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Synthesis of novel halo and tosyloxy nortropane derivatives as efficient precursors for the one-step synthesis of the dopamine transporter PET ligand [18F]FECNT

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The fluorine-18 labeled nortropane derivative 2β-carbomethoxy-3β-(4-chlorophenyl)-8-(2-fluoroethyl)-nortropane (FECNT) is a dopamine transporter (DAT) ligand. Currently, it is considered as reference for positron emission tomography imaging. Herein, the synthesis of novel precursors (*N*-tosyloxy-, chloro-, and bromo- analogues) for one-step radiosynthesis of [^{18}F]FECNT is reported. Using the *N*-mesyloxy- precursor in a one-step radiosynthesis, the crude [^{18}F]FECNT was obtained with the radiolabeling yield of 45 ± 10%, confirming the practical efficiency of this approach in the design of novel precursors for labeling.

Keywords: [^{18}F]FECNT; precursors; one-step; radiofluorination

Introduction

2β-carbomethoxy-3β-(4-chlorophenyl)-8-(2-[^{18}F]-fluoroethyl)-nortropane (FECNT) is a dopamine transporter (DAT) ligand, first reported by Goodman *et al.*[1] Labeled with the positron-emitter fluorine-18 ($T_{1/2}$ = 109.8 min), this radiotracer has demonstrated highly promising properties in positron emission tomography (PET) studies in human. Indeed, the DAT is a presynaptically located protein responsible for the regulation of synaptic concentration of dopamine, and thus dopamine neurotransmission, in the brain. Deregulation of dopaminergic transmission in the basal ganglia is implicated in brain neurodegenerative disorders such as Parkinson's disease and psychiatric disorders,[2–4] and as such, DAT has been for several years a highly investigated target for development of selective PET-tracers.

[^{18}F]FECNT has high-binding affinity, low-nonspecific binding, and favorable kinetics towards the DAT compared with other fluorine-18-labeled ligands.[1,5,6] Moreover, high degree of test–retest reproducibility and extremely high sensitivity of [^{18}F]FECNT for imaging the DAT in PET studies were recently demonstrated.[7] However, the use of this radioligand as a clinical marker for the state of the DAT system is highly dependent on the robustness of the radiochemical process used for its preparation, and this in particular in terms of efficiency and speed. To date,[1,8] [^{18}F]FECNT has been synthesized in a two-step chemical process, involving the preparation of 2-[^{18}F]-fluoroethyl tosylate or brosylate and subsequent *N*-(2-fluoroethyl) alkylation of a dedicated nortropane moiety. These methods provided the overall radiochemical yield of 21% and 16% (decay corrected) in total time of 122 and 150 min, respectively. More recently, Chen *et al.*[9] reported that [^{18}F]FECNT could be synthesized in one single chemical step by direct [^{18}F]fluorination of *N*-mesyloxy tropane precursor for labeling. Using the latter method, [^{18}F]FECNT was obtained in 33% decay-corrected yield and in total synthesis time of 80 to 90 min.

The use of a mesylate as a leaving group in such a nucleophilic substitution reaction (SN2) has some disadvantages. Mesylates are rather hard to detect using ultraviolet (UV)-absorption, which may complicate the final HPLC purification of the radiotracer from its precursor-for-labeling and reaction side-products. In addition, mesylates are often characterized by high reactivity and thus, limited long-term storage stability.

Tosylates as well as halogens such as bromo- and chloro-groups are also often reported leaving groups in [^{18}F]fluorination reaction. Tosylate is one of the most commonly used leaving groups in SN2 reaction. [^{18}F]fluoro-for-tosylate exchange reactions usually work well under mild conditions. The tosylate precursor and tosylated derivatives can be easily separated from the [^{18}F] products by HPLC purification with UV detection because of their high-UV absorption at 254 nm and differences in lipophilicity. However, one drawback of tosyloxy-containing structures is their limited shelf life. Bromo- group is another

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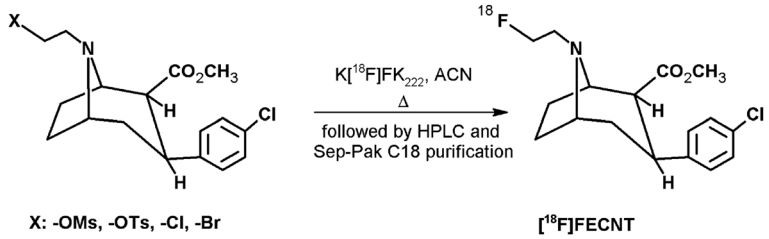
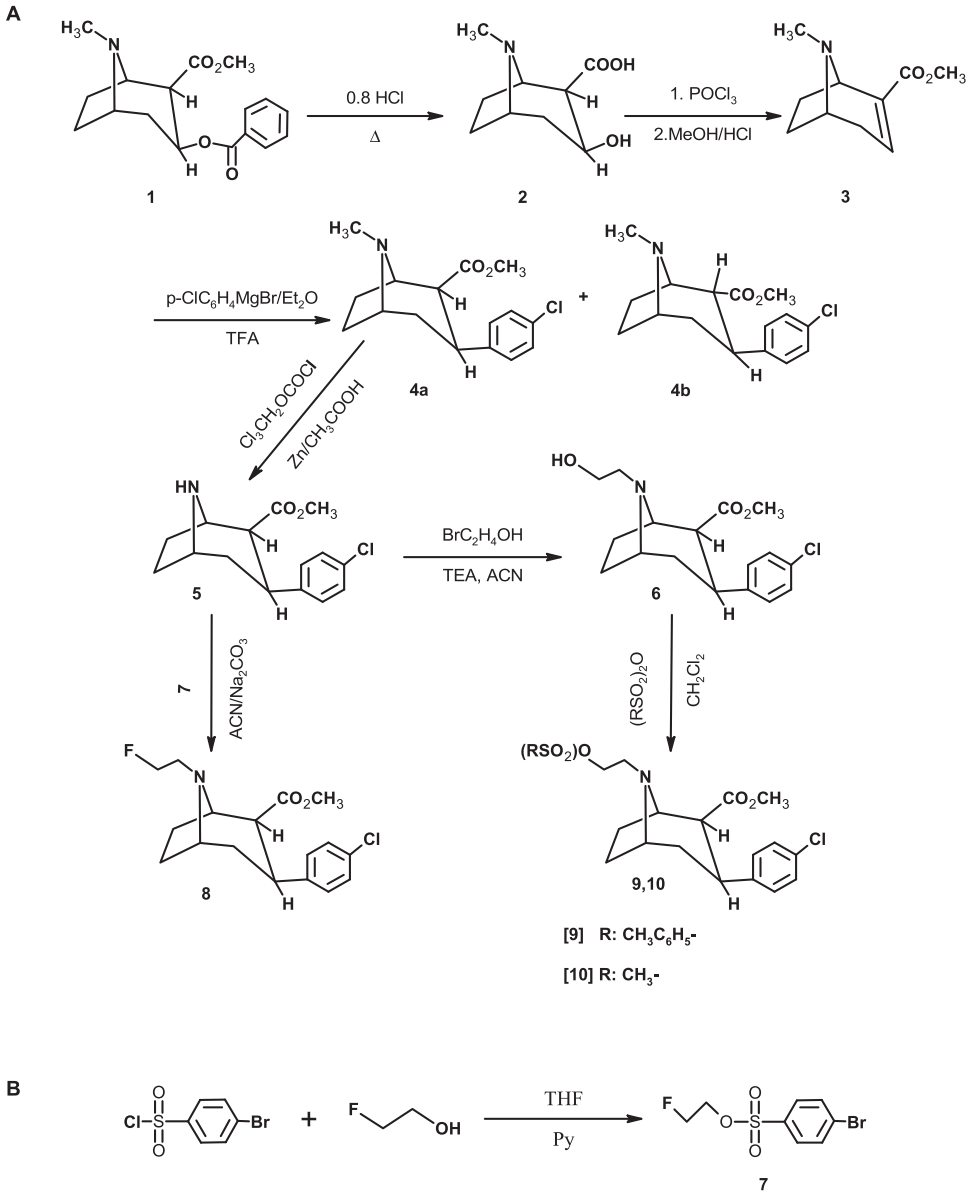
possible leaving group, and bromo-bearing precursors for fluorine-18-labeling have been described.[11] Chloro- group is much less reactive, especially when compared with the tosyloxy- moiety and bromine atom, but provides a higher-stability of compounds containing this halogen.[12] Chloro- precursor has moreover been used for one-step radiosynthesis of another tropane-based DAT-radioligand, [^{18}F]LBT-999.[10]

