Carborane-containing Matrix Metalloproteinase (MMP) enzyme inhibitors as tumor-targeting ligands for Boron Neutron Capture Therapy (BNCT)

Boron neutron capture therapy (BNCT) is a non-invasive modality of treating brain tumors as well as head and neck tumors through delivery of a molecule containing $^{10}$B atoms to the tumor, which absorb a neutron under low-energy neutron irradiation to yield unstable $^{11}$B nuclei that undergo fission to yield high energy alpha particles ($^4$He nuclei) and high energy lithium-7 ($^7$Li) nuclei that are limited in range to 5–9 µm, approximately the diameter of the target cell. The challenge for improving BNCT is to target tumor cells to enable selective and efficient delivery of the $^{10}$B atoms. Recognizing that matrix metalloproteinase (MMP) enzymes, especially gelatinases MMP-2 and MMP-2, as well as collagenase MMP-13, are upregulated in tumor cells, we selected to incorporate carborane clusters into scaffolds that are known to bind potently and selectively to these MMP enzymes. Diaryl ether sulfone hydroxamate MMP inhibitors have served as clinical candidates for cancer treatment, and bear a piperidine substituent that is known to project from the MMP active site into solvent when the molecules are bound to MMP enzyme, thus enabling attachment of even very large dyes for imaging of tumors. Hence we have installed boron-rich carborane clusters to the piperidines nitrogen utilizing Click chemistry for attachment of the carborane moiety. Herein we report the successful multistep synthesis of these BNCT agents and the potent MMP enzyme inhibition by these molecules as we proceed toward in vivo efficacy testing.

Biography

Daniel Becker earned his PhD at Indiana University in Bloomington, Indiana and worked in the pharmaceutical industry in Searle, Pharmacia and then Pfizer as a Project Leader and Research Fellow in cancer, arthritis, and cardiovascular diseases. He moved from industry and joined Loyola University Chicago in 2004 where he serves as a Full Professor of Chemistry performing research in synthetic organic and medicinal chemistry, especially in antibiotics and in cancer, as well as in supramolecular chemistry. He has published more than 50 scientific papers in various areas of chemistry and is an inventor on over 50 U.S. patents.

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