Neopentyl glycol as a scaffold to provide radiohalogenated theranostic pairs of high *in vivo* stability†

H. Suzuki,[*1] Y. Kaizuka,[*1] M. Tatsuta,[*2] H. Tanaka,[*2] N. Washiya,[*1] Y. Shirakami,[*3] K. Ooe,[*4] A. Toyoshima,[*3] T. Watabe,[*4] T. Teramoto,[*3] I. Sasaki,[*5] S. Watanabe,[*5] N. S. Ishioka,[*5] J. Hatazawa,[*6] T. Uehara,[*1] and Y. Arano[*1]

^{211}At is one of the most promising α-emitting radionuclides applicable to targeted α-therapy. Low-molecular-weight targeting molecules are suitable for delivering ^{211}At to target tissues because of its short half-life (7.2 h). Benzoate derivatives have been widely used to prepare radioiodinated low-molecular-weight targeting molecules of high stability against *in vivo* deiodination.[1] Although astatine shares some chemical properties similar to those of iodine, ^{211}At-labeled benzoate derivatives are unstable against *in vivo* deastatination.[2] Therefore, a new scaffold applicable to a radiotheranostic system with ^{211}At and radioiodine needs to be developed.

We focus on a neopentyl glycol structure used for 2-dihydroxymethyl-3-[^{18}F]fluoropropyl-2-nitroimidazole ([^{18}F]DiFA, Fig. 1) that shows high stability against *in vivo* defluorination.[3] In this study, the neopentyl glycol structure was applied for heavier radiohalogens such as radioiodine and ^{211}At; however, the dissociation energy of sp^3 carbon-halogen bonds in alkyl halides is low and decreases with an increase in the atomic number of halogen.[4] Three neopentyl iodide compounds with or without hydroxyl groups ([^{125}I]**1a**, [^{125}I]**2**, and [^{125}I]**3**, Fig. 1) were synthesized to investigate the role played by the hydroxyl groups before studying with ^{211}At-labeled compounds.

All three neopentyl iodides remained stable against the nucleophilic attack. While [^{125}I]**2** and [^{125}I]**3** were deiodinated by cytochrome P450 (CYP)-mediated metabolism, [^{125}I]**1a** remained stable against CYP-mediated metabolism. The biodistribution study was correlated with the *in vitro* study of CYP-mediated metabolism; [^{125}I]**1a** showed the lowest accumulation in the stomach and neck where free [^{125}I]I$^-$ accumulates. The liberation of [^{125}I]I$^-$ was observed via the urine analyses of [^{125}I]**2** and [^{125}I]**3** but it was not observed for [^{125}I]**1a**, which indicates that the C-I bond of [^{125}I]**1a** was stable against in vivo deiodination.

The structure of [^{125}I]**1a** was applied for ^{211}At to prepare [^{211}At]**1b**. ^{211}At used in this work was produced in the ^{209}Bi(α, 2n)^{211}At reaction using the RIKEN AVF cyclotron. [^{211}At]**1b** showed high *in vitro* stability against nucleophilic attack and the CYP-mediated metabolism.

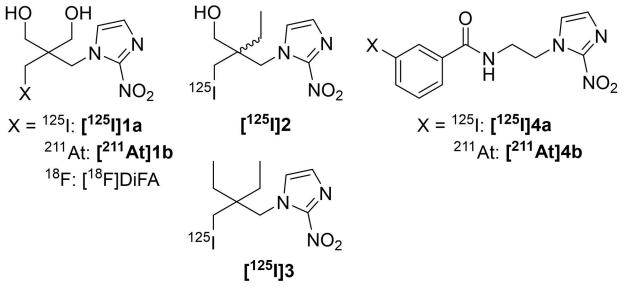

Fig. 1. Chemical structures of neopentyl and benzoate derivatives evaluated in this study.

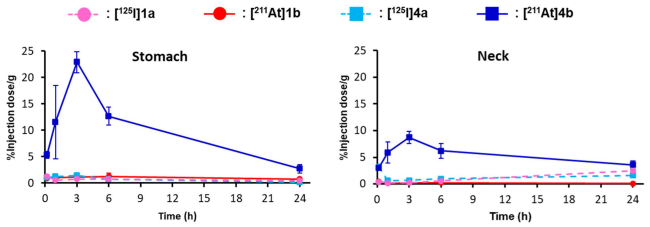

Fig. 2. Biodistribution in selected organs after the injection of [^{125}I]**1a**, [^{211}At]**1b**, [^{125}I]**4a**, and [^{211}At]**4b**.

When injected into normal mice, the radioactivity levels in the stomach and the neck registered low levels. The biodistribution profiles of [^{211}At]**1b** were similar to those of [^{125}I]**1a** (Fig. 2). However, the reference compound [^{211}At]**4b** (Fig. 1) exhibited pharmacokinetics different from [^{125}I]**4a**, with high radioactivity levels observed in the stomach and the neck. Further, the urine analysis showed that [^{211}At]At$^-$ was liberated from [^{211}At]**4b** but not from [^{211}At]**1b**, which implies that the C-At bond of [^{211}At]**1b** was stable against *in vivo* deastatination.

In this study, a neopentyl structure with two hydroxyl groups (neopentyl glycol) provided ^{125}I- and ^{211}At-labeled compounds with high stability against nucleophilic attack and the CYP-mediated metabolism. Furthermore, both compounds registered similar biodistribution profiles and metabolic fate. These findings indicate that neopentyl glycol would constitute a useful scaffold for developing a radiotheranostic system with radioiodine and astatine as radiolabels for further applications.

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*1 Graduate School of Pharmaceutical Sciences, Chiba University
*2 Department of Chemical Science and Engineering, Tokyo Institute of Technology
*3 Institute for Radiation Sciences, Osaka University
*4 Graduate School of Medicine, Osaka University
*5 Takasaki Advanced Radiation Research Institute, National Institutes for Quantum Science and Technology
*6 Research Center for Nuclear Physics, Osaka University

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