[^{18}F]stilbene and [^{18}F]styrylpyridine as PET-tracers for the early diagnosis of Alzheimer's disease

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Neurodegenerative disorders like dementia are one of the major reasons for serious handicap and care dependency. Furthermore, they cause immense costs for the healthcare system which is due to the huge amount of people suffering from them. It is estimated that in 2010 35,6 million people worldwide were affected by dementia and the number will increase greatly. For 2050 a prevalence of 115,4 million people is predicted assuming that there is no breakthrough in treatment effectiveness [1].

Alzheimer's disease (AD) is the most common type of these disorders. It is characterized by slowly progressing dementia which leads to death after 3 to 10 years depending on the age by which the disease is diagnosed [2]. Clinical symptoms comprise cognitive dysfunctions, such as memory loss and language problems as well as non-cognitive symptoms, such as depressions and delusions. On cellular level β-amyloid (Aβ) plaques and neurofibrillary tangles built up from hyperphosphorylated tau proteins can be observed. These pathological aggregates result in an impairment of neurons and finally in neuron loss and decline of cerebral matter [3].

It has already been 100 years since the first description of AD [4]. Despite, a distinct diagnosis is still only possible *post mortem* by staining the Aβ plaques with fluorescence dye. However, an early diagnosis is essential for therapy, since the few available drugs slow down the progression of AD only if applied early during the course of the disease [5]. A promising approach towards early diagnosis uses positron emission tomography (PET) to detect radioligands that bind to Aβ plaques which occur at a preclinical stage of the disease.

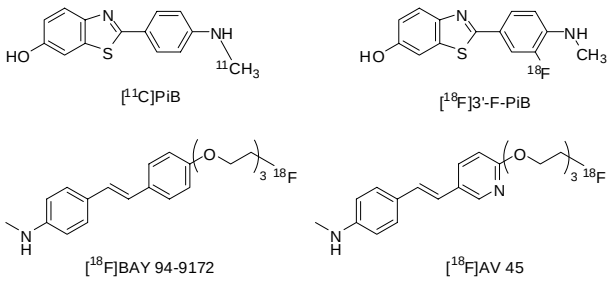

Fig.1. Chemical structures of Aβ plaque targeting radioligands.

Based on the fluorescence dye Thioflavin T, one of the first imaging agents developed was the benzothiazole [^{11}C]PiB (Fig. 1) which shows excellent brain penetration and high binding affinity to Aβ plaques [3]. However, the short half- life of ^{11}C ($t_{1/2}$=21 min) limits the use to medical centers with an on-site cyclotron. Further development of [^{11}C]PiB resulted among others in [^{18}F]3'-F-PiB (Fig. 1). Due to the longer half-life of ^{18}F ($t_{1/2}$=110 min), ^{18}F tracers simplify the logistics of transportation and enable medical centers without an on-site cyclotron to do PET scans. The recognition of the structural similarity between benzothiazoles and stilbenes led to stilbene- and styrylpyridine-based Aβ tracers including [^{18}F]BAY 94-9172 and [^{18}F]AV-45 (Fig. 1) [3]. Although, [^{18}F]AV-45 received the FDA approval in April 2012 and [^{18}F]BAY 94-9172 is currently in phase 3 clinical trials [6] the fast development and evaluation of these molecules give raise to doubts whether they bind to Aβ plaques is specifically [7].

The aim of this project is to evaluate and compare [^{18}F]BAY 94-9172, [^{18}F]AV-45 and a new [^{18}F]styrylpyridine derivative in small animal PET studies. The new styrylpyridine derivative will be synthesized starting from commercially available 2-chloro-5-((trimethylsilyl)ethynyl)pyridine, which has to be deprotected first. In a subsequent step the alkine will be addressed to hydroboration with catecholborane giving a boronic ester, which will be coupled with commercially available 5-amino-2-bromopyridine in a Suzuki reaction. The amino group of the resulting styrylpyridine derivative will be monomethylated via reductive alkylation with paraformaldehyde then boc-protected. Following this, the styrylpyridine derivative will be coupled with triethylene glycol. To enable a nucleophilic radiolabelling with ^{18}F the hydroxyl group will be tosylated.

In initial studies the radiosynthesis of [^{18}F]BAY 94-9172 has been optimized. Radiochemical yields over 90 % have been reached. In further experiments the reaction conditions will be tested with the [^{18}F]AV-45 precursor as well as the new [^{18}F]styrylpyridine derivative precursor. With the three radiotracers in hand small animal PET studies will be accomplished.

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