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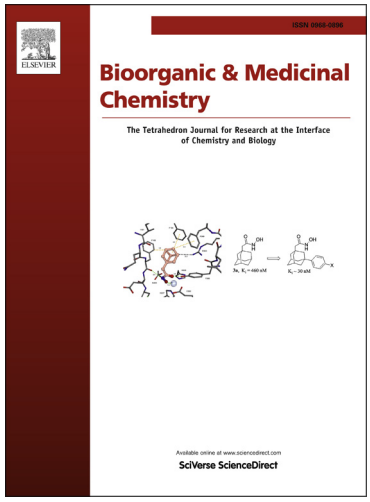

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Fluorescent rhodanine-3-acetic acids visualize neurofibrillary tangles in Alzheimer's disease brains

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ABSTRACT

There is a high demand for the development of an imaging agent for neurofibrillary tangles (NFTs) detection in Alzheimer's diagnosis. In the present study, a series of rhodanine-3-acetic acids was synthesized and evaluated for fluorescence imaging of NFTs in brain tissues of AD patients. Five out of seven probes have shown excellent binding affinity to NFTs over amyloid plaques in the *Thiazine red R* displacement assay. However, the selectivity in this *in vitro* assay is not confirmed by the histopathological evaluation, which indicates significant differences in the binding sites in the assays. Probe 6 showed binding affinity (IC_{50} = 19 nM) to tau aggregates which is the highest among this series. Probes 2, 3, 4 and 5 display IC_{50} values of lower than 100 nM to tau aggregates to displace *Thiazine red R*. Evaluation of the cytotoxicity of these five probes with human liver carcinoma cells revealed that these compounds excert negligible cytotoxicity. The *in vivo* studies with zebrafish embryos confirmed negligible cytotoxicity at 24 and 72 hours post fertilization.

1. Introduction

Alzheimer's disease (AD) is one of the most common forms of dementia. This disease is a progressive neurodegenerative disorder associated with cognitive decline, disorientation and language impairment. Incidence of new AD cases worldwide is growing with the age of the baby boomer generation.[1, 2] The major cause is still unknown for the disease but it is usually accepted that the formation of two abnormal proteins; extra cellular senile plaques (SPs) and neurofibrillary tangles (NFTs) are the two key pathological findings in postmortem histology. They are observed in hippocampus and cerebral cortex but also in other areas of the brain. SPs are composed of aggregated β-amyloid (Aβ) peptides and NFTs are formed by the aggregated microtubule associated tau protein.[3]

Non-invasive imaging is vital for early diagnosis of AD. Currently there are few positron emission tomography (PET) imaging agents available for the early diagnosis. PET imaging is a very well-known technique which provides good sensitivity deep in tissue.[4] Nevertheless it is limited by a time-consuming

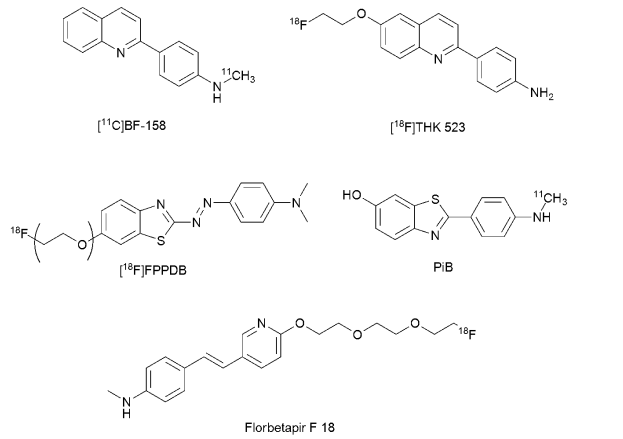

Figure 1. Structure of PET imaging probes for the detection of NFTs and Aβ plaques in AD brain tissues