Chapter 11
Strategies of Virtual Screening in Medicinal Chemistry

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ABSTRACT

Virtual screening represents an effective computational strategy to rise-up the chances of finding new bio-active compounds by accelerating the time needed to move from an initial intuition to market. Classically, the most pursued approaches rely on ligand- and structure-based studies, the former employed when structural data information about the target is missing while the latter employed when X-ray/NMR solved or homology models are instead available for the target. The authors will focus on the most advanced techniques applied in this area. In particular, they will survey the key concepts of virtual screening by discussing how to properly select chemical libraries, how to make database curation, how to applying and- and structure-based techniques, how to wisely use post-processing methods. Emphasis will be also given to the most meaningful databases used in VS protocols. For the ease of discussion several examples will be presented.

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1. INTRODUCTION

Virtual screening (VS) is a computational technique developed since early 1990s to meet the needs of pharmaceutical companies to maximize their profit when minimizing time and cost (Lavecchia & Di Giovanni, 2013). It is well known that developing a new drug is a complex process, which can take approximately 12-15 years and huge investments of about $1 billion (Hughes et al., 2011).

In the last decades, pharmaceutical companies have radically changed the approach to the discovery and development of new drugs (Everts et al., 2017; Mangiatordi et al., 2016; Myers & Baker 2001) in the attempt to increase competitiveness and innovativeness. The need to speed-up the entire pipeline of drug discovery and development has given new credit to VS approaches as a viable alternative to the High-Throughput Screening (HTS) (Shoichet, 2004; Klebe, 2006). In this scenario, VS has gained a key role for anticipating the discovery of novel hits by reducing the likelihood of failure and, thus, time and costs (Kar& Roy, 2013).

In addition, VS is effective to investigate ligands promiscuity for unveiling polyphamacological actions for the design of multi-target compounds and/or to detect off- target affinity (Chaudhari et al., 2017). The old paradigm of drug design "one-drug one-target" has been overtaken by the need of having polypharmacological drugs enabling to replace combination therapy with multitarget therapy (Anighoro et al., 2014). VS could be also valuable to draw a preliminary toxicological spectrum and especially about drug efficacy and safety (Chaudhari et al., 2017; Nicolotti et al., 2014). In this respect, main causes of market withdrawal are associated with the occurrence of idiosyncratic adverse liver effects, which are often fatal for people (M. Chen et al., 2011; Fontana et al., 2009). Well known is the case of nimesulide, a non-steroidal anti-inflammatory drug (NSAID) marketed as one of the first selective COX-2 inhibitors and currently banned from several countries in Europe and USA.

Traditionally, VS relies on two main strategies that are ligand-based (LBVS) and structure-based (SBVS) virtual screening approaches (Lionta et al., 2014; Nicolotti et al., 2008). The LBVS strategies are based on the assumption that similar chemical structures should exhibit similar binding properties with respect to a given target (Klabunde, 2007; Koeppen et al., 2011). To carry out LBVS studies, at least one active compound (e.g., agonist for a given target) and a pool of structurally similar compounds are necessary (Koeppen et al., 2011; Rognan, 2017).

On the other side, SBVS approaches are employed when the 3D solved structure, or as alternative a reliable homology model, of a target protein is available. For the sake of clarity, homology models having at least 50% sequence identity compared to the template are suitable for SBVS, being docking studies usually able to globally reproduce the reference interactions with high level of accuracy (Bordogna et al., 2011; Cavasotto & Phatak, 2009; Hillisch et al., 2004; Oshiro et al., 2004).

Generally, a SBVS approach is based on two basic steps: (1) one or more libraries of compounds are screened by biasing the active site of the targets protein (or its model) with a number of different molecular poses; (2) the compound-target affinity is evaluated by means of a scoring function whose value is used for ranking compound. A post-processing phase can be also implemented to refine the selection of the top-ranked compounds for prioritizing experimental tests (i.e., *in vitro* and/or *in vivo* assays) (Rognan, 2017). An example of efficient application of SBVS is the identification of molecular scaffolds for developing selective ligands towards human histamine H4 receptor (hH4R). This study was conducted using a library of about 8.7 million 3D-structures screened on a homology model of the hH4R, with 255 compounds selected and successfully tested (Kiss et al., 2008).