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Applications of Computational Chemistry in Drug Designing

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ABSTRACT

Computational Chemistry in drug designing has played a major role in the development of therapeutically important small molecules for over three decades. These methods are broadly classified as either structure-based or ligand-based methods. Structure-based methods are in principle analogous to high-throughput screening in that both target and ligand structure information is imperative. Structure-based approaches include ligand docking, pharmacophore, and ligand design methods. The article discusses theory behind the most important methods and recent successful applications. Ligand-based methods use only ligand information for predicting activity depending on its similarity/dissimilarity to previously known active ligands. We review widely used ligand-based methods such as ligand-based pharmacophores, molecular descriptors, and quantitative structure-activity relationships. In addition, important tools such as target/ligand data bases, homology modeling, ligand fingerprint methods, etc., necessary for successful implementation of various computer-aided drug discovery/design methods in a drug discovery campaign are discussed. A wide range of illustrative applications, focusing on chemical materials are discussed briefly.

Keywords: calculate structure, computational chemistry, drug designing, structures and properties of molecules and solids, theoretical chemistry

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INTRODUCTION

Computational chemistry is a branch of chemistry that practices computer simulation to support in resolving chemical problems. It uses methods of theoretical chemistry, merged into efficient computer programs, to determine the structures and properties of molecules and solids. Computational chemistry uses result of theoretical chemistry incorporated into efficient computer programmed to determine structure and properties of molecule. It calculates the properties of molecule for example relative energy, dipole moment, structure, charge distribution, vibrational frequency, reactivity and other spectroscopic quantity [1]. Computational chemistry range is highly precise in drug designing (Figures 1–3).

As per World Health Organization (WHO)

- It is a natural or synthetic substance which (when taken into the living body) affects its functioning.
- An inventive process of finding new medications based on knowledge of biological target [1].

Fig. 1. *Synthetic or natural drugs.*

Purpose of Drug Design

- It is for treatment purpose
- It is for preventive purpose
- It is for diagnostic purpose

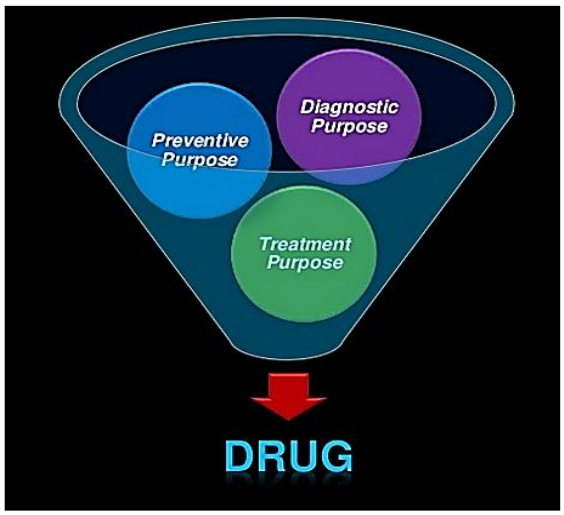

Fig. 2. *Purpose of drug designing.*

Advantage of Computational Chemistry

- It allows the medicinal chemist for use the computational power of computer for measurement of molecular geometry, electron density, electrostatic potential, conformational analysis, different types of energies.
- Determination of structure of ligand and target through X-ray crystallography and NMR spectroscopy.
- Docking of ligand in receptor active sites and exact measurement of geometric and energetic favor ability of such interaction.
- Comparison of various ligands through various parameters [2].

