

[¹⁸F]Difluoromethyl Heteroaryl-Sulfones

Subjects: Others

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The suitability of the ¹⁸F radioisotope in positron emission tomography (PET) demanded novel approaches for ¹⁸F-fluorination and ¹⁸F-fluoroalkylation. The difluoromethyl (CF₂H) group has gained increasing attention in medicinal chemistry due to its lipophilic hydrogen-bond donor properties. In non-radioactive chemistry, difluoromethyl heteroaryl-sulfones has been extensively used in difluoromethylation of substrates bearing C=C, C≡C, and C≡N bonds by visible light photoredox catalysis. Herein, we highlight our recent work on the synthesis of [¹⁸F]difluoromethyl heteroaryl-sulfones with improved molar activities and their application in photoinduced C-H ¹⁸F-difluoromethylation of *N*-containing heteroarenes *via* a radical-mediated pathway.

Keywords: fluorine-18 ; difluoromethylation ; heteroarenes ; visible light ; photocatalysis

1. Introduction

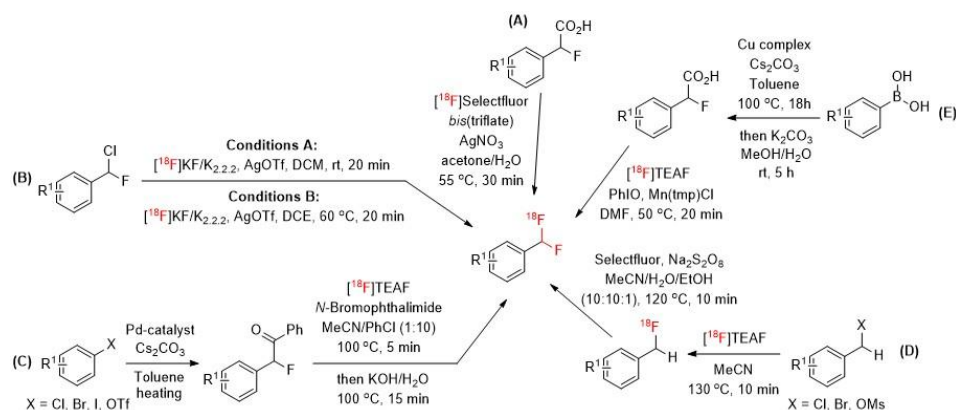
The fluorine-18 radioisotope has been regarded the "radionuclide of choice" for in vivo positron emission tomography (PET) imaging in living subjects since it provides a unique combination of nuclear and physical features over alternative short-lived positron emitters such as carbon-11, nitrogen-13, and oxygen-15^{[1][2][3][4]}. Fluorine-18 has a high positron yield resulting from an almost exclusive β⁺ emission (97%) with this mode of decay producing the stable oxygen-18 isotope. The half-life of 109.8 min allows sufficient time for multistep synthetic labeling reactions and the transport of ¹⁸F-labeled radiotracers over considerable distances. Furthermore, the relatively low positron energy of fluorine-18 (0.635 MeV) is highly advantageous in the acquisition of high-resolution PET images^{[1][2][3][4]}. The distinctive sensitivity of PET makes this technique suitable for the study of absorption, distribution, metabolism, and excretion (ADME) properties of radiopharmaceuticals and the evaluation of their pharmacodynamic profile. In addition, PET technology has proven highly valuable in the observation of biochemical and physiological changes that may take place before the anatomical alterations of a certain disease are detected^{[5][6][7][8]}. The suitability of the ¹⁸F radioisotope in PET has encouraged radiochemists to invest much effort in the development of efficient ¹⁸F-fluorination and ¹⁸F-fluoroalkylation reactions^{[9][10][11]}.

