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Research Article

Synthesis of *N*-(3-[^{18}F]Fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{18}F]FP-β-CIT)

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Summary

N-(3-[^{18}F]fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{18}F]FP-β-CIT) was synthesized in a two-step reaction sequence. In the first reaction, 1-bromo-3-(nitrobenzene-4-sulfonyloxy)-propane was fluorinated with no-carrier-added fluorine-18. The resulting product, 1-bromo-3-[^{18}F]-fluoropropane, was distilled into a cooled reaction vessel containing 2β-carbomethoxy-3β-(4-iodophenyl)-nortropane, diisopropylethylamine and potassium iodide. After 30 min, the reaction mixture was subjected to a preparative HPLC purification. The product, [^{18}F]FP-β-CIT, was isolated from the HPLC eluent with solid-phase extraction and formulated to yield an isotonic, pyrogen-free and sterile solution of [^{18}F]FP-β-CIT.

The overall decay-corrected radiochemical yield was $25 \pm 5\%$. Radiochemical purity was $>98\%$ and the specific activity was 94 ± 50 GBq/μmol at the end of synthesis. Copyright © 2006 John Wiley & Sons, Ltd.

Key Words: F-18; [^{18}F]FP-β-CIT; dopamine transporter; positron emission tomography

Introduction

The *in vivo* visualization and quantification of the dopamine transporter by positron emission tomography (PET) can be achieved by the utilization of radiolabelled cocaine derivatives. Cocaine analogues where the benzoic ester moiety has been replaced by a 4-halogenophenyl group (CFT,[1–3] CIT,[4–6] CNT,[7,8] CBT[9]) or a 4-methylphenyl group (CMT[10]) and the *N*-methyl is substituted by a *N*-fluoropropyl or *N*-fluoroethyl moiety (FP,[1,3–6,8–10] FE[2,7]) are often used and give satisfactory results.

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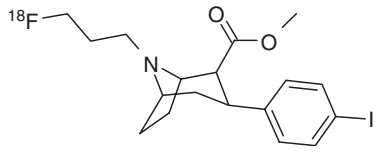


Figure 1. N-(3-[^{18}F]fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{18}F]FP-β-CIT)

Table 1. Yields and specific activity of literature methods

Entry	Reference	Radiochemical yield (%)	Specific activity (EOS, GBq/μmol)	Remarks
1	Kazumata[6]	NR	37	
2	Lundkvist[4]	2-4	55	90% chemically pure
3	Chaly[5]	1-2	NR	

NR, not reported.

We focussed our efforts on the synthesis of *N*-(3-[^{18}F]fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ([^{18}F]FP-β-CIT, Figure 1). The I-123-labelled analogue (DATScan) is a well known and investigated SPECT ligand. We chose to label this compound with ^{18}F for use in PET. Methods for the synthesis of [^{18}F]FP-β-CIT described in literature thus far showed either low yields or moderate specific activities, or a combination of the both (see Table 1).

We assume that the moderate specific activity is caused by side-products, since the employed no-carrier-added methods cannot cause that much [^{18}F]FP-β-CIT carrier. One can only speculate on the nature of such side-products since the authors have not explored these possibilities. However, it must be assumed that these are caused by alkylation of nor-β-CIT by unreacted starting material of the fluorination reaction. It is beyond the scope of this paper to elaborate on such speculations, but the mediocre results urged us to explore a different synthesis route with a higher yield, reproducibility and specific activity.

It was our hypothesis that splitting the synthesis of [^{18}F]FP-β-CIT in two separate reactions steps, with intermediate purification of ω-[^{18}F]fluorohalogenopropane by distillation and subsequent alkylation of 2β-carbomethoxy-3β-(4-iodophenyl)-nortropane (nor-β-CIT), would be an improvement on the described synthesis procedures in literature.