On the basis of the latter result, we assumed that [^{18}F]FECNT could analogously be synthesized at high yield, with high-specific radioactivity and in relatively short time by direct nucleophilic [^{18}F]fluorination of the chloro- analog, and also the bromo- and tosyloxy- derivatives as precursors for labeling. Thus, we report herein the synthesis of these novel derivatives. We also described the synthesis of FECNT as standard and the



Scheme 1. One-step radiosynthesis of [^{18}F]FECNT.



Scheme 2. (A) Synthesis of FECNT (**8**, standard compound) as well as the *N*-mesyloxy and *N*-tosyloxy nortropane (**9** and **10** as precursors for labeling); (B) synthesis of (2-fluoroethyl)-4-bromobenzenesulfonate (**7**).

N-mesyloxy- derivative as precursor, followed by the development of novel, sensitive, and selective HPLC quality control methods. We also investigated and compared by HPLC the preparation of FECNT from the four precursors using non-radioactive fluoride, in order to propose novel conditions for subsequent radiofluorination and to confirm suitability of these precursors for radiopharmaceutical preparation. As a proof of concept, we also prepared [^{18}F]FECNT from the *N*-mesyloxy tropane precursor *via* a one-step radiosynthetic process (Scheme 1).

Results and discussion

Chemistry

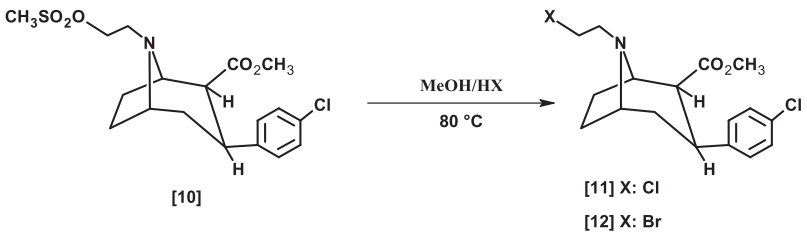
FECNT and precursors for labeling syntheses

FECNT as standard (**8**) as well as its tosyloxy-, mesyloxy-, chloro-, and bromo- derivatives (**9–12**) were all prepared from cocaine hydrochloride (**1**) as outlined in Schemes 2–4.

The critical intermediate, R-(−) anhydroecognine methyl ester (**3**) was prepared as described previously[13–15] from (−) cocaine HCl (**1**) by (i) hydrolysis in 0.8 N HCl followed by (ii) dehydratation with $POCl_3$ and subsequent (iii) Fisher esterification with dry MEOH (Scheme 2A). Compound **3** was obtained in 77% yield after purification by distillation under reduced pressure. 2β-Carbomethoxy-3β-(4-chlorophenyl)tropane **4a** was prepared from **3** by treatment with (4-chlorophenyl)magnesium bromide as previously reported by Caroll *et al.*[16] and Goodmann *et al.*[17] with minor modifications. Reaction of the Grignard reagent with **3** at −45°C in diethyl ether followed by trifluoroacetic acid treatment at −78°C gave 70% yield of both C-2 epimers mixture (ratio C-2β **4a**/C-2α**4b**: 7/3). The unwanted, biologically inactive α-isomer[18,19] was separated by flash chromatography (diethyl ether/triethylamine, 9:1) on silica gel, followed by fractional crystallization from hexane. In this manner, a total yield of β-isomer **4a** of about 60% was obtained. 2β-Carbomethoxy-3β-(4-chlorophenyl)nortropane **5** was prepared by *N*-demethylation of compound **4a**. This reaction involved conversion of **4a** to its 2,2,2-trichloroethyl carbamate followed by reduction with zinc/acetic acid mixture. Compound **5** was obtained in 59% yield and with purity exceeding 99% (HPLC – method B) after purification by crystallization from hexane according to previously described procedures,[13,15,17] with some modifications. The 2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-hydroxyethyl)nortropane **6** was prepared by *N*-hydroxyethylation of **5** using 2-bromoethanol[9] and was obtained in 89% yield after purification by crystallization from petroleum ether and with above 99% purity (HPLC – method A).

FECNT (**8**) as standard was prepared by direct *N*-(2-fluoroethyl) alkylation of **5** with (2-fluoroethyl)-4-bromobenzenesulfonate (**7**). The crude product was purified by recrystallization from hexane and obtained in 71% yield and with purity exceeding 99% (HPLC – method A). Noteworthy, the synthesis of **7** from 2-fluoroethanol and 4-bromobenzenesulfonyl chloride was already described by Voll *et al.*,[8] but extremely low yields (5%) were reported. Using anhydrous pyridine as acid neutralizer (Scheme 2B) allowed to increase the yield up to 47%.

For the synthesis of the *N*-tosyloxy- derivative **9**, two ways were used. First, the alkylation of compound **5** with 1,2-ethanediol di-(4-toluenesulfonate) (**13**) was used (Scheme 4).

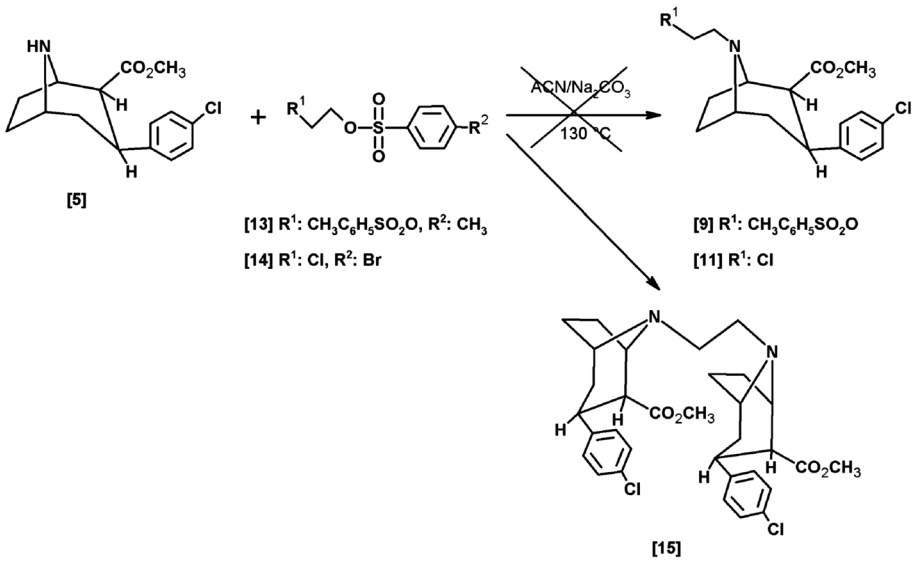


[10]

[11] X: Cl

[12] X: Br

Scheme 3. Synthesis of the chloro- and bromo- nortropane analogs (**11** and **12** as alternative precursors for labeling).



