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# Efficient automated syntheses of high specific activity 6-[18F]fluorodopamine using a diaryliodonium salt precursor†

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**6-[$^{18}$F]Fluorodopamine (6-[$^{18}$F]F-DA) is a positron emission tomography radiopharmaceutical used to image sympathetic cardiac innervation and neuroendocrine tumors. Imaging with 6-[$^{18}$F]F-DA is constrained, in part, by the bioactivity and neurotoxicity of 6-[$^{19}$F]fluorodopamine. Furthermore, routine access to this radiotracer is limited by the inherent difficulty of incorporation of [$^{18}$F]fluoride into electron-rich aromatic substrates. We describe the simple and direct preparation of high specific activity (SA) 6-[$^{18}$F]F-DA from no-carrier-added (n.c.a.) [$^{18}$F]fluoride. Incorporation of n.c.a. [$^{18}$F]fluoride into a diaryliodonium salt precursor was achieved in 50–75% radiochemical yields (decay corrected to end of bombardment). Synthesis of 6-[$^{18}$F]F-DA on the IBA Synthera® and GE TRACERlab FX-FN automated platforms gave 6-[$^{18}$F]F-DA in >99% chemical and radiochemical purities after HPLC purification. The final non-corrected yields of 6-[$^{18}$F]F-DA were 25 ± 4% ($n$ = 4, 65 min) and 31 ± 6% ($n$ = 3, 75 min) using the Synthera and TRACERlab modules, respectively. Efficient access to high SA 6-[$^{18}$F]F-DA from a diaryliodonium salt precursor and n.c.a. [$^{18}$F]fluoride is provided by a relatively subtle change in reaction conditions – replacement of a polar aprotic solvent (acetonitrile) with a relatively nonpolar solvent (toluene) during the critical radiofluorination reaction. Implementation of this process on common radiochemistry platforms should make 6-[$^{18}$F]F-DA readily available to the wider imaging community.**

**Keywords:** 6-[$^{18}$F]fluorodopamine; positron emission tomography; emission computed tomography; diaryliodonium salts; fluorine-18

## Introduction

Early work by Kirk and coworkers[1,2] demonstrated that 6-fluorodopamine (6-F-DA)[3] is readily converted to 6-fluoronorepinephrine *in vivo*.[4] The observation of 6-F-DA metabolism suggested that 6-[$^{18}$F]fluorodopamine (6-[$^{18}$F]F-DA) could be used as a positron emission tomography radiotracer to image cardiac sympathetic innervation.[5] Imaging studies in dogs,[6,7] baboons,[8–10] and humans[11–13] subsequently established the utility of this radiotracer in cardiac imaging. 6-[$^{18}$F]F-DA is also taken up selectively in neuroendocrine tumors, which accumulate and store catecholamine derivatives recognized by the cell membrane norepinephrine transporter (NET).[14,15] Pacek and coworkers demonstrated that 6-[$^{18}$F]F-DA is more sensitive and effective at localizing pheochromocytomas and paragangliomas than either *meta*-[$^{131}$I]iodobenzyl guanidine ([$^{131}$I]MIBG) or [$^{123}$I]MIBG, the clinically used NET-mediated radiopharmaceuticals.[16–21] Given these observations and the inherent advantages of $^{18}$F compared with $^{123}$I/$^{124}$I/$^{131}$I-radionuclides (decay purity, tissue penetration range, half-life), 6-[$^{18}$F]F-DA may prove to be superior compared with MIBG for imaging neuroendocrine tumors and micrometastases. Neuroblastoma (NB) is a neuroendocrine tumor of neural crest origin and, as such, possesses sympathetic neuronal behavior.[22] Currently, functional imaging of NB, is performed with [$^{123}$I]MIBG and/or [$^{18}$F]FDG.[23] However, owing to the limitations of these imaging agents for the specific staging of NB, our interest lies in investigating the potential use of [$^{18}$F]F-DA as an NB imaging agent.

