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Radiosynthesis of [^{18}F] *N*-3-fluoropropyl-2-β-carbomethoxy-3-β(4′ methylphenyl) nortropane (FPCMT)

Thomas Chaly Jr.[a,*], Ralph Matacchieri[a], Robert Dahl[a,b], Vijay Dhawan[c], David Eidelberg[c]

[a]*Department of Research, North Shore University Hospital, NYU Medical College, Cyclotron/PET Facility, Manhasset, NY 11030, USA*

[b]*Department of Medicine, North Shore University Hospital, NYU Medical College, Cyclotron/PET Facility, Manhasset, NY 11030, USA*

[c]*Department of Neurology, North Shore University Hospital, NYU Medical College, Cyclotron/PET Facility, Manhasset, NY 11030, USA*

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Abstract

A synthetic procedure for the routine preparation of [^{18}F] *N*-3-fluoropropyl-2-β-carbomethoxy-3-β-(4′ methylphenyl) nortropane (^{18}F FPCMT) has been developed. The synthesis is based on alkylation of nortropane with ^{18}F labeled fluoropropyl tosylate. Purification of the final product was achieved by a preparative HPLC procedure using Alltech Econosil column. Separation of the desired compound was achieved and the product was clean. The radiochemical yield (without decay correction) is 4 to 5%, calculated at the end of the synthesis based on the total amount of fluorine recovered from the target. Radiochemical purity was in the range of 98 to 99%.

1. Introduction

There is a great deal of interest in studying dopamine transporters (DAT) to assess the disease process in patients with Parkinson's disease (Wagner and Wong, 1990). [^{18}F] fluorodopa has played an important role in evaluating patients with Parkinson's disease using PET (Brooks, 1993; Takikawa et al., 1994; Eidelberg et al., 1995). Recently cocaine and its analogues have been investigated as a positive alternative to evaluate the condition of patients with Parkinson's disease using short-lived radiopharmaceuticals. Many cocaine analogues have been synthesized and evaluated for their biological activity (Clarke et al., 1973; Boja et al., 1990; Abraham et al., 1992; Carroll et al., 1992). Several groups have investigated the usefulness of these analogues as imaging agents to measure dopamine transporter function using SPECT and PET (Fowler et al., 1989; Volkow et al., 1990; Chaly et al., 1996). Even though there are a number of cocaine analogues available as imaging agents, the ones with the phenyl group attached directly to the tropane ring at the C-3 position in place of cocaine's benzoate group (CFT, CIT, etc.) have been found to be more potent and useful as a dopamine transporter marker (Madras et al., 1989; Neumeyer et al., 1991; Frost et al., 1993; Innis et al., 1993; Baldwin et al., 1995). Replacement of the methyl group in β-CIT by a fluoropropyl group at the amino group of the tropane ring has been shown to be advantageous in terms of selectivity and

* Corresponding author. Tel.: +1-516-562-1042; fax: +1-516-562-1120.

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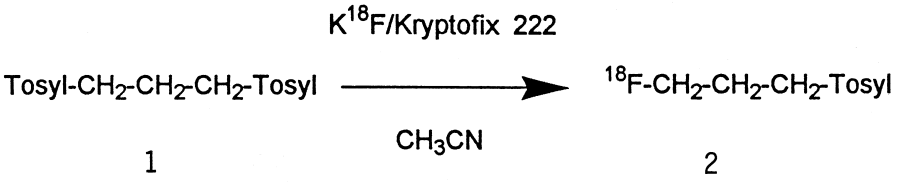

Fig. 1. Synthesis of [^{18}F] fluoropropyl tosylate.