Results and discussion

Synthesis of ω-[^{18}F]fluorohalogenopropane

An effective synthesis of a ω-[^{18}F]fluorohalogenopropane as a radiofluorinated intermediate in the synthesis of [^{18}F]FP-β-CIT would be beneficial for two

reasons. Firstly, the boiling point of such intermediates is in such a range that distillation is feasible and secondly the starting material will be retained in the reaction vessel, due to their very high boiling points, thus eliminating the risk of formation of pseudo-carrier. Moreover, the fluorination chemicals will not be present during the alkylation reaction, in contrast to the one-pot synthesis procedure described in literature,[6] resulting in a less tedious purification procedure as well as a possibly higher alkylation yield.

Fluorination was performed as depicted in Scheme 1, starting from compounds **1a–h**, which were synthesized according to literature procedures.

Fluorination yielded a mixture of the products **2** and **3** of which the individual yields were dependent on the characteristics of the leaving groups. The tosylates and nosylates were preferably substituted by ^{18}F, while the bromide was substituted in favor of the mesylate as the leaving group. In this way the yield of **2** could be controlled in such a way that the yield increased up to 75% (decay corrected) for **1g** Results are shown in Table 2.

Reaction time and temperature were also investigated. The fluorination is a fast reaction, already after 5 min yields are at their maximum. Upon elongation of the reaction time, yields decreased significantly, probably caused by decomposition of the product. The temperature was varied between 50 and 125°C. Best results were obtained between 100 and 110°C, at higher temperatures the volatile product can leak away from the reaction vessel, due to the elevated pressure inside.

Precursor (**1**) Main product (**2**) Side product (**3**)

Compound	R	R'	Compound	R	R'
1a	Br	Mesylate	**1e**	Br	Tosylate
1b	Cl	Triflate	**1f**	I	Tosylate
1c	Br	Triflate	**1g**	Cl	Nosylate
1d	Cl	Tosylate	**1h**	Br	Nosylate

Scheme 1. Fluorination reaction

Table 2. Results of the fluorination of 1a–h

Precursor	*R*	*R′*	% **(2)**	% **(3)**	% Unreacted ^{18}F	% Undefined
1a	Br	Mesylate	25	46	21	8
1b	Cl	Triflate	16	0	75	9
1c	Br	Triflate	7	5	83	5
1d	Cl	Tosylate	58	1	19	21
1e	Br	Tosylate	41	5	37	17
1f	I	Tosylate	31	0	41	28
1g	Cl	Nosylate	75	1	19	5
1h	Br	Nosylate	57	1	24	18

The precursors **1a–h** in acetonitrile were added to the dried ^{18}F/Kryptofix K_{222}/K_2CO_3 solution (see Experimental section). This mixture was heated for 5 min at 100°C, after which the products were distilled, together with the solvent acetonitrile, into a cold vessel. The distillate was subjected to HPLC to determine the yield of product **2**. The amount of unreacted fluoride and all other non-volatile products **3** (identified with cold reference compounds) was determined by adding acetonitrile to the residue in the reaction vessel for subsequent HPLC analysis.

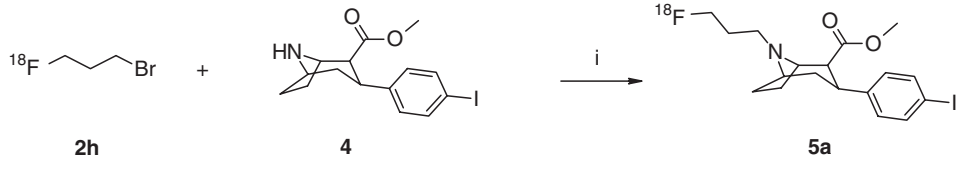
Best results were obtained with the nosylate precursors. Giving the fact of a decreasing yield of **1d–1f** and a decreasing yield of **1g–1h**, the iodopropylnosylate precursor was not investigated, since it was anticipated that this compound would result in lower yields. Furthermore, the iodopropylfluoride has a higher boiling point than the chloro- and bromopropylfluoride, making the distillation of this intermediate less feasible.

*Synthesis of N-(3-[^{18}F]fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl) nortropane **(5a)***

Initially, compound **1g** was selected to be used for the alkylation of the nor-β-CIT **4**, Scheme 2. However, alkylation yields were low, despite increasing the reaction temperature (80–160°C). Also the addition of potassium iodide as a catalyst did not improve the alkylation yield. However, 1-bromo-3-[^{18}F]fluoropropane gave better results, caused by the better leaving group characteristics of the bromine atom, which also has been shown by Bauman *et al.*[11] Compound **1h** was therefore selected for optimization of the alkylation reaction (Table 3).