Historically, electrophilic methods provided the most direct access to 6-[$^{18}$F]F-DA. Direct electrophilic fluorination methods rely typically on [$^{18}$F]$F_2$ gas as the source of the label to produce low specific activity (SA) 6-[$^{18}$F]F-DA.[6,24,25] Although sufficient yields for patient studies are attainable using these strategies, precautions are required to avoid injecting a high mass dose of dopamine and 6-[$^{19}$F]fluorodopamine that are present in the final product.[26] In addition, electrophilic syntheses require a

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dedicated $F_2$ cyclotron target and the appropriate equipment for handling corrosive fluorine gas in the facility. Classical electrophilic methods provide the advantage of a single-step, regioselective radiolabeling, but these methods often employ heavy-metal reagents (e.g., mercury[27] and tin[28,29]) that must be removed from the final product, and they afford final product with relatively low SA (<370 MBq/μmol). More recently, Eskola and coworkers reported that fluorodestannylation with high SA [$^{18}$F]$F_2$[30] could be used to prepare relatively high SA (13 GBq/μmol) 6-[$^{18}$F]F-DA in small-scale syntheses (660 MBq); however, this methodology still requires sophisticated equipment, which is not readily available, to generate the high SA [$^{18}$F]$F_2$.

Nucleophilic $^{18}$F-labeling of aromatic compounds that do not feature strong electron-withdrawing groups (such as in F-DA) remains a significant chemistry challenge. As a testament to the difficulty of no-carrier-added (n.c.a.) [$^{18}$F]fluoride radiopharmaceutical preparation, several methodologies have recently been reported utilizing nickel,[31] palladium[32], and copper[33]-mediated catalysis, and iodonium ylides.[34] A multistep n.c.a. synthesis of 6-[$^{18}$F]F-DA was pioneered by Ding and coworkers[8] to yield high SA 6-[$^{18}$F]F-DA (74–185 GBq/μmol). This tour de force, manual radiochemical synthesis required 105 min, included several synthetic and intermediate purification steps, and proceeded in 9% radiochemical yield (RCY; end of synthesis). Routine synthesis of n.c.a. 6-[$^{18}$F]F-DA by this multistep route remains a challenge.

Despite 20 years of human imaging with 6-[$^{18}$F]F-DA, there is no direct synthesis that uses n.c.a. [$^{18}$F]fluoride, avoids heavy-metal reagents, and provides high SA 6-[$^{18}$F]F-DA in good yield and quantity. The thermal decomposition of diaryliodonium salt precursors to produce [$^{18}$F]fluoroarenes, an approach pioneered by Pike,[35–37] is a promising alternative method to introduce n.c.a. [$^{18}$F]fluoride into electron-rich aromatic substrates. In mechanistic studies over several years, the DiMagno laboratory optimized the important experimental parameters required to perform high-yield [$^{19}$F]fluorination reactions with diaryliodonium salt substrates. The key observation from this work was that the use of relatively nonpolar solvents suppressed a number of troublesome side reactions of diaryliodonium salts, including internal electron transfer and disproportionation. Finally, the syntheses of diaryliodonium salt precursors were refined so that fairly densely functionalized precursors could be prepared without using heavy-metal reagents.[38–40] Taken together, these preliminary data from [$^{19}$F]fluorination reactions indicated that $^{18}$F-labeled electron-rich aromatic compounds should be readily accessible from diaryliodonium salt precursors.

Here, we demonstrate that a modest change in reaction conditions dramatically improves the yield of 6-[$^{18}$F]F-DA obtained from a diaryliodonium salt precursor (Figure 1). The result is a new method for providing a reliable, high-yielding, and scalable radiosynthesis of high SA 6-[$^{18}$F]F-DA.

## Experimental

All commercial reagents were purchased from Sigma-Aldrich (St. Louis, MO, USA) or TCI America (Portland, OR, USA) and used as received, unless otherwise specified. Diaryliodonium salt **1** was prepared as previously reported.[37–40] All reagents used were of >95% purity. All aqueous solutions were prepared using distilled, deionized water (Milli-Q Integral Water Purification System, Millipore Corp., Billerica, MA, USA; 18.2 MΩ cm resistivity). Radioactive samples were analyzed in a CRC-15R Dose Calibrator (Capintec, Inc., Ramsey, NJ, USA). Thin-layer chromatography (TLC) sample analysis was performed on an AR-2000 radio-TLC Imaging Scanner (Bioscan, Hopkinton, MA, USA) using WinScan 3. Analytical HPLC was performed on an Agilent 1200 Series LC System (Agilent Technologies, Cedar Creek, TX, USA) using both diode array detection and a Bioscan Flow-Count radioisotope detector.

