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Preparation of [^{18}F]β-CFT-FP and [^{11}C]β-CFT-FP, Selective Radioligands for Visualisation of the Dopamine Transporter Using Positron Emission Tomography (PET)

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SUMMARY

In this study the N-fluoropropyl analogue of the cocaine congener β-CFT (**I**), N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-fluorophenyl)nortropane (β-CFT-FP, **III**), was labelled with ^{18}F or ^{11}C. Syntheses of the precursors nor-β-CFT (**II**) and β-CFT-FP acid (**IV**) as well as **III** itself are described. [^{18}F]β-CFT-FP was prepared starting from **I** using two different labelling reagents: [^{18}F]fluoropropyl bromide (**V**) and [^{18}F]fluoropropyl tosylate (**VI**). A reversed–phase HPLC system proved to be effective in separating the labelled product from precursor **II**. The radiochemical incorporation of **V** or **VI** to yield [^{18}F]β-CFT-FP (**^{18}F-III**) was in general 30-50% and the radiochemical purity was higher than 99%. [^{11}C]β-CFT-FP (**^{11}C-III**) was synthesised by esterification of **IV** using [^{11}C]methyl triflate (**VII**). An HPLC-purification system using a reversed-phase column proved to be effective in separating the product from the acid precursor. The radiochemical yield starting from [^{11}C]carbon dioxide was 30-40% and the radiochemical purity was better than 99%. **^{18}F-III** and **^{11}C-III** have potential as radioligands for visualisation of the dopamine transporter (DAT) using Positron Emission Tomography (PET).

Key Words: [^{18}F]β-CFT-FP, [^{11}C]β-CFT-FP, Dopamine Transporter, PET

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INTRODUCTION

Several compounds have been labelled and used in PET studies in order to evaluate the physiology and pharmacology of the central dopamine transporter (DAT) *in vitro* and *in vivo* (1). However, poor selectivity or/and unfavourable kinetics of most of the compounds limit their use in quantitative PET. The cocaine analogue, 2β-carbomethoxy-3β-(4-iodophenyl)tropane, β-CIT (Fig. 1) has been suggested as a lead structure in the development of radioligands for DAT. However, radiolabelled β-CIT itself proved to be unsuitable for PET as it does not reach peak equilibrium within the time course of the PET-experiment (2). The fluorine analogue, 2β-carbomethoxy-3β-(4-fluorophenyl)tropane (β-CFT), has been labelled with either ^{11}C or ^{18}F (3, 4). Radiolabelled β-CFT has a higher selectivity and faster kinetics than β-CIT, but the time to reach peak equilibrium is still too slow. This is particularly true for the ^{11}C-form, [^{11}C]β-CFT (3).

Two N-fluoroalkyl analogues of β-CIT, which reach peak equilibrium more rapidly, have also been developed for PET (5, 6, 7). They are, N-(3-fluoroethyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (β-CIT-FE) and N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)nortropane (β-CIT-FP) and both are more selective for DAT than the parent compound β-CIT (8) but still have considerable affinity for the serotonin reuptake site. The estimated order of selectivity for DAT is β-CIT-FP > β-CIT-FE > β-CIT. A fluorine analogue, N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-fluorophenyl)nortropane (β-CFT-FP) (**III**) (Fig. 1), labelled with ^{18}F has in preliminary experiments indicated accumulation in the rat striatum (9). Altogether it is suggested that β-CFT-FP should have a higher selectivity for DAT and should reach peak equilibrium faster than the cocaine analogues mentioned above.

We report the labelling of β-CFT-FP with fluorine-18 or carbon-11 to be subsequently used for a detailed PET examination of the regional distribution of radioactivity in brain. The syntheses of the appropriate precursors, 2β-carbomethoxy-3β-(4-fluorophenyl)nortropane (nor-β-CFT) (**II**) and N-(3-fluoropropyl)-2β-carboxylic acid-3β-(4-fluorophenyl)nortropane (β-CFT-FP-acid) (**IV**) as well as the reference compound N-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-fluorophenyl)nortropane (β-CFT-FP) (**III**), are described. The labelling of **III** was performed with either ^{18}F via [^{18}F]fluoropropyl bromide (**V**) or [^{18}F]fluoropropyl tosylate (**VI**) or with ^{11}C via [^{11}C]methyl triflate (**VII**).

