A Bead-Supported Kit-Like Preparation of [^{18}F]SiFB (([^{18}F]-di(t-butyl)silyl)benzoic Acid N-hydroxylsuccinimidyl Ester) and Its Derivatives Greatly Simplifies Radiolabeling and Purification of PET Imaging Agents

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The introduction of fluorine-18 into peptides, polymers, or small molecules via prosthetic groups for diverse applications in positron emission tomographic (PET) imaging generally involves multi-step reaction sequences with long overall operational times, which are cumbersome and reduce radiochemical yield (RCY). Recently, F-18 labeling of PET tracers through fluorophilic silicon has attracted great interest because this one-step method is rapid and convenient, and gives high RCY. The conventional methods, however, have disadvantages because of the requirement of harsh condition or difficulty in obtaining high specific activity (SA). We recently developed versatile prosthetic group containing a silyl ester function which achieved high RCY and SA under mild conditions. Furthermore, this method allowed us to simplify F-18 labeling and purification by using a silicon-based bead-supported F-18 labeling protocol that releases only the F-18 incorporated silicon-based prosthetic compound after radiolabeling in a form that is ready for injection or conjugation to proteins or other PET agents.

Most silyl esters have poor hydrolytic stability. Nevertheless, the hindered silyl acetate **1** exhibited surprisingly good stability and showed little decomposition after 7 days at rt in an aqueous solvent system. F-18 incorporation into compound **1** was conducted under two conditions: (*a*) aqueous condition using F-18 activity in $H_2[^{18}O]O$ obtained directly from the cyclotron or (*b*) after typical azeotropic drying using $K[^{18}F]F$, K_2CO_3, K_{222}Kryptofix. Both methods consistently gave product **2** in >94% RCY with SA 3650 Ci/mol. This hindered silyl acetate group has two very favorable characteristics: good hydrolytic stability and very high fluorophilicity. Thus, the acetate group in compound **1** is easily substituted with F-18 without any NHS group decomposition to give the very useful [^{18}F]fluorosilylbenzoate prosthetic group.

The silyl compound was loaded onto beads by *(a)* reaction of a silyl chloride with COOH-terminated beads or *(b)* copper-free click chemistry with DBCO (dibenzocyclooctyne)-modified silyl compound and azide-terminated beads. The F-18 incorporation into the bead-supported succinimidyl-oxy-carbonylphenyl-(di-t-butyl)silyl ester (**3**) to produce [^{18}F]SiFB (**2**) was carried out under direct aqueous conditions: F-18 activity in $H_2[^{18}O]O$, obtained directly from the the cyclotron target without drying, was diluted into DMSO containing the beads, and compound **2** was released during a 30-min reaction at rt. After simple isolation from the beads by passage through a silica gel plug, compound **2** was obtained in 93% RCY, >98% radiochemical purity, and at more than 3200 Ci/mmol SA, high enough for further conjugation with other compounds of interest for PET imaging of diverse targets.