### Preliminary testing of n.c.a. $^{18}$F incorporation using a microfluidic reactor

Investigation of the radiolabeling step was performed using the Nanotek® Microfluidic Synthesis System (Advion Biosciences, Ithaca, NY). [$^{18}$F]Fluoride was separated from [$^{18}$O]$H_2O$ using a QMA anion exchange resin (ORTG, Inc., Oakdale, TN, USA) cartridge that was pretreated with 1 M sodium bicarbonate and rinsed with water. The trapped [$^{18}$F]fluoride was eluted from the QMA cartridge into the concentrator vial with 450 μL of an acetonitrile : water solution (90:10) containing potassium carbonate (0.5 mg) and Kryptofix® [2.2.2.] (K2.2.2) (3.5 mg). The K2.2.2.-[$^{18}$F]fluoride complex was dried azeotropically (105 °C, 3 × 100 μL dry acetonitrile), and the concentrator vial was cooled to 35 °C. A freshly prepared precursor solution (34.2 mg of **1** in 450 μL acetonitrile) was added. For experiments in which solvent composition was varied, this mixture was transferred to the precursor storage loop. For reactions performed in benzene alone, the solvent was removed under reduced pressure, benzene (250 μL) was added, and the reconstituted solution was transferred to the precursor storage loop. Dry benzene was loaded into a second reagent loop. The separate volumes were mixed by passing through a microreactor containing a 15.7-μL loop at a flow rate of 30 μL/min and a reactor temperature of 180 °C. Fluorinated intermediate (**2**) product samples were removed and spotted onto silica TLC plates which were developed in an ethyl acetate : hexanes (20:80) mixture and analyzed for radioactivity by comparison to a protected 6-[$^{19}$F]F-DA ($^{19}$F-**2**) standard ($R_f$ (product) = 0.3). Once effective radiofluorination conditions were identified, the same general synthesis protocol was performed on both the Synthera® (V1, Ion Beam Application (IBA), Louvain-la-Neuve, Belgium) and TRACERlab FX-FN (GE Healthcare, Waukesha, WI, USA) automated radiosynthesizers.

### Synthesis of 6-[$^{18}$F]fluorodopamine using the IBA Synthera® module

The Synthera® platform utilizes a sterile, single-use Integrated Fluidic Processor™ (IFP, ABX Advanced Biochemical Compounds, Radeberg, Germany) that is mounted on the synthesis module for chemical manipulations. For this synthesis, two Synthera® modules were connected in series. An external compressed air line was directed toward the reactor vial on each synthesizer to provide manual cooling.

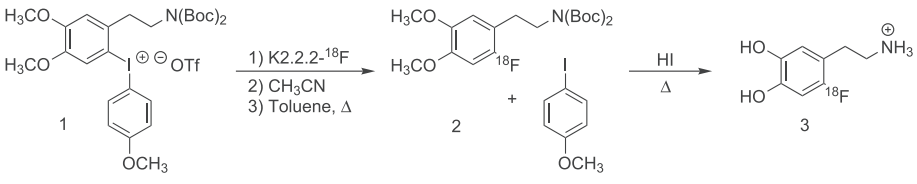


**Figure 1.** Synthetic scheme for 6-[$^{18}$F]F-DA (**3**) from the diaryliodonium precursor **1**. Initial ion exchange at the hypervalent iodine center of **1** is conducted in acetonitrile to afford the diaryliodonium–[$^{18}$F]fluoride complex. Solvent is removed and thermolysis is conducted in toluene to produce **2**. Deprotection of the radiolabeled intermediate **2** in HI produces **3**.

