Derisking the Cu-Mediated ^{18}F-Fluorination of Heterocyclic Positron Emisssion Tomography Radioligands

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ABSTRACT: Molecules labeled with fluorine-18 (^{18}F) are used in positron emission tomography to visualize, characterize and measure biological processes in the body. Despite recent advances in the incorporation of ^{18}F onto arenes, the development of general and efficient approaches to label radioligands necessary for drug discovery programs remains a significant task. This full account describes a derisking approach towards the radiosynthesis of heterocyclic PET radioligands using the copper-mediated ^{18}F-fluorination of aryl boron reagents with ^{18}F-fluoride as a model reaction. This approach is based on a study examining how the presence of heterocycles commonly used in drug development affects the efficiency of ^{18}F-fluorination for a representative aryl boron reagent, and on the labeling of more than fifty (hetero)aryl boronic esters. This set of data allows for the application of this derisking strategy to the successful radiosynthesis of seven structurally complex pharmaceutically-relevant heterocycle-containing molecules.

INTRODUCTION

Therapeutic innovation is increasingly challenging due to the complexity of the physiopathology of diseases where there is a high unmet medical need. For known and new biological targets, positron emission tomography (PET) is a quantitative molecular imaging technology that can provide valuable insight on the in vivo behavior of drug candidates much earlier in the drug discovery pipeline. In practice, PET requires molecules labeled with a positron-emitting radioisotope. For these studies, ^{18}F is one of the radioisotopes of choice since a significant proportion of drugs on the market contain a fluorine substituent, and the half-life of ^{18}F (110 minutes) poses less constraint for radiosynthesis and imaging time in comparison with that of ^{11}C (20 minutes).[1] Despite the recent progress made in the field of ^{18}F-radiochemistry, one outstanding challenge is the labeling of complex molecules, especially those featuring one or multiple heterocycles often seen in medicinal chemistry.[2] The molecular properties of these ring systems have benefited drug discovery due to their unique electronic distribution, shape and scaffold rigidity.[3] These motifs can tailor potency, physicochemical and pharmacokinetic properties, and are therefore equally important in PET radioligand design. Today, most studies aimed at defining the scope of a new ^{18}F-labeling method consider the steric and electronic properties of the substrate, as well as functional group tolerance, but lack information on compatibility with heterocycles. As a result, late stage ^{18}F-incorporation can become a high-risk process for the labeling of molecules possessing one or more heterocyclic systems; indeed, significant time is invested in the synthesis of precursors, which may not be suitable for the intended ^{18}F-radiolabeling reaction. Chemists have developed high-throughput screening approaches for the rapid evaluation of functional group compatibility and the generality of the selected reaction conditions, including tolerance to heterocyclic rings. Particularly noteworthy is the chemical robustness screen developed by Glorius and co-workers.[4] However, no substantial studies of this kind have been carried out in radiochemistry.[5]

Herein, we describe a derisking strategy towards the ^{18}F-labeling of complex molecules, using the Cu-mediated oxidative nucleophilic ^{18}F-fluorination of aryl boronic esters as a model reaction.[6] Our approach is based on screening experiments which provide information regarding the tolerance of this reaction towards a selection of heterocycles, in addition to offering insights on the parameters affecting oxidative nucleophilic ^{18}F-radiofluorination. With this study, we aim to aid potential users of this reaction in conceiving retro-radiosynthetic plans that maximize the chances of successfully radiolabeling complex heterocyclic PET radioligands (Fig. 1A,B). We exemplify this approach with the radiosynthesis of seven ^{18}F-labeled medicinally-significant molecules **[^{18}F]1**-**[^{18}F]7**, all featuring one or more heteroatom-containing ring systems (Fig. 1C).

RESULTS AND DISCUSSION

Our first study, borne from an academic-industrial partnership between our laboratory and UCB Biopharma, showed that aryl boronic esters are amenable to

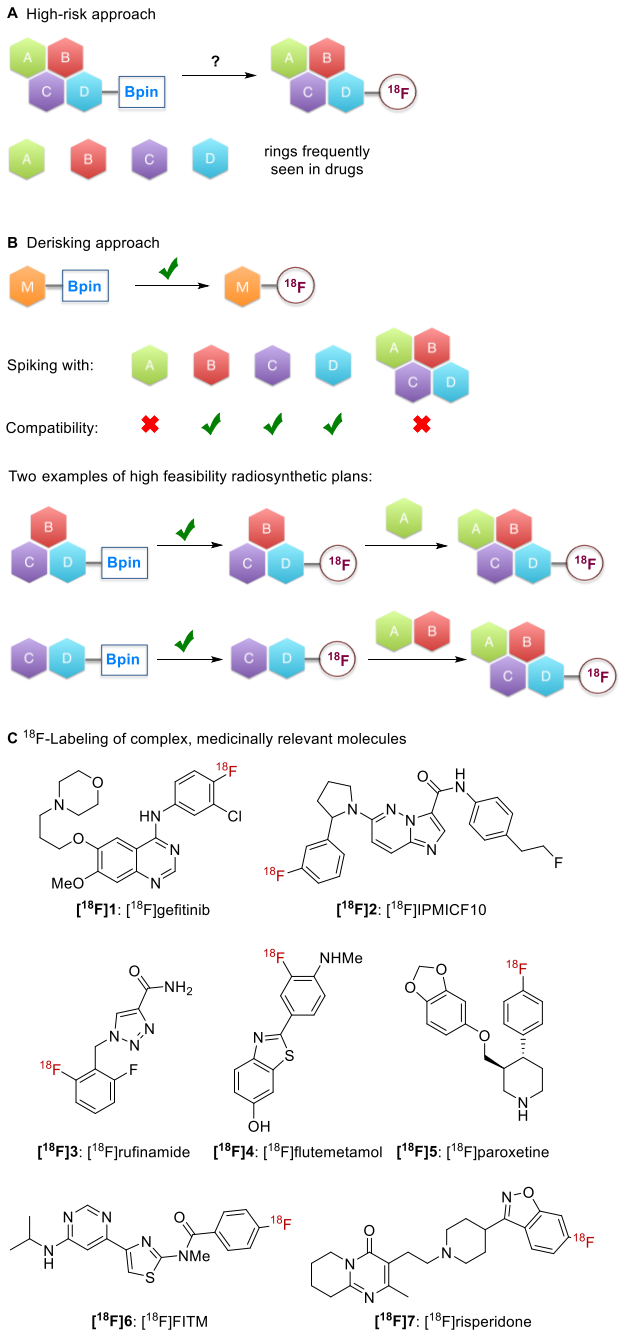
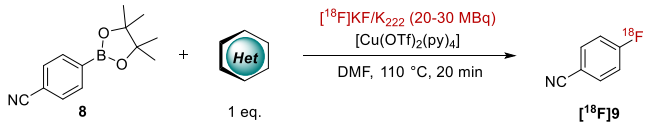


Figure 1. (A) Late-stage ^{18}F-fluorination of complex targets featuring multiple heterocycles (A, B, C, D) is a high-risk approach. **(B)** A rapid screen on the compatibility of the reaction of a readily available model substrate (M) in the presence of each heterocycle and/or the target molecule provides information on feasibility for a final step ^{18}F-radiofluorination. As a result, new high feasibility retrosynthetic schemes can be designed featuring a post-fluorination step to introduce any incompatible heterocycle (here A). **(C)** Seven medicinally-relevant molecules successfully ^{18}F-labeled using the derisking strategy.

