Arene Radiofluorination Enabled by Photoredox-Mediated Halide Interconversion

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Article

Keywords: Positron Emission Tomography, Molecular Probes, Drug Candidates, C-18F Bonds, Halide Precursors, Site-selective Introduction

Posted Date: December 4th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-111390/v1

Version of Record: A version of this preprint was published at Nature Chemistry on December 13th, 2021.
See the published version at https://doi.org/10.1038/s41557-021-00835-7.

Abstract

Positron emission tomography (PET) is a powerful imaging technology that could visualize and measure metabolic processes in vivo and/or obtain unique information about drug candidates at early stages. Identification of new and improved molecular probes plays a critical role in PET, but its progress is limited in many situations due to the lack of efficient and simple labeling methods to modify biologically active small molecules and/or drugs. Although various approaches have been reported, current methods to radiofluorinate unactivated arenes are still limited. Here we document the discovery of a robust method for constructing C–18F bonds through direct halide/18F conversion in electron-rich halo(hetero)arene substrates. Based on readily available halide precursors and mild photoredox conditions, [18F]F- is efficiently introduced into a broad spectrum of organic molecules, including pharmaceutical compounds in a site-selective manner. Notably, the direct 19F/18F conversion method is demonstrated to be a simple and robust protocol for PET probe screening/preparation: this methodology not only identifies a new cancer imaging agent L-61-18F-COOH after a rapid screening of a tyrosine isomer library; but also allows the simple and high-yielding synthesis of the widely used PET agent L-[18F]FDOPA. Taken together, photoredox-mediated halide/18F interconversion strategies represent an innovative chemical tool to prepare new and clinically significant PET agents that are synthetically inaccessible or cumbersome to achieve by traditional methods.

Introduction

Positron emission tomography (PET) is one of the most sensitive non-invasive imaging techniques used in diagnosis and treatment monitoring of various human diseases, including oncological and neurological disorders[1,2]. Advances in imaging probe development have accelerated clinical adoption of PET, which in return also fostered a growing interest in establishing robust methodologies for synthesizing highly specific PET agents via the late-stage installation of short-lived radionuclides[3]. Because many small molecule pharmaceuticals and therapeutics contain aromatic or heteroaromatic systems within their framework[4-6], it is highly desirable to introduce radionuclides on these moieties in a synthetically facile and efficient manner. Fluorine-18 is arguably the most widely used short-lived PET isotope ($t_{1/2}$ ~110 min) due to its excellent imaging properties, wide availability and ideal half-life. It is often introduced using ^{18}F fluoride ($^{18}F^-$) although its incorporation into organic scaffolds is nontrivial as fluoride is a recalcitrant nucleophile[7-10]. A common strategy used for constructing aryl C(sp^2)–^{18}F bonds is nucleophilic aromatic substitution (S_NAr), which substitutes a (pseudo)halide with $^{18}F^-$ (Fig.1A). This is routinely used for the synthesis of PET agents with high molar activity[11-14]; however, its application is limited to electron-deficient (hetero)aromatic systems[15], thus restricting the classes of small molecules towards which radiofluorination is amenable. Consequently, systems detailing the nucleophilic radiofluorination of electron-neutral and -rich aromatics have been widely investigated over the past decade[3,16]. Progress towards this goal have largely focused on transition-metal mediated methods[17-23] or the development of specialized nucleofuges [24-28]. Despite notable advances, the widespread adoption of

these methods for radiotracer preparation is limited by the synthetic challenges associated with designing arene precursors for late-stage radiofluorination. Of the extant aromatic ^{18}F-fluorination approaches, aryl (pseudo)halides are typically used as intermediates enroute to prepare precursors based on aryl-palladium[17]/nickel complexes[18], aryl boronic acids[21]/esters[19], aryl stannanes[22]and aryl iodonium salts/ylides[20,23,24,29], which will then be radiofluorinated to generate the PET agent (Fig.1B). Clearly, there is a dearth of methods for the direct radiofluorination of electron-rich aryl halides[30]. Such a strategy is highly desirable given the stability and abundance of aryl chlorides and fluorides in therapeutics[31-33]. More importantly, this strategy would enable direct translation of readily available fluorinated therapeutics into ^{18}F-labeled radiopharmaceuticals though simple late-stage ^{19}F to ^{18}F conversion [34-36].

We recently disclosed two acridinium photoredox-mediated methods for arene radiofluorination in which arene cation radicals are used to selectively radiofluorinate C(sp^2)–H[37] and C(sp^2)–O[28] bonds. Inspired by our previous success, we explored the feasibility to directly convert an aryl halide into ^{18}F in electron-rich arenes. Upon single electron oxidation, we envisioned the resulting electron-deficient cation radical would trap the $^{18}F^-$ at the halide-bearing carbon. Reduction and expulsion of the halide nucleofuge will give the desired radiofluorinated arene (Fig. 1C). This radiofluorination strategy would obviate the need for lengthy, multi-step precursor synthesis, greatly simplifying product isolation in various situations, and lead innovative ways to prepare new and clinically significant PET agents that are synthetically inaccessible or cumbersome to prepare previously.

Results

To evaluate whether acridinium photocatalysts could promote halide/^{18}F exchange in electron-rich arenes, 1-chloro-4-methoxybenzene (1-Cl) was first tested with acridinium S1 in a multicomponent solvent system containing DCE/^{t}BuOH/MeCN. [^{18}F]TBAF and tetrabutylammonium bicarbonate (TBAB) were added to the solution which was then irradiated with a 450 nm laser along with air bubbling for 30 min at 0 ºC. We previously demonstrated these conditions promote efficient radiodeoxyfluorination and we were encouraged when we observed the formation of 1-^{18}F, albeit in 1.7% radiochemical conversion (RCC) as calculated by HPLC isolation. In our previous (radio)deoxyfluorination study[28], methoxy groups did not act as effective nucleofuges for the chemistry developed. However, the increased acidity of the C-H bonds in *O*-methyl group did represent a potential oxidation site that would compete with halide/^{18}F conversion in the presence of oxygen[38]. To avoid this potential side-reaction, the radiofluorination of 1-Cl was then conducted under nitrogen atmosphere, which successfully increased the isolation yield of 1-^{18}F to 12.8 ± 0.3% (n=3) with 71.25 GBq/μmol molar activity (MA).