Best results for the alkylation were achieved in 1 ml of acetonitrile with 5 µl diisopropylethylamine as a base at 150°C. Also DMSO at 130°C gave good results, but we did not investigate higher temperatures with DMSO because at 130°C already no intact fluorobromopropane was left and polar side-products are formed. We believe that at higher temperatures the reaction yield will not increase, but decrease and more polar side-products will be formed.

In contrast to all literature methods[1,2,4,6–10] where DMF is used as solvent for the alkylation reaction, the alkylation in acetonitrile shows higher yields



Scheme 2. Alkylation of nor-β-CIT (4). Reaction conditions: (i) potassium iodide, diisopropylethylamine, acetonitrile, 150°C, 30 min

Table 3. Optimization of the alkylation reaction conditions[a]

Solvent	Temperature (°C)	Yield **5a** (%)	Yield undefined product (%)
DMF	100	23	35
DMF	130	30	44
DMF	150	29	71
THF	130	39	10
DMSO	130	49	46
CH_3CN	130	41	27
CH_3CN	150	52	22

[a] Three milligrams of **4**, 30 min reaction time; yields relative to 1-bromo-3-[^{18}F]fluoropropane.

with less impurities. Diisopropylethylamine is a well known, sterically hindered base, which itself is non-nucleophilic, and enhances the alkylation reaction also in this case, improving the yield by 10%. The addition of potassium iodide proved to be essential for the alkylation. Without the *in situ* formation of iodo **2h** via exchange of Br for I, alkylation occurred only in very low yields of 5–10%. The iodo **2h** could clearly be recognized on HPLC. The formation of the iodo intermediate is probably also the reason why **2g** shows much less alkylation, since in that case no exchange of the Cl by the I occurs and therefore a low alkylation yield was observed.

The alkylation reaction mixture was subjected to semi-preparative HPLC for the purification of **5a**, on a Kromasil 250 × 21 mm column with methanol/water/diisopropylamine 90/10/0.2 as the eluent. At a flow rate of 10 ml/min the retention time of [^{18}F]FP-β-CIT was 15 min. However, from the chromatogram (Figure 2), the presence of a contamination in the UV channel which co-eluted with [^{18}F]FP-β-CIT was observed.

One likely possibility for this contamination could be *N*-(1-propene-3-yl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane **5b**. This product could result from the alkylation of **4** by 3-bromo-1-propene **6** and might even be a potent dopamine transporter ligand, and can as such act as a pseudo-carrier. The very reactive alkylating agent **6** could be formed under the alkaline reaction conditions of the fluorination by elimination of the nitrophenylsulphonyl group (Scheme 3).

In order to verify this hypothesis, commercially available 3-bromo-1-propene, was reacted with **(4)**, and a single reaction product was formed within 5 min at room temperature. The obtained compound from this synthesis co-eluted on HPLC analysis with the observed contamination in the synthesis of [^{18}F]FP-β-CIT proving that this compound was indeed the contamination. The chemical structure of the reaction product was determined with NMR and proved to be compound **5b**. The product **5b** is also formed when other sulfonate esters **1a–1g**, were used.