faster kinetics (Neumeyer et al., 1994; Abi-Dharam et al., 1996). It has also been reported in the literature that replacement of the methyl group by a fluoropropyl group at the amine function on β-CIT gives the cocaine analogue a longer biological half-life and increased uptake in the striatum with increased specificity (Neumeyer et al., 1994). There are several related compounds reported in the literature as DAT imaging agents for both SPECT and PET (Neumeyer et al., 1994; Goodman et al., 1994; Kuikka et al., 1995; Kung et al., 1995; Ishikawa et al., 1996; Mozley et al., 1996; Booij et al., 1997). We have reported the use of [^{18}F] *N*-3-fluoropropyl-2-β-carbomethoxy-3-β-(4-iodophenyl) nortropane (^{18}F FPCIT) as an important DAT imaging agent for PET (Chaly et al., 1996). An age-related decline in DAT binding as well as a significant bilateral reduction in putaminal DAT binding in patients were reported in a recent publication based on a number of PET studies performed at our center (Kazumata et al., 1998). Recently Guilloteau et al. (1998) have demonstrated the use of (*E*)-*N*-(3-iodoprop-2-enyl)-2β-carbomethoxy-3-β-(4′methylphenyl)nortropane(PE2I) as an imaging agent for dopamine transporter sites. The major structural difference in this compound from [^{18}F] FPCIT is the replacement of the iodo group by a methyl group on the aromatic ring and the double bond on the propenyl group. According to their report, kinetic studies in the rat brain showed a maximal striatum/cerebellum ratio within the first 30 min of the injection. They also indicate that striatal accumulation reaches a plateau between 30 and 80 min post-injection. This situation is ideal for the in vivo imaging of the dopamine transporter sites. Therefore, development of such a compound for PET studies will be complimentary. Since the methyl ester group has a tendency to cleave at the physiological conditions after injection, the label on the methyl group may not provide an appropriate condition for PET imaging. The compound PE2I has a propenyl group attached to the nortropane structure. The unsaturation on the propenyl group makes it difficult to label that group with [^{18}F] F^-. Therefore, by assuming that the unsaturation on the side chain is not critical to achieve an ideal equilibrium for PET imaging, one could substitute the propenyl group with a fluoropropyl group. As in the case of [^{18}F]FPCIT, the new compound is expected to retain the biological activity (Kozikowski et al., 1998). Thus, the compound under consideration is the one with a methyl group on the aromatic ring and a fluoropropyl group attached to the amino group of the tropane ring. The target compound is [^{18}F] *N*-3-fluoropropyl-2-β-carbomethoxy-3-β-(4′ methylphenyl) nortropane (FPCMT) and has a very close structural relationship to that of FPCIT and PE2I. There are several ways one can prepare this compound. A direct approach involves the preparation of a precursor in which a propyl mesylate or a tosylate is attached to the amino group of the tropane ring followed by a one step fluorination of this compound to obtain the target compound. In our experience with [^{18}F] FPCIT, the direct labeling gives several breakdown products and isomers and is not the method of choice for the preparation of this compound.

The second approach is a two step procedure in which the side chain containing a leaving group is fluorinated to produce [^{18}F] labeled fluoropropyl tosylate or bromide. In the second step the [^{18}F] labeled fluoropropyl group is attached to the amino group of the tropane ring by an *N*-alkylation reaction. Preparation of the [^{18}F] labeled fluoropropyl group can be achieved by direct nucleophilic fluorination of either 1,3 fluoropropyl dibromide or ditosylate. In this regard 3-bromopropyl-1-triflate may have some advantage over the dibromide or ditosylate to prepare the fluoropropyl bromide due to the fact that the reaction may proceed faster (Kim et al., 1997). However, 3-bromopropyl-1-triflate is very unstable and the fluorination is not very reliable. Therefore we decided to use the ditosylate for the preparation of the [^{18}F] fluoropropyl tosylate. In fact, we are currently using the [^{18}F] fluoropropyl tosylate as the alkylating agent to make [^{18}F] labeled FPCIT.

2. Materials and methods

2,β-Carbomethoxy-3-β-(*p*-tolyl) nortropane, **3**, was custom synthesized by Research Biochemical International. 1,3-Propanediol-di-*p*-tosylate is available from the Aldrich Chemical company. Purification of the final product was achieved by HPLC separation using Alltech Econosil C-18 column (10 × 250 mm, 10

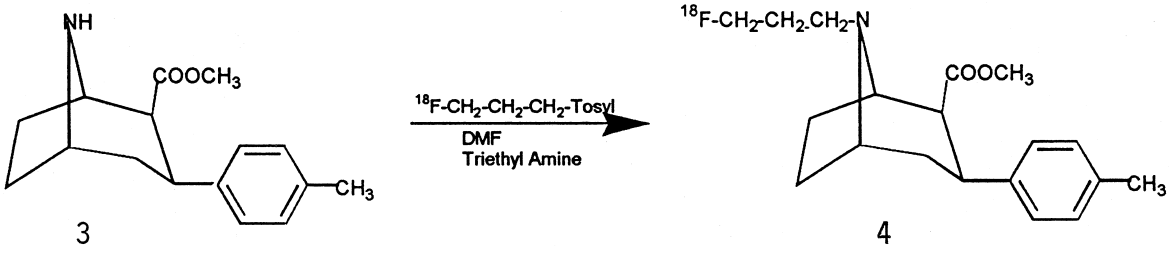

Fig. 2. Synthesis of [^{18}F] FPCMT.

