DOI: 10.31703/gdddr.2017(II).01

URL: http://dx.doi.org/10.31703/gdddr.2017(II-I).01 Vol. II, No. I (2017) Pages: 1 – 8

Arif Paiman [a] Ahmad Mohammadi [b] Mubashar Rehman [c]

# Role of Computer Aided Drug Design in Modern Drug Discovery and Pharmacokinetic Prediction

## Abstract

*In modern day, Data on different diseases and drug substances with their properties like modification, side effects, and dose requires documentation data and building library exploring, such library with vast information in every aspect needs computational methods used in CADD. Recognition of specific targets for the drug tested and defining pharmacological activity of a drug candidate based on the structure of both drug and its target, finding outside effects of drugs at the molecular level and calculation of toxicity caused by metabolism of drug applications of Computer aided drug design in the drug discovery process. We can get additional tools and websites which serve As a tool for the source of data and computational drug design are available on the web interface and being used extensively by researchers and scientists to save time and budget for speeding up the process of experiments for Novel Drug compound.*

**Key Words:** Computer Aided Drug Design, Pharmacokinetics, Computational Methods, Drug Discovery, Novel Drug Candidate, Target -Drug Interaction

## Introduction

Search for the discovery of new drug candidate or vaccine that shows required safety, specificity, efficacy and potency is progressing fast since the covid-19 pandemic started searching for the new drug candidate to minimize mortality and testing existing drugs on patients hoping so it will treat them.

Various techniques involving combinatorial chemistry, high through put-out screening enables us to find various new compounds out of which only some of them are filtered and selected for further studies. Computer-aided drug design emerging techniques to improve, Creation, and modification of active principles of biological activity that affects the human body. Drug Discovery involves three main processes first of all recognition of potential binding sites for hit and trials various targets stitches receptors, active sites and allosteric site of enzymes protein and DNA structure parts are selected for docking and binding trial called hit finding second step development of Pharmaceutical formulation in all three steps of clinical trials needs to be implemented using in Vivo and in vitro modellings costs of which is increasing from 8.6 to 2.4 million dollars.

at the final step, the registration of Pharmaceutical formulation should be done another forget a patent for open markets distribution and monitoring closely the problems such as drug interactions and tension side effects of appearing along with administration drug and trying to modify Pharmaceutical formulation to eliminate defects Research and development Computer-aided drug design minimizes the budget used in the clinical trials by the reduction in animal experimentation and saves as time speeding up the total entire procedure of drug Discovery Computer aided drug design uses computational tools filtering out Novel Drug compounds for identifying targets by using techniques of structure-activity relationship, Docking techniques and Corporation with various techniques success cabinet Royal chemistry artificial intelligence and high through put out screening to filter out most probable drug candidate for special diseases

[a] Department of Pharmacy, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan.

[b] Department of Pharmacy, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan

[c] Assistant Professor, Department of Pharmacy, Faculty of Biological Sciences, Quaid-i-Azam University, Islamabad, Pakistan. Email: mrehman@qau.edu.pk (*Corresponding Author*)

www.gdddrjournal.com GDDDR GLOBAL DRUG DESIGN & DEVELOPMENT REVIEW

Inclusion of pharmacological and pharmacokinetic and pharmacodynamic prediction of drug characteristics for example drug toxicity, metabolism to test the safety of formulation at early stages of drug development.

## A Summary of Recent Approaches Used in Computer Aided Drug Design

In past thirty years with improving the power and availability of computer and chemo genomic data have allowed the computational chemistry method discovery many new drugs. For example, many drugs like Zanamivir, Nelfinavir and Imatinib have discovered with the help of molecular modeling methods.

