Poonsiri Thipnate 2009: Theoretical Investigation on the Binding of DNA-Topoisomerase I Complex With Lamellarin Derivatives and Molecular Design. Doctor of Philosophy (Chemistry), Major Field: Chemistry, Department of Chemistry. Thesis Advisor: Associate Professor Supa Hannongbua, Dr.rer.nat. 104 pages.

Currently, cancer is one of leading causes of death in the world. It continued to be a serious problem because the number of death from cancer increases every year. Hence, this work focuses on anticancer compounds, especially from marine source, so called lamellarins. Molecular docking methods were applied to investigate the orientation and the binding energies of lamellarins in the binding pocket of a possible known target, topoisomerase I-DNA complex. Several lamellarins can intercalate at the site of DNA cleavage, forming base-stacking interactions with both the upstream and downstream base pairs. The hydrogen-bond interactions occurred with amino acid residues of topoisomerase I such as Asn352, Glu356, Arg364, and Asn722. The different interactions between the lamellarins containing a saturated D-ring and those with a C5-C6 double bond and common structural requirements for their cytotoxic activities against human breast cancer cell lines were determined using comparative molecular field analysis (CoMFA) and comparative molecular similarity indices analysis (CoMSIA) techniques. The best CoMFA and CoMSIA models for both cell lines yielded satisfactory predictive ability with r^2_{cv} values in the range of 0.659-0.728. Moreover, 4D-QSAR and 4D-fingerprint virtual screening models were built and investigated for the cytotoxicity of lamellarins against human hormone-dependent T47D breast cancer cells. 4D-QSAR models were first constructed from the exploration of eight possible receptor binding alignments for the entire training set. Since the training set is small (25 compounds), the generality of the 4D-QSAR paradigm was then exploited to devise a strategy to maximize the extraction of binding information from the training set, and to also permit virtual screening of diverse lamellarin chemistry. 4D-QSAR models were sought for only six of the most potent lamellarins of the training set as well as another subset composed of lamellarins with constrained ranges in molecular weight and lipophilicity. Overall, it was found that formation of an intermolecular hydrogen bond and hydrophobic interactions for substituents on the E ring modulate most of the cytotoxicity against T47D breast cancer cells. Hydrophobic substitutions on the F-ring can also enhance cytotoxic potency. The 4D-fingerprint QSAR model was constructed using absolute molecular similarity. This 4D-fingerprint virtual high throughput screen permits a larger range of chemistry diversity to be assayed than the 4D-QSAR models. The optimized 4D-QSAR 3D-pharmacophore model has $r^2_{cv} = 0.947$, while the optimized 4D-fingerprint virtual screening model has $r^2_{cv} = 0.719$. This work reveals that it is possible to develop significant 3D-QSAR, 4D-QSAR and virtual screening models for a small set of lamellarins showing cytotoxic behavior in breast cancer screens that can guide future drug development based upon lamellarins.

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