

Iodonium Ylide–Mediated Radiofluorination of ^{18}F -FPEB and Validation for Human Use

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Translation of new methodologies for labeling nonactivated aromatic molecules with ^{18}F remains a challenge. Here, we report a one-step, regioselective, metal-free ^{18}F -labeling method that uses a hypervalent iodonium(III) ylide precursor, to prepare the radiopharmaceutical ^{18}F -3-fluoro-5-[(pyridin-3-yl)ethynyl]benzonitrile (^{18}F -FPEB). **Methods:** Automated radiosynthesis of ^{18}F -FPEB was achieved by reaction of the ylide precursor (4 mg) with ^{18}F -Et₄NF in dimethylformamide at 80°C for 5 min and formulated for injection within 1 h. **Results:** ^{18}F -FPEB was synthesized in 20% ± 5% (*n* = 3) uncorrected radiochemical yields relative to ^{18}F -fluoride, with specific activities of 666 ± 51.8 GBq (18 ± 1.4 Ci)/μmol at the end of synthesis and was validated for human use. **Conclusion:** Radiofluorination of iodonium (III) ylides proved to be an efficient radiosynthetic strategy for synthesis of ^{18}F -labeled radiopharmaceuticals.

Key Words: ^{18}F -FPEB; mGlu₅; iodonium ylide; PET; fluorination

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Historically, the formation of aromatic C–F bonds has been challenging in the field of synthetic organic chemistry, and even more so in radiochemistry, with the short-lived radionuclide ^{18}F (half-life, 109.7 min) for molecular imaging by PET. Electrophilic fluorination reactions with carrier-added ^{18}F -F₂ gas and its derivatives (e.g., ^{18}F -CH₃CO₂F) have enabled the development of ^{18}F -labeled aromatics by direct electrophilic substitution or demetalation reactions with organometallic reagents such as aryl stannanes (1,2). Electrophilic radiosynthesis with ^{18}F -F₂ and its derivatives involves the use of carrier-added fluorine gas and consequently results in products with relatively low specific activities. Such reactions also require specialized equipment as well as technical expertise for the safe handling of F₂(g). Commercial availability of high-specific-activity, no-carrier-added ^{18}F -fluoride has led to this reagent becoming the most widely used radiofluorinating species. Aromatic molecules with ^{18}F -fluoride are typically synthesized by nucleophilic aromatic substitution reactions with electron-deficient (activated) aromatics, and these reactions have been used extensively to prepare high-

specific-activity radiopharmaceuticals (3). However, labeling of electron-rich (nonactivated or deactivated) aromatics with ^{18}F -fluoride remains a long-standing and unmet challenge in routine PET radiopharmaceutical production.

Early efforts to expand the scope of reactions of electron-rich aromatics with ^{18}F -fluoride include inefficient and low-yielding thermal decomposition processes such as the Balz–Schiemann and Wallach reactions (3). Isotopic exchange via ^{18}F -for- ^{19}F displacement reactions can be used to label electron-rich aromatics and have been applied to prepare low-specific-activity radiotracers (3,4). Strategies that convert electron-withdrawing aryl substituents to electron-donating groups after radiofluorination (e.g., reduction of fluoronitrobenzene or fluorobenzaldehydes and decarbonylation reactions) are useful to access electron-rich ^{18}F -fluoroaromatics in high specific activity but are known to have limited chemical scope, involve multistep labeling approaches, and are challenging to adapt to radiopharmaceutical production. Recent strategies for reactions of ^{18}F -fluoride with electron-rich aromatics include the development of transition metal-mediated reactions with isolable aryl palladium or nickel complexes, copper-mediated fluorinations with aryl borate esters, oxidative fluorination with phenolic substrates, and fluorination of diaryliodonium or sulfonium salts as well as diarylsulfoxides, and most of these methods have been recently reviewed (5). These newer methods appear promising for preparing radiolabeled aromatics. However, drawbacks include the use of air-sensitive or toxic transition metals, limited substrate scope, or poor regioselectivity. Furthermore, radiotracer syntheses by the above-mentioned methods generally result in low isolated radiochemical yields. Such limitations have hampered the use of these alternative labeling reactions for clinical translation. To our knowledge, none of these methodologies have been applied to radiolabel a nonactivated aromatic ring with ^{18}F -fluoride for synthesis of a radiopharmaceutical and validate it for human use.

