Synthesis of 6-[^{18}F]Fluorodopamine, 6-[^{18}F]Fluoro-*m*-Tyramine and 4-[^{18}F]Fluoro-*m*-Tyramine+

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Summary

A new method for the preparation of 6-[^{18}F]fluorodopamine (**3**) and [^{18}F]fluorinated analogs of *m*-tyramine based on a regioselective radiofluorodestannylation reaction has been developed. The radiofluorodestannylation of 6-trimethylstannyldopamine derivative **1** was carried out with [^{18}F]F_2 to give the corresponding [^{18}F]fluoro intermediate **2**. Acid deprotection of **2** with 48% HBr followed by HPLC purification afforded 6-[^{18}F]fluorodopamine (**3**) in 18% radiochemical yield. Similarly, 6- and 4-[^{18}F]fluoro-*m*-tyramines (**6a** and **6b**) were prepared from their corresponding trimethylstannyl-*m*-tyramine derivatives in 25 and 8% radiochemical yields, respectively. In all cases, after HPLC purification of the final products, tin concentrations were found to be <15 ppb.

Key words: 6-[^{18}F]fluorodopamine, 6-[^{18}F]fluoro-*m*-tyramine, 4-[^{18}F]fluoro-*m*-tyramine, fluorine-18, fluorodestannylation, PET

Introduction

6-Fluorodopamine, an analog of the neurotransmitter dopamine, has been reported to follow the biochemical pathways of dopamine in peripheral tissues (1). This has been the impetus for the synthesis of 6-[^{18}F]fluorodopamine (6-FDA, **3**) as a potential positron emission tomography (PET) tracer for

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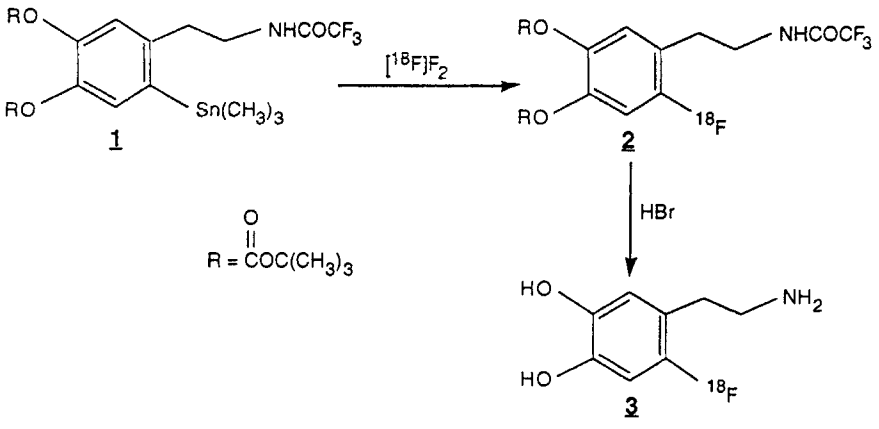
investigating the sympathetic nervous function *in vivo* (2). For example, similar to dopamine, 6-FDA is converted into 6-[^{18}F]fluoronorepinephrine in the adrenergic nerve terminals by the enzyme dopamine β-hydroxylase. This conversion probably reflects the turnover rate of endogenous norepinephrine. The initial synthesis of 6-FDA was achieved by the decarboxylation of 6-[^{18}F]fluoro-*L*-dopa using the enzyme aromatic amino acid decarboxylase (4). Unfortunately, this method as reported provides only modest yields of 6-FDA. The direct fluorination of dopamine in liquified HF provided an alternative for the preparation of 6-fluorodopamine. In this case a mixture of 2- and 6- fluoro regioisomers is produced, which requires a very careful HPLC separation (5). On the other hand, a regioselective synthesis based on the fluorodemercuration reaction has been recently described (6). However, the fluorodemercuration reaction, in general, is amenable only with acetyl hypofluorite as the fluorinating agent (7).

In contrast, the fluorodestannylation of arylstannanes is a more versatile reaction from the stand point of higher yields and the nature of the fluorinating agents that could be used (8,9). Recently, the syntheses of 6-[^{18}F]fluoro-*L*-dopa (10) and [^{18}F]fluoro-*m*-tyrosines (11) based on the fluorodestannylation reaction have been disclosed. Described herein is a high yield synthesis of 6-FDA from the aryltin derivative **1**. A similar reaction methodology is also extended with ease to synthesis of 6-[^{18}F]fluoro-*m*-tyramine (6-FMA, **6a**) and 4-[^{18}F]fluoro-*m*-tyramine (4-FMA, **6b**), potential peripheral dopamine probes. The fluorotyramines are biochemically interesting analogs of dopamine in that they retain the structural necessities (an ethylamine moiety *meta* to a phenolic function) for the dopamine agonistic activity while conspicuously differing in not being substrates for the enzyme catechol-O-methyltransferase (12).