With these preliminary results on hand, we then screened other nucleofuges commonly used in S_NAr reactions. As shown in Fig 2, 1-bromo-4-methoxybenzene (**1-Br**) gave comparable RCC with **1-Cl** whereas the 1-iodo-4-methoxybenzene (**1-I**) analog unsurprisingly gave much lower but still noticeable labeling efficiency. Interestingly, 1-fluoro-4-methoxybenzene (**1-F**) was found to provide the highest yield of

radiofluorinated product through direct ^{19}F to ^{18}F conversion (80.1%). This observation represents a significant breakthrough in the field because it allows simple and efficient conversion of electron-rich fluorinated bioactive compounds or pharmaceuticals to ^{18}F-labeled PET radiotracers directly. Before our report, arene-fluorine isotopic exchanges are mainly restricted to electron-deficient fluorinated compounds, which generally requires relatively high temperatures to proceed[35,36,39-41]. One potential limitation of this strategy is the relatively low molar activity (MA) due to the presence of inseparable aryl ^{19}F precursor. However, the MA could be significantly improved to acceptable levels by limiting the amount of precursors used in the reaction[42]. We also found that the aryl triflate (**1-OTf**) analog could be successfully radiofluorinated, albeit with lower yields. Interestingly, 1-methoxy-4-nitrobenzene (**1-NO_2**) was not a suitable substrate for this conversion despite the well-documented substitution of nitro groups in traditional S_NAr reactions. This is likely due to the oxidation potential of **1-NO_2** is higher than the excited state reduction potential of the catalyst.

To better understand the effect of substitution pattern on the halogen/^{18}F interconversion, we evaluated the scope of this method with a range of aromatic and heteroaromatic substrates (Fig 2). Increasing alkylation at the a-carbon relative to oxygen in *O*-alkylated 4-chlorophenol derivatives resulted in a 2- to 4-fold RCC increase, suggesting that labile C–H bonds adjacent to the *O*-atom could decrease reaction yields (**2**, **3**, **4-Cl**, **5-Cl**). This effect is less pronounced for ^{19}F to ^{18}F conversion, where minimal RCC differences were observed, for example both **4-F** and **5-F** were obtained in >80% RCC based on isolation. We also discovered Cl/^{18}F conversion could proceed efficiently under irradiation by blue LEDs on **5-Cl**, albeit with lower RCC. A *meta*-methyl substituent (**6**) resulted in moderate RCC improvement, while substituents *ortho* to the chlorine nucleofuge resulted in more efficient halide/^{18}F conversion (**7-9**). This observation is tentatively attributed to the enhanced stability of a putative captodative cation radical intermediate suggested in our previous findings[28,43-45]. 2,4-Dimethoxy-substituted aryl halides (**10-Cl**, **10-Br**, **10-I**) were labeled with $^{18}F^-$ leading to **10-^{18}F** in good, moderate and low RCCs, respectively. Interestingly, **10-NO_2** which is more electron rich than mono-methoxy **1-NO_2**, was successfully radiofluorinated in 49% RCC. The radiofluorination of 2,4,6- and 2,3,4-substituted chlorobenzenes (**11-14**) was accomplished with moderate to excellent RCCs. Desymmetrization of dihalogenated aromatics (**15** and **16**) was also demonstrated, although the reduced solubility of dibrominated **16** resulted in a lower RCC than the more soluble dichlorinated analog (**15**). More pronounced changes in radiofluorination efficiency were observed *O*-alkylated haloarenes bearing *ortho*-nucleofuges (**17-20**). Chloro- and fluoro-naphthalenes and their alkoxy-substituted derivatives were also successfully radiofluorinated (**21**-**23**). Aryl fluorides containing protected amines (**24, 25-F, 26-27**) undergo $^{19}F/^{18}F$ conversion with moderate to good RCC under the standard labeling conditions, with aryl chloride **25-Cl** demonstrating lower radiofluorination efficiency. Chloro- and fluoro-substituted heterocycles were also successfully radiofluorinated via Cl/^{18}F or $^{19}F/^{18}F$ conversion, as demonstrated for carbazoles **28-F** and **28-Cl**, *N*-benzyl indolinone **29**, 3,3-dimethy-3*H*-indoles **30-F** and **30-Cl**, *N*-methyl indazoles **31** and **32**, benzo[*b*]thiophene **33**, quinazoline-2,4(1H,3H)-dione **34**, pyridine **35**, and chromanone **36**. Additionally, 4-

(arylamino)quinazoline fragment **37** and its analog **38**, common pharmacophores in kinase inhibitors[46], were found to be competent substrates for radiofluorination via direct $^{19}F/^{18}F$ conversion.

To probe the chemo- and regioselectivity of the halide/^{18}F conversion, we studied substrates bearing more than one potential halogen nucleofuge (Fig. 3a). Radiofluorination of compound **39** provides both Br/^{18}F and Cl/^{18}F conversion products (**15-^{18}F**, **16-^{18}F**) in 1:1.4 ratio in favor of chlorine substitution. When the bromide was shifted to the *meta* position relative to the methoxy groups (**40**), selective Cl/^{18}F conversion (**40-^{18}F**) was observed. These results suggest that 1) chlorine is a better nucleofuge than bromine, and 2) the site of S_NAr is largely dependent on arene electronics. Next, we explored the selectivity between Cl/^{18}F conversion (S_NAr) and bimolecular nucleophilic substitution (S_N2), which is a commonly employed strategy to introduce ^{18}F into alkyl groups in PET radiotracer design[3]. Compound **41** is a substrate containing both aryl and alkyl chlorides (Fig. 3b). Selective Cl/^{18}F conversion (S_NAr) (**41-^{18}F**) was observed under photoredox conditions while heating the reaction to 100 °C resulted in the exclusive displacement of the alkyl chloride (**41-^{18}F-a**). Next, we probed the chemoselectivity between electron-rich and electron-deficient arenes within one molecule (Fig. 3c). Using compound **42** as our model substrate, we obtained exclusive $^{19}F/^{18}F$ conversion (**42-^{18}F**) with no traditional S_NAr product (**42-^{18}F-a**)[47]. Taken together, these results suggest that our halide exchange strategy is selective for electron-rich substrates using photoredox conditions. Additionally, radiofluorination of alkyl halides can be conducted in the presence of aryl halides through thermal activation.

