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Technical note

# Automated electrophilic radiosynthesis of [$^{18}$F]FBPA using a modified nucleophilic GE TRACERlab FX$_{FDG}$

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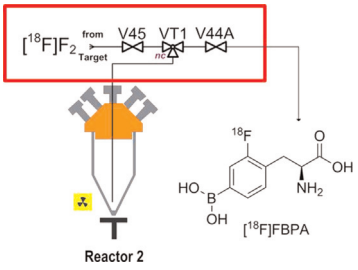
## HIGHLIGHTS

- Automated synthesis of [$^{18}$F]FBPA was developed *via* reaction of BPA with [$^{18}$F]$F_2$.
- [$^{18}$F]FBPA was obtained with a RCY of 8.5 ± 2.0%.
- Nucleophilic synthesis module was adapted for electrophilic [$^{18}$F]fluorinations.
- Modified synthesis module may also enable other electrophilic [$^{18}$F] fluorinations.

## GRAPHICAL ABSTRACT

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## ABSTRACT

We modified a commercially available synthesis module for nucleophilic [$^{18}$F]fluorinations (TRACERlab™ FX$_{FDG}$, GE Healthcare) to enable the reliable synthesis of 2-[$^{18}$F]fluoro-4-borono-L-phenylalanine ([$^{18}$F]FBPA) *via* direct electrophilic substitution of 4-borono-L-phenylalanine with [$^{18}$F]$F_2$ gas. [$^{18}$F]FBPA was obtained with a RCY of 8.5 ± 2.0% and a radiochemical purity of 98 ± 1% in a total synthesis time of 72 ± 7 min ($n$=22). The modified synthesis module might also be useful for the synthesis of other [$^{18}$F]radiopharmaceuticals *via* electrophilic substitution reactions while still being suitable for nucleophilic substitution reactions.



## 1. Introduction

Boron neutron capture therapy (BNCT) is a form of radiotherapy for treatment of malignant tumors (Barth et al., 2005). The patient is injected with a tumor targeting drug containing the boron isotope boron-10 ($^{10}$B) followed by external neutron irradiation, resulting in nuclear capture reactions. This produces secondary particles of high energy and short range that kill malignant cells. The efficacy of this approach critically depends on the amount of $^{10}$B delivered *in vivo* to malignant cells relative to normal cells through appropriate boron carriers. The most commonly used $^{10}$B carrier in BNCT is $^{10}$B-enriched 4-borono-L-phenylalanine (BPA). The fluorine-18-($^{18}$F) labelled analogue of BPA, 2-[$^{18}$F]fluoro-4-borono-L-phenylalanine ([$^{18}$F]FBPA), can be used as surrogate marker to predict the biodistribution and kinetics of BPA in tumor and non-tumor tissue by non-invasive positron emission tomography (PET) imaging (Imahori et al., 1998a, b).

[$^{18}$F]FBPA is synthesized by direct electrophilic fluorination of BPA (Ishiwata et al., 1991; Vähätalo et al., 2002). Due to the high

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reactivity of $[^{18}F]F_2$, radiosyntheses based on electrophilic $[^{18}F]$fluorinations normally require the availability of dedicated automated synthesis modules. In this work we report a simple and straightforward procedure to adapt a commercially available nucleophilic synthesis module (TRACERlab™ $FX_{FDG}$, General Electric Healthcare, Uppsala, Sweden) to the synthesis of [$^{18}$F]FBPA *via* electrophilic $[^{18}F]$fluorination.

## 2. Materials and methods

### 2.1. General

All chemicals were purchased from Sigma-Aldrich Handels GmbH (Vienna, Austria) and used without further purification. Unlabelled FBPA reference standard was purchased from FluoroTech, LLC (Gainesville, FL, USA). $[^{18}F]F_2$ was produced using a PETtrace cyclotron (GE Healthcare) *via* the $^{18}O(p,n)^{18}F$ reaction with a two shot method by irradiation of a gas target containing highly enriched $[^{18}O]O_2$ gas for first bombardment with a 16.5 MeV proton beam (Nickles et al., 1984; Solin and Bergman, 1986). After evaporation of the target gas the adherent $[^{18}F]F_2$ was released by a second bombardment using an argon/helium gas mixture containing 0.3% $[^{19}F]F_2$.

Radiochemical purity and specific activity of [$^{18}$F]FBPA were determined with analytical high-performance liquid chromatography (HPLC) using an Agilent 1200 system (Agilent Technologies Österreich GmbH, Vienna Austria) consisting of a quaternary pump, an auto-sampler and a column oven. Ultraviolet (UV) absorption was detected with an Agilent 1200 diode array detector at a wavelength of 225 nm in series with a Raytest "Gabi Star" detector (raytest Isotopenmessgeraete GmbH, Straubenhardt, Germany) for radioactivity detection. An Eclipse XDB C18 column (150 × 4.6 mm, 5 μm, Agilent Technologies Österreich GmbH, Vienna Austria), heated to 40 °C, was isocratically eluted with a 70/30 (v/v) mixture of aqueous (aq.) 0.1% (v/v) acetic acid containing 1 mM sodium dodecyl sulfate and 1 mM ethylenediaminetetraacetic acid disodiumsalt dehydrate, and methanol at a flow rate of 2 mL/min. Osmolality (mosmol/kg) of formulated [$^{18}$F]FBPA solution was measured using a Wescor Vapro 5520 Pressure Osmometer (Wescor Inc., Logan, USA). The pH value was determined with a pH-Meter Inolab pH720 (WTW Wissenschaftlich-Technische Werkstätten GmbH, Weilheim, Germany).

