Systematic labeling studies exemplified for a novel DO2A-tyrosine-derivative

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Introduction: The synthesis of radio-pharmaceuticals with high specific activities requires a time-efficient and high yield-labeling procedure [1], ideally avoiding final chromatographic separation. A lot of different parameters affect the ^{68}Ga-labeling yields of macrocyclic labeling precursors. On the example of a novel DO2A-amino acid derivative (DO2A-(butyl-L-tyrosine)$_2$) we performed systematical labeling studies in order to quantify the influence of reaction time, temperature of the reaction mixture and amount of precursor. Different pH-values were examined in presence and absence of buffer. Labeling yields of the pure labeling precursor were compared with those of its TFA-salt. Furthermore, a well working, time-effective solid phase extraction method was investigated to avoid a time-wasting HPLC-run to remove possible impurities. With all these optimization-steps the labeling yields and the specific activities of the products should be significantly increased.

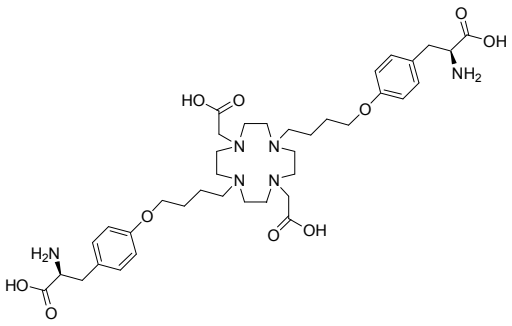

Figure 1: Structure of the labeling precursor DO2A-(butyl-L-tyrosine)$_2$

Experimental: The established ^{68}Ge/^{68}Ga-generator post-processing utilizing a cation-exchange resin was carried out prior to every labeling process [2]. The labeling experiments were carried out with the resulting ^{68}Ga fraction N2 in 5 ml labeling solution, like water or buffer, using different amounts of generator-eluate and labeling precursor at various temperatures. The mixture of labeling solution and precursor was preheated, then the ^{68}Ga was added. Different pH-values were reached, depending on the volume of generator eluate and the labeling solution. The starting pH-values were reaching from 8 to 10,5 utilizing aqeous sodiumhydroxid solution. A reaction under high pressure conditions was performed, too. The labeling mixture was heated to 175 °C for four minutes. The TFA-salts, as received from the HPLC, were removed from the labeling precursors using and ion-exchange resin.

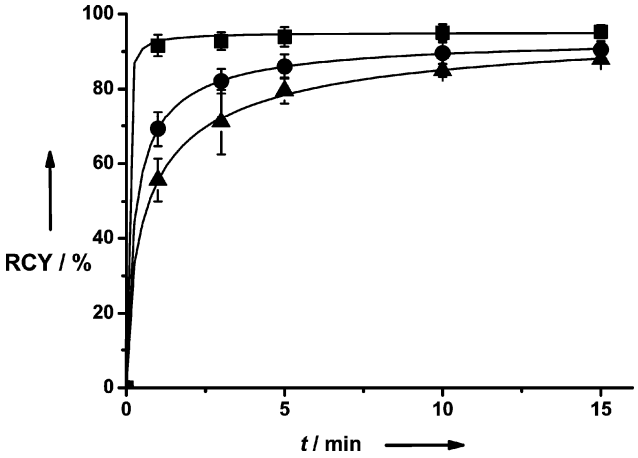

Figure 2: Radiochemical yields (RCY) of labeling of DO2A-(but-L-tyr)$_2$ with ^{68}Ga (50 ml generator eluate) at three different temperatures (90 °C (squares), 70 °C (circles), 50 °C (triangles)) in aqueous solution

The labeling yields of the desalted compounds were compared to the TFA-salts. Different solid-phase-extraction cartridges were tested for the purification of the product.

Results: Under the optimized conditions, with the desalted labelling precursor under the high pressure conditions, we achieved labeling yields of more than 99 %. Furthermore we established a solid-phase extraction method, to obtain, absolutely independent of the labeling yield, a radiochemical purity of more than 97 % ready to inject. The time for the total labeling and purification process including the ^{68}Ga-post-processing was reduced to only 13 minutes. The method showed a very high reproducibility and provides a low radiation dose. With all the optimizations we established a method to receive very high labeling yields in very short times. We achieved high specific activities up to 100 GBq/µmol ready to inject in a multi injection vial after just 13 minutes. This method is well suited for the production of radiopharmaceuticals to be used in further evaluations, e.g. small animal PET-studies.

References:

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