **9a**, **8b** (0.25 g, 0.76 mmol) gave **9b** (0.19 g, 0.66 mmol, 87%) and disulfide dimer **10b** (0.014 g, 0.02 mmol, 7%) as white solids. **9b**: mp 67–69 °C; ^{1}H NMR δ 7.50 (d, J = 7.5 Hz, 2H), 7.31 (t, J = 8.0 Hz, 2H), 7.25 (br s, 1H), 7.10 (t, J = 7.4 Hz, 1H), 4.67 (dt, J = 36, 7.5 Hz, 1H), 3.15–3.24 (m, 2H), 2.35 (t, J = 7.5 Hz, 2H), 2.05–2.10 (m, 2H), 1.68–1.81 (m, 3H), 1.38–1.42 (m, 4H); ^{13}C NMR δ 171.2, 155.4 (d, J = 252 Hz), 137.9, 128.9, 124.2, 119.7, 106.5 (d, J = 16 Hz), 37.7, 28.8 (d, J = 1.3 Hz), 28.6, 25.7, 25.2, 23.5; ^{19}F NMR δ −114.7 (dt, J = 37 Hz, 18 Hz); HRMS (FAB) (M+H)$^+$ calculated for $C_{15}H_{21}NOFS$ 282.1328, found 232.1346. Compound **10b**; mp 96–98 °C; ^{1}H NMR δ 7.45 (d, J = 7.8 Hz, 4H), 7.40 (br s, 2H), 7.23 (t, J = 7.8 Hz, 4H), 7.02 (t, J = 7.7 Hz, 2H), 4.74 (dt, J = 36, 7.5 Hz, 2H), 3.29 (d, J = 20 Hz, 4H), 2.28 (t, J = 7.5 Hz, 4H), 2.04–2.06 (m, 4H), 1.66 (quin, J = 7.2 Hz, 4H), 1.33–1.35 (m, 8H); ^{13}C NMR δ 171.4, 155.3 (d, J = 253 Hz), 137.9, 129.0, 124.2, 119.8, 109.9 (d, J = 16 Hz), 40.3 (d, J = 31 Hz), 37.7, 28.8, 28.7, 25.3, 23.7; ^{19}F NMR δ −114.9 (dt, J = 35 Hz, 18 Hz); HRMS (FAB) (M+H)$^+$ calculated for $C_{30}H_{39}N_2O_2F_2S_2$ 561.2421, found 561.2429.

4.13. *N-tert*-Butoxycarbonyl-6-aminohexanoic acid methyl ester (11)

To a chilled solution of thionyl chloride (2.3 mL, 30 mmol) in methanol (20 mL) was slowly added 6-aminohexanoic acid (1.31 g, 10.0 mmol). The mixture was stirred for 24 h at room temperature and then concentrated in vacuo to give a white solid. The solid was suspended in 10 mL of THF. To this suspension was added triethylamine (1.7 mL, 10 mmol) and di-*tert*-butyl-dicarboxylate (2.31 g, 10.5 mmol). The solution was stirred overnight at room temperature. Precipitates were filtered off and solvent was removed with a rotary evaporator to give an oily product. The oil was dissolved in AcOEt, washed with 1 M HCl, saturated $NaHCO_3$, and brine, and then dried over Na_2SO_4. Solvent was removed in vacuo to give **11** as a colorless oil (2.45 g). The compound was used without further purification. Compound analysis is consistent with published data.[30]

4.14. *N-tert*-Butoxycarbonyl-6-aminohexanol (12)

To a suspension of $LiAlH_4$ (0.37 g, 10.0 mmol) in THF (70 mL) was slowly added a solution of **11** (2.45 g, 10.0 mmol) in THF (10 mL). The mixture was stirred for 40 min, and then quenched with 10% KOH aqueous solution (20 mL) at 0 °C. Inorganic precipitates were filtered and the solution was concentrated. The oil was dissolved in AcOEt, washed with 1 M HCl, saturated $NaHCO_3$, and brine, and then dried over Na_2SO_4. Solvent was removed in vacuo to give **12** as colorless crystals (2.11 g, 97%). Mp 36–37 °C; ^{1}H NMR analysis is consistent with published data.[31]

4.15. *N-tert*-Butoxycarbonyl-1-amino-6-bromohexane (13)

To a solution of **12** (4.26 g, 20.0 mmol) dissolved in toluene (200 mL) was added triphenylphosphine (5.46 g, 21 mmol), imidazole (1.51 g, 23 mmol), and CBr_4 (7.30 g, 22 mmol) at 0 °C, and this mixture was stirred for 3 h. The reaction mixture was extracted with AcOEt, and the extract was washed with brine and dried over Na_2SO_4. Solvent was removed in vacuo and the residue was purified by flash chromatography (hexane/ethyl acetate = 2:2), yielding **13** as a colorless oil (3.57 g, 65%). ^{1}H NMR analysis is consistent with published data.[32]

