ECRONICON OPEN ACCESS

EC PROTEOMICS AND BIOINFORMATICS
Editorial

# Structure Based Drug Design: Past, Present and Future

**Anand Gaurav***

*Faculty of Pharmaceutical Sciences, UCSI University, Kuala Lumpur, Malaysia*

***Corresponding Author**: Anand Gaurav, Faculty of Pharmaceutical Sciences, UCSI University, Kuala Lumpur, Malaysia.

**Received:** August 10, 2017; **Published:** August 12, 2017

Drug discovery is a time-consuming, high-risk and costly process and on an average, takes about 15 years for the transformation of lead molecules to approved drugs. Over the last three decades, computer-aided drug design (CADD) has become an invaluable tool for studying relation between structure and pharmacological properties of chemical compounds as well as their adverse effects. CADD is mostly used to filter the most promising molecules from a large number of candidate molecules, for further experiments in wet lab. The application of computational methods as a means to identify and design novel drugs started in the 1980's when first report explaining relation between specific physicochemical properties and potency of known inhibitors was published [1]. The impact of CADD on the overall process of drug discovery has been quite huge over the last three decades [2,3]. Application of CADD along with high throughput synthesis and screening has resulted in significant reduction of the cost as well as time of drug discovery. While impacting the drug discovery process the computational methods themselves have evolved at immense pace and newer and more accurate methods have come up. Traditionally computational methods have been classified into structure based drug design (SBDD) methods and ligands based drug design (LBDD) methods [3]. Structure based methods like docking based virtual screening (VS) has been used for new lead identification, while ligand based methods such as quantitative structure activity relationships (QSAR) have been mostly used for lead optimisation [4-7]. However, ligand based methods such as pharmacophore development has played important role in many lead discovery programs.

Structure based methods like docking and molecular dynamics (MD) simulations have been used to study the binding of PDE inhibitors with the enzymes, receptors and other drug targets. While the information derived from these methods have been used to optimise the structure of inhibitors [8-12].

The advent of high performance computing (HPC) and modern parallel accelerator architectures along with selected parallel programming models such as OpenMP, OpenCL, MPI and HPX have allowed CADD in general and structure based methods in particular to be implemented on a large-scale drug discovery projects [13]. This allows accelerated drug discovery projects by applying heterogeneous systems equipped with parallel computing devices. Virtual screening of large databases of compounds using docking based VS programs has become significantly faster due to the evolution of HPC and the computational cost has also become significantly cheaper.

HPC also allows the study of intricate molecular mechanisms such as allostery using computational methods, this was previously unheard of. Molecular Dynamics has been applied recently to study allostery, a long-range macromolecular mechanism of internal regulation [14,15]. This phenomenon can be exploited to achieve important therapeutic effects, since specific ligands able to bind allosteric sites can be designed. From the drug design point of view, it's important to characterize the allosteric mechanisms behind long-range interactions. These interactions have been characterised by exploiting HPC and accelerated approaches to perform simulations able to describe these mechanisms. Indeed, development of HPC and soft computing techniques have provided solution to problems with extreme computational costs which were previously not easy to solve. One such example is the protein folding problem which falls under the ambit of structure based drug design itself.

As clearly illustrated by the numerous and wide-ranging application of SBDD, it has clearly brought about a revolution in the field of drug design/discovery. However, it should be borne in mind that the cases of successful application of SBDD that are reported are fewer than the ones that have led to failure. The reasons for failure are many and cannot be always attributed to the shortcomings of SBDD, rather they are mostly related to the incorrect approach to the application of SBDD. Despite all these challenges, SBDD has shown its immense potential in the discovery of novel drugs and it is believed that SBDD will make a difference in the future as well. The continuing development and evolution of biochemical technology, as well as the software/algorithms and hardware will accentuate the success stories of SBDD in future.

## Bibliography

1. Timothy Robert B. "Imidazoquinazolinone based inhibitors of Phosphodiesterase 3" (2017).

2. Sliwoski G., *et al*. "Computational Methods in Drug Discovery". *Pharmacological Reviews* 66.1 (2014): 334-395.

3. Leelananda SP and Lindert S. "Computational methods in drug discovery". *Beilstein Journal of Organic Chemistry* 12 (2016): 2694-2718.

4. Kovalishyn V., *et al*. "Predictive QSAR modeling of phosphodiesterase 4 inhibitors". *Journal of Molecular Graphics and Modelling* 32 (2012): 32-38.

5. Dong X., *et al*. "A novel structure-based multimode QSAR method affords predictive models for phosphodiesterase inhibitors". *Journal of Chemical Information and Modeling* 50.2 (2010): 240-250.

6. Antunes JE., *et al*. "Bioactivities of a series of phosphodiesterase type 5 (PDE-5) inhibitors as modelled by MIA-QSAR". *European Journal of Medicinal Chemistry* 43.8 (2008): 1632-1638.

7. Gaurav A and Singh R. "3D QSAR pharmacophore, CoMFA and CoMSIA based design and docking studies on phenyl alkyl ketones as inhibitors of phosphodiesterase 4". *Medicinal Chemistry* 8.5 (2012): 894-912.

8. Xing M., *et al*. "Structure-based design of selective phosphodiesterase 4B inhibitors based on ginger phenolic compounds". *Journal of Biomolecular Structure and Dynamics* 27 (2016): 1-15.

9. Hassaan EA., *et al*. "Mining ZINC Database to Discover Potential Phosphodiesterase 9 Inhibitors Using Structure-Based Drug Design Approach". *Medicinal Chemistry* 12.5 (2016): 472-477.

10. Rauf A., *et al*. "Elucidation of Phosphodiesterase-1 Inhibitory Effect of Some Selected Natural Polyphenolics Using In Vitro and In Silico Methods". *Current Topics in Medicinal Chemistry* 17.4 (2017): 412-417.

11. Nunes IK., *et al*. "Synthesis, Pharmacological Profile and Docking Studies of New Sulfonamides Designed as Phosphodiesterase-4 Inhibitors". *PLoS One* 11.10 (2016): e0162895.

12. Kumar J., *et al*. "Identification of lead BAY60-7550 analogues as potential inhibitors that utilize the hydrophobic groove in PDE2A: a molecular dynamics simulation study". *Journal of Molecular Modeling* 23.1 (2017): 7.

13. Wei F and Michal B. "Structure-Based Drug Discovery Accelerated by Many-Core Devices". *Current Drug Targets* 17.14 (2016): 1595-1609.

14. Chiappori F., *et al*. "HPC Analysis of Multiple Binding Sites Communication and Allosteric Modulations in Drug Design: The HSP Case Study". *Current Drug Targets* 17.14 (2016): 1610-1625.

15. Naithani A., *et al*. "A Molecular Dynamics Study of Allosteric Transitions in Leishmania mexicana Pyruvate Kinase". *Biophysical Journal* 109.6 (2015): 1149-1156.

**Volume 1 Issue 1 August 2017**
**© All rights are reserved by Anand Gaurav.**