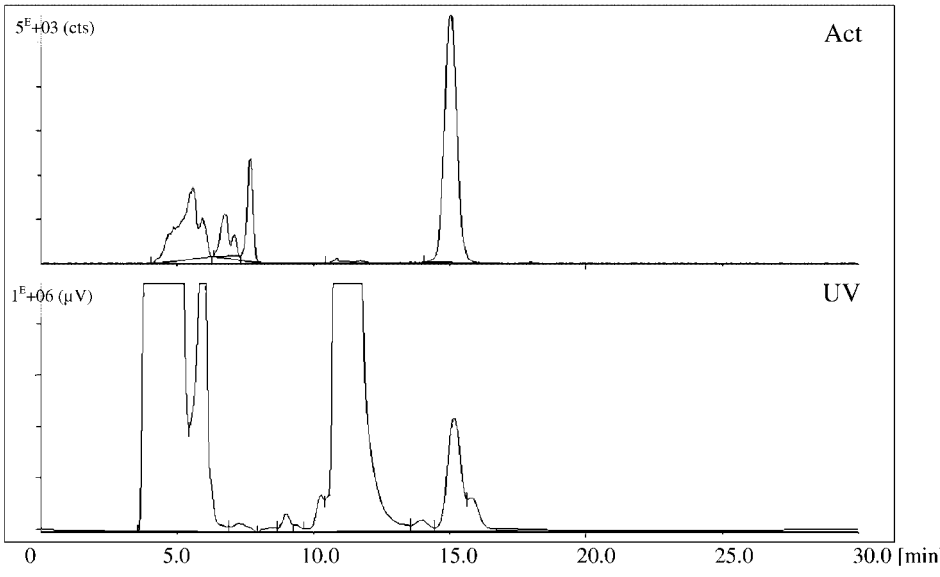
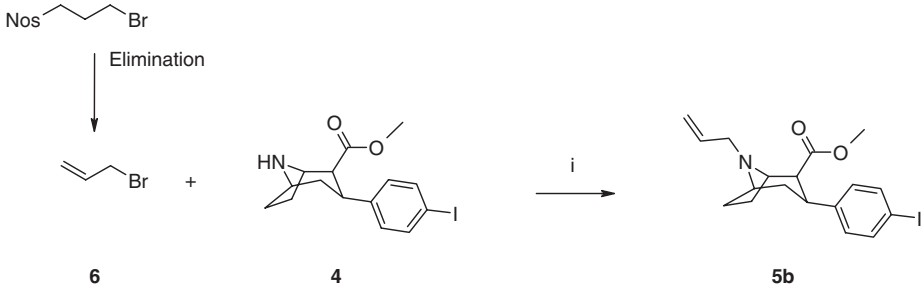


Figure 2. Semi-prep HPLC of [^{18}F]FP-β-CIT, using a Kromasil 250 $\times$ 21 mm column



Scheme 3. Alkylation of the nor-β-CIT precursor yielding the pseudo-carrier 5b. Reaction conditions: (i) potassium iodide, diisopropylethylamine, acetonitrile, 150°C, 30 min

Semi-preparative HPLC purification

Compound **5b** shows a remarkable resemblance with [^{18}F]FP-β-CIT on various semi-preparative HPLC systems. Results are depicted in Table 4, these were the maximum achieved resolution for these columns, despite the variation of the eluent. Only by using a Phenomenex Luna C18(2) 5 µm, 250 $\times$ 10 mm and acetonitrile/water/diisopropylamine 57.5/42.5/0.2 (v/v/v) as eluent, sufficient separation could be achieved between FP-β-CIT (R_t 52 min) and the pseudo-carrier (R_t 48 min) (Figure 3).

Table 4. Selection of the investigated HPLC purification systems

Column	Eluent	R_t FP-β-CIT	R_t propene-CIT	Resolution (R_s) between investigated peaks[a]
Kromasil 250 × 21 mm	MeOH/H_2O/DiPA 90/10/0.2	15	16	0.64
Spherisorb 250 × 8 mm	MeCN/NH_4Ac 75/25	17	16	1.00
Sperimage 250 × 16 ODS2	5 mM $NH_4H_2PO_4$ pH 7.4/MeCN 15/85	17	19	0.93
Xterra 150 × 3.9 mm[b]	MeOH/H_2O/DiPA 75/25/0.2	19	20	0.28
Bondapak 300 × 7.8 mm	0.01 M H_3PO_4/MeCN 75/25	27	21	0.88
Luna C18(2) 250 × 10 mm	MeCN/H_2O/DiPA 65/35/0.2	30	29	0.29
Luna C18(2) 250 × 10 mm	MeCN/H_2O/DiPA 57.5/42.5/0.2	52	48	1.82

[a] $R_s < 1.25$ no baseline separation; $R_s > 1.5$ baseline separation between UV propene-CIT and radioactive FP-β-CIT.
[b] Analytical amount.

