Automated synthesis of $^{18}\text{F}$ FBEM for labeling of thiol containing compounds

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Objectives: $^{18}\text{F}$FBEM, i.e. $\text{N-}[2-(4-[^{18}\text{F}]\text{fluorobenzamido})\text{ethyl}]\text{maleimide}$, is a useful synthon employed for the specific radiolabeling of thiol containing compounds, including peptides and proteins$^{[1]}$. The aim of the present work was to develop a fast, reproducible and fully automated synthesis of this compound in order to improve its availability as well as for obvious radioprotection matters.

Methods: A three-step synthetic pathway was followed (scheme 1) and implemented on a GE FastLab$^\text{TM}$ system by modifying the original $^{18}\text{F}$FDG sequence and reagents cassette configuration. The process starts with the $^{18}\text{F}$ F nucleophilic substitution of the trimethylammonium ethylbenzoate compound 1 followed by NaOH hydrolysis performed in the same labeling reactor$^{[2]}$. After acidification (HCl 0.25M), the resulting $^{18}\text{F}$Fluorobenzoic acid 3 was trapped and purified on a solid phase extraction cartridge before being coupled to amino-maleimide compound 4 in the next step. This was carried out using diethylcyanophosphonate$^{[3]}$ in acetonitrile at 70°C. Then $^{18}\text{F}$FBEM could be isolated and purified on a second SPE cartridge.

Results: The fully automated process takes around 55 minutes and the desired product is obtained with a decay-corrected radiochemical yield of $41\%$ (n=11) and a radiochemical purity $\geq 90\%$ as determined by HPLC and TLC. Subsequent conjugation to thiol containing compounds was also carried out.

Conclusions: A completely automated radiosynthesis of $^{18}\text{F}$FBEM has been developed with good radiochemical yields and purity. The resulting SPE purified maleimide synthon is suitable for the labeling of various thiol containing compounds under mild conditions.

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![Scheme 1: Radiosynthesis of $^{18}\text{F}$FBEM](image-url)