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Design, radiosynthesis, and evaluation of radiotracers for positron emission tomography imaging of stearoyl-CoA desaturase-1

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ABSTRACT

Design, radiosynthesis, and biological evaluation of two radiotracers (*N*-(3-[^{18}F]fluoropropyl)-6-(4-(trifluoromethyl)benzoyl)-piperazin-1-yl)pyridazine-3-carboxamide (^{18}F-FPPPT) and (*N*-(4-[^{18}F]fluoroaniline)-6-(4-(trifluoromethyl)benzoyl)-piperazin-1-yl)pyridazine-3-carboxamide (^{18}F-FAPPT)) are described for noninvasive assessment of stearoyl-CoA desaturase-1 (SCD-1). The overexpression of SCD-1 in multiple solid tumors associates with poor survival in cancer patients. The two radiotracers, ^{18}F-FPPPT and ^{18}F-FAPPT, were each prepared in three steps in radiochemical yields of 21% and 3%, respectively. The practicality of imaging SCD-1 with ^{18}F-FPPPT was tested in two mouse models bearing xenograft tumors with different levels of SCD-1 expression, which afforded a 1.8-fold uptake difference correspondingly. Our work indicates that it is possible to develop SCD-1 specific imaging probes from previously reported SCD-1 inhibitors.

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The family of stearoyl-CoA desaturase (SCD) enzymes catalyzes the formation of a double bond at the C9 position in saturated fatty acids (SFAs) to create monounsaturated fatty acids (MUFAs).[1–3] Of the two isoforms in humans, SCD-1 is predominant and ubiquitously expressed in the brain, liver, fat, heart and lung.[4] Upregulated expression of SCD-1 has been reported in multiple solid tumors (e.g., prostate, breast, lung, and ovarian cancer) with implications in cancer progression, which is indicative of poor prognosis in cancer patients.[5,6] The important role of SCD-1 in *de novo* fatty acid (FA) metabolism, a pathway elevated across all cancer types, makes it an ideal target for cancer therapy. To date, small organic inhibitors of SCD-1 have shown desired anti-cancer effects by inducing cancer cell apoptosis and slowing tumor-growth in preclinical tumor xenograft mouse models.[6–8] Given the reported correlation of SCD-1 expression with cancer progression, measurement of SCD-1 levels can potentially serve as a biomarker for cancer treatment planning and prognostic evaluation post-treatment.

Clinically, the expression of SCD-1 is often measured by the desaturation index (DI) from plasma and tissue or immunohistochemical analysis on tissue biopsies.[5,9,10] Suboptimal accuracy of biopsies aside, major drawbacks of both methods include the invasiveness of obtaining biopsies from tissues and long sample processing times. A noninvasive imaging technique would be highly desirable in the clinic for the assessment of SCD-1 expression.

To date, numerous SCD-1 inhibitors with sub-μM binding affinities have been reported for cancer treatment.[11–15] These inhibitors can potentially serve as lead compounds for SCD-1 targeted radiotracer development.

To enable positron emission tomography (PET) imaging of SCD-1, the design of radiotracers labeled with ^{18}F ($t_{1/2}$ = 109.8 minutes; β^+ 0.63 MeV, 97%) was based on two previously reported SCD-1 inhibitors, *N*-pentyl-6-(4-(2-(trifluoromethyl)benzoyl)piperazin-1-yl)pyrazine-3-carboxamide and *N*-phenethyl-6-(4-(2-(trifluoromethyl)benzoyl)piperazin-1-yl)pyrazine-3-carboxamide.[15] Their half maximal inhibitory concentrations (IC_{50}) were measured at 25 and 18 nM, respectively, for human SCD-1. Shown in Scheme 1, the ^{18}F synthon (**1**) for ^{18}F-FAPPT (*N*-(4-[^{18}F]fluoroaniline)-6-(4-(trifluoromethyl)benzoyl)-piperazin-1-yl)pyridazine-3-carboxamide) was synthesized as previously described.[16] To make the synthon (**5**) for ^{18}F-FPPPT (*N*-(3-[^{18}F]fluoropropyl)-6-(4-(trifluoromethyl)benzoyl)-piperazin-1-yl)pyridazine-3-carboxamide), the desired tosylated precursor (**3**) was first prepared through reacting *N*-(*tert*-butoxycarbonyl)-3-hydroxypropylamine (**2**)[17] with *p*-toluenesulfonyl chloride in the presence of triethylamine (Et_3N) (63% yield).[18] Synthesis of ^{18}F-FPPPT was accomplished in 3 steps within 120 min, as outlined in Scheme 1.[19] Radiolabeling of **3** with ^{18}F was performed under basic conditions in the presence of kryptofix 2,2,2 ($K_{2,2,2}$)/K_2CO_3 and the reaction was carried out at 110 °C for 15 min. The resulting protected 3-[^{18}F]fluoro-propylamine **4** was isolated