Among the existing fluorinated motifs, the difluoromethyl (CF₂H) group has received considerable attention in medicinal chemistry due to its lipophilic hydrogen-bond donor properties. The CF₂H substitution may offer a viable alternative to conventional hydrogen-bond donors [e.g., hydroxy (OH) and thiol (SH) groups] in terms of lipophilicity, cell membrane permeability, and metabolic stability, thus modulating the pharmacological activity of pharmaceuticals and agrochemicals^{[12][13]}. Thus, the synthesis of radiotracers with ¹⁸F-difluoromethyl groups has been recently explored due to the attractive characteristics of fluorine-18 and CF₂H motifs in radiopharmaceutical chemistry.

2. Overview of the different strategies for the synthesis of [¹⁸F]aryl-CF₂H derivatives

Despite the recent progresses in the preparation of CF₂H-containing derivatives in organofluorine chemistry^{[14][15][16]}, methodologies for the ¹⁸F-labeling of CF₂H groups are still relatively scarce and mainly relied on the radiosynthesis of [¹⁸F]aryl-CF₂H derivatives *via* ¹⁸F-fluorination reactions (Figure 1). In 2013, Gouverneur and co-workers disclosed a silver(I)-mediated protocol enabling the ¹⁸F-fluorodecarboxylation of 2-fluoro-2-arylacetic acids with [¹⁸F]Selectfluor *bis*(triflate), an electrophilic ¹⁸F-fluorinating reagent^[17] (Scheme 1A). The cyclotron-produced [¹⁸F]fluoride was employed for the first time to access [¹⁸F]aryl-CF₂H derivatives by AgOTf-mediated ¹⁸F-fluorination of aryl-CHFCI precursors^[18] (Scheme 1B). In 2016, Ritter developed an alternative approach for the construction of [¹⁸F]aryl-CF₂H functionalities starting from aryl (pseudo)halides *via* activation of a benzoyl auxiliary followed by benzylic bromination and *in situ* halogen exchange with [¹⁸F]fluoride^[19] (Scheme 1C). Later, Liang and co-workers described an alternative approach for the preparation of [¹⁸F]aryl-CF₂H with improved molar activity^[20]. This synthetic approach consisted in the initial nucleophilic ¹⁸F-fluorination of benzyl (pseudo)halides and subsequent oxidative benzylic C-H fluorination with Selectfluor under transition metal-free conditions (Scheme 1D). In 2019, Gouverneur reported the utilization of aryl

boronic acids as substrates to afford [^{18}F]aryl- CF_2H through copper-mediated cross-coupling with ethyl bromofluoroacetate and manganese-mediated ^{18}F -fluorodecarboxylation with [^{18}F]tetraethylammonium fluoride ([^{18}F]TEAF) and iodosobenzene (PhIO)^[21] (Scheme 1E).



These methods allowed the radiosynthesis of [^{18}F]aryl- CF_2H derivatives with low-to-moderate molar activities (up to 22 $\text{GBq}\cdot\mu\text{mol}^{-1}$). The production of radiotracers with high molar activity is mandatory for PET imaging studies, especially for targeting low-density biomacromolecules. Obtaining a high molar activity still constitutes a major challenge in the preparation of [^{18}F]CF $_2$ H-bearing compounds, due to the unwanted ^{18}F - ^{19}F isotopic exchange reactions.

3. Radiosynthesis of [^{18}F]difluoromethyl heteroaryl-sulfones for C-H ^{18}F -difluoromethylation of heteroarenes by visible light photoredox catalysis

