Investigation into the metabolic stability of $^{18}$F-labeled PSMA inhibitor derivatives bearing aryl-fluorosulfates for PET tracer development applications

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Introduction

- Radiolabeled PSMA inhibitors are used in clinics for non-invasive molecular imaging and treatment of prostate cancer [1].
- The sulfur [18]F-fluoride exchange ([18]F)SuFEx) radiolabeling approach has had promising results to prepare [18]F-labeled radiotracers with high RCY and RCP in the absence of metal additives and under mild conditions [2,3].
- Recently, the [18]F(SuFEx) radiolabeling approach was used on FAP inhibitors. Fibroblast Activation Protein alpha (FAPα) inhibition potency was not affected by the addition of aryl-fluorosulfates [4]. However, defluorination in serum (37 °C) and in vivo was observed.
- This work aims to study the influence of aryl-fluorosulfates on PSMA-inhibitors with [18]F(F2) and subsequently (not this work) without [18]F(F4) electron withdrawing group.
- Both radiotracers will be evaluated with respect to their relative stability to aid future radiotracer development using the [18]F(SuFEx) radiolabeling approach.

Methods

- Two step radiosynthetic preparation of [18]F(F2) via the [18]F(SuFEx) reaction and deprotection. The identity and radiochemical purity (RCP) of [18]F(F2) was confirmed by U-HPLC (Fig. 1A).
- Real-time radiogold binding experiments of [18]F(F2) on LNCaP cells (Fig. 1B) were performed using LigandTracer Yellow (Ridgeview Instruments AB).
- Stability studies were performed by incubating a sample of [18]F(F2) in three different media: PBS buffer (pH 7.4), EiOH and human serum (37 °C) (Fig. 1C).
- Xenograft tissue binding studies were performed using [18]F(F2) and [18]GaGa-PSMA-11 as the reference tracer (Fig. 1D).
- PET imaging of LNCaP tumor-bearing mouse using [18]F(F2) (8.5 MBq equivalent to 1.7 nmol) (Fig. 1E).
- PET imaging of LNCaP tumor-bearing mouse using [18]F(F2) and blocking agent 2-PMPA (6.6 µmol; ~4×10-fold molar excess) (Fig. 1F).

Results


- Radiosynthesis: An [18]F-labeled PSMA inhibitor [18]F(F2) was obtained with activity yield (AY) of 40 ± 3% (n = 3) and >95% RCP in 60 min.
- Binding affinity was found to be 1 nm in real-time radiogold binding experiments. The low dissociation rate constant indicates internalization. Affinity for [18]F(F2) was found to be in the nanomolar range as [18]F-PSMA-107 [5].
- Stability experiments show partial (~20%) in 120 min degradation in human serum but no degradation in PBS or EiOH.
- In vivo PET images show tumor accumulation, but apparent tracer degradation (defluorination) occurs shown by bone accumulation ~60 min post-injection.
- Competitive blocking experiment (Fig. 1F) (2-PMPA, 6.6 µmol) show that tumor accumulation is target-specific.

Conclusions & Further work

- [18]F(F2) shows good binding kinetics compared to known radiotracers (1 nm) but ~20% defluorination occurs in human serum after 120 min.
- [18]F(F2) binds to LNCaP xenograft sections in a similar pattern as [18]GaGa-PSMA-11.
- PET imaging experiments show defluorination but also accumulation in LNCaP tumor xenografts (SUVmax = 4.4).
- Further work: Radiosynthesis of [18]F(F4) starting from precursor 3 (Fig. 2).

References


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