JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
*J Label Compd Radiopharm* 2003; **46**: 1151–1160.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.747

**Research Article**

# Synthesis of [$^{18}$F]Fluoroclofilium as a potential cardiac imaging agent for PET studies

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## Summary

*N*-4-(4-chlorophenyl)butyl-*N*,*N*-diethyl-7-[$^{18}$F]fluoroheptylammonium ([$^{18}$F]-fluoroclofilium) has been prepared as a potential cardiac imaging agent. For the synthesis of this radiolabelled ammonium salt, its tosyloxylated analogue was prepared as a precursor, and the non-radioactive fluorine analogue was synthesized as a reference compound. Radiofluorination was achieved by the treatment of *N*-4-(4-chlorophenyl)butyl-*N*,*N*-diethyl-7-(*p*-toluenesulfonyloxy)-heptylammonium *p*-toluenesulfonate with $^{18}F^-$ in the presence of Kryptofix-2.2.2 in acetonitrile. Copyright © 2003 John Wiley & Sons, Ltd.

**Key Words:** fluoroclofilium; [$^{18}$F]fluoroclofilium; radiofluorination; PET

## Introduction

The quaternary ammonium derivative clofilium (**1**) is well known for its class III antiarrhythmic properties.[1] HERG potassium channels are

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Contract/grant sponsor: Korean Science and Engineering Foundation; contract/grant number: KOSEF 951-0710-007-2
Contract/grant sponsor: Nuclear R&D Program from the Ministry of Science & Technology
Contract/grant sponsor: Dongguk University Research Fund

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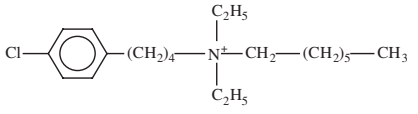
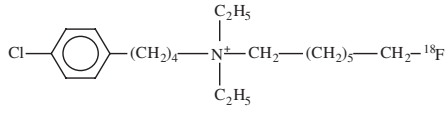
*Received 2 April 2003*
*Revised 3 July 2003*
*Accepted 11 July 2003*

blocked by clofilium in a nanomolar range and this binding is believed to be the reason for its antiarrhythmic action.[2] [$^{14}$C] labelled clofilium showed high myocardial uptake[3] and radioactive labelling of its aromatic residue by several iodine isotopes has been carried out.[4] Here we report on the synthesis of [$^{18}$F]fluoroclofilium (**2**).



**1**



**2**

## Results and discussion

Previously labelling of clofilium with iodine isotopes was carried out in the aromatic ring by iodine exchange yielding a product of low specific activity. We decided to introduce the F-18 into the $\omega$-position of the heptyl side chain. This approach allowed no carrier added (n.c.a) introduction of F-18 by nucleophilic substitution.[5] As leaving group the *p*-tosyloxy residue was chosen. Before starting the F-18 labelling we had to synthesize the reference compound **5** and the precursor **10**. Retrosynthesis led us to the known tertiary amine **9**,[6] the previously described heptyl ditosylate **3**[7] and fluoroheptyl tosylate **4**.

For the synthesis of the amine **9** we started with the reduction of the commercially available 4-(4-chlorobenzoyl)propionic acid **6** by the borane-tert-butylamine complex in dichloromethane. Contrary to published data[8] the reaction time required 9 days stirring at 40°C in a closed-reaction vessel to yield the substituted butanol **7**, after purification on a silica gel column, in a good yield (71%). Compound 7 was treated with an excess of tosyl chloride in pyridine to give the tosylate **8**, after chromatographic purification, in 70% yield. Stirring compound **8** in diethylamine at 50°C for 1 day led to the amine **9** in 90% yield.

Reaction of the commercially available 1,7-heptandiol with tosyl chloride was carried out in 58% yield to give the known ditosylate **3**, which was treated thereafter with tetrabutylammonium fluoride (TBAF) in acetonitrile, generating the fluoro compound **4** in moderate yield (31%). The reference compound **5** was synthesized in a closed vessel in acetonitrile as solvent by reaction of a slight excess of the fluoro compound **4** with the amine **9** at 85°C; the yield was 80%. The produced ammonium salt (cation **5** and tosylate as anion) was precipitated as an oil by addition of petrol ether (see Scheme 1).