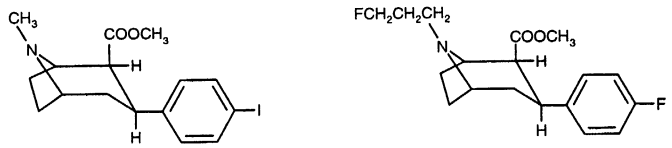

Figure 1. Structures of β-CIT (left) and β-CFT-FP (**III**) (right)

RESULTS AND DISCUSSION

Chemistry

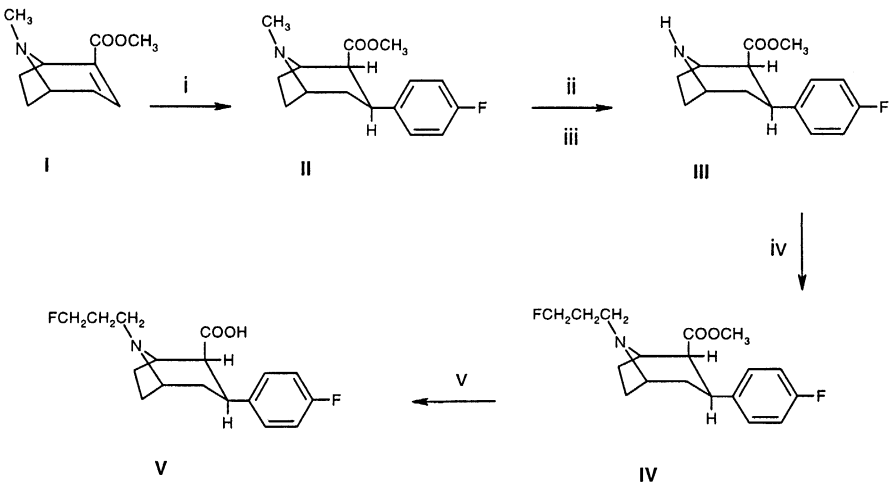

Figure 2. Synthesis scheme for the precursors i) 4-F-PhMgBr in diethyl ether, TFA, -50°C. ii) 1-Chloroethylchloroformate, 100°C. iii) MeOH, reflux. iv) 1-Bromo-3-fluoropropane, TEA, KI, EtOH, reflux. v) 6M HCl, reflux.

Anhydroecgonine methyl ester **I** was synthesised according to previously described methods (10) and reacted with 4-fluorophenylmagnesium bromide to give β-CFT (**II**) in a yield of 28% (Fig. 2). Compound **II** was desmethylated by use of I-chloro-ethylchloroformate affording the N-desmethyl compound **III** in a yield of 45%. The N-fluoropropyl compound **IV** was synthesised from compound **III** by refluxing with bromo-3-fluoropropane in the presence of triethylamine and a catalytic amount of KI. The free acid form, β-CFT-FP-acid (**V**), was synthesised by refluxing with HCl. The formation of the acid form was monitored by ^{1}H NMR spectroscopy. The product was crystallised as the sodium salt. The purity of the products was over 90% before labelling, unless stated otherwise.

Radiochemistry

Fluoroalkylation with [^{18}F]fluoropropyl bromide (V) to yield [^{18}F]β-CFT-FP ([^{18}F-III)(Fig. 3A)