We next applied our halide/^{18}F interconversion strategy towards the radiolabeling of known pharmaceuticals and bioactive molecules (Fig. 4a). Clofibrate (**43**) and Boc-protected atomoxetine (**44**) were directly converted to ^{18}F-fluorinated analogs (**43-^{18}F**, **44-^{18}F**) through aryl-Cl/^{18}F exchange while ^{18}F-labeled flurbiprofen methyl ester (**45**) and diflunisal (**46**) were obtained (**45-^{18}F, 46-^{18}F**) through direct $^{19}F/^{18}F$ conversion. Mono-Boc protected fluorodopamine (**47-F**) was efficiently labeled through $^{19}F/^{18}F$ conversion (**47-^{18}F**) in excellent RCC. Fluorinated dopamine **47-^{18}F** could also be synthesized through Cl/^{18}F exchange with a lower RCC but higher molar activity. ^{18}F labeled 2-phenoxyaniline derivatives have been investigated as translocator protein (TSPO)-specific PET agents for neuroinflammation imaging[48-50]. Using our aryl-Cl/^{18}F conversion method, ^{18}F successfully replaced the chlorides in 2-phenoxyaniline derivatives, leading to potential new imaging agents (**48-^{18}F**, **49-^{18}F**, and **50-^{18}F**) targeting TSPO. Additionally, [^{18}F]fluorouracil (**53-^{18}F**), an important PET agent in oncology, is readily obtained through aryl-Cl/^{18}F conversion from **52** followed by a simple deprotection (Fig. 4b). Given that **52** is easily synthesized from the inexpensive, commercial trichloropyrimidine **51**, our labeling route offers a promising alternative to existing methods for synthesizing [^{18}F]fluorouracil[24,51,52].

We further evaluated the application of direct $^{19}F/^{18}F$ conversion in electron rich arenes, due to its exceptional efficiency and simplicity. Although the resulting PET agents may have reduced molar activity, it still represents a broadly useful technology for studying the pharmacokinetics/pharmacodynamics of

fluorine-containing drugs[34-36] or imaging transporter-mediated processes[53,54], such as synthesizing fluorinated amino acid agents for large neutral amino acid transporter (LAT1) imaging[39,41]. We were particularly interested in synthesizing ^{18}F-labeled tyrosine analogs.[55-59] Amino acid metabolism represents another important class of pathways in cancer progression in addition to glucose metabolism. Using our direct ^{19}F/^{18}F conversion, ^{18}F could be easily installed on the aromatic core of a small library of fluorinated *O*-methyl tyrosine derivatives (**54-63**) (Fig. 5a). Good to excellent RCCs were observed when the fluorine nucleofuge is located at the *ortho* or *para* position relative to the methoxy group (**54**, **56-60**, **62**, **63**). Lower but still significant labeling efficiency was observed when the fluorine is located at *meta* position of the methoxy group (**55**, **61**). After a simple deprotection (See SI for details), a total of ten ^{18}F-labeled *O*-methyl tyrosines were easily obtained as potential PET agents, which were then evaluated in the MCF7 breast cancer tumor model. Although **54-58, 60-62** all bearing one methoxy and one fluorine group on the electron rich arene ring, the position of substitution significantly impacted their tumor uptake and clearance profile (Fig. 5b). Most of the PET tracers demonstrated initial prominent tumor uptake at 1h post injection followed by obvious washout at 3h (**54-^{18}F-COOH**, **55-^{18}F-COOH**, **56-^{18}F-COOH**, **58-^{18}F-COOH, 59-^{18}F-COOH, 62-^{18}F-COOH, 63-^{18}F-COOH**). In contrast, PET agents **57-^{18}F-COOH**, **60-^{18}F-COOH, 61-^{18}F-COOH** showed high and persistent retention in the MCF-7 tumor within the same timeframe. While amino acid analogs with initial high uptake and clearance (leading to high contrast) are great candidates for imaging applications, other analogs with prolonged tumor retention provides amino acid backbones for potential therapy applications in which radioiodinated (^{131}I) or boronated (^{10}B) analogs can be used as cancer treatments via radioactive iodine therapy[60] or boron neutron capture therapy[61], respectively. Although most of the ^{18}F-labeled tyrosine analogs demonstrated apparent pancreatic uptake, simply introducing one extra fluorine to the arene ring (difluorinated **63-^{18}F-COOH**) greatly reduced uptake in pancreas while still maintaining prominent tumor uptake. The agent was washed out through gallbladder with increased tumor to muscle ratio. The effect of stereo definition of amino acids was also studied based on **61-^{18}F-COOH**, which demonstrated high and persistent tumor uptake. Although the contrast remains comparable at 1h post-injection (p.i.), *L*-**61-^{18}F-COOH** doubled the tumor uptake along with increased tumor retention at 3h p.i. compared with *D*-**61-^{18}F-COOH**. Clearly, the potential transformative impact of our direct ^{19}F/^{18}F conversion was successfully demonstrated by the discovery of the innovative PET agent *L*-**61-^{18}F-COOH** for cancer imaging.

In addition to developing new and improved PET agents, our halide/^{18}F interconversion could revolutionize the preparation of existing PET agents that are complicated and/or challenging to synthesize traditionally (Fig. 6). For example, 6-[^{18}F]Fluoro-L-DOPA ([^{18}F]FDOPA) is employed as an important PET agent for Parkinson's disease (PD), brain cancer, and other diseases since the 1980s[62]. Despite recent progress, its synthesis remains a challenge in many radiochemistry labs due to the complicated procedures associated with tracer preparation[63-68]. Based on our halide/^{18}F interconversion methods, *O*-methylated DOPA precursors ***L*-64-Cl** and ***L*-64-F** were successfully radiofluorinated in 4.2% RCC (***L*-64-Cl**), and 73.4% RCC (***L*-64-F**) respectively. The resulting product ***L*-64-^{18}F** could be easily

deprotected to *L*-[^{18}F]FDOPA with 97.1% RCC and >99% enantiomeric excess (*ee*). No racemization was observed under our labeling conditions. We also found the ^{19}F/^{18}F conversion in ***L*-64-F** remains highly efficient after replacing the laser with more readily available LEDs, performing the reaction without ice cooling, reducing precursor concentration, or shorten the reaction to 5 min at room temperature. The methoxymethyl (MOM)-protected analog (***L*-65**) and three constitutional isomers of DOPA (**66-68**) were efficiently labeled via Cl/^{18}F and/or direct ^{19}F/^{18}F conversion as well. Encouraged by the initial successes of our method, we explored the feasibility of synthesizing *L*-[^{18}F]FDOPA on scales more relevant to clinical application. Starting from 0.93–1.11 GBq [^{18}F]TBAF, [^{18}F]FDOPA was isolated in 42% and 37.5% n.d.c. RCY (non-decay corrected radiochemical yield) when 0.01 and 0.005 mmol of ***L*-64-F** were used respectively (Fig. 6b). Further increasing the scale to ~37 GBq [^{18}F]F$^-$ leaded to > 11 GBq of [^{18}F]FDOPA with >30% n.d.c. RCY (> 99% *ee,* 1.51GBq/mmol) in 100 min (Fig. 6c). The obtained molar activity is much higher than early [^{18}F]F_2 gas method[69] and comparable with other isotopic exchange strategies[39]. Although high molar activity is not mandatory for the investigation of the neuronal dopaminergic metabolism[63], it could be further improved by reducing precursor loading and starting from higher amounts of activity. Taken together, this new strategy demonstrates a notable advance for [^{18}F]FDOPA preparation over the existing methods, considering the use of stable, readily available precursors, a simple and mild labeling procedure, and high labeling efficiency.

