Computer Aided Drug Design: A Promising Approach for Drug Discovery

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ABSTRACT
In the field of pharmaceutical sciences, the drug discovery is an interdisciplinary approach by which new potential drug candidates are discovered. Traditionally, new drug molecules were discovered through identifying the active principles from natural sources or by serendipitous discovery. But it was time consuming and expensive. As a result, in the last few years there has been a technological switch in the methodology of drug design from synthetic approach to new computer-aided drug design (CADD) methods that expedite the drug discovery process and generate more accurate, viable lead compounds. In CADD process so many computational tools are used such as over viewing tools, homology modelling, and homology modelling programs, molecular dynamics, molecular docking and QSAR descriptors. The objective of this review article is to shed light on the role of computer aided drug design in drug discovery process.

Keywords
Lead compounds, homology modelling, molecular docking, QSAR descriptors.

1. INTRODUCTION
The process of drug discovery is very intricate and requires a multidisciplinary approach to design effective and commercially feasible drugs. Failure of a candidate molecule can occur as a result of combination of reasons such as poor pharmacokinetics, lack of efficacy, side effect and commercial reasons (Bharath et al. 2011). Traditionally, new drug molecules were discovered through identifying the active ingredient from traditional remedies or by serendipitous discovery. For an individual drug candidate a pharmaceutical industry synthesizes >1000 structural derivatives and depending on the initial screening results protection of such data is carried out, which significantly increases the cost of drug discovery procedure in its initial phases which is directly proportional to the number of molecules to be designed, synthesized and tested (Pramod, 2014). Regulatory agencies as well as pharmaceutical industry are actively involved in development of computational tools that will improve effectiveness of drug discovery and development process, decrease use of animals and increase predictability (Kapetanovic, 2008). Computer aided drug design is the process which provides computational methods and softwares that are used in design and discovery of new molecules of therapeutic interest. In the postgenomic era, owing to the dramatic increase of small molecule and biomacromolecule information, CADD tools have been applied in almost every stage of drug R & D, greatly changing the strategy and pipeline for drug discovery (Jorgensen et al. 2004). This review focuses on CADD techniques with special emphasis on the role of CADDs in drug discovery.

2. COMPUTER-AIDED TECHNIQUES USED IN DRUG DESIGN AND DISCOVERY
Some of the important CADD techniques include:

Homology modelling: Homology modelling means similarity searching for drug analogs. Homology modelling is used to predict the 3D structure of proteins (Qian *et al.* 2008). The user provides an alignment of a sequence to be modelled with known related structures and modeller automatically computes a model containing all non hydrogen atoms.

Molecular dynamics: Molecular dynamics deals with the study of movement of molecule. Every molecule has its own characteristic frequency of vibration. It can oscillate position one to two through zero, where the molecule has high potential energy at one and two position and least at zero position (Luis *et al.* 2009).

Docking: Docking represents ligand binding to its receptor protein. Docking is used to identify and optimize drug candidates by examining & modelling molecular interactions between ligand and target macromolecules (Perdo *et al.* 2010).

QSAR: Traditional QSAR methods are based on association of biological activity with local features of atoms, whole molecular properties (e.g. charge) and substituent effects (e.g. fragment hydrophobicity indices). QSAR provides a number of descriptors that one can use in determining new QSAR relationships. A descriptor is a molecular property that can be calculated by QSAR.

3. IN SILICO DRUG DISCOVERY PROCESS
It consists of 3 Stages (Pranita *et al.* 2012) -

Stage 1: The first stage is identification of a therapeutic target and building a heterogeneous small molecule library to be tested against it. Then, a virtual screening protocol is developed initialized by either docking of small molecules from the library or building these structures in the active site by using De novo design methods.

Stage 2: The selected hits from the stage 1 are checked for specificity by docking at binding sites of other known drug targets.

Stage 3: A detailed *in silico* ADMET profiling studies are performed on selected hits and those molecules that pass such studies are called leads (Pranita *et al.* 2012).

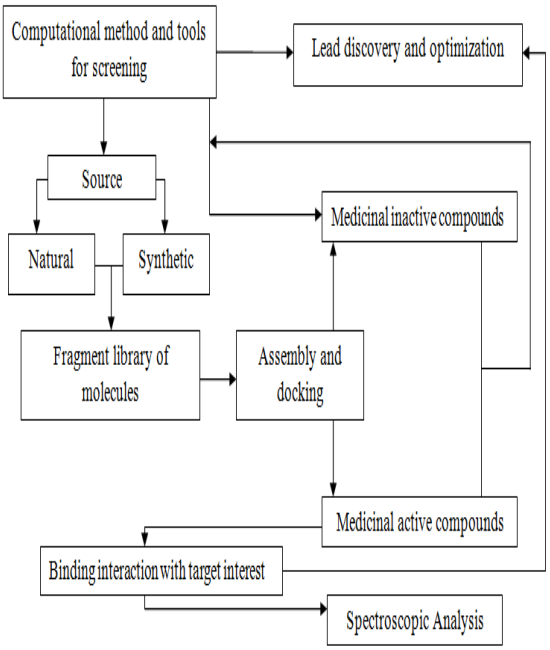

Figure 1: The Process of Drug discovery

4. BENEFITS OF CADDS

CADD methods and bioinformatics tools offer significant benefits for drug discovery programs (Perun *et al.* 1989).

