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Automated radiosynthesis of no-carrier-added 4-[^{18}F]fluoroiodobenzene: a versatile building block in ^{18}F radiochemistry

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4-[^{18}F]Fluoroiodobenzene ([^{18}F]FIB) is a versatile building block in ^{18}F radiochemistry used in various transition metal-mediated C–C and C–N cross-coupling reactions and [^{18}F]fluoroarylation reactions. Various synthesis routes have been described for the preparation of [^{18}F]FIB. However, to date, no automated synthesis of [^{18}F]FIB has been reported to allow access to larger amounts of [^{18}F]FIB in high radiochemical and chemical purity. Herein, we describe an automated synthesis of no-carrier-added [^{18}F]FIB on a GE TRACERlab™ FX automated synthesis unit starting from commercially available (4-iodophenyl)diphenylsulfonium triflate as the labelling precursor. [^{18}F]FIB was prepared in high radiochemical yields of 89 ± 10% (decay-corrected, $n = 7$) within 60 min, including HPLC purification. The radiochemical purity exceeded 95%, and specific activity was greater than 40 GBq/μmol. Typically, from an experiment, 6.4 GBq of [^{18}F]FIB could be obtained starting from 10.4 GBq of [^{18}F]fluoride. Copyright © 2013 John Wiley & Sons, Ltd.

Keywords: 4-[^{18}F]fluoroiodobenzene; automation; sulfonium salts; building block

Introduction

The success of positron emission tomography (PET) for functional molecular imaging depends largely on the availability of suitable radiotracers. Recent advancements in radionuclide production,[1] automation of radiotracer synthesis,[2,3] and significant improvement of PET scanner instrumentation,[4–7] including small animal PET scanners,[8] have further stimulated clinical and preclinical research activities focused on the visualization and assessment of biochemical processes in living organisms. However, the design and synthesis of innovative PET radiotracers remain a special challenge, and as such, PET chemistry has evolved into a complex chemical science. Special attention is attributed to radiochemistry with the short-lived positron emitter fluorine-18 (^{18}F, $t_{1/2} = 109.8$ min). The relatively long half-life, the low maximal positron energy (0.635 MeV), and the ease of large scale cyclotron production make ^{18}F an ideal radionuclide for the design and synthesis of PET radiotracers.

The PET chemistry of [^{18}F]fluoride[9] and the applications of ^{18}F-labelled radiotracers[10,11] have been reviewed frequently over the last decades. Within the plethora of ^{18}F-labelled radiotracers, only a few have been prepared by the use of transition metal-mediated cross-coupling reactions. These transition metal-mediated cross-coupling reactions mainly exploited palladium complexes and 4-[^{18}F]fluorohalobenzenes as an electrophilic coupling partners for the preparation of PET radiotracers containing a 4-[^{18}F]fluorophenyl group.

Over the last decades, numerous methods have been reported for the preparation of 4-[^{18}F]fluorohalobenzenes. Methods include hot atom recoil chemistry and direct electrophilic and nucleophilic aromatic radiofluorination chemistry.[12–16] Significant improvements were achieved by using iodonium[17,18] and sulfonium[19] salts as labelling precursors. Moreover, novel technologies like microwave activation and microfluidic devices have also been applied to prepare 4-[^{18}F]fluorohalobenzenes. A comprehensive summary of methods and technologies for the preparation of 4-[^{18}F]fluorohalobenzenes has recently been published.[20] This review also discusses all the advantages and disadvantages for the selections of available precursors for the preparation of 4-[^{18}F]fluorohalobenzenes. Based on the reported radiochemical yields and the availability of starting materials, nucleophilic aromatic radiofluorination reactions using sulfonium salts as labelling precursors seem to be the most promising synthesis route for the preparation of 4-[^{18}F]fluorohalobenzenes. Therefore, we decided to adapt sulfonium salt-based chemistry to an automated synthesis procedure enabling the preparation of large amounts of no-carrier-added (n.c.a.) 4-[^{18}F]fluorohalobenzenes with special focus on 4-[^{18}F]fluoroiodobenzene ([^{18}F]FIB).