Conclusion And Outlook

In conclusion, the photoredox-mediated halide/^{18}F conversion represents a simple and innovative tool to radiofluorinate electron-rich haloarenes, which has been a longstanding problem in the field. The success of this strategy is most pronounced for aryl chlorides and fluorides, with the latter enabling direct ^{19}F/^{18}F isotopic exchange. Applications of our method were demonstrated by the success radiofluorination of electron-rich halo(hetero)arene substrates, known pharmaceuticals and bioactive molecules, which were highlighted by the discovery of innovative cancer imaging agent *L*-61-^{18}F-COOH and the simple/robust preparation of [^{18}F]FDOPA. The discovery of direct ^{18}F labeling of aryl halides complements recent advances on other labeling methods, which would provide direct access to new and/or clinically significant PET agents that are synthetically inaccessible or cumbersome to prepare previously.

Methods

General procedure for the photoredox-mediated halide/^{18}F interconversion. The substrate (0.01-0.05 mmol) and photocatalyst (**S1**, 1.5 mg) were weighed into a 1.5 ml Eppendorf tube and transferred (with solvent when the substrate is liquid or oil) into a 5 ml V-vial via pipette. DCE (300 µl), anhydrous MeCN (45-65 µl), ^{t}BuOH(400 µl) and 25 µl of TBAB in MeCN solution (~60 mg/ml) were sequentially added to the V-vial. Then a 10-30 µl aliquot of [^{18}F]TBAF in MeCN (typically 10-30 mCi) was added to the reaction vial via pipette. The reaction V-vial was then fixed either on an iron support and cooled using an ice bath or on a block without cooling. A needle connected to an N_2 filled balloon was inserted to the bottom of

the V-vial and the reaction medium was continuously sparged throughout the entire reaction time. The reaction was then irradiated top-down with a laser (MDL-D-450, 450 nm, 3.5 W after fibre coupling) (Supplementary Figure 6) or an A160WE Tuna Blue Kessil LED lamp (Supplementary Figure 7) for 30 min. The resulting solution was diluted and evenly mixed with MeCN (0.5-1ml). An aliquot of the reaction mixture (typically 300-1000 μCi) was taken for radio-HPLC analysis. The activity injected into HPLC was measured (this activity was denoted by α) and the time was recorded. The fraction corresponding to radiolabelled product was collected and the activity was measured (this activity was denoted by β) and the time was recorded. The decay-corrected β could be calculated from the recorded isolation time of each substrate. The radiochemical conversion (RCC) was obtained by dividing the decay-corrected β by α. Co-injection of the purified ^{18}F-labelled compound with commercial or synthesized ^{19}F standard via HPLC was used to confirm the identity of the radiolabelled compound.

Radio-HPLC analysis and characterization for ^{18}F-radiolabelled arenes. All ^{18}F-labelling reactions were performed according to the general procedure unless otherwise noted. Each labelling reaction, starting activity ([^{18}F]TBAF), injected and collected activities, isolation time, decay corrected activity and calculated radiochemical conversion (RCC) are summarized in a table for each substrate. All ^{18}F-labelled products were analyzed and characterized according to the general HPLC conditions listed in supplementary information at section 3.3. Crude radio-HPLC traces of each reaction (labelled with reaction number), HPLC traces of purification and co-injection were listed. The collected ^{18}F-labelled product from crude HPLC analysis may require further HPLC-purification before co-injection with its corresponding ^{19}F standard. The red HPLC traces in the following spectra were obtained with a UV signal at 212 nm unless otherwise noted. The black HPLC traces represent the radio signal.

Synthesis of [^{18}F]FDOPA from preformed [^{18}F]TBAF. The FDOPA precursor *L*-64-F (0.01 or 0.005 mmol) and Photocatalyst S1 (1.5 mg) were dissolved in the solution of DCE/^{t}BuOH/MeCN in a 5 ml V-vial. After addition of the [^{18}F]TBAF and $TBAHCO_3$ (25 μl), the resulted solution (~1 ml) was top-down irradiated for 20 min under 450 nm laser (450 nm, 3.5 W after fibre coupling) with a N_2 balloon sparge at room temperature. The resulting reaction solution was diluted with 1 ml MeCN and passed through an aluminum cartridge (preconditioned with 5 ml DI water) to remove the unconverted ^{18}F-fluoride. Rinse the reaction vial with another 1 ml MeCN which was then passed through the same aluminum cartridge. The elution was collected in another 5 ml V-Vial and caped with a Teflon-lined septum screw cap equipped with a vent needle. The solvent was removed under 100 ^{o}C with argon stream. Argon flow was then stopped and the vent needle was removed. 200 μl HI (57 wt.% in H_2O) were then added into the V-vial and the mixture was heated under 160 ^{o}C for 10 min. A vent needle was then equipped before water (300 μl) and saturated $NaHCO_3$ solution (400 μl) was slowly added to the V-vial. The resulting aqueous solution

was passed through a HPLC filter to remove the insoluble catalyst residue. The collected solution was then purified on HPLC to give the product [^{18}F]FDOPA.

Scale-up synthesis of [^{18}F]FDOPA starting from [^{18}F]F$^-$. The aqueous solution of [^{18}F]F$^-$ fluoride produced via the ^{18}O(p,n)^{18}F reaction by proton irradiation (40 μA) was delivered to a hot cell equipped with manipulators and collected in a 5 ml V-vial containing 5 ml TBAB (20%) water solution . This aqueous solution was azeotropically dried with anhydrous MeCN (1 ml × 5) under a stream of Argon at 100 °C. After removing the water, the V-vial was removed from the heater. The solution of precursor *L*-64-F (0.01 mmol) and photocatalyst (S1, 1.5 mg) in DCE/^{t}BuOH/MeCN (5/4/1, 1 ml) was then added into the V-vial. The [^{18}F]FDOPA was then obtained after the same reaction and purification procedure as the synthesis starting from preformed [^{18}F]TBAF.

Data availability

All the data generated or analysed during this study are included in this article (and its Supplementary Information files).

