Docking of Dictyostatin, 16-Normethyldictyostatin, Discodermolide and 14-Normethyldiscardermolide, to β-Tubulin

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Due to their crucial role in cell division, microtubules have become a primary target for chemotherapeutic drugs. Two families of compounds, the taxanes and epothilones function by binding to β-tubulin, thereby strengthening the lateral contacts between protofilaments and stabilizing microtubules against disassembly. By hindering the dynamic behavior of microtubules, they inhibit mitosis, eventually causing the cell to die by apoptosis. Despite exhibiting similar mechanisms, these two families of compounds, based on cryoelectron crystallography analysis, have unique binding modes and interact with different residues of β-tubulin. Two other families of compounds – discodermolides and dictyostatins – have been found to competitively inhibit the binding of and have activities similar to the taxanes and epothilones. No crystallographic studies of the complexes of tubulin with discodermolides or dictyostatins have been reported. Therefore, docking simulations were performed with CAChe and MOE in order to develop hypotheses about their binding that agree with experimental data.