Optimizing the radiosynthesis of [^{11}C]vorozole by selective methylation with [^{11}C]methyl triflate

Svenja Winzen[1], Sung Won Kim[2], Joanna S. Fowler[2]

[1]Fachbereich Chemie, Johannes Gutenberg-Universität Mainz, 55122 Mainz, Germany

[2]Medical Department, Brookhaven National Laboratory, Upton, NY-11973, USA

Introduction: Vorozole is an aromatase inhibitor and its ^{11}C-analog is a commonly used radiotracer (Figure 1). It is produced using *nor*-vorozole as a precursor and labelled with [^{11}C]methyl iodide. Unfortunately, this reaction gives three different isomers in equal yields of which only one is the desired product. Due to the similarity of the three products, the HPLC separation is difficult and results in long retention times. This reduces the amount of available radioactivity significantly, so that sometimes even administration to a patient has to be cancelled.

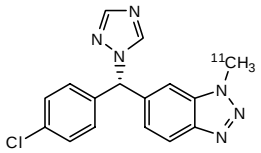

Figure 1: Structure of [^{11}C]vorozole.

Our approach was the optimization of the [^{11}C]vorozole production by developing a selective methylation of the N1-position of the triazole ring. Because vorozole is expensive and very difficult to synthesize, we developed a model system for optimization of the methylation. We chose simple benzotriazole, which basically mimics the labeling site of vorozole. Later the symmetric benzotriazole were replaced by substituted and therefore asymmetric benzotriazoles. To establish some selectivity, the main approach was to change the ^{11}C-methylation reagent from [^{11}C]methyl iodide to [^{11}C]methyl triflate, which is more reactive (Figure 2). Because of that no base was needed for the reaction so that the triazole remains in its neutral form. Now the varying reactivity of the triazole nitrogens controls the reaction.

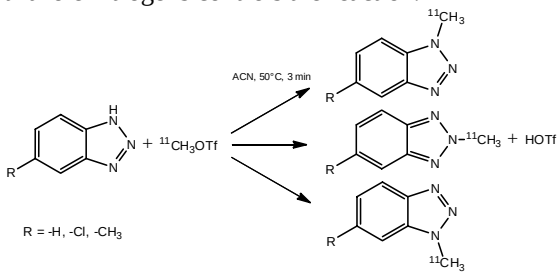

Figure 2: General radiosynthesis reaction scheme.

Experimental: For all radiolabeling reactions, 1 mg of precursor was dissolved in 0.3 mL of acetonitrile and [^{11}C]methyl triflate was trapped at -78 °C. Afterwards the reaction mixture was heated at 50 °C for 3 min and injected into a semi-preparative HPLC system for purification.

Results: The reaction yielded the product in a total radiochemical yield of 33-80%. One side-product could be identified as [^{11}C]methanol (Figure 3).

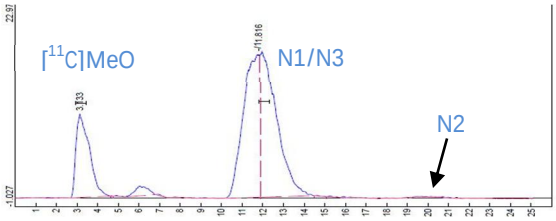

Figure 3: Exemplary HPLC chromatogram of -1,5-di-[*N*-^{11}C]methylbenzotriales.

All labeling reactions gave similar results. N1- and N3-isomers still cannot be separated by the given HPLC system. But using [^{11}C]methyl triflate instead of [^{11}C]methyl iodide seems to be a promising way to reduce the amount of the N2-isomer significantly.

Conclusions and Outlook: So far, the goal to enhance the selectivity in the ^{11}C-methylation reaction has been reached for the model systems. This knowledge now will be transferred to [^{11}C]vorozole, which the most crucial part. Can the transferability of the method for [^{11}C]vorozole be shown, in addition, the selectivity between the N1- and N3-isomer has to be investigated.

References:

[1] S. W. Kim, A. Biegon, Z. E. Katsamanis, C. W. Ehrlich, J. M. Hooker, C. Shea, L. Muench, Y. Xu, P. King, P. Carter, D. L. Alexoff, J. S. Fowler; *Nuclear Medicine and Biology* **36**, 323-334 (2009).

[2] S. T. A. Shah, S. Singh, P.J. Guiry; *Tetrahedron Letters* **22 (36)**, 3455-3458 (1981).

[3] E. J. Corey, H. Cho, C. Rücker, D. H. Hua; *J. Org. Chem.* **54**, 4496-4497 (1989).

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