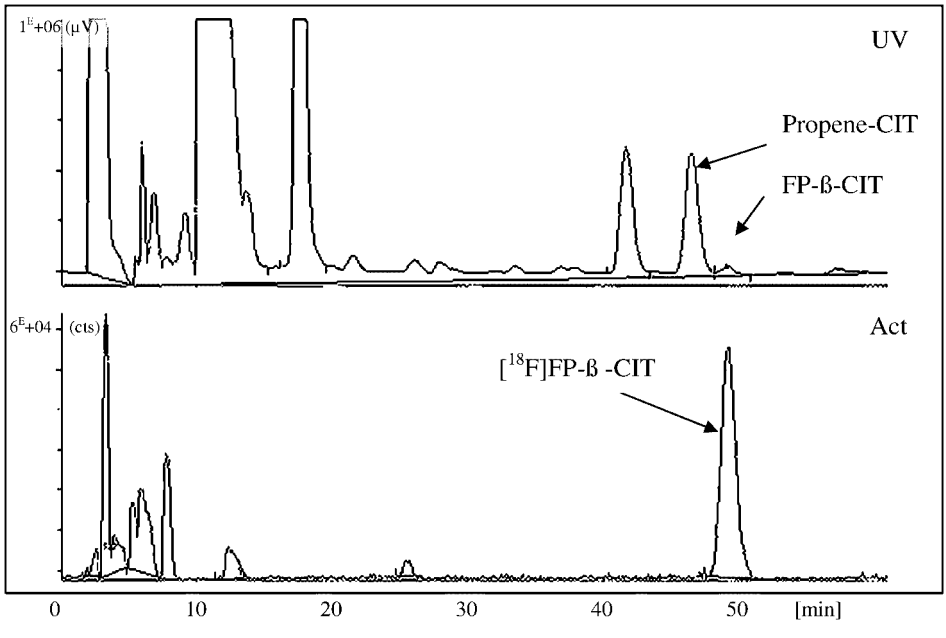


Figure 3. Representative semi-preparative HPLC purification of [^{18}F]FP-β-CIT, using a Phenomenex Luna C18(2) 250 × 10 mm column

Stability of [^{18}F]FP-β-CIT

QC HPLC analysis of the formulated [^{18}F]FP-β-CIT showed that radiochemical purity of [^{18}F]FP-β-CIT was irreproducible. Sometimes the radiochemical purity was even less than 98%. QC showed a side-product (SP1) which was formed during the formulation of [^{18}F]FP-β-CIT (Figure 4(A)) and did not increase in time. We hypothesized that the impurity might be the product of the hydrolysis of the ester function of [^{18}F]FP-β-CIT.

However, upon addition of 1 M NaOH to the formulated solution of [^{18}F]FP-β-CIT and heating at 50°C for 10 min, a different side-product was formed instead of SP1, since the retention time of the alkaline hydrolysis product was clearly different from the retention time of SP1 (Figure 4(B)). One must conclude from this experiment that SP1 is not the product of the hydrolysis of the ester moiety of [^{18}F]FP-β-CIT, but another, yet unidentified impurity. When the HPLC fraction itself was analysed, it was shown that [^{18}F]FP-β-CIT remained 100% pure in time (Figure 4(C)). One can only speculate on the nature of this impurity, but Chaly *et al.*[5] reported a decomposition or epimerization into the 2-α isomer on a silica cartridge, also Xing *et al.*[12] reported an epimerization in the [^{18}F]FP-β-CIT synthesis. We assume that SP1 is also this epimerization product, since in the formulation of

