



One-step preparation of [¹⁸F]FPBM for PET imaging of serotonin transporter (SERT) in the brain



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ABSTRACT

Serotonin transporters (SERT) in the brain play an important role in normal brain function. Selective serotonin reuptake inhibitors such as fluoxetine, sertraline, paroxetine, escitalopram, etc., specifically target SERT binding in the brain. Development of SERT imaging agents may be useful for studying the function of SERT by in vivo imaging. A one-step preparation of [¹⁸F]FPBM, 2-(2'-(dimethylamino)methyl)-4'-(3-([¹⁸F]fluoropropoxy)phenylthio)benzenamine, for positron emission tomography (PET) imaging of SERT binding in the brain was achieved. An active OTs intermediate, **9**, was reacted with [¹⁸F]F⁻/K₂₂₂ to produce [¹⁸F]FPBM in one step and in high radiochemical yield. This labeling reaction was evaluated and optimized under different temperatures, bases, solvents, and varying amounts of precursor **9**. The radiolabeling reaction led to the desired [¹⁸F]FPBM in one step and the crude product was purified by HPLC purification to give no-carrier-added [¹⁸F]FPBM (radiochemical yield, 24–33%, decay corrected; radiochemical purity >99%). PET imaging studies in normal monkeys (n = 4) showed fast, pronounced uptakes in the midbrain and thalamus, regions known to be rich in SERT binding sites. A displacement experiment with escitalopram (5 mg/kg iv injection at 30 min after [¹⁸F]FPBM injection) showed a rapid and complete reversal of SERT binding, suggesting that binding by [¹⁸F]FPBM was highly specific and reversible. A one-step radiolabeling method coupled with HPLC purification for preparation of [¹⁸F]FPBM was developed. Imaging studies suggest that it is feasible to use this method to prepare [¹⁸F]FPBM for in vivo PET imaging of SERT binding in the brain.

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1. Introduction

The serotonin transporter (SERT) plays a central role in maintaining the balance of the serotonergic system in the brain [1,2]. Changes in serotonin function have been implicated in a variety of psychiatric diseases including major depressive disorder, obsessive–compulsive

Abbreviations: DASB, N,N-dimethyl-2-(2-amino-4-cyanophenylthio)benzyl-amine; (+)-McN5652, trans-1,2,3,5,6,10-β-hexahydro-6-[4-(methylthio)phenyl]-pyrrolo-[2,1-α]isoquinoline]]]; PET, positron emission tomography; SPECT, single photon emission computed tomography; SERT, serotonin transporter; SSRI, selective serotonin reuptake inhibitor; ADAM, 2-(2-((dimethylamino)methyl)-phenylthio)-5-iodo-phenylamine; 4-FADAM, (N,N-dimethyl-2-(2-amino-4-fluorophenylthio)benzyl amine); FPBM, 2-(2'-(dimethylamino)methyl)-4'-(3-fluoropropoxy)phenyl-thio)benzenamine; K₂₂₂, Kryptofix 222.

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disorder (OCD), alcohol dependence, and others [3–7]. This transporter, SERT, is often a target for drug therapy in many psychiatric disorders and drugs — selective serotonin reuptake inhibitors, such as fluoxetine, sertraline, paroxetine, escitalopram, etc., are commonly prescribed anti-depressants. In vivo positron emission tomography (PET) imaging of SERT binding in the brain may be useful as a method for probing pathophysiological and therapeutic mechanisms in various psychological diseases [8–10] such as OCD [11], eating disorders, and addiction [3,4,12].

A number of SERT ligands for in vivo imaging (Fig. 1) have been developed [13–25]. [¹¹C]McN5652 was the first SERT PET imaging tracer used in humans. However, use of this tracer is limited due to high non-specific binding, slow uptake kinetics in SERT-rich brain regions [23,26,27], and being a [¹¹C]tracer. Development of [¹⁸F]FMe-(+)-McN5652, an S-[¹⁸F]fluoromethyl analogue of (+)-McN5652, showed favorable features for SERT imaging with PET in humans [23]. It is also suitable for in vivo quantification of SERT with PET.