[5]

[13] R^1: $CH_3C_6H_5SO_2O$, R^2: CH_3

[14] R^1: Cl, R^2: Br

[9] R^1: $CH_3C_6H_5SO_2O$

[11] R^1: Cl

[15]

Scheme 4. Synthesis of 1,2-di-[2β-carbomethoxy-3β-(4-chlorophenyl)nortropanyl]ethane (**15**).

Table 1. HPLC characteristic of FECNT and its derivatives (Method A)

Compound		Known impurities		
Number	Retention time (min) ($n = 10$)	Number	Retention time (min) ($n = 10$)	Resolution[a]
8	11.6	**5**	11.2	1.6
		7	15.8	12.4
9	15.3	**6**	11.3	15.7
10	12.4	**6**	11.3	6.7
11	12.6	**6**	11.3	7.6
		10	12.4	1.3
12	12.7	**6**	11.3	8.3
		10	12.4	2.0

[a]Resolution was calculated in accordance with Ph. Eur. requirements (monograph: 20246) between peak of analyzed compound and known impurities (substrates or degradation products).

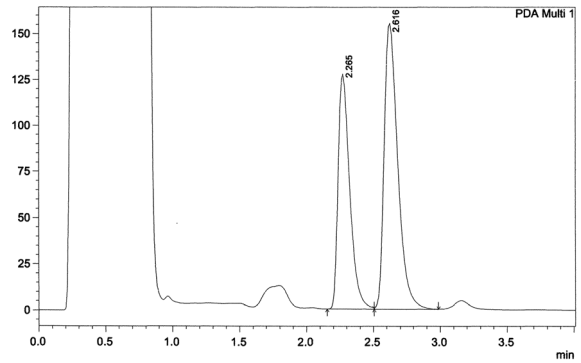


Figure 1. HPLC typical analytical chromatogram (method C) of the *N*-mesyloxy-derivative **10** reaction with fluoride (3 h, 80°C). Peak A, FECNT (**8**, Rt 2.26 min); peak B, side-product (Rt 2.62 min).

The only recovered product from this reaction was compound **15** that could be isolated in 80% yield. Mass spectroscopy analysis confirmed its structure as the 1,2-di-[2β-carbomethoxy-3β-(4-chlorophenyl)nortropanyl]ethane. In the second method,[9] the tosylation reaction of alcohol **6** with p-toluenosulfonic anhydride gave compound **9** in 58% yield after purification using preparative HPLC described previously.

The *N*-mesyloxy- derivative **10** was prepared and purified as described previously but using methanesulfonic anhydride, and was obtained in 81% yield. Both sulfonates, that is, compounds **9** and **10**, were obtained with purities exceeding 99% (HPLC – method A).

Synthesis of the chloro- derivative **11** was attempted by alkylation of **5** with (2-chloroethyl)-4-bromobenzenesulfonate (**14**) (Scheme 4), but only compound **15** could be isolated as confirmed by mass spectroscopy. Compounds **11** and **12** were therefore prepared from the *N*-mesyloxy- derivative **10** by nucleophilic substitution reaction using chloride and bromide, respectively, and were obtained in 75% and 73% yield (Scheme 3). Both halogenated compounds (**11**, **12**) were obtained with purities exceeding 98% (HPLC – method A).

In conclusion, the four proposed precursors for labeling and FECNT as standard were prepared in a few chemical steps from (−) cocaine HCl (**1**) in moderate overall yield: 12% for **9**, 16% for **10**, 11% for **11** and **12**, and 16% for **8**. All synthesized compounds were characterized by mass spectroscopy, ^{1}H and ^{13}C NMR spectroscopy and m.p. measurement.

Robust HPLC methods were developed and used to separate products from substrates. Purity of the compounds was determined by analytical HPLC method (method A) with values over 98% for all derivatives. The high purity obtained for the synthesized compounds permits direct use of these precursors for labeling without further purification. The calculated resolution[20] between the peaks of obtained compounds and main impurities is presented in Table 1. For all analyzed compounds, the resolution from impurities is higher than 1.3, while the Ph. Eur. requires min. 1.0.

Table 2. HPLC-determined, FECNT and its side-product synthesis yields

		Yields (%) ($n = 3$)				
	Temp.	80°C				110°C
Time	Precursor	**9** (−OTs)	**10** (−OMs)	**11** (−Cl)	**12** (−Br)	**11** (−Cl)
5 min	Ya	93.4	96.0	39.3	94.2	85.1
	Yb	4.2	2.6	2.2	5.3	12.7
10 min	Ya	94.5	95.6	64.4	90.2	80.4
	Yb	5.5	3.7	6.1	9.5	17.2
20 min	Ya	—	—	76.6	—	—
	Yb	—	—	9.2	—	—
30 min	Ya	—	—	83.6	—	—
	Yb	—	—	12.4	—	—
3 h	Ya	—	41.8	—	—	—
	Yb	—	57.6	—	—	—

Ya: FECNT synthesis yield calculated as the ratio of the HPLC-peak area (method C) corresponding to FECNT (Rt 2.2 min) over the sum of the HPLC-peak areas corresponding to the starting compound, FECNT, and side-product.
Yb: Side-product formation yield calculated as the ratio of the HPLC-peak area corresponding to the side-product (Rt 2.6 min) over the sum of the HPLC-peak areas corresponding to the starting compound, FECNT, and side-product.

The stability of all compounds was tested when stored at room temperature. FECNT as standard is stable under these conditions and can be stored for at least 36 months without decomposition, whereas all precursors decomposed and therefore should be stored in sealed vials at −20°C under inert gas atmosphere. At least 6 months stability was confirmed by HPLC.