nucleophilic ^{18}F-fluorination with potassium ^{18}F-fluoride in the presence of [Cu(OTf)$_2$py$_4$] when the reaction is performed in *N,N*-dimethylformamide (DMF) at 110 °C.[6] The reaction is compatible with automation, and both higher Cu:substrate ratio (up to 1.5:1) and the replacement of DMF with *N,N*-dimethylacetamide (DMA) improved the radiochemical conversions (RCCs) for electron-deficient arenes;[7] in addition, [Cu(OTf)$_2$py$_4$] could be replaced with Cu(OTf)$_2$ and pyridine.[7,8] The influence of heterocycles on the feasibility of this process is best contextualized with some mechanistic considerations. Ribas followed by Wang demonstrated that the Cu-catalyzed nucleophilic fluorination of arenes proceeds via Cu(III) intermediates in geometrically-constrained systems.[9] The fluorination of aryl iodides with [Cu(OTf)(*t*BuCN)$_2$] and AgF was proposed by Hartwig and co-workers to occur by oxidative addition to form a Cu(III) intermediate followed by C–F reductive elimination from an aryl copper(III) fluoride.[10] A high valent Cu(III) species was also invoked by Sanford and co-workers in the reaction of (hetero)aryltrifluoroborate salts with KF and Cu(OTf)$_2$.[11] These precedents led us to examine the reactivity of a preformed aryl-Cu(III) complex derived from azacalix[1]arene[3]pyridine with [^{18}F]KF in DMF at 110 °C.[12] Successful ^{18}F-fluorination under carrier-added conditions provided experimental evidence that a high-valent aryl-Cu(III) species is amenable to ^{18}F–C bond formation, and is therefore a plausible intermediate on the pathway converting pinacol-derived aryl boron reagents into ^{18}F-labeled aryl fluorides.[12] In the ^{18}F-labeling of aryl boronic esters, air is highly beneficial for ^{18}F-fluorination,[12] indicating that the Cu(III) species could be produced by direct oxidation; however a Cu(II) into Cu(III)/Cu(I) disproportionation pathway cannot be discounted. We anticipated that some heterocycles could influence ^{18}F-fluorination by facilitating the transmetalation of the aryl group from boron to copper, or the reductive elimination from Cu(III)^{18}F intermediates, whilst others with strongly Lewis basic coordinating heteroatoms could prevent ^{18}F-fluorination by generating unreactive copper species.

Our first objective was to categorize heterocycles by their compatibility with the Cu-mediated ^{18}F-fluorination of aryl boron reagents. The ^{18}F-fluorination of a model aryl boronic ester was performed in the presence of one molar equivalent of heterocycle in order to emulate the presence of the heterocycle within a target molecule, and to assess the impact on ^{18}F-labeling efficacy. We selected 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzonitrile **8** for these experiments, a substrate affording 4-[^{18}F]fluorobenzonitrile **[^{18}F]9** in moderate radiochemical conversion (RCC) (34% ± 15%, n = 122) upon treatment with [^{18}F]KF and [Cu(OTf)$_2$py$_4$] in DMF for 20 minutes at 110 °C (Table 1).[12] The heterocycles used in the additive screen are present in a greater than ten-fold excess with respect to the copper complex (molar ratio for **8**:heterocycle:[Cu] = 11:11:1, Table 1); the effects of the heterocycles are therefore pronounced. The reactions were analyzed using radio-TLC/HPLC, providing a

Table 1. Use of 8 as a Model Substrate for Studying the Influence of Heterocycles on Radiochemical Conversion



RCC (No heterocycle): 34% ± 15% (n = 122)

Minimum RCC: 3%
Maximum RCC: 73%

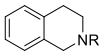
Key: RCC < 5% | 5% ≤ RCC < 20% | RCC ≥ 20%

10a R = H: 0%, 0%
10b R = Me: 0%, 0%
10c R = Bn: 2% ± 2%[a]
10d R = Boc: 40% ± 17%[a]

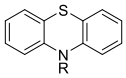
11a R = H: 0%, 0%
11b R = Me: 0%, 0%
11c R = Bn: 4% ± 2%[a]
11d R = Boc: 24%, 61%

12a $R^1 = R^2$ = H: 0%, 0%
12b R^1 = Me, R^2 = H: 4%, 4%
12c R^1 = Bn, R^2 = H: 21%, 26%
12d R^1 = Bn, R^2 = Boc: 54%, 76%

13a R = H: 0%, 0%
13b R = Me: 7%, 15%
13c R = Bn: 39% ± 13%[a]

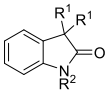


14a R = H: 0%, 0%
14b R = Bn: 33%, 41%



15a R = H: 0%, 0%
15b R = Me: 12%, 26%

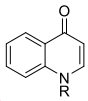
16a R = H: 1%, 1%
16b R = Me: 40%, 44%



17a $R^1 = R^2$ = H: 0%, 0%
17b R^1 = H, R^2 = Me: 13%, 24%
17c $R^1 = R^2$ = Me: 38%, 42%

18a $R^1 = R^2$ = H: 0%, 1%
18b R^1 = H, R^2 = Me: 3%, 5%
18c $R^1 = R^2$ = Me: 34%, 36%

19a $R^1 = R^2$ = H: 2%, 9%
19b R^1 = H, R^2 = Me: 12% ± 6%[a]
19c $R^1 = R^2$ = Me: 26%, 35%



20a R = H: 2%, 2%
20b R = Me: 45%, 59%

21 17%, 34%

22 31%, 35%

23 27%, 63%

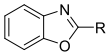
24 37%, 62%

25 13%, 42%

26 42% ± 8%[a]

27 61%, 69%

28 37%, 40%



29a R = H: 19%, 23%
29b R = Ph: 24%, 32%

30 45%, 58%

31a R = H: 15%, 21%
31b R = Me: 40%, 44%

32 53% ± 14%[a]

33 42% ± 12%[a]

34 25%, 45%

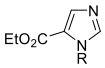
35 37% ± 9%[a]

36a R = H: 0%, 0%
36b R = Me: 74%, 81%

37a R = H: 0%, 0%
37b R = Me: 40%, 48%

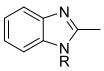
38a R = H: 0%, 0%
38b R = Me: 7%, 7%

39a R = H: 0%, 0%
39b R = Me: 29%, 31%



40a R = H: 0%, 0%
40b R = Me: 62%, 78%

41a R = H: 0%, 0%
41b R = Me: 0%, 0%
41c R = Boc: 7%, 9%



42a R = H: 0%, 0%
42b R = Me: 33%, 77%

43a R = H: 0%, 0%
43b R = Bn: 53%, 68%

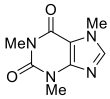
44a R = H: 0%, 0%
44b R = Me: 44%, 46%

45a R = H: 0%, 0%
45b R = Bn: 72% ± 13%[a]

46a R = H: 0%, 0%
46b R = Bn: 42%, 47%

47 14%, 22%

48a R = H: 1%, 1%
48b R = Me: 17%, 32%



49 36%, 53%

50 69% ± 6%[a]

51 0%, 0%

52 26%, 28%

53 30%, 39%

54 26%, 34%

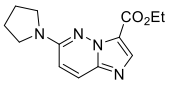
55 20%, 30%

56 69%, 72%

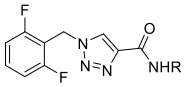
57 22%, 28%

58 45%, 48%

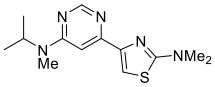
59 80% ± 8%[a]