**Table 1.** Examples of drugs recently discovered with Computer Aided Drug Design

| Drug | Indication | Computer-Aided Drug Design Method | Target | Status |
|---|---|---|---|---|
| Oxymorphone | Peripheral opioid receptor antagonists | 3D molecular docking | Gene name: OPRD1<br>Gene name: OPRM1 | Clinical trials 2015 |
| Saquinavir | Inhibitor of HIV-1 and HIV-2 proteases | Pharmacophore | Uniprot id:Q72874<br>Gene name: pol | Approved 1995 |
| Zanamivir | Antiviral (influenza A and influenza B) | Modeling de novo-design | Neuraminidase<br>Uniprot id: P27907<br>Neuraminidase<br>Uniprot id: 06818<br>Sialidase-2<br>Uniprot id: P27907 | Approved 2000 |
| Dorzolamide | Glaucoma and ocular hypertension | Fragment-based screening | Gene name: CA2<br>Gene name: CA4<br>Gene name: CA1<br>Gene name: CA3 | Approved 2012 |
| Norfloxacin | Inhibitor of bacterial DNA gyrase | QSAR | Gene name: gyrA<br>Gene name: parC<br>Gene name: TOP2A | Approved 1998 |

## Classification Computer Aided Drug Design Methods

Computer aided drug design methods are divided into three methods hybrid method, ligand-based method structure method.

## Hybrid Method

Availability of 3D structure of a target and structure of active substance enables to utilize certain methods such as structure-based method and ligand-based binding to find the biological activities of the lead compound to be clarified however the combination of mentioned methods can be used to predict the biological activity of a lead compound to be tested in single or multiple targets in pharmacophore determination.

## Ligand-based Methods

Ligands with specific biological activities have known and specific structures by testing and docking various active compounds against ligand Structures we can obtain various biological activities of trucks and also improve the existing activity of active substances.

## Structure-based methods

The structure-based method relies only on the targets spatial structure, for example, docking an active substance against a structure of the binding site and allosteric site of an enzyme and testing the mechanism of action of specific drugs at molecular level clarify the binding Kinetic ligand Target interactions.

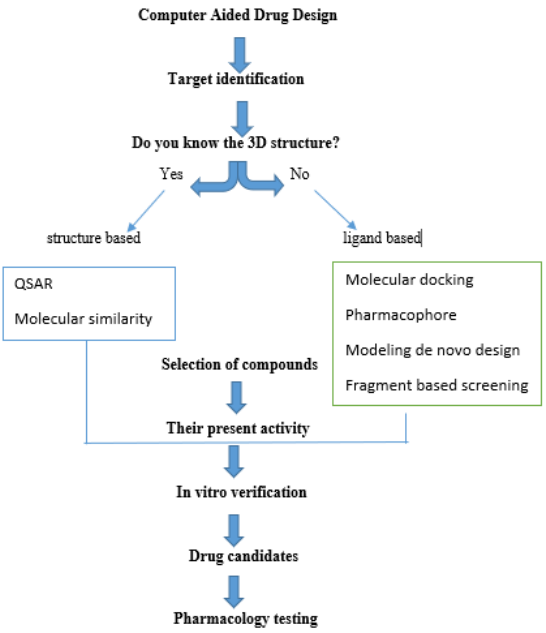


**Figure 1:** Schematic Representation of the process of Computer Aided Drug Design & Discovery (CADD).

## Main Applications of Computer-Aided Drug Design

To measure the scope of Computer-aided drug design for to find new biological substance is known as lead compounds in Novel Drug Discovery, for example, finding in Sourcing new antibiotics which is a solution to the antimicrobial resistance and prediction of pharmacokinetic parameters such as absorption, distribution, metabolism and toxicity of drugs safe time in many in clinical trials during drug discovery process.

## Hit Finding

virtual screening of large compounds for specific activities and filtering drugs activities using structured like and hybrid method or ligand method software is used in Computer-aided drug design help service to speed up the process of finding a new lead compound for specific novel diseases and Rare diseases. Experimental evaluation Relies on filtration process during experimental procedure which helps us to find the specific biological activity of drug substances and this helps us to find the targets for binding for small molecules for better specificity of Pharmaceutical formulation.

