An Approach Toward Radioiodination and Radiopharmacological Evaluation of a Carborane-Containing Analog of Indomethacin

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Abstract

Dicarbadodecaboranes (12) (carboranes) are versatile molecular building blocks with unique properties, which allow the expansion of classical medicinal-chemical space. To enable single-photon emission computed tomography (SPECT) imaging of cyclooxygenase-2 (COX-2), we investigated the feasibility of introducing iodine-123 into nido-indoborin 1, a nido-carborane analog of indomethacin with potent and selective cyclooxygenase-2 inhibitory activity. An electrophilic iodination strategy afforded two regioisomers, 2a and 2b, bearing the iodine at the carborane cluster. Compared to nido-indoborin, a reduced COX-2 inhibition potency and selectivity were observed, with 2b exhibiting the more favorable inhibition profile. Radiosynthesis of [123I]2b was achieved by N-chlorosuccinimide–mediated electrophilic substitution of 1, and conditions were optimized, leading to an isolated radiochemical yield of 4%. While the radiotracer displayed high stability in phosphate buffer, ester hydrolysis was observed in human plasma and murine liver microsomes with no significant deiodination in vitro. Cell uptake studies indicated partial COX-2–dependent accumulation but also revealed substantial non-specific uptake and unexpected enhancement of radiotracer uptake in the presence of carborane-based blocking agents. In vivo pilot imaging studies in mice bearing U87 xenografts showed renal and hepatobiliary clearance without measurable tumor accumulation but evidence of deiodination over time. Overall, iodination was feasible, but the resulting compounds lacked the required COX-2-selective tumor accumulation for further radiotracer development.