Preliminary experiments demonstrated that significant (40–55%) radioactivity adhered to the reactor vial upon addition of toluene. To minimize radioactivity loss to the reactor vial, each reactor was pretreated for at least 15 min with a base wash (saturated potassium hydroxide in ethanol). The solution was removed, and the reactor and lines were thoroughly rinsed with 4 × 4 mL aliquots each of water, ethanol, and finally acetonitrile. The lines and reactor were dried by flushing with nitrogen and heating the reactor vial to 80 °C for 10 min. IFP reactor vials prepared in this manner retained significantly less [$^{18}$F]fluoride (15–20%).

[$^{18}$F]Fluoride was trapped on a QMA cartridge and eluted into the reactor vial with 600 μL of an acetonitrile : water solution (90:10) of Kryptofix® [2.2.2] (3.0 mg) and potassium carbonate (0.5 mg). The solvent was removed at 90 °C under reduced pressure over 90 s, and the reactor vial was cooled to room temperature. Anhydrous acetonitrile (600 μL) containing 10–12 mg of the diaryliodonium precursor **1** was introduced to the reactor. Acetonitrile was removed under reduced pressure (30 kPa) with argon flow at 50 °C. Dry toluene (900 μL) was added to the reactor vial, and the solution was heated to 150 °C for 4 min. The reactor was cooled to room temperature, and the contents were transferred from the reactor vial onto a silica Sep-Pak® Plus cartridge (Waters Corp, Milford, MA). Toluene was purged from the cartridge using argon (200 kPa), and protected 6-[$^{18}$F]F-DA (**2**) was eluted with ethyl acetate (2.7 mL) and transferred to the second Synthera® reactor vial. Ethyl acetate was removed under argon flow and reduced pressure at 90 °C followed by addition of 57% hydroiodic acid (600 μL). The sealed reactor vial was heated at 155 °C for 4 min. The solution was cooled to room temperature and neutralized to pH 3 with 4 mL of a 0.32 M potassium phosphate buffer (pH 12). The solution was transferred from the reactor vial to the HPLC injector loop (5 mL) connected to an Agilent 1100 series HPLC pump equipped with a Zorbax Eclipse XDB-C18 semi-prep (9.4 × 250 mm, 5 μm) column. Eluent: 20% ethanol, 55 mM citric acid, pH 3 at 2 mL/min. The radioactive peak corresponding to 6-[$^{18}$F]F-DA (retention time 8.5 min) was collected and neutralized with 0.1 M ammonium acetate (pH 8.2).

A sample of 6-[$^{18}$F]F-DA final product was analyzed for radiochemical identity, purity, and SA by analytical HPLC using an Agilent Zorbax SB-Aq (3.5 μm, 4.6 mm × 100 mm) chromatography column with a mobile phase of 10% acetonitrile and 90% aqueous buffer (0.1 M monosodium phosphate, 0.27 mM disodium EDTA, 0.92 mM octanesulfonic acid, pH 3.5). The flow rate was 1.0 mL/min, and UV (220 nm) and radioactivity detectors were used for the analysis. For determination of radiochemical identity, purity, and SA, the HPLC retention time and peak area of 6-[$^{18}$F]F-DA were compared with those for a standard solution of 6-[$^{19}$F]F-DA (ABX) of known concentration.

An aliquot of the final product, 6-[$^{18}$F]F-DA, was analyzed for residual solvents by gas chromatography (GC) using an Agilent Technologies 7890A GC System, Carbowax column (J&W; 30 m × 250 μm × 0.25 μm), inlet and detector temperatures of 250 and 300 °C, respectively, oven temperature of 80 °C, and flow of 1.5 mL/min. The GC peak retention times and areas were compared with standards of acetone (0.1%, v/v), ethyl acetate (0.1%), ethanol (0.1%), acetonitrile (0.01%), and toluene (0.01%). The amount of each volatile solvent was calculated based on the ratio of peak areas for the samples versus the standard.