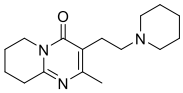
60 43%, 84%



3 R = H: 0%, 0%
61 R = CPh_3: 17%, 19%



62 0%, 0%



63 1%, 3%

Conditions: **8** (0.06 mmol), heterocycle (0.06 mmol), [Cu(OTf)2(py)4] (0.0053 mmol), [^{18}F]KF/K_{222} (20-30 MBq.), DMF (300 µL), air, 110 °C, 20 mins. In the absence of a heterocyclic additive, ^{18}F-fluorination affords **[^{18}F]9** in 34% ± 15% RCC (n = 122). Radiochemical conversions for the ^{18}F-labeling of **8** in the presence of each heterocycle, using a 11:11:1 molar ratio for **8**:heterocycle:[Cu(OTf)2(py)4]. Radiochemical conversions were determined by radio-TLC and radio-HPLC. Screening reactions were performed twice (n = 2); the radiochemical conversion of **[^{18}F]9** for each run is given. [a] Selected screening reactions were performed eight times (n = 8); in these cases, radiochemical conversions are given in the form mean ± standard deviation.

quantitative assessment of the RCC and therefore the tolerance of the reaction towards each heterocycle.

When **8** was subjected to labeling conditions in the presence of heterocycles containing an unprotected cyclic secondary amine able to act as nucleophile in Chan-Lam coupling, **[^{18}F]9** was not observed. An appropriate protecting group was important for this class of molecules. For pyrrolidine and piperidine (pK_{aH} = 11.3 and 11.2, respectively), *N*-methylation did not influence basicity to a point that allowed for the ^{18}F-labeling of **8** to occur in the presence of **10b** (*N*-methyl pyrrolidine, pK_{aH} = 10.5) or **11b** (*N*-methyl piperidine, pK_{aH} = 10.1).[13] *N*-Protection with an electron-withdrawing group restored reactivity, as demonstrated with **10d** and **11d**. For the less basic piperazine **12a** (pK_{aH1} = 9.4) or morpholine **13a** (pK_{aH} = 8.5), *N*-alkylation was sufficient for these heterocycles to be compatible with labeling, as demonstrated with *N*-benzyl piperazine **12c** (pK_{aH1} = 9.0) and *N*-methyl morpholine **13b** (pK_{aH} = 7.4).[13,14] Heterocyclic tertiary amines are frequently incorporated into pharmaceutical agents in order to improve pharmacokinetic profiles, so the finding that **12c-d, 13b-c, 14b** and **15b** are tolerated is significant. For amides and ureas, *N*-protection was mandatory to minimize detrimental effects on RCC (**16a-21**). Substitution of weakly acidic C–H positions is beneficial, as exemplified with comparative experiments undertaken with *N*-methyl indolin-2-one **17b** and the C3-dimethylated indolin-2-one **17c**.

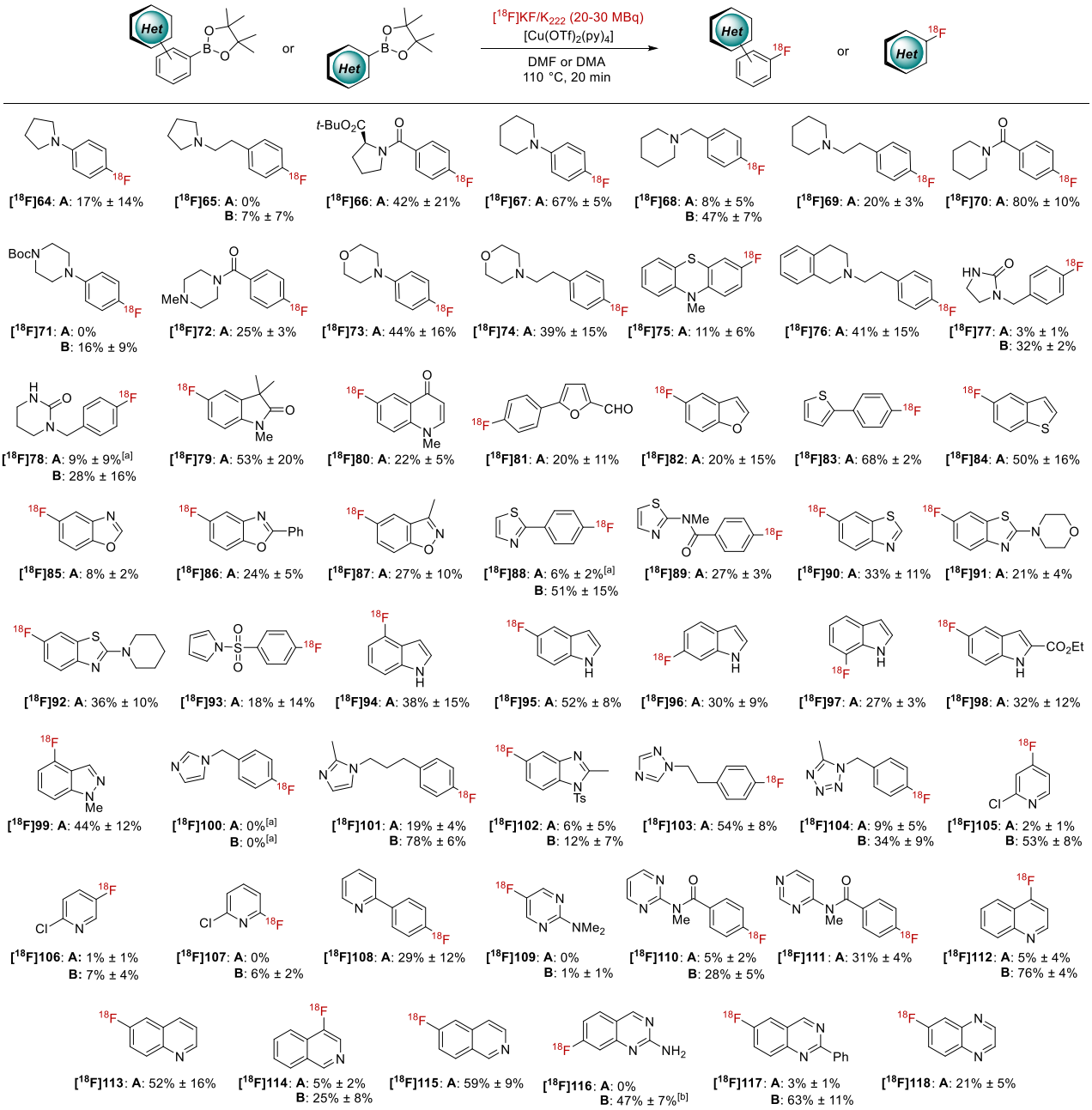
We investigated next the influence of heteroarenes on the ^{18}F-labeling of **8**. Furan **24**, benzofuran **25**, thiophene **26**, benzothiophene **27**, oxazole **28**, benzo[*d*]oxazoles **29a-b**, isoxazole **30**, benzo[*d*]isoxazoles **31a-b**, thiazole **32**, benzo[*d*]thiazole **33**, pyrrole **34**, indole **35**, pyrrolo[3,2-*b*]pyridine **47**, pyridine **50**, pyridazine **52**, pyrimidine **53**, pyrazine **54**, quinoline **55**, isoquinoline **56**, quinazoline **57**, quinoxaline **58** and imidazo[1,2-*b*]pyridazine **59** were all compatible with ^{18}F-fluorination. Heteroarenes containing a very weakly acidic N–H group such as pyrrole **34** (pK_a = 23.0) and indole **35** (pK_a = 21.0) are tolerated without the need for *N*-protection.[15] In contrast, we found that pyrazole **36a**, imidazole **38a**, triazoles **43a** and **45a,** and tetrazole **46a** (pK_a = 19.8, 18.6, 13.9 and 8.2, respectively) all required *N*-protection to prevent interference with the formation of **[^{18}F]9**. When not *N*-protected, these heteroarenes are possible Chan-Lam partners in the coupling with aryl boron reagents, and/or could coordinate strongly to Cu(II) complexes leading to deactivation. The structures of complexes [Cu(OTf)$_2$(py)$_4$], [Cu(OTf)$_2$(im)$_4$] and [Cu(OTf)$_2$(pz)$_4$] are known,[16] and show that the distance between the metal centre and the nitrogen is shorter in the cases of imidazole (im) (1.991 Å) and pyrazole (pz) (2.006 Å) in comparison with pyridine (py) (2.026 Å), indicating that imidazole and pyrazole are more strongly coordinated to Cu. Radiofluorination of **8** did not proceed when the reaction was performed using [Cu(OTf)$_2$(pz)$_4$] instead of [Cu(OTf)$_2$(py)$_4$].[12] Complex [Cu(OTf)$_2$(pz)$_4$] is also ineffective for the coupling of *para-tert*-butyl phenol and *para*-tolylboronic acid. This reaction afforded 10% of 1-(*para*-tolyl)-1*H*-pyrazole along with unreacted phenol; a similar outcome was observed with complex [Cu(OTf)$_2$(py)$_4$] in the presence of 4 equivalents of pyrazole.[12] These considerations likely account for the ^{18}F-fluorination intolerance to indazole **37a**, benzo[d]imidazole **41a** and benzo[d][1,2,3]triazole **44a**.

