Int. J. Chem. Sci.: 7(3), 2009, 2000-2008

COMBINATORIAL DRUG DESIGN- FORMULATION OF THE ERA

- A REVIEW

SUBIN MARY ZACHARIAH*, K. LEENA PAPPACHEN, K. N. FASMI, STIMSON JOSE and ARATHI VIMAL

Department of Pharmaceutical Chemistry, Amrita School of Pharmacy, Amrita Viswavidyapeedam University, Elamakkara P. O. KOCHI - 682026 (Kerala) INDIA

ABSTRACT

The field of medicinal chemistry and drug design is in a state of development and is at present undergoing major restructuring. The molecular biological revolution and the progressing mapping of the human genome have created a new biochemical and biostructural great order. These developments have provided new challenges and opportunities for drug research and drug design. The aim of this review is to know more about the newly formulated drugs with the use of computer aided designed drugs and molecular modeling. One can site the advances in the understanding in the reaction mechanism, conformational analysis, host - guest interactions, quantum mechanics and so on. The major objective of the medicinal chemist is in designing molecules interacting with the degenerating process in the diseased organisms.

Key words : Structure based drug design, Dock, Computational chemistry, Drug modelling, Designed drugs

INTRODUCTION

Medicinal chemistry is concerned with the determination of structure and the synthesis and isolation of compounds, which may be used in medicine[1]. It involves the relationship between structures of medicinal compounds and their biological activity. The general format of presentation of each compounds include introduction, preparation, physical character, chemical property, identification test, purity test and assay. Drug design is the approach of finding drugs by design based on their biological targets. Typically, a drug target is a key molecule involved in a particular metabolic or signaling pathway i. e.,

* Author for correspondence; E-mail : smz78@rediffmail.com

specific to a disease condition or pathology, or to the infectivity or survival of a microbial pathogen.

The structure of the drug molecule that can specially interact with the bimolecular can be modeled using computational tools[2]. Using knowledge of its active site, construction of the drug molecule can be made inside out or outside in depending on whether the core of the R -groups are chosen first. Newer approaches have also suggested the use of drug molecules that are large and proteinaceaous in nature rather than as small molecules. There are suggestions to make this using mRNA. Gene slicing may be used, which have therapeutic applications.

Structure-based design refers specifically to finding and complementing the 3D structure of a target molecule such as a receptor protein[3]. From the geometry and functional features of the binding site, complementary structures of a compound are so designed as to have high binding affinity with the target molecule. It is a powerful technique to design a corresponding ligand specifically interacting with the target, particularly for the development of a novel therapeutic through stimulation or inhibition of the receptor protein. Structure-based drug design represents the idea that you can see exactly how your molecule interacts with its target protein[4]. This structural information can be obtained with X-ray crystallography or nuclear magnetic resonance spectroscopy (NMR). Ideally, these two techniques complement one another. Structure-based drug design was equated with de novo design or building a molecule from the ground up. The active site of the protein was a space to be filled with a molecule that complemented it in terms of shape, charge and other binding components.

A major development that has given structure-based methods a place of prominence in drug discovery has been increased rapidly[6, 7]. Structure based drug design can help lead to better compounds more quickly. It was a success in using structure-based methods to discover inhibitors for refractory targets as the SH2 domain of SRC, a tyrosine kinase implicated in osteoporosis and other bone-related diseases.

One of the driving forces behind structure-based drug design is lead optimization. Structure is a really good way of quickly getting a handle on how the lead compound binds to the target of interest and what one might be able to do with chemistry to modify the molecule to get the desired properties.

Structure-based drug design plays a major role in the development of novel therapeutic agents (drugs) against all types of diseases. Major focus is on the

computational/knowledge-based aspect of drug design, but experimental methods such as NMR, Biacore and ITC are also described. It is also used in amyloid diseases. Current structure-based drug design efforts for HIV, SARS, cancer and G-protein coupled receptors are also found[11].

The DOCK suite of programs focuses on molecular recognition, with wide-ranging applications to enzyme systems, protein-protein interfaces, nucleic acids and protein-nucleic acid complexes[17, 18]. However, combinatorial chemistry is the best thing that ever happened to structure-based drug design. Purely random combinatorial chemistry has evolved into focused combinatorial libraries, which can be considered an abstract form of structure-based drug design; Researchers realized that specific knowledge of the target could guide the power of combinatorial chemistry to rapidly make many compounds.

Structure-based drug design is at its most powerful, when coupled with combinatorial techniques.