### Synthesis of 6-[$^{18}$F]fluorodopamine on the GE TRACERlab FX-FN

For this method, the automated radiochemistry setup with a GE TRACERlab FX-FN and an adjacent customized module has been previously described.[41] As significant $^{18}$F-radioactivity adhered to a borosilicate glass reactor vial, a glassy carbon reactor vessel was used instead of the glass vial. [$^{18}$F]Fluoride (n.c.a.) in [$^{18}$O]water was added directly to the reactor, which was previously charged with Kryptofix® [2.2.2] (3 mg) and $K_2CO_3$ (0.5 mg) in 95:5 acetonitrile : water (2 mL). Residual water was removed by azeotropic distillation with an additional aliquot of acetonitrile (2 mL). An acetonitrile solution containing diaryliodonium precursor **1** (10 mg in 0.5 mL) was added to the reactor. Acetonitrile was removed under vacuum and heat (50 °C), toluene (1 mL) was added, and the vial was heated at 150 °C for 5 min. The crude reaction mixture was passed through a silica Sep-pak® Plus cartridge (Waters), and the protected 6-[$^{18}$F]F-DA intermediate was eluted using ethyl acetate (3.5 mL) and transferred to a secondary reactor in the adjacent customized module. The solvent was removed under reduced pressure using helium and vacuum, and 47% aqueous HI (250 μL) was added to the dry residue. The resulting solution was heated at 155 °C for 5 min, cooled, and neutralized with 2 M sodium citrate (800 μL). The crude product was purified by semi-preparative HPLC (Luna C18(2), (5 μm, 10 mm × 250 mm) 0.1% acetic acid and 0.02% ascorbic acid in water; flow rate = 2.0 mL/min, product retention time ~ 10.5 min), and the isolated product was confirmed by analytical HPLC and formulated as described earlier.

## Results and discussion

This study demonstrates the feasibility of using n.c.a. [$^{18}$F] fluoride and a diaryliodonium salt precursor to prepare high SA 6-[$^{18}$F]F-DA rapidly, efficiently, and at a scale that is sufficient for preclinical and clinical work. Preliminary radiochemical experiments performed using the general approach depicted in Figure 1 demonstrated that radiofluorination of the catechol ring could be performed rapidly (30-s reaction time) at 180 °C in benzene and with good incorporation of [$^{18}$F]fluoride (~40–50%). Owing to the high toxicity of benzene as compared with toluene, toluene was later used for developing the radiochemical syntheses on the automated platforms that had intended *in vivo* use, and benzene was not considered further. However, for purposes of chemistry, the aromatic solvents may be used interchangeably.

### Preliminary testing of n.c.a. $^{18}$F incorporation using microfluidics

Like many prior reports of the use of diaryliodonium salts as radiofluorination precursors, the overall process incorporates a high-temperature thermolysis reaction and a deprotection step. The key variable that distinguishes this new methodology from previously reported methods is that the ion exchange and thermolysis reactions (Figure 2 and Figures S1 and S2) are performed in a relatively nonpolar solvent. Investigation of these labeling conditions was performed using the Advion Nanotek® system.

While the thermolysis yielded negligible amounts of **2** in 100% acetonitrile (data not shown), Figure 2 shows that a modest yield (~10%) of **2** was produced when 50% of the acetonitrile was

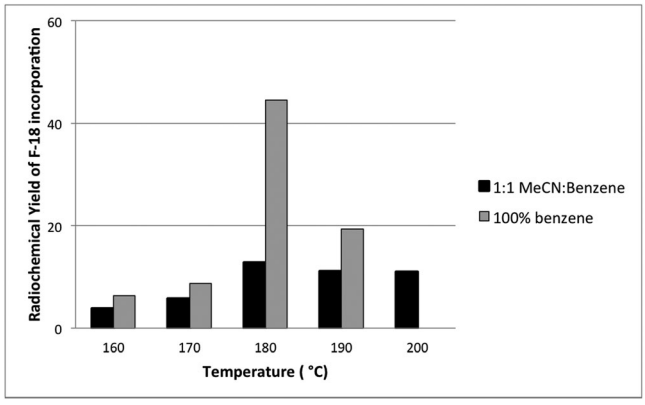


**Figure 2.** Optimization of thermal decomposition of **1** conducted at various temperatures for 30 s in 1:1 acetonitrile : benzene (black bars) and 100% benzene (gray bars) ($n = 3$ for each condition) (precursor (**1**) (5 mg/mL); reactor loop 15.7 μL; flow rate = 31.4 μL/min).

