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Research Article

Utility of azetidinium methanesulfonates for radiosynthesis of 3-[^{18}F]fluoropropyl amines

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Summary

3-Methanesulfonyloxypropyl tertiary amines were observed to cyclize to form azetidinium methanesulfonate moieties. Heat-induced cyclization of 3-methanesulfonyloxypropyl amines was utilized for preparation of azetidinium methanesulfonates. The azetidinium methanesulfonates were found to incorporate radioactive [^{18}F]fluoride (decay-corrected yields $>60\%$) efficiently, resulting in an efficient synthesis of 3-[^{18}F]fluoropropyl tertiary amines. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: fluorine-18; aliphatic fluorination; sigma receptor; radiopharmaceutical

Introduction

Although there are many strategies for preparing fluorine-containing compounds, the introduction of [^{18}F]fluoride ($t_{1/2}$ = 109.8 min) requires methods that incorporate fluorine very late in the synthetic scheme. The most common aliphatic radiofluorinations are effected by treating a highly reactive sulfonate ester precursor with [^{18}F]fluoride in the presence of K_2CO_3 and Kryptofix [2.2.2].[1,2] During the course of our efforts to prepare a methanesulfonate precursor of a hydroxypropyl amine, we observed cyclization to an azetidinium structure. We have studied the reactivity of this azetidinium moiety toward [^{18}F]fluoride. We also report a comparison of radiochemical yields between the azetidinium methanesulfonate and its analogous methanesulfonate ester.

Results and discussion

We set out to prepare F-18 labeled 4-{[1-(3-fluoropropyl)-4-piperidinyl]-methoxy}benzonitrile (**9**), a compound with reportedly high selectivity for

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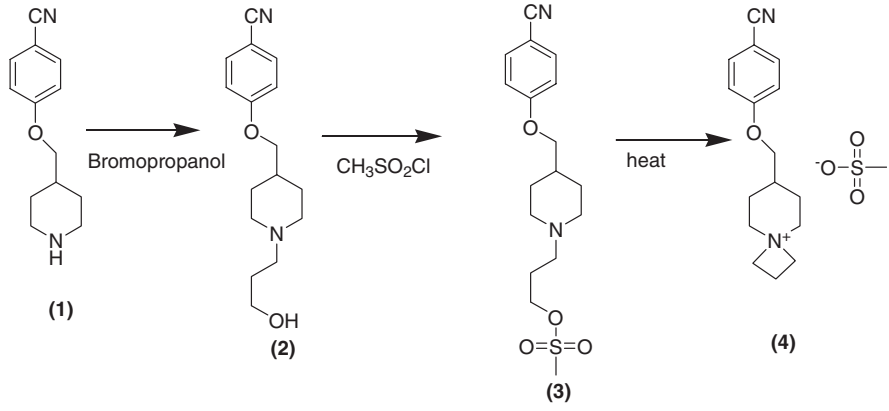


Scheme 1. Synthesis of azetidinium salts

sigma-1 receptors.[3] The synthetic sequence for the radiolabeling employs an alkyl methanesulfonate precursor (**3**, Scheme 1). The secondary amine (**1**) was first alkylated with bromopropanol; the resultant hydroxypropyl amine (**2**) was subsequently reacted with methanesulfonyl chloride to form the methanesulfonate ester (**3**). Following chromatography on silica gel, an impurity that later proved to be the azetidinium salt (**4**) was observed by ^{1}H-NMR. In $CHCl_3$ or CH_3CN solution, **3** slowly converted into **4**. No attempt was made to measure the conversion rate. Once the conversion to azetidinium **4** was complete, the ^{1}H-NMR spectrum compared favorably with that previously reported in the literature[3] for the alkylmethanesulfonate (**3**) (Table 1).

For the purpose of elucidating the structure, a comparative ^{13}C-NMR spectrum of **3** was desirable. However, the instability of **3** in solution prevented the acquisition of the required spectrum. The conversion of **3** into **4** could be prevented if **3** existed as a methanesulfonate salt. This salt was prepared by reaction of alcohol **2** with methanesulfonic anhydride in the presence of K_2CO_3 in a manner inspired by the method of Erhardt and Owens.[4] Although this alkyl methanesulfonate, methanesulfonate salt could not be induced to crystallize, HPLC analysis suggested 96% purity. Because this compound also has a positive charge on the tertiary nitrogen, its NMR spectra provided important comparative information.

The use of conventional 1D and 2D (COSY and HETCOR) NMR techniques provided sufficient evidence for elucidating the structure of **4** as an azetidinium methanesulfonate. The 1D ^{1}H-NMR and ^{13}C-NMR peak assignments for **4** are shown in Figures 1 and 2. An upfield $\underline{C}H_2$ signal at about 14 ppm in the ^{13}C-NMR spectrum compares favorably with that reported in the literature for the 3-carbon of an azetidium salt.[4] This characteristic ^{13}C resonance was observed for all the azetidinium

Table 1. ^{1}H-NMR spectra of products from the reaction of alcohol (2) with methanesulfonyl chloride

Literature (ppm)([3])[a]		*J* (Hz)	(4) (ppm)		*J* (Hz)	(3)[b] base (ppm)		*J* (Hz)	(2) (ppm)		*J* (Hz)
1.65–1.8	m, 2H		1.6–1.8	m, 2H		1.3–1.51	m, 2H		1.2–1.5	m, 2H	
2.12	d, 2H	12	2.07	d, 2H	14.2	1.7–2.1	m, 7H		1.7–2.09	m, 7H	
2.28–2.40	m, 1H		2.2–2.35	m, 1H		2.46	t, 2H	6.8	2.62	t, 2H	5.9
2.75–2.88	m, 5H		2.77	s, 3H		2.94	d, 2H	11.2	3.09	d, 2H	11.2
			2.64–2.84	m, 2H		3.01	s, 3H				
3.60–3.75	m, 2H		3.62	dt, 2H	12.7, 2.9						
3.93	d, 2H	6.1	3.92	d, 2H	5.9	3.83	d, 2H	5.8	3.7–3.85	m, 4H	
4.05	d, 2H	10	4.04	brd, 2H	12.2	4.31	t, 2H	6.5			
4.39	t, 2H	5.5	4.40*	t, 2H	8.3						
4.5	t, 2H	5.5	4.51*	t, 2H	8.3						
6.95	d, 2H	9	6.92	d, 2H	8.8	6.92	d, 2H	8.8	6.92	d, 2H	8.8
7.59	d, 2H	9	7.58	d, 2H	8.8	7.57	d, 2H	8.8	7.57	d, 2H	9.3

The first column is the reported literature spectrum for alkyl methanesulfonate. Compound **3** is the alkyl methanesulfonate prior to cyclization and compound **4** is the azetidinium methanesulfonate. Literature values obtained at 400 MHz; experimental data from this study obtained at 200 MHz.
* In more concentrated solution these signals become AB quartet (4.43 ppm).
[a] ^{1}H-NMR 400 MHz reported for structure **3**[3].
[b] The spectrum obtained immediately after dissolution in $CDCl_3$.