Nonactivated aromatics can be radiofluorinated with aryliodonium ylide–based precursors bearing various β-dicarbonyl auxiliaries (6). This technology was introduced by Satyamurthy and Barrio using barbituric or Meldrum acid auxiliaries (7). A recent study by Cardinale et al. demonstrated the satisfactory application of this method using Meldrum acid auxiliaries but led to non-regiospecific labeling and formation of several byproducts (8). Concurrently, we explored the application of iodonium ylide precursors with barbituric acid and Meldrum acid auxiliaries for ^{18}F -labeling but also found yields to be suboptimal (9). We discovered that spirocyclic iodonium(III) ylide precursors, in conjunction with systematic optimization of the reaction conditions, led to efficient, regiospecific, 1-step radiosyntheses of nonactivated

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aromatics with ^{18}F -fluoride (9). These bench-stable precursors involved facile synthesis and demonstrated a broad substrate scope for nonactivated ^{18}F -aromatics including hindered alkyl substituents, benzyl azides, anisoles, amides, heterocycles, and halogenated aromatics. The radiofluorination is operationally simple and was shown to be suitable for routine and automated production of ^{18}F -labeled aromatics. The conceptual advantages of excellent regioselectivity and viability of incorporating ^{18}F into a wide array of nonactivated (hetero)arenes makes this methodology attractive for routine radiopharmaceutical production.

^{18}F -3-fluoro-5-[(pyridin-3-yl)ethynyl]benzonitrile (^{18}F -FPEB) is a metabotropic glutamate receptor subtype 5 (mGlu₅) antagonist used in preclinical (10,11) and clinical PET neuroimaging research (12,13). Radiosynthesis of ^{18}F -FPEB and several structurally related radiotracers for mGlu₅ has been challenging as nucleophilic aromatic substitution by ^{18}F -fluoride is not a favored reaction because of the absence of electron-withdrawing groups located *ortho* or *para* to the labeling site. High temperatures are generally required, and several chemical impurities are generated during the labeling reactions. Isolated ^{18}F -FPEB is typically obtained in low radiochemical yields (1%–5% uncorrected yield relative to ^{18}F -fluoride) (10,14–16).

The goals of the present work were to exploit our new spirocyclic iodonium(III) ylide precursor technology to develop a high-yield radiosynthesis of ^{18}F -FPEB and to demonstrate that this methodology is suitable for routine radiopharmaceutical production.

MATERIALS AND METHODS

Full details of precursor synthesis and characterization, radioisotope production, analytic methods, spectra, and radiosynthesis with a TRACERlab FX_{FN} radiosynthesis module (GE Healthcare), as well as human validation data, are provided in the supplemental materials (available at <http://jnm.snmjournals.org>).

Manual and Automated Radiosynthesis of ^{18}F -FPEB

Precursor (**1**, **2** or 4 mg) was dissolved in *N,N*-dimethylformamide (DMF, 400 μL) and added to a glass V-vial containing azeotropically dried ^{18}F -Et₄NF (typically 37–111 MBq [1–3 mCi]). The reaction was heated at 80°C for 5 min. The reaction mixture was cooled for 3 min and then quenched with a 60:40 CH₃CN:H₂O + 0.1N ammonium formate solution (mobile phase; 2 mL). The reaction was further diluted with water (16 mL) and passed through a preactivated (ethanol [1 mL] and water [5 mL]) solid-phase extraction (C18 Sep-Pak; Waters) cartridge. The solid-phase extraction cartridge was flushed with water (2 mL), and the product was eluted with ethanol (1 mL). Product identity and purity were confirmed by radio-high-performance liquid chromatography and radio-thin-layer chromatography (100% EtOAc). The product was more than 99% radiochemically pure. Radiochemical yield was determined as the percentage of radioactivity that was isolated as the final product from the amount of activity present in the V-vial before addition of iodonium precursor to dried ^{18}F -Et₄NF and was not decay-corrected.