The presence of a substituent on a particular heteroarene can strongly influence its electronic and steric properties, and therefore its compatibility with ^{18}F-fluorination. For example, the electron-deficient imidazole **40b** is tolerated without the need for substitution at C2, in contrast to imidazole **39b** for which the presence of a methyl group at that carbon is essential. Heteroarenes such as pyridine **50**, isoquinoline **56** or imidazo[1,2-*b*]pyridazine **59** led to the formation of **[^{18}F]9** in RCC higher than observed in their absence. The Lewis basic ligand pyridine is known to facilitate carbon-heteroatom coupling at a Cu(III) center and was expected to favorably influence carbon-fluorine bond formation.[17] For example, the radiofluorination of **8** was found to be very effective in the presence of pyridine (**50**, pK_{aH} = 5.2, RCC = 63%), a result contrasting with the stronger Lewis base *N,N*-dimethylaminopyridine (DMAP **51**, pK_{aH} = 9.6, RCC = 0%). These data corroborate with the observation that [EtMe$_2$Cu(DMAP)] is a longer lived intermediate than [EtMe$_2$Cu(py)], and undergoes reductive elimination into propane more slowly.[18]

Caution should be taken when extrapolating data secured on single heteroarenes to more complex ring systems. For example, thiazole **32** and pyridimine **53** are well-tolerated individually, but the bicyclic 4-(pyrimidin-4-yl)thiazole **62**, a molecule with two nitrogen atoms N3 and N'3 arising from different heteroarenes and ideally positioned for bidentate Cu(II) coordination, inhibits the formation of **[^{18}F]9**. In this respect, the ideal derisking experiment is to carry out the ^{18}F-labeling of **8** (or an alternative model aryl boron reagent) in the presence of the target molecule itself or a close analogue. Noteworthy, we found that altering the reaction conditions applied for screening to the conditions found to be beneficial for electron-deficient arenes (molar ratio **8**:heterocycle:[Cu] = 1:1:1.5)[7] could accommodate certain heterocycles that failed when these are added in large excess with respect to the copper complex (molar ratio **8**:heterocycle:[Cu] = 11:11:1).[12]

The next step was to verify the value of the screening approach detailed in Table 1 with the ^{18}F-labeling of boron reagents all containing a heterocyclic system; selected precursors feature the boronic ester substituent on the heteroarene itself. We chose scaffolds seen in drug compounds, including those that would be a challenge for ^{18}F-labeling using conventional methods.[2a,3a-b] The (hetero)aryl boron reagents were prepared by subjecting hetero(aryl) halides to Miyaura borylation conditions.[19] This process was generally efficient, although some heteroaryl boron reagents proved difficult to prepare and/or purify, for example 2-pyridyl, 5-thiazolyl, 4- and 5-pyrazolyl derivatives. The propensity of some

Table 2. Cu(II)-Mediated ^{18}F-Fluorination of (Hetero)aryl Pinacol-Derived Boronic Esters with [^{18}F]Fluoride



Conditions A: (Hetero)aryl boronic ester (0.06 mmol), $[Cu(OTf)_2(py)_4]$ (0.0053 mmol), [^{18}F]KF/K_{222} (20-30 MBq.), DMF (300 µL), air, 110 °C, 20 mins; Conditions B: (Hetero)aryl boronic ester (0.02 mmol), $[Cu(OTf)_2(py)_4]$ (0.03 mmol), [^{18}F]KF/K_{222} (20-30 MBq.), DMA (300 µL), air, 110 °C, 20 mins. Reactions were performed four times (n = 4); radiochemical conversions were determined by radio-TLC and radio-HPLC and are given in the form mean ± standard deviation. [a] Reactions were performed twice (n = 2). [b] Starting from *N,N*-di-Boc protected starting material; deprotection occurred under reaction conditions.

(hetero)aryl boron reagents to either gain stability or decompose via protodeboronation in the presence of Lewis acid additives such as Cu(II) salts has been recently rationalized.[20] A successful radiosynthesis therefore relies as much on the accessibility of the precursor and its stability under the reaction conditions as on the feasibility of the ^{18}F-radiofluorination step itself. In this study, we subjected more than fifty substrates to ^{18}F-fluorination applying conditions A or B (Table 2). Conditions A consist of a 11:1 ratio of substrate:Cu(II) complex in DMF at 110 °C. Under conditions B, a 1:1.5 ratio of substrate:Cu(II) complex was used in DMA at 110 °C. Conditions B were typically required for the more demanding tertiary amines (**[^{18}F]65**, **[^{18}F]68**) and substrates bearing unprotected N–H functionalities (**[^{18}F]77**, **[^{18}F]78**). The use of an excess of Cu(II) complex was also found beneficial for electron-deficient heterocycles (**[^{18}F]105**-**[^{18}F]107**, **[^{18}F]110**, **[^{18}F]112**, **[^{18}F]114**).