4.16. (*Z*)-8-(*N-tert*-Butoxycarbonyl)amino-2-fluoro-2-octenoic acid ethyl ester (14)

Sodium hydride (60% in mineral oil, 0.56 g, 14 mmol), in which oil was previously washed out with petroleum ether, was suspended in 9 mL of DMF under an Ar atmosphere. The suspension was cooled to 0 °C, and a solution of ethyl phenylsulfinylfluoroacetate (2.65 g, 12 mmol) dissolved in DMF (5 mL) was added dropwise. The mixture was stirred for 30 min at 0 °C, compound **13** (2.65 g, 13 mmol) dissolved in 3.3 mL of DMF was slowly added at 5 °C, and the reaction mixture was stirred for 17 h. The progress of adduct formation was monitored by TLC, and then the reaction mixture was warmed to 95 °C and maintained at this temperature for 3 h. After cooling to room temperature, the reaction was quenched with the NH_4Cl aqueous solution, and the mixture was extracted with AcOEt. The organic extracts were washed with brine and dried over Na_2SO_4. Solvent was removed in vacuo and the residue was purified by flash chromatography (hexane/ethyl acetate = 3:1), yielding **14** as a pale yellow oil (2.77 g, 79%). ^{1}H NMR δ 6.16 (dt, J = 33, 7.5 Hz, 1H), 4.46 (br s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.12 (q, J = 6.3 Hz, 2H), 2.21–2.29 (m, 2H), 1.29–1.54 (m, 6H), 1.44 (s, 9H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR δ 160.6 (d, J = 36 Hz), 155.9, 146.4 (d, J = 257 Hz), 120.2 (d, J = 12 Hz), 79.1, 61.5, 40.4, 29.8, 28.4, 27.9, 26.3, 24.1, 14.1; ^{19}F NMR δ −132.1 (d, J_{HF} = 34 Hz); HRMS (FAB) (M+H)$^+$ calculated for $C_{15}H_{27}NO_4F$ 304.1924, found 304.1926.

4.17. (*Z*)-8-(*N-tert*-Butoxycarbonyl)amino-2-fluoro-2-octenol (15)

Compound **14** (0.64 g, 2.1 mmol) in THF (10 mL) was slowly added to a stirring suspension of $LiAlH_4$ (0.089 g, 2.3 mmol) in THF (20 mL) so as not to exceed 40 °C. After 1.5 h, the reaction mixture was cooled 0 °C, 10% KOH aqueous solution (5 mL) was added cautiously. The formed precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in AcOEt. The organic solution was washed with brine and dried over Na_2SO_4. Solvent was removed in vacuo to give **15** as a colorless oil (0.36 g, 65%). An analytical sample was purified by flash chromatography (hexane/ethyl acetate = 1:1). ^{1}H NMR δ 4.74 (t, J = 37, 7.5 Hz, 1H), 4.50 (br s, 1H), 4.07 (dd, J = 16, 6.5 Hz, 2H), 3.07 (q, J = 6.6 Hz, 2H), 2.08 (q, J = 6.7 Hz, 2H), 1.90 (br s, 1H), 1.27–1.50 (m, 6H), 1.42 (s, 9H); ^{13}C NMR δ 159.5 (d, J = 255 Hz), 156.1, 107.4 (d, J = 13 Hz), 79.1, 61.0 (d, J = 33 Hz), 40.5, 29.7, 28.6, 28.4, 26.1, 23.1; ^{19}F NMR δ −122.4 (dt, J = 37, 16 Hz); HRMS (FAB) (M+H)$^+$ calculated for $C_{13}H_{25}NO_3F$ 262.1813, found 262.1840.

4.18. *N*-((*Z*)-7-Fluoro-8-hydroxyoct-6-enyl)benzamide (16a)