The [^{18}F]β-CFT-FP was prepared by a two step synthesis via [^{18}F]fluoropropyl bromide (**V**). The incorporation of **V** to yield [^{18}F]β-CFT-FP (**^{18}F-III**) was in general 30-50%. The identity of the product was confirmed by comparing the chromatogram of the [^{18}F]β-CFT-FP with the authentic unlabelled reference material. Using 2 mg (7.5 μmol) or 4 mg (15 μmol) of the nor-β-CFT (**II**) precursor did not significantly change the labelling yield, which was contrary to the results obtained in the synthesis

of [^{18}F]β-CIT-FP (6). In all cases the addition of base (2-3 mg) improved the yield, being 37-85% with addition of K_2CO_3 and 25-58% without addition, respectively. The best incorporation yield, 85%, was achieved after 30 min heating time (37% after 10 min) with the addition of 2-3 mg of K_2CO_3. It can be concluded that both longer reaction time and the addition of base improved the yield (Fig. 4). The HPLC-system used to separate the product from the precursor and by-products using a reversed-phase column and acetonitrile/H_2O/triethylamine (60:40:0.1) as the mobile phase failed. With this separation method the product (**^{18}F-III**) and the precursor **II** eluted at the same time. A mobile phase consisting of acetonitrile/0.01 M phosphoric acid (22:78) proved to be effective and the product eluted with a retention time of 5-6 min. The total radiochemical yield of **^{18}F-III**, calculated from end of bombardment (EOB) and corrected for decay, was 2-3% with a total synthesis time of about 120 min.

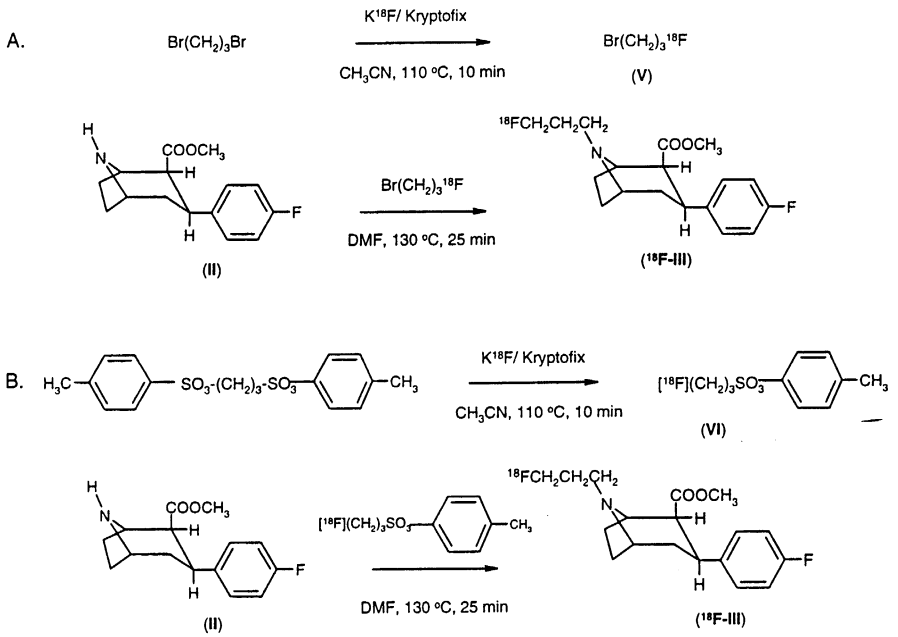

Figure 3. Radiolabelling of [^{18}F]β-CFT-FP (**^{18}F-III**) starting from nor-β-CFT (**II**) and using [^{18}F]fluoropropyl bromide (**V**) (**A**) or [^{18}F]fluoropropyl tosylate (**VI**) as labelling reagent (**B**).

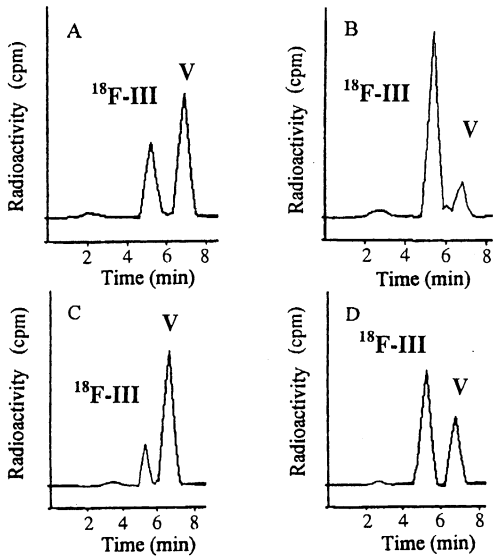

Figure 4. Analytical HPLC-chromatograms of [^{18}F]β-CFT-FP (**^{18}F-III**) from [^{18}F]fluoropropyl bromide (**V**) **with K_2CO_3** after 10 min (**A**) and 30 min (**B**) heating time at 130°C and respectively **without K_2CO_3** after 10 min (**C**) and 30 min (**D**) heating time at 130°C.