Results and Discussion

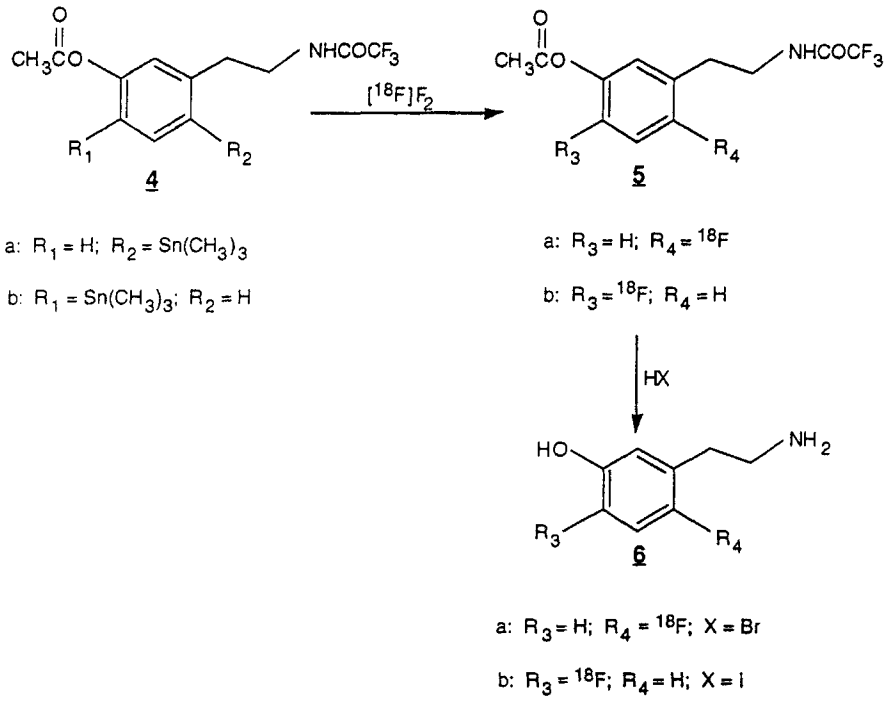
The synthetic approach to 6-FDA is depicted in Scheme 1. The precursor N-(trifluoroacetyl)-3,4-di-t-butoxycarbonyloxy-6-(trimethylstannyl)phenylethylamine (**1**) was prepared starting from the commercially available β-(3,4-dimethoxyphenyl)ethylamine (13). The radiofluorodestannylation of **1** with



Scheme 1. Synthesis of 6-[^{18}F]fluorodopamines (3).

[^{18}F]F_2 at room temperature gave the corresponding 6-[^{18}F]fluoro derivative 2 which upon hydrolysis with 48% HBr and subsequent semi-preparative HPLC purification yielded 6-[^{18}F]fluorodopamine (3). The products 2 and 3, after ^{18}F decay, were analyzed by ^{1}H and ^{19}F NMR and found to be consistent with the assigned structures.

6-[^{18}F]Fluoro-*m*-tyramine (6a) and 4-[^{18}F]fluoro-*m*-tyramine (6b) were regioselectively prepared according to Scheme 2. In this regard, the present method is superior to the direct fluorination of *m*-tyramine with [^{18}F]F_2 which yields a mixture of ring fluorinated derivatives along with unidentified fluorinated products (14). The tin precursors 4a and 4b were prepared starting from (3-methoxyphenyl)acetonitrile (13). The fluorodestannylation of 4a and 4b with [^{18}F]F_2 yielded the [^{18}F]fluoro intermediates 5a and 5b which were purified by silica column chromatography (see Experimental). A careful fractionation of the silica column effluent was required to get pure 5b without the contamination of the starting material 4b. Failure to do so resulted in the contamination of the final product 4-[^{18}F]fluoro-*m*-tyramine (6b) by *m*-tyramine. The [^{18}F]fluoro derivatives 5a and 5b were smoothly hydrolyzed with HBr and HI, respectively, to yield the [^{18}F]fluorotyramines 6a and 6b. The relatively lower radiochemical yield obtained in the case of 6b (Table 1) is probably due to the presence of the



Scheme 2. Synthesis of 6- and 4-[^{18}F]fluoro-*m*-tyramines (6a and 6b).

electron withdrawing acetyl group at C-4 in 4b which deactivates the reaction center, and thereby decreases the efficiency of the electrophilic fluorodestannylation reaction. Analogous results have been reported for the fluorodestannylation reaction of simple arylstannyl derivatives substituted with electron withdrawing groups (9). However, replacement of the acetyl group in 4b with electron donating alkyl groups compromised the regioselectivity of the fluorination reaction (15).