replaced with benzene. Figure 2 also demonstrates the marked improvement in RCY of the fluoroarene when the thermolysis reaction is performed in 100% benzene. These data are consistent with previous work performed with [$^{19}$F]fluoride that showed that the use of polar aprotic solvents in the thermal decomposition reaction of diaryliodonium fluorides led to very poor yields of fluorinated arenes.[40]

Yields of **2** were evaluated with respect to thermolysis time in benzene at 180 °C (Figure S1). Maximum yields of **2** were observed after only 30 s of heating, and prolonged heating times showed no increase in labeling; the yield of **2** plateaued at approximately 40–45%. These results obtained with n.c.a. [$^{18}$F]fluoride were at odds with experiments conducted with [$^{19}$F]fluoride under nearly identical conditions, which produced [$^{19}$F]**2** in 80% yield; the salient difference between the non-radioactive control and the radioactive synthesis was the presence of solubilized $K_2CO_3$ in the acetonitrile solution used to perform the ion exchange reaction. It appeared likely that carbonate ions competed with [$^{18}$F]fluoride for the iodine(III) center and that this problem might be solved by an increase in the concentration of the diaryliodonium salt precursor. This simple change allowed the yields of **2** to approach those of the [$^{19}$F]fluorinated arene observed previously at precursor concentrations above 10 mg in 900 μL of 100% benzene (Figure S2).

### Synthesis of 6-[$^{18}$F]fluorodopamine on the IBA Synthera® and the GE TRACERlab FX-FN

The radiosynthesis of 6-[$^{18}$F]F-DA was performed on two commercially available automated radiochemical synthesizers, the Synthera® (IBA) and the TRACERlab FX-FN (GE). RCYs were measured after the fluorination and thermolysis of **1** to produce **2** and also after the purification of the final product (**3**).

Production of the fluorinated intermediate (**2**) on the IBA Synthera® using the optimized conditions resulted in a yield of 35 ± 4% ($n$ = 9), uncorrected (46 ± 7% corrected to end of bombardment (EOB)). Thermal decomposition was performed at 150 °C rather than optimal 180 °C determined in preliminary experiments as the optimized conditions on the flow system (Nanotek) do not correlate directly with conventional heating conditions of the Synthera. The final yield of 6-[$^{18}$F]F-DA (**3**) after deprotection and purification by HPLC was 25 ± 4% ($n$ = 4), uncorrected (36 ± 4% corrected to EOB), and was achieved in an average of 65 min from EOB. SA was calculated at >74 GBq/μmol (2 Ci/μmol) ($n$ = 8) for this system from a starting activity of 18.5 GBq (500 mCi).

The semi-prep HPLC purification provided a simple separation of 6-[$^{18}$F]F-DA from radiochemical impurities (Figure S3). Different semi-prep HPLC conditions were used on the Synthera and TRACERlab FX-FN to demonstrate the versatility of the method. Analytical validation (Figure S4) against a 6-[$^{19}$F]F-DA standard (ABX) confirmed the final product to be >99% radiochemically pure and >95% chemically pure **3**. Analysis of the UV signal shows a small amount of dopamine (calculated to be 7.7 μg/mL in this case) but no detectable fluorodopamine. Peaks earlier than 2 min are due to the purification eluent (citric acid).

Residual solvent analysis of the final product showed no detectable amount of the class II solvents[42] acetonitrile or toluene. As determined by standard curve comparison, residual ethanol was routinely detected at a 1–2% concentration (Figure S5).

Production of fluorinated intermediate (**2**) on the GE TRACERlab FX-FN using the same conditions described earlier resulted in a yield of 51 ± 6% ($n$ = 3), uncorrected (75 ± 9% corrected to EOB). The final yield of purified 6-[$^{18}$F]F-DA was 31 ± 6% ($n$ = 3), uncorrected (72 ± 10% corrected), and was achieved in an average of 130 min from EOB. Using a lower starting $^{18}$F activity of 11.1–14.8 GBq (300–400 mCi), the specific radioactivity of final product was 11.1–7.4 GBq/μmol (0.3 ± 0.2 Ci/μmol).

The use of toluene and ethyl acetate in the synthesis limits the number of radiosynthesis platforms that can use this methodology currently. Cassettes that employ relatively robust polymers such as polyethylene, polypropylene, or fluoroelastomers are compatible. Cassettes constructed from other materials need to be tested on a case-by-case basis. Purification methods involving widely cassette-compatible solvents are currently being optimized.

