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Automated synthesis of n.c.a. [^{18}F]FDOPA via nucleophilic aromatic substitution with [^{18}F]fluoride

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ABSTRACT

An improved, automated synthesis of [^{18}F]FDOPA including four synthetic steps (fluorination, reductive iodination, alkylation and hydrolysis) is reported with each step optimized individually. In a home-made automatic synthesizer, 9064 ± 3076 MBq of [^{18}F]FDOPA were produced within 120 min from EOB ($n = 5$). Radiochemical purity and enantiomeric excess were both ⩾95%. Specific activity was ca. 50 GBq/μmol at EOS. This automatically operable synthesis is well suited for the multi-patient-dose routine production of n.c.a. [^{18}F]FDOPA.

1. Introduction

[^{18}F]FDOPA is a well accepted and applied radiotracer especially for the evaluation of the presynaptic dopaminergic function by means of PET (Seibyl et al., 2007). The labeling of [^{18}F]FDOPA can be accomplished either by electrophilic or nucleophilic substitution. In most cases, the routine production of [^{18}F]FDOPA is still realized by electrophilic methods (Fuechtner et al., 2002; Dollé et al., 1998). However, low yields of [^{18}F]F_2 produced at the cyclotron using the ^{20}Ne(d,α)^{18}F nuclear reaction or at least the need of a dedicated gas target using the ^{18}O(p,n)^{18}F reaction make a synthetic route via a nucleophilic mechanism with [^{18}F]fluoride highly attractive. In addition, only in the latter case high specific activities can be achieved. Since 1990s, several approaches employing the nucleophilic method have been reported (Reddy et al., 1993; Kaneko et al., 1999; Tierling, 2002; Krasikova et al., 2004). The strategy of Lemaire et al. (2004) seems the most promising for routine production of [^{18}F]FDOPA, as disadvantages for a remote operation, i.e. low temperature and chiral preparative HPLC separation, can be avoided. Moreover, the product is provided in high specific activities and enantiomeric excess. Therefore, the synthesis described in this paper was developed based on this method. In order to realize a reliable large-scale production of [^{18}F]FDOPA, the automated synthesis was improved regarding two aspects: chemical improvements (increased radiochemical yields (RCYs) for every single synthetic step) and technical optimization (e.g. to prevent marked radioactivity losses during the entire process).

2. Experimental

2.1. General

Acetonitrile (for DNA synthesis) for azeotropic distillation as well as Kryptofix 2.2.2 were obtained from Merck (Darmstadt, Germany). For radiolabeling DMF (dried over molecular sieve) was used as solvent (Fluka, Germany). The compound 2-nitro-4,5-dimethoxybenzaldehyde as labeling precursor was from ABCR (Germany). O-allyl-N-(9-anthracenylmethyl)cinchonidinium as chiral phase transfer catalyst (PTC) in the alkylation reaction was prepared according to a published procedure (Zhang et al., 2002). All other chemicals and solvents (Sigma-Aldrich or Fluka) were of highest purity available and used as received. Cartridges were obtained either from Waters (USA; Sep-Pak® Light QMA, Sep-Pak® Light Alumina N, Sep-Pak® Plus C18, Sep-Pak® Accell Plus CM, Sep-Pak® Light NH_2, Sep-Pak® Light Diol, Sep-Pak® Plus Silica) or from VARIAN (Germany; Na_2SO_4, 38 mm, 2.2 g).

2.2. Production of [^{18}F]fluoride

N.c.a. [^{18}F]fluoride was produced at the PETtrace cyclotron (GE Healthcare, Uppsala, Sweden) via the ^{18}O(p,n)^{18}F nuclear reaction by irradiating 1.5 mL of >95% enriched [^{18}O]water with 16.5 MeV protons.

2.3. Synthetic procedure

The automated synthesis was carried out in a remote controlled module which was built in our laboratory (Fig. 1).

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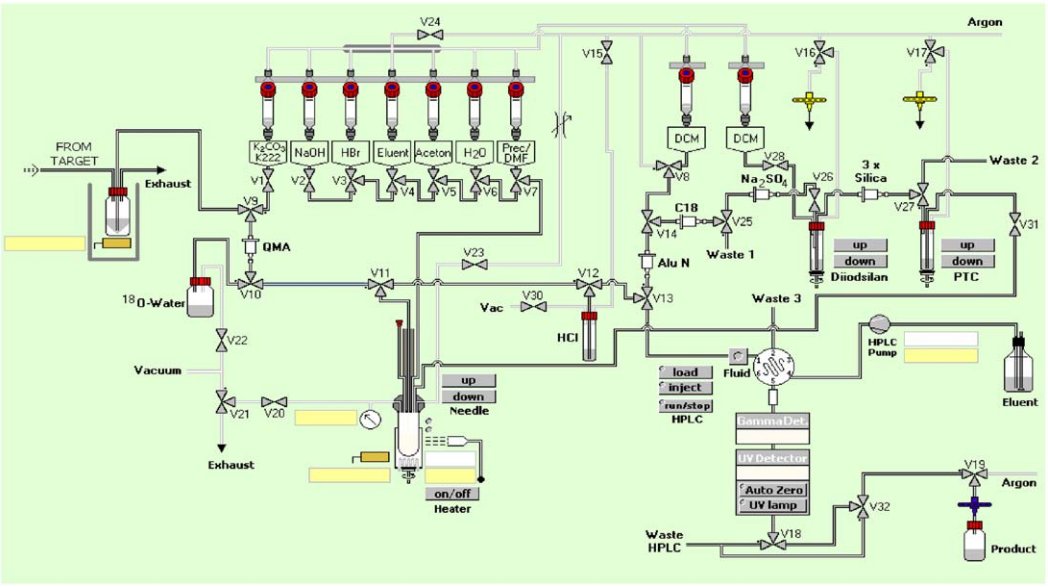

Fig. 1. Scheme for the automated synthesis of [^{18}F]FDOPA.