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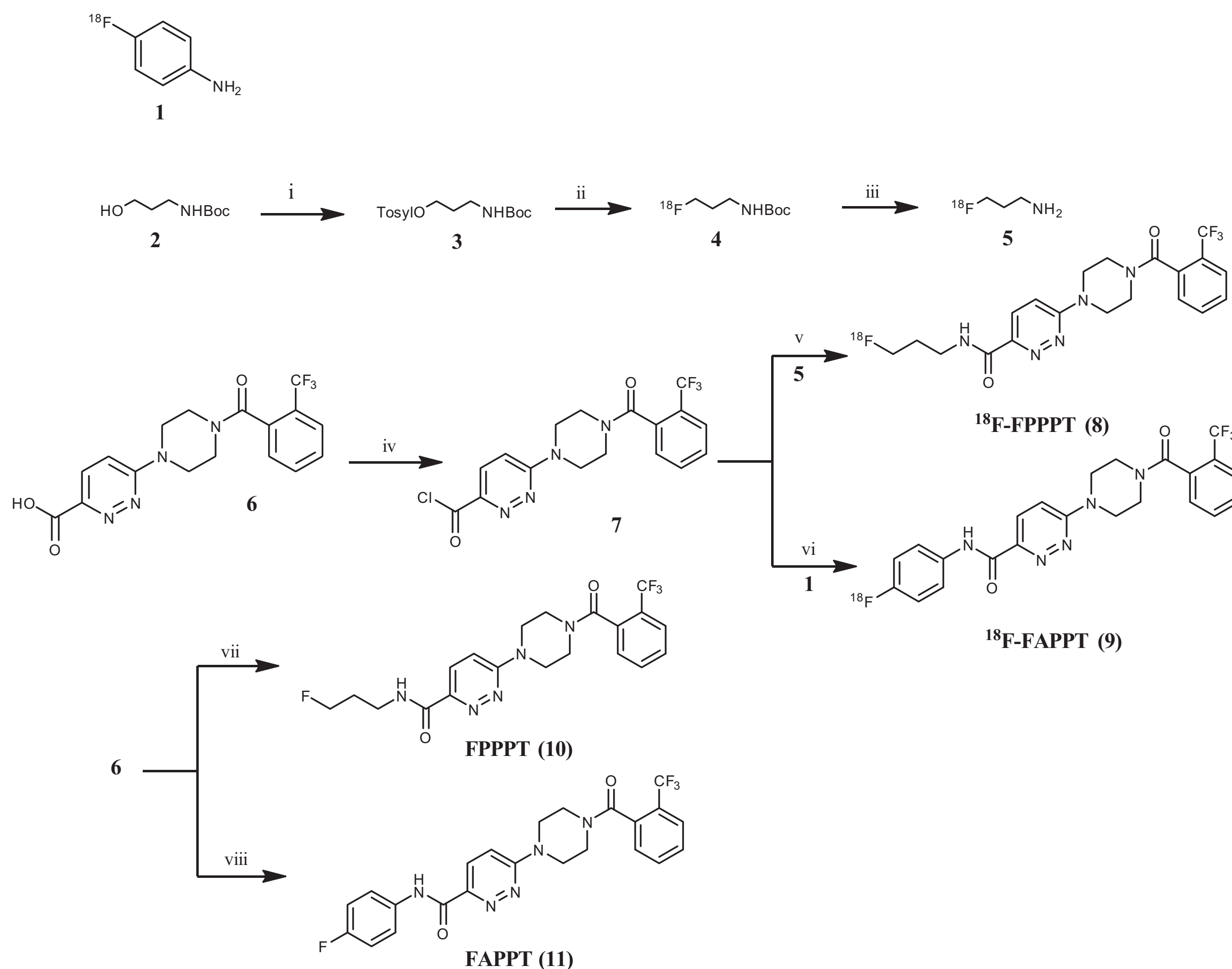