Process of Drug Design and Formation of New Drug

Stage 1: Drug discovery
Stage 2: Preclinical developments
Stage 3: Clinical developments
Stage 4: Regulatory approvals

A New Drug is Formed

Phase 1: Safety in human
Phase 2: Effectiveness in treating disease
Phase 3: Larger scale safety and effectiveness
Phase 4: Long-term safety

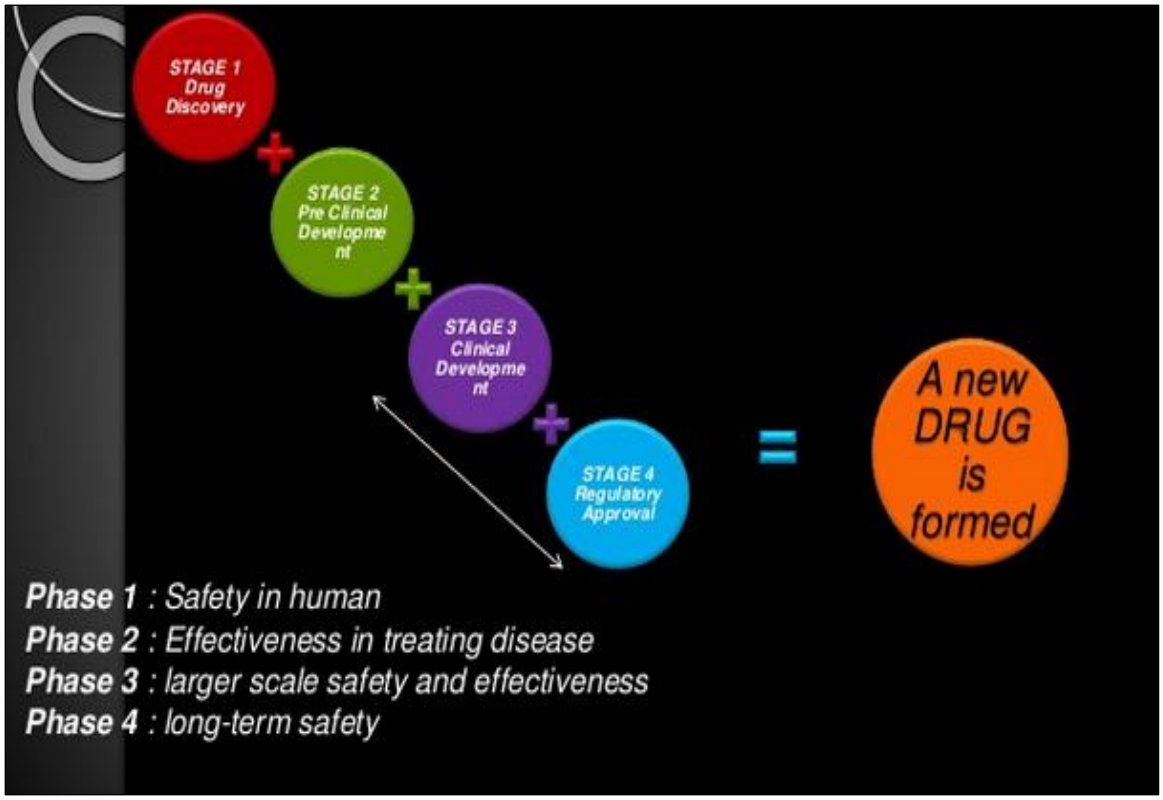

Fig. 3. *Drug designing process.*

Types of Drug Design

- Ligand based drug designing: It relies on knowledge of other molecules that binds to the biological target of interest. It is used to derive a pharmacophore.
- Structure-based drug designing: It relies on the knowledge of three-dimensional structure of the biological target obtained through following techniques: X-ray crystallography, NMR spectroscopy, homology modelling.

Quality Attribute of Drug Design

- Size: Organic small molecules
- Shape: Complimentary to the target receptor
- Charge: Opposite to the target receptor

Computer Aided Drug Design

- It represents computational methods and resources that are used to facilitate the design and discovery of new therapeutics.

Application of CADD

- Elimination of compounds with undesirable effects
- Identify and optimize new drugs [3].

Techniques of Drug Designs

- QSAR
- X-ray crystallography
- NMR
- Homology modeling

Docking

"Docking is a method which predicts the preferred orientation of one molecule to a second when bound to each other to form a stable complex."