The specific activity of the [^{18}F]fluoroamines 3, 6a and 6b ranged between 2 and 6 Ci/mmol at the end of the synthesis (EOS). While 6-[^{18}F]fluorodopamine with specific activities 1,000 - 2,500 Ci/mmol (EOS) (16) is more desirable for in vivo applications, 6-FDA with a mean specific activity of 0.25 Ci/mmol (an order of magnitude less than that obtained in this study) has been successfully used in human PET investigations (17). Thus, the [^{18}F]fluorophenylethylamines

prepared via the methodology described in this paper are anticipated to be useful for in vivo utilization.

Experimental

General

The preparations of 6-FDA (3), 6-FMA (6a) and 4-FMA (6b) were carried out with a remote semi-automated system similar to that previously described for the synthesis of 6-[^{18}F]fluoro-*L*-dopa (18). The ^{1}H (360.14 MHz) and ^{19}F (338.87 MHz) NMR spectra in D_2O were recorded on a Bruker AM-360 WB spectrometer. The concentration of tin in the final products was determined by the inductively coupled plasma (ICP) analysis using an Applied Research Laboratories 1.5 m grating spectrometer (detection limit: 7 ppb). The semi-preparative HPLC purifications were carried out on a Beckman 110 system equipped with an Alltech Econosil C-18 column (5 μ; 1 cm x 50 cm; mobile phase: 55% 100 mM ammonium acetate/acetic acid, pH = 4.6 and 45% methanol; flow rate: 2.5 mL/min). The chemical and radiochemical purities of the final preparations were determined with an analytical HPLC system equipped with a Waters μBondapak C-18 column (5 μ; 0.46 cm x 30 cm; eluent: 84% 80 mM NaH_2PO_4, 1.85 mM octanesulfonic acid sodium salt, 0.08 mM EDTA and 16% methanol, pH = 3.5; flow rate: 0.9 mL/min; uv: 282 nm and radioactivity detection). The final products were tested for sterility and pyrogenicity using standard procedures and found to be sterile and pyrogen-free.

General Procedure for the Synthesis of the Trimethylstannyl Derivatives 1 and 4

The details of the synthesis and characterization of the tin precursors 1 and 4 have been communicated (13). A brief description of the preparation of the tin derivatives is as follows: appropriately protected dopamine and *m*-tyramine derivatives were iodinated by acetyl hypoiodite or iodine/thallium acetate to give the corresponding iodo analogs. An oxidative coupling reaction of the iodo

derivatives with hexamethylditin, as previously utilized for the synthesis of stannyl precursors of amino acids (10, 11), gave the tin analogs **1** and **4** in good yields.

Synthesis of 6-[^{18}F]Fluorodopamine (3)

The [^{18}F]F_2 (100 μmol) produced via ^{20}Ne(d,α)^{18}F or ^{18}O(p,n)^{18}F nuclear reaction in an aluminum target body (19) was bubbled into a solution of the 6-trimethylstannyl derivative (**1**) (58 mg, 95 μmol) in freon-11 (7 mL) at room temperature over a period of 15 min. The solvent was evaporated with a gentle stream of nitrogen at 50°C, the residue dissolved in methylene chloride (5 mL) and transferred onto a chromatography column (1 cm i.d.) packed with $Na_2S_2O_3$ (2.5 cm) and silica gel (10 cm). The column was eluted with 25 mL of hexane-diethyl ether (1:1). Only the effluent containing the radioactivity was collected and the solvents were evaporated to give the [^{18}F]fluoro intermediate **2**. Hydrobromic acid (48%, 2.0 mL) was added to the residue and the reaction mixture was hydrolyzed at 140°C for 20 min. The mixture was cooled (room temperature) partially neutralized with 3N NaOH (1.7 mL) and diluted with 1.3 mL of the preparative HPLC system mobile phase (see above). The solution was filtered through a Millipore Millex-GS filter (0.22 μm) and the filtrate was loaded onto the semi-preparative HPLC column. The radioactive fraction containing the product **3** (retention time: ~13 min) was collected, diluted with 0.3 mL of 1 mM EDTA containing 0.01% ascorbic acid and evaporated to dryness under vacuum. The residue was dissolved in water (USP, 3 mL), made isotonic with NaCl and filtered through a 0.22 μm sterile filter into a multidose vial. The radiochemical yield and the synthesis time are given in Table 1. The radiochemical and chemical purities were determined to be >99% by the analytical HPLC method (retention time for **3**: 5.7 min). The product was also analyzed by NMR spectroscopy after the decay of ^{18}F-isotope. ^{1}H NMR (D_2O/DSS) δ 2.90 (t, 2H, J = 7.0 Hz, benzylic H), 3.20 (t, 2H, J = 7.0 Hz, CH_2N), 6.77 (d, 1H, $J_{H,F}$ = 10.9 Hz, H-5), 6.84 (d, 1H, $J_{H,F}$ = 7.5 Hz, H-2); ^{19}F NMR (D_2O/$CFCl_3$) δ -125.2 (s, proton decoupled). These data are in agreement with the literature values (20). The concentration of tin in the final preparation, as determined by the ICP analysis, was <15 ppb.