Herein, we describe a fully automated synthesis of n.c.a. [^{18}F]FIB on a GE TRACERlab™ FX (General Electric Company, Fairfield, CT, US) automated synthesis unit (ASU) starting from commercially available (4-iodophenyl)diphenylsulfonium triflate as the labelling precursor.

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Experimental

General

All chemicals used were obtained from Sigma-Aldrich® (St. Louis, MO, US) and used as received without further purification. Water was obtained from a Barnstead Nanopure water filtration system (Barnstead Diamond Nanopure pack organic free RO/DIS, Thermo Scientific™ (Waltham, MA, US)).

The HPLC purification and analysis of ^{18}F-radiolabelled products were performed using a Phenomenex (Torrance, CA, US) Luna® C18(2) column (100 Å, 250 × 10 mm, 10 µm) using gradient elution specific to the given compound (Gilson (Middleton, WI, US) 321 pump, 171 diode array detector, Berthold Technologies Herm LC). Radio-thin layer chromatography (TLC) were performed using either EMD Merck (Darmstadt, Germany) F254 silica gel 60 aluminum-backed TLC plates or Analtech (Newark, DE, US) RP18 with UV254 aluminum-backed TLC plates (Bioscan AR-2000 (Washington, DC, US)). Quantification of radioactive samples during chemistry was achieved using a Biodex Atomlab™ 400 dose calibrator (Shirley, NY, US). Reaction parameters were screened using an IKAMAG® Ret-G stir plate (IKA® Works Inc., (Wilmington, NC, US)) with an oil bath.

Preparation of kryptofix 2.2.2. solution

Into a 50 mL volumetric flask, K_2CO_3 (92.3 mg, 668 µmol) in water (7.0 mL) is added. Next, kryptofix 2.2.2. (TCI America, (Portland, OR, US)) (500 mg, 1.38 mmol) is added with CH_3CN (43.0 mL) to the mark of the flask. The solution is then sealed in an amber vial and stored at 4 °C.

Manual synthesis of 4-[^{18}F]fluoroiodobenzene

The n.c.a. [^{18}F]fluoride was produced via the ^{18}O(p,n)^{18}F nuclear reaction from [^{18}O]H_2O (Rotem Industries Ltd (Mishor, Israel), Hyox oxygen-18 enriched water, min. 98%) on an ACSI TR19/9 Cyclotron (Advanced Cyclotron Systems Inc., Richmond, Canada). Cyclotron-produced [^{18}F] fluoride was then trapped on a Waters (Milford, MA, US) Sep-Pak® light QMA anion-exchange cartridge (filled with quaternary ammonium chloride polymer) and eluted off with 86% K(2.2.2.)/K_2CO_3 (1.5 mL) into a long screw top test tube. This solution was then dried azeotropically with additional CH_3CN (6 mL) under nitrogen at 95 °C in an oil bath. Once fully dried, the reaction vessel was allowed to cool for 5 min, the labelling precursor (4-iodophenyl)diphenylsulfonium triflate (7 mg) was added in CH_3CN (1 mL), and the reactor was sealed. The reaction proceeded for 15 min at 85 °C. Upon completion, the reaction mixture was diluted with water (20 mL) and trapped on a Waters Sep-Pak® tC18 plus light cartridge. The solid phase extraction (SPE) cartridge was then washed with additional water (10 mL), and the final product of [^{18}F]FIB was eluted off in CH_3CN (3 mL).

Fully automated synthesis of 4-[^{18}F]fluoroiodobenzene

Radiosynthesis of [^{18}F]FIB was performed on a GE TRACERlab™ FX. This ASU was modified in terms of program and hardware (Figure 1).

Synthetic procedure started with the elution of resin-bound cyclotron-produced [^{18}F]fluoride from the Waters Sep-Pak® light QMA anion-exchange column into reactor 1 (R1) of the GE TRACERlab™ FX using a solution of 86% K(2.2.2.)/K_2CO_3 (1.5 mL). [^{18}F]Fluoride was dried azeotropically under vacuum under a steady stream of nitrogen at 50 and 95 °C. To dried [^{18}F]fluoride, (4-iodophenyl)diphenylsulfonium triflate (V3, 10 mg) in CH_3CN (1 mL) was added and reacted for 15 min at 90 °C. Once the reaction was completed, the mixture was diluted with water (V5, 12 mL) and passed through a Waters Sep-Pak® tC18 plus light cartridge (300 mg). The cartridge was washed with additional water (V6, 10 mL), and [^{18}F]FIB was eluted off in CH_3CN (V4, 3.0 mL) into a 20 mL sealed sterile collection vial with a vent needle.

