QSAR of Microtubule Stabilizing Dictyostatins

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Introduction

The discovery and advancement of new chemotherapeutic agents for the treatment of cancer is currently of high significance. Some of the most useful chemotherapeutic agents are natural products or natural product analogs. For example, paclitaxel is a natural product that is currently being used to treat patients with breast, lung and ovarian cancers.[3] Paclitaxel belongs to a group of chemicals known as taxanes, which functions through binding to the β-tubulin subunits of microtubules. A number of analogs of paclitaxel, including docetaxel, are also clinically useful anticancer agents.

The mechanism by which paclitaxel hinders cancer cell growth is the stabilization of microtubules. Microtubules are polymers made up of α- and β-tubulin heterodimers. Tubulin polymerizes at each end with the α-subunit of one tubulin dimer connecting to the β-subunit of the next. Therefore, one end of the microtubule will have the α-subunit (minus or – end, where microtubule shrinking can occur) exposed, while the other end will have the β-subunit (plus, +, or growing end) exposed. The stacked heterodimers form a line called a protofilament, The microtubules are composed of typically 13 protofilaments parallel to one another in a three-start left handed helix, so that the microtubule will have one end, the (+) end, with only β-subunits exposed, whereas the other end, the (−) end, only has α-subunits exposed.

The α- and β-tubulin subunits each bind one mole of guanosine triphosphate (GTP). The GTP bound to α-tubulin is stable, but the GTP bound to β-tubulin can be hydrolyzed to guanosine diphosphate (GDP) shortly after a heterodimer adds to the growing polymer. The GTP-bound β-tubulin therefore forms a cap at the (+) end of the microtubule, keeping it from disassembling. When hydrolysis catches up to the tip of the microtubule, it begins to quickly depolymerize and shrink. GTP-bound tubulin can begin adding to the tip of the microtubule again, providing a new cap and protecting the microtubule from shrinking. However, when a drug such as the taxanes is attached, it hyperstabilizes microtubules by binding to the β-tubulin of the microtubule and preventing the disassembly from the (–) end.

Like paclitaxel, discodermolide, a polyketide natural product, was discovered to be a very potent inhibitor of cancer cell growth. It was isolated in 1990 from the marine sponge *Discodermia dissoluta*. Discodermolide has been proven to inhibit the growth of human cells by blocking them at G2/ M phase of the cell cycle. It was a clinical candidate for cancer chemotherapy due to its high potency in microtubule stabilization and its strong activity against multiple drug resistant cancers. Unfortunately, discodermolide only made it to Phase II clinical trials when tested in humans, where it failed due to unexpected toxicity.

Because discodermolide showed promising effects, it was important in the fields of chemotherapy and drug discovery to uncover an agent quite similar in structure and activity. It was determined that another marine sponge-derived natural product discovered in 1994, dictyostatin, shares much structural similarity to discodermolide, including identical configurations at all common stereocenters. Dictyostatin also has

very similar biological activity to discodermolide. It is active against paclitaxel-resistant cell lines and is one of the most potent microtubule stabilizers known, potently competing with paclitaxel and discodermolide for the taxoid binding site on microtubules. With the recent withdrawal of discodermolide from clinical development, the importance of uncovering a dictyostatin with the potential for clinical development has increased. Several analogs of dictyostatin have been synthesized and some of their biological activities have been measured. Using the structures of these analogs and their biological activities, along with those of discodermolide and a potent, structurally-related analog, the purpose of this work will be to develop a quantitative structure-activity relationship (QSAR) useful in further analog design.

Methods

The first step will be to build molecular models of dictyostatin and its analogs and find their global minimum energy conformations. The next will be to superimpose these molecular models to provide maximum structural overlap. The structural and physiochemical differences for each compound will then be determined. This will be done by calculating a number of descriptors for the structures, such as thermodynamic properties, electronic properties, steric (size) properties, the linear free energy term, and many others, using the software suite Cerius^2 (Accelrys, Inc.). The descriptors for each structure will be calculated and then tabulated (in a "study table"). The next step to be performed is to use a multiple regression analysis to find the most statistically significant descriptors that explain the differences in activity, the fifty percent growth inhibitory concentration (GI_{50}) against 1A9 human ovarian carcinoma cells. Because the study

table will have a number of descriptors far larger than the number of compounds, it is essential to use a non-traditional regression method known as the Genetic Function Approximation (GFA) to assist in the regression analyses.

The GFA is a method that produces a population of statistically compelling structure-activity models, rather than single models. Cerius[2] uses as one available method the GFA to calculate QSARs.[1] GFA is a component of a class of techniques known as genetic algorithms. These algorithms use a correlation with progress in solving complex combinational problems. GFA begins with a population of randomly-constructed QSAR models, where the models are rated using an error measure that estimates each model's relative predictiveness.[1] QSAR is a multivariate, mathematical relationship between a set of 2D and 3D physiocochemical properties (descriptors) and biological activity.[1] It allows one to choose the best candidate compounds, based on the biological activity, as well as gain insight into a variety of fundamental biological processes.[1]

The GFA algorithm was initially formulated by combining inspiration from two apparently dissimilar algorithms, Holland's genetic algorithm (1975) and Friedman's multivariate adaptive regression splines (MARS) algorithm (1990).[2] MARS is a statistical algorithm for modeling data. It provides an error measure, called a lack-of-fit (LOF) score, which routinely penalizes models with too many features. It also stimulated the use of splines as an influential tool for nonlinear modeling.[2]

The GFA algorithm approach has several advantages. Some advantages of using the GFA approach are that it is better at discovering combinations of features that take advantage of correlations between multiple features. Use of Freidman's LOF error measure, which estimates the most appropriate number of features, resists over fitting,

and allows control over the smoothness of fit. It also provides additional information not available from standard regression analysis, such as the preferred model length and useful partitions of the dataset.[2]

References

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