Abstract

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

Method

The genetic function approximation, which is a special multiple linear regression analysis, was used to find a minimum number of descriptors that best explained the difference in activity. The classes of descriptors include structural, thermodynamic, spatial, electrical, and quantum mechanical, for all descriptors the best models were selected from the group of calculation. After the population of equations was developed, the best five equations (i.e., those with the best statistical scores, particularly Friedman’s rank of 1 and 2) were then studied. The five equations produced a set of predicted activities. The predicted activity was plotted as a function of the actual activity on a scatter graph to determine the difference between the actual and predicted values.

Results

Using plots of predicted versus actual activities and the regression line for each equation, the outliers were further examined to determine the role each descriptor played in causing a poor prediction of activity. A “save one (descriptor) out” exercise was performed to identify descriptors with the highest influence on predicted activity.

Conclusion

The understanding of descriptors used in QSAR equations can provide excellent opportunity for identifying their features and becoming aware of how they affect each compound. Furthermore, the simpler the equation, the easier it is to use that equation to make chemical modifications; and, in general, the more likely it will be useful in drug design.

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References


GUSAR of Microtubule Stabilizing Dictostatyclicin

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