INTRODUCTION

The development of new drugs with potential therapeutic applications is one of the most complex and difficult processes in the pharmaceutical industry. Millions of dollars and man-hours are devoted to the discovery of new therapeutic agents. There is an ever growing effort to apply computational power to the combined chemical and biological space in order to streamline drug discovery, design, development and optimization. In biomedical arena, computer-aided or in silico design is being utilized to expedite and facilitate hit identification, hit-to-lead selection, optimize the absorption, distribution, metabolism, excretion and toxicity profile and avoid safety issues. Commonly used computational approaches include ligand-based drug designs (pharmacophore, a 3-D spatial arrangement of chemical features essential for biological activity), structure-based drug design (drug-target docking), and quantitative structure-activity and quantitative structure-property relationships.

Molecular docking is a widely-used computational tool for the study of molecular recognition, which aims to predict the binding mode and binding affinity of a complex formed by two or more constituent molecules with known structures. An important type of molecular docking is protein-ligand docking because of its therapeutic applications in modern structure-based drug design.

OBJECTIVES

A binding interaction between a small molecule ligand and an enzyme protein may result in activation or inhibition of the enzyme. Docking is most commonly used in the field of drug design as most drugs are small organic molecules, and docking may be applied to:

1. Hit identification: Docking combined with a scoring function can be used to quickly screen large databases of potential drugs in silico to identify molecules that are likely to bind to protein target of interest.
2. Lead optimization – docking can be used to predict in where and in which relative orientation a ligand binds to a protein. This information may in turn be used to design more potent and selective analogs.

METHODOLOGIES

Structure (target)-based drug design represents docking i.e. ligand binding to its receptor, target protein. Docking is used to identify and optimize drug candidates by examining and modeling molecular interactions between ligands and target macromolecules.

Structure (target)-based design requires structural information for the receptor which can be obtained from X-ray crystallography, NMR or homology modeling. The latter being another computational technique used to predict unknown protein structure from a sequence similarity to known protein structure(s). In the process of docking, multiple ligands and conformations and orientations are generated and the most appropriate ones are selected. Scoring functions are applied to evaluate tightness of interaction i.e. estimate binding free energy. General observation is that consensus (combination of different scoring algorithms) scoring yields better results than individual scoring. Validations may be performed with known active and inactive ligands, comparisons to crystallographic data and prediction of rank-ordering and binding affinities.

The success of a docking program depends on two components: the search algorithm and the scoring function.

STRATEGIES

Currently, two major modeling strategies are used for the conception of new drugs. They are:

i) Direct drug design: In the direct approach, the three-dimensional features of the known receptor site are determined from X-ray crystallography to design a lead molecule. In direct design, the receptor site geometry is known; the problem is to find a molecule that satisfies some geometric constraints and is also a good chemical match. After finding good candidates according these criteria, a docking step with energy minimization can be used to predict binding strength.

ii) Indirect drug design: The indirect drug design approach involves comparative analysis of structural features of known active and inactive molecules that are complementary with a hypothetical receptor site. If the site geometry is not known, as is often the case, the designer must base the design on other ligand molecules that bind well to the target.

The aim of this review is to give an outline of studies in the field of medicinal chemistry in which Molecular Modeling has helped in the discovery process of new drugs.

EXAMPLE

Docking, combined with other computational techniques and experimental data, also could be involved in analyzing drug metabolism to obtain some useful information from the cytochrome P450 system. Here example of successful applications of docking are presented.

DNA gyrase is a bacterial enzyme that introduces negative supercoils into bacterial DNA and unwinds of DNA, thus being studied as antibacterial target. HTS failed to find novel inhibitors of DNA gyrase. Boehm et. al. used de novo design for this enzyme and successfully obtained several new inhibitors. Firstly, 3D complex structures of DNA gyrase with known inhibitors, ciprofloxacin and novobiocin, were carefully analyzed to get a common binding pattern, in which both inhibitors donate one hydrogen bond to Asp73 and accept one hydrogen bond from a conserved water molecule. In addition, some lipophilic fragments should be included in the molecule to have lipophilic interaction with the receptor. Based on this information, LUDI and CATALYST were employed to search the Available Chemicals Directory (ACD) and a part of the Roche compound inventory (RIC), respectively, and collected about 600 compounds. Close analogs of these compounds were also considered, thus in total 3000 compounds were further tested using biased screening. Consequently 150 hits were selected and clustered into 14 classes of which 7 classes were proven to be the true and novel inhibitors. Subsequent hit optimization relied strongly on the knowledge of 3D structures of the binding site and eventually generated a series of highly potent DNA gyrase inhibitors.

CONCLUSION

Molecular modeling, an inexpensive, safe and easy to use tool, helps in investigating, interpreting, explaining and identification of molecular properties using three-dimensional structures. Molecular docking tries to predict the structure of the intermolecular complex formed between two or more constituent molecules. The techniques are used in the fields of computational chemistry, computational biology and materials science for studying molecular systems ranging from small chemical systems to large biological molecules.

REFERENCES


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