(i) Economic: To bring a new drug to the market is very expensive with the current price reaching approximating US$800 million, according to data reported in a recent study. The addition of computer aided drug design technologies to the R&D approaches of a company, could lead to a reduction in the cost of drug design and development by up to 50% (Werner *et al. 2006*).

(ii) Time-to-Market: By focusing drug research on particular lead molecules and avoiding potential "dead-end" compounds, biopharmaceutical companies can launch their drugs to the market more quickly (Choudhary *et al.* 2011).

(iii) Information about drug-receptor interactions: Softwares can give an idea about potential therapeutic compounds, their protein targets and binding of drug with protein targets thereby helping in modification of drug compounds for improvement.

(iv) Rapid Drug Development: With the advent of bioinformatics tools, discovery and designing of drugs for cancer, arthritis, AIDS and other diseases heavily depends on the computer, instead of relying on the trial-and-error methods of the past (Choudhary *et al.* 2011). In silico methods show promise in identifying new lead compounds much faster than combinatorial approaches and HTS.

5. LIMITATION OF COMPUTER AIDED DRUG DESIGN

Some of the limitations of CADD are that it is lengthy, expensive, and intellectually inelegant (Rahman *et al.* 2012).

6. SOFTWARES USED IN CADD

It includes the software programs in Grid computing, window based general PBPK/PD modelling software, PKUDDS for structure based drug design, APIS, JAVA, Perl and Python as well as software including software libraries.

Table 1: List of commonly used *in silico* software for the intermediate steps in the drug discovery process (Bharath *et al.* 2011)

Programs	Company
TOPKAT, Tsar, LigandGel, ZDOCKPro, DS MedChem Explorer, AEI,	Accelrys
ACD/LogD Suite and ACD/Log Sol Suite, ACD/LogD Batch and ACD/Log Sol Batch, ACD/Structure Design Suite, ACD/PhysChem batch	ACD/Labs
ADMET Modeller, ADMET Predictor, Class Pharmer 4.0, Gastro Plus, DDD Plus	Simulations Plus, Inc.
ToxML, Lead Scope Toxicity Database, Lead Scope Known Drugs Databases, Lead Scope Enterprise, Lead Scope Personal	Lead Scope
Algorithm Builder, QSAR Builder, ADME Boxes v. 3.0, Tox Boxes v. 1.0, ADME/Tox WEB, DMSO Solubility, ADME Batches, Absolv	Pharma Algorithms

Table 2: List of drug discovery software packages available commercially (Bharath *et al.* 2011)

S. No.	Software name	Company	Provided utilities and URL
1.	Insight II, Discovery studio, Cerius	Accelrys	Molecular modelling and de novo drug design. http://www.accelrys.com/products
2.	Sybyl	Tripos	Computational informatics software for drug discovery. http://www.tripos.com
3.	Phase, Glide,	Schrodinger	Pharmacophore

	Liasion		modelling, Ligand-receptor docking. http://www. Schrodinger.com
4.	Bio-suite	Tata consultancy services	Genomics, Protein modelling, structural analysis, simulation and drug design. http://www. Atc.tcs.com/biosuite
5.	Sanjeevini	Indian institute of technology, Delhi	Active site directed drug design http://www.scfbioitd.in/research/drugdesign.htm

7. CONCLUSION

Computational chemistry and molecular modeling are assuming an increasingly important role in understanding the basis of drug-receptor interactions and assisting the medicinal chemist in the design of new therapeutic agents. Improvements in computer graphics, computational power, and software have led to a better understanding of the three-dimensional aspects of ligand receptor interactions and receptor specificity. CADD approaches can provide valuable information for target identification and validation, lead selection, small-molecular screening and optimization. In particular, these sub disciplines of CADD) have demonstrated promising application for design of drug. The latest technological advances (QSAR/ QSPR, structure-based design, combinatorial library design, chemoinformatics & bioinformatics), the growing number of chemical and biological databases and an explosion in currently available software tools provide a much improved basis for the design of ligands and inhibitors with desired specificity. In future, this review will be helpful for design of drug with minimal side effects and high potency. Furthermore, excessive application of computational approaches with higher precision could reduce the overall cost and failure of drug designing process.

8. ACKNOWLEDGMENTS

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9. REFERENCES

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