Editorial

Recent Advances in the Structure-Based Drug Design and Discovery

Dear Readers!

Md. Imtaiyaz Hassan

It gives me great pleasure and a distinguished honor to release the special issue of Current Topics in Medicinal Chemistry with a theme of Recent Advances in the Structure-based Drug design (SBDD) and Discovery which is focusing on the state of the art for drug discovery procedure and new insights into structural biology. SBDD is a rapidly growing field, providing a new paradigm for drug discovery targeting for many potential drugs. Designing a selective small molecules have a potential to offer better potency, selectivity and drug-like properties than previously achievable, establishing a strong basis for the development of much improved medicines.

This issue will discuss how the recent availability of X-ray structures of various target's ligand-bound conformations, and the subsequent computational analyses of the ligand-binding sites in these conformations, provided a new way to design a potential drug. This special issue contains a total of 10 articles presenting different aspects of drug design and discovery process using varying drug targets, providing a significant stimulation to a reasonable segment of readers.

The first article of this issue is presenting advances in structure-based drug design and its application in drug discovery process by **Mian-Bin Wu group from Zhejiang University**, Hangzhou, China. During the past few decades, the great potentials and success of SBDD have been seen in the field of drug design and discovery. In this review, authors present an overview of the key mechanisms of SBDD, the frequently used computer programs in SBDD and some successful cases. Several typical design processes of lead components from SBDD were also highlighted in detail, such as the discovery of inhibitors of G protein-coupled receptors (GPCRs), antibacterial drugs, and anti-cancer drugs. Though, SBDD has made a revolution in the field of drug design/discovery, it should be borne in mind that the successful cases reported are fewer than the failed ones, which can be attributed to several factors. Despite such challenges, SBDD has shown its great potential in the discovery of novel drugs and it is believed that SBDD will make a difference in the future with the development of biochemical technology, as well as the software and hardware of computers.

The second article of this issue is really very interesting. **Professor Yechun Xu from Drug Discovery and Design Center**, Chinese Academy of Sciences, Shanghai, China reviewed structure-based discovery of phosphodiesterases (PDEs) Inhibitors. PDEs catalyse the hydrolysis of cAMP and cGMP, thereby regulating the cyclic nucleotide signalling pathways and biological responses, and therefore, considered as an attractive drug target for structure-based discovery. In past decades PDE inhibitors have impeded their therapeutic success and therefore spurred the pharmaceutical industry to develop family-selective PDE inhibitors. In this review authors summarize developments and achievements in structure-based search, design and optimization of PDEs inhibitors, and highlighted the challenges that need to be addressed.

Third article of this issue will be focusing on recent advances in computer-assisted structure-based identification and design of histone deacetylases (HDAC) inhibitors, by **Dr. Mohammad Imran Siddiqi** from Molecular and Structural Biology Division, CSIR-Central Drug Research Institute, Lucknow, India. HDAC inhibition induces various tumour cells to enter apoptosis and consequently cell cycle arrest therefore, a large number of HDAC inhibitors have been reported to develop as a new class of anti-cancer agents. Here, authors have reviewed the current status of structure based computational studies that has helped to rationalize the successful identification of HDAC inhibitors. This review provides an overview of contribution of structure-based computational studies that have helped in identifying HDAC inhibitors with an emphasis on the perspectives of its insight, current status, advances and future opportunities as well as the evolving efforts to characterize the structural dynamics of HDACs.

The cysteine biosynthetic pathway is of fundamental importance for the growth, survival, and pathogenicity of the many pathogens. The *de novo* cysteine biosynthetic pathway, on account of its being important for the survival of pathogens and at the same time being absent in mammals, is an important drug target for diseases such as amoebiasis, trichomoniasis & tuberculosis. **Dr. S. Gourinath from School of Life Sciences**, Jawaharlal Nehru University, New Delhi highlighted structural similarities of O-acetylserine sulfhydrylase enzyme in different organisms and the attempts for inhibitor development so far. They also proposed that the intermediate state of the enzyme may be the ideal target for the design of effective high-affinity inhibitors.

The loss of effectiveness of current antibiotics caused by the development of drug resistance today's become a great challenge. Hence, a great interest has emerged in the discovery of novel drugs and therapies to tackle antimicrobial resistance, in particular drugs that target other essential processes for bacterial survival. A review by Professor **Concepción González-Bello from Universidad de Santiago de Compostela, Santiago de Compostela, Spain**, is focusing on enzymes involved in the biosynthesis of aromatic amino acids are may be attractive targets for the development of new antibacterial agents, because they are essential in important pathogenic bacteria. This review is focused on two key enzymes of this pathway, shikimate kinase and type II dehydroquinase. An overview of the use of structure-based design and computational studies for the discovery of selective inhibitors of these enzymes will be provided.