Examples for designed drugs

Cimetidine

Cimetidine is the prototypical H_2-receptor antagonist from, which the later members of the class were developed, which inhibits the production of acid in stomach. It is largely used in treatment of heartburn and peptic ulcer.

Other is the Dorzolamide, which is a carbon anhydrase inhibitor used to treat glaucoma and also, it can be topically applied in the form of eye drops. The drug was the first drug in human therapy, which resulted from structure based drug design. Another drug is Zanamivir, which is an antiviral drug and a neuraminidase inhibitor used in the treatment and prophylaxis of both influenza virus A and B. Also, Enfavirtid**,** which is a peptide HIV entry inhibitor and an antivitriviral drug used in combination therapy for HIV infection. Probenecid also included in the group, which is an uricosuric drug primarily used in treating gout or hyperuricemia that is uric acid removal in the urine.

Bimolecular interactions and computer-assisted drug design

The goal is to develop a set of computational methods for the analysis of molecular kinematics and molecular conformations that are relevant to receptor-ligand interactions. We also focus in studying geometric and the problems arising, when the three-dimensional structure of molecules is considered in the analysis of receptor ligand interactions. Our target application is computer-assisted drug design, [5, which] is a significant component of

rational drug design. Computer assisted drug design is becoming more relevant as the understanding of molecular activity improves and the amount of available experimental data that require processing increases. A fundamental assumption for rational drug design is that drug activity is obtained through the molecular binding of one molecule (the ligand) to the pocket of another, usually larger molecule (the receptor, commonly a protein). In their active, or bound, conformations, the molecules exhibit geometric and chemical complementarity, both of, which are essential for successful drug activity. An example is shown in the Fig. below. The left side shows the protease thermolysin and one of its inhibitors. Thermolysin is the large molecule shown in the picture (PDB code 1TMN), while the inhibitor (a carboxymethyl dipeptide, CDP) is drawn in green near the center of the molecule. The right half of the Fig. below shows the folding of the polymer chain of thermolysin as a ribbon and the inhibitor.

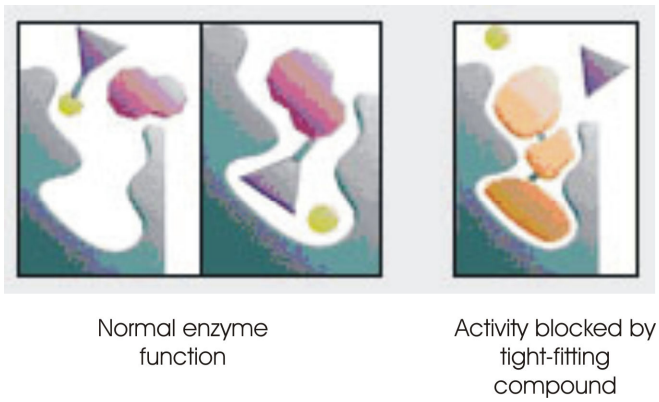

Fig. 1 : Showing structure-based drug design

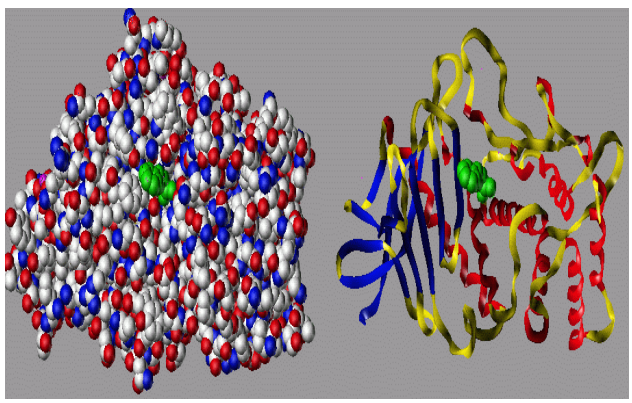

Fig. 2 : Showing molecular binding of protease thermolysin and one of its inhibitors

Drug modelling

The modeling of molecular structure is a complex task, in particular because most molecules are flexible, being able to adopt a number of different conformations that are of similar energy. Although chemists strive to obtain models that are as accurate as possible, several approximations have to be made in practice. In general, bond lengths, bond angles and torsional angles are considered the degrees of freedom of the molecule. It is clear that the more accurate the model used, the better is the chances in predicting molecular interactions. Nevertheless, this has encouraged researchers to build tools that use approximate models and investigate the extent to, which these tools can be useful. More accurate molecular modeling, gained through better theoretical understanding or increased computational power, can only improve the techniques developed with simpler models.

