Chapter 3
An Introduction to the Basic Concepts in QSAR-Aided Drug Design

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ABSTRACT

The need for the development of new drugs to combat existing and newly identified conditions is unavoidable. One of the important tools used in the advanced drug development pipeline is computer-aided drug design. Traditionally, to find a drug many ligands were synthesized and evaluated for their effectiveness using suitable bioassays and if all other drug-likeness features were met, the candidate(s) would possibly reach the market. Although this approach is still in use in advanced format, computational methods are an indispensable component of modern drug development projects. One of the methods used from very early days of rationalizing the drug design approaches is Quantitative Structure-Activity Relationship (QSAR). This chapter overviews QSAR modeling steps by introducing molecular descriptors, mathematical model development for relating biological activities to molecular structures, and model validation. At the end, several successful cases where QSAR studies were used extensively are presented.

INTRODUCTION

Drug design and discovery is a multidimensional task necessitating collaboration across a broad range of disciplines and areas of research. Computational drug discovery is an essential component in drug design process that accelerates drug discovery and development by providing useful preliminary infor-

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mation at the early stages of the process. Quantitative structure-activity relationship (QSAR) is one of the effective data mining strategies of the computational approaches which have opened up a number of informative perspectives in modern and profitable drug design process. The chapter will focus on rational drug design and the importance of relevant computational approaches in this area. Moreover, the chapter will introduce the QSAR studies as a part of computational methods in drug design and development processes. Different kinds of molecular descriptors, data analysis, descriptor selection, model building and evaluation will be discussed. Application of QSAR studies by providing some specific case studies will also be highlighted.

BACKGROUND

Drugs are vital, essential, and inevitable part of our life which is always being threatened by different diseases. Therefore, administration of safe and effective drugs is necessary. According to the side effects being reported in clinic, finding novel drugs with minimum toxicity is always a need. Drug discovery is a patient-oriented, complex, and time consuming process associated with spending huge amount of investment and involves many experts from different disciplines such as biology, biochemistry, pharmacology, mathematics, computing and molecular modeling. It has been estimated that of 9.000-10.000 new chemical entities identified or synthesized, one can reach the market within an average time of 16 years. Previously, drugs have been discovered either by identifying chemicals by trial-and-error or by serendipity. Today, attempts have been focused on rational drug design. Its fundamental principle lies in logical reasoning before synthesizing any therapeutic agent for the evaluation. In this context, computer-assisted drug design is a valuable and promising tool in rational drug design and discovery pipeline and plays an important role in pharmaceutical research by reducing the costly failures of drug candidates in clinical trials.

One of the strong appeals of QSAR studies deals with chemical safety and risk of toxicity. Toxicological profile and safety assessment of new chemical entities is of paramount importance in drug design and development process. Compounds with improved biological activity do not necessarily reach the market and most of them are discarded from clinical trials just for toxicity concerns. Therefore, toxicity is a major source of attrition for potential drug candidates. Drug toxicity and safety assessment of chemicals is time consuming and is accompanied with spending millions of dollars. In this context, structure-toxicity predictive models of pharmaceutically relevant molecules can provide an estimation of risk assessment and safety of drug candidates and it can be regarded as a promising and fundamental way to reduce the need for animal testing as well as ethical and monetary cost. As a consequence, potentially toxic compounds can be identified during early stages of drug discovery process. Carcinogenicity, mutagenicity, teratogenicity, hepatotoxicity, cardiotoxicity, and nephrotoxicity are the most important endpoints in toxicity evaluation (Sullivan, Manuppello, & Willett, 2014; Toropov, Toropova, Raska, Leszczynska, & Leszczynski, 2014).

Computational approaches can be classified into structure-based drug design (SBDD), ligand-based drug design (LBDD) and sequence-based approaches (Ou-Yang et al., 2012). In the presence of experimentally determined structure of target molecule, molecular docking and *de novo* drug design can be used in the SBDD procedures. In situations in which three dimensional (3D) structure of target molecule is not available, LBDD methods are applied. Quantitative structure-activity relationship (QSAR), molecular field analysis, pharmacophore modeling, and 2D/3D similarity assessment are examples of