Scheme 1. Synthesis of ^{18}F-FPPPT, ^{18}F-FAPPT, synthons **1** and **5**, FPPPT, and FAPPT. Reagents and conditions: (i) *p*-toluenesulfonyl chloride, DMAP, Et_3N, dichloromethane (DCM); (ii) $K_{2,2,2}/K_2CO_3$, acetonitrile (ACN), 110 °C, 15 min; (iii) TFA, rt, 8 min; (iv) thionyl chloride, DCM, 50 °C, overnight; (v) **5**, Et_3N, ACN, rt, 15 min; (vi) **1**, Et_3N, ACN, rt, 15 min; (vii) 3-fluoropropylamine hydrochloride, HBTU, DIPA, dimethylformamide (DMF); (viii) 4-fluoroanline, HBTU, DIPEA, DMF.

on a C-18 Sep-Pak cartridge, which was eluted into a vial and dried under a nitrogen flow. Compound **4** was then deprotected by trifluoroacetic acid (TFA, neat) for 8 min generating ^{18}F-fluoro-propylamine (**5**) in 51% radiochemical yield (RCY). After removal of TFA, the silica Sep-Pak cartridge trapped **5** was eluted with acetonitrile for further radiochemistry. For the synthesis of ^{18}F-FPPPT and ^{18}F-FAPPT, 6-(4-(2-(trifluoromethyl)benzoyl)piperazine-1-yl)-pyridazine-3-carboxylate (**6**) was prepared according to a published procedure, from which the amine reactive acid chloride analog **7** was obtained by reacting with thionyl chloride. Compound **7** is the common precursor to make both ^{18}F-FPPPT and ^{18}F-FAPPT by reacting with synthons **5** and **1**, respectively.[20] The coupling reaction between **5** and **7** was carried out at room temperature (rt) for 15 min, followed by HPLC purification of ^{18}F-FPPPT on a semi-preparative C-18 column. The decay corrected RCY at the end of synthesis (EOS) was 21%. The radiochemical purity of the obtained ^{18}F-FPPPT was 99%. The synthesis of ^{18}F-FAPPT was accomplished in a similar way by reacting **1** with **7**.[21] The decay corrected RCY of ^{18}F-FAPPT was lower at 3% at the EOS, due to the poor reactivity of aromatic amines as opposed to the aliphatic in ^{18}F-FPPPT synthesis, and its radiochemical purity was 99%. The average ($n = 3$) specific radioactivity for ^{18}F-FPPPT and ^{18}F-FAPPT was 507 ± 148 MBq μmol^{-1} and 61 ± 28 MBq μmol^{-1}, respectively. The reference standard compounds, the ^{19}F counterparts of ^{18}F-FPPPT and ^{18}F-FAPPT, were synthesized by reacting **6** with 3-fluoropropylamine or 4-fluoroaniline in the presence of *N*,*N*-diisopropylethylamine (DIPEA) using *O*-(benzotriazo-1-yl)-*N*,*N*,*N*′*N*′-tetramethyluronium hexafluorophosphate (HBTU) as the coupling agent at yields of 85% and 80%, respectively, as shown in Scheme 1.[22,23]

The lipophilicity of ^{18}F-FPPPT and ^{18}F-FAPPT measured by partition coefficient ($\log P$) was assessed in a bi-phasic mixture of *n*-octanol and water.[24] The $\log P$ values of ^{18}F-FPPPT and ^{18}F-FAPPT were determined to be 1.23 and 2.08, respectively. The lipophilicity difference of ^{18}F-FPPPT and ^{18}F-FAPPT can be attributed to the fact that different linkers, phenyl and propyl, were used for their construction. The stability of ^{18}F-FPPPT and ^{18}F-FAPPT in fetal bovine serum (FBS) was assessed by radio-HPLC after 3 h of incubation at 37 °C. Both radiotracers were found nearly 100% intact.

The SCD-1 mediated retention of ^{18}F-FPPPT and ^{18}F-FAPPT was assayed in SCD-1 positive prostate cancer cells (C4-2; Fig. 1a) with a commercially available SCD-1 inhibitor, 4-(2-chlorophenoxy)-*N*-[3-[(methylamino)carbonyl]phenyl]-1-piperidinecarboxamide ($IC_{50} = 37$ nM for human SCD-1) (Fig. 1b).[25,26] Briefly, ~2.0 μCi of each radiotracer was incubated with or without the inhibitor in C4-2 cells for 30 min, followed by rinsing with fresh media to remove non-specifically bound radiotracer. The cells were later trypsinized and the activity was measured and normalized to the cell numbers. Shown in Figure 1b, the SCD-1 mediated C4-2 cell uptake reduced by 40% and 39% for ^{18}F-FPPPT and ^{18}F-FAPPT,

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