Synthetic study of At-211 labeled cancer targeting amino acids

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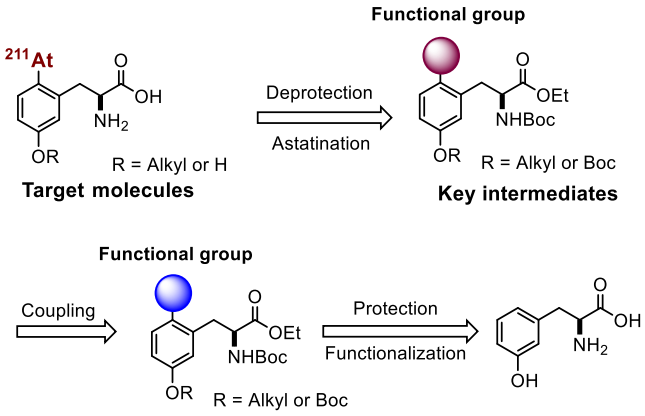
Targeted α-particle therapy (TAT) is a new method for cancer treatments by targeting small amounts of α-particle emitting radionuclides to tumor cells. α-particles have high relative biological effectiveness due to their high linear energy transfer. ^{211}At has the apparent advantage among α-radionuclides, since ^{211}At has suitable half-life only 7.2 h which is long enough for the therapy and easily be cleared from a patient body. In this research, I focus on amino acids which can accumulate to cancer cells via L-type amino acid transporter 1 (LAT1). LAT1 is highly expressed in cancer cells but rarely expressed in normal cells.[1] Therefore, LAT1 is an excellent molecular target for cancer treatment. LAT1 specific substrates α-methyl-L-tyrosine (AMT) and *m*-tyrosine have the benzene moiety to be labeled by ^{211}At. Kaneda-Nakashima *et. al.* in Osaka University thus prepared ^{211}At-labeled α-methyl-L-tyrosine (^{211}At-AAMT) and showed the remarkable anti-cancer effect of ^{211}At-AAMT in mouse model.[2] On the other hand, *m*-tyrosine derivative was also proven to show good accumulation in cancer cells.[3] Therefore, ^{211}At labeled *m*-tyrosine derivative should seem to be promising for cancer treatment.

Although astatination was carried out via mercuriation of AMT, I planned to synthesize ^{211}At labeled *m*-tyrosine and its derivative by using the special precursors to avoid the use of toxic metal reagents. Two kinds of precursor amino acids were thus synthesized from DL-*m*-tyrosine through the protection, functionalization, coupling reaction and deprotection (Scheme 1). We are performing astatination to obtain target molecules.



Scheme 1. Target molecules and synthetic strategy

1) Y. Kanai et al., *J. Biol. Chem.***1998**, *273*, 23629.
2) K. Kaneda-Nakashima et al., *Cancer Sci*., **2020**, doi: 10.1111/cas.14761.
3) T. Watabe et al., *J. Nuclear Medicine*, **2020**, *61*, 627