

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

**Objectives:** Astatine-211 ( $^{211}\text{At}$ ) is an  $\alpha$ -emitting radionuclide appropriate for medical use. To expand the application of  $^{211}\text{At}$ -labeled compounds to radiotheranostics, we developed neopentyl derivatives as a novel scaffold for radioiodination and astatination. The stability, biodistribution, and metabolism of  $^{125}\text{I}$ -labeled neopentyl derivatives were evaluated. The biodistribution of a  $^{211}\text{At}$ -labeled compound was compared with its  $^{125}\text{I}$ -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  $\text{Na}^{125}\text{I}$ . The stability to the nucleophilic substitution was evaluated in a 10 mM glutathione solution at pH 7.4 for 24 h. The biodistribution of  $^{125}\text{I}$ BHIN or  $^{125}\text{I}$ DEIN was evaluated in normal male mice. Urine samples collected for 6 h after injection were analyzed by a reversed-phase HPLC.  $^{211}\text{At}$ *N*-[2,2-bis(hydroxymethyl)-2-(astatomethyl)ethyl]-2-nitroimidazole ( $^{211}\text{At}$ BHAN) was prepared under the procedure similar to  $^{125}\text{I}$ BHIN and was subjected to biodistribution study in normal male mice.

**Results:** Both  $^{125}\text{I}$ -labeled compounds were obtained in 40 to 90% radiochemical yields and over 98% radiochemical purities after HPLC purification. Both  $^{125}\text{I}$ -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  $^{125}\text{I}$ DEIN showed high radioactivity levels in the neck ( $10.60 \pm 0.03\%$  ID at 24 h), such radioactivity was hardly observed with  $^{125}\text{I}$ BHIN ( $0.03 \pm 0.02\%$  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  $^{125}\text{I}$  for  $^{125}\text{I}$ DEIN,  $^{125}\text{I}$ BHIN showed the majority of the radioactivity as the glucuronide-conjugate.  $^{211}\text{At}$ BHAN was obtained in about 14% radiochemical yields and over 98% radiochemical purities after HPLC purification.  $^{211}\text{At}$ BHAN exhibited the pharmacokinetics similar to  $^{125}\text{I}$ BHIN with low radioactivity levels in the neck and the stomach.

**Conclusions:** Both  $^{125}\text{I}$ -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.  $^{125}\text{I}$ BHIN and  $^{211}\text{At}$ 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  $^{211}\text{At}$ -labeled compounds.

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