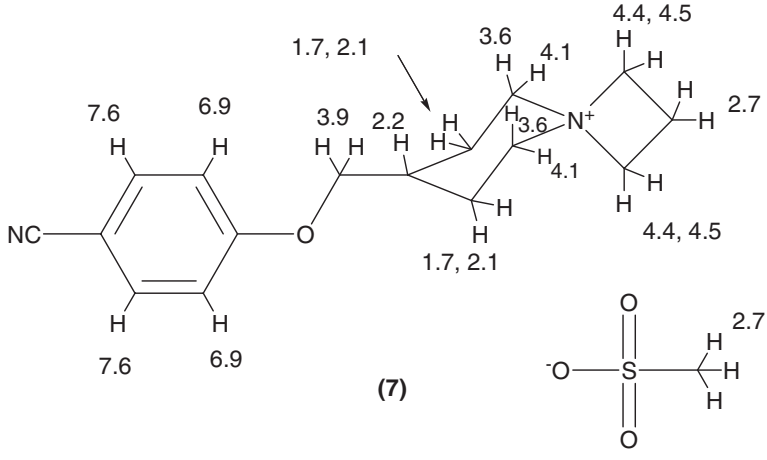


Figure 1. ^{1}H-NMR signal assignments of 4

methanesulfonates prepared for this study. In contrast, the methanesulfonate salt of **3** showed no ^{13}C resonance above 24 ppm. In the ^{1}H-NMR, the methanesulfonate salt of **3** contains two singlets, one for the covalently bound methanesulfonate (3.10 ppm) and one for the ionic methanesulfonate (2.78 ppm), while **4** shows only the ionic methanesulfonate. **4** showed an ion of $m/z = 257$, consistent with the cationic azetidinium moiety, upon analysis

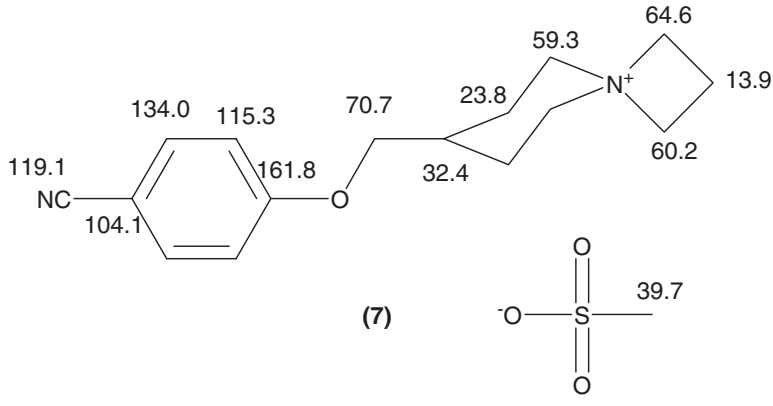


Figure 2. ^{13}C-NMR signal assignments of 4

with ESI-MS and FAB-MS and was soluble in water. HPLC-ESI-MS of **3** showed an M + H signal at m/z 353, indicative of the covalently bound methanesulfonate. All of this evidence supported our assignment of an azetidinium structure for **4**.

Despite the increase in strain energy, cyclization of tertiary *N*-3-methanesulfonyloxypropyl moiety into an azetidinium is quite facile. Even with the strain energy of the four-membered ring, examples of such cyclization reactions are known to occur at room temperature to form azetidinium salts,[4,5] or azetidines.[6–8] Azetidinium ring opening with nucleophiles such as alkoxides, amines, phenoxides, cyanide, and chloride is reported to be facile.[6] In addition, one literature reference demonstrated the ability of an azetidinium methanesulfonate to serve as substrate for the incorporation of fluoride.[9]

We prepared several other azetidinium methanesulfonates by heat-induced cyclization of purified methanesulfonates (Figure 3). Studies of [^{18}F]fluoride incorporation were undertaken to evaluate the utility of these azetidinium methanesulfonates as substrates. The authentic fluoropropyl products were obtained via an independent route, by treating the corresponding secondary amine with bromofluoropropane. [^{18}F]Fluoride reactions were conducted on the various substrates under identical conditions (Scheme 2). Aqueous [^{18}F]fluoride was placed into a test tube along with Kryptofix [2.2.2] and K_2CO_3. The water was removed by azeotropic drying using three portions of CH_3CN. Then, the substrates in CH_3CN were added and the resulting solution heated. HPLC buffer was added and the solution injected onto a semipreparative C-18 HPLC column. The product peak was collected and the radiochemical yield calculated. No attempt was made to achieve chemical purity, but the collected product was analyzed for radiochemical purity and identity (retention time and authentic product co-injection) on an analytical HPLC system. The radiochemical yields, corrected for decay, under these

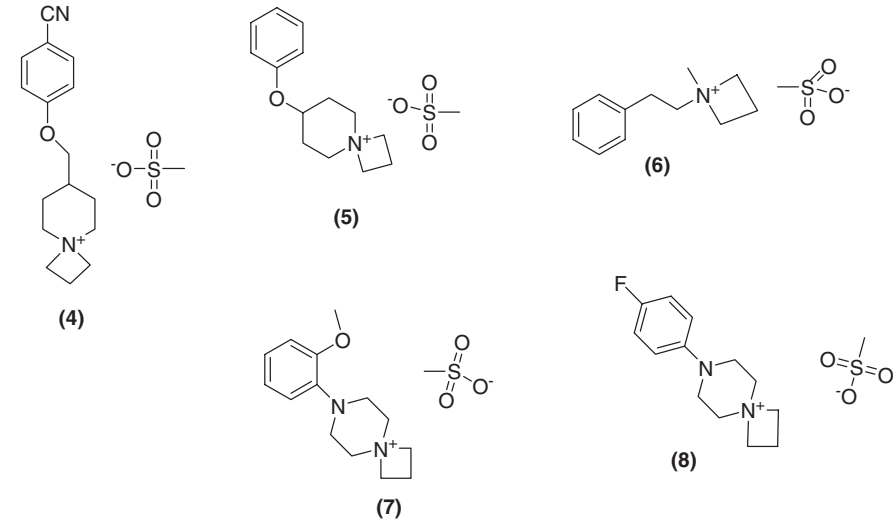
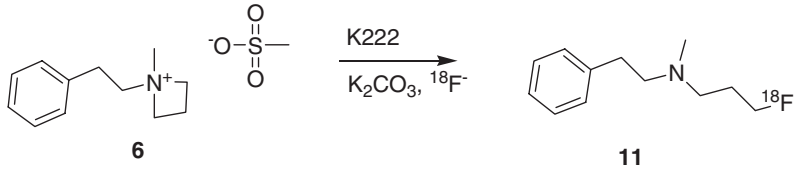
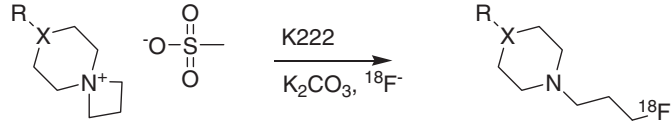


