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An efficient synthesis of dopamine transporter tracer [^{18}F]FECNT ☆

D. Murali [a,*], T.E. Barnhart [a], N.T. Vandehey [a,b,1], B.T. Christian [a,b], R.J. Nickles [a], A.K. Converse [b], J.A. Larson [c], J.E. Holden [a], M.L. Schneider [c], O.T. DeJesus [a]

[a] Department of Medical Physics, University of Wisconsin-Madison, Madison, 1111 Highland Ave, 1005 WIMR, Madison, WI 53705, United States
[b] Waisman Center, University of Wisconsin-Madison, Madison, WI 53705, United States
[c] Department of Kinesiology, University of Wisconsin-Madison, Madison, WI 53706, United States

HIGHLIGHTS

- An efficient synthesis of dopamine transporter tracer [^{18}F]FECNT is presented.
- Coupling using isolated labeling synthon reduces side products formation.
- Higher radiochemical yields and mild reaction conditons achieved.
- Very low amounts of expensive precursor used reducing the cost per synthesis.
- Suitable for routine production of [^{18}F]FECNT.

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ABSTRACT

A simple synthesis of the dopamine transporter ligand [^{18}F]FECNT with high radiochemical yield and short synthesis time, suitable for routine production is reported. Reaction of 2β-carbomethoxy-3β-(4-chlorophenyl)nortropane with [^{18}F]2-fluoroethyl triflate ([^{18}F]FEtOTf) at room temperature for 4 min provided [^{18}F]FECNT in 84% decay corrected radiochemical yield. Since [^{18}F]FEtOTf was prepared from [^{18}F]2-fluoroethyl bromide that was isolated from its starting material, formation of unwanted side products and the amount of expensive precursor used could be greatly reduced. The overall radiochemical yields of [^{18}F]FECNT were 40% (n=29) and the total synthesis time was ca. 100 min. The average specific activity of [^{18}F]FECNT was 377.4 GBq/μmol (10.2 Ci/μmol).

1. Introduction

Dopamine (DA) is a neurotransmitter involved in motor control, cognition and reward mechanisms. DA is mainly produced in the cell bodies of neurons found in midbrain. The axonal projections of these dopaminergic neurons form synapses with other regions of brain. Dopamine transporter (DAT), an integral membrane protein present in the terminals of dopaminergic cells, mediates the reuptake of dopamine from the synaptic cleft, thus terminating the signal of the neurotransmitter. DAT transports the dopamine back into dopaminergic cells, where it is metabolized or stored for future use. It has been reported that in the dendritic release of DA leading to auto-inhibition the role of DAT is reversed (Blakely, 2001; Falkenburger et al., 2001). DAT facilitates regulation of DA signal that underlies several aspects of cognition and reward. DAT is a major target for various psychologically active drugs and environmental toxins.

Though DAT is selective for transporting DA compared to other monoamine neurotransmitters, it can also transport some structural analogs of DA into neurons. It is reported (Storch et al., 2004) that the neurotoxicity of 1-methyl-4-phenylpyridinium (MPP+), the active metabolite of 1-methyl-4-phenyl-1,2,3,4-tetrahydropyridine (MPTP), involves transportation of MPP+ into the DA cells by DAT.

PET imaging using positron emitter labeled DAT ligands provides an important tool to quantitatively assess DAT availability in various pathological and psychological conditions. Since cocaine exhibits high-affinity binding towards DAT, [^{11}C]cocaine (Volkow et al., 1995) and several other ^{11}C and ^{18}F labeled nortropane cocaine analogs have been reported for PET imaging

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* Corresponding author.
E-mail address: dmurali@wisc.edu (D. Murali).
[1] Present address: Lawrence Berkeley National Laboratory, Berkeley, CA 94720, United States.

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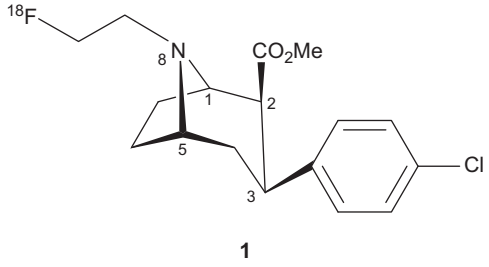
of DAT (Varrone and Halldin, 2010). 2β-Carbomethoxy-3β-(4-chlorophenyl)-8-(2-[^{18}F]fluoroethyl)nortropane ([^{18}F]FECNT, **1**; Fig. 1), reported by Goodman et al. (2000) is a highly selective low nanomolar affinity DAT ligand with low specificity for serotonin transporter (SERT) and norepinephrine transporter (NET). The affinity of FECNT for SERT and NET is 25- and 156-fold lower, respectively, than for DAT (Goodman et al., 2000).



1

Fig. 1. [^{18}F]FECNT structure.

Because of its high selectivity towards DAT and shorter equilibration time [^{18}F]FECNT (**1**) makes an excellent tracer for PET imaging of DAT. Davis et al. (2003) have reported human studies using **1**, involving normal and Parkinson's disease subjects.