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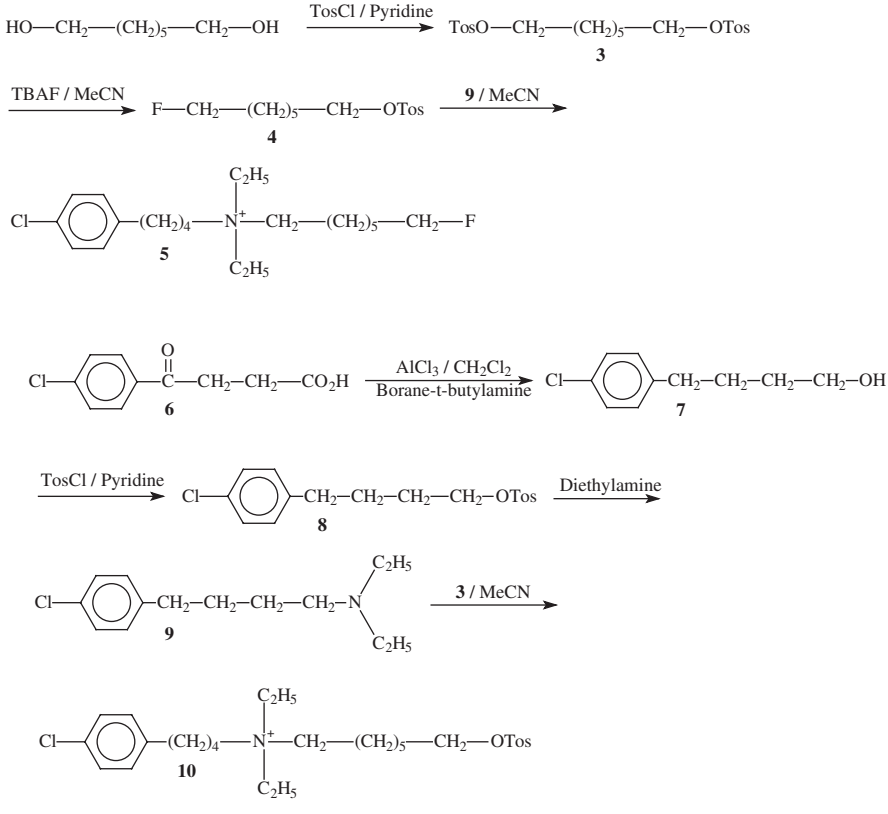


**Scheme 1.**

After crystallization in ether the elemental analysis (CHN) corresponded to the expected ammonium salt. The $^{1}$H-NMR was consistent with the presence of two different *p*-substituted aromatic rings, three methyl groups and 13 methylene groups. The methylene group in $\omega$-position of the heptyl side chain at 4.41 ppm was split into a doublet of triplets (dt; $^{2}J_{HF} = 47.3$ Hz, $^{3}J_{HH} = 6.0$ Hz). The $^{19}$F-NMR signal at $-218.7$ ppm can be analyzed as a triplet of triplet (tt;$^{2}J_{HF} = 46.8$ Hz, $^{3}J_{HF} = 24.3$ Hz). The intense peak (100%) at *m*/*e* 356 in the FAB mass spectrum corresponded with the mass of cation **5**.

Treating the amine **9** with a three-fold excess of the ditosylate **3** at 85°C generated as main product the desired precursor **10** as ammonium salt (cation **10** and tosylate as anion) but also as by-product a 1,7-disubstituted heptane di-ammonium compound. The by-product was extracted with water from a dichlormethane solution. The MS spectrum (FAB) of the main product **10** and of the by-product showed strong

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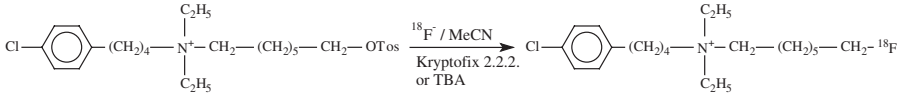
peaks at *m*/*e* 508 and 748, respectively, consistent with the cation **10** and the not shown di-ammonium cation. In a separate experiment in which the amine **9** was used in excess with respect to the ditosylate **3**, the di-ammonium compound was generated as the main product. HPLC analysis on a RP-18 column indicated that the purity of the precursor **10** after clean up was $\geqslant$95%. Compound **10** was treated with TBAF in acetonitrile at 85°C for 1 h. Resulting compound **5** was identified by its retention time on a RP-18 column. The $^{19}$F-NMR showed the expected pattern in the form of a triplet of triplets.