Declarations

Acknowledgments

This work was supported in part by the National Institutes of Health (NIBIB) R01EB029451 (Z.L. and D.A.N.), 5R01CA233904 (Z.L.), UNC LCCC pilot grant (Z.L. and D.A.N.), 1S10OD023611 (Z.L.) and the startup fund from UNC Department of Radiology, Biomedical Research Imaging Center, and UNC Lineberger Comprehensive Cancer Center (Z.L.). N.E.S.T. and V.A.P are grateful for NSF Graduate Research Fellowships. We thank Dr. Gerald T. Bida for assistance with cyclotron operation, and the University of North Carolina's Department of Chemistry Mass Spectrometry Core Laboratory, especially Diane Weatherspoon, for their assistance with mass spectrometry analysis.

Author contributions

W.C. discovered the halides/^{18}F conversion project, prepared the substrates, ^{19}F-standards and performed the radiolabeling reactions. H.W. conducted the animal imaging studies and accomplished PET imaging data collection and analysis. N.E.S.T. was involved in the discovery of the ^{19}F/^{18}F exchange reaction. V.A.P. and K.L. assisted in the synthesis and analysis of substrates. T.Z. assisted in the animal studies. Z.W. contributed to the initial discussion. D.A.N. and Z.L. conceived and supervised the project and

experiments. W.C., D.A.N. and Z.L. wrote the manuscript. N.E.S.T. and V.A.P assisting in editing the manuscript.

Competing interests

The authors have filed a provisional US patent on the basis of the research in this manuscript.

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Figures

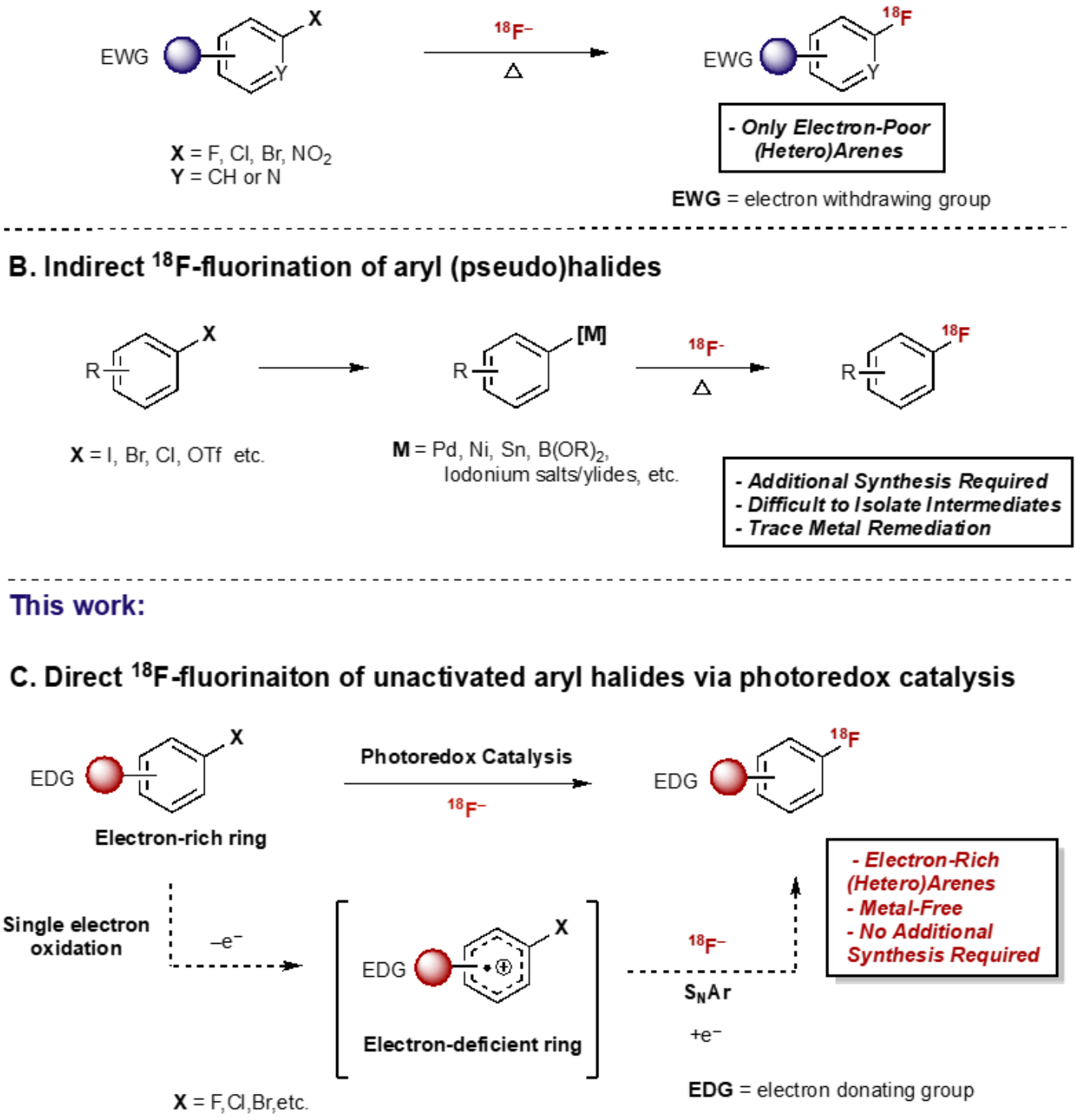

Figure 1

Nucleophilic arene 18F-fluorination. (A) SNAr reaction on activated (electron-deficent) arenes (B) Indirect 18F-fluorination of aryl(pseudo) halides (C) Direct 18F-fluorinaiton of unactivated(electron-rich) aryl halides via photocatalysis

