Chapter 4

QSAR and Lead Optimization

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ABSTRACT
There are many diseases for which suitable drugs have not been identified. As the population increases and the environment gets polluted, new infections are reported. Random screening of synthesized compounds for biological activity is time consuming. QSAR has a prominent role in drug design and optimization. It is derived from the correlation between the physicochemical properties and biological activity. QSAR equations are generated using statistical methods like regression analysis and genetic function approximation. Both 2D parameters and 3D parameters are involved in generating the equation. Among several QSAR equations generated, the best ones are selected based on statistical parameters. Validation techniques usually verify the predictive power of generated QSAR equations. Once the developed QSAR model is validated to be good, the results of that model may be applied to predict the biological activity of newer analogues. This chapter illustrates the various steps in QSAR and describes the significance of statistical parameters and software used in QSAR.

INTRODUCTION

Introduction to Drug Design

The cost involved in the drug discovery process is very high. It is also time consuming because of extensive clinical testing. Drug design is the process of inventing drugs depending on their ability to bind with biological targets. The process of drug design consists of various stages.
Choosing a Disease

Drug design begins by choosing a disease. There are many ailments which can affect human body. Infections by pathogens or due to faulty function of organs may be the cause for the disease. Genetic or congenital factor may also cause disease. Overproduction or under production of some metabolites is also the reason for disease. Thus, the medicinal chemist must be very careful in choosing the disease for drug design. The pathology of the disease must be studied thoroughly before designing a drug.

Choosing a Drug Target

Biochemical processes are important for functioning of human body. This biochemical process produces many chemicals necessary for normal body functioning. Enzymes regulate these biochemical processes. Therefore, the most common biological target for drug design is enzyme which catalyzes the biochemical process. Many drugs available in the market are enzyme inhibitors. The mode of action of anti-inflammatory drugs involves the inhibition of the enzyme cyclooxygenase. It produces prostaglandins. The prostaglandin causes pain, fever and inflammation. The other important biological target is receptors. Receptors produce their effect through hormones. Some of the antihypertensive drugs like atenolol act by blocking beta adrenergic receptors. Another biological target is nucleic acid. The mechanism of antitubercular antibiotic rifampin is inhibition of RNA synthesis. Hence, the study of structure of biological target is very important step in drug design.

Validating the Target

After selection of biological target, it becomes necessary to confirm that correct target has been identified. The validation of biological target may use *in vitro* tools which involves the use of whole animals. Antisense technology which uses RNA like chemical oligonucleotides is another method of target validation. Transgenic animals are powerful validation tools. Other validation tools include monoclonal antibodies, chemical genomics etc.

Lead Identification

“Lead compound” is the structure that has some activity against the biological target, but not yet good enough to be the drug itself (Franz, 2008). The lead molecule has various structural features for further development of the structure to a complete drug. Lead molecule can be identified from natural and synthetic products viz random screening, high throughput screening, pharmacophore mapping, virtual screening; NMR based screening, chemical genetics etc.

Lead Optimization

Once the lead structure is identified, the next step is to optimize the lead structure. In this stage, the medicinal chemist utilizes Structure Activity Relationships (SAR) to improve certain features of lead compound. These features include increasing activity against the biological target, reducing the biological activity against unrelated targets, and improve the drug likeness and ADME properties. The various