Ligands with a core structure of bisphenylthiol also showed promising results as in vivo imaging agents (Fig. 1) [28]. The most commonly used PET SERT imaging agent is [¹¹C]DASB [29,30]. It shows excellent selectivity, high reproducibility, and simple kinetic modeling for

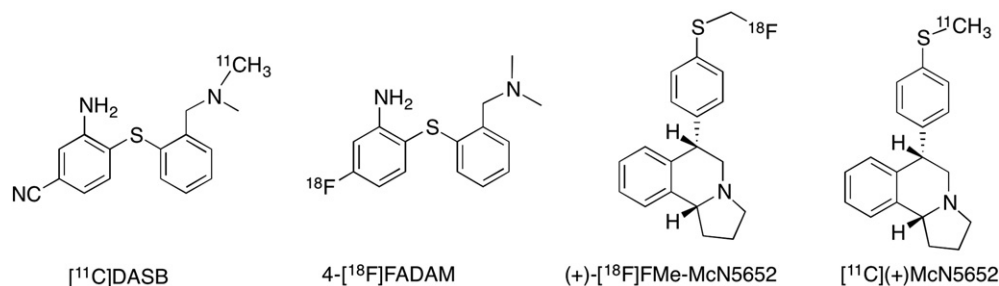


Fig. 1. Chemical structures of known imaging agents for serotonin transporters (SERT) are shown.

quantification [6,31]. A recent report suggests that an altered SERT availability is seen in OCD by $[^{11}\text{C}]\text{DASB}/\text{PET}$, despite treatment with escitalopram [4]. However, $[^{11}\text{C}]\text{DASB}$ is a ^{11}C -labeled radiotracer that is limited by a short physical half-life (20 min), which is unsuitable for widespread clinical application. ^{18}F has a longer half-life (110 min) and can be produced in several curies of activity by a cyclotron. This makes it feasible to radiolabel at a radiopharmacy and distribute the ligand regionally, thus making it available to many hospitals. Additionally ^{18}F has a lower positron energy (0.64 MeV) than ^{11}C (20 min, 0.96 MeV). Due to this low positron energy, ^{18}F has a short positron linear range in tissue, leading to particularly high resolution in PET imaging.

An ^{18}F -labeled SERT imaging agent may be valuable for commercial delivery via radiopharmacies. Significant efforts have been made to develop such ^{18}F -labeled radiotracers for SERT imaging [22,28,32,33]. One promising ^{18}F -labeled ligand is 4- $[^{18}\text{F}]\text{FADAM}$ (*N,N*-dimethyl-2-(2-amino-4- $[^{18}\text{F}]\text{fluorophenylthio})\text{benzyl amine}$) [25,34] (Fig. 1). Results from the first human study of 4- $[^{18}\text{F}]\text{FADAM}$ [25] showed that it is safe and effective for mapping SERT regional binding sites. The regional specific uptake in the human brain correlated well with the known distribution of SERT. The optimal imaging time (about 120 min) was slightly long, but acceptable for routine clinical use. However, there is one less favorable property which may preclude a widespread use of 4- $[^{18}\text{F}]\text{FADAM}$ as a SERT imaging agent: its relatively low and less reliable radiochemical yield. 4- $[^{18}\text{F}]\text{FADAM}$ was originally synthesized from a dinitro precursor, *N,N*-dimethyl-2-(2,4-dinitrophenyl-thio)benzylamine. The radiochemical yield was $5.7 \pm 2.4\%$ (decay corrected). An improved radiochemical precursor for 4- $[^{18}\text{F}]\text{FADAM}$ has been reported in which it was synthesized by nucleophilic aromatic fluorination of the precursor with $\text{K}[^{18}\text{F}]\text{F}^-/\text{K}_{222}$ followed by a reduction of the nitro group with BH_3 . The radiochemical yield for 4- $[^{18}\text{F}]\text{FADAM}$ improved to $14.8 \pm 4.0\%$ (decay corrected) in a synthesis time of 120 min. However, the radiochemical procedure required a reduction reaction with BH_3 , which is problematic when using an automatic synthesizer [35]. An automated synthesis of 4- $[^{18}\text{F}]\text{FADAM}$ without the reduction step was reported from precursor *N,N*-dimethyl-2-(2,4-dinitrophenylthio)benzylamine, however low radiochemical yields were reported ($1.5 \pm 0.3\%$, decay corrected) [25,36]. Taken together, it is evident that the radiochemical yield of preparation of 4- $[^{18}\text{F}]\text{FADAM}$ is too low for routine clinical applications.