The conditions required for removal of the methyl ether protective groups are somewhat aggressive, which is a minor drawback for this synthesis, as HI is a very corrosive reagent. A diaryliodonium precursor containing more labile protecting groups, which require milder hydrolysis conditions, is currently being developed.

The diaryliodonium salt (**1**) showed excellent long-term stability when stored at room temperature under dry argon. No decline in yield of 6-[$^{18}$F]F-DA from a single batch of **1** was noted in runs conducted over the course of 18 months.

The easy implementation and efficiency of the overall method means that amounts of 6-[$^{18}$F]F-DA adequate for a single human dose (180–370 MBq) may be readily prepared from modest amounts of [$^{18}$F]fluoride (0.75–1.2 GBq). Importantly, the yield of 6-[$^{18}$F]F-DA did not decline with increasing amounts of radioactivity; more than 3.7 GBq of pure, high SA 6-[$^{18}$F]F-DA was obtained from 9.3 GBq of [$^{18}$F]fluoride.

Both automated synthesis platforms used in this work provided 6-[$^{18}$F]F-DA in sufficient quantity, SA, and purity for use in clinical studies. Method automation is simple, and overall $^{18}$F-radiosynthesis times are comparably short. While the overall yield of 6-[$^{18}$F]F-DA was higher on the GE system, the single-use cassette capabilities of the Synthera® make regulatory compliance less cumbersome. In our hands, the ability to add a second azeotropic evaporation of the Kryptofix/[$^{18}$F]fluoride complex with anhydrous acetonitrile generally resulted in higher overall RCYs. The GE system is able to accommodate this extra aliquot of acetonitrile and, thus, provided higher yields of 6-[$^{18}$F]F-DA. The GE system is also able to accommodate a more detailed intermediate solid phase extraction purification of the fluorinated intermediate (**2**). Taken together, these additional steps extend the synthesis time on the GE system, as compared with the IBA system. Nevertheless, this study demonstrates that these methods are easily adaptable for use on synthesis platforms that are stable to the use of organic solvents.

While several other methods for incorporation of n.c.a [$^{18}$F] fluoride have been reported in the past few years,[31–34] many of these methods utilize heavy-metal catalysts, necessitating additional quality control analyses for human use to verify that residual metal concentrations are below allowable injection limits. Our diaryliodonium method does not use heavy metals for either radiolabeling or precursor synthesis. Only the spirocyclic iodonium ylides are comparable in this regard. The main advantage of the ylide chemistry appears to be the stability of the precursor; however, we have demonstrated that the diaryliodonium 6-[$^{18}$F]F-DA precursor (**1**) is completely stable for at least 18 months at room temperature under argon atmosphere.

## Conclusions

We have demonstrated production of the clinically relevant radiopharmaceutical 6-[$^{18}$F]F-DA in >25% RCY (end of synthesis) with an SA of >74 GBq/μmol and a total synthesis time of approximately 1–2 h, including HPLC purification. The methodology described here is easily implemented on commercially-available, automated, radiosynthesis modules, and the synthesis has been conducted successfully in multiple laboratories. This adaptability and ease of automation make this method very attractive for the routine preparation of 6-[$^{18}$F]F-DA in compliance with typical regulatory requirements for single-center or multi-center clinical research. The generality and scope of the [$^{19}$F]fluoride chemistry suggest that the methodology may have significant breadth of application in the production of $^{18}$F-radiopharmaceuticals and provide efficient access to previously known, synthetically challenging, and/or new $^{18}$F-radiopharmaceuticals.

## Conflict of interest

Dr. Neumann is currently a consultant for and shareholder of Ground Fluor Pharmaceuticals (GFP), Inc., Lincoln, NE, who now produces the diaryliodonium salt precursor material for 6-[$^{18}$F]-fluorodopamine. Dr. DiMagno holds a patent for the nucleophilic fluorination of aromatic ring systems (US Patent 8,604,213 B2, 10 December 2013), which includes the chemistry described herein, and is a shareholder in GFP, Inc. Other authors declare no conflict of interest.

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