[^{18}F]FECNT (**1**) has been previously synthesized by coupling nortropane precursor **4** (Fig. 2) with either [^{18}F]2-fluoroethyl tosylate (**3a**) (Goodman et al., 2000) or brosylate (**3b**) (Voll et al., 2005), in overall decay corrected radiochemical yields of 20 and 17% respectively and with a synthesis time of about 122 and 150 min respectively. In these syntheses, ^{18}F-synthons **3a** and **3b** were prepared by nucleophilic
^{18}F-fluorination of the corresponding disulfonates **2a** and **2b**. The product mixture containing both the ^{18}F-synthon and the starting material was then subjected to coupling with the precursor **4**, producing, in addition to the required **1**, large amounts of side products formed by the reaction of **2a–b** with **4**. Also, since the ^{18}F-synthon has to compete with more reactive disulfonate esters **2a** or **2b** present in several fold excess, large amounts of the expensive ($80–120 per mg) precursor **4** (3–4 mg) have to be used. In order to reduce the amount of precursor used and also to reduce the side products formed, Musachio et al. (2005) isolated the ^{18}F-synthons **3a–e** using HPLC separation and solid-phase extraction (SPE) procedure before making them react with **4**. However, the yields were affected by considerable loss of synthon in the coupling step. Chen et al. (2008) reported that **1** could be prepared by the nucleophilic fluorination of **5** (X=–OSO_2CH_3). However, in this method there is a high probability of epimerization of chiral center at position 2 next to the carboxylic ester group catalyzed by the base present in the reaction mixture. Base catalyzed epimerization of similar cocaine analogs (**6**, R=–OC(O)Ph, –OH, –Ph) has been reported in literature (Casale et al., 1992). The epimerization products, 2α-carbomethoxy nortropane derivatives have been shown to be biologically inactive (Madras et al., 1989). Nevertheless, formation of labeled epimerization products reduces the yield and also requires their separation from the final product.

Thus, the reported syntheses of **1** are of low radiochemical yields, time consuming and not cost-effective to be carried out on a routine basis. We herein report a simple, practical and cost-efficient synthesis of **1** that is suitable for routine production.

2. Materials and methods

2.1. Materials

2β-Carbomethoxy-3β-(4-chlorophenyl)nortropane (**4**), and the cold standard 2β-carbomethoxy-3β-(4-chlorophenyl)-8-(2-fluoroethyl)nortropane (FECNT) were purchased from ABX Advanced Biochemical Compounds, Germany. Graphpac-GC 80/100 was purchased from Alltech Associates (Deerfield, IL). All other chemicals, reagents and solvents were purchased from either Sigma-Aldrich (St. Louis, MO) or Fisher Scientific (Pittsburgh, PA). Thin-layer chromatography (TLC) was carried out using plastic backed silica gel plates containing fluorescent indicator and the spots were made visible using UV light. Melting points were determined using an Electrothermal® melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker 400 MHz instrument at NMRFAM, University of Wisconsin, Madison, WI. Chemical shift values are reported using TMS as external standard.

2.2. Preparative HPLC

The preparative HPLC system consisted of a Rainin HPX or a Gilson 302 pump, a Gilson 116 or an Applied Biosystems 785A UV detector and a NaI(Tl) single event radioactivity detector. For preparative HPLC purification of the reaction mixture a Waters XTerra Prep RP18 19 × 100 mm HPLC column (Waters Corporation, Milford, MA) and a mobile phase consisting of ethanol-water-triethylamine (50:50:0.1) at a flow rate of 6 mL/min and UV detection at 254 nm were used. The retention time of **1** was 26.5 min under these conditions.

2.3. Analytical HPLC

The analytical HPLC system consisted of a Shimadzu LC-10AS pump, an Applied Biosystems 785A UV detector and a radioactivity detector. For analysis of the final product to determine specific activity and radiochemical purity, a Waters Xterra MS C18 5 μ 4.6 × 20 mm IS column and a mobile phase consisting of methanol-water-triethylamine 60:40:0.1 at a flow rate of 1 mL/min and UV detection at 220 nm were used.

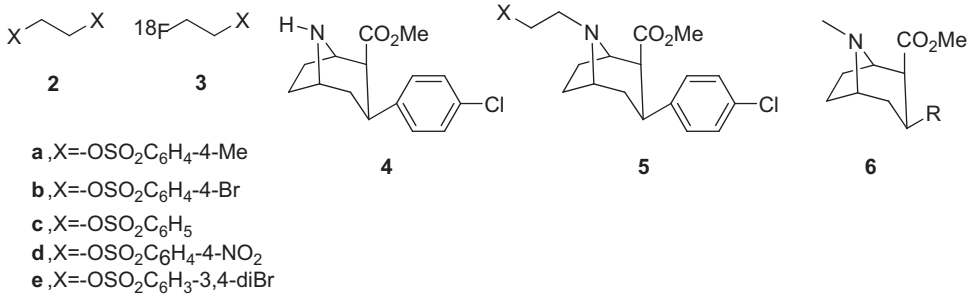


Fig. 2. Previous syntheses of **1**.