[^{18}F]Fluoride was trapped on a QMA cartridge and eluted with 900 μL of acetonitrile (containing 100 μL of 3.5% K_2CO_3 and 15.0 mg Kryptofix 2.2.2) into the fluorination vial. This mixture was dried for 10 min in vacuum under a weak stream of argon at 140 °C by azeotropic distillation. Precursor (2-nitro-4,5-dimethoxybenzaldehyde, 5 mg) in 1.0 mL of DMF was added to the dry residue of the complex $[K/222]^+$ $^{18}F^-$. The fluorination vial was kept heated at 140 °C for 10 min. The reaction solution was cooled down and diluted with 15 mL of water; then this solution was passed through two cartridges (Alumina N and C18). The ^{18}F-labeled benzaldehyde, trapped on the C18 cartridge, was eluted with 4 mL of dichloromethane (DCM) and was passed through a Na_2SO_4 cartridge (for drying) into the iodination vial. Diiodosilane (prepared *in situ*: 250 μL of phenylsilane, 250 mg I_2 and 15 μL of ethylacetate mixed at room temperature) was added. The reductive iodination reaction was carried out at room temperature for 10 min. The ^{18}F-labeled benzyliodide was trapped on silica cartridges and eluted with 7 mL of DCM into a vial already containing 250 mg CsOH, 40 mg PTC and 45 mg N-(diphenylmethylene)glycine-*tert*-butylester. After the alkylation reaction (r.t., 10 min) the reaction solution was transferred back into the fluorination vial and DCM was evaporated. Added 500 μL of 48% HBr containing 10 mg of potassium iodide and hydrolysis carried out at 150 °C for 10 min. The reaction mixture was cooled down and adjusted to pH = 2–3 by adding 500 μL of 6 N NaOH and loaded into a HPLC injection loop after on-line filtration through a micro glass fiber filter (diameter: 13 mm; pore size: 1.6 μm; WHATMAN, USA). Purification was performed using a precolumn (Phenomenex, Luna, C18 (2), 5 μm, 50 mm × 10 mm) and a second reversed phase column (Phenomenex, Luna, C18 (2), 5 μm, 250 mm × 10 mm) with 0.1% acetic acid and 200 mg/L ascorbic acid in water as eluent at a flow rate of 5.0 mL/min. The fraction containing [^{18}F]FDOPA (retention time: 9–11 min) was collected and sterile filtered (Millex GV, Millipore, USA).

2.4. Analyses

Radiochemical yields and purities of the intermediate products were confirmed by TLC: an aliquot of the intermediate product solution was applied to silica gel plates (Polygram® Silica G/UV_{254}, 8 × 4 cm, Macherey&Nagel, Germany) and developed with ethyl acetate/petroleum ether $\frac{60}{90}$ ($\frac{1}{2}$, v/v); the R_f values were 0.59, 0.73 and 0.58 for 2-fluoro-4,5-dimethoxybenzaldehyde, 2-fluoro-4,5-dimethoxybenzyliodide and methyl-N-(diphenylmethylene)-2-fluoro-5-methoxy-O-methyltyrosinate, respectively.

Determination of radiochemical purity and enantiomeric excess of [^{18}F]FDOPA was carried out using HPLC with either a reversed phase column (Phenomenex, Luna, C18 (2), 5 μm, 250 mm × 4.6 mm, at r.t.), the same eluent as used for preparative HPLC (flow: 1 mL/min) or a chiral column (Chirosil, 5 μm, 150 mm × 4.6 mm, eluent: MeOH/water $\frac{85}{15}$ (v/v) with 6 mM acetic acid, 0.6 mL/min, at 0 °C), respectively. The retention time was 8.7 min on the reversed phase column and 7.7 min ([^{18}F]fluoro-L-DOPA) on the chiral column. The D-enantiomer had a retention time of 13.2 min.

3. Results and discussion

3.1. Fluorination

The first synthetic step was ^{18}F-fluorination of the precursor 4,5-dimethoxy-2-nitrobenzaldehyde via nucleophilic aromatic substitution. In literature, usually DMSO was used as solvent in this labeling reaction (Lemaire et al., 1992, Rengan et al., 1993). However, we previously observed the potential of DMSO to oxidize the benzaldehyde precursor to benzoic acid (Shen et al., 2007). Therefore, DMF was used instead of DMSO for the fluorination resulting in a RCY of 71 ± 4% ($n = 40$). In addition, it was found that when using a glassy carbon reaction vial for the labeling reaction, the amount of adsorbed and, therefore, lost radioactivity in the vial could be reduced to 2.0 ± 0.7% ($n = 15$), compared to normal glass (16 ± 6%; $n = 10$).

3.2. Reductive iodination

Conversion of 4,5-dimethoxy-2-[^{18}F]fluorobenzaldehyde to 4,5-dimethoxy-2-[^{18}F]fluorobenzyliodide was done using diiodosilane. A strong dependence of the RCY was observed on the time when diiodosilane was prepared before the reductive iodination. Diiodosilane is extremely unstable; even at room temperature it decomposes very fast (Keinan and Perez, 1987). Therefore, we studied the effect of the time diiodosilane was prepared before