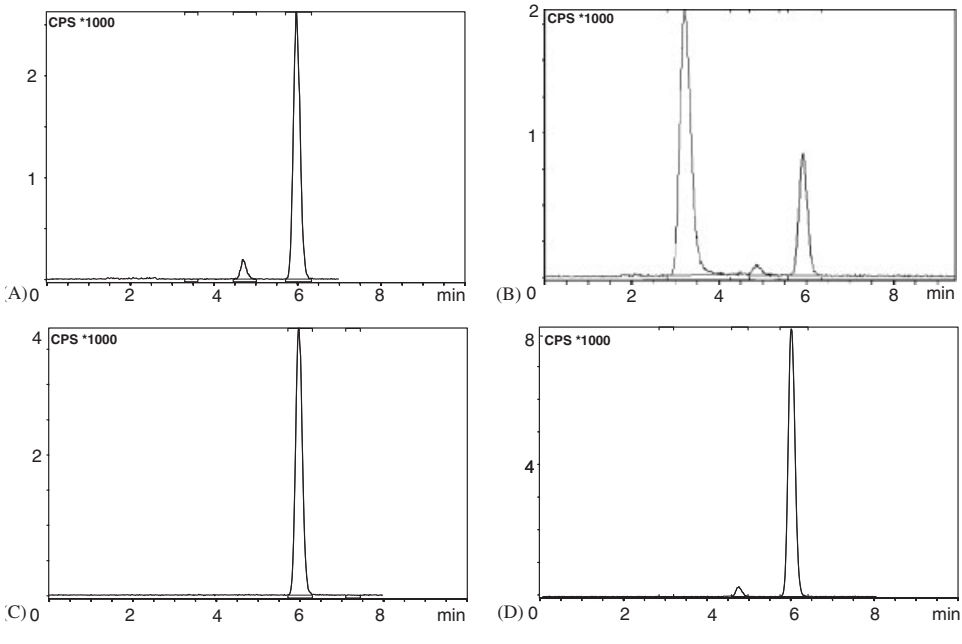


Figure 4. QC radiochromatograms of formation of SP1. (A) Formulated product, with side-product. (B) Formulated product partially hydrolysed. (C) Collected HPLC fraction. (D) Ethanol fraction of solid-phase extraction

Table 5. Purity of [^{18}F]FP-β-CIT during formulation

Step in SPE	[^{18}F]FP-β-CIT (%)	SP1 (%)
HPLC fraction	100	0
HPLC fraction, after 1 h	100	0
Washing	ND	ND
Ethanol fraction	95	5
Formulated product	95	5

ND, not determined; products present on SPE cartridge; HPLC analysis not possible.

[^{18}F]FP-β-CIT, also a solid-phase extraction (SPE) is employed. Table 5 shows the results of the analysis of the various intermediate steps in the SPE procedure.

From these results it was concluded that SP1 originates after the washing of the SPE cartridge and before the elution with ethanol (Figure 4(D)). In between these two successive steps, the SPE cartridge runs dry and during this period SP1 originates. Indeed it was shown that upon elongation of the period the SPE cartridge runs dry, the amount of SP1 impurity also increases. Preventing the SPE cartridge to run dry during the formulation resulted in a reproducible purity of [^{18}F]FP-β-CIT which exceeded 98%.

Experimental

Material and methods

Acetonitrile, Kryptofix 222, potassium carbonate and potassium iodide were obtained from Merck, other chemicals were obtained from Aldrich. All chemicals were used as received.

HPLC for semi-preparative separation was performed with a Jasco PU1587 pump, an in-line Jasco UV1575 UV detector (wavelength 235 nm), a flow-through radioactivity detector with GM tube (home-made) and Jasco-Borwin software for data acquisition and processing. HPLC Column Phenomenex Luna C18(2) 5 µm, 250 × 10 mm (Bester). Seppak C18 plus (Waters). Radioactivity was quantified with a VDC-405 dose calibrator (Veenstra instruments). All reactions were carried out utilizing a home-made, remotely controlled apparatus.[13] Analytical HPLC was performed with a Jasco PU1580 pump, an in-line Jasco UV2075 UV detector (wavelength 235 nm), a flow-through NaI (Tl) crystal scintillation detection system and Raytest Gina-NT for data acquisition.

Synthesis of sulphonic esters

All esters, except for the 3-chloropropyl-trifluoromethanesulfonate, were synthesized according to literature.[14] This was successful for all the esters

except for 3-chloropropyl-trifluoromethanesulfonate, this compound was prepared according to Chi *et al.*[15]

NMR data

3-*Bromoprophyl-methanesulfonate*. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.36 (t, 2H, $J = 5.8$ Hz, H-1), 3.50 (t, 2H, $J = 6.2$ Hz, H-3), 3.02 (s, 3H, methyl), 2.25 (m, 2H, H-2).

