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Synthesis and evaluation of ^{18}F-trifluoroborate derivatives of triphenylphosphonium for myocardial perfusion imaging

Zhengxing Zhang [a], Silvia Jenni [a], Chengcheng Zhang [a], Helen Merkens [a], Joseph Lau [a], Zhibo Liu [b], David M. Perrin [b], François Bénard [a,c,*,†], Kuo-Shyan Lin [a,c,*,‡]

[a] Department of Molecular Oncology, BC Cancer Agency, Vancouver, BC V5Z 1L3, Canada
[b] Department of Chemistry, University of British Columbia, Vancouver, BC V6T 1Z1, Canada
[c] Department of Radiology, University of British Columbia, Vancouver, BC V5Z 4E3, Canada

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ABSTRACT

Four trifluoroborate derivatives of phosphonium cations **2a–d** were radiolabeled with fluorine-18 (^{18}F) and evaluated for imaging myocardial perfusion with positron emission tomography (PET). Tracers were radiolabeled simply via ^{18}F–^{19}F isotope exchange reaction in acidic (pH 2) aqueous solution. On average, [^{18}F]**2a–d** were obtained in 10–17% non-decay-corrected radiochemical yield with 25.9–48.1 GBq/μmol specific activity, and >96% radiochemical purity. In vitro stability study showed no decomposition of [^{18}F]**2a–d** after being incubated in mouse plasma for up to 2 h. Myocardial uptake in mice was visualized in PET images by using [^{18}F]**2b–d** but not [^{18}F]**2a**. [^{18}F]**2a–d** were stable against in vivo defluorination as no significant bone uptake was observed. Despite sub-optimal heart uptake of [^{18}F]**2b–d**, we successfully demonstrated that ^{18}F–^{19}F isotope exchange reaction on trifluoroborates could be a promising strategy for the design of potential ^{18}F-labeled tracers even for intracellular targets.

Nuclear imaging modalities including single photon emission computed tomography (SPECT) and positron emission tomography (PET) are used routinely in the clinic for evaluating myocardial perfusion to detect and characterize coronary artery disease.[1,2] The most widely used radiotracers for myocardial perfusion imaging are mitochondria-targeting cations ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin for SPECT.[2] Mitochondria are present in abundance within the myocardium, and these radiolabeled cations are drawn to the enhanced negative membrane potential of mitochondria.[2] Due to superior sensitivity and quantification capability of PET, the development of myocardial perfusion imaging agents in the past few years has focused on using positron emitters especially fluorine-18 (^{18}F) as imaging radioisotopes.[3] ^{18}F has a 109.7-min physical half-life, and can be produced in large quantity using a medical cyclotron. ^{18}F-labeled tracers can be prepared at a centralized radiopharmacy and distributed to regional hospitals for imaging. The pharmacophores commonly used for the design of ^{18}F-labeled myocardial perfusion imaging agents include phosphonium and rhodamine cations, and mitochondrial complex I inhibitors.[4–19] Among them, phosphonium has received the most attention due to the simplicity of its chemical structure.

Although several ^{18}F-labeled phosphonium cations have been reported and evaluated as potential myocardial perfusion imaging agents (Fig. 1),[4–14] most of these tracers suffer from tedious multi-step radiolabeling procedures[4,5,12,7] and/or in vivo defluorination leading to undesired high bone uptake (22.6%ID/g for [^{18}F]FMBTP at 2-h post-injection).[7,9] For example, [^{18}F]FBnTP (Fig. 1), developed by Dannals' group, is currently the most well-studied ^{18}F-labeled phosphonium cation.[20–23] However, its preparation involves four synthetic steps: ^{18}F-fluorination, reduction, bromination, and final coupling reaction with triphenylphosphine.[4] Such multi-step radiolabeling procedures could potentially limit its clinical applications due to the challenge of adapting the synthetic procedures to a commercial GMP-compliant automated synthesizer. Suitable ^{18}F-labeled phosphonium cations that are stable in vivo, and can be prepared in a single ^{18}F-fluorination step would be more appealing for routine use in the clinic.