Figure 3. Azetidinium methanesulfonates prepared for this study





4 X = C, R = CH_2O(p-CNphenyl)
5 X = C, R = Ophenyl
7 X = N, R = 2-OCH_3phenyl
8 X = N, R = 4-fluorophenyl

9 X = C, R = CH_2O(p-CNphenyl)
10 X = C, R = Ophenyl
12 X = N, R = 2-OCH_3phenyl
13 X = N, R = 4-fluorophenyl

Scheme 2. Radiosynthesis

conditions are reported in Table 2. All the substrates provided similar radiochemical yields.

Three different lots of the azetidinium methanesulfonate **4** were prepared for this study; two were prepared as described from isolated alkyl methanesulfonate by cyclization in $CHCl_3$. These two lots provided similar radiochemical yields at 105°C and were used for the comparison reactions described in this manuscript. The third lot was obtained by a different route. Following

Table 2. Radiochemical yield corrected for decay for various azetidinium methanesulfonates

Substrate	NCA yield (%)	CA yield %
(**5**)	63 ± 5^a	76 ± 3^a
(**6**)	60 ± 2^b	86 ± 3^a
(**7**)	63 ± 7^a	80 ± 9^a
(**8**)	66 ± 5^a	70 ± 5^b
(**4**) lot 1	70 ± 5^b	83 ± 4^a
(**4**) lot 2	72^c	NA
(**4**) lot 3	27 ± 6^a	NA
(**3**)	72 ± 3^b	NA

(NCA = no-carrier-added reaction; CA = 0.1 equivalent KF added to reaction; NA = not attempted). All reactions run at 105°C.
[a] $n = 3$.
[b] $n = 4$.
[c] $n = 2$ (individual values: 70, 73).

chromatography to isolate **3**, the ^{1}H-NMR showed the presence of a mixture of **3** and **4**. The mixture, in chloroform was extracted with aqueous sodium carbonate. The aqueous layer was evaporated and the resulting solid extracted with CH_2Cl_2. This organic soluble material gave the same ^{1}H-NMR and HPLC data as the previous two lots, but the radiochemical yield at 105°C was significantly lower (Table 2). The melting point of the third lot obtained from the aqueous extraction had a melting range about 10°C higher than the other two lots. We have no definitive explanation for the lower yields of the aqueously extracted azetidinium methanesulfonate other than the possibility that the counterion may contain some carbonate or bicarbonate.

There is one major difficulty in drawing a conclusion from these results concerning the reactivity of the azetidinium methanesulfonates. How can we be sure that the reaction occurred between [^{18}F]fluoride and the azetidinium ion? If a very small amount of the alkyl methanesulfonate was a contaminant and this contaminant reacted very rapidly with fluoride, a high yield could be observed even if the azetidinium salt did not react at all. The presence of minor amounts ($<1\%$) of alkyl methanesulfonate were observed with two of the substrates and could not be ruled out based on our ^{1}H-NMR and HPLC analyses in the others. ^{1}H-NMR is not extremely sensitive to small impurities and the dissolution of the sample for ^{1}H-NMR or HPLC can result in conversion of alkyl methanesulfonate into azetidinium methanesulfonate. In order to address this issue, we studied the reaction of azetidinium salt with addition of carrier-added [^{18}F]fluoride. If the reaction was occurring between fluoride and minute amounts of alkyl methanesulfonate but not with a preformed azetidinium salt, addition of carrier fluoride should result in lowered radiochemical yield. The various azetidinium salts (**4**–**8**) were treated with Kryptofix [2.2.2], K_2CO_3, and 0.1 equivalents of KF. These carrier-added

reactions resulted in the same radiochemical yield (corrected for decay) as was observed in the no-carrier-added experiments (Table 2) for all substrates. Therefore, the presence of minor amounts of alkyl methanesulfonate cannot be responsible for the incorporation of [^{18}F]fluoride.

In order to evaluate the utility of azetidinium methanesulfonates for incorporation of non-radioactive fluoride, azetidinium **8** was treated with [^{18}F]fluoride, Kryptofix [2.2.2], and KF (0.88 equivalents) ($n = 1$). Product (**13**) was isolated from the HPLC eluate and its identity confirmed by GC-MS and ^{1}H-NMR. A previous publication reported a 16% yield of fluorination product from the reaction of Et_3N-2HF with an azetidinium methanesulfonate and concluded, 'these ions seem quite unreactive towards fluorinating agents'.[9] Contrarily, the reaction of **4** with carrier-added potassium [^{18}F]fluoride (0.8 equivalents) and Kryptofix [2.2.2] resulted in a radiochemical yield of about 65% (decay corrected). Therefore, these azetidinium substrates may also be useful for incorporation of non-radioactive fluoride.

Since we had determined that [^{18}F]fluoride does react directly with the azetidinium methanesulfonate, we compared the relative reactivity of the azetidinium salt and alkyl methanesulfonate. Utilizing **4**, the azetidinium methanesulfonate, and **3**, the corresponding alkyl methanesulfonate, a comparison of the radiochemical yields as a function of reaction temperature was conducted (Table 3). In order to minimize the conversion of **3** into **4** prior to the reaction, **3** was dissolved in CH_3CN immediately prior to addition to the dried [^{18}F]fluoride. Reducing the reaction temperature from 105 to 79°C did not significantly reduce the radiochemical yield of the no-carrier-added reactions. Surprisingly, the radiochemical yield of **9** obtained from the alkyl methanesulfonate was lower at 60°C and much lower at 40°C compared with the yield from the azetidinium methanesulfonate. This suggests that the azetidinium salt is actually more reactive toward fluoride and therefore, may have applications with comparatively temperature-sensitive substrates.