For the labelling procedure with F-18 two often used phase transfer catalysts were tried out, tetrabutylammonium carbonate and Kryptofix 2.2.2 in acetonitrile, of which the Kryptofix method according to Klatte *et al.*[5] gave the best results. After 30 min at 85°C the yield, as determined by radio-TLC, was $\geqslant$75%.




**10** **2**

First, the reaction solution was passed through a small alumina cartridge to remove unreacted F-18. Further separation from excess of precursor and catalyst by HPLC (Figure 1) occurred on a RP-18 column with aqueous phosphate buffer whereupon the labelled compound was produced in high chemical and radiochemical purity ($\geqslant$95%). The absence of an UV absorption reflects the absence of cold clofilium. The specific activity was $\geqslant$30 GBq/μMol.

## Conclusion

[$^{18}$F]Fluoroclofilium labelled in the $\omega$-position of the heptyl side chain has been synthesized in a specific activity of $\geqslant$30 GBq/μmol and a radiochemical purity of $\geqslant$95%.

## Experimental

All chemicals were purchased from Aldrich, Fluka or Sigma in analytical grade and were used without further purification. Elemental analysis were performed with the CHN-O-RAPID (Analysesystem GmbH, Hanau, FRG ) instrument. Preparative column chromatography (flash

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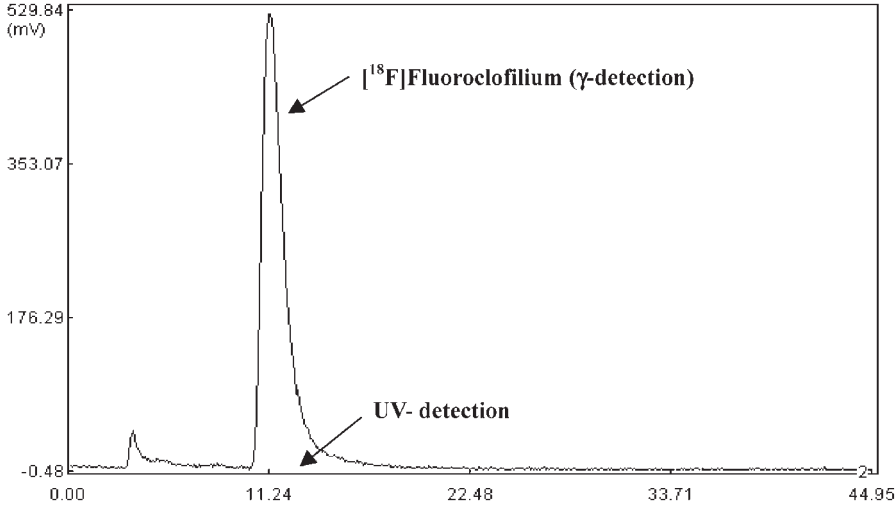


**Figure 1. HPLC analysis of the purified [$^{18}$F]Fluoroclofilium (2). UV (277 nm) and $\gamma$-detection (511 keV) profiles were recorded simultaneously. HPLC was performed on a reverse-phase column (Nova-Pak $C_{18}$, 3.9 × 300 mm, 4 µm. Eluent: MeOH/0.05 M $K_2HPO_4$ with 10% MeOH 60/40 at a flow rate of 1 ml/min)**

mode, 0.5 bar) was carried out on silica gel (15 µm). Gel plates (HPTLC, silica gel 60 $F_{254}$) were purchased from Merck (Darmstadt). Radioactive spots were detected using a Bioscan AC-3000 scanner. For analytical HPLC a Gynkotek System (Column: Lichrospher 100 RP-18 end-capped; 5 µm; 125 × 4 mm; flow: 1 ml/min; $\lambda$: 277 nm) was used and for semipreparative HPLC a Young–Lin system equipped with a Young–Lin UV instrument (Column: RP-18, 300 × 3.9 $mm^2$; 4 µm; flow 1 ml/min; $\lambda$: 277 nm). For $\gamma$-detection a Raytest GABI instrument was used. As components of eluents were used $CH_2Cl_2$ (A), *n*-hexane (B), acetone (C), $CH_3OH$ (D) and 0.05 M $KH_2PO_4$ with 10% MeOH (E). $^1$H-NMR spectra were recorded mostly on a Bruker WP 80 spectrometer and in a few cases on a Bruker AM 360. All chemical shifts were reported on ppm scale with TMS as internal standard. $^{19}$F-NMR spectra were recorded on a Bruker WP 80 with 1% $CDF_3$ in $CDCl_3$ as external standard. MS spectra of non-ionic compounds were recorded on MAT 311 A (70 eV, Varian MAT) mass spectrometer. Organic ammonium compounds were measured by the FAB Method (Xenon gun, *m*-nitrobenzylalcohol as matrix). [$^{18}$F]fluorine was produced on a MC-50 cyclotron by irradiation of a $H_2^{18}O$ water target.

