Synthesis of Radiotracers to Image Neuroinflammation in Alzheimer's Disease

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Alzheimer's disease (AD) remains one of the most devastating neurodegenerative disorders, with 10 million new cases reported every year. Despite decades of research, its early and accurate diagnosis continues to pose a major clinical challenge, emphasizing the need for sensitive molecular imaging techniques. **Positron emission tomography** (PET) imaging, through the use of specific radiotracers, offers a powerful tool to visualize and quantify key molecular targets involved in the disease [1].

Among these targets, **Monoamine Oxidase-B** (MAO-B) has emerged as a promising biomarker for early AD detection, as it is massively upregulated during the neuroinflammatory phase occurring in the early stages of the disease [2]. [^{18}F]SMBT-1, a well-established radiotracer for MAO-B [3], has proven to be a highly promising candidate, although its synthesis has so far remained difficult to achieve reliably. The overarching aim of this project is therefore to develop a robust, reliable, and straightforward automated radiosynthesis process suitable for routine clinical production of [^{18}F]SMBT-1.

Our first objective was to synthesize the non-radioactive SMBT-1, which served (i) to investigate protection and deprotection strategies and (ii) as an analytical reference for the development of QC methods and confirmation of the radiotracer's identity. In a second step, the synthesis of the tosylated precursor was undertaken to enable the subsequent incorporation of radioactive fluorine-18. Initial radiolabelling experiments proved challenging, with radiochemical yields below 5%. Further investigation identified contamination with trace amounts of chloride and chlorinated analogues as a potential cause. To address this, alternative synthetic routes were explored, focusing on the reactivity of **tosylated epoxides, allyl derivatives, and the various alcohol groups** within the molecule.

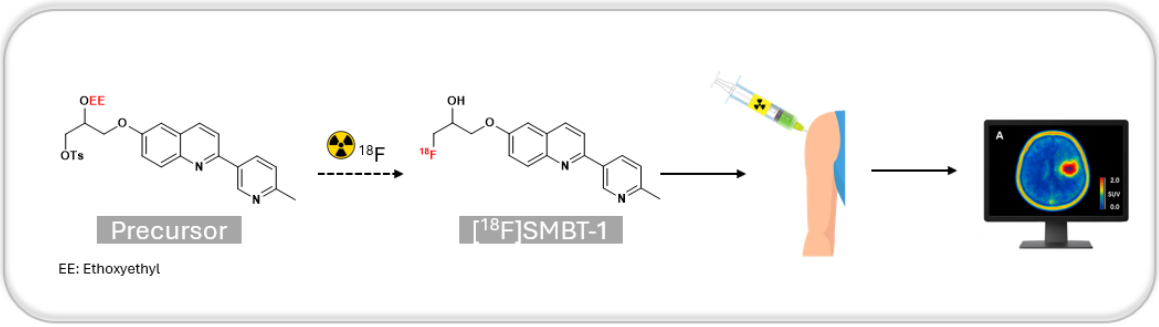

Figure 1: Overview of [^{18}F]SMBT-1 radiosynthesis and application for MAO-B PET imaging.

References

[1] James, M. L.; Gambhir, S. S, *Physiological Reviews* **2012,** *92* (2), 897–965.
[2] Jaisa-Aad M, Muñoz-Castro C, Healey MA, Hyman BT, Serrano-Pozo A**.** *Acta Neuropathol* **2024** 3;147(1):66**.**
[3] Villemagne, V. L.; Harada, R.; Doré, V.; Furumoto, S.; Mulligan, R.; Kudo, Y.; Burnham, S.; Krishnadas, N.; Bozinovski, S.; Huang, K.; Lopresti, B. J.; Yanai, K.; Rowe, C. C.; Okamura, N. *J. Nucl. Med.* **2022**, *63* (10), 1551–1559.