FECNT preparation by nucleophilic substitution reaction from (non-radioactive) fluoride

Pilot studies using non-radioactive fluoride were carried out to investigate the initial conditions for one-step radiosynthesis of FECNT from the four proposed precursors. The same amounts of substrates and the same temperature conditions were used for all precursors in order to compare their reactivity. The synthesis of FECNT was carried out in one step in pressurized reaction vessels and preserving the conditions and reagents similar as in typical radiofluorination. The nucleophilic substitution of the synthesized precursors was performed at 80°C using potassium fluoride, Kryptofix®222, and dry acetonitrile as the solvent. Progress of the reaction was monitored using HPLC (method C), which gave satisfactory separation of FECNT from its precursors and side-products. The

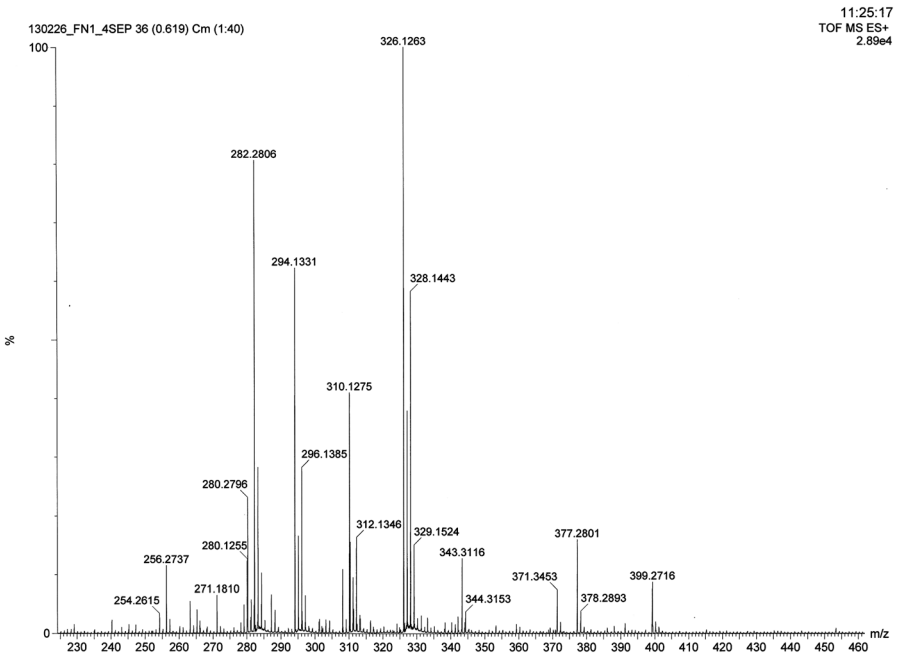


Figure 2. Mass spectrum of the compound corresponding to peak A (Rt 2.26 min, Figure 1), confirming the identity of FECNT.

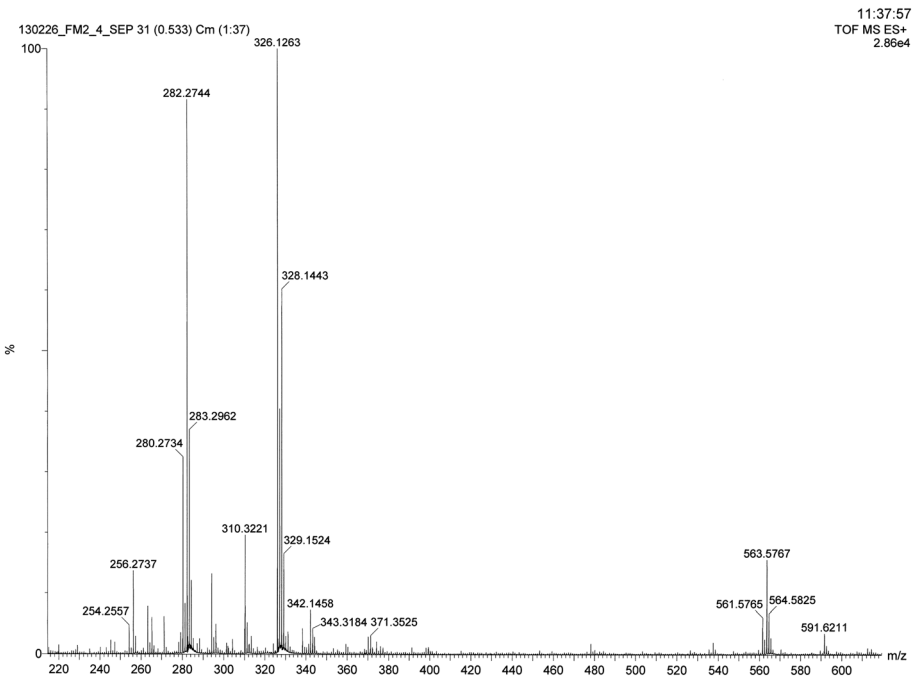


Figure 3. Mass spectrum of the compound corresponding to peak B (Rt 2.62 min, Figure 1), a side-product of the reaction with the same mass as FECNT.

identity of the desired fluorinated product was confirmed by co-injection with FECNT standard (Rt 2.2 min), and all recorded HPLC profiles were in accordance with the formation of FECNT. For compounds **9**, **10**, and **12**, the reaction time of 5 min at 80°C was sufficient to obtain FECNT in yields above 90%, as measured by HPLC (method C). Using compound **11**, the reaction had to be carried out at 110°C to obtain similar yield in the reaction time of 5 min. Fluorination yields obtained for all runs are shown in Table 2.

We noticed, the same as Block *et al.*[24], that the increase of the substitution yields correlates with the following order of leaving groups: Cl < Br < sulfonylates. The mesylate leaving group was a bit more reactive than tosylate group, similar to the report by Wester.[25] Except for the latter precursor, reaction temperature of 80°C seems to be optimal for sufficient fluorine incorporation in these nucleophilic substitution reactions.[21] The yield decreased significantly at temperature lower than 80°C.

For all used precursors and reactions conditions, the formation of more lipophilic side-product was observed; however, the formation yield depended on the reaction time and temperature. For the chlorinated derivate **11**, it was the most abundant because higher reaction temperature was required to increase the fluorination yield.

In order to isolate and identify this unexpected side-product, the fluorination of compound **10** was performed at 80°C in the reaction time extended to 3 h. In this way, the side-product was formed in 58% yield. Results from this experiment are also included in Table 2, and the typical HPLC analytical chromatogram is shown in Figure 1. HPLC purification was performed, and the fraction was collected at retention time corresponding to FECNT as well as the fraction corresponding to the side-product. Both compounds were extracted from the HPLC solvents using a C18 Sep-Pak® cartridge and were analyzed by mass spectrometry. As expected, the parent-ion $[M+H]^+$ for peak A (Figure 2) lead to *m/z* value = 326, confirming the identity of FECNT. Surprisingly, the same *m/z* value was also found for peak B (Figure 3), suggesting that the side-product could be the corresponding α-isomer. Indeed, such a structure may result from α/β epimerization of the tropane ring at the C2 position[21–23], leading to the formation of the thermodynamically more stable but undesired α-isomer.

Radiochemistry

[^{18}F]FECNT was synthesized from the *N*-mesyloxy- precursor **10** using the one-step radiochemical process outlined in Scheme 1. The [^{18}F]fluorination reaction was carried out using the same conditions as described previously for the fluorination involving non-radioactive fluoride. The radiochemical yields of fluorine-18 incorporation, determined by HPLC (method B) and defined as the ratio of radioactivity HPLC area of [^{18}F]FECNT to total fluorine-18 radioactivity HPLC area, were about 45 ± 10% (n = 5). These yields are comparable with those (48 ± 12%) reported by Chen *et al.*[9]

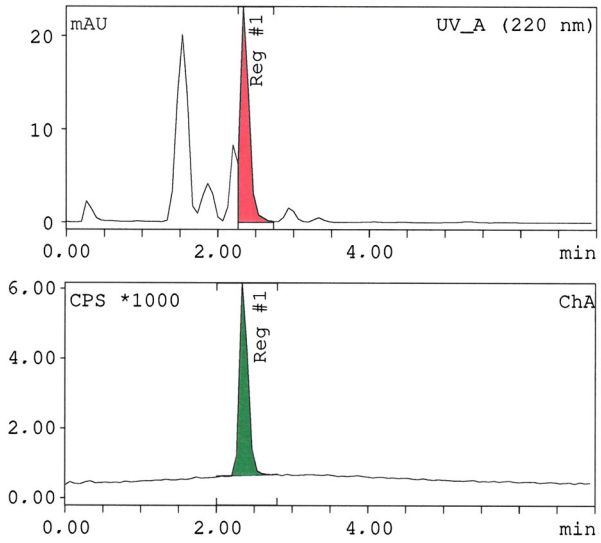


Figure 5. A typical chromatogram (method C) of crude product [^{18}F]FECNT ([^{18}F]-**8**) co-injected with non-radioactive standard. Top, UV (220 nm) detection; bottom, radioactivity detection. This figure is available in color online at wileyonlinelibrary.com/journal/jlcr

The typical HPLC chromatograms of a crude [^{18}F]FECNT are shown in Figures 4 and 5. The identity of [^{18}F]FECNT was confirmed by co-injection with non-radioactive standard. As demonstrated using HPLC (method C), the side-product was not observed.

