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Synthesis of 4-[^{211}At]astato-L-phenylalanine via electrophilic demetallation from a silylprecursor

Background: Astatine-211 (^{211}At) labeled compound, 4-[^{211}At]astato-L-phenylalanine, is one of the promising amino acid derivatives for targeted alpha therapy (TAT) for various cancers. Electrophilic demetallation of stannyl precursor is the most widely used approach for labeling biomolecules with ^{211}At. However, the low acid-resistance of the stannyl precursor necessitates the use of a N- and C-terminus protected precursor, which causes low overall radiochemical yield (RCY) due to the multiple synthetic steps involved. A deprotected organosilyl compound, 4-triethylsilyl-L-phenylalanine, was employed for direct synthesis of the astatinated phenylalanine in this study.
Methods: ^{211}At was produced by irradiating $^{4}He^{2+}$ beams with 28.1 MeV to a bismuth-209 (^{209}Bi) target. ^{211}At was isolated from the irradiated target and recovered with $CHCl_3$ or *N*-chlorosuccinimide-methanol (NCS-MeOH) solution. The ^{211}At solution was evaporated to dryness with the gentle flow of N_2 gas. After adding 4-triethylsilyl-L-phenylalanine (200 μg/5μL MeOH), NCS (400 μg/20 μL MeOH), and 0.3 M of methanol-acetic acid solution (20 μL), the mixture was evaporated to dryness again. For the synthesis of 4-[^{211}At]astato-L-phenylalanine using ^{211}At in NCS-MeOH solution, extra NCS addition to the residue was excluded in this step. Trifluoroacetic acid (20 μL) was then added to the mixture and heated at 70 ℃ for 10 min in both cases. A human colon adenocarcinoma cell line, LS180, was incubated with synthesized 4-[^{211}At]astato-L-phenylalanine at 37 ℃ for up to 30 min. For the inhibition assay, LS180 was incubated with some amino acid derivatives for 10 min., followed the incubation of 4-[^{211}At]astato-L-phenylalanine.
Results: The radiochemical yields obtained from the triethylsilane precursor with ^{211}At in $CHCl_3$ and MeOH-NCS solution, were 75% and 64% respectively. In both cases, the retention time of the desired compound was found to be 20 min, which showed reasonable correlation with the retention time of non-radioactive halogenated phenylalanines. It should be noted that the one step reaction involved mild reaction conditions (70 ℃) and a short time (10 min) compared to the other currently reported procedures for astatination. Uptake of 4-[^{211}At]astato-L-phenylalanine by LS180 was time-dependently increased and then plateaued at about 20 min after incubation. Inhibition assays using several amino acid derivatives demonstrated that uptakes in the presence of BCH, Leu, Phe, and Tyr were significantly reduced compared to uptake of the control. These results clearly showed that 4-[^{211}At]astato-L-phenylalanine was successfully synthesized in this study. In addition, In vitro study would give us valuable information for the characterization of astatinated compounds with no stable isotopes.
Conclusion: Electrophilic desilylation was found to be very effective for the labeling of amino acids with ^{211}At. This method is also applicable to the synthesis of astatinated peptides for TAT.

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