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A detailed view of the structural changes caused by these inhibitors in the catalytic arrangement of these enzymes, which are responsible for the inhibition of their activity, is described. More importantly, it has proved that these enzymes are good targets for the development of inhibitors that can be used as drugs.

An interesting review by **Dr. D. Sriram** from, Birla Institute of Technology and Science-Pilani, Hyderabad campus, provided a deep insight into the *Mycobacterium tuberculosis* Glutamine Synthetase Inhibitors because glutamine synthetase plays a major role in nitrogen metabolism and cell wall biosynthesis of pathogenic mycobacteria. This review focuses on the structural and functional aspects of Mtb glutamine synthetase and an overview of its reported inhibitors till date. Moreover, authors also reported that three compounds found with IC_{50} less than 5 μM to 2.124 μM using computational and differential scanning fluorimetry studies.

Another interesting article on designing prodrugs based on special residues of human serum albumin by **Yi Gou, Feng Yang, Hong Liang** from the Ministry of Science and Technology of China was incorporated. Serum albumin has emerged as one of the most promising drug carriers for active drugs. However, the current strategies for prodrug design, in which chemically modified prodrugs are tethered with residues of human serum albumin, may introduce exogenous compounds and produce unexpected side effects to some extent. In this article author suggested that designing prodrugs based on special human serum albumin residues, such as Cys34 and Lys residues can be employed. This review provided an overview of the development of non-steroidal anti-inflammatory and anticancer prodrugs based on these special residues. Moreover, this review may guide the rational design and development of new prodrugs for future clinical applications.

Philip Prathipati and Kenji Mizuguchi from the National Institute of Biomedical Innovation, Health and Nutrition, Osaka-Japan contributed an excellent review on Systems biology approaches to a rational drug discovery paradigm. In this review author discussed the existing approaches to drug discovery research, the case for systems biology approach, the basic principles and the foundational arguments/ underlying assumptions of systems biology approaches to drug design. They also highlighted the important elements and relationships between the elements of various systems biology datasets, the data models for capturing and retrieving systems biology data, softwares and tools used for either retrospective- or prospective- analysis and the types of hypotheses that can be derived. In addition, this review summarizes some of the existing protocols proposed/ implemented for a systems biology based drug discovery paradigm (NIBIO Toxoicogenomics, DrugMatrix, CMap and LINCs) in terms of their strengths and limitations.

After designing a drug, its delivery to the target is again a challenging step. Hence, we included an article describing challenges and opportunities for biopolymer-based delivery systems by **Professor D. Julian McClements from the University of Massachusetts, USA.** Biopolymer particle suspensions can be used as delivery systems for the protection, controlled release, and targeted delivery of active components to their potential site of action without any harm. The wide variability in the nature of the biopolymers available to assemble these systems with a wide range of physicochemical properties. Biopolymeric delivery systems have been developed in the form of film-, fiber- and particulate like structures with different advantages. Reliable and predictable ingredient properties are therefore important for consistently producing structures with well-defined attributes. Notwithstanding the different challenges that need to be addressed during the production of biopolymer-based delivery systems, they also present some serious opportunities which, in a lot of cases, outweigh the time and effort that have to be invested to optimize their stability and functionality. Biopolymers are also promising with regard to the production of delivery systems optimized for controlled release and target delivery in the gastrointestinal tract. Finally, the author suggested that structure-function relations that will help in the rational design of biopolymer-based delivery systems with specific functional attributes suitable for utilization in food, personal care, supplement, and pharmaceutical applications.

We also included one review article from our group stating the Current advances in the identification and characterization of putative drug and vaccine targets in the bacterial genomes. In this review we are providing a newer opportunities to avail some novel drug target namely, “hypothetical or uncharacterized proteins". This class of proteins draws a significant interest of pharmaceutical research as they can provide new clues regarding the development of novel therapeutics against the multidrug resistant strains of bacteria. *In silico* identification of putative drug and vaccine targets in the set of uncharacterized proteins through comparative and subtractive genomic analyses facilitates the increase usability and efficiency of the present drugs. This review focuses on the current advancement in the field of computational biology that can aid in the identification of putative drug and vaccine targets, prediction of the functionalities of uncharacterized proteins through a variety of sequence and structure based annotation methods. We hope these *in silico* techniques that were listed in this study can facilitate the process of drug designing process.

Finally, I would like to express my considerable appreciation to all authors of the articles in this issue. It is their generous contributions of time and effort that made this issue possible. At the same time I would like to encourage all our readers to avail the content of this issue. I also welcome comments and suggestions that could help to improve the quality further.

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