## Lead Optimization

Problems regarding absorption distribution metabolism excretion and toxicity cause withdrawal from available of Pharmaceutical formulation from the market and cancellation of clinical trials on the new Drug substance entity Crystallization of machine learning and artificial intelligence Technologies communication with structure ligand Hybrid based material Computer-aided drug design improves their activity and reduces drug interactions Toxicity associated with Pharmaceutical product Specific organs of tissues reduced tissue build up and this helps us for the promotion of Pharmaceutical entity to reach human clinical trials and reduces the cost associated with the clinical trials and saves us time during their drug Discovery process.

## Identification and Validation of Target by Chemical Biology

The target validation and identification can be accomplished both at the beginning (target based or reverse chemical genetic) or at the end (phenotype based or forward chemical genetics) of a biological screening. Genetic interaction, through biochemical and computational interpretation techniques are used to confirm the

protein target elaborate in the biological pathway being considered. Enzyme assays and other biochemical tests can convey beneficial proven for primary optimization when target structure data is available. In expansion, various DNA and RNA investigation strategies permit target identification utilizing using genetic or genomic strategies adjust and modify the presence and quality of protein targets in a controlled demonstrate. Computational interpretation techniques are moreover competent to predict the target of identified inhibitors utilizing structure based and ligand-based strategies. In precise, these procedures are as often as possible utilized for medicate moving to depict the off target intelligent medicine discovery research.

The strategies announced over are crucial in gathering data essential to execute CADD and have been broadly examined in a most recent paper by Schenone.

## Assessing the Side Effects and Drug Interactions of a Lead Compound at the Molecular Level

In- silico method can be used for evaluation of side effects associated with Noble compound at early clinical trials by mode of interaction of human proteins with drug compound we are programs and software simulate structures of targets of drugs in three-dimensional structures. Interacting with target structure certain genes are modified on the surface of cultured cells as a result of biological activity of the drug contracted with the target another method we can isolate the targets for example receptors protein targets and active site of enzymes but this method is very cross and requires very high technique perform during installation and experimental premises isolation technique helps us to minimize errors and bias during experimentation due to impurity and environmental errands the quantity and amount of expressed genes produced by drug target interaction facilitates to find pathophysiological processes behind the behind side effects for example Side Effects of drugs on the cardiovascular system can be checked buy amount of genes related to myocardium infraction, ventricular arrhythmias another heart diseases produced when a drug interacts with the targets on the myocardium tissues. We can also determine drug interactions and protect them by checking two more potentials interacting with each other against similar targets to check displacement of one drug bound to target buy another one interacting more potentially with the same target.

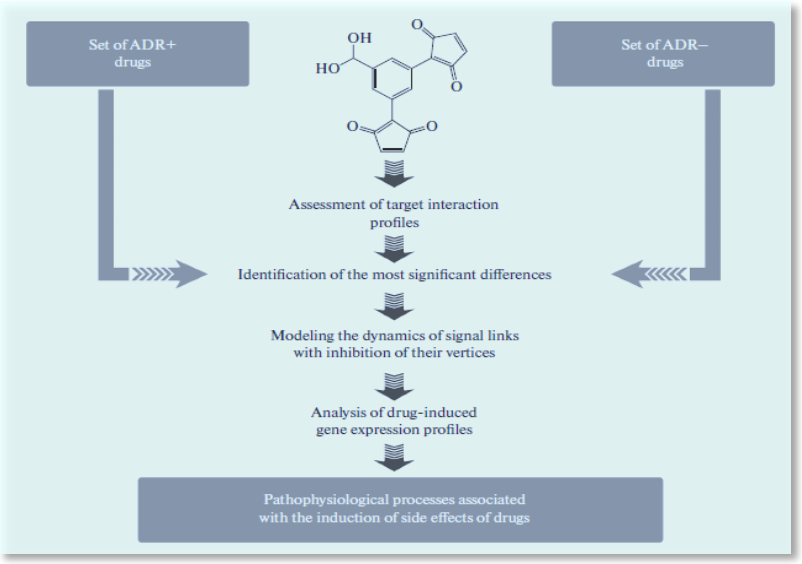


**Figure 2:** Analysis of side effect at Molecular Level Using in-Silico Modelling

## Drug Metabolism Prediction

Drug substances change such as metabolism and biotransformation to form metabolites To facilitate drug excretion by making them water-soluble during biotransformation intermediate structures are formed before production of metabolites certain software related to Computer-aided drug design procedures and machine learning procedures imitate the metabolism of drugs by cytochrome P 450 at certain levels they also generate virtual metabolic sites for every drug by comparing types of metabolites produced during experimentation and

metabolites mention for a specific drug in standard literature like this we can predict metabolism which helps us reduce drug toxicity and side effects during drug formulation and formulating new Drugs.