μm). Analytical HPLC was performed on an Alltech Econosil C18 5U column (4.6 × 250 mm, 5 μm). Thin layer chromatography (TLC) was done on a Bioscan TLC analyzer using silica plates (Analtech uniplate, Silica gel HLF, scored 10 × 20 cm). Anhydrous acetonitrile and DMF were purchased from Aldrich and were used without any purification. Sterility testing was performed by the microbiology laboratory of our hospital and the endotoxin levels were measured in-house using LAL kit available from Associates of Cape Cod.

2.1. Synthetic scheme

The synthetic scheme involves the nucleophilic fluorination of 1,3-propanediol di-*p*-tosylate, **1**, in acetonitrile using [^{18}F] potassium Kryptofix-complex as the fluorinating agent to produce the intermediate compound [^{18}F] fluoropropyl tosylate, **2**, as in Fig. 1. The [^{18}F] fluoropropyl tosylate, **2**, thus produced was directly reacted with the nortropane, **3,** in DMF using triethylamine as the catalyst to synthesize the target compound **4** as in Fig. 2.

2.2. Synthetic unit

The radiochemical synthesis was carried out using a disposable synthesizer similar to the one that was described for the synthesis of [^{18}F]FPCIT (Chaly et al., 1996) operated by a mechanical arm. The synthetic unit consists of sterile syringes, needles, luer adapters and three-way stopcocks.

2.3. Radiochemical synthesis of [^{18}F]fluoropropyl tosylate, 2

The cyclotron-produced [^{18}F]$^-$ was transferred directly into a 10-ml Wheaton vial containing potassium carbonate (3.2 mg) through a Teflon tubing. The target water was distilled off under vacuum with a flow of argon to increase the efficiency of the distillation process. The vial was heated on a heat/stir unit at 105°C. The [^{18}O] water thus recovered was collected in a vial which was cooled in dry ice. After the [^{18}O] water was recovered completely, the vial was cooled and a solution of the Kryptofix (32 mg) in dry ethylether was added dropwise. The vial was heated again at 105°C under argon to remove ether. A solution of the 1,3-propanediol-di-*p*-tosylate (17–19 mg, 51 μmol) in dry acetonitrile was added dropwise and the reaction mixture was heated at 105°C under argon for another 20 min. At the end of 20 min, the excess solvent (acetonitrile) was removed by evaporation under reduced pressure and a flow of argon. The [^{18}F] labeled fluoropropyl tosylate thus prepared was reacted directly with the nortropane to produce [^{18}F]FPCMT.

2.4. Synthesis of [^{18}F] N-3-fluoropropyl-2-β-carbomethoxy-3-β-(4′ methylphenyl) nor-tropane

The [^{18}F] fluoropropyl tosylate, **2**, prepared as in Section 2.3 was dissolved in dry DMF (0.2 ml) and a solution of the 2,β-carbomethoxy-3-β-(*p*-tolyl) nortropane **3** (2.5 mg, 10 μmol) in DMF (0.5 ml) was added to the reaction vial containing the tosylate. Triethylamine (15 μl) in dry DMF (0.5 ml) was added and the reaction mixture was heated at 150°C for 30 min in a closed system. At the end of 30 min, the solvent was removed completely by evaporation under reduced pressure with a flow of argon to improve the efficiency of evaporation. When the solvent was removed completely, the reaction vial was cooled and the crude product was dissolved in methanol (0.5 ml × 2). The crude product was then injected into the HPLC loop by an automatic injector and was purified on an Alltech Econosil C18 column (10 × 250 mm, 10 μm) using methanol, water and triethylamine in the ratio 750:250:2 with a flow rate of 4 ml/min. Unreacted fluoropropyl tosylate was eluted at around 5 min followed by a major peak at 5.8 min. The product peak was eluted at 30 min from the start of the HPLC. Fraction eluting from the HPLC at 30 min was collected in a 100 ml flask and was subjected to rotary-evaporation at 70°C. After complete removal of the solvent by rotary-evaporation, the final product was resolubilized in 50% ethanol (0.5 ml × 2) and sterile