HLPC purification of 4-[^{18}F]fluoroiodobenzene

The HPLC purification of the crude SPE purified [^{18}F]FIB was performed using a gradient elution as follows: (A: water; B: CH_3CN; 0 min 50% B, 8 min 50% B, 21 min 80% B, 33 min 100% B). The flow rate of the system was 3 mL/min, which gave a retention time of approximately 22 min for the [^{18}F]FIB product as confirmed with the use of a commercially available reference compound. The radiochemical purity was determined by the area under the peak of interest compared with the rest of the radiochromatogram; the specific activity of [^{18}F]FIB was calculated against a standard curve as well.

Results and discussion

Optimization of reaction parameters for manual synthesis of 4-[^{18}F]fluoroiodobenzene

Radiosynthesis of [^{18}F]FIB **2** starting from (4-iodophenyl) diphenylsulfonium triflate **1** is depicted in Figure 2. Manual

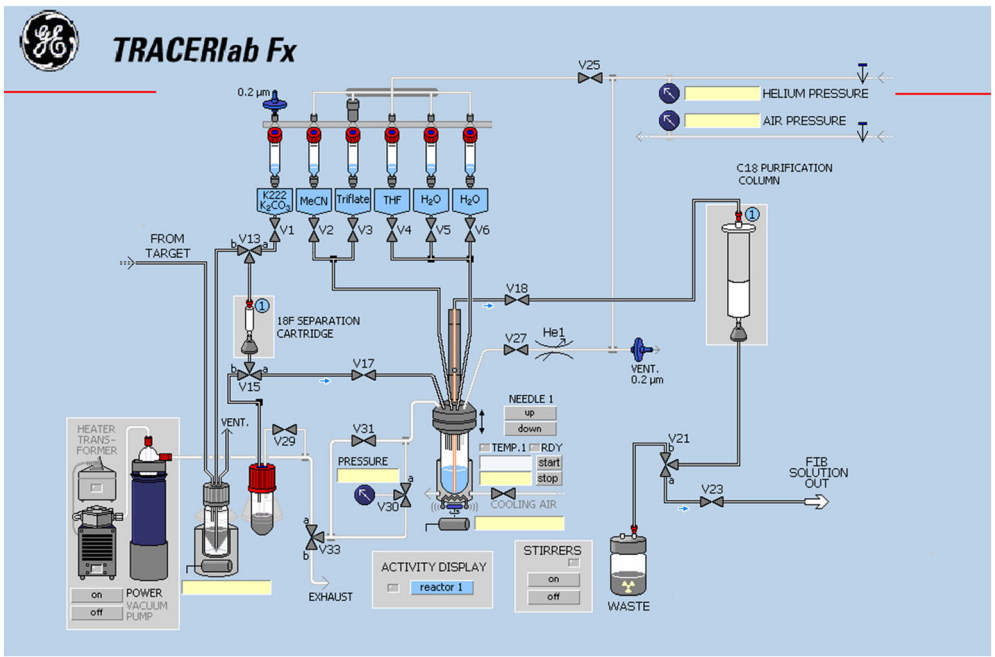

Figure 1. Scheme of the automated synthesis unit for the synthesis of 4-[^{18}F]fluoroiodobenzene.

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Figure 2. Synthetic procedure for the radiosynthesis of 4-[^{18}F]fluoroiodobenzene **2**.

syntheses were performed to optimize reaction conditions by screening various reaction parameters (solvent, temperature, synthesis time, and precursor concentration) and SPE methods aimed at increasing the radiochemical yield and radiochemical purity of [^{18}F]FIB **2** and decreasing the amount of inevitably formed by-product [^{18}F]fluorobenzene **3**.