The developed HPLC isocratic analysis method (method B) could be successfully used for the preparative purification of [^{18}F]FECNT from all precursors, degradation products, and fluorine-18 labeled side-product. Using these conditions, [^{18}F]FECNT (Rt 7.9 min) was completely separated from compound **11** (Rt 11.2 min) and compound **12** (Rt 12.0 min). [^{18}F]FECNT was also efficiently separated from derivative **5** (Rt 5.1 min), a compound resulting from the degradation of both the tosyloxy- and mesyloxy-precursors (**9** and **10**) during the fluorination reaction.

These results confirmed the usefulness of one-step radiosynthesis method for the preparation of fluorinated radiotracers, herein exemplified with [^{18}F]FECNT.

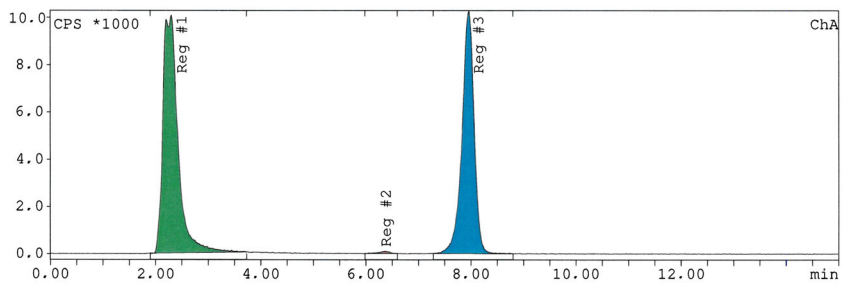


Figure 4. Typical radioanalytical HPLC chromatogram (method B) of the reaction mixture corresponding to the preparation of [^{18}F]FECNT. First peak, [^{18}F]fluoride (Rt 2.0–2.5 min); second peak, [^{18}F]FECNT (Rt 7.5–8.0 min). Radiochemical yield of around 45% was obtained using 5 mg of the *N*-mesyloxy- derivate **10** as precursor for labeling and at 80°C for 10 min. This figure is available in color online at wileyonlinelibrary.com/journal/jlcr

Conclusion

Non-radioactive FECNT as standard and four analogs as potential precursors for the one-step radiosynthesis of [^{18}F]FECNT were prepared with good overall yields and high-chemical purities. Improved purification and HPLC quality control procedures were also developed for all compounds. In addition, the initial parameters of the fluorination substitution reaction for the four precursors were developed using non-radioactive fluoride, and these procedures were confirmed in a one-step radiosynthesis of [^{18}F]FECNT from the *N*-mesyloxy- precursor for labeling. The results presented will be a good starting point for the implementation of the radiosynthesis of [^{18}F]FECNT from other precursors using automated synthesizers.

Experiment

Materials and methods

Materials. All reagents and solvents used in reactions were of commercial quality and purchased from Sigma-Aldrich Co. (USA) and POCH (Poland). Low-UV PIC B7 reagent, C18 Sep-Pak® cartridges, and Sep-Pak® Light QMA cartridges were obtained from Waters (USA). Solvents were dried as required. ^{1}H and ^{13}C NMR spectra were recorded using Bruker 500 MHz and Varian 600 MHz spectrometers. $CDCl_3$ was used as solvent, and chemical shifts (δ) were reported in parts per million relative to TMS as an internal standard. Mass spectra were obtained on API 365PESciex turboionspray tandem mass spectrometer (ESI method) and GCT Premier Waters (FD-TOF) spectrometer (FD-method). m.p. were determined using an OptiMelt (SRS) apparatus and are uncorrected. Flash chromatography was used for routine purification of reaction products using silica gel (Kieselgel 100, 230–400 mesh, Merck). Compound detection was accomplished under UV or in an iodine chamber.

[^{18}F]Fluoride was prepared *via* the ^{18}O(p,n)^{18}F nuclear reaction by irradiation of a 2.4 mL [^{18}O]H_2O (≥97% enriched, CIL (USA) and ≥98% enriched, Rotem GmbH (Germany)) target on an 11 MeV negative-ion cyclotron RDS 111 (Siemens, USA). Typical production of [^{18}F]fluoride at the end of bombardment for 60 μA, 10–15 min irradiation: 10–15 GBq. All radiolabeling reactions were conducted with the use of a multifunction synthesizer SynChrom R&D (Raytest, Germany).

Preparative HPLC. Preparative HPLC was run on Gilson (USA) system, consisting of a Gilson 306 pump, a Gilson 151 UV/VIS detector, a Gilson 506C controller system, and the Unipoint software. Purification of compounds **9**, **10**, **11**, and **12** was performed using Phenomenex Luna C18(2) column (15 μm, 250 × 30 mm, 100 Å). A gradient method using the following two mobile phases was used: A: 0.1% TFA in water; B: 0.1% TFA in acetonitrile/water (9:1). The gradient profile and timing were identical for all purifications: (i) 0–10 min: linear gradient from 0% to 60% B, followed by (ii) 10–20 min: 60% B, and finally, (iii) 20–21 min: linear gradient from 60% to 0% B. A maximum of 20 mg of each substance dissolved in acetonitrile (1 mL) was loaded onto the column. Flow rate of 15 mL/min and UV detection at 220 nm were used. Each purification run lasted 35 min.

Analytical HPLC. Analytical HPLC was run on Shimadzu (USA) system consisting of LC-20AD pump, SPD-M20A diode array detector, CBM-20A controller, and the LC Solution software. Radioanalytical HPLC was run on Agilent system (Agilent Technology 1200 series, USA) consisting of G311A quaternary pump, DAD G1315D diode array detector, Gabi (Raytest, Germany) radiodetector, and a Gina Star station (Raytest, Germany) software. Chemical purity analyses of compounds **8**, **9**, **10**, **11**, and **12** were performed using Phenomenex Luna C18(2) column (5 μm, 250 × 4.6 mm, 100 Å). Gradient method (method A) using the following mobile phases was used: A: 0.1% TFA in water; B: 0.1% TFA in acetonitrile/water (9:1). The gradient profile and timing were as follows: (i) 0–10 min: linear gradient from 0% to 60% B; (ii) 10–14 min: 60% B; and finally, (iii) 14–15 min: linear gradient from 60% to 0% B. Flow rate of 1 mL/min and UV detection at 220 nm were used. Radiochemical yields were also determined using the same column but applying isocratic method (method B). In this case, the mobile phase consisted of MEOH/water mixture (80:20), pH 8 (triethylamine, HCOOH). Flow rate of 1 mL/min and a UV detection at 220 nm were used. Non-radioactive fluorination reactions were monitored using a Waters Symmetry C18 column (3.5 μm, 50 × 4.6 mm) and isocratic method (method C). The eluent was 58:42 mixture of water containing 2% of low-UV PIC B7 reagent and acetonitrile/water (70:30) also containing 2% of low-UV PIC B7 reagent. Flow rate of 2 mL/min and UV detection at 220 nm were used.