At 40 and 60°C, HPLC of the reaction mixture from substrate **3** indicated that a significant amount of the alkyl methanesulfonate, **3**, survived the

Table 3. Radiochemical yield corrected for decay (no-carrier-added) as a function of temperature to compare azetidinium methanesulfonate with alkyl methanesulfonate

Temperature	(**4**) lot 1 azetidinium	(**3**) alkyl mesylate
105	70 ± 5	72 ± 3
79	69 ($n = 2$)[a]	65 ($n = 2$)[b]
60	56 ± 12	32 ($n = 2$)[c]
41	26 ± 4	1.4 ± 2.0

$N = 3$ unless otherwise stated.
[a] Individual numbers 72, 66.
[b] Individual numbers 66, 64.
[c] Individual numbers 33, 30.

reaction. This observation is consistent with the labeling studies of Collier *et al.*[3] in which hydroxide was added to the reaction at the end to destroy remaining substrate **3**. With all reactions utilizing **4** as substrate, the major mass component following the reaction with [^{18}F]fluoride was unreacted **4**.

Experimental

General

4-Hydroxybenzonitrile and 4-hydroxymethyl piperidine were purchased from Lancaster Synthesis (Pelham, NH). Kryptofix [2.2.2] was obtained from EM Reagents. All other reagents were purchased from Aldrich Chemical Company (Milwaukee, WI) and used as received. Solvents were obtained from commercial sources and used as received with the exception of tetrahydrofuran, which was distilled from sodium prior to use. ^{1}H-NMR and ^{13}C-NMR were obtained on a Varian Gemini 2000 spectrometer at 200 and 50 MHz, respectively. The chemical shifts are reported downfield from tetramethylsilane (TMS). Some C-13 assignments are based on calculations using ChemDraw's (Ultra 8.0, CambridgeSoft, Cambridge, MA) spectrum prediction module. HPLC-MS was obtained on a ThermoFinnigan LCQ spectrometer coupled to a HP1100 HPLC system using electrospray as the ionization method with HPLC employing a Phenomenex Luna C-18 (4.6 mm × 150 mm) and isocratic elution (35% CH_3CN: 65% NH_4OAc) unless otherwise noted. Analytical HPLC employed a Phenomenex C-18 column (4.6 × 150 mm) eluted with CH_3CN and NH_4OAc (50 mM) at 1 ml/min. Percent purity from HPLC was determined by integrated peak area but ignoring any peak eluting at the void time. The calculated void volume for this column is 1.75 ml. GC-MS employed a ThermoFinnigan TraceDSQ instrument. Gas chromatography utilized a Restek RTX5-MS column with oven temperature programming (50°C for 2 min, programmed at 30°C/min to 270°C). Microanalyses were conducted by Galbraith Laboratories, Inc. (Knoxville, TN).

1-(tert-Butyloxycarbonyl)-4-(4-cyanophenoxymethyl)piperidine

1-(*tert*-Butyloxycarbonyl)-4-hydroxymethyl piperidine[10] (1 g, 4.65 mmol), 4-hydroxybenzonitrile (554 mg, 4.65 mmol), and triphenylphosphine (1.21 g, 4.65 mmol) were dissolved in tetrahydrofuran (20 mL). Diisopropyl azodicarboxylate (DIAD) (1.03 g, 5.11 mmol) was added. The solution was stirred at room temperature for 3 days. The tetrahydrofuran was evaporated, the residue taken up in ether (50 mL) and washed with 1 M NaOH, water, and brine. The ether layer was dried and evaporated. The residue was subjected to flash chromatography on silica gel eluting with 20% ethyl acetate in hexane. The major component was collected and recrystallized from ethyl acetate-

hexane to yield the product (1.03 g, 69%). A trace of the diisopropyl 1,2-hydrazinedicarboxylate could be seen due to the isopropyl signals in the ^{1}H-NMR. ^{1}H-NMR δ 1.2–1.4 (m, 2H), 1.47 (s, 9H), 1.82 (brd, 2H, J = 13.7 Hz), 1.9–2.0 (m, ^{1}H), 2.75 (brt, 2H, J = 12.0 Hz), 3.85 (d, 2H, J = 6.4 Hz), 4.17 (brd, 2H, J = 13.2 Hz), 6.92 (d, 2H, J = 9.2 Hz), 7.58 (d, 2H, J = 8.7). ^{13}C-NMR δ 28.6, 28.8, 28.9, 36.2, 43.6, 72.7, 79.7, 104.1, 115.3, 119.4, 134.1, 155.0, 162.4. GC-MS 8.88 min, m/z (relative abundance) 316 (M+, 3), 142 (70), 57 (100).

*1-[(3-Hydroxypropyl)-4-(4-cyanophenoxymethyl)]piperidine (**2**)*

The secondary amine (**1**) was obtained by treatment of 1-(*tert*-butyloxycarbonyl)-4-(4-cyanophenoxymethyl)piperidine with trifluoroacetic acid as previously described[10] and used without additional purification. **1** was alkylated following the literature procedure[3] with two minor modifications: time of reaction and chromatography conditions. **1** (500 mg, 2.31 mmol) was dissolved in 10 mL CH_2Cl_2 and anhydrous K_2CO_3 (956 mg, 6.93 mmol) and 3-bromopropanol (81.1 mg, 52.7 µl, 0.575 mmol) were added. The resulting mixture was stirred at room temperature for 4 days, at which time TLC (silica, 90% $CHCl_3$, 9% CH_3OH, 1% NH_4OH) indicated that only a small proportion of **1** remained. Water (20 mL) and CH_2Cl_2 (20 mL) were added and the layers mixed and separated. The aqueous layer was extracted with one portion of CH_2Cl_2 (20 mL) and the combined organic layers were dried (Na_2SO_4) and evaporated. The residue was subjected to flash chromatography, eluting with $CHCl_3$:MeOH:NH_4OH (90:9:1) to give the desired product (504 mg, 80%). ^{1}H-NMR see Table 1. ^{13}C-NMR δ 27.3, 29.2, 35.8 (CH from APT experiment), 53.7, 59.3, 64.9 (CH_2OH), 72.8 (CH_2OAr), 104.0, 115.3 (CN), 119.4, 134.1, 162.5.

4-Phenoxypiperidine

4-Hydroxypiperidine (2.95 g, 29.2 mmol) was dissolved in tetrahydrofuran (40 mL) and 12 mL 10% NaOH was added.[11] Di-*t*-butyl-dicarbonate (7.01 g, 32.1 mmol) was added dropwise over 30 min and the resulting mixture stirred overnight. The mixture was then diluted with $CHCl_3$ (70 mL) and partitioned with 40 mL water. The aqueous layer was extracted with two portions of $CHCl_3$ (40 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). The organic solvent was evaporated and the residue subjected to flash chromatography eluting with 15% ethanol in ethyl acetate. The product (*N*-BOC-4-hydroxy piperidine) was collected and used in the next step without additional purification. ^{1}H-NMR δ 1.46 (s, 3H), 1.3–1.5 (m, 2H), 1.7–1.9 (m, 2H), 2.9–3.1 (m, 2H), 3.8–3.9 (m, 3H); second *t*-butyl signal at 1.55 (1/3 mole equivalent).