3-*Chloropropyl-trifluoromethanesulfonate*. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.69 (t, 2H, $J = 5.9$ Hz, H-1), 3.65 (t, 2H, $J = 6.0$ Hz, H-3), 2.25 (m, 2H, H-2).

3-*Bromopropyl-trifluoromethanesulfonate*. ^{1}H NMR (200 MHz, $CDCl_3$) δ 4.63 (t, 2H, $J = 5.8$ Hz, H-1), 3.44 (t, 2H, $J = 6.2$ Hz, H-3), 2.28 (m, 2H, H-2).

1-*Chloro-3-(toluene-4-sulfonyloxy)-propane*. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.76 (d, 2H, $J = 8.3$ Hz, aryl), 7.32 (d, 2H, $J = 8.3$ Hz, aryl), 4.15 (t, 2H, $J = 5.9$ Hz, H-3), 3.53 (t, 2H, $J = 6.2$ Hz, H-1), 2.42 (s, 3H, methyl), 2.07 (m, 2H, H-2).

1-*Bromo-3-(toluene-4-sulfonyloxy)-propane*. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.75 (d, 2H, $J = 8.0$ Hz, aryl), 7.30 (d, 2H, $J = 8.0$ Hz, aryl), 4.12 (t, 2H, $J = 6.0$ Hz, H-3), 3.35 (t, 2H, $J = 6.0$ Hz, H-1), 2.40 (s, 3H, methyl), 2.12 (m, 2H, H-2).

1-*Iodo-3-(toluene-4-sulfonyloxy)-propane*. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (d, 2H, $J = 8.0$ Hz, aryl), 7.32 (d, 2H, $J = 8.0$ Hz, aryl), 4.08 (t, 2H, $J = 6.0$ Hz, H-3), 3.14 (t, 2H, $J = 6.0$ Hz, H-1), 2.45 (s, 3H, methyl), 2.10 (m, 2H, H-2).

1-*Chloro-3-(nitrobenzene-4-sulfonyloxy)-propane*. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.41 (d, 2H, $J = 8.8$ Hz, aryl), 8.12 (d, 2H, $J = 8.8$ Hz, aryl), 4.29 (t, 2H, $J = 5.8$ Hz, H-3), 3.57 (t, 2H, $J = 6.1$ Hz, H-1), 2.13 (m, 2H, H-2).

1-*Bromo-3-(nitrobenzene-4-sulfonyloxy)-propane*. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.40 (d, 2H, $J = 8.9$ Hz, aryl), 8.11 (d, 2H, $J = 8.8$ Hz, aryl), 4.28 (t, 2H, $J = 5.8$ Hz, H-3), 3.41 (t, 2H, $J = 6.1$ Hz, H-1), 2.21 (m, 2H, H-2).

Synthesis of N-(1-propene-3-yl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane ***(5b)***

3-Bromo-1-propene **(6)** (2 µl, 23 µmol), was reacted with 5 mg (13 µmol) nortropane **(4)** in acetonitrile, for 30 min at 50°C. Compound **5b** was isolated with the same semi-prep and SPE procedure as for [^{18}F]FP-β-CIT.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55 (d, 2H, $J = 8.4$ Hz, aryl), 7.00 (d, 2H, $J = 8.3$ Hz, aryl), 5.75 (m, 1 H, ═ CH), 5.10 (t, 2H, CH_2 ═), 3.67 (s, 1 H,

H-1), 3.48 (s, 3H, OCH_3), 3.41 (s, 1 H, H-5), 3.0 (m, 2H, H-3 and H-2), 2.55 (m, 1 H, H-4a), 2.05 (m, 2H, H-6a and H-7a), 1.65 (m, 5 H, CH_2, H-6b, H-7b and H-4b).

Production of [^{18}F]F$^-$

[^{18}F]F$^-$ was produced by the ^{18}O(p,n)^{18}F nuclear reaction with an IBA 18/9 cyclotron. An irradiation of 40 min with 40 μA of 18 MeV protons yielded 55–65 GBq of [^{18}F]F$^-$ at EOB. After irradiation the ^{18}F was trapped on a BioRad AG-1-X8 column (carbonate form), while the enriched water was collected for re-use.

