Radiolabeling of small molecules with astatine ($^{211}$At) for theranostics
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Background:
Astatine ($^{211}$At, $T_{1/2}=7.2$hr) is an alpha particle emitter which is known as the promising radionuclide for nuclear medicine therapy. Furthermore, $^{211}$At allows SPECT imaging since the daughter nuclide of $^{211}$At, polonium ($^{211}$Po, $T_{1/2}=5$sec), emits X-rays (77 and 79 keV). Thus, $^{211}$At and its labeled compounds are considered to be useful not only for the rapetutics but also for diagnostics (theranostics). No $^{211}$At labeled agents were launched yet in the world at present. A clinical trial of $^{211}$At labeled BC8-B10 was initiated in the U.S. as the world’s first clinical trial of $^{211}$At labeled agents in 2017 (Phase 1/2 for leukemia, NCT03128034). While the chemical properties of astatine have not been well elucidated since there are no stable isotopes of astatine, which make difficult or slow the development of $^{211}$At labeled agents. This article describes the chemistry of $^{211}$At aiming to develop sodium astatide ($^{211}$Na) as a potential agent for thyroid cancer and also explains methods for radioastatination of small molecules.

Sodium astatide ($^{211}$Na):
Sodium astatide ($^{211}$Na) has been investigated for treatment of thyroid cancer as an alternative to sodium iodide ($^{131}$Na) which is currently used in a clinical setting. It is well known that $^{211}$Na is accumulated in tumors expressing sodium iodide symporters (NIS) as well as in normal thyroid in small animals. Several papers pointed out that the thyroid uptake of $^{211}$Na is lower than that of $^{131}$I (3 to 20 times, vary by paper) [1]. The reason of lower accumulation of astatide in thyroid is not well understood. Astatide anion might not be able to couple to thyroxine (a hormone of thyroid), unlike iodide anions, since the ionic radius of astatide (2.3 Å) is a little larger than that of iodide (2.16 Å). Astatine-211 is produced by a nuclear reaction of $^{209}$Bi($\alpha$,2n)$^{211}$At. The produced $^{211}$At is separated and purified by a dry distillation method or a wet solvent extraction method and obtained as an aqueous solution in a cold trap. It is assumed that, in contrast to iodine, astatine prefer to present as higher oxidation states, such as At[+1] and At[0], in addition to At[-1] in the aqueous solution. We tried to prepare an aqueous solution of pure $^{211}$Na using reducing agents. Ascorbic acid was one of the best agents for reducing the higher oxidation states of At-species into astatide anions. The radiochemical yield of $^{211}$Na with 1% ascorbic acid was more than 90%. The solution of $^{211}$Na with 1% ascorbic acid showed 3 to 5-times greater thyroid uptake in rats and mice comparing with the solution without ascorbic acid. This result demonstrated that the oxidation states of $^{211}$At affects pharmacokinetics of $^{211}$At labeled compounds as well as chemical properties of them.
**Astatination of small molecules:**

Trialkylstannylated precursors can be used for preparation of astatinated molecules as well as for preparation of iodinated molecules since the chemical properties of both astatine and iodine are alike [2]. The astatination reactions often require organic solvents and complicated procedures for heating, deprotection and purification. The residual precursors including tin and by-products in the reaction mixtures should be eliminated from final drug products. We attempted to develop a new method for astatination of phenylalanine (Phe) by substitution reaction of a borono-group in a precursor molecule (Fig.1).

Boronophenylalanine (BPA) or 2-fluoro-boronophenylalanine (FBPA) was reacted with $^{211}$At-aqueous solution (1-10MBq) in the presence of N-bromosuccinimide as an oxidant at room temperature for 30min. Radiochemical yields of $^{211}$At-(F)-Phe were more than 90%. The products were stable in the aqueous solution at pH8.5 for 24hr. The borono-substitution reaction is applicable for the astatination of the other arylboronates.

![Fig. 1 Astatination of phenylalanine analogue by substitution reaction of borono group in precursor molecule](image)

**Future aspects:**

Our goals of the studies are to prepare and supply $^{211}$At labeled agents for theranostics. Both Na$^{211}$At and $^{211}$At-(F)-Phe analogues will be the potential candidates. We need careful about the designs of molecular structures and formulations of the drug products due to some limitations of astatine from the chemical point of view as follows: 1) Astatine presents as various oxidation states from +7 to -1 resulting in complicated properties for labeling, 2) The energy of covalent bonding between astatine and carbon atoms are relatively weak. It is crucial to ensure the stability of $^{211}$At labeled agents both in vitro and in vivo.

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**References:**