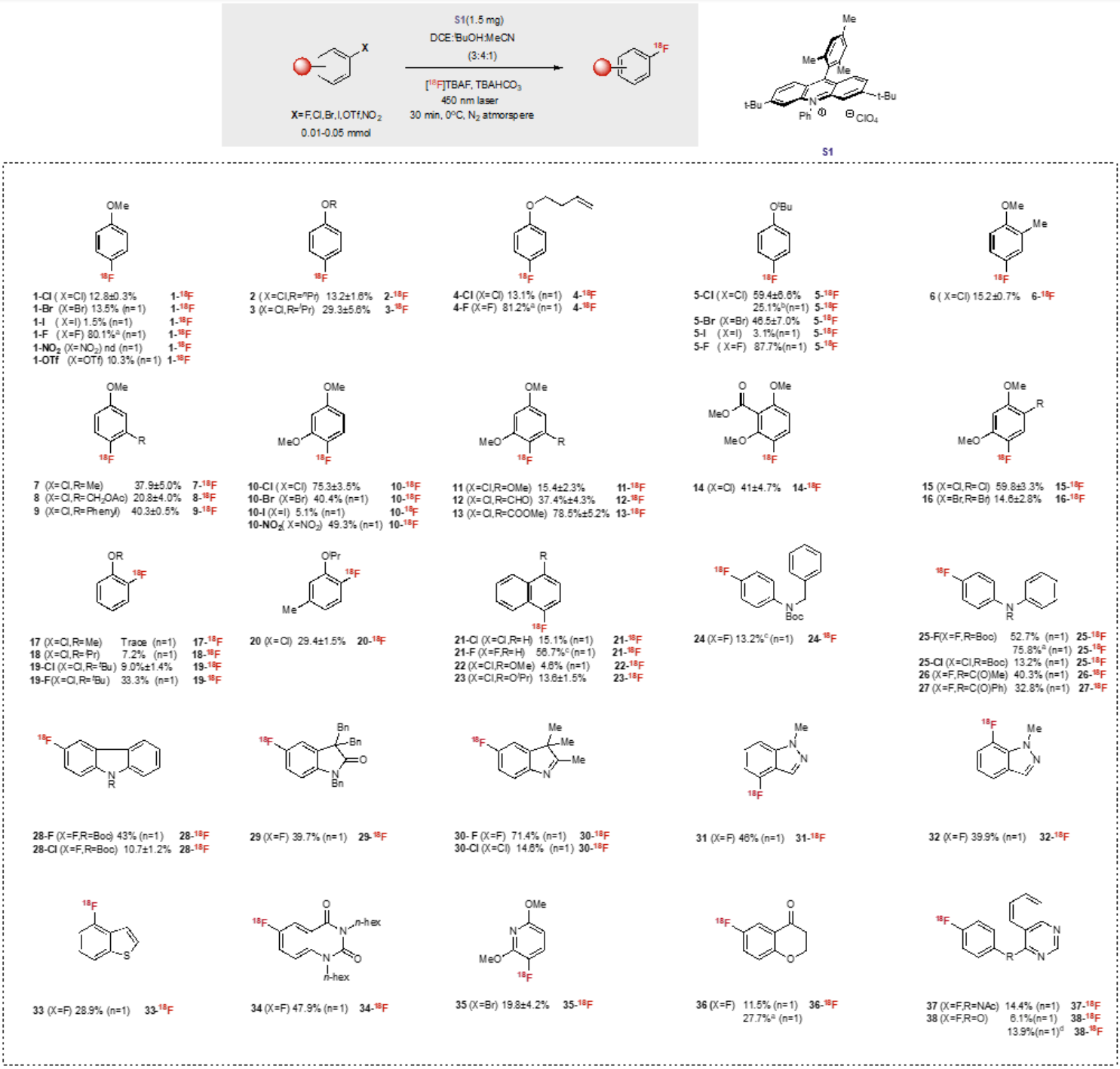

Figure 2

Reaction scope of direct 18F-fluorination of aryl halides via halide/18F exchange. All radiochemical conversions (RCCs) were calculated by HPLC isolation and averaged over 3 experiments unless otherwise noted. 0.37-1.11 GBq [18F]TBAF were generally used for the labeling. 0.05 mmol substrate were used for all the labeling reactions except Ar-F which used 0.01 mmol unless otherwise noted.a0.05 mmol substrate. bBlue LED instead of laser. c0.02 mmol substrate. dReaciton was performed under air.

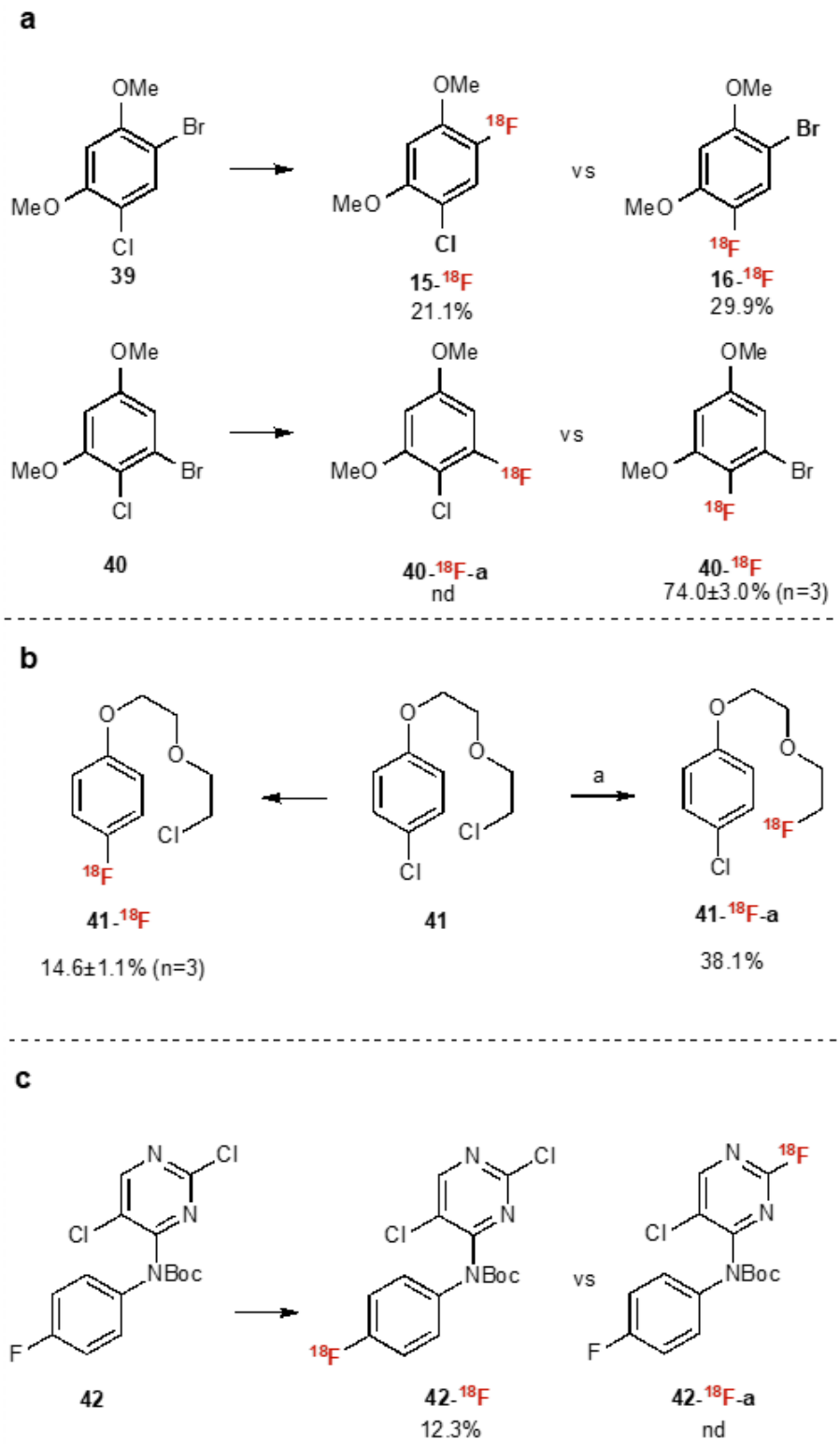

Figure 3

Chemo-and regioselectivity study of aryl halide/18F exchange. All halide/18F exchange reactions were conducted under standard condition listed on Fig.2. a,comparison reactivity of ArBr and ArCl. b, Comparison of reactivity of SNAr and SN2 under light condition. c, Comparison of reactivity of electron rich and electron deficient SNAr reaction. a[18F]TBAF, MeCN, 100oC, 10 min (See SI for detail).