To a solution of **15** (0.37 g, 1.4 mmol) dissolved in dioxane (2.5 mL) was slowly added 4 M HCl/dioxane (4.0 mL) at 0 °C and the mixture was stirred for 1 h at room temperature. The reaction mixture was diluted with methanol, concentrated in vacuo to give a pale, yellow oil. The residue was dissolved in DMF (1.4 mL) and cooled to 0 °C. To this solution was successively added *N*-methylmorpholine (0.15 mL, 1.4 mmol), a solution of benzoic acid (0.18 g, 1.5 mmol) and HOBt (0.25 g, 1.8 mmol) dissolved in DMF (1.4 mL), and EDCI (0.28 g, 1.5 mmol). The reaction mixture was stirred for 26 h at room temperature and diluted with AcOEt. The organic solution was successively washed with water, saturated $NaHCO_3$ solution, 1 M aqueous HCl, and brine. After drying the organic phase over Na_2SO_4, solvent was removed in vacuo and the residue was purified by flash chromatography (hexane/ethyl acetate = 1:1) yielding **16a** as colorless oil (0.30 g, 80%). ^{1}H NMR δ 7.71 (d, J = 8.4 Hz, 2H), 7.37–7.49 (m, 3H), 6.24 (br s, 1H), 4.73 (dt, J = 37, 7.5 Hz, 1H), 4.03 (d, J = 16 Hz, 2H), 3.40 (q, J = 6.6 Hz, 2H), 2.30 (br s, 1H), 2.08 (q, J = 6.6 Hz, 2H), 1.59 (quin, J = 6.9 Hz, 2H), 1.31–1.46 (m, 4H); ^{13}C NMR δ 167.6, 156.2 (d, J = 256 Hz), 134.8, 131.4, 128.5, 126.8, 107.4 (d, J = 14 Hz), 61.1 (d, J = 27 Hz), 39.9, 29.4, 28.6, 26.3, 23.1; ^{19}F NMR δ −122.2 (dt, J = 38, 16 Hz); HRMS (FAB) $(M+H)^+$ calculated for $C_{15}H_{21}NO_3F$ 266.1556, found 266.1557.

4.19. 4-(Dimethylamino)-*N*-((*Z*)-7-fluoro-8-hydroxyoct-6-enyl)benzamide (16b)

Starting from **15** (0.46 g, 1.8 mmol), **16b** was obtained as a white powder (0.34 g, 62%) following a procedure similar to that described for **16a**. Mp 89–90 °C; ^{1}H NMR δ 7.61–7.66 (m, 2H), 6.61–6.66 (m, 3H), 6.06 (br s, 1H), 4.85 (dt, J = 37, 7.5 Hz, 1H), 4.08 (d, J = 15 Hz, 2H), 3.40 (q, J = 6.7 Hz, 2H), 2.98 (s, 6H), 2.44 (br s, 1H), 2.09 (q, J = 6.5 Hz, 2H), 1.57 (quin, J = 6.9 Hz, 2H), 1.33–1.41 (m, 4H); ^{13}C NMR δ 167.6, 156.3 (d, J = 256 Hz), 152.3, 128.3, 121.4, 111.1, 107.2 (d, J = 14 Hz), 60.9 (d, J = 33 Hz), 40.1, 39.7, 29.5, 28.6, 26.2, 23.1; ^{19}F NMR δ −122.2 (m); HRMS (FAB) $(M+H)^+$ calculated for $C_{17}H_{26}FN_2O_2$ 309.1978, found 309.1981.

4.20. *N*-((*Z*)-8-Bromo-7-fluorooct-6-enyl)benzamide (17a)

To a solution of **16a** (0.29 g, 1.1 mmol) dissolved in toluene (11 mL) was added PPh_3 (0.36 g, 1.4 mmol), imidazole (0.10 g, 1.4 mmol), and CBr_4 (0.45 g, 1.4 mmol) at 0 °C, and the mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with AcOEt, washed with brine, and dried over Na_2SO_4. The solvent was removed in vacuo and the residue purified by flash chromatography (hexane/ethyl acetate = 1:1) yielding **17a** as colorless crystals (0.20 g, 60%). ^{1}H NMR δ 7.72–7.76 (m, 2H), 7.37–7.50 (m, 3H), 6.14 (br s, 1H), 4.89 (dt, J = 34, 7.5 Hz, 1H), 3.87 (d, J = 20 Hz, 2H), 3.42 (q, J = 7.2 Hz, 2H), 2.10 (q, J = 6.9 Hz, 2H), 1.61 (quin, J = 6.6 Hz, 2H), 1.35–1.44 (m, 4H); ^{13}C NMR δ 167.7, 159.3, 134.5, 131.4, 128.5, 126.9, 110.8 (d, J = 16 Hz), 40.0, 29.3, 28.8, 28.4, 26.3, 23.4; ^{19}F NMR δ −115.8 (dt, J = 35, 20 Hz); HRMS (FAB) $(M+H)^+$ calculated for $C_{15}H_{20}NOBrF$ 328.0712, found 328.0678.

