

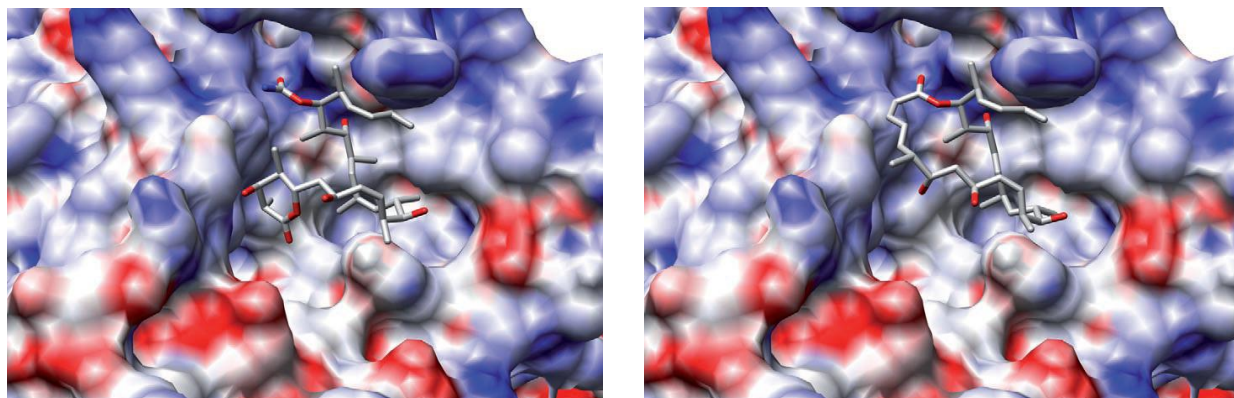
The Bound Conformation of Microtubule-Stabilizing Agents: NMR Insights into the Bioactive 3D Structure of Discodermolide and Dictyostatin

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A protocol based on a combination of NMR experimental data with molecular mechanics calculations and docking procedures has been employed to determine the microtubule-bound conformation of two microtubule-stabilizing agents, discodermolide (DDM) and dictyostatin (DCT). The data indicate that tubulin in assembled microtubules recognizes DDM through a conformational selection process, with minor changes in the molecular skeleton between the major conformer in water solution and that bound to assembled microtubules. For DCT, the deduced bound geometry presents some key conformation differences around certain torsion angles, with respect to the major conformer in solution, and still displays mobility even when bound. The bound conformer of DCT resembles that of DDM and provides very similar contacts with the receptor. Competition experiments indicate that both molecules compete with the taxane-binding site. A model of the binding mode of DDM and DCT to tubulin is proposed.



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