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*4-(4-Chlorophenyl)butanol (***7***)*[8]

Borane-*tert*-butylamine-complex in an amount of 24.4 g (281 mmol) was added to an ice cold solution of 18.7 g (140 mmol) of aluminum chloride in 200 ml of $CH_2Cl_2$. After 10 min 10.0 g (46.8 mmol) of 3-(4-chlorobenzoyl)propionic acid (**6**) was slowly added to the reaction mixture. The suspension was refluxed for 9 days in a closed system under dry nitrogen. After cooling the mixture was poured under vigorous stirring into 500 ml of ice with 200 ml of 0.1 M HC1. After 2 h stirring the organic phase was separated and washed 3 times with 50 ml of water, saturated aqueous $NaHCO_3$ and then dried over anhydrous sodium sulfate and filtered. After evaporation the product was purified by column chromatography (A:C 9/1). After Kugelrohr distillation (150°C at 12 mm Hg) 6.1 g (71%) of an oil was obtained. TLC: $R_f$ = 0.5 (A:C 9/1). $^1$H-NMR ($CDCl_3$): δ = 7.24 (*d*; 2 H, Ar-H), 7.07 (*d*; 2 H, Ar-H), 3.62 (*t*; 2 H, HOC$H_2$), 2.57 (*m*; 3 H, Ar-C$H_2$ and OH), 1.7–1.4 (*m*; 4 H, C$H_2$–C$H_2$). MS (*m*/*e*): 184 (20%, $M^+$), 166 (4%), 151 (10%), 138 (100%), 131 (40%), 125 (94%).

*4-(4-Chlorophenyl)butyltosylate (***8***)*

Tosyl chloride in an amount of 7.20 g (38.0 mmol) was added slowly to 3.50 g (19.0 mmol) of compound **7** in 50 m1 of anhydrous pyridine at 0°C. The mixture was stirred for 30 min at 0°C, stirred for an additional 3 h at room temperature and quenched with 3 ml of water. After 15 min and addition of 100 ml of $CH_2Cl_2$ the pyridine was extracted with 100 ml of conc. HCl in 600 ml of ice water. The organic layer was separated and washed twice with 70 ml of water and dried over anhydrous sodium sulfate and filtered. Concentration in vacuum followed by purification by column chromatography (A:B:C 48/50/2) yielded 4.5 g (70%) of an oily product. TLC: $R_f$ = 0.6 (A:B:C 45/50/5). $^1$H-NMR ($CDCl_3$): δ = 7.70 (*d*; 2 H, $CH_3$ Ar-H), 7.33 (*d*; 2 H, $CH_3$Ar-H), 7.20 (*d*; 2 H, ClAr-H), 7.05 (*d*; 2 H, C1Ar-H), 4.01 (*m*; 2 H, OC$H_2$), 2.55 (*m*; 2 H, ClAr-C$H_2$), 2.44 (*s*; 3 H, C$H_3$), 1.80–1.50 (*m*; 4 H, $CH_2$C$H_2$–C$H_2$$CH_2$). MS (*m*/*e*): 338 (4%, $M^+$), 166 (14%), 138 (100%), 131 (46%), 125 (50%). Anal. for $C_{17}H_{19}ClO_3S$ (M 338.9) cal. C 60.26 H 5.65, exp. C 60.21 H 5.80.