In 2019, our laboratories described an innovative and efficient protocol enabling the late-stage introduction of ^{18}F -difluoromethyl moieties in *N*-containing heteroarenes with the [^{18}F]difluoromethyl benzothiazolyl-sulfone ([^{18}F]1) with improved molar activity [A_m ([^{18}F]1) = $54 \pm 7 \text{ GBq}\cdot\mu\text{mol}^{-1}$]^{[22][23]} (Figure 1A). In non-radioactive chemistry, difluoromethyl heteroaryl-sulfones have been extensively employed in photoredox-catalyzed difluoromethylation of substrates bearing C=C, C \equiv C, and C \equiv N bonds because of the ability of these compounds to be reduced to CF $_2$ H radicals in the presence of appropriate photocatalysts in their photoexcited state. In 2016, Hu and Fu reported the use of difluoromethyl benzothiazolyl-sulfone (1) in the radical difluoromethylation of biphenyl isocyanides^[24] and olefinic amides^[25], respectively. The reagent 1 was also employed in the preparation of CF $_2$ H-substituted heterocycles of biological relevance, including isoquinolinediones^[26], coumarins^[27], isoxazolines^[28], and oxindoles^[29]. In 2019, Liu and co-workers developed a procedure for the difluoromethylation of *N*-arylacrylamides with the reagent difluoromethyl pyridyl-sulfone (2), under visible light photoredox conditions^[30] (Figure 1B).

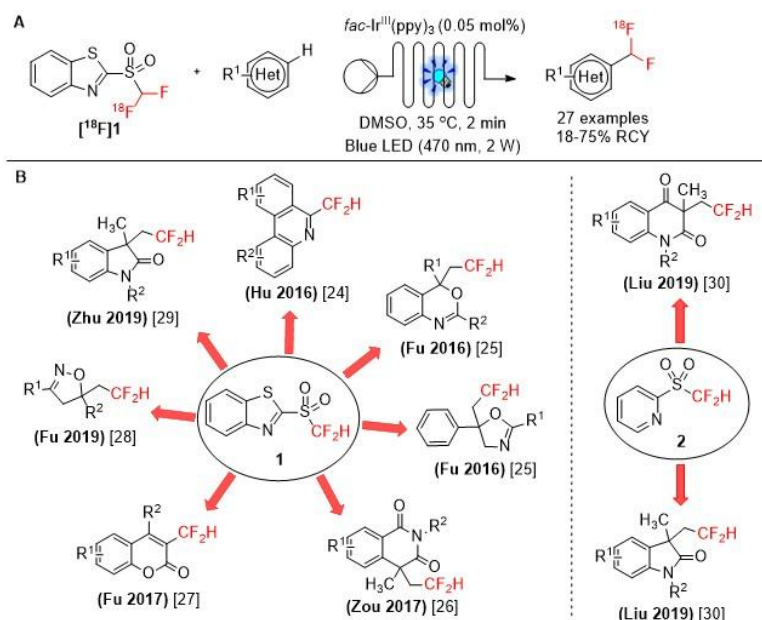


Figure 1. (A) Photoredox C–H ^{18}F -difluoromethylation of *N*-containing heteroarenes with [^{18}F]difluoromethyl benzothiazolyl-sulfone ([^{18}F]1), under continuous-flow conditions^{[22][23]}. **(B)** Application of the difluoromethyl sulfones **1** and **2** in the preparation of heterocycles of biological relevance, under visible light photoredox catalysis^{[24][25][26][27][28][29][30]}.

Taking advantage of the reported efficiency of the [^{18}F]1 as ^{18}F -difluoromethylating reagent^{[22][23]}, our laboratories planned to study the influence of certain molecular modifications in the structure of [^{18}F]1 in the reactivity toward the photoredox C–H ^{18}F -difluoromethylation of heteroarenes, under continuous-flow conditions^[31]. The molecular modifications consisted in the single introduction of an electron-donating (EDG) or an electron-withdrawing group (EWG) either at position 5 or 6 of the benzothiazolyl ring and the modification of the original benzothiazolyl moiety to other heteroaryl rings (*N*-methyl-benzimidazolyl and *N*-phenyl-tetrazolyl rings). Six structurally-related [^{18}F]difluoromethyl heteroaryl-sulfones ([^{18}F]5a–[^{18}F]5f) were synthesized on a GE FASTlabTM synthesizer via a two-step sequence (Scheme 2). The nucleophilic ^{18}F -fluorination of bromofluoromethyl heteroaryl-sulfides (**3a–3f**) was carried out in the presence of potassium carbonate (K_2CO_3) and Kryptofix[®] 222 ($\text{K}_{2.2.2}$), and afforded the cartridge-purified [^{18}F]difluoromethyl heteroaryl-sulfides ([^{18}F]4a–[^{18}F]4f) in 8.3–14.8% RCYs [decay-corrected at the start-of-synthesis (SOS)]. After optimization of the oxidation step with sodium (meta)periodate (NaIO_4) and ruthenium (III) chloride hydrate ($\text{RuCl}_3 \cdot x\text{H}_2\text{O}$), the sulfones [^{18}F]5a–[^{18}F]5f were afforded in 70.6–91.9% RCYs (decay-corrected at the SOS).