## Approaching Problems in Computer Aided Drug Design Field

Computer-aided drug design faces many problems regarding these shoes, but problems faced isn't Limited true regarding the list.

Development in-silico in studies and techniques and genetic engineering using computational tools searches software machines certain Technologies like artificial intelligence nanotechnology.

Improving in prediction specificity Regarding side effects and toxicity of drug substances. Increasing Precision of virtual screening for checking of the docking of drugs at multi-molecular targets increasing numbers and Precision of online software in tools used in Computer-aided drug design and setting standards for inclusion in professional scope to be recognized defining specificity and sensitivity in the detection of targets simulation of structures Docking sensitivity remains a big concern that should be solved by a legal organization to supervise companies making this software tools and machines to set international units of measurement concerning sensitivity, precision, in the specific performance required by that tool.

## Training Educating and Commitment

To continue the regeneration of knowledge of Computer-aided drug design skills any improvement in this field special commitment step is necessary to make Computer-aided drug design field of study in undergraduates and further graduate-level this requires budget, holding various seminars training workshops and internships given to students and also various Publications such as sources like textbooks and creation of libraries for sources of reference standards to compare intermediate structures formed during metabolism specific and reference standards for structure of every enzymes and target known to create Reference standard library.

## Prediction of Pharmacokinetic Parameters of a Drug

Pharmacokinetic characterization of a drug is rate-limiting step during clinical trials all methods are playing important role introduction of pharmacokinetic profiles of a drug such as prediction of metabolism intermediates, side effects and mechanism of toxicity associated with Drug entity we can speed up drug discovery process and clinical trials by the help of pharmacokinetic characterization at early stages by the reduction in animal experimentation and the cost associated with it and also errors due to the variations in the targets and gene expression.

## Internet Resources for Biological Activity Prediction

There are different methods available for implementation of computer aided drug design either, as local version of programs or WEB services freely searchable on the internet.

Pass INet or PASS Online is the first available internet based resource that allowed the user to predict the biological activity spectra via internet, the PASS Online and some other web sources have been used for numerous computational investigations to match the correctness of prediction of experimentally verified types of biological activity. The establishment of freely available record having material and data on the structure and organic activity of compounds such as PubChem, CheMbl and Drug Bank stimulated the development of other web services that predict biological activity profiles. Several online available facilities make prediction based on evaluating the parallel structural formula of a chemical formula of a chemical compound that's why the accuracy of assessment will reach 100% provided that training set used is sufficiently complete. In this case two test sets are prepared, the first one have 50 well known repositioned drugs while the other has 12 drugs recently patented for a new indication, analysis of the prediction allowed to compare the accuracy of prediction of several web services like SuperPred, Target hunter, ChemPort, SEA and Tar Pred. the sensitivity value has been utilized for valuation of quality of prediction as the proportion of number of properly expected pharmacotherapeutic effects to the number of known pharmacotherapeutic effects for all drugs. In regard to the initial set the sensitivity values differ from 0.64 (**Tar Pred**)-1.00 (**PASS**) for initial indication and 0.64 (**Tar Pred**)-0.98 (**PASS**) for repositioned indication, in the case of second set of drugs the sensitivity values range from 0.08 (**Super Pred**)-1.00 (**PASS**) for initial indication and 0.00 (**Super Pred**) to 1.00 (**PASS**) repositioned

indication, the accuracy of PASS is near to 100% for both initial and repositioned indications. This outcome specifies there is no need for agreement predictions based on the combination of PASS result and many other internet services.

