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DRUG DISCOVERY AND DRUG DESIGN

Drug design

A drug can be defined as a small molecule which interacts with targets usually receptors of proteins in the body and through such interactions it causes various physiological responses leading to beneficial therapeutic remedies to the patients.

Drug design or rational drug design, is an intensive process that involves the design of small molecules that are complementary to the bio-molecular targets or receptor proteins with which they will bind and interact. The process of designing and development of a new drug is called drug discovery. The development of a new drug is a complex, lengthy and expensive process. The biggest challenge faced by the pharmaceutical industries is the design of a new novel drug. The use of computers exponentially accelerates the intensive process of drug design and reduces the cost of whole process. Computational modeling techniques are used in the discovery of new drugs and this type of modeling is often referred to as computer-aided drug design (CADD).

Bioinformatics in drug development

Bioinformatics plays an important role in the development of new drug by tracking, storing and providing tools for the analysis of massive amount of data developed by the pharmaceutical industries. The functional annotation of genes is known as functional genomics and it includes areas such as searching, structural analysis, homology, expression analysis, large scale mutagenesis and analysis of protein interactions. Each of these areas is important in the

development of drugs. New techniques are constantly being developed to boost productivity of the drug design process. One such process includes the Computer-aided-drug-design (CADD).

Computer-aided-drug-design (CADD)

Computational chemistry is used in CADD to discover or study the effectiveness of drug and its related biologically active molecules. The main basic principle of CADD is to predict the binding affinity of a given molecule to a target.

Various semi-quantitative methods are available to predict the binding affinity of a molecule to its target, such as molecular mechanics or molecular dynamics. Binding affinity estimates can be done by knowledge-based scoring function. These methods use statistical techniques, linear regression, neural nets or machine learning to derive the predictive binding affinity equations.

Optimization of the parameters for the calculation of the molecular mechanics and estimation of the electronic properties (electrostatic potential, polarization etc.) of the candidate drug that will influence binding affinity are done by semi-empirical, ab initio functional theory.

Drug design with the help of computers may be used at any of the following stages of drug discovery.

1. Identification of 'Hits' using virtual screening (structure or ligand based design).
2. Hit – to – lead (H2L) optimization of affinity and selectivity (structure-based design, QSAR etc).

Virtual screening is a computational method used in CADD to search structures of small molecules (which have the affinity to bind to a drug target) in databases libraries e.g. ZINC databases, Pubchem etc. These are automatically evaluating large libraries of compounds using computer programs and has become the integral part of drug discovery process.

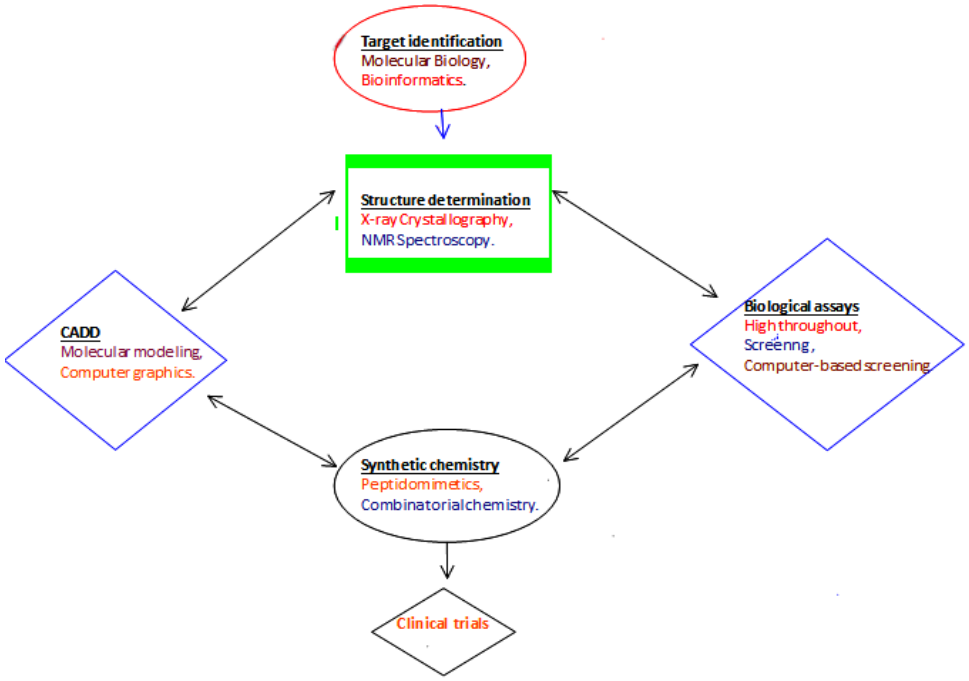

Fig. Schematic diagram of working of CADD

Drug design can be categorized into two types as given hereunder –

1. Ligand based drug design (LBDD)
2. Structure based drug design (SBDD)

1. Ligand based drug design (LBDD)

LBDD, also called indirect drug design is an approach used in the absence of the receptor 3D information and relies on knowledge of other molecules that bind to the biological target of interest. The most important and widely used tools in LBDD are the 3D quantitative structure activity relationship (3D QSAR) and pharmacophore modeling. They can provide predictive models suitable for lead identification and optimization.

QSAR is an alternative approach and widely used in CADD, in absence of reliable structural informations. It is defined as a process that quantitatively assumes the structural molecular properties of a molecule e.g. its geometric and steric fields (shape of the

molecule), the hydrophobic regions (water soluble surfaces) and the electrostatic fields must contain the responsible features for its physical, chemical and biological activity.

2. Structure based drug design (SBDD)

SBDD is an iterative approach where the structural information of the targeted drug is exploited for the development of its inhibitors. Structure of the receptor is prerequisite for this method and most commonly it is determined by experimental techniques which include the cloning, purification and structural determination of the target protein or nucleic acid by X- ray crystallography, NMR or homology modeling (the first cycle). These compounds are then scored and ranked based on their steric and electrostatic interactions with the target site and the best compounds are tested with biochemical assays. Protein structure can be detected by computational methods like threading and homology modeling if the structure of the protein drug target is not available.

The second cycle includes the complex structural determination of the target with a promising 'lead' from the first cycle.

Other important additional cycles includes synthesis of the new target: lead complex and future optimization of the lead compound. The optimized compounds usually show marked improvement in binding and specificity for the target after several cycles of the drug design in SBDD