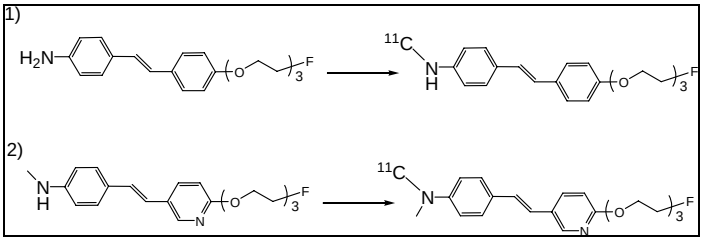
LABELLING OF STILBENE DERIVATIVES FOR PET STUDIES OF AMYLOID PLAQUE

J.S. Fowler[1], S.Wessmann[2], A. Reid[1]
[1]Broohaven National Laboratory, Chemistry Department, Upton, NY, USA
[2]Johannes-Gutenberg-Universität, Fachbereich Biomedizinische Chemie, Mainz

Introduction: The ^{11}C-methylation of two stilbene derivatives as potential diagnostic imaging agents binding to amyloid plaques in Alzheimer´s disease (AD) was studied.
Different methylation pathways were applied in order to produce the labelled 4´-fluoroethoxy-stilbene precursor (1 and 2).



To determine the stilbene binding character towards Aß-plaque, Positron Emission Tomography (PET) imaging was planned.

Methods: The precursors were provided by Hank Kung. The standard curves were performed successfully by HPLC in order to determine yields. For methylation, [^{11}C]methyl iodide and [^{11}C]methyl triflate were used. The cold and hot synthesis were made with a precursor excess of 5:1 over methyl triflate. In addition, a methyl iodide carrier-added hot run was performed. The radioactivity was measured by the well counter (Picker) directly after reaction and after HPLC, when the hot fraction was eluted from the column.

Results: The hot reaction with ^{11}C-methyl iodide failed at 100°C without using a base with 2 and 3 min beam time. Because the aromatic amine is relatively non-basic, both TBAF and NaH were also used without success. Even when the amount of NaH was increased and the temperature raised to 120°C, no labelled product was detected. Thus, the methylation was modified and [^{11}C]-methyl triflate instead of methyl iodide was used as methylation agent. In the cold reactions, [1] seems to be more reactive than [2] which needs to be verified. Cold product of [1] with MeI and [2] with methyl triflate were obtained although no NaH was added. The base-added cold reactions show a high yield of [1] and [2] when using methyl iodide in excess. The same reaction conditions were applied with [^{11}C] methyl iodide but no labelling occurred. According to the fact that product synthesized under cold reaction but the same reaction conditions did not work to receive hot product, a carrier-added reaction with methyl iodide and [2] was performed.
The second carrier-added hot run was successful but only a small amount of labelled product was detected.

Conclusion: Different methylation pathways were applied in order to produce the labelled 4´-fluoroethoxystilbene, but although successful in the cold reaction, neither methyl iodide nor methyl triflate as methylation agents were successful to synthesize the labelled product. Because it was just working in the cold reaction, this could indicate a competing reaction in the hot runs (possibly an impurity produced in the cyclotron target) that prevents synthesizing product in the non-carrier-added reaction. Although methyl triflate shows very high reactivity to form product in shorter reaction time, with a smaller amount of precursor and lower reaction temperature, the stilbene compounds did not react as expected.

Future studies are needed to systematically investigate the methylation of these precursors as well to determine what is really suppressing the labelling reaction.

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