### 2.2. Automated synthesis of [$^{18}$F]FBPA

Radiosynthesis of [$^{18}$F]FBPA was performed as a one-step one-pot reaction (Fig. 1) in a dual-reactor TRACERlab™ $FX_{FDG}$ synthesis module (GE Healthcare). This synthesis module originally contained two independent synthesis units in a single housing and was designed to operate two consecutive [$^{18}$F]FDG syntheses without reloading and opening the hot cell. Our synthesis module was custom-modified by the manufacturer to enable two-pot nucleophilic [$^{18}$F]fluorinations (Fig. 2). In this work we further modified the synthesis module to enable electrophilic [$^{18}$F]fluorinations (Fig. 2).

Prior to start of synthesis reactor 2 (borosilicate glass, 15 mL) was loaded with 4-borono-L-phenylalanine hydrochloride (BPA, 40 mg, 191 μmol in 2 mL trifluoroacetic acid) and storage vial 7 was loaded with aq. acetic acid (0.1%, v/v, 3 mL). After end of bombardment $[^{18}F]F_2$ was bubbled for 2 min at room temperature at a flow rate of 12 mL/min through the radiolabelling precursor solution in reactor 2. After delivery of $[^{18}F]F_2$ had been completed, the reaction solution was dried under vacuum (85 °C, 5 min) and then re-dissolved in aq. 0.1% acetic acid (3 mL) added from storage vial 7, and cooled to room temperature. The solution was then injected into the built-in HPLC system. A semipreparative HPLC column (YMC-Pack ODS-A, 150 × 20 mm, YMC Europe GmbH, Dinslaken, Germany) equipped with a Nucleosil® C18 pre-column (10 × 10 mm, MACHEREY-NAGEL GmbH & Co. KG, Düren, Germany) was isocratically eluted with 0.1% aq. acetic acid at a flow rate of 5 mL/min. The HPLC eluate was monitored in series for radioactivity and UV absorption at a wavelength of 220 nm. [$^{18}$F]FBPA and radiolabelling precursor BPA eluted with retention times of approximately 33 min and 25 min, respectively (Fig. 3). The fraction containing [$^{18}$F]FBPA was collected. After evaporation of the HPLC solvent, [$^{18}$F]FBPA was formulated for intravenous injection into rodents by adding aq. saline solution (0.9%, w/v).

## 3. Results and discussion

[$^{18}$F]FBPA was synthesized by direct electrophilic $[^{18}F]$fluorination of commercially available BPA with $[^{18}F]F_2$ gas (Fig. 1) as described in the literature (Ishiwata et al., 1991; Vähätalo et al., 2002). We produced $[^{18}F]F_2$ gas by using the $^{18}O(p,n)^{18}F$ reaction from enriched $[^{18}O]O_2$ gas, which gives higher specific activities of $[^{18}F]F_2$ as compared with the $^{20}Ne(d,\alpha)^{18}F$ reaction on a neon/$F_2$ gas mixture (Nickles et al., 1984; Solin and Bergman, 1986). For the automated synthesis of [$^{18}$F]FBPA we used a custom-modified commercially available automated synthesis module for nucleophilic $[^{18}F]$fluorinations (TRACERlab™ $FX_{FDG}$, GE Healthcare), which is similar to the TRACERlab™ $FX_N$ synthesis module, which has been shown to be a versatile synthesis platform for the production of a range of different $^{18}$F-labelled radiopharmaceuticals (Shao et al., 2011). The nucleophilic synthesis module contains two reactors (reactor 1 and 2, Fig. 2) to enable two-pot nucleophilic $[^{18}F]$fluorinations. In order to support electrophilic $[^{18}F]$fluorinations we modified reactor 2 by directly connecting a stainless steel line from the cyclotron target for delivery of $[^{18}F]F_2$ into reactor 2 (Fig. 2). In the target delivery line an additional 2/2 solenoid valve (V45) was placed in order to prevent recoil of liquid into the tubing, since reaction of $F_2$ gas with moisture may lead to the formation of hydrofluoric acid, which can result in an unwanted surface enhancement in the target delivery line. Moreover a 3/2 way valve (VT1) was placed in line, configured normally closed to V45 (Fig. 2). Activating valve VT1 delivers $[^{18}F]F_2$ into the reactor. All tubings of the synthesis module except for the polyether ether ketone (PEEK) reactor needle were made of ethylene tetrafluoroethylene (ETFE) capillaries (OD 1/16″ and ID

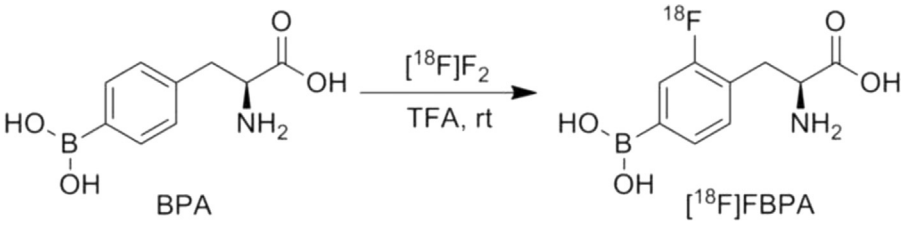


**Fig. 1.** Reaction scheme for the synthesis of [$^{18}$F]FBPA.