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In Silico Evaluations of Activity/Toxicity Profiles of Chemotherapeutic Agents

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The goal of drug discovery is to identify a compound that can modulate the effect of a molecular target, usually a receptor or an enzyme, that regulates a biological process related to a disease. *In silico* approaches are often made by utilizing virtual screening to explore candidate molecules and promising hits. The hits are analyzed and usually clustered into structural classes. The promising clusters with excellent physico chemical properties are then subjected to further chemical exploration for generating a lead compound of the series. The most promising compounds from the synthesized compounds in the lead series are then evaluated through activity prediction by quantitative structure activity relationships along with pharmacokinetic and pharmaco dynamic profiles. The final phase in preclinical research is the transformation of a lead structure into a candidate drug, which is then considered for testing in clinical trials. It is estimated that it usually takes about 10-15 years to develop a drug, and that it costs around US$ 800 million. So, many parallel processes are run so as to minimize the risk of erosion involved in the process of transforming hits into good leads, which can in turn become good candidate drugs with a high probability of succeeding in clinical trials. It is needless to mention here that target validation plays a key role in drug discovery procedure and is often run throughout the development. The importance of computational modeling towards predicting the properties and activities of the various compounds at all stages of drug discovery creates an entire gamut of studies known as Computer-Aided Drug Design (CADD), which is a completely new field with enormous opportunity and goes hand in hand with computational chemistry. Such in-silico design of new useful compounds reduces the high cost of experimental research in the drug development strategy. CADD has become undoubtedly an essential tool for the discovery of novel compounds with specific pharmaceutical properties and is an integral part of rational drug design. Rational drug design with an aim of arriving at some lead compound is an ever expanding area of research. The canvass of the entire gamut of studies in molecular design being too wide, the key feature restricts itself to the development of some leading aspects including molecular similarity analysis, virtual library design and most importantly, a rationalized and systematized approach, better known as structure activity-property relationship. Although theoretical/computer-aided drug design (CADD) approach cannot replace laboratory experiment with actual molecule, it can give a clear insight by generating and analyzing massive amounts of data in relatively short period of time. Thus the whole system of such discovery processes is not limited within the science of medicinal chemistry only. High throughput screening, protein-ligand docking, protein-protein interactions, drug-protein interactions are several other important areas playing key roles leading to drug like molecules. In computational modeling, one is mainly concerned with design of new lead compounds using computer programs relating to chemotherapeutic and other causative agents which ultimately helps in predicting important biological properties at all stages of drug discovery. Such *in silico* design will definitely boost up the opportunity of predicting novel compounds with useful properties and will reduce the time as well as high cost of experimental research in the drug development strategy.

The rapid development and utilities of CADD may be witnessed in Quantitative Structure Activity Relationship (QSAR) problems, to perform a rational analysis of different pharmacological activities. One can mention the application of Topological Substructural Molecular Design (TOPS-MODE) method for the description of physicochemical property of organic compounds as well as for the design of the biologically active compounds. The method is not only very useful for the discovery of novel leads, but also to the study of the physicochemical and absorption properties of drugs. The rationality in the search of the novel antibacterial drugs using the TOPS-MODE approach and the validation of the method for describing the biological activity of a heterogeneous series of compounds have been studied in details in very recent years. Exploration of TOPS-MODE for generating good predictive linear models in connection with anti-microbial and anti cancer activity of a large number of molecular structures is a typical incident. The Markovian Chemicals *in silico* design (MARCH-INSIDE), is another useful approach in drug design, that have been utilized for developing QSAR in order to classify compounds as anti bacterial or not, within structurally heterogeneous series. QSAR is a modeling technique employing linear regression method with an aim to find the optimal drug in the set of congeneric compounds. When data set are diverse and of complicated nature, applicability of non-linear methods like self-organizing maps (SOM) or Kohonen network and counter propagation artificial neural network (CP-NN) are justified in QSAR/QSPR modeling. Differential QSAR using computed structural descriptors are of remarkable use in the design of drugs where resistance is a problem.

However, it is important to note here that only biological activity does not guarantee a compound to be a drug. There may be many drawbacks for even a highly active compound to reach the shelves of a medicine shop as a drug. Preclinical toxicity and lack of adequate efficacy in human trials are two major causes responsible for grinding down in the drug development process. Some significant factors are stretched out between a successful drug and a biologically active compound. A few of the more common problems encountered include bioavailability, unfavorable ADME property and more importantly,

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toxicity. Many active drugs have been withdrawn from the market mainly due to toxic effects that are very injurious for the living system. QSAR/QSTR models are frequently used for *in silico* prediction of in vivo toxicity endpoints. Virtual screening techniques for determining potential toxicity of a wide variety of chemical structures benefit candidate selection in drug development. They also contribute in the process of replacing compounds already in the market with less toxic ones. While experimentally-derived toxicity data had been difficult to obtain on large number of chemicals in the past, recent efforts by the National Center for Environmental Assessment (NCEA) and US Environmental Protection Agency (EPA) to routinely use TOPKAT to screen and rank chemicals that lack experimental toxicity data is highly encouraging. One can mention some TOPKAT models concerning hydrophobicity or lipophilicity (logP), rat oral lethal dose (LD_{50}), rat chronic oral lowest observed adverse effect level (LOAEL), daphnia magna EC_{50} for reproduction ability, mutagenicity (Ames test), and developmental toxicity profile (DTP) which are frequently used for assessment of newly reported compounds. Since most of the anticancer compounds show toxicity at moderate doses, a management between activity and toxicity is very important for development of such new effective compounds. Use of TOPKAT in such situations is expected to throw newer insights in chemotherapeutic drug design.