Production of 1-bromo-3-[^{18}F]-fluoropropane

The ^{18}F was eluted from the anion exchange column by using 1 ml acetonitrile/water (9/1 v/v) containing 13 mg (34 μmol) of Kryptofix 222 and 2 mg (14 μmol) of potassium carbonate. The solution was dried under a Helium flow and reduced pressure at 90°C. To remove residual water, 0.5 ml of acetonitrile was added, and the solution was dried again. At room temperature the precursor 1-bromo-3-(nitrobenzene-4-sulfonyloxy)-propane in 0.5 ml acetonitrile was added. Fluorination reaction was carried out for 5 min at 110°C. At the end of the reaction, the formed 1-bromo-3-[^{18}F]fluoropropane was distilled, together with the solvent, acetonitrile, into a cooled (−30°C) second reaction vessel, which contained 5.5 mg (15 μmol) of 2*β*-carbomethoxy-3*β*-(4-iodophenyl)-nortropane **(4)**, and 4 mg (24 μmol) of potassium iodide in 0.5 ml acetonitrile and 5 μl (29 μmol) diisopropylethylamine.

Production of [^{18}F]-N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)-nortropane

After the distillation step, the reaction vessel was closed and heated at 150°C for 30 min. The reaction mixture was then cooled to room temperature and quenched with 0.5 ml of water and subsequently transferred to the HPLC unit using a remote-control-operated HPLC injection system and subjected to a semi-preparative HPLC purification using a Phenomenex Luna C18(2) 5 μm, 250 × 10 mm column. Eluent was acetonitrile:water:diisopropylamine 57.5:42.5:0.2 (% v/v/v) at a flow of 5 ml/min.

[^{18}F]-*N*-(3-fluoropropyl)-2*β*-carbomethoxy-3*β*-(4-iodo-phenyl)nortropane had a retention time of 52 min, as detected by UV (235 nm) and radioactivity flow-through GM detector. Specific activity was determined by calculation of the peak area of radioactive product combined with the peak area of the UV peak, quantified with a calibration curve of the non-radioactive FP-*β*-CIT.

The collected fraction was diluted with 60 ml of sterile water in the formulation unit.[13] The diluted product was passed over a Sep-Pak plus C_{18}

cartridge using helium overpressure, followed by a washing with 60 ml sterile water. The desired product was eluted with 2 ml of sterile ethanol, followed by 17 ml of sterile citrate/acetate buffer (0.038 M citric acid, 0.054 M sodiumcitrate, 0.051 M sodiumacetate, pH 5) and filtered through a sterile 0.22 μm Millipore GV filter using helium overpressure, yielding a sterile and pyrogen-free solution, ready for injection. Total synthesis time was 125 min including the purification and the formulation. The product was obtained in 25 ± 5% ($n = 34$) decay-corrected isolated radiochemical yield with a specific activity at the end of synthesis of 94 ± 50 GBq/μmol ($n = 34$).

An aliquot was analyzed by HPLC using a Kromasil C18, 10 μm, 250 × 4.6 mm column, with acetonitrile:water:diisopropylamine 90:10:0.2 (% v/v/v) as mobile phase, at a flow rate of 1 ml/min. Radiochemical purity was >98%.

Residual solvent analysis on GC showed less than 18, 18, 26 and 1 ppm of acetone, acetonitrile, diisopropylamine and diisopropylethylamine, respectively. The ethanol concentration was found to be 10%.[16]

Conclusion

A fully automated, GMP compliant, reproducible procedure for the synthesis of [^{18}F]-FP-β-CIT has been developed. The product was obtained in 25 ± 5% ($n = 34$) decay-corrected isolated radiochemical yield in 125 min after end of bombardment. The specific activity at the end of synthesis was 94 ± 50 GBq/μmol ($n = 34$). Radiochemical purity was >98%, and no other mass peaks other than the carrier product were detected. Although the synthesis time is longer than the previously described synthesis routes, the yield and specific activity are significantly improved.

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