QSAR of Microtubule Stabilizing Dictyostatins

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Microtubule stabilization is a validated mechanism for cancer chemotherapy. Dictyostatin, an analog of the failed drug discodermolide, binds to the β-tubulin subunit of microtubules, inhibiting cell growth by blockage at the G2/M phase of the cell cycle. Dictyostatin and analogs were synthesized and their antiproliferative activities against ovarian cancer cells were measured. These data, along with that from some discodermolides, were used to determine a quantitative structure-activity relationship (QSAR). Molecular models of the dictyostatins were built from NMR coordinates of discodermolide and their global minimum energy conformations determined. Models were superimposed to provide maximum structural overlap and a collection of electronic, thermodynamic and steric descriptors were calculated for each model. A special multiple linear regression analysis, the genetic function approximation, was then used to find the descriptors that best explained the differences in activity. A population of statistically-compelling QSAR equations was found and may be useful in future analog design.