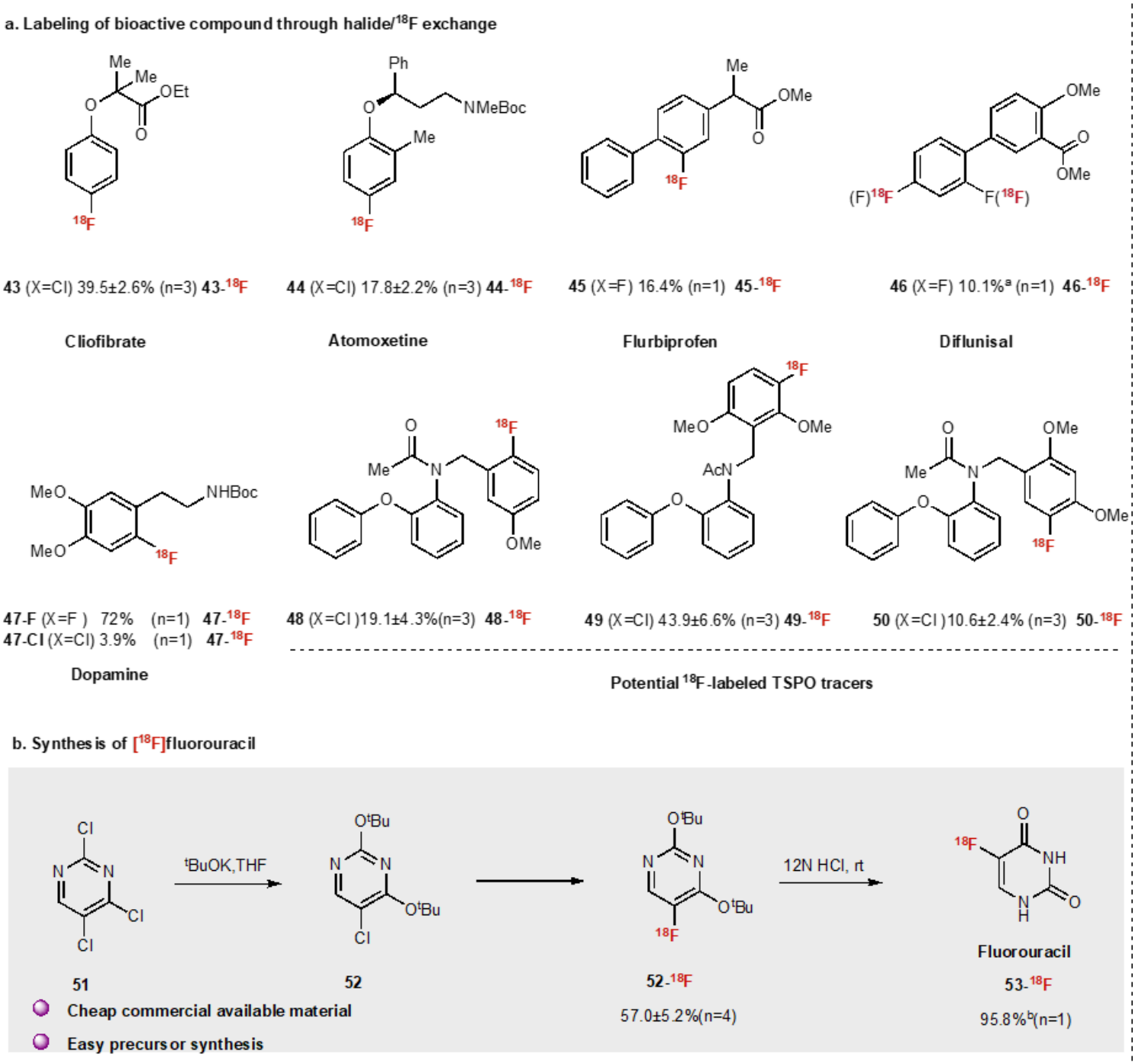

Figure 4

Application of the halide/18F strategy. All halide/18F exchange reactions were conducted under standard condition listed on Fig.2. a, Labeling of bioactive compound. b, Synthesis of [18F]fluorouracil. a0.05 mmol substrate. bDeprotection yield.