Automated synthesis of ^{18}F -FPEB was performed on a TRACERlab FX_{FN} radiosynthesis module. The final product was formulated and found suitable for injection in compliance with the quality control protocols and guidelines of the International Conference of Harmonization of Technical Requirement of Pharmaceuticals for Human Use (supplemental materials).

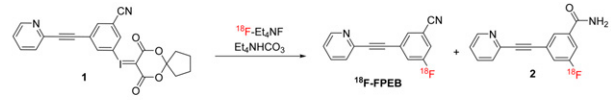
RESULTS

The iodonium ylide precursor, **1**, was synthesized in 6 steps starting with 4-amino-3,5-diiodobenzoic acid. A Sandmeyer reaction

furnished 3,5-diiodobenzoic acid, which was converted to the nitrile via acid chloride formation, amidation, and dehydration. Sonogashira coupling with 3-ethynylpyridine provided the aryl iodide (IPEB). We anticipated that oxidation of the iodine could be problematic in the presence of a pyridine functional group, which is known to undergo efficient transformation to the pyridine *N*-oxide under conditions analogous to those used in 3-iodo-5-(pyridin-2-ylethynyl)benzonitrile. Oxidants such as *m*-chloroperoxybenzoic acid and H₂O₂/urea in acetic acid resulted in complex mixtures of products. To our delight, Oxone (DuPont) in trifluoroacetic acid was successfully used to oxidize IPEB, partially attributed to a protonation event on nitrogen of pyridine, which prevented the formation of *N*-oxide. Removal of trifluoroacetic acid, resolubilization in ethanol, treatment with the auxiliary in aqueous sodium carbonate, and subsequent purification with silica gel chromatography provided **1** in 40% yield (Fig. 1).

Initial efforts toward the radiosynthesis of ^{18}F -FPEB using precursor **1** (2 mg) were performed manually with 37–111 MBq (1–3 mCi) of starting ^{18}F -fluoride. Using our previously optimized radiolabeling conditions for these reactions (9), with Et₄NHCO₃ (7 mg) in DMF (400 μL) at 120°C, only 6% radiochemical conversion (via radio-thin-layer chromatography) of ^{18}F -fluoride to ^{18}F -FPEB was attained, along with formation of a radioactive byproduct (**2**; see below) in 18% radiochemical conversion (Scheme 1, entry I). Monitoring the reaction over time indicated that ^{18}F -FPEB formed with high conversions during the initial 3 min of the reaction and subsequently decomposed. Control reactions with nonradioactive FPEB demonstrated that the compound was stable in DMF at 120°C. However, in the presence of an excess (2 equivalents) of Et₄NHCO₃ at the same temperature, FPEB underwent a rapid, quantitative base-mediated hydrolysis of the nitrile group to form 3-fluoro-5-(pyridin-2-ylethynyl)benzamide, **2**. To suppress amide formation, the concentration of Et₄NHCO₃ was reduced from 90 to 40 mM. Reduced base concentration resulted in increased ^{18}F -fluoride incorporation into products and favored distribution between ^{18}F -FPEB and byproduct **2**. Increased radiochemical conversion from 6% to 27% for ^{18}F -FPEB was observed, and formation of byproduct **2** decreased to 12% (Scheme 1, entry II). Furthermore, the temperature was lowered to 80°C and the reaction time was reduced to 5 min, affording ^{18}F -FPEB in excellent radiochemical conversion of 49% \pm 6% (*n* = 3; Scheme 1, entry III).