Two classes of problems

The problems that arise can be classified into two broad categories : If the receptor is known, chemists are interested in finding if a ligand can be placed inside the binding pocket of the receptor in a conformation that results in a low energy for the complex. This problem is referred to as the docking problem[16]. Very often the binding pocket is unknown. In fact, the 3D structure of relatively few macromolecules has been determined experimentally. In this case, indirect approaches must be adopted, which use a number of ligands that interact with that specific receptor.

Methods

The techniques that are used in computer-aided drug design include robotics (kinematics and planning), graphics algorithms (visualization of molecules), geometric calculations (surface computation), numerical methods (energy minimization), graph theoretic methods (invariant identification), randomized algorithms (conformational search), dimension recution methods (analysis of motion), computer vision methods (docking) and a variety of other techniques

The Computer-Aided Drug Design (CADD) center was created to foster collaborative research between biologists, biophysicists, structural biologists and computational scientists[8]. The major goal of the CADD center is to initiate these collaborations leading to the establishment of research projects to discover novel chemical entities with the potential to be developed into novel therapeutic agents.

Rational drug design employs the tools of *Bioinformatics* to identify genes and

proteins as potential drug targets. Sequence databases are doubling in size every 15 months and we now have the complete genome sequences of more than 100 organisms. This ability that generates vast quantities of data surpasses current means to use this data meaningfully for rational drug design[10]. Bioinformatics is used to bridge the enormous gap between rapidly-growing new gene sequence data, predicted proteins and the related structural information that is required to design, synthesize, or efficiently screening new drugs. The manner in, which new drugs are being developed has changed radically due to our increased understanding of molecular biology. Fortunately, there is only a limited set of data, one needs to gather about potential drug targets and different bioinformatics tools can be used to gather this information, interpret it and make associations leading to new discoveries. The relevant data includes nucleotide and protein sequences and variation, associations of homologous sequences, genetic maps, gene/protein/disease associations, gene to metabolic pathway associations.

In the age of human genome being deciphered and 3-dimensional structures of proteins available in an increasing number, drugs may now be designed in advance guessing possible 3-dimensional shape of the targets. In drug design, potential compounds may be conceptualized for the performance of required function based on essential characteristics (pharmacophores), including idealized structural and physical properties. These essential pharmacophores may be expressed in 3-dimensional atomic orientation for optimal activity and binding to the target proteins. The pharmacophores may be used to search database for compounds with similar pharmacophores and to design new compounds with desired activity and binding. Molecular models of these new compounds can be built and virtual tests, which are cheaper, faster and safer than real experiments may be run to assess its suitability before an expensive synthesis attempt is made. These are now essential tools for data management and cost-effective development processes in pharmaceutical R & D.

Structural genomics is poised to have a tremendous impact on traditional structure-based drug design programmes[6]. As a result, there is a growing need to obtain rapid structural information in a reliable form that is amenable to rational drug design.

Computational chemistry

Computational chemistry[17] screens small molecules in the database and identify potential candidate compounds. Such databases are published or commercially available, for instance, at MSI (Molecular Simulations) and other similar service organizations active-analog approach assists the design of a legend based on similarities to a set of

compounds known to possess the desired activity. The affinity score is calculated to select candidate compounds with strong binding to the target site. In addition, when the target site is not known for a ligand, various programs allow characterizing likely sites through computational approaches[13] for functional site mapping that involves repeatedly placing small functional groups into the possible site to approximate the shape of the binding region. Likely sites may also be inferred from similarity to known site structures.

Computational chemistry is used to design combinatorial libraries of molecules for the purpose of biological screening[20]. For instance, statistical techniques such as QSAR[11, 12] (quantitative structure activity relationship) analysis may be used in order to choose targeted compounds with required features and for diverse libraries, techniques such as PCA (principal component analysis) may be used for ensuring as wide a range as possible of compounds in the library. The component here may be activities, properties or substructures of the molecule. In QSAR[14] or still another QSPR (quantitative structure property relationship), statistical correlation is explored between an activity or a property and geometric or chemical characteristics (pharmacophores) of the molecule[19]. It is often used to analyze the effect of a particular substructure on the activities or properties of compounds. In the past 10 years, computational chemistry[9] led to the development of a large number of soft wares that helped design combinatorial libraries. For obvious synergy, these combinatorial chemistry companies are now getting allied with those of computational chemistry and structure modeling.

As powerful as rational drug design has proven, molecular design opens still more frontiers in biomedical research. In the age of human genome being deciphered and 3-dimensional structures of proteins available in an increasing number, drugs may now be designed in advance guessing possible 3-dimensional shape of the targets[8]. In drug design, potential compounds may be conceptualized for the performance of required function based on essential characteristics, including idealized structural and physical properties[15]. The pharmacophores may be used to search database for compounds with similar pharmacophores and to design new compounds with desired activity and binding.

