



INSTITUTIONEN FÖR KEMI OCH MOLEKYLÄRBIOLOGI

Computer-aided drug design approaches in developing anti-cancer inhibitors

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ABSTRACT

The thesis entitled “computer-aided drug design approaches in developing anti-cancer drug” is divided into a total of six chapters. In the first chapter, an overview of drug discovery and development are introduced. The whole process of drug discovery and development is lengthy and complicated, which require huge input of time, money, and resources. Acknowledging that drug discovery is complicated in general, oncology has one of the poorest records for developing into clinical trial phases, however, we have moved into a new “golden era” for cancer drug development through molecular targeting recently. In the second chapter, computer-aided drug design (CADD), which is effective methods for facilitating and expediting drug discovery and development process, are introduced. Some approved drugs that credited their discovery in large part to the tools of CADD were reported, and the application of CADD has extended to two directions in drug discovery and development. In the third chapter, a detailed introduction of the anti-cancer targets in this thesis is given. The targets include tyrosine kinase RET, kinesin Eg5 and KIF18B, histone transferase Tip60 and the GTPase K-Ras. The involving signalling pathway, the cancer induced mechanism and the current available inhibitors for the targets are discussed. In the fourth chapter, the methodologies applied for different projects will be discussed, including homology modelling, docking, molecular dynamics simulations, structure-based pharmacophore, ligand-based pharmacophore and 3D-QSAR. The detailed theoretical background and the main steps involve in the use of these methods are outlined. In the fifth chapter, I provide a summary of seven papers or manuscripts, which are related to this thesis. In the final chapter, conclusions and future perspective is given, CADD is indeed a very useful tool for pharmaceutical companies and academic research groups to search for potential drug candidates, meanwhile, it is also necessary to improve the current CADD methods. The different projects included in this thesis have the potential for further development.

Key words: Computer aided drug design, cancer, RET, Eg5, KIF18B, Tip60, K-Ras