© 2017 IJSRST | Volume 3 | Issue 10 | Print ISSN: 2395-6011 | Online ISSN: 2395-602X
National Conference on Research and Developments in Synthetic Organic Chemistry

Computer Aided Drug Design

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ABSTRACT

In the fast pace world fast pace development of drug is essential. This has been boosted by Computer aided drug design(CADD). The methodology has been cost-effective reducing the labour and time of design and discovery by almost fifty percent. The paper discusses mainly those approaches of CADD mainly developed based the structure of macromolecule protein.

Keywords: CADD, Structure Based Drug Design, Docking, Homology Modelling

I. INTRODUCTION

The field of medicinal chemistry basically deals with discovery newer drugs for the benefit of the general populace. These should reach them with easy availability and at economic prices. However in the past drug discovery and developing a new medicine is/was assumed to be a long, complex, costly and highly risky process that had few peers in the commercial world. But by the introduction of computer-aided drug design (CADD) approaches the scenario has changed. During the 1980s, the ability to rationally design drugs using protein structures was an unrealized goal for many structural biologists. However, now the human genome project has made available a substantial amount of sequence data that can be used in various drug discovery projects. Additionally, increasing knowledge of biological structures, as well as increasing computer power has made it possible to use computational methods effectively in various phases of the drug discovery and development has become the major subject of research for many academic laboratories. It is being widely used in the pharmaceutical industry to accelerate the process. The use of computational tools in the lead optimization phase of drug development leads to substantial cost benefit.

In the earlier scenario it took on 10-15 years and US $500-800 million to introduce one drug in the market, with synthesis and testing of lead analogs being highest cost areas.The greatest cost benefit was achieved in application of computational tools in hit-to-lead optimization which covers a wider chemical space while reducing the number of compounds that must be synthesized and tested in vitro. The computational optimization of a hit compound involves a structure-based analysis of docking poses and energy profiles for hit analogs, ligand-based screening for compounds with similar chemical structure or improved predicted biological activity, or prediction of favorable affinity or optimize drug metabolism and pharmacokinetics (DMPK) or absorption, distribution, metabolism, excretion, and the potential for toxicity (ADMET) properties. The comparably low cost of CADD compared with chemical synthesis and biological characterization of compounds make these methods attractive to focus, reduce, and diversify the chemical space that is explored. Today CADD has become an effective and indispensable tool in therapeutic development. The importance of in silico tools is greater than ever before and has advanced pharmaceutical research.[1]

Methods

The two methodologies involved are structure based drug design and ligand based drug design.

II. STRUCTURE BASED DRUG DESIGN

The structure based drug design is the best suited at present for emerging diseases/disorders. If the three-dimensional structure of a disease-related drug target is known, the most commonly used CADD techniques are structure-based. In SBDD the therapeutics are designed

based on the knowledge of the target structure. Two commonly used methods in SBDD are molecular docking approaches and de novo ligand (antagonists, agonists, inhibitors, etc. of a target) design. Molecular dynamics (MD) simulations are frequently used in SBDD to give insights into not only how ligands bind with target proteins but also the pathways of interaction and to account for target flexibility. This is especially important when drug targets are membrane proteins where membrane permeability is considered to be important for drugs to be useful. Successes have been reported for SBDD and it has contributed to many compounds reaching clinical trials and get FDA approvals to go into the market. Examples include Saquinavir[2] and Amprenavir[3] which were developed targeting HIV-1 protease based on SBDD. Also Dorzolamide[4] is a carbonic anhydrase II inhibitor was also sought on SBDD approach. SBDD methods rely on the protein structure and in the cases where the target structure is not possible to be determined by experimental methods, computational methods become useful. Several methods have been used for protein structure prediction including homology modeling, threading approaches, and ab initio folding.

III. HOMOLOGY MODELING

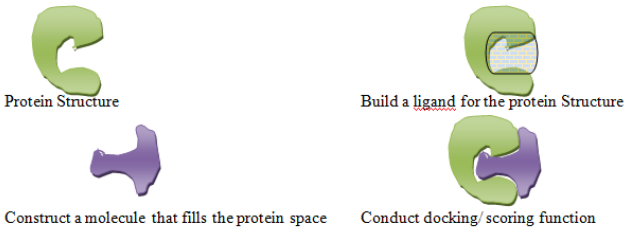
Homology modeling is a popular computational structure prediction method for obtaining the 3D coordinates of structures. Here we first use NCBI Basic Local Alignment Search Tool (BLAST) to identify a homologous protein structure on which model for the target structure is built using comparative modeling algorithms. The models built are evaluated and refined for stereochemistry. Once the models are verified to be acceptable in terms of their stereochemistry, they are then evaluated using 3D profiles or scoring functions that were not used in their generation.

Examples include homology modeling of HIV protease from a distantly-related structure has been used in the design of inhibitors for this structure.[5] Also, structure prediction of M antigen by homology modeling has given insights into its function by revealing that the structures and domains are similar to fungal catalases.[6] Homology servers used are SWISS-MODEL, MODELLER, 3D-JIGSAW, HHpred, etc.

IV. DOCKING AND SCORING

Docking of small molecules to receptor structures has become increasingly important in the context of drug discovery. Generally speaking, docking is carried out using a computer program in order to dock computer-generated representations of small molecules to a receptor (or to a user-defined part thereof, e.g. the active site of an enzyme), followed by evaluation of the molecules with respect to complementarities in terms of shape and properties, such as electrostatics. Good complementarities of a molecule indicate that the molecule is potentially a good binder. The outcome of a docking exercise normally includes some sort of affinity prediction for the molecules investigated, yielding a relative rank-ordering of the docked compounds with respect to affinity.

V. DE NOVO LIGAND DESIGN



It involves fragment-based approach for designing of ligand wherein assembling of different fragments of drug-like molecules is done to develop new ligand. The approach can be restricted by complexity of the molecule predicted. When a high resolution target structure is available, ligand growing programs such as biochemical and organic model builder (BOMB) can be used to design ligands that bind to the target without using ligand databases.[7,8] Using BOMB it is possible to grow molecules by adding substituents into a core structure. Examples include designing inhibitors for Escherichia coli RNS polymerase and inhibitors for Enterococcus faecium ligase VanA using hydroxyethylamine as the base template structure.[9]

VI. LEAD OPTIMIZATION AND ADME

Once the target structure/s is determined the next step includes lead optimization. Lead optimization indicates effectiveness of promising hits with the desired pharmacological profiles to reach the required affinity,

pharmacokinetic properties, drug safety, and ADME properties. Software includes QikProp, an ADME program offered by Schrodinger.

VII. ACKNOWLEDGEMENT

We are grateful to Gokhale Education Society members for their continuous encouragement and support for the preparation of this paper.

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