Previously, we reported a facile strategy for the preparation of ^{18}F-labeled tracers via ^{18}F–^{19}F isotope exchange reaction using trifluoroborate derivatives.[24–27] This one-step reaction proceeds well in acidic aqueous solution (~pH 2) and obviates the lengthy drying

* Corresponding authors. Tel.: +1 604 675 8206; fax: +1 604 675 8218 (F.B.); tel.: +1 604 675 8208; fax: +1 604 675 8218 (K.-S.L.).
E-mail addresses: fbenard@bccrc.ca (F. Bénard), klin@bccrc.ca (K.-S. Lin).
† Present address: 675 West 10th Avenue, Rm 4-113, Vancouver, BC V5Z 1L3, Canada.
‡ Present address: 675 West 10th Avenue, Rm 4-123, Vancouver, BC V5Z 1L3, Canada.

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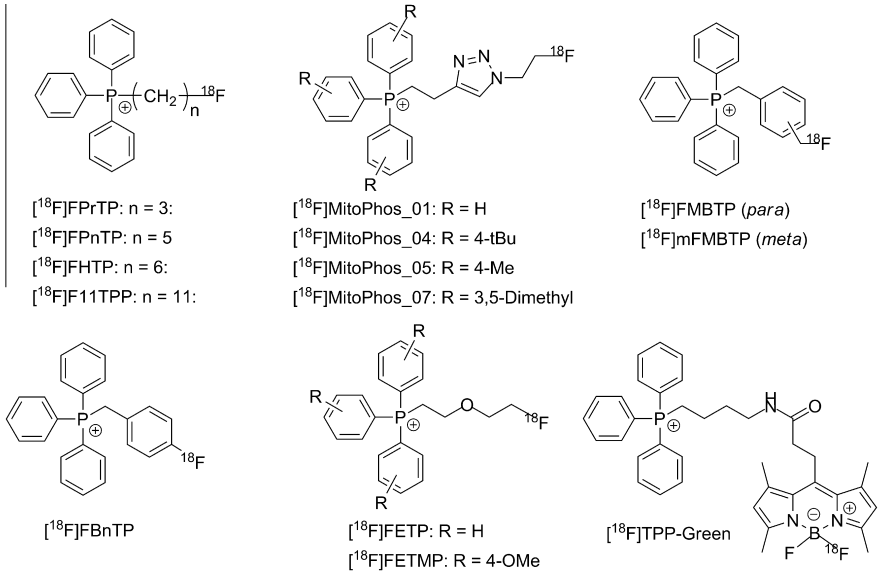


Figure 1. Structures of reported ^{18}F-labeled phosphonium cations for myocardial perfusion imaging.

step (to remove water from [^{18}F]fluoride) that is typically required for tracers prepared via aliphatic/aromatic nucleophilic substitution using [^{18}F]fluoride. Since the ^{18}F-labeled product and the radiolabeling precursor are chemically identical, in most cases, the ^{18}F-labeled trifluoroborates can be purified via solid phase extraction using a C18 Sep-Pak cartridge instead of HPLC purification. This facile radiolabeling and purification strategy can be easily implemented for clinical production using an automated synthesizer. Furthermore, we have successfully applied this strategy for the design of ^{18}F-labeled trifluoroborates targeting extracellular membrane-bound carbonic anhydrase IX,[28] integrin $\alpha_v\beta_3$,[29–31] and receptors of somatostatin,[32] bombesin,[33,34] and bradykinin.[35] None of these reported ^{18}F-labeled trifluoroborate derivatives exhibited significant bone uptake, demonstrating the stability of ^{18}F-labeled trifluoroborates against in vivo defluorination.