Chemistry

*2β-Carbomethoxy-3β-(4-chlorophenyl)nortropane (**5**).* 2β-Carbomethoxy-3β-(4-chlorophenyl)tropane (**4**, 5 g, 17 mmol) was dissolved in 2,2,2-trichloroethyl chloroformate (12.5 mL, 93 mmol) and the solution heated at 120°C for 2 h. The reaction mixture was then cooled to room temperature and vacuum distilled to remove unreacted 2,2,2-trichloroethyl chloroformate. The residue was dissolved in 40 mL of 96% acetic acid and treated with zinc dust (4 g, 61 mmol). Then, the mixture was stirred at room temperature for 16 h and filtered. The filtrate was adjusted to pH 7 with 25% ammonium hydroxide, saturated with NaCl, and extracted once with diethyl ether (50 mL) and four times with methylene chloride (4 × 50 mL). The combined extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to afford 3.5 g (12 mmol) of crude product. Purification by crystallization from hexane gave compound **5** (2.8 g, 9.5 mmol, 59%) as a white solid and with a purity >99% (HPLC, UV, 220 nm). m.p.: 118–120°C (lit. 118–119°C)[12]; MS: $[M+H]^+ = 280$; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.65–1.69 (m, 1H, H-4α), 1.71–1.83 (m, 2H, H-6α, H-7α), 2.13–2.17 (m, 1H, H-6β), 2.20–2.50 (m, 1H, H-7β), 2.40–2.46 (td, 1H, H-4β), 2.75–2.77 (m, 1H, H-2), 3.21–3.25 (m, 1H, H-3), 3.40 (s, 3H, O-CH_3), 3.80–3.81 (m, 1H, H-5), 3.82–3.87 (m, 2H, H-1, N-H), 7.11–7.27 (m, 4H, ArCl); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 27.2, 28.5, 33.1, 35.0, 50.3, 51.4, 53.5, 56.2, 128.5 (2C), 128.7 (2C).

*2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-hydroxyethyl)nortropane (**6**).* 2β-Carbomethoxy-3β-(4-chlorophenyl)nortropane (**5**, 0.56 g, 2 mmol) 2-bromoethanol (1.02 g, 8 mmol) and triethylamine (1.11 g, 11 mmol) were dissolved in acetonitrile (30 mL) and the resulting solution heated at 80°C for 5 h under argon atmosphere. The reaction mixture was then concentrated under reduced pressure to dryness and the residue dissolved in methylene chloride (30 mL). The solution was then washed with water (30 mL), aqueous saturated $NaHCO_3$ (30 mL), water again (30 mL), and finally dried over anhydrous Na_2SO_4 for 12 h followed by evaporation to dryness. The crude product (0.70 g) was purified by crystallization from petroleum ether to afford 0.58 g of compound **6** (1.78 mmol, 89%) as colorless needles and with a purity >99% (HPLC, UV, 220 nm). m.p.: 102–104°C; (lit. 103–104.5°C);

[9] MS: $[M+H]^+ = 324$; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.65–1.69 (m, 1H, H-4α), 1.71–1.83 (m, 2H, H-6α, H-7α), 2.13–2.17 (m, 1H, H-6β), 2.20–2.50 (m, 1H, H-7β), 2.40–2.46 (td, 1H, H-4β), 2.75–2.77 (m, 1H, H-2), 3.21–3.25 (m, 1H, H-3), 3.40 (s, 3H, O-CH_3), 3.80–3.81 (m, 1H, H-5), 3.82–3.87 (m, 2H, H-1, N-H), 7.11–7.27 (m, 4H, ArCl); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 27.2, 28.5, 33.1, 35.0, 50.3, 51.4, 53.5, 56.2, 128.5 (2C), 128.7 (2C).

*(2-Fluoroethyl)-4-bromobenzenesulfonate (**7**).* A mixture of 2-fluoroethanol (2.5 g, 39 mmol), anhydrous pyridine (15 mL), and anhydrous THF (30 mL) under an argon atmosphere was cooled to 5°C using an ice/water bath. The solution of 4-bromobenzenesulfonyl chloride in anhydrous THF (15mL) was added dropwise; the reaction mixture was then allowed to warm to room temperature and stirred for 2 days. After this time, water with ice (100mL) was added to the reaction solution, which was then adjusted to pH 2 by addition of concentrated HCl. The product was then extracted with methylene chloride (3 × 100 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, and concentrated *in vacuo* to afford 7.1 g (25 mmol, 58%) of crude product **7** as yellow oil. Purification by flash chromatography (hexane/EtOAc, 4:1) on silica gel gave compound **7** (5.7 g, 20 mmol, 47%) as a white solid and with a purity >98% (HPLC, UV, 220 nm). m.p.: 44–45°C (lit. 43.5–45°C);[8] MS: $[M+Na]^+ = 307$; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.65–1.69 (m, 1H, H-4α), 1.71–1.83 (m, 2H, H-6α, H-7α), 2.13–2.17 (m, 1H, H-6β), 2.20–2.50 (m, 1H, H-7β), 2.40–2.46 (td, 1H, H-4β), 2.75–2.77 (m, 1H, H-2), 3.21–3.25 (m, 1H, H-3), 3.40 (s, 3H, O-CH_3), 3.80–3.81 (m, 1H, H-5), 3.82–3.87 (m, 2H, H-1, N-H), 7.11–7.27 (m, 4H, ArBr); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 27.2, 28.5, 33.1, 35.0, 50.3, 51.4, 53.5, 56.2, 128.5 (2C), 128.7 (2C).

*2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-fluoroethyl)nortropane (FECNT, **8**).* 2β-Carbomethoxy-3β-(4-chlorophenyl)nortropane (**5**, 0.25 g, 0.89 mmol) and (2-fluoroethyl)-4-bromobenzenesulfonate (**7**, 0.3 g, 1.06 mmol) were dissolved in anhydrous acetonitrile (3 mL), and Na_2CO_3 (0.3 mg, 2.9 mmol) was added. The solution was heated at 130°C for 2 h using oil bath. The reaction mixture was then cooled to room temperature, filtered, and concentrated to dryness. The solid residue was finally purified by crystallization from hexane to afford compound **8** (0.215 g, 0.66 mmol, 74%) as white solid and with purity >99% (HPLC, UV, 220 nm). m.p.: 81–82°C; MS: $[M+H]^+ = 326$; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.65–1.69 (m, 1H, H-4α), 1.71–1.83 (m, 2H, H-6α, H-7α), 2.13–2.17 (m, 1H, H-6β), 2.20–2.50 (m, 1H, H-7β), 2.40–2.46 (td, 1H, H-4β), 2.75–2.77 (m, 1H, H-2), 3.21–3.25 (m, 1H, H-3), 3.40 (s, 3H, O-CH_3), 3.80–3.81 (m, 1H, H-5), 3.82–3.87 (m, 2H, H-1, N-H), 7.11–7.27 (m, 4H, ArCl); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 27.2, 28.5, 33.1, 35.0, 50.3, 51.4, 53.5, 56.2, 128.5 (2C), 128.7 (2C).