## Future Research Opportunities

- Compound structures docking to the allosteric active size of targets such as enzymes active sites
- Studies of structural and virtual simulation of macromolecules for example proteins DNA structure and structures of receptors
- Determination of free energy required for binding of a drug with its specific target
- Operation of Computer-aided drug design with various other techniques and technologies used in Novel Drug Discovery, for example, combinatorial chemistry, simulation software, artificial intelligence, and many more
- Defining a specific class of drug planning to micro molecular structures
- Discovery of new Diagnostic techniques based on the principle of fluorescence
- Production of high definition structural simulation of direct and its target and monitoring drug-target interactions during an experimental evaluation

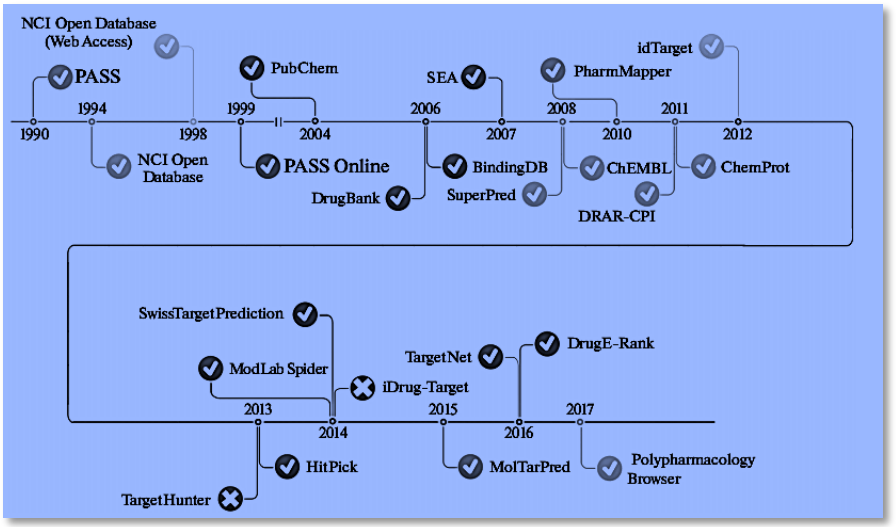


**Figure 3:** Development of Webs in the Pharmaceutical Field over 2 decades

## Artificial Intelligence

Artificial intelligence as machine learning could be a branch data and computer science interested with the embedding of intelligence within the machine and computer. Artificial intelligence is widely used in different parts of hospitals like ICU care, surgical scheduling and diagnostic purposes. Surprising result has been found in acknowledgment and imaging investigation, where it has been proposed that, in spite of the fact that in its earliest stage, artificial intelligence may supplant doctors in near future.

The current studies and improvements in artificial intelligence have been encouraged the neuro-science improvements to promote model complication and its abilities. In the field of medicinal chemistry Artificial intelligence was used for structure activity relationship and quantitative structure activity relationship studies to increase their implementation and expectation power and this has prolonged to molecular docking, drug design and predictive toxicology.

## Conclusion

Computer aided drug design is a technique which is a part of drug Discovery process used in early development of a pharmaceutical formulation involves several computational processes like Docking, QASR, real

chemistry and chemo-informatics its benefit on one hand It faces several challenges and defects regarding education and training in this technique the scientists and researchers neglect to use this technique because it requires exhaustive techniques and are concerned about the errors produced from using of this technique.

## References


Akoka, J., Comyn-Wattiau, I., & Laoufi, N. (2017). Research on big data—a systematic mapping study. *Computer Standards & Interfaces, 54*, 105–115.

Aldeghi, M., Heifetz, A., Bodkin, M. J., Knapp, S., & Biggin, P. C. (2016). Accurate calculation of the absolute free energy of binding for drug molecules. *Chemical Science, 7*(1), 207–218.

Alonso, H., Bliznyuk, A. A., & Gready, J. E. (2006). Combining docking and molecular dynamic simulations in drug design. *Medicinal Research Reviews, 26*(5), 531–568.

