Chapter 5
Virtual Screening and Its Applications in Drug Discovery Process

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ABSTRACT

Virtual screening plays an important role in the modern drug discovery process. The pharma companies invest huge amounts of money and time in drug discovery and screening. However, at the final stage of clinical trials, several molecules fail, which results in a large financial loss. To overcome this, a virtual screening tool was developed with super predictive power. The virtual screening tool is not only restricted tool small molecules but also to macromolecules such as protein, enzyme, receptors, etc. This gives an insight into structure-based and Ligand-based drug design. VS gives reliable information to direct the process of drug discovery (e.g., when the 3D image of the receptor is known, structure-based drug design is recommended). The pharmacophore-based model is advisable when the information about the receptor or any macromolecule is unknown. In this ADME, parameters such as Log P, bioavailability, and QSAR can be used as filters. This chapter shows both models with various representative examples that facilitate the scientist to use computational screening tools in modern drug discovery processes.

INTRODUCTION

Lead discovery is the vital step in drug discovery programme. Advancements in genetics and computational biology boost up the modern drug discovery methods. The genetic scientists provide a lot of information about human genome along with gene requirement which codes for a particular protein that is prerequisite for the development of a particular organism. As a consequence, the targets for drugs and the mechanistic pathway can be traced with the support of genetic information. The drug targets may soon rise from 500 to 10,000 in future (Debouck C & Metcalf B, 2000).

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Meanwhile, the advent of combinational chemistry also revolutionised the basic research to provide an infinite number of compounds in a short span of time. The high throughput screening (HTS) played a very vital role to automate the conventional assay methods (Hertzberg RP & Pope AJ, 2000). There are various combinatorial methods is available to create a wide range of chemical libraries like peptides, non-peptide oligomers, peptidomimetics, small molecules, and natural product-like organic molecules. Each combinatorial approach possesses unique high-throughput screening and encoding strategy. But still, it is in the infant stage due to its exorbitant economic implications. The virtual screening came to the practice as a complementary approach that can analyse the large databases.

The computational screening is otherwise known as *in silico* screening since the screening is done by silicon graphics interface (Walters WP 1998; Lyne PD 2002; Schneider G & Böhm HJ, 2002). Virtual screening is based on knowledge of either ligand or receptor. The virtual screening methods yield the information of the receptor based on the input information. For example, the three-dimensional image of the receptor is known, the virtual screening will direct as to receptor-based Drug Design . When the information about receptor is known, the virtual screening directs to pharmacophore drug discovery considering ADME parameters as a filter. In the following sections, application of virtual screening in drug discovery process are described with schematic representation.

VIRTUAL DRUG SCREENING

A pharmacophore is an abstract description of molecular features that are necessary for molecular recognition of a ligand by biological macromolecules. Gund proposed the pharmacophores could be used to search the database based on similarity in structure (Gund P, 1977). It paves the way to develop and apply 3D databases pharmacophore to discover novel leads (Kurogi Y & Guner OF, 2001; Langer T & Hoffmann RD, 2001). There are two steps in pharmacophore-based screening: one is identification of pharmacophore model and the second step is 3-D search based on the specific constraints. The most benefit of VS is that it can be applied to large databases.

Pharmacophore models are generally used when the active lead is identified, but the 3D image of the target is unknown. The active molecules are considered as training set and used for pharmacophore identification which is atoms/groups interact with the receptor.

The pharmacophore generation poses some problems due to conformational flexibility of the molecule Catalyst (Accelrys, (http://www.accelrys.com) Discotech and GASP (Tripos, (http://www.tripos.com; Jones G *et al.,* 1995) are commercially available programs for pharmacophore modeling. Conformational flexibility is the key feature to develop the algorithm which play pivotal role for the program development. These programs are based on the algorithms used for the alignment and the way in which conformational flexibility is handled. A pharmacophore model is obtained not only from active ligand but also from 3D receptor. Such a structure of receptor or receptor/ligand complex provides information on possible and essential points of interactions between receptor and drug. The active binding site in 3D receptor is analyzed and the same information which can be used in 3-D database screening. For instance, when a drug-receptor complex is available, the atoms of ligand which interacts with receptor can be defined as features in a pharmacophore modeling. The protein backbone atoms are also used in pharmacophore model. The information of protein backbone atoms are merged with the feature points into a single pharmacophore. When three-dimensional image is only protein, multiple queries are needed in order to correlate and explore various possible binding modes. The programmes such as UNITY (Tripos, http://