Influence of solvent on radiosynthesis of 4-[^{18}F]fluoroiodobenzene

Based on the publication of Linjing *et al.*[19] as a general guide, the following solvents were tested for the synthesis of solvents of [^{18}F]FIB: acetonitrile (CH_3CN), toluene, dioxane, *N,N*-dimethylformamide (DMF), and THF. The labelling precursor (4-iodophenyl)diphenylsulfonium triflate **1** was only poorly soluble in toluene, THF and dioxane. Only CH_3CN and DMF proved to be suitable solvents for (4-iodophenyl)diphenylsulfonium triflate **1**. Results of using DMF (Figure 3a/3b) and CH_3CN (Figure 3c/3d) as solvents for the synthesis of [^{18}F]FIB are depicted as respective radio-HPLC and ultraviolet (UV) traces of the reaction mixture (Figure 3). The reaction in both solvents proceeded with a comparable 40% radiochemical yield. However, radiochemical purity of [^{18}F]FIB in the reaction mixture was higher in CH_3CN (91%) compared with that of using DMF as the solvent (70%).

Also, the UV traces as determined by HPLC (displayed in the right panels) clearly demonstrate that there are more possible contaminants pushed near the retention time of the peak of interest in DMF as the solvent versus CH_3CN. Overall, CH_3CN was chosen to be the solvent of choice, and it was used in all further experiments.

Influence of temperature on radiosynthesis of 4-[^{18}F]fluoroiodobenzene

The reaction between (4-iodophenyl)diphenylsulfonium triflate **1** and n.c.a. [^{18}F]fluoride requires elevated temperatures. However, at an elevated temperature, significant amounts of nonradioactive by-products were present in the reaction mixture. Careful testing of reaction temperature on the radiochemical yield and formation of nonradioactive by-products is necessary. Various reaction temperatures were tested to determine their influence on radiochemical yield and the formation of nonradioactive