*Fluorination with the sulfonate ester [^{18}F]fluoropropyl tosylate (**VI**) to yield [^{18}F]β-CFT-FP (**^{18}F-III**) (Fig. 3B)*

The preparation via [^{18}F]fluoropropyl tosylate (**VI**) was also carried out via a two step procedure. In all cases 2 mg of **II** was used. The radiochemical incorporation of **VI** to yield **^{18}F-III** after 10 min or 30 min reaction time was 27% and 40%, respectively. The longer reaction time improved the yield to some extent. However, better yields were obtained using **V** as the labelled reagent as described above.

*Preparation of [^{11}C]β-CFT-FP (**^{11}C-III**) from [^{11}C]methyl triflate (**VII**) (Fig.5)*

[^{11}C]β-CFT-FP (**^{11}C-III**) was labelled by esterification of the corresponding carboxylic acid using [^{11}C]methyl triflate (**VII**) (11, 12, 13). The reaction proceeded instantaneously during trapping of **VII**. No extra reaction time and heating was necessary. The radiochemical yield was optimal with an equimolar ratio of base (TBAH) and reagent. If using extra base, it possibly reacts with **VII** and thus lowers the yield. The radiochemical incorporation of **VII** to yield **^{11}C-III** was about 40-50% measured at the end of **VII** trapping. Normal-phase HPLC failed to separate **^{11}C-III** from by-products (analytical purity 87%). However, the reversed-phase HPLC worked well (analytical purity >99%) (Fig. 6). The product eluted with a retention time of

5-6 min. The total synthesis time was 25-30 min and the radiochemical yield was 30-40% calculated from [^{11}C]carbon dioxide.

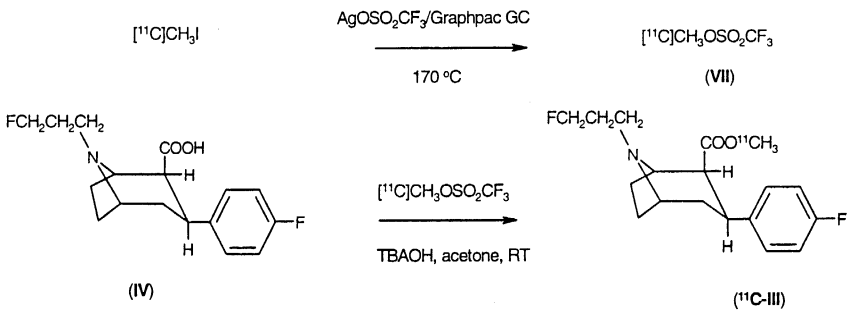

Figure 5. Preparation of [^{11}C]methyl triflate (**VII**) from [^{11}C]methyl iodide and its use in labelling [^{11}C]β-CFT-FP (**^{11}C-III**)

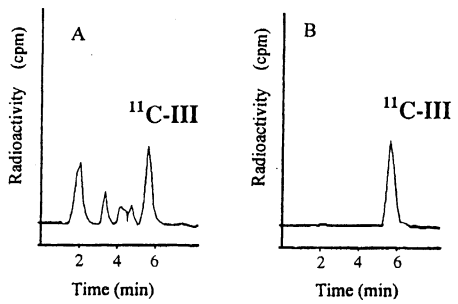

Figure 6. Analytical HPLC-chromatograms of [^{11}C]β-CFT-FP (**^{11}C-III**) before HPLC-purification (**A**) and after HPLC-purification (**B**)

EXPERIMENTAL

Chemistry

Materials and Methods

Materials

Silver triflate was purchased from Aldrich and graphpac GC (80-100 mesh) from Alltech. DMF was obtained from Merck, distilled under vacuum and dried over molecular sieves (4Å). Silica gel for column chromatography was Merck Kieselgel 60 (0.063 - 0.200 mm). Other chemicals and reagents were obtained from commercial sources and were of analytical grade.

