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Radiohalogenated neopentyl derivatives: A novel scaffold for radioiodinated and astatinated compounds of high stability to in vivo dehalogenation

Objectives: Astatine-211 (²¹¹At) is an α-emitting radionuclide appropriate for medical use. To expand the application of ²¹¹At-labeled compounds to radiotheranostics, we developed neopentyl derivatives as a novel scaffold for radioiodination and astatination. The stability, biodistribution, and metabolism of ¹²⁵I-labeled neopentyl derivatives were evaluated. The biodistribution of a ²¹¹At-labeled compound was compared with its ¹²⁵I-labeled counterpart.

Methods: Two iodinated neopentyl derivatives with a nitroimidazole group were synthesized; *N*-[2,2-bis(hydroxymethyl)-2-(iodomethyl)ethyl]-2-nitroimidazole (BHIN) and *N*-[2,2-diethyl-2-(iodomethyl)ethyl]-2-nitroimidazole (DEIN). The radioiodination was conducted by reacting their sulfonyl precursors with Na[¹²⁵I]I. The stability to the nucleophilic substitution was evaluated in a 10 mM glutathione solution at pH 7.4 for 24 h. The biodistribution of [¹²⁵I]BHIN or [¹²⁵I]DEIN was evaluated in normal male mice. Urine samples collected for 6 h after injection were analyzed by a reversed-phase HPLC. [²¹¹At]*N*-[2,2-bis(hydroxymethyl)-2-(astatomethyl)ethyl]-2-nitroimidazole ([²¹¹At]BHAN) was prepared under the procedure similar to [¹²⁵I]BHIN and was subjected to biodistribution study in normal male mice.

Results: Both ¹²⁵I-labeled compounds were obtained in 40 to 90% radiochemical yields and over 98% radiochemical purities after HPLC purification. Both ¹²⁵I-labeled compounds remained stable after incubation in a glutathione solution for 24 h (>95%), indicating that the two radioiodinated compounds possess high stability to the nucleophilic substitution reaction. In biodistribution study, while [¹²⁵I]DEIN showed high radioactivity levels in the neck (10.60 ± 0.03 %ID at 24 h), such radioactivity was hardly observed with [¹²⁵I]BHIN (0.03 ± 0.02 %ID at 24 h). Both radioiodinated compounds were mainly excreted into urine. The analysis of urine samples indicated that while the majority of the radioactivity was present as [¹²⁵I]I⁻ for [¹²⁵I]DEIN, [¹²⁵I]BHIN showed the majority of the radioactivity as the glucuronide-conjugate. [²¹¹At]BHAN was obtained in about 14% radiochemical yields and over 98% radiochemical purities after HPLC purification. [²¹¹At]BHAN exhibited the pharmacokinetics similar to [¹²⁵I]BHIN with low radioactivity levels in the neck and the stomach.

Conclusions: Both ¹²⁵I-labeled compounds possessed high stability to the nucleophilic substitution. The presence of the hydroxyl groups in BHIN provided further stabilization to the enzymatic dehalogenation reaction. [¹²⁵I]BHIN and [²¹¹At]BHAN exhibited similar pharmacokinetics each other with dehalogenation being hardly observed. These findings indicate that the neopentyl derivatives would serve as a useful scaffold to develop a radiotheranostic pair consisting of radioiodinated and ²¹¹At-labeled compounds.

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