Table 1. Radiochemical yields and synthesis times

Fluoroalkylamine	Radiochemical yield[a] (%)	Synthesis time (min)
6-FDA (3)	18	70
6-FMA (6a)	25	70
4-FMA (6b)	8	90

[a] Decay corrected and based on the total amount of $[^{18}F]F_2$ recovered from the target. Theoretical maximum yield in all these reactions is 50%, 50% of the activity is lost with the trimethyltin moiety.

Synthesis of 6- and 4-[^{18}F]Fluoro-*m*-tyramines (6a and 6b)

The above procedure for the synthesis of 3 could also be applied to the preparation of 6a and 6b. $[^{18}F]F_2$ (100 μmol) was bubbled into a solution of the trimethylstannyl derivative 4a or 4b (42 mg, 96 μmol) in freon-11 (7 mL). After evaporation of the solvent, the residue was dissolved in methylene chloride (5 mL) and transferred to a chromatography column (see preparation of 3). The column was eluted with 25 mL of hexane-ether (1:1). In the case of the 4-fluorotyramine 1 mL fractions were collected and only those fractions that contained significant radioactivity were utilized in the subsequent reaction. However, for 6-fluorotyramine the major radioactive fraction was collected similar to 6-fluorodopamine. The fluoro intermediates 5a and 5b were hydrolyzed at 140°C for 20 min with 48% HBr (2.0 mL) and HI (57%, 2.0 mL), respectively. The rest of the procedure was identical to that described for the preparation of 3. Both 4- and 6-[^{18}F]fluoro-*m*-tyramines eluted off the semi-preparative HPLC column with retention times ~14 min. The radiosynthesis times and the isolated radiochemical yields are provided in Table 1. The final products 6a and 6b were found to be >99% radiochemically and chemically pure as determined by analytical HPLC (retention times for 6a and 6b were 6.9 and 7.0 min, respectively). As an example, the analytical HPLC trace (uv and radioactivity) for 6a is shown in Figure 1. The final products were also analyzed

by ^{1}H and ^{19}F NMR spectroscopy and the data were identical to reported values (12,13). The concentrations of tin in the final preparations of **6a** and **6b** were also determined by ICP and found to be <15 ppb.

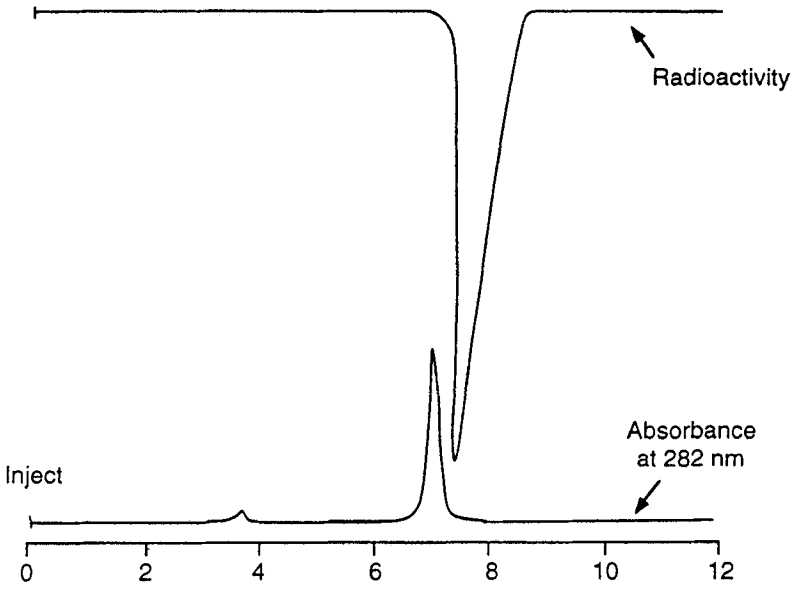


Fig. 1. Typical analytical HPLC profile of **6a**

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