Crude *N*-BOC-4-hydroxypiperidine (2.00 g, 9.95 mmol), phenol (936 mg, 9.95 mmol) and triphenylphosphine (2.61 g, 9.95 mmol) were dissolved in THF (40 mL). Diisopropyl azodicarboxylate (2.05 mL, 10.4 mmol) was added in one portion. The resulting solution was stirred at room temperature for 3 h at which time GC indicated complete conversion of *N*-BOC-4-hydroxypiperidine into the phenolic ether. The solvent was then evaporated and the residue purified by flash chromatography eluting with 10% ethyl acetate in hexane. The product, *N*-BOC-4-phenoxypiperidine, was collected as a solid (1.37 g, 50%), mp 65–68°C. ^{1}H-NMR. δ 1.47 (s, 9H), 1.6–2.0 (m, 4H), 3.2–3.4 (ddd, J = 13, 3.7, 3.6 Hz, 2H), 3.6–3.8 (ddd, J = 13.7, 3.7, 3.6 Hz, 2H), 4.46 (sept, J = 3.5 Hz, 1H), 6.9–7.0 (m, 3H), 7.2–7.35 (m, 2H). ^{13}C-NMR δ 28.6, 30.7, 40.9, 72.3, 79.8, 116.4, 121.2, 129.8, 155.1, 157.4.

N-BOC-4-phenoxypiperidine (1.34 g, 4.83 mmol) was dissolved in CH_2Cl_2 (15 mL). Trifluoroacetic acid (4 mL) was added. The resulting solution was stirred at room temperature for 4 h. The solvent was evaporated and the residue taken up in CH_2Cl_2. The solution was washed with 30 ml 1N NaOH and the aqueous layer was back extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were dried (Na_2SO_4) and evaporated. The crude title product was obtained in 99% yield from the BOC-protected precursor and was used directly in the next step to make the hydroxylpropyl analogue without any additional purification. ^{1}H-NMR δ 1.6–1.8 (m, 2H), 1.95–2.1 (m, 2H), 2.65–2.80 (m, 2H), 3.1–3.2 (m, 2H), 4.37 (sept, J = 4.1 Hz, 1H), 6.9–7.0 (m, 3H), 7.2–7.35 (m, 2H).

3-[4-(2-Methoxyphenyl)piperazin-1-yl]propan-1-ol

The corresponding secondary amine (1.32 g, 6.86 mmol) was dissolved in CH_2Cl_2 (25 mL) and treated with 3-bromopropanol (1.15 g, 8.24 mmol) and K_2CO_3 (2.94 g, 20.6 mmol).[12] The reaction was stirred at room temperature for three days and refluxed for 8 h. The mixture was diluted with water and the layers separated. The organic phase was dried with Na_2SO_4 and evaporated. The residue was chromatographed on silica gel, eluting with chloroform: methanol:ammonia (90:9:1) to obtain the amino alcohol containing 3-bromopropanol as a minor contaminant. The desired product was obtained by formation of the oxalate followed by conversion to the free base (952 mg, 55%).

^{1}H-NMR δ 1.76 (quin, J = 6 Hz, 2 H), 2.62–2.84 (m, 7H), 3.00–3.20 (brs, 5H), 3.75–3.90 (m, 2H), 3.85 (s, 2H), 6.8–7.1 (m, 4 H).

3-(4-Phenoxypiperidin-1-yl)propan-1-ol

This compound was prepared in 42% yield following the method for 3-(4-(2-methoxyphenyl)piperazin-1-yl)propan-1-ol. ^{1}H-NMR. δ 1.67–2.05 (m, 6H),

2.25–2.35 (m, 2H), 2.63 (t, J = 5.2 Hz, 2H), 2.7–2.9 (m, 2H), 3.82 (t, J = 5.2 Hz, 2H), 4.36 (sept, J = 3 Hz, 1H), 5.44 (br s, 1H), 6.8–7.0 (m, 3H), 7.20–7.35 (m, 2H).

3-[Methyl(2-phenylethyl)amino]-1-propanol

The corresponding secondary amine was dissolved in DMF (1.5 mL/mmol) and treated with 1.05 equivalent of bromopropanol and 1.5 equivalents of diisopropyl ethylamine.[13] The resulting solution was heated at 80°C for 3 days. The reaction was cooled, diluted with water and extracted with three portions of ether. The organic extracts were dried and the solvent evaporated. The residue was subjected to flash chromatography on silica gel eluting with chloroform:methanol: ammonia (90:10:1). The product was obtained as an oil (63%). A small amount of DMF was present, but the sample was utilized in the next step without additional purification. ^{1}H-NMR δ 1.70 (quin, J = 5.4 Hz, 2H), 2.33 (s, 3H), 2.60–2.68 (m, 4H), 2.68–2.81 (m, 2H), 3.78 (t, J = 4.7 Hz), 7.10–7.35 (m, 5H).

3-(4-(4-Fluorophenyl)piperazin-1-yl)propan-1-ol

This compound was prepared in 70% yield following the same method as for 3-[methyl(2-phenylethyl)amino]-1-propanol.[14]

^{1}H-NMR δ 1.76 (quin, J = 5.4, 2H), 2.6–2.7 (m, 6H), 3.05–3.12 (m, 4H), 3.83 (t, J = 5.2 Hz, 2H), 5.0 (br s, 1H), 6.8–7.00 (m, 4 H).