Electron-donating groups in benzothiazolyl ring	Electron-withdrawing groups in benzothiazolyl ring	Other heteroaryl rings
<p>[^{18}F]4a (X=S): 14.2 ± 0.7% RCY [^{18}F]5a (X=SO₂): 70.9 ± 6.1% RCY 10.1 ± 0.8% RCY (2 steps)</p>	<p>[^{18}F]4c (X=S): 13.6 ± 0.6% RCY [^{18}F]5c (X=SO₂): 88.2 ± 0.2% RCY 12.0 ± 0.5% RCY (2 steps)</p>	<p>[^{18}F]4e (X=S): 8.3 ± 1.9% RCY [^{18}F]5e (X=SO₂): 86.1 ± 3.0% RCY 7.2 ± 0.2% RCY (2 steps)</p>
<p>[^{18}F]4b (X=S): 11.8 ± 1.9% RCY [^{18}F]5b (X=SO₂): 70.6 ± 5.1% RCY 8.3 ± 0.6% RCY (2 steps)</p>	<p>[^{18}F]4d (X=S): 12.7 ± 0.2% RCY [^{18}F]5d (X=SO₂): 88.4 ± 2.8% RCY 11.2 ± 0.3% RCY (2 steps)</p>	<p>[^{18}F]4f (X=S): 14.8 ± 0.8% RCY [^{18}F]5f (X=SO₂): 91.9 ± 2.8% RCY 13.6 ± 0.4% RCY (2 steps)</p>

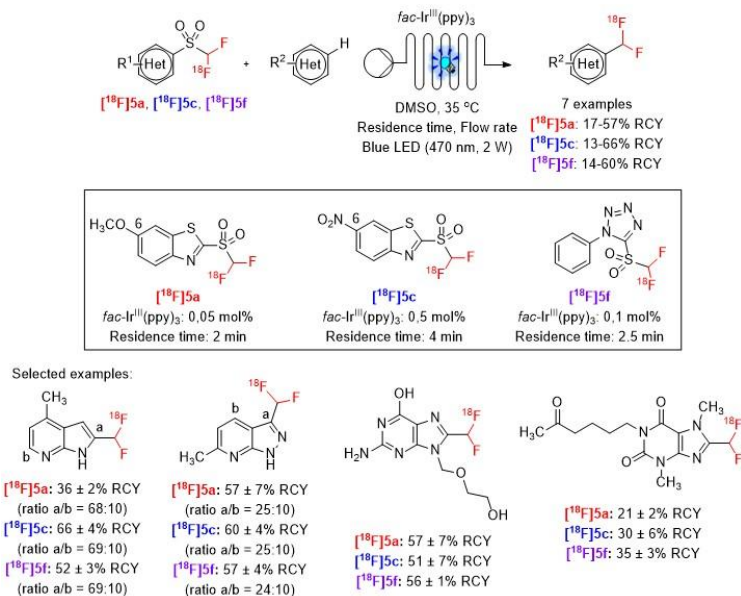
Scheme 2. Two-step radiosynthesis of [^{18}F]difluoromethyl sulfones bearing electron-rich ([^{18}F]5a and [^{18}F]5b) and electron-poor benzothiazolyl groups ([^{18}F]5c and [^{18}F]5d) and other heteroaryl rings ([^{18}F]5e and [^{18}F]5f). All radiochemical yields (RCYs) are of the cartridge-purified products and decay-corrected at the SOS.