*N-4-(4-Chlorophenyl)butyl-N,N-diethylamine (***9***)*[6]

A mixture of 3.45 g (10.2 mmol) of compound **8** in 50 ml of dry diethylamine was stirred for 24 h at 50°C. After evaporation of the

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excess of diethylamine 50 ml of 2 M NaOH was added to the resulting white solid. The aqueous phase was extracted twice with 70 ml of $CH_2Cl_2$. The combined organic extract was dried over sodium sulfate, filtered and evaporated. Purification by column chromatography (A:B:C 45/50/5) followed by Kugelrohr distillation gave 2.20 g (90%) of compound **9** as a yellow oil ( b.p 158–160°C at 50 mm Hg). TLC: $R_f$ = 0.3 (A:B:C 45/50/5). $^1$H-NMR ($CDCl_3$): δ = 7.20 (*d*; 2 H, Ar-H), 7.05 (*d*; 2 H, Ar-H), 2.50 (*q*, 7.1 Hz; 4 H, $CH_2$-$CH_3$), 2.50 (*m*; 4 H, $CH_2(CH_2)_2$-$CH_2$), 1.7–1.4 (*m*; 4 H, $CH_2$–$CH_2$–$CH_2$–$CH_2$), 1.00 (*t*, 7.1 Hz; 6 H, $CH_3$). MS (*m*/*e*): 239 (1%, $M^+$), 224 (3%), 125 (8%), 86 (100%). Anal. for $C_{14}H_{22}ClN$ (M 239.8) cal. C 70.1 H 9.25 N 5.84, exp. C 69.4 H 8.98 N 6.04.

### *1,7-Di-tosyloxyheptane*[7] (**3**)

Three grams (22.6 mmol) of 1,7-heptandiol in 35 ml of anhydrous pyridine was added 13.2 g (67.7 mmol) of tosyl chloride at 0°C. The mixture was stirred for 15 min, allowed to reach ambient temperature and stirred for a further 3 h. Then it was quenched with 3 ml of water and stirred for a further 1 h. 100 ml of $CH_2Cl_2$ was added and the pyridine removed by extraction with a solution of 40 ml of conc. HC1 in 200 ml of ice water. The dichloromethane phase was washed twice with 50 ml of water, dried over sodium sulfate and filtered. After evaporation of the solvent, purification by column chromatography (A:B:C 48/50/2) and recrystallization from $CH_2Cl_2$/*n*-hexane yielded 5.6 g (58%) of compound **3**. mp: 76–78°C. TLC: $R_f$ = 0.45 (A:B:C 45/50/5). $^1$H-NMR ($CDCl_3$): δ = 7.73 (*d*, 8.2 Hz; 4 H, Ar-H), 7.30 (*d*, 8.2 Hz; 4 H, Ar-H), 3.96 (*t*, 6.1 Hz; 4 H, O-$CH_2$), 2.44 (*s*; 6 H, $CH_3$), 1.7–1.1 (*m*; 10 H). MS (*m*/*e*): 440 (0.7%, $M^+$), 268 (0.4%, $M^+$-Tos-OH), 173 (8%), 155 (10%), 97 (100%), 91 (40%).

### *7-Fluoroheptyltosylate* (**4**)

Five milliliters of anhydrous acetonitrile was added to 1.43 g (4.54 mmol) of tetra butyl ammonium fluoride trihydrate. The mixture was evaporated in vacuum to remove the water. This procedure was repeated twice. Compound **3** in an amount of 2.05 g (4.54 mmol) in 10 ml of anhydrous acetonitrile was added to the reaction flask. The mixture was stirred for 4 h at 85°C in a closed tube. The solvent was evaporated in vacuum. Flash column chromatography (A:B:C 49/50/1) provided

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400 mg (31%) of compound **4** as an oil. TLC: $R_f$ = 0.65 (A:B:C 45/50/5). $^1$H-NMR ($CDCl_3$): δ = 7.79 (*d*, 8.2 Hz; 2 H, Ar-H), 7.33 (*d*, 8.2 Hz; 2 H, Ar-H), 4.70 (*t*, 5.9 Hz; 1 H, $CH_2$-F), 4.11 (*m*; 1 H, $CH_2$-F), 4.02 (*t*, 6.2 Hz; 2 H, $CH_2O$), 2.45 (*s*; 3 H, $CH_3$), 2.0–1.1 (*m*, 10 H). $^{19}$F-NMR: δ = −218.74 (tt, $^2J$ = 46.4 Hz, $^3J$ = 24.4 Hz). MS (*m*/*e*): 288 (2%, $M^+$), 173 (90%), 155 (68%), 116 (30%), 96 (22%), 91 (100%). Anal. for $C_{14}H_{21}FO_3S$ (M 288.3) cal. C 58.3 H 7.34, exp. C 57.8 H 7.29.

