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Dissecting the mechanism of adenosine kinase inhibition: new insights for drug designing

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As a promising therapeutic drug target, adenosine kinase (AK) has recently attracted great interest in the search of potent and selective inhibitors against a variety of diseases including hypertension, epilepsy, pain, diabetes, and inflammation [1]. Nucleoside kinases, such as AK, cytidine kinase, thymidine kinase, catalyze phosphorylation of a variety of nucleosides, including nucleoside-based drugs, giving rise to nucleoside-5'-O-phosphates which are incorporated into RNA or DNA via the corresponding triphosphates [2]. Thus, 5'-O-phosphates of these nucleosides are responsible not only for the pharmacological activity but also for their cytotoxic side effects. Therefore designing molecules having different scaffold than the nucleosides is required. Here molecular modeling of known inhibitors was conducted to gain better insights about the role of waters in their different degrees of binding and activity to AK. The two docking algorithms, Ligandfit and GOLD were utilized and compared. It was found that results from both the methods, if complemented, give more meaningful answers for docking and binding modes. The docking study proposed an interesting classification of the considered molecules according to their binding with two different conformations (open or closed forms) of protein. A comparison of various clustering methodologies indicates that 2d topological fingerprints are able enough to differentiate the molecules according to their binding to various conformations. Using a combined approach of docking and clustering various databases were screened for novel molecules interacting with both forms of enzyme. Finally, focused libraries were generated that could stabilize both the conformations of enzyme utilizing a strategy by giving weights to various fragments according to their water replacing tendency or hydrogen bonding capacity.

References

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