Conformational Analysis of Natural Products: Shishijimicin A, Brevetoxin A, Brevetoxin B, and Ciguatoxin

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Naturally occurring anticancer agents, such as calicheamicin, esperamicin, dynemicin A, and neocarzinostatin chromophore, are structurally diverse yet each contains a reactive, electron-rich enediyne moiety. Under certain conditions, the enediyne group undergoes a Bergman cyclization resulting in a *p*-benzyne diradical. This highly reactive diradical can abstract hydrogen atoms from cancer cell DNA resulting in cell death. Brevetoxins, a class of polycyclic marine ethers and neurotoxins, function by binding to a voltage-sensitive sodium channel. Binding induces prolonged ion channel opening times at lower membrane potentials. In an effort to understand the role of molecular flexibility in drug preorganization and DNA binding we have performed an exhaustive analysis of the flexibility of Shishijimicin using the LM:MC 50:50 conformational searching method. In a similar attempt, we attempted to understand the molecular flexibility in the aqueous solvent by exhaustively analyzing the flexibility of Brevetoxins using the same LM:MC 50:50 method. An ensemble of low energy structures was generated for each system and this yielded information about flexibility and conformationally accessible structures.