Chapter 33
Application of Docking Methodologies in QSAR-Based Studies

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ABSTRACT

The computational strategies permeate all aspects of drug discovery such as virtual screening techniques. Virtual screening can be classified into ligand based and structure based methods. The ligand based method such as Quantitative Structure Activity Relationship (QSAR) is used when a set of active ligand compounds is recognized and slight or no structural information is available for the receptors. In structure based drug design, the most widespread method is molecular docking. It is widely accepted that drug activity is obtained through the molecular binding of one ligand to receptor. In their binding conformations, the molecules exhibit geometric and chemical complementarity, both of which are essential for successful drug activity. The molecular docking approach can be used to model the interaction between a small drug molecule and a protein, which allow us to characterize the performance of small molecules in the binding site of target proteins as well as to clarify fundamental biochemical processes.

INTRODUCTION

The Molecular modeling expression is used to describe the use of computers to build compounds and carry out a variety of calculations on these compounds in order to predict their chemical characteristics and behavior. The computational strategies also permeate all aspects of drug discovery such as virtual screening techniques in comparison to the process of trial and error that was used in the search for novel drugs.

DOI: 10.4018/978-1-5225-1762-7.ch033

The most important challenges that medicinal chemists face today is the design of new drugs with improved potency and less side-effects for treating human diseases such as AIDS and others. Medicinal chemists begin the process by taking a lead structure and then finding analogs exhibiting the preferred biological activities. Next, they use their experience and chemical insight to eventually choose a candidate analog for further development. This process was not only difficult but also expensive and time consuming. The conventional methods of drug discovery are now being supplemented by shorter approaches made possible by the accepting of the molecular processes involved in the original disease. In this view, the preliminary point in drug design is the molecular target, which is a receptor or enzyme in the body as an option of the existence of the known lead structure.

The effective design of chemical structures with the desirable therapeutic properties is directed towards Computer Aided-Drug Design (CADD) a well-established area of Computer Aided-Molecular Design (CAMD). The main applications of CAMD are the clarification of the basic requirements for a compound to obtain a determined activity, the simulation of the binding between a ligand and the receptor, the discovery of new active compounds and the prediction of activities for non-synthesized analogues. Two major modeling strategies right now are used in the designing of new drugs. In the first strategy, the design is based on the comparative analysis of the structural features of known active and inactive molecules that are interpreted in terms of their complementarily with a supposed receptor site model. This strategy is called *ligand based design* and one of its approaches is quantitative structure activity relationships (QSAR). This discipline was promoted by Hansch and his group (Fujita, 1990). In the second strategy, the three-dimensional features of a known receptor site are directly considered and this strategy is called *structure based design* method. In structure based drug design, the most widespread method is molecular docking (Mahajan A., Gill N.S & Arora R., 2014; Xuan-Yu Meng, Hong-Xing Zhang, Mihaly Mezei & Meng Cui, 2011) The molecular docking approach which will be discussed in details in the coming section can be used to model the interaction between a small drug molecule and a protein, which allow us to characterize the performance of small molecules in the binding site of target proteins as well as to clarify fundamental biochemical processes.

This chapter deals with the two strategies that are used in designing new drugs. At first, focus will be on the ligand based design or QSAR approach. The QSAR section starts with history and the earliest efforts made in this field, types of descriptors and statistical analysis methods. Moreover, validation of QSAR models, the internal as well as the external validations. Second, the focus will be on the structure based design or molecular docking approach. The different types of docking methods will be discussed including the different software used. At the end, applications or case studies done by the authors and others will be discussed also. For example, Exploration of human serum albumin binding sites by docking and molecular dynamics, Docking study related to non-peptide HIV-1 protease inhibitors, Homology modeling, molecular dynamics and docking simulations of rat A2A receptor, Exploring the ligand recognition properties of the human vasopressin V1a receptor using QSAR and molecular modeling studies and others. These studies will introduce the reader to the field of molecular docking and its use in structure based drug design. Finally, more attention must be dedicated to the combination of the two approaches in designing new drugs.