Based on the RCYs of the two-step radiosyntheses of the cartridge-purified [^{18}F]5a–[^{18}F]5f, the electron-rich benzothiazolyl derivative [^{18}F]5a, the electron-poor benzothiazolyl derivative [^{18}F]5c, and the *N*-phenyl tetrazolyl derivative [^{18}F]5f were selected for the investigation of their reactivity toward ^{18}F -difluoromethylation of *N*-containing heteroarenes. In order to circumvent any potential radioprotection issues, the radiosyntheses of the three ^{18}F -labeled compounds were fully automated on a FASTlabTM synthesizer (GE Healthcare) in conjunction with an additional high performance liquid chromatography (HPLC) purification. The fully automated radiosyntheses of [^{18}F]5a, [^{18}F]5c, and [^{18}F]5f (^{18}F -labeling, oxidation, HPLC purification, and formulation) were performed in 73 min, 70 min, and 65 min, respectively. Starting from 125–150 GBq of [^{18}F]fluoride, the [^{18}F]5a, [^{18}F]5c, and [^{18}F]5f were isolated in 2.9 ± 0.1%, 5.7 ± 0.5%, and 8.0 ± 0.9% RCYs (decay-corrected at the SOS), respectively. Improved molar activities at the end of the synthesis (EOS) were achieved under these radiolabeling conditions [A_m ([^{18}F]5a) = 139 ± 17 GBq·μmol^{−1} > A_m ([^{18}F]5f) = 113 ± 17 GBq·μmol^{−1} > A_m ([^{18}F]5c) = 62 ± 12 GBq·μmol^{−1} > A_m ([^{18}F]1) = 54 ± 7 GBq·μmol^{−1}] (Table 1).

Table 1. Radiochemical yields and molar activities of [^{18}F]5a, [^{18}F]5c, and [^{18}F]5f.

[^{18}F]Difluoromethyl Heteroaryl-Sulfones	[^{18}F]5a	[^{18}F]5c	[^{18}F]5f
Duration of the radiosynthesis (min)	73	70	65
RCY (%)	2.9 ± 0.1	5.7 ± 0.5	8.0 ± 0.9
Molar activity (GBq·μmol ^{−1})	139 ± 17	62 ± 12	113 ± 17

Subsequently, the efficiency of [^{18}F]5a, [^{18}F]5c, and [^{18}F]5f as ^{18}F -difluoromethylating reagents was evaluated using the antihypertensive drug acyclovir as a model substrate. The ^{18}F -difluoromethylation reactions were carried out under continuous-flow conditions, in the presence of the photocatalyst *fac*-Ir^{III}(ppy)₃. Our results demonstrated that the introduction of molecular modifications in the structure of [^{18}F]1 can modulate the reactivity of the resulting ^{18}F -difluoromethylating reagents, influencing the amount of *fac*-Ir^{III}(ppy)₃ and the residence time needed to ensure a complete C-H ^{18}F -difluoromethylation reaction. The photocatalytic ^{18}F -difluoromethylation protocol with the reagents [^{18}F]5a, [^{18}F]5c, and [^{18}F]5f was extended to other heteroarenes (Scheme 3; [^{18}F]5a: 17-57% RCYs; [^{18}F]5c: 13-66% RCYs; [^{18}F]5f: 14-60% RCYs). Radical-trapping experiments demonstrated the likely involvement of radical species in the ^{18}F -difluoromethylation process.



Scheme 3. Scope of [^{18}F]heteroaryl- CF_2H derivatives. All RCYs were determined based on the radio-TLC and radio-UPLC purities of the crude products.

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