Software's are

- Dock
- Auto dock
- Molecular operating environment
- Visualization of dock complex

Selection of Disease

- Determine the biochemical basis of the disease process.
- Physiological pathway (the exact steps in the pathway that are altered in the diseased state).
- Knowledge about the regulation of the pathway.

Target Selection

- Knowledge of the molecular basis of the disease is important in order to select a target at which to disrupt the process
- Enzyme as a target
- Receptor as a target
- Nucleic acid as a target

Determination of Active Site of Target Protein

Only a small part of a lead compounds may be involved in the appropriate interaction, i.e., a pharmacophore.

Selection of Ligands/Drugs

Docking like DOCK, AutoDock and Molecular Operating Environment (MOE), Visualization of docking complex.

Application of Drug Captopril

- Captopril is an ACE inhibitor. ACE stands for angiotensin converting enzyme.
- Captopril is used to treat high blood pressure (hypertension), congestive heart failure, kidney problems caused by diabetes, and to improve survival after a heart attack.

Lilly/Protherics (LY-517717)

- Researchers developed inhibitors of factor Xa serine protease, an important target in the blood coagulation cascade.
- Amidine-containing compounds have antithrombotic activity but poor oral bioavailabilty, because of the presence

of the basic benzamidine moiety, which is known to hinder absorption from the gastrointestinal tract.

- Replacing the benzamidine moiety with an uncharged indole, exhibiting Ki= 0.005 micrometer and good oral pharmacokinetic properties.
- (LY-517717) is currently under phase II clinical development for the prevention of venous thromboembolism [4–6].

Cyclin-Dependent Kinase-2

- Cyclin-dependent kinase-2 (CDK2) is a member of protein kinase family.
- Role in regulating various events of eukaryotic cell division cycle.
- Over expression of CDK2 causes the abnormal regulation of cell-cycle, which is directly associated with hyper- proliferation in cancer cells.
- CDK-2 is regarded as a potentially therapeutic target for cancer therapy.
- Knowledge of crystallography and availability of X-ray crystal structure of CDK-2 have enabled us to understand the mode of CDK-2 inhibition, which facilitated the development of numerous CDK-2 inhibitors (Figures 4, 5) [5].

Nonpeptide Antigen

- The antigen α4β1 plays an important role in the migration of white blood cells to sites of inflammation.
- It has been implicated in the pathology of various diseases like asthma, multiple sclerosis and rheumatoid.

Nonpeptide Antigen Antagonist

- Scientists described a series of potent inhibitors of α4β1 that were discovered using computational screening.
- The most potent compound was evaluated in a sheep model of asthma, and a 30 mg nebulized dose was able to inhibit early and late airway responses in allergic sheep following antigen challenge and prevented the development of nonspecific airway hyper-responsiveness to Carbachol [7].