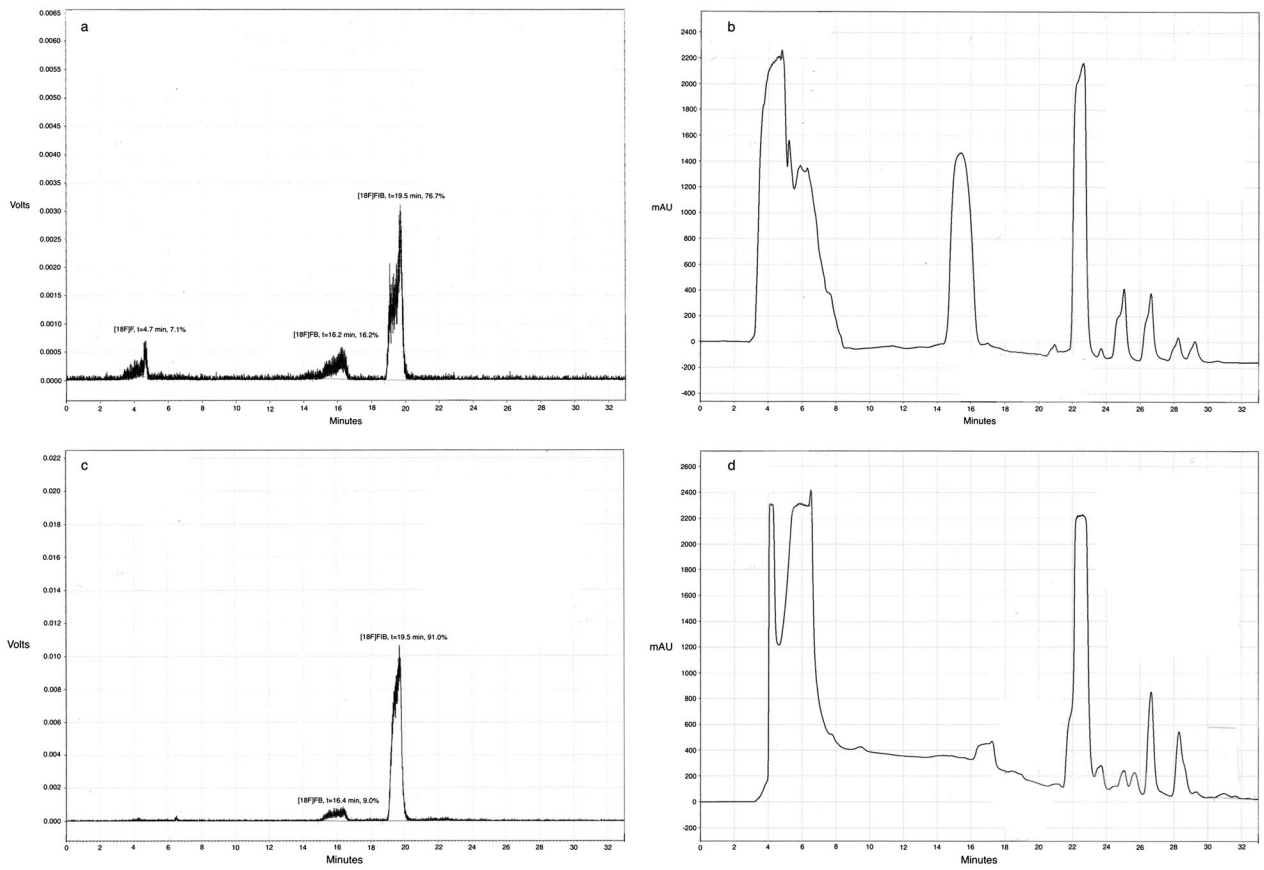

Figure 3. (a–d) Comparison of *N,N*-dimethylformamide and CH_3CN as solvents for the radiolabelling of (4-iodophenyl)diphenylsulfonium triflate **1** with no-carrier-added [^{18}F]fluoride.

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by-products as represented by their respective HPLC profiles. The results are summarized in Figure 4a.

Reaction temperature of 70 °C resulted in only low radiochemical yields of 1–2%. Radiochemical yields increased significantly at elevated temperatures of 85 (61%) to 120 °C (44%). However, only the reaction temperature of 85 °C gave sufficient radiochemical yields while showing low amount of nonradioactive by-products in the UV trace of the HPLC trace. Therefore, a reaction temperature of 85 °C was used for further optimization of reaction conditions.

Influence of reaction time on radiosynthesis of 4-[^{18}F]fluoroiodobenzene

All reactions were performed at 85 °C using different reaction times varying from 5 to 30 min. At each time point, aliquots of the reaction mixture were taken and analyzed via radio-TLC with 50% EtOAc/hexane as the solvent to develop TLC plates. As shown in Figure 4b, no significant improvement of radiochemical yield was observed at reaction times longer than 15 min.

Influence of labelling precursor amount on radiosynthesis of 4-[^{18}F] fluoroiodobenzene

After the optimization of reaction temperature, solvent, and reaction time, the needed amount of the labelling precursor **1** was tested using the reaction conditions of 85 °C in CH_3CN for 15 min. Progress of the reaction was monitored using radio-TLC. Results are summarized in Figure 4c.

Results in Figure 4c indicate that 5 to 7 mg of the labelling precursor **1** provided sufficient radiochemical yields of [^{18}F]FIB (50–59%). Further increases in the mass of sulfonium salt **1** did not result in significantly higher radiochemical yields. To reduce the amount of potential cold contaminations in the reaction mixture, a labelling precursor amount of 5–7 mg seems to be optimal.

Influence of solid phase extraction cartridges on radiosynthesis of 4-[^{18}F]fluoroiodobenzene

Four different SPE cartridges were tested for their ability to retain and purify [^{18}F]FIB. SPE cartridges tested included Mackerey-Nagel (Düren, Germany) Chromafix® HR-P (M), Phenomenex Strata® C18-U (500 mg), Waters Sep-Pak® tC18 plus light, and Waters Sep-Pak® C18 plus light.