NMR

NMR spectra were recorded on a Bruker AM 400 WB spectrometer using tetramethylsilane as an internal standard. Normal $^{3}J_{HH}$ couplings are indicated by the letter "J" and all J values are given in Hz.

Separation and analysis of radioligands

Each radioligand was purified to >99% radiochemical purity by HPLC on a system comprising the specified mobile phase, pump (type 420; Kontron), automatic sample injector (type VICI with 1 mL loop) and UV-detector (type 43, set 254 nm; Kontron). The crude fluorine-18 labelled product was purified by semipreparative reversed-phase HPLC using a μ-Bondapak C-18 (300 x 7.8 mm, 10 μm; Waters) column with acetonitrile and 0.01 M phosphoric acid (22:78) as the mobile phase with a flow rate of 6 mL/min. HPLC-separation of the carbon-11 labelled compound was carried out using the same column as described above with acetonitrile/H_2O/triethylamine (60:40:0.1) as the mobile phase. Each radioligand was analysed for radiochemical purity by reversed-phase HPLC on a system comprising the specified mobile phase, PC-controlled module with intelligent pump (type L-6200A; Merck-Hitachi), injector (type 7125 with 50 μL loop; Rheodyne) and UV absorbance detector in series with a radioactivity detector (Flo-one, Radiomatic) equipped with a PET flow-cell (600 μL; Packard). The radiochemical purity of both **^{18}F-III** and **^{11}C-III** was analysed using a μ-Bondapak C-18 (300 x 3.9 mm, 10 μm; Waters) column with acetonitrile and 0.01 M phosphoric acid (30:70) as a mobile phase with a flow rate of 2 mL/min.

Preparation of 2β-Carbomethoxy-3β-(4-fluorophenyl)tropane (β-CFT) (**I**). A solution of anhydroecgonine methyl ester (308.7 mg, 1.70 mmol) in dry diethyl ether (5 mL) was added dropwise over the course of 0.5 h and under a nitrogen atmosphere to a vigorously stirred solution of 4-fluorophenylmagnesium bromide (2M in dry diethyl ether, 1.9 mL, 3.8 mmol) in dry diethyl ether (10 mL) at –50°C. The reaction mixture was stirred at this temperature for 2 h. The mixture was cooled to –70°C and trifluoroacetic acid (425.0 mg in 2 mL of dry diethyl ether) was added. The reaction mixture was allowed to warm to –5 °C and 10 mL distilled water was added in small portions. The aqueous layer was acidified (pH 1) using a small amount of concentrated HCl and the layers separated. The aqueous layer was made alkaline by addition of NH_3 (aq., 25%), saturated with NaCl, and extracted with CH_2Cl_2 (4 x 5 mL). The combined organic layers were dried, filtered and evaporated to dryness to give a dark yellow oil, which was purified by silica column using 5-10% triethylamine-diethylether as an eluent to give 130.0 mg (28 %) of the pure product. ^{1}H NMR ($CDCl_3$): δ (ppm) 1.56-1.77 (m, 3H), 2.04-2.15 (m, 1H), 2.16-2.26 (m, 1H), 2.23 (s, 3H), 2.56 (ddd, 1H, J = -12.8 Hz, 12.6 Hz, 3.1 Hz), 2.86 (m, 1H), 2.97 (dm, 1H, J = 12.8 Hz), 3.36 (m, 1H), 3.50 (s, 3H), 3.55 (dd, 1H, J = 7.0 Hz, 3.1 Hz), 6.95 (m, 2H), 7.21 (m, 2H).