Molecular models of these new compounds can be built and virtual tests may be run to assess its suitability before an expensive synthesis attempt is made. Virtual experiments are cheaper, faster and safer than real experiments and the data can help scientists to eliminate compounds that would not perform the required function. These are now essential tools for data management and cost-effective development processes in pharmaceutical R & D and other bone-related diseases

CONCLUSION

Scientific knowledge by itself is morally neutral, understanding more perfectly the relationship between chemical structure and the factors will greatly facilitate, drug design and discovery. Increasing use of structure based drug design techniques will take place enhancing our ability to craft more potent and more specific agents. The central objective of each branch of chemistry is to posses such an understanding of the relationship between chemical structure and molecular properties that given a set of desired characteristics, a molecule can be proposed and prepared that should come close to possessing them. The pharmaceutical industry is still in the process of centripetal separation into fewer but much larger firms on the one hand and a number of much smaller specialized firms on the other. The large firms carry on drug discovery and development the whole way from inception to marketing. They become increasingly risk averse as a consequence and only drugs promising to earn major sales can be justified to the share holders, so the new drugs are inevitable and should be developed.

ACKNOWLEDGEMENT

The authors are thankful to Dr K. G. Revikumar, Principal, Amrita School of Pharmacy and all others members of Department of Pharmaceutical Chemistry, Amrita School of Pharmacy for continuous encouragement in accomplishing this work.

REFERENCES

1. P. Krosgaard, T. Liljefros and U. Madsen, Textbook of Drug Design and Drug Discovery, 3rd Edn.
2. Richard B. Silverman, Textbook of Organic Chemistry of Drug Design and Drug Action, 2nd Edn., Academic Press, USA, (2004) p. 34.
3. C. M. Henry, Chem. Eng. News, **29**, 69-74 (2001).
4. J. Greer, J. W. Erickson, J. J. Baldwin and M. D. Varney, Application of the Three-Dimensional Structures of Protein Target Molecules in Structure-Based Drug Design., J. Med. Chem., **37(8)**, 1054 (2004).
5. K. Gubernator, Structure-Based Ligand Design, in Methods and Principles in Medicinal Chemistry, Weinheim, Wiley-VCH. (1998).
6. P. Robert, J. Stru. Func. Genom., **2(2)**, 113- 115 (2002).
7. R. L. Affleck, Solutions for Library Encoding to Create Collections of Discrete Compounds, Curr. Opin. Chem. Biol., **5**, 257-263 (2001).

8. C. Barnes and S. Balasubrhamanian, Curr. Opin. Chem. Biol., **4**, 346 (2003).
9. A. W. Czarnick, Encoding Methods of Combinatorial Chemistry. Curr. Opin. Chem. Biol., **1**, 60-66 (1997).
10. H. Fenniri, Combinatorial Chemistry. A Practical Approach, Oxford University Press, UK (2000).
11. S. J. Singer and G. L. Nicolson, Science., **175**, 720 (1972).
12. M. C. Richet, Compt. Rend. Soc. Biol., **45**, 775 (1893).
13. C. V. Gorswant, P. Theoren and S. Engstorm, J. Pharm. Science., **87**, 200 (1998).
14. C. Hansch and A. Leo, Exploring QSAR, Fundamentals and Applications in Chemistry and Biology, Vol I, Washington, DC (1995).
15. M. A. Gallop, R. W. Barrett and W. J. Dower, J. Med. Chem., **37**, 1233 (1994).
16. I. D. Kuntz, C. C. Huang and T. E. Ferrin, J. Med. Chem., **49**, 17 (2006).
17. I. D. Kuntz, Structure-based Strategies for Drug Design and Discovery, Science, **257**, 1078-1082 (1992).
18. P. Charifson and I. D. Kuntz, Recent Successes and Continuing Limitations in Computer-Aided Drug Design, in Practical Application of Computer-Aided Drug Design, Marcel-Dekker, NewYork, (1997) pp. 1-37.
19. I. Ojima, S. Chakravarthi, T. Inoe and S. Lin, Proc. Nat. Acad. Science., **96**, 4256 (1999).
20. S. C. Stinson. Chem. Eng. News, 29 (2001).
21. www. wikipedia.org
22. www.fatmanbiodesign.com
23. www.chem.iupui.edu
24. www.cgl.ucsf.edu
25. www.chem.unp.ca
26. www.netsci.org
27. www.uspharmacist.com
28. www.evotec.com

Accepted : 07.04.2009