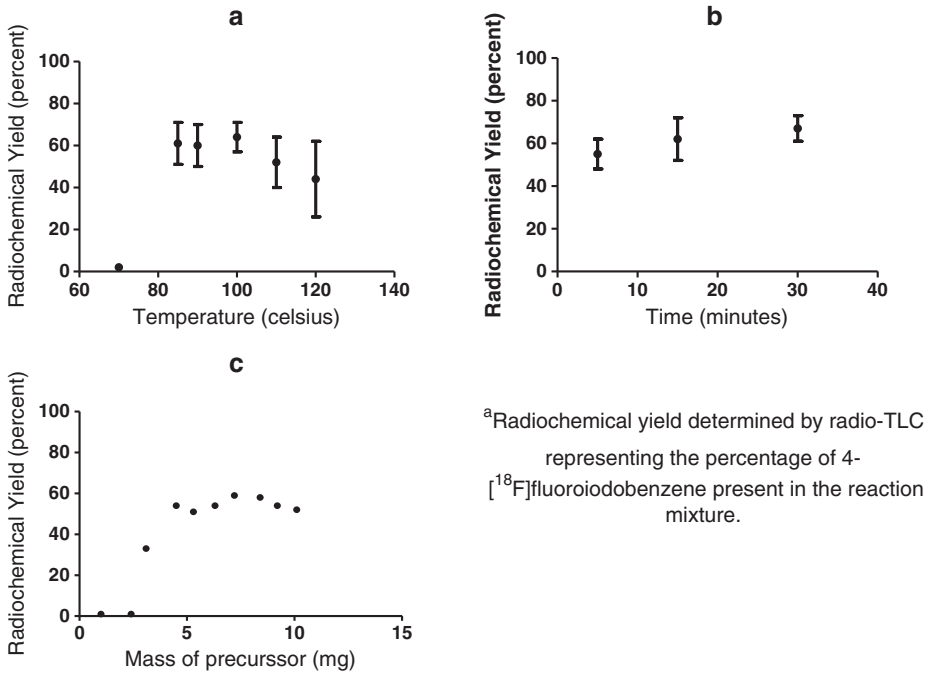
All cartridges gave comparable results, and we decided to use Waters Sep-Pak® tC18 plus light cartridges for further experiments.

Summary of optimized reaction parameters for the manual synthesis of 4-[^{18}F]fluoroiodobenzene

Optimal reaction conditions resulted in the following manual radiosynthesis of [^{18}F]FIB. Radiosynthesis of [^{18}F]FIB was performed using (4-iodophenyl)diphenylsulfonium triflate as the labelling precursor (7 mg) in CH_3CN (1 mL) at a temperature of 85 °C for 15 min. Application of these reaction conditions afforded [^{18}F]FIB in 41 ± 9% decay-corrected radiochemical yields after SPE and HPLC purification within a total synthesis time of over a 64 ± 4 min (n = 17). Radiochemical purity was greater than 99%. In a typical experiment, 235 MBq of [^{18}F]FIB was prepared starting from 850 MBq of n.c.a. [^{18}F]fluoride. These optimized reaction parameters are very similar to that of Linjing *et al.*[16] and provide confirmation that [^{18}F]FIB can be produced selectively and sufficiently over [^{18}F]fluorobenzene as by-product. Moreover, application of HPLC purification afforded [^{18}F]FIB in high radiochemical and chemical purity suitable for subsequent reactions like transition metal-mediated cross-coupling reactions.

Automated synthesis of 4-[^{18}F]fluoroiodobenzene

Reaction conditions from optimized manual synthesis were directly transferred to the GE TRACERlab FX fully ASU. Radiosynthesis of



[a]Radiochemical yield determined by radio-TLC representing the percentage of 4-[^{18}F]fluoroiodobenzene present in the reaction mixture.

Figure 4. (a–c) Influence of reaction temperature (n = 3), reaction time (n = 3), and concentration of labelling precursor **1** (n = 1) on radiochemical yield[a] of 4-[^{18}F] fluoroiodobenzene.

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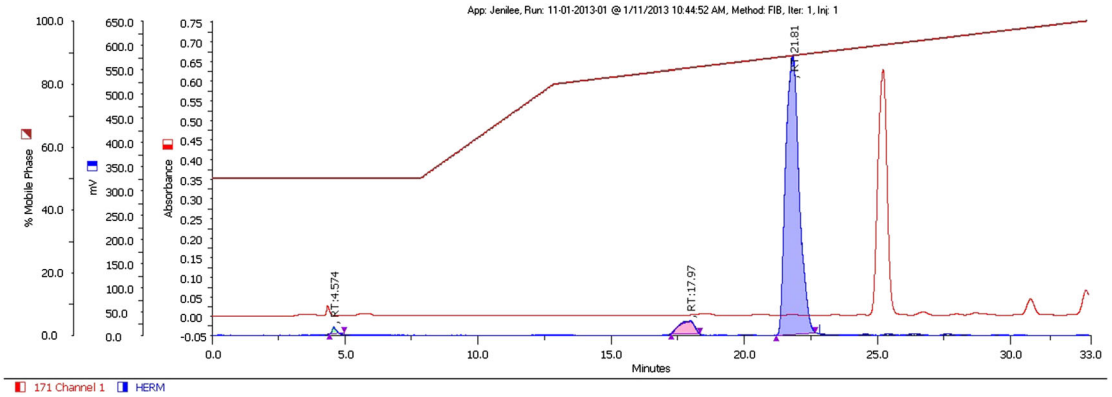