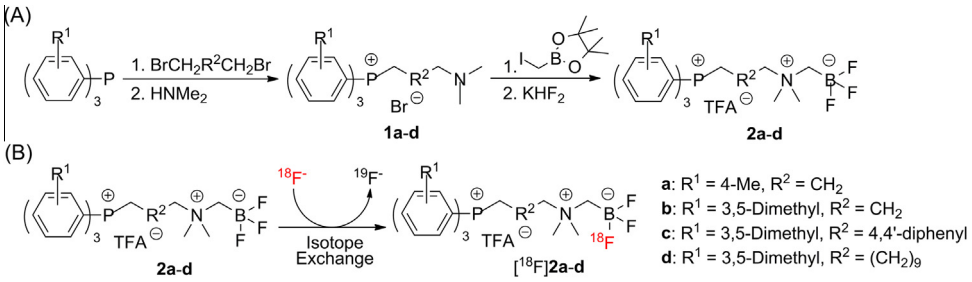
To exploit this radiolabeling strategy for the design of mitochondria-targeting tracers, we synthesized and compared four triphenylphosphonium bioconjugates **2a–d** (Scheme 1) that were differentially linked to an ^{18}F-labeled trifluoroborate. Instead of triphenylphosphine which was used in most ^{18}F-labeled phosphonium cations, we started with tris(4-methylphenyl)phosphine (for **2a**) or tris(3,5-dimethylphenyl)phosphine (for **2b–d**). It has been suggested that the phosphonium cations designed for heart imaging should have moderate lipophilicity (Log*P* values in the range of 0.5–1.3).[36] The extra methyl substitutions in tris(4-methylphenyl) phosphine and tris(3,5-dimethylphenyl)phosphine should provide compensation for the potential reduction in overall lipophilicity caused by the introduction of the polar dimethylammoniomethyl trifluoroborate motif. We also used different linkers between tris (3,5-dimethylphenyl)phosphine and the dimethylammoniomethyl trifluoroborate moiety in **2b** (propylene), **2c** (4,4′-bis-methylenebiphenyl) and **2d** (undecylene), so that the effect of linker selection on imaging contrast (heart-to-background) could be compared directly.

Table 1
Molecular weight, lipophilicity (Log$D_{7.4}$) and radiochemical data of [^{18}F]**2a–d**

Radiotracer	[^{18}F]**2a**	[^{18}F]**2b**	[^{18}F]**2c**	[^{18}F]**2d**
Molecular Weight (dalton)	471.4	513.4	651.6	625.6
Log$D_{7.4}$	0.11 ± 0.01 (n = 3)	1.16 ± 0.01 (n = 3)	1.90 ± 0.02 (n = 3)	2.46 ± 0.01 (n = 3)
Radiochemical Yield (%)	12 ± 4 (n = 3)	17 ± 4 (n = 3)	14 ± 4 (n = 2)	10 ± 1 (n = 2)
Radiochemical Purity (%)	98.8 ± 1.3 (n = 3)	97.2 ± 1.9 (n = 3)	96.7 ± 1.8 (n = 2)	96.7 ± 4.7 (n = 2)
Specific Activity (GBq/μmol)	40.7 ± 14.8 (n = 3)	48.1 ± 25.9 (n = 3)	25.9 ± 3.7 (n = 2)	33.3 ± 11.1 (n = 2)

The data except molecule weight are presented as mean ± SD.

The cold standards **2a–d** were prepared as depicted in Scheme 1A. First, tris(4-methylphenyl)phosphine or tris(3,5-dimethylphenyl)phosphine was reacted with excess dibromide (1,3-dibromopropane for **a** and **b**; 4,4′-bis(bromomethyl)biphenyl for **c**; 1,11-dibromoundecane for **d**) in toluene. The precipitated phosphonium bromides were filtered and reacted directly with *N*, *N*-dimethylamine to yield the intermediates **1a–d** in 13–35%



Scheme 1. Synthesis of (A) trifluoroborate derivatives of triphenylphosphonium **2a–d**, and (B) their ^{18}F-labeled analogs prepared via isotope exchange reaction.