3 -(4-((4-Cyanophenoxy)methyl)piperidin-1-yl)propyl methanesulfonate, methanesulfonate salt (3, methanesulfonate salt)

2 (100 mg, 0.365 mmol) was dissolved in CH_2Cl_2 (6 mL) and treated with methanesulfonic anhydride (127 mg, 0.730 mmol) and K_2CO_3 (201 mg, 1.46 mmol). The reaction was stirred at room temperature overnight, filtered through Celite and evaporated. The resulting oil was triturated at dry ice temperature with ether and the ether decanted. Crystallization from 2-propanol was unsuccessful leading to an oil. The solvent was decanted, the residue taken up in $CHCl_3$ and CH_3CN and evaporated to provide 84 mg (50%) as an oil. HPLC (35% CH_3CN) T_R 6.4 min, 96% at 230 nm. HPLC (Phenomenex Luna (2 × 150 mm, 100% 50 mM NH_4OAc to 65% CH_3CN, 35% 50 mM NH_4OAc over 10 min, 1 ml/min) ESI-MS m/z 353 (M + H). ^{1}H-NMR δ 1.82–2.24 (m, 5H), 2.24–2.55 (m, 2H), 2.78 (s, 3H), 2.75–3.00 (m, 2H), 3.10 (s, 3H), 3.18–3.42 (m, 2H), 3.70 (brd, J = 11 Hz, 2H), 3.92 (d, J = 5.0 Hz, 2H), 4.40 (t, J = 4.9 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 7.58 (d, J = 8.7 Hz, 2H), 10.34 (brs, 1H). Some impurity signals were observed. ^{13}C-NMR δ 24.2, 25.9, 33.8, 37.5 (CH_3), 39.7 (CH_3), 52.9, 54.2, 67.2, 71.2, 104.3, 115.3 (CH), 119.2, 134.1(CH), 161.8.

General synthesis method for azetidinium methanesulfonates

The appropriate 3-hydroxypropylamine was dissolved in dichloromethane and treated with 1.1 equivalent of methanesulfonyl chloride and **4** equivalents of triethylamine. The reaction was stirred at room temperature for 30–45 min. The solvent was evaporated and the residue subjected to flash chromatography on silica gel. The sample was loaded in ethyl acetate and the column eluted with 10% ethanol in ethyl acetate (unless otherwise stated). This procedure follows the literature preparation of **3** except for a change in the eluant for the silica gel column purification.[3] Fractions containing product were collected and the solvent evaporated *in vacuo* with a bath temperature of 25°C. ^{1}H-NMR was acquired on these intermediates; spectra showed a preponderance of alkyl methanesulfonate with varying amounts of azetidinium salts. The product mixtures were dissolved in chloroform and heated at 65°C overnight to effect complete cyclization to the azetidinium methanesulfonate. The solvent was evaporated and the resulting oil triturated with ethyl acetate. Two of the five azetidinium methanesulfonates did not solidify upon trituration.

*7-[(4-Cyanophenoxy)methyl]-4-azoniaspiro[3.5]nonane methanesulfonate (**4**)*

Following the general procedure for azetidinium methanesulfonates, alkyl methanesulfonate **3** was obtained as a solid in 72% yield (mp 72–74°C, lit.[3] 67–68°C). ^{1}H-NMR of (**3**) is reported in Table 1. Analytical HPLC (35% CH_3CN) showed two components 3.17 min (azetidinium **4**) and 6.69 min (alkyl methanesulfonate **3**). Following cyclization, recovery of hygroscopic azetidinium methanesulfonate **4** from alkyl methanesulfonate **3** was 89% (overall yield from alcohol 65%). mp 139–141°C. ^{1}H-NMR for **4** is reported in Table 1 and Figure 1. ^{13}C-NMR is reported in Figure 2. HPLC-ESI-MS: m/z 257. HPLC (20% CH_3CN) 7.46 min, 99% at 250 nm.

Analysis: Calculated for $C_{17}H_{24}N_2O_4S \cdot 1/3\ H_2O$: C, 56.96; H, 6.94; N, 7.82; S, 8.95. Found: C, 57.36; H, 6.79; N, 7.81; S, 8.56.

A second sample was obtained in a similar manner, mp 135–138°C. A third sample of **4** was obtained from the alkyl methanesulfonate by partitioning with aqueous Na_2CO_3 and evaporating the aqueous layer. The residue from the aqueous layer was washed with CH_2Cl_2 and evaporated to yield an oil. This oil was crystallized from 2-propanol, mp 150–153°C. FAB-MS $m/z + 257$. ^{1}H-NMR for lots 2 and 3 were identical to lot 1.

*7-Phenoxy-4-azoniaspiro[3.5]nonane methanesulfonate (**5**)*

Following the general procedure for azetidinium methanesulfonates, the alkyl methanesulfonate precursor of **5** was prepared. Chromatography of alkyl methanesulfonate utilized 10% acetonitrile in ethyl acetate to give 87% yield. ^{1}H-NMR of alkyl methanesulfonate showed CH_3 at 3.02 ppm and

$CH_2OSO_2CH_3$ at 4.3 ppm (*t*). The azetidinium methanesulfonate, resulting from heat-induced cyclization, did not solidify upon treatment with ethyl acetate. The resulting oil solidified after standing overnight at −20°C, but melted on warming to room temperature. The product contained <1% alkyl methanesulfonate as determined by ^{1}H-NMR.

^{1}H-NMR δ 2.0–2.3 (m, 4H), 2.79 (s, 3H), 2.82 (quin, J = 8.3 Hz, 2H), 3.61 (dt, J = 12, 3.4 Hz, 2H), 3.97 (t, J = 4.0, 1H), 4.03 (t, J = 4.4 Hz, 1H), 4.40, (t, J = 8.3 Hz, 2H), 4.63 (t, J = 8.3 Hz, 2H), 6.89 (d, J = 7.8 Hz, 2H), 7.00 (t, J = 7.3 Hz, 1H), 7.30 (t, J = 8.3 Hz, 2H).

^{13}C-NMR δ 156.25, 130.0, 122.1, 116.2, 66.6, 63.9, 61.4, 56.3, 39.9, 25.8, 14.1.

HPLC-ESI-MS: m/z 218. HPLC (20% CH_3CN): T_R 6.5 min, 95% purity at 250 nm.

Analysis: Calculated for $C_{15}H_{23}NO_4S$: C, 57.48; H, 7.40; N, 4.47; S, 10.23. Found: C, 54.79, H, 7.49, N, 4.20, S, 9.94.

*1-Methyl-1-(2-phenylethyl)azetidinium methanesulfonate (**6**)*

Following the general procedure for azetidinium methanesulfonates, the alkyl methanesulfonate was obtained in 85% yield. ^{1}H-NMR of alkyl methanesulfonate showed CH_3 at 2.95 ppm and $CH_2OSO_2CH_3$ at 4.20 ppm. Following cyclization, the azetidinium methanesulfonate was recovered as a hygroscopic solid in 70% yield after trituration with EtOAc. mp 83–85°C. ^{1}H-NMR δ 2.72 (s, 3H), 2.45–2.9 (m, 2H), 2.95–3.05 (m, 2H), 3.35 (s, 3H), 3.75–3.90 (m, 4H), 4.2–4.4 (m 2H), 4.4–4.65 (m, 2H), 7.2–7.4 (m, 5H). ^{13}C-NMR δ 135.3, 129.2, 129.2, 127.6, 65.1, 64.4, 49.1, 39.9, 29.7, 14.3.