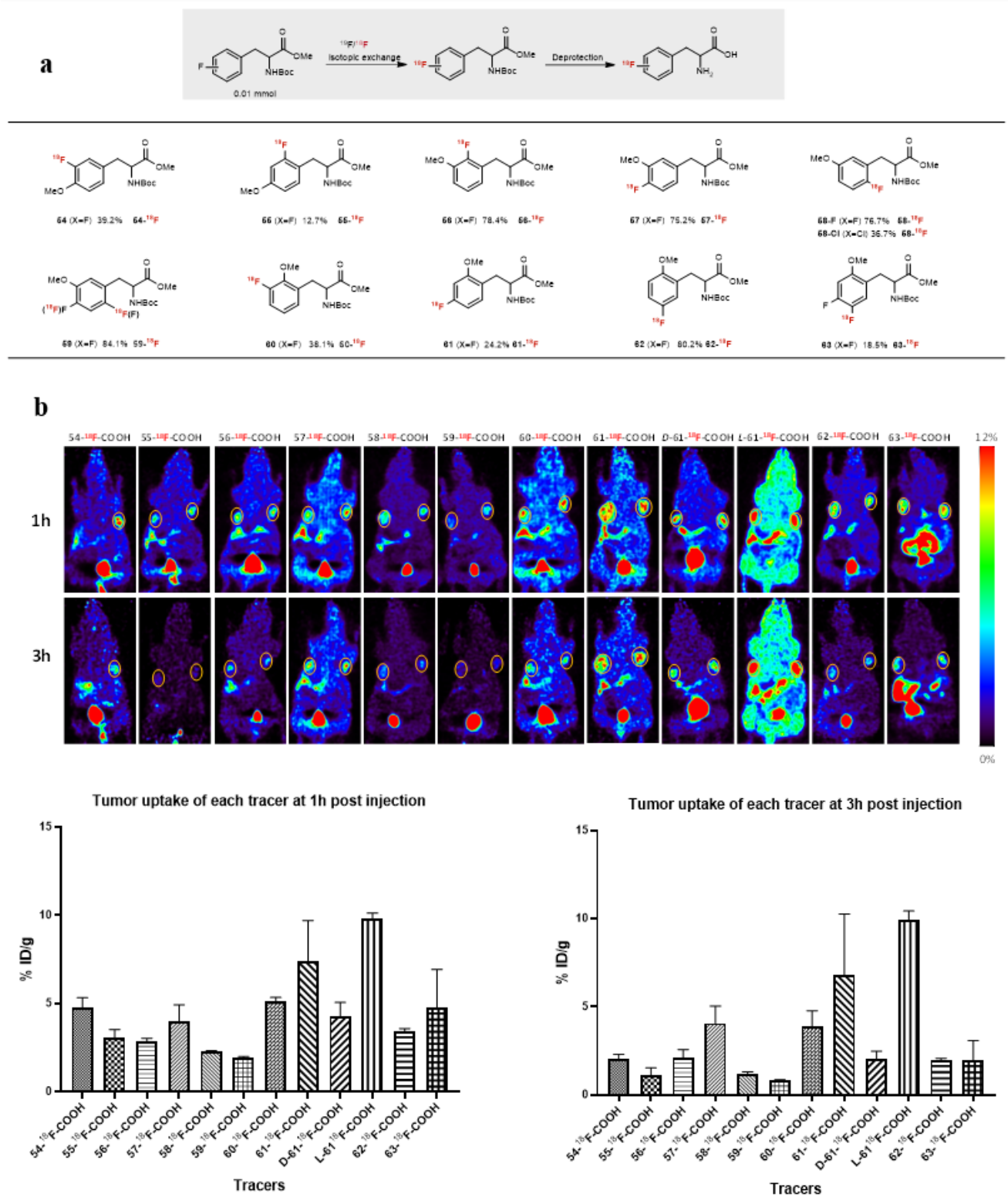

Figure 5

Screening of 18F-labeled tyrosines in the MCF7 breast cancer tumor model system. All the labeling reactions were conducted under standard condition listed on Fig. 2. a. Labeling of tyrosine derivatives. b. PET imaging of 18f-labeled tyrosines in the MCF7 breast cancer tumor (circled in the pictures).

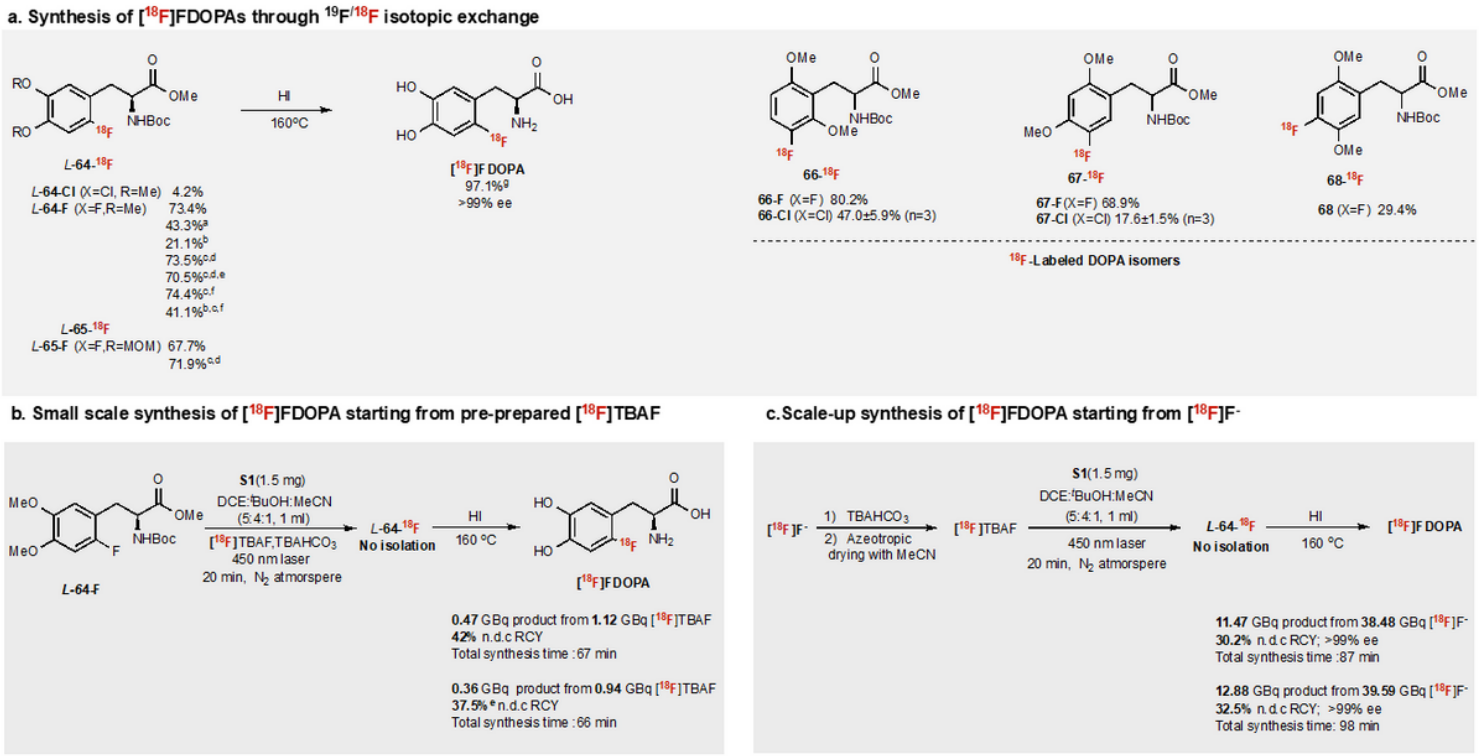

Figure 6

Synthesis of [18F]FDOPA. All halide/18F exchange reactions were conducted under standard condition listed on Fig.2 unless otherwise noted. Radiochemical conversions (RCCs) were calculated by HPLC isolation. 0.05 mmol substrates were used for Cl/18F exchange labeling reactions; 0.01 mmol substrate used for 19F/18F exchange reaction unless otherwise noted . aBlue LED was used instead of laser. bNo DCE were added in the reaction. cNo ice cooling and 500 l DCE were used. dReaction ran 20 min. e0.005 mmol substrate. fReaction ran 5 min. gDeprotection yield.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- 18FexchangeSI.pdf