# Cutting off Cancer: Design, Analysis, and Synthesis of Novel Vascular Disrupting Agents

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Cancer remains a pervasive and ominous threat as the second leading cause of death in the United States, accounting for one in four fatalities. The survival and proliferation of tumors in cancer patients requires a vascular network to provide sufficient nutrients and oxygen to tumor cells. Recent research has focused on developing Vascular Disrupting Agents (VDAs) to selectively destroy tumor vasculature and initiate secondary tumor cell death. Combretastatin-A-4 (CA-4), a tubulin-binding agent, has reported preclinical successes as a VDA and set the precedent for further exploration. However, only one of CA-4's geometric isomers has anti-cancer properties and previously synthesized analogs have failed to match its activity. This study aims to discover VDAs with improved efficacy and selective toxicity. While previous research has tended to analyze analogs of only one scaffold/model structure at a time, in this study many completely new molecular scaffolds were rationally designed and a library of 210 compounds based on analogs of these novel scaffolds was created. Following computational modelling and analysis, SB-BC-160, an analog of an original scaffold design, emerged as the most promising compound demonstrating geometric stability, desired hydrogen bonding, and ten-fold improved binding affinity to tubulin. A synthetic scheme for SB-BC-160 was created. When fully synthesized, SB-BC-160 will be biologically evaluated and serve as the basis to a new class of more potent, structurally stable VDAs, opening up new treatment options for the millions affected by cancer.

**Awards Won:**
Fourth Award of $500