Chapter 8
Integrated *in Silico* Methods for the Design and Optimization of Novel Drug Candidates: A Case Study on Fluoroquinolones – *Mycobacterium tuberculosis* DNA Gyrase Inhibitors

Nikola Minovski
National Institute of Chemistry, Slovenia

Marjana Novič
National Institute of Chemistry, Slovenia

ABSTRACT

Although almost fully automated, the discovery of novel, effective, and safe drugs is still a long-term and highly expensive process. Consequently, the need for fleet, rational, and cost-efficient development of novel drugs is crucial, and nowadays the advanced in silico drug design methodologies seem to effectively meet these issues. The aim of this chapter is to provide a comprehensive overview of some of the current trends and advances in the in silico design of novel drug candidates with a special emphasis on 6-fluoroquinolone (6-FQ) antibacterials as potential novel Mycobacterium tuberculosis DNA gyrase inhibitors. In particular, the chapter covers some of the recent aspects of a wide range of in silico drug discovery approaches including multidimensional machine-learning methods, ligand-based and structure-based methodologies, as well as their proficient combination and integration into an intelligent virtual screening protocol for design and optimization of novel 6-FQ analogs.

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INTRODUCTION

The discovery process of novel, effective and safe drugs, from day to day is becoming more advanced and sophisticated. Today, the profit- and innovation-based competition between the pharmaceutical companies is increasingly growing (Cavazzani, 2010). In addition to the profit, the process of discovery a new drug is not only long-term, but also highly expensive. It was estimated that a new drug discovery program is approximately 12-15 years long and takes around 200-300 millions to one billion dollars (Rawlins, 2004; Bartfai & Lees, 2006; Hughes et al., 2011). To alleviate this growing problem, nowadays the drug research efforts are mainly directed toward reducing the discovery costs as well as the time required. In that regard, the *in silico* drug discovery methods were found as particularly important to effectively meet these issues.

As depicted in Figure 1, the lead discovery part (which is constructed of several interconnected sub-phases) of the drug discovery pipeline can be considered as the essential one (Kenny et al., 1998; Langer & Hoffmann, 2001). Owing to the rapid development of various computational methods that today could readily and efficiently be applied in different lead discovery segments, one can observe a significant progress in reducing its durability to amazing 2-3 years (Figure 1). However, within the framework of the entire drug discovery process it is still a long period of time and therefore a further time reduction is certainly welcomed.

In the seventies of the previous century, the discovery of novel lead compounds was substantially based on a random screening of large chemical libraries comprised of chemicals of different origin. This approach has been initially used for discovery of new antibiotics. The drug discovery practice demonstrated that on average only one potential lead from a library containing around 20.000 molecules could be identified using the random screening approach (Young et al., 1996). Since the 1980s, with the growth and development of robotics and miniaturization of the *in vitro* testing methods, it became possible to screen hundreds of thousands of compounds on a large number of biological targets (Gribbon & Sewing, 2005), i.e., a methodology widely known as high-throughput screening (HTS). Nevertheless, such a philosophy postulated under the idea, the greater is the starting chemical library, the higher are the chances to identify a biologically-active molecule, was disappointing for many pharmaceutical companies (O'Driscoll, 2004). These failures as well as the daily progresses in molecular and structural biology were the major driving force to elevate the discovery of novel drugs to a significantly higher, knowledge-based level commonly known as the rational drug design (Mavromoustakos et al., 2011). Moreover, the advances in the computation and strategies such as 2D/3D computer-aided molecular design (CAMD) opened a new perspective into the drug discovery world. Nowadays, the *in silico* screening methods are indeed an efficient supplement to the experimentally grounded HTS methods, becoming an integral segment of the hit identification and lead generation processes (Klebe, 2006; Stahura & Bajorath, 2004; Bajorath, 2002; Shoichet, 2004; Bleicher et al., 2003).

The present text aim to report some of the recent trends and advances in the *in silico* design of novel drug candidates – from chemical sketches to predicted active conformations. Specifically organized in two, tutorial-like parts (theoretical and practical), this chapter is not strictly intended to expose the thorough theoretical and mathematical background behind the *in silico* methodologies employed, but rather to guide the reader through the different steps of the *in silico* design and prediction of novel biologically-active hits. Put differently, the theoretical part gives an overview of various attentively selected computational methodologies proficiently integrated into an efficient *in silico* screening framework including quantitative structure-activity relationship (QSAR) methods, virtual combinatorial library