In light of this promising result—automated radiosynthesis of ^{18}F -FPEB—validation was subsequently performed to demonstrate the utility of the iodonium(III) ylide precursor for clinical translation. Three consecutive productions of ^{18}F -FPEB were isolated with more than 7,400 MBq (200 mCi) at the end of synthesis and formulated for injection within 1 h. Analysis of the formulated product (10% ethanol



Entry	Et ₄ NHCO ₃ / mg	Temp / °C	Time / min	^{18}F -FPEB [†]	2 [†]
I	7	120	10	6 \pm 1 %	18 \pm 4 %
II	3	120	10	27 \pm 1 %	12 \pm 4 %
III	3	80	5	49 \pm 6 %	\leq 1 %

SCHEME 1. Manual optimization of ^{18}F -FPEB radiosynthesis based on crude reaction mixtures. Conditions: precursor **1** (2 mg), Et₄NHCO₃, DMF (400 μL). [†]Incorporation: percentage radiochemical conversion as determined by radio-thin-layer chromatography (*n* = 3). Product identity was confirmed by coinjections of authentic **1** and **2** via radio-high-performance liquid chromatography.

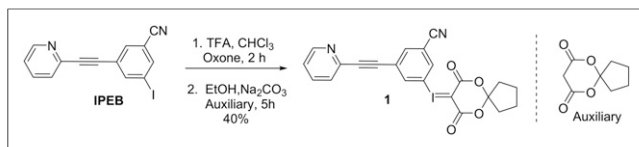


FIGURE 1. Synthesis of iodonium ylide precursor (**1**) for radiofluorination. IPEB = 3-iodo-5-(pyridin-2-ylethynyl)benzonitrile; TFA = trifluoroacetic acid.

in 0.9% sodium chloride) by high-performance liquid chromatography showed high specific activity (666 ± 51.8 GBq/ μ mol [18 ± 1.4 Ci/ μ mol]) as well high radiochemical purity ($\geq 99\%$) and chemical purity ($\geq 98\%$). Validation via an established quality control protocol (16) demonstrated that ^{18}F -FPEB synthesized from iodonium ylide precursor **1** is suitable for human injection (the supplemental materials present full validation data).

DISCUSSION

Radiosynthesis of ^{18}F -FPEB is low yielding by most traditional nucleophilic aromatic substitution reactions ($<5\%$ radiochemical yields), because nucleophilic displacement of common leaving groups (e.g., Cl, Br, or NO_2) by ^{18}F -fluoride is not favored when the electron-withdrawing group, that is, nitrile, is at the *meta* position. Harsh conditions, including high temperatures and prolonged reaction times, are generally required and several chemical and radiochemical impurities are usually generated during these reactions, thereby complicating purification. The original radiosynthesis of ^{18}F -FPEB used a chlorinated precursor (Scheme 2, entry I) (14). We and other laboratories (10,15,16) have validated a reproducible radiosynthesis of ^{18}F -FPEB via 3-nitro-5-(pyridin-2-ylethynyl)benzonitrile (Scheme 2, entry II), which resulted in 1%–5% radiochemical yield for clinical research studies. Notably, our efforts to further optimize the radiochemical yield of ^{18}F -FPEB by use of the nitro-precursor in the presence of reduced base concentrations still required high temperatures to proceed ($\sim 150^\circ\text{C}$) and continued to yield a problematic ^{18}F -labeled hydrolysis product as well as chemical byproducts that are difficult to separate (comparison of semipreparative high-performance liquid chromatograms is provided in the supplemental materials). Use of the bromo-precursor or use of microfluidic technologies demonstrated that the radiotracer could be prepared suitably for human use by conventional radiofluorination or flow chemistry, albeit without an increase in isolated radiochemical yield or simplified purification (16). In the present work, attempts to prepare a trimethyl ammonium triflate precursor (17) proved to be a chemical challenge and consistently led to the formation of an undesired methyl pyridinium salt, as predicted to be the thermodynamically favored product (supplemental materials). The spirocyclic iodonium ylide (**1**) was explored as a novel precursor for ^{18}F -FPEB on the basis of our recent demonstration of the viability of this strategy for radiolabeling a wide range of compounds (Scheme 1, entry III) (9).