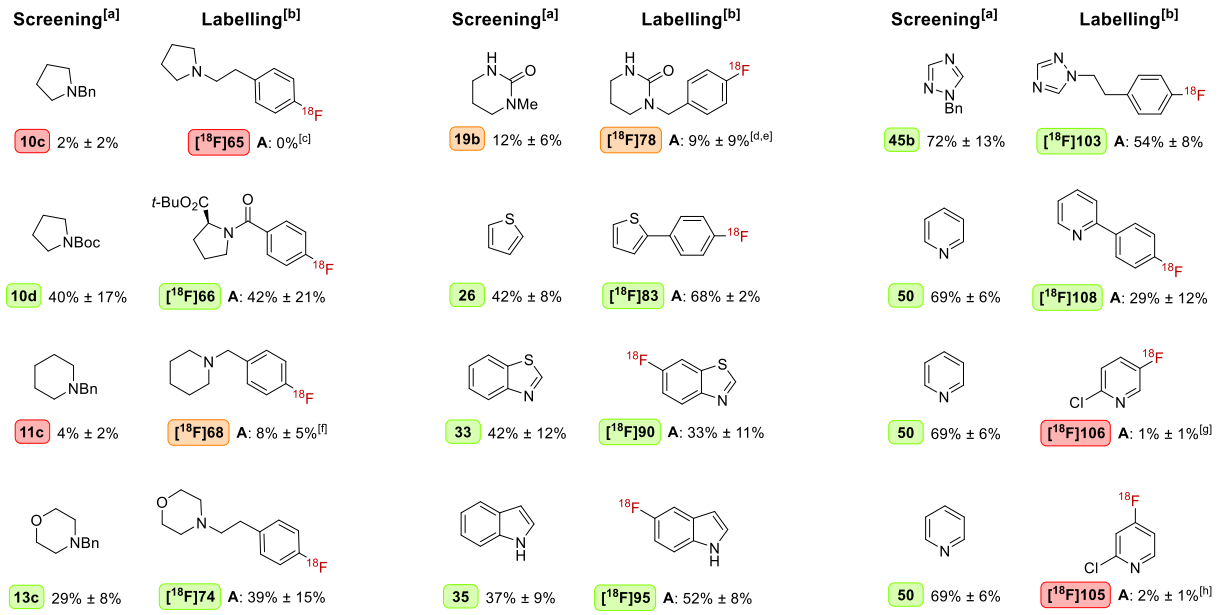
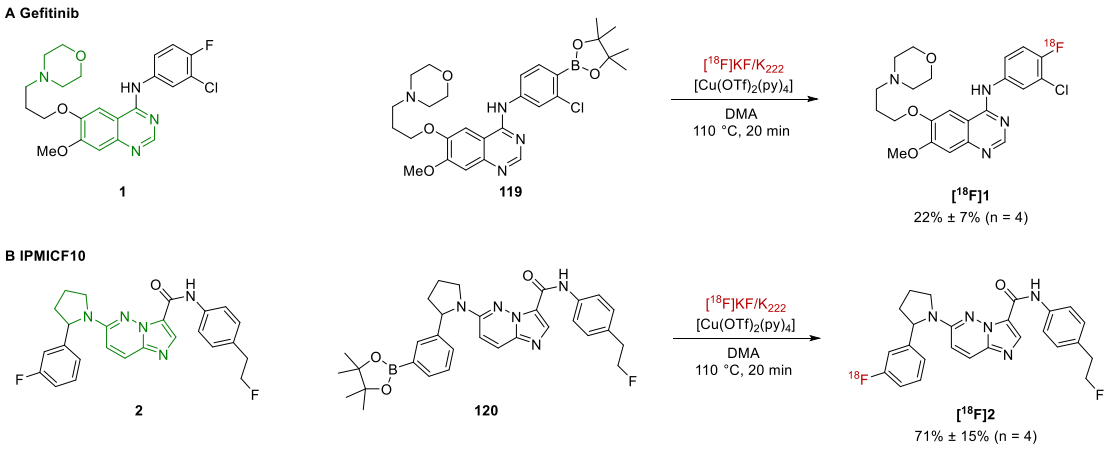


Figure 2. A comparison of the heterocyclic additive screening and corresponding labeling results for selected substrates. Red highlight: RCC < 5%. Orange highlight: 5% ≤ RCC < 20%. Green highlight: RCC ≥ 20%. Screening conditions: **8** (0.06 mmol), heterocycle (0.06 mmol), [Cu(OTf)2(py)4] (0.0053 mmol), [^{18}F]KF/K222 (20-30 MBq.), DMF (300 µL), air, 110 °C, 20 mins. Labelling conditions (A): (Hetero)aryl boronic ester (0.06 mmol), [Cu(OTf)2(py)4] (0.0053 mmol), [^{18}F]KF/K222 (20-30 MBq.), DMF (300 µL), air, 110 °C, 20 mins. Radiochemical conversions were determined by radio-TLC and radio-HPLC and are given in the form mean ± standard deviation. [a] Reactions were performed eight times (n = 8). [b] Reactions were performed four times (n = 4). [c] Under conditions B, RCC = 7% ± 7% (n = 4). [d] Reactions were performed twice (n = 2). [e] Under conditions B, RCC = 32% ± 2% (n = 4). [f] Under conditions B, RCC = 47% ± 7% (n = 4). [g] Under conditions B, RCC = 7% ± 4% (n = 4). [h] Under conditions B, RCC = 53% ± 8% (n = 4).

Applying both conditions A and B, we labeled fluorine-containing drug fragments with heterocycles and basic amines in RCCs up to 80%, including pyrrolidines **[^{18}F]64**-**[^{18}F]66**, piperidines **[^{18}F]67**-**[^{18}F]70**, piperazines **[^{18}F]71**-**[^{18}F]72,** morpholines **[^{18}F]73**-**[^{18}F]74**, phenothiazine **[^{18}F]75**, and tetrahydroisoquinoline **[^{18}F]76**. The monoprotected imidazolidin-2-one **[^{18}F]77** and tetrahydropyrimidin-2(1H)-one **[^{18}F]78** were formed under conditions B in 32% and 28% RCC, respectively. Indolinone **[^{18}F]79** was formed in good RCC when both the nitrogen and C3 were protected, a result corroborating the data presented in Table 1 for **17a-c**. Furans **[^{18}F]81**-**[^{18}F]82**, thiophenes **[^{18}F]83**-**[^{18}F]84** and a range of heterocycles **[^{18}F]85**-**[^{18}F]92** containing multiple heteroatoms (N,O and N,S) underwent ^{18}F-fluorination in good RCC. Indoles **[^{18}F]94**-**[^{18}F]98** were labeled at position 4, 5, 6 or 7 in RCC up to 52% without *N*-protection. For some substrates, substitution had a strong influence on reactivity. For example, imidazole **[^{18}F]100** could not be labeled under conditions A or B. In contrast, C2-methylated imidazole **[^{18}F]101** was labeled in 78% RCC under conditions B. Benzimidazole **[^{18}F]102** was radiolabeled in low RCC (12%). *N*-Alkylated azoles containing multiple nitrogen atoms such as indazole **[^{18}F]99**, triazole **[^{18}F]103** and tetrazole **[^{18}F]104** underwent ^{18}F-fluorination in good RCC (up to 54%). The chloro-substituted pyridines **[^{18}F]105**-**[^{18}F]107** were labeled on position C4, C5 and C6, as well as pyrimidines **[^{18}F]109**-**[^{18}F]111**, quinolines **[^{18}F]112**-**[^{18}F]113**, isoquinolines **[^{18}F]114**-**[^{18}F]115**, quinazolines **[^{18}F]116**-**[^{18}F]117**, and quinoxaline **[^{18}F]118**. In this series, the ^{18}F-fluorination was most challenging for pyridines **[^{18}F]106**-**[^{18}F]107** and pyrimidine **[^{18}F]109**. For **[^{18}F]105**-**[^{18}F]107**, it is noteworthy that the boronic ester functionality is displaced with ^{18}F in preference to the chloro substituent.[12]