HPLC-ESI-MS: m/z 176. HPLC (20% CH_3CN): T_R 4.1 min, 95% purity at 250 nm.

Analysis: Calculated for $C_{13}H_{21}NO_3S \cdot \frac{1}{2} H_2O$: C, 55.69; H, 7.91; N, 5.00; S, 11.44. Found: C, 55.29; H, 7.99, N, 5.62, S, 11.06.

*7-(2-Methoxyphenyl)-7-aza-4-azoniaspiro[3.5]nonane methanesulfonate (**7**)*

Following the general procedure for azetidinium methanesulfonates, the alkyl methanesulfonate was obtained in 83% yield. ^{1}H-NMR of the alkyl methanesulfonate showed OCH_3 at 3.05 ppm and $CH_2OSO_2CH_3$ at 4.33 ppm. Following cyclization, **7** was obtained as an oil and could not be induced to solidify. **7** was observed to contain <1% alkyl methanesulfonate by ^{1}H-NMR.

^{1}H-NMR δ 2.76 (s, 3H), 2.84 (quin, J = 8.3 Hz, 2H), 3.2–3.3 (m, 4H), 3.83 (s, 3H), 3.8–3.9 (m, 4H), 4.54 (t, J = 8.0 Hz, 4H), 6.8–7.9 (m, 3H), 7.0–7.15 (m, 1H). ^{13}C-NMR δ 152.3, 138.6, 124.6, 121.2, 118.9, 111.6, 62.4, 59.9, 55.6, 45.5, 39.8, 14.1. HPLC-ESI-MS: m/z 233. Analytical HPLC (35% CH_3CN): T_R

4.5 min, 97% purity at 250 nm. Analysis: Calculated for $C_{15}H_{24}N_2O_5S\ H_2O$: C, 52.00; H, 7.56; N, 8.09; O, 23.09; S, 9.26. Found: C, 52.08; H, 7.02; N, 7.91; S, 9.36.

*7-(4-Fluorophenyl)-7-aza-4-azoniaspiro[3.5]nonane methanesulfonate (**8**)*

Following the general procedure for azetidinium methanesulfonates, the alkyl methanesulfonate was obtained in 86% yield. ^{1}H-NMR of alkyl methanesulfonate δ 1.97 (pent, J = 6.8 Hz, 2H), 2.35 (t, J = 7.0 Hz, 2H), 2.55–2.65 (m, 4H), 3.02 (s, 3H), 3.05–3.15 (m, 4H), 4.33 (t, J = 6.3 Hz, 2H), 6.8–7.05 (m, 4H). Following cyclization, **8** was obtained as a hygroscopic solid in 86% yield from the alkyl methanesulfonate. mp 143.5–146°C. ^{1}H-NMR δ 2.75 (s, 3H), 2.82 (quin, J = 8.3 Hz, 2H), 3.2–3.3 (m, 4H), 3.8–3.9 (m, 4H), 4.55 (t, J = 8.3 Hz, 4H), 6.8–7.1 (m, 4H). ^{13}C-NMR δ 158.2 (J = 241 Hz), 145.8 (J = 2.4 Hz), 119.1 (J = 7.8 Hz), 116.1 (J = 22.4 Hz), 62.4, 59.3, 45.7, 39.9, 14.1. HPLC-ESI-MS: m/z 221. HPLC (20% CH_3CN): T_R 2.97 min, 97% purity at 250 nm.

Analysis: Calculated for $C_{14}H_{21}FN_2O_3S \cdot 1/3\ H_2O$: C, 52.16; H, 6.77; N, 8.69; S, 9.95. Found: C, 52.55; H, 6.82; N, 8.68; S, 9.69.

General procedure for preparation of fluoropropyl analogues

Secondary amine (1 equivalent) was dissolved in a solvent (CH_2Cl_2, CH_3CN, or DMF). 1-Bromo-3-fluoropropane (1.02 equivalent) and base (K_2CO_3, 4 equivalents; or diisopropyl amine, 1.5 equivalents) were added. The reaction was stirred at room temperature for 2 days (CH_2Cl_2), heated at 85°C overnight (CH_3CN) or heated at 60°C for 3–4 days (DMF). The reaction was partitioned with water, evaporated and dried (Na_2SO_4). The product was purified by flash chromatography on silica gel. The free base was precipitated from acetone solution by addition of oxalic acid.

*4-{[1-(3-Fluoropropyl)-4-piperidinyl]methoxy}benzonitrile (**9**)*[3]

Using the general procedure, alkylation was conducted in CH_2Cl_2 for 2 days. Flash chromatography employed $CHCl_3$:MeOH:NH_4OH (95:4.5:0.5). The free base was analyzed by GC-MS (EI), T_R 8.23 min, 276 (4), 230 (100). The oxalate was obtained in 51% yield. ^{1}H-NMR (oxalate salt in $CDCl_3$/DMSO-d_6) δ 1.8–2.4 (m, 7H), 2.65–2.9 (m, 2H), 3.1–3.25 (m, 2H), 3.68 (br d, J = 7.8 Hz, 2H), 3.90 (d, J = 7.8 Hz, 2H), 4.53 (dt, J = 46.9, 5.4 Hz, 2H), 6.93 (d, J = 8.8 Hz, 2H), 7.59 (d, J = 8.8 Hz, 2H). HPLC (35% CH_3CN) T_R 5.5 min, >98% at 230 nm.

Analysis: Calculated for $C_{16}H_{21}FN_2O \cdot C_2H_2O_4$: C, 59.01; H, 6.33; N, 7.65. Found: C, 58.75; H, 6.49; N, 7.58.

*1-(3-Fluoropropyl)-4-phenoxypiperidine (***10***)*

Following the general procedure, alkylation was conducted in CH_3CN at 85°C overnight. The free base was obtained in 92% yield following flash chromatography ($CHCl_3$:MeOH:NH_4OH (95:4.5:0.5)) and characterized by ^{1}H-NMR. The oxalate salt was obtained in 71% yield. GC-MS (EI) T_R 7.6 min 237 (15), 190 (100), 144(45). HPLC (35% CH_3CN) T_R 7.6 min, >99% at 230 nm. ^{1}H-NMR (free base) δ 1.7–2.1 (m, 6H), 2.2–2.4 (m, 2H), 2.48 (two overlapping doublets, J = 7.8, 6.8, 2H), 4.35 (sept, J = 3.9 Hz, ^{1}H), 4.50 (dt, J = 47.4, 5.9 Hz), 6.8–7.0 (m, 3H), 7.2–7.35 (m, 2H). ^{13}C-NMR δ 157.6, 129.6, 120.9, 116.3, 82.7 (J = 164), 72.7, 54.4 (J = 5.9), 50.8, 31.0, 28.4 (J = 19.5).

