Docking Studies of the Binding Mode of Dictyostatin and Its Analogues to the Taxoid Binding Site on Beta-Tubulin

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The division of a cell's contents during mitosis is highly dependent on the dynamic growth and breakdown of microtubules. Because quickly dividing cancerous cells are especially susceptible to disruption of this process, many treatments for cancer have targeted this behavior of microtubules, hyperstabilizing the tubulin polymers they are composed of to arrest the cell cycle and trigger apoptosis. These agents have been successful in some respects, but they do face certain problems, particularly the emergence of resistant tumors.

Computer docking simulations were used to examine binding modes of the promising new antimitotic agent dictyostatin and several of its analogues with wild-type tubulin and a mutated form that is resistant to dictyostatin and some similar drugs. Our goal was to discover protein-ligand interactions that could help explain the resistance of cells expressing this mutant form of tubulin and thereby facilitate the formulation of hypotheses regarding new agents to synthesize.