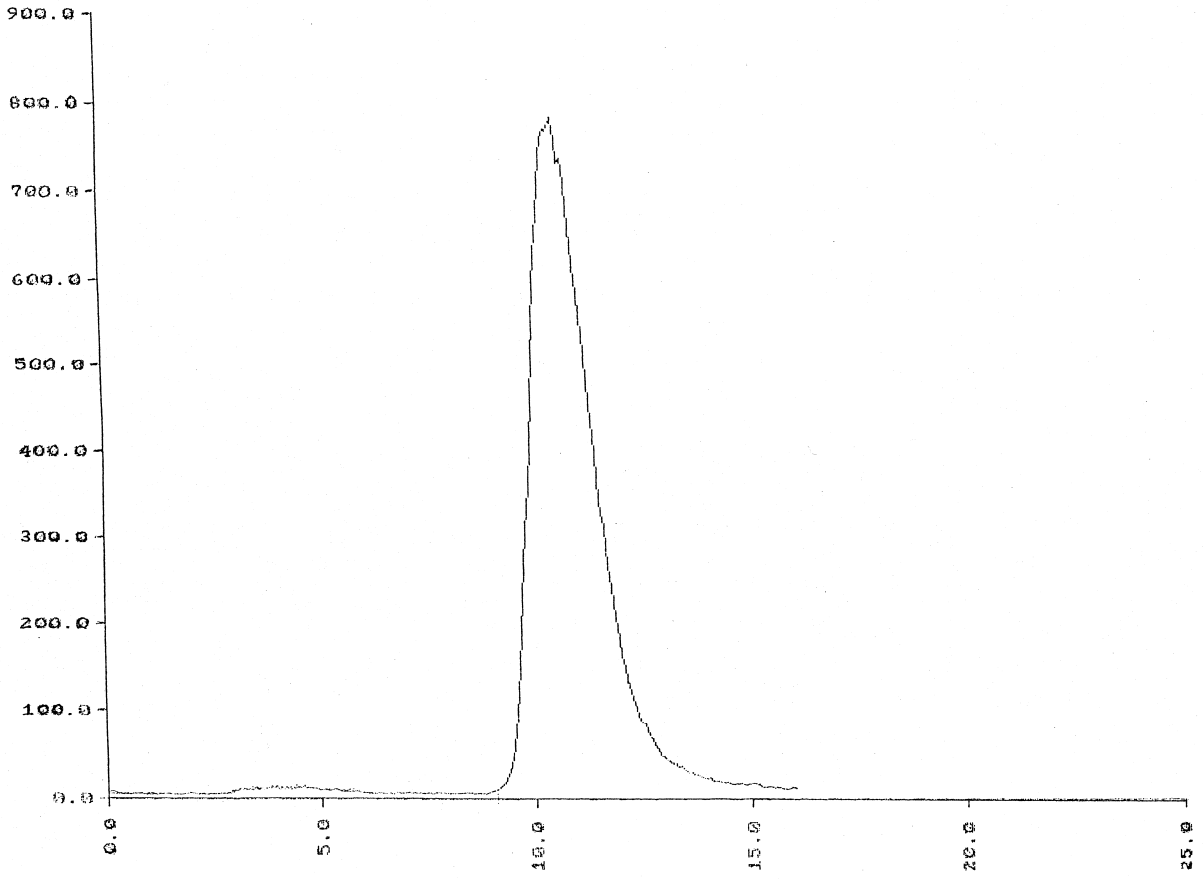

Fig. 3. Analytical HPLC of the product.

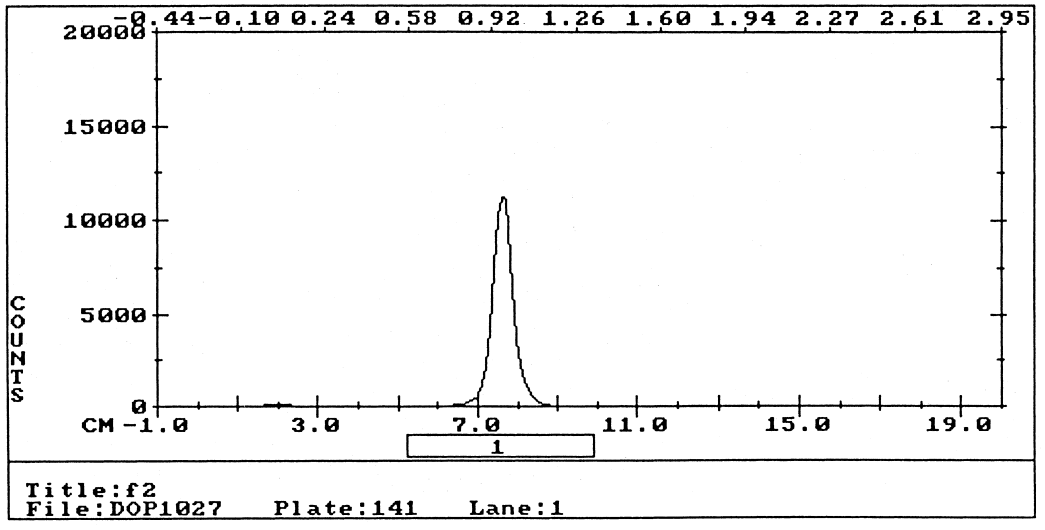

Fig. 4. Radiochromatogram (TLC) of the final product.

