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Short Research Article

Synthesis and evaluation of fluorine-18 and copper-64 labelled PBR radioligands†

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Introduction

Imaging peripheral-type benzodiazepine receptors (PBRs) by positron emission tomography (PET) is a powerful approach for *in vivo* assessment of various inflammatory pathologies. However, the most widely used PBR radioligand, (*R*)-[^{11}C]PK11195[1] has methodological problems with regard to its use for PET imaging. Consequently, there is a need for PBR radioligands with improved properties, in particular with longer-lived radionuclides for clinical PET studies.

Results and discussion

Based on a class of aryloxyanilide derivatives, which have been shown to have high affinity for PBR,[2] we have developed a synthetic pathway for precursors to enable the radiosynthesis of PBR ligands labelled with a variety of positron-emitting radioisotopes (Figure 1).

For [^{18}F]FEDAA1106[3] we developed a high-yielding automated radiosynthesis on a GE FXn module from a tosyl precursor (TsEDAA1106). After preparative HPLC we can produce 8–11 GBq of [^{18}F]FEDAA1106 with specific activity (SA) of 212–370 GBq/μmol at the end of synthesis (EOS) with a total synthesis time of 43 min.

For a preliminary biological evaluation of these radioligands we initially compared [^{11}C]DAA1106 (**A**) with (*R*)-[^{11}C]PK11195 (**B**) using a small animal scanner (MicroPET P4) (Figure 2). A New Zealand white rabbit was injected with 104 MBq of (**B**) and data were acquired for 75 min and subsequently (after 15 min) with 79 MBq of (**A**, SA>100 GBq/μmol at injection) and data were acquired for 75 min. The results indicate comparable data *in vivo* for the PBR distribution using A and B (kidney cortex uptake (%ID/g) ratio 1–1.25 h post-injection **A : B** = 2.11 : 1).

To fully characterize the binding properties of the DAA1106 series of tracers to the PBR, we used [^{18}F]FEDAA1106 to perform *in vitro* binding assays on rat heart showing a diffuse PBR expression mainly in the ventricle wall and rat kidney where the PBR expression occurred mainly in the cortex (Figure 3).

To conclude we have developed methods to radiolabel the DAA1106 series of compounds with various positron-emitting isotopes, including, (i) synthetic routes for the required precursors for labelling with ^{18}F and ^{64}Cu and (ii) a high-yielding one-step automated radiosynthetic method for [^{18}F]FEDAA1106. Our preliminary *in vivo* and *in vitro* studies indicate these radioligands are markers of the PBR.

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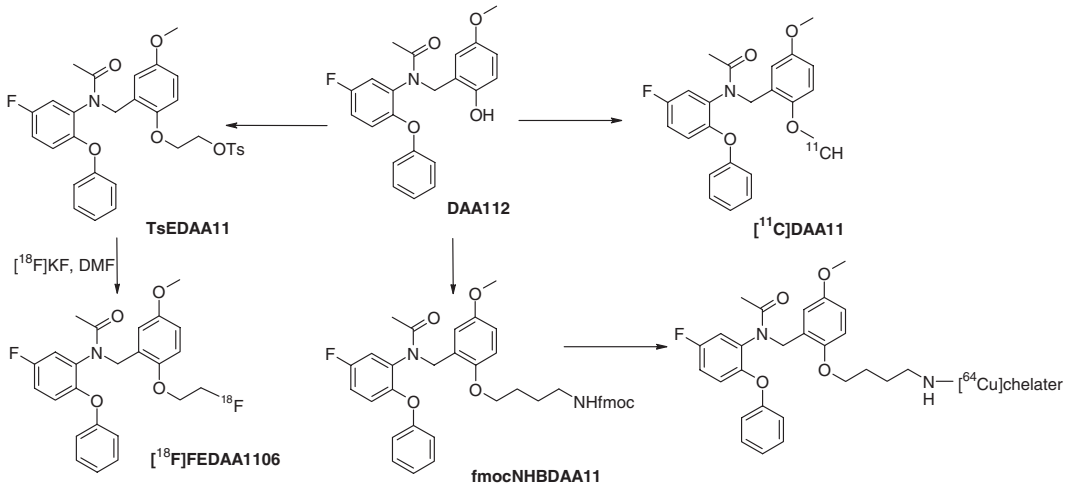

Figure 1 Synthesis of DAA1106 family and radiosynthesis of [^{18}F]FEDAA1106.

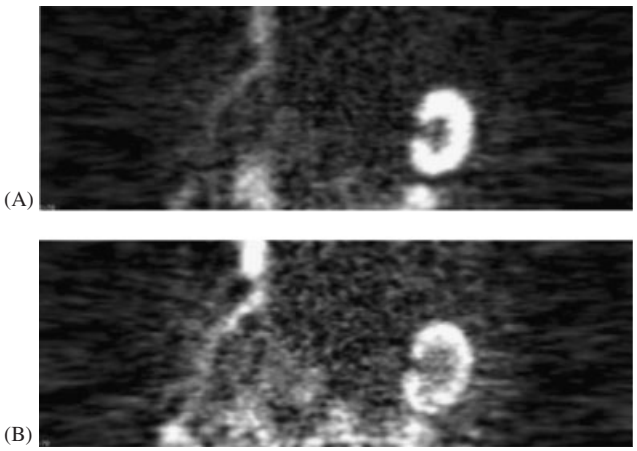

Figure 2 MicroPET scan of [^{11}C]DAA1106 (**A**) and (*R*)-[^{11}C]PK11195 (**B**) in the kidney of a New Zealand white rabbit (1 h–1 h 15 min post injection).

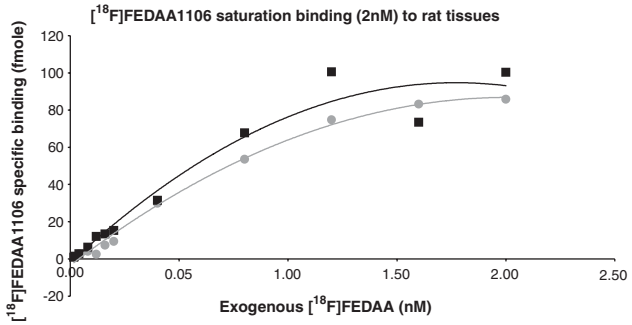

Figure 3 Saturation binding curves for rat heart (●) and rat kidney (■) using [^{18}F]FEDAA1106.

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