Analysis: Calculated for $C_{14}H_{20}FNO \cdot C_2H_2O_4$: C, 58.71; H, 6.77; N, 4.28. Found: C, 58.12; H, 6.85, N, 4.26.

*N-(3-Fluoropropyl)-N-methyl-N-(2-phenylethyl)amine (***11***)*

Using the general procedure, alkylation was conducted in DMF for 3 days. The free base was isolated after flash chromatography ($CHCl_3$:MeOH:NH_4OH (95:4.5:0.5)) and analyzed by NMR. The oxalate salt was obtained in 63% overall yield. GC-MS (CI-CH_4) T_R 4.99 min. 196 (M + 1). HPLC (35% CH_3CN) T_R 4.8 min, >98% at 230 nm. ^{1}H-NMR δ (free base) 1.70–2.0 (dm, J = 25.4, 2H), 2.30 (s, 3H), 2.53 (t, 7.0), 2.55–2.65 (m, 2H), 2.65–2.80 (m, 2H), 4.46 (dt, J = 47.3, 5.8 Hz, 2H), 7.1–7.35 (m, 5H). ^{13}C-NMR δ 140.7, 128.9, 128.5, 126.1, 82.7 (J = 163.6), 59.8, 53.4 (J = 5.3), 42.3, 34.0, 28.6 (J = 9.6).

Analysis: Calculated for $C_{12}H_{18}FN \cdot C_2H_2O_4$: C, 58.94; H, 7.17; N, 4.91. Found: C, 58.85; H, 7.17; N, 4.91.

*1-(3-Fluoropropyl)-4-(2-methoxyphenyl)piperazine (***12***)*

Following the general procedure, alkylation was conducted in DMF for 3 days. The free base was isolated by flash chromatography ($CHCl_3$:MeOH:NH_4OH (95:4.5:0.5)). The oxalate was obtained in 86% overall yield. GC-MS (CI-CH_4) T_R 6.92 min, 253 (M + 1), 281 (M + 29). HPLC (35% CH_3CN) T_R 7.0 min, >99% at 230 nm. ^{1}H-NMR (free base) δ 1.8–2.1 (dm, J = 25.4 Hz, 2H), 2.55 (t, J = 7.3 Hz, 2H), 2.6–2.7 (m, 4H), 3.05–3.15 (m, 4H), 3.85 (s, 3H), 4.53 (dt, J = 47.4, 5.8 Hz, 2H), 6.8–7.1 (m, 4H). ^{13}C-NMR δ 152.5, 141.5, 123.1, 121.1, 118.4, 111.4, 82.8 (J = 164), 55.5, 54.5 (J = 5.4), 53.6, 50.8, 28.1 (J = 20). Analysis: Calculated for $C_{14}H_{21}FN_2O \cdot C_2H_2O_4$: C, 56.13; H, 6.77; N, 8.18. Found: C, 54.22; H, 6.67; N, 7.58.

*1-(4-Fluorophenyl)-4-(3-fluoropropyl)piperazine (***13***)*

Following the general procedure, alkylation was conducted in DMF for 4 days. After flash chromatography ($CHCl_3$:MeOH:NH_4OH (97:2.7:0.3)) **13** was obtained in 89% yield. The oxalate salt was obtained in 88% overall yield.

GC-MS (CI-CH_4) T_R 6.48 min, 241(M + 1), 221 ((M + 1)–20). HPLC (35% CH_3CN) T_R 13.1 min, >99% at 230 nm. ^{1}H-NMR (free base) δ 1.75–2.05 (dm, J = 24.9 Hz, 2H), 2.53 (t, J = 7.3, 2H), 2.5–2.7 (m, 4H), 3.0–3.2 (m, 4H), 4.55 (dt, J = 47.3, 5.9 Hz, 2H), 6.8–7.0 (m, 4H).

Analysis: Calculated for $C_{13}H_{18}F_2N_2 \cdot C_2H_2O_4$: C, 54.54; H, 6.10; N, 8.48. Found: C, 54.63; H, 6.38; N, 8.19.

Radiofluorination of azetidinium methanesulfonates

Stock solutions of Kryptofix [2.2.2] (9 mg/100 μL), K_2CO_3 (0.1 M), and KF-H_2O (0.147 M) were prepared. A 13 × 100 mm test tube was charged with 100 μL (24 μmol) of Kryptofix [2.2.2] solution, 120 μL (12 μmol) K_2CO_3 solution, and an aliquot of [^{18}F]fluoride (1–5 mCi). The solvents were evaporated under a stream of argon while heating at 100–110°C. Three portions of CH_3CN (200 μL) were added and each, in turn, evaporated. A solution of the azetidinium methanesulfonate (5.7 μmol) in 300 μL CH_3CN was added and heated for 5 min in the same heating block. The reaction solution was then removed from heat, cooled briefly, and diluted with 500 μL of 50 mM NH_4OAc solution. (If the reaction went dry during heating, CH_3CN (200 μl) was added first.) The entire solution was injected onto a semipreparative HPLC column (Phenomenex Luna C-18(2) 9.4 × 250 mm) and eluted with 30% CH_3CN, 70% 50 mM NH_4OAc at 5 ml/min. The eluate was monitored with online radioactivity and UV detectors (230 nm). The two largest radioactivity peaks, [^{18}F]fluoride, near the solvent front, and product, at the appropriate retention time, were collected. Radioactivity assay of the product was corrected for decay to the start of the reaction and the decay corrected radiochemical yield calculated. An aliquot of the product was reinjected onto an analytical HPLC column (Phenomenex Luna C-18(2) 4.6 × 150 eluted with 35% CH_3CN: 65% 50 mM NH_4OAc at 1 mL/min) to verify radiochemical purity and identity based on retention time. The retention time for each individual fluorinated product on the analytical system can be found with its experimental description above.

Conclusion

A variety of quaternary azetidinium methanesulfonates were prepared with a relatively facile cyclization procedure that involved heating of the alkyl methanesulfonate in chloroform. Azetidinium methanesulfonates could be used as substrate for incorporation of both no-carrier-added and carrier-added [^{18}F]fluoride. At 40 and 60°C the azetidinium methanesulfonate **4** provided a higher radiochemical yield based on [^{18}F] fluoride than the corresponding alkyl methansulfonate **3**. Higher radiochemical yields are obtained at the higher temperatures studied but either substrate provided equivalent yields.

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