Alpaydin, E. (2004). Introduction to machine learning (adaptive computation and machine learning). *Cambridge, MA: The MIT Press.*

Andrade, C. H., Neves, B. J., Melo-Filho, C. C., Rodrigues, J., Silva, D. C., Braga, R. C., & Cravo, P. V. L. (2018). In silico chemogenomics drug repositioning strategies for neglected tropical diseases. Current Medicinal Chemistry. https:// dx.doi.org/10.2174/0929867325666180309114824 [in press].

Arcon, J. P., Defelipe, L. A., Modenutti, C. P., Lo´pez, E. D., Alvarez-Garcia, D., Barril, X., ... Mart´ı, M. A. (2017). Molecular dynamics in mixed solvents reveals protein-ligand interactions, improves docking, and allows accurate binding free energy predictions. *Journal of Chemical Information and Modeling, 57*, 846–863.

Atkinson, S. J., Soden, P. E., Angell, D. C., Bantscheff, M., Chung, C., Giblin, K. A., ... Prinjha, R. K. (2014). The struc- ture based design of dual HDAC/BET inhibitors as novel epigenetic probes. *Medicinal Chemical Communications, 5*, 342–351.

Bajorath, J. (2013). A perspective on computational chemogenomics. Molecular Informatics, 32, 1025–1028. Bajorath, J. (2017). Molecular similarity concepts for informatics applications: (pp. 231–245). *New York, NY: Humana Press.* https://dx.doi.org/10.1007/978-1-4939-6613-4_13.

Barmania, F., & Pepper, M. S. (2013). C-C chemokine receptor type five (CCR5): an emerging target for the control of HIV infection. *Applied & Translational Genomics, 2*, 3–16.

Beauchamp, K. A., Lin, Y.-S., Das, R., & Pande, V. S. (2012). Are protein force fields getting better? A systematic benchmark on 524 diverse NMR measurements. *Journal of Chemical Theory and Computation, 8*, 1409–1414.

Beisken, S., Meinl, T., Wiswedel, B., de Figueiredo, L. F., Berthold, M., & Steinbeck, C. (2013). KNIME-CDK: workflow-driven cheminformatics. *BMC Bioinformatics, 14*, 257.

Best, R. B., Buchete, N.-V., & Hummer, G. (2008). Are current molecular dynamics force fields too helical? *Biophysical Journal, 95*, L07–L09.

Bini, S. A. (2018). Artificial intelligence, machine learning, deep learning, and cognitive computing: what do these terms mean and how will they impact health care? *The Journal of Arthroplasty, 33*, 2358–2361.

Bornmann, L. (2012). Measuring the societal impact of research. *EMBO Reports, 13*, 673–676.

Brindha, S., Vincent, S., Velmurugan, D., Ananthakrishnan, D., Sundaramurthi, J. C., & Gnanadoss, J. J. (2017). Bioinformatics approach to prioritize known drugs towards repurposing for tuberculosis. *Medical Hypotheses, 103*, 39–45.

Computer Aided Drug Design: from Discovery of Novel Pharmaceutical Agents to Systems Pharmacology

February 17, 2020, V.V. Poroikov, Institute of Biomedical Chemistry, ul. Pogodinskaya 10, bldg. 8, Moscow, 119121 Russia pages (222-223).

Saldıvar-Gonza´lez, F. I., Prieto-Mart´ınez, F. D., & Medina-Franco, J.L. (2017). Descubrimiento y desarrollo de

Wassermann, A. M., Lounkine, E., Hoepfner, D., Le Goff, G., King, F. J., Studer, C., ... Glick, M. (2015). Dark chemical matter as a promising starting point for drug lead discovery. *Nature Chemical Biology*, 11, 958–966.

WHO. (2018). World Health Organization. Retrieved from http://www.who.int/en/. Accessed 24 March 2018. Yadav, D. K., Kumar, S., Saloni, Singh, H., Kim, M. H., Sharma, P.,

Yang, H., Sun, L., Li, W., Liu, G., & Tang, Y. (2018). In silico prediction of chemical toxicity for drug design using machine learning methods and structural alerts. Frontiers in Chemistry, 6, 30.