

DEVELOPMENT OF CANCER TARGETED NAMPT INHIBITORS

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ABSTRACT

The purpose of this research is the discovery of a highly potent pharmaceutical that can selectively cause apoptosis in various cancer cells. To utilize hydrophobic properties of carboranes, 1,7-dicarba-*closo*-dodecaborane (*m*-CB) has been selected as a template to synthesize new targeted antitumor agent. These drugs selectively bind to nicotinamide phosphoribosyltransferase (Nampt), preventing cancer cells from replenishing nicotinamide adenine dinucleotide (NAD⁺) through their recycle pathway, leading to apoptosis.

Previously, our group reported a family of potent small molecule inhibitors of Nampt. Herein an improved, gram-scale synthesis of our most potent agent (MC4-PPEA), as well as several other derivatives is reported. Additionally, the carborane moiety of the molecule has been modified with a hydroxymethyl functional group to allow for its covalent attachment to targeted prodrugs.

In this dissertation, several linker models capable of reacting with drug molecules containing primary alcohols are also proposed. These molecules are covalently linked through different hydrolytically or enzymatically cleavable moieties, each bearing an azide at its distal end. Using click chemistry, several prodrugs were proposed and their activity were investigated.

The association constants (K_a') of unsubstituted *o*-, *m*-, and *p*-carborane, adamantane, their derivatives, and CB containing drug with β -cyclodextrin (β -CD) are reported for the first time using displacement binding in an aqueous solution.