2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-tosyloxyethyl) nortropane (**9**)

*Method I [1,2-di-[2β-carbomethoxy-3β-(4-chlorophenyl)nortropanyl] ethane (**15**)].* 2β-Carbomethoxy-3β-(4-chlorophenyl)nortropane (**5**, 0.3 g, 1.07 mmol) and 1,2-ethanodiol di-(4-toluenosulfonate) (**13**, 0.47 g, 1.26 mmol) were dissolved in anhydrous acetonitrile (5 mL). Then, Na_2CO_3 (0.3 mg, 2.9 mmol) was added, and the mixture was heated at 130°C for 8 h using an oil bath. The reaction mixture was then cooled to room temperature, filtered, and washed with methylene chloride (2 × 2 mL) and diethyl ether (2 × 2 mL). The filtrate and combined washes were concentrated to dryness, and the solid residue was purified by crystallization from acetonitrile to afford compound **15** (0.25 g, 0.43 mmol, 80%) as white solid and with purity >95% (HPLC, UV, 220 nm). m.p.: 225–231°C; MS: $[M+H]^+ = 585$; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.56–1.79 (m, 6H, H-4α, H-6α, H-7α, H-4α′, H-6α′, H-7α′), 2.07–2.11 (m, 2H, H-6β, H-6β′), 2.12–2.19 (m, 2H, H-7β, H-7β′), 2.21–2.37 (m, 2H, CH_2), 2.39–2.46 (m, 2H, CH_2), 2.47–2.51 (td, 2H, H-4β, H-4β′), 2.85–2.86 (m, 2H, H-2, H-2′), 2.94–3.03 (m, 2H, H-3, H-3′), 3.39 (m, 2H, H-5, H-5′), 3.49 (m, 6H, O-CH_3, O-CH_3′), 3.68–3.76 (m, 2H, H-1, H-1′), 7.16–7.30 (m, 8H, ArCl, ArCl′); ^{13}C NMR (600 MHz, $CDCl_3$) δ: 25.9 (2C), 26.0 (2C), 33.0 (2C), 33.7 (2C) 34.0 (2C), 51.4 (2C), 52.8 (2C), 53.8 (2C), 61.4 (2C), 63.7 (2C), 127.9 (4C), 128.7 (4C).

Method II. 2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-hydroxyethyl) nortropane (**6**, 0.10 g, 0.31 mmol) was dissolved in anhydrous methylene chloride (20 mL), and this solution was then added dropwise to a cooled (ice/water bath) solution of p-toluenesulfonic anhydride (0.20 g, 0.62 mmol) in anhydrous methylene chloride (50 mL). The mixture was then heated at 45°C under argon atmosphere for 20h or until total disappearance of compound **6** (HPLC-monitoring of the reaction). The crude product (0.12 g, 0.25 mmol, 82%) was then diluted in acetonitrile and purified by preparative HPLC. The fractions containing the desired product were collected, combined and concentrated to dryness to afford compound **9** (85 mg, 0.18 mmol, 58%) as colorless oil and with purity >99% (HPLC, UV, 220 nm). MS: $[M+H]^+ = 478$; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.99–2.11 (m, 1H, H-4α), 2.15–2.24 (m, 2H, H-6α, H-7α), 2.49–2.55 (m, 4H, H-6β, CH_3–Ar (Ts)), 2.64–2.67 (m, 1H, H-7β), 2.89–2.94 (td, 1H, H-4β), 3.03–3.04 (m, 1H, H-2), 3.40–3.46 (m, 4H, O-CH_3, H-3), 3.58–3.62 (m, 1H, H-5), 3.80–3.84 (m, 1H, H-1), 4.32–4.44 (m, 2H, CH_2-N), 4.53–4.56 (m, 2H, O-CH_2), 7.10–7.33 (m, 4H, ArCl), 7.38–7.82 (m, 4H, Ar (Ts)); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 21.7, 23.8, 24.6, 32.1, 34.0, 49.3, 51.9 (2C), 53.0, 64.0, 65.2, 128.1 (2C), 128.6 (2C), 129.1 (2C), 130.3 (2C).

*2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-mesyloxyethyl)nortropane (**10**).* 2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-hydroxyethyl) nortropane (**6**, 100 mg, 0.31 mmol) was dissolved in anhydrous methylene chloride (3 mL) and pyridine (0.59 g, 0.75 mmol) was added. The mixture was then cooled (ice/water bath), and a solution of methanesulfonic anhydride (0.10 g, 0.57 mmol) in anhydrous dichloromethane (3 mL) was added dropwise. The mixture was then heated at room temperature under atmosphere of dry argon for 1.5 h or until total disappearance of compound **6** (HPLC-monitoring of the reaction). Anhydrous ether (5 mL) was then added to the reaction mixture. The oily layer was separated, redissolved in dichloromethane (1 mL), and diethyl ether (5 mL) was again added. This operation was repeated twice. Finally, the oily layer was dried in vacuum to give 0.14 g of **10** as colorless oil, which was then redissolved in acetonitrile and purified by preparative HPLC. The fractions containing the desired product were collected, combined and concentrated to dryness to afford compound **10** (100 mg, 0.25 mmol, 81%) as colorless oil and with purity >99% (HPLC, UV, 220 nm). MS: $[M+H]^+ = 402$; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.00 (m, 1H, H-4α), 2.17–2.21 (m, 2H, H-6α, H-7α), 2.51–2.63 (m, 2H, H-6β, H-7β), 3.04 (td, 1H, H-4β), 3.18 (s, 3H, CH_3-S), 3.40–3.44 (m, 4H, O-CH_3, H-3), 3.58 (m, 1H, H-5), 3.82 (m, 1H, H-1), 4.75 (m, 2H, CH_2-N), 4.85 (m, 2H, O-CH_2), 7.10–7.33 (m, 4H, ArCl); ^{13}C NMR (600 MHz, $CDCl_3$) δ: 23.8, 25.0, 32.0, 34.0, 37.5, 49.3, 52.1, 52.9, 53.3, 63.8, 64.0, 128.6 (2C), 129.2 (2C).

2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-chloroethyl)nortropane (**11**).