Overall, the data show reasonable agreement between the screening and ^{18}F-labeling experiments detailed in Tables 1 and 2, respectively. Figure 2 compares data based on a larger number of screening experiments (n = 8) applied to a narrower selection of twelve heterocyclic systems. Any pair with the same color code indicates agreement between the screening experiments and ^{18}F-labeling; this was the case for ureas **19b** and [^{18}F]**78**, thiophenes **26** and [^{18}F]**83**, benzo[*d*]thiazoles **33** and [^{18}F]**90**, indoles **35** and [^{18}F]**95**, and triazoles **45b** and [^{18}F]**103**. The screening experiments predict correctly that *N*-alkylated pyrrolidines **10c** and piperidines **11c** are highly

Scheme 1. Final-Stage ^{18}F-Fluorination of Medicinally-Relevant Molecules with [^{18}F]Fluoride



Heterocycles shown by screening experiment to be tolerated are highlighted in green. ^{18}F-Fluorination conditions: (Hetero)aryl boronic ester (0.02 mmol), [Cu(OTf)2(py)4] (0.03 mmol), [18F]KF/K222 (20-30 MBq.), DMA (300 µL), air, 110 °C, 20 mins. Reactions were performed four times; radiochemical conversions were determined by radio-TLC and radio-HPLC and are given in the form mean ± standard deviation. (A) Gefitinib. (B) IPMICF10.

challenging substrates (0% RCC and 8% for [^{18}F]**65** and [^{18}F]**68**, respectively), and that reduced basicity restores reactivity, as illustrated with the successful labeling of [^{18}F]**66** and [^{18}F]**74**. For low yielding heterocycles such as [^{18}F]**68**, we recommend applying conditions B consisting of a higher Cu:substrate ratio in the reaction solvent DMA. These conditions afforded [^{18}F]**68** in an improved RCC of 47%. The comparative data selected in Figure 2 indicate that caution should be exercised when attempting to extrapolate the result of the screening experiment to predict feasibility for the labeling of the heterocycle itself. This is best illustrated with pyridine and the contrasting data for [^{18}F]**108**, [^{18}F]**106** and [^{18}F]**105**. The screening experiment predicts correctly that [^{18}F]**108** with a pyridyl substituent can be labeled successfully; this is in contrast to the outcome for the ^{18}F-labeling on the pyridine itself. As anticipated, the position of the ^{18}F on the heterocycle impacts on reactivity considerably; the 3-fluoropyridine [^{18}F]**106** is afforded in very low RCC under both conditions A (1%) and B (7%), whereas the pinacol-derived boronic ester leading to 4-fluoropyridine [^{18}F]**105** responded well for ^{18}F-fluorination, but only under conditions B (RCC = 53%).

The results assembled in Table 1, Table 2 and Figure 2 are instructive at various levels:

1) The screening experiments are in good agreement for ^{18}F-labeling an arene that features the heterocycle as a substituent. Caution should be exercised if one requires that the heterocycle itself is ^{18}F-labeled;

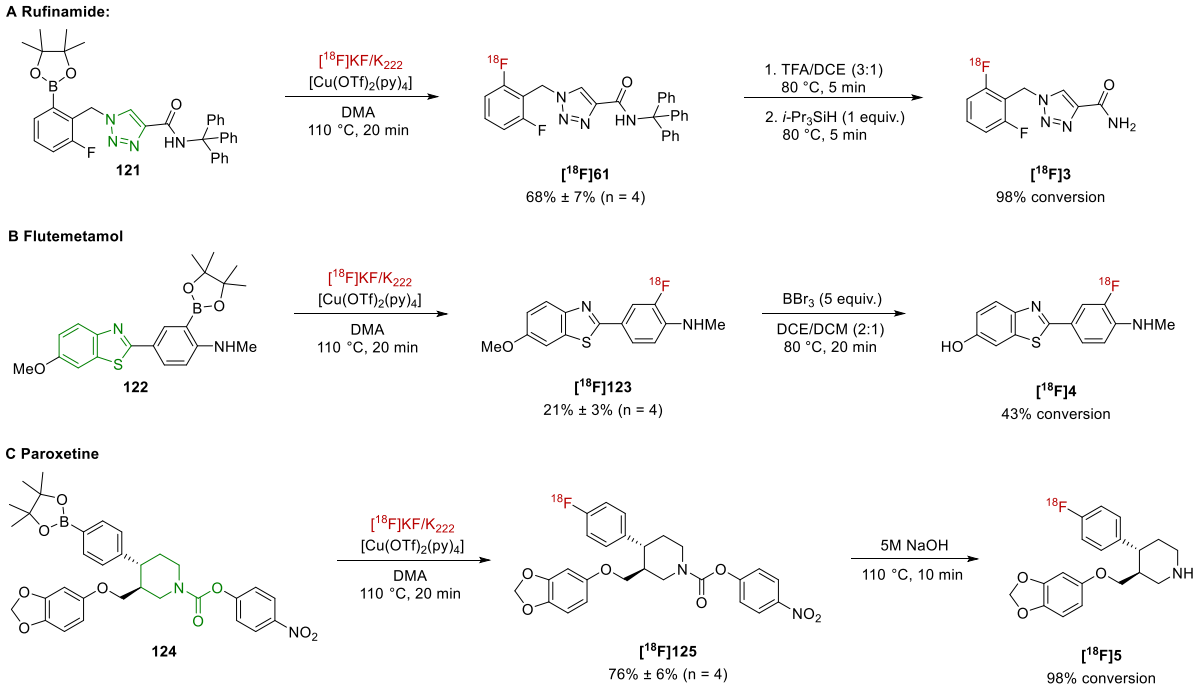
2) The radiochemical yield is dependent on the reaction conditions. We have applied two sets of conditions A and B in this study, and have demonstrated that conditions B rescue some of the most challenging substrates;

3) The reaction is sensitive to steric and electronic effects, and this should be taken into account in addition to any compatibility issue with a particular heterocycle;

4) For complex target, we recommend conducting a screening experiment with the target itself.

When planning for the optimal copper-mediated radiosynthetic route towards complex targets possessing one or more heterocyclic sub-motifs, one should consider several criteria: 1) ^{18}F-incorporation should be late stage, ideally taking place in the final step; 2) the ^{18}F-fluorination should be compatible with the functional groups *and* any heterocyclic motif(s) present on the aryl boron precursor; 3) if ^{18}F-fluorination is not the final step of the radiosynthesis, any post ^{18}F-fluorination transformation should be rapid and facile; and 4) the aryl boron reagent should be readily accessible and stable. With these considerations in mind, our final objective was to demonstrate that the approach described in Figure 1, combined with the data in Tables 1 and 2, can guide a low-risk retro-radiosynthesis for molecules featuring one or more heterocyclic motifs. Our target molecules consist of seven drugs and radioligands, namely [^{18}F]gefitinib **[^{18}F]1**, [^{18}F]IPMICF10 **[^{18}F]2**, [^{18}F]rufinamide **[^{18}F]3**, [^{18}F]flutemetamol **[^{18}F]4**, [^{18}F]paroxetine **[^{18}F]5**, [^{18}F]FITM **[^{18}F]6** and [^{18}F]risperidone **[^{18}F]7** (Fig. 1C). The synthesis of the pinacol boronic ester precursors is required to access these molecules in their ^{18}F-labeled form, a process that may be time-consuming and therefore best initiated if late-stage ^{18}F-fluorination is likely to be successful.