### *N-4-(4-Chlorophenyl)butyl-N,N-diethyl-7-fluoroheptylammonium p-toluenesulfonate (**5**)*

Four hundred milligrams (1.39 mmol) of compound **4** and 330 mg (1.38 mmol) compound **9** were dissolved in 2 ml of anhydrous acetonitrile and stirred for 24 h at 85°C. After cooling with an ice bath the reaction mixture was added dropwise under stirring to 70 ml of cold *n*-hexane. An oily compound was separated from solution. The hexane was decanted. The oily residue was stored in a refrigerator until compound **5** was produced as an amorphous white solid. The solid was treated with ether whereupon the material crystallized in a yield of 80% (580 mg). mp: 48–50°C. HPLC: $t_R$ = 4.1 min (D:E 60/40), $t_R$ = 9.9 min (D:E 50/50). $^1$H-NMR ($CDCl_3$, 360 MHz): δ = 7.74 (*d*; 2 H, $CH_3$Ar-H), 7.21 (*d*; 2 H, ClAr-H), 7.09 (*d*; 2 H, $CH_3$Ar-H), 7.08 (*d*; 2 H, ClAr-H), 4.41 (dt, $^2J$ = 47.3 Hz, $^3J$ = 6.0 Hz; 2 H, $CH_2$-F), 3.3 1(*q*;$^3J$ = 7.2 Hz, 4 H, $NCH_2CH_3$), 3.20 (*m*; 2 H, N-$CH_2$), 3.1 (*m*; 2 H, N-$CH_2$), 2.60 (*t*; $^3J$ = 6.8 Hz; 2 H, $ArCH_2$), 2.29 (*s*; 3 H, $ArCH_3$), 1.60 (*m*; 8 H,$CH_2CH_2CH_2$), 1.30 (*m*; 6 H, $CH_2$), 1.24 (*t*, $^3J$ = 7.2 Hz; 6 H, $CH_2CH_3$). $^{19}$F-NMR: δ = −218.7 (tt, $^2J$ = 46.8 Hz, $^3J$ = 24.3 Hz). MS (*m*/*e*): 356 (4%, $M^+$-OTos), 336 (1%), 327 (1%), 312 (1%), 224 (44%), 174 (44%), 155 (20%), 125 (48%), 91 (54%), 86 (00%), 72 (50%). MS (FAB): *m*/*e* 356.3 (100%, $M^+$-Anion). Anal. for $C_{28}H_{43}ClFNO_3S$ (M 528.2) cal. C 63.7 H 8.21 N 2.65, exp. C 63.4 H 8.25 N 2.91.

### *N-4-(4-Chlorophenyl)butyl-N,N-diethyl-7-tosyloxyheptylammonium p-toluenesulfonate (**10**)*

Four hundred and eighty milligrams (2.00 mmol) of compound **9** and 2.64 g (6.00 mmol) of compound **3** were dissolved in 3 ml of anhydrous acetonitrile and stirred for 8 h at 85°C in a closed tube. After cooling with an ice bath the reaction mixture was added dropwise to 70 ml of ice cold diethylether. An oily product separated from the solution and was

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taken up in 30 ml of $CH_2Cl_2$. The solution was washed 3 times with 100 ml of water. The dichloromethane layer was dried over sodium sulfate, filtered and evaporated in vacuum. Anhydrous acetonitrile in an amount of 20 ml was added to the oily residue. The reaction mixture was evaporated again. Storage in a refrigerator provided a crystalline product in 68% (920 mg) yield. mp: 58–60°C. HPLC: $t_R = 8.1$ min (D:E 60/40). $^1$H-NMR ($CDCl_3$, 360 MHz): $\delta = 7.77$ (*d*, 5.4 Hz; 2 H), 7.75 (*d*, 5.4 Hz; 2 H), 7.35 (*d*, 5.4 Hz; 2 H), 7.21 (*d*, 5.4 Hz; 2 H), 7.09 (*d*, 5.4 Hz; 4 H), 3.99 (*t*, 6.3 Hz; 2 H, C$\underline{H}_2$O), 3.32 (*q*, 7.3 Hz; 4 H, NC$\underline{H}_2$CH$_3$), 3.21 (*m*, 2 H; N-C$\underline{H}_2$), 3.12 (*m*, 2 H, N-C$\underline{H}_2$), 2.61 (*t*, 6.7 Hz; 2 H, C1ArC$\underline{H}_2$), 2.44 (*s*; 3 H, C$\underline{H}_3$ tosylester), 2.30 (*s*; 3 H, C$\underline{H}_3$Ar, tosylanion), 1.66 (*m*; 8 H, C$\underline{H}_2$), 1.30 (*m*; 6 H, C$\underline{H}_2$), 1.24 (*t*, 7.2 Hz; 6 H, C$\underline{H}_3$CH$_2$N). MS (FAB) *m*/*e*: 508.3 (100%, $M^+$-OTos). Anal. for $C_{35}H_{50}ClNO_5S$ (M 680.3) cal. C 61.8 H 7.41 N 2.06, exp. C 61.6 H 7.46 N 2.11.