4.21. *N*-((*Z*)-7-Fluoro-8-mercaptooct-6-enyl)benzamide (18a)

To a solution of **17a** (0.19 g, 0.57 mmol) dissolved in EtOH (2.0 mL) was added AcSK (0.24 g, 2.1 mmol) and the mixture was stirred for 20 h at room temperature. To this mixture was added THF–AcOEt, washed with water and brine. After drying of the organic phase over Na_2SO_4, solvent was removed in vacuo and the residue purified by flash chromatography (hexane/ethyl acetate = 3:2) yielding a thioacetate derivative as a colorless oil. The thioacetate was dissolved in MeOH (5.0 mL) and K_2CO_3 (34 mg, 0.25 mmol) was added to this solution. The mixture was stirred for 30 min at room temperature, diluted with AcOEt, washed with water and brine, and dried over Na_2SO_4. Solvent was removed in vacuo and the residue purified by flash chromatography (hexane/ethyl acetate = 3:2) yielding **18a** (0.12 g, 1.0 mmol, 78%) as a oil. ^{1}H NMR δ 7.72–7.76 (m, 2H), 7.37–7.50 (m, 3H), 6.13 (br s, 1H), 4.78 (dt, J = 36, 7.5 Hz, 1H), 3.34–3.47 (m, 2H), 3.13–3.23 (m, 2H), 2.09 (q, J = 6.3 Hz, 2H), 1.72–1.77 (m, 1H), 1.61 (quin, J = 6.8 Hz, 2H), 1.34–1.41 (m, 4H); ^{13}C NMR δ 167.5, 155.5 (d, J = 252 Hz), 134.8, 131.3, 128.5, 126.8, 106.5 (d, J = 16 Hz), 39.9, 29.4, 28.7, 26.3, 25.2, 23.4; ^{19}F NMR δ −115.3 (dt, J = 37, 18 Hz); HRMS (FAB) $(M+H)^+$ calculated for $C_{15}H_{21}NOFS$ 282.1328, found 282.1331.

4.22. 4-(Dimethylamino)-*N*-((*Z*)-7-fluoro-8-mercaptooct-6-enyl)benzamide (18b)

To a solution of **16b** (130 mg, 0.42 mmol) and Et_3N (0.09 mL, 0.64 mmol) dissolved in THF (3.7 mL) was slowly added $MeSO_2Cl$ (50 μL, 0.63 mmol) at 0 °C. After the addition, the mixture was stirred for 2 h at room temperature. The precipitate was filtered off and the filtrate was concentrated in vacuo. The residue was dissolved in ethanol (3.0 mL), AcSK (240 mg, 2.1 mmol) was added to the solution, and the mixture was stirred for 20 h at room temperature. This mixture was diluted with AcOEt, washed with water and brine. After drying the organic phase over Na_2SO_4, solvent was removed in vacuo and the residue purified by flash chromatography (hexane/ethyl acetate = 3:2) yielding a thioacetate derivative as a colorless oil. The oil was dissolved MeOH (2.2 mL) and K_2CO_3 (14 mg, 0.10 mmol) was added. After the mixture was stirred for 30 min at room temperature, it was diluted with AcOEt, washed with water and brine, and dried over Na_2SO_4. Solvent was removed in vacuo and the residue purified by flash chromatography (hexane/ethyl acetate = 3:2) yielding **18b** (32 mg, 46%) as a white solid. Mp 84–86 °C; ^{1}H NMR δ 7.57–7.62 (m, 2H), 6.56–6.61 (m, 2H), 5.97 (br s, 1H), 4.72 (dt, J = 36, 7.5 Hz, 1H), 3.36 (q, J = 6.5 Hz, 2H), 3.14 (dd, J = 14, 8.1 Hz, 2H), 2.94 (s, 6H), 1.97–2.03 (m, 2H), 1.70 (t, J = 8.0 Hz, 1H), 1.48–1.55 (m, 2H), 1.31–1.33 (m, 4H); ^{13}C NMR δ 167.4, 155.4 (d, J = 252 Hz), 152.4, 128.2, 121.6, 111.0, 106.6 (d, J = 16 Hz), 40.1, 39.7, 29.6, 28.8, 26.4, 25.2, 23.5; ^{19}F NMR δ -115.4 (dt, J = 37, 18 Hz); HRMS (FAB) $(M+H)^+$ calculated for $C_{17}H_{26}N_2OFS$ 325.1750, found 325.1748.

4.23. HDAC inhibition assay

The HDAC activity assay was performed using an HDAC fluorescent activity assay/drug discovery kit (AK-500, BIOMOL Research Laboratories). HeLa cell nuclear extract was used as the source of HDAC activity. Test compounds were prepared as 5 mM stock solutions in EtOH. HeLa nuclear extracts (15 μL) were incubated at 37 °C with 25 μL of Fluor de Lys substrate and various concentrations of samples. The reaction was allowed to proceed for 10 min at room temperature before stopping the reaction by adding Fluor de Lys Developer with trichostatin A. Twenty minutes after addition of this developer, the mixture was diluted with 150 μL of buffer, and then the fluorescence was measured on a fluorometric reader with excitation set at 360 nm and emission detection set at 460 nm. The concentration of the compound, which results in 50% inhibition, was determined by plotting as a logistic function of the log[Inh] and the % inhibition. We report the means values of the three independent experiments.

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