Scheme 2. Medicinally-Relevant Molecules Requiring Deprotection Following ^{18}F-Fluorination



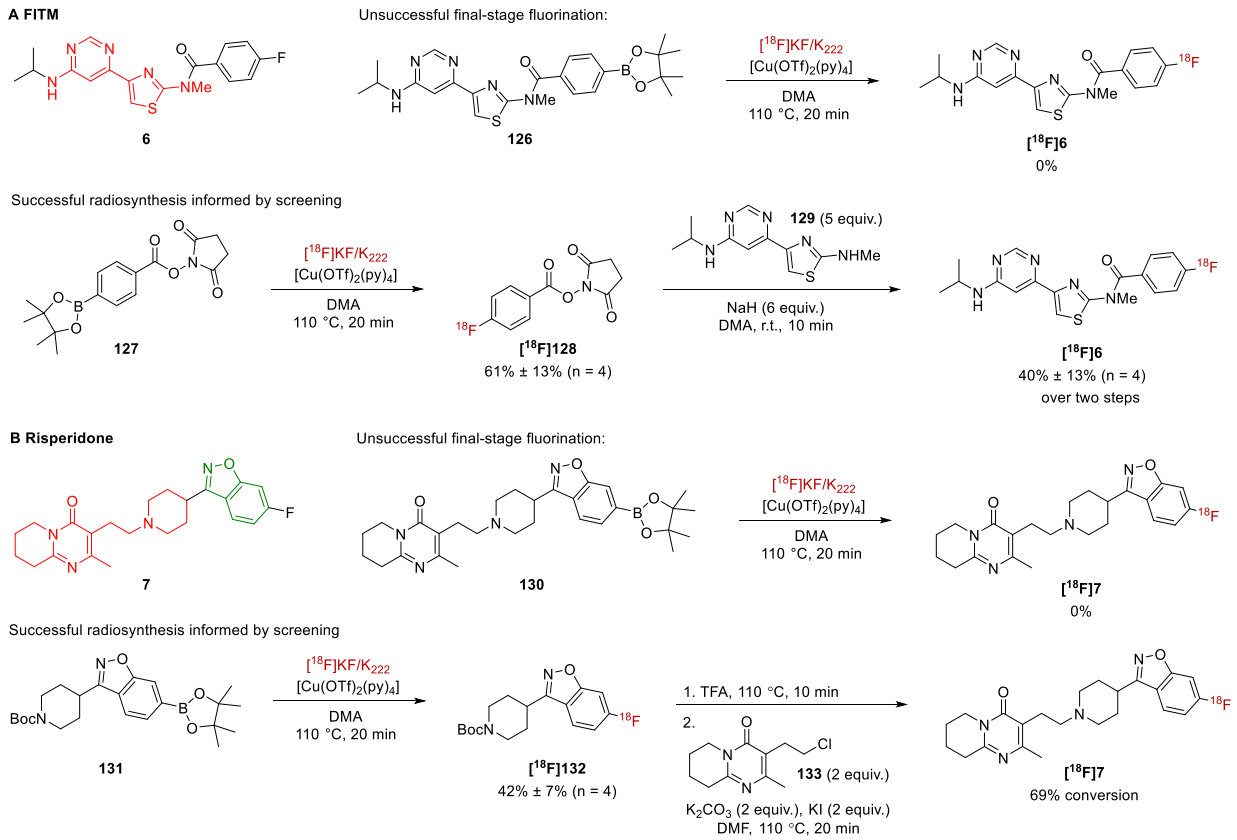
Heterocycles shown by screening experiment to be tolerated are highlighted in green. ^{18}F-Fluorination conditions: Protected (hetero)aryl boronic ester (0.02 mmol), $[Cu(OTf)_2(py)_4]$ (0.03 mmol), $[^{18}F]KF/K_{222}$ (20-30 MBq.), DMA (300 µL), air, 110 °C, 20 mins. Cu(II)-mediated ^{18}F-fluorination reactions were performed four times; radiochemical conversions were determined by radio-TLC and radio-HPLC and are given in the form mean ± standard deviation. The conversions of the deprotection steps were determined by radio-HPLC. **(A)** Rufinamide. **(B)** Flutemetamol. **(C)** Paroxetine.

Gefitinib **1** is an inhibitor of the epidermal growth factor receptor–tyrosine kinase (EGFR-TK) that has shown potent effects in patients carrying specific EGFR-TK mutations in non-small-cell lung cancer.[21] Measurement of intratumoral drug concentration by PET with [^{18}F]gefitinib can provide insights into the mechanisms of gefitinib resistance in clinical studies. [^{18}F]Gefitinib was previously prepared in a three-step radiosynthesis starting with the [^{18}F]fluorination of 3-chloro-4-trimethylammonium-nitrobenzene.[22] With the knowledge that quinazoline and *N*-alkyl morpholine did not disrupt the ^{18}F-labeling of **8**, and are amenable to labeling themselves (**[^{18}F]74**, **[^{18}F]116**, **[^{18}F]118**), we envisaged the radiosynthesis of [^{18}F]gefitinib applying a final step ^{18}F-fluorination of the aryl boron precursor **119** possessing the unprotected diaryl amino functionality. As planned, [^{18}F]gefitinib **[^{18}F]1** was obtained in 22% RCC applying conditions **B** (Scheme 1A).

[^{18}F]IPMICF10 **[^{18}F]2** is a tropomyosin receptor kinase (Trk) inhibitor possessing pyrrolidine and imidazo[1,2-*b*]pyridazine sub-motifs; this PET radioligand was originally labeled on the fluoroethyl chain by S_N2 with [^{18}F]KF,[23] but the presence of the fluoroarene motif of IPMICF10 persuaded us to envisage instead a copper-mediated ^{18}F-fluorination of the aryl ring. This decision was reinforced by the observation that imidazo[1,2-*b*]pyridazine **59** and 6-(pyrrolidin-1-yl)imidazo[1,2-b]pyridazine **60** had a beneficial effect on the ^{18}F-labeling of **8** (Table 1). Accordingly, we obtained [^{18}F]IPMICF10 **[^{18}F]2** in 71% RCC applying a final step ^{18}F-fluorination of boronic ester **120** (Scheme 1B).

Rufinamide **3** is an anticonvulsant broadly used as an adjunctive seizure therapy in children and older adults suffering from Lennox-Gastaut syndrome.[24] The mechanism of action of rufinamide remains unclear; ^{18}F-labeling for PET studies is therefore of interest. The *N*-benzylated triazole **43b** was not detrimental to the labeling of **8**. Moreover, the results obtained by spiking experiments with rufinamide itself **3** and *N*-protected rufinamide **61** suggest that the synthesis of [^{18}F]rufinamide would be within reach from precursor **121** protected at the amide group (Table 1). This was verified experimentally; *N*-trityl-[^{18}F]rufinamide **[^{18}F]61** was formed in 68% RCC, and subsequent deprotection with

Scheme 3. Medicinally-Relevant Molecules Requiring a Coupling Reaction Following ^{18}F-Fluorination



Heterocycles shown by screening experiment to be tolerated are highlighted in green; fragments not tolerated are highlighted in red. ^{18}F-Fluorination conditions: (Hetero)aryl boronic ester (0.02 mmol), $[Cu(OTf)_2(py)_4]$ (0.03 mmol), $[^{18}F]KF/K_{222}$ (20-30 MBq.), DMA (300 µL), air, 110 °C, 20 mins. Successful Cu(II)-mediated ^{18}F-fluorination reactions were performed four times. Radiochemical conversions were determined by radio-TLC and radio-HPLC and are given in the form mean ± standard deviation. **(A)** FITM. RCC of **[^{18}F]6** was 40% ± 13% (n = 4) over both steps, starting from **127**. **(B)** Risperidone. Conversion of **[^{18}F]132** into **[^{18}F]7** was determined by radio-HPLC.