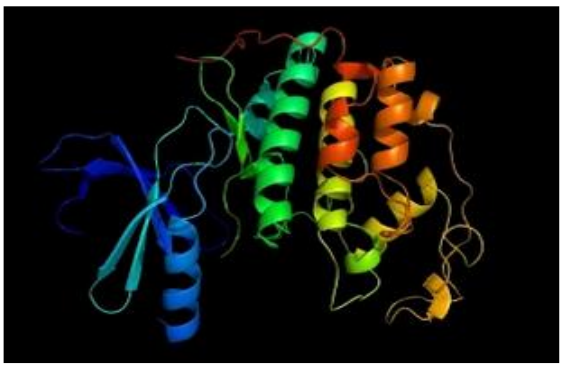

Fig. 4. *Cyclin dependent kinase -2 inhibitor, non-peptide antigen antagonists.*

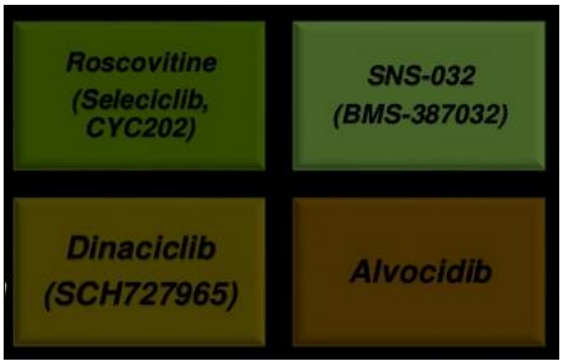

Fig. 5. *CDK2 inhibitors.*

APPLICATION OF COMPUTATIONAL CHEMISTRY IN DRUG DESIGNING

The term theoretical chemistry may be defined as a mathematical description of chemistry, whereas computational chemistry is usually used when a mathematical method is sufficiently well developed that it can be automated for implementation on a computer. In theoretical chemistry, chemists, physicists, and mathematicians develop algorithms and computer programs to predict atomic and molecular properties and reaction paths for chemical reactions. Computational chemists, in contrast, may simply apply existing computer programs and methodologies to specific chemical questions [8].

- Computational studies, used to find a starting point for a laboratory synthesis, or to assist in understanding experimental data, such as the position and source of spectroscopic peaks.
- Computational studies, used to predict the possibility of so far entirely unknown molecules or to explore reaction mechanisms not readily studied via experiments.
- Thus, computational chemistry can assist the experimental chemist or it can challenge the experimental chemist to find entirely new chemical objects.
- Several major areas may be distinguished within computational chemistry:
- The prediction of the molecular structure of molecules by the use of the simulation of forces, or more accurate quantum chemical methods, to find stationary points on the energy surface as the position of the nuclei is varied.
- Storing and searching for data on chemical entities.
- Identifying correlations between chemical structures and properties and quantitative structure–activity relationship (QSAR).
- Computational approaches to help in the efficient synthesis of compounds.
- Computational approaches to design molecules that interact in specific ways with other molecules (e.g. drug design and catalysis) [8].

CONCLUSION

The extensive variety of computational tools used in drug discovery campaigns suggests that there are no fundamentally superior techniques. The performance of methods varies greatly with target protein, available data, and available resources. The process of drug discovery and development is a long and difficult one, and the costs of developing are increasing rapidly. Mechanism-based drug design tackles medical problems directly. It provides an opportunity to discover entirely new lead compounds not possible using other techniques for drug development. The successful application of crowd-sourced biomolecule design and prediction suggests further potential of CADD methods in drug discovery.

REFERENCES

[1] S. Wu-Pong, Y. Organismal. *Biopharmaceutical Drug Design and Development*. 2nd Edn. Totowa, NJ: Humana Press, Humana Press; 2008. ISBN 978-1-59745-532-9.

[2] P. Imming, C. Sinning, A. Meyer. Drugs, their targets and the nature and number of drug targets, *Nat Rev Drug Discov*. 2006; 5(10): 821–34p. PMID17016423.

[3] A.C. Anderson. The process of structure-based drug design, *Chem Biol*. 2003; 10(9): 787–97p. PMID 14522049. doi:10.1016/j.chembiol.2003.09.002.

[4] W.F. de Azevedo, R. Dias. Computational methods for calculation of ligand-binding affinity, *Curr Drug Targets*. 2008; 9(12): 1031–9p.

[5] A.R. Leach, H. Jhoti. *Structure-Based Drug Discovery*. Berlin: Springer; 2007. ISBN 1-4020-4406-2.

[6] H. Mauser, W. Guba. Recent developments in de novo design and scaffold hopping, *Curr Opin Drug Discov Dev*. 2008; 11(3): 365–74p.

[7] G. Klebe. Recent developments in structure-based drug design, *J Mol Med*. 2000; 78(5): 269–81p.

[8] A.C. Anderson. The process of structure-based drug design, *Chem Biol*. 2003; 10(9): 787–97p.