saline containing 0.1 mM L-ascorbic acid (2 ml). The solution containing the product was then filtered through a sterile filter into a sterile syringe and was again diluted with sterile saline according to the dose requirement. 5 μl of the product was subjected to analytical HPLC separation using an Alltech Econosil C18 column (5 μm, 4.6 × 250 mm). An eluent containing a mixture of methanol, water and triethylamine in the ratio 750:250:2 was used with a flow rate of 1 ml/min and the radiochromatogram appeared at 9.9 min as a single peak (Fig. 3). The radiochemical purity of the final product was determined again by TLC using silica glass plate as the stationary phase and a solvent system containing hexane, diethyl ether, methanol and triethyl amine in the ratio 10:10:2:1. The TLC radiochromatogram indicated that the product was >99% pure (Fig. 4). The radiochemical yield calculated from the end of bombardment was 4–5% without decay correction and the total time required for the synthesis was 90 min. The authenticity of the final product was confirmed by analytical procedures using an authentic sample.

3. Results and discussion

[^{18}F] *N*-3-Fluoropropyl-2-β-carbomethoxy-3-β(4′ methylphenyl)nortropane was synthesized by a two step procedure as described in Figs. 1 and 2. Preparation of the intermediate [^{18}F] fluoropropyl tosylate, **2**, is a straightforward reaction and is presently used at our center to produce [^{18}F] FPCIT. Fluorination of the ditosylate was completed in 20 min with an average yield of 75%. The intermediate [^{18}F] fluoropropyl tosylate was reacted directly with the nortropane without further purification. A large excess of the fluoropropyl tosylate was used for the *N*-alkylation to avoid the presence of any unreacted nortropane in the crude product. Complete removal of the solvent acetonitrile from the intermediate **2** was needed for the alkylation reaction, but at the same time overheating the reaction vial was avoided. DMF was removed completely from the crude product before it was injected into the HPLC column. Preparative HPLC chromatogram displayed a number of peaks and the two major peaks between 5 and 5.8 min are attributed to the unreacted [^{18}F] fluoropropyl tosylate and the α-isomer of the target compound. These results are very similar to those observed during the synthesis of [^{18}F] FPCIT. Even though the separation of the target compound in the preparative HPLC takes almost 30 min, the separation was very effective and the product was clean. We have tried other combinations of solvents to separate the final product from impurities, but were not successful. Analytical HPLC indicated one peak and the radiochromatogram from the TLC indicated a clean product. A disposable synthesizer containing sterile components is the method of choice at our center for the production of any radiopharmaceuticals to meet the sterility and apyrogenicity standards. Sterility and apyrogenicity tests were performed on each sample prepared and were negative. Since the synthesizer can be operated by a mechanical arm, radiation exposure to personnel is considerably reduced. Even though the radiochemical yield is low (4–5%), the synthesis gives enough radiopharmaceutical to perform research as well as clinical studies in the future. Acetonitrile was used as a solvent for the alkylation reaction to improve the yield, but the reaction was found to be very slow. In the synthesis of cocaine analogues by the alkylation of nortropane with fluoropropyl tosylate or bromide, there is evidence that epimerization of the tropane ring at the 2-position may occur and will result in the formation of the α-isomer, which is thermodynamically more stable than the β-isomer (Clarke et al., 1973). The α-isomer was also found to be much more polar than the β-isomer (Wang, 1995). We can only speculate that this might have contributed to the low yield of [^{18}F] FPCMT. We have made similar observations during the synthesis of [^{18}F] FPCIT.

4. Conclusion

We have synthesized [^{18}F] FPCMT, a new cocaine analogue for imaging DAT using PET. Synthesis is based on a two step procedure and can be completed in 90 min. Preparative HPLC procedure separates the target compound from the impurities with a >98% pure product. This is further validated by analytical HPLC and TLC. Animal studies are under way to evaluate the use of this radiopharmaceutical as a potential PET imaging agent for DAT.

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