TFA/*i*-Pr_3SiH in DCE at 80° C afforded [^{18}F]rufinamide **[^{18}F]3** in 98% conversion (Scheme 2A).

Flutemetamol **[^{18}F]4** is a PET radiopharmaceutical used to estimate beta-amyloid neuritic plaque density in adult patients with cognitive impairment who are being evaluated for Alzheimer's disease.[25] This radioligand has been prepared upon treatment of a nitro precursor with [^{18}F]fluoride,[26] and in its protected form, from an iodonium precursor.[27] The results obtained with fragments **90** and **91** (Table 2) led us to consider the copper-mediated ^{18}F-fluorination of the *O*-protected aryl boronic ester **122** as an alternative route (Scheme 2B). This reaction led to **[^{18}F]123** in 21% RCC; demethylation with BBr_3 in DCE/DCM at 80 °C afforded [^{18}F]flutemetamol **[^{18}F]4** in 43% conversion.

Paroxetine **5** is an antidepressant which selectively inhibits serotonin reuptake.[28] The Ritter group reported the synthesis of [^{18}F]paroxetine applying a palladium-mediated ^{18}F-fluorination.[29] We started our investigation with the knowledge that the piperidine motif is best protected with an electron-withdrawing group (Table 1). Since the *para*-nitrophenyl carbamate was an intermediate in the synthesis of the aryl boronic ester, this carbamate was chosen for ^{18}F-fluorination. Product **[^{18}F]125** was obtained in 76% RCC and subsequent treatment with aqueous NaOH for 10 minutes at 110 °C proceeded in 98% conversion to afford [^{18}F]paroxetine **[^{18}F]5** (Scheme 2C).

Since our screening method decouples the heterocyclic motifs from the entire structure of the target, caution should be taken when assessing the steric and/or electronic impact of multiple heterocyclic fragments on

the reaction center. One representative example is the labeling of the metabotropic glutamate 1 (mGlu1) receptor antagonist [^{18}F]FITM **[^{18}F]6**,[30] a molecule currently accessible by ^{18}F-fluorination of a nitro precursor.[31] Our screening study indicated that copper-mediated ^{18}F-fluorination was compatible with pyrimidine **53** and thiazole **32** but failed in the presence of 4-(pyrimidin-4-yl)thiazole **62** (Table 1). Late stage ^{18}F-fluorination is therefore a high-risk operation, as verified experimentally by the failure to access [^{18}F]FITM **[^{18}F]6** from boronic ester **126** (Scheme 3A). An alternative retrosynthesis featuring an amide coupling step following ^{18}F-fluorination was therefore implemented. *N*-(Hydroxysuccimidyl)-[^{18}F]fluorobenzoate **[^{18}F]128** was prepared in 61% RCC and coupled with heterocyclic amine **129**. This two-step radiosynthesis led to [^{18}F]FITM **[^{18}F]6** in 40% RCC over two steps.

The last molecule investigated in this study is risperidone **7**, an antipsychotic drug that has never been labeled with ^{18}F.[32] Benzo[*d*]isoxazoles **31a-b** and *N*-protected pyrimidin-4(3*H*)-one **21** are compatible with ^{18}F-labeling, in contrast to *N*-alkylated piperidines **11b-c** (Table 1). Late stage ^{18}F-fluorination of **130** failed under our conditions (Scheme 3B); this result was expected since the 2-methyl-3-(2-(piperidin-1-yl)ethyl)-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-4-one fragment **63** is not tolerated (Table 1). An alternative synthetic approach introducing this motif post ^{18}F-fluorination was therefore necessary. We started the radiosynthesis by ^{18}F-fluorinating the Boc-protected fragment **131** in 42% RCC; *in situ N*-deprotection of **[^{18}F]132** with TFA followed by alkylation under basic conditions afforded [^{18}F]risperidone **[^{18}F]7** in 69% conversion.

CONCLUSION

The radiosynthesis of complex radioligands is typically attempted when there is a clinical need, rarely as an exercise to demonstrate the generality of a new radiochemical transformation. As a result, the ^{18}F-labeling of complex targets remains a high-risk endeavor. Since its discovery, the Cu-mediated ^{18}F-radiofluorination of aryl boron reagents has emerged as an attractive methodology for the labeling of arenes, and is finding increasing application for the labeling of imaging agents.[33] Post-labeling purification with HPLC has demonstrated that ^{18}F-fluoroarenes can be isolated in high radiochemical purity and copper can be sufficiently removed for clinical applications. However, the reaction lacked predictability for heterocyclic radioligands. These considerations prompted us to provide radiochemists with guidelines on the compatibility of the Cu-mediated ^{18}F-radiofluorination with the rings most frequently used in medicinal chemistry. Our empirical approach consists of monitoring fluctuation in the RCC of a model reaction carried out in the presence of heterocyclic additives. Categorization of these ring systems as compatible or not compatible with our Cu-mediated ^{18}F-fluorination, combined with the ^{18}F-labeling of more than fifty (hetero)aryl boron reagents, provides a convenient starting point to establish low-risk retrosynthetic routes towards complex molecular radioligands. This was illustrated with the preparation of seven heterocycle-containing radioligands. Two radiosyntheses feature the ^{18}F-radiofluorination as the final step, three require a deprotection step post ^{18}F-fluorination, and two feature a coupling reaction following ^{18}F-incorporation. These three scenarios were implemented by design, a guided approach that we view as highly advantageous in comparison with time-consuming and costly trial and error ^{18}F-experimentation. The approach considered in this study brings into focus the value of low risk retro-radiosynthesis, and is geared for practicing radiochemists who are looking for a rapid route to complex PET radioligands. Beyond the Cu-mediated ^{18}F-fluorination selected here as our model reaction, this type of study applied to other ^{18}F-labeling methods combined with a rapid assessment of precursor availability should lower the barrier of adoption of one particular method over another when a radiolabeled molecule is needed either for a diagnostic or drug development program.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, spectral and analytical data, radio-HPLC traces and additional ^{18}F-radiolabeling experiments.
This material is available free of charge on the ACS Publications website at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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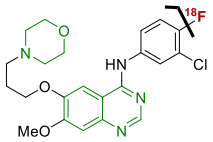
All heterocycles tolerated

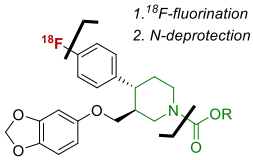
Final-stage ^{18}F-fluorination



Heterocycle tolerated when *N*-protected

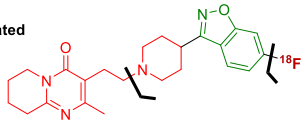
1. ^{18}F-fluorination

2. N-deprotection



Heterocycle not tolerated

1. ^{18}F-fluorination

2. N-deprotection

3. N-alkylation