Radiofluorination of nonsymmetric diaryliodonium compounds is believed to involve a distinct mechanistic pathway compared with traditional nucleophilic aromatic substitution-type reactions, that is, ^{18}F -fluoride capture followed by reductive elimination to produce ^{18}F -labeled aromatics with C– ^{18}F bond formation occurring at the more electron-deficient substituent (18). Diaryliodonium precursors for structurally related mGlu₅ radiotracers have been radiolabeled (19) but were not pursued herein because of the lack

of regioselectivity. Nonetheless, diaryliodonium salts have been widely used for preclinical studies and were recently shown to be suitable for human use with an activated (electron-deficient) aromatic precursor of ^{18}F -flumazenil (20). Unlike diaryliodonium salts, which rely on an aryl auxiliary, diaryliodonium ylides use an electron-rich β -dicarbonyl auxiliary, resulting in a selective C– ^{18}F bond formation and increased chemical stability (9). Iodonium ylides were easily purified by silica flash chromatography, which is a challenge with diaryliodonium salts, and are bench-stable compounds at room temperature.

A high-yield radiosynthesis of ^{18}F -FPEB, via the iodonium ylide-based precursor **1**, resulted in $20\% \pm 5\%$ ($n = 3$) radiochemical yield ready for injection (Scheme 2, entry III) and represents a 10-fold increase over our previous methodology based on the NO_2 precursor (16). The present method is achieved (ready for injection) in 60 min, compared with 90 min by our previous method, with more than a 2-fold increase in specific activity (18 Ci/ μ mol). The production was easily automated and validated for routine radiopharmaceuticals, passing our quality control protocol (16). A reduced base concentration and temperature was able to suppress formation of an amide impurity (**2**), identified as a major byproduct formed by base-promoted hydrolysis of ^{18}F -FPEB (Scheme 1). Compound **1** has been stored at room temperature for 2 mo and has not shown signs of decomposition by structural characterization and chromatography and has not lost labeling efficiency when reacted with ^{18}F -fluoride. The radiochemical methodology demonstrated herein should prove to be widely applicable to several diagnostic PET imaging agents for mGlu₅ that share a similar structural scaffold to ^{18}F -FPEB (13).

CONCLUSION

The use of a spirocyclic hypervalent iodine(III)-mediated radiofluorination was shown to provide a high-yielding synthesis of the nonactivated aromatic ring of ^{18}F -FPEB and was validated for human imaging studies. A 10-fold increase in radiochemical yield (20%, non-decay-corrected) and more than a 2-fold increase in specific activity (666 GBq [18 Ci]/ μ mol) compared with our established clinical production procedure was achieved. The methodology described herein not only should facilitate widespread preclinical and clinical use of ^{18}F -FPEB but also represents the utility of iodonium ylides as a viable strategy for the practical

Entry	X	Labeling Conditions	Reported RCY of ^{18}F -FPEB	Reference
I	Cl	^{18}F -KF / K_{222} MW(45 W)	4%	14
II	NO_2	^{18}F -KF / K_{222} 150 $^\circ\text{C}$ or ^{18}F -TBAF, 150 $^\circ\text{C}$	1–5%	10, 15, 16
III		^{18}F -Et ₃ NF, 80 $^\circ\text{C}$	20%	This work

SCHEME 2. Comparison of ^{18}F -FPEB production yields for clinical research. *Non-decay-corrected radiochemical yield at end of synthesis relative to starting ^{18}F -fluoride.

radiofluorination of nonactivated aromatics with ^{18}F -fluoride and is suitable for human use.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18-USEC section 1734. We thank the Alzheimer’s Drug Discovery Foundation as well as Dr. Ivan Greguric and the Australian National Science and Technology Organisation for financial support. No other potential conflict of interest relevant to this article was reported.

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