Preparation of 2β-Carbomethoxy-3β-(4-fluorophenyl)nortropane (nor-β-CFT) (**II**). β-CFT (**I**) (130.0 mg, 0.47 mmol) was heated at 100°C with 1-chloroethyl-chloroformate (2.0 mL) for 1 hour and the reaction mixture was evaporated to dryness. The residue was dissolved in methanol (2.5 mL), refluxed for 30 minutes, followed by evaporation to dryness. The residue was dissolved in CH_2Cl_2 and washed with saturated sodium bicarbonate, dried and evaporated to dryness. The crude product (133.9 mg) was purified by column chromatography with isopropylamine-ethylacetate-hexane (3:47:50) as eluent to give 55.0 mg of product as a white solid (45%). ^{1}H NMR ($CDCl_3$): δ (ppm) 1.57-1.82 (m, 3H), 1.95-2.06 (m, 1H), 2.06-2.18 (m, 1H), 2.39 (ddd, 1H, J = -14.4 Hz, 13.0 Hz, 2.9 Hz), 2.71 (dd, 1H, J = 5.9 Hz, 1.9 Hz), 3.23 (dm, 1H, J = 13.0 Hz), 3.38 (s, 3H), 3.69 (dd, 1H, J = 7.0 Hz, 1.9 Hz), 3.73 (dm, 1H, J = 6.7 Hz), 6.96 (m, 2H), 7.16 (m, 2H)

Preparation of N-(3-Fluoropropyl)-2β-carbomethoxy-3β-(4-fluorophenyl)nortropane (β-CFT-FP) (**III**). 1-Bromo-3-fluoropropane (44.0 μL, 0.9 mmol) was added to a solution of nor-β-CFT (**II**) (55.0 mg, 0.21 mmol) in ethanol (2.2 mL) containing triethylamine (44 μL) and a catalytic amount of KI. The reaction mixture was refluxed overnight and evaporated to dryness. The residue was purified by column chromatography using diethylether-triethylamine (90:10) as eluent yielding 48.9 mg (72%) of crude product. ^{1}H NMR ($CDCl_3$): δ1.58-1.84 (m, 5H), 1.95-2.16 (m, 2H), 2.37 (m, 2H), 2.55 (ddd, 1H, J = -14.1 Hz, 12.5 Hz, 3.0 Hz), 2.88 (m, 1H), 2.98 (dm, 1H, J = 12.5 Hz), 3.39 (m, 1H), 3.48 (s, 3H), 3.66 (m, 1H), 4.52 (dt, 2H, $^2J_{HF}$ = 47.2 Hz, J = 6.0 Hz), 6.95 (m, 2H), 7.21 (m, 2H)

N-(3-Fluoropropyl)-2β-carboxylic acid-3β-(4-fluorophenyl)nortropane (β-CFT-FP-acid) (**IV**) β-CFT-FP (**III**) (48.6 mg, 0.15 mmol) was dissolved in 6 M HCl (850 μL) and refluxed in an NMR tube until the OMe-peak at 3.8 ppm disappeared. ^{1}H NMR (D_2O): δ (ppm) 1.94-2.69 (m, 7H), 3.15-3.33 (m, 2H), 3.64 (dm, 1H, J = 13.4 Hz), 4.17 (m, 1H), 4.32 (d, 1H, J = 6.2 Hz), 4.62 (dt, 2H, $^2J_{HF}$ = 47.0 Hz, J = 5.6 Hz), 7.08 (m, 2H), 7.21 (m, 2H).
The reaction mixture was evaporated to dryness, followed by adding 2 eq of NaOH and evaporated to constant weight to give 52.9 mg of mixture, containing 42.3 mg (91%) of product and 10.6 mg NaCl.

Radiochemistry

Production of [^{18}F]fluoride. [^{18}F]Fluoride was produced by the nuclear reaction ^{18}O(p,n)^{18}F at the Karolinska Hospital with a Scanditronix RNP 16 cyclotron using 16 MeV protons and at the Radiochemistry laboratory of the University of Helsinki with Cyclone 10/5 cyclotron using 10 MeV protons.