An alternative bisphenylthiol derivative, 2-(2'-((dimethylamino)methyl)-4'-(3- $[^{18}\text{F}]\text{fluoropropoxy})\text{-phenylthio})\text{benzenamine}$, $[^{18}\text{F}]\text{FPBM}$, (Scheme 1) with a different substitution on the phenyl ring has been shown to possess high selective binding ($K_i = 0.38 \text{ nM}$), high brain uptake (0.99% dose/g at 2 min post iv injection), and an excellent in vivo target-to-non-target ratio (7.7 at 120 min post injection) [15,37,38]. Previously, the labeling of this diarylsulfide was performed by two different methods: either a nucleophilic fluorination with $\text{K}[^{18}\text{F}]\text{F}/\text{K}_{222}$ via precursor **1**, followed by the reduction of the nitro group to an amine group or via a two-step coupling reaction (Scheme 1A) [39]. The desired product, $[^{18}\text{F}]\text{FPBM}$ was further purified by either high-performance liquid chromatography (HPLC) or solid phase extraction (SPE) (see Scheme 1A). Similar to that of 4- $[^{18}\text{F}]\text{FADAM}$, the whole

procedure took 75–90 min and the radiochemical yield was 9–25% (decay corrected). The reduction reaction was unreliable, and this radiolabeling method suffered from low and variable radiochemical yield. An improved two-step radiolabeling method for $[^{18}\text{F}]\text{FPBM}$, was mentioned earlier (Scheme 1A) [39]. An alternative labeling reaction was tested in which $[^{18}\text{F}]\text{3-fluoropropyltosylate}$, **3**, was employed as an active intermediate. It was reacted with 4-(2-aminophenylthio)-3-((dimethylamino)methyl)phenol, **4**, to produce $[^{18}\text{F}]\text{FPBM}$ (Scheme 1A). The radiochemical yield was 31–39% (decay corrected) and the total preparation time was 70 min. The preparation efficiency has been considerably improved, however the labeling of precursor **4** needed to be pre-activated, treated with strong base (NaH), heated at a high temperature, and then reacted with the radiolabeled building block $[^{18}\text{F}]\text{3-fluoropropyltosylate}$, **3**. This procedure for making $[^{18}\text{F}]\text{FPBM}$ is also difficult to perform in an automatic synthesizer, and a connection to the problem encountered for 4- $[^{18}\text{F}]\text{FADAM}$ regarding automation can be made [25,35,36].

Reported herein, is an improved one-step radiolabeling method for the preparation of $[^{18}\text{F}]\text{FPBM}$ using a different precursor (OT's precursor **9**, see Scheme 1B). The desired $[^{18}\text{F}]\text{FPBM}$ was purified by HPLC to remove the pseudo-carrier, **10**. The resulting “no-carrier added” $[^{18}\text{F}]\text{FPBM}$ was tested in PET imaging studies in normal cynomolgus monkey brains.

2. Materials and methods

All reagents were commercial products and were used without further purification unless indicated. Solid-phase extraction cartridges (Oasis HLB 3 cm³ cartridge, light QMA cartridge) were obtained from Waters (Milford, MA, USA). Thin-layer chromatography (TLC) was run on pre-coated plates of silica gel 60F254. Proton and carbon nuclear magnetic resonance (NMR) spectra were recorded on a Bruker DPX-200 spectrometer and are reported in parts per million (ppm) from the residual solvent peak (CDCl_3). High-resolution mass spectrometry (HRMS) was measured on Agilent (liquid chromatography/mass selective detector with time of flight) mass spectrometry. Microwave reactions were performed on a Biotage Initiator microwave reactor. High performance liquid chromatography was performed on an Agilent 1200 series system with a reverse phase column (C18 reverse phase, Phenomenex).

Four healthy cynomolgus monkeys were employed for PET imaging studies. The animal protocol was approved and certified by Wincon Theracells Biotechnologies Co., Ltd. Nanning, China, which is certified by and meets the standards of care guidelines of the Council on Accreditation of the Association for Assessment and Accreditation of Laboratory Animals Care (AAALAC) (protocol no. W00103).

2.1. Chemical synthesis

Comparison of previously reported two-step labeling (A) and the new one-step labeling reaction (B) are described in Scheme 1. Synthesis of a new precursor, **9**, for the one-step labeling in preparation of $[^{18}\text{F}]\text{FPBM}$ was prepared as outlined in Scheme 1B.

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