Figure 5. HPLC trace of reaction mixture of 4-[^{18}F]fluoroiodobenzene synthesis in an automated synthesis unit. This figure is available in colour online at wileyonlinelibrary.com/journal/jlcr

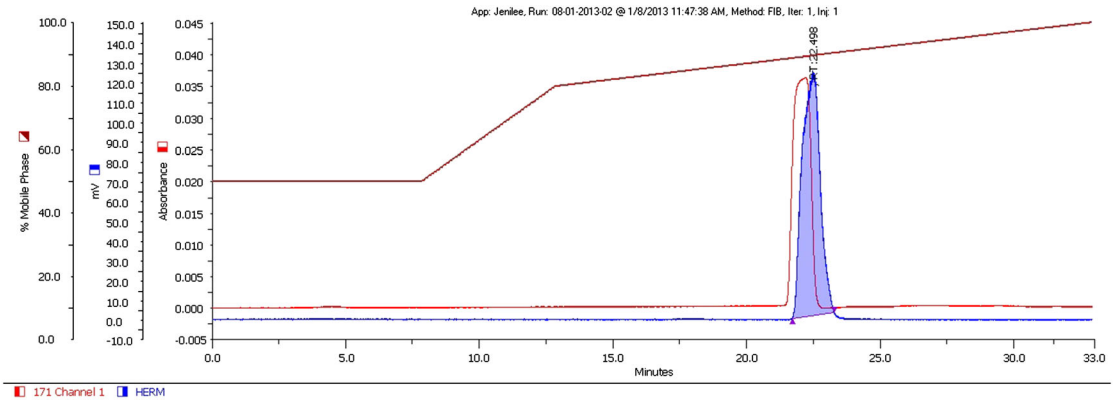

Figure 6. HPLC purified 4-[^{18}F]fluoroiodobenzene with co-injection of [^{19}F]fluoroiodobenzene. This figure is available in colour online at wileyonlinelibrarycom/journal/jlcr

[^{18}F]FIB in the ASU gave comparable results as found for the manual synthesis. The reaction temperature was slightly increased to 90 °C because larger amounts of nonreacted [^{18}F]fluoride were found in the reaction mixture, when a reaction temperature of 85 °C was applied. In summary, the ASU synthesis provided [^{18}F]FIB in decay-corrected radiochemical yields of 89 ± 10% (n = 7) within a reaction time of 59 ± 2 min including HPLC purification. Radiochemical purity was 97 ± 3%. Specific activity of [^{18}F]FIB was greater than 40 GBq/μmol. In a typical ASU synthesis, 6.4 GBq of [^{18}F]FIB could be prepared from 10.4 GBq of n.c.a. [^{18}F]fluoride.

HPLC purification of 4-[^{18}F]fluoroiodobenzene

Purification was completed as described in the experimental section, eluting [^{18}F]FIB at 22 min as shown in Figure 5. Co-injection with cold reference compound as displayed in Figure 6 confirmed the identity of [^{18}F]FIB.

Conclusions

A fully automated synthesis for the production of [^{18}F]FIB has been developed from a commercially available precursor material. Automated synthesis resulted in reliable, very high radiochemical yields of [^{18}F]FIB within 60 min including HPLC purification. HPLC purification of [^{18}F]FIB was also fully optimized to allow for the synthesis of highly radiochemically and chemically pure radiotracer. Application of ASU-based synthesis of [^{18}F]FIB provides large quantities of this ^{18}F-building block suitable for a broad variety of different buildup syntheses, including transition metal-mediated cross-coupling reactions.

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Conflict of Interest

The authors did not report any conflict of interest.

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