*1,7-Heptanediyl-di-[N-4-(4-chlorophenyl)butyl-N,N-diethylammonium] di-p-toluenesulfonate*

Forty eight milligrams (0.20 mmol) of compound **9** and 29 mg (0.06 mmol) of compound **3** were dissolved in 2 ml of anhydrous acetonitrile. The reaction mixture was stirred for 72 h at 85°C in a closed tube. After cooling the reaction mixture was added dropwise to 10 ml of diethyl ether and was stored in a refrigerator for 2 weeks to give a crystalline compound in a yield of 36 mg (60%). HPLC: $t_R = 4{,}2$ min (D:E 60/40), $t_R = 12.0$ min (D:E 50/50). $^1$H-NMR ($CDCl_3$, 360 MHz): $\delta = 7.73$ (*d*, 8.1 Hz; 4 H), 7.20 (*d*, 8.4 Hz; 4 H, ClAr-$\underline{H}$), 7.08 (*d*; 7.8 Hz; 4 H), 7.05 (*d*, 8.4 Hz; 4 H, ClAr-$\underline{H}$), 3.30 (*m*; 4 H; NC$\underline{H}_2$), 3.27 (*q*, 7.4 Hz; 8 H, C$\underline{H}_2$CH$_3$), 3.18 (*m*, 4H; NC$\underline{H}_2$), 2.56 (*t*, 6.8 Hz; 4H, C1ArC$\underline{H}_2$), 2.30 (*s*; 6 H, C$\underline{H}_3$), 1.75–1.35 (*m*; 18 H, CH$_2$C$\underline{H}_2$CH$_2$), 1.18 (*t*, 7.2 Hz; 12H, NCH$_2$C$\underline{H}_3$). MS (FAB) *m*/*e*: 748.0 (100%, $M^+$-OTos), 730.1 (40%), 547.9 (95%). Anal. for $C_{49}H_{72}Cl_2N_2O_6S_2$ (M 920.1) cal. C 64.0 H 7.89 N 3.04, exp. C 63.4 H 7.85 N 3.43.

*Radiochemistry: N-4-(4-Chlorophenyl)butyl-N,N-diethyl-7-([$^{18}$F]fluoroheptyl)ammonium salt (**2**)*

The reaction was carried out in a device developed for FDG synthesis.[9] The F-18 activity (50 mCi) was produced by $^{18}$O (p, n) $^{18}$F reaction. The activity was extracted from $H_2^{18}O$ by a small anion exchanger and then eluted by aqueous potassium carbonate into the reaction vessel. The

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radioactive solution was evaporated together with 20 mg of Kryptofix 2.2.2 in 1 ml of acetonitrile in a nitrogen stream at 85°C under a slight vacuum. One milligram of acetonitrile was added twice to repeat the drying procedure. Then 10 mg of compound **10** dissolved in 1 ml of anhydrous acetonitrile was added. The reaction mixture was heated for 30 min at 85°C in the closed-reaction vessel. Radio-TLC showed a yield of more than 75% of compound **2**. Thereupon the solvent was evaporated, the residue was dissolved in 1 ml of HPLC eluent (E) and passed through a small aluminum oxide Sep-Pak cartridge. 0.2 ml of the resulting eluent (1.5 ml) was purified on HPLC (Column: RP-18, $300 \times 3.9$ mm; 4 μm; flow 1 ml/min; $\lambda$: 277 nm). The radiochemical purity of the [$^{18}$F]fluoroclofilium was more than 95%. After purification the solvent was removed in a nitrogen flow and the residue dissolved in 2 ml of isotonic solution.

**Acknowledgements**

This work was supported by grant no. KOSEF 951-0710-007-2 from the Korean Science and Engineering Foundation, Nuclear R&D Program from the Ministry of Science & Technology in Korea and Dongguk University Research Fund.

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