*Method I [1,2-di-[2β-carbomethoxy-3β-(4-chlorophenyl)nortropanyl] ethane (**15**)].* 2β-Carbomethoxy-3β-(4-chlorophenyl)nortropane (**5**, 0.33 g, 1.18 mmol) and (2-chloroethyl)-4-bromobenzenesulfonate (**14**, 0.425 g, 1.42 mmol) were dissolved in anhydrous acetonitrile (5 mL). Then, Na_2CO_3 (0.3 mg, 2.9 mmol) was added, and the mixture was heated at 130°C for 2 h using an oil bath. The reaction mixture was then cooled to room temperature, filtered, and washed with methylene chloride (2 × 2 mL) and diethyl ether (2 × 2 mL). The filtrate and combined washes were concentrated to dryness, and the solid residue was purified by crystallization from acetonitrile to afford compound **15** (0.3 g, 0.51 mmol, 86%) as white solid and with purity >98% (HPLC, UV, 220 nm). Mp: 225–231°C; MS: $[M+H]^+ = 585$; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.63–1.70 (m, 6H, H-4α, H-6α, H-7α, H-4α′, H-6α′, H-7α′), 2.00 (m, 2H, H-6β, H-6β′), 2.18 (m, 2H, H-7β, H-7β′), 2.21–2.22 (m, 2H, CH_2), 2.39–2.40 (m, 2H, CH_2), 2.50–2.51 (td, 2H, H-4β, H-4β′), 2.85–2.86 (m, 2H, H-2, H-2′), 2.95 (m, 2H, H-3, H-3′), 3.39–3.40 (m, 2H, H-5, H-5′), 3.41–3.49 (m, 6H, O-CH_3, O-CH_3′), 3.68–3.69 (m, 2H, H-1, H-1′), 7.16–7.23 (m, 8H, ArCl, ArCl′); ^{13}C NMR (600 MHz, $CDCl_3$) δ: 25.8 (2C), 26.0 (2C), 33.75 (2C), 34.0 (2C), 50.1 (2C), 52.8 (2C), 53.9 (2C), 61.4 (2C), 63.7 (2C), 128.0 (4C), 128.7 (4C).

Method II. 2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-mesyloxyethyl) nortropane (**10**, 50 mg, 0.12 mmol) was dissolved in MEOH saturated with HCl (10 mL). The mixture was heated at 80°C using an oil bath for 3 h or until total disappearance of compound **10** (HPLC-monitoring of the reaction). The reaction mixture was then cooled to room temperature, concentrated to dryness and the crude recovered product purified by preparative HPLC. The fractions containing the desired product were collected, combined, and concentrated to dryness to afford compound **11** (31 mg, 0.091 mmol, 75%) as colorless oil and with purity >98% (HPLC, UV, 220 nm). MS: $[M+H]^+ = 342$; ^{1}H NMR (600 MHz, $CDCl_3$) δ: 2.08 (m, 1H, H-4α), 2.21 (m, 2H, H-6α, H-7α), 2.50–2.65 (m, 2H, H-6β, H-7β), 2.85 (td, 1H, H-4β), 3.07 (m, 1H, H-2), 3.46–3.47 (m, 4H, O-CH_3, H-3), 3.58–3.80 (m, 2H, CH_2-Cl), 4.05 (m, 2H, CH_2-N), 4.39 (m, 1H, H-5), 4.56 (m, 1H, H-1), 7.10–7.34 (m, 4H, ArCl); ^{13}C NMR (600 MHz, $CDCl_3$) δ: 24.0, 25.0, 32.5, 34.0, 39.0, 53.0, 53.6, 63.1, 64.4, 128.5 (2C), 129.2 (2C).

*2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-bromoethyl)nortropane (**12**).* 2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-mesyloxyethyl) nortropane (**10**, 50 mg, 0.12 mmol) was dissolved in MEOH saturated with HBr (10 mL). The mixture was heated at 80°C using oil bath for 3 h or until total disappearance of compound **10** (HPLC-monitoring of the reaction). The reaction mixture was then cooled to room temperature, concentrated to dryness and the crude recovered product purified by preparative HPLC. The fractions containing the desired product were collected, combined, and concentrated to dryness to afford compound **12** (33 mg, 0.090 mmol, 73%) as colorless oil and with purity >98% (HPLC, UV, 220 nm). MS: $[M+H]^+ = 366$; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.00–2.10 (m, 1H, H-4α), 2.15–2.31 (m, 2H, H-6α, H-7α), 2.61–2.78 (m, 2H, H-6β, H-7β), 2.91–2.97 (td, 1H, H-4β), 3.11–3.15 (m, 1H, H-2), 3.45–3.48 (m, 4H, O-CH_3, H-3), 3.71–3.78 (m, 2H, CH_2-Br), 3.94–4.42 (br, 2H, CH_2-N), 4.53 (m, 1H, H-5), 5.02 (m, 1H, H-1), 7.14–7.34 (m, 4H, ArCl); ^{13}C NMR (500 MHz, $CDCl_3$) δ: 24.3, 25.2, 32.3, 34.2, 39.5, 49.3, 53.2, 54.6, 63.4, 64.7, 128.6 (2C), 129.2 (2C).

Non-radioactive fluorination assays at the micromolar scale

*Preparation of FECNT (**8**) via nucleophilic substitution reactions with fluoride.* One-step syntheses of FECNT (**8**) by direct fluorination of compound **9**, **10**, **11**, or **12** were carried out in pressure vessels. For this, solutions containing the appropriated precursor (1 mg, 2.1 μmol for **9**, 2.5 μmol for **10**, 2.9 μmol for **11**, 2.7 μmol for **12**), Kryptofix®222 (18 mg, 47.8 μmol) and KF (2.8 mg, 47.8 μmol) in dry acetonitrile (1 mL) were loaded into dedicated glass vials which were then sealed with a stopper. The vials were then put into the pressure vessels and the solutions heated at 80°C (for compound **9**, **10**, **11**, and **12**) and 110°C (for compound **11** only) using oil bath until total disappearance of the starting material (HPLC-monitoring of the reaction). Reaction times were 5, 10, 20, or 30 min. Identity of the reaction product, FECNT (**8**), was established by comparison with standard by HPLC.

FECNT side-product formation and isolation. Syntheses were also carried out in pressure vessels, using the conditions described previously for compound **10** but with a heating period of 3 h. Samples were then cooled to room temperature and analyzed by HPLC. The fractions at retention time corresponding to FECNT and to the main side-product were collected separately. These operations were repeated four times in order to obtain sufficient materials for further analysis. Fractions isolated by HPLC with the expected elution time were combined and five-fold diluted with water. The resulting solution was drawn through a C18 Sep-Pak® cartridge (pre-activated with 10 mL of ethanol followed by 10 mL of water). The cartridge was then rinsed with 20 mL of water to remove residual traces of organic solvents and then rinsed with 0.5 mL of ethanol which was collected separately. Most FECNT as well as the side-product was then eluted with an additional 1.0 mL portion of ethanol. These solutions were finally concentrated to dryness, and their contents were characterized by mass spectrometry (ESI method).

Radiochemistry

The automated radiosynthesis of [^{18}F]FECNT ([^{18}F]-**8**) from compound **10** was carried out using SynChrom synthesizer with computer interface. First, 10–15 GBq of cyclotron-produced H[^{18}F]F in 2.4 mL of [^{18}O]H_2O was trapped on the QMA Sep-Pak® cartridge followed by fluorine-18 elution using a solution containing Kryptofix®222 (18 mg) in 0.8 mL of CH_3CN and K_2CO_3 (2.8 mg) in 0.2 mL of H_2O. The resulting mixture was then heated at 105°C for 10 min under flow of nitrogen (70 mL/min) in order to evaporate solvents and to form the K[^{18}F]F-Kryptofix®222 complex. Then, 1 mL of CH_3CN was added, and the content of the vessel was heated at 105°C for additional 10 min to completely dry the [^{18}F]fluoride complex. After cooling below 50°C, the compound **10** (4–5 mg dissolved in 1 mL CH_3CN) was added, and the solution was heated at 80°C for 10 min. To evaluate the [^{18}F]fluorination yields, an aliquot of the reaction mixture was diluted with some HPLC eluent and subjected to analytical HPLC (method B and method C).

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Conflict of Interest

The authors did not report any conflict of interest.

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