*Preparation of [^{18}F]β-CFT-FP ([^{18}F]**III**) via [^{18}F]fluoropropyl bromide (**V**) (Fig. 3A).* The synthesis of [^{18}F]**III** was performed by N-fluoroalkylation of nor-β-CFT (**II**) with **V** according to a previously described method (6). N.C.A aqueous [^{18}F]fluoride was

added to a solution of Kryptofix-222 (3 mg) and K_2CO_3 (10-20 mg) in dry acetonitrile. To the dried residue (3 x 1.5 mL acetonitrile, 110°C) was added 1,3-dibromopropane (20 mg) in acetonitrile (500 μL) and the solution heated at 110°C for 10 minutes. The reaction mixture was cooled to room temperature and water (2.5 mL) added to the solution. The combined mixture was eluted through a Sep-Pak (C-18). The eluate containing acetonitrile, unreacted [^{18}F]fluoride and labelled by-products was discarded. The product **V** was eluted from the Sep-Pak with DMF (2 mL). The separated alkylation reagent **V** was distilled (110°C, under nitrogen flow) into another reaction vessel containing **II** (2-4 mg) in DMF (250 μL) with or without potassium carbonate (2-3 mg). The vessel was sealed and heated at 130-140°C for at least 10 minutes. Subsequently, the crude product was purified with HPLC.

*Preparation of [^{18}F]β-CFT-FP (**^{18}F-III**) via [^{18}F]fluoropropyl tosylate (**VI**) (Fig. 3B).* The labelling procedure was only slightly different to what was described above in the preparation via **V**. To the dried residue was added 1,3-propanediol di-p-tosylate (2-3 mg) in acetonitrile (500 μL) and the solution heated at 80°C for 10 min. The reaction mixture was cooled to room temperature and water (2.5 mL) added to the solution. The mixture was eluted through a Sep-Pak (C-18) and the eluate containing by-products was discarded. The product **VI** was eluted from the Sep-Pak with DMF (2 mL). After elution the labelling agent (**VI**) was transferred to another reaction vessel containing **II** (2 mg). The reaction mixture was heated for 10-30 min at 120°C. The crude product was analysed by HPLC.

Production of [^{11}C]carbon dioxide. [^{11}C]Carbon dioxide was produced at the Karolinska Hospital with a Scanditronix RNP cyclotron using 16 MeV protons by the $^{14}N(p,\alpha)^{11}C$ nuclear reaction on nitrogen. The [^{11}C]carbon dioxide produced was trapped in a stainless steel coil cooled with liquid nitrogen before being transferred to the [^{11}C]methyl iodide/[^{11}C]methyl triflate system (11).

Preparation of [^{11}C]methyl triflate. [^{11}C]Methyl iodide was prepared from cyclotron produced [^{11}C]carbon dioxide and passed through a heated soda glass column (oven temperature 170°C) containing silver triflate impregnated graphitised carbon. Subsequently, [^{11}C]methyl iodide was converted to the [^{11}C]methyl triflate (**VII**) (Fig. 5) (11, 12, 13).

*Preparation of [^{11}C]β-CFT-FP (**^{11}C-III**) (Fig. 5).* [^{11}C]β-CFT-FP was prepared by esterification of **IV** with [^{11}C]methyl triflate (**VII**). **VII** was trapped in a sealed vial (1 mL, Minivial Alltech), containing **IV**, (0.5 mg in 25 μL of acetone), acetone (300-375 μL) and variable amounts of freshly prepared aqueous tetrabutylammonium hydroxide (TBAH) solution (0.4 M; 4-8 μL). After completion of reagent trapping (3-4 min) the crude product was purified by HPLC.

CONCLUSION

The synthesis of β-CFT-FP (**III**) and its appropriate precursors **II** and **IV** has been described. Both ^{18}**F-III** and ^{11}**C-III** could be prepared from the appropriate reagents in good radiochemical yield and purity. The examination of ^{11}**C-III** in post mortem human autoradiography cases has already demonstrated high selectivity for the dopamine transporter (14), which makes radiolabelled **III** potentially valuable for quantitation of dopamine transporters in the human brain *in vivo* by PET .

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